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The Treatment and Risk Factors of Peptic Ulcer Bleeding

Doctoral dissertation

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ABSTRACT

The incidence of acute upper gastrointestinal bleeding has been 100/100000 inhabitants in Western countries. Peptic ulcer bleeding (PUB) was the source of bleeding in 50% of these cases. The incidence of non-complicated peptic ulcer has decreased while that of PUB has increased. The mortality of bleeding patients has not significantly decreased despite new therapeutic options. Controversial results in few studies concerning the medical treatment of PUB after endoscopic treatment complicates sound clinical decision making in patient care. Furthermore, the risk profile of these patients and the impact of treatment on H.pylori have been studied seldom, especially in Finnish patients.

The significance of gastric acid inhibition following successful endoscopic therapy in preventing rebleeding and reducing mortality in PUB was studied by testing the equivalence of a regular dose (20 mg once a day for 72 hours, n = 73) and a high dose of omeprazole (80 mg bolus + 8 mg/h for 72 hours, n = 69) in a prospective randomised double blind trial. Both doses were equally effective based on rebleeding rates, need of emergency surgery and mortality. The factors associated with rebleeding were shock on admission and duodenal ulcer (DU).

In PUB an intragastric pH-level > 4 is considered necessary to prevent dissolving of the formed fibrin clot. Therefore, intragastric pH monitoring for 72 hours was performed in 7 of patients of the regular and 6 of the high dose group. The regular dose of omeprazole raised both mean and median 24-hour intragastric pH > 4 in patients with PUB. This reduction in the acidity together with endoscopic therapy is probably sufficient to maintain haemostasis. The high dose kept the pH almost constantly > 6.

A case-control study of PUB patients (n = 94) and controls (n = 94) of age (≥ 5 years) and sex matched non-ulcer patients attending elective endoscopy was undertaken to analyse risk factors for PUB. A questionnaire concerning possible risk factors was completed. H.pylori was determined positive if histology and/or urease test were positive. CagA antibodies of IgG class of H.pylori were determined by an immunoblot method. H.pylori infection, the use of ASA, other NSAIDs with ≥ 1 defined daily doses, smoking ≥ 20 cigarettes daily and previous DU were independent risk factors for PUB. Two of them were present simultaneously in 2/3 of the patients. However, the combination of risk factors did not increase the risk. Of H.pylori positive subjects, 97% of the cases and 96% of the controls had CagA strains. ASA, ibuprofen, ketoprofen and smoking had a dose-dependent association with PUB.

The effect of a 3-day treatment of omeprazole on the colonisation of H.pylori in the stomach was studied in patients with PUB. H.pylori status was assessed by histology and urease test of gastric biopsies at pre-entry and after 3 days of therapy in 51 patients receiving the regular dose and in 50 patients receiving the high dose of omeprazole. A marked disappearance of H.pylori was found with both regimens, but with the high dose, tests for the diagnosis of H.pylori became negative significantly more often than with the regular dose, 60% vs. 27.5%, p = 0.001 (any test), 67.6% vs. 31.7%, p = 0.003 (histology) and 82.2% vs. 43.6%, p = 0.001 (urease test). Samples to find H.pylori should be taken before any omeprazole treatment, or the presence of the bacteria may be overlooked.
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ABBREVIATIONS

ASA    acetylsalicylic acid
ASA-TP ASA as thrombosis prophylaxis
ASA-P  ASA as pain medicine
CagA   cytotoxin associated gene A
DDD    defined daily dose
DU     duodenal ulcer
GU     gastric ulcer
H2 blocker histamine-2 receptor antagonist
H. pylori Helicobacter pylori
IgG    immunoglobulin G
IV     intravenous
NBVV   non-bleeding visible vessel
NSAID  non-steroidal anti-inflammatory drug
NANSAID non-ASA-NSAID
OGD    oesophagogastroduodenoscopy
PPI    proton pump inhibitor
PUB    peptic ulcer bleeding
SD     standard deviation
DEFINITIONS

Change of *H. pylori* colonisation by histology:

- **change to negative colonisation**: 1-0: (from grade 1 to grade 0), 2-0: (from grade 2 to grade 0) and 3-0: (from grade 3 to grade 0)
- **decrease in density**: 2-1: (from grade 2 to grade 1), 3-1: (from grade 3 to grade 1), 3-2: (from grade 3 to grade 2)
- **no change in density**: 1-1: (remains grade 1), 2-2: (remains grade 2), 3-3: (remains grade 3)
- **increase in density**: 1-2: (from grade 1 to grade 2), 1-3: (from grade 1 to grade 3)

**Defined daily dose**

- the assumed average maintenance dose per day for a drug used for its main indication in adults

**Duodenal ulcer**

- bulbar or duodenal ulcer

**Gastric ulcer**

- gastric, prepyloric or pyloric ulcers

**High dose of omeprazole infusion**

- 80 mg bolus + 8 mg/h for 72 hours

**Long-term mortality**

- > 30 day mortality

**Rebleeding**

- rebleeding found in OGD necessitating endoscopic therapy and/or surgery; or persistent bleeding (haematemesis, melena, shock) necessitating repeated endoscopic therapy or emergency operation

**Regular dose of omeprazole infusion**

- 20 mg once a day for 72 hours

**Short-term mortality**

- ≤ 30-day mortality
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1. INTRODUCTION

The incidence of upper gastrointestinal bleeding has been 100/100000 habitants per year in Western world (Rockall et al. 1995). Of these patients 40 - 57% have been reported to have a peptic ulcer (Soplemann et al. 1997a; van Leerdam et al. 2003). It has been estimated that altogether 10 - 20% of all peptic ulcers bleed. Especially in the elderly, this bleeding event may be the first sign of the ulcer disease (Imhof et al. 1997; Kemppainen et al. 1997).

Although the majority of bleeding episodes cease spontaneously, still 20% require intervention (Choudari et al. 1994; Williams et al. 1993). Before the era of endoscopic therapy, patients with major bleeding events underwent emergency surgery (Wara et al. 1983). Most of the other patients had an early elective operation.

Today the diagnosis of PUB is made by endoscopy. Signs of acute or recent bleeding found on diagnostic endoscopy can predict the risk of rebleeding. Some form of endoscopic therapy is usually indicated when these high risk signs exist. After endoscopic therapy there is still a 20% risk of rebleeding (Thomopoulos et al. 2001; Villanueva et al. 1993).

Medical treatment is considered necessary to reduce the risk of rebleeding. PPIs decrease gastric acid secretion and heal ulcers (Graham et al. 1990). These drugs have also been used in the acute bleeding phase to increase intragastric pH and thereby control bleeding. Although high doses of PPIs have been found superior to placebo in this respect, the role of regular doses has remained obscure.

In case-control studies NSAIDs (Imhof et al. 1997; Labenz et al. 1999; Wu et al. 1999), smoking (Stack et al. 2002; Tzourmakiotis et al. 2004; Weil et al. 2000) and *H.pylori* (Labenz et al. 1999; Stack et al. 2002; Wu et al. 1999) have been reported as individual single risk factors for PUB, but their concurrence in patients has seldom been studied. Furthermore, the role of multiple risk factors in the same patient has gained little attention in various investigations. Helicobacter pylori is regarded as one of the most important causes of peptic ulcer. Its early detection is fundamental for the purpose of eradication to prevent ulcer recurrence. However, there are only scant data of the early effect of PPI treatment on the detection of *H.pylori*.

The purpose of the present work was to assess the risk profile of PUB patients and to study the effect of modern medical treatment after endoscopic therapy on the clinical outcome of PUB, on the intragastric acidity and on the detection of *H.pylori* in PUB in a prospective randomised double blind setting.
2. REVIEW OF LITERATURE

2.1. Definition of peptic ulcer

Peptic ulcer is a chronic defect in the gastrointestinal mucosa extending through muscularis mucosae (Oi and Sakurai 1959; Oi et al. 1959). The defect persists as a function of the acid peptic activity in gastric juice. Major bleeding occurs when the ulcerative process reaches underlying submucosal vessels.

2.2. Historical aspects of PUB

The first suggested description of gastric haemorrhage attributed to an ulcer is in the Egyptian Papyrus Ebers (Kravetz 2003). There are cases of PUB in the medical literature since 12th century.

The treatment of PUB became a clinical option when gastric surgery was begun in the 1880s. Roux and von Mikulicz succeeded with suture-ligation in a few cases, and others tried local excision of the bleeding ulcer. Eventually, gastrectomy prevailed in these cases (Weil and Buchberger 1999). In the 1920s, the Sippy regimen, which consisted of hourly milk and cream feedings alternating with hourly calcium and sodium bicarbonate, was used to neutralise hydrochloric acid. Antacids to neutralise acidic gastric juice and anticholinergics to reduce secretion of gastric acid were given in combination products to heal ulcers from the beginning of the 1900s (Scheindlin 2005). Rigid endoscopes were available already in 1930s (Douthwaite and Lintott 1938), but they were rarely used in acute upper gastrointestinal bleeding (Palmer 1969). Fiberoptic endoscopes have been used since the 1960s. Therapeutic endoscopy became a rational therapeutic option in the 1980s (Pitcher 1990). Before that era, patients with major bleeding events had an emergency operation, but mortality following emergency surgery has been as high as 36% (Wara et al. 1983).

2.3. Epidemiology of the PUB

2.3.1. Incidence of gastrointestinal bleeding

The overall incidence of gastrointestinal bleeding has varied between 63/100000 (Soplepmann et al. 1997a; van Leerdam et al. 2003) and 100/100000 hospitalisations per year in England (Rockall et al. 1995), in the USA (Longstreth 1995) and in Tartu, Estonia (Soplepmann et al. 1997a). In Scotland the incidence was even 67% higher (Blatchford et al. 1997). The rate increases markedly with age (Rockall et al. 1995; Soplepmann et al. 1997b). However, at the end of the second millennium the overall incidence of PUB has further decreased in Netherlands to 47.7 per 100000 habitants (van Leerdam et al. 2003). PUB has been reported to account for 40-57% of all cases with upper gastrointestinal bleeding (Longstreth 1995; Rockall et al. 1995; Soplepmann et al. 1997a; van Leerdam et al. 2003).
2.3.2. Incidence of peptic ulcer and bleeding

The clinical presentation and frequency of peptic ulcer has varied during previous decades. The incidence of uncomplicated peptic ulcer in terms of hospitalisations has decreased, like in the United States between 1970 and 1985 (Kurata and Corboy 1988). In the Netherlands the incidence was halved between 1992 and 2003 (Post et al. 2006). In Finland elective operations for peptic ulcer disease decreased by 89% between years 1972 and 1999 (Paimela et al. 2002).

In contradiction to the overall decline in the incidence of peptic ulcer complications like bleeding have increased in the United States from 1970 - 1985 (Kurata and Corboy 1988), in Denmark from 1981 - 1993 (Andersen et al. 1998) and in England from 1989 - 1999 (Higham et al. 2002). Between the years 1974 – 1986 in Massachusetts there was a decline in elective peptic ulcer operations, but the operations performed due to perforation or bleeding remained constant (Welch et al. 1986).

The incidence of emergency operations increased by 44 % (from 5.2 to 7.5 /100000 inhabitants) in Finland during the period 1972 - 1999 (Paimela et al. 2002). The number of hospitalisations for PUB increased at least twofold between 1979 and 1984 (Tilvis et al. 1987).

More recently in Denmark the incidence of uncomplicated and perforated peptic ulcers decreased further, in DU from 55 to 37/100000 and in GU from 56 to 40/100000, but that of PUB remained the same, 55/100000 inhabitants (Lassen et al. 2006).

On the other hand, the annual incidence of surgery for PUB remained stable during 1977-1988 in Northern Finland (Mäkelä et al. 1992). In Düsseldorf, Germany, the incidence of PUB has been stable between the years 1990 and 2000, at 50 per 100000 inhabitants per year (Ohmann et al. 2005).

2.3.3. Incidence of DU and GU bleeding

In the Amsterdam area, the incidence of GU (10/100000 inhabitants per year) and DU bleeding (13/100000 inhabitants per year) has remained the same between years 1993/1994 and 2000 (van Leerdam et al. 2003). In Tartu, Estonia, the incidence has been much higher, 57/100000 adults per year (Soplepmann et al. 1997b). It was 82.7/100000 per year for men and 36.1 for women while the male to female ratio for GU was 1.6:1 and for DU 4.4:1.

In Denmark in 1981-2003 the hospitalisation rates of PUB in women increased (standardised rate ratio 1.22 for gastric ulcer bleeding and 1.7 for duodenal ulcer bleeding) but that of men remained almost the same (Andersen et al. 1998).
2.3.4. Recurrence

After the first episode of PUB, further episodes of bleeding can occur. Recurrence rate of 6% has been found in 3 months follow-up (Hasselgren et al. 1998), 9% after follow-up of 36 months (median) (Kubba et al. 1997) and 18% after 8 years (Fischer et al. 1994).

2.3.5. 30-day mortality

Despite improvements in therapeutic methods, intensive monitoring and new acid-suppressing medication, the mortality of PUB has remained stable during last decades in Western countries. The mortality of PUB in general has been 15% in Northern Finland between 1977 and 1988 (Mäkelä et al. 1992), 8% in 1993 and 1995 (Mäkelä et al. 1996) and 5.5% in Gothenburg in 1989 and 1993 (Hasselgren et al. 1998) whereas that of complicated peptic ulcer was 11% in Denmark 1993 - 2000 (Lassen et al. 2006). The combined mortality of peptic ulcer perforation and bleeding increased from 4.2 to 7.3/100000 inhabitants per year in Finland 1972 - 1999 (Paimela et al. 2002).

Age and Forrest class (Rockall et al. 1996a; Chow et al. 1998; Hasselgren et al. 1998), concomitant diseases, rate of rebleeding (Rockall et al. 1996a) and need for emergency surgery (Chow et al. 1998) have influenced mortality. In another study the number of concomitant diseases but not age increased mortality among PUB patients (Mueller et al. 1994).

