Risk Stratification in Upper Gastrointestinal Bleeding: Prediction, Prevention and Prognosis

Risk stratification in upper gastrointestinal bleeding; Prediction, prevention and prognosis
Thesis with summary in Dutch, University of Utrecht

ISBN: 9789461085016
Printing, Cover, Layout: J. Grashof, P van Limbeek, Gildeprint drukkerijen, Enschede, the Netherlands

The printing of this thesis was financially supported by:
Afdeling Maag-, Darm- en Leverziekten UMC Utrecht, Nederlandse Vereniging voor Gastroenterologie, Ferring Pharmaceuticals BV, Chipsoft BV, Olympus Nederland BV, Vifor Pharma Nederland BV and Zambon Nederland BV

Risk Stratification in Upper Gastrointestinal Bleeding: Prediction, Prevention and Prognosis

Risicostratificatie in bovenste tractus digestivus bloedingen:
Predictie, preventie en prognose

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht op gezag van de rector magnificus,
prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op dinsdag 8 oktober 2013 des middags te 4.15 uur

door

Nicolette Louise de Groot

geboren op 28 augustus 1984 te Beverwijk

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Contents

Chapter 1

General introduction and outline of the thesis

Gastrointestinal toxicity

Non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin are among the most frequently prescribed drugs worldwide. NSAIDs are most commonly prescribed as painkillers, but also used for their anti-pyretic and anti-inflammatory properties. NSAIDs are indicated for various conditions in multiple organ systems, but NSAIDs are particularly used for musculoskeletal disorders. Low-dose aspirin on the contrary is mainly used for the prevention and treatment of (cardio)vascular diseases.

Both drugs work through a pathway in which the enzyme cyclooxygenase (COX) is inhibited, and with this the formation of prostaglandins and thromboxane. The COX enzyme has two subtypes: COX-1 and COX-2. The main function of COX-1 is to regulate various physiological processes such as protection of the gastric mucosa and platelet aggregation. COX-2 on the other hand is mainly involved in inflammation. Most NSAIDs and also low-dose aspirin inhibit both COX-1 and COX-2. This gives low-dose aspirin the ability to reduce cardiovascular events (by inhibiting platelet aggregation).

COX-1 inhibition also results in gastrointestinal side effects of these drugs, as it reduces the protection of the gastric mucosa against acid[1]. Frequent occurring GI side effects in NSAID and low-dose aspirin users are therefore dyspeptic symptoms, peptic ulcer disease and upper GI bleeding. A recent meta-analysis showed that NSAIDs increase the risk of dyspeptic symptoms such as upper abdominal pain, bloating, fullness and tenderness on palpation, with 36%[2]. The most serious side effect of COX inhibition is upper GI bleeding. The risk of such an event is overall low, but the relative risk is high and up to 4 times higher in patients using either NSAIDs or low-dose aspirin[3-6].

PART I

Predicting upper gastrointestinal bleeding

Identified predictors of upper GI bleeding in NSAID and low-dose aspirin users

In order to prevent serious GI complications of NSAID use several guidelines have been developed over the years[7-9]. The most important predictors for GI complications reported in guidelines and in the literature are prior GI complications, increasing age, concomitant use of NSAIDs or low-dose aspirin, and concomitant use of oral anticoagulants. Male gender has also been associated with an increased risk as is concomitant use of corticosteroids and SSRIs[10-13]. The guidelines stratify patients in various risk categories based on the presence or absence of these predictors.

However, the risk stratification tools that are mentioned in the guidelines are based on consensus agreement and not validated on individual patient data. In **Chapter 2** we aim to develop a prediction score for NSAID users and for low-dose aspirin users, based on individual patient data and we compare these scores with risk stratification tools from clinical guidelines.

Preventing upper gastrointestinal bleeding and other gastrointestinal complications

Gastroprotection overview

If it is possible to identify patients with an increased risk profile for GI complications, these patients can be treated preemptive with gastroprotective agents. Several gastroprotective agents have been developed and studied for their ability to reduce complications. The most commonly used gastroprotective agents are proton pomp inhibitors (PPI), histamine-2 receptor antagonist (H2RA) and misoprostol. Also replacement of non-selective NSAIDs with selective COX-2 inhibitors (coxibs) has been proven to be effective[14;15]. Yet, clear head-to-head comparisons between the different gastroprotective agents have not been made and PPIs are the most frequently recommended and prescribed gastroprotective agents. All these strategies are shown in the table below[3;16-18].

Gastroprotective strategy	Pro's	Con's
Proton pump inhibitors	Proven effective in reducing dyspepsia, gastric and duodenal ulcers and complications from these ulcers	Uncommon but serious side effects: *C. difficile* infections, bone fractures
H2 receptor antagonists	Proven effective in reducing gastric and duodenal ulcers	Poor compliance due to twice daily dosing
Misoprostol	Proven effective in reducing gastric and duodenal ulcers	Poor compliance due to commons side effects: abdominal pain, diarrhea
Coxibs	Proven effective in reducing gastric and duodenal ulcers	Less effective in prevention of dyspepsia The gastroprotective power negated when used concomitantly with low-dose aspirin Associated with an increased risk of cardiovascular events

Compliance and cost-effectiveness of different gastroprotective strategies

Gastroprotective agents together with NSAIDs or low-dose aspirin may be effective yet only when patients use these gastroprotective agents correctly. For example, several studies have shown that compliance to gastroprotective agents use is

suboptimal and the risk of upper GI complications increases with a decrease in compliance[19;20].

Therefore coxibs and recently developed combination tablets of NSAID or low-dose aspirin with gastroprotective agents in one pill may resolve compliance issues, and thereby be more effective in preventing GI complications. Several cost-effectiveness analyses have been performed to study which gastroprotective strategy is most effective in preventing upper GI complications in NSAID and low-dose aspirin users[21-23]. However, compliance was not taken into account in these models. Furthermore, another important aspect to consider is that the costs of PPIs have decreased to large extent more recently due to generic availability. So the question remains which strategy could be most cost-effective. In **Chapters 3 and 4** we perform two up to date cost-effectiveness analyses for NSAID and for low-dose aspirin users in which we will look at compliance but also incorporate the recently developed combination tablets in the models.

PART II

Predicting the outcome of upper gastrointestinal bleeding

Developed prediction scores for the outcome of GI bleeding

There is a large variation in severity of upper GI bleedings, with the spectrum varying from minor hematemesis in reflux oesophagitis to rapid exsanguination and death from bleeding from a aorto-enteral fistula[24]. Because of the potential disadvantageous outcome, almost all patients who present with upper GI bleeding are hospitalized and undergo endoscopy within twenty-four hours[25]. This leads to a high pressure on the hospital wards and endoscopy units, to a high burden for the patients and to high health care costs. An adequate prediction as to whether a patient requires an intervention and therefore hospital admission could therefore be helpful. For patients with a high risk for rebleeding and/or mortality closer monitoring in an intensive or medium care unit should ideally be arranged in advance. Unfortunately, predicting these outcomes tends to be difficult in this specific population. Many prediction scores have been developed over the last decades[26-29]. In **Chapter 5** we aim to identify all published prediction scores for the outcome of GI bleeding and we compare their predictive power and methodological quality. The most popular and most often recommended scores in guidelines are the Blatchford score – a score based on pre-endoscopic predictors, which predicts the need for an intervention – and the Rockall score, which also includes endoscopic predictors and is developed to predict mortality[25;30]. However, the implementation of these scores in clinical practice is still low. A possible reason could be that

gastroenterologists continue to use their own clinical intuition or believe that their 'gut feeling' is sufficient for predicting the outcome of patients presenting with upper GI bleeding. Indeed, these risk stratification scores have never been compared to the current risk estimation of clinical judgment. In **Chapter 6** we report a study that actually compares the gut feeling of experienced gastroenterologists with the Blatchford and the Rockall prediction scores.

Predictors for the outcome of upper GI bleeding

A predictor for the outcome of upper GI bleeding which has often been studied over the last few years is 'day of admission', that is the difference between weekend and weekday, or even more detailed differences between during and after office hours. Conflicting results exist as to whether weekend admission is associated with an increased risk of mortality in this patient population[31;32]. In **Chapter 7** we aim to study whether there is a possible association between time and day of admission and the outcome of patients presenting with upper GI bleeding.

Another commonly used predictor for outcome of patients with peptic ulcer bleeds is the Forrest classification. The Forrest classification was introduced in 1974 and thereafter this classification has been used as predictor for rebleeding and to a lesser extent mortality[33]. Although this classification was originally developed to classify peptic ulcers, more than three decades later, we still use the Forrest classification as a prognostic index. Since then, much has however changed in the etiology and treatment of peptic ulcer bleeds. More and more patients are now using prescribed but also over-the-counter NSAIDs, low-dose aspirin and anticoagulants, all known for their increased risk for peptic ulcer bleeding. Although infection with *Helicobacter (H.) Pylori* is still a risk factor for peptic ulcer bleeding, the incidence rate of this infection is declining and eradication reduces the recurrence and chronicity of ulcers[34]. Moreover, endoscopic advancements such as combination treatments including injection therapy, bipolar coagulation and endoscopic clip placement have changed management of peptic ulcer bleeds considerably. Perhaps the most significant improvement since the development of the Forrest classification has been the use of (intravenously administered) PPIs[35]. With these changes the predictive power of the Forrest classification may also have changed. In **Chapter 8**, we investigate the predictive power of the Forrest classification and aim to update the Forrest classification for the prediction of rebleeding. In the final **Chapter 9** of this thesis we aim to incorporate the gut feeling of the gastroenterologist and objective variables in a newly developed prediction score to identify patients who need to be admitted to the hospital.

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PART

Prediction and prevention of upper GI bleeding in NSAID and low-dose aspirin users

Chapter 2

Primary non-variceal upper gastrointestinal bleeding in NSAID and low-dose aspirin users: development and validation of risk scores for either medication in two large Dutch cohorts

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Accepted for publication in Journal of Gastroenterology

ABSTRACT

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose acetylsalicylic acid (ASA) have several adverse gastrointestinal (GI) effects, including upper GI bleeding. We aimed to develop a simple risk score to identify high risk NSAID and ASA users for primary upper GI bleeding.

METHODS

Using data from two large anonymized health insurance databases, we defined a development and validation cohort with NSAID and ASA users which were followed-up for the occurrence of a primary upper GI bleeding. Cox regression analyses identified risk factors which were combined into simple risk scores. C-statistics were used to evaluate the discriminative ability of these scores in a validation cohort.

RESULTS

In total, 421 cases of upper GI bleeding were identified in the initial cohort of 784,263 NSAID users (incidence rate 54.2 per 10,000 person-years), while 1295 cases of upper GI bleeding were identified in 235,531 ASA users (incidence rate 37.9 per 10,000 person-years). The risk of upper GI bleeding increased with a higher risk score, which for NSAID users included age, male gender, anemia and concomitant use of ASA or anticoagulants. For ASA users, age, anemia, diabetes and concomitant use of other antiplatelet drugs or anticoagulants were included in the risk score. The C-statistics in the validation cohort were 0.68 and 0.63 or NSAID and ASA users, respectively.

CONCLUSION

Risk factors for primary upper GI bleeding are to a large extent similar for NSAID and ASA users. Using a risk score based on these risk factors, patients at the highest risk can be identified with moderate accuracy.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose acetylsalicylic acid (ASA) use are two major risk factors for gastrointestinal bleeding. NSAID use is associated with an up to 5-fold increased risk for upper GI bleeding[1;2]. For ASA the risk for gastrointestinal bleeding was almost two times higher compared to patients using placebo[3-5]. Although the absolute risks are relatively low, the use of NSAIDs and ASA is extensive, and the numbers will increase in the near future with expansion of treatment indications and aging of the population. For example, an estimated 50 million US citizens have started taking aspirin over the last twenty years[6].

Several risk factors for developing upper GI bleeding in patients using NSAIDs and ASA have been identified[7-9]. In a recent systematic review of the current guidelines, we identified a history of peptic ulcer disease, older age, concomitant use of anticoagulants and corticosteroids and the use of multiple NSAIDs (including ASA) as the most commonly applied risk factors in current guidelines[10]. Other risk factors, i.e. use of high-dose NSAIDs, concomitant use of SSRIs (selective serotonin reuptake inhibitors), severe rheumatoid arthritis and cardiovascular disease were not indicated in all guidelines.

In order to support clinical decision-making, and to provide input for guidelines for GI risk management in NSAID or ASA users, an analysis of individual patient data is needed. We hypothesized that individual risk profiles could lead to a more accurate prediction of GI bleeding. Risk stratification has been proposed based on these risk factors identified from previous studies, yet these risk stratifications were based on consensus among experts[11;12]. Although many studies have focused on risk factors for NSAID and/or ASA related GI complications, no proper risk score has been developed so far. The aim of our study was therefore to identify predictive factors for upper GI bleeding in patients using NSAIDs and/or ASA and to incorporate these risk factors in an easy to use score. We chose to include patients without a history of previous GI bleeding as this is the area where guidelines need a proper risk score to see what subgroup of patients are at an increased risk for a GI bleed.

METHODS

Data sources

For the purpose of this study we analyzed two different databases, both using data from Dutch health insurance companies (AGIS and ACHMEA). These cohorts were very similar, and have been used before, mostly combined in one large cohort[13;14].

For this study we used the databases separately as a development and a validation cohort. The development cohort contained data from a large anonymized database of one of the Dutch health insurance companies covering 2.8 million Dutch inhabitants which is approximately 17% of the total population. Data included patient characteristics, pharmaceutical prescriptions and in-hospital diagnoses based on DRGs (diagnosis related groups). Each reimbursed prescription record contained information on the dispended product according to the Anatomical Therapeutic Chemical (ATC) classification, date and number of doses provided. Prescribed number of units per day was not available. Registration of drugs is based on reimbursement of costs that is strictly controlled. For the validation cohort, data were extracted from a different large anonymized Dutch health insurance database with comparable data covering 1.2 million Dutch inhabitants.

Study cohort

The development cohort had a time span of four years (January 1st 2006 until January 1st 2010). Patients were included if they were 18 years or older and registered for at least one year with the insurance company on January 1st 2005. Patients were considered NSAID or low-dose aspirin users if they had a minimum of one filled prescription (≥7 defined daily dose) for NSAID or ASA or a combination of these medications. The study cohort was restricted to new (no prescription the past 30 days) NSAID and ASA users. Patients with documented use of NSAIDs/ASA in the 30 days before the index NSAID prescription date were excluded from the analysis in order to solely study new users. Patients were followed until the end of medication use (with an extra 30 days after ending the medication to account for carryover effects) , until developing an upper GI bleeding or until death.

NSAID and ASA users in the cohort used for validation were identified in the same manner as the development cohort. However, in this cohort we used a nested case-control design over a time span of five years (January 1st 2005 until January 1st 2010). Case patients were defined as patients with a first upper GI bleeding episode identified by an automatic electronic search on DRGs. We sampled up to 100 random controls per case from the cohort of new users of NSAIDs and low-dose aspirin, matched on index date.

Exposure definition

We considered a patient to be exposed to the medication from the time of the initial dispensation of a prescription to the following dispensation or end of prescription, as long as the calculated overall medication possession rate did not fall under 0.7 standard doses per day. We used the following ATC-codes for NSAIDs: M01AB01, M01AB02, M01AB05, M01AB55, M01AC01, M01AE01, M01AE02, M01AE03, M01AE52, N02BA01 and for low-dose aspirin: B01AC06, B01AC08 N02BA15.

Outcome and case definition

Our primary outcome was presence of primary upper gastrointestinal bleeding, defined by diagnosis related groups (DRGs), while on NSAID and/ or ASA use. Patients with a history upper GI bleeding were excluded from the analysis. We considered a case to be exposed to either NSAID and/ or ASA if that patient was exposed within 30 days before the event date. We used this cut-off to account for carryover effects associated with the medication that may persist for a time following the last prescription.

