Peptic Ulcer Bleeding

Towards Improved Outcome

by

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Göteborg 1998

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I Hasselgren G, Keelan M, Kirdeikis P, Lee J, Röhss K, Sinclair P, Thomson ABR. To optimize acid suppression for patients with peptic ulcer bleeding — an intragastric pH-metry study with omeprazole. Accepted for publication in Eur J Gastroenterol Hepatol.

II Hasselgren G, Lind T, Lundell L, Aadland E, Efskind P, Falk A, Hyltander A, Söderlund C, Eriksson S, Fernström P. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. Scand J Gastroenterol 1997;32:328-333.

III Schaffalitzky de Muckadell OB, Havelund T, Harling H, Boesby S, Snel P, Vreeburg EM, Eriksson S, Fernström P, Hasselgren G. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers. Scand J Gastroenterol 1997;32:320-327.

IV Hasselgren G, Blomqvist A, Eriksson S, Henningsson A, Lundell L. The short and long term course of elderly patients with peptic ulcer bleeding — Analysis of factors influencing fatal outcome. Accepted for publication in Eur J Surg.

V Hasselgren G, Carlsson J, Lind T, Schaffalitzky de Muckadell O, Lundell L. Risk factors for rebleeding and fatal outcome in elderly patients with acute peptic ulcer bleeding. Accepted for publication in Eur J Gastroenterol Hepatol.

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ABSTRACT

Bleeding from a peptic ulcer is a common and life threatening event. To reduce the risk for further bleeding, normal coagulation and a stable clot formation are pivotal factors. In vitro studies have shown that neither coagulation nor platelet aggregation can take place if pH is below 5.4. Efforts have therefore been made to improve intragastric hemostasis by administrating antacids or histamine-2-receptor antagonists to raise intragastric pH to or above this level. The effect of these treatments has, however, been limited. In vivo studies have shown that if omeprazole is given as a primed continuous infusion a stable intragastric pH above 5.4 can be reached.

The aims of the present study were: 1) To determine the dose regimens for intravenous omeprazole infusion and subsequent per oral administration to stabilize intragastric pH at a levels alleged to allow hemostasis and facilitate further ulcer healing. 2) To study if this omeprazole dose regimen improved the outcome for high risk patients with peptic ulcer bleeding (PUB). 3) To identify risk factors for fatal outcome in both short and long term perspective in patients with PUB.

Healthy volunteers and duodenal ulcer patients in remission were included in the dose-finding study. An omeprazole infusion, 80 mg + 8 mg/h for 72 hours, followed by omeprazole 20 mg orally once daily fulfilled the requirements set up based upon intragastric pH measurements. This dose regimen was evaluated in two separate clinical studies enrolling patients with acute PUB. One study included patients 60 years or over (n = 322), while the other study included patients in hemorrhagic shock (n = 265). Both studies showed consistently better outcomes in the groups treated with omeprazole when either assessed by a defined overall outcome score, blood transfusions requirements or need for surgical/endoscopic interventions. The cumulative mortality was approximately 1% after the first three days of admission but rose almost linearly during the subsequent three weeks reaching about 6% at day 21. Most deaths were caused by cardiovascular events.

In a multiple logistic regression analysis performed on a subset of the data, age, coronary heart disease, blood pressure on admission and absence of previous ulcer were significantly associated with mortality.

Patients above 60 years admitted to hospital due to a PUB in Göteborg during 1989 to 1993 (n=687) were found to have a 5.5% cumulative mortality at 30 days. Age and Forrest class significantly influenced mortality during this period. During the subsequent 5 year follow-up mortality was significantly higher in women compared to matched controls while no significant difference was found in men.

Finally, 1020 patients with a PUB were selected from the General Practitioners Research Database in the UK. Day 30 mortality was 4.4% and again high age and absence of previous ulcer had a significant impact upon mortality.

In conclusion, an omeprazole infusion 80 mg + 8 mg/h for 72 hours significantly improved clinical outcome in high risk patients with PUB. Mortality occurred almost linearly over the first month of admission and most patients died due to cardiovascular events. High age and absence of previous ulcer significantly increased the mortality risk.

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ABBREVIATIONS

ASA	Acetylsalicylic acid
ASGE	American Society for Gastrointestinal Endoscopy
AUC	Area under the plasma concentration curve
B.i.d.	Twice daily
CI	Confidence interval
OR	Odds ratio
GP	General practitioner
GPRD	General Practice Research Database
H2RA	Histamine-2-receptor antagonist
NSAID	Non steroidal anti-inflammatory drugs
O.d.	Once daily
OTC	Over the counter
PU	Peptic ulcer
PUB	Peptic ulcer bleeding
RR	Relative risk
UGIB	Upper gastrointestinal bleeding

HISTORICAL ASPECTS

On April 15th, 1830 a 29 years old Parisian carpenter experienced a burning epigastric pain. The pain increased in intensity and on the 30th he began to vomit red blood and was admitted to a hospital in Paris. He was found to be in shock with vague pulse and severe anemia. The next day he had recovered somewhat, but on May the 2nd he had a further massive hematemesis and abruptly died. When the autopsy was performed a large peptic ulcer was found with a solitary artery extruding from its base.

This patient history was described in "Anatomie pathologique du corps human" 1829 - 35 by Jean Cruveilhier (1791-1874) who was professor of anatomy in Paris and the first person to fully describe the peptic ulcer, its complications and treatment (*37*). Up until this time ulcers had been looked upon as merely a curious autopsy finding. The production of hydrochloric acid in the stomach had been described by Prout a few years before (1823), which had led to Abercrombie's recommendation of a diet of milk and flour products . Shortly thereafter antacids i.e., soda and chalk were recommended as an effective therapy (*16*).

It was, however, Cruveilhier who brought these different recommendations together and outlined a detailed diet therapy, he also emphasized the need for prolonged treatment.

During the subsequent years the diet therapy became more and more specific and the need for strict confinement to bed for several weeks was seriously recommended. Boas (*15*) gave detailed instructions on how to treat a patient with a peptic ulcer bleeding (PUB) and besides rest and complete fasting he suggested "injection of a full syringe of ergot in the stomach region" instead of the traditional medication with lead acetate, iron chloride or turpentine oil. In those patients who required nutrients, a specific recipe for an enema with milk, egg yolk, salt flour and red wine was given. In certain cases, warm port wine was added to the enema to further improve the efficacy. If the patient needed something to improve his general health status, 2 mg arsenic up to ten

times daily was recommended. This therapy was continued for several weeks after the bleeding.

The fundamentals of this therapy with starvation for several days before oral nutrients were resumed remained until the introduction of the "Sippy regime" in 1915,(*144*). Sippy suggested frequent feeding and administration of alkalids, "Sippy powder", and gastric aspiration at night. Some years later the radical recommendations by Meulengracht was presented (*115*). He presented a study on 251 patients who were given a combination of pureed diet, antacids, sedation and iron replacement starting already the day after admission and claimed a drastic reduction of mortality, to only 1.5%, in contrast to the 7.9% which was reported from a neighboring hospital in Copenhagen.

The same year Marriot and Kekwick (*110*) reported on a method where blood was continuously infused by a drop. Blood transfusions had been used early this century when blood grouping was first established by Landsteiner in 1901 but until 1935 these entailed direct intravenous only which limited the usefulness.

The combination of antacids, sedation and commencing a specific diet within 24 hours together with blood transfusions constituted the fundamentals of medical ulcer bleeding treatment until the introduction of more potent acid inhibition agents in the middle of 1970's.

Gastroduodenal surgery in the treatment of peptic ulcers was first described in the 1880's when various procedures were presented by Billroth, Heinecke and Rydygier (*83*). Mikulicz (*116*) was the first to describe an operation for a bleeding peptic ulcer in 1888 opening the pylorus and cauterizing a bleeding posterior duodenal ulcer. Vagotomy, combined with pyloroplasty in the treatment of bleeding ulcers was not described until 1952 by Dorton (*41*) despite the fact that Latarjet described the vagal effects upon the acid secretion already in 1922 (*102*).

Surgery for bleeding peptic ulcers was for long considered as a very risky procedure until Gordon Gordon-Taylor (being both surgeon and rear-

admiral), pointed out in a very readable article in 1946 (*53*) that much of this disrepute came from the fact that surgery was often seen as a last, desperate measure to save a patients life. He reported that if he could operate shortly after hospital admission he could reduce mortality from 36% to 5.5% and that patients could "be rescued from the jaws of death by courageous surgery" if the operation was performed at the right time. The surgical procedures varied from simple hemostasis and oversewing to extensive resections. It is interesting to note that the importance of early surgery was confirmed many years later by several authors (*83, 119*).

Gastric cooling was introduced by Wangensteen in 1958 (*160*) with the aim to reduce peptic activity, secretion of acid, gastric blood flow and gastric motility. The cooling was accomplished by intragastric balloons, cooling machines or ice water installation. Despite the findings by McFarland in 1968 (*111*) indicating that gastric cooling had no advantage in comparison with conservative treatment, the procedure has kept its popularity until today.

A significant step forward in the clinical management of ulcers was taken with the introduction of fiberoptic instruments in the early 1960's (*71*) allowing the precise identification of the bleeding source. The technique for endoscopic hemostasis was first described in the middle of the 1970's, however, it took almost 20 years until the use of therapeutic endoscopy came into routine clinical practice. The first results from randomized clinical trials using laser to photocoagulate the ulcer were published in 1981 (*77, 149*). Results of electrocoagulation (*127*) and injection techniques (*31*) were presented later. The results of therapeutic hemostasis through the endoscope in the treatment of PUB has been described in many studies (*34, 151*) and constitutes the cornerstone for the treatment of bleeding ulcers today. As a consequence, the need for surgery has again been limited to those patients in whom the bleeding cannot be controlled by other methods.

BACKGROUND

Epidemiology of peptic ulcer bleeding

Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency and the annual hospital admission rates vary from 45 - 120/100 000 persons (*69, 81, 139, 171*). The proportion of patients admitted with UGIB being > 60 years old has steadily increased from 6% - 17% in series presented during 1921 - 36 to 40% - 48% from 1953 - 73 (*2*). This trend has further progressed also during subsequent years as well, and Rockall presented a figure as high as 68% in 1995, (*133*).

Peptic ulcer bleeding (PUB) is the single most common cause of UGIB, comprising 37%-50% of patients with UGIB which is equal to a hospitalization rate of 30 - 50/100,000 and year (*39, 51, 67, 84, 118*).

The true incidence of peptic ulcers is difficult to estimate since not all patients with ulcers will seek medical care. Schöön and co-workers reported (*140*), 1402 ulcers in 1137 adults during one year (1985) the city of Gothenburg with, at that time, had an adult population of 360,000. Of the ulcers, 222 presented as a bleeding ulcer.. The majority of hospitalized patients with PUB are men (*20, 107, 159*) reflecting the sex ratio in peptic ulcer disease in general (*140*). Gastric ulcer patients are generally older than patients with duodenal ulcer, and a difference in median age of 10 years was reported by Branicki(*18, 19*).

Mortality in peptic ulcer disease

It is estimated that the current death rate, in western countries, due to peptic ulcers, is 2 - 4/100 000 (*95*) based upon death certificate figures. This implies that 20 - 30 000 patients die due to peptic ulcers in Europe every year. Sweden has a corresponding death rate of 200 - 300 per year.

The number of deaths due to peptic ulcer, i.e. including both deaths due to bleeding and to perforation, has, however, declined by more than 50% since 1955 (*95*). The major part of this decline occurred between 1975 and 1984, a period during which H2 receptor antagonists (H2RA) were introduced, but a causal relationship between use of these drugs and a decline in death rates is difficult to substantiate. Data from the US, however, indicates hat only minor changes have occurred since 1979 (*94*).

The decline in overall mortality due to peptic ulcers is not paralleled by reductions in the proportion of the patients admitted with a PUB that die, i.e., the case-fatality rate, which is still as high as 5% - 15%, Table 1. All comparisons of case fatality rates are, however, hampered by variations in follow-up time. Most authors do not state the follow-up period at all, and instead they simply declare that patients were followed until discharge or, they present data for a limited period of follow-up, say 7-10 days. The vast majority of deaths occur among patients who are over 60 years (*128*) and half of the deaths occur during the second half of the month (IV, V and VI). Consequently, it is of pivotal importance to report the age profile of patients studied and also to precisely define the length of follow-up, which should be at least 3- 4 weeks for <u>all</u> patients.

The cause of death in patients admitted with a PUB is most often cardiovascular events and only rarely due to exsanguination, (*47*).

Table 1. Mortality in studies including patients with PUB. Figures in brackets represent the mortality for the subgroup of patients over 60 years.