Treating these patients remains a clinical challenge, since many are elderly, with concurrent illnesses and multiple medications. In these circumstances not only the endoscopic signs of acute or recent bleeding, but also background factors predict the outcome.

2.3.6. Long-term mortality

After an episode of PUB, the risk of death is estimated to be 2-fold compared with the general population. This risk is less than 2-fold in the elderly but 7-fold in the middle aged, suggesting that PUB could be a marker of a general deterioration in health (Ruigomez et al. 2000).

Worsened long-term survival after an episode of PUB has been found in Scottish population (Kubba et al. 1997) and in Gothenburg (Hasselgren et al. 1998). In elderly PUB patients the 6 year survival estimate was almost 20% worse than expected according to national death rates despite prophylaxis with H2 blockers. Decreased survival was associated with other concomitant diseases (cancer, respiratory, cardiovascular) rather than recurrence of peptic ulcer complications (Hudson et al. 1995a).
2.4. Risk factors of PUB

2.4.1. Previous history of peptic ulcer and bleeding

Previous peptic ulcer increases the risk of a new episode of ulcer and bleeding. The risk has been estimated to be 4 to 6 fold (Stack et al. 2002; Weil et al. 2000). Typically 26% to 40% of PUB patients have had peptic ulcer or bleeding earlier (Henriksson et al. 1998; Leivonen and Kivilaakso 1991; Savage et al. 1993; Stack et al. 2002). This risk scenario may change in the future, since in years 1999-2000 PUB patients were less likely to have a history of ulcer (25% versus 59%) compared with PUB patients treated 10 years earlier (Ohmann et al. 2005). Previous upper gastrointestinal bleeding also increases the risk of PUB (Gabriel et al. 1991). However, there are also studies indicating that previous ulcer treatment has been a protective factor for new bleeding episode (Imhof et al. 1997).

2.4.2. Concomitant diseases and age

In a meta-analysis (Gabriel et al. 1991) and an overview of epidemiologic studies (Hernandez-Diaz and Rodriguez 2000), the risk of PUB increases with age. Lung diseases increased the risk of PUB according to a case-control study (Imhof et al. 1997).

2.4.3. H.pylori

*H. pylori* is a spiral-shaped gram-negative bacterium colonizing the gastric mucosa that was first discovered by Marshall and Warren (Marshall and Warren 1984). *H.pylori* causes chronic gastritis (Goodwin et al. 1986, Sipponen et al. 1994) and increases the risk of peptic ulcer (Voutilainen et al. 2001), especially duodenal ulcer (Graham 1989, Blaser 1998). *H.pylori* is also considered a risk factor for gastric adenocarcinoma (Parsonnet et al. 1991, Kokkola et al. 2005, Knekt et al. 2006), and it is associated with gastric MALT lymphoma (Wotherspoon et al. 1991). Although half of the population of the world is infected with *H.pylori*, only 20% of *H. pylori*-positive subjects developed ulcer disease during long-term follow-up (Forbes et al. 1994). The lifetime risk for ulcer disease in *H. pylori*-positive subjects is nonetheless 3 times higher than in *H. pylori*-negative subjects (Nomura et al. 1994).

Duodenal gastric metaplasia is associated with high acid output and it is suggested to be prerequisite for duodenal ulcer, because in the duodenum, *H.pylori* is found only in areas with gastric metaplasia (Graham 1991). Widespread duodenal gastric metaplasia has been associated with *H.pylori*-positive duodenal ulcer disease (Veijola et al. 2006).

Due to a birth cohort effect, the *H.pylori* seroprevalence has fallen over the last decades in developed countries (Banatvala et al. 1993, Sipponen et al. 1994, Kosunen
et al 1997). In developing countries, most people are infected with the bacteria (Graham et al. 1991).

In PUB the prevalence of *H. pylori* infection has been lower than in noncomplicated peptic ulcer disease (Stack et al. 2002; Wu et al. 1999). This may be due to ongoing PPI medication and inaccurate testing. According to several case-control studies *H. pylori* has been a risk factor for PUB, with 2 to 3-fold risk (Labenz et al. 1999; Stack et al. 2002; Wu et al. 1999). In one case-control study *H. pylori* was inversely associated with gastric ulcer bleeding (Pilotto et al. 1997).

### 2.4.3.1. CagA strains of *H. pylori*

Virulence factors are related to the ability of a microbe to induce disease. True virulence factors should have a disease association, like increased mucosal inflammation.

Cytotoxin-associated gene A has been studied vigorously, as a potential virulence factor. CagA in *H. pylori* positive subjects has been associated with peptic ulcer disease in Western Europe (Covacci et al. 1993) and the United States (Cover et al. 1995; Nomura et al. 2002). Cag A has also been associated with PUB (Henriksson et al. 1998; Santolaria et al. 1999; Stack et al. 2002; Tzourmakliotis et al. 2004).

In a few case-control (Hsu et al. 2000; Lanas et al. 2002) and other studies (Graham et al. 1996a) there was no association between CagA and peptic ulcer disease, and the prevalence of CagA was low in both peptic ulcer, PUB and control patients. On the other hand, in North America (Evans et al. 1998; Go and Graham 1996), Sweden (Hamlet et al. 1999), Estonia (Andreson et al. 2002) and among Asian populations (Park et al. 1998) the prevalence of CagA has been similarly high in patients with peptic ulcer and controls. Therefore CagA may not serve as an appropriate marker of more virulent *H. pylori* strains.

The results from studies comparing the prevalence of antibodies against CagA in patients with and without peptic ulcer are inconsistent. CagA itself may not be responsible for the inflammatory process. It is unclear if it has any specific role in peptic ulcer disease. Neither CagA nor VacA seropositivities are better predictors of increased peptic ulcer risk than antibodies against *H. pylori*. More than 90% of strains in East Asia are CagA and VacA positive. These factors may not be sufficient to cause more severe gastroduodenal disease (Gonzalez et al. 2003). Cytotoxin associated gene pathogenicity island PAI, the duodenal ulcer-promoting gene, and the blood group antigen binding adhesion are possible virulence factors (Lu et al. 2005).
2.4.4. NSAIDs including ASA

The ability of ASA to damage gastric mucosa was first described in 1938 (Douthwaite and Lintott 1938). NSAIDs cause damage in the gastroduodenal mucosa by several mechanisms. They are topically irritable and suppress mucosal prostaglandin synthesis which regulates mucosal defence mechanisms (Wallace 2000).

Cyclo-oxygenase enzyme (COX) is responsible for prostaglandin synthesis by converting arachidonic acid to prostaglandins and thromboxane. Gastrointestinal prostaglandins protect against injury by stimulating mucosal bicarbonate and mucus secretion and by increasing mucosal blood flow. COX exists in two isoforms, COX-1 and COX-2. The former predominates in the stomach and the whole gastrointestinal tract. With COX-2 inhibitor NSAIDs, the incidences of gastroduodenal lesions have been lower than with the traditional NSAIDs (Bombardier et al. 2000). However, serious cardiovascular side effects restrict the use of COX-2 inhibitors to rare patients (Grosser et al. 2006; Hernandez-Diaz et al. 2006). On the other hand, they are not without the risk of upper gastrointestinal complications (Garcia Rodriguez and Barreales Tolosa 2007, Helin-Salmivaara et al. 1997) especially when used in combination with aspirin (Garcia Rodriguez and Barreales Tolosa 2007).

In Finland during year 2000, the total NSAID consumption was 61.2 DDD/1000 inhabitants per day. The 1-year prevalence of NSAID use was 17.7% in a sample of 500,000 persons. Paracetamol is less often used and the consumption of NSAIDs is higher in Finland than in other Nordic countries (Helin-Salmivaara et al. 2003).

The use of NSAIDs including ASA (Weil et al. 1995) have been reported to be important risk factors for PUB, with a 3 to 8-fold higher risk according to meta-analyses of cohort (Gabriel et al. 1991) and case-control studies (Imhof et al. 1997; Labenz et al. 1999; Wu et al. 1999). There has been a 4-fold risk of PUB with NSAIDs (Cullen et al. 1997) and NNSAIDs among the elderly (Griffin et al. 1991).

2.4.4.1. Recent use of NSAIDs

The bleeding event may often occur soon after the initiation of NSAIDs and mostly during the first month of the therapy (Somerville et al. 1986). The risk of PUB has been estimated to be 11-fold within the first week of use (Lewis et al. 2002) and 7- to 8-fold within the first month in case-control studies (Griffin et al. 1991; Lanas et al. 2006) and a meta-analysis (Gabriel et al. 1991).

2.4.4.2. Different NSAIDs

The risk of PUB associated with different traditional NSAID drug regimens varies. According to a meta-analysis and case-control studies the risk of upper gastrointestinal bleeding or PUB has been the highest with ketoprofen, from 6- to 30-fold (Hernandez-Diaz and Rodriguez 2000; Lanas et al. 2006; Lewis et al. 2002) and with piroxicam...
(Hernandez-Diaz and Rodriguez 2000; Lanas et al. 2006). With ibuprofen and diclofenac the risk has been the lowest (Hernandez-Diaz and Rodriguez 2000; Lewis et al. 2002).

Ketoprofen 50 mg caused significantly more gastroduodenal injury than ibuprofen 400 mg, whereas ketoprofen 12.5 mg was equal to ibuprofen 400 mg (Donnelly et al. 2000). The recommended single dose of ketoprofen is 50–100 mg, and that of ibuprofen 200-600 mg.

2.4.4.3. Dose-dependence of NSAIDs

The risk of PUB is dependent on the dose of NSAIDs according to meta-analyses (Gabriel et al. 1991), case-control (Lewis et al. 2002; Stack et al. 2002; Weil et al. 1995) and prospective cohort studies (Hernandez-Diaz and Rodriguez 2000). Similarly, the risk of upper gastrointestinal bleeding and perforation increases with increasing the dose (Gutthann et al. 1997). In the recent study of Stack et al. (2002) half of the cases consumed some NSAID which may explain the high odds ratios: OR 10.6 for doses ≤ 1 defined daily doses (DDD) and OR 20.6 for doses ≥ 1 DDD. Furthermore, the use of multiple NSAIDs has been claimed to increase the risk further compared with single NSAID use (Gutthann et al. 1997; Weil et al. 1995).

2.4.4.4. Deaths and bleeding associated with NSAIDs

In England, over 40% of the 8528 episodes of ulcer bleeding in patients over 60 years and over 40% of the estimated 981 deaths per year are related to NSAID use (Langman 2001). The frequency of episodes of bleeding and deaths would be expected to be reduced by 70%, if NSAID was converted to the regimen with lowest risk. If the dose of prophylactic ASA was lowest (75 mg) the frequency of bleeding episodes and deaths would be expected to reduce by 30%. It has been estimated that on average 1 in 1200 patients taking NSAIDs for at least 2 months will die from gastroduodenal complications (Tramer et al. 2000). On the other hand, in women current use of low dose ASA was associated with significantly lower risk of all-cause mortality when compared with women who never used ASA regularly (Chan et al. 2007a).

2.4.5. Anticoagulants

Warfarin is the most used anticoagulant and acts as a vitamin K antagonist. Warfarin and other anticoagulating drugs delay the coagulation cascade. In placebo-controlled trials of warfarin there has been no risk of bleeding, but these studies usually exclude patients with history of peptic ulcer (Mant et al. 2003). In a Finnish study 11.3% of PUB patients but only 1.4% of hospital controls were on anticoagulants (Leivonen and Kivilaakso 1991).
The clinical outcome has been similar in patients with acute upper gastrointestinal bleeding using warfarin and in bleeding patients not using warfarin (Thomopoulos et al. 2005). In patients on warfarin and having signs of upper gastrointestinal bleeding 44% had PUB (Tabibian 1989). The use of oral anticoagulants is a risk factor for PUB according to a meta-analysis of 3 studies (Lewis et al. 2002). The risk has varied from almost 2-fold (Lanas et al. 2006; Stack et al. 2002) to 8-fold (Weil et al. 2000) in case-control studies.

Clopidogrel is a platelet adenosine diphosphate P2Y12- receptor antagonist that is used to prevent vascular events across a wide spectrum of atherothrombotic cardiovascular diseases (Gachet 2001). Clopidogrel seems to be associated with fewer upper gastrointestinal tract side effects compared with aspirin (Liberopoulos et al. 2006). The use of various anticoagulating drugs like ASA and clopidogrel in combination is increasing, thus increasing the risk of gastrointestinal bleeding (Hallas et al. 2006, Chan et al. 2005).

2.4.6. Corticosteroids

The association between corticosteroid therapy and peptic ulceration has been a source of debate. In an earlier review of randomised controlled trials steroids did not cause peptic ulcers unless used over a month or with high doses (Conn and Blitzer 1976).

On the other hand, corticosteroid therapy has been associated with an increased risk of peptic ulcer and gastrointestinal bleeding in an analysis of controlled trials (Messer et al. 1983), a population-based cohort study (Nielsen et al. 2001), a case-control report (Weil et al. 2000) and a meta-analysis of case-control studies (Gabriel et al. 1991).

The concurrent use of corticosteroid and NSAIDs did not increase the risk of PUB in a case-control study (Lanas et al. 2006), but in another study the risk was multiplicative (Weil et al. 2000). The clinical picture is thus far from clear. In patients on high doses of corticosteroids, previous history of peptic ulcer, advanced malignant disease, or concurrent consumption of NSAIDs, ulcer prophylaxis should be considered (Ellershaw and Kelly 1994).

2.4.7. Other drugs

During recent years pharmacoepidemiological studies have suggested that oral bisphosphonates (Kane et al. 2004), calcium channel antagonists (Kaplan et al. 2000) and selective serotonin reuptake inhibitors (de Abajo et al. 2006; Yuan et al. 2006) can increase the risk of upper gastrointestinal lesions especially if used simultaneously with NSAIDs. The results are partly contradictory (Smalley et al. 1998) and particularly with respect to PUB (Graham and Malaty 1999; Kaplan et al. 2000; Wessinger et al. 2006).
2.4.8. Smoking

Smoking causes ulcers by stimulating basal acid output and increasing duodenogastric reflux. It increases also production of platelet activation factor and endothelin, which are ulcerogens. Smoking decreases prostaglandin generation in gastric mucosa, reduces angiogenesis and blood flow and inhibits mucosal cell proliferation (Ma et al. 1998; Maity et al. 2003).