Study variables

We considered a limited set of candidate risk factors based on plausibility, reliability and distribution: age, gender, prior episodes of NSAID/ ASA use, history of peptic ulcer disease, anemia, comorbidities (i.e. cardiovascular diseases, cerebrovascular diseases, rheumatoid arthritis, osteoarthritis, diabetes mellitus, gastro-esophageal reflux disease and dyspepsia) and concomitant use of other NSAIDs, previous episodes of NSAID use, antiplatelet therapy (including ASA), anticoagulants, systemic corticosteroids, SSRIs and gastroprotective agents (GPAs) (proton pump inhibitors, H2 receptor antagonist and misoprostol). Concomitant use of other drugs was defined as a minimum of 80% overlap between the drug of interest and NSAIDs and/or ASA; or concurrent use of both medications within 7 days prior to the time of an event. Patients with a history of the above mentioned diseases were defined as those with a running DRG for that diagnosis in the year before the index date.

Statistical analysis

Standard descriptive statistics were used to assess baseline characteristics of the study cohorts.

We analyzed the data by episodes of NSAID or ASA use. Univariable analyses with the Pearson χ^2 and Student's t-test were used whenever appropriate to compare baseline characteristics between cases and controls of both NSAID and ASA users. Candidate risk factors with p-values less than 0.10 in univariable analyses were entered in a Cox proportional hazard regression analysis to determine their independent contribution to risk estimation of upper GI bleeding per unit of time. Statistical significance was considered if $p<0.05$.

To develop an easy to use score, we then identified the five most important risk factors, based on a backward stepwise elimination using likelihood ratio statistics. Risk factors were assigned an integer point based on a common denominator across all beta coefficients of the risk factors[15]. We quantified the discriminatory value with a C-statistic, with a C statistic of 0.5 indicating no, and a value of 1.0, indicating perfect discrimination between high and low risk patients.

For each ASA user the risk stratification tool from the ACCF/ACG/AHA guideline by Bhatt et al[16] was calculated and for NSAID users also the risk stratification tool from the ACG guideline by Lanza et al[12]. As our goal was to predict and prevent a patient's primary upper GI bleeding, history of upper GI bleeding could not be extracted. Sensitivity and specificity rates were calculated for both risk scores (with different cut-off points) compared to the risk stratification tool from the guidelines. The percentage of the cohort that would be treated according to the risk stratification tools was calculated. We validated the risk scores in the validation cohort by calculating the C statistics in these cohorts. We also validated our score in a subgroup of patients who did not use gastroprotective agents.

Ethical considerations

This study was carried out with the approval of and in accordance with the privacy and ethical guidelines of the research committee of the Agis Health Database. This study was financed by an unrestricted research grant from AstraZeneca B.V. the Netherlands. The sponsor had no access to the study data.

RESULTS

NSAIDs

The initial cohort comprised 784,263 NSAID users. Over a median follow-up of 15 (Interquartile range (IQR) 10.0-22.5) days, a total of 421 (absolute risk 0.05%) cases of primary upper GI bleeding were identified corresponding with an incidence rate of 54.2 per 10,000 person years of follow-up. Mean time to event was 115 days with a median of 35 (IQR 12-119) days (**Figure 1**). Baseline characteristics of NSAID users that did (cases) and did not (controls) develop upper GI bleeding are displayed in **Table 1.** All variables with a p-value of <0.10 were entered in a multivariate Cox regression analysis to analyze factors that could be incorporated in our risk score. At this point, we did not include concurrent PPI and H2RA use. Independent risk factors of upper GI bleeding were increasing age, male gender, ASA and/or anticoagulants, corticosteroid use, a history of peptic ulcer disease, anemia, gastroesophageal reflux disease (GERD) and liver cirrhosis. One or more previous episodes of NSAID use were independently associated with a lower risk of upper GI bleeding. The adjusted hazard ratios are displayed in **Table 1**.

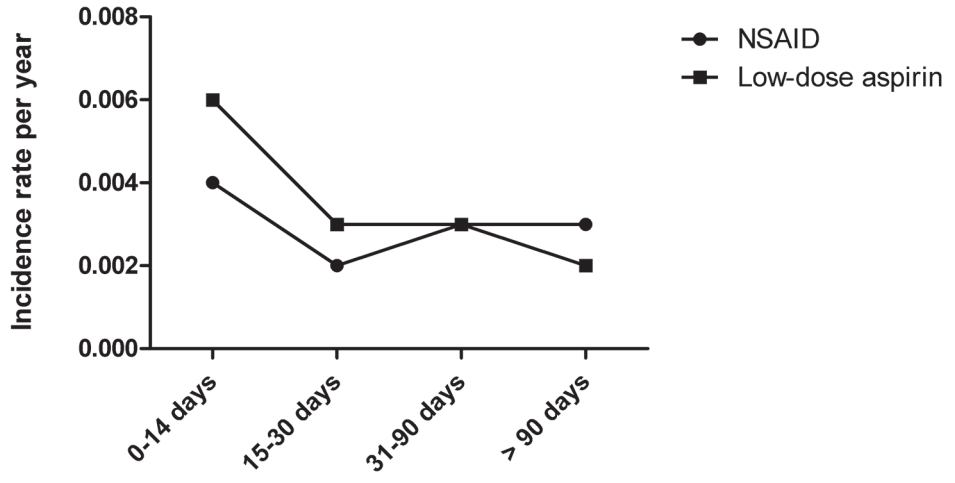

Figure 1 Time to primary upper GI bleeding for both NSAID and ASA users

Table 1 Baseline characteristics of NSAID users in the development cohort (n=784,263)

	NSAID					
	Cases 421 (%)	Controls 783,842 (%)	p-value	Unadjusted HR	Adjusted HR	95% CI
Age	66 (SD 17)	50 (SD 17)	<0.01	1.03 (1.03-1.04)		
Age						
18-60	139 (33.0)	553,168 (70.6)	<0.01	Reference	Reference	
60-70	79 (18.8)	117,768 (15.0)		1.7 (1.3-2.2)	1.3	0.99-1.8
>70	203 (48.2)	112,906 (14.4)		3.5 (2.8-4.4)	**2.4**	**1.9-3.0**
Sex (male)	199 (47.3)	356,043 (45.4)	0.46	1.3 (1.1-1.6)	**1.4**	**1.1-1.7**
NSAIDs						
Non-selective NSAID	333 (79.1)	684,533 (87.3)	<0.01	1.02 (0.8-1.3)		
COXIB	64 (15.2)	45,256 (5.8)	<0.01	0.9 (0.7-1.1)		
Single tablet NSAID+PPI	66 (15.7)	69,918 (8.9)	<0.01	1.2 (0.9-1.5)		
Combination of above	32 (9.5)	15,448 (2.0)	< 0.01	1.04 (0.8-1.5)		
Concomitant drug use						
ASA	102 (24.2)	53,320 (6.8)	<0.01	3.9 (3.1-4.8)	**2.5**	**2.0-3.3**
Other antiplatelet therapy	10 (2.4)	5799 (0.7)	<0.01	3.2 (1.7-5.9)	1.1	0.6-2.1
Anticoagulant therapy	24 (5.7)	11,421 (1.5)	<0.01	6.1 (4.0-9.2)	**3.9**	**2.5-6.1**
Corticosteroids	12 (2.9)	6531 (0.8)	<0.01	3.3 (1.8-5.8)	**1.8**	**1.0-3.2**
SSRIs	17 (4.0)	21,687 (2.8)	0.08	1.5 (0.9-2.4)		
Gastroprotective drugs						
PPI	202 (48.0)	202,685 (25.9)	<0.01	2.0 (1.7-2.4)		
H2RA	8 (1.9)	5268 (0.7)	<0.01	2.5 (1.2-5.0)		

	NSAID					
	Cases 421 (%)	Controls 783,842 (%)	p-value	Unadjusted HR	Adjusted HR	95% CI
History of PPI use	201 (47.7)	167,344 (21.3)	<0.01	1.6 (1.3-1.9)	1.2	0.9-1.4
Comorbidity						
Dyspepsia	1 (0.2)	1329 (0.2)	0.51	1.3 (0.2-9.2)		
GERD	6 (1.4)	2058 (0.3)	<0.01	4.5 (2.0-10.2)	**3.9**	**1.7-9.2**
History of PUD	1 (0.2)	78 (0.0)	0.04	17.6 (2.5-125.1)	**10.2**	**1.4-73.3**
Treated H Pylori in past	3 (0.7)	2443 (0.3)	0.15	2.2 (0.7-6.7)		
Cardiovascular disease	33 (7.8)	13,668 (1.7)	<0.01	3.8 (2.6-5.4)	1.7	1.1-2.6
Cerebrovascular disease	5 (1.2)	5076 (0.6)	0.07	1.2 (0.5-2.8)		
DM	61 (14.5)	46,683 (6.0)	<0.01	1.7 (1.3-2.2)	1.1	0.7-1.6
Rheumatoid arthritis	21 (5.0)	5789 (0.7)	<0.01	1.3 (0.8-2.0)		
Osteoarthritis	6 (1.4)	3474 (0.4)	0.01	0.9 (0.4-2.1)		
Liver cirrhosis	2 (0.5)	292 (0.0)	0.01	12.1 (3.0-45.6)	**9.6**	**2.4-39.1**
Anemia	66 (15.7)	33,226 (4.2)	<0.01	1.9 (1.5-2.5)	**1.5**	**1.0-2.2**
More than 1 comorbidity	151 (35.9)	95,495 (12.2)	<0.01	2.1 (1.7-2.6)	1.1	0.7-1.6
More than 1 episode of prior NSAID use	180 (42.8)	326,703 (41.7)	0.66	0.8 (0.7-0.96)	**0.8**	**0.7-0.98**

ASA = low-dose aspirin, DM = Diabetes Mellitus, GERD = gastroesophageal reflux disease, GI = gastrointestinal, HR = Hazard ratio H2RA = H2 receptor antagonist, NSAID = non-steroidal anti-inflammatory drugs, PPI = proton pump inhibitors, PUD = peptic ulcer disease, SSRI = selective serotonin reuptake inhibitors

Risk score

The five most important risk factors were used in a simplified risk score (**Table 2**). The score ranges from 0 to 11. The risk profile of patients was divided into a low (score <1 point) and an elevated risk (≥1 points). **Figure 2** shows the observed upper GI bleeding rate for each score. The C statistic in the initial cohort, measuring the discriminative power of the score, was 0.68 (CI 0.63-0.71). This risk score was externally validated in a second population with 107,012 NSAID users, wherein a total of 207 cases of upper GI bleeding were identified. The mean age was 49 years (SD 18) and median follow-up time was 15 days (IQR 10-25). The prognostic score, developed in the initial cohort, was calculated for each patient in the validation cohort, and plotted against the observed upper GI bleeding rate. The C statistic for the NSAID validation cohort was 0.68 (CI 0.63-0.74). The risk score was then validated in a subgroup of patients who did not receive a GPA concomitant to NSAID. The C statistic in this group was 0.65 (CI 0.59-0.70). With the developed risk score a sensitivity of 85.1% could be reached at a cut-off of ≥1 point, with 64% of the cohort requiring additional gastroprotective treatment (**Table 3**).

Table 2 The risk score for NSAID users

Risk factors	Adjusted HR	95% CI	B coefficient	Score
Age				
18-60	Reference			
60-70	1.4	1.1-1.8	0.33	1
>70	2.6	2.0-3.3	0.95	2
Male gender	1.4	1.2-1.7	0.34	1
Comorbidities				
Anemia	1.4	1.3-2.2	0.53	1
Medication				
ASA	2.7	2.1-3.4	0.99	2
Anticoagulants	4.8	3.1-7.3	1.56	4
Total score				**11**

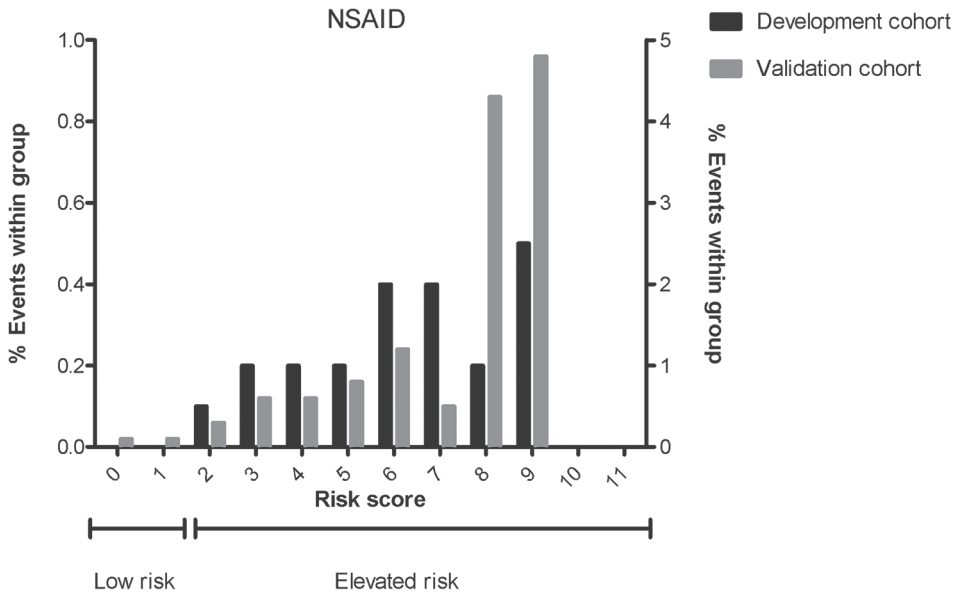

Figure 2 Performance of the NSAID risk score

Low-dose acetylsalicylic acid (ASA)

A total of 1295 cases (absolute risk 0.5%) were identified in 235,531 ASA users. The median follow-up time was 530 (IQR 146-1014) days. The incidence rate per 10,000 follow up years was 37.9. The mean time to event was 319 days with a median of 248 days to event (IQR 90-484) (**Figure 1**). Baseline characteristics of ASA users of the cases and controls are displayed in **Table 4.** At multivariable analyses, increasing age, male gender and concomitant use of NSAIDs, coxibs, antiplatelet therapy, anticoagulant therapy, SSRIs, a history of PPI use and corticosteroids were found to be independent risk factors for upper GI bleeding. Presence of the following comorbid entities were also significantly associated with a higher risk of upper GI bleeding: diabetes mellitus, anemia, peptic ulcer disease and liver cirrhosis. One or more previous episodes of ASA use were independently associated with a lower risk of upper GI bleeding

Risk score

A total of five risk factors were retained for a simple risk score (**Table 5**). Based on their risk profile, patients could score a maximum of 15 points, and the scores were subdivided into a low (score <1 point) and an elevated risk (≥1 points). **Figure 3** shows the observed upper GI bleeding rate for each score. The C statistic, measuring the discriminative power of the score, was 0.64 (CI 0.63-0.66). This risk score was externally validated in 32.613 ASA users, wherein a total of 470 cases were identified. The mean age was 69 year (SD 13) and the median follow-up time 359 days (IQR 116-902). The prognostic score had a C statistic of 0.63 (CI 0.60-0.66) in the validation cohort and 0.63 (CI 0.61-0.65) in the subgroup of patients who did not receive GPAs concomitant to low-dose aspirin. Depending on the cut-off point of the developed score, the risk score showed high sensitivity rates for identifying patients at risk (90.9% at a cut-off ≥1 point), but with 83.1% of the patients requiring gastroprotective treatment (**Table 3**).