Author	Year	No. of patients	Mortality	Follow-up period
Schiller (*139*)	1970	947	6.9% (12.6%)	NG
Duggan (*43*)	1972	830	8.3% (23.6%)	NG
Wara (*162*)	1985	276	10.5%	NG
Collins (*33*)	1985	2500	5-8%	Vary
Katchinsky (*85*)	1989	471	10.4%	Discharge
Branicki (*20*)	1990	701	4.9% (10.0%)	NG
Wheatley (*164*)	1990	342	4% (5.6%)	NG
Daneshmend (*39*)	1992	503	7.2%	40 days
Henriksson (*67*)	1991	592	3.5%	30 dgr
Walt (*159*)	1992	1005	5.6% (9.1%*)	Discharge
Herold (*70*)	1994	85	22.3%	NG
Hsu (*73*)	1994	227	0.9%	10 days
Vreeburg (*171*)	1997	379	15%	Discharge

* over 65 years

Current treatment options

There are several prerequisites that a treatment must fulfill to become efficacious in the treatment of PUB. It should be safe, ideally be effective both in stopping the bleeding and preventing rebleeding. Furthermore, it should

be easily accessible and possible to use in all patients as well as by all hospitals irrespective of the level of expertise and experience and cost effective. The ultimate goal is, of course ,to reduce mortality, but a reduction in the need for intervention in terms of endoscopic intervention, surgery or blood transfusions is also of major importance.

Since continued bleeding or rebleeding is the event leading to intervention, efforts have been focused on reducing their occurrence.

Stanching the bleeding can either be accomplished by improving the physiochemical conditions for hemostasis (i.e., suppress acid or inhibit fibrinolysis) or by achieving hemostasis by means of mechanical methods, that is, by endoscopic or surgical intervention.

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Acid suppressing agents

The rationale for the use of acid inhibitory drugs in the treatment of PUB is based upon *in vitro* data showing that hemostatic mechanisms are highly pH dependent and that coagulation and stable platelet aggregation do not occur at pH levels below 6 (*27, 45, 56*). Furthermore, pepsin exerts its maximal proteolytic effect at a pH around 2 and gradually decreases to negligible activity at pH 5 (*10, 131*). It is therefore reasonable to assume that for an acid suppressing therapy to improve hemostasis, it should have the capacity to maintain the intragastric pH at a level of approximately 6 or above.

Antacids of various potency have been used in the treatment of PUB for many years. However, most often in rather low doses and with infrequent dosing. Curtis and co-workers, 1973, (*38*) described the results of aggressive administration of antacids to patients with massive bleeding from the upper gastrointestinal tract. The aim was to keep intragastric pH at 7.0 or above with hourly titration and administration of antacids. With this very laborious regimen the bleeding was stopped in 23 out of 25 patients (92%). In one of the

two treatment failures pH could not be raised above 4.5 despite massive instillation of antacids. Two later studies (*90, 172*) , however, indicated that antacids were of limited value. None of them, however, measured intragastric pH and the lack of effect could simply be due to insufficient control of the intragastric acidity.

The introduction of cimetidine, the first histamine-2-receptor antagonist (H2RA) in the mid-seventies paved the way for a new era in acid inhibition therapy and studies soon erged using this new drug or its later successor ranitidine in patients with PUB. An early meta-analysis based on 27 randomized clinical studies (*33*) indicated that results were "moderately promising" but five years later Langman concluded that "available data, is, however, inadequate to establish the usefulness of pharmacological measures" (*101*). The disappointment was further underlined by the results from the, up uitil this point of time, largest randomized clinical trial in PUB patients presented by Walt 1992 (*159*). This study showed no significant reductions in mortality, rebleeding rate or the need for surgery in PUB patients randomized to famotidine infusion compared to placebo.

There are at least two reasons why H2RA may have failed in PUB. Firstly, they only competitively block the stimulation of acid secretion mediated by the histamine-2 receptors and stimulation mediated by gastrin, acetylcholin or other stimuli may still lead to acid secretion. A second reason is a rapidly evolving tachyphylaxis which occurs already within 24 hours and rapidly leads to decreasing control of intragastric pH (*113, 166*). The reasonable conclusion from these studies is that the concept of profound and sustained acid inhibition has actually never been properly tested.

Omeprazole has a different mode of action and binds, after protonation in the highly acidic intragastric milieu and conversion to a sulfenamide form strongly to the H^+K^+-ATPase. This is the final step in gastric acid production, the "acid pump" , that is present in the secretory surface of the gastric parietal cell. There is a constant circulation between "active" H^+K^+-ATPase in the secretory cell surface and "resting" enzyme in the intracellular tubulovesicles.

The enzyme can, however, only be blocked in its "active" phase on the secretory surface. In the stimulated human parietal cells, it is reasonable to assume that about half of the H^+K^+-ATPase is present in the secretory surface but this figure remains somewhat uncertain (*63*). The half life of omeprazole at the secretory surface is in the range of 1-2 hours; after which it circulates back with its bound H^+K^+-ATPase to the tubulovesicles in the cytoplasm (*141*). A continuous infusion of omeprazole is therefore necessary to block pumps that migrate to the surface if a high degree of blockade is requested.

The first study with omeprazole given as repeated injections was performed by Lind and co-workers (*105*) who showed profound reductions of acid output. Several more studies have later been performed to investigate what dose of omeprazole is required to stabilize intragastric pH values above 6. Repeated i.v. injections of omeprazole (80 mg + 40 mg + 40 mg + 40 mg over 24 hours) did not reach these levels (*5*) but Cederberg could, after a series of dose-finding experiments (*24, 25*), show that a primed continuous infusion of omeprazole, (i.e., 80 mg given i.v. over 30 min followed by a continuous infusion of 8mg/h), maintained stable and high pH values also after a pentagastrin challenge. Nielsen and co-workers (*123*) could shortly thereafter show, that the effect was stable up to 22 hours. Corresponding, similar effects upon intragastric pH were later demonstrated in duodenal ulcer patients (*26, 89*), in patients with PUB (*96*) and in healthy volunteers during 72 hours infusion (*122*). In contrast to H2RA, no tolerance development has been described with omeprazole (*113*).

Based on available data (published and unpublished) it can be concluded that the dose 80 mg + 8 mg/h is needed during the first 24 hours to create an intragastric pH likely to be optimal for hemostasis. However, no formal comparative study has addressed the possibility of a lower infusion dose after the initial 24 hours when most acid pumps are likely to be blocked. Furthermore, no data exists on the effect that standard oral healing doses of omeprazole has on intragastric pH after of these high i.v. doses have ceased.

The clinical effects of omeprazole given in a variety of doses and dosing regimens have been evaluated in several studies including patients with upper gastrointestinal bleeding. Most of these studies have reported small or no effects. In the largest of these, which was a randomized clinical trial including 1147 patients with UGIB (*39*), omeprazole was administered as repeated injections (80 mg + 40 mg + 40 mg + 40 mg) over 20 to 27 hours which was followed by oral treatment 40 mg twice daily for three days.. The study, however, showed only minor advantages for patients treated with omeprazole. Oral administration of omeprazole has also been evaluated in patients with PUB (*87*). This study showed a better outcome for patients in the omeprazole group but the results need confirmation. Indian ulcer patients, as in this study, are suggested to have a lower parietal cell mass than Western patients (*86*) which can have influenced the result.

The present situation is therefore confusing and a number of questions are still to be answered before the definitive role of omeprazole in the treatment of PUBs can be established. Firstly, we have to identify the dose of omeprazole to be given to patients with a peptic ulcer bleeding both during the acute bleeding phase and the subsequent ulcer healing phase. Secondly, we need to study the effects of this dose regimen upon the clinical outcome for patients admitted with a PUB in large randomized clinical studies.

Antifibrinolytic drugs

The rationale behind the use of antifibrinolytic substances in the treatment of ulcer bleeding is based on the report of a plasminogen activator in the gastric mucosa in patients with peptic ulceration and the finding that free plasmin in the gastric venous blood were more commonly detected in peptic ulcer patients than in controls (*36*). A subsequent study, however, challenged whether this actually applies to anything but a small subset of patients (*108*).

Henriksson and collaborators (*65*) showed a normal fibrinolytic activity in peripheral blood of PUB patients at admission and the results indicated a development of a hypofibrinolytic state the following day.

The effect of antifibrinolytic drugs has been evaluated in several studies. Unfortunately most of these studies have included a rather heterogeneous study population (*7, 11*) which complicates the evaluation. In a well designed study in which patients with benign bleeding lesions in the stomach and duodenum were included, tranexamic acid was given i.v. for three days followed by oral treatment for another three days. The authors reported reduced blood transfusion requirements and need for emergency surgery (*147*). A meta-analysis of studies performed concluded that tranexamic acid may be of value (*68*) but also emphasizes the lack of definitive trials. Despite this efficacy potential, tranexamic acid is not routinely used as a first line therapy (*126*) which may be a result of concerns about adverse events (*68, 163*).

Somatostatin

Somatostatin or its more long-acting analogue octreotide has been studied separately or in combination with acid reducing agents. Two studies have compared somatostatin with H2RAs i.e., cimetidine or ranitidine and both presented better results in the somatostatin group. The studies were unfortunately either open (*35*) or rather small (*154*) and firm conclusions can not be drawn. Other studies could not show any significant benefits in the somatostatin treated groups compared with placebo (*8, 109, 145*).

Christiansen (*30*) reported no significant differences for octreotide versus placebo in a well designed study in PUB patients.

Somatostatin combined with ranitidine was compared with omeprazole infusion in one small study (n = 20) (*52*). No significant differences in clinical effect could be shown between the two treatment arms.

Endoscopic treatment

The introduction, in 1961, of the flexible endoscope in clinical gastroenterology by Hirschowitz (*71*) suddenly offered a unique diagnostic precision in patients with UGIB. Patients' outcome did not, however, change significantly despite the use of early endoscopy per se (*42, 55, 129*). The great break-through came with the advent of the possibility of a therapeutic intervention directed towards the bleeding source through the endoscope. The extent to which *therapeutic* endoscopy may decrease further bleeding, reduce the need for surgical intervention and mortality has been addressed in several controlled clinical trials. Injection with sclerosing agents combined with adrenaline or adrenaline alone are most commonly used. Other techniques include laser coagulation, heater probes or electro coagulation (*151*).

Recently other endoscopic hemostatic methods have been introduced such as the hemoclip and fibrin glue injection. The clip was designed in the mid 1970s by Hayashi (*62*) and later modified by Hachisu (*59*). Large comparative studies are lacking but good results have been presented (*13*). Fibrin glue was first introduced in the mid eighties (*57*) and in a recent large study promising results were presented (*70*). The method is, however, rather laborious since it requires re-endoscopy and further injections until the ulcer base is free from stigmata of recent bleeding.

The results from studies of all these different techniques have, however, often been inconclusive or conflicting, possibly because of small sample sizes, variable inclusion criteria and differences in patient characteristics.

The first meta-analysis by Sacks et al (*138*) included 25 studies in which PUB patients had been endoscopically treated and showed a 69% reduction in rebleeding, a 62% reduction in surgery and 30% reduction in mortality.

Cook (*34*) included 30 randomized clinical trials in a meta-analysis evaluating three main types of hemostatic endoscopic therapy (i.e., thermal contact, laser treatment or use of sclerosing agents) in patients admitted due to UGIB. From

the 30 studies, 22 presented data for PUB patients. The results showed that these treatments, when applied in PUB patients, significantly reduced further bleeding by 43% (95% CI ; 15% - 61%) and surgery by 63% (95% CI; 54% - 73%). Also hospital mortality was significantly reduced by 60% (95% CI 52% - 69%). However, only one (*149*) of the 22 studies in the meta-analysis showed, by itself, statistically significant improvements. This is an important illustration of the problems associated with meta-analyses which has been thoroughly discussed in several recent articles (*3, 6*).

In 1991 Swain (*151*) concluded after a very comprehensive review of different techniques that "the results have provided fairly convincing evidence that endoscopic intervention is of value to patients with PUB".

Mortality after a PUB is not solely confined to the early hospitalization period but rather to a period up to 30 days after the initial bleeding (II, III, IV and VI). Very few studies have reported the length of follow-up and it is therefore not yet clear whether the mortality reduction seen in these meta-analyses actually implies a significant higher proportion of patients surviving long-term or whether the hemostasis achieved only postpones death with the patients dying later in a cardiovascular complication. Any long term data on this topic is unfortunately not presented.

Consequently, even though results presented so far are rather promising further studies must confirm the benefits of these treatments also outside clinics with special interest. Irrespective of which endoscopic treatment is used, each mode requires expertise and continued training to be effective.

In fact, most patients with PUB will not be treated in a referral center with devoted and experienced endoscopists available 24 hours a day. Thus there is a need for other methods that can be safely and effectively used by all doctors at all hospitals in patients with peptic ulcer bleedings.

Surgery

The need for surgery in a patient with PUB has decreased during the last decades despite the increasing age among PUB patients. Gustavsson (*58*) reported a decline in the rate of emergency operations, between 1956 and 1985, from 16% to 12%. Further decline could be expected after the introduction of endoscopic hemostatic techniques as an alternative to surgery in patients with rebleedings. The figures presented by Qvist and co-workers (*132*) confirm this, when he reported in 1994 that only 1% of patients needed immediate surgery on admission and only 5% in total, in his material of 341 patients with PUBs.

The mortality after surgery is highly dependent upon the timing of the operation. Those despairing cases where surgery must be undertaken without previous endoscopy or blood transfusion still carry a high mortality rate from 12% even up to 50% (*75, 130*) . In contrast, early elective surgery (i.e., after initial endoscopy with or without endoscopic hemostasis) has been shown to carry a lower risk (*119, 130*).