Smoking has been an independent risk factor for peptic ulcer disease in a prospective cohort study in a Danish population (Rosenstock et al. 2003). Furthermore, smoking is a risk factor for PUB in some studies (Aalykke et al. 1999; Henriksson et al. 1998; Savage et al. 1993; Stack et al. 2002; Tzourmakliotis et al. 2004; Weil et al. 2000) but not all (Gisbert et al. 2001a; Ng et al. 2000; Schubert et al. 1993). However, the risk of PUB has been found not (Aalykke et al. 1999) or only slightly increased among NSAID users who smoke compared with non-smokers (Tzourmakliotis et al. 2004; Weil et al. 2000). On the other hand, smoking doubles the risk of PUB in *H. pylori* positive patients, and they act synergistically (Stack et al. 2002). There was a dose dependence of smoking in the risk of upper gastrointestinal bleeding according to a meta-analysis (Lewis et al. 2002). In another study, smoking was not a risk factor for PUB, but was for perforated peptic ulcer (Andersen et al. 2000). At present, there are no data concerning risk of PUB and smoking in a Finnish population.

2.4.9. Alcohol consumption

Ethanol causes severe epithelial damage and necrosis of deeper layers of gastric mucosa. Further microvascular damage leads to increased permeability and intramucosal haemorrhage (Tarnawski et al. 1987). Gastric emptying is also disturbed by ethanol (Jian et al. 1986).

In Finland alcohol consumption has been significantly more common among PUB patients than in controls (Leivonen and Kivilaakso 1991). The regular use of alcohol is a risk factor for PUB (Labenz et al. 1999), also in patients on low-dose of ASA (Lanas et al. 2002). Alcohol intake has had a dose-dependent risk for PUB in New Zealand (Savage et al. 1993) as well as in Denmark (Andersen et al. 2000).

However, in several studies alcohol consumption did not differ among cases and controls (Schubert et al. 1993; Stack et al. 2002; Tzourmakliotis et al. 2004). Because many PUB patients are infected with *H. pylori*, alcohol and *H. pylori* may have some interaction. Helicobacter lipopolysaccharides induce formation of nitric oxide synthase (iNOS), cyclo-oxygenase (COX-2) and heat shock protein 70 (HSP 70) known to increase resistance to damage caused by ethanol in vivo. Indeed, *H. pylori* increases resistance of the gastric mucosa to injury caused by ethanol in vitro (Brzozowski et al. 2003).
2.4.10. Combination of risk factors

When 2 or more risk factors are present concurrently, their effect can be inhibitory, simply additive (sum of single risk factors), or synergistic (the effect is more than a simple addition).

2.4.10.1. *H. pylori* and NSAIDs

The role of underlying *Helicobacter* infection in NSAID-related bleeding ulcers is still unclear and the effect of their combination is under debate. According to a meta-analysis of 9 studies of PUB NSAID and *H. pylori* act synergistically (Huang et al. 2002). Compared with a *H. pylori*-negative non-NSAID user, a *H. pylori*-positive NSAID user has a 6-fold increased risk for PUB.

In another study, the combination has been only simply additive, and not synergistic (Cullen et al. 1997). NSAID use in *H. pylori*-positive persons increases the risk of gastric ulcer bleeding (Ng et al. 2000).

In NSAID users *H. pylori* infection (Aalykke et al. 1999) and CagA-positive *H. pylori* infection (Tzourmakliotis et al. 2004) increase the risk for PUB by 2-fold. In regular low-dose ASA users, *H. pylori* infection has almost 5-fold higher risk for PUB (Lanas et al. 2002).

The combination of NSAID and *H. pylori* has also had an inverse effect on the risk of PUB in general (Stack et al. 2002) and on gastric ulcer bleeding (Santolaria et al. 1999). In a Taiwanese case-control study the interaction was negative, though not statistically significant (Wu et al. 1999).

2.4.10.2. Anticoagulants and NSAIDs

In a large case-control study, oral anticoagulants increased the risk for PUB by 2-fold, but when combined to NSAIDs the risk ratio was 19.3 (Lanas et al. 2006). In a population based case-control study the combination of warfarin and low-dose ASA acted synergistically on the risk of PUB (Hallas et al. 2006). The concurrent use of warfarin and low-dose aspirin (325 mg/day) caused upper gastrointestinal bleeding in 20% of the patients compared with none in the group using only ASA (Younossi et al. 1997). When a patient with an earlier history of PUB receives low-dose ASA medication, the risk of new bleeding episode of peptic ulcer is increased 15 –fold (Lanas et al. 2002).

2.4.11. *Helicobacter pylori*-negative non-NSAID peptic ulcer

An increasing proportion of ulcers occur in the absence of *H. pylori* infection, because the prevalence of *H. pylori* is decreasing. In Finland, the rate of *H. pylori*-negative patients has been as high as 35% among older peptic ulcer patients who do not use
NSAIDs (Kemppainen et al. 1997). A prevalence of 20% of non-\textit{H. pylori} non-NSAID ulcers has been found in Poland in 2000 (Konturek et al. 2003) and in Sweden (Aro et al. 2006).

In patients with \textit{H. pylori}-negative DU some other obvious reason may be present, such as NSAID use, Crohn’s disease, or Zollinger-Ellison syndrome. \textit{H. pylori}-negative DU may also be associated with hypergastrinaemia, increased acid secretion and rapid gastric emptying (McColl et al. 1993). Also increased parietal cell mass, reduced mucosal blood flow, or Cytomegalovirus infection might be explanations for \textit{H. pylori} negative ulcers (Peura 2000). \textit{H. pylori} negative ulcer may also be explained by recent peptic ulcer medication, antibiotics or inaccurate test.

2.5. Endoscopic and clinical factors associated with PUB

2.5.1. Forrest classification

Signs of haemorrhage seen at endoscopy include localised active bleeding (arterial spurting or oozing) and signs of recent bleeding, like an adherent clot, a non-bleeding visible vessel (NBVV), or a flat black base. These signs are used in the modified Forrest classification: Ia = spurting bleeding, Ib = oozing bleeding, IIa = visible vessel, IIb = clot, IIc = black base covering ulcer, III= clean ulcer base (Forrest et al. 1974). The Forrest classification characterises the bleeding point and can predict the rebleeding risk in PUB.

Major peptic ulcer bleeding is typically from a small (mean external diameter 0.7mm) single submucosal artery just below the ulcer base, which can be seen as a visible vessel (Swain et al. 1986). It is defined as a protruding red, blue, or white mount, a pulsatile pseudoaneurysm or a yellow-white rod sticking out of the ulcer base (Swain et al. 1986; Wara 1985). Sentinel clot covers a side hole of the bleeding artery running beneath ulcer base and the vessel is actually invisible (Johnston 1984). The generic term protuberance includes both visible vessel and sentinel clot (Consensus statement on therapeutic endoscopy and bleeding ulcers 1990). The prevalence of these signs of bleeding among PUB patients are: active bleeding 18%, NBVV 17%, adherent clot 17%, flat spot 20%, clean base 42% (Laine and Peterson 1994).

2.5.2. Endoscopic signs of acute or recent haemorrhage predicting rebleeding

Endoscopic signs of acute or recent haemorrhage are important predictors of rebleeding and need of endoscopic therapy or surgery (Branicki et al. 1992; Jaramillo et al. 1994; Mueller et al. 1994). When endoscopy is performed within 24 hours after the onset of bleeding, NBVV can be found in 48% of patients, and other signs of acute or recent haemorrhage in 18% of patients, whereas 34% have no signs (Storey et al. 1981).
When no endoscopic treatment or surgery is undertaken, the rebleeding risk associated with each sign are: active arterial bleeding (Forrest Ia and Ib) 55%, NBVV (Forrest IIa) 43%, adherent clot (Forrest IIb) 22%, flat spot/black base (Forrest IIc) and clean base (Forrest III) 5% (Laine and Peterson 1994). However, there has been a considerable inter-observer disagreement in the interpretation of the presence of endoscopic stigmata of recent haemorrhage (Laine et al. 1994). Endoscopic Doppler ultrasound has shown that not all NBVV have submucosal arterial flow (Fullarton and Murray 1990) and that even pigmented spots may have it. Hypovolaemic shock increases the rebleeding rate of NBVV from 25 to 40%, and that of an adherent clot from 17% to 50% (Hsu et al. 1994).

2.5.3. Other endoscopic predictors of rebleeding

The rebleeding risk is associated with ulcers > 1cm in diameter (Branicki et al. 1992), and more so with giant duodenal ulcers (≥ 2 cm) (Brullet et al. 1996a; Brullet et al. 1996b; Collen et al. 1994). An ulcer location high on the lesser curvature (Brullet et al. 1996b) or posterior duodenal wall (Brullet et al. 1996a) and possible pulsation are also risk factors.

2.5.4. Clinical risk factors for rebleeding

Haematemesis (Jaramillo et al. 1994), a low haemoglobin level (Choudari et al. 1994) and shock on admission are risks for rebleeding (Branicki et al. 1992; Brullet et al. 1996b; Choudari et al. 1994; Jaramillo et al. 1994; Mueller et al. 1994). Regarding other clinical risk factors, the situation is not clear. Old age has been a risk factor in some studies (Chow et al. 1998; Inadomi et al. 1995; Jaramillo et al. 1994) while in others it did not increase the rebleeding risk or mortality (Choudari et al. 1994; Mueller et al. 1994). A similar lack of clarity prevails with alcoholism and concomitant diseases. They have been associated with the risk for rebleeding in one study (Inadomi et al. 1995), but in another study concomitant diseases did not increase the risk (Choudari et al. 1994). Even the reports of recent use of NSAID or ASA are inconsistent, because they may (Godil et al. 2000) or may not (Choudari et al. 1994; Inadomi et al. 1995) be associated with rebleeding.

2.5.5. Timing of rebleeding

Rebleeding occurs mostly within 72 hours after the initial incidence (Lin et al. 1996; O’Brien et al. 1986). In cases with NBVV 97% of the occasions took place in 72 hours (Lin et al. 1994). The rest of such episodes in general occur within one week (Hsu et al. 1994; Inadomi et al. 1995; Lin et al. 1994).
2.5.6. Risk of rebleeding and early discharge

Different scoring systems to identify those at increased risk of rebleeding may be used in patient management and decision making for discharge. The idea of Rockall’s risk score (age, presence of shock, comorbidity, diagnosis, endoscopic stigmata) (Rockall et al. 1996b) and other scoring systems (Gisbert et al. 2006; Guglielmi et al. 2002; Saeed et al. 1995) are to identify those with the risk. Patients at a low risk can accordingly be safely discharged after endoscopy.

These scoring systems have been criticised, because they are not practical and are too complex to use in a real-life setting. The Rockall score may predict death, but performs poorly for endpoints of rebleeding and surgical procedures (Enns et al. 2006).

By Saeed et al. (1993) the risk associated with endoscopic signs of bleeding can be eliminated by endotherapy. Therefore clinical factors become primary determinants of rebleeding. On the other hand, endoscopic factors are more important than clinical ones predicting rebleeding following endoscopic therapy according to Chung et al. (2001).

Routine second-look endoscopies are not recommended (Barkun et al. 2003). In the study of Messmann et al. (1998) scheduled second-look endoscopy did not improve outcome compared with second endoscopy performed only at recurrent hemorrhage. Though, by Chiu et al. (2003) scheduled repeat endoscopy with appropriate therapy 16–24 hours after initial endoscopic haemostasis reduced the number of cases of recurrent bleeding.

2.6. Treatment

Patients with signs of upper gastrointestinal bleeding should be carefully monitored following initial fluid resuscitation even on special observation wards. Plasma expanders are needed, if patient remains shocked following initial fluid resuscitation. Blood transfusions are often needed, when patient has ongoing bleeding, or when haemoglobin concentration is less than 100g/l (Sanderson et al. 1990; Lin et al. 2002; British Society of Gastroenterology Endoscopy Committee 2002).

The schedule of diagnostic endoscopy depends on the bleeding status. If patient has major bleeding, urgent endoscopy is to be performed without delay. Otherwise routine endoscopy is undertaken during routine working hours. The mortality associated with acute gastrointestinal bleeding has diminished to 5-8% by forming specialised gastrointestinal units with strict protocols for resuscitation, transfusion and surgery (Sanderson et al. 1990, Barkun et al. 2003).

2.6.1. Endoscopic therapy

Endoscopic therapy in PUB is possible in almost all cases. Permanent haemostasis can be achieved in 83 % (Choudari et al. 1994). According to Williams et al. (1993),
before the era of endoscopic therapy, 15-27% of the PUB patients were operated on, with an overall mortality of 22%. During the period of endoscopic therapy, the operation rate has been 6% and the mortality 7%.

Endoscopic therapy was presented as a procedure of choice for PUB in 1989 by a Consensus Conference of Therapeutic endoscopy and bleeding ulcers (1989) at the National Institutes of Health. There has been speculation that when therapeutic endoscopy fails, emergency surgery may be delayed and mortality may increase (Wheatley and Dykes 1990). On the other hand, endoscopic therapy was as effective as emergency surgery for PUB in terms of rebleeding, but mortality rates were 0% for endoscopic therapy and 20% for surgery (Ralph-Edwards and Himal 1992).

Adrenaline causes vasoconstriction and has a local tamponade effect. Injection of sclerosants (like polidocanol and alcohol) results in tissue necrosis, ulceration and thrombosis (Rajgopal et al. 1992). A second method in addition to adrenaline injection is superior to adrenaline alone according to a meta-analysis of 16 trials (Calvet et al. 2004) and Cochrane analysis (Vergara et al. 2007). Several other haemostatic methods are used during endoscopy, like bipolar coagulation (O'Brien et al. 1986), heater probe thermocoagulation (Lin et al. 1990), fibrin glue (Rutgeerts et al. 1997) or hemoclip (Lin et al. 2002).