Table 3 Score and guideline; sensitivity and specificity

	NSAID development cohort			NSAID validation cohort		
	Percentage of cohort	Sensitivity	Specificity	Percentage of cohort	Sensitivity	Specificity
Cut off score ≥1 point	65.0%	86.8%	35%	64.2%	85.1%	35.8%
Cut off score ≥ 2 points	25%	64.2%	75.1%	27.0%	64.0%	73.1%
Guideline ACG‡	24.3%	62%	75.7%	24.4%	62.2%	75.6%
Guideline ACG/AHA†	8.9%	31.4%	91.1%	9.2%	29.3%	90.9%
	ASA development cohort			**ASA validation cohort**		
Cut off score ≥ 1 point	83.1%	93.5%	17%	83.1%	90.9%	18.8%
Cut off score ≥ 2 points	62.1%	78.5%	38%	60.4%	76.8%	39.9%
Guideline ACG/AHA†	7.9%	14.8%	92.2%	8.6%	16.8%	91.5%

† ACCF/ACG/AHA guideline Bhatt et al[16]
‡ ACG guideline Lanza et al 12

Table 4 Baseline characteristics of ASA users in the development cohort (n=235,531)

	ASA					
	Cases 1295 (%)	Controls 234,236 (%)	p-value	Unadjusted HR	Adjusted HR	95% CI
Age	73 (SD 11)	69 (SD 13)	<0.01	1.02 (1.02-1.03)		
Age						
18-60	149 (11.5)	53,247 (22.7)	<0.01	Reference	Reference	
60-70	296 (22.9)	59,488 (25.4)		1.6 (1.3-1.9)	**1.6**	**1.3-1.9**
>70	850 (65.6)	121,501 (51.9)		2.2 (1.9-2.7)	**2.2**	**1.9-2.6**
Sex (male)	736 (56.8)	126,318 (53.9)	0.04	0.9 (0.8-1.1)	**1.3**	**1.1-1.4**
ASPIRIN						
Low-dose aspirin	1286 (99.3)	232,201 (99.1)	0.65	1.2 (0.6-2.3)		
Single tablet aspirin + antiplatelet	19 (1.5)	3369 (1.4)	0.92	0.96 (0.6-1.5)		
Concomitant drug use						
Non-selective NSAIDs	15 (1.2)	1489 (0.6)	0.03	3.5 (2.1-5.8)	**2.7**	**1.6-4.5**
Coxib	12 (0.9)	561 (0.2)	<0.01	6.0 (3.4-10.6)	**5.1**	**2.9-9.0**
Single tablet NSAID+PPI	9 (0.7)	381 (0.2)	<0.01	7.0 (3.6-13.4)	**5.2**	**2.7-10.1**
Anticoagulant therapy	24 (1.9)	1082 (0.5)	<0.01	16.7 (11.1-25.1)	**14.6**	**5.6-22.1**
Antiplatelet therapy	145 (11.2)	14,800 (6.3)	<0.01	2.3 (1.9-2.7)	**2.2**	**1.8-2.7**
Corticosteroids	22 (1.7)	2106 (0.9)	<0.01	3.8 (2.5-5.8)	**2.3**	**1.5-3.5**

	ASA					
	Cases 1295 (%)	Controls 234,236 (%)	p-value	Unadjusted HR	Adjusted HR	95% CI
SSRIs	35 (2.7)	4558 (1.9)	0.05	1.7 (1.2-2.4)	**1.5**	**1.1-2.1**
Gastroprotective drugs						
PPI	281(21.7)	36,503 (15.6)	<0.01	1.8 (1.6-2.1)		
H2RA	19 (1.5)	1407 (0.6)	<0.01	2.7 (1.7-4.3)		
History of PPI use	522 (40.3)	81,227 (34.7)	<0.01	1.4 (1.3-1.6)	**1.2**	**1.1-1.4**
Comorbidity						
Dyspepsia	3 (0.2)	467 (0.2)	0.75	1.5 (0.5-4.5)		
GERD	6 (0.5)	906 (0.4)	0.65	1.4 (0.6-3.1)		
History of PUD	4 (0.3)	108 (0.0)	<0.01	7.1 (2.7-18.9)	**3.9**	**1.4-10.4**
Treated H Pylori in past	8 (0.6)	774 (0.3)	0.08	2.2 (1.1-4.5)	1.7	0.9-3.5
Cardiovascular disease	143 (11.0)	24,301 (10.4)	0.43	1.3 (1.1-1.5)	1.1	0.9-1.4
Cerebrovascular disease	98 (7.8)	15,236 (6.5)	0.12	1.2 (0.98-1.5)	0.9	0.8-1.2
DM	315 (24.3)	42,354 (18.1)	<0.01	1.4 (1.3-1.6)	**1.4**	**1.1-1.7**
Rheumatoid arthritis	23 (1.8)	2041 (0.9)	<0.01	2.2 (1.4-3.3)	1.0	0.7-1.6
Osteoarthritis	9 (0.7)	1117 (0.5)	0.26	1.7 (0.9-3.3)	1.4	0.7-2.8
Liver cirrhosis	6 (0.5)	183 (0.1)	<0.01	8.4 (3.8-18.8)	**5.3**	**2.3-11.9**
Anemia	229 (17.7)	18,941 (8.1)	<0.01	2.7 (2.3-3.1)	**2.3**	**1.9-2.8**
More than 1 comorbidity	578 (44.6)	77,834 (33.2)	<0.01	1.7 (1.5-1.9)	0.97	0.8-1.2
More than 1 episode prior	367 (28.3)	93,548 (39.9)	<0.01	0.9 (0.8-1.1)	**0.9**	**0.8-0.99**

ASA = low-dose aspirin, DM = Diabetes Mellitus, GERD = gastroesophageal reflux disease, GI = gastrointestinal, HR = Hazard ratio H2RA = H2 receptor antagonist, NSAID = non-steroidal anti-inflammatory drugs, PPI = proton pump inhibitors, PUD = peptic ulcer disease, SSRI = selective serotonin reuptake inhibitors

Table 5 The risk score for low-dose aspirin users

Risk factors	Adjusted HR	95% CI	B coefficient	Score
Age				
18-60	Reference			
60-70	1.6	1.3-1.9	0.46	1
>70	2.2	1.8-2.6	0.77	2
Comorbidities				
Anemia	2.4	2.1-2.8	0.88	2
DM	1.4	1.2-1.5	0.30	1
Medication				
Other antiplatelet use	2.2	1.9-2.7	0.80	2
Anticoagulants	16.5	10.9-24.8	2.80	7
Total score				**15**

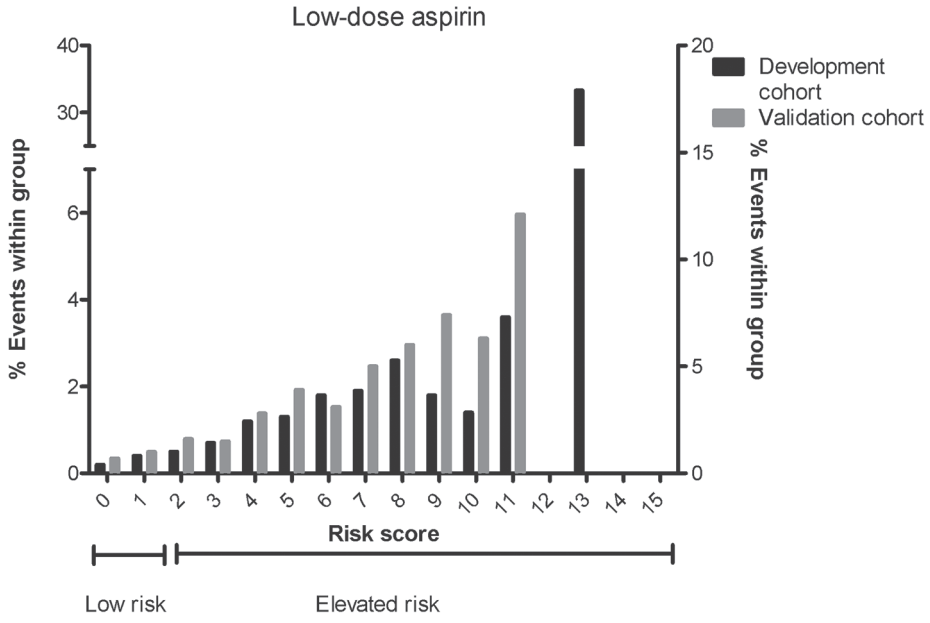

Figure 3 Performance of the ASA risk score

DISCUSSION

NSAIDs and ASA are among the most commonly prescribed drugs worldwide and account for an up to 4 times increased risk for upper GI bleeding. In two large databases, we showed that age, a history of anemia, and antiplatelet and anticoagulant use were the most important risk factors for upper GI bleeding in both NSAID and low-dose aspirin users. Based on the risk factors found, we developed easy-to-use risk scores enabling the identification of patients at a high risk of a primary GI bleeding while using NSAIDs or ASA. Although the risk of upper GI bleeding increased with a higher score, we found that the predictive power of the scores was only moderate. External validation was performed within a second cohort. The predictive power of the scores in the validation cohort was comparable to the initial cohort and the validation cohort showed high sensitivity rates for identifying upper GI bleeding in both scores. However, many patients were found to be at an increased risk and might need additional gastroprotective treatment to accomplish such a high sensitivity.

Recently, a considerable number of studies have focused on risk factors for upper GI bleeding in NSAID and ASA users[7-9;17-22]. Laine et al. performed two studies in arthritis patients using NSAIDs, and identified prior GI events, increasing age and concomitant use of low-dose aspirin as being the most important risk factors for upper GI bleeding[7;9]. Castellsague et al. performed a case-control study in a health insurance database to assess the risk of upper GI bleeding in patients using NSAIDs and identified similar risk factors: age, male gender, prior GI events, ischemic heart disease, anemia, ASA use and anticoagulant use[8]. A large study in almost 3,000 arthritis patients showed similar results, however, the authors focused on GI related hospitalization and/or death. Apart from the already mentioned risk factors, Hansen et al[19] reported that dyspepsia was a risk factor for ulcer complications. Four other studies focused on the risk and possible risk factors for upper GI bleeding in low-dose aspirin users[17;21;22;23]. They found that prior complications in the GI tract, aspirin dose, concomitant use of NSAIDs and dual antiplatelet therapy and anticoagulant use were risk factors.

Partially based on these studies, clinical guidelines have been developed incorporating recommendations for the prevention of GI complications. These guidelines differentiate between low/ medium/ high risk groups for upper GI complications, but the stratifications are based on consensus statements. Interestingly, in these guidelines different risk factors were included, even when the same publications were available from a systematic review[10;24]. This encouraged us to develop a risk stratification tool based on individual patient data and to assess the predictive power of such a tool. We also compared the sensitivity and specificity of recommendations in the current guidelines with those of our risk scores in the validation cohort. The risk stratification tools from the guidelines revealed lower sensitivity rates, and relatively low numbers of patients to be treated (**Table 3**). However, we were not able to account for 'a history of previous GI bleeding' which was a important risk factor in both guidelines and 'high dose NSAIDs' which was a risk factor in one guideline[12].

Apart from confirming known risk factors, we also identified new risk factors which were not included in current guidelines. For both NSAID and ASA users, men were more prone to develop upper GI bleeding compared to women. For NSAID users, male gender was one of the five most influential risk factors and was incorporated in the risk score. Castellsague et al[8] also found that men had a higher risk compared to women and Laine et al[9] reported that women experienced fewer upper GI clinical events, although this was not present in their results when they focused on complicated upper GI events as an outcome. We also found that patients were at highest risk for developing an upper GI bleeding in the first weeks after start of their NSAID/ASA. In other words, if a patient will develop upper GI bleeding, most bleeding cases will occur during the first 14 days. Our prediction

score is therefore most accurate for predicting early events, even though we have analyzed data using a proportional hazards approach. Weil et al. found comparable results and hypothesized that this can be explained by the use of aspirin for relieving symptoms from an incipient peptic ulcer[25]. However, the exact underlying mechanisms for this trend over time could unfortunately not be analyzed with our dataset.

A potential limitation of our study was that our choice of risk factors in our conceptual model was based on previous studies, and the plausibility, reliability and distribution of factors between cases and controls. We excluded gastroprotective agents (GPAs, i.e. PPI, H2RA and misoprostol use) from our risk score, even although patients using GPAs were at an increased risk of upper GI bleeding. Including GPAs in our final risk score as risk factor for upper GI bleeding would make our score less plausible and probably confusing in clinical practice. We chose not the exclude patients who started using a GPA concomitantly with the NSAID/ASA as this would have resulted in the selection of lower risk patients. We did however validate our score in subgroups of patients not using gastroprotective agents during NSAID or ASA use and found a comparable predictive power of the score in these populations. Our score can also not be applied to patients with a history upper GI bleeding, as these were excluded from our analyses. Risk management and treatment of this group of patients has been established over the years. Secondly, although we found an increasing risk for upper GI bleeding with a higher score, the C statistic was moderate. An C statistic of 0.5 would indicate no predictive power and our scores ranged between a C statistic of 0.63 and 0.68. Future research should focus on improving the predictive power of comparable risk scores. Thirdly, our analyses were based exclusively on administrative claims, which did not include over-the-counter (OTC) medication use. OTC aspirin, NSAIDs and PPIs can be obtained in the Netherlands; however, when these drugs are prescribed they are reimbursed by the health insurance companies and therefore OTC use is expected to be relatively low in the Netherlands. Furthermore, OTC use of gastroprotective agents is no problem for the findings of this study as PPIs only became available over-the-counter in 2010 and our dataset ends in 2010. Moreover, we analyzed NSAID/ ASA use on the quantity supplied on the reimbursed prescriptions under the assumption that the dispensed medication was actually ingested by that particular patient. Finally, the use of administrative data is also subject to incompleteness and inaccuracy of coding. For example we had no access to data regarding the prescribed number of units per day and therefore we were not able to account for dosage of NSAID and/or ASA.

An important strength of our study is the large population that we included which is a good reflection of the Dutch population. We were able to develop and validate a prediction score for NSAID and ASA users separately. This was necessary as ASA might reflect a different population than NSAID users and ASA is

often used for a longer duration than NSAIDs, which we also found in our cohorts. Secondly, we performed an external validation, which showed comparable performance results, assuming application of this score in other populations will result in a comparable predictive power as well. Extrapolation of our score was further improved by including all users (i.e. short and long term users, selective and non-selective NSAID users). The use of cox regression analyses enabled us to take duration of drug use into account. Lastly, by developing a conceptual model with a tight selection of variables included in the analyses, the risk of overfitting the data was minimized.

The development of our risk score may have several implications for clinical practice. Patients at an increased risk of upper GI bleeding should be co-treated with gastroprotection. If patients are already prescribed gastroprotection, physicians could pay more attention to compliance of gastroprotection or convert GPA co-therapy to a single tablet formulation. In patients at an increased risk of upper GI bleeding, physicians should reconsider the indication of the NSAIDs and/or low-dose aspirin, and the possibility for alternative treatment strategies, which have less GI toxicity. Patients at a low risk of upper GI bleeding probably do not need extra gastroprotective measures. However, it can be considered to prescribe all patients on NSAIDs and low-dose aspirin a PPI as it might be cost-effective due to the low costs of generic PPI availability[26;27].

In conclusion, risk factors for upper GI bleeding in NSAID and ASA users were largely similar. The easy-to-use risk score showed an increasing risk with an increasing score and had moderate discriminative power for both groups. With this validated risk score, treatment measures like co-prescribing GPAs can be applied for patients at increased risk for upper GI bleeding. Further validation and improvement of the proposed risk scores is required.

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The final publication is available at; http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s00535-013-0817-y

Chapter 3

Gastroprotective strategies in chronic NSAID users: a cost-effectiveness analysis comparing single tablet formulations with individual components

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Accepted for publication in Value in Health

ABSTRACT

BACKGROUND

To evaluate the cost-effectiveness of competing gastroprotective strategies, including single tablet formulations, in the prevention of gastrointestinal (GI) complications in chronic arthritis patients taking non-steroidal anti-inflammatory drugs (NSAIDs).

METHODS

We performed a cost-utility analysis to compare eight gastroprotective strategies including NSAIDs, cyclooxygenase-2 inhibitors, proton pump inhibitor (PPI), histamine-2 receptor antagonists, misoprostol, and single tablet formulations. We derived estimates for outcomes and costs from medical literature. Primary outcome was incremental cost per quality adjusted life year gained. We performed sensitivity analyses to assess the effect of GI complications, compliance rates, and drug costs.

