The continuing story of peptic ulcer bleeding
van Leerdam, M.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 9

General Discussion
General Discussion

In this thesis several aspects of peptic ulcer bleeding are being evaluated. The main results are summarized below. Furthermore, practical implications and recommendations for prevention and management of PUB in general practice are discussed. Finally, future research topics are suggested.

**Overall incidence of acute upper gastrointestinal bleeding**

Acute upper gastrointestinal bleeding is still common, although the incidence did decrease significantly, as presented in the study evaluating two epidemiological cohorts (1993/94 versus 2000) in the greater Amsterdam area. Compared to data from other countries in Europe and the United States of America, the overall incidence rate in The Netherlands is in the lower range.\(^1\) It is not known why the incidence is low in the Netherlands. The decrease in incidence might partly be explained by the use of strong acid suppressants and by a lower prevalence of *H. pylori* infection. However, this remains speculative and case-control studies are necessary to confirm this.

**Incidence of peptic ulcer bleeding**

Peptic ulcer bleeding (PUB) is the cause of bleeding in almost half of all cases of upper gastrointestinal bleeding in the greater Amsterdam area. Despite the lower overall incidence of upper gastrointestinal bleeding, the incidence of both duodenal and gastric ulcer bleeding remained stable, resulting in a higher proportion of PUB.

**Why did the incidence of PUB remain stable?**

In 2000, more than half of all patients presenting with PUB were using aspirin and/or non-steroidal anti-inflammatory drugs (NSAIDs), which is a well-known risk factor for the development of PUB. Also in a recent epidemiological study performed in Greece, the intake of NSAIDs was 49% among patients with upper gastrointestinal bleeding.\(^2\) Of all aspirin and/or NSAIDs users with a previous history of ulcer disease, only a minority (12%) was using a proton pump inhibitor (PPI) prophylactically despite the results of several studies advocating PPIs to prevent recurrent ulcer disease and ulcer complications.\(^3,4\)
Aspirin and NSAIDs, both over-the-counter and per prescription, are one of the most widely used classes of drugs. Of all patients who are using NSAIDs, 1-2% per year will develop complications such as PUB. This seems only a small fraction, but given the fact that so many people are using such drugs, the development of this complication has a major health care impact.

It is rather surprising that significantly fewer patients with PUB did have a previous history of peptic ulcer disease in the 2000 cohort. This might be explained by the effect of eradication/disappearance of H. pylori infection or by the widely increased use of powerful acid suppressants.

A large proportion of PUB is probably preventable; either by eradication of H. pylori infection and/or discontinuation or more selective prescription of aspirin and/or NSAIDs. It is clear that prevention of PUB should have high priority. All physicians prescribing aspirin and/or NSAIDs should be aware of the risk of gastrointestinal complication and should be aware of the current treatment strategies in patients at risk for ulcer bleeding. Established risk factors for the development of serious gastrointestinal complications while using aspirin/NSAIDs are advanced age (linear increase in risk), history of ulcer disease, concomitant use of corticosteroids or anticoagulants, higher doses of NSAIDs, including the use of more than one NSAID, and serious comorbidity, especially cardiovascular disease. High-risk patients should either be switched to a COX-2 inhibitor instead of non-selective NSAIDs or therapy with aspirin/NSAID should be combined with a PPI. Meta-analyses including all published and unpublished data comparing COX-2 inhibitors with non-selective NSAIDs will be necessary to determine the ultimate benefit and safety profile of COX-2 inhibitors. Also misoprostol is highly effective for preventing NSAID-induced ulcers. The disadvantage of this group of medicine however, is the development of diarrhea and abdominal pain in many patients. Attention for the prevention of aspirin/NSAID related gastroduodenal ulcers and ulcer bleeding at a national level should have high priority.

Data about the incidence of H. pylori infection in our epidemiological cohort of 2000 are still being investigated. These data are important to determine the respective etiological role of
aspirin and NSAIDs and H. pylori infection. Thereby, we should know the incidence of non-NSAID, non-H. pylori associated ulcer disease and look for additional risk factors.

*Outcome of peptic ulcer bleeding*

Neither rebleeding nor mortality rates did decrease. Rebleeding rate was still 20% and mortality rate 14% in the 2000 cohort. Age, comorbidity and rebleeding were risk factors significantly associated with higher mortality. In both cohorts the mean age was high and more than 40% of patients had severe or life-threatening comorbidity. This makes it extremely difficult to reduce mortality. Because only rebleeding can be influenced, an aggressive approach to prevent rebleeding is necessary.

*Therapy for peptic ulcer bleeding*

Unfortunately, both the data from a national inquiry regarding management of PUB as well as data from our epidemiological cohort did show that management is sub optimal. Endoscopy performed as soon as safely possible, but at least within 24 hours, favors a better outcome of the patient.\(^9\) Because endoscopy in a bleeding patient is difficult, an experienced endoscopy-team is important. However, even in a regional hospital, without a 24-hour endoscopy team, it should be possible to arrange emergency endoscopy within 24 hours.

From the literature, it is beyond doubt that all ulcers with active bleeding (spurting bleeding and oozing bleeding) and with a non-bleeding visible vessel are at risk for further bleeding\(^11\) and should be treated by endoscopic hemostatic therapy. Even today, 18% of patients with high-risk stigmata did not receive endoscopic hemostatic therapy. It is important to treat ulcers with these stigmata to prevent rebleeding and all endoscopists should handle accordingly.