According to a meta-analysis of 25 randomised controlled trials comparing endoscopic therapy to standard therapy (common antiulcer drugs and emergency surgery if necessary), endoscopic therapy reduces rebleeding by 68% (Sacks et al. 1990). In another meta-analysis of 30 randomised controlled trials, endoscopic therapy significantly reduced rates of rebleeding (OR 0.57), surgery (OR 0.37) and mortality (OR 0.40) in PUB (Cook et al. 1992). Endoscopic haemostasis is the first line therapy for PUB.

2.6.2. Operative treatment

Before the era of endoscopic therapy, patients with ongoing bleeding and unstable haemodynamics were operated on and in the rest the semi-elective acid controlling surgery was performed. Due to major improvements in medical and endoscopic treatment, the role of surgery has changed. Emergency surgery in PUB is a life-saving procedure in situations where endoscopic treatment fails or cannot be performed.

The overall mortality was 12% in 145 PUB patients who had undergone emergency surgery in Turku, Finland between the years 1973 - 1985. In this study only a few (2%) patients rebled following gastric resection, whereas 19% of those operated with transfixation rebled. Furthermore, 44% of the patients who rebled died (Kuttila et al. 1991). The mortality of PUB patients with emergency operation was significantly lower (9.8%) than in patients who were operated on after an observation period (16.9%) in Helsinki, Finland in the years 1975 and 1986 (Ovaska et al. 1992). Between 1974 and 1986 mortality was 22.1% in Massachusetts when operations were performed for
massive peptic ulcer bleeding. Deaths were attributed to sepsis and organ failure, not rebleeding (Welch et al. 1986).

Endoscopic treatment has failed in 20 to 25% of the PUB patients with active bleeding or a NBVV (Thomopoulos et al. 2001; Villanueva et al. 1993). Failure is related to shock on admission, spurting bleeding at endoscopy, anastomotic ulcer, concomitant diseases, large ulcer size and posterior duodenal ulcer. Therefore, patients with these risk factors should be carefully monitored and considered as candidates for second look endoscopy or early elective surgery (Thomopoulos et al. 2001; Villanueva et al. 1993).

Following endoscopic therapy, PUB patients with acute spurting bleeding or NBVV were randomised to early definitive surgery (n = 23) or repeated endoscopic therapy (n = 32) (Imhof et al 2003). Rebleeding occurred in 1 and 16 patients, respectively. Repeated endoscopic therapy succeeded in 9 of the 16 patients and 7 were further operated on.

In the era of endoscopic treatment, primary emergency surgery is considered when the ulcer is inaccessible to endoscopic treatment, e.g. in the posterior duodenal wall with spurting arterial bleeding, when endoscopic therapy is unable to stop the bleeding, or when the patient has life-threatening bleeding that does not allow endoscopy (Ohmann et al. 2000). Rebleeding after endoscopic therapy can be treated by repeated endoscopic treatment, and permanent haemostasis is achieved in half of these patients (Villanueva and Balanzo 1997). In the rest, rebleeding is an indication for secondary emergency surgery (Ohmann et al. 2000).

In a randomised study of 120 patients with massive, persistent or recurrent bleeding of DU there was no difference between local (oversewing and vagotomy) and radical surgery (gastric resection and ulcer excision) concerning mortality (23 % vs. 22%), but the rebleeding rates were higher in the local surgery group (17% vs. 3%) (Millat et al. 1993).

Once the decision to operate has been made, it is important to gain control of the bleeding vessel quickly. For bleeding duodenal ulcers, oversewing and ligation is a procedure of choice, and for bleeding gastric ulcer excision of the ulcer or ligation of the bleeding vessels (Ohmann et al. 2000). In cases of deformed or penetrated ulcer, gastric resections may be an alternative, but in most cases ligation of the bleeding site and further acid-suppressing medication is effective with a low mortality and low recurrence rate (Rogers et al. 1988; Teenan and Murray 1990).

2.6.3. Angioembolisation

New non-surgical treatment modalities have been used in cases when endoscopic therapy or surgery fails and when the endoscopic access is difficult, like in massive duodenal ulcer bleeding. In these circumstances arterial embolisation succeeded in all but 1 of the 13 patients (Toyoda et al. 1995). In another study of bleeding DU
permanent haemostasis was achieved in 26 out of 40 patients, but the overall mortality was 25% (Holme et al. 2006).

2.6.4. Drug treatment

2.6.4.1. Theory

The gastric proton pump H⁺K⁺ATPase situated within the parietal cell is able to produce large amounts of acidic gastric juice. If a fibrin clot is placed in gastric juice with a pH < 4, it is dissolved by pepsin in minutes (Berstad et al. 1979). If similar concentration of hydrochloric acid without pepsin is used, almost nothing happens.

At pH 5.4 both platelet aggregation and plasma coagulation are virtually abolished. In vitro, acid and pepsin together inhibit platelet plug formation and fibrin clot generation. They also destroy previously established platelet plugs. Pepsin also digests fibrin clots at a pH < 4 (Berstad 1982; Green et al. 1978). This is also confirmed by in vitro studies with thrombelastography (Patchett and O’Donoghue 1995). In vivo more fibrinolytic activity is found in the gastroduodenal mucosa in biopsies obtained from PUB patients with signs of acute or recent bleeding than in patients without such signs. Acid suppression by drugs decreases this activity (Vreeburg et al. 2001).

In early stages, the major factors affecting peptic ulcer healing are intragastric acidity and pepsin activity (Tarnawski et al. 1991). Pepsin can be inhibited by acid neutralisation and clots remain stable at a near neutral intragastric pH (Berstad 1982). Therefore, the pharmacologic treatment of PUB is aiming to preserve intragastric pH near neutral. Keeping the intragastric pH at ≥ 6 requires almost complete inhibition of acid secretion (Green et al. 1978).

2.6.4.2. H2 receptor antagonists

H2 blockers act on histamine receptors outside the parietal cell. These agents reduce acid secretion from parietal cells and therefore help to heal ulcers.

According to 2 meta-analyses (Collins and Langman 1985; Levine et al. 2002) the H2 antagonists are only comparable to placebo in acute PUB. Their use should be re-evaluated, because they fail to reduce rates of rebleeding, surgery or mortality significantly in patients with bleeding duodenal ulcers. On the other hand, H2 blockers may prevent recurrent bleeding and the need for surgery in patients with bleeding gastric ulcers, but there was no effect on mortality (Collins and Langman 1985; Levine et al. 2002).

In a meta-analysis of 11 studies comparing the use of H2 blockers and PPIs for bleeding peptic ulcer, PPIs have been superior in preventing rebleeding, especially in cases with high-risk endoscopic signs of bleeding. However, there was no difference in the need for surgery or mortality (Gisbert et al. 2001b).

The modest acid suppression and rapid development of pharmacological tolerance to H2 antagonists occurring as early as 24 h after the onset of therapy are the main reasons for the lack of their efficacy.

2.6.4.3. Proton pump inhibitors

PPIs inhibit H\(^+\)K\(^-\)ATPase in the parietal cell. The drugs are the most effective suppressors of gastric acid secretion. Omeprazole was the first PPI brought to the market, in Finland in 1991. Omeprazole was soon followed by lansoprazole, rabeprazole and pantoprazole. In recent years esomeprazole has been available and studies with tenatoprazole have been published recently (Hunt et al. 2005).

Oral omeprazole, the most used PPI, is relatively slow to reduce acid secretion. As an intravenous infusion with an initial bolus dose, however, acid secretion has been shown to be quickly inhibited and intragastric pH level stays between 4 and 6 in most cases (Kiilerich et al. 1995).

2.6.4.3.1. Proton pump inhibitors without endoscopic therapy

In PUB patients with endoscopic signs of high-risk bleeding, but without endoscopic therapy oral omeprazole 40 mg twice a day has been superior to placebo, with a lower rebleeding rate (10.9% vs. 36.4%) and lower rate of surgery (7.3% vs. 23.6%), but no difference in mortality (Khuroo et al. 1997). Though PPIs without endoscopic therapy reduce rebleeding and need for surgery and repeated endoscopic treatment by a meta-analysis (Leontiadis et al. 2007), therapeutic endoscopy is considered the standard of the care of patients with acute PUB.

2.6.4.3.2. Proton pump inhibitors compared with endoscopic therapy

In cases with NBVV omeprazole (80 mg/day) is a valid alternative to endoscopic combination (adrenaline injection + 0.5% polidocanol) treatment with equal 19% rebleeding rates (Grosso et al. 1995). Similarly, in cases with NBVV or adherent clots omeprazole 40 mg orally twice a day and endoscopic ethanol injection therapy are comparable for preventing rebleeding, with rebleeding rates of 22.9% and 20.8%, respectively (Jung et al. 2002). On the other hand, in cases with adherent clots the rebleeding rate was significantly lower (0%) after endoscopic treatment with adrenaline injection and bipolar probe coagulation than after high-dose oral PPI therapy (35.3 %), the exact dose of which was not mentioned (Jensen et al. 2002).

According to a meta-analysis of 6 studies comparing endoscopic therapy with medical therapy in PUB with an adherent clot, rebleeding rate was 8.2% vs. 24.7%, indicating that endoscopic therapy is superior to PPI in preventing rebleeding (Kahi et al. 2005). However, there was no difference in mortality, 9.8% vs. 7%. 
2.6.4.3.3. Proton pump inhibitors versus placebo following endoscopic therapy

Several studies comparing PPI with placebo following endoscopic therapy indicate that high dose of PPI is superior to placebo in PUB patients with high-risk endoscopic signs of bleeding in preventing rebleeding (Table 1). In most of the studies a continuous infusion of a high-dose omeprazole (80 mg bolus following infusion of 8 mg/h) was compared with placebo for 72 hours (Hasselgren et al. 1997; Lau et al. 2000; Schaffalitzky de Muckadell et al. 1997) or a high dose pantoprazole (Zargar et al. 2006) was used. Oral omeprazole with doses 40 mg x 2 (Javid et al. 2001) or 20 mg x 4 (Kaviani et al. 2003) were also superior to placebo in reducing rebleeding.

In these studies, there was no difference in the mortality, or in the need for emergency surgery, except in the study of Hasselgren et al. (1997), which was discontinued due to a high mortality rate in the omeprazole group (6.9% vs. 0.6% in the placebo group, p = 0.012). In another study the number of deaths was similar in both groups (Schaffalitzky de Muckadell et al. 1997).

2.6.4.3.4. Proton pump inhibitors versus H2 blockers following endoscopic therapy

In 100 PUB patients with active bleeding or NBVV after endoscopic therapy (with heater probe or multipolar electrocoagulation) omeprazole with a 40 mg bolus, followed by 160 mg of continuous infusion daily for 3 days is superior to cimetidine with 300 mg bolus followed by 1200 mg continuous infusion daily for 3 days based on the rate of rebleeding (4% vs. 24% by day 14 after the enrolment) but there was no difference in surgery rate or deaths (Lin et al. 1998).

A lower dose of pantoprazole (40 mg bolus followed by 40 mg every 12 hours for 3 days) was compared with ranitidine (bolus of 50 mg followed by 50 mg every 8 hours for 3 days) in 102 patients with high-risk bleeding peptic ulcers following endoscopic therapy. The rebleeding rate was significantly lower with pantoprazole (4% vs. 16%), but there was no difference in deaths, 2% in both groups (Hsu et al. 2004).

Altogether 200 PUB patients with active bleeding or NBVV after endoscopic therapy with adrenaline injection received either high or a low-dose omeprazole (40 mg every 6 hours, n = 67 or 40 mg every 12 hours, n = 66) as a continuous infusion, or cimetidine (400 mg every 12 hours, n = 67) as a continuous infusion for 3 days. The rebleeding rates and volume of blood transfusion were significantly lower with the high-dose omeprazole than with cimetidine, 9% versus 33%. There was no significant difference in hospital stay, number of operated patients, and deaths. The lower dose of omeprazole had a rebleeding rate of 21% in contrast to 9% with the higher dose. This may have clinical significance, suggesting that a higher dose of PPI should perhaps be favoured in high-risk patients (Lin et al. 2006).
2.6.4.3.5. **Proton pump inhibitors and endoscopic therapy**

In a study of PUB patients with high-risk endoscopic signs of bleeding (active bleeding or NBV) patients received a high-dose intravenous omeprazole (80 mg bolus + 8 mg/h) and were randomised to have endoscopic therapy or sham therapy (Sung et al. 2003). The importance of endoscopic therapy in preventing rebleeding was affirmed, since none of the patients treated with endoscopic therapy rebled, compared with 9% of the patients treated only with the high dose of omeprazole.

PUB patients with concomitant illnesses received 200 or 80 mg/day omeprazole after endoscopic treatment with adrenaline injection or heater probe, respectively, as a continuous infusion for 3 days. Increasing the dose of intravenous PPI from 80 mg to 200 mg was not adequate to control rebleeding, with rebleeding rates of 15.4% and 11.3% by day 3 and 35.4% and 33.3% by day 28, respectively (Cheng et al. 2005). An albumin level < 3 g/dl was a risk factor for rebleeding suggesting that poor background disease and poor nutritional status results in poor tissue repair. In these patients rebleeding occurred during the days 4-14. End stage liver disease was associated with rebleeding occurring between days 15-28.