RESULTS

For average risk patients, NSAID+PPI co-therapy was most cost-effective. The NSAID/PPI single tablet formulation only became cost-effective when its price decreased from €0.78 to €0.56 per tablet, or when PPI compliance fell below 51% in the NSAID+PPI strategy. All other strategies were more costly and less effective. The model was highly sensitive to the GI complication risk, costs of PPI and NSAID/PPI single tablet formulation, and compliance to PPI. In patients with a 3-fold higher risk of GI complications, both NSAID+PPI co-therapy and single tablet formulation were cost-effective.

CONCLUSION

NSAID+PPI co-therapy is the most cost-effective strategy in all chronic arthritis patients irrespective of their risk for GI complications. For patients with increased GI risk, the NSAID/PPI single tablet formulation is also cost-effective.

INTRODUCTION

The prevalence of osteoarthritis and rheumatoid arthritis is high and the incidence of these chronic and expensive conditions is rising. Empirical treatment for osteoarthritis and rheumatoid arthritis often begins with non-steroidal anti-inflammatory drugs (NSAIDs) for symptom relief[1,2].

NSAIDs are associated with a wide spectrum of gastrointestinal (GI) side effects, including dyspepsia, peptic ulcers, peptic ulcer bleeding, and ulcer perforations. NSAIDs cause an approximately 3 to 4-fold increase in these upper GI complications[3]. GI complications are expensive; for example a Dutch observational study showed that for each €1.00 spent on NSAIDs, an additional €0.68 is needed for the treatment of GI adverse events[4].

Gastroprotective agents (GPAs) can reduce GI complications of NSAID, and are therefore widely recommended for use in high-risk users[5]. Physicians can choose between several gastroprotective strategies, including co-prescription of NSAIDs with acid suppressive medication (proton pump inhibitors (PPIs) and histamine-2-receptor antagonist (H2RAs)), misoprostol (prostaglandin analogue), or selective cyclooxygenase-2 inhibitors (coxibs). Previous analyses revealed that PPI co-therapy is cost-effective[6,7], especially in patients with a high risk of GI complications. Several guidelines recommend PPI co-prescription for patients with moderate-to-high risk profiles[5,8]. The national institute for health and clinical excellence (NICE) guidelines even recommends PPI co-prescription in all patients on chronic NSAID-therapy[1]. H2RA may be cost-effective when used in high-doses. Only one study directly compared H2RA versus PPI co-therapy and concluded that PPI co-therapy was more effective in healing ulcers[9]. Misoprostol is also equally efficacious to PPIs, although common GI side-effects (e.g. diarrhea and dyspepsia) reduce compliance and possibly its effectiveness. Another alternative is to replace non-selective NSAIDs with coxibs, which maintain anti-inflammatory capability while reducing GI complications through selective cox-2 inhibition[10,11]. Cost-effectiveness analyses reveal that coxibs provide an acceptable cost-effectiveness ratio compared with NSAID+PPI combination therapy in high-risk patients with a history of bleeding ulcers[12].

Although physicians are more aware than ever regarding the clinical and economic burden of NSAIDs, adherence to prescribing guidelines for GPA-use remained low; up to 60% of high-risk patients are not prescribed adequate gastroprotection[13,14]. Furthermore, patient compliance with GPAs is also inadequate, leading to sub-optimal gastroprotection[15]. The risk of NSAID-related GI complications increases by 16% for every 10% decrease in GPA compliance[16].

Due to the low compliance with effective and cost-effective GPAs, efforts have been made to enhance patient adherence with prescribed therapies. In particular, new single tablet formulations (i.e. NSAID/PPI or NSAID/H2RA) have

been developed; which may limit poor clinical outcomes associated with non-compliance by ensuring GPA is administered with each NSAID dose. Recent randomized controlled trials have shown that both esomeprazole+naproxen and ibuprofen+famotidine single tablet formulation are superior to placebo in reducing gastric ulcers[17,18]. Previous data also found that the single tablet formulation of diclofenac+misoprostol is effective in protecting patients at medium and high-risk for GI complications[19].

In order to assist the clinical decision making process for patients with rheumatoid arthritis or osteoarthritis requiring chronic NSAIDs treatment, we aimed to evaluate the costs and effectiveness of eight different treatment strategies, including (co)prescription of GPAs and single tablet formulations while accounting for patient compliance.

METHODS

Decision model framework

We developed a Markov model using decision-analysis software (TreeAge Pro 2009, TreeAge Software Inc., Williamstown, MA). We evaluated 8 strategies for managing a hypothetical cohort of 60-year-old patients with rheumatoid- or osteoarthritis and requiring chronic NSAID therapy: 1) NSAID monotherapy (naproxen 500mg b.i.d.); 2) NSAID + PPI (naproxen 500mg b.i.d. and omeprazole 20mg q.d.); 3) NSAID/PPI single tablet formulation (naproxen 500mg combined with esomeprazole 20 mg b.i.d.); 4) NSAID + H2RA (naproxen 500mg b.i.d. and cimetidine 400mg b.i.d.); 5) NSAID/H2RA single tablet formulation (ibuprofen 800mg combined with famotidine 26.6mg t.i.d.); 6) NSAID + misoprostol (naproxen 500mg b.i.d. and misoprostol 200µg b.i.d.); 7) NSAID/misoprostol single tablet formulation (diclofenac 75mg combined with misoprostol 200µg b.i.d.); 8) coxib monotherapy (celecoxib 100mg b.i.d.) (**Figure 1**).

Coxib in combination with PPI was left out of the model as no literature is available for this strategy. The model tracked differential rates of compliance with these competing strategies, and evaluated variations in compliance (**Table 1**). In our base-case analysis, patients entering the model were 60 years old, did not have any GI symptoms or a history of peptic ulcer disease. Through a series of 3-month Markov transition cycles, we followed the cohort over a 5-year time horizon. During each cycle, patients could develop GI complications, including dyspepsia, ulcer complications (bleeding), and related mortality. After these initial health states, patients either could become symptom free, or go to health state in which dyspepsia persists. In the “dyspepsia persists” health state patients had different costs because of physician visits and medication, but comparable utilities. If a patient got a peptic ulcer bleeding (PUB), they will thereafter transfer to a ‘post’ health state (post-PUB) in which they remained at higher risk for a recurrent event,

had a different utility and higher health care costs compared to “no complications”. In a ‘post’ health state, the patient could still develop other complications (e.g. dyspepsia or recurrent PUB), yet they could never return to a “non-post” health state (**Figure 2**).

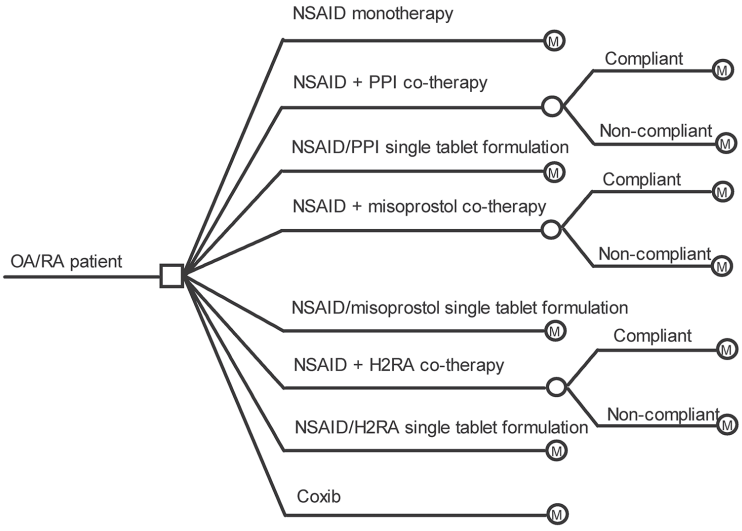

Figure 1 Decision model. The “M” is where the Markov model was incorporated in the decision tree

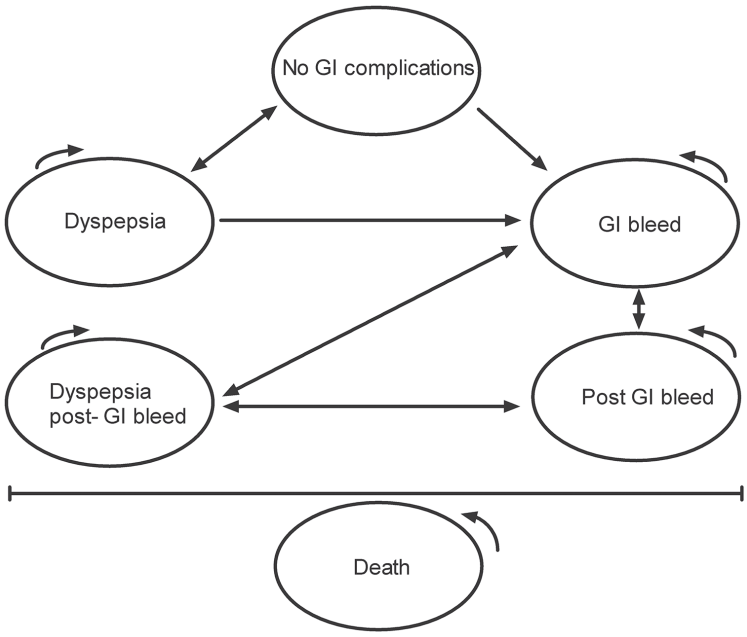

Figure 2 Markov model structure; the cohort was followed through three-month Markov cycles over a 5-year horizon. All patients started in a health state in which they were free of gastrointestinal complications

Table 1 Model parameters; probabilities for GI complications by treatment strategy based on 3 months Markov cycles

	Base-case Probability	Range tested in sensitivity analysis	Reference
Average risk of death of 60jr old RA/OA	0.01		(20)
Probability to die of PUB	0.08	0.02-0.15	(21,22)
NSAID THERAPY			
Probability to develop dyspepsia while on NSAID	0.13	0.05-0.29	(10,23-25)
Probability to develop PUB while on NSAID	0.004	0.001-0.005	(11, 25-28)
NSAID+PPI THERAPY			
Probability to develop dyspepsia while on NSAID+PPI	0.06	0.04-0.20	(29-31)
Probability to develop PUB while on NSAID+PPI	0.002	0.0003-0.01	assumption
Probability PPI compliance in NSAID+PPI users	0.68	0.2-1.0	(14-16)
NSAID+H2RA THERAPY			
Probability to develop dyspepsia while on NSAID+H2RA	0.08	0.08-0.12	(30)

	Base-case Probability	Range tested in sensitivity analysis	Reference
Probability of PUB while on NSAID+H2RA	0.003	0.001-0.004	assumption
Probability H2RA compliance in NSAID+H2RA users	0.68	0.3-1.0	(15,16)
NSAID+MISOPROSTOL THERAPY			
Probability to develop dyspepsia while on NSAID+Misoprostol	0.13	0.02-0.74	(30,31)
Probability to develop PUB while on NSAID + Misoprostol	0.0025	0.001-0.004	assumption
Probability misoprostol compliance in NSAID+Misoprostol users	0.33	0.3-1.0	(30,31)
COXIB THERAPY			
Probability to develop dyspepsia while on COXIB	0.095	0.04-0.11	(29,32)
Probability to develop PUB while on COXIB	0.003	0.001-0.009	(27, 28,33)
UTILITIES			
Utility for dyspepsia	0.87		(34)
Utility for persisting dyspepsia	0.87		
Utility for GI bleeding	0.82		(35)
Utility post GI bleed	0.98		(6)
Utility of dyspepsia post GI bleed	0.85		
Utility for persisting dyspepsia post GI bleed	0.85		
Utility of no GI complications	1		
COSTS (€)			
Costs embolization/surgery	1329.47	600-2000	
Cost 3 months NSAID	13.50	4.5-28.8	
Cost 3 months Acetaminophen	21.42	9.57-21.42	
Cost 3 months PPI 20mg	2.99	2-90	
Cost 3 months COXIB	71.28	1-100	
Cost 3 months PPI 40mg	6.13	3.98-90	
Cost 3 months NSAID/PPI single tablet	69.33	1-100	
Cost 3 months H2RA	23.58	11.26-35.90	
Cost 3 months misoprostol	175.92	100-200	
Cost 3 months NSAID/H2RA single tablet	70	1-100	
Cost 3 months Arthrotec	66.65	1-100	
Cost blood transfusion	405.35	200-600	
Cost diagnostic endoscopy	343.79	175-525	
Cost GE visit	72	35-105	
Cost GP visit	28	10-35	
Cost hospital admission 10 days	4570	2000-6000	
Cost HP test CLO	3.5	2-5	
Cost HP test breath	63.92	30-90	
Cost IV PPI 72hr	163.61	100-200	
Cost month PPI	0.99	0,67-29	
Cost therapeutic endoscopy	850	350-1200	

	Base-case Probability	Range tested in sensitivity analysis	Reference
Cost triple therapy	11.39	5-16	
ADDITIONAL PROBABILITIES			
Probability for need of embolization/surgery	0.09	0.02-0.22	(36,37)
Probability to rebleed within 3 months	0.067	0.05-0.09	(36,38)
Probability for ulcus ventriculi	0.18	0.11-0.24	(37)
Probability need for blood transfusion	0.6	0.2-0.9	(36,37)
Probability HP positive	0.48	0.42-0.92	(36,38)
Probability that dyspepsia resolves while on NSAID+PPI	0.55	0.53-0.76	(39,40)
Probability to develop dyspepsia post GI bleed on acetominophen and PPI	0.05	0.01-0.07	assumption
Probability that dyspepsia resolves post GI bleed on acetominophen and PPI	0.61	00.55-0.68	(41,42)
Probability to rebleed post GI bleed while on acetominophen and PPI	0.1	0.07-0.17	(31,43)

Model assumptions

We applied the following assumptions regarding physician and patient behavior. To closely simulate clinical practice we based these assumptions on a combination of clinical guidelines and expert opinion.

1. If dyspepsia develops, patients first visit their primary care provider. Patients will be prescribed a 4-week trial of PPI therapy. If dyspepsia persists despite this treatment, the patient is referred to a gastroenterologist and undergoes diagnostic endoscopic examination and testing for *Helicobacter pylori (H. pylori)*. In case of *H. pylori* positivity, a 1-week course of triple therapy is prescribed and a 13C urea breath test is subsequently performed to confirm *H. pylori* eradication.
2. If dyspepsia persists in patients without endoscopic findings or *H. pylori* negativity, then patients visit their primary care provider again and receive another 3 months of PPI therapy.
3. Patients presenting with GI bleeding visit the emergency department and are admitted to the hospital. If necessary, patients are stabilized with blood transfusion. A therapeutic endoscopy is then performed. The patient is treated with intravenous PPI therapy for 72 hours, followed by indefinite PPI therapy. Survivors are tested for *H. pylori*, and treated with triple therapy if positive. If the bleeding recurs, a second endoscopy is performed and endoscopic treatment is employed if needed. If endoscopic intervention fails, the patient undergoes radiographic embolization or surgical intervention and hospital stay is extended. If a patient has an ulcer bleeding from a gastric ulcer a second look endoscopy

will be performed. Patients with GI bleeding will be converted to acetaminophen and a PPI for the remainder of the time horizon.

4. Patients developing dyspepsia after a previous peptic ulcer bleed first visit their primary care provider, and are then referred to a gastroenterologist to undergo diagnostic endoscopic examination and *H. pylori* testing. Patients testing positive for *H. pylori* are treated with a 1–week course of triple therapy and undergo breath testing to confirm cure. PPI therapy is then continued for the remainder of the time horizon.

