Bleeding Peptic Ulcer
A Systematic Review

Summary and Conclusions
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Summary and Conclusions of the SBU Report:

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Bleeding peptic ulcer is a common condition, affecting 7–10 people a day in Sweden. Over 10% of patients suffer a recurrence of bleeding peptic ulcer or a different form of gastrointestinal haemorrhage within 12 months of the initial episode. Most serious cases of gastrointestinal bleeding, which has a high mortality rate, are caused by ulcers of the stomach or duodenum. This report covers the treatment and prevention of bleeding peptic ulcer.

**SBU’s Conclusions**

Bleeding peptic ulcer is an acute, life-threatening condition, but there are several effective methods of treatment. Even so, almost a quarter of patients die within a year of receiving treatment. Some of these fatalities could probably be avoided with improved preventive measures.

- Treatment to eradicate the bacterium *H. pylori*, by the administration of two antibiotics combined with a proton pump inhibitor, reduces the risk of a recurrence of bleeding peptic ulcer. This is true in patients who are not concurrently taking medication that can damage the lining of the gastrointestinal tract. Despite strong scientific evidence in support of this treatment approach, data from the Swedish Prescribed Drug Register indicate that many patients are currently not receiving this type of treatment.

- In patients who have suffered a bleeding peptic ulcer but who need continuing treatment with low-dose aspirin, the risk of re-bleeding can be reduced by preventive treatment, ie, *H. pylori* eradication, followed by the administration of a proton pump inhibitor.
Following an episode of bleeding peptic ulcer, patients should, if possible, avoid taking NSAIDs, including so-called coxibs. When, however, NSAID treatment must be continued, the risk of re-bleeding can be reduced by preventive measures, ie, \textit{H. pylori} eradication, followed by the administration of a proton pump inhibitor.

In patients who have not suffered an episode of bleeding peptic ulcer, but who have recognised risk factors for this, and who require long-term medication with an NSAID or low-dose aspirin, the risk of developing a bleeding peptic ulcer can be reduced by preventive treatment with a proton pump inhibitor.

Endoscopic examination (gastroscopy) of a patient with bleeding peptic ulcer is made easier if the patient is given a single dose of erythromycin before the investigation. This improves visibility for the endoscopist.

In patients with active bleeding, or a non-bleeding blood vessel in the base of the ulcer, the risk of re-bleeding and the need for surgery is reduced by endoscopic treatment with adrenaline injection combined with mechanical or thermal haemostasis.

Administration of a proton pump inhibitor after endoscopic treatment of a bleeding peptic ulcer further reduces the risk of re-bleeding and the need for surgery.

After endoscopic treatment of a bleeding peptic ulcer, systematic endoscopic review and further treatment as indicated, reduce the risk of recurrent bleeding.
Background and aims

Bleeding peptic ulcer is an acute, life-threatening condition that requires hospital admission. A recent survey shows that in 2005, around 38 per 100,000 of the Swedish population suffered an episode of bleeding peptic ulcer. There is a marked increase with advancing age, regardless of gender. In those aged over 75 years, 170 people per 100,000 are affected annually. This rate is gradually decreasing, probably because the prevalence of the bacterium implicated in the development of peptic ulcer, *Helicobacter pylori* (*H. pylori*), is decreasing in the population. It is currently estimated that in Sweden, 7–10 people develop a bleeding peptic ulcer every day, and there is a death from the condition every two or three days.

Although a bleeding peptic ulcer is a very common acute diagnosis in surgical units, acute medical units and emergency departments worldwide, there are many unanswered questions about how the condition should be managed and treated. The aim of this evaluation is to establish the scientific evidence base for the different treatments and combinations of treatment, and to highlight their ethical, social and health economic aspects.
The scope and purpose of the report

The purpose of this evaluation is to determine the benefits and risks associated with

- drug treatment of bleeding peptic ulcer (Chapter 3.1)
- endoscopic treatment of bleeding peptic ulcer (Chapter 3.2)
- surgical and endovascular treatment of bleeding peptic ulcer (Chapter 3.3)
- preventive treatment for patients after admission for bleeding peptic ulcer (Chapter 3.4)
- preventive treatment for patients with known risk factors for bleeding peptic ulcer (Chapter 3.5).