In one study the effect of a high dose of pantoprazole (40 mg intravenous bolus followed by 8 mg/h for 3 days) was compared with a regular dose (40 mg intravenous bolus for 3 days) in endoscopically treated patients. There was no difference the in rebleeding rate, 8% versus 12% (Shonekas et al. 1999).
Table 1. Randomized trials comparing PPIs in the treatment of PUB after endoscopic therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Treatment</th>
<th>Rebleeding</th>
<th>Surgery</th>
<th>Mortality</th>
<th>F Ia</th>
<th>F Ib</th>
<th>F IIa</th>
<th>F IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaffalitzky de Muckadell et al. 1997*</td>
<td>130/135</td>
<td>OME IV 80mg+8mg/h Placebo</td>
<td>9/19</td>
<td>5/11</td>
<td>2/0</td>
<td>6</td>
<td>24</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Hasselgren et al. 1997 **</td>
<td>159/163</td>
<td>OME IV 80mg+8mg/h Placebo</td>
<td>3.1/2.5</td>
<td>4/10</td>
<td>6.9/0.6</td>
<td>7</td>
<td>25</td>
<td>16</td>
<td>52</td>
</tr>
<tr>
<td>Lau et al. 2000</td>
<td>120/120</td>
<td>OME IV 80mg+8mg/h Placebo</td>
<td>7/23</td>
<td>3/8</td>
<td>4/10</td>
<td>10</td>
<td>4</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Kaviani et al. 2003</td>
<td>71/78</td>
<td>OME PO 20mg/6h Placebo</td>
<td>17/33</td>
<td>2/1</td>
<td>0/1</td>
<td>8</td>
<td>54</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Javid et al. 2001</td>
<td>82/84</td>
<td>OME PO 40mg/12h Placebo</td>
<td>7/21</td>
<td>2/8</td>
<td>1/2</td>
<td>16</td>
<td>25</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Schonekas et al. 1999</td>
<td>82/86</td>
<td>PAN IV 40mg x1 PAN IV 40mg+8mg/h</td>
<td>10/12</td>
<td>-/-</td>
<td>2/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* endoscopic therapy in 71% and 73%
** endoscopic therapy only in F Ia bleeding,
OME= omeprazole, PAN= pantoprazole, IV= intravenous, PO= peroral, F= Forrest classification
2.6.4.4. Somatostatin, tranexamic acid and sucralfate

Somatostatin is presumed to be effective in arresting PUB by inhibiting gastric secretion and reducing splanchnic blood flow (Bloom et al. 1974). In a meta-analysis of PUB it has reduced rebleeding (Imperiale and Birgisson 1997). Somatostatin intravenously (250 µg bolus +500 µg/h) had a similar effect as intravenous pantoprazole (80 mg bolus + 8 mg/h) in maintaining a high intragastric pH during 24 hours (pH > 4: 83 % vs. 70% of time and pH > 6: 64% vs. 57% of time, respectively) (Avgerinos et al. 2005). Somatostatin is not recommended in the routine management of patients with acute nonvariceal upper GI bleeding (Barkun et al. 2003).

The antifibrinolytic agent tranexamic acid impairs plasmin-mediated fibrinolysis by gastric juice (Patchett et al. 1989). Administration of tranexamic acid has reduced the total amount of blood loss and need for emergency surgery (von Holstein et al. 1987). On the other hand, tranexamic acid partially inhibited gastric juice-induced clot lysis but did not have beneficial effect on coagulation in an in vitro study with thrombelastography (Patchett and O'Donoghue 1995).

Sucralfate has been used as a protectant of the mucosa, because it forms an ulceradherent complex at ulcer site and reduces pepsin activity. Sucralfate inhibited fibrinolysis, but it had an adverse effect on the dynamics of clot formation. Drugs like omeprazole that profoundly neutralise gastric acid seem to be more appropriate in upper gastrointestinal bleeding than tranexamic acid or sucralfate (Patchett and O'Donoghue 1995).

2.7. The effect of drug treatment on intragastric pH

2.7.1. Intragastric pH in healthy volunteers

Gastric acid secretion is studied by the measurement of the intragastric pH expressed in a logarithmic scale. Each increase or decrease of 1 pH unit reflects a 10-fold change in acid concentration. There are several studies of intragastric pH measurement performed in healthy volunteers to find an ideal acid suppressing drug to be used in PUB.

During the first 24 hours, ranitidine at doses of 150 mg-300 mg/day has been superior to intermittent boluses of omeprazole (160 mg/day) in increasing the intragastric pH above 6, 60% vs. 20-42% of time, respectively. This is probably caused by considerable interindividual variation in response to omeprazole (Teyssen et al. 1995).

When intragastric pH measurement is continued beyond 24 hours, H2 blockers fail to increase the intragastric pH constantly above 4 after the first 24 hours. This phenomenon of tolerance has been observed with ranitidine at doses of 300 mg q.d.s
(Hurlimann et al. 1994), at mean doses of 503 mg and 542 mg (Merki and Wilder-Smith 1994), and with an infusion of 50 mg bolus + 0.25 mg/h (Labenz et al. 1997; Netzer et al. 1999) or injection of 100 mg/6h (Netzer et al. 1999).

With omeprazole 40 mg intravenously, the maximal effect on intragastric acidity has been obtained instantly and maintained for 5 days. In contrast, with omeprazole at doses of 10 mg intravenously and 20 mg orally, the maximal effect on gastric acidity (60% reduction) was obtained only after 5 days. However, the reduction of intragastric acidity in these healthy subjects was less than in duodenal ulcer patients (Cederberg et al. 1993). In a study of Hurlimann et al. (1994), the response of intragastric pH to the administration of omeprazole 40 mg or ranitidine 300 mg orally was studied in healthy volunteers. With ranitidine, the maximum acid-suppressing effect was present on day 1 (median pH 4.4). Thereafter the effect faded, implying tolerance. With omeprazole, the antisecretory effect (median pH 3.8 on day 1) further increased during the first week.

With a continuous omeprazole infusion (80 mg bolus + 8 mg/h) intragastric pH stayed > 4 over 95% of the time during the first day and at 100% on the third day. In contrast, with the injection of omeprazole (80 mg bolus + 40 mg every 6 hours) the result was significantly less effective on day 1, but after that pH increased to a similar level with omeprazole infusion (Netzer et al. 1999).

2.7.2. Intragastric pH in peptic ulcer bleeding

There are only a few studies in which intragastric pH measurements have been performed in patients with PUB. Omeprazole 120 mg/day has been superior to ranitidine 300 mg/day (Lanas et al. 1995), omeprazole infusion superior to cimetidine infusion (Lin et al. 1998) and omeprazole infusion (80 mg bolus + 8 mg/h) superior to ranitidine infusion (50 mg bolus +0.25 mg/kg/h) (Labenz et al. 1997) in increasing the pH above 6. Both 200 mg and 80 mg of omeprazole intravenously increased the median 24h intragastric pH above 6 (Cheng et al. 2005). With higher doses of pantoprazole infusion (80 mg bolus + 6 mg/h vs. 8 mg/h) there was better control and lower interindividual variability of the acidity (pH ≥ 6 during 48 hours 47% and 64% of the time, respectively).

In Taiwan, 88 PUB patients who underwent endoscopic therapy were placed on omeprazole (40 mg + 40 mg every 6h) for 3 days. The mean intragastric pH was < 6 in 25 patients and < 4 in 4 patients, defined as poor responders to intravenous omeprazole. These patients with pH < 4 had a higher rebleeding rate (Hsieh et al. 2004). On the other hand, the rebleeding was not related to the increase of pH, since patients with adequate pH control rebled and also deaths occurred (Labenz et al. 1997; van Rensburg et al. 2003). So far, in Finland there is no study reporting the control of intragastric acidity with the treatment of PUB.
2.7.3. The effect of H. pylori on intragastric pH

The increase in pH with omeprazole has been more constant and profound in patients with DU than in healthy controls (Cederberg et al. 1993). Omeprazole 20 mg increased the intragastric pH less after the eradication of H. pylori than before the pre-eradication phase in DU patients (median 24-hour pH 5.5 vs. 3.0) (Labenz et al. 1996). Similarly, the median intragastric 24 hour pH decreased from 7.95 in H. pylori-positive to 3.75 in H. pylori-negative healthy volunteers after 6-8 weeks of treatment with omeprazole 40 mg daily (Gillen et al. 1999). This difference may be caused by higher content of buffer substances in the infected stomach or by a higher volume of gastric secretions. Therefore, the dose of PPI in H. pylori-negative subjects should be re-evaluated (Gillen et al. 1999; Labenz et al. 1996).

2.7.4. CYP2C19 genotype and intragastric pH

Omeprazole is completely metabolised by the liver with hydroxylation which is catalysed by the polymorphic cytochrome P450 isoenzyme CYP2C19. This CYP2C19 genotype status can affect the efficacy of the PPI omeprazole (Furuta et al. 1999). In homozygous carriers this isoenzyme is absent. Of Caucasians 3-6% and of Orientals 18-30% lack this isoezyme and are called poor metabolisers of omeprazole. Therefore, in Orientals the clearance of omeprazole is on average slower than in Caucasians (Bertilsson 1995; Sagar et al. 1998; Sagar et al. 2000). When combining homozygous and heterozygous carriers of this mutation, almost 60% of Asian populations have a slower metabolism of CYP2C19 substrates than the majority of Caucasians (Meyer 1996). Genotyping test of CYP2C19 might be valuable in determining an effective dose of omeprazole in some treatment-resistant, acid-related diseases (Ishizaki and Horai 1999).

2.8. Omeprazole and H. pylori

2.8.1. Effect of omeprazole on H. pylori

H. pylori colonises the gastric epithelium and its urease activity is probably essential for colonisation. The base produced by the urease may protect the organism from gastric acid (Eaton et al. 1991).

In vitro studies indicate that the survival of H. pylori below pH 4 may be urease dependent (Bugnoli et al. 1993). Omeprazole inhibits the urease enzyme of H. pylori in a dose-dependent manner (Bugnoli et al. 1993). On the other hand, omeprazole decreases H. pylori survival at low pH also through a mechanism independent of its effect on urease. The drug also has an antibacterial effect on other bacteria (McGowan et al. 1994).
2.8.2. Detection of H. pylori

*H. pylori* eradication is defined as absence of the bacterium when detection is carried out at least one month after the cessation of the treatment (Rauws et al. 1988). In several studies omeprazole transiently affects the detection of *H. pylori* (Stolte and Bethke 1990; Yamamoto et al. 1995).

After 4 weeks (Fukuda 1996; Logan et al. 1995; Marzio et al. 1995), 2 weeks (Hui et al. 1991) or even after one week of treatment (Verdu et al. 1994) some *H. pylori*-positive subjects temporarily turned *H. pylori* negative. The lack of detection of *H. pylori* from the antral mucosa after omeprazole treatment was dose-dependent and the density of *H. pylori* decreased with omeprazole, but not with ranitidine (Hui et al. 1991).

After 4 weeks of omeprazole treatment *H. pylori* colonisation decreased in the antrum and corpus and increased in the fundus (Logan et al. 1995). It was speculated that *H. pylori* migrated from the antrum to the corpus (Marzio et al. 1995). Later this speculation has been rejected, because in another study the number of *H. pylori* decreased both in the antrum and corpus (Graham et al. 1996b).

The distribution of *H. pylori* in gastric mucosa between GU and DU is different, since the bacteria is found only in antrum in 7% of GU and 43% of DU cases, but both in antrum and corpus in 82% or 56% of the patients, respectively (Vorobjova et al. 1991).

2.8.3. PUB and test reliability for *H. pylori*

The prevalence of *H. pylori* infection in PUB has been lower than in cases of uncomplicated peptic ulcer (Lee et al. 2000; Liao et al. 2003). This may be due to the biopsy-based methods (rapid urease test, histology, culture), which have low sensitivity (45-70%) but high specificity (90-98%) to detect *H. pylori* in cases of upper gastrointestinal bleeding (Gisbert and Abraira 2006; Grino et al. 2001; Lee et al. 2000; Liao et al. 2003). In contrast, urea breath test has been sensitive (93%) and specific (92%) (Gisbert and Abraira 2006; Liao et al. 2003).

Blood in the stomach may interfere the result of rapid urease test (Lee et al. 2000) and also prior PPI medication induces false-negative results. To increase the accuracy, other additional tests should be used (Grino et al. 2001; Liao et al. 2003). The low rate of *H. pylori* infection in the acute bleeding phase may also be due to a different pathogenesis in bleeding peptic ulcers than in uncomplicated ulcers. This is clinically important because a patient with an overlooked *H. pylori* infection is more likely to experience recurrent ulcer and bleeding (Gisbert and Abraira 2006).

2.8.4. Recurrent bleeding after eradication of *H. pylori*

Eradication of *H. pylori* infection reduces the rate of ulcer recurrence and rebleeding in complicated ulcer disease (Graham et al. 1993). After the occurrence of PUB,
eradication of *H. pylori* has been superior to maintenance antisecretory treatment in preventing recurrence of peptic ulcer and rebleeding (Santander et al. 1996).

2.9. Clinical practice today and future aspects

Studies of patients with a history of PUB has revealed that only from 12% (van Leerdam et al. 2003) to 20% (Hudson et al. 1995b) of the NSAID prescriptions has had co-prescription of antiulcer drugs. Altogether 50% of the NSAID consuming patients at risk of ulcers (history of peptic ulcer, > 60 years of age) do not use gastroprotective therapy (Lanas and Fernandez 2007). Guidelines of pain management recommend for patients at risk NSAID with PPI or COX2 inhibitors. Still, in patients with history of PUB, combination of COX2 inhibitor and PPI was more effective than COX inhibitor alone in preventing a new episode of PUB (Chan et al. 2007b).

The routine administration of intravenous PPI to all persons admitted due to upper gastrointestinal bleeding until diagnostic endoscopy is performed and thereafter discontinuing the drug in those other than PUB would prevent 40 rebleeding episodes, 9 emergency operation and 223 hospital days/1000 patients. This policy is estimated to be a cost-effective treatment strategy in the USA (Gagnon et al. 2003).

In Canada, only 13.4% of all patients who had intravenous PPI when admitted to hospital due to suspected upper gastrointestinal bleeding had PUB with high risk signs of bleeding. After diagnostic endoscopy, intravenous PPI was unnecessarily continued in 57% of the patients with low-risk or even nonulcer lesions (Enns et al. 2004). In the Canadian practice intravenous PPI infusions before endoscopy compared with after endoscopy may lower the proportion of actively bleeding peptic ulcer lesions found on endoscopy, but this does not affect the rates of rebleeding, surgery or mortality (Andrews et al. 2005).

In Amsterdam, between years 1993/1994 and 2000 the use of H2 blockers has decreased from 54% to 6%. High dose intravenous PPI has been administered to 37% of the high risk PUB patients. Despite these new treatment modalities, rate of rebleeding, emergency surgery and mortality has remained the same (van Leerdam et al. 2003).

On the other hand, PPI use and endoscopic haemostasis in patients with high-risk stigmata decreased the rebleeding rate in a Canadian registry of nonvariceal upper gastrointestinal bleeding in 1999 and 2002. Generally, rebleeding rate was 14%, surgery rate 7% and mortality 5% (Barkun et al. 2004a).

Peptic ulcer is believed to be a disappearing disease, because powerful ulcer-healing drugs and eradication of *H. pylori* should abolish the disease. At the same time, there is a clear increase of life-threatening complications of peptic ulcer disease in older people. This most probably results from comorbidities and increased consumption of NSAIDs in the elderly. Despite the progress in the treatment of chronic peptic ulcer disease in the past decades, peptic ulcer bleeding remains a therapeutic challenge.
3. AIMS OF THE PRESENT STUDY

The purpose of the current clinical study was to examine controversial aspects of peptic ulcer bleeding and its treatment with modern strategies. The following issues were addressed:

1. Does a high-dose of omeprazole-infusion offer any benefit compared to the regular-dose in patients with PUB who have been treated endoscopically?

2. How do different omeprazole doses affect the intragastric acidity in PUB?

3. What are the important risk factors and their possible concurrence in patients with PUB?

4. Do different doses of omeprazole have any impact on the detection of \textit{H. pylori} in gastric mucosa of patients suffering from PUB?
4. PATIENTS

This prospective study was performed between June 1994 and December 1996 in the Central Hospital of Central Finland, Jyväskylä, Finland and Kuopio University Hospital, Kuopio, Finland. The hospitals serve a population of 500 000. During the study period 591 patients were admitted with suspected acute upper gastrointestinal bleeding.

Comparison of intravenous omeprazole doses on PUB after endoscopic treatment (Study I)

There were 314 patients with suspected PUB. The characteristics of patients primarily excluded, randomised and later excluded are presented in Table 2.

Table 2. Patients excluded and randomised to Study I.

| Patients with upper gastrointestinal bleeding | n = 591 |
| Patients with non-peptic-ulcer bleeding     | n = 277 |
| Patients with peptic ulcer                  | n = 314 |
| peptic ulcer patients excluded from the randomisation | n = 146 |
| Forrest classification III                  | n = 58  |
| H2 blocker or proton-pump inhibitor medication on admission | n = 32  |
| no definitive diagnosis in first endoscopy   | n = 15  |
| terminal illness                            | n = 11  |
| refusal to participate                      | n = 9   |
| inability to give informed consent, no co-operation | n = 8   |
| immediate failure of endotherapy and operation | n = 5   |
| anastomotic ulcer                           | n = 5   |
| no endoscopy                                | n = 3   |
| Peptic ulcer patients randomised            | n = 168 |
| Randomised but excluded from analysis       | n = 26  |
| Forrest III                                 | n = 13  |
| malignancy                                  | n = 4   |
| unwilling to continue                       | n = 2   |
| bleeding and perforation                    | n = 1   |
| study drug unknown                          | n = 6   |
| Included in the study                       | n = 142 |
Effect of different doses of omeprazole on intragastric pH in PUB (Study II)

Intragastric pH monitoring was available only in Kuopio University Hospital and during the working days. Altogether 86 out of 142 acute PUB patients attended the basic study in Kuopio. Of these patients 17 had diagnostic endoscopy during the weekend. Altogether only 15 of the remaining 69 subjects were willing and gave their oral consent to participate in the 3-day pH monitoring of gastric acidity. Two patients were later excluded because they removed the nasogastric catheter only two and six hours after the initiation of the pH monitoring leaving 13 patients for the analysis. Table 3 shows that the demographics of the patients with PUB in the basic study (Study I) and those of the patients participating in the intragastric pH monitoring are comparable.

Table 3. Demographics of 129 patients with peptic ulcer bleeding in the basic study and of the 13 patients with intragastric pH monitoring.

<table>
<thead>
<tr>
<th></th>
<th>Patients of basic study* (n = 129)</th>
<th>Patients with intragastric pH monitoring (n = 13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>77/52</td>
<td>8/5</td>
<td>0.89</td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>64.9 ± 14.5</td>
<td>62.6 ± 15.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Forrest Ia, Ib</td>
<td>56 (43.4%)</td>
<td>7 (53.8%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Forrest IIa, IIb, IIc</td>
<td>73 (56.6%)</td>
<td>6 (46.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>NSAID</td>
<td>72 (58.5%)</td>
<td>7 (58.3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ASA</td>
<td>22 (17.1%)</td>
<td>2 (15.4%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>13 (10.1%)</td>
<td>1 (7.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Antisecretory drug**</td>
<td>12 (9.3%)</td>
<td>1 (7.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Haemoglobin, mean, on admission (g/l)</td>
<td>91.0 ± 27.4</td>
<td>81.1 ± 25.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Size of ulcer (mm)</td>
<td>13.2 ± 14.3 x</td>
<td>12.8 ± 8.5 x</td>
<td>0.9</td>
</tr>
<tr>
<td>(mean±SD)</td>
<td>12.7 ± 11.9</td>
<td>15.4 ± 12.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>13 /10.1%</td>
<td>2 /15.4%</td>
<td>0.78</td>
</tr>
<tr>
<td>Mortality</td>
<td>6 /4.7%</td>
<td>0</td>
<td>0.43</td>
</tr>
</tbody>
</table>

ASA-TP: acetylsalicylic acid for thrombosis prophylaxis
NSAID: non steroidal anti-inflammatory drug
*basic study = Study I
**antisecretory drug used during last month but not on admission.
Risk factors and their combinations in PUB (Study III)

Of the 591 patients with upper gastrointestinal bleeding in 277 patients the cause of bleeding was not peptic ulcer disease. Of the 314 suspected PUB patients in 3 patients endoscopy was not performed, in 15 patients no definitive diagnosis was found in endoscopy, 4 patient had malignancy and 1 patient had bleeding and perforation. The characteristics of the 291 patients with PUB excluded and finally included in the risk factor analysis is presented in Table 4.

Table 4. Patients included in the Study III.

<table>
<thead>
<tr>
<th>Patients with peptic ulcer bleeding</th>
<th>n = 291</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded from the case-control study</td>
<td>n = 197</td>
</tr>
<tr>
<td>Terminal illness</td>
<td>n = 11</td>
</tr>
<tr>
<td>Refusal to participate or no co-operation</td>
<td>n = 17</td>
</tr>
<tr>
<td>Previous subtotal gastrectomy</td>
<td>n = 4</td>
</tr>
<tr>
<td>Ongoing H2 blocker/ PPI medication</td>
<td>n = 32</td>
</tr>
<tr>
<td>H. pylori eradication previously</td>
<td>n = 13</td>
</tr>
<tr>
<td>No biopsies in endoscopy</td>
<td>n = 35</td>
</tr>
<tr>
<td>Forrest III</td>
<td>n = 52</td>
</tr>
<tr>
<td>Not interviewed</td>
<td>n = 33</td>
</tr>
</tbody>
</table>

The control group consisted of 94 age (± 5 years) and sex-matched non-ulcer patients attending elective endoscopy during the same year. Because many patients with pulmonary diseases were sent to exclude reflux esophagitis, there were more patients with pulmonary disease in the control group, 7 vs. 17, p = 0.047.
Effect of different doses of omeprazole on the detection of *H.pylori* (Study IV)

Of the 168 randomised patients, 114 were *H.pylori* positive. Thirteen patients were excluded from this study because of the lack of control endoscopy or biopsies taken on day 3. There were 101 *H.pylori*-positive patients left for the analysis.

**All patients**

Summary of age and sex of the patients participating in studies I-IV is presented in Table 5.

Table 5. Age and sex of patients in studies I, II and IV with reference to omeprazole dose and study III with reference to case/control status.

<table>
<thead>
<tr>
<th>Study</th>
<th>Regular/High</th>
<th>Regular/High</th>
<th>Case/Control</th>
<th>Regular/High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>73/69</td>
<td>7/6</td>
<td>94/94</td>
<td>51/50</td>
</tr>
<tr>
<td>Age (years, mean)</td>
<td>66/63.4</td>
<td>63/60.8</td>
<td>63.7/63.8</td>
<td>62.8/62.7</td>
</tr>
<tr>
<td>Males/Females</td>
<td>44/29 vs. 41/28</td>
<td>4/3 vs. 4/2</td>
<td>59/35 vs. 59/35</td>
<td>23/17 vs. 29/15</td>
</tr>
</tbody>
</table>

Regular = Regular dose of omeprazole, High = High dose of omeprazole
5. METHODS

OGD was to be performed by experienced endoscopists within one to 72 hours of admission. No drug treatment for ulcer was given prior to endoscopy. Bleeding was classified using a modified Forrest classification (Ia = spurting bleeding, Ib = oozing bleeding, Ila = visible vessel, Iib = clot, IIc = black base, III = clear ulcer base).

**Endoscopic therapy**

Clots covering ulcers were to be washed gently away. Endoscopic haemostasis using adrenaline 1/10000 in 0.5 ml doses four to six times around the bleeding site and/or heater probe (Heatprobe unit, model HPY; Olympus Optical Co. Ltd. Japan), or sclerotherapy with ethanolamineoleate was performed. Indications for endoscopic therapy were Forrest classification I-II ulcers (spurting, oozing, non-bleeding visible vessel, clot and black base). Patients had been assigned to receive endoscopic therapy, but the endoscopist decided whether the endoscopic treatment was necessary.

In study I endoscopic therapy was given on demand to 50 (68.5%) patients in the regular omeprazole and to 52 (75.4%) in the high dose omeprazole group. Thirty seven (90.2%) of the regular dose group and 35 (85.4%) of the high-dose group patients with high risk of rebleeding (Forrest Ia, Ib, and Ila) had endotherapy. Second look endoscopy on day 3 was performed in 67 (91.8%) and 65 (94.2%) patients, respectively. Ten patients did not undergo control endoscopy after 72 hours. Three of them had undergone control endoscopy earlier, 6 underwent operation and 1 was suffering from continuous ischaemic heart pain.

**Proton pump inhibitor treatment**

Patients with acute PUB (Forrest I-II) were randomised to receive a continuous infusion of high-dose omeprazole (Losec® as an 80 mg bolus +8 mg/h for 72 hours, i.e. 652 mg/72 hours) or a regular dose of omeprazole (20 mg once a day followed by saline infusion, i.e. 60 mg of omeprazole/72 hours). The infusion was started during 1 hour after the endoscopy at a surgical ward. All investigators were unaware of the patients' drug treatment assignment.

Patients received only intravenous fluids during the 72 hours and were not allowed to eat or drink, since in case of rebleeding, food in the stomach would have made performing of re-endoscopy difficult. No other ulcer medication was given. Patients with haemoglobin concentrations below 100 g/l received blood products until haemoglobin reached 100 g/l. When a patient had clinical signs of continuing bleeding or rebleeding (haematemesis, new signs of melena, shock) endoscopy with the therapeutic options were repeated or emergency operation was undertaken.
Any signs of continuing bleeding or rebleeding were recorded in the control OGD after 72 hours, after which H2-receptor antagonist treatment was given for 8 weeks.

**Diagnosis of H.pylori infection**

H.pylori infection was assessed by histology (2 biopsies from the antrum and 2 biopsies from the corpus) and urease test (1 antrum and 1 corpus biopsy; Jatrox®; H.p Test, CiH.R. Heim Arzneimittel GmbH, Darmstadt). Biopsies were taken before and after the 3-day omeprazole treatment. The diagnosis of H.pylori was made if either of the tests was positive. Biopsies were analysed by histology after Giemsa staining to grade H.pylori infection: no bacteria (grade 0), occasional bacteria (grade 1), scattered bacteria in most fields (grade 2) and numerous bacteria in most fields (grade 3).

**Detection of CagA antibodies**

Serum CagA antibodies of the IgG class of H.pylori were determined by an immunoblot method (I.D. Blot H.pylori IgG, DPC, Los Angeles, CA, USA).

**Intragastric pH monitoring**

A flexible glass pH catheter with internal reference (Synectics Medical Inc., Stockholm, Sweden) was introduced through the nostril to reach the stomach within 1 hour after the endoscopy. When the pH turned clearly acidic (pH < 3) and the distance from the tip of the electrode to nostrils was > 55 cm, the electrode was considered to reach the acid secretion environment and it was firmly fixed with adhesive tape to the nose and face. All recordings were performed with Digitrapper Mk III recorders (Synectics Medical Inc.) and analysed with EsopHogram software (version 5.60C4, Synectics Medical). The recorder was calibrated according to manufacturer’s instructions before each recording. Sampling interval was set to 16 s to enable up to 96 h recordings. In all patients included the initial intragastric pH was < 3.

For the purposes of this study, all time periods with intragastric pH less than 4 and less than 6 were identified and compared with the total measurement time. In addition, by using pH-time curves, the average pH-level during each 30 min period was measured with 0.2 pH unit accuracy.

**Statistics**

*Comparison of intravenous omeprazole doses on PUB after endoscopic treatment (Study I)*

Significance of differences in categorical data was determined using the χ²-test or Fisher’s exact test. The t-test was used to assess the significance of differences between means of normally distributed continuous variables. The Mann-Whitney-U -
test was used when variables were not normally distributed. Results are reported as means and standard deviations (SD). A level of \( p < 0.05 \) was regarded as statistically significant.

The normal statistical techniques finding differences between treatments is not valid when the goal is to assess whether the treatments are equally efficacious. Therefore, equivalence testing, which actually reverses the roles of null and alternative hypotheses, was used (Dunnet and Gent 1977; Blackwelder 1998). The study was designed to detect equivalence with equivalence threshold of 0.15 for the difference in proportions presuming 0.1 failure rate, zero hypothesised difference, 0.9 power and 0.95 confidence. This would be ensured with 69 patients in each group. In equivalence testing it is necessary to define tolerance limits and the range of equivalence. Equivalence is thereafter confirmed or rejected by observing if the confidence intervals (CI) of difference of proportions lie totally within the range of equivalence. The predefined value for the difference in proportions is +15\%, as mentioned above.