Recently a prospective study was presented where all PUB patients (n = 253) underwent emergency endoscopy and injection therapy (*167*). In patients regarded as being at high risk an early elective operation was performed (n = 126). The mortality in this group was 9% while no patient died in the non-operated, low-risk group giving an overall mortality of 4%.

The indications for emergency surgery in general and particularly the number of transfusions that should have been transfused before deciding to operate have always been a matter of debate. In a recent study it was suggested that besides those cases with an ongoing exsanguinating bleeding, surgery may be indicated in elderly patients with an arterial bleeding or visible vessel or blood transfusion requirement exceeding 5 units (*32*). Patients with large ulcers in the posterior duodenal wall may also be candidates for surgery due to the near proximity to the gastroduodenal artery (*32*) (*83*).

Due to of effective and safe medical remedies for causal treatment of ulcer disease such as Helicobacter pylori eradication or long-term antisecretory medication, the operative strategy in a patient with a PUB has now changed to a more conservative approach with only ulcer ligation/underrunning the bleeding vessel in duodenal ulcers. A more definite surgery is not reasonable and should be avoided (*136*). A higher rebleeding rate seen after simple underrunning/excision than after more extensive procedures may challenges this statement (*93*).

For gastric ulcers an excision of the ulcer is important. However, in a patient in shock, the risk of a difficult excision may be outweighed by an increase in mortality or morbidity and in such a case an individual solution may be necessary. The same applies to the role of resective procedures which may be considered in, for instance, ulcers located high on the lesser curvature which are likely to carry a particularly high rebleeding risk since the ulcer is close to the left gastric artery (*150*).

Risk factors

It is of special clinical importance to identify those factors which imply a low or high risk to a patient with a PUB. Knowledge of these factors will offer the clinician important guidance tools when setting priorities in a busy emergency ward. It will be possible to provide true high risk patients intensive care and a rapid start of specific therapeutic measures while low risk patients can safely be directed to other ward facilities and even be quickly discharged. The most commonly analyzed response variables in this respect are rebleeding or mortality.

Risk factor analyses in PUB patients have been performed in a large number of studies. There are, however, several difficulties to be considered when

performing such studies. Unfortunately, there are often many deficiencies hampering the published studies in this area.

All risk factors are more or less related to each other and the value of an isolated risk factor can depend very much upon other related variables. To study, for instance, the prognostic value of a gastric ulcer relative to a duodenal ulcer requires that a correction is made for influencing factors such as age since gastric ulcers are more common among elderly, age is therefore a so called confounder. If this correction in the analysis is not made, it is impossible to separate the prognostic value of the gastric ulcer from that of higher age. A *multiple* logistic regression analysis takes into account all variables in the model and thereby compensates for influence by the other factors when the prognostic value for a certain factor is calculated. This contrasts to the *univariate* logistic regression which analyzes the value of a certain variable without compensation for other confounding factors. Consequently, a univariate approach cannot give any reliable estimate of the true value of a single variable unless only one risk factor is operating. Most studies in this area have still used this approach.

In analyses of prognostic factors for mortality, factors like rebleeding, blood transfusions and the need for surgery have often been included in the models (*20, 155*). This is problematic since these factors are actually response variables observed during the course of events and as such cannot be seen as true independent prognostic variables. They may *predict* a less favorable outcome but it is not possible to study their prognostic value without specifically designed studies.

It is of crucial importance that the data to be analyzed for prognostic importance represents the true situation. To collect valid information, under emergency conditions, from an elderly and possibly exsanguinated patient with respect to current medication and medical history is by necessity almost impossible. If such variables are to be analyzed, a carefully designed study with prospective collection of data must be performed. Other data such as, age and sex can also safely be collected in other types of studies while data on

therapeutic procedures, blood transfusions and blood pressure at admission represent an intermediate group.

Most commonly reported risk factors for mortality have been: age over 60 (65) years (*20, 78, 82*) and signs of recent hemorrhage at endoscopy (*134, 155*). Corresponding risk factors for rebleeding are: shock (*17, 20*) and stigmata of recent hemorrhage (*17, 21*).

The Forrest classification (*46*), Table 2, has frequently been used in attempts to ascribe a certain Forrest class a high or low risk of rebleeding and mortality. The problems with a large inter-observer variation has recently been shown (*98, 103*) and this may partly explain the differences in reported results.

Table 2. The Forrest classification

Active bleeding	Spurting	Forrest Ia
	Oozing	Forrest Ib
Recent bleeding	Visible, non-bleeding vessel	Forrest IIa
	Adherent blood clot or black base	Forrest IIb*
No bleeding	Lesion with no stigmata of bleeding	Forrest III

* A Forrest IIc class has also been suggested (ulcers with black base).

In summary, although there are quite a few publications in this field, data are of poor quality and further studies comprising high quality data are needed to provide the clinicians with true guidance tools.

AIM OF THE PRESENT STUDY

Several questions remain to be answered regarding the treatment and prognosis of patients with peptic ulcer bleeding as illustrated by the given review. The aim of the present study was therefore to address the following questions:

- What intravenous infusion dose of omeprazole should be used to ensure an increase of intragastric pH to levels alleged to ensure hemostasis during the first three days of treatment days for a PUB?
- What oral dose regimen of omeprazole should be used subsequent to the infusion period in order to ensure healing of the ulcer based upon intragastric pH observations?
- Is omeprazole, if administered as above, effective in high risk patients with a PUB to reduce continued bleeding, prevent rebleeding and decrease the need for therapeutic intervention?
- What is the short and long term mortality after admission for a PUB and how does it relate to mortality among matched controls?
- What risk factors can be defined for recurrent bleeding, short and long term mortality in patients admitted with a PUB?

PATIENTS AND METHODS

Study I

The aim of this study was to identify the intravenous infusion dose of omeprazole that increases the intragastric pH to levels alleged to ensure a durable hemostasis during the first three days of a PUB. Furthermore, to identify an oral dose regimen of omeprazole to be used subsequent to the infusion dose regimen in order to ensure that the ulcer heals.

Since most rebleedings occur during the first three days of admission (*118*) it was decided that the infusion should continue for three days and after that an oral dose regimen should start.

Based upon published and unpublished data we were convinced that a primed continuous infusion of 80 mg + 8 mg/h was needed to keep intragastric pH at levels alleged to be sufficient for hemostasis during day one. Consequently, it was decided to study whether it was necessary to continue with the infusion of 8 mg/h also after the first 24 hours as well or if it was possible to reduce it to 4 mg/h or 2 mg/h and still keep intragastric pH at requested levels.

A reference level during the infusion period was set at pH 5.4 based on *in vitro* data on coagulation and platelet aggregation (*27, 45, 56*). The corresponding reference level for the healing phase with oral dosing was pH 3. This was based upon data from compilations of results from clinical studies using different dosing regimens with various pH increasing potency (*23, 72, 76*). These studies have suggested that if the intragastric pH is kept above pH 3 for more than 75% of the day a predictable and high healing rate of both gastric and duodenal ulcers are reached.

The true target population for therapy with these intravenous doses of omeprazole in these doses is patients with an acute PUB. It has, however, been suggested that patients with an acute PUB may, in circumstances of

acute bleeding, actually have a reduced acid production. Chandler, (*28*) described a low acid output in patients shortly after admission with a PUB and Fullarton (*48*) showed that gastric acid secretion was reduced by intraduodenal infusion of autologous blood in healthy volunteers. Since we wanted to test the possibilities of a dose reduction under "worst scenario" conditions but still in a population, mimicking the actual target population as much as possible, we chose to include duodenal ulcer patients in remission. Consequently, 12 *H. pylori (+)* patients were included and they all received 80 mg + 8 mg/h during 48 hours. In a subsequent experiment, with the same group of patients but separated from the first with at least 14 days, omeprazole infusion 80mg + 8 mg/h was again given but only during the first 24 hours whereupon six patients were randomized to a subsequent dose of 4 mg/h and the other six to 2 mg/h during the period 24 - 48 hours. Intragastric pH was measured continuously during the 48 hour periods.

Later, data emerged to indicate that intragastric pH may be different in H. pylori (+) than in H. pylori (-) individuals after omeprazole administration (*9*). Consequently, in part two of the study, where the aim was to find the optimal *oral* dose to be used after the first 3 days of intravenous infusion, we included 12 healthy, H. pylori (-), volunteers. These subjects received omeprazole 80 mg + 8 mg/h during 72 hours after which they were randomized to either omeprazole 20 mg o.d. or b.i.d. Intragastric pH was measured continuously during days2, 3, 4, 6 and 10.

All intragastric pH measurements were made using the Gastrograph Mark II, (MIC AG, Solothurn, Switzerland), a well validated and recommended data logger (*153*). The electrodes were of bipolar glass design (Ingold, Urdorf, Switzerland) with high accuracy and widely used for intragastric pH measurements (*50*). The electrode was calibrated using the Gastrograph© standard buffers at pH 1.7 and 7.0 and was positioned in the stomach by inserting it slowly until a clear drop in pH readings was seen after which the electrode was withdrawn just enough to again record neutral pH. From that

position the electrode was further inserted 8 cm which is approximately 10 cm below the lower esophageal sphincter.

From the collected pH data we calculated a mean pH for each group based upon the (12)24 hour median pH values from each individual which is in agreement with current recommendations (*137*). Furthermore, since our specific interest was to study how various dose regimens influenced the time with pH levels over 5.4, the mean is a rather insensitive variable and therefore the fraction of time (%) with pH above 5.4 was also calculated.

According to Merki (*114*) the intra-individual day to day variation of pH, as currently assessed, is minimal and the reproducibility good if food intake and daily activities are standardized. The reproducibility of variables such as "fraction of time above pH 5.4" has, however, not yet been fully tested.

Studies II, and III

Studies II and III were performed in parallel and with very similar protocols. In both studies we chose to include patients with an acute PUB in the stomach or duodenum with ongoing or signs of recent bleeding (that is Forrest I or II), Table 2. Furthermore, patients should have a high risk of rebleeding and death.

Thus two risk groups were chosen which were; patients over 60 years of age (II) and patients with hemodynamic instability (III),

Patients

The following inclusion criteria applied for Study II:

Patient's age $\geq$ 60 years, current melena or hematemesis (starting less than 48 hours before admission), endoscopy performed within 12 hours of admission showing a peptic ulcer in the stomach or duodenum classified as Forrest Ia, Ib, IIa or IIb.

The following inclusion criteria applied in Study III:

Patient's age above 18 years, current melena or hematemesis, endoscopy performed within 12 hours of admission showing a peptic ulcer in the stomach or duodenum classified as Forrest Ia, Ib, IIa or IIb and clinical signs of circulatory stress or blood loss (at least two of the following three conditions had to be fulfilled at least once during the time span from presentation of the UGIB until the endoscopy): Systolic BP < 100 mm Hg, HR > 100/min or B-Hb < 7.0(men), 6.5(women) mmol/l. (Conversion factor to g/l - x 16.1).

The main exclusion criteria applied in both studies (II and III) comprised: gastrointestinal malignancy, esophageal varices, Mallory-Weiss syndrome, intake of anticoagulants during the last five days/last week, deficient hemostasis (simplastin < 40% or platelet count < 100 x 10^9/l or similar) severe concomitant disease reducing life expectancy to less than 6 months/ making study compliance questionable.

The assignment of treatment was made according to computer-generated randomization lists. The lists were made separately for each centre and within blocks of 2 consecutive patients. This block-size was only known by the statistician.

Methods

In both studies administration of study medication started within 30 min of the endoscopy. Omeprazole (or matching placebo) was given as a bolus infusion, 80 mg over 30 min, followed by start of an intravenous infusion of 8 mg/h,which was continued for a total of 72 hours wherafter all patients received oral treatment, omeprazole 20 mg once daily.

Mannitol was used as a placebo since it has an identical appearance to the omeprazole formulation and has no known therapeutic effects in these doses (80 mg of omeprazole resembles 40 mg mannitol in volume and appearance).

In Study II no endoscopic intervention was allowed except in ulcers classified as Forrest Ia. Consequently, patients with ongoing bleeding (Forrest Ib) could also be studied. In Study III endoscopic hemostasis was the main aim in all Forrest I patients. Forrest IIa ulcers should also be treated. In case of endoscopic intervention, injection techniques should be used as the first alternative.

The treatment effect was, according to the protocol, evaluated after the infusion was stopped, which was after 3 days. A safety follow up was done at day 21. The primary variable in both studies was a composite, ordinal scale, variable which classified the outcome for each patient from worst to best as follows:

5) death, 4) surgery, 3) additional endoscopic treatment, 2) > 3 units of blood transfused, 1) 0 - 3 units of blood transfused. By using this systematic characterization we obtained an overall evaluation of the treatment effect and avoided the problem of counteracting effects between efficacy variables always ranking the patient according to worst outcome. In Study II, the number of transfused blood units was also analyzed as a primary variable while it was a secondary variable in Study III. Other secondary variables were: degree of bleeding, duration of bleeding, need for surgery, need for additional endoscopic treatment and mortality. Degree of bleeding was evaluated every 12 hours and reflected the worst degree of bleeding during the 12 hour period preceding the evaluation. Duration of bleeding was defined as the number of such 12 hour periods with bleeding, (maximum 6 periods).