Whether ulcers with an adherent clot should be treated endoscopically is still arguable.\(^12\) On the other hand, two recent studies showed a beneficial effect of endoscopic therapy for ulcers with an adherent clot compared to no endoscopic therapy.\(^13,14\) As long as the rebleeding rate remains this high, endoscopic therapy is also advocated for ulcers with an adherent clot, awaiting further studies.
The question what endoscopic modality should be used for PUB is difficult to answer. In the Netherlands endoscopic injection therapy is most often used, either with adrenaline alone or combined with a sclerosant. Several studies did not find a beneficial effect of the addition of a sclerosant, and because of the adverse effects, a sclerosant should probably not be used (chapter 2). On the other hand, there is discussion about the efficacy of adrenaline injection therapy alone. Several experts recommend the use of adrenaline injections combined with the heat-probe.\textsuperscript{15,16} Up to now randomized controlled trials are lacking, but one can imagine that adrenaline injection to stop the bleeding and heat-probe therapy to target the vessel might be superior to adrenaline alone. To determine the value of combination therapy, a large randomized controlled trial will be necessary.

Four randomized controlled trials did show improved outcome, including reduction of rebleeding and/or surgery rate, in patients with PUB, comparing high dose i.v. PPI in the first 72 hours and placebo.\textsuperscript{17} No effect on mortality rate was found in these studies. In the greater Amsterdam region, high dose i.v. PPI was only administered to 37% of patients with high-risk stigmata for further bleeding. Knowing this, we should convince all endoscopists to treat patients at risk for recurrent bleeding (active bleeding, visible vessel or adherent clot) with high dose i.v. PPI (80 mg bolus injection followed by 8 mg per hour). The optimal dose of PPI after the first 24 hours might be less, but we are awaiting further studies evaluating dose reduction.

\textit{H. pylori infection in patients with PUB}

It is beyond doubt that all patients with PUB should be tested for \textit{H. pylori} infection. One should realize that all invasive diagnostic tests are less sensitive in the acute bleeding phase. Urea breath test is less sensitive when acid suppressants are used. The HpSA test gives a high number of false positive results, probably due to blood constituents cross reacting in the enzyme immunoassay. Serology cannot always differentiate between a past or recent infection, but is probably most sensitive. This implicates that we should realize that when a patient with PUB has negative test results for \textit{H. pylori} infection and has no other risk factors for ulcer disease, the test might have been false negative. A repeated test to determine \textit{H. pylori} infection is advised after the acute phase. We keep on searching for a reliable, simple and fast \textit{H. pylori} test.
The interaction between H. pylori infection and aspirin and/or NSAID use is still not clear. For management in clinical practice, we recommend eradication of all H. pylori-infected patients with duodenal or gastric ulcer bleeding, irrespective of the use of aspirin and/or NSAIDs. Furthermore, H. pylori eradication should always be confirmed in patients with PUB. However, this is only done by 64% of endoscopists.

Classifying the ulcer

In this thesis, we again showed the subjectivity of the Forrest classification when we evaluated 19 video fragments of peptic ulcers among 56 endoscopists. We also performed a clinical trial comparing the Forrest classification with Doppler assessment. We hoped to overcome the subjectivity of the Forrest classification by using an objective diagnostic tool to assess the vascularisation of the ulcer base. However, despite the results of other studies, we could not confirm the diagnostic value of the endoscopic Doppler assessment of the ulcer base in predicting clinical outcome. There was no difference in primary outcome (rebleeding, surgery and mortality within 96 hours) between patients with and without a positive Doppler flow signal. Early rebleeding did also occur in 3 of 23 patients without a Doppler flow signal. Important is the fact that less than a quarter of all patients presenting with PUB were eligible for Doppler investigation. The main reason for exclusion was the presence of more than one potential bleeding lesion. This might be due to NSAID use, causing mucosal damage at different places in the stomach and/or duodenum.

It is obvious that we do need alternative methods to assess the risk for rebleeding and make decisions about endoscopic therapy and early discharge. Several studies have used a scoring system to determine which patients can be safely discharged after endoscopy. One of the problems of these scoring systems is the fact that the patient population consists of predominantly elderly patients, with a high prevalence of severe or life-threatening comorbidity, which predominantly dictates the level of care. For the subgroup of young patients (<60 years of age) with no or only mild co-morbidity, scoring systems for early discharge or outpatients management, using objective criteria, should be further validated in clinical practice. Because there is no objective tool to assess the ulcer base, we should also realize that patient inclusion based on subjective stigmata (Forrest classification) are easily
erroneous. In an overview by Laine and Peterson\textsuperscript{11} this is clearly visualized. Incidence, rate of further bleeding and mortality rate differed widely within the same group of stigmata.

\textit{Surgery for peptic ulcer bleeding}

Our retrospective study, evaluating the outcome of emergency surgery for PUB did show a high rebleeding (27\%) and mortality (37\%) rate. Mortality was associated with co-morbidity and arterial bleeding at the initial endoscopy. Transcatheter arterial embolisation (TAE) might be a valid alternative. TAE has made major improvements with the possibility of selective embolisation with a low incidence of ischaemic complications. Furthermore, compared to surgical treatment, TAE is a less traumatic intervention, which might be beneficial in patients with severe comorbidity. A prospective study has just started to evaluate the outcome of TAE in endoscopically uncontrolled PUB.

Despite centuries of research and recent new developments, the chapter about PUB is still not closed, especially because rebleeding and mortality are still substantial and did not decrease in the last 6½ years. At a national level we should focus on continuous education and the development of protocols. Prevention of PUB should have high priority. Furthermore we should focus on the possibilities to reduce rebleeding. Beside this, further research is necessary to improve the quality of care received by patients with PUB. The story of PUB continues.
References