The goal of this study was to assess whether the regular dose of omeprazole was at least as effective as high dose of omeprazole in preventing rebleeding in ulcer patients. Therefore one-sided equivalence testing was used and only upper tolerance limit for difference in proportions was defined. For one-sided tests at 0.05 level the confidence coefficient has to be 90\% in equivalence testing. Exact confidence limits used in equivalence testing are quite conservative, but they are necessary due to the low incidence rate. The hypothesis testing for equivalence was performed by testing the null hypothesis \( H_0: \theta \geq \theta_0 \) against the alternative hypothesis \( H_1: \theta < \theta_0 \), where \( \theta \) is the difference in proportions or odds ratio, and \( \theta_0 \) is the respective tolerance limit.

**Effect of different doses of omeprazole on intragastric pH in PUB (Study II)**

For continuous data and median values Wilcoxon’s rank-sum was applied. The longitudinal data was analysed with linear mixed models using the first order autoregressive covariance structure and restricted maximum likelihood method for estimation (Singer and Willett 2003). The covariance structure was chosen by comparing the -2 logarithm of restricted maximum likelihood. Omeprazole dose (high/regular) and measurement time were included in the model. The data are presented also as mean ± standard deviation (SD). The stratified Cochran-Armitage trend test was used to assess significant trends in proportions of time that intragastric pH is below 4.0.

**Risk factors and their combinations in PUB (Study III)**

Single risk factors and combinations of risk factors were analysed by calculating single odds ratios. Conditional logistic regression analysis was used as a multivariate analysis to account for simultaneous risk factors in matched data (LogExact, Cytel Software Corp., Cambridge, MA). Interaction terms of different combinations of risk factors...
factors were added one by one into the model to test possible mutual interference of
the combination of two separate risk factors. Significant interaction term indicates that
simultaneous risk factors potentiate or attenuate the risk. The Cochran-Armitage trend
test was used to detect possible trends in proportions of naturally ordered factors. The
effect of the dose of ASA, ketoprofen, ibuprofen, cigarettes and alcohol on the risk of
bleeding was studied by trend analyses.

*Effect of different doses of omeprazole on the detection of H.pylori (Study IV)*

Significance of differences in categorical data was determined using the Fisher’s
exact test. The T-test was used when appropriate. Results are reported as means and
standard deviations (SD).

*Ethical aspects*

Informed consent was obtained from all subjects. The study was approved by the
ethics committee of each centre and was conducted in accordance with the Declaration
of Helsinki.
6. RESULTS

Regular-dose versus high-dose omeprazole after endoscopic treatment in PUB (Study I)

Rebleeding occurred in 6 (8.2%) of the 73 patients receiving the regular dose of omeprazole and in 8 (11.6%) of the 69 patients receiving the high dose (p = 0.002 for equivalence, equivalence limit 0.15). Three (4.1%) of the former and 5 (7.2%) patients of the latter group underwent surgery. Four (5.5%) patients in the regular and 2 (2.9%) in the high dose group died in 30 days from the admission. There was no difference between the regular and the high dose group in blood transfusions (regular vs. high dose: 5.3 units, SD 7.7 vs. 5.5 units, SD 5.2) or mean hospital stay (5.7 days, SD 2.5, vs. 5.9 days, SD 2.7).

In patients with spurting or oozing bleeding or non-bleeding visible vessel ulcers (Forrest Ia, Ib, Iia) the rate of rebleeding was 7.3% in the regular dose group and 12.2% in the high-dose group (p = 0.7). The rate of rebleeding was 9.7% and 10.3%, respectively in patients with Forrest IIb and IIc ulcers (clot/black base), (p = 0.6). Since the rate of rebleeding was similar regardless of the Forrest classification (7.3% vs. 9.7% in the low dose and 12.5% and 10.3% in the high dose group), the bleeding data was combined (Table 6).

Table 6. Rebleeding according to Forrest classification in peptic ulcer bleeding patients receiving a regular or a high-dose of omeprazole

<table>
<thead>
<tr>
<th>Forrest classification</th>
<th>Patients with rebleeding / Regular dose omeprazole n = 73</th>
<th>Patients with rebleeding / High dose omeprazole n = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest Ia, Ib, Iia</td>
<td>3/42</td>
<td>5/40</td>
</tr>
<tr>
<td>Spruting bleeding (Forrest Ia)</td>
<td>2/11</td>
<td>2/5</td>
</tr>
<tr>
<td>Oozing bleeding (Forrest Ib)</td>
<td>0/20</td>
<td>2/27</td>
</tr>
<tr>
<td>Non-bleeding visible vessel (Forrest Ila)</td>
<td>1/11</td>
<td>1/8</td>
</tr>
<tr>
<td>Forrest IIb, IIc</td>
<td>3/31</td>
<td>3/29</td>
</tr>
<tr>
<td>Clot (Forrest IIb)</td>
<td>3/9</td>
<td>2/13</td>
</tr>
<tr>
<td>Black base (Forrest IIc)</td>
<td>0/22</td>
<td>1/16</td>
</tr>
<tr>
<td>All</td>
<td>6/73</td>
<td>8/69</td>
</tr>
</tbody>
</table>
**Effect of regular and high doses of omeprazole on the intragastric acidity in PUB treated endoscopically (Study II)**

The mean 24-hour intragastric pH (regular versus high dose) on day 1 was 4.9±1.6 vs. 6.3±0.5, p = 0.035; on day 2: 4.9±1.8 vs. 6.7±0.3, p = 0.001, and on day 3: 5.7±1.1 vs. 6.7±0.5, p = N.S. Medians of intragastric pH were: day 1: 6 vs. 6.5, p = 0.082; day 2: 5.8 vs. 6.8, p = 0.001, and day 3:6.2 vs. 6.8, p = 0.17. The mean and median of intragastric pH in PUB patients during 72 hours is presented in Figures 1 and 2. Both figures reveal the efficacy of the high dose of omeprazole in increasing the intragastric pH. There was no statistical difference in the means of the proportion of the time with an intragastric pH < 4 between the regular- and the high-dose groups on day 1: 29.2% ±34.1 versus 5.4% ±5.7, p = N.S; day 2: 24.8% ±41.8 versus 0%; day 3:14.2% ±16.5 versus 0%.

There was a significant difference in the percentage of time when pH was below 6 on day 1 (46.5%±34 versus 10.5% ±13.8, [p = 0.034]) and day 2 (50.7%±35.5 versus 0.3%±0.9, [p = 0.001]), but not on day 3 (30.9% ±27.3 versus 3.2%±6.4 [p = 0.14]). However, there was a significant decrease in the proportion of time the intragastric pH was below 4.0 over the 3-day period in the regular dose group (p=0.029 for a trend). With the regular dose of omeprazole, both mean and median intragastric pH, however, increased > 4.
Figure 1. Intragastric pH (mean) during administration of regular and high doses of omeprazole in patients with peptic ulcer bleeding after endoscopic treatment

Figure 2. Intragastric pH (median) during administration of regular and high doses of omeprazole in patients with peptic ulcer bleeding after endoscopic treatment
**Analysis of risk factors and their combinations in PUB (Study III)**

*H. pylori* infection (OR=odds ratio) (OR 8.79, 95%CI:3.65-23.3), the use of ASA-P (OR 3.45, 95%CI:1.18-10.8), ASA-TP (OR 4.07, 95%CI:1.12-16.29), smoking ≥ 20 cigarettes daily (OR 6.43, 95%CI:1.19-44.2), previous DU (OR 8.96, 95%CI:2.07-50.43) and NANSAID with ≥ 1 defined daily doses (OR 6.56, 95%CI:1.77-28.37) were independent risk factors for PUB in the logistic regression analysis. ASA, ibuprofen, ketoprofen and smoking had dose-dependent associations with PUB as shown by trend analyses (Table 7).

Altogether 75 of the cases and 35 of the controls were defined as *H. pylori* positive, p <0.001. Of them, 66 (97.1%) and 26 (96.3%) had the CagA strain of *H. pylori*, respectively. There were only 5 patients who were *H. pylori* negative and were not using NSAIDs compared to 25 of the controls, p < 0.001. Seven patients among the cases were on warfarin therapy, but none among the controls, p < 0.001. The mean number of independent risk factors (history of DU, *H. pylori*, ASA, smoking ≥ 20 cigarettes, ≥ 1 DDD of NANSAID) in the group of cases was 1.88 (± 0.89) and in the control group 0.73 (± 0.61), p < 0.001. Of the cases 4 did not have any of these risk factors compared to 33 of the controls, p < 0.001. Furthermore, ≥ 3 risk factors were present in 24 of the cases but in none of the controls, p < 0.001. One of the following risk factors, namely the use of ASA, ≥ 1 DDD of NANSAID and smoking ≥ 20 cigarettes was present in 63 of the cases and in 31 of the controls, p < 0.001. Two of them were present in 16 of the cases but in none of the controls, p < 0.001. Two thirds of the PUB patients had at least 2 independent risk factors, indicating accumulation of risk factors in the affected patients.
Table 7. Trend analysis of risk factors with a dose effect in PUB.

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>&lt;500mg</th>
<th>500-1000mg</th>
<th>&gt;1000mg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n)</td>
<td>57</td>
<td>17</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Control (n)</td>
<td>74</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Proportion</td>
<td>0.8</td>
<td>1.3</td>
<td>3.3</td>
<td>∞</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>&lt;150 mg</th>
<th>&gt;150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n)</td>
<td>82</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Control (n)</td>
<td>84</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Proportion</td>
<td>1.0</td>
<td>0.2</td>
<td>6.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>≤1200 mg</th>
<th>&gt;1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n)</td>
<td>81</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Control (n)</td>
<td>86</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.9</td>
<td>1.8</td>
<td>6.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>&lt; 20 cigarettes</th>
<th>&gt;20 cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n)</td>
<td>59</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Control (n)</td>
<td>73</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.8</td>
<td>0.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>&lt;1 dose</th>
<th>1-3 dose</th>
<th>≥ 3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n)</td>
<td>51</td>
<td>18</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Control (n)</td>
<td>58</td>
<td>25</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.9</td>
<td>0.7</td>
<td>2.0</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Effect of short-term treatment with regular or high doses of omeprazole on the detection of Helicobacter pylori in PUB (Study IV)

After 3-day omeprazole treatment the diagnostic tests (urease test, histology) of *H.pylori* (any test) were negative in 14 (27.5%) of 51 patients in the regular and in 30 (60%) of 50 in the high dose group, *p* = 0.001.

A subanalysis of the patients with positive histology (*n* = 78) in the first endoscopy and information on the biopsies of the antrum and corpus in both of the endoscopies (pre-entry and after 3 days) (*n* = 78) revealed that the negative result of *H.pylori* colonisation was found in 13 patients (31.7%) of the regular-dose and in 25 (67.6%) of the high-dose group; *p* = 0.003. Another similar subanalysis was carried out in patients assessed by urease test (*n* = 84). Of the 39 *H.pylori*-positive patients in the regular-dose and of the 45 *H.pylori*-positive patients in the high-dose group, 17 (43.6%) and 37 (82.2%), became *H.pylori* negative, *p* = 0.001. The change in the distribution of *H.pylori* in gastric mucosa after the omeprazole treatment is shown in Table 8. The change in colonisation of the bacterium is presented in Table 9.

Table 8. Distribution of *H.pylori* in gastric mucosa after 3-day omeprazole treatment in patients with the bacterium both in antrum and corpus (A+C+) assessed by histology.

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>Regular dose omeprazole (20 mg/ day)</th>
<th>High dose omeprazole (80 mg + 8 mg/h)</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>A+C+</td>
<td>n = 38</td>
<td>n = 34</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A+C+</td>
<td>20</td>
<td>8</td>
<td>0.016</td>
</tr>
<tr>
<td>A+C-</td>
<td>2</td>
<td>1</td>
<td>N.S</td>
</tr>
<tr>
<td>A-C+</td>
<td>5</td>
<td>2</td>
<td>N.S</td>
</tr>
<tr>
<td>A-C-</td>
<td>11</td>
<td>23</td>
<td>0.002</td>
</tr>
</tbody>
</table>

A+C+: antrum positive and corpus positive; A+C- : antrum positive and corpus negative; A-C+: antrum negative and corpus positive; A-C- : antrum negative and corpus negative for *H.pylori*
Table 9. Change in colonisation of \textit{H.pylori} (grades 0,1,2,3) in antrum and corpus after regular and high dose of omeprazole treatment.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Antrum</th>
<th></th>
<th></th>
<th>Corpus</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular dose</td>
<td>High dose</td>
<td>Regular dose</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 77</td>
<td>n = 37</td>
<td>n = 79</td>
<td>n = 38</td>
<td></td>
</tr>
<tr>
<td>Negative colonisation</td>
<td>16</td>
<td>27**</td>
<td>15</td>
<td>27**</td>
<td></td>
</tr>
<tr>
<td>1-0</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2-0</td>
<td>5</td>
<td>13</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3-0</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Decrease in density</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2-1</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3-1</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3-2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Density remained the same</td>
<td>13</td>
<td>2***</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1-1</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2-2</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
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<tr>
<td>3-3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increase in density</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Regular vs. high dose of omeprazole: negative colonisation of \textit{H.pylori} infection in antrum * $p = 0.006$, or in corpus ** $p = 0.004$; density of \textit{H.pylori} remained the same in antrum *** $p = 0.003$. 
7. DISCUSSION

The present study gives information on the treatment of acute PUB, of the pH response in gastric juice during regular- and high-dose omeprazole treatment under these circumstances and on the detection of *H. pylori* in the bleeding phase. Also the risk factor profile of PUB patients is presented.