Rebleeding was not included as an efficacy variable. Even if this variable allows comparisons between studies, these may often be misleading due to inconsistent definitions both from a quantitative and qualitative point of view in different studies.

An independent, external statistician, was responsible for sequentially monitoring mortality in both studies. The Steering Committees for the studies should only be informed if there was a concern for safety.

The sample size calculations for both studies were based upon the number of blood units transfused. The assumption was to detect a reduction of blood transfusions by one-third in the omeprazole treated groups, established with a power of 80 % and the risk of false significance less than 5%. Depending upon slightly different assumptions for the relation between the mean and standard deviation of the number of transfused blood units, the calculations resulted in a sample size of 400 patients in Study II and 350 in Study III.

Study IV

This study was performed to generate data to form hypotheses to be further tested in Studies V and VI and also to substantiate the findings from Studies II and III. The study was conducted as a retrospective cohort study in patients aged 60 years or older who had been hospitalized at Sahlgren Hospital or Östra Hospital in Gothenburg for a peptic ulcer bleeding during a five years period, 1 January, 1989 to 31 December, 1993. The following discharge diagnoses were included (International Classification of Diseases, revision no. 9, codes 531, 532, 533 and 534 with subgroups - 0, - 2, -4 and -6 (that is , chronic or acute gastric, (pre)pyloric, duodenal, peptic, gastrojejunal, stomal or anastomotic ulcers with bleeding). Patients, experiencing a peptic ulcer bleeding during their stay in hospital due to other diseases or in whom the bleeding came from a stress-induced ulcer were excluded after the hospital records had been reviewed manually.

Given the retrospective design of the study we primarily collected data which we considered to be accurate and not hampered by this design. The data collected concerned age, sex, ulcer site, number of transfused blood units, subsequent treatment (that is operation, endoscopic treatment or pharmacological treatment only) and length of hospital stay. Other data, such as Forrest class, presence of hemorrhagic shock on admission, past or present diseases and current medication that could potentially influence healing, (such as non-steroidal anti-inflammatory drugs, aspirin, or anticoagulants)

were also collected but was evaluated with caution due to the retrospective study design.

The hospital records were also scrutinized for any rehospitalization due to a recurrent bleeding during the 90 days after the index bleed. This cut-off level was chosen arbitrarily.

The hospital records of 676 of the 687 patients who fulfilled the inclusion criteria could be located and were subsequently reviewed.

A review of all patients with respect to survival was carried out by 31 December, 1995 using the Swedish National Population Register and the follow-up period was therefore from two to seven years.

A traditional control group should contain individuals free from the disease under study. It is, however, practically difficult to find a group that is virtually identical to study cohort except for peptic ulcer bleeding. To circumvent this problem we identified, from the same geographical area, a comparatively high number of controls (n=9464) which equaled 14 control individuals to each patient. The controls were matched according to age and sex by using the Swedish National Population Register from 1980. Survival data for the controls during 1980 - 1986 was obtained from the Population Register and these were compared with survival data from our patients.

Given the relatively low occurrence of peptic ulcer bleeding in the population, < 1/1000/year, it can thus be estimated that among the controls less than 9 PUB occur during one year which is less than 63 during the seven years of follow up. It is therefore reasonable to believe that the impact of these individuals, representing a fraction of about 6‰, is negligible when studying survival in the whole control group. Following the controls during a different time period (1980 - 86) than the cases (1989 - 95) can infer a problem. In this case the population in Gothenburg did not show any significant demographic/survival changes between 1980-86 compared with 1989-95 based upon data from National Statistics (Statistiska Centralbyrån, Sweden) (*146*) and this is thus not likely to influence the conclusions.

Multiple logistic regression analyses were performed including the variables collected and listed above. Analyses included possible influence upon short and long term mortality, as well as rehospitalisation due to rebleeding within 90 days of admission. The multiple logistic regression analyses are described on page 40.

Study V

This study included a subset of patients from Study II and III (that is, the patients over 60 years). While Study II and III evaluated the *therapeutic* effect of omeprazole in two well defined risk groups of patients with PUB, Study V analyzed which factors had *prognostic importance* for short term survival and rebleeding. The cut-off point for rebleeding was set at 3 days (72 hours) since less than 10% of rebleedings occur after this point in time (*118*). The cut-off point for mortality was 1 month (30 days) based upon experience from Study II, III and IV.

Merging of data from two separate studies must be done with caution. In this case it was considered scientifically valid and correct due to the following facts: 1) Both studies (II and III) were performed during the same time period. 2) The protocols were almost identical. 3) There was no reason to believe that patients in one study would respond differently from patients in the other study. 4) The difference between centres within each study was likely to be larger than the average difference between the two studies. 5) "Study" was included as a prognostic variable in the analysis and had no prognostic value (OR=0.99).

Study V thus recruited patients with a peptic ulcer bleeding (PUB) admitted to 63 hospitals in Sweden, Denmark, Holland, France and Norway. Eligible patients should have been included previously in Study II or III and, furthermore, to be included in Study V, also be over 60 years of age.

From a total of 587 patients in the two parent studies, 508 patients met the current inclusion criteria and were consequently included. Six patients had incomplete data sets and were not included in the multiple logistic regression analyses (one of them died).

Table 3 displays the variables that were included in the multiple logistic regression analyses. Even though it could have been interesting to separate, for instance the prognostic value of angina from that of a myocardial infarction during last month, we chose to limit the number of variables included in the analyses. The risk of both false correlations by chance and very wide confidence intervals could thereby be reduced. One common variable, "coronary heart disease", was thus created including angina, congestive heart failure or myocardial infarction. "Diabetes" was defined as need for insulin or oral antidiabetic drugs. " Intake of ASA/NSAID" reflected intake during the last two weeks prior to admission. Daily intake of less than 250 mg ASA was not included in this variable .

Table 3. Variables included in the multiple logistic regression in Study V.

Category variables	Continuous variables
Shock at admission	Age
Ulcer localization	Systolic blood pressure on admission
Forrest class (Ia, Ib, IIa, IIb)	(mm below 100)
Previous ulcer history	
Sex	
Current smoker	
Diabetes[1]	
Coronary heart disease[2]	
Intake of ASA/NSAID[3]	
Chronic obstructive airway disease	
Study drug	

[1,2,3] For definition see text.

Study VI

The aim of this study was to study risk factors for short term mortality in a different cohort than in Study IV and V. The General Practice Research Database (GPRD) was selected for this study since it is a large, well validated and population based. This base is currently the most widely used European data base for pharmacoepidemiological research (*49*).

The base was started in the late 1980s, by VAMP Health, a commercial company, which on a commercial basis started to install computer systems in general practioners' (GPs) offices throughout UK. It was predicted that such collected data could be used for both administrative and research purposes. Since 1994, the acquired information belongs to the UK Department of Health and is maintained by the Office of National Statistics in UK. Until now about 1500 GPs participate in this system covering a population in excess of three millions. The data base contains computerized information on demographics, details of every visit to the GP, referrals, summaries of specialists' clinical notes, discharge letters, results of lab tests and a free text section. Prescriptions issued by the GP are directly generated from the computer ensuring a complete record of all prescriptions.

The base is very well validated and covers all segments of the UK population both from a geographical as well as from a social point of view and has hitherto been the data source for more than 60 publications (*49*).

We identified in the GPRD patients aged 30 to 89 years who had been admitted to hospital for an episode of upper gastrointestinal bleeding between January 1991 and March 1994. Patients had to be free from cancer, esophageal varices, cirrhosis, Mallory-Weiss syndrome and intestinal vascular abnormalities. The computerized patient profiles of these patients (n=3953) were automatically reviewed to include only patients in whom a peptic ulcer in the stomach or duodenum was the cause of bleeding. Furthermore, patients with one or more of the following conditions were excluded: patients with hemorrhagic gastritis or duodenitis only, patients with perforated peptic ulcer

and patients experiencing their bleed while hospitalized for other causes. After this revision, 1070 patients with an episode of peptic ulcer bleeding involving the stomach or duodenum, remained in the cohort. In 772 of these patients data was partly missing or insufficient and questionnaires were sent out to their GP asking for further information. Replies were received from 716 of these and based on this complementary information 50 more patients had to be excluded due to violation of any of the selection criteria above. Consequently, our final study population comprised 1020 patients.

Table 4 lists all variables included in the final Cox proportional hazard analysis for influence upon mortality. Given the nature of our data source, use of non prescribed drugs, for instance, aspirin purchased over-the-counter (OTC) was not included as current intake.

In the final presentation of the relative risks (RR) for the variable of interest adjustments were only made for age, sex and the variable of interest. This was decided upon after an initial analysis including all variables in Table X where it was found that the major modifiers of risk were age and sex. Including only these factors (+ the variable under analysis) in the final model increased the precision of the RR estimate.

Table 4. Variables included in Cox proportional hazard analysis for influence on mortality within one month of admission.

Variable	Categorization	Comment
PU antecedent	Yes	Included PU or PUB
	No	
Age	30 - 59 years	
	60 - 69 years	
	70 - 79 years	
	80 - 89 years	
Sex	Male	
	Female	
Ulcer site	Gastric/pyloric	
	Duodenal	
	Gastric and Duodenal	
	Undiagnosed	
Co-morbidity	Yes	Cerebrovascular, cardiovascular, respiratory or diabetes
	No	
Surgical treatment	Yes	
	No	
Acid suppressing drug use	None	
	Current	Prescription within 60 days
	Past	Prescription > 60 days
Aspirin use	None	Incl OTC use
	Current	Prescription within 60 days
	Past	Prescription > 60 days
NSAID use (excl. ASA)	None	Incl OTC use
	Current	Prescription within 60 days
	Past	Prescription > 60 days
Alcohol consumption	< 2 units/week	1 unit = 8 - 10 g (*142*)
	2 - 15 units/week	
	>15 units /week	
Body Mass Index	<25	kg/m^2
	25 - 30	
	>30	
Smoking	None	
	Current smoker	
	Past	

RISK FACTOR ANALYSIS (IV, V, VI)

Variable selection

Causes of diseases or events are studied with the objective to explain and eventually prevent the occurrence of the event. Commonly, a causal relation can be said to exist if the probability of a particular outcome would be different in the absence than in the presence of a factor (*1*). Several forms of co-variation between two factors, A and B, can exist. Such a co-variation can arise in two different ways (given that A occurs before B).

1) A causes B

or,

2) A and B have the same, common cause (X)

In alternative 1) a true causal association exists between the risk factor (prognostic factor) A and the factor (in this case, event) B while in alternative 2) the co-variation between A and B is not causal but called a "confounding" co-variation. If the ultimate aim is to reduce occurrence of the event B, it is essential to distinguish between alternative 1) and 2) since it is only by eliminating factor A in an association of type 1) that an event rate (B) can be reduced.

In the current investigation the aim was to identify factors that are true risk factors for death and that they, if eliminated or reduced, should ultimately reduce death rate. Those risk factors must therefore be of category 1) as indicated above.

Rebleeding, blood transfusions and surgery, in this context, all fall into category 2) since they, together with death, all have a common cause, namely bleeding. Consequently, factors of this type were not included in the analyses. Still surgery, for instance, can have an association to mortality of type 1). However, to be able to investigate this, studies strictly randomizing patients

to either operation or no operation must be done. Such designs raise justified ethical concern.

Statistical models

In the present investigation mortality has been a factor for which we have tried to find the true risk factors. It is likely that mortality depends upon several variables and not only upon a single one. It can also be assumed that there is a co-variation between certain explanatory variables. It is, for instance, well known that patients with gastric ulcers are older than patients with duodenal ulcers (*18, 19*) and NSAID intake is more common among the lderly. Consequently, an analysis of risk factors must include all factors of interest in the model (a multivariate approach) to compensate for this co-variation between variables and not just take one factor at a time into consideration (a univariate approach). To analyze such complex relations a multiple logistic regression model (*91*) is often used which is based on a logistic function, Figure 1 . The following logistic function is used:

$$f(z)= \frac{1}{1+e^{-z}} \qquad (1)$$

This function has, for several reasons, gained a lot of popularity. It has a range, $0 \leq f(z) \leq 1$, for all values of z. Thus we can never get a risk estimate above 100% or below 0% in contrast to, for instance, a linear multiple regression model. This is appealing in our perception of the term "risk". Furthermore, the S-shape of the logistic curve; first a minimal risk after which the risk increases more rapidly and then levels off and remains extremely high once z gets large enough. This is in agreement with a common perception of risk influence.

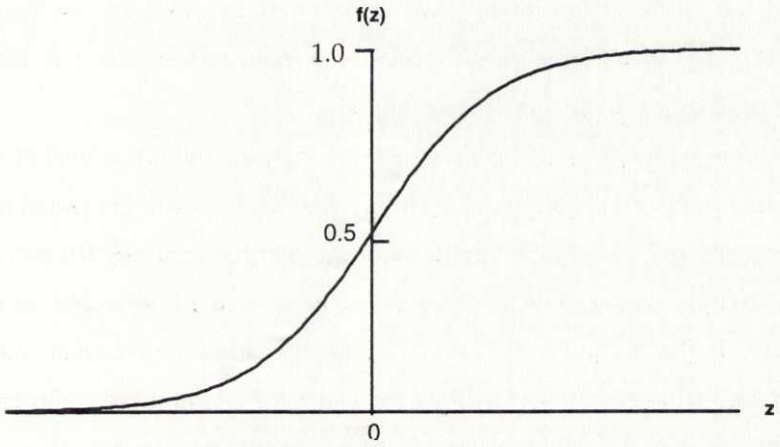


Figure 1. The logistic function representing the risk, f(z), as a function of the risk index, z.

