NCGC National Clinical Guideline Centre

Acute upper gastrointestinal bleeding

Management

Clinical Guideline

Methods, evidence and recommendations

June 2012

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Foreword

Acute upper gastrointestinal bleeding is a major life threatening medical emergency. A recent UK wide audit showed that crude mortality has not significantly changed since the 1950s; yet modern management based upon endoscopic diagnosis and therapy has the potential to stop active bleeding, prevent further bleeding and save lives. Furthermore advances in drug therapies, interventional radiology and operative surgery have occurred and are used when endoscopic therapies prove unsuccessful. Why is there an obvious disparity between modern effective therapies that on the face of it should improve outcome and the continued high mortality observed in routine clinical practice? Part of the answer undoubtedly relates to differences in case mix since patients presenting with acute upper gastrointestinal bleeding are older and have greater medical co-morbidity than ever before. The audit demonstrated great variation in service provision across the UK, including availability of emergency therapeutic endoscopy and interventional radiology, and variation in the expertise of endoscopists. It is therefore possible that inequities in service provision are an important contributor to the relatively poor outcome of this patient group. We anticipate that by providing the evidence base for optimum diagnosis and management, this guideline will help hospitals provide best care for patients presenting with acute upper gastrointestinal bleeding and that this will in turn reduce their risk of death.

Our guideline development group included doctors, a nurse and patients. The remit principally concerned hospitalised patients but a general practitioner provided insight into issues concerning primary care. Our deliberations focused upon a series of key questions that were developed from a large meeting of stakeholders. These questions addressed the important steps in diagnosis and management. Analysis was based upon critical appraisal of published literature followed by discussion and consensus. The quality of the available information varied widely from questions that could be addressed by analysis of high quality randomised clinical trials to informed opinion and whilst some of our recommendations are solidly evidence based, others are based upon clinical experience and what we believe is good common sense. The guideline therefore may be open to criticism since all of our recommendations cannot be justified by quantitative research; there are no randomised trials relating to patient experience and attitudes, trials of rescue therapies following failed endoscopic treatment are extremely difficult to undertake because of patient heterogeneity and relative infrequency within any one unit; there are other examples that will be obvious to the reader. Despite this caveat we are confident that we have produced a useful document that will inform and improve clinical practice.

I am greatly indebted to the guideline development team who showed great skill and expertise in data analysis, who continually questioning the data yet were able through high quality discussion arrive at a series of clinically relevant recommendations that can be adopted by all clinical teams for the benefit of patients.

Dr Kelvin Palmer, November 2011

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Abbreviations

Acronym	Abbreviation
ACA	Available Case Analysis
APACHE II	Acute Physiology and Chronic Health Evaluation II
APTT	Activated Partial Thromboplastin Time
ARR	Absolute risk reduction
AUC	Area under curve (diagnostic test statistic)
BNF	British National Formulary
CI	Confidence Interval
CC	Complications and Comorbidities
CCT	Controlled Clinical Trial
CEAC	Cost Effectiveness Acceptability Curve
CUA	Cost Utility Analysis
DH	Department of Health
EHT	Endoscopic Haemostatic Therapy
EQ5D	EuroQol 5 Dimension
FG	Fibrin Glue
FFP	Fresh Frozen Plasma
GBP	Great British Pound
GDG	Guideline Development Group
GI	Gastro-Intestinal
GRADE	Guidelines Recommendations Assessment Development Evaluation
GRP	Guideline Review Panel
H2RA	Histomine 2 Receptor Antagonist
HDU	High Dependency Unit
Hr	Hour
HR	Hazard Ratio
HRG	Health Resource Group
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
ITU	Intensive Therapy Unit/Intensive Treatment Unit
INR	International Normalised Ratio
IQR	Interquartile Range
IV	Intravenous
LY	Life Year
LYG	Life Year Gained
M/F	Male to Female Ratio
MD	Mean Difference
MID	Minimal Important Difference
N	Number in study
NA	Not applicable

NCGC	National Clinical Guideline Centre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMB	Net Monetary Benefit
NR	Not Reported
NS	Non Significant
NSAID	Non steroidal anti inflammatory drug
PA	Probabilistic Analysis
PICO	Framework incorporating patients, interventions, comparisons, outcomes
PPI	Proton Pump Inhibitors
PSSRU	Personal Social Services Research Unit
PT INT	Pro thrombin time, International Normalised Ratio
QALD	Quality Adjusted Life Day
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RBC	Red blood cells
RCT	Randomised controlled trial
RFVlla	Recombinant Factor VIIa
RR	Risk Ratio
RRR	Relative risk reduction
SD	Standard Deviation
SMD	Standardized Mean Difference
SRH	Stigmata of Recent Haemorrhage
TIPS	Transjugular Intrahepatic Portosystemic Stent shunt
STD	Sodium tetradecyl sulphate
UGIB	Upper Gastro-intestinal bleeding
UK	United Kingdom
UNG	Understanding NICE Guidance
USA	United States of America
USD	United States Dollars

Acknowledgments

The development of this guideline was greatly assisted by the following people:

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- Sharon Swain (NCGC Senior Research Fellow)
- Richard Whittome (NCGC Information Scientist)

1 Introduction

The incidence of acute upper gastrointestinal haemorrhage in the United Kingdom ranges between 84-172 /100,000/year, equating to 50-70,000 hospital admissions per year [1-4]. This is therefore a relatively common medical emergency; it is also one that more often affects socially deprived communities [1-3].

A recent large UK wide audit[5] showed that the hospital mortality of patients admitted to hospitals in the UK for acute gastrointestinal bleeding is about 7%, rising to approximately 30% in patients who bleed as inpatients. A recent analysis has shown only modest age and co-morbidity corrected mortality decreases in recent years[3] . The audit demonstrated considerable inequities in clinical care; some hospitals provided a comprehensive 24/7 service involving endoscopy, interventional radiology and emergency surgery, whilst others did not provide out of hours endoscopy or interventional radiology. The reported expertise of endoscopists varied widely with approximately 30% being unable to manage bleeding oesophageal varices, yet it is obvious that rotas must be populated by teams trained to deliver all aspects of endoscopic haemostatic therapy.

A guideline is therefore required to demonstrate the clinical utility of the diagnostic and therapeutic steps needed to manage patients, and to stimulate hospitals to develop a structure to enable clinical teams to deliver the optimum service.

The guideline concerns patients who present with haematemesis (vomiting of blood) and/ or melaena (the passage of black, tarry stools). Acute blood loss leads to collapse with low blood pressure, rapid pulse, sweating and pallor. In severe cases poor blood flow to the kidneys leads to acute renal failure and in patients with underlying vascular disease to stroke or myocardial infarction. Elderly patients and those with chronic medical diseases withstand acute gastrointestinal bleeding less well than young fitter patients and have a higher risk of death. Almost all patients who develop acute gastrointestinal bleeding are managed in hospital (rather than in the community), there is no published literature concerning primary care and the guideline is therefore focused upon hospital care.

Peptic ulcer is the most frequent cause of major, life-threatening acute gastrointestinal bleeding and accounts for approximately 35% of cases. Bleeding occurs as the ulcer erodes into an underlying artery. A history of previous ulcer disease, aspirin or non-steroidal anti-inflammatory drug use is common. ‘Stress Ulcers’ that can develop in critically ill patients (typically burns patients or patients with severe head injury in Intensive Care Units) are thought to occur as a result of mucosal ischemia. Acutely bleeding stress ulcers have a poor prognosis since bleeding tends to be severe, often develops in multiple sites and arises in the context of multiple organ failure.

Oesophago-gastric varices occur as a consequence of severe liver disease; as alcohol consumption has increased and obesity has become more prevalent. In the UK audit the incidence of variceal bleeding has more than doubled over twenty years and was responsible for about 12% of cases of acute bleeding in the UK. Others[2,3] have not confirmed this trend but gastroenterologists dealing with patients day by day are only too aware of the increasing incidence of decompensated liver disease within their practices variceal bleeding tends to be severe and other complications of liver failure commonly develop. Consequently the impact of this patient group upon service utilisation is disproportionately great.

The guideline focuses upon peptic ulcer bleeding and bleeding from varices. This is partly because the available published literature concentrates upon these diseases. It is also because the other causes of acute gastrointestinal bleeding are either rare or do not usually result in poor outcome. Other causes of acute upper gastrointestinal bleeding include oesophageal tears that are due to prolonged retching (most commonly from alcohol), oesophagitis due to gastro-oesophageal acid reflux, gastritis, duodenitis and gastroduodenal erosions (associated with consumption of aspirin,

non steroidal anti-inflammatory drugs and H. pylori infection), vascular malformations and a range of benign and malignant upper gastrointestinal tumours. Bleeding from these causes is not usually life threatening and in the great majority of cases ceases spontaneously. In most patients, supportive therapy, stopping NSAID use or H. pylori eradication therapy achieve a favourable outcome.

At the time of first assessment it is important to identify patients who have significant liver disease; most will have a history of alcohol abuse or exposure to hepatitis B or C, have clinical evidence of liver disease and abnormal serum liver function tests. Patients with liver disease tend to present complex management problems and are best managed by gastroenterologists or hepatologists.

When patients present with acute upper gastrointestinal haemorrhage, it is crucial to define factors that predict outcome. Several risk assessment scoring systems have been developed for use in patients with bleeding varices and for non-variceal (principally peptic ulcer) bleeding. The purpose of these scores is to define patients at high risk of dying or re-bleeding, who may be best managed in high dependency units, need urgent investigation and specific treatments to stop active bleeding, and, at the other end of the severity spectrum, to identify patients with an excellent prognosis who can be fast tracked to early hospital discharge. Indeed, approximately 70% of peptic ulcer bleeds settle with conservative management, do not rebleed or need endoscopic therapy there are several published risk assessment scoring systems and the guideline recommends the optimum system that should be used at presentation and after endoscopy (Chapter 5).

After initial assessment the first step in managing the patient with acute upper gastrointestinal bleeding is resuscitation; the principles of ‘airway, breathing and circulation’ apply. Patients with major bleeding are often elderly and have significant cardiorespiratory, renal and cerebrovascular co-morbidity. It is vital that these conditions are recognized and supported. In critically ill patients it is wise to enlist the services of specialists in critical care and to support the patient in a high dependency unit. Blood transfusion is administered to patients who are shocked and bleeding actively, but there are controversies concerning the use of blood products in patients with less severe bleeding. The guideline addresses these controversies and recommends when whole blood, platelets and clotting factors should be used (Chapter 7). Patients with liver disease present specific problems; hepatic encephalopathy, renal failure and ascites may all develop or worsen as a consequence of bleeding and warrant specific management. Broad spectrum antibiotics are advocated for this patient group (Chapter 9).

Endoscopy is the primary diagnostic investigation but is undertaken only after optimum resuscitation has been achieved. The optimal timing of endoscopy is a complex issue; other guidelines state that endoscopy should be done within 24 hours of admission in the great majority of cases, and that facilities should be available for urgent endoscopy in unstable, actively bleeding patients. These statements make good sense since late endoscopy is likely to unnecessarily prolong the duration of hospital admission in stable patients, whilst the need to stop active potentially life threatening bleeding by endoscopic therapy is obvious. There are no clinical trials comparing early verses elective endoscopy in severely ill acutely bleeding patients (and nor should there be) and the guideline development group recommendations concerning this patient group were based upon consensus. We did however have access to data from the UK audit that allowed us to make recommendations concerning the overall timing of endoscopy and this related to the great majority of patients who did not require very urgent, emergency therapeutic endoscopy but underwent semi-urgent endoscopy. An economic analysis allowed us to make recommendations concerning the timing of endoscopy and these may have considerable implications for service changes in some hospitals (Chapter 7). We are grateful to the National Blood Service and the British Society of Gastroenterology for providing the information that allowed us to make these statements.

Endoscopy is done to give an accurate diagnosis and to provide prognostic information (the presence of blood within the upper gastrointestinal tract and specific appearances of ulcers and varices predict whether bleeding is likely to continue or recur). Probably of more importance has been the

development of a range of endoscopic techniques that can stop active bleeding and prevent re-bleeding- both from varices and non-variceal lesions. A large number of clinical trials have demonstrated the efficacy of therapeutic endoscopy and the guideline recommends particular endoscopic therapies for varices (Chapter 9) and ulcer (Chapter 8) bleeding.

A range of drugs is relevant. Drugs that suppress gastric acid secretion may be of use in the prevention of ulcer bleeding (for example in patient groups at high risk of ulcer development in the community and in the ITU setting to reduce the risk of stress ulcer development (Chapter 11); and following endoscopic therapy in some cases of peptic ulcer bleeding (Chapter 8). Patients who present with acute gastrointestinal bleeding whilst taking anti-platelet drugs for vascular diseases pose difficult clinical decisions-; stopping these drugs could reduce the risk of continuing bleeding yet increase the risk of death from myocardial infarction or stroke. We produce specific recommendations concerning this issue (Chapter 10). Patients with variceal haemorrhage may benefit from drugs that reduce portal hypertension, and we define the role of these drugs in relation to endoscopic therapy (Chapter 6).

Whilst endoscopic therapy has become the mainstay of therapy for variceal and peptic ulcer bleeding, it is not universally successful and both interventional radiological and surgical approaches have an important role in the management of patients who continue to bleed despite endo-therapy. Trans-jugular intrahepatic portosystemic shunt (TIPS) insertion reduces portal pressure and we recommend this procedure as optimal rescue therapy for patients with both oesophageal and gastric varices (Chapter 9). Transarterial embolisation of the bleeding artery is also recommended as an effective and safe treatment for peptic ulcer bleeding (Chapter 8). The precise roles of these approaches that require highly specialist interventional radiological teams are yet to be defined and in many institutions these treatments are unavailable, particularly out of hours. The UK audit1 demonstrated that emergency surgery is now rarely undertaken for acute upper gastrointestinal bleeding, but when it is done, the operative mortality is approximately 30%.

As with all guidelines, patients are at the heart of our recommendations. We recognise that acute gastrointestinal bleeding can be an extremely unpleasant and worrying event for the patient with concerns about bleeding to death, the underlying cause of bleeding (particularly a fear of cancer) and those relating to endoscopy and surgery. We also recognise that in the emergency setting, patients and their carers are not always able to make informed decisions about their care and that provision of informed consent for diagnostic and therapeutic interventions is sometimes difficult in the midst of life threatening gastrointestinal haemorrhage. Nevertheless we recommend at the end of our guideline steps that clinical teams should undertake to inform patients and carers, both during their time in hospital and in the period after admission (Chapter 12).

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- Information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

"To prepare a clinical guideline on the management of acute upper gastrointestinal bleeding"

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Kelvin Palmer in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every six weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B)

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

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

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

<u>Key clinical issues</u>

- Primary prophylaxis for acutely ill patients in high dependency and intensive care units

- Assessment of risks (such as mortality, re-bleeding and the need for further intervention), including the use of scoring systems

- Initial management 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

- Timing of endoscopy

- Management of non-variceal upper gastrointestinal 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 re-bleeding in patients on NSAIDs, aspirin or clopidogrel

- Management of variceal upper gastrointestinal 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 [TIPS])
    - Interventions for uncontrolled bleeding (oesophageal or gastric) including balloon tamponade, TIPS, surgery and repeat endoscopy

- Information and support for patients and carers

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.

For further details please refer to the scope in Appendix A [and review questions in section 3.1].

2.5 What this guideline does not cover

- Adults with chronic upper gastrointestinal bleeding
- Children (15 years and below)
- Patients with a bleeding point lower than the duodenum

Clinical issues that will not be covered

- Treatment for *Helicobacter pylori*

2.6 Relationships between the guideline and other NICE guidance

2.6.1 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

- Stent insertion for bleeding oesophageal varices. NICE interventional procedure guidance 392 (2011). Available from www.nice.org.uk/guidance/IPG392

- Prevention of cardiovascular disease. NICE Public Health guidance 25 (2010). Available from www.nice.org.uk/guidance/PH25

- Alcohol use disorders. NICE Public Health guidance 24 (2010). Available from www.nice.org.uk/guidance/PH24

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009[6].

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section.

Chapter	Review questions	Outcomes
8	Question 1 Are proton pump inhibitors the most clinical /cost effective pharmaceutical treatment compared to H_2 receptor antagonists or placebo to improve outcome with regards to mortality, risk of re-bleeding, length of hospital stay and quality of life in patients presenting with likely non-variceal upper gastrointestinal bleeding prior and after endoscopic investigation?	• Mortality (early and late mortality) • Re-bleeding • Surgery or other procedures to control bleeding • Need for transfusion • Length of hospital stay
8	Question 2 Are proton pump inhibitors administered intravenously more clinical / cost effective than administered in tablet form for patients with likely non-variceal upper gastrointestinal bleeding?	• Mortality (early and late mortality) • Re-bleeding • Surgery or other procedures to control bleeding • Need for transfusion • Length of hospital stay
5	Question 3 In patients with gastrointestinal bleeding (with or without comorbidities) is there an accurate scoring system (Rockall, Blatchford [aka Glasgow], Addenbrooke) to identify which patients are high risk and require immediate intervention and those at low risk who can be safely discharged?	• Mortality • Re-bleeding • Need for intervention • Need for surgery
7	Question 4 In patients with gastrointestinal 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 re-bleeding or mortality?	• Mortality • Failure to control bleeding • Re-bleeding • Surgical intervention • Length of hospital stay • Blood transfusion requirements

Chapter	Review questions	Outcomes
6	Question 5 In patients presenting with likely variceal upper gastrointestinal bleeding at initial management, is terlipressin compared to octreotide or placebo the most clinical / cost effective pharmaceutical strategy?	• Mortality • Numbers failing initial haemostasis • Re-bleeding • Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events were subdivided into 2 categories: • Adverse events causing withdrawal of treatment • Adverse events causing death
6	Question 6 In patients with confirmed variceal upper gastrointestinal bleeding after endoscopic treatment, how long should pharmacological therapy (terlipressin or octreocide) be administered to improve outcome in terms of clinical and cost effectiveness?	• Mortality • Numbers failing initial haemostasis • Re-bleeding • Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events were subdivided into 2 categories: • Adverse events causing withdrawal of treatment • Adverse events causing death
6	Question 7 In patients with upper gastrointestinal 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?	• Mortality • Re-bleeding • Surgical intervention • Length of hospital stay (ICU stay, total stay) • Adverse events – myocardial infarction
6	Question 8 In patients with upper gastrointestinal bleeding with low platelet count and / or abnormal coagulation factors, pre-endoscopy,	• Mortality • Failure to control bleeding • Re-bleeding

Chapter	Review questions	Outcomes
	what is the most clinical and cost effective threshold and target level at which platelets and clotting factors should be administered to improve outcome?	• Surgical intervention • Length of hospital stay (ICU stay, total stay) • Red blood cell transfusion • Adverse events – serious • Adverse events - fatal
8	Question 9 In patients with upper gastrointestinal bleeding after first endoscopic treatment, is a routine second-look endoscopy more clinically / cost effective than routine clinical follow-up?	• Mortality • Re-bleeding • Additional treatments (salvage surgery, TIPS etc) • Failure to control bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events (leading to death, leading to withdrawal from treatment)
8	Question 10 In patients who re-bleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolisation / angiography to stop bleeding?	• Mortality • Re-bleeding • Additional treatments (salvage surgery, TIPS etc) • Failure to control bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events (leading to death, leading to withdrawal from treatment)
8	Question 12 In patients where endoscopic therapy fails is angiography / embolisation more clinical / cost effective than surgery to stop bleeding?	• Mortality • Re-bleeding • Additional treatments (salvage surgery, TIPS etc) • Failure to control bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events (leading to death, leading to withdrawal from treatment)
9	Question 13	• Mortality

Chapter	Review questions	Outcomes
	In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of re-bleeding and death?	• Re-bleeding • Treatment failure (no initial haemostasis) • Other procedures to control bleeding • Blood transfusion requirements • Number of treatments required for eradication • Adverse event stricture • Adverse events causing death
10	Question 14 In patients presenting with upper gastrointestinal bleeding 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?	• Mortality • Re-bleeding • Treatment failure (no initial haemostasis) • Other procedures to control bleeding • need for transfusion • Length of hospital stay • Adverse events (adverse events causing death and adverse events causing withdrawal from treatment)
11	Question 15 For acutely ill patients in high dependency and intensive care units are Proton Pump Inhibitors (PPIs) or H2-receptor antagonists better than placebo in the primary prophylaxis of Upper Gastrointestinal Bleeding?	<u>Primary outcome:</u> • Upper GI bleeding <u>Secondary outcomes:</u> • Ventilator associated pneumonia • Mortality • Duration of ICU stay • Duration of intubations • Blood transfusions • Adverse events
9	Question 16 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?	• Mortality • Re-bleeding • Treatment failure • Rate of unresolved varices • Blood transfusion requirements • Length of hospital stay • Adverse events – encephalopathy • Adverse events - sepsis
9	Question 17 What is the evidence that TIPS is better than repeat endoscopy	• Mortality • Re-bleeding • Blood transfusion

Chapter	Review questions	Outcomes
	or balloon tamponade in patients where the variceal bleed remains uncontrolled?	requirements • Length of hospital stay • Adverse events – encephalopathy • Adverse events - sepsis
8	Question 18 In patients with non-variceal upper gastrointestinal bleeding are combinations of endoscopic treatments more clinically/cost effective than adrenaline injection alone?	• Mortality • Re-bleeding • Failure to achieve initial haemostasis • Emergency procedures • Length of hospital stay • Transfusion requirements
9	Question 19 In patients with likely variceal bleeding at initial management, are antibiotics better than placebo to improve outcome (mortality, re-bleeding, length of hospital stay, rates of sepsis)?	• Mortality • Re-bleeding • Length of hospital stay • Transfusion requirements • Any infections • Bacteraemia • Spontaneous bacterial peritonitis • Pneumonia
12	Question 20 What information is needed for patients with acute upper gastrointestinal bleeding and their carers (including information at presentation, prophylaxis and information for carers)?	• Any outcome that is reported by patients and carers

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual [6]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. Additional subject specific databases were used for some questions: e.g. PsycInfo for patient experience. All searches were updated on 23/9/11. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix C.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2009, to ensure recent publications that had not yet been indexed by these databases were identified. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix C. All searches were updated on 23/7/11. No papers published after this date were considered.

3.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix D).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual [6].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: data presented as a range of values in GRADE profiles
  - Diagnostic studies: data presented as a range of values in adapted GRADE
  - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.
- Fifteen percent of the sift and checklists as well as whole reviews were quality assured by a second reviewer to eliminate any potential of section bias or error.

3.3.1 Inclusion/exclusion

The inclusion/exclusion of studies was based on the review protocols. The GDG were consulted about any uncertainty regarding inclusion/exclusion of selected studies. With regards to review

question 16 the GDG agreed that studies with a mixed patient population, i.e. patients with gastric varices and also patients with oesophageal varices should be permitted as indirect evidence. The GDG agreed that there was insufficient evidence if this was restricted to studies entirely of patients with gastric variceal bleeding.

Patients bleeding from upper GI varices due to schistosomiasis were excluded since the cause of bleeding compared to those patients bleeding due to cirrhosis of the liver. Schistosomiasis is a parasitic illness originating from Africa and is uncommon in the UK.

In the antibiotic review question (question 19) erythromycin was excluded since this is used in a different clinical context to that specified in the review question.

See the review protocols in Appendix D for full details.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes. Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio.

Statistical heterogeneity between individual study results in a meta-analysis was assessed by considering the Chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out predefined subgroup analyses for – length of follow-up, severity of cirrhosis (for groups of patients with variceal bleeding), severity of illness in intensive care / high dependency patients (question 15). Intravenous and oral drug administration of Proton Pump Inhibitors (question 2) and type of combination treatment (question 18) were a priori subgroups due to the specific nature of the questions.

Assessments of potential differences in effect between subgroups were based on the Chi-squared tests for heterogeneity statistics between subgroups. If no subgroup analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as “less than”, a conservative approach was undertaken. For example, if p value was reported as “$p \leq 0.001$”, the calculations for standard deviations will be based on a p value of 0.001.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Data synthesis for risk assessment (risk scoring) review (question 3 / chapter Error! Reference source not found.**)**

Data and outcomes

In studies for the risk assessment review all patients received a formal risk assessment which was then scored according to the particular system(s) under investigation. Patients could then be categorised into those that scored above or below a clinically specified cut-off points (as described in more detail in chapter 5. This allowed us to extract the proportion of those above and those below the cut-off who experienced a particular outcome. From this we derived components of "2x2 tables" (true positives, false positives, true negatives and false negatives) and then calculated accuracy parameters: sensitivity, specificity, positive / negative predictive value and positive / negative likelihood ratios. For some studies areas under curve of a receiver operating characteristics curve (AUC, which is another accuracy measure) was also extracted. When data were only graphical presented (with sufficient levels of detail), frequencies were extracted from the figures to create 2x2 tables (this is noted in the extraction Tables in section 2 of Appendix F).

Data synthesis for risk assessment data

When data from 5 or more studies were available, a diagnostic meta-analysis was carried out. Graphs of point estimates for sensitivity and specificity with 95% confidence intervals were presented side-by-side for individual studies using Cochrane Review Manager (RevMan5) software. To show the differences between study results on graphical space, pairs of sensitivity and specificity were plotted for each study on one receiver operating characteristics (ROC) curve in Microsoft EXCEL software (for RevMan5 and Excel plots please see Appendix L). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (in WinBUGS® software - for the program code see Appendix L). This model also assesses the variability by incorporating the precision with which sensitivity and specificity have been measured in each study. A confidence ellipse is shown in the graph that indicates the confidence region around the summary sensitivity / specificity point. A summary ROC curve is also presented. From the WinBUGS® output we report the summary estimate of sensitivity and specificity (plus their standard deviations) in the graphical presentation of the meta-analysis results. The bivariate meta-analysis method is described in more detail in Appendix L.

3.3.3 Type of studies

Systematic reviews, triple blinded, double blinded, single blinded and unblinded parallel randomised controlled trials (RCTs) as well as observational studies were included in the evidence reviews for this guideline. We included randomised trials, as they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects.

The GDG decided to include observational studies in questions where ethical considerations would not permit randomisation. These were for the question regarding resuscitation with blood products (questions 7 and 8) and for the question assessing the treatment options when the bleeding remained uncontrolled after first line intervention (question 12).

Randomised control trials are not the appropriate study type for risk assessment test accuracy analysis. For this review (question 3) prospective as well as retrospective case reviews were analysed.

3.3.4 Type of analysis

Estimates of effect from individual studies were based on Intention To Treat (ITT) analysis with the exception of the outcome of experience of adverse events whereas we used Available Case Analysis (ACA). ITT analysis is where all participants included in the randomisation process were considered in

the final analysis based on the intervention and control groups to which they were originally assigned. We assumed that participants in the trials lost to follow-up did not experience the outcome of interest (for categorical outcomes) and they would not considerably change the average scores of their assigned groups (for quantitative outcomes).

It is important to note that ITT analyses tend to bias the results towards no difference. ITT analysis is a conservative approach to analyse the data, and therefore the effect may be smaller than in reality.

However, the majority of outcomes selected to be reviewed were continuous outcomes, very few people dropped out and most of the studies reported data on an ITT basis.

3.3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings is presented in landscape tables in this guideline. The GRADE summary table includes details of the quality assessment as well as pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2: The main criteria considered in the rating of these elements are discussed below (see section 3.3.6 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the pre-determined clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level

Level	Description
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

3.3.7 Study limitations

The main limitations for randomised controlled trials are listed in Table 4.

The GDG accepted that investigator blinding in surgical intervention studies was impossible and participant blinding was also impossible to achieve in most situations. In these instances blinding was not downgraded for objective outcomes (such as mortality or re-bleeding) in quality ratings across the guideline. However, in case of subjective outcomes (for instance Quality of Life scores if reported) evidence from non-blinded trials was downgraded for study limitation since subjective scores would be prone to be influenced by blinding regardless of whether or not the study design made blinding possible or not.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomised trials with allocation by day of week, birth date, chart number, etc)
Lack of blinding	Blinding refers to people’s awareness of what type of treatment is administered after people have been randomised. Ideally in randomised control studies all groups should be unaware of the treatment, i.e people receiving an intervention, people

Limitation	Explanation
	administering the intervention and people who analyse the resulting data. When all groups are blinded it is referred to as a triple blinded study, two groups double blinded and so on. Lack of blinding is a situation when one or all of the groups are aware of which intervention arm a patient has been randomised to.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials

3.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded. The most common factor of subgroup analysis was severity of cirrhosis in groups of patients with variceal upper GI bleeding.

3.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. The GDG agreed to permit indirect evidence for the treatment of patients with gastric varices as long as patients with gastric varices were not explicitly excluded (i.e. studies with mixed populations of patients with either oesophageal or gastric varices or both).

3.3.10 Imprecision

The minimal important difference in the outcome between the two groups was the main criterion considered.

The thresholds of important benefits or harms, or the MID (minimal important difference) for an outcome are important considerations for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management [7-10]. An effect estimate larger than the MID is considered to be "clinically important". For dichotomous outcomes, the MID is considered in terms of changes of absolute risk.

The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of "clinical importance"; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

We searched the literature for published studies which gave a minimal important difference point estimate for the outcomes specified in the protocol and agreement was obtained from the GDG for their use in assessing imprecision throughout the reviews in the guideline. Table 5 presents the MID thresholds used for the main upper GI bleeding outcomes which were all reached by GDG consensus. For those outcomes where no specific MID was set by the GDG, the default GRADE pro MIDs were used. For categorical data, we checked whether the confidence interval of the effect crossed one or two ends of the range of 0.75-1.25. For continuous outcomes two approaches were used. When only one trial was included as the evidence base for an outcome, the mean difference was converted to the standardized mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the Grade tables. If two or more included trials reported a quantitative outcome then the default approach of multiplying 0.5 by standard deviation (taken as the median of the standard deviations across the meta-analyzed studies) was employed. When the default MIDs were used, the GDG would assess the estimate of effect with respects to the MID, and then the imprecision may be reconsidered.

The confidence interval for the pooled or best estimate of effect was considered in relation to the MID, as illustrated in Figure 1. Essentially, if the confidence interval crossed the MID threshold, there was uncertainty in the effect estimate in supporting our recommendation (because the CI was consistent with two decisions) and the effect estimate was rated as imprecise.

To decide on the MIDs for the main outcomes the GDG took into consideration their best estimates of current rates (by consensus) and then decided an acceptable drop in the rate.

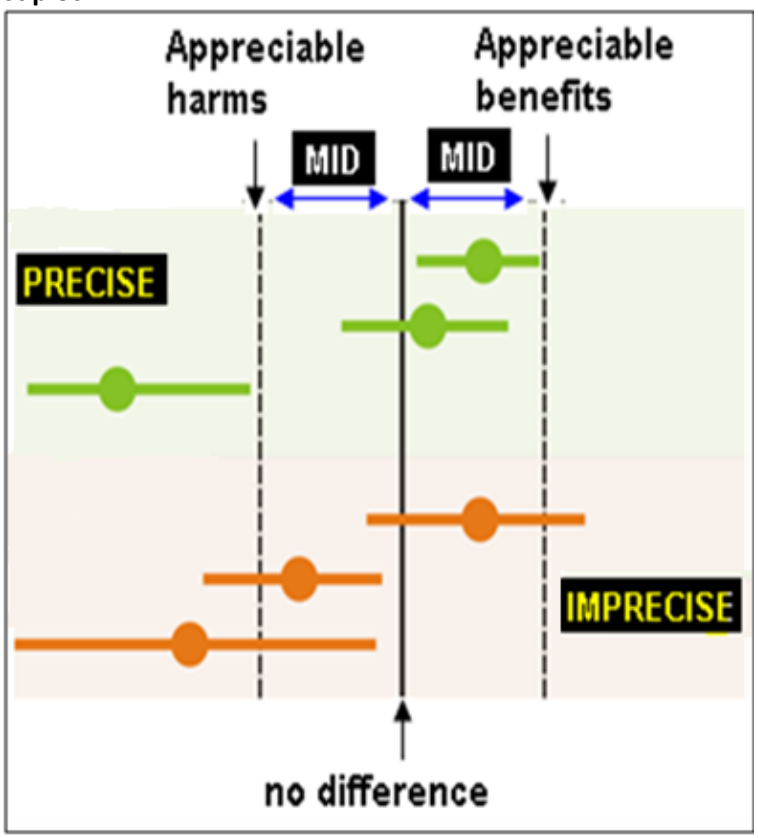
Table 5: Decision process for MID consensus of main upper GI bleeding outcomes.

Outcome	Current % in UGIB (untreated) population	Acceptable rate	Absolute risk reduction (ARR)	Relative risk reduction (RRR)	Critical threshold 1± RRR
Mortality	7.0%	6%	1%	14.3%	0.847 to 1.143
Re-bleeding	15.0%	10%	5%	33.3%	0.667 to 1.333
Surgery	3.3%	2.8%	0.5%	15.2%	0.848 to 1.152
Continuous outcomes	Mean	Clinical difference	Mean difference threshold		
Length of hospital stay	4 days	Half a day	-0.5 to + 0.5		

Outcome	Current % in UGIB (untreated) population	Acceptable rate	Absolute risk reduction (ARR)	Relative risk reduction (RRR)	Critical threshold 1± RRR
Blood transfusion requirements	2.5 units	Half a unit	-0.5 to +0.5		

Note: The ARR is the current minus the acceptable rate (second column subtracted from the first column) and the RR is the ARR divided by the current rate. The critical threshold is the RR beyond which point an effect can be considered to have a clinical benefit or harm.

Figure 1: Illustration of precise and imprecision outcomes based on the confidence interval of outcomes in a forest plot



Source: Figure adapted from GRADEPro software.

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

3.3.11 Adaptation of GRADE for risk scoring outcomes

GRADE rating tables were adapted for this review. In the first section they were presented for each risk assessment system and each outcome. Another adapted GRADE table is presented for the results of the diagnostic meta-analyses for which outcomes of some of the pre-endoscopy scoring systems were combined.

Compared to intervention studies, in risk scoring assessment studies different study designs and statistics are appropriate. Therefore the intervention GRADE table was adapted for this review to reflect these differences. For each risk outcome (mortality, rebleeding and need for intervention) results were summarised across studies. For each a range of sensitivity, specificity, positive/negative predictive value, negative likelihood ration and area under curve were reported. The aspects of GRADE were then assessed across studies. Currently no standard risk of bias checklist is used for these types of studies at the NCGC. Study limitations were assessed by considering patient selection. These were: retrospective study design, representativeness of study population, study population size, whether all patients received the assessment and how much loss to follow-up was reported and whether or what type of validation sample was used in the development of the rating system). Imprecision was downgraded whenever there was a difference in the range of reported diagnostic statistics that was ≥10%.

For data in the diagnostic meta-analyses study limitations were assessed according to the same criteria. Inconsistency was assessed by inspection of the sensitivity / specificity plots and imprecision was rated according to the confidence region of the summary plots (please see Appendix L).

3.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

3.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[6].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix H[6]) and the health economics research protocol in Appendix D.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix H[6]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity [11].

Table 6: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective

Item	Description
	QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix H[6]

Where economic studies compare multiple strategies, results are generally presented in the economic evidence profiles as an incremental analysis where possible. This is where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Otherwise results were presented for the pair-wise comparison specified in the review question.

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendix I and J for details of the health economic analysis/analyses undertaken for the guideline.

3.4.3 Cost-effectiveness criteria

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 [6,12].

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. 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
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'[12].

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices F and G
- Summary of clinical and economic evidence and quality (as presented in chapters 5-12)
- Forest plots and summary ROC curves (Appendix H)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendices I and J)
- Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG.
- The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section preceding the recommendation section.

3.5.1 Validation process

The guidance is subject to an eight week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.2 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.3 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.4 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

4 Guideline summary

From the full set of recommendations, the GDG selected 10 key priorities for implementation. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients
- Have a high impact on reducing variation in care and outcomes
- Lead to a more efficient use of NHS resources
- Promote patient choice
- Promote equality

In addition to this, the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Relates to an intervention that is not part of routine care
- Requires changes in service delivery
- Requires retraining of staff or the development of new skills and competencies
- Highlights the need for practice change
- Needs to be implemented across a number of agencies or settings (complex interactions)
- May be viewed as potentially contentious, or difficult to implement for other reasons

The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

The recommendations identified as priorities for implementation are listed below:

Assessment of risks

1. Use the following formal risk assessment scores for all patients with acute upper gastrointestinal bleeding:

    - the Blatchford score at first assessment, **and**
    - the full Rockall score after endoscopy

Timing of Endoscopy

2. Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation.

3. Offer endoscopy within 24 hours of admission to all other patients with upper gastrointestinal bleeding.

4. Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances.

Management of non-variceal upper gastrointestinal bleeding

5. Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.

6. For the endoscopic treatment of non-variceal bleeding, use one of the following:

- a mechanical method (for example, clips) with or without adrenaline

- thermal coagulation with adrenaline

- fibrin or thrombin with adrenaline

7. Offer interventional radiology to unstable patients who re-bleed after endoscopic treatment. Refer urgently for surgery if interventional radiology is not promptly available.

Management of variceal upper gastrointestinal bleeding

8. Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding.

9. Consider transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from oesophageal varices is not controlled by band ligation.

Control of bleeding and prevention of re-bleeding in patients on NSAIDs, aspirin or clopidogrel

10. Continue low-dose aspirin for secondary prevention of vascular events in patients with upper gastrointestinal bleeding in whom haemostasis has been achieved.

4.1 Full list of recommendations

Assessment of risks

1. Use the following formal risk assessment scores for all patients with acute upper gastrointestinal bleeding:

    - the Blatchford score at first assessment, **and**
    - the full Rockall score after endoscopy.

2. Consider early discharge for patients with a pre-endoscopy Blatchford score of 0.

Resuscitation and initial Management

Blood products:

3. Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding.

4. Base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.

5. Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable.

6. Offer platelet transfusion to patients who are actively bleeding and have a platelet count of less than 50×10^9/litre.

7. Offer fresh frozen plasma to patients who have either:

- a fibrinogen level of less than 1g/litre **or**
- a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal.

8. Offer prothrombin complex concentrate to patients who are taking warfarin and actively bleeding.

9. Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols.

10. Do not use recombinant factor Vlla except when all other methods have failed.

Terlipressin:

11. Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive haemostasis has been achieved, or after 5 days, unless there is another indication for its use[a].

Timing of endoscopy

11. Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation.

12. Offer endoscopy within 24 hours of admission to all other patients with upper gastrointestinal bleeding.

13. Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances.

Management of non-variceal bleeding

Endoscopic treatment:

12. Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.

13. For the endoscopic treatment of non-variceal upper gastrointestinal bleeding, use one of the following:

- a mechanical method (for example, clips) with or without adrenaline
- thermal coagulation with adrenaline
- fibrin or thrombin with adrenaline

Proton Pump Inhibitors:

14. Do not offer acid-suppression drugs (proton pump inhibitors or H2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.

a At the time of publication (June 2012), terlipressin was indicated for the treatment of bleeding from oesophageal varices, with a maximum duration of treatment of 72 hours (3 days). Prescribers should consult the relevant summary of product characteristics. Informed consent for off-label use of terlipressin should be obtained and documented.

15. Offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.

Treatment options after first or failed endoscopic treament

16. Consider a repeat endoscopy, with treatment as appropriate, for all patients at high risk of re-bleeding, particularly if there is doubt about adequate haemostasis at the first endoscopy.

17. Offer a repeat endoscopy to patients who re-bleed with a view to further endoscopic treatment or emergency surgery.

18. Offer interventional radiology to unstable patients who re-bleed after endoscopic treatment. Refer urgently for surgery if interventional radiology is not promptly available.

Management of variceal bleeding

Antibiotics:

19. Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding

Oesophageal varices

20. Use band ligation in patients with upper gastrointestinal bleeding from oesophageal varices.

21. Consider transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from oesophageal varices is not controlled by band ligation.

Gastric varices

22. Offer endoscopic injection of N-butyl-2-cyanoacrylate to patients with upper gastrointestinal bleeding from gastric varices

23. Offer transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from gastric varices is not controlled by endoscopic injection of N-butyl-2-cyanoacrylate.

Control of bleeding and prevention of re-bleeding

24. Continue low-dose aspirin for secondary prevention of vascular events in patients with upper gastrointestinal bleeding in whom haemostasis has been achieved

25. Stop other non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 [COX-2] inhibitors) during the acute phase in patients presenting with upper gastrointestinal bleeding.

26. Discuss the risks and benefits of continuing clopidogrel (or any other thienopyridine antiplatelet agents) in patients with upper gastrointestinal bleeding with the appropriate specialist (for example, a cardiologist or a stroke specialist) and with the patient.

Primary prophylaxis

27. Offer acid-suppression therapy (H2-receptor antagonists or proton pump inhibitors) for primary prevention of upper gastrointestinal bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug.

28. Review the ongoing need for acid-suppression drugs for primary prevention of upper gastrointestinal bleeding in acutely ill patients when they recover or are discharged from critical care.

Information and support for patients and carers

29. Establish good communication between clinical staff and patients and their family and carers at the time of presentation, throughout their time in hospital and following discharge. This should include:

- giving verbal information that is recorded in medical records
- different members of clinical teams providing consistent information
- providing written information where appropriate
- ensuring patients and their families and carers receive consistent information.

5 Risk Assessment (risk scoring)

5.1 Introduction

Risk assessment scoring systems have been devised to define the likelihood of death, re-bleeding and the need for intervention (e.g. endoscopy or operative surgery). Scoring systems are developed by multivariate analysis of clinical observations and investigations in series of patients who develop acute upper gastrointestinal bleeding. In order for a risk scoring system to be accepted, there has to be both internal and external validation.

Three risk scoring systems have been published within the UK over the past few years. The most widely used system is the Rockall score which was developed from an audit of patients presenting with acute gastrointestinal bleeding to several English regions[4]. This score is based upon age, the presence of shock, medical co-morbidity and a range of endoscopic findings. The Rockall score was developed to define the risk of death, but has also been use for other end-points including re-bleeding and duration of admission. It is simple to calculate, performs well for both non-variceal and variceal bleeding and is currently used in many units. The full Rockall score can only be calculated after endoscopy has been undertaken, yet clinicians may need guidance of risk at an early stage in order to ascertain the need for urgent investigation; a 'pre-endoscopy or 'modified'' Rockall Score', based upon clinical observations is therefore frequently used in clinical practice. The Blatchford score was developed from an audit of patients presenting with acute upper gastrointestinal bleeding in the west of Scotland[1,1] . It aspires to define the need for intervention (particularly urgent endoscopy) and is based upon simple clinical observations, haemoglobin and blood urea concentrations and, whilst it is a little more cumbersome to use than the Rockall score, it has the advantage that it can be calculated at an early stage after hospital admission, and does not require the results of endoscopy.

The Rockall and Blatchford scoring systems are used widely in clinical trials of therapy and are useful to define case mix in audit study; their use in clinical decision making in routine practice is less clear. The Addenbrookes scoring system has not been externally validated and was therefore not considered.

5.2 Clinical question and methodological introduction

In patients with upper gastrointestinal bleeding (with or without co-morbidities) is there an accurate scoring system (Rockall, Blatchford)[1,13,14] 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?

Table 7: PICO characteristics of the review question

Clinical Methodological Introduction	
Population:	Patients with GI bleeding (with or without co-morbidities)
Scoring system	• Clinical (i.e. pre-endoscopy) and full (i.e. post endoscopy) Rockall • Blatchford • Addenbrooke
Comparison:	Any validation studies or studies that compare one scoring system to another
Outcomes:	• Mortality

Clinical Methodological Introduction	
	• Re-bleeding • Need for intervention • Need for surgery
Statistics to be presented	Whenever possible the following diagnostic / prognostic values are provided: • Prevalence • Sensitivity • Specificity • Negative predictive value • Positive predictive value • Likelihood ratio +ve • Likelihood ratio –ve • Area under the curve

5.2.1 Details of the three scoring systems considered in the review

5.2.1.1 Clinical and full Rockall score

Details of the clinical and full Rockall scores are shown in Table 8. Scores are additive which means that possible values for the first three rows (lighter shaded and referring to the clinical Rockall) range from 0 to 7 (i.e. a person coming to health services who is younger than 60 years without shock and has no comorbidities would receive a score of 0 whereas someone 80 years or older with hypotension and renal failure has a risk score of 7). Scores from the darker shaded cells (last two rows) are added post endoscopy to create the full Rockall. A score of 0 for the clinical and scores from 0-2 are the clinical cut-offs to indicate patients at low risk of re-bleeding or death.

Table 8.Clinical (pre endoscopy) and full (post endoscopy) Rockall scoring systems

	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, ischemic heart disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
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	

5.2.1.2 Blatchford score

Blatchford risk assessments are designed to be used pre-endoscopy (the clinical details are shown in Table **9**). Scores in the right column are added up for each component. A score of 0 is the cut-off with any patient scoring >0 at risk of requiring an intervention.

Table 9: The Blatchford score 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	
≥120 <130	1
≥100<120	3
<100	6
Haemoglobin (g/L) for woman	
≥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
Hepatic disease	2
Cardiac failure	2

5.2.1.3 Addenbrooke

Another risk scoring index is the Addenbrooke system which is also only used pre-endoscopy. This system is more descriptive and places patients with specific combinations of clinical characteristics into categories of low, intermediate or high risk.

Table 10. The Addenbrooke system.

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

Risk group	Variable
	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

5.3 Clinical evidence review

This review assesses the prognostic accuracy of risk scoring systems in the initial management of upper gastrointestinal bleeding (see flowchart in Appendix E for study selection).

This evidence review includes a total of 19 case review studies (plus an additional study [15] which was consulted for baseline characteristics of another included study). Of those, 9 studies directly validated the Rockall scoring system, 2 studies validated the Blatchford index and another one describes the creation of another different scoring scale (Addenbrooke). The remaining 7 were comparative studies between accuracy of the Rockall scores with those of the Blatchford scale. Another study included the Rockall as a comparator to another scale (not reviewed here), where data could be extracted for the current review (see Appendix F for evidence tables and Appendix H for forest plots).

Table 11: Characteristics of included studies

STUDY	STUDY TYPE AND POPULATION	RISK SCORE	ANOTHER RISK SCORE AS COMPARATOR?	PROGNOSTIC OUTCOMES
Bessa 2006[16]	Retrospective Spanish Rockall validation study N=222	Post-endoscopy Rockall	No	Re-bleeding (defined as a new episode of bleeding during hospitalisation, after the initial bleeding had stopped, manifested as a recurrence of haematemesis, hematochezia or fresh blood in the nasogastric aspirate.), mortality was defined as death within the hospitalisation period.
Blatchford 2000[1]	Development (study 1 – N=1748) and prospective validation (study 2 – N=197) of a risk scoring system for UGIB (aka Glasgow)	Blatchford	Rockall	Need for treatment (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, re-bleed, or

STUDY	STUDY TYPE AND POPULATION	RISK SCORE	ANOTHER RISK SCORE AS COMPARATOR?	PROGNOSTIC OUTCOMES
				had a substantial fall in haemoglobin concentration after admission)
Cameron 2002[13]	Prospective UK risk score creation study N=1349 episodes	Addenbrooke	No	2-week, all-cause mortality (selected because the authors felt that this was most likely to represent mortality directly from GIB), re-bleeding, urgent treatment intervention
Chen 2007[17]	Retrospective Taiwanese risk score comparison N=354	Pre- and post-endoscopy Rockall score	Blatchford	Mortality and Re-bleeding 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)
Church 2006[18]	Retrospective UK Rockall validation study N=247	Post-endoscopy Rockall score	No	Re-bleeding (defined as fresh haematemesis or melaena associated with the development of shock or a fall in haemoglobin concentration of 2 g/dl over 24 h), 30 day mortality and failed haemostasis.
Enns 2006[19]	Retrospective Canadian Rockall validation study in non-variceal UGIB population N=1869	Post-endoscopy Rockall	No	Re-bleeding (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 re-bleeding were combined to a single re-bleeding category.**
Gralnek 2004[20]	Retrospective US risk score comparison case	Pre and post-endoscopy Rockall score	Blatchford	Re-bleeding (if one of the following events occurred: repeat

STUDY	STUDY TYPE AND POPULATION	RISK SCORE	ANOTHER RISK SCORE AS COMPARATOR?	PROGNOSTIC OUTCOMES
	study N=175			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
Kim 2009[21]	Prospective South Korean risk score comparison study N=343	Rockall	Blatchford, Forest classification, Baylor college score, Cedars-Sinai Medical Centre index	Mortality and Re-bleeding (defined as objective evidence of UGIB with unstable vital signs, with a decreased haemoglobin 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 haemoglobin concentration after initial endoscopic haemostasis and stabilisation of the vital signs in 24 h.)
Masaoka 2007[22]	Retrospective Japanese Blatchford validation study N=93	Blatchford	No	High and low risk groups (high defined as requiring blood transfusion, operative or endoscopic interventions)
Pang 2010[23]	Prospective Chinese risk score comparison study N=1087	Pre-endoscopy Rockall	Blatchford	Primary outcome: Need for endoscopic treatment
Phang 2000[24]	Prospective New Zealand Rockall risk score validation study. N=565	Pre-endoscopy Rockall score	No	Mortality
Rockall 1996[4]	Development of index score including a validation sample. N=4185 and N=1625 validation population (audit data from	Rockall (pre and post-endoscopy)	No	Mortality and re-bleeding

STUDY	STUDY TYPE AND POPULATION	RISK SCORE	ANOTHER RISK SCORE AS COMPARATOR?	PROGNOSTIC OUTCOMES
	4 health regions in England – North West Thames, South West Thames, Trent and West Midlands).			
Rotondano 2011[25]	Prospective Italian Multi-centre Risk score comparison study N=2380	Post-endoscopy Rockall	Artificial neural network	30 day mortality
Sanders 2002[26]	Prospective UK risk score validation study N=325	Post-endoscopy Rockall score	No	Re-bleeding (defined as overt fresh bleeding after initial stabilization or a fall in Hb of more than 2 g within 24 h.) mortality
Sarwar 2007[27]	Prospective Pakistani Rockall validation study in patients with cirrhosis N=402	Post-endoscopy Rockall score	No	Mortality and re-bleeding (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) mortality (defined as death within the hospitalisation period)
Srirajaskant han [28] 2010	Retrospective UK risk score comparison study (single centre) N=166	Pre-endoscopy Rockall	Blatchford	Patients correctly identified as high risk Definition of 'high risk' was: those who required blood transfusion, operative or endoscopic interventions to control haemorrhage, required admission to the high dependence or intensive care units, had episodes of re-bleeding, were re-admitted with further UGI bleeding within 6 months, or who died.

STUDY	STUDY TYPE AND POPULATION	RISK SCORE	ANOTHER RISK SCORE AS COMPARATOR?	PROGNOSTIC OUTCOMES
Stanley [29]2009	**Phase one:** three UK centre (prospective data collection) and one UK centre (retrospective data collection) N=676 **Phase two:** two UK centres (prospective data collection) N=572	Blatchford score	No	Endoscopic or surgical procedure Blood transfusion Hospital stay In-hospital mortality
Stephens [30]2009	Prospective UK Blatchford validation study (study 1 – N=232) with a second cohort to assess management in the community (study 2 – N=304)	Blatchford	No	Need for endoscopic therapy, blood transfusions, surgery, mean length of stay and death
Tham [31]2006	Retrospective Rockall validation study in non-variceal UGIB population Country: Northern Ireland N=102	Pre-endoscopy Rockall score	No	Mortality and re-bleeding
Vreeburg [32]1999	Prospective Dutch Rockall validation study N=951	Post-endoscopy Rockall score	No	Re-bleeding (defined as a new episode of bleeding during hospitalisation after the initial bleeding had stopped. Further haemorrhage necessitating surgery was also defined as re-bleeding) mortality (defined as death within the hospitalisation period)

Pre-endoscopy (also known as 'clinical') Rockall score

Table 12: GRADE table for prognostic/diagnostic studies – for Pre-endoscopy Rockall cut-off value 0 to indicate low risk all other scores considered high risk

Study characteristics			Quality Assessment*					Summary of findings							
No. of studies	Design	No. of patients	Limitation	Inconsistenc	Indirectness	Imprecision	Other consideratio	Prevalence (%)	Sensitivity (%)	Specificity (%)	Negative predictive value	Positive predictive value	Likelihood ratios (+ve / -ve)	Area under curve	Quality
Mortality (within 30 days or less)															
4: Chen 2007 [17]; Phang 2000 [24]; Rockall 1996 [4], Tham, 2006 [31]	Cross-sectional	Range: 102 to 1625	S (a)	N	N	N	S (b)	Range: 2.0 to 14.3	Range: 98.4 to 100	Range: 12.7 to 38	Range: 98.5 to 100	Range: 3.1 to 17.5	Ranges: +ve 1.13 to 1.61 / -ve 0 to 0.13	Range: 0.80 to 0.99	LOW
Re-bleeding (within 30 days or less)															
2: Chen 2007 [17]; Tham 2006 [31]	Cross-sectional	Range: 102 and 354	S (a)	N	N	S (c)	S (b)	4.9 and 6.5	69.6 and 100	31.1 and 39.2	89.2 and 100	5.5 and 7.8	+ve 1.64 / -ve 0	0.98	VERY LOW
Need for intervention (within 30 days or less)															

Study characteristics			Quality Assessment*					Summary of findings							
4: Blatchford 2000 [1]; Pang 2010 [23]; Srirajaskantha n, 2010 [28]; Stanley, 2009 [29]	Cross-sectional	Range: 166 to 1087	S (a)	N	N	S (c)	S (b)	34.7; 27.3; 43 and 43.9	88.8; 63.3; 97.2; 86.0	38.0; 23.4; 45.7; 35.0	80.4; 50.4; 95.6; 82.4	54.1; 84.7; 57.9; 41.3	+ve 11.43 / -ve 0.30; +ve 2.70 / -ve 0.48; +ve 1.32 / -ve 0.40; +ve 1.79 / -ve 0.06	Range: 0.71; not reported ; 0.81 and 0.72	VERY LOW

**Quality Assessment for all tables: N=no serious risks of bias; S=Serious risks of bias and VS=very serious risk of bias*
(a) Two studies were retrospective case reviews
(b) One study had an insufficiently small sample with a very low event rate
(c) The two studies had large differences in sensitivity values and / or data could only be extracted from a graph.

Non- analysed data

Tham et al. 2006 (surgery)

No. of participants: (n=102 non-variceal upper GI bleeding patients)

The number of surgeries in relation to the Rockall scores was also an outcome that was investigated in addition to mortality and re-bleeding. There was only one instance of a patient needing surgery and this patient had a Rockall score of 4.

Post-endoscopy Rockall score

Table 13: GRADE table for Post-endoscopy Rockall score at the cut-off value of ≤ 2 to indicate low risk all other scores considered high risk

Study characteristics			Quality Assessment					Summary of findings							
No. of studies	Design	No. of patients	Limitation	Inconsistenc	Indirectness	Imprecision	Other consideratio	Prevalence (%)	Sensitivity (%)	Specificity (%)	Negative predictive value	Positive predictive value	Likelihood ratios (+ve / -ve)	Area under curve	Quality

Study characteristics			Quality Assessment					Summary of findings							
Mortality (within 30 days or less)															
10: Bessa 2006 [16]; Chen 2007 [17]; Church 2006 [18]; Enns 2006 [19], Kim 2009 [21]; Rockall 1996 [4]; Rotondano 2011 [25]; Sanders 2002 [26]; Sarwar 2007 [27]; Vreeburg 1999 [32]	Cross-sectional	Range: 222 to 1869	S (a)	N	N	S (b)	S (c)	Range: 5.4 to 14.3	Range: 33.3* to 100	Range: 2.5 to 52.0	Range: 97.2 to 100	Range: 0.4 to 16.0	Range: +ve 1.03 to 1.73 / -ve 0 to 0.55	Range: 0.67 to 0.84	VERY LOW
Re-bleeding (within 30 days or less)															
9: Bessa 2006 [16]; Chen 2007 [17]; Church 2006 [18]; Enns 2006 [19], Kim 2009 [21]; Rockall 1996 [4]; Sanders 2002 [26]; Sarwar 2007 [27]; Vreeburg 1999 [32]	Cross-sectional	Range: 222 to 1869	S (a)	N	N	S (b)	S (c)	Range: 5.5 to 23.4	Range: 77.1 to 100	Range: 2.9 to 39.2	Range: 90.9 to 100	Range: 0.4 to 24.1	Range: +ve 1.03 to 1.35 / -ve 0 to 0.60	Range: 0.56 to 0.80	VERY LOW
Need for intervention (within 30 days or less)															

Study characteristics			Quality Assessment					Summary of findings							
2: Blatchford 2000 [1]; Stanley 2009 [29]	Cross-sectional	197 and 676	S (a)	N	N	N	S (d)	Range: 43.2 and 43.9	74.4	58.6	63.0	70.7	+ve 1.80 / -ve 0.44	Range: 0.75 and 0.80	LOW

Note. N= no serious risk of bias, S=serious risk of bias
(a) Four studies are retrospective case reviews.
(b) Wide ranges of sensitivity / specificity values and / or extracted from graph only. Imprecision was rated according to the range of study results. Most had differences of more than >10% and in one case up to 66%.
(c) Three studies had an insufficiently small sample with a very low event rate which means that the sample could be unrepresentative of the population under investigation.
(d) In one study a lower number of patients received post-endoscopy Rockall scores but the number was not given in the publication. The other study does not present sensitivity values and presents data in a graphical format that cannot be extracted.
**As reported in a study by Chen where 3 patients died of which 2 patients had a score below the complete Rockall cut-off value of 2.*

Blatchford scale

Table 14: GRADE table for the Blatchford scale at cut-off value 0 to indicate low risk all other scores considered high risk

Study characteristics			Quality Assessment					Summary of findings							
No. of studies	Design	No. of patients	Limitation	Inconsistenc	Indirectness	Imprecision	Other consideratio	Prevalence (%)	Sensitivity (%)	Specificity (%)	Negative predictive value	Positive predictive value	Likelihood ratios (+ve / -ve)	Area under curve	Quality
Need for intervention (within 30 days or less)															

Study characteristics			Quality Assessment					Summary of findings							
7: Blatchford 2000 [1]; Masaoka 2007 [22]; Pang 2010 [23]; Srirajaskantha 2010 [28]; Stanley 2009 [29]; Stephens 2009 [30](two cohorts)	Cross-sectional	Range: 93 to 1087	S (a)	N	N	N (c)	S (b)	Range: 20.4 to 75.3*	Range: 98.9 to 100	Range: 6.3 to 44.7	Range: 97.2 to 100	Range: 24.0 to 58.1	+ve Range: 1.10 to 1.81 / -ve Range: 0 to 0.03	Range: 0.63 and 0.96	LOW
Mortality (within 30 days or less)															
2: Chen 2007 [17]; Kim 2009 [21]	Cross-sectional	239 and 354	VS (a, d)	N	N	N	S (b)	Range: 0.8 and 8.4	100 each	Range: 1.8 and 8.0	100 each	Range: 0.9 and 8.5	n/a	n/a	LOW
Re-bleeding (within 30 days or less)															
2: Chen 2007 [17]; Kim 2009 [21]	Cross-sectional	239 and 354	VS (a, d)	N	N	N	S (b)	Range: 6.5 and 14.6	Range: 94.3 and 100	Range: 1 and 8.5	Range: 50 and 100	Range: 7.1 and 14.0	n/a	n/a	LOW

Note. N= no serious risk of bias, S=serious risk of bias and VS=very serious risk of bias
(a) One study is a retrospective case reviews.
(b) One study has a very small sample size and / or insufficient data could be extracted
(c) Due to the small sample size (and therefore very different prevalence rate) of one study there was a wide range of AUC values.
(d) Both studies are restricted to patients with nonvariceal bleeding and therefore not representative of all patients with UGIB
** This prevalence rate in this study (Masaoka 2007) was an outlier 70 out of 93 patients were classified as being at 'high risk' (high defined as requiring blood transfusions, operative or endoscopic interventions). The next highest prevalence was 45.3%*

Addenbrooke scale

Table 15: GRADE table for the Addenbrooke's scoring system category 'low' indicates the cut-off whereas patients from both 'intermediate' and 'high' are counted as the higher category.

Study characteristics			Quality Assessment					Summary of findings							
No. of studies	Design	No. of patients	Limitation	Inconsistenc	Indirectness	Imprecision	Other consideratio	Prevalence (%)	Sensitivity (%)	Specificity (%)	Negative predictive value	Positive predictive value	Likelihood ratios (+ve / -ve)	Area under curve	Quality
Mortality (within 30 days or less)															
1: Cameron 2002 [13]	Cross-sectional	1349	VS (a)	N	N	N	S (b)	6.5	100	6.0	100	6.9	+ve 1.06 / -ve 0	0.69	VERY LOW
Re-bleeding (within 30 days or less)															
1: Cameron 2002 [13]	Cross-sectional	1349	VS (a)	N	N	N	S (b)	19.8	100	7.0	100	21.0	+ve 1.08 / -ve 0	0.83	VERY LOW
Urgent intervention (within 30 days or less)															
1: Cameron 2002 [13]	Cross-sectional	1349	VS (a)	N	N	N	S (b)	51.3	99.7	11.3	97.4	54.2	+ve 1.12 / -ve 0.03	0.69	VERY LOW

Note. N= not downgrade for this column, S=serious (one downgrade of outcome rating) and VS=very serious (i.e. the overall rating of the outcome is downgraded twice)
(a) Study used the same sample for risk score creation and to validate the index.
(b) Study reported episodes of UGIB without specifying sample size. Lowest score is defined by exclusion 'none of the aforementioned factors'.

Rockall versus Blatchford comparisons

Table 16: Summary table for direct Rockall – Blatchford comparison studies (In the Chen 2007 and Kim 2009 studies normal font refers to the outcome re-bleeding and bold font refers to the outcome Mortality)

Study	Risk scale	Outcome	Prevalence (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC	Interpretation
Blatchford 2000 [1]*, Stanley 2009 [29], Srirajaskanthan 2010 [28]*, Pang 2010 [23]*	Blatchford (score of 0)	Need for any intervention or need for therapeutic endoscopy	Range of 20.4 to 45.2	98.7 to 100	6.3 to 44.7	97.2 to 100	28.6 to 57	0.72 to 0.96	In all the four studies for this outcome Blatchford was as good as or better than Rockall
	Pre-endoscopy Rockall (score of 0)			63.3 to 100	23.4 to 45.7	63.0 to 100	14.5 to 53.7	0.71 and 0.72 otherwise not reported	
	Post-endoscopy Rockall (score ≤ 2)			74.4	58.6	63	70.7	0.75 and 0.80	
Chen 2007 [17]	Blatchford (score of 0)	Re-bleeding **Mortality**	6.5 **0.8**	100 **100**	8.5 **8.0**	100 **100**	7.1 **0.9**	Not reported	Blatchford better for re-bleeding and as good as the Rockall for mortality
	Pre-endoscopy Rockall (score of 0)			69.6 **100**	17.5 **18.5**	89.2 **100**	5.5 **1.0**	Not reported	
	Post-endoscopy Rockall (score ≤ 2)			87.0 **33.3**	31.1 **29.6**	97.2 **98.1**	8.1 **0.4**	Not reported	
Kim 2009 [21]**	Blatchford (score of 0)	Re-bleeding **Mortality**	14.6 **8.4**	94.3 **100**	1.0 **1.8**	50.0 **100**	14.0 **8.5**	Not reported	Blatchford better for re-bleeding and as
	Post-endoscopy Rockall (score			77.1 **100**	39.2 **40.2**	90.9 **100**	17.9 **13.3**	Not reported	

Study	Risk scale	Outcome	Prevalence (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC	Interpretation
	≤ 2)								good as the Rockall for mortality

** Values based on data extracted from graph. Patient level data not available in the publication.*
*** This publication also compared to further scoring systems but for the purpose of the current review these are not reported here. Graphical presentation not clear enough to extract data from.*

Non- analysed data

Gralnek et al. 2004[20] (number of 'low risk' patients identified)

No. of participants: (n=175 patients with non-variceal upper GI bleeding)

The yield of identifying low risk patients was compared between the Blatchford, the pre-endoscopy and the post-endoscopy Rockall score. The Blatchford identified 14 (8%) and the pre-endoscopy Rockall 21 (12%) patients as low risk which was significantly fewer than those identified by the post-endoscopy Rockall 53 (30%). None of the patients identified by the Blatchford and pre-endoscopy Rockall rebled or died, whereas 2 patients in the low risk group of the post-endoscopy Rockall rebled.

5.3.1 Diagnostic meta-analysis

Four separate diagnostic meta-analyses were carried out to establish whether the clinically used cut-off points were sensitive enough to rule out patients that are at a high risk of further severe adverse events (need for intervention / surgery, rebleeding and mortality). Two of these analyses were also used to compare the Blatchford and clinical Rockall to assess which might be a better risk assessment system to use at the time of admission pre-endoscopy. For the clinical Rockall score outcomes were combined in one meta-analysis as a 'risk of adverse events' (some studies reported risk of rebleeding, mortality or need for intervention). However, whenever a study reported risk scoring for more than one outcome, for reasons of caution the most severe outcome (i.e mortality) was selected to ensure that an assessment would be sensitive enough to rule out patients at risk of experiencing a fatal adverse event. The raw data, forest plots and meta-analysis graphs are included in Appendix L.

Table 17: Adapted GRADE table for the diagnostic meta-analyses. For summary plots see Appendix L.

Scoring system	Outcome	Studies	N	Summary sensitivity (SD)	Summary specificity (SD)	Study limitations	Inconsistency	Indirectness	Precision	Quality
Clinical (pre-endoscopy) Rockall	Need for intervention / rebleeding / mortality	1,4,23,24,28,29,31	7274	96% (6%)	29% (6%)	S	VS	N	S	VERY LOW
Blatchford	Need for intervention / rebleeding / mortality	1,22,23,28-30	2728	99% (0.5%)	20% (7%)	S	S	N	N	LOW
Full (post endoscopy Rockall*	Rebleeding	4,16,18,19,26,32,33	7006	96% (3%)	11% (7%)	S	S	N	S	VERY LOW
Full (post endoscopy) Rockall*	Mortality	4,16,18,19,26,32,33	7103	98% (2%)	12% (6%)	S	N	N	N	MODERATE

Note. N= no serious risk of bias, S=serious risk of bias and VS=very serious risk of bias

(a) We downgraded for study limitations when studies used retrospective case reviews or when there was a large amount of loss to follow-up or not all patients received risk assessment or where the study population was not very clearly described.

(b) Inconsistency was assessed by inspection of the sensitivity / specificity RevMan 5 plots. When both sensitivity and specificity were inconsisted the quality was downgrade two increments and when either sensitivity or specificity was inconsistent across studies quality was downgraded once.

(c): The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta analysis.

** One of the studies in the full Rockall analysis was using only patients with variceal bleeding and this study and was therefore not overall representative of the upper GI bleeding population. Results from this study were not considered in the inconsistency and imprecision analysis.*

5.4 Health Economic evidence

No relevant economic evaluations were identified. There were no excluded studies.

5.5 Evidence statements

5.5.1 Clinical evidence

Clinical (pre-endoscopy) Rockall score

Mortality

Four studies with patient numbers ranging from 102 to 1625 reported risk scoring for the outcome mortality with good ability in ruling out those patients who died (sensitivity values at the cut-off score of 0 ranged from 98.4 – 100%). The AUC values ranged from 0.80 – 0.99 (LOW QUALITY).

Re-bleeding

For the outcome re-bleeding, two studies with 102 and 354 patients respectively, reported clinical Rockall values with lower ability (and wide variability) for the prediction of who would have an episode of re-bleeding , i.e. a sensitivity of between 69.6 -100% and an AUC of 0.98 (VERY LOW QUALITY).

Need for intervention

This outcome was reported by four studies (usually those studies that compared Rockall and Blatchford scales). Patient numbers ranged from 166 to 1087. There was wide variability in the number of patients that were correctly ruled out as having a need for intervention (sensitivity values ranged from 63% to 97%) and the AUC ranged from 0.71 to 0.81 (VERY LOW QUALITY).

Diagnostic meta-analysis clinical Rockall score (combined outcomes)

Results from a diagnostic meta-analysis of 7 studies comprising 7274 patients showed that the clinical Rockall score was 96% sensitive (6% standard deviation) in ruling out patients that are at risk of severe adverse events (VERY LOW QUALITY).

Full (post-endoscopy) Rockall score

Mortality

Ten studies used the post-endoscopy Rockall score to investigate risk for mortality. Patient numbers ranged from 222 to 1869. The ability to rule out mortality showed wide ranges of sensitivity between 33.3 and 100% and AUC 0.67 to 0.84. Only three studies reported any mortality for patients with complete Rockall scores ≤ 2. In one of those 106 patients had a score ≤ 2 of which 2 (1.9 %) died. In the second study 118 patients had scores ≤ 2 and 1 patient died (0.8%). Another study reported an overall mortality rate of 4.7% (112 of 2380). According to the authors the Rockall was only 52.9% accurate in predicting death.

In patients with *variceal upper GI bleeding* the complete Rockall score at the cut-off of 2 identified the risk for mortality with 85.2 % sensitivity and the AUC was 0.83. 4 patients died out of 230 patients with a score ≤ 2 or 1.7% (VERY LOW QUALITY).

Diagnostic meta-analysis full Rockall score (mortality)

Results from a diagnostic meta-analysis of 7 studies comprising 7103 patients showed that the full Rockall score was 98% sensitive (2% standard deviation) in ruling out patients that are at risk of fatal adverse events (MODERATE QUALITY).

Re-bleeding

There were nine studies that investigated the complete Rockall score for the prediction of re-bleeding. Patient numbers in these studies varied from 222 to 1869. The complete Rockall was between 91.9 and 100% sensitive in ruling out those patients that later had an episode of re-bleeding. However, AUCs for the entire scale were lower than those for mortality ranging from 0.56 to 0.80. When restricted to patients with *variceal bleeding* sensitivity was 86.4% an AUC of 0.80 (VERY LOW QUALITY).

Diagnostic meta-analysis full Rockall score (rebleeding)

Results from a diagnostic meta-analysis of 7 studies comprising 7006 patients showed that the full Rockall score was 96% sensitive (3% standard deviation) in ruling out patients that are at risk of rebleeding (VERY LOW QUALITY).

Need for intervention

Two studies with 197 and 676 patients respectively investigated the complete Rockall score's ability to rule out need for intervention. Only one of those reported sensitivity data (74.4%). The AUC in the two studies was 0.75 and 0.80 (VERY LOW QUALITY).

Blatchford scale

Mortality

Two studies reported this risk score for the outcome of mortality (one with 239 and the other with 354 patients). In both these studies none of the patients with a Blatchford score of 0 (cut-off) died which makes it 100% sensitive (AUCs were not reported) (LOW QUALITY).

Re-bleeding

Two studies reported used this risk score for the outcome re-bleeding (one with 239 and the other with 354 patients). In one of these studies none of the patients with a Blatchford score of 0 (cut-off) re-bled which makes it 100% sensitive. In the other study 2 patients were incorrectly classified making it 94.3% sensitive (AUCs were not reported) (LOW QUALITY).

Need for intervention

Seven studies with patient numbers ranging from 93 to 1087 reported the Blatchford's ability to rule out need for intervention. In 6 out of these 7 the Blatchford cut-off value of 0 ruled out every patient who needed an intervention (100% sensitive). In the study one patients who was classified as not needing intervention later needed treatment (1out of 89 patients who needed treatment – a sensitivity of 98.9%). AUCs for the whole scale showed wide variability between studies (from 0.63 to 0.96).

Diagnostic meta-analysis Blatchford score (combined outcomes)

Results from a diagnostic meta-analysis of 6 studies (with 1 study reporting results of 2 different groups of patients) comprising 2728 patients showed that the Blatchford score was 99% sensitive (0.5% standard deviation) in ruling out patients that are at risk of severe adverse events (LOW QUALITY).

Addenbrooke

Mortality

One study with 1349 patients showed high sensitivity for ruling out those patients who later died (sensitivity of 100%). The AUC was 0.69 (VERY LOW QUALITY).

Re-bleeding

One study with 1349 patients showed high sensitivity for ruling out those patients who later re-bled (sensitivity of 100%). The AUC was 0.83 (VERY LOW QUALITY).

Urgent intervention

One study with 1349 patients showed high sensitivity for ruling out those patients who later needed urgent intervention (sensitivity of 99.7%). The AUC was 0.69 (VERY LOW QUALITY).

Rockall and Blatchford comparisons

Mortality

Two studies with 239 and 354 patients respectively compared Rockall and Blatchford directly for the outcome mortality (one with 239 and the other with 354 patients). Apart from the complete Rockall score which missed out 2 of an overall 3 patients who died, the pre-endoscopy Rockall and Blatchford scores were 100% correct in ruling out patients at risk of dying.

Re-bleeding

Two studies, with 239 and 354 patients respectively, reported accuracy in ruling out patients who later re-bleed for the Blatchford compared to the Rockall scores. In both studies the Blatchford showed better sensitivity than the Rockall index. For the Blatchford the two studies reported 100% and 94.3% sensitivity respectively whereas it was 69.6% for the pre-endoscopy Rockall (which was only reported by one of the studies), and 87.0% / 77.1% for the post-endoscopy Rockall. In other words the Rockall failed to identify more patients who later re-bled.

Need for intervention / classification of high risk groups

Five studies with patient numbers ranging from 166 to 1087 compared Rockall with Blatchford scores for this outcome. One of those showed better sensitivity as well as AUC values for the Blatchford as compared to either the pre-endoscopy or the post-endoscopy Rockall (sensitivity: 98.9% compared to 88.8% and 74.4%; AUC: 0.92 compared to 0.71 and 0.75 respectively). Another study reported better AUC values for the Blatchford 0.92 compared to the pre-endoscopy Rockall 0.72 and the post-endoscopy Rockall 0.80. In one study the Blatchford scale ruled out 100% of patients who later required therapeutic endoscopy whereas the Rockall was, according to the authors, unable to do this with a sensitivity of only about 63% (as extracted from a graph). A fourth study with a total of 174 patients showed that 2 patients who had a pre-endoscopy Rockall score of 0 later required clinical intervention, whereas none of those with a Blatchford score of 0 needed this (AUC reported in this study were 0.81 for the pre-endoscopy Rockall and AUC of 0.96 for the Blatchford scale). The last study with 175 participants aimed to identify low risk patients and compared the yield of the Blatchford with the pre-endoscopy and the post-endoscopy Rockall score. The Blatchford identified 14 (8%) and the clinical Rockall 21 (12%) patients as low risk which was significantly fewer than those identified by the complete Rockall 53 (30%). None of the patients identified by the Blatchford and pre-endoscopy Rockall re-bled or died, whereas 2 patients in the low risk group of the post-endoscopy Rockall re-bled.

5.5.2 Health economic evidence

No studies were identified on the cost-effectiveness of the accuracy of scoring systems.

5.6 Recommendations and link to evidence

In patients with upper gastrointestinal bleeding (with or without co-morbidities) is there an accurate scoring system (Rockall, Blatchford [aka Glasgow], Addenbrooke)[1,13,14] 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?

Recommendations	• **Use the following formal risk assessment scores for all patients with acute gastrointestinal bleeding:** - **the Blatchford score at first assessment, and** - **the full Rockall score after endoscopy.** • **Consider early discharge for patients with a pre-endoscopy Blatchford score of 0.**
Relative values of different outcomes	Outcomes were considered in terms of mortality, re-bleeding and the need for intervention. The ability of a scoring system to predict mortality and re-bleeding was considered paramount. Of note, the available scoring systems were not developed with the purpose of predicting both of these outcomes. The evidence indicated to the GDG that they had a choice between the Blatchford and the Rockall scores: these had been more extensively evaluated than any other scoring system, and performed well. Across the available studies, the Blatchford score appeared to be the better predictor of re-bleeding, and comparable with the Rockall for prediction of mortality. One paper was identified reporting a third scoring system (Addenbrooke's) but there was no direct comparison with either the Rockall or Blatchford score. The GDG did not feel that they had enough evidence to consider this score within a recommendation.
Trade off between clinical benefits and harms	The clinical benefits and harms of a Risk Assessment Score are clearly bound up with the accuracy of its predictions, as set out in the evidence statements. The only additional issue considered by the GDG was the ease of use of each of the available scores. It was felt that the Rockall score was commendably simple, and is the system in widest current use. However, although currently used in less centres, the Blatchford score was regarded as being reasonably straightforward and the GDG felt that adopting it in place of the Rockall should not be difficult. It is clearly undesirable to routinely encourage the early discharge of patients where there is a risk of mortality or re-bleeding, but there are also obvious practical benefits to early discharge where this is safe. The GDG debated whether a safe level of either the Blatchford or the Rockall score could be identified. The lower scores on both scales were associated with little risk of adverse outcomes, but the GDG did not feel that they could make a confident recommendation above a score of 0.

	It was also noted that a pre-endoscopy Rockall score of 0 as well as a post-endoscopy Rockall score ≤2 were somewhat less sensitive in predicting re-bleeding than mortality.
Economic considerations	No health economic evidence was available to review. In discussion the GDG felt that there was unlikely to be significant incremental cost implications attached to the implementation of any of the scoring systems considered; however, it was noted that early discharge of patients with a pre-endoscopy Rockall or Blatchford score of 0, could result in reduced hospital stay and associated cost.
Quality of evidence	The evidence upon which this recommendation is made is predominantly of low to very low quality by GRADE criteria. Study numbers varied considerably but there were some studies with substantial patient populations.
Other considerations	The GDG noted that scoring systems facilitate consistent standards of communication and measurement. They also allow a concise, semi-objective description of a patient's clinical condition. It had been hoped that it might be possible to make a recommendation based on the use of scoring systems in primary care, advising whether or not patients with GI bleeding needed urgent assessment in secondary care; unfortunately, no evidence specific to primary care was found. The GDG recognised that the Rockall and Blatchford scoring systems were each designed for a different primary purpose and this was one reason for their differing sensitivities and specificities in relation to the outcomes considered. However, it was felt undesirable to recommend the use of multiple scoring systems for practical reasons. The Rockall score was recognised as being well validated and already in widespread usage. Furthermore, there is a post-endoscopy Rockall score and although this is clearly not useful as a means of selecting patients for early discharge and later endoscopy, it is a useful score for prediction of mortality and patients at high risk of re-bleeding. However, the Blatchford score has emerged more recently, and in direct comparison to the Rockall score is a better predictor of re-bleeding and / or need for intervention. Although they recognised that Units well versed in use of the Rockall might not wish to change, the GDG felt that the evidence in favour of the Blatchford score in pre-endoscopy assessment could not be ignored and that its use should be recommended The GDG noted that consideration for early discharge is based upon a number of factors in addition to the risk of mortality or re-bleeding and that any recommendation had to be couched in terms which allowed discretion.

6 Resuscitation and initial management

6.1 Blood Products

6.1.1 Introduction

When acute upper gastrointestinal bleeding is very severe blood transfusion can be life saving; hospitals should have written policies in place for massive blood loss including the use of O-ve blood for extreme cases. For bleeding of lesser severity the role of blood transfusion is less clear cut. Circulation can be supported in shocked patients by intravenous infusion of crystalloids or colloids and blood transfusion is only necessary when haemoglobin concentrations fall to less than 7g/dL- tissue oxygenation is then significantly impaired and cardiac function is compromised[34,34]. Patients in intensive care units are generally only transfused at such haemoglobin levels. Decisions regarding blood transfusion in actively bleeding patients are more difficult because haemoglobin concentrations only fall after haemodilution occurs; haemoglobin concentration may be normal in the first few hours after a major bleed and to rely upon the haemoglobin level in acutely bleeding patients is potentially dangerous since at this early stage this may grossly under-estimate blood loss and tissue hypoxia. For these reasons previously published guidelines recommend a haemoglobin concentration of 10 g/dL (rather than 7 g/dL) as the threshold for giving blood in acute gastrointestinal bleeding[35], and this may be particularly pertinent for patients with vascular diseases who may be less able to tolerate anaemia.

The issue is complicated by the observation that blood transfusion may be associated with significant adverse effects. Whilst transfusion reactions are now relatively infrequent and transmission of infection via blood is very rare, there is increasing evidence that outcome in a range of settings is adversely affected by blood products. Mortality is higher in patients admitted for major trauma to intensive care units who receive a blood transfusion compared to matched patients not receiving blood[36]. The outcome of patients undergoing cardiac surgery is also adversely affected by blood transfusion [37]. The 2008 UK wide audit of acute upper gastrointestinal bleeding found that re-bleeding was more frequent in patients receiving blood transfusion as compared to matched patients who did not receive blood products and there was a strong trend towards increased mortality in transfused patients[5,5].

Finally blood products are precious. Approximately 14% of all transfused blood in the UK is used to treat acute gastrointestinal bleeding and the UK audit suggested that local decisions regarding transfusion were not always appropriate. It is clear that clinicians would value evidence-based guidance concerning decisions regarding blood transfusion in acute gastrointestinal bleeding and that those in charge of blood transfusion laboratories would value advice in regulating the use of blood in this context.

Administration of platelets to thrombocytopenic bleeding patients, and of clotting factors to patients with deranged clotting, is considered in several situations. The most common is probably patients with significant liver disease who may have a low platelet count as a result of consumption by an enlarged spleen or of bone marrow suppression (particularly by alcohol abuse), and of coagulopathy from liver failure. Other clinical situations when platelet transfusion is contemplated include patients with immune or drug-induced thrombocytopenia and that occurring after massive blood transfusion. Administration of clotting factors may be also considered in bleeding patients who are receiving anticoagulant drugs.

Whilst platelet and clotting factor administration may be intuitive management steps in these clinical situations, there are reasons to consider their appropriateness. Stable patients who have stopped bleeding may derive little benefit from these products, the efficacy of platelet transfusion may be

modest since they have a short biological half life and transfusion of clotting factors and platelets may cause complications. Finally harvesting platelets and clotting factors is relatively expensive.

6.1.2 Clinical question 1 and methodological introduction

Clinical question 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?

Table 18: PICO characteristics of clinical question

Clinical Methodological Introduction	
Population:	Patients with upper GI bleeding with low level of haemoglobin
Intervention:	Red blood cell transfusion (low / high levels)
Comparison:	No red blood cells, red blood cells (low/high levels)
Outcomes:	• Mortality • Re-bleeding • Surgical intervention • Length of hospital stay (ICU stay, total stay) • Adverse events – myocardial infarction

6.1.3 Clinical evidence review

We searched for randomised control trials or observational studies comparing the effectiveness of red blood cell resuscitation for patients with upper GI bleeding with low levels of haemoglobin with either no transfusion or lower / higher levels of transfusions (see flowchart in Appendix E for study selection).

This evidence review included a total of 3 studies, 1 of which is a randomised control study and cross-references one Cochrane meta-analysis [38-41]. One study addressed the question to either transfuse blood compared to a control group without transfusions. The other two observational studies compared cohorts with early versus late transfusions (see Appendix F for evidence tables and Appendix H for forest plots).

Table 19: Characteristics of included studies

Study	Study design	Patient population	Definition of transfusion treatment	Any other comments
Baradarian, 2004 [38]	Prospective case review	Patients with UGIB complicated by hemodynamic instability	In the early intensive resuscitation group physician provided guidance to the health care team managing the patients to allow a rapid correction of hemodynamic instability. In the control group no specific guidance on rapid resuscitation was provided. In the comparison such direct guidance was not provided.	For the control group hemodynamic stability was achieved on average in 4 hours compared to under 2 hours in the early transfusion group

Study	Study design	Patient population	Definition of transfusion treatment	Any other comments
Blair, 1986[39]	RCT	All patients presenting with acute severe gastrointestinal haemorrhage with onset within the last 24 hours	≥ 2 units or red blood cell transfusion compared to no transfusions	5/26 patients in the control group required transfusions but were analysed in the control group according to ITT principles
Hearnshaw, 2010[42]	Prospective case review (national NHS audit)	All patients (16 years or over) presenting with acute UGIB	Early RBC transfusion, i.e. within 12 h of presentation with acute UGIB.	Overall statistical analyses in this study were presented unadjusted as well as adjusted for Rockall and initial haemoglobin concentration

Comparison of red cell transfusions versus no transfusion

Table 20: GRADE summary table for red blood cell transfusion versus non transfusions

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Red cell transfusions, Frequency	No transfusion Frequency	Relative Risk (95% CI)	Absolute effect (95% CI)	
Mortality*										
Blair, 1986 [39]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/24 (8.3%)	0/26 (0%)	RR 5.4 (0.27 to 107.09)	[c]	VERY LOW
Re-bleeding[a]										
Blair, 1986 [39]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	9/24 (37.5%)	1/26 (3.8%)	RR 9.75 (1.33 to 71.33)	337 more per 1000 (from 13 more to 2705 more)	LOW

[a] *No clear allocation concealment. Randomisation sequence generation not specified and there is no blinding.*
[b] *The confidence interval of the total risk ratio ranges from appreciable harm to appreciable benefit.*
[c] *Absolute effect could not be calculated due to 0 events in the control group.*

Comparison of early versus late red blood cell transfusions

Table 21: GRADE rating for observational studies investigating early versus late transfusions

No. of studies	Design	Early transfusion (n)	Late transfusion (n)	Results - p	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Mortality (unclear length of follow up)										
Baradarian, 2004 [38]	Prospective case review	1/36	4/36	p=0.04	VS (i)	N	N	S (ii)	N	Very low
Outcome: Mortality (30 days)										
Hearnshaw, 2010 [42]	Prospective NHS audit	Initial haemoglobin < 8 gm/dl 130/1025 (CI 11-15%)	Initial haemoglobin < 8 gm/dl 14/112 (CI 7.0-20%)	Not significant	N	N	N	N	N	low
		Initial haemoglobin > 8 gm/dl 91/819 (CI 9.4-13%)	Initial haemoglobin > 8 gm/dl 94/2208 (CI 3.5-5.2%)	p-value not given but CIs do not overlap						
Outcome: Re-bleeding										
Baradarian, 2004 [38]; Hearnshaw et al. 2010 [41]	Prospective case review and prospective NHS audit, respectively	8/36	7/36	P=0.33	VS (i)	S (iii)	N	N	N	Very low
		Initial haemoglobin < 8 gm/dl	Initial haemoglobin < 8 gm/dl	p-value not given but even with a slight						

No. of studies	Design	Early transfusion (n)	Late transfusion (n)	Results - p	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
		234/1015 (CI 21-26%)	17/111 (CI 8.6-22%)	overlap in CIs logistic regressions were significant						
		Initial haemoglobin > 8 gm/dl 192/812 (CI 21-27%)	Initial haemoglobin > 8 gm/dl 147/2196 (CI 5.7-7.8%)	p-value not given but CIs do not overlap and odds ratios are significant						
Outcome: Mean days in hospital										
Baradarian, 2004 [38]	Prospective case review	5.8 (8.3)	7.2 (13.8)	p=0.06	VS (i)	N	N	S (ii)	N	Very low
Outcome: Mean days in ICU										
Baradarian, 2004 [38]	Prospective case review	3.9 (3.8)	2.4 (2.5)	p=0.04	VS (i)	N	N	S (ii)	N	Very low
Outcome: Surgical intervention										
Baradarian, 2004 [38]	Prospective case review	4/36	6/36	p=0.09	VS (i)	N	N	S (ii)	N	Very low
Outcome: Adverse events – myocardial infarction										
Baradarian, 2004 [38]	Prospective case review	2/36	4/36	p=0.04	VS (i)	N	N	S (ii)	N	Very low

N = no serious; S = serious; VS = very serious

(i) No formal protocol was followed with an unclear description of how and when resuscitation was so-called 'intensive'. Physicians were aware of the group that each patient was in. Small sample size. Since no direct protocol was followed it is hard to interpret whether the results stem from the resuscitation or the difference in care provided.

(ii) Small sample size would lead to wide confidence intervals and confidence intervals were not reported.

(iii) One of the studies showed no effect of early blood transfusion whereas the other shows a large and significant difference in favour of later transfusion, i.e. after 12 hours.

6.1.4 Health economic evidence review

No relevant economic evaluations were identified that assessed the target haemoglobin concentration at which red blood cell transfusions should be administered in patients with upper gastro intestinal bleeding before endoscopy.

6.1.5 Evidence statements

6.1.5.1 Clinical evidence

Red blood cell transfusions versus no transfusions

Mortality (30 day follow-up)

One study comprising 50 participants with non variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of mortality between the groups who had blood transfusions compared to those that had not (VERY LOW QUALITY).

Re-bleeding

One study comprising 50 participants with non variceal upper gastrointestinal bleeding found that there was a statistical significant difference in the rate of re-bleeding in favour of the group that did not receive blood transfusions rather than those who did. This increased rate of re-bleeding with transfusion was large enough to be potentially clinically harmful (LOW QUALITY).

Early versus late red blood cell transfusions

Evidence from two observational studies, one comprising 72 patients the other with 4441 participants, were not pooled.

Mortality (30 days or less follow-up)

One of the observational studies with 72 participants showed a significant lower mortality in patients receiving blood transfusion compared to those not transfused with blood. The second study with 4441 patients showed another pattern with significantly lower rates of mortality favouring those with late transfusions, but this effect was only seen in those patients with an initial haemoglobin > 8 gm/dl. In this second study there was no significant difference in the rate of mortality when considering those patients with an initial haemoglobin < 8 gm/dl (VERY LOW QUALITY).

Re-bleeding

One of the observational studies with 72 participants reported no significant difference in the rate of re-bleeding between the group that received early transfusion and the group that received late transfusion. The second study with 4441 patients showed significantly smaller rate of re-bleeding in patients undergoing late transfusions or no transfusion regardless of initial haemoglobin level (VERY LOW QUALITY).

Length of hospital stay – total days

One study comprising 72 participants showed no significant lower average number of days in hospital in the group of participants who had early transfusions (VERY LOW QUALITY).

Length of hospital stay – ICU days

One study comprising 72 participants showed significantly lower average ICU days in the group of participants who had late transfusions (VERY LOW QUALITY).

Surgical interventions

One study comprising 72 participants showed no significant differences in the rate of surgery between the group that received early transfusion and the group that received late transfusions (VERY LOW QUALITY).

Myocardial infarctions

One study comprising 72 participants showed that myocardial infarction was significantly more common in the group of participants who had late transfusions (VERY LOW QUALITY).

6.1.5.2 Health economic evidence

No studies were identified on the cost-effectiveness of the threshold and target level at which red blood cell transfusions should be administered to improve outcome in patients with upper GI bleeding with low level of haemoglobin, pre-endoscopy.

6.1.6 Recommendations and link to evidence

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?

Recommendations	• **Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding.** • **Base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.**
Relative values of different outcomes	Mortality and re-bleeding rates were considered the most important outcomes.
Trade off between clinical benefits and harms	The GDG noted that the evidence available relating to blood transfusion in the context of upper GI haemorrhage suggests that liberal, rather than restrictive, transfusion does not improve outcomes and may in fact be detrimental (increasing the rate of re-bleeding). This parallels evidence relating to transfusion in other clinical settings. The GDG was clear that where there was hemodynamic or clinical compromise the appropriate administration of blood should not be delayed but in stable patients clinicians should exercise caution when deciding if and when to transfuse.
Economic considerations	Blood products are an expensive resource and are extensively used in UGIB. There was no cost-effectiveness evidence available to review. The appropriate use of blood transfusions in UGIB is essential and is likely to be cost-effective.
Quality of evidence	The evidence available to the GDG was categorised as of low or very low quality by GRADE criteria
Other considerations	In discussion the GDG noted that the only available RCT in this area suggested that transfusion was associated with more re-bleeding than no transfusion. This was consistent with evidence from a large

	prospective case review that demonstrated higher rates of re-bleeding in those transfused early, the effect being particularly pronounced in low risk groups. Whilst a third paper demonstrated the opposite finding the GDG felt this study to be less reliable due to small numbers and an unclear comparator arm. The GDG discussed the issue of massive haemorrhage at length and felt this to be a special clinical situation requiring different management to less severe blood loss. There was no formal evidence to review here. However, trusts are already required to have a massive transfusion protocol and where upper GI blood loss is sufficiently severe the GDG felt they should recommend that this should be invoked. The GDG also noted in discussion that clinicians should be encouraged not to consider the administration of blood (packed red cells) in isolation but also, where indicated, the concomitant administration of blood products. The GDG debated whether they could set a definite threshold below which transfusion was unlikely to help, and could be potentially harmful. Although a transfusion threshold of 8g/dL is safe in other patient cohorts, it is unclear whether this can be translated to patients with acute upper gastrointestinal bleeding in the absence of a randomised clinical trial.

6.1.7 Clinical question 2 and methodological introduction

Clinical question 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?

Table 22: PICO characteristics of clinical question 2

Clinical Methodological Introduction	
Population:	Patients with upper GI bleeding with low level of platelets and / or coagulation factors
Intervention:	Platelets, coagulation factors
Comparison:	Placebo or different thresholds / target levels
Outcomes:	• Mortality • Failure to control bleeding • Re-bleeding • Surgical intervention • Length of hospital stay (ICU stay, total stay) • Red blood cell transfusion • Adverse events – serious • Adverse events - fatal

6.1.8 Clinical evidence

We searched for RCTs and observational studies investigating the best threshold and target levels for platelets and coagulation factors in the initial resuscitation of patients with upper GI bleeding (see flowchart in Appendix E for study selection).

This evidence review includes a total of 2 RCTs and cross-referenced one Cochrane meta-analysis [43-45] addressing coagulation factors only (i.e. Recombinant factor VIIa). No studies were identified that addressed platelet levels in this population of patients. No observational studies were retrieved. The evidence did not directly answer the question of thresholds and target levels, but rather the efficacy of treatment (comparing rFVIIa to placebo). The population of patients with upper GI bleeding was also restricted to those with liver cirrhosis and variceal upper GI bleeding. The results of the review have been analysed according to whether rFVIIa was administered to patients with cirrhosis with a Child-Pugh grade A or to those with the more severe condition, i.e. Child-Pugh grade B-C. Some results were also subdivided by the dosage of rFVIIa that was administered (see Appendix F for evidence tables and Appendix H for forest plots).

Table 23: Characteristics of included studies

Study	Study design	Patient population	rFVIIa treatment	Any other comments
Bosch, 2004[43]	Multi centre multi country (Europe) RCT	Patients with signs of active acute UGIB suspected to be of variceal origin	100 µg/kg rFVIIa - 8 doses (the first dose was administered as a slow intravenous injection before first endoscopy and within 6 hours of admission, further doses were administered at 2, 4, 6, 12, 18, 24 and 30 hours after first dose).	Well conducted study with clear allocation concealment, randomisation, blinding, power calculations etc (N=245)
Bosch, 2008[44]	Multi centre multi country (Europe and Asia) RCT	Patients with acute UGIB and advanced cirrhosis, i.e. a Child-Pugh score > 8;	600 µg/kg rFVIIa (200 plus 4 X 100 µg/kg) or 300 µg/kg rFVIIa (200, 100 plus 3 X placebo)	Well conducted study with clear allocation concealment, randomisation, blinding, power calculations etc (N=256) The first interim analysis showed an unexplained 'stop' signal but the trial was continued after ruling out any safety concerns.

Comparison of rFVIIa versus placebo (all patients)

Table 24: GRADE summary table for rFVIIa versus placebo – lighter coloured and indented outcomes indicate subgroup analyses

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	rFVIIa, Frequency (%), Mean (SD), Median (range)	Placebo, Frequency (%), Mean (SD), Median (range)	Relative Risk (95% CI)	Absolute effect / Mean difference (95% CI)	
Mortality (5 day follow-up)										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	18/291 (6.2%)	18/207 (8.7%)	RR 0.62 (0.33 to 1.17)	33 fewer per 1000 (from 58 fewer to 15 more)	LOW
Mortality (42 day follow-up)										
Bosch 2004, [43]Bosch 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	55/291 (18.9%)	36/207 (17.4%)	RR 0.95 (0.66 to 1.38)	9 fewer per 1000 (from 59 fewer to 66 more)	LOW
Failure to control bleeding within 24h										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	22/291 (7.6%)	18/207 (8.7%)	RR 0.81 (0.44 to 1.51)	17 fewer per 1000 (from 49 fewer to 44 more)	LOW
Re-bleeding (5 day follow-up)										

Quality assessment						Summary of findings				
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	19/291 (6.5%)	18/207 (8.7%)	RR 0.76 (0.41 to 1.42)	21 fewer per 1000 (from 51 fewer to 37 more)	LOW
Emergency procedures at Day 5 (balloon catheters, TIPS, further endoscopy)										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	27/170 (15.9%)	16/86 (18.6%)	RR 0.85 (0.49 to 1.5)	28 fewer per 1000 (from 95 fewer to 93 more)	LOW
Red cell transfusion (24 hour follow-up) divided by dose of rFVIIa						**-**	***Low dose rFVIIa***			
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N=121; 0.9 (1.2); N=85; 1.5 (1.7)	N=121; 0.7 (1.8); N=86; 2.3 (2.3)		MD 0.09 lower (0.41 lower to 0.24 higher)	HIGH
Red cell transfusion (24 hour follow-up) divided by dose of rFVIIa						**-**	***High dose rFVIIa***			
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=85; 1.7(1.9)	N=86; 2.3(2.3)		MD 0.6 lower (1.23 lower to 0.03 higher)	MODERATE
Red cell transfusion (5 day follow-up) divided by dose of rFVIIa						**-**	***Low dose rFVIIa***			
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=121; 1.5(3.7); N=85; 2.3 (2.2)	N=121; 1.3 (1.9); N=86; 3.3 (3.1)		MD 0.35 lower (0.9 lower to 0.19 higher)	MODERATE
Red cell transfusion (5 day follow-up) divided by dose of rFVIIa						**-**	***High dose rFVIIa***			

Quality assessment						Summary of findings				
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=86; 2.8 (2.6)	N=86; 3.3 (3.1)		MD 0.5 lower (1.36 lower to 0.36 higher)	MODERATE
Serious adverse events (mainly thromboembolic events, such as portal vein thrombosis, arterial thromboembolic events) by day 42										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	176/629 (28%)	111/404 (27.5%)	RR 0.96 (0.78 to 1.17)	11 fewer per 1000 (from 60 fewer to 47 more)	MODERATE
Fatal adverse events (such as bleeding related, related to liver disease, infection related) by day 42										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	54/629 (8.6%)	35/404 (8.7%)	RR 0.71 (0.49 to 1.04)	25 fewer per 1000 (from 44 fewer to 3 more)	HIGH

[a] *When the confidence interval of the effect ranges from appreciable benefit to no effect imprecision is downgraded once and whenever it ranges from appreciable benefit to appreciable harm imprecision is downgraded twice.*

Comparison of rFVIIa versus placebo (restricted to Child-Pugh B/C patients)

Table 25: GRADE summary table for rFVIIa versus placebo (restricted to Child-Pugh B/C patients) – outcome names are italicised to indicate subgrouping by dosage

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	rFVIIa, Frequency (%),	Placebo, Frequency (%), Mean (SD), Median	Relative Risk (95% CI)	Absolute effect / Mean differenc	

Quality assessment						Summary of findings				
						Mean (SD), Median (range)	(range)		e (95% CI)	
Mortality (5 day follow-up) – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	4/85 (4.7%)	11/86 (12.8%)	RR 0.37 (0.12 to 1.11)	81 fewer per 1000 (from 113 fewer to 14 more)	MODERATE
Mortality (5 day follow-up) – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	10/85 (11.8%)	11/86 (12.8%)	RR 0.92 (0.41 to 2.05)	10 fewer per 1000 (from 75 fewer to 134 more)	LOW
Mortality (42 day follow-up) – low dose										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	26/85 (30.6%)	25/86 (29.1%)	RR 1.05 (0.66 to 1.67)	15 more per 1000 (from 99 fewer to 195 more)	LOW
Mortality (42 day follow-up) – high dose										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	13/85 (15.3%)	25/86 (29.1%)	RR 0.53 (0.29 to 0.96)	137 fewer per 1000 (from 12 fewer to 206 fewer)	MODERATE
Failure to control bleeding – low dose										

Quality assessment						Summary of findings				
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	8/148 (5.4%)	15/151 (9.9%)	RR 0.56 (0.25 to 1.25)	44 fewer per 1000 (from 75 fewer to 25 more)	MODERATE
Failure to control bleeding – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	8/85 (9.4%)	8/86 (9.3%)	RR 1.01 (0.4 to 2.57)	1 more per 1000 (from 56 fewer to 146 more)	LOW
Re-bleeding – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	8/148 (5.4%)	16/151 (10.6%)	RR 0.51 (0.22 to 1.16)	52 fewer per 1000 (from 83 fewer to 17 more)	MODERATE
Re-bleeding – high dose										
Bosch 2004 [43], Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	5/85 (5.9%)	8/86 (9.3%)	RR 0.63 (0.22 to 1.86)	34 fewer per 1000 (from 73 fewer to 80 more)	LOW
Emergency procedures at day 5 – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	8/85 (9.4%)	16/86 (18.6%)	RR 0.51 (0.23 to 1.12)	91 fewer per 1000 (from 143 fewer to 22 more)	MODERATE
Emergency procedures at day 5 – high dose										

Quality assessment						Summary of findings				
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	19/85 (22.4%)	16/86 (18.6%)	RR 1.2 (0.66 to 2.18)	37 more per 1000 (from 63 fewer to 220 more)	LOW
Red blood cell transfusions (first 24 hrs) – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=85; 1.5 (1.7)	N=86; 2.3 (2.3)	-	MD 0.8 lower (1.41 to 0.19 lower)	MODERATE
Red blood cell transfusions (first 24 hrs) – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=85; 1.7 (1.9)	N=86; 2.3 (2.3)	-	MD 0.6 lower (1.23 lower to 0.03 higher)	MODERATE
Red blood cell transfusions (5 days) – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=85; 2.3 (2.2)	N=86; 3.3 (3.1)	-	MD 1 lower (1.8 to 0.2 lower)	MODERATE
Red blood cell transfusions (5 days) – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	N=85; 2.8 (2.6)	N=86; 3.3 (3.1)	-	MD 0.5 lower (1.36 lower to 0.36 higher)	MODERATE
Serious adverse events – low dose										

Quality assessment						Summary of findings				
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	63/172 (36.6%)	56/155 (36.1%)	RR 1.01 (0.76 to 1.35)	4 more per 1000 (from 87 fewer to 126 more)	MODERATE
Serious adverse events – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	46/169 (27.2%)	56/155 (36.1%)	RR 0.75 (0.55 to 1.04)	90 fewer per 1000 (from 163 fewer to 14 more)	MODERATE
Fatal adverse events – low dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	35/172 (20.3%)	35/155 (22.6%)	RR 0.9 (0.59 to 1.36)	23 fewer per 1000 (from 93 fewer to 81 more)	LOW
Fatal adverse events – high dose										
Bosch 2008 [44]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	18/169 (10.7%)	35/155 (22.6%)	RR 0.47 (0.28 to 0.8)	120 fewer per 1000 (from 45 fewer to 163 fewer)	MODERATE

[a] *When the confidence interval of the effect ranges from appreciable benefit to no effect imprecision is downgraded once and whenever it ranges from appreciable benefit to appreciable harm imprecision is downgraded twice.*

6.1.9 Health economic evidence review

No relevant economic evaluations were identified that assessed the most cost effective threshold and target level at which platelets and clotting factors should be administered to patients with upper GI bleeding with low platelet count and/or abnormal coagulation factors.

It was possible to use the results of the clinical review to inform the likely cost effectiveness of the use of the recombinant factor VIIa in patients with variceal bleeding.

Bosch and colleagues (2008) [44] concluded that the use of this agent is beneficial in patients with cirrhosis and Child-Pugh class B and C: results showed a significant improvement in mortality at 42 days (Risk ratio [95% CI]: 0.53 [0.29, 0.96]). Approximately 14 fewer patients per 100 patients using the intervention would have died by 42 days.

The dosage used for this effect was 600 µg/kg (200 +4 X 100 µg/kg). For a patient weighting 70kg, the cost of this treatment was estimated to be £19,303 (5mg costing £2,298 including hospital discount – personal communication with Novo Nordisk, 2009). The total cost of treating 100 patients would cost £1,930,300. The cost per life saved at 42 days therefore is £140,124.

6.1.10 Evidence statements

6.1.10.1 Clinical evidence

rFVIIa versus placebo (all participants)

Mortality (5 day follow-up)

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of 5 day mortality between the groups who received rFVIIa compared to those who did not (LOW QUALITY).

Mortality (42 day follow-up)

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of 42 day mortality between the groups who received rFVIIa compared to those who did not (LOW QUALITY).

Failure to control bleeding

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of bleeding control between the groups who received rFVIIa compared to those who did not (LOW QUALITY).

Re-bleeding

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of re-bleeding between the groups who received rFVIIa compared to those who did not (LOW QUALITY).

Emergency procedures at day 5

Evidence from 1 study comprising 256 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of emergency procedures between the groups who received rFVIIa compared to those who did not (LOW QUALITY).

Red blood cell transfusions (24 hours) – divided into low and high dose rFVIIa treatment

Evidence from 2 studies comprising 416 participants with variceal upper gastrointestinal bleeding who received a lower dose of rFVIIa (100/300 microgram / kg) found that there was no statistical significant / clinical difference blood transfusion requirements between the group who received

low dose rFVIIa compared to those who received a placebo in the first 24 hours (HIGH QUALITY). One of these studies with 85 additional patients who received a higher dose of rFVIIa (600 microgram / kg) showed a non-significant difference with a lower average amount of blood transfused in the treatment group (MODERATE QUALITY).

Red blood cell transfusions (5 days) – divided into low and high dose rFVIIa treatment

Evidence from 2 studies comprising 416 participants with variceal upper gastrointestinal bleeding who received a lower dose of rFVIIa (100/300 microgram / kg) found that there was no statistical significant / clinical difference 5 day blood transfusion requirements between the group who received low dose rFVIIa compared to those who received a placebo (MODERATE QUALITY). 1 of the studies with a further 85 patients receiving a higher dose treatment (600 microgram / kg) showed that there was no statistical significant / clinical difference 5 day blood transfusion requirements between the group who received high dose rFVIIa compared to those who received a placebo (MODERATE QUALITY).

Severe adverse events

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference in the rate of severe adverse events between the groups who received rFVIIa compared to those who did not (MODERATE QUALITY).

Fatal adverse events

Evidence from 2 studies comprising 498 participants with variceal upper gastrointestinal bleeding showed a non-significant difference with lower rates of fatal adverse events in the group who received rFVIIa compared to those who did not (LOW QUALITY).

rFVIIa versus placebo divided into low and high dose treatment (moderate to severe cirrhosis participants – Child-Pugh grade B/C)

Mortality (5 day less follow-up)

One study with 171 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed a non-significant difference with a lower rate of 5 day mortality for patients receiving a low dose of rFVIIa compared to those receiving placebo (MODERATE QUALITY). The same study with a further group of 85 patients treated with a high dose of rFVIIa showed no statistical / clinical improvement in rate of 5 day mortality compared to those who received placebo (LOW QUALITY).

Mortality (42 day less follow-up)

One study with 171 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed no statistical / clinical improvement in rate of 42 day mortality in those receiving low dose rFVIIa compared to those who received placebo (LOW QUALITY). The same study with a further group of 85 patients treated with a high dose of rFVIIa showed a statistically / clinical significant improvement in rate of 42 day mortality compared to those who received placebo (MODERATE QUALITY).

Failure to control bleeding

Two studies with 299 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed no statistical or clinical improvement in the rate of bleeding control for patients receiving a low dose of rFVIIa compared to those receiving placebo (MODERATE QUALITY). In one of those studies a further group of 85 patients treated with a high dose of rFVIIa showed no statistical / clinical improvement in rate of bleeding control compared to those who received placebo (LOW QUALITY).

Re-bleeding

Two studies comprising 299 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed no statistical or clinical improvement in the rate of re-bleeding for patients receiving a low dose of rFVIIa compared to those receiving placebo (MODERATE QUALITY). One of those studies provided an additional group of 85 patients treated with a high dose of rFVIIa showed no statistical / clinical improvement in rate re-bleeding compared to those who received placebo (LOW QUALITY).

Emergency procedures at day5

One study with 171 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed a non-significant difference with a lower rate of emergency treatments at 5 day follow-up for patients receiving a low dose of rFVIIa compared to those receiving placebo (MODERATE QUALITY). The same study with a further group of 85 patients treated with a high dose of rFVIIa showed no statistical / clinical improvement in rate of 5 day emergency procedures compared to those who received placebo (LOW QUALITY).

Red blood cell transfusion (24 hrs)

Evidence from 1 study comprising 171 participants with moderate to severe cirrhosis and variceal upper gastrointestinal bleeding who received a lower dose of rFVIIa (100/300 microgram / kg) found that there was a statistical significant decrease in blood transfusion requirements between the group who received low dose rFVIIa compared to those who received a placebo in the first 24 hours (MODERATE QUALITY). One of these studies with 85 additional patients who received a higher dose of rFVIIa (600 microgram / kg) showed a non-significant difference with a lower average amount of blood transfused in the treatment group (MODERATE QUALITY).

Red blood cell transfusion (5 days)

Evidence from 1 study comprising 171 participants with moderate to severe cirrhosis and variceal upper gastrointestinal bleeding who received a lower dose of rFVIIa (100/300 microgram / kg) found that there was a statistical significant decrease in blood transfusion requirements between the group who received low dose rFVIIa compared to those who received a placebo in the first 5 days (MODERATE QUALITY). One of these studies with 85 additional patients who received a higher dose of rFVIIa (600 microgram / kg) showed that the lower average amount of blood transfused was not significantly different from those that received a placebo (MODERATE QUALITY).

Serious adverse events

Evidence from 1 study comprising 171 participants with moderate to severe cirrhosis and variceal upper gastrointestinal bleeding who received a lower dose of rFVIIa (100/300 microgram / kg) found that there was no statistical significant / clinical difference in the frequency of severe adverse events in those who received a low dose rFVIIa compared to those who received a placebo (MODERATE QUALITY). One of these studies with 85 additional patients with moderate to severe cirrhosis and upper GI bleeding who received a higher dose of rFVIIa (600 microgram / kg) showed a non-significant difference with a lower rate of serious adverse events in the treatment group compared to the placebo group (LOW QUALITY).

Fatal adverse events

One study with 171 patients with moderate to severe cirrhosis and variceal upper GI bleeding showed no statistical / clinical improvement in the rate of fatal adverse events in those receiving low dose rFVIIa compared to those who received placebo (LOW QUALITY). The same study with a further group of 85 patients treated with a high dose of rFVIIa showed a statistically / clinical significant improvement in the rate of fatal adverse events compared to those who received placebo (MODERATE QUALITY).

6.1.10.2 Health economic evidence

There was no economic evidence assessing the cost effective pre-endoscopy threshold and target level at which platelets and / or clotting factors should be administered to improve outcome acute upper GI bleed patients of low platelet count and / or abnormal coagulation factors.

Considering the cost of treatment and the effect on mortality of the intervention, routine use of factor VIIa is not likely to be cost-effective.

6.1.11 Recommendations and link to evidence

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?

Recommendations	• **Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable.** • **Offer platelet transfusion to patients who are actively bleeding and have a platelet count of less than 50 x 10^9/litre.** • **Offer fresh frozen plasma to patients who have either:** - **a fibrinogen level of less than 1g/litre, or** - **a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal.** • **Offer prothrombin complex concentrate to patients who are taking warfarin and actively bleeding.** • **Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols.** • **Do not use recombinant factor VIIa except when all other methods have failed.**
Relative values of different outcomes	Mortality and re-bleeding rates were considered the most important outcomes.
Trade off between clinical benefits and harms	The GDG discussed recently published concerns regarding the safety of recombinant factor VIIa, but were reassured that one of the included studies [43] had not demonstrated a significant difference in adverse event rates
Economic	Based on the costing presented to the GDG, the GDG felt that the

considerations	routine administration of recombinant factor V11a to patients with upper GI bleeding was very unlikely to be cost effective. There was no cost-effectiveness evidence available to review in relation to the other forms of treatment. The GDG discussed the standards and findings of current use from a national UK audit [46] to prompt discussion regarding economic considerations of platelet transfusion and fresh frozen plasma transfusion and reach consensus. The audit standard for platelet transfusion is to do so in actively bleeding patients with a platelet count <50x10^9/L. Findings from the audit found 61% (213/352) of patients with upper gastrointestinal bleed and a platelet count <50x109/L did not receive a platelet transfusion; and 42% of platelet transfusions were given inappropriate. Given this high estimate of unnecessary use of platelets, the GDG felt that platelet transfusion in actively bleeding patients with a platelet count <50x109/L. was likely to be cost effective when compared to current practice. The audit standard for fresh frozen plasma (FFP) transfusion is in patients actively bleeding with INR >1.5x normal or PT > 3 seconds prolonged. In 57% (314/550) of patients with an INR >1.5 (or PT > 3 seconds prolonged) who were not on warfarin did not receive FFP transfusion where this may have been appropriate. In 27% of patients receiving FFP transfusion the INR was <1.5 or the PT was 3 seconds prolonged (FFP transfusion was inappropriate). Given that 27% of patients who received a transfusion of FFP did not need it, the GDG felt that use of fresh frozen plasma (FFP) transfusion in patients actively bleeding with INR >1.5x normal or PT > 3 seconds was likely to be cost effective when compared to current practice.
Quality of evidence	With the exception of recombinant factor VIIa no direct evidence was available to the GDG for consideration in relation to the administration of platelets and clotting factors. The quality of evidence available when considering recombinant factor VIIa ranged from low to high depending upon the outcome considered.
Other considerations	In discussion the GDG noted that although the evidence from individual trials suggested a reduction in 42-day mortality with high dose factor VIIa, and in red cell transfusion requirements at 24 hours for low dose factor VIIa, these findings are inconsistent with an effect of factor VIIa in early control of bleeding. There was insufficient evidence of significant benefit across all outcomes. Overall the GDG felt that there were circumstances in which it would be appropriate to try recombinant factor VIIa as a measure of last resort, but that its use could not be supported routinely The GDG received expert opinion relating to when to administer platelets and clotting factors to patients with upper gastrointestinal bleeding. In the absence of evidence, threshold values were reached by consensus. The GDG was keen to emphasise the importance of making a distinction between platelet numbers and function; the platelet count alone may be falsely re-assuring. However, It was felt that the routine use of tests

	of platelet function was unlikely to be practical in most sites. In addition, particularly in the context of chronic liver disease, it was felt that coagulation tests could also be misleading. The GDG discussed the use of near-patient tests of global haemostasis and their role in guiding the administration of platelets and clotting factors. Those who had used in them in practice reported a significant impact upon clinical decision-making. The GDG recognised the difficulty of making a recommendation for their routine use due to lack of availability. The GDG discussed local policies related to patients developing acute gastrointestinal bleeding whilst taking Warfarin. They felt that these should be based on local guidelines. These will vary according to the reasons for anticoagulation, but in general Warfarin therapy should be discontinued and the INR normalised using Vitamin K and (for actively bleeding patients) administration of clotting factors.

6.2 Terlipressin treatment and treatment duration

6.2.1 Introduction

Variceal bleeding is a consequence of portal hypertension and the severity of bleeding is proportional to the magnitude of portal venous pressure [47]. In the majority of cases cirrhosis of the liver (usually due to alcohol abuse or chronic viral hepatitis) is responsible for portal hypertension. It has long been recognised that pharmacological reduction of portal pressure using vasopressin can stop active variceal bleeding, although trials undertaken in the last Century demonstrated that this did not confer survival benefit. Furthermore vasopressin, that works by causing constriction of Splanchnic arterioles, has significant side effects principally related to vasoconstriction of the coronary and peripheral vascular arteries and has to be used with great care in patients with coronary or peripheral vascular disease[48] . Terlipressin, the long acting analogue of vasopressin, is used in clinical practice since it is given as intravenous boluses rather than as a constant infusion. Somatostatin and its analogue octreotide also reduce portal pressure by reducing splanchnic flow and have been used to treat variceal bleeding [49,49] .

Current treatment of bleeding varices is principally based upon variceal ablation by endoscopic band ligation for oesophageal varices or tissue glue injection for gastric varices (Chapter 9). Surgical approaches including porta-caval shunt operations or oesophageal transection are now rarely undertaken. Pharmacological approaches (terlipressin, somatostatin and octreotide) are best considered as complementary therapies and cannot be considered as substitutes for endoscopic treatment. These drugs could, for example, be used at presentation in patients with probable variceal haemorrhage to stop active bleeding and help stabilise the patient prior to definitive endoscopic therapy; they could have other positive effects including the support of renal function.

Clinicians need guidance concerning the choice of drug, the timing of therapy (whether treatment should be started at presentation or only after endoscopic confirmation of variceal bleeding), duration of drug use and clarity concerning side effects and exclusions.

6.2.2 Clinical questions and methodological introduction

Clinical question 1

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?

Table 26: PICO Characteristics of clinical question 1

Clinical Methodological Introduction	
Population:	Adults with upper GI bleeding with likely or confirmed variceal upper GI bleeding
Intervention:	• Terlipressin
Comparison:	• Somatostatin, Octreotide or placebo
Outcomes:	Mortality Numbers failing initial haemostasis Re-bleeding Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding Blood transfusion requirements Length of hospital stay Adverse events were subdivided into 2 categories: Adverse events causing withdrawal of treatment Adverse events causing death

Clinical question 2

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

Table 27: PICO Characteristics of clinical question 2

Clinical Methodological Introduction	
Population:	Adults with upper GI bleeding with likely or confirmed variceal upper GI bleeding
Intervention:	• Terlipressin long / short duration of treatment
Comparison:	• Terlipressin long / short duration of treatment
Outcomes:	Mortality Numbers failing initial haemostasis Re-bleeding Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding Blood transfusion requirements Length of hospital stay Adverse events were subdivided into 2 categories: Adverse events causing withdrawal of treatment Adverse events causing death

6.2.3 Clinical evidence review

This combined review compares terlipressin to placebo, octreotide or somatostatin in the treatment of likely or confirmed variceal UGIB and also the best duration for terlipressin treatment. The search was restricted to randomised control trials (see flowchart in Appendix E for study selection).

This evidence review included a total of 8 RCTs and cross-references one Cochrane meta-analysis [50-58]. The results of the review have been analysed according to whether terlipressin treatment was compared to placebo, octreotide or somatostatin treatment. The most clinical effective length of treatment (≤5 days versus > 5 days) was also reviewed. Three of the 8 randomised control trials provided evidence for the duration of treatment. One study compared directly a 5 day regime to a10 day terlipressin treatment duration (see Appendix F for evidence tables and Appendix H for forest plots).

The main results of the review are presented as follows:

- Terlipressin versus Placebo
- Terlipressin versus Octreotide
- Terlipressin versus Somatostatin
- Duration of Terlipressin treatment

Table 28: Characteristics of included studies

Study	Confirmed varices	Diagnosis of cirrhosis	Patients or episodes	Terlipressin doses of treatment and comparator	Any other comments
Bruha, 2009 [50]	Yes	Clinical and histological	Patients	1 mg i.v. every 4 hours 5 day versus 10 day treatment	25 patients randomised. Study terminated early due to slow recruitment. Direct short versus long treatment duration comparison
Feu, 1996 [51]	Both confirmed and unconfirmed	Histological or clinical	Patients	2 mg i.v. every 4 hours versus Somatostatin	No major problems to report here.
Freeman, 1989 [52]	Yes	Clinical	Episodes	2 mg i.v. every 4 hours versus placebo	Only 29 patients randomised (31 episodes)
Pedretti, 1994 [54]	Both confirmed and unconfirmed	Histological	Episodes (patient number unclear)	2 mg every 4 hours versus Octreotide	Results stratified by Child-Pugh classification (treatment duration 7 days)
Silvain, 1993 [55]	Yes	Histological or clinical	Episodes	2 mg once then 1 mg every 4 hours versus Octreotide	Study terminated early due to 2 major side effects in the terlipressin group and also due to the results of the intermediate analysis
Söderlund, 1990 [56]	Both confirmed and unconfirmed	Histological and clinical	Patients	2 mg i.v. every 4 hours versus placebo	Baseline differences: Patients with more prior episodes of bleeding in the terlipressin group
Walker, 1986 [57]	Yes	Histological	Episodes	2 mg once then 1 mg	In 39 of 50 bleeding episodes balloon tamponade was used at entry to the

Study	Confirmed varices	Diagnosis of cirrhosis	Patients or episodes	Terlipressin doses of treatment and comparator	Any other comments
				every 4 hours versus placebo	study
Walker, 1996 [58]	Both confirmed and unconfirmed	Histological or clinical	Episodes	2 mg once then 1 mg every 4 hours versus Somatostatin	Sclerotherapy performed in all patients after 24 hours.

Clinical question 1:

Comparison of Terlipressin versus placebo

Table 29: GRADE summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Terlipressin, Rate, Mean (sd), Median (range)	Placebo, Rate, Mean (sd), Median (range)	Relative risk (95% CI),	Absolute effect or Mean difference (95% CI)	
Mortality (within 6 weeks or less)										
Walker 1986 [57], Freeman 1989 [52], Soderlund 1990 [56]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	9/71 (12.7%)	23/70 (32.9%)	RR 0.39 (0.19 to 0.78)	200 fewer per 1000 (from 72 fewer to 266 fewer)	MODERATE
Failure to achieve initial haemostasis										
Walker 1986 [57], Freeman 1989 [52], Soderlund 1990 [56]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	14/71 (19.7%)	34/70 (48.6%)	RR 0.41 (0.25 to 0.69)	287 fewer per 1000 (from 151 fewer to 364 fewer)	MODERATE
Re-bleeding										
Walker 1986 [57], Freeman 1989 [52]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	6/40 (15%)	8/41 (19.5%)	RR 0.76 (0.29 to 2.01)	47 fewer per 1000 (from 139 fewer to 197 more)	VERY LOW
Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding										
Walker 1986 [57], Freeman 1989 [52], Soderlund 1990 [56]	randomised trial	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	15/71 (21.1%)	35/70 (50%)	RR 0.43 (0.27 to 0.7)	285 fewer per 1000 (from 150 fewer to 365 fewer)	MODERATE
Units of blood transfusions										
Walker 1986 [57]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	N=25, Mean (sd) = 5.4 (4.3)	N=25, Mean (sd) = 7.5 (6.1)	-	MD 2.1 lower (5.03 lower to 0.83 higher)	VERY LOW
Adverse events causing withdrawal from treatment										
Walker 1986 [57],	randomised trial	serious[a]	no serious	no serious	very serious[b,c]	1/71	0/70 (0%)	RR 2.81	0 more per 1000 (from	VERY LOW

Quality assessment						Summary of findings				
Freeman 1989 [52], Soderlund 1990 [56]			inconsistency	indirectness		(1.4%)		(0.12 to 66.4)	0 fewer to 0 more)	
Fatal adverse events										
Walker 1986 [57], Freeman 1989 [52], Soderlund 1990 [56]	randomised trial	serious[a]	no serious inconsistency	no serious indirectness	very serious[b,c]	0/71 (0%)	0/70 (0%)	not pooled	not pooled	VERY LOW

[a] *None of the studies report clear allocation concealment or randomisation sequence generation.*
[b] *The overall confidence interval range from appreciable benefit / harm to no effect imprecision is downgraded to 'serious' and when it ranges from appreciable benefit to appreciable harm it would be downgraded twice to very serious status*
[c] *Event rate too low (no or only one event)*

Comparison of Terlipressin versus Octreotide

Table 30: GRADE summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Terlipressin Rate, Mean (sd), Median (range)**	**Octreotide Rate, Mean (sd), Median (range)**	**Relative risk (95% CI),**	**Absolute effect or Mean difference (95% CI)**	
Mortality (within 6 weeks or less)										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	15/71 (21.1%)	13/76 (17.1%)	RR 1.26 (0.65 to 2.44)	44 more per 1000 (from 60 fewer to 246 more)	VERY LOW
Failure to achieve initial haemostasis										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	31/71 (43.7%)	17/76 (22.4%)	RR 1.95 (1.19 to 3.2)	212 more per 1000 (from 43 more to 492 more)	VERY LOW
Re-bleeding										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	8/71 (11.3%)	17/76 (22.4%)	RR 0.52 (0.24 to 1.11)	107 fewer per 1000 (from 170 fewer to 25 more)	VERY LOW

Quality assessment						Summary of findings				
Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trial	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	31/71 (43.7%)	24/76 (31.6%)	RR 1.39 (0.9 to 2.12)	123 more per 1000 (from 32 fewer to 354 more)	VERY LOW
Units of blood transfusions										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trials	very serious[a]	seriou[c]	no serious indirectness	serious[b]	N=25, Mean (sd) = 5.4 (4.3)	N=25, Mean (sd) = 7.5 (6.1)	-	MD 2.1 lower (5.03 lower to 0.83 higher)	VERY LOW
Adverse events causing withdrawal from treatment										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[b,d]	1/71 (1.4%)	0/70 (0%)	RR 2.81 (0.12 to 66.4)	-	VERY LOW
Fatal adverse events										
Silvain 1993 [55], Pedretti 1994 [54]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[b,d]	1/71 (1.4%)	0/70 (0%)	RR 2.81 (0.12 to 66.4)	-	VERY LOW

[a] *None of the two studies describe clear allocation concealment. One study is single blind and the other is not blinded.*
[b] *The overall confidence interval range from appreciable benefit / harm to no effect imprecision is downgraded to 'serious' and when it ranges from appreciable benefit to appreciable harm it would be downgraded twice to very serious status*
[c] *Evidence of heterogeneity – due to more variability in one study's results (may be related to different follow-up lengths)*
[d] *Event rate too low (no or only one event)*

Comparison of Terlipressin versus Somatostatin

Table 31: GRADE summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Terlipressin Rate, Mean (sd), Median (range)**	**Somatostatin Rate, Mean (sd), Median (range)**	**Relative risk (95% CI),**	**Absolute effect or Mean difference (95% CI)**	
Mortality (within 6 weeks or less)										

Quality assessment						Summary of findings				
Feu 1996 [51]; Walker 1996 [58]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	24/133 (18%)	24/134 (17.9%)	RR 1.01 (0.6 to 1.68)	2 more per 1000 (from 72 fewer to 122 more)	VERY LOW
Failure to achieve initial haemostasis										
Feu 1996 [51]; Walker 1996 [58]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[2]	17/133 (12.8%)	14/134 (10.4%)	RR 1.23 (0.64 to 2.34)	24 more per 1000 (from 38 fewer to 140 more)	VERY LOW
Re-bleeding										
Walker 1996 [58]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[2]	5/53 (9.4%)	5/53 (9.4%)	RR 1 (0.31 to 3.25)	0 fewer per 1000 (from 65 fewer to 212 more)	VERY LOW
Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/re-bleeding										
Feu 1996 [51]; Walker 1996 [58]	randomised trial	serious[a]	no serious inconsistency	no serious indirectness	very serious[2]	21/133 (15.8%)	23/134 (17.2%)	RR 0.92 (0.53, 1.58)	14 fewer per 1000 (from 81 fewer to 100 more)	VERY LOW
Units of blood transfused										
Feu 1996 [51]; Walker 1996 [58]	randomised trial	serious[a]	no serious inconsistency	no serious indirectness	serious[2]	N=80, Mean (sd) = 2.4 (2.1); N=53, Mean (sd) = 5.5 (5.1)	N=81, Mean (sd) = 2.6 (2.3); N=53, Mean (sd) = 5.5 (6.3)		MD 0.18 lower (0.83 lower to 0.47 higher	LOW
Length of hospital stay										
Walker 1996 [58]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[2]	N=53, Mean (sd) = 17.4 (11.9)	N=53, Mean (sd) = 16.0 (11.3)	-	MD 1.4 higher (3.02 lower to 5.82 higher)	VERY LOW
Adverse events causing withdrawal from treatment										
Feu 1996 [51]; Walker 1996 [58]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[b,d]	1/133 (0.8%)	0/134	RR 1.42 (0.89 to 2.25)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Fatal adverse events										
Feu 1996 [51]; Walker 1996 [58]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[b,d]	31/133 (23.3%)	22/134 (16.4%)	RR 1.42 (0.89 to 2.25)	69 more per 1000 (from 18 fewer to 205 more)	VERY LOW

[a] *One of the studies does not describe clear allocation concealment and the randomisation sequence generation is also unclear. Study limitations are therefore*
[b] *The overall confidence interval range from appreciable benefit / harm to no effect imprecision is downgraded to 'serious' and when it ranges from appreciable benefit to appreciable harm it would be downgraded twice to very serious status*
[c] *Event rate too low (no or only one event)*

Clinical question 2:

Terlipressin 5 days versus Terlipressin 10 days

Table 32: GRADE summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Terlipressin 5 days, Rate, N, Mean (sd), Median (range)	Terlipressin 10 days, Rate, N, Mean (sd), Median (range)	Relative risk (95% CI),	Absolute effect (95% CI) or Mean difference (95% CI)	
Mortality (within 6 weeks)										
Bruha 2009 [50]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	1/15 (6.7%)	2/10 (20%)	RR 0.33 (0.03 to 3.2)	134 fewer per 1000 (from 194 fewer to 440 more)	VERY LOW
Re-bleeding (within 6 weeks)										
Bruha 2009 [50]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	5/15 (33.3%)	4/10 (40%)	RR 0.83 (0.29 to 2.37)	68 fewer per 1000 (from 284 fewer to 548 more)	VERY LOW
Transfusion need (units of fresh frozen plasma)										
Bruha 2009 [50]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	N=15, Mean (sd) = 4.1 (5.8)	N=10, Mean (sd) = 2.7 (2.6)	-	MD 1.43 higher (1.92 lower to 4.78 higher)	VERY LOW
Transfusion needs (units of packed red cells)										
Bruha 2009 [50]	randomised trial	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	N=15, Mean (sd) = 2.9 (3.9)	N=10, Mean (sd) = 0.9 (1.76)	-	MD 2 higher (0.26 lower to 4.26 higher)	VERY LOW
Adverse events causing withdrawal from treatment										
Bruha 2009 [50]	randomised trial	very serious[a]	no serious	no serious	very serious[b,c]	1/15	0/10 (0%)	RR 2.06	-	VERY LOW

Quality assessment						Summary of findings				
			inconsistency	indirectness		(6.7%)		(0.09 to 46.11)		
Fatal adverse events										
Bruha 2009 [50]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b,c]	0/15 (0%)	0/10 (0%)	-	-	VERY LOW

[a] *This study does not describe clear allocation concealment and the randomisation sequence generation is also unclear. Very small sample size.*
[b] *The overall confidence interval range from appreciable benefit / harm to no effect imprecision is downgraded to 'serious' and when it ranges from appreciable benefit to appreciable harm it would be downgraded twice to very serious status*
[c] *Event rate too low (no or only one event)*

6.2.4 Health economic evidence review

One economic study [59] was included that compared terlipressin to octreotide and no treatment in the UK NHS. This is summarised in the economic evidence profile below. See also the Evidence Table G.1.1 in Appendix G. Two cost-effectiveness analyses assessing vasoactive agents for the initial management of patients with acute variceal upper GI bleeding, from Belgium [60] and France [61], were identified and excluded. The former was based on the findings of the included study, and the later had potential serious limitations and less applicability to the current UK healthcare system in comparison to the included study.

No relevant economic evaluations that assessed the optimal length of treatment with vasoactive agents for patients with acute variceal upper GI bleed were identified.

Table 33: Treatment A – Economic study characteristics

Study	Limitations	Applicability	Other comments
Wechowski 2007	Minor limitations (a)	Directly applicable	Cost utility analysis developed from a UK perspective and over a time horizon up to 5 years (1 year for base case)

Very serious limitations/Potentially serious limitations/Minor limitations; Directly applicable/Partially applicable/Not applicable.

(a) Based on Cochrane reviews, a discrete event simulation model was developed over a time horizon up to 5 years. The model adequately reflects the nature of the health condition. Cost components included were appropriate. Appropriate incremental analyses were presented. A univariate sensitivity analysis and a probabilistic sensitivity analysis were performed.

The analysis from Wechowski and colleagues showed that terlipressin is highly cost effective and likely to be cost saving compared to octreotide and to placebo. This was explained by the observed survival benefit with terlipressin, and by the improvement of bleeding control which consequently reduced the length of hospital stay and the need for costly therapeutic interventions.

Table 34: Economic summary of findings of Wechowski (2007)

Intervention	Total cost (£) (1 year)	Total effects (1 year)	Cost effectiveness	Uncertainty
Terlipressin [a]	£2623 [b]	Terlipressin produced, respectively, 0.079 and 0.078 QALYs more than octreotide and no treatment per patient in 1 year [c] Terlipressin resulted in a gain of 0.107 LY (1.3 months) compared with octreotide and placebo. Octreotide produced 0.001 QALYs more than no treatment per patient in 1 year. There is no detectable LY gain advantage for	Base case (1 year): 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 (shorter time horizon) to 2 years, and was cost effective at 3 years (ICER of £356 per QALY gained) and at 5 years (£775 per QALY gained);	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; Probability of cost effectiveness at 1 year was
Octreotide (somatostatin analogues) [c]	£2758			
No treatment	£2890			

Intervention	Total cost (£) (1 year)	Total effects (1 year)	Cost effectiveness	Uncertainty
		octreotide compared with no treatment.	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). [d]	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).

Abbreviations: QALY = Quality-Adjusted Life-Years; LY = Life Year;

(a) Treatment doses were based on the proceedings of the 4th Bavero International Consensus workshop recommendation: terlipressin = 12mg/day, dose was halved after bleeding was controlled, for up to a maximum of 5 days; octreotide = initial bolus of 50µg, followed by 50µg/h, up to a maximum of 5 days. When the Baveno guidance differs from the licensed dosing, this was tested in the sensitivity analysis.

(b) Cost components incorporated: i) hospitalisation cost; ii) vasoactive drug treatment costs (terlipressin and octreotide); iii) secondary prophylaxis costs (endoscopic treatment, treatment with β-blockers, general practitioner follow-up visits, and surgical therapy costs for salvage surgery and TIPS); and iv) cost of death (excess cost of treatment immediately preceding death).

(c) The baseline utility score for non-bleeding patient of 0.75 was obtained based on previous studies [62]. In the model, disutilities were applied from expert opinion for bleeding episodes, for TIPS intervention, and for salvage surgery. Reduction from baseline following TIPS and salvage surgery were based on observations by Rubenstein 2004[63].

(d) As the time horizon increased, the cost effectiveness of terlipressin decreased. This was due to improved survival, which also came with the associated cost of follow up in primary care and endoscopic treatment and treatment with β- blokers with any subsequent re-bleed (the annual probability of which was assumed to be 40%).

6.2.5 Evidence statements

6.2.5.1 Clinical evidence

Clinical question 1

Terlipressin versus Placebo

Mortality (within 6 weeks or less)

Three studies comprising 141 patients found a statistically significantly lower rate of mortality in the group of patients treated with terlipressin compared to those given a placebo. The size of this reduction in mortality was large enough to show appreciable clinical benefit [MODERATE QUALITY].

Failure to achieve initial haemostasis

Three studies comprising 141 patients found a statistically significant improvement in the rate of patients achieving initial haemostasis in the group of patients treated with Terlipressin compared to those given a placebo. The size of this improvement was large enough to show appreciable clinical benefit of terlipressin treatment [MODERATE QUALITY].

Re-bleeding (within 6 weeks or less)

Two studies comprising 81 patients found no significant statistical / clinical improvement in rate of re-bleeding in patients treated with terlipressin compared to those given a placebo [VERY LOW QUALITY].

Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding / re-bleeding

Three studies comprising 141 patients found a statistically significant improvement in the rate of patients needing additional procedures in the group of patients treated with terlipressin compared to those given a placebo. The size of this improvement was large enough to show appreciable clinical benefit of terlipressin treatment [MODERATE QUALITY].

Blood transfusion requirement

One study with 50 participants found no statistical / clinical significant improvement in the average units of blood transfusions comparing patients treated with terlipressin compared to those given a placebo [MODERATE QUALITY].

Adverse events causing withdrawal from treatment

Three studies with 141 participants found no statistical / clinical difference in the rate of adverse events that caused patients to terminate the treatment in the group of patients treated with terlipressin compared to those given a placebo [VERY LOW QUALITY]. However, just one withdrawal of treatment due to adverse events was reported.

Fatal adverse events

Three studies with 141 participants reported no adverse events causing death in either the terlipressin or the placebo groups [VERY LOW QUALITY].

Terlipressin versus Octreotide

Mortality (within 6 weeks)

Two studies comprising 147 patients found no significant statistical / clinical difference in the rate of mortality in the group of patients treated with terlipressin compared to those given octreotide [VERY LOW QUALITY].

Failure to achieve initial haemostasis

Two studies comprising 147 patients found a statistically lower rate of patients achieving initial haemostasis in the group of patients treated with terlipressin compared to those given treated with octreotide. The size of this decrease in initial haemostasis was not large enough to show clear appreciable clinical harm of terlipressin treatment [VERY LOW QUALITY].

Re-bleeding (within 6 weeks)

Two studies comprising 147 patients showed a non-significant difference with a lower rate of re-bleeding in patients treated with terlipressin compared to those given octreotide [VERY LOW QUALITY].

Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding / re-bleeding

Two studies comprising 147 patients found that the difference in the rate of patients needing additional procedures in the group of patients treated with terlipressin compared to those given octreotide was not statistically or clinically significant [VERY LOW QUALITY].

Blood transfusion requirement

Two studies with a total of 50 participants found statistically significant higher average units of blood transfusions comparing patients treated with terlipressin compared to those given octreotide. The size of this higher average in transfusion requirement was not large enough to show appreciable clinical harm of terlipressin treatment [VERY LOW QUALITY].

Adverse events causing withdrawal from treatment

Two studies comprising 147 patients found no statistically / clinically significant increase in the rate of patients experiencing adverse events that lead to withdrawal of treatment in the group of patients treated with terlipressin compared to those given octreotide. However, only one person in total withdrew due to treatment [VERY LOW QUALITY].

Fatal adverse events

Two studies comprising 147 patients found no statistically / clinically significant increase in the rate of patients needing additional procedures in the group of patients treated with terlipressin compared to those given octreotide. However, only one person in total withdrew due to treatment [VERY LOW QUALITY].

Terlipressin versus Somatostatin

Mortality (within 6 weeks)

Two studies comprising 167 patients found no significant statistical / clinical improvement in the rate of mortality in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Failure to achieve initial haemostasis

Two studies comprising 167 patients found no significant improvement in the rate of patients achieving initial haemostasis in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Re-bleeding (within 24 hours)

One study comprising 106 patients found no statistical / clinical significant improvement in the rate of re-bleeding in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Re-bleeding (within initial hospital stay but after 24 hours weeks)

One study comprising 106 patients found no statistical / clinical significant improvement in the rate of re-bleeding in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Re-bleeding (within 6 weeks)

Two studies comprising 167 patients found no statistical / clinical significant improvement in the rate of re-bleeding in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Number of patients needing procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding / re-bleeding

Two studies comprising 167 patients found no statistical / clinical significant difference in the rate of patients needing additional procedures to control bleeding / re-bleeding in the group of patients treated with terlipressin compared to those given somatostatin [VERY LOW QUALITY].

Blood transfusion requirement

Two studies with a total of 167 participants found no statistically / clinically significant difference in the average units of blood transfused comparing patients treated with terlipressin to those given somatostatin [LOW QUALITY].

Length of hospital stay

One study with 106 participants found no statistically / clinically significant difference in the average length of hospital stay comparing patients treated with terlipressin to those given somatostatin [VERY LOW QUALITY].

Adverse events causing withdrawal from treatment

Two studies comprising 167 patients found no statistically / clinically significant increase in the rate of patients experiencing adverse events that lead to withdrawal of treatment in the group of patients treated with terlipressin compared to those given somatostatin. However, only one person in total withdrew due to treatment [VERY LOW QUALITY].

Fatal adverse events

Two studies comprising 167 patients reported no adverse events causing death in either the terlipressin group or the Somatostatin group [VERY LOW QUALITY].

Clinical question 2

Terlipressin 5 days versus Terlipressin 10 days

Mortality (within 6 weeks)

One study with a total of 25 patients found no statistical / clinical significant improvement in the rate of mortality in the group of patients treated with terlipressin for 5 days compared to those that were treated for 10 days [VERY LOW QUALITY].

Re-bleeding (within 6 weeks)

One study comprising 25 patients found no statistical / clinical significant improvement in the rate of re-bleeding in patients treated with terlipressin for 5 days compared to those that were treated for 10 days [VERY LOW QUALITY].

Blood transfusion requirement (fresh frozen plasma)

One study with a total of 25 participants found no statistically / clinically significant average transfusion amount of units of fresh frozen plasma comparing patients treated with terlipressin for 5 days to those that were treated for 10 days [VERY LOW QUALITY].

Blood transfusion requirement

One study with a total of 25 participants found a non-significant difference with a higher average amount of fresh frozen plasma units in patients treated with terlipressin for 5 days compared to those that were treated for 10 days. However, the size of this difference was not large enough to constitute appreciable benefit [VERY LOW QUALITY].

Adverse events causing withdrawal from treatment

One study comprising 25 patients found no statistically significant increase in the rate of patients experiencing adverse events that lead to withdrawal of treatment in the group of patients treated with terlipressin for 5 rather than 10 days. However, only one person in total withdrew due to treatment [VERY LOW QUALITY].

Fatal adverse events

One study comprising 25 patients reported no adverse events causing death in neither the Terlipressin treatment for 5 or for 10 days in duration [VERY LOW QUALITY].

6.2.5.2 Health economic evidence

Terlipressin is highly cost effective and is likely to be cost saving compared to octreotide and to placebo for the initial management of patients with acute variceal upper GI bleeding over the time horizon of 2 years subsequent to the initial bleed. This conclusion is from the assessment of giving terlipressin at 12mg/day, with the dosage halved after the bleeding controlled, for up to a maximum of 5 days.

No relevant economic evaluations that assessed the optimal length of treatment with vasoactive agents for patients with acute variceal upper GI bleed were identified.

6.2.6 Recommendations and link to evidence

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?

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

Recommendations	• **Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive haemostasis has been achieved, or after 5 days, unless there is another indication for its use[b].**
Relative values of different outcomes	Mortality was considered the most important outcome. The number of procedures needed for uncontrolled bleeding and blood transfusion requirements were also considered particularly relevant to this clinical question. Adverse event rates, particularly those resulting in discontinuation of therapy, were also taken into account. Terlipressin was shown to be superior to placebo on several outcome measures, but there were no differences when terlipressin was compared to somatostatin. The clinical evidence comparing terlipressin to octreotide showed, in general, non-significant trends in favour of octreotide, and a significant result in favour of octreotide for adequacy of initial haemostasis. However, in addition to concerns over the data quality (see below) the GDG noted that the failure of haemostasis with terlipressin seen in this comparison versus octreotide was markedly greater than that seen with the drug in studies versus placebo or versus somatostatin.
Trade off between clinical benefits and	The GDG noted that the side effect profiles of all the drugs considered (terlipressin, somatostatin and octreotide) were reassuring. There was

b At the time of publication (June 2012), terlipressin was indicated for the treatment of bleeding from oesophageal varices, with a maximum duration of treatment of 72 hours (3 days). Prescribers should consult the relevant summary of product characteristics. Informed consent for off-label use of terlipressin should be obtained and documented.

harms	an increase in the number of minor adverse events when comparing terlipressin to placebo, but for all 3 drugs there were low frequencies of serious adverse events causing death or leading to discontinuation of therapy. There were no significant differences in the rates of adverse events between terlipressin and either of the other drugs.
Economic considerations	The health economic evidence reviewed identifies the use of terlipressin as cost-saving compared to octreotide over a time horizon of 2 years, and is highly cost effective when considering a longer time horizon. The GDG noted that the clinical data used in this model was taken from studies comparing each of terlipressin and octreotide to placebo rather than studies comparing terlipressin to octreotide directly (due to the poor quality of the latter). There was some concern that the clinical efficacy of octreotide in comparison to placebo may have been underestimated, and therefore the efficacy of terlipressin to octereotide may have been overestimated in the indirect comparison. None the less, given the reviewed clinical evidence for this question and that estimates used in the model were derived from a Cochrane review, the GDG agreed Terlipressin was very likely to be cost effective in the initial management of variceal bleeding.
Quality of evidence	The evidence comparing terlipressin to placebo was predominantly of moderate quality. The available evidence comparing terlipressin to octreotide was of very low quality for most outcomes, and for the outcomes of transfusion requirements and numbers failing initial haemostasis it was of low quality. Data comparing terlipressin to somatostatin was also of very low quality. The GDG expressed some concern that many of the studies considered were old and carried out prior to the advent of effective endoscopic interventions for variceal bleeding. As such the design of many of the studies was without current clinical practice – i.e. they investigated the efficacy of vasoactive drugs in isolation rather than as currently used in conjunction with endoscopic therapy.
Other considerations	In discussion the GDG noted that terlipressin is the most widely used of the three drugs considered. Additionally the group noted that there are other therapeutic indications for the administration of terlipressin such as hepatorenal syndrome, which may be present in conjunction with variceal bleeding. However, the GDG noted that the direct clinical data, albeit of low quality, did not show terlipressin to be superior to octreotide although the available health economic analysis, containing otherwise unpublished clinical data on octreotide, favoured terlipressin. The GDG was reassured that the studies considered showed terlipressin to be significantly superior to placebo for the outcomes of mortality, numbers failing initial haemostasis and procedures required for uncontrolled bleeding, and noted that there was no comparable data available for octreotide or somatostatin. After some debate they agreed that there was enough data to make a positive recommendation for terlipressin. The group felt it difficult to

	make a recommendation to not use octreotide or somatostatin, as the available evidence which suggested inferiority of these agents was considered to be of low quality. None of the direct or indirect considered evidence favoured a prolonged duration of therapy, evidence which was however of very low quality. The summary of product characteristics for terlipressin informs that therapy with this drug should be for no more than 72 hours. However, the available evidence to inform this recommendation assessed terlipressin over a longer time frame and it was felt appropriate to make a recommendation outside the drug's indication

7 Timing of endoscopy

7.1 Introduction

The principle diagnostic test for patients with acute upper gastrointestinal bleeding is endoscopy. Endoscopy defines a specific cause for bleeding in more than 80% of cases, provides prognostic information and facilitates delivery of a range of haemostatic therapies. Endoscopy is associated with complications, and whilst these are uncommon in the context of diagnostic endoscopy in relatively fit individuals, they are relatively common in patients who are actively bleeding and may be life threatening in unstable patients with medical co-morbidities. Patients should therefore be optimally resuscitated before endoscopy to minimise their risk of complications and the procedure should not be undertaken whenever possible until cardiovascular stability is achieved.

The optimal timing for endoscopy relates to the severity of bleeding.

At one end of the spectrum are patients with active haematemesis /melaena who could benefit from urgent diagnostic and therapeutic endoscopy done as soon as possible after resuscitation; accepting that endoscopic haemostasis improves outcome it can be argued that endoscopy should be readily available night and day, during the week and at weekends. Does the available evidence justify a policy that facilitates endoscopy in selected patients within a very few hours of presentation? Such an approach clearly requires an out of hours endoscopy rota and this is resource intensive, stresses other medical and surgical hospital rotas, and may not be justified in smaller hospitals where major acute upper gastrointestinal bleeding events are relatively unusual and the number of endoscopists is low . On the other hand urgent therapeutic endoscopy could save lives, prevent unnecessary surgery, reduce blood transfusion and reduce duration of hospital admission. The guideline group therefore addressed the evidence that endoscopy done within a very few hours of presentation improves patient outcomes and is cost effective for patients with major gastrointestinal bleeding.

At the other end of the severity spectrum are patients who present with relatively trivial bleeding, who have no cardiovascular instability and are free from major medical co-morbidities. These patients are at low risk of death yet are almost invariably admitted to hospital and may wait several days for semi-elective endoscopy. It is possible that early endoscopy might obviate the need for hospital admission or at least greatly reduce the duration of stay, but this has to be balanced against the resource implications of developing urgent endoscopy.

Between these extremes lie the majority of patients who present to hospital with significant gastrointestinal haemorrhage or who bleed as established inpatients, yet respond well to resuscitation and achieve cardiovascular stability. What is the optimal timing for endoscopy in this patient group? Endoscopy is clearly needed to provide a diagnosis and to guide treatment; urgent out of hours endoscopy does not appear warranted, but is it cost effective to delay endoscopy over a weekend in patients who present on a Friday afternoon or should all patients undergo this investigation within 24 hours of presentation?

7.2 Clinical question and methodological introduction

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 re-bleeding or mortality?

Table 35: PICO characteristics of clinical question

Clinical Methodological Introduction	
Population:	Patients with upper GI bleeding
Intervention:	Early endoscopy (below one day)
Comparison:	Late endoscopy
Outcomes:	• Mortality • Failure to control bleeding • Re-bleeding • Surgical intervention • Length of hospital stay • Blood transfusion requirements

7.3 Clinical evidence review

This review assesses the effectiveness of early compared to late endoscopy in the initial management of upper gastrointestinal bleeding (see flowchart in Appendix E for study selection).

This evidence review includes a total of 3 randomised control trials[64-66] with timing to endoscopy ranging from 2 to 12 hours after admission to the emergency department compared to later endoscopy. The results of the review have been analysed according to whether the patient population included patients at risk (according to hemodynamic factors, had co-morbid illnesses or those with variceal bleeding etc) or whether the study only used a 'stable' low risk patient population (see Appendix F for evidence tables and Appendix H for forest plots).

Table 36: Characteristics of included studies

Study	Design	Patient population	Exclusions criteria	Sample size	Timing and other comments
Bjorkman, 2004[64]	RCT	'Stable' patients with non-variceal UGI bleeding	Patients who started bleeding whilst in hospital and patients with Rockall scores >5	N=93	Endoscopy within 6 hours. Discharge recommendation numbers reported. Baseline differences: significantly higher number of patients with high risk lesions in the early endoscopy group. Study was terminated early, due to a smaller than expected group difference in outcomes impacting on interim power calculation.
Lee 1999[67]	RCT	'Stable' patients with non-variceal UGI bleeding	Co-morbid illness requiring intensive care, hemodynamic instability, cirrhosis, hypertension, coagulopathy, upper GI bleeding within the preceding 1 month	N=110	Endoscopy within 2 hours. Early discharge numbers reported.

Study	Design	Patient population	Exclusions criteria	Sample size	Timing and other comments
Lin, 1996[66]	RCT	'Unstable' patients (according to hemodynamic factors were included	Patients with a bleeding tendency or bleeding from the upper airway or lower gastrointestinal tract, a bleeding source that could not be pinpointed, bleeding due to malignancy	N=325	Endoscopy within 12 hours. Patients stratified according to their nasogastric aspirate. Overall 36% of patients with shock.

Comparison early versus delayed endoscopy

Table 37: GRADE summary table for early versus delayed endoscopy (early endoscopy times varied from 2 hours to 12 hours from admission, or before admission to the emergency department). Italicised, indented outcome names indicate subgroups within a particular outcome

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Early endoscopy (within 12 hours) Frequency, rate, N, mean (sd), median (range)	Delayed endoscopy Frequency, rate, N, mean (sd), median (range)	Relative Risk (95% CI)	Absolute effect / Mean difference (95% CI)	
Mortality (30 day or less)										
See subgroups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/265 (0.75%)	3/263 (1.1%)	RR 0.81 (0.13 to 5.29)	2 fewer per 1000 (from 10 fewer to 49 more)	VERY LOW
Mortality (30 day or less) - Only stable patients										
Lee 1999[67], Bjorkman, 2004[64]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	0/103 (0%)	2/100 (2%)	RR 0.19 (0.01 to 3.93)	16 fewer per 1000 (from 20 fewer to 59 more)	VERY LOW
Mortality (30 day or less) – High risk patients included										
Lin, 1996[66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/162 (1.20%)	1/163 (0.61%)	RR 2.01 (0.18 to 21.97)	6 more per 1000 (from 5 fewer to 129 more)	VERY LOW

Quality assessment						No of patients		Effect		Quality
Re-bleeding (30 day or less)										
See subgroups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	9/218 (4.10%)	10/217 (4.60%)	RR 0.89 (0.37 to 2.18)	5 fewer per 1000 (from 29 fewer to 54 more)	VERY LOW
Re-bleeding (30 day or less) - Only stable patients										
Lee 1999[67]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	3/56 (5.40%)	2/54 (3.70%)	RR 1.45 (0.25 to 8.32)	17 more per 1000 (from 28 fewer to 271 more)	VERY LOW
Re-bleeding (30 day or less) - High risk patients included										
Lin, 1996[66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	6/162 (3.70%)	8/163 (4.90%)	RR 0.75 (0.27 to 2.13)	12 fewer per 1000 (from 36 fewer to 55 more)	VERY LOW
Surgery for continued bleeding										
See subgroups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	3/265 (1.10%)	4/263 (1.50%)	RR 0.86 (0.18 to 4.05)	2 fewer per 1000 (from 12 fewer to 46 more)	VERY LOW
Surgery for continued bleeding - Only stable patients										
Lee 1999, Bjorkman, 2004[64]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	1/103 (0.97%)	3/100 (3%)	RR 0.47 (0.06 to 3.57)	16 fewer per 1000 (from 28 fewer to 77 more)	VERY LOW
Surgery for continued bleeding - High risk patients included										

Quality assessment						No of patients		Effect		Quality
Lin, 1996[66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/162 (1.20%)	1/163 (0.61%)	RR 2.01 (0.18 to 21.97)	6 more per 1000 (from 5 fewer to 129 more)	VERY LOW
Mean units of blood transfused - Only stable patients (Better indicated by lower values)										
Lee 1999, Bjorkman, 2004[64]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	47, 2.14 (3.78); 56, 1.2 (2.4)	46, 1.54 (1.92); 54, 1.1 (1.7)	-	MD 0.24 higher (0.41 lower to 0.9 higher)	VERY LOW
Length of hospital stay (mean days) (Better indicated by lower values)										
See subgroups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	47, 3.98 (3.87); 162, 2.89 (4.4)	46, 3.26 (3.18); 163, 3.88 (10.8)	-	MD 0.05 higher (1.07 lower to 1.17 higher)	VERY LOW
Length of hospital stay (mean days) - Only stable patients (Better indicated by lower values)										
Bjorkman, 2004[64]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	47, 3.98 (3.87);	46, 3.26 (3.18)	-	MD 0.72 higher (0.72 lower to 2.16 higher)	VERY LOW
Length of hospital stay (mean days) - High risk patients included (Better indicated by lower values)										
Lin, 1996[66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	162, 2.89 (4.4)	163, 3.88 (10.8)	-	MD 0.99 lower (2.78 lower to 0.8 higher)	VERY LOW

[a] *All studies describe clear allocation concealment, but none report randomisation sequence generation. No baseline differences were reported and dropout rates / loss to follow-up were low. Risk of bias was downgraded once.*

[b] *Results were downgraded once when the confidence interval of the total effect crossed one MID (appreciable benefit in favour of one or the other arm of the studies) and the line of no effect. When the confidence interval ranged from appreciable benefit to appreciable harm imprecision was downgraded twice.*

7.4 Health economic evidence

One study [64,67] was identified that included the relevant comparison. Due to the limited applicability of the identified study to the UK NHS setting, it was decided to build an original economic model to compare four different strategies, three of which would allow for earlier endoscopy than currently observed in the UK's current practice. The included study and the original economic model are summarised in the economic evidence profile below. See also Evidence Table G.2.1 and G.2.1 in Appendix G. No studies were selectively excluded.

In the RCT by Lee and colleagues, early endoscopy was undergone in the emergency department within 1 to 2 hours, and patients were triaged based on the endoscopic findings. Patients with low-risk findings on early endoscopy were discharged directly from the emergency department. Late endoscopy was undergone for elective patients within 1 to 2 days of admission. This study was conducted in the United States and randomised 110 patients.

In the NCGC economic model, four staffing service strategies were compared which assumed endoscopy would occur within 4 hours of presentation, 12 hours of presentation and 24 hours of presentation. As a baseline comparator the model also examined a strategy where endoscopy would occur in the same timeframe as observed by a national UK audit of providers which have a weekday service without out of hours service arrangements. The four respective staffing models to allow for the different timings of endoscopy were: having endoscopy staff onsite 8am-5pm every day, with an on call service 5pm-8am every day; onsite 8am-5pm everyday, with an on call service 5pm-12am everyday; onsite 8am-5pm Monday to Friday and onsite 8am-12pm Saturday and Sunday; and having endoscopy staff onsite 8am-5pm Monday to Friday. Many of the model inputs, including the rates of mortality, discharge, and endoscopy, were estimated from data collected by a national prospective UK audit [42, 46]. Further detail is available in Appendices I and J.

Table 38: Treatment A – Economic study characteristics

Study	Limitations	Applicability	Other comments
Lee et al (1999) [67]	Minor limitations (a)	Partially applicable (b)	Randomized controlled trial including a comparative cost analysis. Assessed patients with low risk endoscopic lesions and thought of having negligible risk of further bleeding
NCGC economic model (Appendices I and J)	Potentially serious limitations (c)	Directly applicable (d)	Cost utility analysis based on a UK prospective audit of gastrointestinal services. Assessed patients with low risk and high risk of mortality together, with results disaggregated according to Rockall score.

Very serious limitations/Potentially serious limitations/Minor limitations; Directly applicable/Partially applicable/Not applicable.

(a) Economic assessment based on a RCT. A cost analysis was developed costing patient-level resource use data, allowing reporting the distribution of the results – the interquartile range was reported. No additional sensitivity analysis was performed. A 30-day time horizon was used. Cost components included were appropriate.

(b) Cost-consequence analysis developed from a US healthcare system perspective assessing relevant interventions and a relevant population of patients. The study neither assessed patient quality of life nor calculated QALYs.

(c) Cost utility analysis based on observational patient level data collected by a national prospective 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. Potentially confounding variables within the observational dataset were not controlled for. Both determinist and probabilistic sensitivity analysis were 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

(d) Resource use and quality of life assessment developed from a UK NHS healthcare system perspective. Quality of life assessment used EuroQol 5D questionnaire given to UK patients having experienced a nonvariceal acute upper gastrointestinal bleed. Probabilities derived from data collected by a UK audit. Costs were estimated using NHS reference costs 2009-2010. Interventions assessed relevant to the UK NHS.

Results from the Lee (1999) study show that early endoscopy is less costly than late endoscopy. The main cost component was the hospitalisation stay, which was significantly lower for the early group. This is explained by the 46% of patients discharged directly from the emergency department and because of a significant shorter stay in the medical ward from early endoscopy. In addition, unplanned visit to the physician during the 30-day follow-up period was significantly lower for the early group. Finally, none of the patient discharged directly from the emergency department suffered an adverse outcome.

In the NCGC model, the main cost component was hospital stay, which was lowest for patients endoscoped within 24 hours. However, when all costs were considered, the strategy that had staff onsite only between 8am-5pm on weekdays had the lowest cost per patient. When the number of presentations per year is above approximately 330, the cost per patient decreases sufficiently that the strategy offering endoscopy within 24 hours has the lowest cost per patient. This reflects the trade off between fixed staff costs to provide a weekend morning service with the cost of hospital stay for patients waiting for endoscopy. In the subgroup analysis which looked at patients by pre-endoscopy Rockall score, the lowest cost of hospital stay in patients with low risk of mortality (i.e. Rockall score 0-1) was seen in the strategy that allowed endoscopy to occur within 4 hours. Please refer to Appendix I for further detail of the model results, including the subgroup analysis

Table 39: Treatment A – Economic summary of findings

Study and Intervention	Cost (£)	Effects	Cost effectiveness	Uncertainty
Lee 1999 Early endoscopy (within 1 to 2 hours; n=56) Late endoscopy (within 1 to 2 days; n=48)	**Median total cost (IQR)[a][b]:** Early endoscopy: £1350 (606-2586) Late endoscopy: £2391 (1615-4754) P=.00006	**Recurrent haemorrhage (median, IQR):** Early endoscopy: 2 (3.6) Late endoscopy:3 (5.6) P=.63 **Deaths (no, %):** Early endoscopy: 0/56 Late endoscopy: 2/48 [c] P=.54	Early endoscopy is less costly than late endoscopy; and fewer deaths and haemorrhages occurred.	Results of the cost analysis were presented with IQR. No additional sensitivity analysis was performed
NCGC economic model 1. Endoscopy in timeframe observed in providers without on call service	**Mean cost per patient (d)** 1. £3382 2. £3428 3. £3999 4.£4012	**Mean QALY per patient** 1: 0.051 2: 0.052 3: 0.051 4: 0.051	3 and 4 were dominated by 2. 2 versus 1: £ 36,590 per QALY gained	The results were most sensitive to change in the number of presentations a provider expects in a year. Results in the base case PSA showed

Study and Intervention	Cost (£)	Effects	Cost effectiveness	Uncertainty
2. Endoscopy within 24 hours 3.Endoscopy within 12 hours 4. Endoscopy within 4 hours				that the probability of Intervention 1 being cost effective was 53% and the probability that intervention 2 was cost effective was 47% (assuming 300 presentations annually).

Abbreviations: ICER = Incremental cost effectiveness ratio; Inc.= Incremental; IQR = Interquartile Range; CI = Confidence Interval; ICU = Intensive Care Unit; n = number of patients in study; DSA =deterministic sensitivity analysis; PSA=probabilistic sensitivity analysis

(a) Cost components: Units of transfusion required; hospital stay (including readmissions); endoscopic procedures (including repeat endoscopy); surgical procedures; and unplanned visit to any physician.

(b) Published costs in USD were converted in pound sterling using Purchasing Power Parities.

(c) Both deaths in the late group were unrelated to GI bleeding or endoscopy.

(d) Cost components: Endoscopy consultant and nurse (band 5); endoscopy procedural costs (maintenance and consumables); and hospital stay cost. Based on 300 expected presentations of acute upper GI bleeding per provider per year.

7.5 Evidence Statements

7.5.1 Clinical evidence

Early versus delayed endoscopy

Mortality (30 days or less follow-up)

Three studies comprising 528 participants showed that the overall rate of mortality (which was an overall 0.9%) did not differ significantly between patients who were endoscoped early compared to those that had a delayed endoscopy (VERY LOW QUALITY). The three studies were then subdivided according to whether they included only ‘stable’ patients and those that included ‘stable’ as well as ‘unstable’ patients as measured by hemodynamic factors.

- Two studies comprising 203 ‘stable’ participants showed no clear statistical or clinical difference in rate of mortality between the earlier scoped and later scoped patients (VERY LOW QUALITY).
- One study with 325 which included 36% ‘unstable’ patients showed no clear statistical or clinical difference in rate of mortality between the earlier scoped and later scoped patients (VERY LOW QUALITY).

Re-bleeding (30 days or less follow-up)

Two studies comprising 435 participants showed that the overall rate of re-bleeding (which was an overall 4.4%) did not differ significantly between patients who were endoscoped early compared to those that had a delayed endoscopy (VERY LOW QUALITY). The two studies were divided into subgroups according to whether they included only ‘stable’ patients and those that included ‘stable’ as well as ‘unstable’ patients as measured by hemodynamic factors.

- One study comprising 110 ‘stable’ participants showed no clear statistical or clinical difference in rate of re-bleeding between the earlier scoped and later scoped patients (VERY LOW QUALITY).

- One study with 325 subjects which included 36% 'unstable' showed no clear statistical or clinical difference in rate of re-bleeding between the earlier scoped and later scoped patients (VERY LOW QUALITY).

Surgery for continued bleeding

Three studies comprising 528 participants showed that the overall rate of surgery (which was an overall 1.3%) did not differ significantly between patients who were endoscoped early compared to those that had a delayed endoscopy (VERY LOW QUALITY). The three studies were then subdivided according to whether they included only 'stable' patients and those that included 'stable' as well as 'unstable' patients as measured by hemodynamic factors.

- Two studies comprising 203 'stable' participants showed no clear statistical or clinical difference in rate of surgery for continued bleeding between the earlier scoped and later scoped patients (VERY LOW QUALITY).
- One study with 325 subjects which included 36% 'unstable' patients showed no clear statistical or clinical difference in rate of surgery for continued bleeding between the earlier scoped and later scoped patients (VERY LOW QUALITY).

Mean units of blood transfused

Evidence from 2 studies comprising 203 'stable' participants found that there was no statistical significant / clinical difference in the average volume of blood transfused between those patients scoped early and those who had a delayed endoscopy (VERY LOW QUALITY).

Length of hospital stay

Two studies comprising 418 participants showed that the overall average length of hospital stay did not differ significantly between patients who were endoscoped early compared to those that had a delayed endoscopy (VERY LOW QUALITY). The two studies were divided into subgroups according to whether they included only 'stable' patients and those that included 'stable' as well as 36% 'unstable' patients as measured by hemodynamic factors.

- One study comprising 93 'stable' participants showed no clear statistical or clinical difference in average length of hospital stay between the earlier scoped and later scoped patients (VERY LOW QUALITY).
- One study with 325 subjects which included 36% 'unstable' showed no clear statistical or clinical difference in rate of re-bleeding between the earlier scoped and later scoped patients (VERY LOW QUALITY).

7.5.2 Health economic evidence

For stable patients with low risk of mortality and rebleeding, endoscopy within the first 24 hours is likely to be more cost effective than endoscopy later than 24 hours. This is based in part on evidence with minor limitations and partial applicability, and in part on evidence with direct applicability and with potentially serious limitations.

The provision of endoscopy services on weekend mornings in addition to those provided 8am-5pm on the weekday is likely to be cost-effective, provided that

- this allows all patients to be endoscoped within 24 hours of presentation and
- that the provider expects approximately 330 or more presentations of acute upper gastrointestinal bleed per year.

This is based on evidence of direct applicability and with potentially serious limitations.

7.6 Recommendations and link to evidence

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 re-bleeding or mortality?

Recommendations	• **Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation.** • **Offer endoscopy within 24 hours of admission to all other patients with upper gastrointestinal bleeding.** • **Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances.**
Relative values of different outcomes	Endoscopy for stable patients within 24 hours of presentation facilitates early intervention and, where appropriate, early discharge of patients and reduction in length of hospital stay. The clinical papers available to the GDG did not show any consistent significant differences between timing strategies, and the GDG's deliberations centred mainly on the health economic data.
Trade off between clinical benefits and harms	Stable patients who are not in clear need of urgent intervention should nevertheless ideally receive endoscopy within 24 hours of the bleeding episode; re-bleeding may occur and could be prevented by therapeutic endoscopic interventions. Moreover, delayed endoscopy lengthens hospital stay. For high risk patients requiring urgent endoscopy, particularly if out-of-hours, the GDG emphasised the importance of appropriate facilities and trained staff and that the safety and quality of any endoscopic procedure should not be compromised by its timing.
Economic considerations	There are no published economic analyses of timing of endoscopy in patients at high risk of uncontrolled bleeding or death. One published study shows significant economic benefit in stable patients at low risk of death for endoscopy undertaken within 2 hrs of admission. This was a US study that may not be applicable to UK practice where very urgent endoscopy is generally unavailable for this patient group. Additionally the GDG raised concern that endoscopy within the short time frames associated with the RCT may not be practical in the UK setting. The GDG felt an original economic decision model was essential in order to assess more realistic time frames for endoscopy (i.e. 4 hours, 12 hours and 24 hours) in the UK setting. The economic model was devised to assess the trade-off between the additional cost of implementing a service that allowed for endoscopy within a given time period and the potential savings which could be realised through early discharge and reduced length of stay. The GDG agreed that the key cost

of implementing a service to reduce delay to endoscopy was the cost of additional staff hours.

The GDG agreed on 4 service models which should allow endoscopy to occur for all patients within a given timeframe, these were as follows:

Endoscopy available 8am-5pm, Monday to Friday only; Endoscopy available 8am-5pm on Monday to Friday, and 8am-12pm on weekends; Endoscopy available 8am-5pm everyday, with oncall services between 5pm and 12am; Endoscopy available 8am-5pm everyday, with oncall services between 5pm-8am.

As detailed in Appendix I and J, the economic Markov model assumed a 28 day horizon and used data derived from the UK audit of acute upper gastrointestinal bleeding that was completed by the British Society of Gastroenterology and the National Blood Service in 2007.

The economic model suggested that the first two strategies listed above were optimal from a health economic point of view. Further, the model indicated that investing in additional staff hours to provide endoscopy on the weekend mornings was most likely to be cost effective when providers expected more than 330 presentations per year (either in new admissions or in established inpatients). This threshold is likely to be conservative due to the assumptions made in the model. The model does not capture the possibility that the increased availability of endoscopy and associated staff members could bring benefit to patients other than those requiring endoscopy for acute upper GI bleed (thus resulting in an increase of activity for the hospital trust and subsequent QALYs gains for the patients treated). In addition, our cost-effectiveness estimates are also likely to be conservative in that we do not capture the health benefit after 28 days or consider the other potential resource savings associated with reduced re-bleeding and need for transfusion.

The subgroup analysis suggested that for the lowest risk patients, an endoscopy within 4 hours was likely to result in the greatest reduction in length of stay in these patients. It is the reduced length of stay in these patients that for the most part offsets the cost of implementing a strategy that provides endoscopy within 24 hours.

The potential limitations of using an observational dataset were discussed with the GDG, and considered in the interpretation of the model results. It is likely that not all factors were adequately controlled in the analysis to allow firm conclusions in terms of the clinical outcomes, especially those resulting from endoscopy before 12 hours.

The GDG considered the limitations of the model and the secondary outcomes of clinical effectiveness given by the model, noting the decreased mortality and reduced length of stay seen when endoscopy was offered within 24 hours when compared to current practice. As such, the GDG acknowledged that daily lists could be cost effective in smaller centres, although the probability of this diminished with reducing caseload. If smaller centres suspect that additional endoscopy lists would bring benefit not captured in the model, or could find alternative strategies that make use of economies of scale, provision of endoscopy within 24 hours could still be cost effective. Although not

	formally assessed in the model, the GDG cited networks as a possible strategy for smaller centres to consider. It was also felt that units that have established 24/7 services should not abandon these, but could represent referral centres for bleeding 'networks' (see other considerations section below).
Quality of evidence	The available clinical evidence in relation to the timing of endoscopy for stable patients is predominantly of very low quality by GRADE criteria. Little clinical evidence is available which addresses the timing of endoscopy in unstable or high risk patients. That which is available is predominantly of very low quality. The economic analysis performed as part of the guideline development process is based upon NHS costs, models of care and representative UK audit data – and therefore directly applicable. However as it is based on observational data, it potentially has serious limitations.
Other considerations	The experience of the GDG is that urgent endoscopy for unstable and high risk patients reduces mortality, length of hospital stay and transfusion requirements, and that this is intuitively the correct recommendation. Despite a lack of formal evidence on this issue, a research recommendation is not made as trials in this area are likely to be unethical as a result of delaying an intervention known to be of benefit. Arrangements for urgent therapeutic endoscopy in actively bleeding, haemodynamically unstable patients must be put in place. How this is done will depend upon local circumstances. In referral centres fully trained teams could provide 24/7 endoscopic cover, supported by surgery and interventional radiology. Smaller hospitals could develop networks that will result in transfer of relevant patients to referral centres or, in rare circumstances, of teams from the referral centre undertaking therapeutic endoscopy in peripheral hospitals. For the stable patient group, the GDG were conscious that the output of the health economic model posed a problem. It seems inequitable to offer endoscopy to patients within 24 hours only if they find themselves in a hospital with an annual caseload above 330 cases per year, and not if they are in a smaller unit. The consensus view of the GDG was that endoscopy within 24 hours should ideally be offered to all patients rather than a subgroup. However, they also acknowledged the trade-off between staff costs of a daily service to provide a quick discharge and “hotel” costs of the wait to a slower discharge of a weekday service noting that smaller providers would need to explore these factors in deciding how best to provide services for stable patients. It is worth noting that the majority of endoscopies in the UK currently occur in units dealing with more than 330 cases per year. Provision of endoscopy within 24 hours of presentation might be possible in smaller units by providing facility for safe transfer, or peripatetic endoscopy. However, these strategies were not considered in the health economic model, and the GDG therefore could not make firm recommendations along these lines. The GDG therefore developed a recommendation which encourages all units to offer endoscopy within 24 hours, but only specifying that this should be achieved by arranging daily endoscopy lists in hospitals seeing >330 cases of acute upper GI bleeding per year. Smaller units should consider what model

	would best allow them to arrange endoscopy within 24 hours. The advantages to patients and carers in terms of the peace of mind associated with rapid diagnosis (and intervention where appropriate) were also acknowledged.

8 Management of non-variceal bleeding

8.1 Endoscopic combination therapy versus adrenaline injection alone

8.1.1 Introduction

Three approaches to endoscopic therapy for non-variceal bleeding have been examined in clinical trials. These trials have focused upon peptic ulcer bleeding and have included patients with active, arterial haemorrhage and other major stigmata of recent haemorrhage (a visible vessel and adherent blood clot), but it is reasonable to conclude that other causes of non-variceal bleeding including selected patients with Mallory Weiss tears or those with vascular malformations may also respond to endoscopic therapy. The three approaches are:

1. Injection into the bleeding point of either dilute adrenaline (to induce vasoconstriction of the bleeding artery) or thrombin (to thrombose the bleeding artery)
2. Coagulation of the bleeding point, either by diathermy or direct application of heat (the 'heater probe' or Argon Plasma Coagulation).
3. Mechanical occlusion of the bleeding point, principally by endoscopic application of clips.

Randomised clinical trials have generally shown that each of these approaches can control active bleeding, reduce the rate of re-bleeding and need for blood transfusion compared to patients not receiving endoscopic therapy. It is more difficult to show survival benefit, although this has been demonstrated in meta-analyses [68,69]. Trials have failed to show superiority of any one approach and clinical experience has shown that these three approaches should not be regarded as competitors; rather they should be considered to be complementary. For example it may be relatively easy to inject or coagulate a bleeding ulcer at the junction of the first and second part of the duodenum, but very difficult to apply a clip, whilst an obvious protruding vessel within a lesser curve gastric ulcer can be a relatively easy target for clip application. Endoscopists should therefore have a range of therapies that can be tailored according to clinical need.

If randomised trials have shown that endoscopic therapy improves outcome, there remain questions about the benefits associated with combining types of endoscopic therapy as compared to mono-therapy? It could be argued for example that the haemostatic benefit of adrenaline may be transient since its vasoconstrictor effect is relatively short- lived and that the addition of a thermal treatment would achieve more permanent haemostasis by thrombosing the feeding artery. It is possible that the efficacy of clip placement could be improved by application of a thermal treatment since the latter will deal with other potential defects within the artery that courses through the ulcer bed. On the other hand, complications of endoscopic therapy – particularly ulcer bleeding and precipitation of bleeding from a visible vessel -are well documented. Such complications are reported infrequently in trials of endoscopic monotherapy, but the more aggressive approach of combination therapy could make these complications more frequent. Additionally, the placement of endoscopic clips can be a useful adjunct in difficult to control bleeding as it allows identification of the site of haemorrhage for secondary radiological intervention if required.

8.1.2 Clinical question and methodological introduction

In patients with non-variceal upper gastrointestinal bleeding are combinations of endoscopic treatments more clinically/cost effective than adrenaline injection alone?

Table 40: PICO Characteristics of the question

Clinical Methodological Introduction	
Population:	Patients with non-variceal UGIB
Intervention:	Combination of thermal / mechanical with adrenaline / thrombin injection endoscopic treatment
Comparison:	Adrenaline injection treatment alone
Outcomes:	• Mortality • Re-bleeding • Failure to achieve initial haemostasis • Emergency procedures • Length of hospital stay • Transfusion requirements

8.1.3 Clinical evidence review

We searched for randomised control trials comparing the effectiveness of different combinations of endoscopic treatment compared to adrenaline injection alone. Combinations under investigation were adrenaline combined with a mechanical method such as application of clips, adrenaline combined with a thermal method, or adrenaline injection combined together with thrombin / fibrin glue injection (see flowchart in Appendix E for study selection).

Nine randomised control studies were identified and cross-references one Cochrane review [70]. Four of those compared adrenaline in combination with a mechanical endoscopic method, two used the adrenaline and thermal combination and three further studies investigated adrenaline with thrombin injection; all of these compared the combined treatments to adrenaline alone. The aim of all these papers was to assess a combination of endoscopic procedures were the more effective means than adrenaline injection alone to improve outcomes in patients with non-variceal UGIB. One further study was included which compared to adrenaline combinations to each other (adrenaline plus thermal versus adrenaline plus mechanical) (see Appendix F for evidence tables and Appendix H for forest plots).

Outcomes analysed were:

- Mortality
- Re-bleeding
- Failure to achieve haemostasis
- Emergency procedures
- Length of hospital stay
- Transfusion requirements

Table 41: Characteristics of included studies

Adrenaline injection endoscopic treatment compared to those specified in the top row or combination comparison as specified in the title of the fifth column.

STUDY	Adrenaline plus Mechanical	Adrenaline plus Thermal	Adrenaline plus Thrombin	Adrenaline plus Thermal versus Adrenaline plus Mechanical	Adjunct pharmaceutical treatment	COMMENTS
Balanzo, 1990[71]			✓		None described	Only some basic baseline characteristics provided
Chung 1997[72]		✓			PPI or H_2-RAs given on discharge from hospital	All patients had actively bleeding ulcers (spurting / oozing), NBVV[c] patients were excluded
Chung, 1999[73]	✓				After initial haemostasis ranitidine (50 mg) was given i.v. every 6 hours	Only most basic baseline characteristics provided
Gevers, 2002[74]	✓				All patients received ranitidine, 50 mg i.v. 4 times daily and after 3 days if bleeding was stopped treatment was initiated with oral PPI/	Patients taking NSAIDs, aspirin, or anticoagulants were not excluded, but use of these medications was stopped at inclusion.
Kubba, 1996[75]			✓		Management after endoscopy was left in the hands of the admitting teams who were unaware of what was injected (no details provided)	Reported deaths in the study were restricted to patients who had severe comorbid disease.
Lin, 1999[76]		✓			Omeprazole was given i.v. every 6 hrs for 3 days then 20 mg / day orally for 2 months	2/3 of patients had comorbid diseases and 1/3 of patients had shock
Lo, 2006[77]	✓				After initial haemostasis i.v. administration	Over half of the patients had comorbid diseases and

c *Non bleeding visible vessels*

STUDY	Adrenaline plus Mechanical	Adrenaline plus Thermal	Adrenaline plus Thrombin	Adrenaline plus Thermal versus Adrenaline plus Mechanical	Adjunct pharmaceutical treatment	COMMENTS
					of pantoprazole (40 mg for 2 days)	14% patients with shock
Park, 2004[78]	✓				After initial haemostasis patients were treated with ranitidine, i.v. 50 mg every 6 hours, and oral omeprzole 40 mg twice daily as soon as oral intake was possible	More than half of the participants were actively bleeding
Pescatore, 2002[79]			✓		Prior to treatment all patients received omeprazole 80 mg i.v. bolus followed by 40 mg 3 times daily and antibiotics if necessary	Four patients with outcome data (failure to achieve haemostasis and emergency surgery) were excluded in the study
Taghavi, 2009[80]				✓	Pantoprazole administered i.v. (80 mg stat, 8 mg/h) for one day on arrival before endoscopic treatment. After treatment omeprazole 20 mg twice daily.	The rate of ulcer history was more than double in the adrenaline plus thermal group (32.6% versus 14.5%)

Comparison: Adrenaline injection versus Combinations (adrenaline injection with either mechanical or thermal) - GRADE characteristics and clinical summary of findings

Table 42: GRADE table of outcome quality assessments – main outcome headings are labelled on the left, whereas subgroup outcomes are indented on a slightly lighter background.

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Adrenaline combination Frequencies (%), Means (SD) or Medians (range)	Adrenaline alone Frequencies (%), Means (SD) or Medians (range)	Relative Risk (95% CI)	Absolute effect, Mean difference (95% CI)	
Mortality by type of combination										
Balanzo, 1990, Kubba, 1996, Chung 1997, Chung 1999, Lin 1999, Gevers 2002, Pescatore 2002, Park 2004, Lo 2006	randomised trials	serious[a, b]	no serious inconsistency	no serious indirectness	very serious[c]	17/510 (3.3%)	22/513 (4.3%)	RR 0.8 (0.44 to 1.44)	9 fewer per 1000 (from 24 fewer to 19 more)	VERY LOW
Mortality by type of combination - Adren + Mechanical										
Chung 1999, Gevers 2002, Park	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	5/171 (2.9%)	2/173 (1.2%)	RR 1.89 (0.53 to 6.78)	10 more per 1000 (from 5 fewer to	VERY LOW

Quality assessment						Summary of findings				
2004, Lo 2006									67 more)	
Mortality by type of combination - Adren + Thermal										
Chung 1997, Lin 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	9/172 (5.2%)	10/168 (6%)	RR 0.88 (0.37 to 2.12)	7 fewer per 1000 (from 38 fewer to 67 more)	VERY LOW
Mortality by type of combination - Adren + Thrombin										
Balanzo, 1990, Kubba, 1996, Pescatore 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	3/167 (1.8%)	10/172 (5.8%)	RR 0.35 (0.11 to 1.13)	38 fewer per 1000 (from 52 fewer to 8 more)	LOW
Re-bleeding by type of combination										
Balanzo, 1990, Kubba, 1996, Chung 1997, Chung 1999, Lin 1999, Gevers 2002, Pescatore 2002, Park 2004, Lo 2006	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	35/412 (8.5%)	83/418 (19.9%)	RR 0.43 (0.3 to 0.63)	113 fewer per 1000 (from 73 fewer to 139 fewer)	MODERATE
Re-bleeding by type of combination - Adren + Mechanical										
Chung 1999, Gevers 2002, Park	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	12/171 (7%)	31/173 (17.9%)	RR 0.4 (0.21 to 0.74)	108 fewer per 1000 (from 47	LOW

Quality assessment						Summary of findings				
2004, Lo 2006									fewer to 142 fewer)	
Re-bleeding by type of combination - Adren + Thermal										
Chung 1997, Lin 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	4/74 (5.4%)	17/73 (23.3%)	RR 0.23 (0.08 to 0.66)	179 fewer per 1000 (from 79 fewer to 214 fewer)	MODERATE
Re-bleeding by type of combination - Adren + Thrombin										
Balanzo, 1990, Kubba, 1996, Pescatore 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	19/167 (11.4%)	35/172 (20.3%)	RR 0.56 (0.34 to 0.94)	90 fewer per 1000 (from 12 fewer to 134 fewer)	LOW
Failure to achieve haemostasis by type of combination										
Balanzo, 1990, Kubba, 1996, Chung 1997, Chung 1999, Lin 1999, Gevers 2002, Pescatore 2002, Park 2004, Lo 2006	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	15/510 (2.9%)	22/513 (4.3%)	RR 0.69 (0.36 to 1.3)	13 fewer per 1000 (from 27 fewer to 13 more)	VERY LOW
Failure to achieve haemostasis by type of combination - Adren + Mechanical										
Chung 1999, Gevers	randomised trials	serious[a]	no serious inconsistenc	no serious indirectness	very serious[c]	6/171 (3.5%)	9/173 (5.2%)	RR 0.68 (0.25 to		VERY LOW

Quality assessment						Summary of findings				
2002, Park 2004, Lo 2006			y					1.87)		
Failure to achieve haemostasis by type of combination - Adren + Thermal										
Chung 1997, Lin 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	3/172 (1.7%)	4/168 (2.4%)	RR 0.74 (0.17 to 3.23)	6 fewer per 1000 (from 20 fewer to 53 more)	VERY LOW
Failure to achieve haemostasis by type of combination - Adren + Thrombin										
Balanzo, 1990, Kubba, 1996, Pescatore 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	6/167 (3.6%)	9/172 (5.2%)	RR 0.67 (0.25 to 1.81)	17 fewer per 1000 (from 39 fewer to 42 more)	VERY LOW
Emergency surgery by type of combination										
Balanzo, 1990, Kubba, 1996, Chung 1997, Chung 1999, Lin 1999, Pescatore 2002, Park 2004, Lo 2006	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	17/478 (3.6%)	40/479 (8.4%)	RR 0.44 (0.25 to 0.75)	47 fewer per 1000 (from 21 fewer to 63 fewer)	MODERATE
Emergency surgery by type of combination - Adren + Mechanical										
Chung 1999, Park 2004, Lo 2006	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	2/139 (1.4%)	13/139 (9.4%)	RR 0.18 (0.05 to 0.7)	77 fewer per 1000 (from 28 fewer to 89 fewer)	MODERATE

Quality assessment						Summary of findings				
Emergency surgery by type of combination - Adren + Thermal										
Chung 1997, Lin 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	3/172 (1.7%)	11/168 (6.5%)	RR 0.27 (0.08 to 0.94)	48 fewer per 1000 (from 4 fewer to 60 fewer)	LOW
Emergency surgery by type of combination - Adren + Thrombin										
Balanzo, 1990, Kubba, 1996, Pescatore 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	Very serious[c]	12/167 (7.2%)	16/172 (9.3%)	RR 0.77 (0.38 to 1.58)	21 fewer per 1000 (from 58 fewer to 54 more)	VERY LOW
Transfusion requirements – mean units transfused (Better indicated by lower values)										
Park 2004, Gevers 2002, Balanzo 1990	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	N=45, Mean (SD) = 4.4 (1.66), N=32, Mean=4.03 N=32, Mean=3.14	N=45, Mean (SD) = 4.1 (1.66), N=34, Mean=4.93, N=32, Mean=3.94	Gevers: overall p-value (3 arms of study) given as 0.53) Balanzo: no p-value given (described as 'similar')	MD 0.3 higher (0.39 lower to 0.99 higher) – no standard deviation or individual p-value given for the second and third study.	LOW
Transfusion requirements – median ml / units transfused										
Kubba, 1996, Chung, 1997	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	N=70, Median (no range provided) = 219 ml, N=140,	N=70, Median (no range provided) = 297 ml, N=136,	1st study P=0.041 2nd study P=0.93	No pooled effect could be derived	VERY LOW

Quality assessment						Summary of findings				
						Median (range) = 3 units (0-29)	Median (range) = 2 units (0-18)			
Length of hospital stay by type of combination – mean days (Better indicated by lower values)										
Lin 1999, Park 2004, Lo 2006	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very Serious[c]	N=21, Mean (SD) = 6.2 (2.64), N=45, Mean (SD) = 12.5 (6.99), N=52, Mean (SD) = 7.2 (7.1)	N=21, Mean (SD) = 8.3 (4.83), N=45, Mean (SD) = 11 (4.65), N=53, Mean (SD) = 10.5 (11)	-	MD 0.92 lower (2.45 lower to 0.61 higher)	VERY LOW
Length of hospital stay by type of combination - Adren + Mechanical (Better indicated by lower values)										
Park 2004, Lo 2006	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	N=45, Mean (SD) = 12.5 (6.99), N=52, Mean (SD) = 7.2 (7.1)	9 N=45, Mean (SD) = 11 (4.65), N=53, Mean (SD) = 10.5 (11)8	-	MD 0.06 lower (2.08 lower to 1.96 higher)	VERY LOW
Length of hospital stay by type of combination - Adren + Thermal (Better indicated by lower values)										
Lin 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	N=21, Mean (SD) = 6.2 (2.64)	N=21, Mean (SD) = 8.3 (4.83)	-	MD 2.1 lower (4.45 lower to 0.25 higher)	LOW
Length of hospital stay – median days										
Chung 1997	randomised trials	No serious limiation	no serious inconsistency	no serious indirectness	serious[c]	N=140, Median (range)= 4 (1-59)	N=136, Median (range)= 4 (0-34)	P=0.06	-[d]	VERY LOW

[a] *In 5 out of 10 studies allocation concealment was unclear but below 50% of the weight of the evidence in the meta-analysis; none of the studies had clear blinding (which is difficult to achieve with a combination of different endoscopic procedure); in 4 studies the sequence generation for randomisation is unclear. Blinding is downgraded when subjective outcome measures*

are rated. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly. Since the majority of studies suffer from at least 1 serious limitations this section was downgraded at least once and twice for some combinations of studies.
[b] *Subgroup analysis did not reach significance*
[c] *If the CIs were consistent with both appreciable benefit and no effect the imprecision was graded as serious; if the CIs were consistent with both a clinically appreciable benefit and harm then imprecision was graded as very serious.*
[d] *No effect size could be derived since only medians were reported.*

Narrative summary

Length of hospital stay was also reported by Kubba et al. 1996. Medians and ranges were provided, but each arm was subdivided into active and nonbleeding vessel patients (combinations: active bleeding: median (range) = 6(2-25) nonbleeding vessel median (range) = 6 (4 – 35); adrenaline alone: active bleeding median (range) = 6(2-37), nonbleeding vessel median (range) = 7(3-65)). The authors state that 'duration of hospital stay was similar in both groups'.

Comparison: Adrenaline injection plus Argon Plasma Coagulation versus Adrenaline injection plus Hemoclip - GRADE characteristics and clinical summary of findings

Table 43: GRADE outcome quality rating for the treatment comparison

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Adrenaline + Thermal Frequency (%)or mean (SD) or Median (range)	Adrenaline + Mechanical Frequency (%)or mean (SD) or Median (range)	Relative Risk (95% CI)	Absolute effect or Mean Difference (95% CI) or other measure of effect	
Mortality (30 day follow-up)										
Taghavi, 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/89 (2.2%)	1/83 (1.2%)	RR 1.87 (0.17 to 20.19)	10 more per 1000 (from 10 fewer to 231 more)	VERY LOW

Quality assessment						Summary of findings				
Re-bleeding										
Taghavi, 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	10/89 (11.2%)	4/83 (4.8%)	RR 2.33 (0.76 to 7.15)	64 more per 1000 (from 12 fewer to 296 more)	LOW
Failure to achieve initial haemostasis										
Taghavi, 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	3/89 (3.4%)	1/83 (1.2%)	RR 2.8 (0.3 to 26.37)	22 more per 1000 (from 8 fewer to 306 more)	VERY LOW
Emergency procedures										
Taghavi, 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/89 (2.2%)	0/83 (0%)	RR 4.67 (0.23 to 95.8)	-	VERY LOW
Length of hospital stay										
Taghavi, 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	N=89, Mean=5.34 (no sd provided)	N=83, Mean=5.5 (no sd provided)	P=0.396	MD (derived from p-value) 0.18 lower (from 0.59 lower to 0.23 higher)	LOW

[a] *This study has unclear allocation concealment. Apart from this it is well conducted. Study limitations are downgraded once.*

[b] *When confidence intervals of the total effects are consistent with appreciable benefit or no effect imprecision is downgraded once and whenever these intervals lie in the range of appreciable benefit and also appreciable harm imprecision is downgraded twice.*

8.1.4 Health economic evidence

No relevant economic evaluations comparing combinations of endoscopic treatment with and without adrenaline injection alone were identified. No studies were selectively excluded.

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were considered. The treatment modalities which might be used in addition to adrenaline injection fall within the same Health Resource group (HRG). For example fibreoptic endoscopic cauterisation, diathermy and cryotherapy to a lesion of upper gastrointestinal tract fall within the HRG group for Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed (code FZ29Z). As a non elective short and long stay inpatient procedure, and taking into account average bed days, these treatment modalities have an associated weighted unit cost of £1,299.64 (interquartile range of £910 to £1,543)[81].

8.1.5 Evidence statements

8.1.5.1 Clinical evidence

Combination treatments versus adrenaline injection alone

Mortality (30 day or less follow-up)

9 studies comprising 1073 participants with non- variceal upper gastrointestinal bleeding found that mortality was not significantly decreased by using combination endoscopic treatments rather than adrenaline injection alone (VERY LOW QUALITY).

These 9 studies were then divided into 3 subgroups according to type of combination that was used:

- 4 studies comprising 344 participant showed no statistical / clinical significant difference in mortality in the adrenaline combined with hemoclip compared to the adrenaline alone group (VERY LOW QUALITY).
- 2 studies with 340 patients provided evidence that there was no statistical / clinical significant difference in mortality in the adrenaline combined with thermal treatment compared to the adrenaline alone group (VERY LOW QUALITY).
- 3 studies with 339 patients showed a non-significant difference with a lower rate of mortality in patients receiving adrenaline combined with thrombin injections compared to those receiving adrenaline injection alone (LOW QUALITY).

Subgroups effect between subgroups did not differ according to the combination used (VERY LOW QUALITY).

Re-bleeding (30 day or less follow-up)

9 studies comprising 1073 participants with non- variceal upper gastrointestinal bleeding found that the rate of re-bleeding was significantly lower in those receiving combination treatments compared to patients who were treated with adrenaline injection alone. This decrease in the rate of re-bleeding favouring combination treatment was large enough to have appreciable clinical benefit (MODERATE QUALITY).

These 9 studies were then divided into 3 subgroups according to type of combination that was used:

- 4 studies comprising 344 participants showed a significantly lower rate of re-bleeding in the adrenaline combined with mechanical treatment compared to the adrenaline alone group. However, the decrease in rate of re-bleeding was not large enough for appreciable clinical benefit (LOW QUALITY).
- 2 studies with 340 patients found that there was a significantly lower rate of re-bleeding in the adrenaline combined with thermal treatment compared to the adrenaline alone

group. The size of this decrease was large enough to constitute appreciable benefit in favour of adrenaline combined with thermal treatment (MODERATE QUALITY).

- 3 studies with 339 patients provided evidence of a significantly lower rate of re-bleeding in the adrenaline combined with thrombin injection treatment compared to the adrenaline alone group. However, the decrease in rate of re-bleeding was not large enough for appreciable clinical benefit (LOW QUALITY).

Subgroups effect between subgroups did not differ according to the combination used (VERY LOW QUALITY).

Failure to achieve haemostasis

9 studies comprising 1073 participants with non- variceal upper gastrointestinal bleeding found that the rate of treatment failure was not significantly decreased by using combination endoscopic treatments rather than adrenaline injection alone (VERY LOW QUALITY).

These 9 studies were then divided into 3 subgroups according to type of combination that was used:

- 4 studies comprising 344 participant showed no statistical / clinical significant difference in failure to achieve haemostasis in the adrenaline combined with hemoclip compared to the adrenaline alone group (VERY LOW QUALITY)
- 2 studies with 340 patients provided evidence that there no statistical / clinical significant difference in failure to achieve haemostasis in the adrenaline combined with thermal treatment compared to the adrenaline alone group (VERY LOW QUALITY)
- 3 studies with 339 patients provided evidence of no statistical / clinical significant difference in failure to achieve haemostasis in the adrenaline combined with thrombin injection treatment compared to the adrenaline alone group (VERY LOW QUALITY).

Subgroups effect between subgroups did not differ according to the combination used.

Emergency surgery

8 studies comprising 957 participants with non- variceal upper gastrointestinal bleeding found that the decrease in the rate of emergency surgery was significantly lower in those receiving combination treatments compared to patients who were treated with adrenaline injection alone. This decrease in the rate of re-bleeding favouring combination treatment was large enough to have appreciable clinical benefit (MODERATE QUALITY).

These 8 studies were then divided into 3 subgroups according to type of combination that was used:

- 3 studies comprising 278 participants showed a significantly lower rate of re-bleeding in the adrenaline combined with mechanical treatment compared to the adrenaline alone group. The decrease in rate of emergency surgery was large enough for appreciable clinical benefit (LOW QUALITY).
- 2 studies with 340 patients found that there was a significantly lower rate of emergency surgery in the adrenaline combined with thermal treatment compared to the adrenaline alone group. The size of this decrease was, however, not large enough to warrant appreciable benefit in favour of adrenaline combined with thermal treatment (MODERATE QUALITY).
- 3 studies with 339 patients provided evidence that the decrease in the rate of emergency surgery was not significantly lower in the adrenaline combined with thrombin injection treatment compared to the adrenaline alone group (VERY LOW QUALITY).

Subgroups effect between subgroups did not differ according to the combination used (VERY LOW QUALITY).

Blood transfusion requirements

1 study comprising 90 patients with non- variceal upper gastrointestinal bleeding found that the increase in average blood transfusion units in the combination treatment group as compared to adrenaline alone was not statistically / clinically different (VERY LOW QUALITY).

4 further studies reported blood transfusion requirements, but due to reported medians with p-values, or missing standard deviations no estimate of effect could be derived.

Length of hospital stay

3 studies comprising 237 participants with non- variceal upper gastrointestinal bleeding found that the average length of hospital stay was not significantly decreased by using combination endoscopic treatments rather than adrenaline injection alone (VERY LOW QUALITY).
These 3 studies were then divided into 2 subgroups according to type of combination that was used:

- 2 studies comprising 195 participant showed no statistical / clinical significant difference in average length of hospital stay when adrenaline was combined with hemoclip compared to the adrenaline alone group. However, since the two studies showed heterogeneous results with directly opposite effects this would need to be interpreted with caution (VERY LOW QUALITY).
- 1 study with 42 patients showed a statistical / clinical significant difference in the length of hospital stay with a lower average length of stay in the adrenaline combined with thermal treatment compared to the adrenaline alone group (LOW QUALITY).

One further study comprising 176 participants provided length of stay data, however no estimate of effect could be derived since only a median and range was provided (the study gives the p-value as p=0.06 with lower number of days associated with the adrenaline alone group) (VERY LOW QUALITY).

Adrenaline injection plus argon plasma coagulation versus adrenaline injection plus hemoclip

Mortality (30 day follow-up)

1 study comprising 172 participants with non- variceal upper gastrointestinal bleeding found that mortality was not significantly decreased by using adrenaline injection combined with hemoclip as compared to using adrenaline injection plus argon plasma coagulation. However, only 3 deaths were reported which makes interpretation of this result difficult (VERY LOW QUALITY).

Re-bleeding (30 day follow-up)

1 study comprising 172 participants with non- variceal upper gastrointestinal bleeding found that the rate of re-bleeding was not significantly decreased by using adrenaline injection combined with hemoclip as compared to using adrenaline injection plus argon plasma coagulation (LOW QUALITY).

Failure to achieve haemostasis

1 study comprising 172 participants with non- variceal upper gastrointestinal bleeding found that the failure rate for achieving haemostasis was not significantly decreased by using adrenaline injection combined with hemoclip as compared to using adrenaline injection plus argon plasma coagulation. However, only 4 such failures were reported which makes interpretation of this result difficult (VERY LOW QUALITY).

Emergency procedures

1 study comprising 172 participants with non- variceal upper gastrointestinal bleeding found that the rate of patients needing emergency procedures was not significantly decreased by using adrenaline injection combined with hemoclip as compared to using adrenaline injection plus argon plasma coagulation. However, only 2 such procedures were reported which makes interpretation of this result difficult (VERY LOW QUALITY).

Length of hospital stay

1 study comprising 172 participants with non- variceal upper gastrointestinal bleeding found that the average length of hospital stay was not significantly increased by using adrenaline injection

combined with hemoclip as compared to using adrenaline injection plus argon plasma coagulation (LOW QUALITY).

8.1.5.2 Health economic evidence

No studies were identified on the cost-effectiveness of combinations of endoscopic treatments to adrenaline injection alone in the treatment of patients with non- variceal upper gastrointestinal bleeding.

8.1.6 Recommendations and link to evidence

In patients with non-variceal upper gastrointestinal bleeding are combinations of endoscopic treatments more clinically/cost effective than adrenaline injection alone?

Recommendations	• **Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.** • **For the endoscopic treatment of non-variceal upper gastrointestinal bleeding, use one of the following:** - **a mechanical method (for example, clips) with or without adrenaline** - **thermal coagulation with adrenaline** - **fibrin or thrombin with adrenaline.**
Relative values of different outcomes	Mortality data was available for this question and did not show a significant difference between combination and single modes of treatment for bleeding ulcers. However, the GDG questioned whether the numbers in the studies were sufficiently powered to show a mortality difference given the relatively low mortality rates observed in the study populations. The studies showed that re-bleeding rates were significantly lower when two forms of treatment were employed, rather than one or either treatment used alone. Securing initial haemostasis was not significantly improved with combination therapy, but the need for further emergency procedures after initial endoscopy was reduced; this outcome is likely to be influenced strongly by both immediate haemostasis and the rate of re-bleeding. Length of hospital stay tended to be less when combination treatments were used, but was not significantly reduced.
Trade off between clinical benefits and harms	Adverse effects of the different forms of treatment were not compared in the papers. The GDG experience is that these are very rare. The GDG discussed whether they could define a safe upper dose of adrenaline, but concluded that there was no secure data on which to base such a recommendation.
Economic considerations	No formal health economic evidence was found. The treatment modalities which might be used in addition to adrenaline injection are not likely to be significantly different in terms of unit cost, as they are considered to have similar resource use. The reductions in re-bleeding and the need for further emergency

	interventions found with the use of combination treatments compared to adrenaline alone imply that the additional cost of adjunctive treatment may be at least partially offset by reduced down stream health related resource use and associated cost.
Quality of evidence	The formal evidence was usually of low or very-low quality by GRADE criteria, but the GDG felt that the studies had been reasonably well-performed allowing for the difficulties of performing RCT's in acutely ill patient groups. The possible under-powering for mortality outcome has been mentioned above.
Other considerations	The GDG considered whether they could recommend any particular combination as being superior to others but this was not possible. One study compared adrenaline plus thermal coagulation with adrenaline plus Hemoclip, and found no difference between the two. Technically, the GDG agreed that there can be situations where it easier to use one method than another (where hemoclip as monotherapy can be very effective), but this is not consistent between patients, depending on variables such as site and depth of the bleeding ulcer. They therefore felt that use of a combination of treatment modes should be recommended, but that different forms of treatment should be available for use in the varied situations which an endoscopist might face.

8.2 Proton pump inhibitor (PPI) treatment

8.2.1 Introduction

Acid suppressing drugs have been studied in clinical trials of peptic ulcer bleeding. The rationale is that an intra-gastric pH of at least 6.5 stabilises the blood clot that plugs the arterial defect within the bleeding ulcer crater and acid suppressing drug therapy could therefore reduce the risk of continuing bleeding and re-bleeding [82]On this basis, gastric acid secretion should be completely suppressed for many hours after the bleed, without acid 'breakthrough' during this critical period. This can be achieved using high doses of H2 receptor antagonist drugs, but is more assured using the Proton Pump Inhibitors (PPIs).

Use of these powerful (yet well tolerated) drugs in patients with non-variceal bleeding remains a controversial area.

One important question is whether all patients should receive acid suppressing drugs when they present with haematesis or melaena, or whether these drugs should only be used in patients who, at endoscopy, have either active bleeding or major stigmata of recent haemorrhage. The first approach ensures that all patients at greatest risk of uncontrolled bleeding receive potentially effective drug therapy, but this is probably wasteful since approximately 80% of ulcers stop bleeding without any form of intervention and do not re-bleed. Powerful acid suppression may therefore be unnecessary in these patients, at least in improving the prognosis of the acute event, although standard doses of PPIs or H2 receptor antagonists clearly have a role in ulcer healing.

A second controversial area concerns the optimum route of administration of acid suppressing drugs. Accepting that some patients will be fasted or actively vomiting and will require the parenteral route, is it generally reasonable to prescribe oral PPIs in patients with acute gastrointestinal bleeding or is it better to deliver these drugs as an intravenous infusion, in spite of the higher costs, inconvenience and possible complications of intravenous administration?

8.2.2 Clinical questions and methodological introduction

Clinical question 1

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?

Table 44: PICO Characteristics of the protocol

Clinical Methodological Introduction	
Population:	Adults with upper GI bleeding with likely non-variceal upper GI bleeding prior and after endoscopy
Intervention:	PPIs
Comparison:	H_2-RAs or placebo
Outcomes:	Mortality (early and late mortality) Re-bleeding Treatment failure (no initial haemostasis) Other procedures to control bleeding Need for transfusion Length of hospital stay

Clinical question 2

Are proton pump inhibitors administered intravenously more clinical / cost effective than the same agents administered in tablet form for patients with likely non-variceal upper gastrointestinal bleeding?

Table 45: PICO Characteristics of the protocol

Clinical Methodological Introduction	
Population:	Adults with upper GI bleeding with likely non-variceal upper GI bleeding prior and after endoscopy
Intervention:	PPIs intravenous
Comparison:	PPIs oral
Outcomes:	Mortality (early and late mortality) Re-bleeding Treatment failure (no initial haemostasis) Other procedures to control bleeding Need for transfusion Length of hospital stay

8.2.3 Clinical evidence review

This combined review compares PPIs to H_2-RAs or placebo in the treatment of likely non-variceal UGIB and also the best mode of administration for PPI treatment (see flowchart in Appendix E for study selection).

We searched for randomised control trials and included a total of 32 trials and cross-referenced two Cochrane meta-analyses [83,84] as well as one Health Technology appraisal [85]. A different analysis was carried out to the Cochrane and HTA analysis dividing comparisons into placebo or H_2-RA (rather than combining those two into one comparator to PPI treatment) as well as into pre-and post-endoscopy in one analysis. The results of the review have been analysed according to whether PPI treatment was started pre or post-endoscopy and whether PPIs were compared to Placebo or H_2-RA treatment. In post-endoscopy studies, therapy (or placebo) was commenced only in the presence of active bleeding or obvious signs of recent bleeding. The most clinical effective method of administration (oral or intravenous) was also reviewed (separately according to pre or post-endoscopy timing of intervention) (see Appendix F for evidence tables and Appendix H for forest plots).

The main results of the review are presented as follows:

5. Pre-endoscopy
    a. PPI versus Placebo
    b. PPI versus H_2-RAs
    c. Route of administration – pre-endoscopy
6. Post-endoscopy
    a. PPI versus Placebo
    b. PPI versus H_2-RAs
    c. Route of administration – pre-endoscopy

The following studies were identified comparing the clinical effectiveness of PPIs pre and post-endoscopy as well as route of administration for patients with likely non-variceal upper GI bleeding.

Table 46: Characteristics of included studies

Study	Pre - endoscopy	Placebo comparison	H_2-RA comparison	Direct oral versus intravenous PPI comparison	Oral PPI administration	Sample size < 100	Any other comments
Bajaj, 2007[86]				✓		✓	Only 25 patients randomised. No mortality.
Brunner, 1990[87]			✓			✓	Only 39 patients randomised and half of those started bleeding whilst already in hospital
Coraggio, 1998[88]			✓		✓	✓	Only compared 48 patients randomised in PPI versus H_2-RA
Daneshmend, 1992[89]	✓	✓					Unusually high mortality and re-bleeding rate and number of patients requiring surgery (7% mortality and 18% re-bleeding)
Fasseas, 2001[90]			✓			✓	
Hasselgren, 1996[91]		✓					All trial patients were ≥ 60 years old. Trial prematurely terminated – data excluded from meta analysis.
Hawkey, 2001[92]	✓	✓			✓		Even though there was a larger difference between intention to treat and baseline sample size, this was clearly addressed
Hsu, 2004[93]			✓				
Hung, 2007[94]		✓					
Javid, 2001[95]		✓			✓		
Javid, 2009[96]				✓		✓	90 patients were randomised, and were on average younger than in all other studies (35.4

Study	Pre - endoscopy	Placebo comparison	H_2-RA comparison	Direct oral versus intravenous PPI comparison	Oral PPI administration	Sample size < 100	Any other comments
							and 34.7 in the two treatment arms). No mortality
Jensen, 2006[97]			✓				
Kaviani, 2003[98]		✓			✓		
Këlliçi 2010[99]			✓				
Khuroo, 1997[100]		✓			✓		Excluded patients with severe bleeding
Khoshbaten, 2006[101]			✓			✓	There was re-bleeding in half of the 40 patients in the H_2-RA group.
Labenz, 1997[102]		✓				✓	All 40 participants were either infected with H pylori or had taken ulcerogenic drugs or both. Re-bleeding discovered by control endoscopy.
Lanas, 1995[103]			✓			✓	Only 51 patients randomised
Lau, 2000[104]		✓					Trial recruitment terminated early due to significant differences in interim analysis.
Lau, 2007[105]	✓	✓					
Lin, 1997[106]			✓			✓	Only 52 patients randomised into 4 treatment arms. Limited to Non Bleeding Visible Vessel patients.
Lin, 1998[107]			✓				
Lin, 2006[108]			✓				
Mostaghni					✓		

Study	Pre - endoscopy	Placebo comparison	H_2-RA comparison	Direct oral versus intravenous PPI comparison	Oral PPI administration	Sample size < 100	Any other comments
2010[109]							
Schaffalitzky, 1997[110]		✓					Significant baseline differences. Trial prematurely terminated – data excluded from meta analysis
Sheu, 2002[111]			✓				Restricted to H-pylori patients.
Sung, 2009[112]		✓					
Tsai, 2009[113]				✓			
van Rensburg, 2009[114]			✓				Trial was funded by various pharmaceutical companies and the initial data analysis were undertaken by a drug company, writing support was also funded by a drug company
Villanueva, 1995[115]			✓			✓	Only 86 patients were randomised which included 5 with stomal or pyloric bleeding location.
Wallner, 1996[116]	✓		✓			✓	Significant baseline differences
Wei, 2007[117]		✓			✓	✓	Only 70 patients randomised
Yilmaz, 2006[118]				✓			Baseline differences: More patients with multiple ulcer sites in the oral PPI group
Zargar, 2006[119]		✓					Baseline differences: Patients in the PPI group were significantly older (mean age - 52.4 in Placebo and 55.3 PPI group)

Pre-endoscopy PPI treatment

Comparison of PPI versus placebo pre-endoscopy

Table 47: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI, Rate, Mean (SD), Median (range), N	Placebo, Rate, Mean (SD), Median (range), N	Relative risk	Absolute Effect Mean difference (95% CI)	
Mortality (follow-up 30 days)										
Daneshmend, 1992 [89], Hawkey, 2001 [92], Lau, 2007 [105]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	50/994 (5%)	42/989 (4.2%)	RR 1.18 (0.79 to 1.76)	8 more per 1000 (from 9 fewer to 32 more)	LOW
Re-bleeding within 30 days (follow-up 30 days)										
Daneshmend, 1992 [89], Hawkey, 2001 [92], Lau, 2007 [105]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	106/994 (10.7%)	118/989 (11.9%)	RR 0.89 (0.7 to 1.13)	13 fewer per 1000 (from 36 fewer to 16 more)	LOW
Surgery for continued or recurrent bleeding										
Daneshmend, 1992 [89], Hawkey, 2001 [92], Lau, 2007 [105]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	69/994 (6.9%)	75/989 (7.6%)	RR 0.91 (0.67 to 1.24)	7 fewer per 1000 (from 25 fewer to 18 more)	LOW
Blood transfusion requirements (follow-up 30 days; Better indicated by lower values)										
Lau, 2007 [105]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[b]	N = 314; 1.54 (2.41)	N = 317; 1.88 (3.44)	-	MD 0.34 lower (0.8 lower to 0.12 higher)	MODERATE
Patients needing blood transfusions										
Daneshmend, 1992	randomis	serious[a]	no serious	no serious	no serious	365/680	362/672	1.00	539 fewer per	MODERA

Quality assessment						Summary of findings				
[89], Hawkey, 2001 [92]	ed trials		inconsistency	indirectness	imprecision	(53.7%)	(53.9%)	(0.90 to 1.10	1000 (from 539 fewer to 539 fewer)	TE
Length of hospital stay (follow-up 30 days; Better indicated by lower values)										
Lau, 2007 [105]	randomis ed trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[b]	N = 314; 4.5 (5.3)	N = 317; 4.9 (5.1)	-	MD 0.4 lower (1.21 lower to 0.41 higher)	MODERA TE
Daneshmend 1992 [89]	randomis ed trial	serious[a]	no serious inconsistency	no serious indirectness	- [c]	median 5 days	median 6 days		- [c]	VERY LOW

[a] *In 2 out of the 3 studies there was unclear allocation concealment > 50% of the weight in the meta-analysis; in 2 out of 3 studies the randomisation sequence generation was not clearly described; in 1 study baseline statistics were not provided. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly.*

[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

[c] *Imprecision could not be assessed because authors reported only median values*

Comparison of PPI versus H_2-RAs pre-endoscopy

Table 48: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI, Rate, Mean (SD), Median (range), N	H2-RAs, Rate, Mean (SD), Median (range), N	Relative Risk (95% CI)	Absolute Effect, Mean Difference (95% CI)	
Mortality (follow-up length unclear)										
Wallner, 1996 [116]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	3/50 (6%)	5/52 (9.6%)	RR 0.62 (0.16 to 2.47)	37 fewer per 1000 (from 81 fewer to 141 more)	VERY LOW
Surgery for continued or recurrent bleeding										
Wallner, 1996 [116]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	7/50 (14%)	5/52 (9.6%)	RR 1.46 (0.49 to 4.29)	44 more per 1000 (from 49 fewer to 316 more)	VERY LOW
Patients requiring blood transfusion										
Wallner, 1996 [116]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	30/50 (60%)	36/52 (69.2%)	RR 0.87 (0.65 to 1.16)	90 fewer per 1000 (from 242 fewer to 111 more)	VERY LOW

[a] *Unclear allocation concealment, no blinding and significant baseline differences (higher proportion of > 65 year old patients in the H2-RA group); unclear timing of outcome assessment. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly.*

[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

Route of administration (Placebo and H_2-RAs combined) – oral versus intravenous pre-endoscopy (indirect comparison)

Table 49: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI, Rate, Mean (SD), Median (range), N	Control, Rate, Mean (SD), Median (range), N	Relative Risk (95% CI)	Absolute Effect, Mean Difference (95% CI)	
Mortality: subgroup oral administration (30 day follow-up)*										
Hawkey 2001 [92]	randomised trials	serious[a,]	no serious inconsistency	serious[b]	very serious[c]	2/102 (2.0%)	5/103 (4.9%)	RR 0.4 (0.08 to 2.03)	29 fewer per 1000 (from 45 fewer to 50 more)	VERY LOW
Mortality: subgroup intravenous administration (30 day or less follow-up)										
Daneshmend 1992 [89], Lau 2007 [105], Wallner, 1996 [116]	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	51/942 (5.4%)	42/938 (4.5%)	RR 1.21 (0.81 to 1.8)	9 more per 1000 (from 9 fewer to 36 more)	LOW
Re-bleeding: subgroup oral administration (30 day follow-up)*										
Hawkey 2001 [92]	randomised trials	serious[a,]	no serious inconsistency	serious[b]	very serious[c]	10/1032 (9.8%)	10/103 (9.7%)	RR 1.01 (0.44 to 2.32)	1 more per 1000 (from 54 fewer to 128 more)	VERY LOW
Re-bleeding: subgroup intravenous administration(30 day or less follow-up)*										
Daneshmend 1992 [89], Lau 2007 [105], Wallner, 1996 [116]	randomised trials	serious[a,]	no serious inconsistency	serious[b]	Serious[c]	96/892 (10.8%)	108/886 (12.2%)	RR 0.87 (0.68 to 1.12)	16 fewer per 1000 (from 39 fewer to 15 more)	LOW
Surgery for continued or recurrent bleeding: subgroup oral administration*										

Quality assessment						Summary of findings				
Hawkey 2001 [92]	randomised trials	serious[a,]	no serious inconsistency	serious[c]	very serious[c]	3/102 (2.9%)	N6/103 (5.8%)	RR 0.5 (0.13 to 1.96)	29 fewer per 1000 (from 51 fewer to 56 more)	VERY LOW
Surgery for continued or recurrent bleeding: subgroup intravenous administration										
Daneshmend 1992 [89], Lau 2007 [105], Wallner, 1996 [116]	randomised trials	serious[a,] [b]	no serious inconsistency	serious[c]	very serious[c]	73/942 (7.7%)	74/938 (7.9%)	RR 0.98 (0.72 to 1.33)	2 fewer per 1000 (from 22 fewer to 26 more)	VERY LOW

[a] *In 3 out of the 4 studies there was unclear allocation concealment > 50% of the weight in the meta-analysis; in 3 out of 4 studies the randomisation sequence generation was not clearly described; in 1 study baseline statistics were not provided. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly (also see table notes above.*

[b] *indirectness is described as serious since the oral versus intravenous comparison was not assessed within study but rather between studies*

[c] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

Post-endoscopy PPI treatment

PPI compared to placebo post-endoscopy

Table 50: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**PPI, Rate, Mean (SD), Median (range), N**	**Placebo, Rate, Mean (SD), Median (range), N**	**Relative Risk (95% CI)**	**Absolute Effect, Mean Difference (95% CI)**	
Mortality (30 days or less)										

Quality assessment						Summary of findings				
Hung, 2007 [94], Javid, 2001 [95], Kaviani, 2003 [98], Khuroo, 1997 [100], Lau, 2000 [104], Sung, 2009 [112], Wei, 2007 [117], Zargar, 2006 [119]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	13/959 (1.4%)	79/932 (8.5%)	RR 0.40 (0.22 to 0.74)	51 fewer per 1000 (from 22 fewer to 66 fewer)	MODERATE
Re-bleeding within 30 days										
Hung, 2007 [94], Kaviani, 2003 [98], Khuroo, 1997 [100], Labenz, 1997 [102], Lau, 2000 [104], Sung, 2009 [112], Wei, 2007 [117], Zargar, 2006 [119]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	66/936 (7.1%)	159/890 (17.9%)	RR 0.40 (0.31 to 0.52)	107 fewer per 1000 (from 86 fewer to 123 fewer)	MODERATE
Surgery for continued or recurrent bleeding										
Hung, 2007 [94], Javid, 2001 [95], Kaviani, 2003 [98], Khuroo, 1997 [100], Lau, 2000 [104], Sung, 2009 [112], Wei, 2007 [117], Zargar, 2006 [119]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	33/998 (3.3%)	94/954 (9.9%)	RR 0.34 (0.24 to 0.5)	65 fewer per 1000 (from 49 fewer to 75 fewer)	MODERATE
Transfusion requirements (Better indicated by lower values)										
Khuroo, 1997 [100], Lau, 2000 [104], Sung, 2009 [112], Wei, 2007 [117], Zargar, 2006 [119]	randomised trials	serious[a]	serious[c]	no serious indirectness	no serious imprecision	632	645	-	MD 1.06 lower (1.31 to 0.81 lower)	LOW
Length of hospital stay (Better indicated by lower values)										
Khuroo, 1997 [100], Kaviani, 2003 [98], Wei, 2007 [117], Zargar, 2006 [119]	randomised trials	serious[a, c]	serious[c]	no serious indirectness	serious[b]	N = 110; 5.5 (2.1) N = 71; 2.6 (1.2) N = 35; 3.82 (1.8) N = 102; 5.6 (5.3)	N = 110; 6.9 (2.1) N = 102; 5.6 (5.3); N	-	MD 0.77 lower (1.09 to 0.45 lower)	VERY LOW

Quality assessment						Summary of findings				
							= 78; 3.1 (1.6) N = 35; 3.58 (2.17) N = 101; 7.7 (7.3)			
Patients with a median hospital stay > 5days										
Lau, 2000 [104]	randomised trials	serious[a, c]	No serious inconsistency	no serious indirectness	serious[b]	64/120 (53.3%)	82/120 (68.3%)	RR 0.78 (0.63 to 0.96)	150 fewer per 1000 (from 27 fewer to 253 fewer)	LOW

[a] *In 5 out of 8 studies allocation concealment was unclear > 50% of the sample size; in 3 studies there is no or unclear blinding; in 2 studies the sequence generation for randomisation is unclear. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly.*
[b] *The confidence interval of the total mean difference ranges from appreciable benefit to no effect*
[c] *There is substantial heterogeneity between study results – blood transfusion: unexplained but all favouring PPI treatment; length of hospital staydue to the large variability in one study (result to be interpreted with caution).*

Non- analysed data

Hung et al. 2007 (blood transfusion; length of hospital stay)

No. of participants: (n=103 in PPI and n=37 in Placebo)

Patients with PPI treatment after endoscopy had a lower level of units of packed blood cells transfused (bolus: mean = 1.53 and infusion: mean = 2.26) than those in the placebo group (mean = 2.88) but since no standard deviations were given it is unclear whether this difference is significant and what the effect size is.

With regards to length of stay patients with PPI treatment after endoscopy had also a lower length of hospital stay (bolus: mean = 6.57 and infusion: mean = 6.37) than those in the placebo group (mean = 8.15) but since no standard deviations were given it is unclear whether this difference is significant and what the effect size is.

PPI compared to H_2-RAs post-endoscopy

Table 51: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI, Mean (SD), Median (range)	H2-RA, Mean (SD), Median (range)	Relative Risk (95% CI)	Absolute effect, Mean difference (95% CI)	
Mortality within 30 days or less										
Brunner, 1990 [87], Coraggio, 1998 [88], Hsu, 2004 [93], Jensen, 2006 [97], Këlliçi 2010[99], Khoshbaten, 2006[101], Lanas, 1995 [103], Lin 1998 [107], Lin, 2006 [108], Sheu, 2002 [111], Van Rensburg, 2009 [114], Villanueva, 1995 [115]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	25/1154 (2.2%)	38/1161 (3.3%)	RR 0.66 (0.41 to 1.08)	11 fewer per 1000 (from 19 fewer to 3 more)	LOW
Re-bleeding within 30 days or less										
Brunner, 1990 [87], Coraggio, 1998 [88], Fasseas, 2001 [90], Hsu, 2004 [93], Jensen, 2006 [97], Këlliçi 2010[99], Khoshbaten, 2006[101], Lanas, 1995 [103], Lin, 1997 [106], Lin 1998 [107], Lin, 2006 [108], Sheu, 2002 [111], Van Rensburg, 2009 [114], Villanueva, 1995 [115]	randomised trials	serious[a]	serious	no serious indirectness	no serious imprecision	90/1271 (7.1%)	158/1198 (13.2%)	RR 0.49 (0.38 to 0.62)	67 fewer per 1000 (from 50 fewer to 82 fewer)	LOW
Surgery for continued or recurrent bleeding										
Brunner, 1990 [87], Coraggio, 1998 [88], Hsu, 2004 [93], Këlliçi 2010[99], Khoshbaten, 2006[101], Lanas, 1995 [103], Lin 1998 [107], Lin, 2006 [108], Sheu, 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	32/1147 (2.8%)	52/1081 (4.8%)	RR 0.59 (0.39 to 0.88)	20 fewer per 1000 (from 6 fewer to 29 fewer)	LOW

Quality assessment						Summary of findings				
[111], Van Rensburg, 2009 [114], Villanueva, 1995 [115]										
Blood transfusion requirements - mean units transfused (Better indicated by lower values)										
Coraggio, 1998 [88], Hsu, 2004 [93], Jensen, 2006 [97], Këlliçi 2010[99], Lanas, 1995 [103], Villanueva, 1995 [115]	randomised trials	serious[a, d]	no serious inconsistency	no serious indirectness	serious[e]	-[g]	-[g]	-	MD 0.34 higher (0.24 to 0.44 higher)	LOW
Blood transfusion requirement (ml)										
Lin 1997 [106], Lin 2006 [108]	Randomised trials	very serious[a, d]	no serious inconsistency	no serious indirectness	very serious[e]	N = 13; 923 (1156) N = 66; 1241 (3067)	N = 13; 596 (813) N = 67; 1317 (1517)		MD 139.66 higher (422.33 lower to 701.66 higher)	VERY LOW
Lin 1998 [107]	randomised trial	very serious[a, d]	no serious inconsistency	no serious indirectness	-[f]	N = 50; 0 (0-2500)	N = 50; 0 (0-5000)		P=0.05-[f]	VERY LOW
Patients requiring blood transfusions										
Van Rensburg, 2009	randomised trial	serious[a,]	no serious inconsistency	no serious indirectness	serious[e]	334/618 (54%)	313/626 (50%)	RR 1.08 (0.97 to 1.20)	40 more per 1000 (from 15 fewer to 100 more)	LOW
Length of hospital stay (Better indicated by lower values)										
Coraggio, 1998 [88], Hsu, 2004 [93], Jensen, 2006 [97], Këlliçi 2010[99], Lanas, 1995 [103],, Lin, 1997 [106], Lin, 2006 [108], Villanueva, 1995 [115]	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	-[g]	-[g]	-	MD 1.23 lower (1.71 to 0.75 lower)	MODERATE
Lin 1998 [107]	randomised trial	very serious[a, d]	no serious inconsistency	no serious indirectness	-[f]	N = 50; 7 (3-27)	N = 50; 6 (3-31)		P>0.05-[f]	VERY LOW
Fasseas, 2001 [90]	Randomis	very	no serious	no serious	-[f]	N=45	N=47	-	p<0.01[f]	VERY

Quality assessment						Summary of findings				
	ed trial	serious[a, d]	inconsistency	indirectness		mean days = 3.93 no sd	mean days = 6.39 no sd			LOW

[a] *In 9 of the 12 studies allocation concealment was unclear; single or no blinding in 9 studies; randomisation sequence generation not clearly described in 6 studies; baseline differences in 3 studies. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly.*
[b] *The confidence interval of the overall effect ranges from appreciable benefit to no effect*
[c] *Very small event rate*
[d] *Three of the five studies on which this outcome assessment is based have an overall sample size < 100 patients*
[e] *Even though there is statistical significance for lower blood transfusion requirements with H2-RAs there is no appreciable benefit or harm in clinical terms.*
[f] *For these studies insufficient data was provided to calculate the effect size: in one stay (Lin 1998) only medians (range) and p-value was given and in the other study the authors only provided means in a graph without standard deviations.*
[g] *Due to the number of studies for this outcome the means and standard deviations for each study are reported here but can be found in the relevant forest plot in Appendix H.*

Route of PPI administration – oral versus intravenous post-endoscopy (direct comparison)

Table 52: GRADE Summary table

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI i.v. Rate Mean (SD), Median (range)	PPI p. o., Rate, Mean (SD), Median (range)	Relative Risk (95% CI)	Absolute effect, Mean Difference (95% CI)	
Mortality (30 day or less)										
Bajaj, 2007 [86], Javid,	randomise	Serious[a,]	no serious	no serious	very	5/292	5/275	RR 0.93	1 fewer per 1000	VERY

Quality assessment						Summary of findings				
2009, Mostaghni 2011[109], [96], Tsai, 2009 [113], Yilmaz, 2006 [118]	d trials	[b]	inconsistency	indirectness	serious[c]	(1.7%)	(1.8%)	(0.27 to 3.18)	(from 13 fewer to 40 more)	LOW
Re-bleeding (30 days or less)										
Bajaj, 2007 [86], Javid, 2009 [96], Mostaghni 2011[109], Tsai, 2009 [113], Yilmaz, 2006 [118]	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	30/292 (10.3%)	26/275 (9.5%)	RR 1.11 (0.68 to 1.81)	10 more per 1000 (from 30 fewer to 77 more)	VERY LOW
Surgery for continued or recurrent bleeding										
Javid, 2009 [96], Mostaghni 2011[109], Tsai, 2009 [113], Yilmaz, 2006 [118]	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	6/279 (2.2%)	5/263 (1.9%)	RR 1.14 (0.35 to 3.67)	3 more per 1000 (from 15 fewer to 60 more)	VERY LOW
Second endoscopy										
Mostaghni 2011[109]	randomised trial	very serious	no serious inconsistency	no serious indirectness	serious[c]	18/44 (40.9%)	24/41 (58.5%)	RR 0.7 (0.45 to 1.08)	176 fewer per 1000 (from 322 fewer to 47 more)	VERY LOW
Transfusion requirements (Better indicated by lower values)										
Bajaj, 2007 [86], Yilmaz, 2006 [118]	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	Serious[d]	N=112; 1.9 (1.1) N=13; 3.9 (3.7)	N=99; 2.1 (1.7) N=12; 3.6(2.4)	-	MD 0.19 lower (0.57 lower to 0.2 higher)	LOW
Javid, 2009 [96]	randomised trial	very serious[a,d]	no serious inconsistency	no serious indirectness	-[e]	N=45 mean units = 3 no sd	N=45 mean units = 4 no sd	-	not significant[e]	VERY LOW
Transfusion requirements (ml)										
Tsai, 2009 [113]	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[d]	N=78; 1231 (3300)	N=99; 1156 (2958)	-	MD 75 higher (908.49 lower to 1058.49 higher)	VERY LOW

Quality assessment						Summary of findings				
Patients needing blood transfusions										
Mostaghni 2011[109]	randomised trial	very serious	no serious inconsistency	no serious indirectness	serious[c]	31/44 (70.5%)	33/41 (80.5%)	RR 0.88 (0.69 to 1.12)	97 fewer per 1000 (from 250 fewer to 97 more)	VERY LOW
Hospital stay (days mean) (Better indicated by lower values)										
Bajaj, 2007 [86], Tsai, 2009 [113], Yilmaz, 2006 [118]	randomised trials	serious[a, b]	no serious inconsistency	no serious indirectness	very serious[d]	N=112; 4.6 (1.6) N=13; 6.8 (4.8) N=78; 8.5 (4.9)	N=99; 4.5 (2.6) N=12; 5.2 (3.3) N=78; 8.9 (5.3)	-	MD 0.09 higher (0.46 lower to 0.63 higher)	VERY LOW
Javid, 2009 [96]	randomised trial	very serious[a, d]	no serious inconsistency	no serious indirectness	-[e]	N=45 mean days = 3.5 no sd	N=45 mean days = 3.5 no sd	-	not significant[e]	VERY LOW

[a] *No mortality in 2 out of 5 studies; 3 studies reported neither clear allocation concealment nor were blinded. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly.*
[b] *Two of four studies have overall sample sizes < 100 patients*
[c] *The confidence interval of the total effect size ranges from appreciable harm to appreciable benefit*
[d] *The confidence interval of the total effect size ranges from appreciable harm / benefit to no appreciable difference*
[e] *Insufficient data to calculate effect size*

8.2.4 Health economic evidence

The GDG did not consider it necessary to explore the cost-effectiveness of PPIs versus H_2-RAs or placebo pre-endoscopy, as it had concluded from the clinical review that there was no benefit from these agents when given routinely pre-endoscopy. In consideration of the use of acid suppressing drugs post-endoscopy, two studies were included as relevant. These are summarised in the economic evidence profile below. See also Evidence Tables G.3.1.1 and G.3.1.2 in Appendix G.

In regard to the use of acid suppression treatment pre and post-endoscopy, seven studies were selectively excluded due to their limited applicability to the UK setting [120,121 122-126].

Table 53: Acid suppression in patients presenting with likely non-variceal UGIB – Economic summary of findings – Economic study characteristics

Study	Limitations	Applicability	Other comments
Leontiadis (2007)[85]	Potentially serious limitations [a]	Directly applicable [b]	Analysis developed from a UK perspective and over a 28-day and a lifetime horizons
Spiegel (2006)[127]	Potentially serious limitations [d]	Partially applicable [d]	Analysis developed from a US perspective and over a short time horizon

(a) Based on a systematic review of the literature, an individual sampling model was developed over a 28-day time horizon, and then life expectancy was applied to 28-day survivors. The model assumes that patients on oral PPIs have a shorter length of hospital stay than those on IV. Cost components included were appropriate. Appropriate incremental analyses were presented. A probabilistic sensitivity analysis was performed. However, the model assumes that patients on oral PPIs have a shorter length of hospital stay than those on IV.post-endoscopy, which could bias results in favour of oral PPI. Estimates of treatment effect and mortality for interventions given post-endoscopy may not be the best available leading to the study being down graded for this aspect of the analysis.

(b) Analysis developed from a UK NHS perspective, assessing relevant interventions and a relevant population of patients, and reporting cost per QALY gained for the 28-day analysis and cost per life-year gained for the lifetime analysis. Costs of PPIs have decreased since 2004. Mortality rates used within the lifetime horizon were considered high.

(c) Based on a systematic review of the literature, a decision analysis model was developed over a short time horizon (not clearly specified; seemingly 30 days) and there is a lack of consideration of the mortality outcome. The assumption that IV PPI administration results in one extra day of hospital stay than when oral PPI is given is questionable. Appropriate incremental analyses were presented. Multivariable, one-way, and probability sensitivity analyses was performed.

(d) Analysis developed from a US third-party payer perspective, assessing relevant interventions and a relevant population of patients, and reporting cost per QALY gained. However the applicability of the costs from the USA is questionable as they are thought to be high in comparison to UK costs.

Results from the analysis by Leontiadis and colleagues showed that, for patients with likely non-variceal upper gastrointestinal bleeding, the most cost-effective strategy is to offer oral PPI before and after endoscopy, in hospital and at discharge. In addition, haemostatic therapy should be offered at endoscopy to patients with major stigmata of recent haemorrhage. This superior strategy presents, at 28 days, a cost-effectiveness ratio of £24,300 per QALY gained, which is slightly higher than the NICE threshold of £20,000 per QALY gained. When looking at the cost-effectiveness ratio from the lifetime analysis of £140 per LY gained, and considering the utility scores applied to the 28-day analysis (0.45 when the patient is hospitalised and 0.78 when at home), the cost-effectiveness ratio in cost per QALY gain is lower than the NICE threshold of £20,000. However, the mortality rates used in this analysis were considered high, thereby potentially biasing the results.

Results from the analysis by Spiegel and colleagues showed that, for patient with high-risk peptic ulcer haemorrhage in whom successful endoscopic haemostasis was performed, oral PPI is the preferred option compared with IV PPI and IV H2 receptor antagonist. IV PPI is not cost effective compared with oral PPI, even under conservative assumptions favouring IV PPI. The superiority of oral PPI compared with IV PPI is mainly explained by the lower cost of the treatment, a shorter hospital stay, and a higher QALY gained in shortening the hospital length of stay. The reduced length of hospital stay may have in part been driven by the assumption IV PPI administration requires an extra day to oral PPIs. H2 receptor antagonists were found to be more costly and less effective than PPI strategies. This analysis was developed from a US perspective; therefore the applicability of the results to the UK NHS is questionable.

Table 54: Acid suppression in patients presenting with likely non-variceal UGIB – Economic summary of findings of Leontiadis et al (2007)

Intervention before endoscopy, at endoscopy and after endoscopy [a]	Incremental cost versus subsequent option (£)[e]	Incremental effects versus subsequent option 28 days / lifetime horizon [f]	Cost Effectiveness (ICER versus subsequent option)	Uncertainty
Oral PPI, EHT [b], Fixed [c]	£12	0.18 QALDs / 0.08 LYs	£24,300 per QALY gained (22,200 - 26,800) / £140 per LY gained (127 - 157)	Probabilistic sensitivity analysis: For the 28-day analysis, inspection of the cost effectiveness acceptability curves and cost effectiveness plane scatter plots showed a notable probability that other strategies are superior than 'Oral PPI, EHT, Fixed'. However, this strategy is strongly favoured in the lifetime analysis.
Nothing, EHT, Fixed	£28	0.48 QALDs / 0.26 LYs	£21,300 per QALY gained (20,200 - 22,600) / £111 per LY gained (104 - 118)	
Nothing, EHT, Variable [d]	£3	0.08 QALDs / 0.04 LYs	£13,000 per QALY gained (10,700 - 16,600) / £75 per LY gained (61 - 97)	
IV PPI, EHT, Variable	£10	0.91 QALDs / 0.48 LYs	£4120 per QALY gained (3830 - 4460) / £22 per LY gained (20 - 23)	
IV PPI, EHT, fixed	Reference	Reference	Reference	

Abbreviations: QALD = Quality-Adjusted Life-Days; QALY = Quality-Adjusted Life-Years; LY = Life Year; ICER = Incremental Cost-Effectiveness Ratio; PPI = Proton Pump Inhibitors; IV = Intravenous; EHT = Endoscopic Haemostatic Therapy.

(a) Strategies excluded by dominance or extended dominance are not presented.

(b) EHT – Endoscopic haemostatic therapy offered to patients with major stigmata of recent haemorrhage (SRH).

(c) 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.

(d) 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.

(e) Cost components: day in hospital; endoscopy; endoscopy therapy; surgery; oral PPI; IV PPI.

(f) Life expectancy was applied at 28 days among survivors.

Table 55: Acid suppression in patients presenting with likely non-variceal UGIB – Economic summary of findings of Speigel et al (2006)

Intervention	Total cost and incremental cost versus subsequent option (£)[d] [e]	Incremental effects versus subsequent option 28 days / lifetime horizon [f]	Cost Effectiveness (ICER versus subsequent option)	Uncertainty
IV H2 receptor antagonists [a]	Total cost = £6002 Incremental cost = £805	Total = 0.9670 QALYs Incremental = -0.0113 QALYs	Dominated by PPI strategies, being less effective and more costly	A multivariate sensitivity analysis (tornado analysis) was performed, and then a one-way sensitivity analysis on the most influential variables. A probabilistic sensitivity analysis was also performed. The conclusion of the base case was robust, favouring oral PPI in all scenarios. Some scenarios showed oral PPI being dominant over IV PPI. The probability of IV PPI being cost effectiveness compared to oral PI and to a threshold of $50k (£30k) per QALY gained was 8%.
IV PPI [b]	Total cost = £5197 Incremental cost = £743	Total = 0.9783 QALYs Incremental = 0.0016 QALYs	£759,882 per QALY gained	
Oral PPI [c]	Total cost = £4454	Total = 0.9767 QALYs [l]	Reference	

(a) 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.

(b) 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.

(c) 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.

(d) Cost components: drug treatment cost (including IV tubing and pump when IV treatment); intervention cost (endoscopy, surgery); hospital stay; inpatient and outpatient consultations; and cost for treating complicated and uncomplicated ulcer haemorrhage (Medicare DRG cost).

(e) Published costs in USD were converted in pound sterling using Purchasing Power Parities.

(f) To calculate QALYs, utilities for 4 health states were incorporated to the model: dyspepsia; ulcer haemorrhage without surgery; ulcer haemorrhage or ulcer perforation with surgery; and death.

8.2.5 Evidence statements

8.2.5.1 Clinical evidence

Pre-endoscopy

a) PPI versus Placebo:

Mortality (30 day or less follow-up)

Three studies comprising 1983 patients found no statistical / clinical significant difference in the rate of mortality in patients treated with PPIs compared to those given a placebo [LOW QUALITY].

Re-bleeding (30 day or less follow-up)

Three studies comprising 1983 patients found no statistical / clinical significant improvement in rate of re-bleeding in patients treated with PPIs compared to those given a placebo [LOW QUALITY].

Surgery for continued or recurrent bleeding (30 day or less follow-up)

Three studies comprising 1983 patients found no statistical / clinical significant improvement in rate of re-bleeding in patients treated with PPIs compared to those given a placebo [LOW QUALITY].

Blood transfusion requirement / Patients needing blood transfusions

One study with 631 participants found no statistical / clinical significant improvement in the average unit of blood transfusions between the patients treated with PPIs and those given a placebo [MODERATE QUALITY]. Two studies with a total of 1352 patients reported the rate of patients requiring blood transfusions. Similar percentages of patients needing transfusions in groups of patients in the treatment and the control group with no significant differences [MODERATE QUALITY].

Length of hospital stay

One study with 631 participants found no statistical / clinical improvement in the average length of hospital stay between patients treated with PPIs and those given a placebo [MODERATE QUALITY].

b) PPI versus H_2-RAs:

Mortality (30 day or less follow-up)

One study comprising 102 patients found no statistical / clinical difference in the rate of mortality in patients treated with PPIs and those given H_2-RAs [VERY LOW QUALITY].

Surgery for continued or recurrent bleeding (30 day or less follow-up)

One study comprising 102 patients found no statistical / clinical difference in the rate of re-bleeding in patients treated with PPIs and those given H_2-RAs [VERY LOW QUALITY].

Patients needing blood transfusions (30 day or less follow-up)

One study comprising 102 patients found no statistical / clinical difference in the rate of patients requiring blood transfusions treated with PPIs and those given H_2-RAs [VERY LOW QUALITY].

c) Route of administration of PPI treatment (indirect comparison):

The four pre-endoscopy studies of sections 8.2.5.1 a and b comprising a total of 2085 participants were then divided into those that used oral compared to those that used intravenous PPIs mode of administration. This was done regardless of whether a placebo or H_2-RAs comparison group was used. A head to head comparison of oral versus intravenous PPI was not available and therefore this analysis is indirect evidence. In the following sections subgroup analyses are carried out to determine whether orally administered PPIs were more effective than intravenous pre-endoscopy for mortality, re-bleeding and emergency surgery.

Mortality (30 day or less follow-up)

An indirect subgroup analysis with the oral group comprising 105 patients and the intravenous group consisting of 1880 participants showed no statistical / clinically important difference in the rate of mortality between those that had PPIs administered orally or those that were treated intravenously [VERY LOW QUALITY].

Re-bleeding (30 day or less follow-up)

An indirect subgroup analysis with the oral group comprising 105 patients and the intravenous group consisting of 1880 participants showed no statistical / clinically important difference in re-bleeding rates between the group of patients who had PPIs administered orally or those that were treated intravenously [VERY LOW QUALITY].

Patients needing surgery for continued bleeding (30 day or less follow-up)

An indirect subgroup analysis with the oral group comprising 105 patients and the intravenous group consisting of 1880 participants showed no statistical / clinically important difference in rates of patients requiring surgery between the group of patients who had PPIs administered orally or those that were treated intravenously [VERY LOW QUALITY].

Post-endoscopy

a) PPI versus Placebo:

Mortality (30 day or less follow-up)

Ten studies comprising 2523 participants did not show a statistical / clinical significantly lower rate of mortality in patients receiving PPIs compared to the control group (LOW QUALITY).

Re-bleeding (30 day or less follow-up)

Ten studies comprising 2413 participant showed statistically significant lower rates of re-bleeding in patients receiving PPIs compared to the control group. The size of the drop in rate reached clinical significance (LOW QUALITY).

Surgery for continued or recurrent bleeding (30 day or less follow-up

Ten studies comprising 2539 participant showed statistically significant lower rates of surgery in patients receiving PPIs compared to the control group. The size of the drop in rate reached clinical significance (MODERATE QUALITY).

Blood transfusion requirements

Five studies with 1497 participants found a significantly lower average blood transfusion requirement for patients treated with PPIs versus those given a placebo. This significantly lower average amount of units of blood was high enough to reach clinical difference [LOW QUALITY].

Length of hospital stay/ Patients with a median hospital stay > 5 days

Four studies comprising 422 participants found a significantly lower average length of hospital stay for patients treated with PPIs versus those given a placebo. This lower length of stay was statistically significant yet did not reach a level considered to be of clinical importance [VERY LOW QUALITY]. One study comprising 240 patients had a significantly lower rate of patients staying in hospital longer than 5 days in the PPI group compared to the control group. This difference in rate was high enough to reach statistical significance yet it did not reach a level that can be considered to have clinical benefit [LOW QUALITY].

b) PPI versus H_2-RAs:

Mortality (30 day or less follow-up)

Eleven studies comprising 2207 patients found lower rates of mortality in the PPI compared to the H_2-RA group. However this lower rate did not reach statistical or clinical significance [LOW QUALITY].

Re-bleeding (30 day or less follow-up)

Twelve studies comprising 2361 participant provided evidence for statistically significant lower rates of re-bleeding in patients receiving PPIs compared to the control group. The size of the drop in rate reached clinical significance (LOW QUALITY).

Surgery for continued or recurrent bleeding (30 day or less follow-up)

Ten studies with a total of 2122 participants provided evidence for statistically significant lower rates of surgery in patients receiving PPIs compared to the control group. The size of the drop in rate reached clinical significance (LOW QUALITY).

Blood transfusion requirements

Five studies with 431 participants found a statistically significant higher average blood transfusions requirement for patients treated with PPIs versus those given a H_2-RAs. However, the size of this average increase in rate units of blood transfused did not reach clinical significance [LOW QUALITY].

Length of hospital stay

Seven studies comprising 590 participants found a significantly lower average length of hospital stay for patients treated with PPIs versus those given a placebo. This lower length of stay reached a level considered to be of clinical benefit [MODERATE QUALITY].

Route of PPI administration – oral versus intravenous (direct comparison):

Mortality (30 day or less follow-up)

Four studies comprising 482 patients provided evidence for similar rates of mortality for PPIs administered orally compared to PPIs administered intravenously. As such the evidence for this outcome did not reach statistical or clinical significance [VERY LOW QUALITY].

Re-bleeding (30 day or less follow-up)

There were similar rates of re-bleeding in four studies comprising 482 patients when PPIs were administered orally compared to PPIs administered intravenously. As such the evidence for this outcome did not reach statistical or clinical significance [VERY LOW QUALITY].

Surgery for continued or recurrent bleeding (30 day or less follow-up)

In three studies comprising 482 patients there were similar rates of patients requiring surgery when PPIs were administered orally compared to PPIs administered intravenously. As such the evidence for this outcome did not reach statistical or clinical significance [VERY LOW QUALITY].

Blood transfusion requirements

Two studies comprising 236 participants found similar average need for blood transfusions for patients treated p.o. and those given i.v. PPIs. As such the evidence for this outcome did not reach statistical or clinical significance [LOW QUALITY].

Length of hospital stay

Three studies comprising 392 participants found similar average length of hospital stay between the patient group that was given the PPI orally compared to intravenous administration. As such the evidence for this outcome did not reach statistical or clinical significance [LOW QUALITY].

8.2.5.2 Health economic evidence

At the time of endoscopy, offering haemostatic therapy to patients with major stigmata of recent haemorrhage is a cost-effective strategy.

Post-endoscopy, oral PPI in hospital and at discharge is the most cost-effective strategy, compared with in hospital IV PPI or IV H2 receptor antagonists, followed by oral PPI at discharge.

8.2.6 Recommendations and link to evidence

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?

Recommendations	• **Do not offer acid-suppression drugs (proton pump inhibitors or H2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.**
Relative values of different outcomes	When PPIs are considered specifically in the context of routine administration prior to endoscopy in patients with suspected non-variceal bleeding, there is no statistically or clinically significant evidence that acid suppression therapy is beneficial in relation to any of the considered outcomes. When the results of the endoscopy are known, the considered evidence demonstrates statistically and clinically significant benefit of proton pump inhibitors, compared to placebo. Benefit was seen across all outcomes except mortality where there was a trend in favour of PPI which did not reach statistical significance. Proton pump inhibitors were also demonstrably superior to H2 receptor antagonists when considering re-bleeding, surgery and length of hospital stay but not mortality and blood transfusion requirements.
Trade off between clinical benefits and harms	Specific adverse events were not included amongst considered outcomes for this question (although the GDG did consider the possible increase in pneumonia elsewhere – see Chapter 11). The GDG felt that proton pump inhibitors had been available for some time and experience has shown them to be safe drugs.
Economic considerations	The evidence from Leontiadis et al (2007) suggests that giving oral PPI pre-endoscopy is a cost effective strategy when compared with doing nothing or giving intravenous PPIs prior to endoscopy. However, in light of the findings of the clinical review, the GDG felt that the model could have potentially serious limitations. There is no available evidence that makes a direct comparison between the administration of oral and iv. PPI prior to endoscopy. The best available evidence used in the Leontiadis model compares the interventions to placebo and infers that oral PPIs are superior to iv PPI; as one trial showed a trend of decreased risk of mortality for the former, and another single trial showed a trend towards increased risk in the latter. However, the GDG noted this contrasted to the evidence

	in the clinical review which made a direct comparison of oral versus iv administration of PPIs post-endoscopy, where there was not a significant difference in outcome between the two interventions. Using the overview of evidence provided by the clinical review, the GDG questioned whether there was sufficient evidence to be able to subgroup on the basis of administration of the PPI prior to endoscopy, as had been done in the Leontiadis study. In the clinical review, where the interventions had not been sub grouped, there was not a clinical or statistical difference between placebo and PPI in outcome, including those which would infer downstream cost. The GDG noted that a 'do nothing' approach prior to endoscopy would not incur acquisition costs of the drug itself, and that there was no conclusive evidence that downstream costs would be higher with this approach. In consideration of the cost effectiveness of H2-receptor antagonist to PPIs given post-endoscopy, the available analysis by Speigel et al (2006) demonstrates the superior cost-effectiveness of proton pump inhibitors over H2-receptor antagonists.
Quality of evidence	The quality of evidence comparing proton pump inhibitors to placebo and H2 receptor antagonists is predominantly moderate quality by GRADE criteria.
Other considerations	In discussion the GDG noted that proton pump inhibitors administered pre-endoscopy reduce the incidence of major stigmata or recent haemorrhage. However the evidence suggests that this does not translate into improved clinical outcomes. The guideline development group debated and agreed that acid suppression therapy should not be use as a 'holding measure' to replace or delay early endoscopic therapy. Overall, the GDG felt able to recommend the use of PPI when there is evidence of recent bleeding at endoscopy. In patients with non-variceal upper GI bleeding where endoscopy does not demonstrate stigmata of recent haemorrhage clinicians should consider existing NICE guidance, including that relating to the management of dyspepsia and osteoarthritis, and offer acid suppression therapy as indicated in that guidance.

Are proton pump inhibitors administered intravenously more clinical / cost effective than the same agents administered in tablet form for patients with likely non-variceal upper gastrointestinal bleeding?

Recommendations	• **Offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.**
Relative values of different outcomes	The considered evidence does not demonstrate a statistically or clinically significant difference between oral and intravenous proton pump inhibitors across all outcomes.
Trade off between clinical benefits and harms	Specific adverse events were not included amongst considered outcomes. However, the GDG felt that the route of administration of proton pump inhibitors did not impact significantly upon the safety of the drugs.
Economic considerations	The relative cost-effectiveness of oral and intravenous proton pump inhibitors is unclear. The GDG considered the available analysis by Leontiadis et al. 2007 which found oral PPIs to be more cost effective than iv PPI; however the GDG noted several limitations that may bias the analysis towards oral PPI over iv PPI. The inferiority of iv PPI in terms of cost effectiveness was in part driven by the assumption that iv PPI required an increased length of stay regardless of level of comorbidity. The GDG felt this gave too much emphasis on the route of administration of PPI in determining the time of discharge. Iv PPI was only given to patients post-endoscopy if they had stigmata of recent haemorrhage, and this group could have poorer prognosis than the group which had oral PPI. Therefore the results could be biased against iv PPI. It was also noted that the relative risk of mortality rate for iv PPI post-endoscopy used in the model was high in comparison to the estimate derived from the clinical review, which incorporated additional studies to estimate relative risk associated with the intervention post-endoscopy. Further, the clinical review of studies comparing iv PPI to oral PPI found slightly in favour to iv PPI in regards to risk of mortality. The benefit of iv PPI is likely to be underestimated in the Leontiadis et al. 2007 study. Taking into account the above potential limitations, the cost effectiveness of iv PPI could be improved on that indicated by Leontiadis et al. 2007. Therefore the GDG felt that either route of administration could be cost effective.
Quality of evidence	Although direct comparisons exist, the quality of evidence comparing oral and intravenous proton pump inhibitors is of very low quality, and consequently it is inadequate to allow firm conclusions to be drawn.

Other considerations	The GDG did not feel able to make a firm recommendation on the preferred route of administration. A regimen of an 80mg bolus of Omeprazole or Pantoprazole followed by a 72 hour infusion of 8mg per hour was used in the majority of studies. In contrast studies of orally administered proton pump inhibitor drugs used comparable dosage but a shorter duration of therapy. We are therefore unable to recommend a specific dosage regimen. Despite these observations; a research recommendation is not made due to feasibility challenges. In particular the population size required to demonstrate a significant difference would be very large and the outcome of this research is unlikely to have a major impact upon patient care.

8.3 Treatment options after first or failed endoscopic treatment

8.3.1 Introduction

Endoscopic therapies are delivered to ulcers that are either actively bleeding or have major stigmata of recent haemorrhage (a non-bleeding visible vessel or adherent blood clot). Endoscopic therapy is sometimes technically demanding and it is often difficult for the endoscopist to be entirely confident that haemostasis has been secured. Repeat endoscopy within 24 hours may be useful since it will identify residual stigmata that could then be treated. On the other hand repeated endoscopy may be difficult to schedule (in busy routine lists or at weekends) and repeated endoscopic therapies could increase the risk of ulcer perforation. The role of 'second' endoscopy is therefore addressed in this Chapter'

Failed primary haemostasis and re-bleeding are associated with high mortality; in the National UK audit there was a 30% post operative mortality in patients undergoing emergency surgery for uncontrolled ulcer bleeding[5]. Death is rarely due to exsanguination but occurs in the majority of cases either because of decompensation of medical co-morbidity (cardiac events in patients with coronary artery disease, stroke in patients with cerebrovascular disease, renal failure in patients with pre-existing kidney disease etc) or because of a post operative complication after emergency surgery. Management of these critically ill patients is best undertaken by a multi-disciplinary team in a high dependency setting with discussion involving gastroenterologists, surgeons and, where available, interventional radiologists.

Therapeutic options in this group of patients are further endoscopic treatment, emergency surgery or trans-arterial embolisation.

1. Further endoscopic therapy. In most patients who develop further melaena, haematemesis or significant sudden fall in haemoglobin concentration, it is wise to repeat endoscopy to confirm that bleeding has recurred. The finding of a clean ulcer base and absence of blood within the upper gastrointestinal tract is reassuring, but most patients will have evidence of either active bleeding or major stigmata of recent haemorrhage. Management at this point is based upon clinical judgement and experience; for example cases of massive bleeding may be best managed by urgent surgery whilst the presence of a residual visible vessel could be treated by (say) clip application. The benefits of second endoscopic therapy have to be balanced against the risk of delaying definitive haemostasis by operative surgery or interventional radiology should yet further bleeding occur, and by the possible increased risk of complications associated with multiple application of endoscopic therapies.

2. In patients with uncontrolled massive peptic ulcer bleeding emergency surgery is life saving. A relatively conservative approach of under-running the bleeding ulcer is usually undertaken, although in patients with extremely large duodenal ulcers this may be impossible and more extensive surgery is then needed. The majority of patients are extremely ill at the time of surgery; most are elderly and have medical co-morbidities. It is therefore not surprising that post-operative mortality is high. It is possible that delayed surgery, occurring as a consequence of repeat failed endoscopic therapy contributes to high mortality and that an approach of earlier aggressive surgical intervention might lead to lower mortality, albeit at the expense of significant morbidity.
3. Identification of the bleeding point can be achieved by a range of radiological techniques. CT-angiography will identify blood in the lumen of the gastrointestinal tract and may localise the bleeding artery in patients with major active bleeding, but is not usually helpful once bleeding has stopped. CT-angiography can be particularly useful in actively bleeding patients in whom upper endoscopy and colonoscopy fail to identify the bleeding point; missed lesions and bleeding from the small bowel may be revealed. Percutaneous angiography, in which sophisticated catheters are positioned into visceral arteries, are used to localise the bleeding point and embolisation of the artery using foam and coils will stop bleeding. This requires an expert interventional radiologist and a vascular interventional suite. The benefits of embolisation have to be balanced against the risk of causing ischemic necrosis of the gastrointestinal tract. Case series have shown that this approach can be effective and safe, but in the UK the availability of emergency interventional radiology (particularly outside of normal working hours) is limited.

Whether repeated endoscopic therapy, emergency surgery or trans-arterial embolization is the best approach when initial endoscopic therapy is unsuccessful is therefore complex and is related to patient factors such as the severity of bleeding, extent of comorbidity and the endoscopic findings as well as local factors including expertise of endoscopists, surgeons and radiologists and the availability of (particularly) an interventional radiological service.

8.3.2 Clinical questions and methodological introduction

Clinical question 1

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

Clinical question 2

In patients with non-variceal upper gastrointestinal bleeding who re-bleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolization / angiography to stop bleeding?

Clinical question 3

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

Table 56: PICO Characteristics of all three clinical questions combined

Clinical Methodological Introduction	
Population:	• Patients with non-variceal upper GI bleeding • Patients who re-bleed after first treatment • Patients whose first line treatment fails

Clinical Methodological Introduction	
Intervention	• Routine second look • Second endoscopic treatment • Surgery • Embolisation / angiography
Comparison:	• Routine follow-up • Surgery • Embolisation / angiography
Outcomes:	• Mortality • Re-bleeding • Additional treatments (salvage surgery, TIPS etc) • Failure to control bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events (leading to death, leading to withdrawal from treatment)

We searched for RCTs comparing the effectiveness of routine second look and re-treatment as interventions for upper gastrointestinal bleeding for. We also searched for observational studies for the comparison between surgery and embolisation / angiography in patients where first line treatment fails.

8.3.3 Clinical evidence review

We searched for randomised control trials investigating the effects of routine second look (compared to usual follow up) or repeat endoscopy and the treatment options when bleeding remains uncontrolled(see flowchart in Appendix E for study selection).

This combined review includes 6 randomised control trials [128-133], 6 observational studies [134-139] and cross-referenced 2 meta-analyses [140,141]. Five RCTs were included in the routine second look review and the sixth related to the question which type of second line treatment is preferable when patients re-bleed (repeat endoscopy versus surgery). The additional four observational studies were included in the treatment failure evidence review and analyse the comparison of transcatheter arterial embolisation (TAE) / angiography versus surgery.

The results of this review have been analysed according to whether a routine second endoscopy was compared to follow up treatment without this i.e. with a second endoscopy only if it appeared to be clinically necessary. This review was combined with the repeat treatment part of the review since most studies would include the option of providing a repeat treatment if so required in the routine second look endoscopy. A further aspect that was addressed was which repeat treatment is more effective (repeat endoscopy versus surgery). For the third clinical question we also searched for observational studies and included four separate observational reports which provided evidence for the issue of treatment options when the first line approach has failed (embolization compared to surgery) (see Appendix F for evidence tables and Appendix H for forest plots).

The following table summarises study types, study population (at risk percentage) and gives additional comments (please refer to the evidence tables for more details).

Table 57: Characteristics of included studies

Study	Study type (N)	Clinical question	Population characteristics	Comments
Chiu, 2003	RCT	Routine	46.8% / 48% of patients with	Routine look within 16-24

Study	Study type (N)	Clinical question	Population characteristics	Comments
[128]	(N=194)	second look	shock and 49% / 43% with spurting / oozing stigmata in control and treatment group respectively	hours after initial treatment (with re-treatment if needed)
Defreyne, 2008 [136]	Retrospective case review (N=91)	When first treatment fails	APACHE II scores: 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	Patients undergoing surgical exploration without haemostatic action or arteriography without embolization were included on an ''intention-to-treat'' basis.
Eriksson, 2008 [135]	Retrospective case review (N=91)	When first treatment fails	Patients with repeated bleeding (i.e. not only those who failed to achieve haemostasis with treatment) also included. Most patients had at least one co-morbid condition	Embolization was superior to surgery in the short run a Kaplan-Meier estimate showed that initial differences in mortality rates between the two groups were equalised after 1 year.
Larssen, 2008 [137]	Retrospective case review (N=46)	When first treatment fails	Restricted to patients with duodenal ulcers only – non-peptic ulcers excluded	Surgically treated patients had considerably higher pre-treatment blood transfusions (8.9 versus 15.3 units)
Lau, 1999 [129]	RCT (N=92)	Type of re-treatment	35% / 30% of patients with hypotension 42% / 39% vomiting fresh blood on admission in endoscopic re-treatment and surgery group respectively	Overall 16 patients were bleeding whilst in hospital for other conditions
Messman, 1998 [130]	RCT (N=107)	Routine second look	60% / 54% of patients had heart rate >100min or systolic blood pressure < 100 mm Hg in routine second look and single endoscopy group respectively	Follow-up duration only up until end of hospitalisation
Ripoll, 2004 [134]	Retrospective case review (N=70)	When first treatment fails	Patients with hypovolemic shock in embolization group 67.7% and in the surgery group 84.6%	Significant baseline differences for age, rate of cardiac disease and anticoagulation treatment
Rutgeerts, 1997 [131]	RCT (N=107)	Re-treatment	38% of patients with spurting oozing stigmata in both single and repeat treatment groups	All patients underwent daily repeat endoscopies but only patients allocated to the repeated group received daily prophylactic treatment with FG injection until the visible vessel disappeared
Saeed, 1996 [132]	RCT (N=40)	Re-treatment	All patients were selected to be high risk according to the Baylor Bleeding Score scale.	Follow-up duration only up until end of hospitalisation
Villanueva, 1994 [133]	RCT (N=104)	Routine second look	33% / 44% of patients with spurting oozing stigmata in	Follow-up duration only up until end of hospitalisation

Study	Study type (N)	Clinical question	Population characteristics	Comments
			the routine second look and single treatment groups	
Venclauskas 2010[138]	Retrospective case review (N=74)	When first treatment fails	Patients who were treated with embolization or surgery for massive or recurrent bleeding from duodenal ulcer	Significant baseline differences for age, concomitant disease, number of previous gastroscopies and APACHE II scores

Routine second look endoscopy (with or without second treatment) versus routine follow-up

Table 58: GRADE Summary table routine second look versus routine follow-up

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Routine second look (with or without repeat treatment), Rate (%) or Mean (sd) or Median (range)	Usual care follow up, Rate (%) or Mean (sd) or Median (range)	Relative Risk (95% CI)	Absolute effect or Mean difference (95% CI)	Quality
Mortality (follow-up 30 days)										
Villanueva, 1994 [133] Saeed, 1996 [132] Rutgeerts, 1997 [131] Messmann, 1998 [130] Chiu, 2003 [128]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	19/493 (3.9%)	23/486 (4.7%)	RR 0.82 (0.45 to 1.49)	9 fewer per 1000 (from 26 fewer to 23 more)	VERY LOW
Re-bleeding duration of hospital stay (or 7 days)										
Villanueva, 1994 [133] Messmann, 1998 [130] Chiu, 2003 [128]	randomised trials	no serious limitations	serious[3]	no serious indirectness	serious[4]	29/204 (14.2%)	39/199 (19.6%)	RR 0.74 (0.48 to 1.13)	51 fewer per 1000 (from 102 fewer to 25 more)	LOW

Re-bleeding (30 day)										
Saeed, 1996 [132] Rutgeerts, 1997 [131] Chiu, 2003 [128]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	47/389 (12.1%)	69/381 (18.1%)	RR 0.67 (0.48 to 0.94)	60 fewer per 1000 (from 11 fewer to 94 fewer)	LOW
Surgery										
Villanueva, 1994 [133]; Saeed, 1996 [132]; Rutgeerts, 1997 [131] Messmann, 1998 [130]; Chiu, 2003 [128]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	17/493 (3.4%)	29/486 (6%)	RR 0.58 (0.32 to 1.03)	25 fewer per 1000 (from 41 fewer to 2 more)	LOW
Length of hospital stay (Better indicated by lower values)										
Villanueva, 1994 [133]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	N=52, 9.3 (8.6)	N=52, 11.8 (10.8)	-	MD 2.5 lower (6.25 lower to 1.25 higher)	LOW
Blood transfusions (Better indicated by lower values)										
Villanueva, 1994 [133]; Saeed, 1996 [132] Rutgeerts, 1997 [131] Chiu, 2003 [128]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	N=52, 1.7 (1.9); N=19, 0 (0); N=270, 3.7 (5.8); N=100, 1.9 (1.7)	N=52, 2.5 (2.5); N=21, 0.9 (0.4); N=266, 3.2 (4.2); N=94, 2.1 (2.3)	-	MD 0.18 lower (0.59 lower to 0.24 higher)	LOW

[1] *Two studies have unclear allocation concealment*
[2] *The confidence interval ranges from appreciable benefit via no effect to appreciable harm*
[3] *There is considerable heterogeneity between the study results*

[4] *The confidence interval ranges from appreciable benefit to no effect*

Repeat treatment endoscopy versus surgery in patients who re-bleed

Table 59: GRADE table repeat endoscopy versus surgery

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Repeat endoscopy Rate (%) or Mean (sd) or Median (range)	Surgery Rate (%) or Mean (sd) or Median (range)	Relative Risk (95% CI)	Absolute effect, Mean difference (95% CI)	Quality
Mortality (follow-up 30 days)										
Lau, 1999 [129]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	5/48 (10.4%)	8/44 (18.2%)	RR 0.57 (0.2 to 1.62)	78 fewer per 1000 (from 145 fewer to 113 more)	LOW
Failure to achieve haemostasis										
Lau, 1999 [129]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	4/48 (8.3%)	0/44 (0%)	OR 9 (0.47 to 172.15)	-[b]	LOW
Re-bleeding (30 day)										
Lau, 1999 [129]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	0/48 (0%)	3/44 (6.8%)	RR 0.13 (0.01 to 2.47)	59 fewer per 1000 (from 68 fewer to 100 more)	LOW
Salvage surgery										
Lau, 1999 [129]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	13/48 (27.1%)	0/44 (0%)	RR 24.8 (1.52 to 405.12)	-[b]	HIGH

Rate of treatment complications										
Lau, 1999 [129]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	7/48 (14.6%)	16/44 (36.4%)	RR 0.4 (0.18 to 0.88)	218 fewer per 1000 (from 44 fewer to 298 fewer)	LOW

[a] *When the confidence interval shows appreciable benefit / harm as well as no effect imprecision is downgraded once whenever the confidence interval ranges from appreciable benefit to appreciable harm imprecision is downgraded.*
[b] *An absolute effect cannot be derived since there are no events in one of the study arms.*

Embolisation versus surgery when first line treatment fails

Table 60: GRADE table for observational studies of embolisation versus surgery when first line treatment has failed (data was not pooled) – individual study results given in the relevant cells in the same order as in the first column of the table. Lighter shaded rows indicate where the same outcome is divided into different groups.

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Embolisation, Rate (%) or Mean (sd) or Median (range)**	**Surgery, Rate (%) or Mean (sd) or Median (range)**	**Relative Risk (95% CI)**	**Absolute effect, Mean Difference (95% CI)**	**Quality**
Mortality (30 day or less)										
Ripoll 2004 [134] Defreyne 2008 [136], Eriksson 2008 [135], Larssen 2008 [137], Venclauskas 2010[138], Wong 2011[139]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	8/31 (25.8%); 18/46 (39.1%); 1/40 (2.5%); 7/36 (19.4%); 5/24 (20.8%); 8/32 (25%)	8/39 (20.5%); 14/51 (27.5%); 7/51 (13.7%); 2/10 (20%); 11/50 (55%); 17/56 (30.4%)	RR 1.26 (0.53 to 2.97); RR 0.18 (0.02 to 1.42); RR 1.43 (0.80 to 2.53); RR 0.97 (0.24 to 3.97); RR 0.95 (0.37 to 2.42);RR 0.82 (0.40 to 1.69)	-[d]	VERY LOW
Failure to achieve haemostasis										

Defreyne 2008 [136], Eriksson 2008 [135], Larssen, 2008 [137], Wong 2011[139]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	6/46 (13.0%); 10/40 (25%); 3/36 (19.4%); 3/32 (9.4%)	6/51 (11.8%); 9/51 (17.6%); 0/10 0/56	RR 1.11 (0.38 to 3.15); RR 1.42 (0.64 to 3.15); RR 2.08 (0.12 to 37.29); RR 12.09 (0.64 to 226.89)	-[d]	VERY LOW
Re-bleeding (3 day follow-up)										
Defreyne, 2008 [136]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	serious[c]	20/46 (43.5%)	4/51 (7.8%)	RR 5.54 (2.05 to 15.02)	-[d]	VERY LOW
Re-bleeding (30 day follow up or until discharge from hospital)										
Ripoll, 2004 [134] Defreyne, 2008 [136] Larssen, 2008 [137], Venclauskas 2010[138]Wong 2011[139]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	9/31 (29.0%); 20/46 (43.5%); 10/36 (27.8%); 3/20 (15%); 11/32 (34.4%)	9/39 (23.0%); 13/51 (25.5%); 2/10 (20%); 4/50 (8%); 7/56 (8%)	RR 1.26 (0.57 to 2.78); RR 1.71 (0.96 to 3.03); RR 1.39 (0.36 to 5.34); RR 1.88 (0.46 to 7.64); 2.75 (1.18 to 6.38)	-[d]	VERY LOW
Salvage treatment (usually surgery)										
Ripoll, 2004 [134] Eriksson, 2008 [135] Venclauskas 2010[138]	observational studies	serious[a]	serious[e]	no serious indirectness	very serious[c]	5/31 (16.1%); 5/40 (12.5%); 2/24 (8.3%)	12/39 (30.8%) 3/51 (5.9%); 3/50 (6%)	RR 0.52 (0.21 to 1.33); RR 2.13 (0.54 to 8.36);RR 1.39 (0.25 to 7.77)	-[d]	VERY LOW
Length of hospital stay (days) (Better indicated by lower values)										
Ripoll, 2004 [134], Venclauskas 2010[138], Wong 2011[139]	observational studies	serious[a,b]	serious[e]	no serious indirectness	serious[c]	N=31, 30.1 (24.6); N=24 20.1 (15); N=32, 24.5 (24.7)	N=39, 25.8 (20.8); N=50 17.6 (13.9); N=56, 26.1 (22.5)	-	MD 4.3 higher (6.54 lower to 15.14 higher); MD 2.50 (4.63 lower to 9.63 higher); MD 1.60 lower	VERY LOW

									(11.99 lower to 8.79 higher)	
Transfusion requirements (packed red cell units) (Better indicated by lower values)										
Ripoll, 2004 [134], Wong 2011 [139]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[c]	N=31, 4.2(4.6); N=32, 15.6 (14)	N=39, 4.1(4.2); N=56, 14.2 (9.9)	-	MD 0.1 higher (1.99 lower to 2.19 higher); MD 1.40 higher (4.10 lower to 6.90 higher)	VERY LOW
Adverse events - treatment complications										
Eriksson, 2008 [135], Wong 2011 [139]	observational studies	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	8/40 (20%); 13/32 (40.6%)	19/51 (37.3%); 38/56 (67.9%)	RR 0.54 (0.26 to 1.1), RR 0.60 (0.38 to 0.94)	-[d]	VERY LOW

[a] *All studies are retrospective case reviews*
[b] *Data in the GRADE table shows pooled results. Forrest plots are not pooled and individual Risk Ratios are given in the detailed evidence statements*
[c] *All studies have wide confidence intervals*
[c] *Since all studies are observational no absolute effect was derived*
[e] *There is considerable heterogeneity between study results*

8.3.4 Health economic evidence

One study was identified that compared routine second look endoscopy to routine clinical follow up in patients with UGIB after first endoscopic treatment. This is summarised in the economic evidence profile below. See also Evidence Table G.3.2 in Appendix G. There were no excluded studies for this first review question.

One study [142] was identified that compared repeat endoscopy to surgery or embolisation to stop bleeding in patients who re-bleed after the first endoscopic therapy. This was excluded on the basis of lack of applicability since it looked at oesophageal transection which is not current practice in the UK.

No relevant economic evaluations were found comparing angiography/embolisation with surgery in non-variceal UGIB patients where endoscopic therapy failed.

Table 61: Routine second look endoscopy versus routine clinical follow up – Economic study characteristics

Study	Limitations	Applicability	Other comments
Spiegel BMR, Ofman JJ, Woods K, and Vakil NB [143]	Potentially Serious Limitations [a]	Partially applicable [b]	Analysis developed from a US Medicare perspective and over a 30-day time horizon (post-discharge)

(a) The decisional analytic model was developed based on reviews of published literature, and over a 30-day time horizon. The analysis adequately reflects the nature of the health condition. Cost components included were appropriate. The cost-effectiveness ratios presented were inadequate (cost per additional recurrent haemorrhage, surgery, or death prevented). The Baylor Bleeding Score is not commonly used in the UK, however detailed sufficiently for interpretation of economic analysis.

(b) No quality of life or QALY assessment was included. An extensive sensitivity analysis was performed. Analysis developed from a US Medicare perspective, assessing relevant interventions and a relevant population of patients.

The cost-effectiveness analysis by Spiegel and colleagues shows that performing selective second look endoscopy in patients at high risk for re-bleeding as identified by the Baylor Bleeding Score may prevent more recurrent haemorrhage, surgery, or death at a lower cost. The additional cost generated by committing a subset of patients to repeated endoscopy seems to be offset by the significant effectiveness of this strategy.

In addition, it is important to note that the sensitivity analysis suggests that the strategy of Clinical follow-up + iv PPI may be the dominant strategy in certain cases, as this strategy was preferred where the proportion of patients at high risk for re-bleeding increased. This suggests that using iv PPI in high-risk patients may significantly reduce the subsequent endoscopy burden and therefore offset the cost of the medication.

The review in section 8.2 found PPI's to be clinically effective in improving outcomes in upper GI bleeds when given post-endoscopy. The strategy of combining selective second look and PPI was not included in this analysis by Spiegel et al., but when considering both their results and that from the clinical review in section 8.2, this strategy seems likely to be the most cost-effective in patients with peptic ulcer haemorrhage in whom successful endoscopic haemostasis was performed. Administration of oral PPI was not a comparator in this economic analysis.

Table 62: Routine second look endoscopy versus routine clinical follow up – Economic summary of findings

Study comparators for [143] [a] [b]	Total mean cost per patient [c] [d]	Total health effect [e]	Cost Effectiveness	Uncertainty [f]
Clinical follow-up [g]	£4976	81%	Selective second look endoscopy at 24hrs only in patients at high risk for re-bleeding (as identified by the Baylor Bleeding Score) is the base case dominant strategy, being more effective and less costly than the other strategies.	The conclusion of the base case was sensitive to variations in the probability of re-bleeding and proportion of patient with high-risk Baylor Bleeding Score: Clinical follow-up + PPI dominates when its probability of re-bleeding <9% (base case 13.2%; range in the literature 0-29%); or when the proportion of high-risk patients >66% (56% in the base case and literature).
Clinical follow-up + PPI [h]	£4643	87%		
Second look for all patients [i]	£5548	89%		
Selective second look [j]	£4549	91%		

(a) The model was based on systematic reviews of published literature. When there was a range of data available, estimates were selected that would favour clinical follow-up.

(b) Probabilities incorporated to the analysis: re-bleeding for patients in compared strategies; repeat haemostasis in patients with clinically evident re-bleeding; repeat haemostasis in patients with subclinical re-bleeding; endoscopy induced perforation or uncontrollable bleeding; preoperative death; and proportion of patients with high-risk Baylor Bleeding Score.

(c) 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, consultation, surgeon's fee and anaesthesiologist's fee); cost of inpatient gastroenterologist follow-up visit; and cost of inpatient surgical follow-up visit. It was assumed a daily gastroenterologist follow-up when a patient is hospitalised and, when a patient required surgery, it was assumed an initial surgical consultation followed by a daily follow-up visit by the surgeon while hospitalised. Patients with re-bleeding after discharge were readmitted to receive repeat upper endoscopy (10% of re-bleeding happened after 72 hours according to the 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.

(d) Published costs in USD were converted in pound sterling using 2009 Purchasing Power Parities

(e) Proportion of patients with prevented re-bleeding, surgery, or death.

(f) A one-way sensitivity analyses, two-way sensitivity analyses, and a probabilistic sensitivity analysis (2nd order Monte Carlo).

(g) Clinical follow-up: follow patients clinically after haemostasis and repeat endoscopy only in patients with evidence of re-bleeding;

(h) Clinical follow-up + PPI: administer iv PPI after haemostasis and repeat endoscopy only in patients with clinical signs of re-bleeding; I.V. PPI therapy: equivalent of 80mg bolus followed by 8mg/h for 72 hours.

(i) 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;

(j) Selective second look: perform selective second look endoscopy at 24hrs only in patients at high risk for re-bleeding as identified by the Baylor Bleeding Score.

8.3.5 Evidence statements

8.3.5.1 Clinical evidence

Routine second look / repeat endoscopy versus usual care

Mortality (30 day or less)

For mortality five RCTs comprising 979 patients with upper GI bleeding showed no statistical / clinical difference between routine second look (with and without re-treatment) and routine follow-up (VERY LOW QUALITY).

Re-bleeding (7 day or 30 day follow-up)

Three studies with a total of 403 participants indicated that the lower rate of 7 day re-bleeding associated with routine second look (with or without treatment) did not reach statistical / clinical significance (LOW QUALITY).

Three studies with 770 patients with non-variceal upper GI bleeding showed that the rate of re-bleeding at 30 day follow up was significantly lower in the routine second look / repeat endoscopy group compared to usual care follow-up (LOW QUALITY). However, it is unclear whether this represents a clear clinical benefit.

Surgery for continued bleeding

Five RCTs comprising 979 patients with upper GI bleeding showed a non-significant difference with a reduced need for surgical intervention in favour of routine second look (with and without re-treatment) compared to usual care follow-up (VERY LOW QUALITY).

Length of hospital stay

One study with 104 patients showed that the shorter average length of hospital stay favouring the routine second look / repeat treatment group compared to the usual care follow-up was not statistically / clinically significant (LOW QUALITY).

Blood transfusion requirements

Four studies comprising 774 participants showed no statistical / clinical difference in blood transfusion requirement for patients receiving routine second look endoscopy (with or without repeat treatment) compared to usual care follow-up (LOW QUALITY).

Endoscopic re-treatment versus surgery (in patients who re-bleed)

Mortality

One study with 92 participants showed that mortality was not statistically / clinically different in the repeat endoscopy compared to the surgery group (LOW QUALITY).

Failure to achieve haemostasis

In one study with 92 patients, fewer patients achieved haemostasis in the endoscopy group compared to the surgery group which was, however, not a significant difference (statistically and clinically) (LOW QUALITY).

Re-bleeding

In one study with 92 patients, fewer patients experienced re-bleeding in the endoscopy group compared to those receiving surgery which was, however, not a significant difference (statistically and clinically) (LOW QUALITY).

Salvage surgery

In one study with 92 patients significantly more patients were in need of salvage surgery in the endoscopy group compared to those who had surgery in the first instance, a difference that was statistically significant. The size of this effect of surgery over endoscopy was large enough to show appreciable clinical benefit (HIGH QUALITY).

Rate of treatment complications

Evidence from one study with 92 patients indicated that there were statistically / clinically significantly fewer treatment complications in the endoscopy compared to the surgery group (LOW QUALITY).

Treatment when first line endoscopic procedure fails (embolization versus surgery)

Evidence from 5 observational studies (not pooled) with 70, 91, 46, 97 and 88 participants respectively, was used for the comparison between embolisation and surgery for patients in whom first line treatment failed to achieve haemostasis:

Mortality

All six studies (with 70, 91, 46, 97, 74 and 88 participants respectively) showed no significant difference between embolisation and surgical treatment for mortality [VERY LOW QUALITY].

Failure to achieve haemostasis

Four studies reported failure to achieve haemostasis (with 91, 46, 97 and 88 participants respectively) and all showed more patients achieving haemostasis in the surgery group, yet this was not a large enough effect to show a significant difference between embolisation and surgical treatment [VERY LOW QUALITY].

Re-bleeding (divided by follow-up length

One study with 97 participants reported both short term and long term re-bleeding. At 3 day follow-up re-bleeding was significantly less frequent in the surgery group whereas at 30 day follow-up re-bleeding there was no significant difference between the embolisation and surgery groups [VERY LOW QUALITY].

A further 4 studies with 70, 74, 88 and 46 patients reported the outcome re-bleeding at 30 day follow up and each showed a higher rate of re-bleeding in the embolisation group yet this was not large enough in 3 of the studies to indicate a significant difference between embolisation and surgery. In the fourth study there was a statistical difference but it was unclear whether it was a large enough difference to indicate clear clinical benefit favouring surgery over embolisation [VERY LOW QUALITY].

Salvage treatment (usually additional surgery)

Three studies with 70, 74 and 91 subjects reported the rate of salvage treatment, and showed that in one study more salvage treatments were needed in the surgery group whereas the other two studies reported more additional treatment needed in the embolisation group. In all 3 studies the effects were not large enough to show a clear benefit for either embolisation or surgery.

Blood transfusion requirements

Two studies with 70 and 88 patients provided data for the outcome of transfusion requirements and in one study those in embolisation needed an average higher amount of blood transfusion whereas the opposite pattern was seen in the second study. Neither effect was large enough to indicate significant benefit [VERY LOW QUALITY].

Length of hospital stay

Three studies with 70, 74 and 88 patients provided data for the outcomes length of hospital stay and each reported no significant difference in the average length of stay between embolisation and surgery groups [VERY LOW QUALITY].

Rate of treatment complications

Evidence from two studies with 91 and 88 patients showed lower rates of complications in the embolisation group yet this effect was only large enough in one study to be statistically yet not clinically significant [VERY LOW QUALITY].

8.3.5.2 Health economic evidence

The most likely cost-effective strategy in patients with peptic ulcer haemorrhage in whom successful endoscopic haemostasis was performed is to administer PPI and perform selective second look endoscopy at 24 hours only in patients at high risk for re-bleeding as identified by the Baylor Bleeding Score.

There is no economic evidence to inform whether repeat endoscopy is more cost effective than surgery or emobolisation /angiography in patients who re-bleed after the *first* endoscopic therapy has failed.

There is no economic evidence to inform whether surgery is more cost effective than emobolisation /angiography when endoscopic therapy fails in patients with non variceal UGIB.

8.3.6 Recommendations and link to evidence

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

Recommendations	• **Consider a repeat endoscopy, with treatment as appropriate, for all patients at high risk of re-bleeding, particularly if there is doubt about adequate haemostasis at the first endoscopy.**
Relative values of different outcomes	Mortality is clearly the most important outcome, but the GDG were not expecting, nor did they find, any difference in mortality based on routine performance of a second endoscopy. The debate centred around risk and identification of re-bleeding within the first 30 days of endoscopy, with a reduction in those undergoing a second endoscopy. There were no other significant differences, although in general the trends favoured a second endoscopy for most outcomes.
Trade off between clinical benefits and harms	The potential benefit of a repeat endoscopy is the early identification of re-bleeding (or continued bleeding). Endoscopy is a generally safe procedure, and therefore the potential harm involved in this question is principally that related to delay in treating any re-bleeding.
Economic considerations	The only economic paper available suggested that a routine second look endoscopy was not cost-effective, but that selective elective re-endoscopy was worthwhile in patients in whom the risk of re-bleeding was high (based on a Baylor score, which is not used in the UK but which the GDG felt to be equivalent to a high risk patient using the

	post-endoscopy Rockall score). The study was performed in the USA and is therefore not directly transferable to a UK population. The GDG also noted that the evidence dealt with re-endoscopy within 24 hours. To provide this would necessitate availability of endoscopy services at weekend, and this is not routinely available in the UK at present. The set-up cost of a recommendation in favour of routine re-endoscopy would be considerable and not justified by the current evidence However, the GDG also noted that provision of endoscopy services is an important consideration for other recommendations within this guideline (Chapter 7). If endoscopy service provision increases in line with other recommendations in the guideline, the incremental cost of providing second look endoscopy will be less. In light of the cumulative evidence and recommendations made in previous chapters, the GDG came to a consensus that the increased levels of endoscopy service required to enable a second look endoscopy in high risk patients was likely to be cost effective.
Quality of evidence	By GRADE criteria the evidence on this question was low to moderate. The GDG felt that these studies had been reasonably well performed, but also noted that they were several years old and that techniques for arresting bleeding at endoscopy have improved in recent years. The chances of being able to secure haemostasis at first endoscopy are therefore greater that when these studies were performed, which would tend to reduce the benefit of a routine second procedure.
Other considerations	The GDG were not unanimous in their assessment of this evidence, some feeling that the reduction in re-bleeding and the health economic benefits should lead to a positive recommendation in favour of second-look endoscopy, others feeling that the benefits were not sufficient to justify a considerable change in current practice (at present, unless a patient has clearly bled again, repeat endoscopy would only be arranged if the endoscopist feels that the first procedure is unlikely to have secured anything more than temporary haemostasis). They agreed to couch a recommendation in terms which encourages a more pro-active approach in patients at high risk of re-bleeding, but without making this obligatory.

In patients with non-variceal upper gastrointestinal bleeding who re-bleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolization / angiography to stop bleeding?

Recommendations	• **Offer a repeat endoscopy to patients who re-bleed with a view to further endoscopic treatment or emergency surgery.**
Relative values of different outcomes	There was only one clinical study to consider for this question, and it showed no significant difference for most outcomes when second look endoscopy (with attempt to stop bleeding where possible) was compared with proceeding straight to surgery. However, the need for salvage surgery was greater in the group having a second endoscopy,

	whereas overall significant complications were greater in the surgical group. The GDG found both of these outcome measures difficult to evaluate. Thirteen patients in the repeat endoscopy group subsequently went to surgery, yet only 4 had re-bleeding or failure to secure haemostasis; it is unclear why the other nine needed surgery. It was also not clear in either group to what extent the reported complications resulted from the severity of the bleeding as opposed to resulting from the procedures per se.
Trade off between clinical benefits and harms	The GDG agreed that, when weighing up whether to have a second attempt at an endoscopic procedure or to proceed to surgery, individual patient factors are crucial. An experienced endoscopist will be able to estimate the chances of success at a second procedure, and co-morbidity will be important in assessing the risk of surgical anaesthesia.
Economic considerations	There was no published economic evidence to inform this question. The GDG felt that a comparison of the cost of an endoscopy versus surgery based on standard NHS reference costs was not helpful in this case as it was likely to underestimate the cost of the repeated procedure in patients whose first has not succeeded; this group are inevitably more unwell than average and will have a longer hospital stay, driving associated cost upwards.
Quality of evidence	Only a single study was available; there is uncertainty about some of the outcome measures (see paragraph above).
Other considerations	The GDG felt that the formal evidence cannot capture some of the important intangible factors that might influence decision making by an experienced endoscopist. Such an operator will have a reasonable idea, based on the situation at first endoscopy and how well he/she felt that they had been able to identify and address the source of haemorrhage, whether a repeat endoscopy is likely to help. On balance, and allowing for differences in experience of the initial operator, they felt that the safest recommendation would be one which pointed towards a second endoscopy, but that the wording should not rule out proceeding straight to surgery.

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

Recommendations	• **Offer interventional radiology to unstable patients who re-bleed after endoscopic treatment. Refer urgently for surgery if interventional radiology is not promptly available.**
Relative values of different outcomes	A difference was noted in re-bleeding rates, in favour of surgery rather than embolisation under radiological guidance, but all other outcome measure showed no difference between the two treatment modalities. The GDG did not feel that this outcome alone, measured at 3-days post-

	procedure, was sufficient evidence to prompt a clear recommendation.
Trade off between clinical benefits and harms	The GDG noted that, even if the slight difference in favour of surgery was accepted, surgical procedures are not advisable in some circumstances because the patient poses too great an anaesthetic/operative risk.
Economic considerations	No health economic evidence was available for this question.
Quality of evidence	The studies reviewed were all observational, with all the well recognised problems that follow with non-controlled data. The GDG recognised that a truly randomised study on this question would be very difficult to perform because the two procedures are so different and each would appear to have definite advantages in certain circumstances, and because skill and experience of the radiologists and surgeons would have to be taken into account.
Other considerations	Given the absence of any good quality controlled evidence, the GDG debated the practical issues which would follow from any recommendation. They again noted that some people were poor operative risks, for a variety of possible reasons, and that successful embolisation was potentially the safer procedure. There was a strong consensus view that this should be tried first (encompassing all professional groups and the patient representatives). However, at present not all hospitals can offer appropriate interventional radiology. The GDG did not wish to make a recommendation which would prevent timely surgery when an appropriately skilled interventional radiologist was not available, and formed a recommendation which emphasises the need for prompt action whichever treatment modality is to be employed.

9 Management of variceal bleeding

9.1 Antibiotic prophylaxis

9.1.1 Introduction

The hospital mortality of patients presenting with acute variceal bleeding is closely related to the severity of liver disease, rising to 30% in those with Childs-Pugh cirrhosis (Grade C)[d] . Bleeding can be very severe and, particularly in patients with advanced cirrhosis, cause renal failure that has a very poor prognosis. These patients are also prone to develop infection. This is related to defective immunological function and to trans-location of bacteria from the gastrointestinal tract into the peritoneal cavity leading to spontaneous bacterial peritonitis. Infection has adverse effects on renal function and commonly precipitates hepatorenal failure, characterised by oligurea, sodium and fluid retention and death.

Interest has therefore focused upon the potential benefit of prophylactic broad spectrum antibiotic administration to patients who present with variceal bleeding. The benefits of preventing infection, particularly spontaneous bacterial colonisation, have to be balanced against the risks of complications such as Clostridium Difficile infection and development of resistant bacterial species. The choice of antibiotic and duration of therapy are currently unclear.

9.1.2 Clinical question and methodological introduction

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

Table 63: PICO Characteristics of clinical question

Clinical Methodological Introduction	
Population:	Patients with likely variceal bleeding
Intervention:	Antibiotics
Comparison:	Placebo or ‘on demand’ treatment
Outcomes:	• Mortality • Re-bleeding • Length of hospital stay • Transfusion requirements • Any infections • Bacteraemia • Spontaneous bacterial peritonitis • Pneumonia • Adverse events: resistance and clostridium difficile

d Childs-Pugh cirrhosis is a scoring system that allows us to assess the grade of cirrhosis and thus make a prognostic evaluation of the severity of the disease and obtain prognostic values in regard to mortality.

9.1.3 Clinical evidence review

We searched for randomised control trials comparing the effectiveness of antibiotics with placebo or usual care ('on demand' antibiotics) as prophylactic treatment for patients with likely or confirmed variceal bleeding (see flowchart in Appendix E for study selection).

Nine randomised control studies were identified and one Cochrane review was cross-referenced [70,144]. A variety of antibiotics was used (see Table 64: Characteristics of included studiesTable 64). The aim of all papers was to assess whether antibiotics were an effective means of preventing infections and improving mortality in patients with likely variceal bleeding (see Appendix F for evidence tables and Appendix H for forest plots). Levels of adverse events (resistance and c-diff) were searched for but were not reported in the included studies.

Table 64: Characteristics of included studies

STUDY	INTERVENTION / COMPARISON	POPULATION	OUTCOMES	COMMENTS
Soriano, 1992[145]	Number randomised: N=64 antibiotic (oral norfloxacin 400 mg twice/day during seven days) N=64 control group	Patients with cirrhosis and gastrointestinal haemorrhage. 20% of patients Child-Pugh grade C	Presence of infections, mortality (causes of), encephalopathy, re-bleeding, transfusion requirements, need for surgery, length of hospitalisation	Per protocol analysis but acceptable drop out rates <20%
Rolando, 1993[146]	N=47 antibiotic group (i.v. imipenem + cilastin, 500 mg before and after the sclerotherapy); N= 50 control group; 3 patients were excluded due to protocol violation, but not specified which group they stemmed from	Patients with bleeding oesophageal varices	Bacterial infections, mortality	Possible baseline imbalance – but no statistics provided; sponsored by drug company
Blaise, 1994[147]	Randomised: N=58 antibiotic group (intravenous + oral ofloxacin, 400 mg/day, 10 days; amoxicillin + clavulanic acid (bolus, 1g) before each endoscopy procedure); N=59 control (on demand) group	Patients with cirrhosis hospitalised in intensive care units for upper gastrointestinal haemorrhage. >70% of patients Child-Pugh grade C	Occurrence of infections, mortality	Per protocol analysis (>20% of randomised patients excluded)
Selby,	Numbers	Patients with	Presence of infections,	Follow-up period only

STUDY	INTERVENTION / COMPARISON	POPULATION	OUTCOMES	COMMENTS
1994[148]	randomised: N=19 antibiotic group (intravenous cefotaxime, 1 g immediately before sclerotherapy) N=20 control group	bleeding oesophageal varices. 33% of patients Child-Pugh grade C	mortality	24 hrs
Pauwels, 1996[149]	Numbers randomised: antibiotic group N=41 (intravenous + oral ciprofloxacin 400mg per day, amoxicillin-clavulanic acid 3g per day, until three days after cessation of haemorrhage) Control group N=40	Patients with cirrhosis admitted to hospital because of gastrointestinal haemorrhage. Only those with Child-Pugh grade C or patients with less severe cirrhosis, but who rebled, were randomised. >60% of patients Child-Pugh grade C	Bacterial infections, 4 week mortality, length of ICU stay	Per protocol analysis, but for some outcomes numbers could be derived. The authors included a low risk (Child-Pugh grade A/B without re-bleeding) control group, but those patients were not randomised and therefore were not included in this analysis
Hsieh, 1998[150]	N=60 antibiotic (oral ciprofloxacin, 1 g/day, 7 days); N=60 Placebo	Patients with cirrhosis and upper gastrointestinal bleeding. >38% of patients Child-Pugh grade C	Primary endpoint: rate and type of infections Secondary outcomes: mortality, re-bleeding, length of hospital stay, surgery, transfusion requirements	Intention to treat analysis
Lin, 2002	N=47 antibiotic group (i.v. cefazolin at 1 gram per 8 hours); N=50 control group (antibiotics when needed)	Cirrhotic patients admitted because of UGI bleeding. 21% of patients Child-Pugh grade C	patients with infections, type of infections, length of hospital stay, mortality	Intention to treat analysis
Hou, 2004[151]	Numbers randomised: N=68 prophylactic group (i.v. ofloxacin 200 mg every 12h for 2 days and followed by oral ofloxacin 200 mg every 12h for 5	Patients with endoscopy proven gastro-oesophageal variceal bleeding. 22% Child-Pugh grade C.	Re-bleeding, rate of infection, mortality	Per protocol analysis (>20% of randomised patients excluded)

STUDY	INTERVENTION / COMPARISON	POPULATION	OUTCOMES	COMMENTS
	days) N=87 on-demand group			
Jun, 2006[152]	Numbers randomised: N=76 in prophylactic group (i.v. cefotaxime 2 gram q 8 hr for 7 days); N=76 in the 'on-demand' group	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 (Mean Child-Pugh treatment 8.7 [1.9] mean score control 8.3 [2.1])	Primary outcome: re-bleeding Secondary endpoints: treatment failure, infection rates, transfusion requirements, total hospital stay, mortality	Per protocol analysis (>20% of randomised patients excluded), Mean follow-up about 22 months

Comparison of antibiotic prophylaxis versus control treatment (placebo / 'on demand')

Table 65: GRADE summary table for antibiotics versus control (outcome rows in lighter shades with indented and italicized names represent subgroups of an analysis)

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Antibiotics Frequencies (%), Means (SD) or Medians (range)	Placebo / usual care Frequencies (%), Means (SD) or Medians (range)	Relative Risk (95% CI)	Absolute effect, Mean difference (95% CI)	
All cause Mortality*										
9 studies: Soriano 1992 [145], Rolando 1993 [146], Blaise 1994 [147], Selby 1994 [148], Pauwels 1996 [149], Hsieh 1998 [150], Lin 2002 [153], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	84/479 (17.5%)	110/507 (21.7%)	RR 0.81 (0.63 to 1.03)	41 fewer per 1000 (from 80 fewer to 7 more)	VERY LOW
All cause mortality by follow-up - Early mortality (up to 7 days / in hospital)										

Quality assessment						Summary of findings				
4 studies: Rolando 1993 [146], Selby 1994 [148], Lin 2002 [154], Hou 2004 [151]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	16/181 (8.8%)	25/207 (12.1%)	RR 0.70 (0.39 to 1.23)	36 fewer per 1000 (from 74 fewer to 28 more)	VERY LOW
All cause mortality by follow-up - Late mortality (30 days)										
6 studies: Soriano 1992 [145], Bliase 1994 [147], Pauwels 1996 [149], Hsieh 1998 [150], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	37/366 (10.1%)	53/387 (13.7%)	RR 0.71 (0.49 to 1.04)	40 fewer per 1000 (from 70 fewer to 5 more)	VERY LOW
All cause mortality by follow-up - End of study mortality										
Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	36/144 (25%)	37/163 (22.7%)	RR 1.07 (0.72 to 1.59)	16 more per 1000 (from 64 fewer to 134 more)	VERY LOW
Infection related Mortality										
6 studies: Soriano 1992 [145], Bliase 1994 [147], Pauwels 1996 [149], Lin 2002 [153], Hou 2004 [151], Jun 2006	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	6/353 (1.7%)	15/377 (4%)	RR 0.47 (0.20 to 1.11)	21 fewer per 1000 (from 32 fewer to 4 more)	VERY LOW

Quality assessment						Summary of findings				
[152]										
End of study re-bleeding										
Soriano 1992 [145], Bliase 1994 [147], Pauwels 1996 [149], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	75/306 (24.5%)	104/327 (31.8%)	RR 0.77 (0.60 to 0.98)	73 fewer per 1000 (from 6 fewer to 127 fewer)	VERY LOW
Re-bleeding (up to 7 days)										
Hsieh 1998 [150], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	8/204 (3.9%)	31/223 (13.9%)	RR 0.31 (0.15 to 0.65)	96 fewer per 1000 (from 49 fewer to 118 fewer)	LOW
Patients with infections										
8 studies: Soriano 1992 [145], Bliase 1994 [147], Selby 1994 [148], Pauwels 1996 [149], Hsieh 1998 [150], Lin 2002 [153], Hou 2004 [151], Jun	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	45/432 (10.4%)	150/457 (32.8%)	RR 0.31 (0.23 to 0.42)	226 fewer per 1000 (from 190 fewer to 253 fewer)	LOW

Quality assessment						Summary of findings				
2006 [152]										
Bacteraemia										
9 studies: Soriano 1992 [145], Rolando 1993 [146], Bliase 1994 [147], Selby 1994 [148], Pauwels 1996 [149], Hsieh 1998 [150], Lin 2002 [153], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	15/479 (3.1%)	73/507 (14.4%)	RR 0.24 (0.14 to 0.39)	109 fewer per 1000 (from 88 fewer to 124 fewer)	LOW
Spontaneous bacterial peritonitis										
8 studies: Soriano 1992 [145], Rolando 1993 [146], Bliase 1994 [147], Selby 1994 [148], Pauwels 1996 [149], Hsieh 1998	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	10/432 (2.3%)	38/457 (8.3%)	RR 0.28 (0.14 to 0.55)	60 fewer per 1000 (from 37 fewer to 72 fewer)	LOW

Quality assessment						Summary of findings				
[150], Hou 2004 [151], Jun 2006 [152]										
Pneumonia										
5 studies: Rolando 1993 [146], Pauwels 1996 [149], Hsieh 1998 [150], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	10/291 (3.4%)	14/314 (4.5%)	RR 0.79 (0.38 to 1.63)	9 fewer per 1000 (from 28 fewer to 28 more)	VERY LOW
Length of hospital stay (Better indicated by lower values)										
6 studies: Soriano 1992 [145], Bliase 1994 [147], Pauwels 1996 [149], Hsieh 1998 [150], Lin 2002 [153], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	Total N=345 (for means see subgroups below	Total N=350 (for means see subgroups below	-	MD 0.5 lower (0.85 to 0.16 lower)	VERY LOW
Length of hospital stay - ICU stay (Better indicated by lower values)										
2 studies: Bliase 1994 [147], Pauwels 1996 [149],	randomised trials	very serious[a]	serious[c]	no serious indirectness	Serious[b]	N=58, 7.1 (2); N=40, 6.5 (0.9)	N=59, 6.7 (1.2); N=41, 7.4 (1.1)	-	MD 0.45 lower (0.8 to 0.09 lower)	VERY LOW
Length of hospital stay - Total stay (Better indicated by lower values)										

Quality assessment						Summary of findings				
4 studies: Soriano 1992 [145], Hsieh 1998 [150], Lin 2002 [153], Jun 2006 [152]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	N=64, 13.5 (9.2); N=60, 19 (12); N=47, 10.2 (2.4); N=76, 13.6 (9.7)	N=64, 14.4 (10.9); N=60, 26 (18); N=50, 11.4 (7.8); N=76, 14.8 (10)	-	MD 1.61 lower (3.17 to 0.05 lower)	VERY LOW
Transfusion requirements (Better indicated by lower values)										
3 studies: Hsieh 1998 [150], Hou 2004 [151], Jun 2006 [152]	randomised trials	very serious[a]	serious[c]	no serious indirectness	no serious imprecision	N=60, 9.1 (7.4); N=68, 1.4 (0.9); N=76, 1.6 (1.4)	N=60, 10 (15); N=87, 2.8 (2.3); N=76, 2.2 (1.5)	-	MD 0.95 lower (1.3 to 0.61 lower)	VERY LOW

[a] *The 9 RCTs varied in quality. The majority of studies had at least 2 serious limitations. None of the studies had clear allocation concealment, there was no or unclear blinding in all of the studies, and most did not present intention to treat analysis. Blinding in this context is not considered serious for mortality or re-bleeding since blinding is unlikely to affect these outcomes (for other outcomes it is unclear whether blinding introduces bias and those were downgraded accordingly). Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly. Since most studies suffer from at least 2 serious limitations this section was downgraded twice.*

[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

[c] *There was evidence of heterogeneity.*

**Subgroup analysis did not reach significance*

9.1.4 Health economic evidence

One study [149] was identified that included the relevant comparison. This is summarised in the economic evidence profile below. See also Evidence Table G.5.2 in Appendix G. There were no excluded studies.

Table 66: Systemic antibiotic prophylaxis versus placebo – Economic study characteristics

Study	Limitations	Applicability	Other comments
Pauwels et al (1996)	Potentially serious limitations[a]	Partially applicable [b]	Analysis developed from a French perspective and over a 10-day time horizon

(a) Based on a RCT, the cost of antibiotic prophylaxis therapy was assessed over a 10-day time horizon. This short time horizon limits the measurement of later cost components related to the disease or interventions. Source of cost data was not reported and no breakdown of costing provided. Only one source for treatment effect used. No sensitivity analysis was performed.

(b) RCT developed from a French intensive care unit perspective between December 1989 and March 1992 , assessing a relevant population of patients, and reporting the length of stay in intensive care unit, the rates of infection, sepsis, and mortality. Only the cost of antibiotic therapies was reported. Some uncertainty about applicability of French estimates of resource use and relatively old cost estimates (assumed 1996). Source for cost component not reported. No quality of life assessment was performed. Population was cirrhotic patients that authors considered were at high risk of infection (with Child-Pugh's class C or re-bleeding).

Outcomes from the Pauwels 1996 RCT show that, from an intensive care unit perspective, offering antibiotic prophylaxis improves health outcomes and is cost saving compared with no antibiotic prophylaxis. This conclusion was based on the cost of antibiotic treatment being significantly lower for the treatment group as antibiotic use was higher when patients were not given prophylaxis.

The length of hospital stay was not significantly different between groups, but a trend was present favouring the prophylaxis group. A higher proportion of patient died in the control group, but this difference did not reach statistical significance. Rates of infection significantly favoured the prophylaxis group.

Table 67: Systemic antibiotic prophylaxis versus placebo – Economic summary of findings

Study	Incremental cost, mean per patient [d]	Incremental effects (calculated per 100 patients)	Cost effectiveness	Uncertainty
Pauwels et al (1996) Antibiotic prophylaxis [b] versus no antibiotic prophylaxis [c]	Antibiotic prophylaxis: £107 ± 27 Placebo: £133 ± 40 Incremental: -£26 (p<.01)	40 fewer patients with infections (p<.001) 29 fewer patients with sepsis syndrome (P<.01) 10 fewer patients died by 4 weeks (ns). 0.9 fewer days in ICU [mean per patient](ns)	Prophylaxis antibiotic therapy dominates no antibiotic prophylaxis, being more effective and less costly.	No sensitivity analysis performed.

Note: Units reported as the mean ± standard deviation

Abbreviations: ICU = Intensive Care Unit; ns = non significant difference

(c) (e) 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

(d) Patients received prophylaxis antibiotic with amoxicillin and clavulanic acid 1g/200mg three times daily and ciprofloxacin 200mg twice daily. This therapy was given from admission or re-bleeding 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 creatinine level >200mmol/L, doses were reduced to amoxicillin plus clavulanic acid 500mg/100kg twice daily and ciprofloxacin 200mg once daily. In case of re-bleeding 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.

(e) When an infection was suspected, the initial empiric antibiotic treatment was ciprofloxacin and a combination of amoxicillin and clavulanic acid.

(f) Published costs in USD were converted in pound sterling using Purchasing Power Parities.

9.1.5 Evidence statements

9.1.5.1 Clinical evidence

All cause mortality

9 studies comprising 986 participants with variceal upper gastrointestinal bleeding showed a non-significant difference with a lower rate of mortality in patients receiving antibiotics compared to those receiving placebo (VERY LOW QUALITY).

These 9 studies were then divided into 3 subgroups according to length of follow-up:

- Up to 7 day mortality: 4 studies comprising 388 participant showed no statistical / clinical significant difference in mortality in the antibiotic compared to the control group (VERY LOW QUALITY).
- 30 day mortality: 6 studies with 902 patients provided showed a non-significant difference with a lower rate of mortality in patients receiving antibiotics compared to those receiving placebo (VERY LOW QUALITY).
- > 30 day or end of study mortality: 2 studies with 207 patients provided evidence and when pooled no statistical / clinical significant difference for 30 day mortality between antibiotic and control group was found (VERY LOW QUALITY).

Infection related mortality

- 7 studies comprising 879 participants with variceal upper gastrointestinal bleeding showed a non-significant difference with a lower rate of infection-related mortality in patients receiving antibiotics compared to those receiving placebo (VERY LOW QUALITY).

End of study re-bleeding

5 studies comprising 633 participants provided evidence for statistical but not clinically significant difference for a lower rate of total re-bleeding in the antibiotic compared to the control group (VERY LOW QUALITY).

Early re-bleeding (<7 days)

3 studies comprising 427 participants found statistical and clinical difference for a lower rate of total re-bleeding (7 day) in the antibiotic compared to the control group (LOW QUALITY).

Length of hospital stay

6 studies comprising 695 participants with variceal upper gastrointestinal bleeding found that there was statistical but not clinically significant difference for a shorter length of hospital stay in the antibiotic group compared to the control group (VERY LOW QUALITY).

These 6 studies were then divided into 2 subgroups:

- For ICU stay, 2 studies comprising 198 participant provided evidence for a statistical but not clinically significant difference for shorter stay in the antibiotic group. However, the two studies reported opposite patterns of results (VERY LOW QUALITY).
- For total hospital stay: 4 studies with 497 patients provided evidence for statistical but not clinically significant difference for shorter stay in the antibiotic group. However, the two studies reported opposite patterns of results (VERY LOW QUALITY).

Blood transfusion requirements

3 studies with 427 patients provided evidence for this outcome and found statistically and clinically significant difference between antibiotic and the control group with a lower amount of red blood cell unit transfusions in the antibiotic group (VERY LOW QUALITY).

Any infections

8 studies with 889 patients with variceal bleeding provided evidence for this outcome and found statistically and clinically significant difference with lower rates of infections in the antibiotic group compared to the control group (LOW QUALITY).

Bacteraemia

8 studies with 986 patients with variceal bleeding provided evidence for this outcome and found statistically and clinically significant difference with lower rates of bacteraemia in the antibiotic group compared to the control group (LOW QUALITY).

Spontaneous bacterial peritonitis

8 studies with 889 patients with variceal bleeding provided evidence for this outcome and found statistically and clinically significant difference with lower rates of spontaneous bacterial peritonitis in the antibiotic group compared to the control group (LOW QUALITY).

Pneumonia

5 studies with 605 patients with variceal bleeding provided evidence for this outcome and found no statistically or clinically significant difference for a difference in rate of pneumonia between the antibiotic and the control group (VERY LOW QUALITY).

9.1.5.2 Health economic evidence

Prophylactic administration is likely to be both clinically effective and cost saving in patients with advance liver disease who present with acute upper gastrointestinal bleeding, accepting that the relevant economic analyses have only partial applicability and potentially serious limitations.

9.1.6 Recommendations and link to evidence

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

Recommendations	• **Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding.**
Relative values of different outcomes	Mortality particularly that related to infection was considered the most important outcome. Several studies reported mortality after different lengths of follow-up. The GDG considered early mortality more relevant to the question of whether to offer antibiotics in this setting.

	Later mortality was reasoned to reflect the severity of underlying liver disease more than the effectiveness of antibiotic therapy. Although not statistically significant there was a trend towards lower mortality in patients receiving antibiotics with greater impact seen in earlier mortality (less than 30 days). A similar trend was seen for infection-related mortality but the event rate was low for this outcome. A statistically and clinically significant impact was seen for re-bleeding and blood transfusion requirements in patients receiving prophylactic antibiotics. Episodes of infection were less common in patients receiving prophylactic antibiotics. When analysed by type of infection, it was apparent that there was a significant reduction in the incidence of bacteraemia and spontaneous bacterial peritonitis. Statistically and clinically significant reductions were seen in both the length of ITU and total hospital stay.
Trade off between clinical benefits and harms	The GDG felt that the evidence demonstrated a significant beneficial effect for prophylactic antibiotic therapy for patients with variceal bleeding. However, concern was expressed that widespread use of antibiotic therapy could lead to increased rates of antibiotic resistance. Indeed there was some anecdotal evidence from some clinicians that this was occurring. Additionally GDG members worried that increasing the prevalence of antibiotic use in this patient group risked a corresponding rise in the prevalence of Methicillin-resistant *staphylococcus aureus* (MRSA) and *Clostridium difficile* infections. Although these were not reported as specific outcomes in any of the trials evaluated, the GDG was somewhat reassured that the rates of significant infections with these organisms were unlikely to be greatly increased in the studies since these showed lower overall rates of infections and duration of hospital stay with prophylactic antibiotic use. Additionally it was felt that overall the number of patients admitted with variceal bleeding was small when considered in the context of all patients admitted to hospital on antibiotic therapy. Nonetheless it was felt a watchful eye needed to be kept on the situation.
Economic considerations	A randomised controlled trial with a cost component was identified. The study was felt to have potentially serious limitations, particularly with randomisation. Additionally the study did not include a quality of life assessment and only considered the antibiotic cost. This and the short timeframe meant potential benefits of antibiotic prophylaxis noted in the clinical review may not have been fully captured. The GDG also noted that this relatively old study did not explore the potential cost associated with antibiotic resistance. The study supported the cost effectiveness of prophylactic antibiotic administration to patients with Child's C cirrhosis, considered at high risk of infection, due to reduced incidence of infection and associated costs of antibiotic treatment. The GDG also noted antibiotic prophylaxis reduced the incidence of re-bleeding and the associated costs of transfusion and hospital stay. Overall it was felt that the use of antibiotics in this setting was likely to

	be cost effective and even cost saving.
Quality of evidence	The GRADE quality for the reviewed outcomes was generally low to very low. However, the GDG felt that these studies were well conducted given the difficulties of research in this acutely ill patient group.
Other considerations	The GDG considered whether antibiotic therapy would be appropriate in patients with chronic liver disease with non-variceal upper gastrointestinal haemorrhage. It was concluded that because non-variceal bleeding is unrelated to portal hypertension, this extrapolation has no biological plausibility and could not be made. The GDG also discussed whether the available evidence was sufficient to recommend either a specific prophylactic antibiotic or the optimum duration of antibiotic therapy. It was felt that this was not possible and could constitute a possible area for future research. The GDG noted that current practice is to prescribe broad spectrum antibiotics for approximately five days covering gram-negative bacterial infection in patients with probable variceal bleeding. It was accepted that the choice of agent would need to be varied depending upon local patterns of antibiotic resistance.

9.2 Band Ligation

9.2.1 Introduction

The most important complication of portal hypertension is the development of bleeding varices. Portal hypertension is usually due to cirrhosis (most commonly from alcohol abuse, chronic viral hepatitis or obesity), but is occasionally due to portal vein thrombosis or even more rarely from hepatic vein thrombosis or infections such as Schistosomiasis. Bleeding may be extremely severe and the severity of bleeding relates to magnitude of the portal pressure and the severity of underlying liver disease. Whilst this Chapter focuses upon stopping active variceal bleeding and prevention of re-bleeding, it is important to emphasise that other aspects of liver failure including renal failure, salt and water retention, sepsis and hepatic encephalopathy will need intensive management, as these will all potentially worsen as a consequence of the variceal bleed.

A range of drugs reduce portal hypertension and may stop active bleeding but (as mono-therapy) have not been shown to improve hospital mortality (Chapter 6). Portal hypertension can also be reduced by surgical shunting procedures and these effectively stop active bleeding and reduce the risk of re-bleeding. Porta-caval shunt operations are now very rarely undertaken because of high post operative mortality in acutely bleeding patients, frequent development of hepatic encephalopathy in survivors and because porta-caval shunting using transjugular intrahepatic portosystemic shunt (TIPS) can be achieved less invasively by interventional radiology. Other surgical procedures including oesophageal transaction have also been abandoned because of unacceptable mortality. Endoscopic therapies are currently the primary treatment for bleeding varices; whilst the addition of terlipressin may improve the outcome of endoscopic therapy and a range of other approaches (especially TIPS) are needed when endoscopic treatment fails. Balloon tamponade using the Sengstaken- Blakemore tube may be life saving in patients with torrential oesophageal haemorrhage. Balloon tamponade is a

highly specialised procedure that is used to help stabilise the patient by achieving temporary haemostasis prior to definitive endoscopic, radiological or (very occasionally) surgical intervention.

Emergency endoscopy in patients with active variceal bleeding risks life threatening aspiration pneumonia because bleeding tends to be severe, the endoscopy is often protracted and because the patient with liver disease is frequently obtunded. It is therefore wise to enlist anaesthetic support and to undertake endoscopy after endotracheal intubation.

Oesophageal varices are the principal site of variceal formation in 80% of patients with cirrhosis[155]. Veins perforate through defects within the lower oesophagus and, whilst they may spread proximally into the mid-gullet or distally into the upper part of the stomach (type 1 gastric varices), endoscopically directed therapies are focused upon the 2cm or so above the gastro-oesphageal junction and attempt to thrombose the perforating vessels. Endoscopic injection of sclerosants (ethanolamine, polidocanol or STD) into the lower oesophageal varices was shown in trials undertaken in the 1980s to stop active bleeding, reduce the rate of re-bleeding and to improve mortality. Significant complications, particularly oesophageal stricture formation, occurred and over the past decade band ligation has largely replaced sclerotherapy both as treatment for acute bleeding and for eradicating residual varices after the acute bleed. Multiple rubber bands can be delivered endoscopically using disposable devices. Neither band ligation nor injection sclerotherapy represent effective treatment for distal gastric varices. Histo-acryl or thrombin injection should be considered for these cases. The relative merits of sclerotherapy and band ligation for oesophageal bleeding varices requires clarification. This Chapter does not consider primary prophylaxis for varices that have not bled.

9.2.2 Clinical question and methodological introduction

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

Table 68: PICO characteristics of the clinical question

Clinical Methodological Introduction	
Population:	People with confirmed oesophageal varices
Intervention:	Band ligation
Comparison:	Sclerotherapy
Outcomes:	• Mortality • Re-bleeding • Treatment failure (no initial haemostasis) • Other procedures to control bleeding • Blood transfusion requirements • Number of treatments required for eradication • Adverse event stricture • Adverse events causing death

9.2.3 Clinical evidence review

We searched for randomised controlled trials comparing the effectiveness of band ligation for improving outcomes in people with bleeding oesophageal varices. We looked for any randomised controlled trials that compared the effectiveness of band ligation with sclerotherapy (see flowchart in Appendix E for study selection).

Seventeen randomised controlled trials compared ligation with injection sclerotherapy in patients with bleeding oesophageal varices. To investigate possible heterogeneity of study results 'length of follow-up' and 'severity of cirrhosis' (indicated by the percentage of patients with a Child-Pugh Class), was used as the methodological strategy. Severity of liver disease was graded since patients with advanced cirrhosis would probably need more sessions for the eradication of varices, be more likely to re-bleed and have a higher blood transfusion requirements than patients with less advanced liver disease (see Appendix F for evidence tables and Appendix H for forest plots).

Table 69: Characteristics of included studies

Study	Study type (N)	Population characteristics		Mean follow up period (days)	Outcomes
		% in Child -Pugh Class C	Mean Age		
Baroncini et al. 1997 [156]	RCT (111)	27%	62	500	Mortality, re-bleeding, number of sessions to eradication, adverse events causing death.
Bhuiyan et al. 2007 [157]	RCT (150)	19%	34	350	Mortality, re-bleeding, number of sessions to eradication.
De la Pena et al. 1999 [158]	RCT (88)	26%	59	510	Mortality, re-bleeding, units of blood transfused, adverse events causing death.
Gimson et al. 1993 [159]	RCT (103)	26%	51	330	Mortality, re-bleeding, treatment failure, additional therapy requirements, number of sessions to eradication.
Gralnek et al. 1999 [160]	RCT (66)	44%	52	365	Mortality, re-bleeding, treatment failure, additional therapy requirements, number of sessions to eradication, units of blood transfused, Hospital days in ICU, Hospital days out of ICU.
Harras et al. 2010 [161]	RCT (100)	19%	62	730	Mortality, re-bleeding, adverse events causing death.
Hou et al. 2000 [162]	RCT (200)	31%	60	1840	Re-bleeding, units of blood transfused, number of sessions to eradication.
Laine et al. 1993 [163]	RCT (77)	24%	46	300	Mortality, re-bleeding, treatment failure, units of blood transfused, adverse events causing death.
Lo et al. 1994 [164]	RCT (57)	77%	56	730	Mortality, re-bleeding, treatment failure, additional therapy requirements, units of blood transfused.
Lo et al. 1997 [165]	RCT (71)	60%	54	30	Mortality, re-bleeding, treatment failure, units of blood transfused.
Luz 2011[166]	RCT (83)	42%	54	42	Mortality, re-bleeding and treatment success
Masci et al. 1999 [167]	RCT (100)	24%	62	365	Mortality, re-bleeding.
Sarin et al. 1997 [168]	RCT (101)	14%	37	250	Mortality, re-bleeding, number of sessions to eradication.
Shafqat et al. 1998 [169]	RCT (70)	12%	52	168	Mortality, re-bleeding, treatment failure.
Stiegmann et	RCT (129)	19%	52	300	Mortality, re-bleeding, treatment failure,

Study	Study type (N)	Population characteristics		Mean follow up period (days)	Outcomes
		% in Child -Pugh Class C	Mean Age		
al. 1992 [170]					units of blood transfused, adverse events causing death.
Villanueva et al. 2006 [171]	RCT (168)	25%	62	42	Mortality, re-bleeding, treatment failure, units of blood transfused.
Young et al. 1993 [172]	RCT (23)	79%	55	270	Mortality, number of sessions to eradication.

Comparison of band ligation versus sclerotherapy

There were no studies covering the outcome: *adverse events leading to treatment withdrawal*. The adverse event of stricture was added, post-hoc, as an outcome.

Table 70: GRADE assessment of outcomes for band ligation versus sclerotherapy (lighter- shaded rows with italicised outcome names indicate sub-groups for a particular outcome)

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Band Ligation, Frequency (%), N, Mean (sd), Median (range)**	**Sclerotherapy , Frequency (%), N, Mean (sd), Median (range)**	**Relative Risk (95% CI)**	**Absolute effect, Mean difference (95% CI)**	**Quality**
Mortality (follow-up 30-1840 days)*										
See sub-groups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	167/822 (20.3%)	199/809 (24.6%)	RR 0.86 (0.74 to 0.99)	34 fewer per 1000 (from 2 fewer to 64 fewer)	LOW
Mortality by follow up duration - 0-3 months (follow-up 3-42 days)										
Lo 1997 [165], Villanueva 2006 [171], Luz 2011 [166]	*randomised trials*	*serious[a]*	*no serious inconsistency*	*no serious indirectness*	*serious[b]*	*25/171 (14.6%)*	*34/162 (21%)*	*RR 0.68 (0.42 to 1.09)*	*RR 0.68 (0.42 to 1.09)*	*LOW*
Mortality by follow up duration - >3 months to 1 year (follow-up 168-365 days)										
Stiegmann 1992 [170], Gimson 1993 [159], Young 1993 [172], Laine	*randomised trials*	*serious[a]*	*no serious inconsistency*	*no serious indirectness*	*serious[b]*	*82/401 (20.4%)*	*100/400 (25%)*	*RR 0.79 (0.63 to 0.99)*	*52 fewer per 1000 (from 2 fewer to 93 fewer)*	*LOW*

1993 [163], Sarin 1997 [168], Shafqat [169] 1998, Gralnek, 1999 [173], Masci 1999 [167], Bhuiyan 2007 [157]										
Mortality by follow up duration - >1 year (follow-up 500-730 days)										
Lo 1994 [164], Baroncini 1997 [156], De la Pena 1999 [158], Hou 2000 [162], Harras 2010 [161]	*randomised trials*	*serious[a]*	*no serious inconsistency*	*no serious indirectness*	*serious[b]*	*60/250 (24%)*	*65/247 (26.3%)*	*RR 0.94 (0.78 to 1.15)*	*16 fewer per 1000 (from 58 fewer to 39 more)*	*LOW*
Re-bleeding (follow-up 30-1840 days)										
Stiegmann 1992 [170], Gimson 1993 [159], Laine 1993 [163], Lo 1994 [164], Baroncini 1997 [156], Sarin 1997 [168], Lo 1997 [165], Shafquat 1998 [169], Masci 1999 [167],	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	160/807 (19.8%)	235/776 (30.3%)	RR 0.54 (0.52 to 0.76)	139 fewer per 1000 (from 73 fewer to 145 fewer)	LOW

De la Pena 1999 [158], Gralnek 1999 [173], Hou 2000 [162], Villanueva, 2006 [171], Bhuiyan 2007 [157], Harras 2010 [161], *Luz 2011*[166]										
Treatment failure (no initial haemostasis) by severity of cirrhosis										
See sub-groups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	40/377 (10.6%)	60/356 (16.9%)	RR 0.62 (0.43 to 0.9)	64 fewer per 1000 (from 17 fewer to 96 fewer)	LOW
Treatment failure by severity of cirrhosis - 0-20% of patients with Child Pugh grade C										
Stiegman 1992 [170], Sarin 1997 [168], Shafqat 1998 [169],	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	8/49 (16.3%)	12/48 (25%)	RR 0.66 (0.30 to 1.47)	85 fewer per 1000 (from 175 fewer to 118 more)	LOW
Treatment failure by severity of cirrhosis – 21-40% of patients with Child Pugh grade C										
Gimson 1993 [159], Laine 1993 [163], Villanueva, 2006 [171],	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	10/182 (5.5%)	18/177 (10.2%)	RR 0.53 (0.25 to 1.33)	48 fewer per 1000 (from 76 fewer to 34 more)	LOW
Treatment failure by severity of cirrhosis - >40% of patients with Child Pugh grade C										

Lo 1994 [164], Lo 1997 [165], Gralnek 1999 [173], *Luz 2011* [166]	randomised trials	serious[a]	serious[c]	no serious indirectness	serious[b]	22/146 (15.1%)	30/131 (22.9%)	RR 0.66 (0.40 to 1.09)	78 fewer per 1000 (from 137 fewer to 21 more)	LOW
Adverse effects leading to death (follow-up 300-730 days)										
Stiegmann 1992 [170], Baroncini 1997 [156], De la Pena 1999 [158]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	1/163 (0.6%)	6/165 (3.6%)	RR 0.29 (0.06 to 1.38)	26 fewer per 1000 (from 34 fewer to 14 more)	MODERATE
Adverse events – stricture (follow-up 300-730 days)										
Stiegmann 1992 [170], Gimson 1993 [159], Laine 1993 [163], Baroncini 1997 [156], Sarin 1997 [168], Shafqat 1998 [169], Gralnek 1999 [173], De la Pena 1999 [158], Hou 2000 [162], Bhuiyan 2007 [157], Harras 2010 [161]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	2/561 (0.4%)	70/557(12.6%)	RR 0.07 (0.03 to 0.17)	117 fewer per 1000 (from 105 fewer to 122 fewer)	MODERATE
Additional therapy requirements										

Stiegmann 1992 [170], Gimson 1993 [159], Lo 1997 [165], Gralnek 1999 [173]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	15/190 (7.9%)	19/179 (10.6%)	RR 0.75 (0.39 to 1.42)	27 fewer per 1000 (from 65 fewer to 45 more)	VERY LOW
Number of sessions to eradication (follow-up 250-350 days; Better indicated by lower values)[**]										
Please see subgroups for studies	randomised trials	very serious[a]	very serious[c]	no serious indirectness	no serious imprecision	Total N=413 (please see subgroups for means)	Total N=405 (please see subgroups for means)	-	MD 1.28 lower (1.46 to 1.1 lower)	VERY LOW
Number of sessions to eradication by severity of cirrhosis - 0-20% of patients with Child Pugh grade C (follow-up 250-350 days; Better indicated by lower values)										
Stiegmann 1992 [170], Sarin 1997 [168], Bhuiyan 2007 [157]	*randomised trials*	*very serious[a]*	*very serious[c]*	*no serious indirectness*	*no serious imprecision*	*N=64, 4 (2); N=47, 4.1 (1.2); N=75, 2.3 (3.1)*	*N=65, 5 (2); N=48, 5.2 (1.8); N=75, 5.2 (2.1)*	-	*MD 1.47 lower (1.88 to 1.07 lower)*	*VERY LOW*
Number of sessions to eradication by severity of cirrhosis - 21-40% of patients with Child Pugh grade C (follow-up 330-1840 days; Better indicated by lower values)										
Gimson 1993 [159], Baroncini 1997 [156], Hou 2000 [162]	*randomised trials*	*very serious[a]*	*very serious[c]*	*no serious indirectness*	*serious imprecision[b]*	*N=54, 3.4 (2.2); N=57, 3.5 (0.75); N=71, 3.7 (1.6)*	*N=49, 4.9 (3.5 N=54, 4 (0.74); N=70, 5.1 (2.1)*	-	*MD 0.69 lower (0.94 to 0.44 lower)*	*VERY LOW*
Number of sessions to eradication by severity of cirrhosis - >40% of patients with Child Pugh grade C (follow-up 270-365 days; Better indicated by lower values)										
Lo 1994 [164], Lo 1997 [165]	*randomised trials*	*very serious[a]*	*very serious[c]*	*no serious indirectness*	*no serious imprecision*	*N=10, 0.4 (0.4); N=35, 3.3 (2.4)*	*N=10, 6.2 (0.5); N=31, 3.4 (1.5)*	-	*MD 2.28 lower (2.62 to 1.93 lower)*	*VERY LOW*
Units transfused throughout treatment (follow-up 30-1840 days; Better indicated by lower values)[**]										

For study details see subgroups below	randomised trials	very serious[a]	very serious[c]	no serious indirectness	no serious imprecision	Total N=407 (please see subgroups for means)	Total N=401 (please see subgroups for means)	-	MD 0.84 lower (1.16 to 0.53 lower)	VERY LOW
Units transfused throughout treatment by severity of cirrhosis - 0-20% patients with Child Pugh grade C (follow-up mean 300 days; Better indicated by lower values)										
Stiegmann 1992 [170]	*randomised trials*	*very serious[a]*	*no serious inconsistency*	*no serious indirectness*	*serious[b]*	*N=64, 5 (4.2)*	*N=65,4.3(3.2)*	-	*MD 0.7 higher (0.59 lower to 1.99 higher)*	*VERY LOW*
Units transfused throughout treatment by severity of cirrhosis - 21-40% patients with Child Pugh grade C (follow-up 42-1840 days; Better indicated by lower values)										
Laine 1993 [163], De la Pena 1999 [158], Hou 2000 [162], Villanueva, 2006 [171]	*randomised trials*	*very serious[a]*	*no serious inconsistency*	*no serious indirectness*	*no serious imprecision*	*N=38, 1.5 (2.7); N=42, 3.5 (1.8); N=71, 2.7 (3); N=90, 3.1 (2.3)*	*N=39, 1.9 (5.6); N=46, 3.15 (1.8); N=70, 2.6 (2.4); N=89, 3.9 (3)*	-	*MD 0.14 lower (0.59 lower to 0.32 higher)*	*LOW*
Units transfused throughout treatment by severity of cirrhosis - >40% of patients with Child Pugh grade C (follow-up 30-730 days; Better indicated by lower values)										
Lo 1994 [164], Lo 1997 [165], Gralnek 1999 [173]	*randomised trials*	*very serious[a]*	*very serious[c]*	*no serious indirectness*	*no serious imprecision*	*N=30, 1.5 (0.8); N=37, 3.2 (1.2); N=35, 2.2 (3.5)*	*N=27, 3.9(1.5); N=34, 4.5 (1.8); N=31, 2.1 (3.3)*	-	*MD 1.76 lower (2.22 to 1.31 lower)*	*VERY LOW*
Length of ICU stay (follow-up mean 365 days; Better indicated by lower values)										
Gralnek 1999 [173]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	N=35, 7.5 (13.6)	N=31, 7 (10)	-	MD 0.5 higher (5.22 lower to 6.22 higher)	VERY LOW
Length of non-ICU stay (follow-up mean 365 days; Better indicated by lower values)										

Shafqat 1998 [169], Gralnek 1999 [173], Villanueva, 2006 [171]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	N=28, 4.96 (2.58); N=35, 17.3 (20.7); N=90, 13 (7)	N=30, 6.1 (1.7); N=31, 16.8 (21.7); N=89, 15 (9)	-	MD 1.28 lower (2.3 to 0.27 lower)	VERY LOW

[a] *The 16 RCTs varied in quality, with most having serious limitations including selection, performance, attrition and detection bias. 14 RCTs had 2 or more serious limitations and 2 had 1 serious limitation. Each outcome had a differing combination of studies, and so each outcome has been downgraded accordingly in the study limitations column. It should be noted that for some outcomes un-blinding was not regarded as a relevant limitation, and so these outcomes tended to be downgraded less. When downgraded twice the majority of information for the outcome came from studies with very high risk of bias whereas when downgraded once the majority of information stemmed from studies with moderate risk for bias.*

[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

[c] *There was evidence of heterogeneity which remained after subgroup analysis; it was decided by the GDG not to investigate this further since even though the studies were heterogeneous they were all favouring band ligation.*

** No subgroup difference(s)*

***For subgroup difference(s) see evidence statements and forest plots*

9.2.4 Health economic evidence

One study, which was also included in the clinical review, was identified that included the relevant comparison. This is summarised in the economic evidence profile below. See also Evidence Table G.5.3 in Appendix G. There were no excluded studies.

Table 71: Endoscopic injection sclerotherapy versus endoscopic band ligation – Economic study characteristics

Study	Limitations	Applicability	Other comments
Gralnek (1999)[160]	Potentially major limitations [a]	Partially applicable [b]	Analysis developed from a US Medicare perspective and over a 1-year time horizon

(a) Based on RCT, the cost-effectiveness analysis was developed over a 1-year time horizon. The analysis adequately reflects the nature of the health condition. Cost components included were appropriate. The cost-effectiveness ratios presented were inadequate and recalculated to provide incremental analysis. No quality of life assessment was included in the analysis and no sensitivity analysis was performed.

(b) Analysis developed from a US perspective, assessing relevant interventions and a relevant population of patients. The analysis was performed for all included patients in the trial and for two subgroups: i) patients with active bleeding at index endoscopy (emergency treatment); and ii) patients with clean varices or stigmata of recent haemorrhage at index endoscopy (elective treatment). The RCT was conducted between 1990 and 1994. The analysis did not calculate QALYs.

The cost-effectiveness analysis by Gralnek and colleagues showed the cost-effectiveness superiority of endoscopic sclerotherapy compared to endoscopic ligation, most particularly in patients with active haemorrhage. In both assessed sub-populations of patients (active and non-active haemorrhage) sclerotherapy was marginally more expensive than ligation. However, an important improvement in survival was seen in the sub-population of patients with active haemorrhage having sclerotherapy. This led to the cost-effectiveness advantage of sclerotherapy. The relative cost effectiveness in patients without active haemorrhage was inconclusive (similar cost and survival in both groups).

Based on the level of improvement in survival in the sclerotherapy group reported in this study and the likelihood of cost equivalence in compared interventions, there appears to be a cost-effectiveness advantage of sclerotherapy in actively bleeding patients. However, this study did not conduct a sensitivity analysis and reported a wide potential range for the cost parameters. Although significant differences were demonstrated, sample size was small and the power of the study was low.

Table 72: Endoscopic Sclerotherapy [a] versus Band Ligation [b] [c] – Economic summary of findings

Subgroup assessed in Gralnek (1999)	Total mean costs per patient[d][e]	Total health effects (number of patients surviving)	Cost effectiveness	Uncertainty
All patients	Sclerotherapy (n=31): £10,822 Ligation (n=35): £10,498	Sclerotherapy: 22/31 (71%) Ligation: 21/35 (60%)	Sclerotherapy led to a higher survival and to additional costs. The cost per additional life saved was £2,900.	No sensitivity analysis was performed
Patients with active haemorrhage	Sclerotherapy (n=9): £12,181 Ligation (n=12):	Sclerotherapy: 6/9 (67%) Ligation: 4/12 (33%)	Sclerotherapy led to a higher survival and to additional	No sensitivity analysis was performed

	£11,039		costs. The cost per additional life saved was £3,300.	
Patients with clean varices or stigmata of recent haemorrhage	Sclerotherapy (n=22): £10,266 Ligation (n=23): £10,216	Sclerotherapy: 16/22 (73%) Ligation: 17/23 (74%)	Ligation led to 1% higher survival and to savings of £49 per patient.	No sensitivity analysis was performed

(a) The actively bleeding varix or varix with stigmata of recent haemorrhage was injected intravariceally with TES solution (3% tetradecyl sulfate mixed with absolute ethanol and normal saline) up to 2 mL per injection. All remaining oesophageal varices were then similarly injected intravariceally. In this arm n=31.

(b) 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 varices were then ligated. In this arm n=35

(c) 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. 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 re-bleeding thereafter. If varices reappeared after obliteration, endoscopic treatment was repeated using the originally assigned form of endoscopic therapy. When failure of the randomised intervention, patients could undergo the alternative endoscopic therapy or be treated with any other available therapy such as TIPS or surgical shunt.

(d) 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. The cost of orthotopic liver transplantation undergone after random assignment was not included.

(e) Published costs in USD were converted into pound sterling using Purchasing Power Parities.

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were presented to aid consideration of cost effectiveness. These are detailed in Table 73.

Table 73: UK NHS Reference Costs 2009-2010

Item	Unit Cost	Notes
- Open injection sclerotherapy to varices of the oesophagus (FZ16Z.G10.5) - Local ligation of varices of the oesophagus (FZ16Z.G10.4)	£4,604.98 (7.68 days of hospital stay)	NHS reference cost for HRG code FZ16Z: Very Major Procedures for Gastrointestinal Bleed. Cost includes excess bed stays.
- Fibre optic endoscopic injection sclerotherapy to varices of oesophagus (FZ29Z .G14.4) - Endoscopic injection sclerotherapy to varices of oesophagus using rigid oesophagoscope (FZ29Z .G17.4) - Fibre optic endoscopic sclerotherapy to lesion of upper gastrointestinal tract (FZ29Z.G43.4)	£1,073.13 (3.55 days of hospital stay)	NHS reference cost for HRG code FZ29Z : Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed Cost includes excess bed stays.

Source: Department of Health (2011)[81]

9.2.5 Evidence statements

9.2.5.1 Clinical evidence

Ligation versus sclerotherapy for bleeding oesophageal varices

Mortality

16 studies comprising 1548 participants found a statistically significant reduction in mortality in the participants receiving ligation (follow up 30-1840 days) compared to participants in the sclerotherapy group. However, this effect was not large enough to show clear appreciable band ligation treatment benefit (LOW QUALITY).
These 16 studies were then split into 3 sub groups according to length of follow-up (assuming that deaths in the shorter term would be more related to acute bleeding) as follows:

- 2 studies comprising 250 participants (in the short follow-up sub group: up 30-42 days) found a statistically significant reduction in mortality with the proportion of participants receiving ligation occurring up to 3 months post procedure. However, this effect was not large enough to show clear appreciable band ligation treatment benefit (LOW QUALITY).

- 9 studies comprising 801 participants (in the medium length follow up sub group: 168-365 days) found a statistically significant reduction in mortality with the proportion of participants receiving ligation occurring between 3 months and 1 year post procedure. However, this effect was not large enough to show clear appreciable band ligation treatment benefit (LOW QUALITY).

- 5 studies comprising 497 participants (in the long length follow up sub group: 500-1840 days) found that there was no statistical / clinical significant difference between ligation and sclerotherapy for mortality occurring over 1 year post procedure (LOW QUALITY).

- Test of subgroup analysis showed that difference s between the three groups were not significant (VERY LOW QUALITY).

Re-bleeding

16 studies comprising 1583 participants found a statistically significant reduction in re-bleeding with the proportion of participants receiving ligation (follow up 30-1840 days) (LOW QUALITY) compared to participants in the sclerotherapy group. However, this effect was not large enough to show clear appreciable band ligation treatment benefit (LOW QUALITY).

Treatment failure

10 studies comprising 733 participants found a statistically significant reduction in treatment failure with the proportion of participants receiving ligation (no initial haemostasis) (follow up 30-712 days) compared to participants in the sclerotherapy group (LOW QUALITY). It was unclear whether this effect was large enough to warrant clear clinical benefit by using ligation rather than sclerotherapy.
Due to heterogeneity in study results the 10 studies were subgrouped according to the proportion of patients with severe levels of cirrhosis (as indicated by Child-Pugh grade C) as follows:

- 3 studies comprising 97 participants (in the less severe sub group containing <20% of participants with Child Pugh Grade C) found that patients receiving ligation had lower rates of treatment failure (follow up 175-304 days) compared to participants in the sclerotherapy group (LOW QUALITY). However, this effect was not statistically significant and unclear whether this effect was large enough to indicate clear clinical benefit.

- 3 studies comprising 359 participants (in the medium severe sub group containing 21-40% of participants with Child Pugh Grade C) found that patients receiving ligation had a lower rate of treatment failure (follow up 42-337 days) compared to participants in the sclerotherapy group (LOW QUALITY). This result was not statistically significant and it was unclear whether it can be considered to indicate clinical benefit.

- 4 studies comprising 177 participants (in the severe sub group containing ≥40% of participants with Child Pugh Grade C) found that patients receiving ligation had a lower rate of treatment failure (follow up 30-712 days) compared to participants in the sclerotherapy group (VERY LOW QUALITY). This result was not statistically significant and it was unclear whether it can be considered to indicate clinical benefit.

Number of sessions to eradication

8 studies comprising 818 participants found that patients receiving ligation had a statistically significant lower number of sessions to eradication (follow up 250-1840 days compared to participants in the sclerotherapy group (VERY LOW QUALITY).
These 8 studies were then put into 3 sub groups according to percentage of patients with severe cirrhosis (according to Child-Pugh Grading C) as follows:

- 3 studies comprising 374 participants (in the less severe sub group containing <20% of participants with Child Pugh Grade C) found that patients receiving ligation had a statistically significant lower number of sessions to eradication (follow up 250-350 days) compared to participants in the sclerotherapy group (VERY LOW QUALITY).

- 3 studies comprising 355 participants (in the medium severe sub group containing 21-40% of participants with Child Pugh Grade C) found that patients receiving ligation had a statistically significant lower number of sessions to eradication (follow up 330-1840 days) compared to participants in the sclerotherapy group (VERY LOW QUALITY).

- 2 studies comprising 89 participants (in the severe sub group containing ≥40% of participants with Child Pugh Grade C) found that patients receiving ligation had a statistically significant lower number of sessions to eradication (follow up 270-365 days) compared to participants in the sclerotherapy group (VERY LOW QUALITY).

There was a significant subgroup difference, with those studies with the highest percentage of participants in Child Pugh Grade C showing statistically higher band ligation treatment effects (i.e. fewer sessions required to eradication compared to sclerotherapy) than in studies that included fewer patients with severe cirrhosis (VERY LOW QUALITY).

Units transfused throughout treatment

8 studies comprising 808 participants found that patients receiving ligation had a statistically significant lower number of units transfused throughout treatment (follow up 30-1840 days) compared to participants in the sclerotherapy group. This difference was large enough to indicate clinical benefit from band ligation over sclerotherapy (VERY LOW QUALITY).
These 8 studies were then divided into 3 sub groups according to percentage of patients with severe cirrhosis (as indicated by Child-Pugh Grade C) as follows:

- One study comprising 129 participants (in the less severe sub group containing <20% of participants with Child Pugh Grade C) found that there was no statistical / clinical significant difference between ligation and sclerotherapy for units of blood transfused (follow up 300 days) (VERY LOW QUALITY).

- 4 studies comprising 485 participants (in the medium severe sub group containing 21-40% of participants with Child Pugh Grade C) found no statistical / clinical significant difference between ligation and sclerotherapy for units of blood transfused (follow up 42-1840 days) (LOW QUALITY).

- 3 studies comprising 194 participants (in the severe sub group containing ≥40% of participants with Child Pugh Grade C) found that patients receiving ligation had a statistically significant lower number of units transfused throughout treatment (follow up 30-730 days) compared to participants in the sclerotherapy group. This difference was large enough to indicate clinical benefit from band ligation over sclerotherapy (VERY LOW QUALITY).

There was a statistically significant difference between subgroups, with those studies with the highest percentage of participants in Child Pugh Grade C showing a higher band ligation treatment effects (i.e. fewer units of blood transfused compared to sclerotherapy) than in studies that included fewer patients with severe cirrhosis (VERY LOW QUALITY).

Additional therapy requirements

4 studies comprising 369 participants found that there was no statistical / clinical significant difference between ligation and sclerotherapy for additional therapy requirements (follow up 30-365 days) compared to participants in the sclerotherapy group (VERY LOW QUALITY).

Adverse events leading to death

3 studies comprising 328 participants found that there was non-significant difference with a lower rate of fatal adverse events in ligation compared to sclerotherapy group. However this lower rate was not statistically significant and it was inconclusive whether it represented clear clinical benefit events (follow up 300-730 days) (MODERATE QUALITY).

Adverse events - stricture

11 studies comprising 1118 participants found that there was a statistically significant difference between ligation and sclerotherapy for adverse events –with a lower rate of stricture reported in patients who had received band ligation. This effect was large enough to show appreciable clinical benefit from band ligation (follow up 300-730 days) (MODERATE QUALITY).

Length of hospital stay

One study comprising 66 participants found that there was no significant difference between ligation and sclerotherapy for ICU stay (follow up 365 days) (VERY LOW QUALITY).

3 studies comprising 303 participants found that there was a statistically significant difference between ligation and sclerotherapy for Non-ICU stay, with participants in the ligation group having a shorter stay (follow up 365 days). However, it was unclear whether this effect indicated a clear clinical benefit of ligation over sclerotherapy (VERY LOW QUALITY).

9.2.5.2 Health economic evidence

In patients with active upper GI haemorrhage from oesophageal varices, endoscopic sclerotherapy could be superior to endoscopic ligation in terms of cost effectiveness, providing its superiority in improving survival can be demonstrated. This is based on evidence of partial applicability and with potentially serious limitations.

9.2.6 Recommendations and link to evidence

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

Recommendations	• **Use band ligation in patients with upper gastrointestinal bleeding from oesophageal varices.**
Relative values of different outcomes	Mortality is clearly the most important outcome, and a significant mortality benefit for band ligation over injection sclerotherapy was seen. There was a trend towards a stronger effect at shorter follow-up time points suggesting increased importance of the intervention used to control bleeding. Band ligation was also significantly superior to injection sclerotherapy when considering the outcomes of re-bleeding, numbers of additional procedures required to control bleeding, total units of blood transfused, and the number of sessions of treatment required to eradicate varices.
Trade off between clinical benefits and harms	Analysis demonstrated no difference between the two therapies in terms of adverse events leading to death and increased hospital stay (including days spent in ICU). Injection sclerotherapy can cause oesophageal strictures in an appreciable minority of cases, and this is not observed with band ligation.
Economic considerations	The only economic paper addressing this topic favoured injection sclerotherapy over band ligation. No quality of life analysis was performed. The results of the clinical study on which the economic analysis was based ran contrary to all others in the clinical evidence analysis. The GDG felt that the clinical study had potentially serious limitations including a baseline inequivalence favouring sclerotherapy, since those in the band ligation group had a greater prevalence of very large varices. The findings of cost-effectiveness of sclerotherapy were driven by increased survival at one year in this group, but since this was highly unrepresentative of the rest of the clinical evidence the GDG did not feel able to base a recommendation on this.

	In discussion the GDG did not feel that there was significant cost difference between a session of band ligation or sclerotherapy. Given the finding that fewer band ligation sessions were required to eradicate varices the GDG felt that its widespread adoption would be cost-saving.
Quality of evidence	By GRADE criteria the evidence on this question was low to very low. The GDG felt that these studies had generally been well performed given the difficulties inherent in any study of acutely ill patients such as these. The issues with one particular clinical trial (upon which the economic evaluation was based) are covered in the paragraph above
Other considerations	The GDG felt that band ligation should be first-line therapy in all patients with upper gastrointestinal bleeding due to oesophageal varices. However they did not feel that there was sufficient evidence to make a recommendation against the use of injection sclerotherapy because, very occasionally in a patient with particularly dramatic bleeding it might not be possible to secure haemostasis by banding, in which case sclerotherapy might reasonably be attempted. .

9.3 Transjugular intrahepatic portosystemic shunts [TIPS] and endoscopic treatment

9.3.1 Introduction

The TIPS procedure involves insertion of a catheter into a hepatic vein (via the internal jugular vein, then the vena cava). A branch of the intrahepatic portal vein is intubated using a needle passed through the catheter, the tract is then dilated with a balloon placed over a wire and expandable stent is then deployed over a guidewire to lie between the hepatic and portal veins. The pressure within the portal vein falls. Early experience involved uncovered stents, but more recently PTFE coated stents are used as these have a significantly reduced stenosis rate.

The procedure requires an experienced interventional radiologist and a high resolution lab. Many patients are critically ill and optimal resuscitation is essential prior to the procedure being undertaken. Acute complications, including bleeding due to capsular puncture, are relatively uncommon, whilst the major late complication is hepatic encephalopathy.

TIPS is usually undertaken as rescue therapy when endoscopic approaches for oesophageal or gastric varices fail, but also has a role in treating bleeding ectopic varices when these are not amenable to endoscopic intervention, and has a limited role in treating intractable ascites in selected patients.

9.3.2 Clinical questions and methodological introduction

Clinical question 1

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

Table 74: PICO Characteristics of clinical question 1

Clinical Methodological Introduction	
Population:	Patients with confirmed gastric variceal bleeding

Clinical Methodological Introduction	
Intervention:	TIPS
Comparison:	Endoscopic injection of glue or thrombin
Outcomes:	• Mortality • Re-bleeding • Treatment failure • Rate of unresolved varices • Blood transfusion requirements • Length of hospital stay • Adverse events – encephalopathy • Adverse events - sepsis

Clinical question 2

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

Table 75: PICO Characteristics of clinical question 2

Clinical Methodological Introduction	
Population:	Patients with variceal bleeding
Intervention:	TIPS
Comparison:	Repeat endoscopy or balloon tamponade
Outcomes:	• Mortality • Re-bleeding • Blood transfusion requirements • Length of hospital stay • Adverse events – encephalopathy • Adverse events - sepsis

9.3.3 Clinical evidence review

Clinical question 1

For question 1 we searched for randomised control trials comparing the effectiveness of TIPS with injection treatment as interventions for patients with confirmed gastric variceal bleeding (see flowchart in Appendix E for study selection).

Four randomised control studies were identified. Three of those had a study population consisting of patients with variceal bleeding of either oesophageal or gastric origin. These studies were included in the review as a mixed variceal subgroup (oesophageal and gastric) and therefore represent indirect evidence. The fourth study featured only patients with gastric varices and was therefore directly applicable; it used injection of glue as a comparator to TIPS treatment. This is classified as direct evidence since the patient population directly matched the group specified in the protocol. The aim of all papers was to assess whether TIPS is more effective than alternative treatments (sclerotherapy, banding, and glue injection) to improve outcomes (see Appendix F for evidence tables and Appendix H for forest plots).

Table 76: Characteristics of included studies

STUDY	INTERVENTION / COMPARISON	POPULATION	OUTCOMES	COMMENTS
Lo , 2007 [174]	TIPS versus Cyanoacrylate injection N = 72 Randomisation was performed after acute gastric variceal bleeding had been controlled for 3 days.	Patients with acute gastric variceal bleeding 17% Child-Pugh Grade C	Primary end point: gastric variceal re-bleeding Secondary end points: complications, blood transfusion requirements, length of hospital stay, or death.	Baseline indifference with higher rate of patients with previous bleeding episodes in the TIPS group.
Monescillo, 2004 [175]	TIPS versus Non-TIPS (either ß-blockers or banding or both) N=52 All patients received a single session of injection sclerotherapy on admission	Mixed variceal (unspecified what percentage with gastric varices) 46% Child-Pugh Grade C All patients had hepatic venous pressure gradient (HVPG) ≥20 mmHg	Primary endpoints were concerned with prediction of treatment failure (not reported in this analysis) Secondary endpoints: transfusion requirements; intensive care unit stay (n); complications during the first week of treatment; and mortality with causes of death during follow-up in each treatment group.	A low HVPG group was also analysed, but patients of this group were not randomised and their results are not reported here. 12% of patients (2 in TIPS and 4 in Non-TIPS group) already experienced encephalopathy at the time of baseline assessment. Baseline indifference with higher Bilirubin level in patients in the TIPS group.
Rössle, 1997 [176]	TIPS versus Sclerotherapy / Banding N = 126 Patients with acute bleeding received injection sclerotherapy to stop bleeding prior to randomised treatment.	Mixed variceal (unspecified what percentage with gastric varices) Randomisation stratified according to Child-Pugh class and age (<60 yrs or ≥60yrs) 18% Child-Pugh Grade C Variceal bleeding within 2 wks before randomisation	Clinically significant bleeding, re-bleeding, failure to control bleeding, failure of endoscopic treatment (3 or more re-bleedings within 1 year), hepatic encephalopathy-grade 1, clinically significant hepatic encephalopathy, refractory hepatic encephalopathy Failure of the transjugular shunt and shunt insufficiency	Variable follow-up with a median length of 13 months
Sanyal, 1997 [177]	TIPS versus Sclerotherapy N = 80 Prevention of	Mixed active variceal bleeding, 19% patients with gastric varices –	Primary endpoints: mortality and re-bleeding Secondary endpoints: treatment	20% of patients already experienced encephalopathy at the time of baseline assessment

STUDY	INTERVENTION / COMPARISON	POPULATION	OUTCOMES	COMMENTS
	late variceal re-bleeding in clinically stable patients	overall >50% were Child-Pugh grade C	complications and rates of rehospitalisations	

Clinical question 2

For clinical question 2 we searched for either randomised control trials or observational studies. No studies were identified that directly address any treatment comparisons specified in the protocol for patients with uncontrolled variceal bleeding.

Comparison of TIPS versus injection sclerotherapy / glue

Table 77: GRADE summary table for TIPS versus injection with tissues glue/ N-butyl-2-cyanoacrylate

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	TIPS Frequency (%); Mean (SD)	Injection sclerotherapy Frequency (%); Mean (SD)	Relative Risk (95% CI)	Absolute effect, Mean Difference (95% CI)	
Mortality*										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo, 2004 [175], Lo 2007 [174]	randomised trials	no serious limitations	serious[d]	serious[b]	very serious[c]	41/161 (25.5%)	41/169 (24.3%)	RR 1.04 (0.72 to 1.50)	10 more per 1000 (from 68 fewer to 121 more)	VERY LOW
Mortality - Mixed variceal										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo , 2004 [175]	randomised trials	serious[a]	serious[d]	serious[b]	very serious[c]	28/126 (22.2%)	32/132 (24.2%)	RR 0.90 (0.59 to 1.39)	24 fewer per 1000 (from 99 fewer to 95 more)	VERY LOW

Quality assessment						Summary of findings				
Mortality - Gastric varices										
Lo 2007 [174]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[c]	13/35 (37.1%)	9/37 (24.3%)	RR 1.53 (0.75 to 3.12)	129 more per 1000 (from 61 fewer to 516 more)	LOW
Re-bleeding*										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo, 2004 [175], Lo 2007 [174]	randomised trials	no serious limitations	no serious inconsistency	serious[b]	serious[c]	41/161 (25.5%)	68/169 (40.2%)	RR 0.64 (0.47 to 0.87)	145 fewer per 1000 (from 52 fewer to 213 fewer)	LOW
Re-bleeding - Mixed variceal										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo, 2004 [175]	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	26/126 (20.6%)	46/132 (34.8%)	RR 0.60 (0.40 to 0.90)	139 fewer per 1000 (from 35 fewer to 209 fewer)	VERY LOW
Re-bleeding - Gastric varices										
Lo 2007 [174]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	15/35 (42.9%)	22/37 (59.5%)	RR 0.72 (0.45 to 1.15)	166 fewer per 1000	MODERAT

Quality assessment						Summary of findings				
									(from 327 fewer to 89 more)	E
Transfusion requirements (Better indicated by lower values)										
Monescillo 2004, [175] Lo 2007 [174]	randomised trials	serious[a]	serious[d]	no serious indirectness	no serious imprecision	N=26 3.1 (2.6); N=35 3.42 (2.1)	N=26 3.6 (2.4); N = 376.2 (3.3)	-	MD 1.73 lower (2.66 to 0.80 lower)	LOW
Length of hospital stay (Better indicated by lower values)										
Rössle 1997 [176], Lo 2007 [174]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	N= 61; 27 (17) N=35; 7.2 (5.3)	N= 65; 34 (28) N=37; 8.7 (6.5)	-	MD 2.07 lower (4.66 lower to 0.52 higher)	VERY LOW
Treatment failure										
Rössle 1997 [176], Monescillo, 2004 [175]	randomised trials	serious[a]	very serious[d]	serious[b]	very serious[c]	12/91 (13.2%)	13/87 (14.9%)	RR 0.90 (0.44 to 1.87)	15 fewer per 1000 (from 84 fewer to 130 more)	VERY LOW
Adverse event - Hepatic encephalopathy*										
Rössle	no serious	serious[a]	no serious	serious[b]	no serious imprecision	51/161	27/169 (16%)	RR 1.97	155 more	

Quality assessment						Summary of findings				
1997 [176], Sanyal 1997, Monescillo, 2004 [175], Lo, 2007 [174]	limitations		inconsistency			(31.7%)		(1.31 to 2.97)	per 1000 (from 50 more to 315 more)	LOW
Adverse event - Hepatic encephalopathy - Mixed variceal										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo, 2004 [175]	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	42/126 (33.3%)	26/132 (19.7%)	RR 1.69 (1.10 to 2.57)	136 more per 1000 (from 20 more to 309 more)	VERY LOW
Adverse event - Hepatic encephalopathy - Gastric varices										
Lo, 2007 [174]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	9/35 (25.7%)	1/37 (2.7%)	RR 9.51 (1.27 to 71.27)	230 more per 1000 (from 7 more to 1899 more)	HIGH
Sepsis*										
Rössle 1997 [176], Sanyal 1997 [177],	no serious limitations	no serious limitations	no serious inconsistency	serious[b]	serious[c]	21/161 (13%)	13/169 (7.7%)	RR 1.63 (0.90 to 2.94)	48 more per 1000 (from 8 fewer to 149 more)	LOW

Quality assessment						Summary of findings				
Monescillo, 2004 [175], Lo 2007 [174]										
Sepsis - Mixed variceal										
Rössle 1997 [176], Sanyal 1997 [177], Monescillo, 2004 [175]	randomised trials	serious[a]	no serious inconsistency	seriousb	very serious[c]	18/126 (14.3%)	11/132 (8.3%)	RR 1.64 (0.88 to 3.06)	53 more per 1000 (from 10 fewer to 172 more)	VERY LOW
Sepsis - Gastric varices										
Lo, 2007 [174]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[c]	3/35 (8.6%)	2/37 (5.4%)	RR 1.59 (0.28 to 8.93)	32 more per 1000 (from 39 fewer to 429 more)	LOW

[a] *The 4 RCTs varied in quality. 3 RCTs had no serious methodological limitation, and 1 had 1 serious limitation. However, 2 studies had baseline differences as described in the study characteristics table. Blinding in this context is not considered serious for mortality or re-bleeding since these outcomes would not be influenced by blinding and it is difficult to blind using these treatment techniques (for other outcomes it is unclear whether blinding introduces bias and those were downgraded accordingly). Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly. When downgraded once the majority of information from studies for this outcome has one risks of bias.*

[b] *Three studies have a mixed variceal patient population but the review question is restricted to gastric varices only. This evidence is therefore considered indirect.*

[c] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

[d] *There is evidence of heterogeneity – due to differences in patient populations*

** None of the subgroup interactions reached significance.*

9.3.4 Health economic evidence review

One study was identified that included the relevant comparators of endoscopic glue injection and TIPS. This is summarised in the economic evidence profile below. See also Evidence Table G.5.1 in Appendix G.

No economic evaluations were identified that compared TIPS to repeat endoscopy or balloon tamponade in patients where variceal bleeding remained uncontrolled.

There were no excluded studies.

Table 78: Endoscopic glue versus TIPS – Economic study characteristics

Study	Limitations	Applicability	Other comments
Mahadeva 2003[178]	Potentially serious limitations [a]	Partially applicable [b]	Analysis developed from a UK perspective and over a 6-month time horizon

(a) A cost-consequence analysis, based on retrospective cohorts, was developed over a 6-month time horizon. These cohorts came from two separate time periods (with endoscopic glue being more recent) introducing the possibility of bias. Costs were reported as medians instead of means. No sensitivity analysis was performed. No quality of life assessment was included in the analysis and therefore results were not reported in cost per QALY gained.

(b) Analysis developed from a UK NHS perspective, a relevant population of patients was assessed. However, the efficacy data was estimated from relatively old records (dated 1995-1999 for TIPS and 2000 – 2001 for endoscopic glue), which means the applicability of the study findings to current practice is questionable.

Table 79: Endoscopic glue versus TIPS – Economic summary of findings

Intervention	Median cost (Interquartile Range) [c] [d]	Effects	Cost Effectiveness	Uncertainty
Endoscopic injection of glue [a]	£2,592 (1,014-15,864)	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. Re-bleeding rate: Glue injection: 30% TIPS: 15% p=.005 Inpatient stay (mean ± standard error): Glue injection: 13 ± 1 day TIPS: 18 ± 2 day p=.05	Not reported	No sensitivity analysis was performed
TIPS [b]	£7,458 (4,291-23,873) p<.0001			

(a) 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 post endoscopy to evaluate opacification of varices. Follow-up post-index endoscopy was arranged within 48 hrs, then on a weekly or monthly basis, depending on the degree of variceal obliteration.

(b) 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.

(c) Cost components included: cost of TIPS (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); and the inpatient stay (including nursing staff costs, administrative and clerical staff costs, consumables, equipments, overhead, and capital costs). It was assumed no difference between the 2 groups in ward staff fee, routine blood investigations, standard vasoactive drugs, and basic radiology.

(d) Published costs in USD were converted in pound sterling using Purchasing Power Parities.

One UK cost-effectiveness analysis by Mahadeva and colleagues was identified assessing endoscopic injection of glue and TIPS as primary treatment for patients with confirmed gastric variceal bleeding. Retrospective data from a period of 6 months from St. James's University Hospital (Leeds, UK) was analysed. 20 patients who had TIPS between January 1995 and December 1999, and 23 patients who had glue injection between January 2000 and October 2001 were assessed.

The analysis stated there was no significant difference in mortality, and therefore presented a cost-consequence analysis. The study concluded that endoscopic injection of glue is cost saving compared to TIPS as primary treatment for patients with confirmed gastric variceal bleeding. The significantly higher cost of TIPS was mainly related to the cost of the procedure together with the increased length of hospitalisation.

The cost of the procedures in England and Wales were presented to the GDG: a very major procedure for gastrointestinal bleed (i.e. TIPS) has an associated unit cost of £4605, and a therapeutic endoscopic procedure for gastrointestinal bleed has an associated unit cost of £1073[81].

9.3.5 Evidence statements

9.3.5.1 Clinical evidence

Mortality

4 studies comprising 330 participants with variceal upper gastrointestinal bleeding found that there was no statistical significant / clinical difference between TIPS and sclerotherapy / Cyanoacrylate injection to improve survival rates (variable follow up of up to 50 months) (VERY LOW QUALITY).

These 4 studies were then divided into 2 subgroups as follows:

- 3 studies comprising 258 participants provided indirect evidence and found no statistical or clinical significant difference that TIPS treatment is more effective than sclerotherapy / Cyanoacrylate injection to improve survival (VERY LOW QUALITY).
- 1 study with 72 patients provided direct evidence and found no statistical / clinical significant difference between TIPS and sclerotherapy / Cyanoacrylate injection to improve mortality rates (LOW QUALITY).
- There were no subgroup differences between indirect and direct evidence groups.

Re-bleeding

4 studies comprising 330 participants found that there was a statistically significant difference between TIPS and sclerotherapy / Cyanoacrylate injection, in favour of TIPS compared to sclerotherapy / Cyanoacrylate injection treatment with respect to variceal re- bleeding. But this did not meet the pre-determined level for clinical significance (variable follow-up of 50 months or less) (LOW QUALITY).

These 4 studies were then divided into 2 subgroups as follows:

- 3 studies comprising 258 participants provided indirect evidence and found statistical yet not clinical difference that TIPS treatment is more effective than sclerotherapy / Cyanoacrylate injection to improve re-bleeding rates (VERY LOW QUALITY).
- 1 study with 72 patients provided direct evidence and found no statistical / clinical significant difference between TIPS and sclerotherapy / Cyanoacrylate injection to improve re-bleeding rates (MODERATE QUALITY).
- There were no subgroup differences between indirect and direct evidence groups.

Blood transfusion requirements
2 studies with 124 patients provided mixed direct / indirect evidence and found a statistically and clinically significant difference between TIPS and sclerotherapy / Cyanoacrylate injection with lower levels of blood transfusions in the TIPS treatment group (LOW QUALITY).
However, the pooled result is based on inconsistent study results (may be related to either indirect / direct populations or differences in risk status of patients) and should be considered with caution.

Length of hospital stay
2 studies with 198 patients with variceal bleeding provided mixed direct/indirect evidence and found no statistical / clinical significant difference between TIPS and sclerotherapy / Cyanoacrylate injection to shorten length of hospital stay (VERY LOW QUALITY).

Treatment failure
2 studies with 178 patients with variceal bleeding provided mixed indirect evidence and found no statistical / clinical significant difference between TIPS and sclerotherapy / Cyanoacrylate injection for the rate of treatment failure (VERY LOW QUALITY).

Adverse events – Hepatic encephalopathy
4 studies comprising 330 participants found that there was statistical / clinical difference between TIPS and sclerotherapy / Cyanoacrylate injection with lower rates of hepatic encephalopathy associated with the sclerotherapy / Cyanoacrylate injection treatment for patients with variceal bleeding (variable follow-up of 50 months or less) (LOW QUALITY).
These 4 studies were then divided into 2 subgroups as follows:

- 3 studies comprising 258 participants provided indirect evidence found statistical yet not clinical difference that lower rated of hepatic encephalopathy favouring sclerotherapy / Cyanoacrylate injection compared to TIPS (LOW QUALITY).
- 1 study with 72 patients provided direct evidence and found statistical / clinical difference between TIPS and sclerotherapy / Cyanoacrylate injection with lower rates of hepatic encephalopathy associated with the sclerotherapy / Cyanoacrylate injection treatment for patients with variceal bleeding (variable follow-up of 50 months or less) (HIGH QUALITY).
- There were no subgroup differences between indirect and direct evidence groups.

Sepsis
4 studies comprising 330 participants with variceal upper gastrointestinal bleeding found that there was no significant / clinical difference between TIPS and sclerotherapy / Cyanoacrylate injection to improve rates of sepsis (variable follow up of up to 50 months) (LOW QUALITY).
These 4 studies were then divided into 2 subgroups as follows:

- 3 studies comprising 258 participants provided indirect evidence and found no statistical or clinical significant difference that TIPS treatment is more effective than sclerotherapy / Cyanoacrylate injection to improve rates of sepsis (VERY LOW QUALITY).
- 1 study with 72 patients provided direct evidence and found no statistical / clinical significant difference between TIPS and sclerotherapy / Cyanoacrylate injection to improve sepsis rates (LOW QUALITY).
- There were no subgroup differences between indirect and direct evidence groups.

9.3.5.2 Health economic evidence

Endoscopic injection of glue is considerably less costly than TIPS.

No economic evaluations were identified that compared TIPS to repeat endoscopy or balloon tamponade in patients where variceal bleeding remained uncontrolled.

9.3.6 Recommendations and link to evidence

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

Recommendations	• **Offer endoscopic injection of N-butyl-2-cyanoacrylate to patients with upper gastrointestinal bleeding from gastric varices** • **Offer transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from gastric varices is not controlled by endoscopic injection of N-butyl-2-cyanoacrylate.**
Relative values of different outcomes	There were 4 studies available for consideration, and overall these showed no mortality difference between TIPS and endoscopic therapy for bleeding gastric varices (endoscopic treatment typically comprises endoscopic injection of N-butyl-2-cyanoacrylate). However, the GDG noted a difference between the studies in that the Monescillo study [175] employed TIPS at presentation, whereas in other studies it was only used after other attempts to control acute bleeding. The Monescillo study showed a mortality benefit from early TIPS. There appeared also to be advantages to the use of TIPS in terms of re-bleeding and total blood transfusion requirements (both statistically significant although the improvement in re-bleeding rate was modest). The outcome measure “unresolved varices” appeared to favour endoscopic injection of N-butyl-2-cyanoacrylate**.** However, it was felt that this measure was of debatable value since sclerotherapy can lead to encasement of varices and thus give a spurious impression of resolution. There was no noteworthy difference in length of hospital stay
Trade off between clinical benefits and harms	The incidence of encephalopathy was increased after TIPS in comparison to treatment with endoscopic injection of N-butyl-2-cyanoacrylate**.** The GDG believe this to be a real difference and of clinical significance. The encephalopathy is not necessarily acute and obvious; the GDG are aware of case series demonstrating chronic low-grade mental impairment. Concerns have been raised about sepsis after TIPS, but the studies did not demonstrate any significant increase.
Economic considerations	Only one economic study was identified. Unfortunately this was a retrospective study from a Unit in which patients were treated with TIPS until 1999 and then treated using sclerotherapy, with the obvious

	potential for confounding by other time-related changes in medical management (and indeed other non-medical factors, since time to discharge was an important component of the results and this may have been influenced by increasing pressures on hospital beds). Moreover, there was no Quality of Life measurement within the study. The GDG agreed that TIPS is a more expensive procedure than sclerotherapy.
Quality of evidence	The GRADE quality categories were noted. In general the GDG felt that these studies were well conducted given the difficulties of research in this acutely ill patient group. They noted however that the studies performed in the 1990's (those by Rossle and Sanyal) will have used uncovered stents not purposely designed for TIPS, and therefore may not reflect the benefits which can be achieved now.
Other considerations	The GDG were of the opinion that TIPS is the preferred option for bleeding gastric varices, and the available evidence supports this view. In practice patients will always have an endoscopy to assess the source of bleeding, and an attempt to stop the bleeding at that endoscopy is clearly appropriate rather than leaving the bleeding site alone and proceeding to immediately arrange TIPS. However, the GDG felt that TIPS should be the next procedure if bleeding continues. The GDG were aware that there are other materials than N-butyl-2-cyanoacrylate which might be used or have been used for endoscopic sclerotherapy procedures. However, these are currently either not available or are more expensive. Moreover, most of the evidence reviewed related to N-butyl-2-cyanoacrylate. At present not all hospitals receiving patients with GI bleeding have the facility to perform TIPS. The expense of the procedure and of setting up the facility at all sites was discussed, noting the relative rarity of bleeding gastric varices among causes of upper GI bleeding. The GDG felt that it would be preferable to establish networks in localities or regions, designed to permit rapid transfer of appropriate patients to centres with the relevant expertise. However, this need should not prevent them making a recommendation in favour of availability of TIPS.

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

Recommendations	• **Consider transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from oesophageal varices is not controlled by band ligation.**
Relative values of different outcomes	No studies were found comparing the use of TIPS to repeat endoscopy or balloon tamponade in variceal bleeding following an initial attempt at endoscopic treatment.
Trade off between	No formal evidence was available. The GDG believe that TIPS can be an

clinical benefits and harms	appropriate treatment in this scenario. They debated again the relatively limited availability of TIPS and acknowledged the potential risks of transferring a patient with uncontrolled variceal bleeding to another centre, agreeing that ultimately this is a decision which can only be made on an individual patient basis.
Economic considerations	The GDG again acknowledged that TIPS is a relatively expensive procedure, compared to endoscopic methods or balloon tamponade for control of bleeding.
Quality of evidence	No formal evidence was available.
Other considerations	In the absence of formal evidence comparing the options when initial endoscopic treatment has failed, the GDG debated the question in the light of their clinical experience. They were also aware of case series showing that TIPS can be successful in these cases, and also of (older) series showing that a surgical approach tends to have a high mortality. The results of conservative, supportive management alone were felt to be unacceptably poor. They recognised the difficulties in providing TIPS for all of these extremely unwell patients if this required transfer between hospitals, but felt that a recommendation should be made which prompted clinicians to consider TIPS as an option. They noted that this would be consistent with the recommendation for early consideration of TIPS specifically for gastric variceal bleeding

10 Control of bleeding and prevention of re-bleeding in patients on NSAIDs, aspirin or clopidogrel

10.1 Introduction

A significant proportion of acute peptic ulcer bleeds occur in patients taking Aspirin and NSAIDs. Aspirin and NSAIDs both suppress prostaglandin metabolism; this impairs mucosal protective mechanisms and predisposes to ulceration of the gastrointestinal mucosa. In addition, aspirin has direct toxic effects upon the gastroduodenal mucosa mediated by 'ion trapping'. Aspirin and NSAIDs therefore can cause ulcer formation or cause pre-existing ulcers to bleed. Aspirin and Clopidogrel both bind irreversibly to platelets to impair their ability to aggregate and stop bleeding; in clinical practice Clopidogrel is a more potent suppressor of platelet function than Aspirin and whilst this drug does not cause ulcers it does worsen the severity of bleeding once this has started. Since platelet binding by both Aspirin and Clopidogrel is irreversible, their anti-platelet effects persist for approximately 10 days until a new generation of platelets has been manufactured by the bone marrow

Clinicians have therefore withheld these drugs at the time of acute gastrointestinal bleeding, both because Aspirin and NSAIDs cause ulcers and predispose to ulcer bleeding and because Aspirin and Clopidogrel worsen the severity of bleeding by suppressing normal protective platelet function. There remains little controversy in relation to NSAIDs; these are used for pain relief (usually for arthritis); alternative drugs that do not cause peptic ulcers can be used until ulcer healing has been achieved and in selective patients (particularly patients with erosive arthritis) NSAIDs can be then re-introduced with a co-prescription of a Proton Pump Inhibitor drug to reduce the risk of ulcer recurrence. The situation concerning anti-platelet drugs is much less clear. These drugs are used to prevent vascular events (stroke or myocardial infarction) and in some clinical situations, for example in the months following coronary artery stent insertion, stopping Aspirin and/or Clopidogrel risks a life threatening thrombotic event. There is therefore a balance between the need to stop ulcer bleeding, which may have been precipitated by exposure of a patient to anti-platelet drugs, and the risk of vascular complications that could follow their discontinuation.

10.2 Clinical question and methodological introduction

In patients presenting with upper gastrointestinal bleeding 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?

Table 80: PICO Characteristics of the protocol

Clinical Methodological Introduction	
Population:	Adults with upper GI bleeding on any of the medications in the review question
Intervention:	Continuation of NSAIDs, Clopidogrel, Aspirin or Dipyridamol
Comparison:	Discontinuation
Outcomes:	• Mortality • Re-bleeding

Clinical Methodological Introduction	
	• Treatment failure (no initial haemostasis) • Other procedures to control bleeding • need for transfusion • Length of hospital stay • Adverse events (adverse events causing death and adverse events causing withdrawal from treatment)

We searched for RCTs and observational studies comparing the effectiveness of continuing NSAIDs, Clopidogrel, Aspiring or Dipyridamol (in patients presenting with UGIB who are already on this medication) compared to stopping this medication at the time of presentation to improve the outcomes. No studies were retrieved that investigated the continuation versus stopping of Clopidogrel, Dipyridamol and NSAIDs in patients presenting with acute upper gastrointestinal bleeding. One RCT was identified for low dose Aspirin continuation / discontinuation (see below). No other observational studies met inclusion criteria.

10.3 Clinical evidence review

One RCT [179] was identified comparing the clinical effectiveness of continuation of low dose Aspirin to discontinuation for patients with upper GI bleeding who are already on this medication (see flowchart in Appendix E for study selection). The study randomised patients to continue aspirin, or to receive a placebo, for 56 days. Table 49 summarises the main points of the study (see Appendix F for evidence tables and Appendix H for forest plots).

Table 81: Characteristics of included studies

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Sung, 2010 [179]	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.	Aspirin 80 mg once a day (N=78) All patients (intervention and comparison group) received PPIs and had endoscopic therapy	Placebo (N=78)	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); requirement of surgery; and

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOMES
				recurrence of acute ischemic events (the acute coronary syndrome and cerebrovascular accident).

Comparison of low dose Aspirin continuation versus discontinuation

Table 82: GRADE table for the comparison of low dose Aspirin continuation versus discontinuation

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Aspirin continuation (low dose) frequency (%)/Median (range)	Placebo frequency (%)/Median (range)	Relative Hazard ratio/ Median difference/ Risk Ratio (95% CI)	Absolute	
Mortality - Follow-up 30 days										
Sung, 2010 [179]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[a]	1/78 (1.3%)	7/78 (9%)	HR 0.20 (0.05 to 0.85)	71 fewer per 1000 (from 13 fewer to 85 fewer)	MODERATE
Mortality - Follow-up 56 days										
Sung, 2010[179]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	1/78 (1.3%)	10/78 (12.8%)	HR 0.20 (0.06 to 0.63)	101 fewer per 1000 (from 45 fewer to 120 fewer)	HIGH
Re-bleeding (confirmed 30 days)										
Sung, 2010[179]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	8/78 (10.3%)	4/78 (5.1%)	HR 1.9 (0.60 to 6.00)	44 more per 1000 (from 20 fewer to 219 more)	LOW
Surgery										

Quality assessment						Summary of findings				
Sung, 2010 [179]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	0/78 (0%)	1/78 (1.3%)	RR 0.33 (0.01 to 8.06)	9 fewer per 1000 (from 13 fewer to 91 more)	LOW
Length of hospital stay (Better indicated by less)										
Sung, 2010 [179]	randomised trial	serious[b]	no serious inconsistency	no serious indirectness	-[c]	Median (range) 5 (3-25)	4.5 (1-45)	1 (0.0 – 1.0)	-[c]	MODERATE
Blood transfusion requirements (Better indicated by less)										
Sung, 2010 [179]	randomised trial	serious[b]	no serious inconsistency	no serious indirectness	-[c]	Median (range) 2 (0-10)	3 (0-9)	0 (-1.0 – 0.0)	-[c]	MODERATE
Adverse events (acute ischemic - serious nonfatal)										
Sung, 2010 [179]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	2/78 (2.6%)	4/78 (5.1%)	RR 0.5 (0.09 to 2.65)	26 fewer per 1000 (from 47 fewer to 85 more)	LOW

[a] *When the confidence ranges from one appreciable benefit / harm to no effect imprecision is downgraded once and when the confidence interval of the effect spans from appreciable benefit all the way to appreciable harm imprecision is downgraded twice.*

For these outcomes only medians and ranges as well as median differences were reported in the study. However no statistics were provided. We therefore downgraded study quality (as a proxy for reporting of data) for these two outcomes.

[b] *No effect size and level of significance could be extracted – statistics not provided and only medians and ranges reported.*

10.4 Health economic evidence

No relevant economic evaluations were identified that compared discontinuation with continuation of medication for patients presenting with UGIB already on NSAIDs, clopidogrel, aspirin or dipyridamol (single or combination).

10.5 Evidence Statements

10.5.1 Clinical evidence

Mortality (30 day follow-up)

One study comprising 156 patients provided evidence for a lower rate of mortality (with longer length of survival) in patients continuing with a low dose aspirin compared to those that discontinue aspirin treatment. This effect reached both a statistical and clinical significant difference (MODERATE QUALITY).

Mortality (56 day follow-up)

One study comprising 156 patients provided evidence for a lower rate (and longer length of survival) of mortality in patients continuing with a low dose aspirin compared to those that discontinue aspirin treatment. This effect reached both a statistical and clinical significant difference (HIGH QUALITY).

There were 11 deaths at 56 day follow-up. 6 patients died of cardiovascular events (1 in Aspirin group 5 in placebo group); 3 patients had gastrointestinal complications and 2 deaths were related to pneumonia.

Confirmed re-bleeding

In one study with 156 participants the rate of re-bleeding was higher in the aspirin continuation group. However, this relative difference did not reach statistical / clinical significance (LOW QUALITY).

Need for surgery

In one study with 156 patients no patient required surgery in the aspirin continuation group compared to 1 patient in the discontinuation group. This was not a statistical / clinical significant difference (LOW QUALITY).

Length of hospital stay

One study comprising 156 participants showed a median difference of half a day in length of hospital stay in favour of the discontinuation group which was not statistically significant according to the authors. In both groups the hospital stay had a very wide range of 1-45 days (MODERATE QUALITY).

Blood transfusion requirements

Evidence from one study with 156 patients showed that the median difference of 1 unit lower blood transfusion requirement in the continuation group compared to the discontinuation group did not reach significance according to the authors. The range of units transfused was 0 to 10 (MODERATE QUALITY).

Adverse events (acute ischemic - serious nonfatal)

One study comprising 156 patients reported fewer acute ischemic adverse events in the continuation group compared to the discontinuation group. However, the number of these events was very low (2

in the continuation and 4 in the discontinuation group) and this difference did not reach statistical / clinical significance (LOW QUALITY).

10.5.2 Health economic evidence

No relevant economic evaluations were identified that compared discontinuation with continuation of medication for patients presenting with UGIB already on NSAIDs, clopidogrel, aspirin or dipyridamol (single or combination).

10.6 Recommendations and links to evidence

In patients presenting with upper gastrointestinal bleeding 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?

Recommendations	• **Continue low-dose aspirin for secondary prevention of vascular events in patients with upper gastrointestinal bleeding in whom haemostasis has been achieved.** • **Stop other non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 [COX-2] inhibitors) during the acute phase in patients presenting with upper gastrointestinal bleeding.** • **Discuss the risks and benefits of continuing clopidogrel (or any other thienopyridine antiplatelet agents) in patients with upper gastrointestinal bleeding with the appropriate specialist (for example, a cardiologist or a stroke specialist) and with the patient.**
Relative values of different outcomes	Mortality, either from gastrointestinal bleeding or vascular events, was the most important outcome. Evidence was available for aspirin, but not for clopidogrel or NSAID's, and showed that mortality was higher when aspirin was stopped in patients presenting with acute GI bleeding. The occurrence of vascular events (cerebro- or cardiovascular) and re-bleeding rates were also felt to be particularly important. Here the evidence was as expected, and showed that there were fewer acute ischemic events when aspirin was continued, but a greater rate of proven re-bleeding. Neither of these outcomes reached statistical significance.
Trade off between clinical benefits and harms	The GDG noted that the drugs considered here (aspirin, dipyridamole, clopidogrel, and NSAIDs) have distinct features. All have been implicated as potential causes of upper GI bleeding, but unlike the others NSAID's do not have anti-platelet effects which might increase bleeding. Moreover the indications for using them differ. NSAIDs are used as anti-inflammatory agents, whereas aspirin, dipyridamole and clopidogrel are generally used to prevent cardiovascular complications, and the GDG felt that patients with a predisposition to these may be at increased risk of significant events during the acute phase of bleeding due to physiological instability. Clearly this must be balanced against the potential for the agents to increase the severity or duration of GI

	bleeding. When considering the use of non-steroidal anti-inflammatory drugs in patients with upper gastrointestinal bleeding the GDG considered the risks of uncontrolled symptoms against effects on the duration and severity of bleeding.
Economic considerations	No health economic evidence was available for consideration in relation to this question. It was noted that as the question relates to the decision to potentially stop treatments already prescribed, a key consideration was one of patient safety. The GDG considered the trade off between adverse bleeding and vascular events, which is likely to influence the cost effectiveness of the interventions. .
Quality of evidence	A single RCT was found investigating the continuation or discontinuation of low dose aspirin in the setting of acute gastrointestinal bleeding. By GRADE criteria the evidence for outcomes from this study was of predominantly moderate to high quality for the outcomes considered. The paper looked at patients taking aspirin as secondary prophylaxis; where primary prophylaxis was the indication, the patient was excluded from the study. The GDG also noted that aspirin was stopped for 56 days, but that a difference between study arms was apparent at 30 days. This RCT was conducted in Asia and the GDG discussed the applicability to a UK population. However, they were satisfied that this appeared to be a well performed study, and felt that the effects of aspirin in the Hong Kong population are sufficiently similar to the UK to allow extrapolation. No trials were found investigating the continuation or discontinuation of clopidogrel, dipyridamole or non-steroidal anti-inflammatory drugs in the setting of acute gastrointestinal bleeding.
Other considerations	The GDG felt that different considerations apply to the management of these medications during the acute phase and the longer term. The GDG noted that the available RCT demonstrated a significantly reduced mortality when aspirin was continued in patients admitted with upper gastrointestinal bleeding. Excess deaths in those patients in whom aspirin was discontinued were a function of cardiovascular events. No significant effect was noted on the rate of re-bleeding, length of stay or blood transfusion requirements. Additionally the GDG felt it important to emphasise that the patients included within this study had a proven history of vascular disease and were taking aspirin for secondary prophylaxis. Clearly a different balance of risks and benefits applies to those taking aspirin as primary prophylaxis or for uncertain indications. The GDG also noted that the anti-platelet effect of aspirin persists for at least 7 days after discontinuation, and that stopping the drug for a brief period during an acute bleed was unlikely to have a significant impact upon the severity of bleeding. In practice, the likely chain of events is that aspirin will not be given for a brief period while patients with upper GI bleeding are prepared for endoscopy but, providing haemostasis can be secured at endoscopy, the appropriate recommendation is to continue aspirin thereafter.

	Clopidogrel was felt to be worthy of separate consideration as anecdotally it was felt that bleeding in patients taking the drug is more severe than that encountered in patients taking aspirin. Unfortunately no evidence specific to clopidogrel was found, an evidence gap which will become more important since this agent is likely to be prescribed more frequently in the near future as it becomes less expensive and familiarity with its benefits increases. Due to the lack of evidence the GDG felt that it could not make any general recommendation for clopidogrel. The prescription of clopidogrel to maintain the patency of coronary artery stents was considered to be a special and potentially high-risk situation requiring discussion with a cardiologist to decide upon the most appropriate course of management. Where clopidogrel was prescribed for a non-cardiac indication the treating physician may need to seek advice from an alternative specialist. The GDG felt that the lack of evidence relating to the continuation or discontinuation of dipyridamole prevented a meaningful recommendation from being made. However, this seemed less important since use of dipyridamole is likely to become less prevalent due to the off-patent availability of clopidogrel. The GDG felt that, at least during the acute phase, any increase in pain symptoms as a result of the discontinuation of non-steroidal anti-inflammatory drugs could be managed by employing alternative analgesic agents. The need for restarting an NSAID after the acute GI bleed should be based on clinical judgement of each patient's individual circumstance. In all cases it was felt very important to involve patients, and their carers, in discussions relating to the potential risks and benefits of continuing or stopping any of these medications.

11 Primary prophylaxis for acutely ill patients in critical care

11.1 Introduction

Patients who are established inpatients and who then develop acute upper gastrointestinal bleeding have a hospital mortality of approximately 25%. This is because inpatients generally have more medical comorbidity than patients who present in the community. Most deaths from gastrointestinal bleeding occur as a consequence of the physical stress of the bleed or its treatments (particularly a surgical operation) that leads to decompensation of these comorbidities. It follows therefore that patients who bleed whilst undergoing treatment in ITU/HDU settings, and who inevitably have one or more severe medical comorbidities, are at very high risk of death. Strategies that prevent gastrointestinal bleeding in ITU/ HDU are therefore attractive.

The commonest causes of significant bleeding in this group of patients are gastric and duodenal ulcers. In some patients these are assumed to be classical peptic ulcers that develop as a consequence of Helicobacter Pylori infection and/or exposure to NSAIDs or Aspirin, but in some cases (particularly in patients with extensive burns or head injury patients) 'stress ulcers' may be responsible. Stress ulcers are thought to arise from mucosal ischemia as a consequence of altered mucosal blood flow. It is accepted that in both classical peptic ulcers and stress ulcers that acid, secreted by the stomach, is an important factor in causing the ulcer.

Prevention of acute gastrointestinal bleeding in ITU settings has focused upon inhibiting acid secretion using H2 Receptor antagonist and Proton Pump Inhibiting drugs, neutralising gastric acid using antacids and enhancing mucosal protection using Sucralfate. Pharmacological suppression of acid secretion is now most widely used, but the efficacy of this approach has not been defined. There are potential complications of profound reduction in gastric acid secretion. The most important of these relates to bacterial contamination of the upper gastrointestinal tract since acid effectively sterilises the stomach and upper small bowel. It is possible that powerful acid suppression could therefore result in pneumonia as bacteria rich gastric contents are aspirated into the upper airways (so called 'nosocomial pneumonia'). The altered bacterial gastrointestinal fluid could also predispose to the development of Cl Difficile infection; a potentially fatal condition in these seriously ill patients.

11.2 Clinical question and methodological introduction

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?

Table 83: PICO Characteristics of clinical question

Clinical Methodological Introduction	
Population:	• Patients in high dependency / intensive care units: • Patients who require mechanical ventilation • Any patients with at least 1 of the following in addition were classified as higher risk: • Sepsis or hypotension; • Hepatic or renal failure;

Clinical Methodological Introduction	
	• Burns over 35% of total body surface area • Head trauma with Glasgow Coma Scale < 10 • Multiple trauma
Intervention:	PPI or H_2-RA (include patients on sucralfate)
Comparison:	Placebo (H_2-RA versus placebo or PPI versus placebo and PPI versus H_2-RA)
Outcomes:	Primary outcome: • Upper GI bleeding Secondary outcomes: • Ventilator associated pneumonia • Mortality • Duration of ICU stay • Duration of intubation • Blood transfusions • Adverse events

We searched for randomised controlled trials comparing the effectiveness of Proton Pump Inhibitors (PPI) or H_2-receptor antagonists (H_2-RA) as prophylactic interventions for the clinical effectiveness in the prevention of upper GI bleeding for patients in high dependency / intensive care units.

11.3 Clinical evidence review

22 randomised control trials (RCTs) were identified. One trial randomised patients into 3 groups: PPI, H_2-RA and placebo (see flowchart in Appendix E for study selection).18 studies included a comparison between H_2-RA treatment and placebo. The remaining 3 papers directly compared H_2-RA and PPI treatment. The aim of all papers was to investigate which pharmacological treatment works best to prevent upper GI bleeding in patients who are hospitalised in either high dependency or intensive care units. The 'at risk' status of patients, with regards to upper GI bleeding, varied between studies. It was assumed that those with higher risk status would also be at a higher need for prophylaxis and therefore studies were subgrouped by 'high' or 'low' risk status. Often an average risk factors number was given and patient groups from studies using a population with ≥ 3 were placed in the 'high' risk group. Some studies used the Glasgow coma scale to define risks. In other studies patients requiring mechanical ventilation were defined as 'high risk'. When none of these were explicitly reported, patients were categorised on an 'ad hoc' basis as described in Table 2. In case of heterogeneity of results subgroup analysis was undertaken (see Appendix F for evidence tables and Appendix H for forest plots).

Table 84: Characteristics of included studies

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
Apte 1992 [180]	H_2-RA versus Placebo (n=34)	Patients admitted to intensive care units with tetanus and tracheostomy. 5 H_2-RA patients and 4 control patients required mechanical ventilation. The	H_2-RA group had lower median days of intubation (7.5 versus 12.5). Note	Ranitidine 50mg/6 hrs (200mg/24 hrs)	LOW

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
		median maximum tetanus severity score was 11 for the H_2-RA group and 10 in the control group.	also that no placebo given to control group. No statistical testing. Possibly favours H2RA group		
Ben Menachem 1994 [181]	H_2-RA versus placebo (N=200)	All medical ICU admissions. 15% of control group and 10% of H_2-RA group had no further risk factors for stress-related haemorrhage. However mean risk factor scores were 2.5 (1.8) in the H_2-RA group and 2.0 (1.5) in the placebo group.	No significant baseline differences	Cimetidine 300mg bolus initially, followed by a continuous infusion titrated to keep gastric pH >4.	LOW
Burgess 1995 [182]	H_2-RA versus placebo (N=34)	Adults with severe head injury and a Glasgow coma scale score ≤ 10 admitted to ICU. All patients were comatose on admission and required ventilatory support. There were no significant differences in the number or type of risk factors and all patients had at least two risk factors (e.g., mechanical ventilation, multiple trauma, organ system failure, coagulopathy, surgery).	No significant baseline differences	Ranitidine 6.25 mg/hr for a max of 72 hours (150mg/24hrs)	HIGH
Chan 1995 [183]	H_2-RA versus placebo (N=101)	Patients suffering from nontraumatic neurosurgical lesions with 2 or more risk factors for UGIB. Median (range) number of risk factors: H2-RA: 2 (2-5) Placebo 2 (2-5) Median (range) pre-op GCS: H2-RAs: 6 (3-8) Placebo 6 (3-8)	No statistical testing for baseline differences, but groups appeared similar.	Raniditine 50mg iv/6 hrs (200mg/24hrs)	HIGH
Conrad 2005 [184]	H_2-RA versus PPI (N=359)	In ICU with an anticipated stay of 72 hours or more; required mechanical ventilation for 48 hours or more; 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	Significantly higher (worse) APACHE score in the PPI group. Favours H2-RA	Cimetidine (H2-RA) Initial 300mg bolus followed by 50mg/hr (1200mg/24 hrs) Omeprazole (PPI) 40mg 2xpd	HIGH

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
		injury, multiple trauma, major surgery, extensive burns, acute renal failure, acid-base disorder, coagulopathy, marked jaundice, coma, hypotension, shock, sepsis).		on first day, then 40mg/day thereafter 40mg/24 hrs	
Friedman 1982 [185]	H_2-RA versus Placebo (n=25)	Patients receiving mechanical ventilation <12 hours. The duration of ventilation (unknown if mean or median) was 6.2 days for the H_2-RA group and 9.2 days for the placebo group.	No significant baseline differences	Cimetidine 300mg iv/6 hrs (1200mg/24hrs)	LOW
Groll 1986 [186]	H_2-RA versus placebo (N=221)	Patients in ITU, of which 62% had 2 or more risk factors: major operative procedure, respiratory failure, sepsis, shock, trauma, coma, renal failure, liver failure	No statistical testing done on baseline differences but placebo group had double the patients with sepsis. Potentially favouring H2-RA group	Cimetidine 300mg iv/6 hrs (1200mg/24hrs)	LOW
Halloran 1980 [187]	H_2-RA versus Placebo (n=50)	Patients admitted to intensive care units with severe closed head injury within the previous 12 hours; unable to obey simple commands	No significant baseline differences	Cimetidine 300mg iv/4 hrs (1800mg/24hrs)	HIGH
Hanisch 1998 [188]	H_2-RA versus Placebo (n=50)	Patients admitted to intensive care units. Mean APACHE II score was 19 (range 2-30) in the H_2-RA group and 18 (1-28) in the placebo group.	No statistical testing of baseline differences, but appeared comparable.	Raniditine One-off dose of 3x50mg intravenously.	LOW
Kantorova 2004 [189]	H_2-RA versus PPI versus placebo (N=287)	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.	No significant baseline differences	Omeprazole (PPI) 40mg iv 1xpd; 40mg/24 hrs Famotidine (H2-RA) 40mg 2xpd 80mg/24 hrs	HIGH
Karlstadt 1990 [190]	H_2-RA versus	ICU patients had to have at least one of the following	More H2-RA patients with	Cimetidine initial 300mg	LOW

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
	Placebo (n=87)	risk factors: major abdominal or thoracic surgery; major multiple trauma; hypotension (decrease in 30 systolic and 20 diastolic); hypovoleamic shock; sepsis; acute respiratory failure.	3 risk factors. No statistical testing on these differences. Possibly favours placebo.	dose infused over 15-20 minutes, followed by a continuous infusion at the rate of 50mg/hr (1200mg/24 hrs)	
Levy 1997 [191]	H_2-RA versus PPI (N=67)	Admitted to ICU and 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). Mean number of risk factors 2.3. Mean APACHE II score (SD): PPI - 17.5 (7.7); H_2-RA – 20.2 (9.4)	H2-RA group had significantly higher number of risk factors/patien t (2.7 versus 1.9). Favours PPI	Ranitidine (H2-RA) 150mg iv/24hrs Omeprazole (PPI) 40mg orally /24hrs	HIGH
Macdougall 1977 [192]	H_2-RA versus Placebo (n=50)	Patients admitted to liver failure unit with grade IV coma for intensive care	No baseline comparison done. Possible bias either way	Metiamide used in first 10 patients, then cimetidine in final 16 patients of the H2-RA group. 150mg of metiamide or cimetidine iv infused at a rate of 100mg/hr. Dose repeated as necessary to keep gastric pH>5. Unclear 24 hr dose	HIGH
Martin 1993 [193]	H_2-RA versus Placebo (n=131)	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	H_2-RA group significantly higher (worse) APACHE score. Favours placebo	Cimetidine iv infusion of 50-100 mg/hr (1200-2400 mg/24 hrs)	LOW
Metz 1993 [194]	H_2-RA versus Placebo	Patients admitted to intensive care units with an expected stay of at least 72	No significant baseline differences	Ranitidine 6.25 mg/hr (150mg/24 hrs)	HIGH

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
	(N=167)	hours, with severe head injury (Glasgow coma sore ≤10) in previous 24 hours; at least 18 years old; nasogastric tube in place. 93% of the H_2-RA group and 80% of the placebo group had mechanical ventilation at study entry. 41% of each group had a GCS <6.			
Misra 2005 [195]	H_2-RA versus Placebo (N=92)	Patients with CT-proven intra cranial haemorrhage within 7 days of ictus were included. None on ventilator and all on general ward.	No significant baseline differences	Ranitidine 50 mg/8 hr (150mg/24 hrs)	LOW
Nagasue 1984 [196]	H_2-RA versus Placebo (N=52)	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 H_2-RA 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.	No significant baseline differences	Cimetidine 200mg /6hrs for at least one week (800mg/24hrs)	LOW
Reusser 1990 [197]	H_2-RA versus Placebo (N=28)	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)	No significant baseline differences	Ranitidine 50 mg iv /8 hrs (150mg/24 hrs). Increased to 200mg/24 hrs if gastric pH dipped below 4. NB: antacids also given.	HIGH
Ruiz Santana 1991 [198]	H_2-RA versus Placebo (N=49)	Patients admitted to intensive care units with an expected duration of 6 days of mechanical ventilation;	No significant baseline differences	Ranitidine 50mg iv every 6 hrs (200mg/24hrs)	LOW

STUDY	COMPAR-ISON	POPULATION CHARACTERISTICS	Baseline equivalence	Type and dose of H2RA or PIP	RISK LEVEL OF PATIENTS
		metabolic stress; haemodynamically stable; normal hepatic and renal function; on total parenteral nutrition (starting on 3rd day of ICU admission)			
Somberg 2008 [199]	H_2-RA versus PPI (N=202)	ICU patients 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.	No statistical testing of baseline differences, but appeared comparable.	Cimetidine (H2-RA) Initial 300mg bolus followed by 50mg/hr for 2 - 7 days (1200mg/24 hrs) Pantoprazole (PPI). 5 different dosing regimens compared – from 40mg/24 hrs to 240mg/24 hrs	HIGH
van den Berg 1985 [200]	H_2-RA versus Placebo (N=28)	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. Risk factors included mechanical ventilation; fall in systolic blood pressure below 100 mg Hg lasting over 2 h, sepsis, jaundice, renal insufficiency, peritonitis.	9/14 H_2-RA patients and 4/14 placebo patients had 3 or more risk factors. No statistical testing for these differences. Possibly favours placebo	Cimetidine 20mg/kg per 24 hr (1400mg/24 hrs for 70kg patient)	HIGH
Zinner 1981 [201]	H_2-RA versus Placebo (N=200)	Patients admitted for at least 48 hrs to surgical intensive care units. Mean illness severity score was 2.1 in the H2-RA group and 2.3 in the placebo group.	No statistical testing of baseline differences, but appeared comparable.	Cimetidine 300mg/6 hrs iv for entire duration of ICU stay (1200mg/24 hrs)	LOW

Comparison of PPI treatment versus placebo

Table 85: GRADE table for PPI versus placebo

Quality assessment						Summary of findings				
						No of patients				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI Frequency (%), Mean (sd), Median (range)	Placebo Frequency (%), Mean (sd), Median (range)	Relative Risk (95% CI)	Absolute effect, Mean difference (95% CI)	
Mortality (inpatient mortality)										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	14/72 (19.4%)	13/75 (17.3%)	RR 1.12 (0.57 to 2.22)	21 more per 1000 (from 75 fewer to 211 more)	LOW
Bleeding (during hospital admission)										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	1/72 (1.4%)	1/75 (1.3%)	RR 1.04 (0.07 to 16.34)	1 more per 1000 (from 12 fewer to 205 more)	LOW
Nosocomial Pneumonia										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	8/72 (11.1%)	5/75 (6.7%)	RR 1.67 (0.57 to 4.86)	45 more per 1000 (from 29 fewer to 257 more)	LOW
Length of ICU stay (Better indicated by lower values)										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	N=72, 7.7 (7.3)	N=75, 8.6 (11.3)	-	MD 0.9 lower (3.96 lower to 2.16 higher)	LOW
Days on ventilator (Better indicated by lower values)										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	N=72, 6.6 (9.5)	N=75, 6.1 (10.4)	-	MD 0.5 higher (2.72 lower to 3.72 higher)	LOW

[a]The CIs were consistent with both a clinically significant benefit and harm.

Comparison H_2-RA treatment versus placebo

Table 86: GRADE table for H_2RA versus placebo – lighter shaded outcome rows with indented and italicised font indicate subgroups of an outcome.

Quality assessment						Summary of findings				
						No of patients				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	H_2-RA Frequency (%), Mean (sd), Median (range)	Placebo Frequency (%), Mean (sd), Median (range)	Relative Risk (95% CI)	Absolute Effect, Mean Difference (95% CI)	
Mortality (length of follow-up varied from 24 hrs to 6 months*										
Studies – see subgroups below	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	125/818 (15.3%)	132/792 (16.7%)	RR 0.93 (0.77 to 1.11)	12 fewer per 1000 (from 40 fewer to 19 more)	VERY LOW
Mortality by risk level - High risk										
MacDougall 1977 [192], van den Berg 1985 [200], Reusser 1990 [197], Burgess 1995 [182], Kantorova 2004 [189]	*randomised trials*	serious[a]	*no serious inconsistency*	*no serious indirectness*	*very serious[b]*	*41/230 (17.8%)*	*41/234 (17.5%)*	*RR 0.91 (0.72 to 1.15)*	*3 fewer per 1000 (from 74 fewer to 101 more)*	*VERY LOW*
Mortality by risk level - Low risk										
Zinner 1981 [201], Nagasue 1984 [196], Groll 1986 [186], Karlstadt 1990 [190],	*randomised trials*	serious[a]	*no serious inconsistency*	*no serious indirectness*	*very serious[b]*	*84/588 (14.3%)*	*91/558 (16.3%)*	*RR 0.96 (0.72 to 1.26)*	*7 fewer per 1000 (from 46 fewer to 42 more)*	*VERY LOW*

Ruiz-Santana 1991 [198], Martin 1993 [193], Ben Menachem 1994 [181], Hanisch 1998 [188], Misra 2005 [195]										
Bleeding (variable follow-up length to a maximum of 6 months)*										
See subgroups below for studies for this outcome	randomised trials	serious[a]	serious[c]	no serious indirectness	serious[b]	87/1002 (8.7%)	160/978 (16.4%)	RR 0.55 (0.42 to 0.71)	75 fewer per 1000 (from 52 fewer to 95 fewer)	VERY LOW
Bleeding by risk level - High risk										
MacDougall 1977 [192], Halloran 1980 [187], van den Berg 1985 [200], Reusser 1990 [197], Metz 1993 [194], Burgess 1995 [182], Chan 1995 [183], Kantorova 2004 [189]	*randomised trials*	serious[a]	*very serious[c]*	*no serious indirectness*	*no serious imprecision*	*30/391 (7.7%)*	*69/391 (17.6%)*	*RR 0.40 (0.26 to 0.62)*	*106 fewer per 1000 (from 67 fewer to 131 fewer)*	*VERY LOW*
Bleeding by risk level - Low risk										
Zinner 1981 [201], Friedman 1982 [185], Nagasue 1984 [196], Groll 1986 [186], Karlstadt 1990 [190], Ruiz-Santana	*randomised trials*	serious[a]	*no serious inconsistency*	*no serious indirectness*	*serious[b]*	*57/611 (9.3%)*	*91/587 (15.5%)*	*RR 0.65 (0.47 to 0.89)*	*54 fewer per 1000 (from 17 fewer to 82 fewer)*	*LOW*

1991 [198], Apte 1992 [180], Martin 1993 [193], Ben Menachem 1994 [181], Hanisch 1998 [188], Misra 2005 [195]										
Nosocomial Pneumonia										
Karlstadt 1990 [190], Apte 1992 [180], Metz 1993 [194], Martin 1993 [193], Ben Menachem 1994 [181], Hanisch 1998 [188], Kantorova 2004 [189]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	*serious*[b]	58/438 (13.2%)	53/423 (12.5%)	RR 1.1 (0.79 to 1.52)	13 more per 1000 (from 26 fewer to 65 more)[3]	LOW
Length of ICU stay (Better indicated by lower values)										
Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[b]	N=71, 10.1 (9.8)	N=75, 8.6 (11.3)	-	MD 1.5 higher (1.93 lower to 4.93 higher)	LOW
Days on ventilator (Better indicated by lower values)										
Ruiz-Santana 1991 [198], Kantorova 2004 [189]	randomised trials	serious[a]	serious[c]	no serious indirectness	very serious[b]	N=19, 10 (7); N=71, 7.3 (8.4)	N=30, 19 (9); N=75, 6.1 (10.4)	-	MD 0.13 lower (2.66 lower to 2.4 higher)	VERY LOW
Transfusion requirements (mean units of blood transfused - better indicated by lower values)										
Ben Menachem 1994 [181]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	N=100, 1.6 (1.3)	N=100, 1.2 (1.4)	-	MD 0.4 higher (0.03 to 0.77 higher)	VERY LOW

Need for blood transfusion										
Halloran 1980 [187], Zinner 1981 [201], Nagasue 1984 [196], Apte 1992 [180], Chan 1995 [183]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	19/225 (8.4%)	43/212 (20.3%)	RR 0.44 (0.27 to 0.71)	114 fewer per 1000 (from 59 fewer to 148 fewer)	LOW
Adverse events										
Halloran 1980 [187], Friedman 1982 [185], Karlstadt 1990 [190], Martin 1993 [193], Chan 1995 [183]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	41/205 (20%)	38/189 (20.1%)	RR 1.12 (0.77 to 1.63)	24 more per 1000 (from 46 fewer to 127 more)	MODERATE

[a] *The 19 RCTs varied in quality, with most having serious limitations including selection, performance, attrition and detection bias. 13 RCTs had 2 or more serious limitations, 4 had one limitation and 2 had no serious limitations. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly in the study limitations column. It should be noted that un-blinding was not regarded as a relevant limitation for mortality and bleeding, and so these outcomes tended to be downgraded less. When downgraded twice the majority of information from studies for this outcome has two or more risks of bias when downgrade once the majority of information was from studies with one main risk of bias.*
[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*
[c] *If the heterogeneity was moderately high, the inconsistency was graded as serious, and if heterogeneity was high then inconsistency was graded as very serious.*
[*] *Tests for subgroup differences were not significant.*

Comparison PPI versus H_2-RA treatment

Table 87: GRADE table for PPI versus H_2-RA

Quality assessment	Summary of findings		
	No of patients		Quality

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PPI Frequency (%), Mean (sd), Median (range)	H_2-RA Frequency (%), Mean (sd), Median (range)	Relative Risk (95% CI)	Absolute Effect, Mean Difference (95% CI)	
Mortality (whilst in hospital or up to 30 days)										
Levy 1997 [191], Kantorova 2004 [189], Conrad 2005 [184], Somberg 2008 [199]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	70/449 (15.6%)	47/322 (14.6%)	RR 1.22 (0.86 to 1.72)	32 more per 1000 (from 20 fewer to 105 more)	LOW
Bleeding (whilst in hospital or up to 30 days)										
Levy 1997 [191], Kantorova 2004 [189], Conrad 2005 [184]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	10/282 (3.5%)	23/287 (8%)	RR 0.45 (0.22 to 0.93)	44 fewer per 1000 (from 6 fewer to 63 fewer)	LOW
Any overt bleeding										
Conrad 2005 [184]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	34/178 (19.1%)	58/181 (32%)	RR 0.6 (0.41 to 0.86)	128 fewer per 1000 (from 45 fewer to 189 fewer)	LOW
Nosocomial Pneumonia										
Levy 1997 [191], Kantorova 2004 [189], Conrad 2005 [184], Somberg	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	45/449 (10%)	32/322 (9.9%)	RR 1.03 (0.66 to 1.62)	3 more per 1000 (from 34 fewer to 62 more)	VERY LOW

2008 [199]										
Length of ICU stay (Better indicated by lower values)										
Levy 1997 [191], Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[b]	N=32, 8.7 (6.9); N=72, 7.7 (7.3)	N=35, 7.8 (12); N=71, 10.1 (9.8)	-	MD 1.5 lower (3.92 lower to 0.92 higher)	LOW
Days on ventilator (Better indicated by lower values)										
Levy 1997 [191], Kantorova 2004 [189]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[b]	N=32, 8.8 (5.7); N=72, 6.6 (9.5)	N=35, 6.8 (7.8); N=71, 7.3 (8.4)	-	MD 0.51 higher (1.67 lower to 2.69 higher)	LOW
Serious adverse effects										
Somberg 2008 [199]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	73/167 (43.7%)	18/35 (51.4%)	RR 0.85 (0.59 to 1.22)	77 fewer per 1000 (from 211 fewer to 113 more)	LOW

[a] *The 4 RCTs varied in quality. 1 RCT had 2 or more serious limitations, 2 had one limitation and 1 had no serious limitations. Each outcome was covered by a differing combination of studies, and so each outcome has been downgraded accordingly in the study limitations column. It should be noted that un-blinding was not regarded as a relevant limitation for mortality and bleeding, and so these outcomes tended to be downgraded less.*

[b] *If the CIs were consistent with both a clinically significant and non-significant result the imprecision was graded as serious; if the CIs were consistent with both a clinically significant benefit and harm then imprecision was graded as very serious.*

11.4 Health economic evidence

One study was identified that included one of the relevant comparators. This is summarised in the economic evidence profile below. See also Evidence Table G.4 in Appendix G. There were no excluded studies.

Table 88: H2-receptor antagonist versus no prophylaxis – Economic study characteristics

Study	Limitations	Applicability	Other comments
Ben-Menachem 1996[202]	Potentially serious limitations (a)	Partially applicable (b)	Analysis developed from a US healthcare payer perspective (hospital based) and over a 7-day time horizon

Note: Very serious limitations/Potentially serious limitations/Minor limitations; directly applicable/Partially applicable/Not applicable.

(a) Based on systematic literature reviews, a decision analytic model was developed over a 7-day time horizon. The model adequately reflects the nature of the health condition. Cost components included were appropriate. No quality of life assessment was included in the analysis. A limited sensitivity analysis was performed.

(b) Analysis developed from a US perspective, assessing relevant interventions and a relevant population of patients, and reporting cost per bleeding episode averted. No QALY assessment was performed.

The US cost-effectiveness analysis by Ben Menachem and colleagues assessed primary prophylaxis interventions in patients at risk of stress-related haemorrhage admitted to the intensive care unit. Cimetidine, an H2-receptor antagonist, was compared to no prophylaxis. Ben-Menachem and colleagues believed that the length of stay in the intensive care unit was not affected by the prophylaxis. They stated that the additional length of stay reported by some studies was due to underlying diseases and was not directly attributable to the haemorrhage. The cost-effectiveness results were therefore driven by the cost of the medication and the probability of bleeding. The analysis concluded that prophylaxis was likely to be cost-effective in patients with high risk of stress-related haemorrhage. If alternatively it is assumed that the length of stay in ICU was affected by prophylaxis, then the intervention was cost saving.

Table 89: H2-rceptor antagonist versus no prophylaxis – Economic summary of findings

Study	Incremental cost (a,b,c)	Incremental effects	Cost effectiveness	Uncertainty
Ben-Menachem 1996	£153 per patient	3 bleeding episodes averted per 100 patients	£4,829 per bleeding episode averted	Prophylaxis is more cost effective in high-risk patients Prophylaxis is more cost effective when the risk reduction of bleeding with prophylaxis increases

Abbreviations: QALY = Quality-Adjusted Life-Years; LY = Life Year; ICER = Incremental Cost-Effectiveness Ratio.

(a) Published costs in USD were converted in pound sterling using Purchasing Power Parities.

(b) Cost components included: prophylactic medications, esophagogastroduodenoscopy, serial hematocrit determinations, drug therapy, blood transfusions, treatment of nosocomial pneumonia (in sensitivity analysis only – given the uncertainty of published evidence, it was assumed for the base case that prophylaxis does not alter the frequency of nosocomial pneumonia).

(c) The total cost per patient was estimated at £534 and £389 for the H2 antagonist group and the no prophylaxis group respectively.

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were presented to aid consideration of cost effectiveness. Two commonly used primary prophylactic drugs are ranitidine (H2-receptor antagonist) which is given 150mg twice daily (oral or IV) or omeprazole (PPI) which is given 40mg once daily (oral or IV). Ranitidine is less costly than omeprazole; with ranitidine costing 6.57p (oral) or £3.24 (IV) per day and omeprazole costing 13.71p (oral) or £5.18 (IV) per day.

11.5 Evidence statements

11.5.1 Clinical evidence

PPI versus Placebo

Mortality (inpatient mortality)

One study comprising 147 participants found that that the rate of mortality occurring in hospital in the PPI group did not differ significantly in statistical or clinical terms between PPI and placebo (LOW QUALITY).

Bleeding (during hospital stay)

One study comprising 147 participants did not find statistical / clinical significant prophylactic effects of PPIs compared to placebo for the prevention of upper GI bleeding whilst in hospital (LOW QUALITY).

Nosocomial pneumonia

One study comprising 147 participants found that that the rate of nosocomial pneumonia was not statistical / clinical significantly different between PPI and placebo (LOW QUALITY).

Length of ICU stay

One study comprising 147 participants found that the average length of ICU stay was not statistically / clinically significant different between PPI and placebo (LOW QUALITY).

Days on ventilator

One study comprising 147 participants found that the average days spent on ventilator was not statistically / clinically significant different between PPI and placebo (LOW QUALITY).

H_2-RA versus Placebo

Mortality

14 studies comprising 1610 participants found that that the rate of mortality (with all apart from one in-hospital) was not statistically / clinically significant different between H_2-RA and placebo for mortality (VERY LOW QUALITY).

These 14 studies were also sub-grouped into higher and lower risk for GI bleeding levels:

5 studies comprising 464 higher risk participants found that that there was no statistically / clinically significant difference between H_2-RA and placebo for mortality (VERY LOW QUALITY).

9 studies comprising 1146 lower risk participants found that that there was no statistically / clinically significant difference between H_2-RA and placebo for mortality (VERY LOW QUALITY).

Bleeding

19 studies comprising 1980 participants found that a statistically significant higher proportion of participants receiving H_2-RA showed a reduction in bleeding. This difference was large enough to indicate appreciable benefit from H2-RA treatment (VERY LOW QUALITY).

These 19 studies were also sub-grouped into higher and lower risk for re-bleeding levels:

8 studies comprising 782 higher risk participants found that a statistically significant higher proportion of participants receiving H_2-RA showed a reduction in bleeding. This higher proportion in favour of H2-RAs was large enough to indicate appreciable clinical benefit (VERY LOW QUALITY).

11 studies comprising 1198 lower risk participants found that a statistically yet not clinically significant higher proportion of participants receiving H_2-RA showed a reduction in bleeding (LOW QUALITY).

Pneumonia

7 studies comprising 861 participants found that that there was no statistical / clinical significant difference between H_2-RA and placebo for pneumonia (LOW QUALITY).

Length of ICU stay

1 study comprising 146 participants found that that there was no statistical / clinical significant difference between H_2-RA and placebo for length of ICU stay (LOW QUALITY).

Days on ventilator

2 studies comprising 195 participants found that that there was no statistical / clinical significant difference between H_2-RA and placebo for days on ventilator (VERY LOW QUALITY).

Transfusion requirements

1 study comprising 200 participants found that patients taking H2-RAs needed a statistically significant higher average number of units of packed red cell. However, it is unclear whether this increase is large enough to indicate clinical harm (VERY LOW QUALITY).

Need for blood transfusion

5 studies comprising 437 participants found that a statistically and clinically significant higher proportion of participants receiving H_2-RA showed improvement in need for blood transfusion (LOW QUALITY).

Adverse events

5 studies comprising 394 participants found that that there was no statistical / clinical significant difference between H_2-RA and placebo for adverse events (VERY LOW QUALITY).

PPI versus H_2-RA

Mortality

4 studies comprising 771 participants found that that there was no statistical / clinical significant difference between H_2-RA and PPI in rate of mortality (LOW QUALITY).

Bleeding

3 studies comprising 569 participants found that a statistically significant decrease in the proportion of participants experiencing bleeding for those receiving PPI compared to patients receiving H2-RAs. However, it is unclear whether the effect is large enough to indicate clear clinical benefit in favour of PPI treatment (LOW QUALITY).

Any overt bleeding

1 study comprising 359 participants found that a statistically significant higher proportion of participants receiving PPI showed a reduction in overt bleeding. However, it is unclear whether the effect is large enough to indicate clear clinical benefit in favour of PPI treatment (LOW QUALITY).

Pneumonia

4 studies comprising 771 participants found that that there was no statistical / clinical significant difference between PPI and H_2-RA for pneumonia (VERY LOW QUALITY).

Length of ICU stay

2 studies comprising 210 participants found that that there was no statistical / clinical significant difference between PPI and H_2-RA for length of ICU stay (LOW QUALITY).

Days on ventilator

2 studies comprising 210 participants found that that there was no statistical / clinical significant difference between PPI and H_2-RA for days on ventilator (LOW QUALITY).

Adverse events

1 study comprising 202 participants found that that there was no statistical / clinical significant difference between H_2- PPI and H_2-RA for adverse events (VERY LOW QUALITY).

11.5.2 Health economic evidence

Primary prophylaxis interventions in patients at high risk of stress-related haemorrhage admitted to the intensive care unit are likely to be cost effective.

The acquisition cost for H2-receptor antagonist is lower than for proton pump inhibitors.

The acquisition cost for the oral form of both H2-receptor antagonist and proton pump inhibitors is lower than the intravenous form.

11.6 Recommendations and link to evidence

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?

Recommendations	• **Offer acid-suppression therapy (H2-receptor antagonists or proton pump inhibitors) for primary prevention of upper gastrointestinal bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug.** • **Review the ongoing need for acid-suppression drugs for primary prevention of upper gastrointestinal bleeding in acutely ill patients when they recover or are discharged from critical care.**
Relative values of different outcomes	Acid suppressing therapy has not been shown to significantly affect mortality but they clearly do reduce the risk of acute upper gastrointestinal bleeding and blood transfusion requirements. The rates of adverse events, particularly ventilation associated with pneumonia and C Difficile infection were also considered and did not appear to be

	increased when acid-suppression is employed. The GDG noted that the available studies against placebo showed benefit from H2-receptor antagonists but not from PPI's (although only one study looked at this comparison for PPI). However, when the two forms of active agent were compared the only significant differences were in favour of PPI's.
Trade off between clinical benefits and harms	The GDG recognised that upper gastrointestinal haemorrhage may complicate the recovery of patients who are otherwise critically unwell. When this occurs in this group of patients it is often associated with very poor outcomes. Both proton pump inhibitors and H2-receptor antagonists were felt to be generally safe drugs. However the GDG recognised that there were concerns regarding the prescription of proton pump inhibitors and increased risk of hospital acquired pneumonia and *Clostridium difficile* associated diarrhoea. The GDG was reassured that the clinical evidence review showed no significant difference in the rates of pneumonia between patients receiving placebo and those receiving acid suppression therapy. It was felt, in discussion, that at an individual patient level the increased risk of *Clostridium difficile* associated diarrhoea was small, though an impact may be seen at a population level. In order to minimise this risk the GDG felt it important that the ongoing prescription of acid suppression therapy should be continuously reviewed, particularly on discharge from intensive or high dependency care, in order to minimise the duration of treatment.
Economic considerations	A single health economic evaluation of the prescription of H2-receptor antagonists for primary prophylaxis of upper gastrointestinal bleeding in the relevant patient population was found. The study was developed from US health perspective making applicability to the UK healthcare setting challenging. No quality of life evaluation was performed and results were reported in terms of cost per bleeding episode averted. It was noted that the acquistion costs of the drugs in question are cheaper in the current UK setting, with oral administration of H2-RA and PPIs being significantly cheaper than I.V. administration. Oral H2-RA had the lowest acquisition cost. Looking at the health economic evaluation presented and considering the changes in drug costs the GDG felt that acid suppression therapy as primary prophylaxis against upper gastrointestinal bleeding in critically ill patients was likely to be cost-effective.
Quality of evidence	A single study was available comparing the prescription of proton pump inhibitors to placebo. This showed no difference between placebo and proton pump inhibition across all outcomes. By GRADE criteria the quality of evidence was low for most outcomes and the GDG raised concerns that the study was inadequately powered. A number of studies compared the prescription of H2-receptor antagonists to placebo. By GRADE criteria the evidence provided by these studies for the outcomes considered was predominantly very low or low. The only outcome showing a significant difference was the rate of bleeding which came out in favour of H2-receptor antagonists. The

	effect was significant for both low and high risk patient groups, but its size was larger for higher risk patients. One study looked at transfusion need and appeared to indicate a benefit for placebo; however this was a clinical outlier in respect to a number of the other outcomes, those studies looking at the need for transfusion showed no significant difference. Four studies comparing proton pump inhibitors to H2-receptor antagonists were evaluated. A significant difference favouring proton pump inhibitors was found for the outcome of bleeding (or clinically overt bleeding in one study), but no difference was noted for any of the other outcomes. By GRADE criteria the quality of the evidence was assessed as low or very low.
Other considerations	The GDG felt that overall the body of evidence considered showed statistically and clinically significant benefit from acid suppression therapy for the primary prophylaxis of upper gastrointestinal bleeding in critically ill patients. It was felt that there was little to choose between H2-receptor antagonists and proton pump inhibitors and no difference favouring intravenous over oral preparations. Additionally H2-receptor antagonists have not been associated with an increased risk of *Clostridium difficile* associated diarrhoea. This, alongside its low acquisition cost, was likely to make oral H2-receptor antagonists the most appropriate choice. The GDG felt it important to emphasise that the prescription of acid suppression therapy in these patients was to cover a period of increased risk of upper gastrointestinal haemorrhage due to acute illness. Consequently patients started on acid suppressing drugs during this time should have them discontinued upon recovery and certainly upon discharge unless there were other indications for their ongoing prescription.

12 Information and support for patients and carers

12.1 Introduction

Acute gastrointestinal bleeding is obviously distressing for patients and their carers. Both will be very concerned about the consequences of the acute event in terms of being admitted to hospital, undergoing blood transfusion, perhaps undergoing surgery, whether recovery will be complete and the risk of dying from bleeding. Many patients are concerned about the possibility that cancer is responsible. In addition some of the diagnostic and therapeutic procedures are unpleasant and associated with risk of complications; endoscopy can be uncomfortable, particularly if it is prolonged and (as is often the case) difficult in the presence of active bleeding, TIPS insertion risks significant acute complications and may lead to altered consciousness from hepatic encephalopathy, emergency surgery for bleeding ulcer carries a high risk of post operative complications and death. Patients and their carers are concerned about the recurrence of bleeding after the acute event, both in hospital and after discharge into the community.

As with all acute illnesses, good clinical practice will include excellent communication between patient, carer and the clinical team. Such interaction is needed at all stages including the time of presentation, when investigations or treatments are delivered, when diagnostic and prognostic information is available and at time of discharge to home. This will lessen anxiety, facilitate decision making and reduce the risk of dissatisfaction (and litigation) should complications occur. Development of trust between all parties is essential, particularly if long term follow up (for example in patients with chronic liver disease) is necessary. Whilst in some other clinical situations it is correct to provide written information following interaction between doctor and patient, acute gastrointestinal bleeding is such a complex issue that this is usually inappropriate. For example whilst Clopidogrel therapy is stopped in some patients presenting with acute ulcer bleeding, in others (perhaps after recent coronary artery stent insertion) the drug is continued; in one patient with variceal bleeding banding of type 1 gastric varices is done whilst another patients with distal gastric varices is treated by histo-acryl injection. Outcome of bleeding is very much dependant upon the general health of the patient and heterogeneity of comorbidity makes the prediction of outcome very difficult in any one individual and presentation of written information regarding prognosis is unreliable. Having stated this, there are times where delivery of written information is appropriate- for example at the time of endoscopy or a surgical operation, written consent by the patient (or for patients who are incapable of understanding issues, their legal carer) is required. It must however be recognised that informed considered written consent is sometimes impossible to achieve; for example encephalopathic patients with torrential variceal bleeding cannot be reasonably considered to be able to debate and decide about treatment options; bleeding patients who are paralysed and ventilated in ITU are obviously not in a position to give consent to endoscopy and whilst the reasonable wishes of carers must obviously be respected, consent or its denial by others has limited legal status.

There are (very reasonably) no randomised trials relating to provision of information and whilst much has been written about patient attitudes, comfort and tolerance of elective endoscopy, there is no significant literature associated with acute gastrointestinal bleeding.

12.2 Clinical question and methodological introduction

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

Table 90: PICO Characteristics of clinical question

Clinical Methodological Introduction	
Population:	Patients with upper GI bleeding and their carers
Intervention:	Any types of information, experiences, educational leaflets etc.
Outcomes:	Any outcome that is reported by patients and carers

12.3 Clinical evidence review

We searched any studies reporting patient and carer information or patient experience of care provided for this condition (see flowchart in Appendix E for study selection).

No studies were identified for the relevant population of patients / carers.

12.4 Health economic evidence review

No studies were identified for the relevant population of patients / carers. There were no studies which were selectively excluded.

12.5 Evidence Statements

12.5.1 Clinical evidence

No studies were identified.

12.5.2 Health economic evidence

No studies were identified.

12.6 Recommendations and link to evidence

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

Recommendations	• **Establish good communication between clinical staff and patients and their family and carers at the time of presentation, throughout their time in hospital and following discharge. This should include:** - **giving verbal information that is recorded in medical records** - **different members of clinical teams providing consistent information** - **providing written information where appropriate** - **ensuring patients and their families and carers receive consistent information**
Relative values of different outcomes	No evidence was identified
Trade off between clinical benefits and harms	No evidence was identified

Economic considerations	No evidence was identified
Quality of evidence	No published literature available, recommendations were based upon consensus.
Other considerations	These recommendations are not specific to this topic, but represent good standard clinical practice for a clinical team managing all acute diseases. The GDG did discuss whether units should provide written information at all stages of the clinical course but concluded that this could be misleading or inappropriate since the causes, treatments and prognosis of bleeding differ between patients.

13 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.

Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness	An economic study design in which consequences of different

analysis (CEA)	interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.

Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard See 'Reference standard'.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See ‘Product licence’.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of

	transition between them within a given time period (cycle).
Massive bleeding local protocol	A local protocol is an Emergency Blood Management Plan for every hospital and provides guidance on clinical priorities for the use of large volumes of blood components. It includes guidance on the sequence of components, laboratory tests, blood bank arrangements and monitoring.
Massive haemorrhage/bleeding	In the acute care setting, massive haemorrhage/bleeding may be defined as having a 50% blood volume loss within 3 hours or a rate of loss of 150 ml per minute.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge,

	encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
Quality of life	See ‘Health-related quality of life’.
Quality-adjusted life	An index of survival that is adjusted to account for the patient’s quality

year (QALY)	of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the

	proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific

health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

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