**Effect of acid suppression after endoscopic treatment of bleeding peptic ulcer on rebleeding rate and mortality (Study I)**

A regular dose of omeprazole was compared with a high dose in a prospective randomised double blind setting. The high dose of omeprazole was compared with a regular dose rather than placebo, because it was considered unethical to leave patients with acute peptic ulcer and bleeding complication without definitive treatment after the diagnostic endoscopy for 3 days. There is only 1 study with a similar setting, published in an abstract form (Shonekas et al. 1999). In our study, the rebleeding rate was low, and the inclusion of Forrest IIb and c patients has been criticised (Lin et al. 2006). However, in subgroup analyses the rebleeding rate in Forrest IIb and c patients was not significantly different from Forrest Ia, Ib and IIa cases, indicating that after the initial haemostasis by endoscopy some other patient-related factors may cause rebleeding and mortality.

We had similar criteria as in the study of Hasselgren et al. (1997), in which Forrest IIb was defined as a clot/black base, indicating that they also included patients with Forrest IIc, i.e., with a black base. In the study of Lau et al. (2000) 51% of the patients had spurting or oozing bleeding (Forrest I). Of our patients 45%, of the patients in the study of Hasselgren et al. (1997) 30% and of the patients in the study of Schaffalitzky de Muckadell et al. (1997) 32% had such bleeding. There was a protocol violation in the present study, because endoscopic therapy was given as needed to 50 (68.5%) patients in the regular group and to 52 (75.4%) in the high dose group, but not to all patients. On the other hand, 37 (90.2%) of the regular dose group and 35 (85.4%) of the high dose group patients with the highest risk of rebleeding (Forrest Ia, Ib, and IIa) received endotherapy, a rate similar in another North European multicenter study (Schaffalitzky de Muckadell et al. 1997).

In meta-analyses a high dose of continuous infusion of omeprazole is effective, and also other routes and doses of PPIs have reduced rebleeding rate, but none have had a significant effect on mortality (Leontiadis et al. 2005). By meta-analysis of Khuroo et al. (2005), ulcer deaths showed a significant reduction, while non-ulcer deaths showed significant increase. In clinical trials a high dose of intravenous PPIs have been superior to placebo. Routine use of high-dose intravenous PPIs prior to diagnostic endoscopy is recommended (Barkun et al. 2004b) and is a clinical practise in several units around the world. PPIs initiated prior to endoscopy for upper gastrointestinal
bleeding significantly reduced the proportion of patients with stigmata of recent haemorrhage, but PPIs prior to endoscopy did not improve mortality, rebleeding or the need for surgery (Dorward et al. 2006). Prospective studies using doses other than high doses are needed, especially in connection with endoscopic therapy, because it is unclear what the lowest effective dose would be.

**Effect of regular and high doses of omeprazole on the intragastric acidity in PUB (Study II)**

The pH-analysis was available only on working days and in the Kuopio University Hospital participating in the study. There were only 15 patients willing to attend the pH monitoring. In addition 2 of them discontinued the procedure by their own initiative.

The regular dose of omeprazole (20 mg intravenously/day) is sufficient in decreasing the intragastric acidity and raising the pH above 4 in patients with PUB. This should, theoretically hinder the dissolving of the fibrin clot (Berstad 1982; Green et al. 1978) produced primarily by endoscopic treatment and consequently prevent rebleeding. There was a pH difference during the first and second days between regular and high-dose omeprazole dosage groups, but difference was diminished during the third day, indicating the efficacy of the regular dose of omeprazole in the long term. Furthermore, the fluctuation of the intragastric pH in the regular dose omeprazole group causes the rise of intragastric pH temporarily above 6 for a considerably long time period, which might have a promoting effect on platelet aggregation and blood coagulation. On the other hand, the high dose of omeprazole maintains the intragastric pH above 6 for the most of the time. This does not seem necessary if a pH >4 is adequate to prevent rebleeding.

Intragastric pH above 4 seems to be sufficient to maintain haemostasis providing that ulcer bleeding is primarily ceased by endoscopic techniques. The clinical role of acid suppression is thus probably more dependent upon the prevention of fibrin clot dissolution than on its effects on platelet aggregation and blood coagulation.

**Risk factors and their combinations for acute PUB (Study III)**

In general, studies of PUB risk factors have been focused on a single risk factor, or on the combination of *H. pylori* and NSAIDs. Only Stack et al. (2002) have analysed the role of occurrence of several possible risk factors (CagA/ *H. pylori*, the use of NSAID or ASA, smoking) in patients with PUB. The role of alcohol and warfarin is also often neglected. According to the present results the highest risk was with previous duodenal ulcer and *H. pylori* infection. In this study the high rate of *H. pylori* infection among PUB patients can be partly due to the low rate of PPI treatment prior to diagnostic endoscopy. In earlier studies (Labenz et al. 1999; Santolaria et al. 1999) not excluding patients with ongoing PPI treatment may have resulted in underestimation of the risk of
H. pylori. Consequently, H. pylori had a higher OR (8-fold risk of PUB) in the present study than in studies published earlier.

Almost all of the cases and controls infected with H. pylori had CagA status in this study. Therefore CagA did not increase the risk of bleeding. A similar frequency of CagA-positive H. pylori infection between peptic ulcer patients and non-ulcer dyspepsia controls has also been found elsewhere (Evans et al. 1998; Go and Graham 1996; Hamlet et al. 1999; Park et al. 1998). These studies are in accordance with the present results suggesting that CagA is not a marker of a more virulent H. pylori strain with respect to PUB.

Although the overall use of NANSID among the cases was not significantly different from that among the controls, the onset of using NSAID was significantly more often acute and when used, NSAIDs were taken daily and with doses of ≥ 1 DDD by the PUB patients. The findings are similar to earlier reports (Lanas et al. 2006; Wei et al. 1995).

The control patients in the present study used more NSAIDs than control patients in other case control studies. The estimated risk for PUB of using NSAIDs is affected by the relative consumption of the drugs among the cases and the controls. This probably explains why the risk of bleeding was lower than in earlier studies. Concurrent use of NANSID and ASA or 2 NSAIDs, recent beginning to use the NSAIDs, daily consumption and doses of ≥ 1 DDD of NANSID were associated with an increased risk of PUB. ASA for prophylaxis of thrombosis and at analgetic doses were also risk factors.

Altogether 7.2% of the cases but none of the controls in the present study used warfarin. Therefore, numerical calculations of risk are not possible. In an earlier report warfarin doubled the risk for PUB (Lanas et al. 2006).

The majority of PUB patients in this study were affected by at least one of the main risk factors, the use of NSAIDs or H. pylori infection, but the combination of risk factors did not potentiate the risk of bleeding. The combination seemed to increase the risk of PUB in some studies (Aalykke et al. 1999; Labenz et al. 1999). A significant dose response for the risk of PUB with smoking and the use of ASA, ibuprofen and ketoprofen was also found in that study.

When we conducted the study 1994-1996 the selective inhibitors of cyclo-oxygenase -2 (COX-2) were not generally available. Their promise to displace traditional NSAIDs including acetylsalicylic acid (ASA) as anti-inflammatory and pain medication with less upper gastrointestinal complications has failed. The risk of serious cardiovascular side effects by COX-2 inhibitors (Hernandez-Diaz et al. 2006; Grosser et al. 2006) has restricted their use to rare patients. Additionally, their gastrointestinal safety did not differ from traditional NSAIDs in real-life setting in general population (Helin-Salmivaara et al. 2007). Therefore the present study still represents the most usual clinical background of patients with PUB.
Effect of regular and high doses of omeprazole on detection of H.pylori in PUB (Study IV)

PUB patients randomised to receive either the regular or the high dose of omeprazole who were H.pylori positive by histology and/or the urease test were analysed. The finding that H.pylori is less often found in the gastric mucosa after a 3-day administration of the high dose of omeprazole than after the regular dose indicates lack of detection or suppression of the bacteria. With either of the dose regimens the ability to diagnose H.pylori infection by histology or the urease test decreased as compared with pretreatment biopsies.

If samples to find H.pylori are not taken before the treatment, the presence of the bacteria may be overlooked and left untreated. Later on in these patients a possible recurrence of ulcer is a true risk. It is therefore recommended that endoscopy with adequate biopsies for the diagnosis of H.pylori infection is performed before PPI treatment in cases with acute PUB. It is advisable primarily to use other acid-suppressing or neutralising agents other than PPI if diagnostic endoscopy is postponed. If PPIs are given prior to diagnostic endoscopy, H.pylori should be tested after cessation of the PPI treatment (Guell et al. 2006).
8. SUMMARY

A series of studies concerning modern drug treatment of PUB after endoscopic therapy and risk factors of PUB were undertaken. Because profound acid inhibition following endoscopic therapy may prevent rebleeding and reduce ulcer related deaths in PUB, the equivalence of a regular dose (20 mg once a day for 72 hours, n = 73) and a high dose of omeprazole (80 mg bolus + 8 mg/h for 72 hours, n = 69) was tested in a prospective randomised double blind setting in patients with acute or recent bleeding of whom 102 (71.8%) had endoscopic treatment at pre-entry.

The main results for regular vs. high dose omeprazole: rebleeding 6 (8.2%) vs. 8 (11.6%), p = 0.002 for equivalence; emergency surgery: 3 (4.1%) vs. 5 (7.2%) and 30-day mortality: 4 (5.5%) vs. 2 (2.9%). The regular dose of omeprazole seems to be equal to the high dose in preventing rebleeding, provided that endotherapy is given.

In PUB, an intragastric pH-level > 4 is considered necessary to prevent dissolving of the formed fibrin clot. PUB patients received either the regular dose or the high dose of omeprazole for 72 hours. Monitoring of intragastric pH was performed for 3 days in 13 of these randomised patients, 7 of them from the regular and 6 from the high-dose group.

The mean 24-hour intragastric pH (regular vs. high dose) on day 1 was 4.9 ± 1.6 vs. 6.3 ± 0.5, p = 0.035; on day 2 4.9 ± 1.8 vs. 6.7 ± 0.3, p = 0.001 and on day 3 5.7 ± 1.1 vs. 6.7 ± 0.5, p = N.S. The medians of intragastric pH were: day 1 6 vs. 6.5, p = 0.082; day 2 5.8 vs. 6.8, p = 0.001 and day 3 6.2 vs. 6.8, p = 0.17. The proportion of the time that the pH was 4 on day 1 was 29.2% ± 34.1 versus 5.4% ± 5.7, p = N.S. The regular dose of omeprazole raises the mean and median 24-hour intragastric pH > 4 in patients with PUB. This reduction in the acidity together with endoscopic therapy is probably sufficient to maintain haemostasis. The high dose of omeprazole keeps the pH almost constantly > 6.

NSAIDs including ASA (ASA-TP as thrombosis prophylaxis, ASA-P as pain medication) and NANSAs, H.pylori infection, CagA strains of the bacteria and smoking are reported risk factors for PUB, but their combined and dose effects are controversial. Therefore, a case-control study of PUB patients (n = 94) and controls (n = 94) of age and sex matched non-ulcer patients attending elective endoscopy was undertaken. A questionnaire on possible risk factors (previous GU or DU, use of any NSAIDs, warfarin, alcohol and smoking) was completed. H.pylori was classified as positive if histology or the urease test was positive. CagA antibodies of IgG class were determined by an immunoblot method.

H.pylori infection, the use of ASA-P, ASA-TP, NANSAI with ≥ 1 defined daily dose, smoking ≥ 20 cigarettes daily and previous DU were independent risk factors for PUB. Previous DU, H.pylori, the use of any ASA and smoking explained the majority of the PUB episodes. At least 2 risk factors were present in 2/3 of the PUB patients. CagA was present in 97% of the H.pylori-positive cases and in 96% of the respective
controls, and it was not associated with PUB. ASA, ibuprofen, ketoprofen and smoking had a dose-dependent association with PUB.

It is unknown if a short-term regular or high dose of omeprazole has an influence on colonisation of *H. pylori* in the stomach. In PUB the effect of 3-day treatment of two different doses of omeprazole on colonisation of *H. pylori* in the stomach was studied.

PUB patients received either the regular or the high dose of omeprazole for 72 hours. There were 101 *H. pylori*-positive patients, of whom 51 received the regular and 50 the high dose of omeprazole. *H. pylori* status was assessed by histology and urease test of gastric biopsies at pre-entry and after the 3-day treatment. With the high dose of omeprazole, tests for the diagnosis of *H. pylori* became negative significantly more often than with the regular dose, 60% vs. 27.5%, *p* = 0.001 (any test), 67.6% vs. 31.7%, *p* = 0.003 (histology) and 82.2% vs. 43.6%, *p* = 0.001 (urease test). The conversion of the tests to *H. pylori* negative after the 3-day treatment of omeprazole was dose dependent.
9. CONCLUSIONS

1. The regular dose of omeprazole is as good at preventing rebleeding in PUB as the high dose following endoscopic treatment of bleeding and signs of recent bleeding in the ulcer (Forrest I-II).

2. The regular dose of omeprazole raises the mean and median 24-hour intragastric pH > 4 in patients with PUB. An intragastric pH above 4 seems to be sufficient to maintain haemostasis following endoscopic therapy. The clinical role of acid suppression may be more dependent upon the prevention of fibrin clot dissolution than on its effects on platelet aggregation and blood coagulation. Therefore, maintenance of intragastric pH above 6 is not necessary.

3. Previous duodenal ulcer, H.pylori infection and the consumption of any dose of ASA are independent risk factors for PUB. The role of CagA strains of H.pylori is probably unimportant. Smoking and the use of ASA, ibuprofen and ketoprofen have significant dose-dependent association with PUB. A PUB patient typically presents with at least one of these risk factors: history of duodenal ulcer, H.pylori infection, the use of ASA, NSAID dose ≥ 1 DDD and smoking ≥ 20 cigarettes. Two thirds of the PUB patients have at least 2 of these risk factors. However, the combination of the risk factors did not seem to potentiate the overall risk.

4. H.pylori is less often found in the gastric mucosa after a high dose of omeprazole for 3 days than after a regular dose for the same period of time. Using either of the dose regimens for only 3 days decreases the ability to diagnose H.pylori infection when compared to biopsies taken prior to omeprazole. The role of H.pylori may thus be overlooked and necessary eradication not performed. This may result in ulcer recurrence later.
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