The variable, z, is an index that combines the explanatory variables X_1, X_2,... X_k (that could, for instance, be age, duodenal ulcer or shock) according to the following formula

$$z = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k \qquad (2)$$

where α is a reference constant and β_1 to β_k represent coefficients.

These represent the weight of the individual variables X_1, X_2,... X_k in the overall risk index, z. The values of these coefficients are calculated by a method called "maximum likelihood" using data from a study in which the outcome is known for each patient. However,to describe this technique is beyond the scope of this presentation.

The relative risk ratio (RR) can then, in principle, be calculated for each risk variable in the model by dividing the value for f(z), including the explanatory variable under study, with the value of f(z) when this variable has been omitted but all other factors are kept constant. If, for instance, we want to calculate a RR of dying a smoker relative a non-smoker, the f(z) for the smoker is divided by f(z) for the non-smokers

The problem with using a RR is that the level depends upon the level of other risk factors in the particular patient. This means that if we are interested in the RR for mortality for a smoker versus a non-smoker the resulting RR value for a 60 year old smoker will be different to that of a 61 year old smoker. However, if the formulas (1) and (2) above is used to calculate an OR instead,the value for smokers will be the same for all smokers regardless of their age and also independent of the values of other prognostic values. This is often appealing. This calculation is a complicated process which will use the values of α and β in the formula (2) above.

When the patients in a population are at low risk, say below 20%, the relative risk associated with a particular variabel (for instance smoking) only varies slightly with other factors , for instance, age. In this situation it is reasonable to approximate the RR with the OR.

To correctly estimate a RR for a certain variable we must have outcome data from a follow-up study. If the values of one or more risk factor are missing for a certain patient this patient cannot be used when the RR or OR are calculated. This may cause a bias if the reason for the missing data is associated with the outcome of the patient. The results from the analyses can be questioned if a substantial proportion of patients has missing data.

The more complicated Cox hazard regression model used in Study VI and in the long term analysis of mortality in Study IV, takes into account not only the presence or the absence of an event (i.e., the patient being dead or alive at end of study) but also the follow-up time for each individual patient. Cox hazard regression models present the results in terms of RR. A RR calculated from a Cox hazard regression gives, in contrast to RRs based upon multiple logistic

regression analyses, a value that is independent of the value of other risk factors. (See example above.)

As a consequence, the *numerical* values of an OR (or RR) based upon a multiple logistic regression model can not be compared with a RR value obtained from a Cox regression model.

Although not used in this thesis, an OR or RR can also be analyzed from a simple 2 x 2 table as illustrated in Figure 2. This is, by far, the commonest calcualation behind ORs or RRs presented in the PUB literature. However, if more than one variable could have an impact upon the outcome these results may be grossly misleading due to confounding caused by other variables. Nevertheless, the method is often used, even in modern analyses and it is important to identify the method behind the figures presented in order to evaluate their validity.

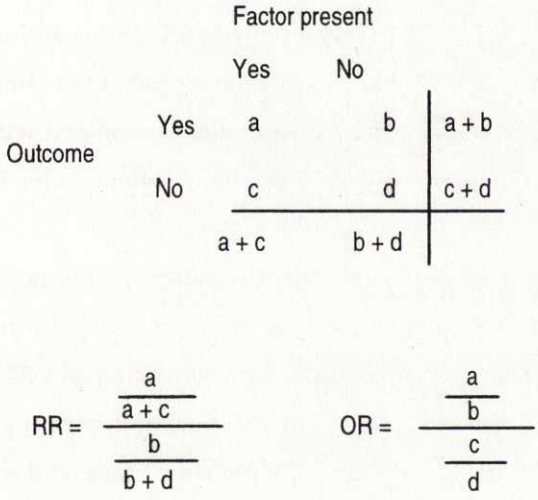


Figure 2. Methods for calculating OR and RR based upon a 2 x 2 table. a, b, c, d denotes number of patients in each cell.

RESULTS AND COMMENTS

Control of intragastric pH (Study I)

Administration of omeprazole as a primed continuous infusion (80 mg given over 30 min followed by infusion of 8 mg /h) resulted in a rapid increase of intragastric pH in all patients. The focus of interest in this part of the study was the possibility of a decrease of the dose after the first 24 hours. Consequently we chose not to include the first 12 hours of the 0 - 24 hours period in the comparisons of results achieved on the 8 mg/h dose and the subsequent doses, administrated during 24 - 48 hours.

The mean pH during the 12 - 24 hour period after start of the study drug administration was 6.7 and the mean fraction of time with pH above 5.4 was 92%. During the second day (24 h - 48 h) mean pH was 6.1 and mean fraction of time with pH above 5.4 was 90%. Nine of the 12 subjects maintained or increased their fraction of time above pH 5.4 during day 2 compared with the preceding 12 hour period. There were, however, three patients who had a decrease, Figure 3.

The patients were also, in a second experiment, randomly allocated to a decrease of the infused dose of omeprazole from 8 mg/h given during the first 24 hours to either 4 mg/h or to 2 mg/h for the subsequent 24 hour period. All of the six patients randomized to a dose reduction from 8 mg/h to 4 mg/h maintained the mean fraction of time with pH above 5.4 as did four of the six patients randomized to a dose of 2 mg/h. The mean pH in the 4 mg and 2 mg/h group was the same (6.1 and 6.2 respectively).

It should be noted that all subjects, received a high energy liquid oral nutrition after the first 24 hours, which may be one reason why a few patients reduced their fraction of time with pH above 5.4 on day 2. There was, however, virtually no difference in mean pH between the three different

dosing groups. Also with respect to fraction of time with pH below 4 there were small differences; (2 mg/h - 2%, 4 mg/h - 3% and 8 mg/h - 0.6%).

These results are difficult to interpretate. The mean pH in the three groups did not differ at all and this could indicate that the true differences between the doses were marginal. Also the differences were small with respect to the patients' fraction of time over pH 5.4. However, in the 8 mg/h dose group there were two patients who increased the fraction of time with pH above 5.4. This was not seen in any of the other two dose groups indicating a possible advantage of the 8 mg/h regimen in those patients who have a sub-maximal response during day 1. There was also three patients who, when on 8 mg/h day 2, decreased their fraction of time above pH 5.4. To further complicate the interpretation these three patients kept their fraction of time above pH 5.4, when they received a lower dose, 4 mg/h during day 2. It is possible that all three tested doses are on the flat part of the dose response curve.

The conclusion is that decreasing the infusion dose to 4 mg (or 2mg/h) may be as effective as continuing on the 8 mg/h dose. Until further data is available, the most secure alternative seems to be to recommend the 8 mg/h dose of omeprazole.

It may be surprising that such high doses are needed to achieve the desirable pH levels. In that respect it should be noted that increasing pH from 2 to 7 implies in fact a 99.999% reduction of the acid concentration. This means that virtually all acid pumps must be blocked. The bolus dose of 80 mg is needed to block all available pumps on the surface of the parietal cell but the short plasma half life of omeprazole, approximately 40 min, implies that pumps coming up to cell surface during subsequent hours are not blocked if omeprazole is not administered as a continuous infusion, ensuring a sufficiently high omeprazole plasma concentration to block these pumps.

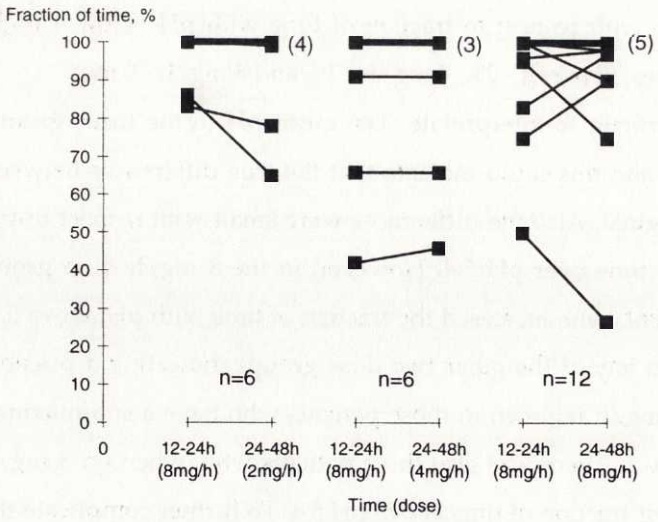


Figure 3. Comparison of fractions of time with pH above 5.4 during 12 - 24h (when all subjects received 8 mg/h) and subsequent interval (24 - 48h - when the subjects received 2, 4 or 8 mg/h)

In part II of Study I all individuals received the same dose regimen (80 mg + 8 mg/h) during the first three days. Intragastric pH data from day 2 shows that this group of healthy *H. pylori* (-) subjects had almost identical intragastric mean pH, 6.3, and mean fraction of time with pH above 5.4, 92%, on day 2 as the *H. pylori* (+) patients in part I of the study (6.1 and 90%, respectively). Since the study was not designed to make a formal comparison between *H. pylori* (-) and *H. pylori* (+) subjects no firm conclusions can be drawn but the results do not support the suggestion that there should be a difference in resulting intragastric pH between infected and non-infected subjects (97) after omeprazole administration, at least not in this dose range.

On day 3, while still infusing 8 mg/h, we noted a reduction of the fraction of time with pH above 5.4 from 92% (day 2) to 75%. The mean pH decreased slightly from 6.3 to 6.0. It could be seen from the individual pH graphs that the decrease in pH was closely related to food intake. During this particular study day, the subjects was given a normal diet and these provisions may

have contained acidic components which could explain the reduction in fraction of time with pH above 5.4.

In previous studies with intragastric pH measurement up to 72 hours it has been shown that omeprazole, in contrast to H2-receptor antagonists, maintains a potent antisecretory efficacy without development of tolerance or decreased effect even during intake of liquid nutrients (*92, 113, 122*). Consequently, we interpret the decrease in fraction of time above pH 5.4 on day 3 as an effect of food intake and not as a sign of drug tolerance.

After cessation of the infusion at 72 hours and start of oral dosing of omeprazole we noted, as expected, a gradual drop of intragastric pH.

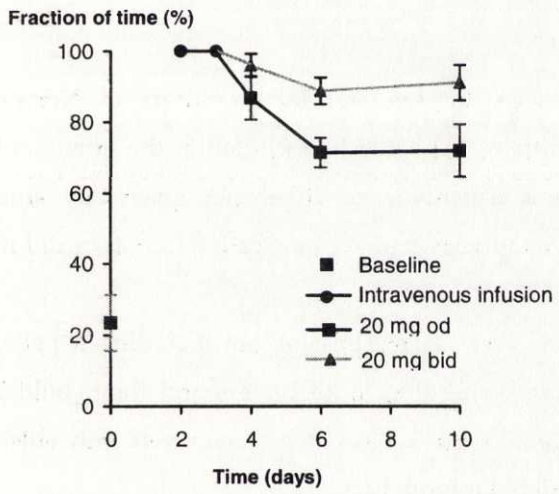


Figure 4. Mean fraction of time (95% CI) with pH above 3.0 before and during intravenous (days 1-3) and oral (days 4 -10) dosing with omeprazole. The difference between the oral doses reached statistical significance during all individual study days ($p<0.05$).

Intragastric pH stabilized in both dose groups (i.e., the 20 mg once or twice daily groups) between day 4 and day 6 with no further changes to day 10 , Figure 4. No signs of rebound phenomenon were seen after the omeprazole infusion ceased.

The 20 mg once daily dose of omeprazole gave a stable reduction of the fraction of time with pH above 3 of approximately 72% which is a level considered sufficient for both duodenal (23) and gastric ulcer healing (72, 76). The corresponding figure for the twice daily dose was 91%. Consequently, there seems to be no reasons to recommend a subsequent twice daily oral treatment regimen in this patient population after the three day infusion of 8 mg/h has been stopped.

Omeprazole infusion in peptic ulcer bleeding (Study II and III)

Patient description

In Study II, the 20 centers in Sweden and the 9 centers in Norway, randomized 333 patients. Of these 322 could be included in the intention to treat analysis. The remaining patients were either not given any study medication at all (n = 4) , given unknown study medication (n = 4) or did not fulfill inclusion criteria (n = 3).

Log-books, intended for recording the reasons for not including a patient admitted due to a PUB, were distributed to all centers and they could be evaluated in 16 of the 29 centers, Table 5. The other centers were only able to provide intermittent and scattered information.

This table gives valuable information regarding the accuracy by which the results from the study can be generally applied to the overall target population. Most patients with PUB who fulfilled the inclusion criteria were, in fact, included. This information consequently suggests that we have no reason to believe that our criteria for exclusion should limit the general applicability of the results.

Table 5. Patients admitted with PUB during the inclusion period but not enrolled by reason.