Clinical probability estimates

We performed a structured literature search in PubMed to identify literature supporting our baseline probability estimates for 30 clinical inputs (**Table 1**). If available, we relied on pre-existing systematic reviews and meta-analyses. If no data from systematic reviews or meta-analyses was available we selected original articles. We aimed to collect data from studies that were comparable in design, follow-up period and in study outcome. Our base-case estimate was based on a sample-size weighted mean of the absolute risks for the outcome extracted from the studies we included. For variables that were not supported by published data or if available data was conflicting, we made assumptions about point-estimates based on expert opinion (2 expert gastroenterologists and 1 expert general practitioner) and evaluation of other cost-effectiveness analyses on this subject[6,7,19]. Because the precision of these estimates varies between different populations, we varied each estimate over a wide range in the sensitivity analysis.

Outcomes

We used quality-adjusted life-years (QALYs) as our effectiveness outcome. The panel on cost-effectiveness in Health and Medicine suggests that QALYs are the most appropriate unit for cost-effectiveness analysis instead of clinical outcomes[44]. QALYs account for both quantity and quality of life generated by health care interventions. In order to calculate QALYs, we obtained 7 relevant health state utility values from the published literature and incorporated these into the model (**Table 1**). Our overall outcome was the incremental cost effectiveness ratio (ICER) evaluating both differences in costs and QALYs. We determined a cost-effectiveness threshold of €20,000 per QALY gained following Dutch national guidelines[45]. We discounted all utilities at an annual rate of 3%, as recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine[44].

Cost estimates

For establishing cost estimates, we only considered direct medical costs using a third party payer's perspective. We present all costs in Euros. The costs of treating

GI complications were estimated on prices for physician services, endoscopic procedures and laboratory tests, derived from the Dutch Healthcare Authority 2010[46]. Costs of the medications studied in this model were derived from the Health Care Insurance Board 2011[47]. As with utilities, we discounted all at an annual rate of 3% as recommended by guidelines[44].

Sensitivity analysis

To assess the influence of all variables in the model, we created a tornado diagram to rank-order the most influential variables. We performed one-way sensitivity analyses and reported thresholds in which the relative order between strategies changed for the most influential variables. To acknowledge the variability of probabilities/risks between individual patients, we then performed a Monte Carlo simulation (probabilistic sensitivity analysis) with 10,000 trials. We assumed triangular probability distributions around the clinical probabilities, meaning that a parameter's base-case value is most likely to occur and the minimum and maximum values are least likely to occur. We assumed that the mean value was equal to the base-case point estimate. The base-case model assumed that patients were at an average risk for developing a GI event from NSAIDs. We also performed additional sensitivity analyses in patients at high risk for GI complications. Patients entered the model with a base-case relative risk of 1.0 for GI complications of NSAIDs; which could increase to a 3-fold higher relative risk for GI complications. A high-risk patient illustrated a patient with a 3-fold higher risk of GI complications. The 3-fold higher risk could be a result of one or any combination of the following risk factors: higher age, concomitant use of low-dose aspirin, anticoagulants or steroids or history of peptic ulcer disease[48]. We subsequently plotted the results on a cost-effectiveness acceptability curve stratified by willingness-to-pay thresholds for patients with average and high-risk profiles.

RESULTS

Base case

NSAID+PPI co-therapy was the most cost-effective strategy in the base-case 60-year old patient with chronic arthritis in need of chronic NSAIDs. NSAID monotherapy was more expensive and less effective in preventing GI complications compared to PPI co-therapy, which rendered the latter a cost-saving approach. Compared to separate NSAID+PPI co-therapy, NSAID/PPI single tablet formulation costs an incremental €35,075 per additional QALY gained. All other strategies were outranked (dominated, i.e. more expensive and less effective) by NSAID+ PPI co-therapy (**Table 2 & Figure 3**).

Table 2 Base case cost-effectiveness

Strategy	Average Cost	Average QALY	ICER (Euro/QALY)
NSAID	€1440	4.27	dominated
NSAID + PPI	€1103.5	4.31	reference
NSAID/PPI Single tablet formulation	€1764	4.33	€35,075*
NSAID + misoprostol	€2156	4.27	dominated
NSAID/misoprostol Single tablet formulation	€1945	4.28	dominated
NSAID + H2RA	€1415	4.29	dominated
NSAID/H2RA Single tablet formulation	€2074	4.30	dominated
Coxib	€2188	4.30	dominated

* compared to NSAID + PPI

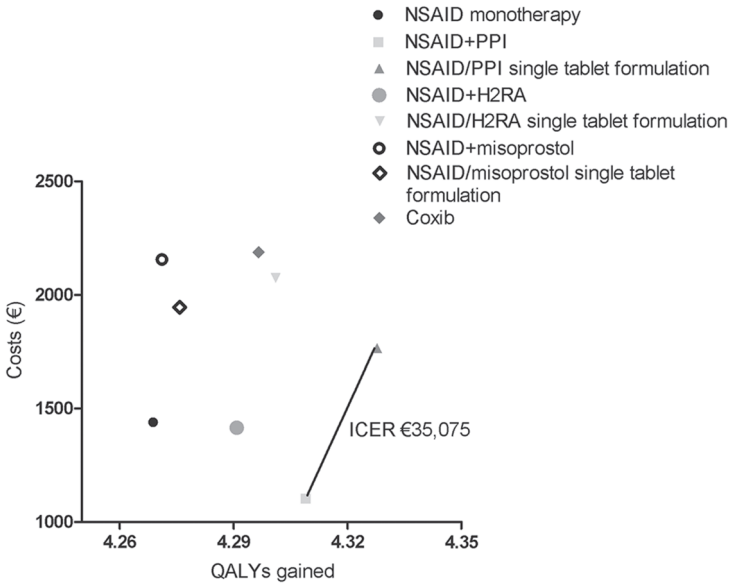

Figure 3 The relative results of all strategies displayed in a cost-effectiveness plane

Sensitivity analyses

The results of one-way sensitivity analysis (displayed in a tornado diagram) show that our model was highly sensitive to the relative risk of GI complications, the probability of PPI compliance, the costs of PPIs and NSAID/PPI single tablet formulation, and probabilities for dyspepsia and peptic ulcer bleeding on NSAID+PPI co-therapy (**Figure 4**). **Table 3** provides the thresholds at which the cost-effectiveness of the different strategies changed. For example, when compliance with PPIs fell below

51% in the NSAID+PPI co-therapy strategy, the NSAID/PPI single tablet formulation is preferred.

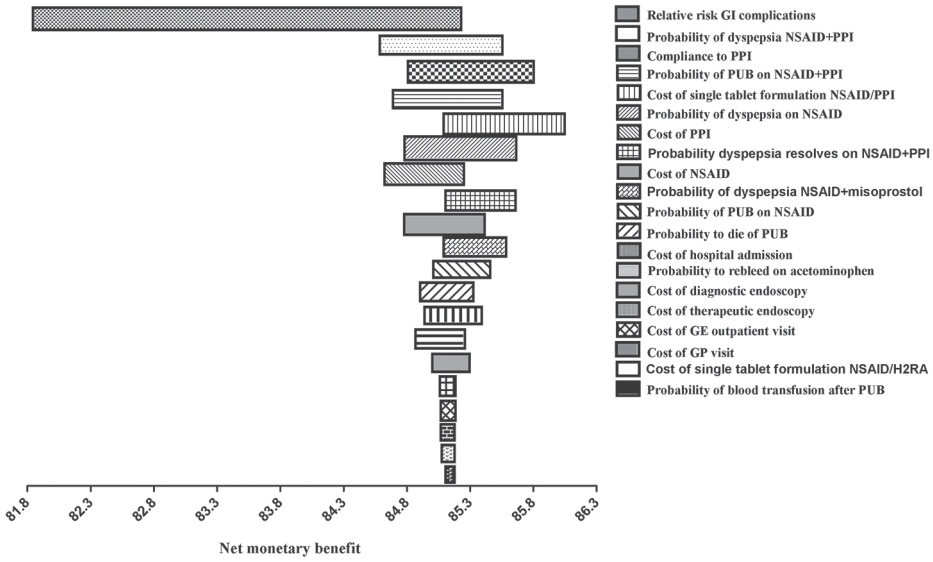

Figure 4 One-way sensitivity analysis: Tornado diagram

Higher gastrointestinal risk

Increasing the relative risk of GI complications from a base case of 1.0 to 3.0 made NSAID/PPI single tablet formulation increasingly cost-effective, with its ICER falling to only €9917 versus NSAID+PPI combination therapy. The single formulation tablet became economically "viable" (i.e. ICER<€20,000) once the relative risk of GI complications exceeded 1.7 times the average risk. When the costs of PPIs exceeded €0.42/day or compliance to PPIs fell below 33%, NSAID+PPI co-therapy became dominated (i.e. both less effective and more expensive) by NSAID/PPI single tablet formulation. Other thresholds at which the relative order of cost-effective strategies changed are displayed in **Table 3.** The remaining strategies were however more expensive and less effective than the above mentioned alternatives (dominated).

Probabilistic sensitivity analysis

Using Monte Carlo analysis, we compared strategies across cohorts of 10,000 patients, each with different probabilities and risks. **Figure 5** and **Figure 6** show the results on a cost-effectiveness acceptability curve. For a willingness-to-pay (WTP) threshold of €20,000 per QALY gained, the probability of being cost-effective was the highest for NSAID+PPI co-therapy users with 57%, followed by NSAID+H2RA (17%) and NSAID/PPI single tablet formulation users (13%). The other strategies had very low probabilities on being cost-effective. For high risk patients these probabilities

were 21%, 19%, and 42% respectively. If the WTP threshold was below €13,000, however, the probability of being cost-effective was the highest for NSAID+PPI co-therapy.

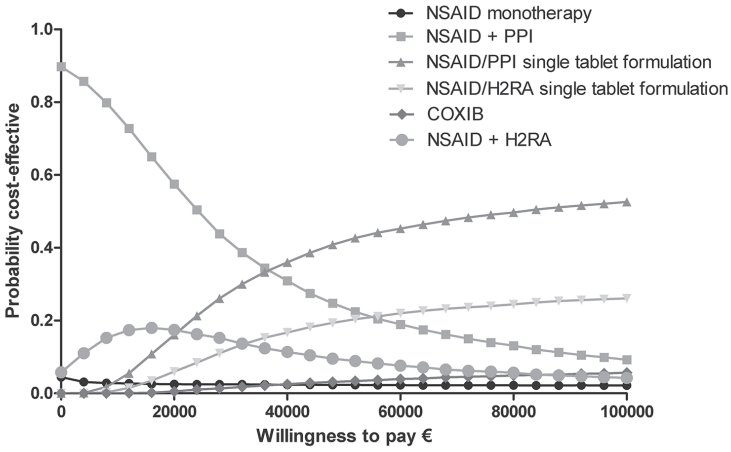

Figure 5 Cost-effectiveness acceptability curves showing the probability of being most effective at different WTP thresholds in average risk patients

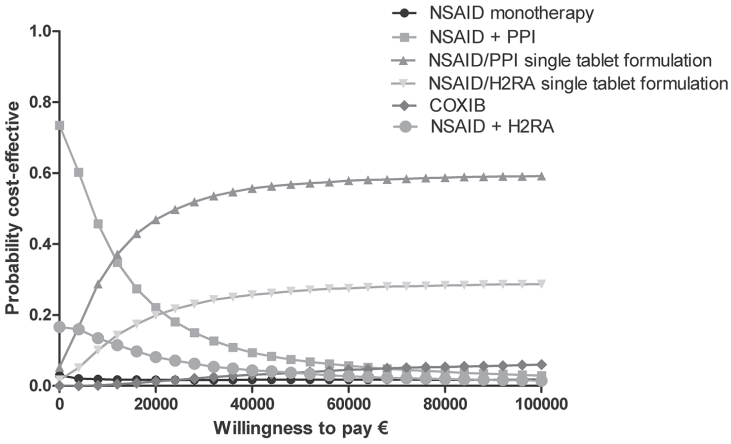

Figure 6 Cost-effectiveness acceptability curves showing the probability of being most effective at different WTP thresholds in high risk patients

Table 3 Results one-way sensitivity analysis

Variable		Base-case estimate	Range tested	Threshold	Comment
Average GI risk	% PPI compliance	68%	0.3-1.0	51%	If less than threshold, then the single tablet formulation NSAID/PPI is cost-effective
	Cost PPI/ tablet	€0.03	0.02-1.0	€0.29	If more than threshold, then the single tablet formulation NSAID/PPI and NSAID+H2RA co-therapy are cost-effective
	Cost single tablet formulation NSAID+PPI/day	€0.77	0.01-1.11	€0.56	If less than threshold, then the single tablet formulation NSAID/PPI becomes cost-effective
	Probability of dyspepsia on NSAID	0.13	0.04-0.20	0.20	If higher than threshold, then the single tablet formulation NSAID/PPI is cost-effective
	Probability of dyspepsia on NSAID + PPI	0.06	0.02-0.20	0.12	If higher than threshold, then NSAID+H2RA co-therapy is cost-effective
High GI risk	% PPI compliance	68%	0.3-1.0	79%	If higher than threshold, then NSAID+PPI co-therapy is the only cost-effective option
				33%	If less than threshold then NSAID+PPI co-therapy is dominated
	Cost PPI/ tablet	€0.03	0.02-1.0	€0.42	If higher than threshold then NSAID+PPI co-therapy is dominated by the single tablet formulation NSAID/PPI
	Cost single tablet formulation NSAID+PPI/day	€0.77	0.01-1.11	€1.07	If higher than threshold, then NSAID+PPI co-therapy is the only cost-effective strategy
	Probability of dyspepsia on NSAID	0.13	0.04-0.20	0.09	If higher than threshold, then the single tablet formulation NSAID/PPI is cost-effective
	Probability of dyspepsia on NSAID + PPI	0.06	0.02-0.20	0.12	If higher than threshold, then NSAID+H2RA co-therapy is cost-effective

DISCUSSION

In this cost-effectiveness analysis comparing different gastroprotective treatment strategies for patients with chronic arthritis using NSAIDs, we found that the combination of NSAID and PPI co-therapy was not only a cost-effective but also cost-saving strategy compared to all other studied strategies. These results are based on a 60-year-old patient with an average-risk profile for GI complications (i.e. dyspepsia and/or peptic ulcer bleeding) in five-year follow-up. However, in patients with an increased GI risk (e.g. previous GI bleed, anticoagulant and/ or steroids use), *both* NSAID+PPI co-therapy and NSAID/PPI single tablet formulation were the preferred strategies. With an ICER of €9917 compared to NSAID+PPI co-therapy, the NSAID/PPI single tablet formulation was optimally cost-effective assuming the willingness to pay threshold was held at €20,000 per QALY. We found that compliance to PPIs affected the cost-effectiveness of the different strategies. If compliance to PPI is low (<51%) in average risk patients, the NSAID/PPI single tablet formulation also becomes a cost-effective strategy. In contrast in high-risk patients with a high compliance (>79%), NSAID+PPI co-therapy is the only cost-effective strategy. Other influential variables included the costs of PPI and of the NSAID/PPI single tablet formulation, and probabilities for dyspepsia on NSAID and NSAID+PPI co-therapy.

This is the first model to demonstrate that NSAID and PPI co-prescription is potentially cost-saving compared to other strategies, including NSAID monotherapy. This finding supports the NICE guidelines to employ GPA co-therapy in all patients on chronic NSAID therapy. In a previously published cost-effectiveness analysis, Latimer et al.[6] also concluded that PPI co-therapy was cost-effective (ICER €1175) for 55-year old patients with osteoarthritis taking traditional NSAIDs with an average risk of GI complications. Our results are however not in line with publications by Spiegel et al. and Cameron et al. which concluded that NSAID monotherapy was the preferred strategy in average risk patients taking NSAIDs.[7,49] An explanation for these conflicting results can be found in differences in the model structure, and in the utilities and probabilities used for the model input. But maybe more important are the costs of PPIs that have decreased significantly over the last few years due generic availability. Spiegel et al., Al et al. and Cameron et al. used PPI costs ranging from €0,22 to €2,52 which resulted in less benefit for the strategies combining NSAIDs with PPIs. This was also supported by our sensitivity analysis in which we found that for average risk patients the costs of PPIs should be below €0,29 and for high risk patients below €0,42. Latimer used a cost of €0,08 for PPIs per day, which also resulted in cost-effectiveness for all NSAID users and our PPI costs are even lower (€0,03)[6,7,12,19,49]. And we also incorporated compliance and

single tablet formulations in the model, which gives a better and closer reflection of clinical practice nowadays.