The ethical, social and health economic aspects are presented in Chapters 4 and 5.

The evaluation is restricted to studies of bleeding ulcers in the stomach and duodenum. Studies of bleeding from other parts of the gastrointestinal tract are not included, nor are studies of ulcers associated with gastrinoma (Zollinger-Ellison syndrome), or gastrointestinal bleeding of other origin, eg, from polyps, varicosities, tumours or other defects of the vascular walls. Studies of bleeding which has occurred during hospitalisation, eg, during intensive care or post-operatively, have also been excluded.
Method

SBU applies a thorough, systematic method, based on a search of the available databases, to identify all publications relevant to the subject in question. Every study included in the evaluation has been assessed for quality and tabulated according to a specially designed method. Quality assessment covers the relevance of the study to the question being addressed, methodological quality – study design, internal relevance (as a reasonable guarantee against systematic error), statistical power and generalisability. Quality assessment of the health economics publications has been made jointly by medical experts and health economists. The results have then been graded according to the strength of the scientific evidence.
**Facts 1** Study Quality, Relevance and Evidence Grading.

*Study quality* refers to the scientific quality of an individual study and its capacity to answer a specific question in a reliable way.

*Evidence grade* refers to the assessed strength of the collective body of scientific evidence and its capacity to answer a specific question in a reliable way. SBU uses an international evidence grading system called GRADE. Study design is the primary factor considered in the overall assessment of each outcome measure. Secondary factors that can increase or decrease the strength of the evidence include: study quality, relevance, consistency, transferability, effect size, data precision, risk of publication bias, and other aspects, eg, the dose-response relationship.

Evidence grades – four levels

**Strong scientific evidence** (⊕⊕⊕⊕)
Based on high or medium quality studies with no factors that weaken the overall assessment.

**Moderately strong scientific evidence** (⊕⊕⊕○)
Based on high or medium quality studies with isolated factors that weaken the overall assessment.

**Limited scientific evidence** (⊕⊕○○)
Based on high or medium quality studies having factors that weaken the overall assessment.

**Insufficient scientific evidence** (⊕○○○)
Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

The stronger the evidence, the lower the likelihood that new research findings would affect the documented results within the foreseeable future.

**Conclusions**
SBU’s conclusions present an overall assessment of benefits, risks, and cost effectiveness.
Evidence-graded results

Drug treatment of bleeding peptic ulcer

Before endoscopic treatment
• Treatment with high doses of a proton pump inhibitor for 24 hours before endoscopic diagnosis of bleeding peptic ulcer does not reduce mortality, the risk of recurrent bleeding, or the need for surgery (strong scientific evidence ⊕⊕⊕⊕). However, this measure may reduce the need for endoscopic treatment\(^1\) (strong scientific evidence ⊕⊕⊕). \(^{1}\)

After endoscopic treatment
• Treatment with a proton pump inhibitor after endoscopic diagnosis of bleeding peptic ulcer and primary endoscopic haemostasis reduces the risk of re-bleeding and the need for surgery\(^2\) (strong scientific evidence ⊕⊕⊕⊕). However, no difference can be demonstrated in total mortality\(^2\).

• Treatment with a proton pump inhibitor after endoscopic diagnosis of bleeding peptic ulcer and primary endoscopic haemostasis reduces the need for repeat endoscopic treatment\(^2\) (strong scientific evidence ⊕⊕⊕⊕).

• There is insufficient scientific evidence to determine the effect of treatment with tranexamic acid after endoscopic diagnosis of bleeding peptic ulcer and primary endoscopic haemostasis (⊕○○○○).

• There is insufficient scientific evidence to determine the effect of treatment with somatostatin after endoscopic diagnosis of bleeding peptic ulcer and primary endoscopic haemostasis (⊕○○○○).

\(^1\) The results are based on systematic reviews, with meta-analyses of studies in which the control groups received placebo, an \(H_2\) blocker or no active treatment.

\(^2\) The results are based on systematic reviews, with meta-analyses of studies in which the control groups received a placebo or an \(H_2\) blocker.
**Eradication of H. pylori**

- Treatment to eradicate *H. pylori* after an episode of bleeding peptic ulcer reduces the risk of recurrent bleeding within the following 12 months (strong scientific evidence ⊕⊕⊕⊕).