Reason for not including a patient	Number	% of total
Inclusion criteria not fulfilled		
Age 60 or over	5	2%
Bleeding within 48 hours of admission	25	11%
Peptic ulcer, Forrest I or II, in stomach or duodenum	28	13%
Informed consent	13	6%
Exclusion criteria fulfilled		
Ulcer of Forrest type III	46	21%
Severe disease making study compliance questionable	19	9%
Anticoagulation therapy within 5 days of admission	11	5%
Phenytoin medication	1	0.5%
Upper gastrointestinal malignancy	3	1%
NSAID intake that could not be withdrawn	8	4%
Omeprazole intake within 5 days of admission	23	10%
Other reasons		
Endoscopy performed > 12 hours of admission	23	10%
Need for immediate surgery	2	1%
Other reasons	14	6%
TOTAL	221	100%

The patients' demographic and baseline characteristics were similar between the omeprazole and placebo groups with the following exceptions: the number of patients with hemoglobin lower than 90g/l were fewer in the placebo group (29%) than in the omeprazole group (43%). Previous ulcer history was more common in the placebo group, (56%) versus (45%).

In Study III, 274 patients were randomized in 34 centers in Denmark, Holland and France. Of these, 265 patients could be included in the intention-to-treat analysis. Patients were excluded from this analysis if they were not given any study medication at all (n = 4) , given unknown study medication (n = 2) ,

violated inclusion criteria (n = 2), or withdrew the informed consent (n = 1). Imbalances in baseline factors were found for the following factors; age (38 patients were above 80 years old in the placebo group compared with 24 in the omeprazole group), systolic blood pressure ≤ than 80 mm Hg (placebo group - 11, omeprazole group 21), heart failure (placebo group - 23, omeprazole group - 13), smoking (omeprazole group - 69, placebo group - 51), previous ulcer (placebo group - 62, omeprazole group - 47) , and Forrest class IIa (placebo group - 37, omeprazole group - 20).

Results (primary efficacy variables)

The composite ranking scale variable was a primary variable in both Study II and III. In both studies we found that patients treated with omeprazole showed a statistically significant improved outcome ($p = 0.017$ and $p = 0.004$, respectively).

This composite variable has several advantages over the alternative approach, that is, to select one individual variable (for instance rebleeding or surgery) as the primary efficacy variable. When treating conditions where several different treatment options are possible there is always a risk of counteracting effects between variables giving in results which are difficult to interpret. The composite variable that we used in the present studies circumvents that problem by always ranking the patient according to worst outcome. This variable also reflects the effect of a treatment in a way that is not necessarily picked up by one individual variable, namely a transition of patients from more "severe" outcomes to "milder" forms. An obvious disadvantage is that the numerical value, the "ranksum" from each treament group, represents something "non-tangible" and thus requires more understanding from the reader than for instance a discrete variable such as number of operations.

In Study II, the number of transfused blood units was an additional primary variable. We found no significant difference between the number of transfused units of blood, with 1.4 units transfused in the omeprazole group

and 1.6 in the placebo group. The transfusion policy was strict in the study and only 166 of the 322 patients received transfusions. Walt (*159*) reported a considerably higher amount of blood transfusions in his study on famotidine in patients with PUB (a mean of 3 and 4 units in the famotidine and placebo groups, respectively). Higher figures than ours were also reported from Branicki (*20*) where a median consumption of 4 units were noted among surviving PUB patients and 10 units among PUB patients who died. In that particular study 58% of the patients had hemoglobin values below 100 g/l and 20 % had a systolic blood pressure below 100 mm Hg on admission. In Study II corresponding figures were 50% and 12% and in Study III 66% and 42%, respectively. The blood transfusion rate in Study III was also rather low, comprising 2.1 units in the group treated with omperazole and 2.9 units in the placebo group.

In Study II only 5 patients in the omeprazole group and 12 patients in the placebo group received more than 5 units of blood. Corresponding figures for Study III were 12 and 20 patients, respectively.

The relative lack of difference between the study groups with respect to the amount of blood units transfused may be due to the use of effective endoscopic or surgical intervention in all patients already at a time when rather few blood units had been transfused. This illustrates the susceptibility of the variable "blood transfusions" to counteraction with intervention variables.

Results (secondary efficacy variables)

The need for surgery was a secondary variable in both studies and we found a consistent and significant reduction when omeprazole was infused. In Study II, 2.5% of patients in the omeprazole group had surgery compared to 9.8% of placebo group patients. The corresponding figures in Study III was 5.4% and 11.1%, respectively.

The logistic regression analysis showed a 87% (95% CI; 97% to 49%, p = 0.003) reduction of the need for surgery for patients treated with omeprazole in Study II and a corresponding 84% (95% CI; 95% to 47%, p = 0.003) reduction in Study III.

The rate of surgical intervention was in both studies, somewhat lower than previously reported in other studies conducted before the era of endoscopic treatment (*120, 159*) but correspond well with the 10% reported in a recent Dutch survey (*171*).

The need for endoscopic treatment was reduced from 6.7% in the placebo group to 3.1% in the omeprazole group in Study II and from 11.1% to 4.6% in Study III. The logistic regression indicated, for the patients treated with omperazole, a 60% (95% CI; 87% to + 28%, p = 0.12) reduction of the need for endoscopic treatment in Study II and a 69% (95% CI; 89% to 14%, p = 0.03) reduction in Study III.

No patient in Study II had both surgery and endoscopic treatment during day 1 - 3. One of the operated patients died during day 1 - 3.

In Study III five of the 15 patients who had surgery in the placebo group had also undergone a previous attempt to endoscopic hemostasis due to rebleeding. This was also the case for three (one died) of the seven patients requiring surgery in the omeprazole group.

Duration of bleeding (that is the number of 12 hour periods with bleeding) was significantly reduced ($p \leq 0.02$) by omeprazole in both studies. In Study II the reduction was from 1.0 (12 hour periods) in the placebo group to 0.6 in the omeprazole group, corresponding figures for Study III were 1.3 to 0.9.

The number of patients with further bleeding with the maximum intensity according to the 3 or 4 graded scale used in the respective study, was in the placebo groups, 26 and 19 (Study II and III, respectively) compared with 12 and 8 in the omeprazole groups. A Wilcoxon test including all classes of bleeding intensity showed significant differences with the advantage of omeprazole treatment in both studies (0.004 and p= 0.03, respectively).

The results from the subgroup analyses of patients who had an ongoing bleeding at admission (Forrest Ib) are of particular interest since they reflect the capacity of omeprazole has to stanch an ongoing bleeding in addition to maintaininghemostasis. In this sub-group, 82 patients were randomized to either omeprazole infusion (n = 41) or placebo infusion (n = 41). The ranking scale variable showed a significantly improved outcome for patients treated with omeprazole, (p=0.01). Other variables showed numerical, but not statistically significant, differences again favoring omeprazole treatment (need for surgery, 1 in the omeprazole group, 7 in placebo group, need for endoscopic treatment, 0 versus 2, mean number of blood transfusions 1.4 versus 2.1).

To summarize, all efficacy variables consistently revealed better results for patients treated with omeprazole infusion regardless of whether the patients had an ongoing or a stanched bleeding when treatment commenced.

These findings are in agreement with some previously presented results after repeated omeprazole bolus injections (*22*) but contrast the relative lack of effect reported in the largest single study including patients with all forms of upper gastrointestinal bleeding (*39*). Several explanations to this discrepancy exist, for instance, the different patient groups. Presumably patients with peptic ulcer bleeding benefit more from omeprazole therapy than patients with any other bleeding sources. Another major reason behind the differences in effects was the difference in level and duration of acid inhibition achieved by the omeprazole dosing regimens used. In the study by Daneshmend (*39*) omeprazole was given as 4 injections of 80 mg, 40 mg, 40 mg and 40 mg, respectively over a period of 20 to 27 hours which was followed by oral treatment 40 mg twice daily for three days. This regimen will not give a stable intragastric pH at the same levels as 80 mg + 8 mg/h during the risk period for rebleeding, i.e., the first three days of admission and thus does not fulfill the theoretical requests for an adequate hemostatic effect (*88*).

Follow-up analyses

The primary objectives of Study II and III were to evaluate the effects of omeprazole in PUB patients during a three day infusion. However, as a safety measure a follow-up analysis of final outcome and further interventions was included day 21 in both study protocols, Table 6. As all patient groups received omeprazole 20 mg daily after day 3, we did not expect any differences between groups during this period (i.e., day 4 to day 21).

Table 6. Results of the follow up analyses. Figures refer to day 4 to day 21. Omeprazole and placebo refers to allocated treatment day 1 - 3.

	Study II		Study III	
Event	Omeprazole	Placebo	Omeprazole	Placebo
Endoscopic or surgical treatm.	9	3	8	6
Rebleeding	5	4	9	16

Therefore it seems as if the advantages shown by omeprazole treatment during the first three days are not counteracted by increased rebleeding rates during the subsequent days.

Mortality

Although a reduction of mortality is the ultimate goal for all therapies in patients with PUB it has to be realized that to be able to show statistically significant reductions, very large studies will be needed. Langman (*101*) drew parallels with the situation for cardiologists who, in their attempts to find significant reduction in mortality had to include more than 10 000 patients in survival studies. For instance, to detect a 20% mortality reduction in an actively treated group of patients would require, if true mortality in the control group is 5%, more than 13 000 patients (α = 5% , 80% power).

Mortality was still included in both studies as an efficacy variable at day 3 and also as a safety variable at the follow-up on day 21 but no significant differences were expected to be found based on the considerations outlined above.

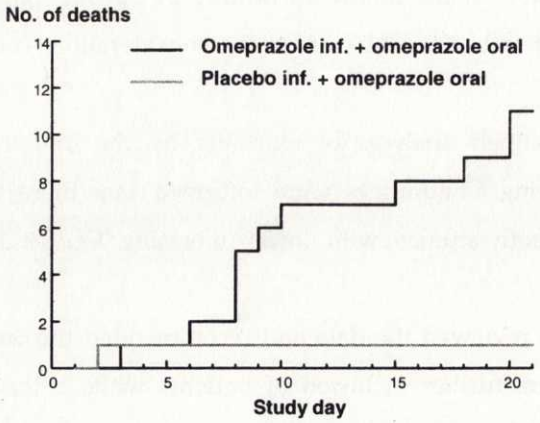
At the third of four planned analyses of mortality by the independent reviewer the study Steering Committees were informed that there was a mortality imbalance in both studies with lower mortality figures in the placebo groups.

An external expert group reviewed the data and recommended the Steering Committees to discontinue further inclusion of patients while a thorough investigation was performed.

The final analysis of mortality revealed that after the three days of infusion one patient in each group (0.6%) in Study II had died and two patients (1.5%) in the omeprazole group in Study III. The cumulated number of deaths at day 21 were, in Study II, one (0.6%) in the group initially treated with placebo infusion and 11 (6.9%) in the group initially treated with omeprazole. In Study III eight patients in each group had died, i.e., for the placebo group a mortality of 5.9%, and 6.2% for the omeprazole group. Figure 5, a and b, shows cumulative number of deaths during days 1 to 21.

The Steering Committees decided later not to resume inclusion and instead perform the efficacy analyses since the included number of patients was sufficient enough to detect true treatment effects very close to those which the studies originally had been planned for.

a)



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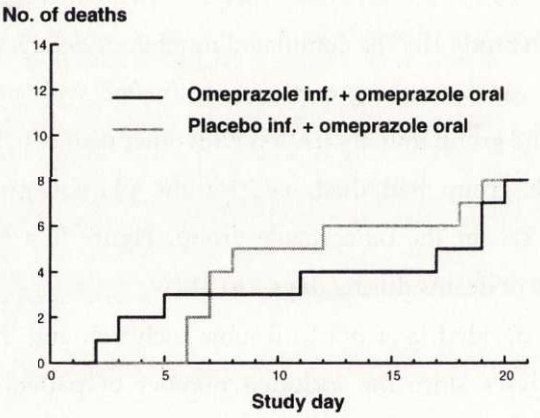


Figure 5 a and b. Cumulated number of deaths in the two treatment groups a) Study II and b) Study III , respectively.

The mortality figures in both active treatment arms are relatively low in comparison to figures reported from similar patient groups , Table 1. The mortality figure in the placebo group in Study II is extraordinarily low in comparison to in the literature as well as from Study III. A thorough investigation was carried out to find any possible causes to the mortality imbalance in Study II. This evaluated both the possibility of a positive effect

on mortality of the placebo formulation, mannitol, as well as the possibility of an adverse effect of omeprazole.

The effect of mannitol has been investigated in a large number of studies, mainly using mannitol as a hydroxyl scavenger to reduce the ishemic damage after thromboembolic events in the brain or myocardium (*54, 60, 117, 125, 156, 168*). The results have, however, been inconclusive and the doses used are at least a 1000-fold higher than the doses we used in our trials (which were about 2mg/kg/24 hours).

However, to exclude effects that the low doses of mannitol used in our studies could have on the coagulation system, which gave a plasma concentration of about 0.5 - 1.0 mg/ml, a few pilot *in vitro* experiments were made. Human plasma with mannitol added in concentrations from 0.1 to 100 mg/ml was used. Mannitol showed no effects in these concentrations in standard APTT analyses as well as in platelet aggregation screen models which are described on page 58.

Imbalances in risk factor distribution between treatment groups at base line might be one factor contributing to the mortality imbalance, see page 48. These differences are, however, not likely to explain the whole difference.