Estimations on compliance were derived from the literature, though little is known about the compliance to misoprostol and H2RAs. We made assumptions for compliance to H2RAs and misoprostol based on best available literature and verified these assumptions with an expert panel. Despite the potential inaccuracy of the point estimates for these values, we found that our basic results did not change even after ranging compliance estimates for H2RA and misoprostol over a wide range. Using sensitivity analyses, we were able to rank order the studied strategies and assess how differences in compliance rates influence our results. Compliance rates differ on population and on a patient level. Van Soest et al. recently showed that compliance with PPIs and NSAIDs in the Netherlands was higher (81%) compared to the compliance rates in the UK (72%) and Italy (58%)[49]. Moreover, Goldstein et al. found a compliance rate of 68% in the USA, whereas another Dutch cohort calculated a GPA compliance rate of 63%[21,22]. On an individual patient level, estimating compliance remains challenging. Potential predictors of low compliance include duration of therapy, indication of therapy (preventive vs. disease controlling), gender and dosing regimen (less frequent dosing results in higher compliance rates)[50,51]. A good profile for GPA compliance, however, has not yet been developed.

Our model has several strengths. First, we built an extensive model and incorporated two clinically meaningful endpoints, i.e. dyspepsia and GI bleeding. Second, we accounted for compliance with GPAs, to our knowledge; this has not been incorporated into previous models. Some other models incorporated the probability of being intolerant to misoprostol; however, they did not incorporate probabilities for being compliant to all different strategies.[19] Compliance appeared to highly affect the cost-effectiveness of different strategies in our model. We also integrated new strategies of single tablet formulations in the model. Nonetheless, little is known about these single tablet formulations with regard to compliance. Finally, we performed our analysis for both average risk patients and increased risk patients (i.e. 3 fold higher risk), making our results more applicable to all NSAID users. This increased risk population can be identified by guidelines developed on this subject in whom patients are stratified towards increased risk and low risk.[5,8]

Our study has also important limitations. We derived probability estimates used in the model from heterogeneous studies. Different patient groups, follow-up periods, and quality of data make it difficult to precisely estimate the mean probability. In order to correct for that, we used systematic reviews and meta-analyses where possible. Furthermore, several probabilities could not be derived from the literature or were supported by only a few studies. For example, little data is available that compared the risk of GI bleeding between coxib and NSAID

+ PPI co-therapy. To account for these uncertainties we performed probabilistic sensitivity analyses across a wide range for each key variable in the model. We found that the model was highly sensitive to the probabilities of dyspepsia in each arm. We therefore verified these probabilities with published data and previous cost-effectiveness studies[6,7,19,49]. Probabilistic sensitivity analyses were also used to account for differences in drug and other health care costs between different health care systems. Subsequently, we did not include side effects of the gastroprotective strategies or NSAIDs in our model as literature is limited and conflicting. Overall, we still believe that it is important not to forget to treat patients on an individual patient level and although we did perform sensitivity analyses with the input of our model to account for uncertainties, we were not able to include all patient characteristics in the model. We would apply our results to a population without any contraindications for PPI use. Moreover, it is possible that NSAID use in clinical practice is more on demand instead of continuous, yet patients with osteoarthritis or rheumatoid arthritis are likely to use NSAIDs chronically. Chronic therapy fits a Markov model perfectly, where intermittent use is less appropriate. Therefore, caution is warranted if our results are extrapolated to all NSAID users. In addition, we did not account for the possibility that patients are non-compliant to their NSAIDs as well as their GPAs. Yet, we assumed good compliance to NSAIDs, as patients use this medication for pain relief.

In conclusion, NSAID+PPI co-therapy is a cost-saving strategy for chronic arthritis patients at average or high risk of GI complications, considering compliance. The NSAID/PPI single tablet formulation is an additional option for average risk patients with low compliance or if the costs of PPIs are higher, and is also a cost-effective strategy for high risk patients. Compliance to PPI was found to be an important and influential factor, for both average and high risk patients.

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Chapter 4

Gastroprotection in low-dose aspirin users for primary and secondary prevention of ACS: results of a cost-effectiveness analysis including compliance

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Accepted for publication in Cardiovascular drugs and therapy

ABSTRACT

BACKGROUND

Low-dose aspirin (ASA) increases the risk of upper gastrointestinal (GI) complications. Proton pump inhibitors (PPIs) reduce these upper GI side effects, yet patient compliance to PPIs is low. We determined the cost-effectiveness of gastroprotective strategies in low-dose ASA users considering ASA and PPI compliance.

METHODS

Using a Markov model we compared four strategies: *no medication*, *ASA monotherapy*, *ASA + PPI* co-therapy and a *fixed combination* of ASA and PPI for primary and secondary prevention of ACS. The risk of acute coronary syndrome (ACS), upper GI bleeding and dyspepsia was modeled as a function of compliance and the relative risk of developing these events while using medication. Costs, quality adjusted life years and number of ACS events were evaluated, applying a variable risk of upper GI bleeding. Probabilistic sensitivity analyses were performed.

RESULTS

For our base case patients using ASA for primary prevention of ACS *no medication* was superior to *ASA monotherapy*. PPI co-therapy was cost-effective (incremental cost-effectiveness ratio (ICER) €10,314) compared to *no medication*. In secondary prevention, *PPI co-therapy* was cost-effective (ICER €563) while the *fixed combination* yielded an ICER < €20,000 only in a population with elevated risk for upper GI bleeding or moderate PPI compliance. *PPI co-therapy* had the highest probability to be cost-effective in all scenarios. PPI use lowered the overall number of ACS.

CONCLUSIONS

Considering compliance, PPI co-therapy is likely to be cost-effective in patients taking low dose ASA for primary and secondary prevention of ACS, given low PPI prices. In secondary prevention, a fixed combination seems cost-effective in patients with elevated risk for upper GI bleeding or in those with moderate PPI compliance. Both strategies reduced the number of ACS compared to ASA monotherapy.

INTRODUCTION

The beneficial effects of low-dose aspirin (ASA) (75-325 mg) in the prevention of acute coronary syndrome (ACS) are well recognized, especially in patients with established cardiovascular (CV) disease (secondary prevention)[1-3]. Guidelines recommend that ASA needs to be administered as soon as possible after an ACS and this should be continued for the remaining lifetime of the patient[4]. The effectiveness of low-dose ASA for primary prevention is less certain. The reduction in CV events needs to be weighed against an increased risk for gastrointestinal (GI) side effects including bleeding, particularly in the upper GI tract, and dyspepsia[5,6]. Randomized placebo controlled trials as well as observational studies have shown that low-dose ASA approximately doubles the risk of GI bleeding compared to placebo[7,8]. Nonetheless, a recent study demonstrated that low-dose ASA for primary prevention is likely to be cost-effective even in patients at moderate risk for CV disease[9], thereby indicating that the CV benefits might outweigh the GI risks.

In order to prevent GI complications in ASA-users, proton pump inhibitors (PPIs) – which reduce the production of gastric acid – are often used as prophylactic therapy. PPI therapy has proven to reduce the risk of dyspeptic symptoms, gastroduodenal ulcers and upper GI bleeding in patients taking low-dose ASA[10-13]. However previous studies showed that the cost-effectiveness of PPI co-therapy in the primary and secondary prevention of CV disease depends on the baseline risk for upper GI bleeding and PPI prices[9,14]. But due to generic availability PPI prices have plummeted in the last several years, which may have enhanced the cost-effectiveness of PPI co-therapy.

To attain the effect of both ASA and PPI, patient compliance is important. Yet it is unclear how patient compliance influences the cost-effectiveness of these therapies. It is known that discontinuation of ASA entails a three-fold higher risk of atherothrombotic events in patients with moderate to high risk for developing an ACS event[15]. The most important reason for ASA discontinuation is the occurrence of GI side effects[16-18].

Also, patient compliance to PPI co-therapy is suboptimal. Herlitz et al. showed that of all patients who were prescribed a daily PPI concomitant to low-dose ASA, less than half took >75% of the prescribed PPIs and almost one-third did not take their PPI at all[19]. The relation between the risk of upper GI complications, CV complications and PPI compliance in low-dose ASA users is not clear, but among non-steroidal anti-inflammatory drug (NSAID) users it was shown that the risk of upper GI complications increased by 9% for every 10% decrease in PPI compliance[20]. Therefore, an important goal in the prevention of an ACS event and upper GI complications is to improve patient compliance to both ASA and PPI. One way to achieve better compliance to PPI, is to combine PPI with low-dose ASA in a

fixed combination. The effectiveness of such a fixed combination has already been demonstrated in chronic NSAID users[21].

In this study, we evaluated the cost-effectiveness of four competing strategies for the primary and secondary prevention of ACS – including the fixed combination of ASA+PPI and its separate components – when GI and CV outcomes and patient compliance are considered.

METHODS

A Markov model was developed to compare the costs and outcomes of competing strategies for the primary and secondary prevention of ACS. We performed two separate analyses using different baseline situations; one in which no previous CV events had occurred, and one in which all subjects had a history of ACS. In the primary prevention analysis we compared 1) *no medication*, 2) low-dose *ASA monotherapy* (enteric coated acetylsalicylic acid 81 mg), 3) low-dose ASA with concomitant PPI therapy (*ASA+PPI*)(omeprazole 20 mg) and 4) a *fixed combination* of low-dose ASA and PPI (enteric coated acetylsalicylic acid 81 mg + omeprazole 20 mg). In the secondary prevention model, only the latter three strategies were incorporated.

In this study the primary outcome was incremental cost per quality adjusted life year (QALY) gained. Using this outcome measure we accounted for both the quantity of a person's life as well as the quality. The third-party payer perspective was applied for the analyses. As a secondary outcome, we looked at the number of ACS events occurring with the different treatment strategies. Additionally, we studied the correlation between PPI compliance and the number of ACS events in 10.000 simulated patients.

Patient population

Primary prevention

The base-case cohort for the primary prevention analysis consisted of 60-year old males with no history of ACS, yet an increased risk (10%) to develop ACS within the next 10 years. This reflects patients with one or more risk factors for ACS (e.g. high blood pressure, high cholesterol, smoker) for whom primary CV prevention with low-dose ASA may be indicated.[24]

Secondary prevention

In order to evaluate the outcome for a patient group taking low-dose ASA for secondary prevention of ACS, we adjusted the baseline situation and created a

second base-case cohort that consisted of 60-year old males with a history of ACS and a 10-year risk of recurrence of 23% (based on annual risk estimates[25-27]), which we also followed over a lifetime horizon. In this model, the treatment strategy *no medication* was eliminated, since these patients have a clear indication to receive at least *ASA monotherapy*. All patients started in the 'ACS' health state from which they could transfer to all other relevant health states as depicted in

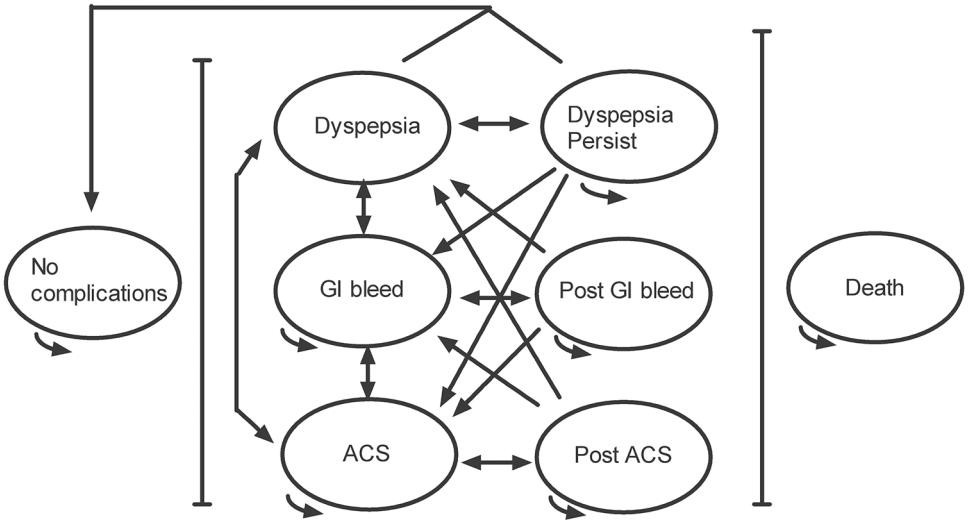

Figure 1 Markov model structure; the cohort was followed through one-year Markov cycles over a lifetime horizon. All patients started in a health state in which they were free of cardiovascular and GI complications. At the end of a cycle patients could either stay in this health state or develop dyspepsia, upper GI bleeding, ACS or die. Patients with upper GI bleeding, ACS or in a post-state on these two and who are developing dyspepsia could not transfer to no complications.

Model structure

The cohort was followed through one-year Markov cycles over a lifetime horizon. All patients started in a health state in which they were free of CV and GI complications. At the end of a cycle patients could either stay in this health state or develop dyspepsia, upper GI bleeding, ACS or die (**Figure 1**). Patients could return to the "no complications" health state only after dyspepsia. After an ACS or upper GI bleeding, patients transferred to a 'post' health state in which they remained at higher risk for a recurrent event, had a different utility and higher health care costs compared to "no complications". In a "post" health state, the patient could still

develop other complications, yet they could never return to a "non-post" health state.

To derive reliable cost approximations, we attempted to reflect a patient's treatment course – within a health state – according to what happens in clinical practice. Therefore, some assumptions regarding clinical practice were incorporated in the model, based on both clinical guidelines and clinical experts' experience (**See Technical Appendix**).

Clinical efficacy

Clinical probability estimates and treatment effectiveness data were primarily derived from the published literature (**Table 1**). We performed a structured search using PubMed and Embase databases, and we created a panel of 4 expert gastroenterologists and 1 cardiologist who provided expert opinions if no published literature was available, or if available information was conflicting.

In order to derive annual transition probabilities, we multiplied baseline risks on the development of ACS, upper GI bleeding and dyspepsia by the relative risks of ASA use and, if appropriate, PPI use. Age-dependent probabilities were used for the development of an ACS and GI bleeding. In addition, we used a risk multiplier to increase the baseline probability of upper GI bleeding to a maximum of three times the average risk. In this way we simulated an additional patient population with a higher GI bleeding risk as compared to the average population to experience more or less benefit from the treatment strategies under evaluation.

Table 1 Input parameters

Variable	Base case estimate	Sensitivity Range	Source
Baseline probabilities	*Probability*	*Probability*	
Dyspepsia	0.17	0.05 – 0.25	(12)
GIB (post GIB)	0.023	0.02 – 0.08	(37)
GIB (after ACS)	0.007	0.003 – 0.025	(38,39)
GIB (after ACS and post GIB)	0.095	0.04 – 0.10	Assumed
ACS (post ACS)	0.04	0.006 – 0.056	(25,26,27)
Mortality GIB	0.08	0.04 – 0.14	(27, 35,40-41)
Mortality ACS	0.09	0.05 – 0.12	(24,42-46)
Relative risks†	*Relative risk*	*Relative risk*	
ASA; dyspepsia	1.09	1 – 1.22	(7)
ASA; GIB	2.07	1.61 – 2.66	(7,26)

Variable	Base case estimate	Sensitivity Range	Source
ASA; ACS Primary prevention Secondary prevention	 0.80 0.78	 0.54 – 0.91	 (1-3,5,30)
PPI; dyspepsia	0.58	0.4 – 0.85	(12)
PPI; GIB	0.32	0.11 – 0.65	(11,13,31,32)
Annual placebo risks	*Probability*		
Death	Age dependent*		(28)
ACS	Age dependent (0.0089 + 0.000336 per year)		(3,28,33)
GIB	Age dependent (0.0014 + 0.00015 per year)		(7, 34-36)
Medication costs (€ per daily dose)	*€ per daily dose*	*€ per daily dose*	
81 mg aspirin	€0.02	€ 0.01 – 0.05	(47)
20 mg omeprazole	€0.022	€ 0.01 – 0.33	(47)
40 mg omeprazole	€0.044	€ 0.02 – 0.66	(47)
Fixed combination	€0.45	€ 0.2 – 0.7	(47)
Annual utilities^	*Utility*	*Utility*	
Dyspepsia	0.94	0.90 – 0.98	(48, 49)
Dyspepsia persist	0.88	0.87 – 0.93	(48, 49)
GI bleeding	0.94	0.88 – 0.97	(48, 49)
Post GIB	0.98	0.95 – 1	(50)
ACS	0.86	0.75 – 0.90	(51,52)
Post ACS	0.90	0.85 – 0.95	(50,52)
Compliance	*Percentages*	*Percentages*	
ASA, no complications	75%	0 – 100	(53)
ASA, GI complications	60%	0 – 100	(16)
ASA, post ACS	90%	0 – 100	(54,55)
ASA, post ACS, GI complications	70%	0 – 100	(16,17,56)
Fixed combination, no complications	75%	0-100	Assumed
Fixed combination, post ACS/ GI complications	90%	0-100	Assumed
PPI, no GI complications	62%	0 – 100	(57,58)
PPI, GI complications	76%	0 – 100	(19, 59)

ASA = low-dose aspirin; PPI = Proton Pump Inhibitor; GIB = upper GI bleeding; ACS = Acute coronary syndrome; GI = gastrointestinal† Annual transition probabilities can be calculated by multiplying baseline probabilities*relative risks; e.g. P(dyspepsia|ASA)= 0.17*1.09 * Figure in appendix

^ References refer to the studies that reported event utilities, which were used as input for the disutility calculations (see appendix). These were performed to derive the annual utilities as reported here, thereby accounting for the duration of the event.

Mortality

Annual, age-dependent probabilities of death (Appendix Figure1) were applied throughout the model, extracted from life tables in The Netherlands[28]. However, in the health states "GIB" and "ACS" event specific mortality estimates (**Table 1 & Appendix Figure 1**) were applied.

Compliance assumptions

We introduced a method to include compliance in our Markov model, by which the probability of an event (e.g. dyspepsia, upper GI bleeding or ACS) was dependent on a patient's compliance. An equation was built into the model as such that every event probability was calculated through this equation;

Risk placebo * (1- (C (1-RR) / 100))

where C stands for compliance rate (0-100%) and RR is the relative risk of developing an event while using medication. The equation can be applied to all individual therapies, as well as to a combination of therapies, in which case the equation should be applied in sequence. The equation implies that patients who are 0% compliant to low-dose ASA/PPI do not experience the benefits nor side effects of ASA or PPI. For example, if a 60-year old patient were 100% compliant to both low-dose ASA and PPI, his risk of GI bleeding equals:

Risk placebo * (1- ((100 (1- RR ASA)) / 100)) * (1- ((100 (1 - RR PPI)) / 100)) =
Risk placebo * RR ASA * RR PPI =
0.0014*2.07*0.32 = 0.0009

We assumed a linear relationship between the compliance rate of both ASA and PPI and their effect, based on a relation which was found for PPI compliance and the risk of upper GI bleeding in NSAID users[20]. Using this method, we were able to model different compliance rates at different health states, thereby emulating reality as a patient's compliance to low-dose ASA and PPIs is dependent on the previous occurrence of GI or CV side effects[16,17]. Based on the available literature we estimated base-case compliance rates as shown in **Table 1**. Patients using the fixed combination of ASA and PPI are by definition 100% compliant to the PPI. Compliance for the fixed combination was assumed equal to compliance for ASA as a single component.

Utilities

Utility values were derived from the literature (**Table 1**). Utility calculations (**Appendix Table 1**) were made in order to derive annual health utilities, thereby accounting

for the duration of the event (technical appendix). All utilities are discounted at an annual rate of 3%.

Costs calculations

Health care costs were estimated from a third-party payer perspective, considering only direct costs. The costs of the medications studied (**Table 1**) were primarily derived from the Dutch Health Care Insurance Board (HCIB) and include cost prizes, claw-back (deduction applied to pharmacies' reimbursement) and taxes[45]. In the model these prizes were increased by a dispensing fee assuming four prescriptions per year. Standardized cost prizes were used for general practitioner (GP) consultations, emergency department and outpatient visits and inpatient hospital stay, following the HCIB guidelines[60]. Specific costs of diagnostic and therapeutic interventions were derived from the Dutch Healthcare Authority (**Appendix Table 2**). We used 2011 prices in euros and discounted all costs at a rate of 3%. The total costs for each health state are displayed in **Table 2**.

Table 2 Annual Costs per state of health

Health state	Costs* (€)
No complications	37.89
Dyspepsia	356.77
Dyspepsia persist	104.36
GI bleed	6389.11
Post GI bleed	84.39
ACS	8836.95
Post ACS	174.57

* Costs include medication costs. Costs displayed are from the treatment strategy "**ASA** monotherapy"

Sensitivity analyses

We performed one way sensitivity analyses to get an overview of the most influential variables on the results (**Table 1**). Plausible ranges were determined by employing the variability that was found in the literature. Applying a willingness to pay (WTP) threshold of €20,000 per QALY, parameter threshold values were obtained at which the relative order between strategies changed. This WTP-threshold is relatively arbitrary as there is no official threshold in the Netherlands. It is, however, the most conservative threshold out of a range of thresholds (€20,000-€80,000) that have been suggested for the Netherlands

Additionally, we performed a probabilistic sensitivity analysis, for which we included probability distributions around all transition probabilities (beta distributions), relative risks (log normal distributions), costs (gamma distributions)

and utilities (beta distributions) (**Appendix Table 3**). Furthermore, we wanted to simulate non-compliance as well as partial and full-compliance. We therefore created compliance distributions with a probability to be non-compliant as well as probabilities for partial and full-compliance (**Appendix Figure 2**). These compliance distributions were based on assumptions verified with our expert panel. A detailed overview of all input parameters for the probabilistic sensitivity analyses is provided in the technical appendix. We conducted a Monte Carlo simulation with 10,000 samples, which resulted in scatter plots and cost-effectiveness acceptability curves for both primary and secondary prevention of ACS and for patients with average and elevated (three-fold) risk of upper GI bleeding.

RESULTS

Primary prevention

Average GI bleeding risk

In a cohort of 60-year old males taking low-dose ASA for primary prevention of ACS the treatment strategies *no medication* as well as *ASA+PPI* were likely to be cost-effective, with the latter strategy yielding an incremental cost effectiveness ratio (ICER) of €10,314 per QALY gained compared to *no medication*. *ASA monotherapy* was not cost-effective, as the ICER of this strategy was higher than the ICER of the next, more effective alternative (*ASA+PPI;* extended dominance). The incremental cost of the *fixed combination* compared to *ASA+PPI* was €35,832 per additional QALY. **Table 3** shows the results of our base case analyses.

Elevated GI bleeding risk

In a cohort of 60-year old patients with a 3-fold increased risk for upper GI complications taking low-dose ASA for primary prevention of ACS, *ASA monotherapy* was dominated since it was more costly and less effective than *no medication* (**Table 3**). *ASA+PPI* yielded an ICER of €10,449 per QALY gained compared to *no medication*. Compared to *ASA+PPI*, the *fixed combination* yielded an ICER of €24,825 per QALY gained.

Sensitivity analyses

We performed one-way sensitivity analyses to assess the influence of individual parameters on the model. The results were most sensitive to 1) compliance of PPI and 2) cost of the fixed combination and the PPI and 3) the probability of developing dyspepsia. A tornado diagram of the full one-way sensitivity analysis for average

and high risk patients, comparing the *fixed combination* to *ASA+PPI*, is presented in the technical appendix.

Threshold analysis for the average risk patient showed that if PPI compliance drops below 40%, the *ASA+PPI* strategy was no longer cost-effective when a WTP threshold of €20,000 was applied. The *fixed combination* then yields an ICER of €21,430 per QALY gained, making *no medication* the only cost-effective strategy. In an average risk population the *fixed combination* was cost-effective only if it costs less than €0.32 per day. In a high risk population the *fixed combination* was cost-effective when it costs less than €0.40 per day, PPI compliance falls below 55%, or PPI costs more than €0.07 per day.

Cost-effectiveness acceptability curves (**Figure 2**) point out that the treatment option *ASA+PPI* has the highest probability of being cost-effective for primary prevention if we hold on to a WTP threshold of €20,000 per QALY gained.

Table 3 Base case results

Analysis	Strategy	Costs (€)	QALYs	Incremental cost-effectiveness ratio (€/QALY gained)
Primary prevention Average GI bleeding risk	*No medication*	3409.60	15.91	-
	ASA monotherapy	3932.90	15.90	**(Dominated)**
	ASA + PPI	4108.60	15.97	**€10,314**
	Fixed combination	5909.60	16.03	**€35,832**
Primary prevention Elevated GI bleeding risk	*No medication*	4004.80	15.85	-
	ASA monotherapy	4855.40	15.80	**(Dominated)**
	ASA + PPI	4682.40	15.91	**€10,449**
	Fixed combination	6335.40	15.98	**€24,825**
Secondary prevention Average GI bleeding risk	*ASA monotherapy*	16,877.70	13.02	-
	ASA + PPI	16,924.90	13.10	**€563**
	Fixed combination	18,953.40	13.17	**€22,927**
Secondary prevention Elevated GI bleeding risk	*ASA monotherapy*	17,844.20	12.92	**(Dominated)**
	ASA + PPI	17,532.50	13.03	-
	Fixed combination	19,353.80	13.12	**€14,682**

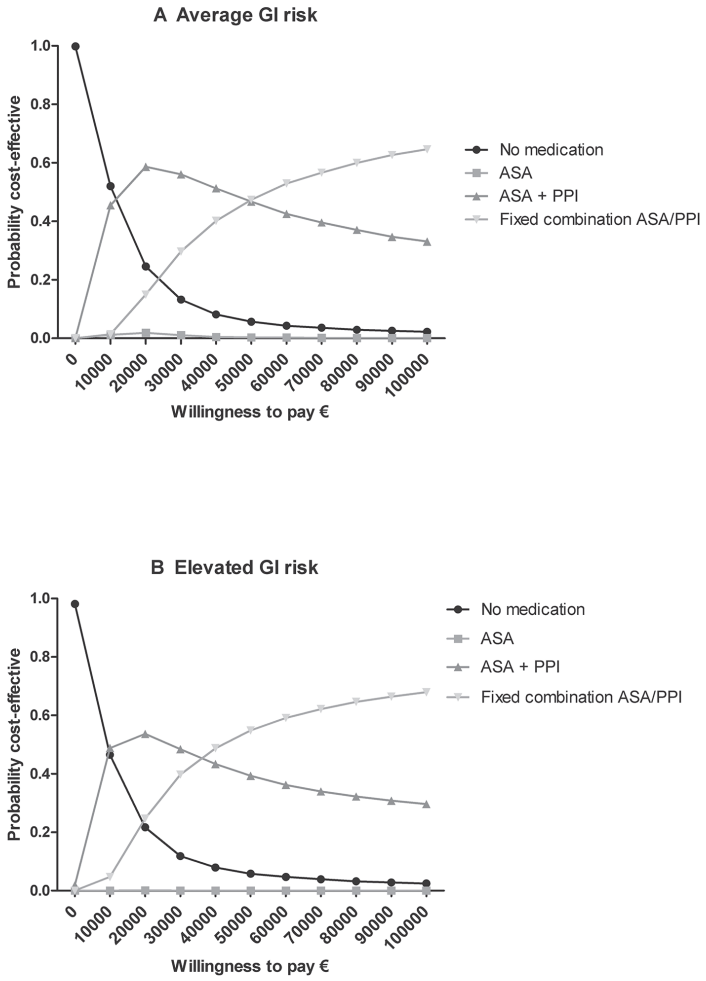

Figure 2 Cost-effectiveness acceptability curves of the primary prevention cohort. A) average GI bleeding risk, B) elevated GI bleeding risk. WTP = Willingness to pay. This figure illustrates the probability that a strategy is cost-effective at various WTP thresholds

Secondary prevention

Average GI bleeding risk

In a cohort of 60-year old males with an average GI bleeding risk profile taking low-dose ASA for secondary prevention *ASA+PPI* was likely to be cost-effective, yielding an ICER of €563 per QALY gained (**Table 2**). Compared to *ASA+PPI*, the *fixed combination* was less cost-effective with an ICER of €22,927 per QALY gained.

Elevated GI bleeding risk

When accounting for a higher GI-complication risk, the treatment option *ASA monotherapy* was dominated by *ASA+PPI*. *ASA+PPI* and the *fixed combination* both seemed acceptable strategies, as the *fixed combination* yielded an ICER of €14,682 per QALY gained compared to *ASA +PPI*.

Sensitivity analyses

One-way sensitivity analyses showed that the results were sensitive to 1) compliance to PPI, 2) cost of PPI and 3) cost of the fixed combination. A tornado diagram of the full one-way sensitivity analysis for average risk patients, comparing the *fixed combination* to *ASA+PPI*, is presented in the technical appendix.

Threshold analysis for the average risk patient showed that if PPI compliance drops below 56%, the *fixed combination* becomes the most effective strategy below the willingness to pay threshold of €20,000 per QALY. If the compliance rate is very low (<21%), the *fixed combination* is the only cost-effective strategy. Should the cost of PPI exceed €0.05 per day or should the *fixed combination* cost less than €0.42, the *fixed combination* becomes cost-effective. In high risk patients, the *fixed combination* was no longer cost-effective at a cost beyond €0.54 or compliance to PPI before GI complications exceeds 72%.

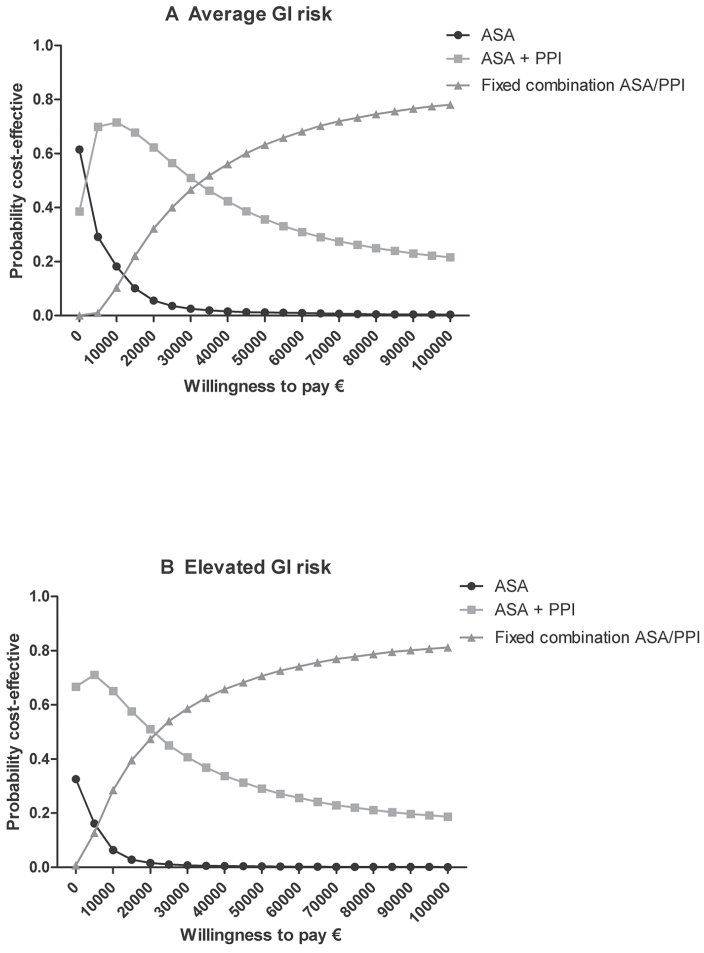

Figure 3 Cost-effectiveness acceptability curves of the secondary prevention cohort. A) average GI bleeding risk, B) elevated GI bleeding risk. WTP = Willingness to pay. This figure illustrates the probability that a strategy is cost-effective at various WTP thresholds

In the probabilistic sensitivity analyses the cost-effectiveness of the *fixed combination* is again not confirmed for average risk patients (**Figure 3**). *ASA+PPI* has the highest probability of being cost-effective at a willingness to pay threshold of €20,000 per QALY. For high risk patients, the probabilities of being the preferred strategy are equal for *ASA+PPI* and the *fixed combination* at a WTP threshold of €20,000 per QALY, yet are higher for *ASA+PPI* at lower thresholds.

Acute coronary syndrome risk

In both primary and secondary prevention, patients treated with the *fixed combination* had the lowest risk of an (recurrent) ACS compared to the other strategies (**Figure 4 & 5**, p<0.01). Notably, patients treated with *ASA+PPI* also had a lower risk of an ACS compared to patients taking *ASA monotherapy* (p<0.01).

In primary prevention, one ACS could be prevented if 435 patients are treated with *ASA+PPI* co-therapy instead of *ASA monotherapy* (NNT (number needed to treat) = 435)). The NNT for the *fixed combination* (compared to ASA monotherapy) is even lower; only 124 patients have to be treated with the *fixed combination* instead of *ASA monotherapy* to prevent one ACS. For secondary prevention the preventive effect of PPIs was stronger; with a NNT of 385 and 74, respectively. The GI bleeding risk did not influence the risk of an ACS among different treatment groups.

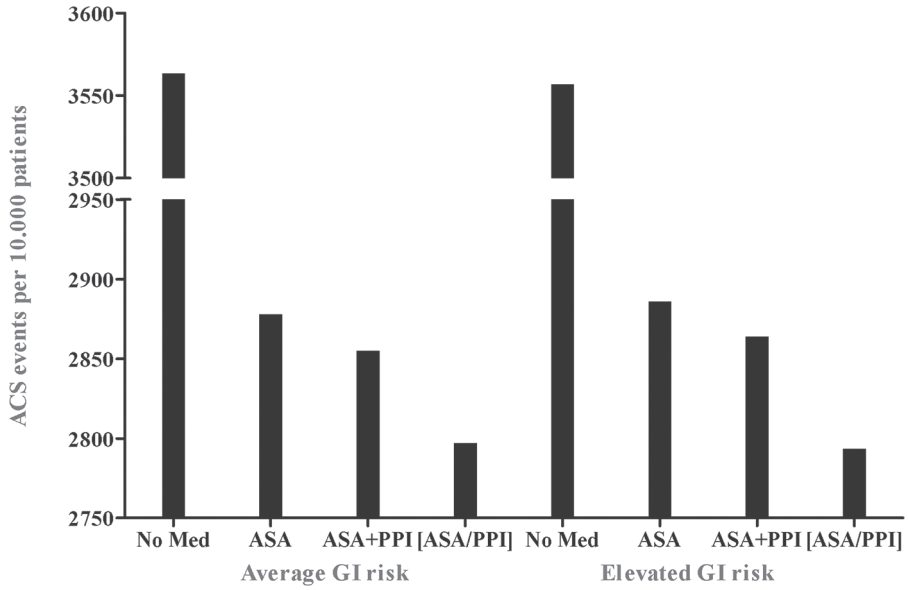

Figure 4 Total number of ACS events during follow-up in 10,000 patients treated with the different treatment strategies for primary prevention. All strategies differed statistically significant p<0.01

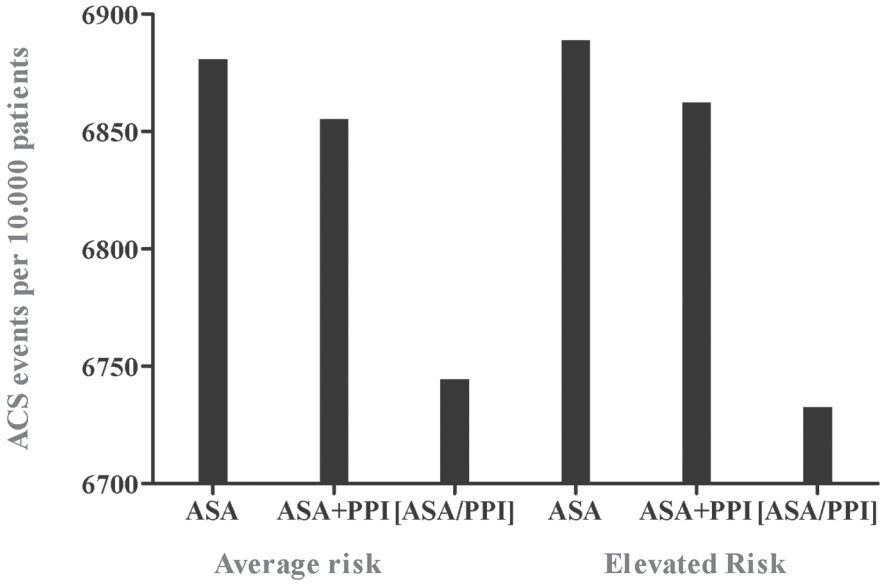

Figure 5 Total number of ACS events during follow-up in 10,000 patients treated with the different treatment strategies for secondary prevention. All strategies differed statistically significant $p<0.01$

Higher patient compliance to ASA is the main driver of the lower ACS risk in patients taking the PPI co-therapy or the fixed combination. Since PPIs reduce GI side effects of ASA, PPI co-therapy indirectly increases ASA compliance. To study the influence of PPI compliance on the risk of an ACS, we plotted the patient compliance to PPI against the number of ACS events (**Figure 6**.). Especially in patients treated with *ASA+PPI* for secondary prevention we found that with every 20% decrease in PPI compliance the risk of an ACS increased by 0.12%. Again, GI bleeding risk did not influence these results.

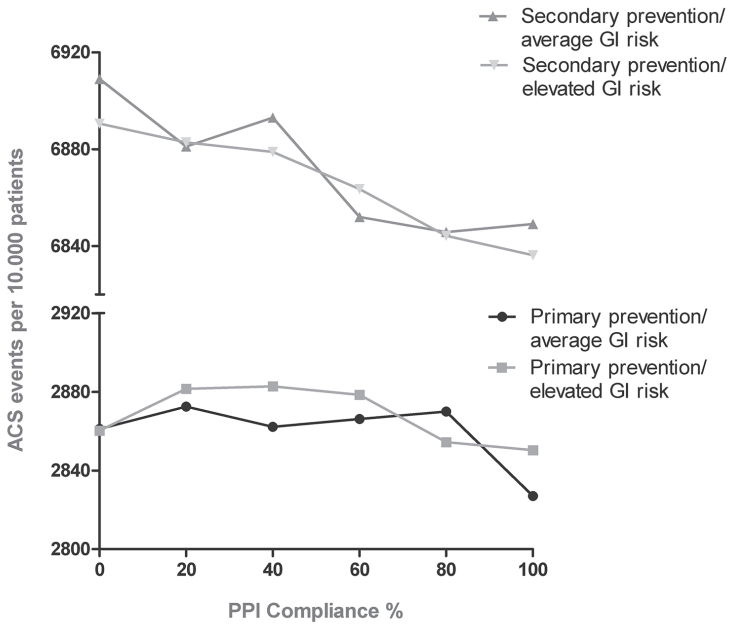

Figure 6 PPI compliance plotted against the total number of ACS events in 10.000 simulated patients.

DISCUSSION

The results of our cost-effectiveness study suggest that use of low-dose ASA for primary prevention is only cost-effective when a PPI is co-administered. *ASA monotherapy* was not cost-effective: we found that both *no medication* and *ASA+PPI* were better treatment options over *ASA monotherapy* for patients with both average and high GI bleeding risk. Our results were however dependent on the costs of PPIs and PPI compliance. For patients with average GI bleeding risk and low compliance to PPI, *no medication* was the best treatment option. For patients with an elevated GI bleeding risk and low compliance to PPI the *fixed combination* of ASA and PPI was likely to be cost-effective. In secondary prevention of ACS, *ASA+PPI* co-therapy was the preferred treatment strategy in all patients taking low-dose ASA and it was even cost-saving for patients with increased GI bleeding risk when it was compared to *ASA monotherapy*. In patients with increased GI bleeding risk, the *fixed combination* seemed an additional cost-effective option.

Prior studies have investigated the cost-effectiveness of low-dose ASA in the prevention of coronary heart disease. Greving et al. concluded that ASA is only cost-effective for men with a 10-year CV disease risk of >10%[61], while Earnshaw et al. concluded that ASA monotherapy is cost-effective in middle-aged men across a range of CV and GI bleeding risk factors[9]. The contrasting results between these studies and our results are mainly due to the effect of structural and parameter model differences. Most importantly, in our model dyspepsia is included as a separate health state, as well as the chronic condition of persisting dyspepsia. Chronic or recurrent dyspepsia is a common GI complication, affecting 20-37% of adults and impacting many domains of health related quality of life[48, 62, 63]. The risk of developing dyspepsia is increased in patients taking low-dose ASA[7,64,65]. On the other hand, PPI therapy increases the proportion of patients with resolution of dyspeptic symptoms[12,13,66]. The inclusion of dyspepsia in our model impairs the cost-effectiveness of ASA monotherapy but favors the cost-effectiveness of PPI co-therapy. The cost-effectiveness of PPI co-therapy is also favored by the low (generic) costs of PPIs in the Netherlands, where a single dose of 20 mg omeprazole is available at a price of €0.02. Another study on the cost-effectiveness of PPI co-therapy in secondary CV prevention was in line with our results, as PPI co-therapy was regarded cost-effective at PPI prices below $250 per year[14]. Yet, we are the first to report PPI co-therapy to be potentially cost-saving.

The analyses were performed from a third-party payer perspective. If we had included costs associated with productivity loss in our analysis, this would have led to more favorable cost-effectiveness outcomes for the strategies ASA+PPI co-therapy and the fixed combination, as these strategies are associated with less events compared to the other strategies, resulting in less incremental costs. Using a third-party payer perspective can therefore be regarded more conservative compared to using a societal perspective.

A secondary outcome of this study was the association between the different treatment strategies and the absolute risk of developing an ACS and the effect of PPI compliance on the absolute ACS risk. We found that patients treated with PPI co-therapy or the fixed combination had a significantly lower ACS-risk compared to patients treated with ASA monotherapy or no medication. This underlines the hypothesis that concomitant prescription of PPI reduces GI side effects and thereby increases patients' compliance to ASA, which in turn reduces the probability of developing an ACS. A recent study by Saini et al. also suggested that PPI co-therapy has the potential to improve CV outcomes[67].

Our study had several important strengths. First, we included patient compliance in our model using a method that enabled us to model partial patient compliance as well as alterations in compliance rates depending on a patient's medical history. Additionally, we modeled both PPI compliance and ASA compliance

and included the effect of compliance on the occurrence of GI events and ACS. Many studies evaluating the cost-effectiveness of low-dose ASA mainly looked at CV outcomes, and therefore often concluded that low-dose ASA is cost-effective in primary prevention of ACS[68]. We also included dyspepsia in our model as well as an age dependent risk of GI bleeding; included both primary and secondary prevention of ACS, and varied the GI bleeding risk to cover a wide patient population. We increased the risk of GI complications up to a 3-fold higher risk, which corresponds to patients who, for example, use anticoagulants or NSAIDs concomitantly[34].

This study had some limitations. First, this study is limited by its hypothetical design. Our base case parameter estimates were derived from literature including studies with heterogeneous designs, populations and follow up periods. In order to correct for that, we used systematic reviews and meta-analyses where possible and to account for uncertainties we performed probabilistic sensitivity analyses across a wide range for each key variable in the model. We chose a 60-year old men as base case patient, as this corresponded with the average patient in clinical trials[2,3,5,27]. Little data is available on primarily women. Possibly, women do not benefit to the same extent from ASA for primary prevention of ACS compared to men, yet results are conflicting and recommendations by guidelines are comparable for males and females[2,69]. A second limitation might have been the generalizability of our results to healthcare systems that differ from the Netherlands. We are aware of higher medication costs in other countries (e.g. USA), especially PPI costs. We therefore included a figure (Appendix Figure 3) which shows the cost-effectiveness estimates for a range of PPI prices. Moreover the WTP may vary between different countries. We applied a WTP-threshold of €20,000 for our threshold analyses, although this threshold is relatively arbitrary as there is no official threshold in the Netherlands. Third, if no published literature was available for input for our model, estimates were based on expert opinion, but were then tested over a wide range in one-way and probabilistic sensitivity analyses. Moreover, we assumed a linear relation between compliance rates and effectiveness of ASA and/or PPI, which might not reflect reality: the antiplatelet effect of ASA is known to last several days after intake, so the influence of compliance on the effectiveness of ASA might have been overestimated. The relation between PPI compliance and the occurrence of GI side effects is unclear in patients using low-dose ASA as well as the exact association between low-dose ASA use and the development of dyspepsia, and we therefore tested a wide range of relative risk values. Last, in order to prevent the model from becoming too cumbersome, we did not include other CV outcomes in our model, nor did we include the preventive effect ASA is thought to have on the development of GI cancer[70]. We did also not include side effects of PPI therapy. Existing data about the potential association between PPI and adverse outcomes such as vitamin and mineral deficiencies, pneumonia and osteoporosis vary and

are based on observational studies; moreover the absolute incidences of these side effects are low[71,72].

In conclusion, this cost-effectiveness study suggest that PPI co-therapy is the preferred treatment strategy in patients taking low-dose ASA for the prevention of ACS, given that PPIs are available at low prices. A fixed combination may be cost-effective in patients who are at increased risk for GI bleeding and who are poorly compliant to PPI. Both PPI co-therapy and the fixed combination were found to be more effective in reducing the ACS risk compared to ASA monotherapy, due to a reduction in dyspepsia and consequent increase in compliance with ASA therapy. These results suggest that the current guidelines may need to be expanded, recommending PPI co-therapy for all low-dose ASA users if generic PPIs can be purchased for relatively low prices. Future clinical trials are needed to assess the effect of PPI and ASA compliance on the occurrence of GI events and ACS.

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PART

Prediction of the outcome of upper GI bleeding

Chapter 5

Prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal

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Accepted for publication in Endoscopy

ABSTRACT

BACKGROUND

Several algorithms predicting outcomes in acute gastrointestinal bleeding have been developed over the past three decades. These algorithms differ substantially and therefore the aim of the current study was to conduct a systematic review to compare their predictive performance and methodological quality in gastrointestinal bleeding.

METHODS

A PubMed literature search was performed up to 1 July 2011. All studies reporting prediction scores in gastrointestinal bleeding were included. Studies were analyzed for predictive performance, and a quality appraisal of these rules was performed for which a score range of 0 (lowest) to 29 (highest) was used.

RESULTS

A total of 372 studies were identified, of which 16 were eligible for inclusion. The studies evaluated different outcomes: mortality (n = 5), rebleeding (n = 2), intervention required (n = 2), or a combination (n = 7). The predictive performance of the identified prediction scores varied between an area under the curve of 0.71–0.92 (if given). The mean overall quality rating was 17 (SD 4.0, range 9–25. Major methodological shortcomings were the absence of validation and absence of impact analyses. Eight of 16 scores (50%) were determined “easy to use,” and five scores (31%) reported some type of action based on the results.

CONCLUSION

Substantial heterogeneity in outcomes and results was seen in the 16 identified prediction scores. