Treatment and prognosis in Peptic Ulcer Bleeding

Stig Borbjerg Laursen

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Tutor(s): Jane Møller Hansen & Ove B Schaffalitzky de Muckadell.

Official opponents: Pål Wara, Torben Jørgensen & Claus Hovendal.

Correspondence: Department of Medical Gastroenterology, Odense University Hospital, Søndre Boulevar 29, 5000 Odense C, Denmark.

E-mail: Stig.Laursen@rsyd.dk

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THE ORIGINAL PAPERS ARE

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INTRODUCTION

Every year around 2000 Danes are diagnosed with peptic ulcer bleeding (PUB) [1]. Even though the disease has been known for centuries, and the treatment has undergone innumerable advancements, it remains associated with high mortality. An American study of 173 patients admitted with bleeding duodenal ulcers in the period 1936-48 identified a 30-day mortality of 8% [2]. Today, more than 60 years later, the 30-day mortality is around 11% [1].

At first sight, the enhanced understanding of the pathogenesis of PUB together with the implementation of advanced endoscopic therapy and effective acid-suppressive treatments only seem to have had limited effect on the outcome. One must, however, take the major changes in patients' characteristics into consideration. In the aforementioned study the majority of patients were younger than 50 years and all of the patients dying within 30 days died of bleeding-related causes. Today, the average age of PUB-patients is 73 years [1] and mortality is in the majority of cases caused by concomitant disease. These changes are challenging and places ever greater demands on the treatment, if the outcome is to be improved. The course of PUB has been further complicated by studies indicating that it is associated with excess long-term mortality.

This thesis evaluates three strategies to improve the outcome of patients presenting with PUB: 1. use of risk scoring systems in the assessment of patients, 2. prevention of rebleeding in high-risk patients by improved hemostatic techniques, and 3. identification of factors predicting fatality, underlying causes of death, and investigation of a possible change in long-term mortality.

BACKGROUND

A. HISTORICAL OVERVIEW

Discovery of peptic ulcer disease and peptic ulcer bleeding

Diocles of Carystus made the first description of a patient presenting with symptoms consistent with peptic ulcer bleeding in Athens in the 4th century BC [3]. Nevertheless, it took until 1586 before Marcellus Donatus of Mantua diagnosed the first peptic ulcer. He performed an autopsy on Camillus Jacinus, who died after an acute illness with excessive vomiting. Marcellus Donatus described how "in the lower part of the stomach at the pylorus or lower orifice the inner coating was ulcerated, and we had no doubt that this had been the cause of his malady" [4-5]. The first duodenal ulcer was later described by Johannes von Murault in 1688 [6]. In 1830 a young man was admitted to a hospital in Paris because of heamatemesis and signs of circulatory collaps. During the admission he developed severe rebleeding and died. At autopsy a gastric ulcer with a protruding artery was found at the lesser curvature. This is the first well-described case of verified peptic ulcer bleeding [7].

Medical treatment in the early days

The first treatment used in peptic ulcer disease was presumably bismuth salts. Bismuth salts have been used for treatment of abdominal pains and dyspepsia since the 18th century [8]. From the first half of the 19th century the main focus was directed towards different regimes of oral intake combined with antacids. It began when Abercrombie recommended a diet consisting of milk and farinaceous foods in 1828 [9]. The discovery of presence of hydrogen chloride in the gastric juice by Prout in 1824 [10] paved the way for treatment with antacidas (sodium bicarbonate, magnesium oxide, and calcium carbonate) in the beginning of the 1830's [11]. The main belief in the period 1830-1870 was that a combination of diets and antacidas could reduce the load of damaging factors on the gastric mucosa. These factors consisted of irritants in food and beverage, gastric acid, and mechanical distress due to rough food [12].

The observation of changes in gastric motility and frequent presence of gastric retention lead to a new regime of treatment in 1870's. In order to prevent these conditions, which were consid-

ered as contributors to mucosal damage, the key elements in treatment of peptic ulcer bleeding became fasting and rest. Absolute fast for minimum three to four days after symptoms of bleeding had ceased, combined with rectal infusion of nutrition and bed rest for several weeks, were strongly recommended for decades [13].

In the beginning of the 1900's there was an increased focus on the malnutritive state caused by the recommended period of fasting. This lead to the presentation of "The Sippy regimen" in 1915 [14]. The Sippy regimen consisted of physical inactivity, frequent feeding, treatment with alkalines (Sippy powder: bismuth subcarbonate, sodium bicarbonate, magnesium oxide) during daytime, and gastric aspiration at night. The effect of feeding was underlined by Meulengracht, who in 1933 demonstrated a 75% relative reduction in mortality achieved by treatment with antacids and early feeding starting the day after admission [15].

Development of surgical treatment

Gastric surgery developed slowly alongside the aforementioned fasting regimes. The first recorded gastric surgery – a gastrostomy – was performed in 1849 [4]. Billroth performed the first successful partial gastrectomy in 1881. In these days gastric surgery was mainly used in treatment of obstructing cancer [16]. However, in 1882 Czerny, a member of Billroth's department, performed the first local excision of a gastric ulcer [17]. In 1887 Mikulicz performed the first recorded successful operation for hematemesis. About five years later the first successful suture of a perforated ulcer was performed in a private house, taking three hours for the operation [4]. In the end of the 19th century, treatment of peptic ulcer bleeding was almost exclusively medical, and surgery was mainly used in relief of stenosis [18].

At the beginning of the 20th century the surgical techniques were well developed and gastric surgery could be performed with acceptable mortality. In 1905 the Mayo Clinic reported a series of 500 cases of surgically treated gastric or duodenal ulcers [4]. However, the general opinion concerning surgery in patients with UGIH were still as expressed by Mikulicz: "it can never be prophesied with certainty in any individual case of haemorrhage is really of sufficient danger to justify surgical interference, so that one should always wait and see whether the bleeding will not be arrested by medical treatment" [19].

Various types of gastric resections were used in the first decades of the 20th century. It was the general belief, that resection of 70% of the stomach was needed in order to achieve an acceptable result [16]. These large gastric resections were often complicated by a long-lasting postgastrectomy syndrome.

The importance of the vagal nerve in gastric acid secretion was shown by Talma, who in 1890 experimentally produced an ulcer by stimulating the vagal nerve [17]. This lead to the use of truncal vagotomy, a procedure which became increasingly popular in the mid 1940'ies [20]. Performance of vagotomy did often result in problems with gastric emptying. This was solved by combining the truncal vagotomi with a gastric drainage procedure. In this manner combined truncal vagotomy and pyloroplasty had become an attractive alternative to gastrectomy in the late 1950'ies [19].

In order to avoid side effects because of extragastric vagal denervation truncal vagotomy was later replaced by selective gastric vagotomy. Performance of selective gastric vagotomy did also lead to altered gastric motility and delayed gastric emptying requiring supplementary drainage. Both types of vagotomies were associated with a noticeable rate of recurring ulcers. This was avoided by combining vagotomy and antrectomy, by which the gastrin producing cells in the antrum were removed. Combined vagotomy and antrectomy reduced the recurrence rate to less than 1% [21].

A considerable proportion of the patients undergoing these procedures developed postoperative meal-related complaints. The desire to maintain a normal pyloric function led Amdrup, among others, to the development of the parietal cell vagotomy where only the part of the stomach containing parietal cells were vagotomised [22]. However, parietal cell vagotomy was also associated with a considerable rate of recurring ulcers so the old combination of vagotomy and antrectomy became the recommended operation of choice for duodenal ulcers in the 1970's and 1980's [23]. The focus on these different vagotomy operations decreased after the discovery of the modern medical acid-suppresive treatments.

Modern acid-suppressive treatments

In the 1970's discovery of the stimulatory effect of histamine on the acid secretion from the parietal cells lead to invention of the H2-histamin receptor antagonists. Cimetidine was introduced in 1975 as the first successful H2-antagonist without unacceptable sideeffects [24]. As with antacids, H2-antagonist were associated with a healing rate of almost 75% of duodenal ulcers after four weeks of treatment [25]. The healing rate of gastric ulcers were for both drugs somewhat lower. Around 50% of gastric ulcers treated with H2-antagonist healed within 4-8 weeks [26]. One of the great advantages with the introduction of the H2-antagonists were the administration, as a single dose H2-antagonist at night replaced regimens where antacids often was taken seven times a day.

The 1970's also formed the setting for identification of the proton pump (H+/K+-ATPase) in the membrane of the parietal cells and its role in acid secretion [27]. This was followed by discovery of the first proton pump inhibitor (PPI), omeprazole, in 1979 [28]. Omeprazole was launched in Europe in 1988. Omeprazole was soon shown to be superior to the H2-antagonists in healing rate of non-bleeding ulcers [29]. The healing rate of duodenal and gastric ulcers after four weeks treatment with omeprazole is around 93% and 85% respectively [30]. Later, treatment with PPI's were also found to be associated with lower rate of persistent ulcer bleeding, recurrent bleeding, and need for surgical haemostasis compared to treatment with H2-antagonists [31,32]. Today, treatment with intravenously infusion of proton pump inhibitors is recommended for endoscopically treated ulcers with active bleeding, or a non-bleeding visible vessel, as this seems to reduce mortality [32]. Proton pump inhibitors remain the most potent acid suppressors available for clinical use.

Helicobacter pylori

Although the presence of bacteria in the margin of gastric ulcers was described as early as 1875 [33], and presence of Helicobacters was demonstrated in the stomach of dogs in 1892 [6], it was not until 1981 that Helicobacter Pylori was isolated and cultered by Warren and Marshall [34-35]. A year later Marshall discovered the association between peptic ulcer disease and presence of Helicobacter pylori. Marshall afterwards proved the pathogenicity of Helicobacter Pylori, and relation to gastric inflammation, by ingestion of an inoculum of Helicobacter Pylori

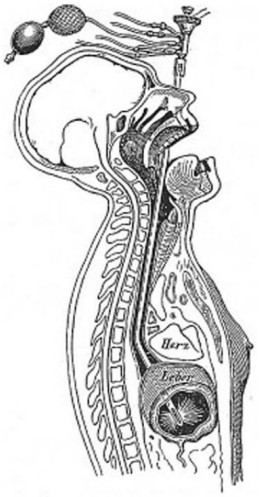
[33]. Several Helicobacter Pylori-eradication-regimens were tested in the late 1980'ies, but satisfactory efficiency was first achieved when Bazzoli presented the PPI-based triple therapy in 1994 [36-37].

The frequency of peptic ulcer bleeding developed on the basis of a Helicobacter Pylori infection seems to have fallen through the last decades [38]. Today, development of PUB seems to be related to infection with Helicobacter Pylori in about 34% of cases [38].

Endoscopic examinations and therapies

Johann Anton von Mikulicz-Radecki, an assistant and student at Billroth's department, was the first to visualize the gastric mucosa and pyloric region using a gastroscope in 1881 (Figure 1) [39].

Figure 1. Original drawing of the first gastroscope, 1881 [40]



Gastroskop von Mikulicz u. Leiter.

The technical development of the gastroscope took mainly place in Germany as the German optical factories were superior in construction of satisfactory optical systems [41]. Production of proper endoscopes began in 1910. The risk of oesophageal perforation decreased when the semiflexible endoscope was introduced in 1932, which at the same time resulted in implementation of clinical gastroscopy in numerous centres worldwide [39]. At that time gastroscopy was mainly used to diagnose gastritis. Therefore, the use of gastroscopy was almost made redundant when the method for gastric suction biopsy was described in 1949 [42]. In the 1950'ies the development of clinical gastroscopy instead focused on advanced gastric photography and aimed biopsies. The optical system was revolutionized when the fully flexible fiber-endoscope was introduced in 1958 [39]. From around 1950 the Japanese developed the gastro-camera that was an intragastric camera that took serial of photographs of the gastric mucosa in high quality [43]. As the transmitting tube only carried the cables for the camera it was thinner and more flexible than the gastroscope. The interpretation of pictures from the early gastro-cameras was, however, often complicated as the gastro-cameras were operated blindly. This dilemma was solved by development of the combined gastric camera and fiber-optic endoscope in 1962 [39]. Although reports of fiber-endoscopy of the duodenum was published from the early 1960'ies [44] it was not until the beginning of the 1970'ies that duodenoscopy became routinely used.

Endoscopic treatment of bleeding lesions in the gastrointestinal tract began in the mid 1970'ies. Injection therapy in peptic ulcer bleeding was introduced in 1976 by Soehendra, who demonstrated that hemostasis could be achieved by submucous injection of 3-5ml Polidocanol (1.5%) around the bleeding site [45]. Later, in 1985, he modified the technique to injection of 5-10 mL of adrenaline (1:10,000) in order to achieve hemostasis followed by injection of 5 mL Polidocanol (1%) in order to obliterate the bleeding vessel [46]. Injection therapy with diluted adrenaline is today the most commonly used method for achieving endoscopic hemostasis in PUB.

The heater probe was presented by Protell and colleagues in a canine experiment in 1978 [47]. They demonstrated how a 3.2mm heater probe could be passed through an endoscope and used successfully to achieve hemostasis in 25 out of 25 dogs with massive bleeding from gastric ulcers. The advantage of the heater probe, compared to injection of diluted adrenaline, is the ability to achieve coaptive coagulation [48].

The use of metallic clips to achieve endoscopic hemostasis was described in a Japanese study already in 1975 [49]. The early clips were, however, very complicated to applicate and relatively inefficient in keeping hemostasis. In the mid-1980'ies the hemoclip was improved in term of easier application and better grasping ability [50].

Today, use of combined therapy (two modalities) with injection of diluted adrenaline, treatment with heater probe or application of clips is recommended in treatment of peptic ulcers with active bleeding, or a visible non-bleeding vessel [51]. Compared to monotherapy with injection of diluted adrenaline additional treatment with a secondary form of therapy will reduce the rate of rebleeding, the need of surgical hemostasis, and the mortality [52]. Likewise, a meta-analysis has indicated that monotherapy with heater probe is associated with a higher rate of rebleeding compared to combined endoscopic therapy [53]. Monotherapy with application of hemoclips does, however, seem to be equally efficient to combined therapy [53-54].

Nowadays it is possible to achieve endoscopic haemostasis in 94% of patients with peptic ulcer bleeding requiring endoscopic therapy [1]. Performance of transcatheter arterial embolization, or surgical hemostasis, is efficient in the few cases not responding to endoscopic treatment. Implementations of effective acid-suppressive treatments, and helicobacter eradication, have made it possible to treat the vast majority of peptic ulcers successfully. In spite of all these advancements, the mortality remains at unchanged levels.

B. RISK SCORING SYSTEMS IN UGIH

Use of risk scoring systems in the assessment of patients has become increasingly popular over the last decades. Several risk scoring systems have been developed for the assessment of patients with upper gastrointestinal haemorrhage (UGIH) [55-62] with some difference in complexity and outcome of interest. None of these are used routinely in Denmark.

Implementation of a risk scoring system could be beneficial in several ways. Use of scoring systems prior to diagnostic endoscopy might improve triage of patients presenting with UGIH. Ideally, this could help in differentiation between patients with serious bleedings requiring admission for haemostatic therapy and low-risk patients who could be safely managed as outpatients. Low-risk patients suitable for early discharge, and potential outpatient management, include patients with minor bleeding

from oesophagitis or Mallory-Weis tears, or patients with normal findings at upper endoscopy. Early discharge is not possible in all of these patients, e.g. due to presence of concomitant disease. Nevertheless, a study from the United Kingdom concluded that 15% of patients presenting with UGIH could be identified and safely treated as outpatients using a risk scoring system [63]. The clinical gain is demonstrated by a significant reduction in the proportion of patients being admitted, as well as length of hospital admission, through use of a scoring system [63-64].

Therefore, use of risk scoring systems in the assessment of patients presenting with UGIH could lead to improved triage as well as reduced resource utilization. The efficiency and safety associated with use of these risk scoring systems in a Danish population has, however, been questioned because of considerable inter-country variation in patients characteristics and proportion of patients handled in the primary health care sector [65]. Thus, external validation is needed prior to implementation of these risk scoring systems in Denmark.

The following section serves as an overview of the risk scoring systems used later in the present thesis including a description of the underlying evidence.

Baylor bleeding score (BBS)

In 1993 Saeed and colleagues published a randomized study comparing the efficacy and safety of endoscopic ethanol injection with heater probe treatment in the management of non-variceal UGIH [55]. In this study the authors presented a scoring system developed to predict patients in high risk of rebleeding. The system was derived on data from 69 patients using logistic regression analysis. All of these patients had major UGIH defined as bleeding associated with syncope, arterial hypotension (systolic blood pressure < 100 mmHg), or orthostatic changes in heart rate (> 20 beats/min) and blood pressure (> 20 mmHg). Included sources of bleeding were peptic ulcers (Forrest I-IIb [66]) and in a few cases Mallory-Weiss tears with active bleeding or a visible vessel. All patients were treated with therapeutic endoscopy. The overall rate of rebleeding was 12%.

The scoring system was divided into three parts: 1) A pre-endoscopy score based on age and number and severity of concurrent diseases, 2) an endoscopy score based on site and stigmata of bleeding, and 3) a post-endoscopy score defined as the sum of the pre-endoscopy and endoscopy score (Figure 2).

Figure 2. Baylor bleeding score

Assigned score	Pre-endoscopy Score[a]			Endoscopy Score[b]		Post-endoscopy score[c]
	Age (yrs)	No. of illnesses	Severity of illnesses	Site of bleeding	Stigmata of bleeding	
0	<30	0				
1	30-49	1 or 2			Clot	
2	50-59					
3	60-69				Visible vessel	
4		3 or 4	Chronic[d]	Posterior		
5	≥70	> 5	Acute[e]	wall bulb	Active bleeding	

[a]Pre-endoscopy score: sum of the scores for age and the number and severity of concurrent illnesses
[b]Endoscopy score: sum of the scores for site and stigmata of haemorrhage
[c]Post-endoscopy score: sum of the pre-endoscopy and endoscopy score
[d]Chronic: presence of a concurrent chronic life-threatening illness
[e]Acute: presence of a concurrent acute life-threatening illness

Using receiver operating characteristic (ROC) curves the authors found that the pre-endoscopy and post-endoscopy scores had favourable discriminative abilities for the prediction of rebleeding. The optimum cut off values were ≥ 6 for the pre-endoscopy score and ≥ 11 for the post-endoscopy score. At these cut off values the pre-endoscopy score had a sensitivity of 100% and a specificity of almost 75%, and the post-endoscopy score had a sensitivity of 100% and a specificity of 79%.

Two years later the same authors presented a prospective validation of the BBS in 45 patients with major ulcer bleeding [67]. Major ulcer bleeding was defined as bleeding from Forrest I-IIb ulcers combined with the previously described symptoms of major bleeding. Cases with ulcer bleeding resistant to endoscopic therapy were excluded. Patients were stratified into low- and high-risk of rebleeding based on the cut off values identified in the original paper. Accordingly, patients with a pre-endoscopy score ≤ 5 and a post-endoscopy score ≤ 10 were categorized as being in low risk of rebleeding. Forty-two percent of patients were classified as being in low risk of rebleeding. None of these patients rebled. In comparison, the rate of rebleeding was 31% in patients classified as high-risk. The difference was within limits of statistical significance. Additionally, there was a tendency towards lower rate of surgical hemostasis (0 versus 3%) and mortality (0 versus 12%) among patients classified as low-risk. The authors concluded that the BBS accurately identifies patients at risk for rebleeding after successful endoscopic haemostasis.

Rockall score (RS)

In 1996 Rockall and colleagues presented a study on risk factors for mortality in upper gastrointestinal haemorrhage [57]. The study was designed as a prospective multicenter study and conducted as part of a national audit in four health regions in England. In the first part of the study the outcome of 4185 cases with UGIH was included. Findings at endoscopy, or surgery, were present in 2956 cases. Overall mortality was 14%. The relative importance of factors associated with mortality was analyzed using multiple logistic regression analyses. The identified risk factors were used in development of the Rockall score; a scoring system that categorised patients by risk of mortality.

The scoring system was divided into two parts: 1. a pre-endoscopy score based on age, signs of shock (presence of tachycardia or arterial hypotension), and categorized level of comorbidity; and 2. a post-endoscopy score that also included endoscopic diagnosis and stigmata of recent bleeding (Figure 3). The pre-endoscopy score is also known as the clinical Rockall score or the admission Rockall score. The post-endoscopy score is often referred to as the complete Rockall score or the full Rockall score.

Figure 3. Rockall score

Assigned score	Age (yrs)	Shock	Comorbidity	Diagnosis	Major SRH
0	< 60	Systolic BP ≥ 100 & pulse < 100	No major comorbidity	MW-tear, no lesion identified, and no SRH	None or dark spot only
1	60-79	Systolic BP ≥ 100 & pulse ≥ 100		All other diagnoses	
2	≥ 80	Systolic BP < 100	Cardiac failure, ischemic heart diease, any major comorbidity	Malignancy of upper GI-tract	Blood in upper GI-tract, adherent clot, visible or spuring vessel
3			Renal failure, liver failure, disseminated malignancy		

Admission score: sum of age, shock, and comorbidity
Full score: sum of age, shock, comorbidity, diagnosis, and major SRH
BP: Blood pressure (measured in mmHg)
GI: Gastrointestinal
MW-tear: Mallory-Weiss tear
SRH: Signs of recent haemorrhage
Yrs: Years

The authors observed that mortality increased stepwise as the admission or full Rockall score increased. They also found increasing rate of rebleeding at increasing level of the full Rockall score. Estimation of the discriminative ability of the Rockall score using ROC-curves was not presented by the authors.

The second part of the study served as a validation study of the Rockall score. A total of 1625 patients were prospectively included. Diagnostic endoscopy, or surgery, was performed in 1190 of these patients. There were no differences between the predicted outcomes, based upon the observed outcomes by risk score in the first part of the study, and observed outcomes in the validation sample in neither admission nor complete Rockall score.

In both cohorts a full Rockall score ≤ 2 was associated with a rate of rebleeding less than 5% and mortality below 1%. The authors concluded that the Rockall score can be used to categorise patients by risk of rebleeding or mortality.

Inspired by Longstreth and Feitelberg, who instituted outpatient management of UGIH in selected cases [68], Rockall and coworkers evaluated the Rockall scores ability to identify low-risk patients [69]. Low-risk patients were defined as patients in negligible risk of further bleeding or death, and for whom early discharge or outpatient management would be possible without adverse effects on standards of care. The study was based on partly the same data as used in derivation of the Rockall score (n=2531). The authors found that patients with a complete Rockall score ≤ 2 (n=744; 29.4%) had a low rate of rebleeding (4.3%) and negligible mortality (0.1%). Thus, use of the complete Rockall score seamed efficient in identification of low-risk patients suitable for early discharge or outpatient management. It was concluded that use of early endoscopy combined with the Rockall score could lead to substantial resource savings through early discharge or outpatient care of these patients.

Cedars-Sinai Medical Center predictive index (CSMCPI)

The CSMCPI was developed as a guideline for determination of the appropriate length of stay (LOS) for patients admitted with UGIH [58]. The components of the CSMCPI were independent predictors of outcome identified through a structural review of the literature.

The guideline scoring system was divided into four parts: 1. findings at upper endoscopy, 2. time from onset of symptoms to admission, 3. gradation of haemodynamics, and 4. number of comorbidities. The total score was calculated as the sum of these sub scores (Figure 4).

Figure 4. Cedars-Sinai Medical Center predictive index

Assigned score	EGD findings[a]	Time[b]	Haemodynamics	Comorbidities
0	PUD (no SRH) MW-tear (NB) Erosive DS (no SRH) NL	> 48 hours	Stable	≤ 1
1	PUD (spot/clot) Erosive DS (SRH) Angiodysplasia	< 48 hours	Intermediate	2
2	PUD (VVNB/SRH)	In hospital	Unstable	3
3				≥ 4
4	Persistent UGIH Varices UGI CA			

[a]Assigned score for endoscopic findings was reduced by 1 point if effective endoscopic therapy was applied (not applicable to varices or cancer)
[b]Time from onset of symptoms to hospitalization
DS: Disease
EGD: Esophagogastroduodenoscopy
M-W Tear: Mallory-Weiss tear
NB: Non-bleeding
NL: Normal findings
PUD: Peptic ulcer disease
SRH: Signs of recent haemorrhage
UGI CA: Upper gastrointestinal cancer
UGIH: Upper gastrointestinal haemorrhage
VVNB: Visible vessel, non-bleeding

In the presentation of the guideline the author's stated that gradation of haemodynamics was based on vital signs, hematocrit, type of symptoms, and nasogastric tube aspirate [58]. Apparently this was done using an adapted version of the recommendations from a national American Society for Gastrointestinal Endoscopy (ASGE) survey on UGIH from 1981 [70]. The exact criteria used are, however, unclear.

Patients with a CSMCPI lower than three were considered suitable for discharge within 24 hours. In cases with a CSMCPI of three or higher continuation of hospital-based care was recommended. In these patients the index was re-evaluated after 24-72 hours, depending on findings at endoscopy. Patients scoring four points in the endoscopy-part were not re-evaluated, as early discharge was not considered safe in these patients.

In order to validate the performance of the CSMCPI with respect to safety and efficacy the authors performed a retrospective study of 500 patients admitted with UGIH [58]. In this study the time of discharge was compared with the recommendations according to the CSMCPI. Additionally, occurrence of complications for the remainder of the inpatient stay, after the patients were evaluated as low-risk according to CSMCPI, was registered.

At the initial assessment 126 (25%) out of the 500 patients were classified as low-risk, and at the final assessment 349 (70%)

were classified as low-risk. Complications occurred in two patients (0.6%) classified as low-risk. Use of the CSMCPI was associated with a reduced time of admission in 79% of all low-risk cases with a mean potential reduction of 2.1 days.

The authors concluded that use of the CSMCPI in determination of LOS was safe and associated with substantial cost savings.

The following year Hay and colleagues validated the CSMCPI in a prospective setting [64]. The study was designed as a prospective, controlled time-series trial with an alternating month design where the guideline only was available every other month. Upper endoscopy was not obligatory. Findings at endoscopy were assumed to be low-risk 72 hours after last evidence of bleeding in patients without cancer or chronic liver disease. Only patients who achieved low-risk status within seven days from time of admission were included.

In the inclusion period 209 out of 299 (70%) patients met the criteria for low-risk status during admission. Mean age was 64.5 years. Endoscopy was performed in 97.1%. The control group and intervention group were similar in most demographic factors although there seemed to be a higher degree of comorbidity among patients in the control group. There were no differences in 30-day mortality (overall: 1.4%), rate of rebleeding (overall: 4.6%), or rate of readmission within 30 days (overall: 8.1%) between the groups. There was no difference in patients self-reported satisfaction. The mean LOS was, however, significantly shorter in the intervention group (2.9 versus 4.6 days; p <0.001) with a mean reduction of 1.7 days. The number of follow-up physician visits within 30 days was not increased in the intervention group.

The authors concluded that early discharge of patients defined as low-risk according to the CSMCPI was safe, satisfying for patients, and associated with reduced resource utilization.

Glasgow Blatchford score (GBS)

In 1997 Blatchford and co-workers published a prospective multicenter study of the epidemiology and mortality of UGIH in the west of Scotland [71]. A total of 1882 patients were included of which the majority underwent endoscopy. The overall rate of mortality was 8.1%.

Data from 1748 of these patients were used to identify factors associated with need of hospital-based intervention using multiple logistic regression analyses [59]. Patients were defined as needing hospital-based intervention if they received blood transfusions, underwent endoscopic or surgical intervention in order to control bleeding, or if they had undergone no intervention but had died, rebled, or had a substantial fall in B-haemoglobin after admission. The identified factors were weighted according to level of associated risk, and used in construction of the Glasgow Blatchford score (Figure 5).

Figure 5. Glasgow Blatchford score

	Assigned score
Blood urea (mmol/L)	
6.5-7.9	2
8.0-9.9	3
10.0-25.0	4
>25.0	6
Hemoglobin for men (g/L)	
120-129	1
100-119	3
<100	6
Hemoglobin for women (g/L)	
100-119	1
<100	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Other markers	
Pulse ≥ 100/min	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease[a]	2
Cardiac failure[b]	2

[a]Known history, or clinical and laboratory evidence, of chronic or acute liver disease
[b]Known history, or clinical and echocardiographic evidence, of cardiac failure

In 2000 Blatchford and colleagues prospectively validated the GBS in a group of 197 patients admitted with UGIH [59]. The performance of the GBS in predicting need of hospital-based intervention was compared to the Rockall score. Using ROC-curve analyses the GBS was found to have a significantly better discriminative ability for the prediction of need of intervention than either of the Rockall scores. Patients with a GBS=0 seemed to have a very low risk of needing intervention (0.5%). Based on this, the ability of the GBS to identify patients with low-risk UGIH suitable for outpatient management seemed encouraging.

Stanley and co-workers examined the GBS and Rockall score in this context in a prospective multicenter evaluation of 676 patients presenting with UGIH [46]. Sixteen percent of patients (n=105) had a GBS=0. None of these needed any intervention or died during admission. By contrast one death, 21 endoscopic or surgical interventions, and 23 transfusions were recorded in patients with an admission Rockall score of 0 (17%).

In the second part of the study the authors validated use of GBS low-risk criteria (GBS=0) in identifying patients suitable for outpatient management. Patients with a GBS of zero were not admitted unless necessary for other reasons. A total of 491 consecutive patients presenting with UGIH were prospectively assessed. Twenty-two percent of patients (n=123) were classified as low-risk. Outpatient management was possible in 68% of these cases. Only 40% (n=23) of low-risk patients offered outpatient endoscopy attended for the procedure. Outpatient endoscopy did not reveal any findings requiring intervention. None of the identified low-risk patients needed any intervention, or died, as a consequence of UGIH. However, one low-risk patient died during follow-up as a result of disseminated non-upper gastrointestinal malignancy two months after endoscopy had indicated gastritis only. Use of the GBS low-risk criteria significantly reduced the proportion of patients presenting with UGIH who were admitted. The authors concluded that selection of patients suitable for outpatient management using the GBS low-risk criteria is safe and reduces costs by lowering the rate of admissions.

The ability of the GBS to predict specific clinical end-points was examined and compared to the Rockall scores in a recent multicenter study including 1555 patients with UGIH [72]. The mean age was 56.7 years, rate of performed endoscopic therapy or surgery 14.3%, and in-hospital mortality 4.8%. Based on ROC curve analyses the GBS was found to be superior to the admission Rockall score, and similar to the full Rockall score, in predicting need for endoscopic therapy or surgical intervention. The GBS and both Rockall scores performed equally in predicting mortality.

In summary, several risk scoring systems have been developed for predicting the outcome in patients with upper gastrointestinal haemorrhage. Many of these differ in outcome of interest. In general, they seem to be capable of predicting need of hospital-

based intervention, appropriate length of stay, risk of rebleeding, and mortality. The majority of these scoring systems have, however, never been externally validated in large prospective settings. The need of external validation is underlined by a considerable inter-country variation in outcome of patients with UGIH due to differences in patients' characteristics. Therefore, validation of these systems in a Danish population seems essential prior to possible implementation in Denmark.

C. RECURRENT BLEEDING

Rebleeding is one of the most important predictors for fatality in PUB. The adverse effect is demonstrated by a considerable lower rate of achievable endoscopic secondary hemostasis compared to the rate of achievable primary hemostasis (74% versus 93%) [1,73]. Thus, TAE or surgical hemostasis is required in a considerable proportion of these patients leading to a markedly increase in mortality. A Danish study of 78 patients undergoing surgical hemostasis for peptic ulcer rebleeding demonstrated a mortality rate of 32% [73].

Rockall and colleagues analyzed the effect of rebleeding on mortality based on data from almost 3000 patients presenting with UGIH [57]. In univariate analysis rebleeding was found to increase mortality by up to a factor of 16. Further analysis demonstrated that the prognostic consequence of rebleeding was highly dependant on age, shock, comorbidity, and findings at endoscopy (bleeding source, and stigmata of bleeding). When adjusting for these factors rebleeding was found to be associated with an Odds ratio for mortality of 5.57. Among patients with a Rockall score of 3-4 rebleeding increased mortality by a factor of five. By contrast, rebleeding was only associated with a twofold increase in mortality among patients with a Rockall score of 8. These findings illustrate how the impact of rebleeding on mortality depends on the existence of other risk factors.

Several studies have intended to identify predictive factors for rebleeding [75-76]. Factors of importance seem to include active bleeding at endoscopy, large ulcer size (>1-2cm), hemodynamic instability (systolic blood pressure < 100 mmHg), location of ulcer (posterior duodenal bulb or minor gastric curvature), and anaemia (B-Haemoglobin < 6.2mmol/L) [75]. Unfortunately, identification of these prognostic factors has not resulted in development of useful guidelines for the prediction of rebleeding after endoscopic therapy.

If left untreated ulcers with an adherent clot, a visible non-bleeding vessel, or active bleeding will have a 22%, 43%, and 55% risk of rebleeding, respectively [76]. Implementation of endoscopic therapy has played a major role in the reduction of these high rates of rebleeding. Additionally, treatment with proton pump inhibitors has contributed to an approximately 6% reduction in risk of rebleeding within the first three days [32]. Concurrent treatment with endoscopic therapy and proton pump inhibitors have reduced the rate of rebleeding to an average of 13-14% [1].

In conclusion, rebleeding continues to be a frequent and dangerous complication of high-risk ulcers (Forrest I-IIb) despite optimal use of the available treatments. Development of new ways to prevent rebleeding is, therefore, of major importance.

D. TRANSCATHETER ARTERIAL EMBOLIZATION

Transcatheter arterial embolization (TAE) is a minimal invasive haemostatic treatment performed by insertion of a haemostatic agent through microselective catheters via the femoral artery. The procedure is performed under local anaesthesia using fluoroscopy. Use of TAE as an alternative to surgical haemostasis in severe PUB was introduced by Rösch in 1972 [77]. Rösch demonstrated that infusion of 2 mL of autogenous blood, preceded and followed by infusion of adrenaline or other vasoconstrictors, could lead to haemostasis through formation of a blood clot in the bleeding artery. Later a variety of different embolic materials have been used in TAE (coils, polyvinyl alcohol particles, cyanoacrylate, Gelfoam). TAE has become increasingly popular throughout the last decade and is today considered as the treatment of choice when endoscopic haemostasis is not achievable [51,78].

Prior to performance of TAE a transfemoral angiographic examination of the celiac artery is performed [79]. The celiac artery is involved in the majority of bleeding ulcers as it gives rise to both the left gastric artery, supplying the lesser gastric curvature, and in particular the gastroduodenal artery, which supply the duodenum as well as the lower part of the stomach. Active ulcer bleeding is often seen during the angiography as extravasation of contrast into the lumen or contractions of the arterial branches due to vasospasms [79-80]. Only an acute transfusion-requiring bleeding of at least 1-2 mL/min is detectable [80]. Signs of bleeding is seen at angiography in up to 61% of patients presenting with upper GI-haemorrhage [81,82].

Localisation of the bleeding site is relatively simple in cases where active bleeding is demonstrated at angiography. If active bleeding is not identified at angiography either "blind embolization" of the most probable bleeding artery based on findings at endoscopy [79,80], or preferable embolization guided by a hemoclip placed in the edge of the ulcer at endoscopy, can be used [83]. Embolization is, nowadays, in the majority of cases performed by insertion of coils. Alternatively, injection of glue can be used, if the blood flow is not blocked by the catheter. Placement of embolic material on both sides of the bleeding site is necessary in order to decrease the risk of rebleeding. Following embolization the effect on bleeding is evaluated at angiography. Additional angiography of the superior mesenteric artery is important as recurrent branches from this artery often contribute to collateral supply of the duodenum.

A review of 819 patients treated with TAE for acute non-variceal UGIH found a rate of technical success in 93% of cases [79]. A third of patients who underwent technically successful embolization did, however, rebleed. Haemostasis could be achieved in half of these patients by repeating TAE. In total 20% of patients underwent surgical haemostasis in order to gain control of bleeding.

Performance of TAE of arteries supplying the stomach or duodenum is generally considered very safe due to rich collateral supply. Embolization-related complications are developed in less than 10% of patients [79]. Complications include access site complications, dissection of target vessel, and infarction of the liver and spleen. The risk of development of contrast-related complications is in the same level as in other endovascular procedures. Misplacement of coils in branches of the celiac artery is reported in rare cases as a consequence of technical difficulties or coil migration [79]. Later development of duodenal stenosis due to ischaemia occurs in 7% of patients undergoing proximal embolization of the gastroduodenal artery [79].

There are no available randomized controlled trials comparing TAE with surgery after failed endoscopic hemostasis. Eriksson and colleagues compared the outcome of surgery and TAE in a retrospective study of 91 patients with upper GI-bleeding not responding to endoscopic intervention [84]. Patients treated with TAE (n=40) had a mean age five years older, and a higher level of comorbidity, compared to patients who underwent surgical haemostasis. Nevertheless, the 30-day mortality seemed lower among patients treated with TAE ($p<0.07$). A retrospective study of 88 patients with PUB resistant to endoscopic therapy demonstrated a higher rate of rebleeding (34.4% versus 12.5%; P=.01) among patients treated with TAE compared to surgery [85]. Surgery was on the other hand associated with a higher rate of complications (67.9% versus 40.6%). There were no differences in 30-day mortality, or mean length of hospital stay, in that study. A retrospective study of 70 patients with PUB not responding to endoscopic treatment found that TAE and surgery were equal with respect to rate of rebleeding and death, despite a mean age ten years older, and higher rate of cardiac diseases, among patients treated with TAE [86].

Overall prospective studies documenting the superiority of TAE over surgery in endoscopy refractory PUB are still missing. Retrospective data do, however, suggest that TAE is associated with an outcome that is at least as good as surgical treatment. Use of TAE as a supplementary treatment of patients with high-risk ulcers (Forrest I-IIb) responding to endoscopic therapy has not previously been evaluated.

E. LONG-TERM MORTALITY IN PUB

Development of PUB is in the vast majority of patients explained by intake of NSAIDs, low-dose aspirin, or infection with Helicobacter Pylori. Discontinuation of any non-essential use of NSAIDs, or low-dose aspirin, combined with treatment with PPI and eradication of possible Helicobacter Pylori-infection will normally result in ulcer healing within weeks. In patients with high-risk bleeding ulcers (Forrest I-IIb) endoscopic therapy is efficient in achieving haemostasis as well as preventing rebleeding and mortality. Possible fatality normally occurs at an early stage as a consequence of severe bleeding not responding to treatment, old age or comorbidity. Therefore, it is a common belief that the prognostic consequence of PUB only affects survival within 30 days from presentation. Nevertheless, several studies indicate that PUB also affects long-term mortality [87-91].

The possible association between PUB and increased long-term mortality was first described by Rørbæk-Madsen and colleagues in 1994 [87]. The authors presented a prospective study of the late outcome of 90 patients discharged after conservative or endoscopic management of bleeding gastric ulcers (Forrest I-IIc). After ulcer healing was verified by endoscopy patients were followed annually for a minimum of five years (median 6.5 years). At time of last follow-up 50% of the patients had died. The vast majority (93%) died of causes unrelated to peptic ulcer disease. The observed mortality rate was significantly higher than expected based on age- and sex-matched life table analysis. This difference was significant even when patients who died of ulcer related causes were excluded.

The following year Hudson and co-workers presented a prospective study of the long-term mortality in 487 elderly patients admitted with verified PUB [88]. Only patients older than 60 years were included. Median time of follow-up was 34.2 months. Data was compared to a matched control group consisting of 480 cases selected from general practice. Despite being matched on age and sex, the community control group was slightly healthier and had a lower intake of most types of drugs. The observed mortality in the control group was a third lower than expected based on life table analyses. Therefore, the authors compared the long-term mortality in the PUB-patients with national death rates. The observed mortality rate was 74% higher than expected. This excess mortality was found to exist three years or more from time of admission. Late complications related to peptic ulcer disease, or gastric cancer, were rare and could not explain the level of increased mortality. Based on data from death certificates the authors found that the largest increases in mortality were for respiratory disease and cancer.

Based on the findings by Rørbæk-Madsen and Hudson, among others, Kubba and colleagues examined the long-term mortality in patients admitted with major PUB [89]. Major PUB was defined as presence of a peptic ulcer requiring endoscopic therapy (Forrest I-IIa) combined with at least one other adverse prognostic factor in term of: Age over 60 years, B-haemoglobin < 10 g/dL or circulatory shock. A total of 121 patients were included. Median length of follow-up was 36 months. Long-term mortality was compared to an age- and sex-matched population using life tables. As previously demonstrated by Rørbæk-Madsen and Hudson, Kubba and colleagues also observed a significantly higher long-term case-mortality compared to the national death rates. Interestingly, Kubba et al found that the excess mortality mainly was restricted to patients who had considerable co-morbid disease present at time of admission. Again, long-term mortality as a result of peptic ulcer disease was rare (6.7%).

Hasselgren et al examined the long-term outcome in PUB in a historic cohort study [90]. A total of 676 elderly PUB-patients with an age of 60+ were included in the case cohort. Only 90% of cases underwent diagnostic endoscopy. Case mortality was compared to an age- and sex-matched control cohort identified using a national population register. Detailed characteristics of the control cohort were, however, not presented by the authors. Follow-up was performed up to seven years from day of admission. Median, or mean, length of follow-up was not reported by the authors. Five-year survival of cases was 60%. The risk of long-term death was significantly higher in the case cohort compared to the control cohort. This difference was, however, only significant for women. Analyses of possible differences in underlying causes of death were not analyzed in that study.

Ruigomez and colleagues evaluated the long-term mortality in a cohort of 978 PUB-patients [91]. Data was compared to a control cohort consisting of 5000 individuals sampled randomly from the source population. The control cohort was unmatched leading to a mean age 11.7 years younger than in the case cohort. Data concerning age, sex, nine different categories of comorbidity (e.g. cardiovascular disease), smoking status, alcohol consumption, and body mass index were registered using administrative data. The cohorts were followed up after a mean period of 39 months. The rate of mortality at follow-up was higher in the case cohort compared to the control cohort. The authors found that PUB was associated with a crude relative risk of death of 4.7. Adjustment for the above mentioned risk factors was performed using Cox proportional hazard regression analysis. The adjusted relative risk associated with having a PUB episode was 2.1 with no difference

according to sex. Stratified analysis indicated that the increased risk of mortality in the case group mainly occurred in the youngest age group. The effect of life-style factors and comorbidity on long-term mortality was similar in cases and controls.

Altogether, there are several studies indicating that PUB is associated with excess long-term mortality. However, in the majority of these studies the survival of PUB-patients was compared to national death rates using life table analyses. This method will undoubtedly be associated with selection bias, as patients admitted with PUB are expected to have a higher degree of comorbidity leading to an increased risk of long-term mortality. Therefore, the observed excess mortality might be a consequence of comorbidity and not peptic ulcer bleeding per se. Only the cohort study presented by Ruigomez et al used both a randomly sampled control group and adjustment for differences in comorbidity by multiple regression analysis. Despite use of multiple regression analysis the considerable difference in age does cast doubt on the general comparability of the cohorts in that study. As the cohorts only were followed for three years the identified excess mortality could be temporary.

Possible effect of blood transfusion on long-term mortality

In addition to the possible bias caused by comorbidity, the observed excess mortality in PUB might be explained by a confounding effect of blood transfusion. Treatment with blood transfusion plays a key role in treatment of patients with severe PUB. Its frequent use is demonstrated in an English survey demonstrating that gastrointestinal bleeding accounts for 13.8% of all red cell transfusions [92]. Although treatment with blood transfusion is essential in severe bleeding, studies have indicated that it could be associated with development of adverse effects.

A large meta-analysis including 13,152 patients concluded that there is overwhelming evidence that allogeneic blood transfusion is associated with an increased risk of post-operative infections [93]. The estimated odds ratio was 3.45. This association is believed to be caused by an immunosuppressive effect of blood transfusion, although the mechanism remains unclear [93,94]. Whether this transfusion-induced immunomodulation is linked to the infusion of red blood cells, or simultaneous infusion of remaining plasma and white blood cells, is unknown.

Several retrospective studies have concluded that perioperative blood transfusion in patients undergoing cardiac surgery is associated with excess long-term mortality [95-99]. One of these studies indicated that the adverse effect on survival exists up to ten years [97].

In the field of cancer research some animal studies have indicated existence of a transfusion-induced immunosuppression followed by enhanced tumor growth [100-107]. These findings have initiated numerous studies of the effect of blood transfusion on cancer recurrence after potentially curative surgery. This association has in particular been examined in patients with colon cancer. A meta-analysis based on 29 studies found a significant overall relative risk of 1.33 of recurrence of colon cancer in transfused patients [94]. Transfusion of plasma and leukocyte-containing products, including whole blood and fresh frozen plasma, seems to increase the cancer-recurrence rate and mortality in patients with colorectal cancer compared to transfusion of isolated red cells [108-110].

The influence of blood transfusion on long-term outcome in patients with UGIH was evaluated in a recent observational study including 1340 patients admitted with non-variceal bleeding [111]. At follow-up two years after the bleeding episode the authors found an increased hazard ratio of mortality of 1.5-2.0 among transfused patients despite adjustment for Rockall score, B-Haemoglobin, age, and comorbidity. The included patients had heterogeneous sources of bleeding (peptic ulcers, Mallory-Weiss tears, oesophagitis, angiodysplasias, and malignacies) and therefore different prognosis. The influence of blood transfusion on long-term mortality in a uniform cohort of PUB-patients has never been examined.

In conclusion a prospective, well-matched cohort study using adjustment for comorbidity and treatment with blood transfusions, and long-term follow-up, is needed in order to conclusively state whether or not PUB is associated with excess long-term mortality. Additionally, such a study would be useful in investigation of a possible association between treatment with blood transfusion and excess long-term mortality in PUB-patients.

AIMS

The overall aim of this thesis was to improve the outcome of patients with peptic ulcer bleeding. The studies focused on: 1. use of risk scoring systems in the assessment of patients presenting with symptoms of peptic ulcer bleeding, 2. improvement of outcome in patients with high-risk PUB (Forrest I-IIb) by use of optimized haemostatic intervention, and 3. examination of the short- and long-term mortality in PUB including identification of predictive factors for fatality and underlying causes of death.

The specific aims of the present studies were:

1. To examine which risk scoring system is best at predicting need of hospital-based intervention, rebleeding, and mortality in patients presenting with upper gastrointestinal bleeding (Study I)

2. To evaluate if supplementary transcatheter arterial embolization after successful endoscopic haemostasis improves outcome in patients with high-risk PUB (Study II)

3. To examine the short- and long-term mortality in PUB compared to a matched control group including identification of predictive factors for adverse outcome, identification of underlying causes of death, and investigation of a possible association between treatment with blood transfusion and long-term mortality (Study III)

METHODS

This thesis is based on three trials (Figure 6):

Study I: A prospective validation of five risk scoring systems in predicting outcome in patients presenting with symptoms of UGIH. The following risk scoring systems were evaluated: The Glasgow Blatchford score (GBS), an age-extended Glasgow Blatchford score (EGBS), the Rockall score (RS), the Baylor bleeding score (BBS), and the Cedars-Sinai Medical Centre predictive index (CSMCPI). The EGBS was constructed as illustrated in Paper 1. The scorings systems were appraised based on ability to predict: 1. need for hospital-based intervention or 30-day mortality, 2. suitability for early discharge, 3. risk of rebleeding, and 4. 30-day

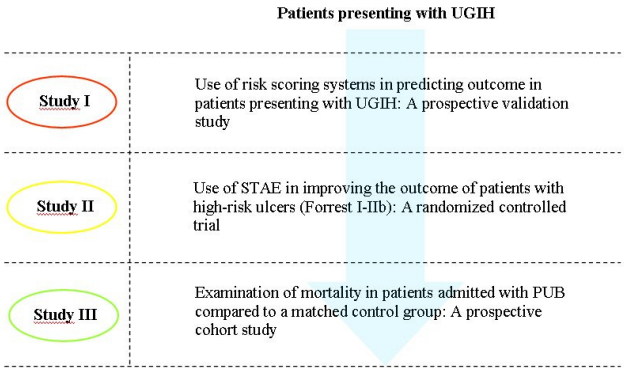
mortality. Area under receiver operating characteristic (AUROC) curves, sensitivity, specificity, positive, and negative predictive values were analyzed for each scoring system. The study included 831 consecutive patients admitted with UGIH over a two-year period.

Study II: A non-blinded, parallel group, randomized controlled trial on the effect of supplementary transcatheter arterial embolization (STAE) after achieved endoscopic hemostasis in patients with high-risk ulcers (Forrest I-IIb). Patients admitted with PUB from Forrest Ia-IIb ulcers controlled by endoscopic therapy were randomized (1:1 ratio) to receive STAE of the bleeding artery within 24 hours or continue standard treatment. Randomization was stratified according to stigmata of haemorrhage. The primary outcome was a composite endpoint based on mortality, severity of possible rebleeding, and need of blood transfusion. Among secondary outcomes were rebleeding, number of blood transfusions received, duration of admission, and mortality. In all, 105 patients were included during 32 months.

Study III: A prospective cohort study of the short- and long-term mortality in patients admitted with PUB. Predictors of mortality were identified using proportional hazards models. A possible effect of blood transfusion on long-term mortality was analyzed. Causes of death were retrieved from death certificates. Results were compared to an age- and sex-matched community control cohort from the same geographical area. A total of 455 cases and 2224 controls were included.

For a more detailed description of the applied methods please refer to Paper 1-3.

Figure 6. Overview of included studies



A. SUPPLEMENTARY DESCRIPTION OF METHODS

The Charlson comorbidity index

In Study III we examined the long-term mortality in patients admitted with PUB compared to an age- and sex-matched control group sampled from the background population. An important confounder in this setting is the effect of a possible difference in level of comorbidity between the case and the control cohort. In order to examine the effect of PUB on long-term mortality adjusted for comorbidity we used a modified version of the Charlson comorbidity index [112] to quantify the degree of comorbidity in all cases and controls.

The Charlson index includes 19 groups of diseases each selected and weighted on the basis of the strength of their association with mortality. The index has been widely used in analyzing mortality based on administrative data and is a valid and reliable method to measure comorbidity in clinical research [113]. Increasing values corresponds to a higher level of comorbidity.

We modified the Charlson index in order to include diagnoses from the 8th and 10th revision of the Worlds Health Organisation's (WHO) International Classification of Diseases (ICD) [114-115]. For practical reasons we chose to merge leukemia, lymphoma, and cancer without metastases in the same group. Therefore, the modified Charlson index used in Study III only consisted of 17 groups of diseases.

RESULTS

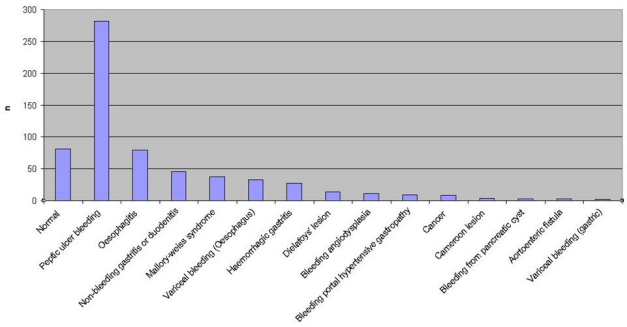
The main results of this thesis are presented in Paper 1-3. The following section serves as an overview of the main findings in Study I to III as well as supplementary results that were excluded in the final manuscripts.

A. STUDY I: THE GLASGOW BLATCHFORD SCORE MOST ACCURATELY ASSESSES PATIENTS WITH UPPER GASTROINTESTINAL HEMORRHAGE

Findings at endoscopy

Eighty percent of the patients (n=663) underwent upper endoscopy. The most common findings are illustrated in Figure 7.

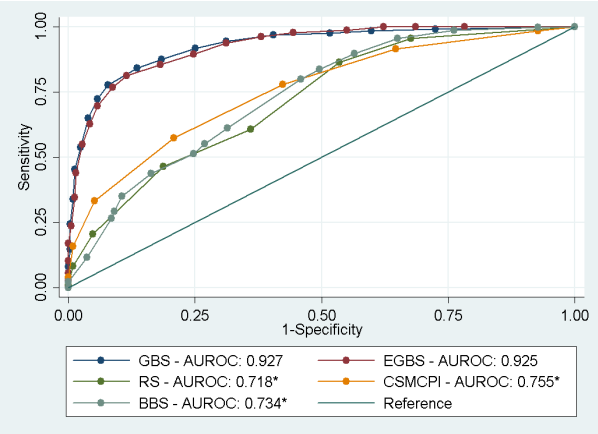
Figure 7. Findings at upper endoscopy (n=663)



Predicting need for hospital-based intervention or 30-day mortality

Using ROC-curve analysis we found that the GBS (AUROC: .927 (.909-.944)) and EGBS (AUROC: .925 (0.907-.942)) were clearly superior to admission RS (AUROC: .718 (.683-.753); p<.001), pre-endoscopy BBS (AUROC: .734 (.699-.769); p<.001), and pre-endoscopy CSMCPI (AUROC: .755 (.723-.787); p<.001) in predicting need for hospital-based intervention or 30-day mortality (Figure 8). The GBS and EGBS both had excellent discriminative ability for the prediction of this endpoint.

Figure 8. Discriminative ability for the prediction of need for hospital-based intervention or 30-day mortality

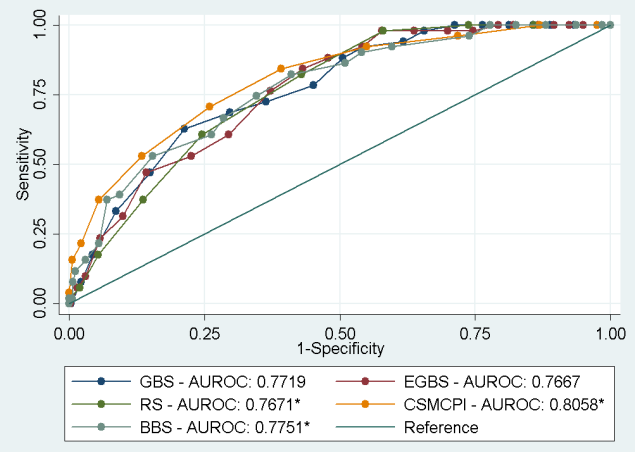


* Pre-endoscopy values

Prediction of rebleeding

Regarding prediction of rebleeding no difference was found in AUROC between the GBS (AUROC: .772 (.714-.830)), EGBS (AUROC: .767 (.711-8.23)), full RS (AUROC: .767 (.715-.819)), post-endoscopy BBS (AUROC: .775 (.713-.837)), and total-CSMCPI (AUROC: .806 (.746-.866)) (Figure 9). As expected the admission RS (AUROC: .669 (.597-.742)), pre-endoscopy BBS (AUROC: .645 (.573-.717)), and pre-endoscopy CSMCPI (AUROC: .708 (.634-.782)) all had low values of AUROC. Calculated sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for each risk scoring system are presented in Paper 1. In general, none of the scoring systems had satisfying discriminative ability for the prediction of rebleeding.

Figure 9. Discriminative ability for the prediction of rebleeding

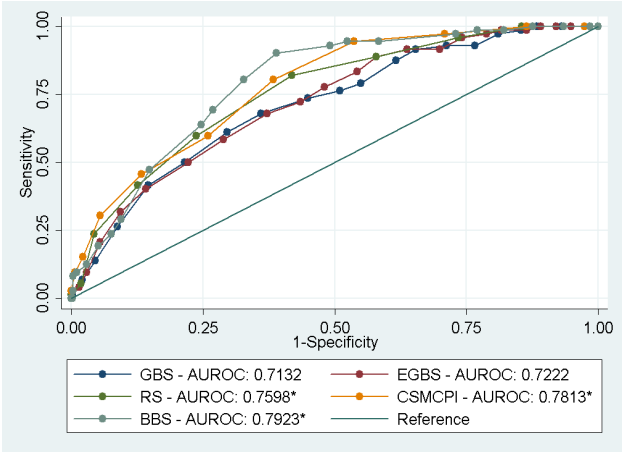


* Post-endoscopy values

Prediction of 30-day mortality

For the prediction of 30-day mortality the post-endoscopy BBS (AUROC: .792 (.746-.839)), total CSMCPI (AUROC: .781 (.732-.831)), and full RS (AUROC: .7598 (.705-.814)) performed best without any significant difference in AUROC (Figure 10). The BBS as well as the CSMCPI had a significantly higher AUROC than both the GBS (AUROC: .713 (.653-.774); P_{BBS_GBS} = .014 and P_{CSMCPI_GBS} = .026) and the EGBS (AUROC: .722 (.664-.780); P_{BBS_EGBS} = .022 and P_{CSMCPI_EGBS} = .049). Calculated sensitivity, specificity, PPV and NPV for each risk scoring system are presented in Paper 1. None of the risk scoring systems had satisfying discriminative ability for the prediction of 30-day mortality.

Figure 10. Discriminative ability for the prediction of 30-day mortality



* Post-endoscopic values

Identification of low-risk patients

Low-risk patients were defined as patients who did not need hospital-based intervention and survived more than 30 days from day of admission. Low-risk patients were considered as suitable for early discharge and potential outpatient management. The association between actual low-risk status and calculated values of the risk scoring systems is presented in Figure 11.

Figure 11. Association between risk score and actual low-risk status

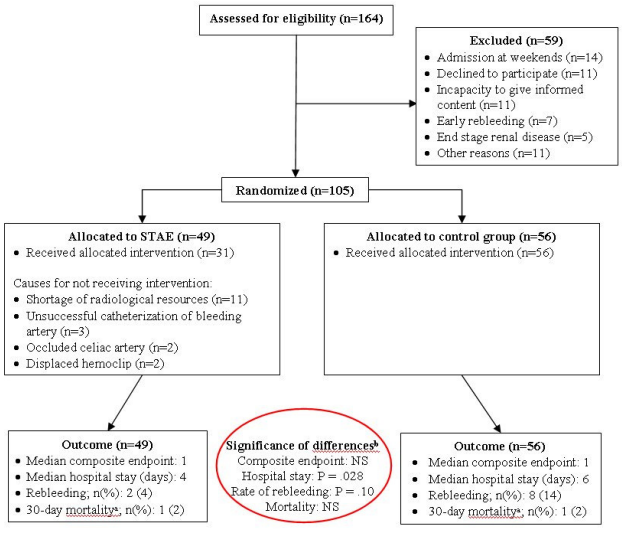
As illustrated in Figure 11, the EGBS and GBS seemed most attractive for identification of low-risk patients. The EGBS identified a larger proportion of correctly classified low-risk patients compared to the GBS (125/331 versus 91/331; Fisher's exact test: P=.006). Additionally, there was a tendency towards a lower rate of mortality (0/125 versus 3/96; Fisher's exact test: P=.081) and performed endoscopic therapy (0/125 versus 2/96; Fisher's exact test: P=.188) among patients classified as low-risk using the EGBS. Calculated sensitivity, specificity, PPV, NPV, and outcome for patients classified as low-risk using each risk scoring system at different cutoff values are presented in Paper 1.

Of the traditional risk scoring systems the GBS seems to be superior in selection of low-risk patients. The present study indicates that use of an EGBS might be associated with identification of a larger proportion of correctly classified low-risk patients compared to the GBS. Further studies of the EGBS are, however, needed in order to demonstrate the external validity of these findings.

B. STUDY II: TRANSCATHETER ARTERIAL EMBOLIZATION AFTER SUCCESSFUL ENDOSCOPIC HEMOSTASIS PREVENTS REBLEEDING IN PEPTIC ULCER BLEEDING

During the period of inclusion 164 patients were assessed for eligibility. A total of 105 of these patients were included in the study. Figure 12 illustrates the flow of participants through the trial and summarizes the key results. For detailed results please refer to Paper 2.

Figure 12. Participant flow and per-protocol outcome



[a]Bleeding related mortality
[b]Level of significance was calculated using Wilcoxon rank sum test and Fisher's exact test
NS: Not significant
STAE: Supplementary transcatheter arterial embolization

Adjusted effect of STAE on rate of rebleeding

For details on patients characteristics please refer to Paper 2. Patients allocated to the STAE group were slightly younger compared to the control group (69 versus 75 years). The effect of STAE on rate of rebleeding was adjusted for imbalances in age and stigmata of recent bleeding using logistic regression analysis. Adjusted data indicated that STAE was associated with a 78% reduction of risk of rebleeding (intention-to-treat analysis; p=.079). Although the association between STAE and rate of rebleeding did not reach statistical significance Study II demonstrates a clear trend towards reduced rate of rebleeding among patients treated with STAE.

C. STUDY III: THE EXCESS LONG-TERM MORTALITY IN PEPTIC ULCER BLEEDING IS NOT EXPLAINED BY COMORBIDITY

30-day mortality

The overall 30-day mortality in the case cohort was 9%. Causes of 30-day mortality are illustrated in Figure 13. Predictive factors for 30-day mortality are listed in Table 1.

Figure 13. Causes of 30-day mortality in case cohort (n=42)

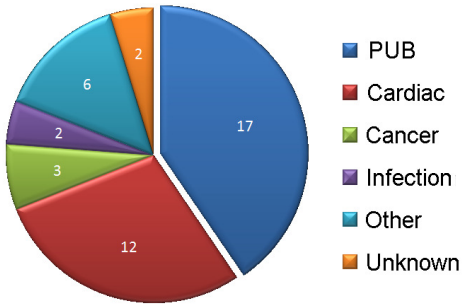


Table 1. Predictive factors for 30-day mortality in case cohort

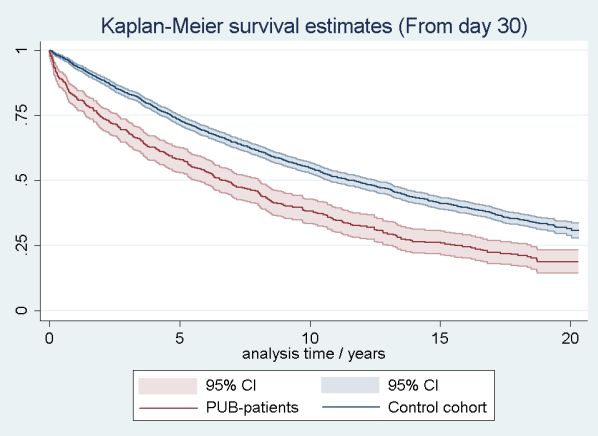
Variable	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	P[a]
Age	1.04 (1.01-1.06)	1.04 (1.01-1.07)	0.005
Rebleeding	2.07 (1.64-2.62)	2.03 (1.60-2.60)	< 0.001
Charlson index	1.31 (1.13-1.52)	1.29 (1.11-1.50)	0.001

[a]Estimates are adjusted by the variables present in the table using a Cox proportional hazards model. See Paper 3 for details
CI: Confidence interval
HR: Hazard ratio

Long-term mortality

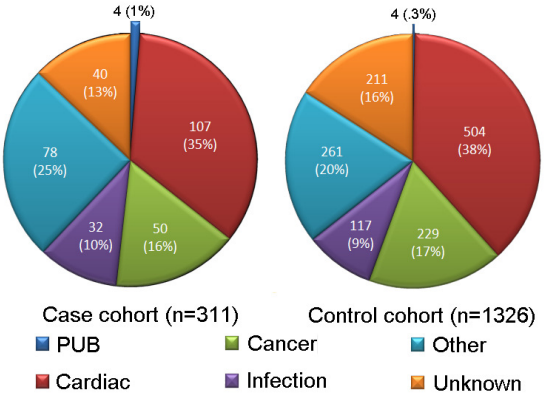
The long-term mortality was higher in the case cohort compared to the control cohort (Log-rank: P <.001) (Figure 14). Although the survival curves seemed fairly parallel after a few years the Log-rank test demonstrated a significant difference in mortality even when only patients surviving nine years after index date were included (P = 0.04). Adjustment for difference in comorbidity (Charlson index) did not change the significance of the observed excess mortality.

Figure 14. Kaplan-Meier survival estimates of long-term mortality (from day 30)



Long-term mortality related to PUB was rare, but occurred more often in cases than in controls (P = .047). No differences in frequencies of other causes of death were found (Figure 15).

Figure 15. Causes of long-term mortality in case and control cohort



Treatment with blood transfusion during admission did neither affect the risk of long-term mortality nor the cause of death. Predictive factors for long-term mortality are listed in Table 2.

Table 2. Predictors of long-term mortality in case cohort

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	P[a]
Age	1.06 (1.05-1.07)	1.08 (1.06-1.09)	< 0.001
Charlson index	1.30 (1.21-1.40)	1.39 (1.27-1.53)	< 0.001
Blood transfusion[b]	1.01 (1.00-1.03)	0.99 (0.97-1.02)	0.615
Sex			
Female	1 (reference)	1 (reference)	
Male	0.89 (0.71-1.12)	1.54 (1.20-1.96)	0.001
Hemoglobin level			
> 5.0 mmol/L	1 (reference)	1 (reference)	
≤ 5.0 mmol/L	1.19 (0.94-1.50)	1.50 (1.15-1.94)	0.003
Glucocorticoid use			
No	1 (reference)	1 (reference)	
Yes	3.08 (1.92-4.92)	2.62 (1.60-4.28)	< 0.001
Tobacco use			
No	1 (reference)	1 (reference)	
Yes	1.04 (0.83-1.31)	1.38 (1.09-1.76)	0.008

[a]Estimates are adjusted by all the variables present in the table using a Cox proportional hazards model. See Paper 3 for details.
[b]Units of blood transfused (250mL)
CI: Confidence interval
HR: Hazard ratio

DISCUSSION

A. HOW CAN WE IMPROVE OUTCOME IN PUB?

Peptic ulcer bleeding continues to be a frequent disease causing significant mortality. The treatment is challenged by the increasing age, and level of comorbidity, in patients presenting with PUB. It is no longer sufficient only to focus on the achievement of primary haemostasis and prevention of rebleeding. This is reflected by the findings of Study III where almost 60% of 30-day mortality was unrelated to ulcer bleeding. One of the major causes of 30-day mortality was pre-existing, or newly developed, cardiovascular disease. Thus, it seems naturally that improvement of the treatment should include a larger perspective on potential factors leading to fatality. The following section discusses the major findings of the present thesis and the possible impact on treatment of PUB-patients and future research.

Use of risk scoring systems

Several risk scoring systems have been developed for the assessment of patients with PUB. The majority of these have never been implemented in everyday practice. This is probably explained by limited impact.

In theory, use of risk scoring systems could be beneficial in identifying subgroups of patients with different prognosis and thus different need of treatment; e.g. low-risk patients suitable for early discharge, or patients in high risk of rebleeding, or mortality, needing close monitoring.

In recent years the GBS has become increasingly popular. This risk scoring system was previously only validated in the United Kingdom, where it was shown to be useful in identification of low-risk patients. The external validation of the GBS has been a subject of debate because of significant inter-country variation in patient's characteristics and proportion of patients handled in primary health sectors.

Study I is the first major prospective study evaluating the discriminative performance of the GBS outside the United Kingdom. The study illustrates that the GBS is attractive in identification of low-risk patients in a population characterized by high age and considerable comorbidity. Identification of low-risk patients without need of hospital-based intervention is important, as admission of the majority of these patients is without benefit and resource-consuming. Post-hoc analyses based on findings of Study I indicated that implementation of the GBS at our institution (a 1000 bed hospital) would be associated with a yearly reduction of 55 hospital admissions and 79 hospital bed days equal to a total savings of 700.000 DKr (90.000 EUR).

Age is not included in the GBS as it was found not to be an independent risk factor of adverse outcome in the logistic regression models used in the initial formulation of the GBS. In spite of this, it is a clinical experience that there is an association between age and outcome. This is supported by Stephens and colleagues who found that the performance of the GBS is age-dependant [116]. The EGBS presented in Study I – as well as the EGBS presented by Stephens et al – both seem to be superior to the original GBS in identifying low-risk patients in our population. The external validity of the EGBS is unknown and studies evaluating the performance of the EGBS in other populations are needed to demonstrate this.

Naturally, the ideal risk scoring system should also be able to predict outcomes as rebleeding and bleeding-related mortality. The GBS has been promoted for performing equal to the Rockall score in the prediction of mortality. Limitations of risk scoring

systems in predicting hard outcomes are, however, clearly demonstrated in Study I. Although the scoring systems are characterized by high sensitivity for predicting rebleeding and mortality, they all have poor specificity for predicting these outcomes. As a result of low specificities none of the scoring systems had PPVs above .16 for predicting rebleeding or mortality. Depending on scoring system used we found that 70-88% of all patients presenting with UGIH were deemed high risk of rebleeding or death. Therefore, implementation of risk scoring systems with the purpose of predicting rebleeding or mortality would only be associated with a negligible impact.

Using need of hospital-based intervention as an outcome measure in patients presenting with UGIH was introduced by Blatchford and colleagues in relation to the development of the GBS. In Study I we used need of hospital-based intervention as one of the primary outcomes. We did, however, define this outcome slightly different than Blatchford et al. We chose also to include patients with cancer found at upper endoscopy in order to secure rapid diagnosis and treatment of these patients. This diversity in definition of outcome could potentially lead to differences in the performance of the scoring systems. However, only 8 patients (1%) were diagnosed with cancer at upper endoscopy. Post-hoc analyses demonstrated that exclusion of these patients did not affect the discriminative ability of the GBS.

Limitations of Study I include that a considerable part of the patients (20%) did not undergo endoscopy. During the study we allowed the attending physicians to discharge patients with very low suspicion of UGIH without performing endoscopy. This could have lead to some degree of measurement bias as these patients might have had undiscovered sources of bleeding, or upper gastrointestinal cancer. All of these patients had a history indicating low risk of UGIH (negligible amount of coffee ground vomiting without presence of melaena) combined with normal B-hemoglobin, and normal or mildly elevated plasma urea. The majority of patients who did not undergo endoscopy were believed to have vomited due to extra-gastrointestinal infection, intake of excessive amounts of alcohol, hyperemesis gravidarum, and other non-gastrointestinal causes. As the patients were followed up for relevant outcomes it seems unlikely that these circumstances had a significant effect on the main conclusions of the study.

Study I was conducted in a normal clinical setting and patients were included consecutively. Data were registered prospectively. The sample size was large compared to previous studies of risk scoring systems in UGIH. Only two patients (0.2%) were excluded as they left the department before they were examined by the attending physician. Ninety-nine percent of patients were followed-up for relevant and well-defined outcomes. As a consequence the study is considered to have high internal validity. The fact that results presented are in accordance with previous trials indicate that the findings also are externally valid.

Study I serves as a validation study of the GBS outside UK and hopefully it will have an impact on two levels. Firstly, it confirms the safety of using the GBS in detecting patients suitable for early discharge. This will hopefully lead to increased level of implementation of the GBS in everyday practice as a valuable tool for the attending physician. Implementation of the GBS will presumably have two major advantages: 1. helping the attending physician in clinical decision making regarding indication for hospital admission, and 2. reduced costs by avoiding hospitalization of a greater proportion of low-risk patients. Secondly, Study I indicates that use of an EGBS is associated with better discriminative ability for the identification of low-risk patients in our population compared to the GBS. This will probably lead to future trials evaluating the external validity of the EGBS and, hopefully, result in identification of a risk scoring system that can identify a larger proportion of the true low-risk patients.

Improved haemostatic techniques

One of the most obvious ways to improve therapy is better prevention of rebleeding. The previously used strategies are all based on an extravascular access sites; e.g. endoscopic or surgical therapy, and improvement of hemostasis by elevation of gastric pH. With the increased use of TAE for treatment of endoscopy-refractory PUB it seemed natural to examine if the rate of rebleeding could be reduced by combining use of extravasal and intravasal haemostatic techniques. In this way haemostasis is secured from both sides of the blood vessel wall.

Study II is the first investigation of the effect of TAE as a supplementary therapy after successful endoscopic haemostasis. It shows a clear trend between STAE and reduced risk of rebleeding. This trend did, however, not reach statistical significance. This is mainly explained by two factors. Firstly, the study was originally designed as a multicenter study with planned inclusion of 200 patients at four university hospitals. Unfortunately, due to various circumstances, the other centres could not reach a satisfying level of inclusion. Therefore, the sample size ended up being considerable lower than planned resulting in reduced power. Secondly, more than half of the patients who re-bled could not be included mainly because of considerable comorbidity leading to incapacity to give informed consent or exclusion due to kidney failure.

The patients who, for various reasons, could not be included were characterized by higher age, ASA-score, rate of rebleeding, and mortality compared to the included patients. Although probably being unavoidable, exclusion of the sickest patients will lead to a degree of selection bias. It is expected that the excluded patients, with a relatively high rate of rebleeding, in general would have had a higher gain of the effect of STAE compared to the included patients. If this is true the described selection bias would result in underestimation of the effect of STAE. The actual value of NNT in order to avoid one case of rebleeding might, therefore, be lower than 10.

Despite use of a randomized design there was a significant difference in age between the STAE and the control group. Therefore, the effect of STAE on rebleeding was adjusted for a possible effect of age using a logistic regression model. Age was found not to be an independent risk factor for rebleeding neither in univariate nor in multivariate analyses. This indicates that the imbalance in age did not influence the main conclusion of the study.

Limitations of Study II include that 37% of the patients allocated to STAE did not undergo the planned procedure. This may have had an adverse effect on the results of the per-protocol analyses as the only patient with a severe rebleeding in the STAE group never underwent embolization due to radiological incapacity.

Study II was conducted as an open randomized controlled trial which is the preferable design in intervention testing. The trail was not blinded as the main outcomes of interests (rebleeding and mortality) were well defined without any possible influence of a placebo effect. Despite the fact that some degree of selection bias cannot be excluded with certainty we believe that the patients included are representative for patients admitted with high-risk PUB in general. The fact that the median age, distribution of stigmata of bleeding, and rate of rebleeding corresponds to previous international studies [76,117-121] indicates that the findings are externally valid. The conclusion that STAE is

associated with reduced rate of rebleeding in PUB is associated with a 7.9% risk of performing a type I-error. However, the overall conclusion of this study is that STAE performed after endoscopic haemostasis most likely is associated with a reduced risk of rebleeding.

One problem associated with use of STAE is how to select the patients who will gain benefit from the procedure. As confirmed in Study II, there is a significant association between the stigmata of recent haemorrhage and risk of rebleeding. The study indicates that each increase in the Forrest-classification (IIb, IIa, Ib and Ia) is associated with more than a doubled risk of rebleeding. The rate of rebleeding was 0%, 10%, 24%, and 20% for Forrest IIb, IIa, Ib, and Ia ulcers respectively. Therefore, use of STAE seems most relevant in patients with Forrest I-ulcers. However, even in these patients the majority will not benefit from STAE. Our experience is that rebleeding not infrequently occurs from Forrest I-IIa ulcers described as having a relatively low risk of rebleeding by the endoscopist. Consequently, better methods to identify ulcers that will be complicated by rebleeding are needed in order to gain the maximal benefits of STAE.

Another factor that can affect the performance of STAE is the ulcer location. For ulcers located in the duodenum, or pyloric region, the underlying artery often originates from the gastroduodenal artery which is relatively easy to catheterize and embolize. Selective catheterization of the arterial branches involved in gastric ulcers not located in the pyloric region, or at the minor or major curvature, can be technically difficult. In study II selective catheterization of the relevant gastric artery was not possible in 15% (n=3) of cases.

Study II demonstrates that STAE is a safe and useful procedure for the prevention of rebleeding in patients with high-risk ulcers. The study will hopefully lead to implementation of STAE in individual cases with suspected very high risk of rebleeding. Future trials are needed in order to identify the optimal indications for STAE.

Short- and long-term mortality; predictive factors, causes of death, and importance of comorbidity

Characteristics of PUB-patients have changed with time in line with the changes in characteristics of the general population. Overall, these patients have become increasingly older with increasingly existence of serious concomitant disease [2,117]. In the 1930'ies and 1940'ies the majority of patients admitted with PUB were under 50 years of age and only very few (<5%) died of concomitant disease [2]. Today, the mean age of Danish patients admitted with PUB is 73 years [1] and the majority of patients dying within 30 days seem to die from causes different than ulcer bleeding.

The 30-day mortality of patients included in Study III was 9%. It calls for reflection that this value seems lower than the average 30 day mortality of these patients in Denmark in 2011 (11%) [1]. The progress in treatment during the last decades (more effective acid suppressive therapy, use of endoscopic combination therapy, and implementation of eradication of Helicobacter Pylori) have apparently not lead to reduced mortality. This lack of decline in mortality cannot be explained by an increasing age as the age of patients included in Study III match the Danish national data from 2011 (73.5 versus 73 years) [1]. A closer look at patients' characteristics does, however, indicate considerable changes. Among patients admitted with PUB in Denmark in 2011 15% were diagnosed with diabetes, 16% with chronic obstructive lung disease, and 53% with heart disease [1]. In comparison, the rates of these concomitant diseases among patients in Study III were 6%, <9%, and 10%. These differences give a clear impression of the increasing level of comorbidity which is the most likely explanation of the absent reduction in mortality. Changes in characteristics seem to have complicated the course of PUB-patients. Identification of patients in high risk of fatality has become more difficult as ulcer bleeding no longer is the, almost, unshared cause of death. A better understanding of the short and long-term mortality including identification of predictive factors for mortality, underlying causes of death and clarification of the possible existence of excess long-term mortality is desirable. This was the focus of Study III.

Study III is the first prospective cohort study of mortality associated with PUB using both a well matched control group, adjustment for comorbidity, and a follow-up period longer than ten years. The study demonstrates that about 60% of patients dying within 30 day die from causes different than PUB. One of the major causes of death was cardiovascular disease (30%). Post-hoc analysis showed that among patients diagnosed with heart disease prior to admission more than three times as many died of heart disease (15%) than ulcer bleeding (4%). Thus, prevention of death of complicating heart disease could play an important part in improvement of the outcome. One important aspect in this context is the cessation of aspirin treatment in patients with established cardiovascular disease presenting with PUB. Increasing amount of evidence indicates that withdrawal of aspirin is associated with a rebound phenomenon characterized by elevated thromboxane production and decreased fibrinolysis resulting in a prothrombotic state [122-124]. Several studies have illustrated an increased risk of cardiovascular events during acute aspirin withdrawal [125-129] also in PUB-patients [130]. As a result of these findings recommendations for the duration of cessation of aspirin have been changed in the more recent guidelines for management of PUB [51]. Therefore, the frequency of PUB patients dying of heart disease might decrease in the forthcoming years compared to the findings in Study III.

Identification of predictive factors confirmed the major prognostic importance of existing comorbidity and rebleeding. According to the results of study III prevalent comorbidity was associated with a 29% increase in risk of 30-day mortality per increase in Charlson index of one. Recurrent bleeding was found to double the risk of 30-day mortality. These findings underline the crucial importance of avoiding destabilization of existing comorbidity and preventing rebleeding.

A possible impact of PUB on long-term mortality has been a subject of debate for several years. Many gastroenterologists do still believe that presentation with PUB only affects short-term survival. This seems natural, as the vast majority of ulcers will heal with within weeks when proper treatment is initiated. Nevertheless, several studies indicate the existence of excess long-term mortality. As demonstrated in Study III this excess mortality is not caused by redevelopment of PUB as this was only the cause of long-term mortality in 1% of patients.

One of the possible explanations of the identified excess mortality is a confounding effect of comorbidity. A great proportion of PUB-patients have developed peptic ulcer disease as a result of use of aspirin or NSAIDs in treatment of comorbidity. These patients must be expected to have a higher degree of comorbidity compared to the background population. As increased level of serious comorbidity will increase the long-term mortality the presence of a confounding effect of comorbidity seems obvious in several of the previous studies based on life table analyses [87-89]. Of the previous studies, only Ruigomez

and colleagues performed adjustments for comorbidity [91]. Their study, however, was based on an unmatched control group that was much younger than the case group (mean age: 64.4 versus 52.7 years). As a consequence this study is associated with a considerable risk of being confounded by age. One of the strengths of Study III is the combination of an age- and sex-matched control group and adjustment for imbalances in comorbidity by use of the Charlson index. Although the Charlson index probably is one of the best available methods it will also be associated some risk of residual confounding. The Charlson index was in study III calculated retrospectively by use of administrative data. The degree of residual confounding could presumably have been minimized if the Charlson index was applied prospectively as part of the structured interview at time of admission. Altogether, six studies based on a total of almost 3000 PUB-patients have identified existence of excess mortality in PUB. This does demonstrate that PUB-patients experience a higher long-term mortality than the background population.

Today, many centres worldwide have implemented outpatient care of a considerable proportion of patients considered as being in low risk of adverse outcomes. Whether or not the excess long-term mortality exists among this subgroup of patients is unknown. Study III does demonstrate that even patients without comorbidity have an excess mortality lasting more than 10 years. Nevertheless, the presence of a normal long-term survival among low-risk PUB patients, defined by use of for example the GBS, cannot be rejected.

The reason for the observed long-term mortality remains unclear. It is presumably not caused by the peptic ulceration itself, as this in most cases responds satisfactory to acid inhibitory treatment and recurrent bleeding after a month from time of presentation is rare. One possible hypothesis is that development of peptic ulcer disease and PUB could be a marker of underlying disease. If this is the case one would expect that the causes of long-term mortality were different compared to non-PUB patients. Regarding causes of long-term mortality the results of Study III seem clear. There are no indications of any change in frequency of death as a consequence of cardiovascular disease, cancer, infection or other diseases among PUB patients. An exception is of course the increased risk of death due to recurrent PUB but this was rare (1%) and cannot explain the level of the observed excess mortality. So if the excess mortality is a result of underlying disease it is a disease that does not seem to affect the cause of death but just increase the overall risk of mortality. The possibility of an impaired physiological response in PUB-patients could be considered. In theory, this could lead to a reduced mucosal barrier increasing the risk of development of PUB as well increasing the risk of long-term mortality of various causes of death. Although studies have indicated changed levels of secretin in PUB patients [131-132] and inappropriate angiographic response in rats with induced peptic ulcer disease [133] the evidence supporting this theory is very limited.

The majority of the identified predictive factors for long-term mortality seem to be general factors for long-term mortality without any specific relation to PUB. It is somewhat surprising that severe anaemia (<5 mmol/L) at time of admission was found to be a predictor for long-term but not 30-day mortality. These findings were not affected by the included variable representing the amount of received blood transfusions. The association between severe anaemia and long-term mortality was significant despite adjustment for the Charlson index. Nevertheless, the most likely cause of this association is residual confounding. Some patients did presumably have undiagnosed concomitant disease such as myelodysplastic syndrome, haemolysis, or cancer leading to anaemia and increased long-term mortality.

As mentioned in the introduction numerous studies demonstrate that treatment with blood transfusion has a much more complex impact than previously believed. Although blood transfusion can be lifesaving in cases with severe bleeding the simultaneous infusion of plasma components might have a long-lasting negative effect. Data indicate existence of a transfusion-induced immunosuppression [93-94], increased risk of cancer recurrence [94], and reduced long-term survival [95-99,111]. Study III is the first evaluation of this association in a homogenous cohort of PUB patients. This study does, however, not indicate any association between treatment with blood transfusion in PUB and changes in the long-term survival. The existence of a possible dose-response effect [93] should result in differences in level of mortality and cause of death according to received amount of blood transfusions. Stratified analyses of data from Study III did not support this hypothesis. The only other study evaluating the mortality following blood transfusion in upper gastrointestinal haemorrhage found a 71% increased risk of death within two years among patients receiving blood transfusions [111]. This study was, however, retrospective and characterized by inclusion of heterogeneous bleeding sources with different prognosis as well as considerable risk of selection bias because of differences in age (73 versus 61 years; $P < .001$) and comorbidity (Ratio of Charlson index=0: 25.6% versus 49.5%; $P<.01$) between transfused and not transfused patients. In conclusion, a possible negative effect of blood transfusion on long-term survival in PUB remains unproven. The current evidence is insufficient to change recommendations of transfusion policies in PUB.

Despite weaknesses in design (discontinuous period of inclusion, retrospective application of Charlson comorbidity index, and registration of causes of death by use of death certificates) Study III clearly demonstrate the importance of concomitant disease for the outcome in PUB. Although ulcer bleeding is the largest single cause of short-term mortality it only accounts for around 40% of 30-day mortality. Similar, only 1% of patients surviving more than 30 days from admission die of redevelopment of PUB. Presence of severe comorbidity is associated with at least the same risk of fatality within 30 day as rebleeding. Treatment of these patients is, therefore, not just a matter of achieving primary haemostasis and preventing rebleeding. One of the potential impacts of Study III is increased focus on prevention of destabilization of prevalent comorbidity and prevention of development of incident comorbidity. This seems crucial in improving the outcome of PUB-patients.

Although the increased level of evidence for the existence of excess long-term mortality in PUB is interesting the impact on treatment for now is limited. As the identified predictive factors and causes of long-term mortality appear non-specific to PUB these aspects are not useful in term of indicating a cause of the identified excess mortality. Thus, further knowledge is needed before a more targeted prevention is possible.

In summary, this thesis may lead to improved treatment in term of: 1. better risk stratification at assessment of patients presenting with UGIH, 2. enhanced prevention of rebleeding in patients with high-risk ulcers, and 3. increased focus on optimizing treatment of comorbidity.

B. DIRECTIONS FOR FUTURE RESEARCH

PUB continues to be a challenge and future trials are needed in order make further breakthroughs in treatment. This section focuses on five high-priority targets for future research: 1. triage, 2. resuscitation, 3. primary hemostasis, 4. rebleeding, and 5. comorbidity. Prevention of development, or recurrence, of peptic ulcer disease is beyond the scope of this thesis.

1. Optimizing triage of patients presenting with PUB

By now, there seem to be convincing evidence of the safety and efficacy of the GBS in the assessment of patients presenting with PUB. Hopefully, this will in the near future result in increased implementation of the GBS in clinical practice. An important weakness of the GBS seems to be low specificity resulting in misclassification of the majority of true low-risk patients. Results from Study I and Stephens et al [116] suggests that the performance of the GBS could be improved by incorporating an age-dependent variable. Examination of the external validity of these findings is an obvious target for future research.

As mentioned previously in this thesis, several risk scoring systems have been developed with the purpose of identifying high-risk patients in risk of rebleeding or death. Data from this thesis, among other studies [72,134-136], demonstrate that these systems perform insufficient in clinical practice. For the time being, prospects for the construction of an efficient risk scoring system for identification of high-risk patients look bleak.

2. Early and effective resuscitation

Although studies of the importance of resuscitation in PUB were not included in the present thesis this subject does deserve a brief description.

Study I illustrated that 29% of patients admitted with PUB had a systolic blood pressure below 100 mmHg at time of admission (data not previously shown). It seems naturally, that presence of hemodynamic instability in these patients is of crucial importance for mortality. Based on data from more than 4000 patients admitted with upper GI-haemorrhage Rockall and colleagues found that the presence of severe shock was associated with an Odds ratio for mortality of 22.3 [57]. Despite this only very few studies have examined the importance of resuscitation in PUB.

Baradarian and co-workers performed an evaluation of the importance of early intensive resuscitation in patients with upper GI-haemorrhage [137]. This study was conducted prospectively, although not randomized, and included 72 patients of which half was assessed by a physician with no other duties than to secure rapid correction of haemodynamics, hematocrit, and possible coagulopathy. Although the authors were later criticized for incorrect use of Chi-squared tests in comparison of outcomes [138] the study illustrated a clear trend towards lower mortality, rate of complicating myocardial infarction, and length of stay among patients receiving intensive resuscitation. Despite these promising results, prober evaluation of the importance of early intensive resuscitation in a randomized setting has not been performed.

Randomized trials investigating the benefits of early intensive resuscitation could be highly beneficial in finding ways to improve the outcome of PUB-patients with hemodynamic instability.

3. Achievement of primary haemostasis

Over the years achievement of primary haemostasis has been a subject for numerous trials. Today, endoscopic haemostasis can be safely achieved in 94% of cases [1]. In the last 6% of patients TAE and surgery are effective in achieving primary hemostasis [79,139]. Therefore, the potential positive effect of new interventions on primary haemostasis is hard to prove in clinical trials due to high risk of performing a type II-error.

One important clarification missing is the determination of possible benefits associated with use of TAE compared to surgery in endoscopy-refractory PUB. As described previously, some retrospective data have indicated advances associated with use of TAE but randomized prospective studies are still lacking. A randomized controlled trial evaluating this problem is currently being performed in Hong Kong [140]. Hopefully; results will be available in 2013.

Another way to achieve higher rate of primary haemostasis could be supplementary treatment with antifibrinolytics or other drugs promoting haemostasis. Comprehensive studies evaluating this kind of treatment in PUB are needed.

4. Prevention of rebleeding

Treatment with endoscopic combination therapy and proton pump inhibitors has resulted in a major reduction in rate of rebleeding to around 13% [1]. Study II indicates that a further reduction of rate of rebleeding is possible. One of the reasons for the missing statistical significance of the findings in Study II was suboptimal recruitment of patients. Although the Forrest classification is a good tool for estimation of the risk of rebleeding in clinical practice only 14% of Forrest I-IIb ulcers re-bleed in the control group. Better selection of patients in risk of rebleeding would make it easier to prove the benefits of STAE. It would also lead to lower NNT and cost savings compared to offering STAE to all patients with high-risk ulcers.

As mentioned previously, development of rebleeding must in the majority of cases be a consequence of inadequate endoscopic treatment resulting in residual flow in the artery lying beneath the ulcer. Therefore, selection of patients in high risk of rebleeding could be improved by examination of the ulcer with endoscopic ultrasound (EUS) including Doppler measurements. This is supported by previous studies [141-142]. A new trial evaluating the effect of EUS after endoscopic treatment, followed by STAE in patients with proved residual flow close to the ulcer surface, seems very interesting.

5. Improved treatment of comorbidity

Future research on how to improve the treatment of comorbidity in PUB-patients is crucial as an increasingly proportion of patients die of concomitant disease. Still, only a limited number of interventional studies have investigated this subject. Improvement of treatment of comorbidity can be subdivided into two groups: 1. optimizing treatment of existing comorbidity and 2. prevention of development of new comorbidity during admission with PUB (incident comorbidity).

Prevention of destabilization of existing comorbidity, in particular ischemic heart disease, is a major challenge. Sung and colleagues demonstrated how continuation of treatment with low-dose aspirin during admission for high-risk PUB seems to reduce mortality [130]. Future studies on continuation of low-dose aspirin, or treatment with other antiplatelets, must be considered despite the tendency towards increased risk of rebleeding.

Further studies of the development of incident comorbidity in PUB are needed in order to pinpoint which types of prophylactic treatment seem most promising and suitable for future trails. In study III nearly ten percent of the PUB-patients dying within 30 days died of infection. Therefore, studies of the effect of prophylactic treatment with antibiotics could be considered.

In conclusion, several possible targets for future research exist. It seems important that future studies include a broad approach to the treatment of PUB instead of focusing on bleeding related parameters only.

ABBREVIATIONS

ASA: Acetylsalicylic acid
ASA-score: The American Society of Anesthesiologists score
ASGE: American Society for Gastrointestinal Endoscopy
AUROC: Area under receiver operating characteristic curve
BBS: Baylor bleeding score
BC: Before Christ
CI: Confidence intervals
COLD: Chronic obstructive pulmonary disease
CSMCPI: Cedars-Sinai Medical Centre predictive index
CT: Computed tomography
EGBS: Age-extended Glasgow Blatchford score
EUS: Endoscopic ultrasound
GBS: Glasgow Blatchford score
GI: Gastrointestinal
ICD: International Classification of Diseases
HR: Hazard ratio
NNT: Numbers needed to treat
NPV: Negative predictive value
NS: Non-significant
NSAIDs: Non-steroidal anti-inflammatory drugs
OR: Odds ratio
PPI: Proton pump inhibitor
PPV: Positive predictive value
PUB: Peptic ulcer bleeding
ROC: Receiver operating characteristic
RS: Rockall score
STAE: Supplementary transcatheter arterial embolization
TAE: Transcatheter arterial embolization
UGIH: Upper gastrointestinal haemorrhage
UK: United Kingdom

SUMMARY

Peptic ulcer bleeding is a frequent cause of admission. Despite several advances in treatment the 30-day mortality seems unchanged at a level around 11%.

Use of risk scoring systems is shown to be advantageous in the primary assessment of patients presenting with symptoms of peptic ulcer bleeding. Studies performed outside Denmark have demonstrated that use of risk scoring systems facilitates identification of low-risk patients suitable for outpatient management. Nevertheless, these systems have not been implemented for routine use in Denmark. This is mainly explained by concerns about the external validity due to considerable inter-country variation in patients' characteristics.

In recent years, transcatheter arterial embolization (TAE) has become increasingly used for achievement of hemostasis in patients with peptic ulcer bleeding not responding to endoscopic therapy. As rebleeding is associated with poor outcome TAE could, in theory, also be beneficial as a supplementary treatment in patients with ulcer bleeding responding to endoscopic therapy. This has not been examined previously.

Several studies have concluded that peptic ulcer bleeding is associated with excess long-term mortality. These findings are, however, questioned as the studies were based on life-table analysis, unmatched control groups, or did not perform adequate adjustment for comorbidity. Treatment with blood transfusion is, among patients undergoing cardiac bypass surgery, shown to increase the long-term mortality. Despite frequent use of blood transfusion in treatment of peptic ulcer bleeding a possible adverse effect of on long-term survival has not been examined in these patients.

The aims of the present thesis were:

1. To examine which risk scoring system is best at predicting need of hospital-based intervention, rebleeding, and mortality in patients presenting with upper gastrointestinal bleeding (Study I)
2. To evaluate if supplementary transcatheter arterial embolization (STAE) after successful endoscopic haemostasis improves outcome in patients with PUB with active bleeding, a non-bleeding visible vessel, or an adherent clot (Study II)
3. To examine the short- and long-term mortality in PUB compared to a matched control group including identification of predictive factors for adverse outcome, identification of underlying causes of death, and investigation of a possible association between treatment with blood transfusion and long-term mortality (Study III)

Study I was conducted as a prospective validation study. During a two-year period 831 patients presenting with upper gastrointestinal haemorrhage were included. The study demonstrated that the Glasgow Blatchford Score (GBS) was superior to the other risk scoring systems at predicting need for hospital-based intervention. The GBS was found to be favourable for the assessment of Danish patients presenting with symptoms of upper gastrointestinal haemorrhage. According to the findings of Study 1 implementation of the GBS at a 1000-bed hospital would be associated with a 90.000 EUR annual saving through avoidance of admission of patients in very low risk of needing hospital-based intervention. None of the examined risk scoring systems were suitable for predicting risk of rebleeding or 30-day mortality.

Study II was designed as a non-blinded, stratified, parallel group, randomized controlled trial. Patients were randomized in a 1:1 ratio to receive STAE within 24 hours from therapeutic endoscopy or to continue standard treatment. A total of 105 patients were included. After adjustment for possible imbalances STAE was associated with a clear trend of reduced rate of rebleeding (P=.079). Numbers needed to treat in order to avoid one case of rebleeding was 10.

Study III was conducted as a prospective cohort study. The long-term survival of 455 patients admitted with peptic ulcer bleeding was compared to an age- and sex-matched control group consisting of 2224 individuals selected from the same geographical area. Long-term mortality was adjusted for differences in comorbidity using the Charlson comorbidity index. The study demonstrated that peptic ulcer bleeding is associated with long-lasting excess mortality. Age, recurrent bleeding, and comorbidity were predictors for 30-day mortality. The underlying cause of 30-day mortality was in the majority of patients related to comorbidity. The main predictors for long-term mortality were old age, comorbidity, male sex, severe anaemia and tobacco use. Although severe anaemia predicted long-term mortality treatment with blood transfusion was not associated with long-term mortality per se.

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