**Endoscopic treatment of bleeding peptic ulcer**

- Compared with no endoscopic treatment, endoscopic treatment of bleeding peptic ulcer classified as Forrest grades I and IIa reduces the need for surgery (strong scientific evidence ⊕⊕⊕⊕).

- Compared with no endoscopic treatment, endoscopic treatment of bleeding peptic ulcer classified as Forrest grades I and IIa reduces the risk of recurrent bleeding (strong scientific evidence ⊕⊕⊕⊕).

- There is contradictory scientific evidence on the effect of endoscopic treatment of bleeding peptic ulcer classified as Forrest grade IIb (insufficient scientific evidence ⊕○○○).

- The scientific evidence is insufficient to assess the effect of OGD and any associated endoscopic treatment within 12 hours of presentation at hospital with bleeding peptic ulcer (⊕○○○).

**The various endoscopic treatment**

- Supplementary thermal or mechanical endoscopic haemostasis of bleeding peptic ulcer reduces the need for surgery, compared with injection of adrenaline only (strong scientific evidence ⊕⊕⊕⊕).

- Supplementary thermal or mechanical endoscopic haemostasis of bleeding peptic ulcer reduces the risk of recurrent bleeding, compared with injection of adrenaline only (strong scientific evidence ⊕⊕⊕⊕).
Planned follow-up endoscopy

• Planned follow-up endoscopy to monitor the outcome of initial endoscopic treatment of bleeding peptic ulcer reduces the risk of recurrent bleeding (moderately strong scientific evidence ⊗⊗⊗○). However, no benefit can be shown with respect to total mortality or the need for surgery (moderately strong scientific evidence ⊗⊗⊗○). These studies evaluated treatment with a variety of acid-suppressing drugs.

Repeat endoscopic treatment

• Repeated endoscopic treatment to control bleeding which recurs following initial endoscopic treatment of bleeding peptic ulcer reduces the need for surgery (moderately strong scientific evidence ⊗⊗⊗○).

• Repeated endoscopic treatment to control bleeding which recurs following initial endoscopic treatment of bleeding peptic ulcer reduces the risk of surgical complications (moderately strong scientific evidence ⊗⊗⊗○).

Treatment before OGD

• Administration of a single dose of erythromycin before OGD for bleeding peptic ulcer improves visibility for the endoscopist during the procedure (strong scientific evidence ⊗⊗⊗⊗).

Risk of complications

• There is insufficient scientific evidence to demonstrate any possible differences in the risk of complications associated with the various endoscopic methods (⊕○○○). The overall frequency of complications associated with endoscopic treatment is low – less than 1%.
Surgical and endovascular treatment of bleeding peptic ulcer

- There is insufficient scientific evidence to identify those patients presenting with bleeding peptic ulcer that have such a high risk of endoscopic treatment failure that an alternative approach (surgery or endovascular treatment) should be considered immediately (⊕〇〇〇).

- There is insufficient scientific evidence to enable a comparison to be made between the effects of various surgical approaches to the treatment of bleeding peptic ulcer (⊕〇〇〇).

- There is insufficient scientific evidence to determine the effect of endovascular treatment of patients with bleeding peptic ulcer in whom endoscopic or surgical treatment has previously failed (⊕〇〇〇).

Lack of studies

- There is a lack of scientific evidence to allow comparison of endovascular and surgical treatment in cases of recurrent bleeding after endoscopic treatment of bleeding peptic ulcer (insufficient scientific evidence ⊕〇〇〇).

Preventive treatment of patients after admission for bleeding peptic ulcer

Patients who need to continue medication for pain relief

- The risk of recurrent bleeding in patients with arthritis or arthrosis who need to take an NSAID is about the same with a combination of diclofenac and omeprazole as it is with celecoxib (limited scientific evidence ⊕⊕〇〇).

- The risk of recurrent bleeding in patients with osteoarthritis or rheumatoid arthritis who need to take an NSAID is about the same with a combination of naproxen and lansoprazole as it is with celecoxib (limited scientific evidence ⊕⊕〇〇).
• In patients with rheumatoid arthritis and a history of NSAID-related bleeding peptic ulcer, celecoxib and esomeprazole in combination may reduce the risk of recurrent bleeding compared with celecoxib alone (limited scientific evidence ⊕⊕○○).

**Patients who need to continue treatment with low-dose aspirin**
• Patients with cardiovascular disease and a history of bleeding peptic ulcer are at lower risk of recurrent bleeding if they receive preventive treatment with low-dose aspirin and esomeprazole in combination rather than clopidogrel alone (moderately strong scientific evidence ⊕⊕⊕○).

• In patients with cardiovascular disease, a history of bleeding peptic ulcer, who need to continue medication with low-dose aspirin, supplementary treatment with lansoprazole may reduce the risk of recurrent bleeding (limited scientific evidence ⊕⊕○○).

**Lack of published research**
• There is a lack of research into the most effective measures to reduce the risk of recurrent bleeding in patients with a history of bleeding peptic ulcer who need to continue medication with both NSAID and low-dose aspirin (insufficient scientific evidence ⊕○○○).

• There is a lack of research into the most effective measures to reduce the risk of recurrent bleeding in patients with a history of bleeding peptic ulcer who need to continue medication with corticosteroids (insufficient scientific evidence ⊕○○○).

• There is a lack of research into the most effective measures to reduce the risk of recurrent bleeding in patients with a history of bleeding peptic ulcer who need to continue medication with SSRI (insufficient scientific evidence ⊕○○○).
• There is a lack of research into the efficacy of continuing treatment with acid-suppressing drugs following *H. pylori* eradication in patients with a history of bleeding peptic ulcer associated with *H. pylori* infection (insufficient scientific evidence ⊕○○○○).

• There is a lack of research into the long-term consequences of failure to monitor the outcome of *H. pylori* eradication after an episode of bleeding peptic ulcer (insufficient scientific evidence ⊕○○○○).

**Preventive treatment for patients with known risk factors for bleeding peptic ulcer**

*Patients who need medication for pain relief*

• Preventive treatment with proton pump inhibitors can reduce the risk of bleeding peptic ulcer in patients on traditional NSAIDs (limited scientific evidence ⊕⊕○○).

• Preventive treatment with H₂ blockers can reduce the risk of bleeding peptic in patients on traditional NSAIDs (limited scientific evidence ⊕⊕○○).

• Treatment with coxibs¹, in the absence of concurrent administration of low-dose aspirin, has a lower risk of bleeding peptic ulcer compared with treatment with traditional NSAIDs (moderately strong scientific evidence ⊕⊕⊕○).

• There is insufficient scientific evidence to determine whether misoprostol affects the risk of bleeding peptic ulcer in patients taking NSAIDs (insufficient scientific evidence ⊕○○○○).

¹ The results are based on systematic reviews and meta-analyses in which treatment was given with a variety of coxibs, some of which are no longer commercially available.
• There is insufficient evidence to determine whether nitrates affect the risk of bleeding peptic ulcer in patients on NSAIDs (insufficient scientific evidence ⊕○○○).

Patients who need treatment with antiplatelet drugs
• Preventive treatment with proton pump inhibitors can reduce the risk of bleeding peptic ulcer in patients taking antiplatelet drugs (limited scientific evidence ⊕⊕○○).

• There is insufficient scientific evidence to determine the preventive effect of H₂ blockers on the risk of bleeding peptic ulcer in patients taking antiplatelet drugs (⊕○○○○).

Lack of published research
• There is insufficient scientific evidence to determine the effect of reducing lifestyle-related risk factors on the risk of bleeding peptic ulcer in patients without other risk factors (⊕○○○○).

• There is insufficient scientific evidence to determine the effect of a change in lifestyle on the risk of bleeding peptic ulcer in those at increased risk because of age, ill-health or medication (⊕○○○○).

• There is insufficient scientific evidence to determine the effect of nabumetone on the risk of bleeding peptic ulcer, compared to other traditional NSAIDs, in people at increased risk (⊕○○○○).

• There is insufficient scientific evidence to determine the effect of meloxicam on the risk of bleeding peptic ulcer, compared with other traditional NSAIDs, in people at increased risk (⊕○○○○).
• There is insufficient evidence to determine the effect of *H. pylori* eradication as a primary prophylactic measure on the risk of bleeding peptic ulcer in people taking traditional NSAIDs, antiplatelet drugs or anticoagulants (⊕◯◯◯).

• There is insufficient scientific evidence to determine whether the risk of bleeding peptic ulcer is affected by the administration of high doses of paracetamol, ie, 3–4 g daily (⊕◯◯◯).

**Discussion – results, knowledge gaps and clinical considerations**

**Drug treatment of bleeding peptic ulcer**
The gastric juices secreted into the stomach and duodenum are highly acidic and this impairs the clotting ability of the blood. Drugs that suppress acid secretion, such as H₂ blockers (histamine 2-receptor antagonists) and proton pump inhibitors, raise the pH of the stomach, which improves the ability of the blood to clot (coagulate) in cases of bleeding and reduces the risk of the clot dissolving.

**Before endoscopic treatment**
It has not been possible to answer the question of whether drug treatment should be given as soon as a patient with suspected bleeding peptic ulcer arrives at the hospital, or whether this treatment can be delayed until the endoscopic diagnosis has been made. Nor has this report identified data that can establish the optimal timing of endoscopic diagnosis and possible treatment. Treatment with proton pump inhibitors for 24 hours before endoscopic diagnosis reduces the need for endoscopic treatment, but it has no effect on the risk of re-bleeding, the need for surgery, or mortality. Treating the symptoms of bleeding before the source has been identified would mean that patients who do not have a bleeding peptic ulcer would also receive this treatment. The
administration of proton pump inhibitors prior to endoscopic diagnosis and treatment is not an important determinant of the outcome of treatment of bleeding peptic ulcer.

After endoscopic treatment
Intravenous administration of proton pump inhibitors for 72 hours immediately following diagnosis of bleeding peptic ulcer and treatment by endoscopic haemostasis reduces the risk of re-bleeding almost by half. This intervention also reduces the need for surgery and repeat endoscopic treatment. Mortality, however, is unaffected. Most of the studies evaluated used high doses of proton pump inhibitors, but the evidence base for optimal dosage is uncertain. Another unanswered question is at what stage proton pump inhibitors can be administered orally.

Treatment with fibrinolysis inhibitors (tranexamic acid) is interesting in theory, as is the administration of drugs that reduce overall gastric secretion of acid and pepsin (eg, somatostatin). There is insufficient scientific evidence to determine the effect of treatment with somatostatin or tranexamic acid during the acute phase of bleeding peptic ulcer.

Eradication of H. pylori
In H. pylori positive patients, eradication of the bacterium following an episode of bleeding peptic ulcer reduces the risk of recurrent bleeding in the ensuing 12 months. Eradication prevents recurrent bleeding more effectively than long-term acid suppression alone. There are insufficient data about the benefits of monitoring the effectiveness of H. pylori eradication. Nor has it been possible to determine whether administration of proton pump inhibitors as a complement to H. pylori eradication improves treatment outcomes in patients who are not on aspirin or NSAIDs.
Endoscopic treatment of bleeding peptic ulcer

Endoscopic treatment of bleeding peptic ulcer is now a well-established method. For the individual endoscopist, the procedure is often technically challenging and requires considerable experience. However, most hospitals only have a few patients who require this treatment. Endoscopic treatment has a low frequency of complications, regardless of the method used.

The various endoscopic treatments

The existence of many different techniques within a particular field may be due to the fact that no single technique is wholly satisfactory. This is the case with endoscopic treatment. We need to know more about the differences between the various techniques and which ones may be preferable for specific clinical conditions. In the case of active bleeding from a visible blood vessel lumen, thermal and mechanical haemostasis are the methods of choice. Adrenaline injection should not be used as sole treatment, but should be complemented by thermal or mechanical haemostasis. Our review of the literature provides no answer to the question of how to proceed when the ulcer is covered by a blood clot. The best time to carry out OGD in cases of acute bleeding represents another significant gap in our knowledge, and this is important for the organisation of patient care.

Treatment before OGD

Prior administration of erythromycin improves visibility for the endoscopist, which makes endoscopy easier.

Planned follow-up endoscopy and repeat endoscopic treatment

Planned follow-up endoscopy after initial endoscopic treatment reduces the risk of recurrent bleeding. Patients who have a recurrence of bleeding should have repeat endoscopic treatment. In practice, repeated endoscopic treatment is often carried out under general anaesthesia, so if a change in treatment plan
proves necessary, transition to surgical intervention can proceed without further delay.

**Surgical and endovascular treatment of bleeding peptic ulcer**

The aim of surgical intervention in cases of bleeding peptic ulcer is to control the bleeding. Since the development of endoscopic techniques, there has been a marked reduction in the need for surgery. Surgery or endovascular surgery can be used in the few cases in which bleeding cannot be controlled by endoscopic and pharmaceutical treatment. Mortality associated with surgery is still high, often due to cardiovascular complications.

*Surgical treatment*

The most appropriate timing for surgical intervention remains undetermined. Research is needed into the factors that may help to determine when to progress beyond endoscopy to other treatments. This would avoid wasting time on further attempts at endoscopic haemostasis while the patient’s condition continues to deteriorate. It is not possible either to demonstrate short-term differences in efficacy between the different surgical methods. Some data on the risk of long-term complications following major surgery may imply that simpler surgical intervention is preferable.

*Endovascular treatment*

There are no comparative or randomised studies to determine whether endovascular treatment is more effective than surgery in patients with bleeding peptic ulcer in whom prior endoscopic or surgical intervention has failed. There are case report series in which haemostasis has been achieved in over 70% of cases. Re-bleeding probably occurs in some cases because it has not been possible to identify the source of bleeding, which is often intermittent. Endovascular treatment is available at relatively few hospitals in Sweden.
Preventive treatment of patients after admission for bleeding peptic ulcer

We found no studies that establish whether patients with bleeding peptic ulcer associated with H. pylori infection derived any benefit from continued administration of acid suppressing drugs following eradication of the infection. There is insufficient scientific evidence to determine whether recurrent bleeding can be prevented by monitoring the outcome of H. pylori eradication treatment. Both these questions require investigation in further studies. The high incidence of recurrent bleeding of unknown cause (eg, peptic ulcer unrelated to H. pylori infection or NSAID treatment) indicates that there is a need for further studies to determine the most appropriate preventive measures for this patient category.

Patients who need to continue medication for pain relief

In patients with a history of bleeding peptic ulcer who need to continue NSAID medication, the risk of a recurrence of bleeding is about the same when taking diclofenac plus omeprazole, naproxen plus lansoprazole, or taking celecoxib alone. Dyspepsia seems to be a commoner side effect with celecoxib than it is with naproxen plus lansoprazole. In patients with a history of bleeding peptic ulcer associated with NSAID, celecoxib plus esomeprazole has a lower risk of recurrent bleeding than celecoxib alone. Naproxen plus esomeprazole has roughly the same efficacy as celecoxib alone. The use of coxibs is currently restricted, for several reasons (see below). Based on the literature review, no specific combination of drugs can be recommended as preferable to any other, provided a proton pump inhibitor is included.

Patients who need to continue treatment with low-dose aspirin

For patients with a history of bleeding peptic ulcer who need to continue medication with low-dose aspirin, preventive treatment with a proton pump inhibitor may be considered. In patients with a history of bleeding peptic ulcer, who have cardiovascular disease and need to continue low-dose aspirin prophylaxis, supplementary
administration of lansoprazole reduces the risk of recurrent bleeding. In these patients, preventive treatment with low-dose aspirin and esomeprazole can also reduce the risk of recurrent bleeding, compared to clopidogrel alone.

Other patient categories
There is a lack of research into the risk of recurrent bleeding in patients with a history of bleeding peptic ulcer who need to continue medication with both NSAID and low-dose aspirin. There is also a lack of research into the risk of recurrent bleeding in patients with a history of bleeding peptic ulcer and a need to continue medication with corticosteroids or SSRIs.

Preventive treatment for patients with known risk factors for bleeding peptic ulcer

Lifestyle factors
It remains unclear as to whether changes in lifestyle affect the risk of developing a bleeding peptic ulcer. Observational studies indicate that alcohol and smoking are lifestyle factors which predispose to the development of bleeding peptic ulcer. However, there is a lack of published research into whether patients at risk of bleeding peptic ulcer can reduce this risk by giving up smoking or reducing alcohol consumption. It should be possible to carry out prospective cohort studies of smokers who either stop smoking or continue to smoke after an episode of bleeding peptic ulcer. It would also be of interest to investigate whether different forms of tobacco consumption affect risk.

Patients who need medication for pain relief
There are few randomised controlled studies of methods of reducing the risk of bleeding peptic ulcer in patients with one or more risk factors. However, several observational studies indicate that preventive treatment with proton pump inhibitors or H$_2$ blockers can reduce the risk of bleeding peptic ulcer in those taking traditional NSAIDs. It is unclear whether $H.~pylori$ eradication prior to
long-term medication with an NSAID can reduce the risk of developing a bleeding peptic ulcer in patients with or without other risk factors.

Meta-analyses of studies of various coxibs show that compared with traditional NSAID medication, coxibs as a group halve the risk of serious complications associated with peptic ulcers. However, the most convincing results are for studies of coxibs that have subsequently been withdrawn from the market. The clinical benefits of this group of drugs came into question following the publication of data linking certain coxibs with an increased risk of myocardial infarction. A further problem is that the results of several studies show a pronounced reduction in or an absence of preventive effect in patients taking low-dose aspirin and coxibs concomitantly.

Paracetamol is often recommended as the drug of choice for patients with painful osteoarthritis. We found no randomised controlled studies which primarily compared the incidence of bleeding peptic ulcer in at-risk patients using paracetamol or traditional NSAIDs. It is unclear which has the lower risk of bleeding peptic ulcer, traditional NSAIDs combined with proton pump inhibitors, or coxibs with or without supplementary proton pump inhibitors. Studies which compare the efficacy and safety of these treatments would therefore be of interest. Monitoring of safety should not only include adverse gastrointestinal effects, but also adverse effects on the cardiovascular system and other clinically important undesirable effects.

Patients who need treatment with antiplatelet drugs
Preventive treatment with proton pump inhibitors may reduce the risk of bleeding peptic ulcer in people who are taking antiplatelet drugs. The scientific evidence is insufficient to assess the effect of H₂ blockers on the risk of bleeding peptic ulcer in people taking antiplatelet drugs.
Ethical and social aspects

Men are at greater risk of developing bleeding peptic ulcer than women, but this difference has decreased. The differences which remain are thought to be related to differences in underlying diseases and lifestyle. Smoking, for example, was previously much more common among men. Men and women did not appear to be treated differently either in the studies we reviewed or in our study of registry data.

Treatment with antiplatelet drugs to prevent myocardial infarction and stroke may increase the risk of bleeding peptic ulcer. Painkilling medication taken by patients with osteoarthritis or rheumatoid arthritis may also increase the risk of bleeding peptic ulcer. These risks must be weighed up very carefully. Myocardial infarction and stroke, like bleeding peptic ulcer, are potentially fatal conditions. Doctors and other healthcare personnel should be prepared to discuss the pros and cons with the patient and reach a joint decision about the most beneficial treatment.

The scientific evidence in support of the prevention and treatment of bleeding peptic ulcer is mainly derived from studies that have been initiated, conducted and financed by the pharmaceutical and biomedical technology industries. Research is very product-driven and there are knowledge gaps in those areas that are not of obvious commercial interest. Commercial aims may also influence study design. One consequence of this is that there is very little research into the optimal duration of treatment. There is also a lack of research into the lifestyle changes that could reduce the risk of bleeding peptic ulcer. There are few studies of the complications associated with bleeding, but in many peptic ulcer studies the conclusions are extrapolated to include complications of bleeding.
There is, therefore, a great need to complement existing studies with research that has a greater emphasis on identifying measures that offer the greatest benefit to the patient.

**Health economics**

It is not possible to determine, on the basis of current knowledge, which treatments are cost-effective following endoscopic diagnosis of bleeding peptic ulcer or which are cost-effective in the prevention of bleeding recurrence.

Health economic consequence analyses are primarily based on the clinical results of studies. The existing empirical studies do not suggest any major cost differences between the various forms of treatment. Health economic considerations do not therefore need to play any great part in the prioritisation of the different treatment methods.

A model analysis has shown that although proton pump inhibitor treatment of bleeding peptic ulcer could well increase healthcare costs to some degree, it can still be regarded as cost-effective. In addition, the medical consequence analysis shows that *H. pylori* eradication can reduce the risk of recurrent bleeding. In another health economic model study, this has been shown to be a cost-effective strategy, but it does result in some increase in cost.

**Register study**

A register study was undertaken to investigate the dispensing of prescription drugs to patients treated for bleeding peptic ulcer, analysing data on treated patients extracted from the Swedish National Patient Register 2006–2008, and data from the Swedish Prescribed Drug Register. This analysis was based on data on prescription medicines dispensed to patients via pharmacies.
The analysis covered prescriptions dispensed during the 90 days immediately prior to the admission, and 0–90 and 91–365 days post discharge. Bleeding from an ulcer in the stomach or duodenum was the primary or secondary diagnosis. Not only were patients presenting for the first time with a bleeding peptic ulcer included, but also those with recurrent bleeding. This group was compared with patients treated during the same year for acute cholecystitis (gall bladder inflammation). This is not an ideal direct comparison because, among other differences, patients with acute cholecystitis are considerably younger than those with bleeding peptic ulcer. The patient groups were therefore matched for age and gender and stratified into two age groups: 45–64 years and 65–99 years.

In the analyses we combined treatment with H₂ blockers and proton pump inhibitors under the heading of acid suppression, but proton pump inhibitors were overwhelmingly predominant. During the total study period, prescriptions dispensed for H₂ blockers accounted for only 2.5% of prescriptions for acid suppressants. Nearly 19 per 100 patients presenting with bleeding peptic ulcer had been on acid suppressants during the three months preceding the event, which suggests that such treatment is not enough to prevent bleeding. During the first three-month period after the bleeding episode, acid suppressants were dispensed to almost 100 per 100 patients, decreasing to about 60 per 100 patients at four months after the bleeding episode.

The study showed that 0–90 days after treatment for a bleeding peptic ulcer, *H. pylori* was eradicated in only around 43 per 100 patients. It is not possible to determine whether this reflects a low prevalence of *H. pylori* in patients with bleeding peptic ulcer, or a lack of awareness on the part of healthcare personnel of the importance of *H. pylori* eradication following an episode of bleeding peptic ulcer. As most of the patients in this population were
quite elderly, we assume that the incidence of *H. pylori* is probably higher than the results suggest, but this is mere speculation.

During the year following the first episode of bleeding peptic ulcer, just over 10% of patients will have recurrent bleeding from the ulcer, or another form of gastrointestinal bleeding. Four to 12 months after discharge from hospital, patients who are not prescribed medication to eradicate the bacterium responsible for peptic ulceration, *H. pylori*, have a 70% higher mortality rate than those who are prescribed medication to treat this infection.
**Glossary**

<table>
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<tr>
<td>Antiplatelet drugs</td>
<td>Drugs which reduce the ability of the blood platelets (thrombocytes) to clump together (aggregate) and form blood clots</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Acetylsalicylic acid</td>
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<tr>
<td>Erythromycin</td>
<td>An antibiotic which also stimulates the peristaltic activity of the gastrointestinal tract</td>
</tr>
<tr>
<td>H₂ blockers</td>
<td>H₂-receptor blockers or histamine 2-receptor antagonists (H2RA); a group of drugs which block the effect of histamine on the parietal cells, ie, the cells in the mucosal lining of the stomach which produce hydrochloric acid</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori, a small Gram-negative bacterium which can colonise the mucosal lining of the stomach and cause a peptic ulcer</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>Aspirin used at a low dose (75–160 mg) to prevent the formation of arterial blood clots. A member of the group of drugs known as antiplatelet drugs</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs; pain relieving and anti-inflammatory drugs which act by inhibiting the synthesis of prostaglandins by the enzyme cyclo-oxygenase</td>
</tr>
<tr>
<td>OGD</td>
<td>Oesophago-gastro-duodenoscopy; examination of the oesophagus, stomach and duodenum by means of a flexible fibre-optic instrument</td>
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<td>SSRI</td>
<td>Selective serotonin uptake inhibitors</td>
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Below is a brief summary of the mission assigned to SBU by the Swedish Government:

• SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.

• SBU shall assess new methods as well as those that are already part of established clinical practice.

• SBU’s assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.

• SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.

• SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.

• SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.
Bleeding Peptic Ulcer

The report on Bleeding Peptic Ulcer from the Swedish Council on Health Technology Assessment (SBU) is a systematic review of the scientific literature in the field.

This document presents the summary and conclusions of the full report approved by SBU’s Board and Scientific Advisory Committee.

The full report is available at www.sbu.se