Another variable of interest in this context is the number of non-fatal serious adverse events. In both Study II and Study III only minor differences between the placebo and the omeprazole groups were found. Major imbalances at base line as well as any harmful effects of omeprazole per se, should have affected the number of non-fatal adverse events seen in the two groups.

Emerging data from Study IV and VI clearly show that the mortality of 0.6% at day 3 with no further deaths occurring up to day 21 found in the placebo group which was found in Study II must be regarded as an extraordinary finding. The mortality in the omeprazole arms in both studies corresponds, however, very well to what was found in Study IV and VI and to figures from the literature, Table 1.

Influence upon mortality by chance is, however, one factor which has to be seriously considered and has in fact provided a likely explanation to

unexpected findings in other studies (*64, 152*). Therefore, influence by chance must be recognized as the most reasonable explanation behind the mortality imbalance also seen in Study II.

Effects of omeprazole upon hemostatic mechanisms (unpubl. data)

The positive effect of omeprazole observed in Study II and III is most likely achieved by the effect of omeprazole reducing intragastric acidity. However, a direct effect of omeprazole on the hemostatic mechanisms can not be excluded from these findings. Therefore we have carried out a series of experiments to investigate the possibility of an effect of omeprazole upon: 1) platelet function, 2) coagulation 3) bleeding time and 4) fibrinolysis.

1) Platelet function

Platelet aggregation was measured in an aggregometer which measures light transmission in a platelet suspension under continuous stirring at 37°C.
The effect is expressed in terms of lag phase (the time between addition of aggregating agent and the start of aggregation) and the final aggregation level. This is a standard method with a reproducibility of ± 3% (final aggregation level) (*12*). Normal maximum aggregation level is 80 - 100%. Normal lag time is less than 60 seconds according to the manufacturer's information.
The platelet aggregation in platelet rich plasma and presence of omeprazole in concentrations of 0, 1, 3, 10, 30, 100 µmol/l was monitored versus time in four parallel experiments both with and without adding the platelet activating agents collagen (2 mg/ml) or adenosine diphosphate, ADP (200 µmol/l). Omeprazole, given as a bolus infusion of 80 mg over 30 min followed by a continuous infusion of 8 mg/h gives a peak plasma concentration of approximately 10 µmol/l and a steady state concentration of 2 µmol/l in healthy volunteers.

Omeprazole had no effect on platelet aggregation as seen from the maximum aggregation level , Figure 6, or lag phase, Table 7.

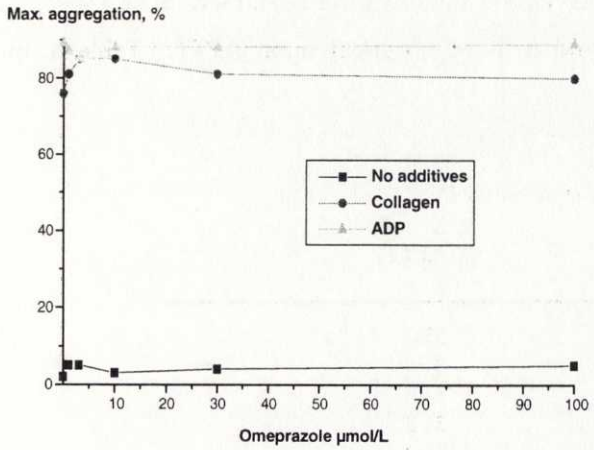


Figure 6. Effect of omeprazole on the maximum platelet aggregation in platelet rich plasma (all values within normal range).

Table. 7. Effect of omeprazole upon lag phase of collagen induced platelet aggregation (all values within normal range).

Omeprazole conc., µmol/l plasma	Lag phase sec.
0	45
1	45
3	45
10	45
30	50
100	44

2) Coagulation

The effect of various concentrations of omeprazole on activated partial thromboplastin time, APTT, was studied using a coagulometer. This is a standard method (*99*) measuring the time to plasma coagulation after adding

an APTT reagent and calcium chloride to a plasma sample. The experiment was performed with and without adding omeprazole (final concentrations of 1, 3, 10, 30, 75, 100 µmol/l) to the plasma sample.

The normal range, given by the manufacturer is 34.5 sec. (SD 2.4 sec.).

Omeprazole, was found to have no effect upon APTT, Table 8, in these concentrations.

Table 8. Effect of omeprazole on APTT

Omeprazole conc., µmol/l plasma	APTT, s
0	35.3
1	34.8
3	34.6
10	34.2
30	34.3
75	34.9
100	34.9

3) Bleeding time

Anaesthetized male Sprague-Dawley rats were used and the dorsal aspect of the tails were incised in a standard manner (*40*) whereupon bleeding time was measured from the moment of incision until the bleeding stopped. The tail incisions were made 10 min. before, 20 and 30 min. after the drug was administered. The study included 10 animals in each of two groups. One group was given vehicle only and the other group was given omeprazole in the vehicle. Omeprazole was given as a bolus i.v. infusion over 6 min. and in a dose of 100 µmol kg^{-1}. Plasma concentrations of omeprazole were measured at the end of the experiment.

The bleeding times was not influenced by omeprazole, Table 9. Plasma concentration of omeprazole 40 min. after start of i.v. infusion was 13.1 (2.1)

µmol/l, (mean (SD), which approximates the maximum plasma levels obtained after infusion of 80 mg over 30 min (approximately 10 µmol/l).

Table 9. Bleeding time, (min.), in the two groups of rats (n=2 x10). Values are mean (SD).

	Group 1 (Vehicle)	Group 2 (Ome+ veh.)
Incision 1 (10 min. before drug)	2.75(0.49)	2.83(0.67)
Incision 2 (20 min. after infusion start)	2.50(0.46)	2.75(0.42)
Incision 3 (30 min. after infusion start)	2.93(0.50)	2.87(0.81)

4) Fibrinolysis

In this experiment a modified euglobulin clot lysis test was used (*169*). Euglobulin was precipitated from human plasma, dissolved and mixed with a plasminogen activator (t-PA). Omeprazole was mixed with reptilase and added to the euglobulin/ (t-PA) mixture in a light absorbance microplate reader. Rapid coagulation took place and the subsequent lysis time (enhanced by adding t-PA) of the euglobulin clot was measured. The final omeprazole concentrations analyzed were 1 ,3, 30, 100µmol/l.

Omeprazole did not influence clot lysis time at these concentrations, Table 10.

Table 10. Euglobulin lysis time at different omeprazole concentrations. (All values within normal range).

Omeprazole conc., µmol/l	Euglobulin lysis time, min.
0	104
1	108
3	110
30	109
100	107

Summary of the effect upon hemostasis

The four pilot studies 1) to 4) above did not show that omeprazole had any effect on platelet aggregation, coagulation, bleeding time or fibrinolysis even at plasma levels up to 10 times maximum levels reached after therapeutic infusion of omeprazole. A reasonable assumption is therefore that the beneficial effects that omeprazole is seen to have in patients with peptic ulcer bleeding occur as a result of omeprazole's effect upon intragastric pH.

Risk factor analyses (Study IV, V, VI)

Rebleeding

From the risk analysis in study V we found that age above 60 years, shock at admission and smoking significantly increased the rebleeding risk. Age showed an OR of 1.03 (95% CI; 1.00 - 1.07) per year over 60 years, shock an OR of 4.52 (2.23 - 10.04) and smoking an OR of 1.74 (0.98 - 3.08). The prognostic importance of these factors is well recognized (*78*) and further substantiates the results from these trials.

We also found that gastric ulcers were associated with a significantly lower risk of rebleeding with an OR = 0.59 (0.36 - 0.98). The importance that ulcer localization has on rebleeding risk is an area of debate and results in the literature are inconsistent (*21, 78, 84*) .

Intake of NSAID/ASA significantly lowered the risk of rebleeding, OR = 0.53 (0.28 - 0.95). This finding can be difficult to comprehend but platelets have been reported to play a minor role in the hemostatic process in the gastric mucosa (*165*) which could explain why, at least, no negative effect upon rebleeding was seen. Again the literature is inconsistent, a recent Dutch report (*170*), showed an increased rebleeding rate for NSAID/ASA users (16.7%

versus 42.9%, p = 0.05) while others, (29) have found no difference with respect to rebleeding, 19% for non-users versus 20 % for users.

Short term mortality

In all studies (IV, V, VI) mortality was registered up to 30 days in all patients. Many deaths occurred outside the hospital shortly after discharge which emphasizes the importance of extending the length of follow-up beyond discharge date as well when data from patients admitted with a PUB are presented. Since most other studies have not specified the length of follow-up or just followed patients until discharge direct comparisons are difficult.
There was an almost linear increase in cumulated number of deaths over the first 30 days in both Study IV and study VI as can be seen in Figures 7 and 8. Both studies also clearly illustrate the high proportion of deaths during the second half of the first 30 days after admission.

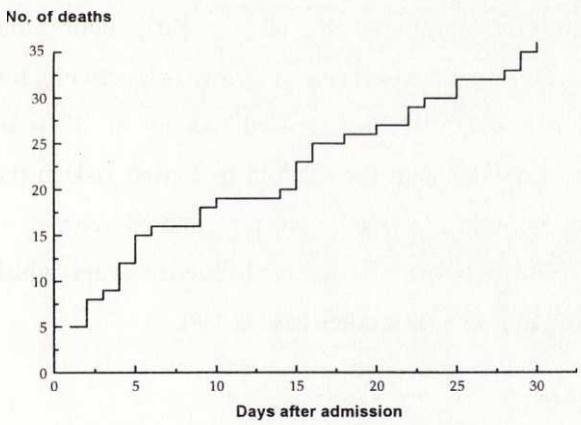


Figure 7. Cumulated number of deaths in Study IV (n=676) .

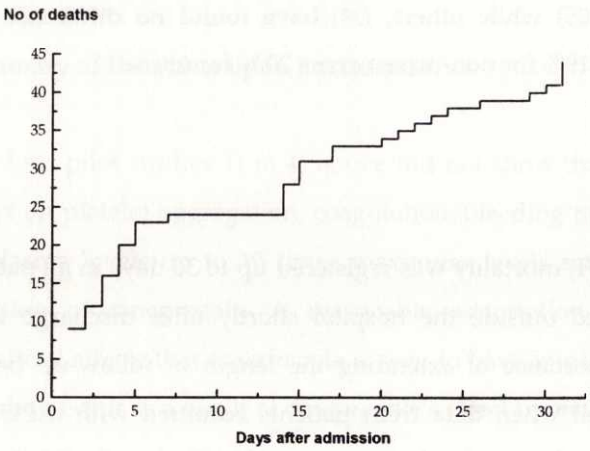


Figure 8. Cumulated number of deaths in Study VI (n=1020).

Age

In all three studies (IV, V and VI) patients over 60 years were found to have a significant increase in mortality compared to a 60 year old patient. Study IV and V showed, a 4.2 and 2.8-fold increased risk of dying, respectively, for a 75 year old patient and a 10.8 and 5.4-fold increased risk for an 85 year old. These figures compares very well with the 4.2-fold increased risk in the age interval 70 - 79 years and 6.2-fold increase between 80 and 89 years of age in Study VI. Our results thereby support the negative influence of age which has consistently been reported in previous studies (*20, 128, 159*).

Sex

In Study IV and V, including patients over 60 years, the variable female sex, indicated a lower mortality risk with an OR of 0.7 (0.3 - 2.0) and 0.6 (0.2 - 1.5) , respectively, thus indicating a non-significant risk reduction of 30 - 40%. In study VI, including patients over 30 years of age the contrary was found with

a 2 - fold increased risk for women. One explanation to this apparent discrepancy may be related to the different age cohorts included and the prognostic impact of female sex may thus be different in young compared to old patients.

Walt (*159*) included sex in his multivariate analysis of risk factors for death but did not list it among factors reported as having significant impact. The influence of sex upon outcome has also been analyzed in other studies, but not with a multivariate approach. These results must therefore be evaluated with caution since the outcome is easily influenced by confounding.

Ulcer site

No consistent pattern was seen regarding the prognostic importance of the ulcer site in studies IV, V and VI. Two of them indicated a 24% - 55% lower, but not significant, risk for gastric ulcers. Study IV showed a 25% higher risk in gastric ulcers, however, with a very wide 95% confidence interval why no firm conclusions can be drawn.

The age factor will distort the results if no proper allowance is made in the analysis since patients with gastric ulcers have a higher mean age than duodenal ulcers patients (*18, 19*). Walt corrected for age and found a numerical, but insignificant increased risk, 32%, for gastric ulcers.

NSAIDs

In Study IV and V, the variable NSAID intake also included ASA intake. Both ASA and non-ASA NSAIDs inhibit prostaglandin-dependent protective processes in the gastric mucosa and may cause ulceration via topical injurious and/or systematic effects (*100, 158*). Both groups of drugs also inhibit platelet aggregation, either irreversibly (ASA) or reversibly (non-ASA NSAIDs). It can thus be assumed that the prognostic influence should be similar for both substance groups at least if mediated through these mechanisms.

In Study V the OR for NSAID intake was 0.45 (0.16 - 1.26) thus indicating a risk reduction of 55% for mortality. It can be assumed that the data in this study reflect the true situation, since it is based upon a prospective collection of data, which was later verified by local study monitors after control of hospital records. In Study IV and VI, reporting a insignificant risk increase, (OR = 1.2 and RR = 2.0, respectively), the accuracy of these data may be comparatively lower. Since the 95% confidence intervals all, to some extent overlap no firm conclusions can be drawn. One possibility is that the latter studies more likely reflect a regular intake of higher doses while, in Study V, also lower and more irregular intake is reported. The possibility of differences in the risk impact of low doses and high doses should also be considered. These speculations need of course to be investigated in future studies but may offer a possible explanation to the confusing and contradicting findings in the literature. Jensen and co-workers (*80*) were unable to show any significant influence of NSAID/ASA intake on rebleeding and mortality in patients with PUB. Both variables showed, however, lower values among those taking NSAID/ASA. Others (*29*) have also reported numerically lower mortality among NSAID users, (2.6% versus 5.3%). Silverstein (*143*), in the ASGE, survey found a lower mortality both among ASA (13.6% versus 4.9%, $p < 0.001$) and NSAID users (6.2% versus 11.0%, n.s.) than in non-users.

In another study (*4*) a significantly higher mortality was reported a among NSAID users but it was also pointed out that these patients were older and had more concomitant diseases. A recent study (*170*), showed a numerically higher mortality (9.5% versus 4.2%,) among NSAID users but no correction for influence of age was done.

Blair (*14*) like others (*66*) have described that patients admitted with a PUB have a hypercoagulable state during the days subsequent to the bleeding and that thromboembolic complications are relatively common after ulcer bleedings (*14*). NSAIDs impair the platelet aggregation, and this may be the reason why NSAID intake may be of benefit in this particular respect.

The question whether NSAID intake may actually decrease short-term mortality after a PUB is not yet answered. Such an hypothesis can, however, be formulated to challenge investigators to carry out formal studies. Data from Walan and co-workers (*157*) and the recently emerging data from Hawkey and co-workers (*61*) ensures the safety of NSAID intake during concomitant omeprazole therapy for ulcer healing, which opens up the possibility for a well designed study.

Shock/Low systolic blood pressure

The prognostic value of hemorrhagic shock on admission was investigated in Study IV and V. In Study V the OR equaled 2.21 (95% CI; 0.71 to 6.82) indicating a pronounced effect compared with the OR of 1.1 (0.4 to 3.7) in Study IV. Again the accuracy of the data in Study V is higher and more likely to represent the true situation.

A systolic blood pressure below 100 mm Hg on admission indicates, as well as shock, a substantial blood loss and it is therefore likely to have the same impact on mortality as shock. This was also found to be true in Study V with a OR of 1.06 (1.01 - 1.11) for each mm below 100 mm Hg. This implies that if a patient has a systolic blood pressure of 80 mm Hg on admission the risk increases with a factor of 3.21 ($1.06^{20} = 3.21$)

Previous ulcer history

In Study IV, 38% patients reported a previous peptic ulcer (bleeding or non-bleeding), in Study V 47% (bleeding or non-bleeding) and in Study VI, 38% (23% non-bleeding and 15% bleeding). Corresponding figures from other studies are 17% and 19% in one study (*44*) and 22% and 10% in another (*135*).

In Study V and VI significant risk reductions were found for patients with an ulcer history with an OR of 0.26 (0.09 to 0.74) and a RR of 0.33 (0.14 to 0.83),

respectively. The retrospective Study IV, however, indicated no prognostic influence (OR of 1.0 (0.4 to 2.5)).

A few previous studies have reported lower mortality rates in patients with previous ulcer history but these findings have not attracted much interest (*43, 81, 139*). Branicki and co-workers (*20*) presented in a study of 701 patients with PUB a mortality of 1.8% among patients with previous ulcer history and a mortality of 6.9% ($p < 0.01$) among those without. Wara (*161*) reported that a history of dyspepsia was also associated with a better overall outcome after PUB.

There may be different explanations why PUB patients with previous ulcer history seem to have a lower case-fatality rate. Most patients with an ulcer history have an *H. pylori* infection and/or NSAID intake as the pathogenic factor. In contrast, in elderly patients admitted due to their first PUB, other pathogenic mechanisms may also be involved, for instance, impaired defense/repair mechanisms. Such impaired defense mechanisms may be a result of a severe general decline in health status and thus it may actually be the underlying condition and health deterioration that causes the ulcer and ultimately leads to death. This theory was also recently been presented by Hudson and co-workers (*74*). The bleeding ulcer in these patients could thus be looked upon more as an epi-phenomenon than a separate disease. A decline in health status may, for instance, be due to a silent myocardial infarction or an, as yet, undetected malignancy.

Based upon autopsy findings, ulcers seem to be a common and often undetected phenomena in terminal disease (*104, 106*) which support the theory that ulcers commonly develop during the terminal phase of a patients life.

Other explanations to the results must of course also be considered. These are, for instance, differences in preventive drug treatment, different treatment policies for an index and a recurrent bleeding, or a higher health awareness among patients with ulcer history.

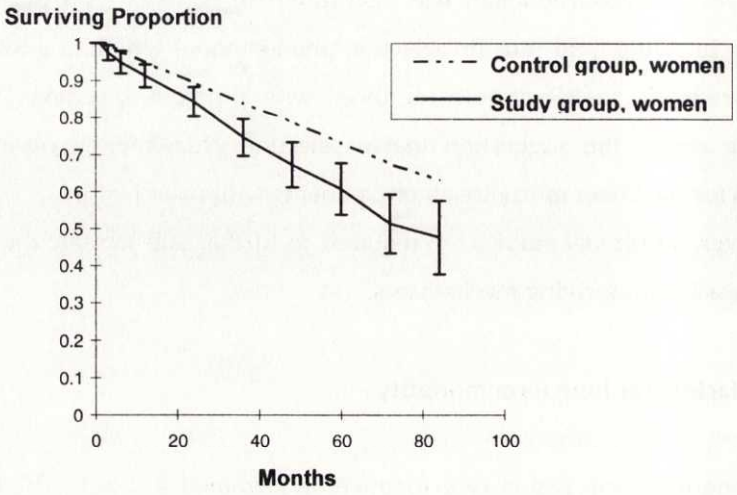
A selection phenomenon may also play a role. Previous *bleeding* episodes, during which the most fragile patients die and thereby selecting the healthier

ones to be exposed to the risk of a second bleeding,could have this effect. However, the risk reduction was also found in patients with ulcer history *without* bleeding (and thus no selection phenomenon) who had a RR of 0.38 compared with a RR of 0.27 for those with previous bleeding (VI). This finding rejects the suggestion that a selection phenomenon could be the reason for the lower mortality among patients with ulcer history.
However, additional studies are required to further substantiate the findings and possible underlying mechanisms.

Risk factors for long term mortality

The long-term survival curves for men and women in Study IV showed a very similar pattern.
Compared with their matched controls, women had a significantly higher risk of dying after the first 30 days of admission. Men showed a small and non-significant increase compared with their controls, Figure 9, a and b.
None of the analyzed factors in Study IV with the exception of age showed any significant association with long term survival despite the finding that women had a significantly increased mortality, adifference of approximately 15% after 5 years, compared with their controls. Whether this finding also applies to women with non bleeding ulcers is not clear.
The magnitude of this mortality difference, however, requires further research in order to find the cause of this increased long term mortality.

a)



b)

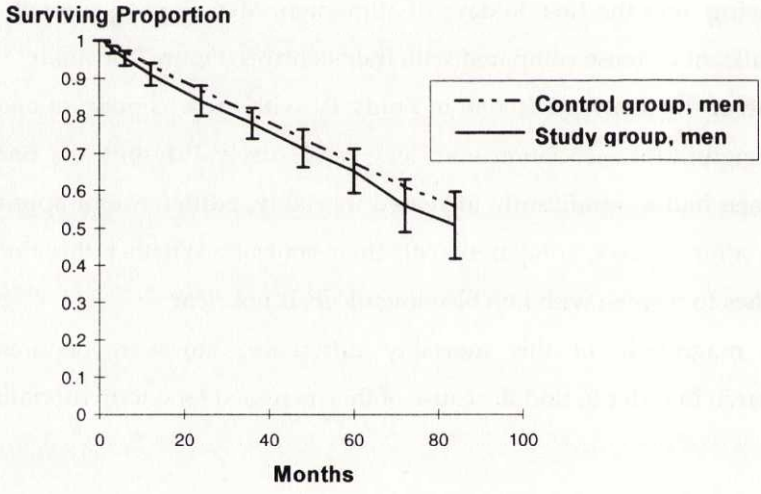


Figure 9, a and b. Surviving proportions (95% CI) among men and women in Study IV compared with their matched controls

A review of the causes of death in Study IV revealed that exsanguination or death due to other ulcer complications occurred only by way of exception and can not explain the increased mortality among PUB patients. The most common causes of death were, as expected in an elderly cohort, mainly cardiovascular events. The recently alleged association between *H. pylori* infection and cardiovascular morbidity/mortality is still an area with conflicting results (*112, 121, 148*) and it will be of great importance to study whether eradication of H. pylori not only prevents rebleedings (*79*) but may also have an impact on mortality in the long-term perspective.

SUMMARY AND CLINICAL CONSIDERATIONS

Peptic ulcer bleedings cause approximately 2500 - 3000 hospital admissions per year in Sweden and the proportion of these patients who are over 60 years is steadily increasing. The primary objective for the initial treatment at the hospital is to achieve rapid hemostasis in order to avoid exsanguination and ultimately death. Endoscopic intervention therapy has gained an increasing popularity and is, in the hands of a skilled endoscopist, highly effective in stopping the index bleeding and secondly it reduces the risk of rebleeding by 30-40%. Still, we have to realize that approximately 20 % of the patients will experience a rebleeding necessitating repeated endoscopic treatment or surgery.

The majority of the admitted patients will not, however, be treated primarily at a hospital with the resources and competence to offer endoscopic hemostatic therapy 24 hours a day 365 days a year. This situation is not likely to change during the coming years. Based on these considerations, there is an apparent need for an effective treatment that can be given to all PUB patients without the need for special equipment or resources. This would allow the patients to stabilize before the subsequent endoscopic treatment or be offered as an effective therapy allowing definitive hemostasis in those instances where a trained endoscopist is not immediately available.

The present study has evaluated the effect of a primed infusion of omeprazole, 80 mg/h + 8 mg/h in high risk patients both after and without endoscopic treatment and we have found that this treatment regimen, significantly improved outcome, reduced the need for surgery by 84% - 87%, and the need for further endoscopic treatment by 60 - 69%.

We can also conclude that infusion of omeprazole administered according to the current regimen exerts an additional effect to that of endoscopic treatment and it also seems to have the capacity to induce hemostasis in ulcers with an ongoing oozing bleeding.

The current results clearly indicate the potential of omeprazole infusion 80 mg + 8 mg/h in the immediate clinical management of patients admitted due to a PUB. It is interesting to note that a similar treatment algorithm has been presented for bleeding complications in patients with portal hypertension (*124*). In this situation resuscitation of the patient and nasogastric intubation coincides with the start of drug therapy to arrest the bleeding, which allows time to prepare for definitive endoscopic therapy.

In the clinical studies we consistently infused a dose of 80 mg + 8 mg/h. It can be argued that the continuous infusion dose of omeprazole could be decreased and the results from the dose-finding study (I) could not exclude this possibility. We can, however, claim that the very strict criteria, to have a stable intragastric pH over 5.4, was essentially fulfilled with the current dose.

The present study also added important data on the overall mortality pattern after a PUB. The risk of a fatal outcome remains high *even though* a durable hemostasis has been achieved and furthermore, the risk seem to be elevated during the entire first month after the bleeding event and not only confined to the hospitalization period. The cause of death was in most cases cardiovascular or cerebrovascular events.

In Sweden, we can estimate that the annual death rate due to a PUB is 200 - 300. In our analysis of risk factors for mortality we have found that the risk was considerably higher in patients being over 60 years of age or in shock on admission. In addition, patients who experienced their first ulcer event had a higher risk.

Traditionally, clinical research in this field has focused on reducing the rate of rebleeding with the belief that this would ultimately reduce mortality as well. However, despite significant reductions in variables related to rebleeding we have not been able to show any corresponding reductions in mortality. Thus, it may be time to challenge the assumed causal relationship that an effective prevention of rebleedings leads, by necessity, to a reduction in mortality. Future research in this field must seriously consider other possibilities of reducing mortality. The finding, in one of the studies, of a lower day 30

mortality in NSAID users raises, together with the fact that patients with a PUB have a hypercoagulable blood status and that thromboembolic events are the most common reason for death, a new and intriguing question. Does thromboembolic prevention measures, for instance with low dose ASA, prevent late cardiovascular complications after a PUB which may eventually lead to death? As early as in 1989, Walan and co-workers (*157*) demonstrated that omeprazole was equally effective in healing gastric ulcers regardless of concomitant ASA/NSAID intake. Recently data emerging from Hawkey and co-workers (*61*) have shown that omeprazole treatment leads to high healing rates of NSAID induced lesions, even if the NSAID treatment is continued. This indicate a safe basis for a potential study design evaluating, for instance, low dose ASA (in combination with omeprazole) as a preventive measure of cardiovascular events during the first month after a PUB.

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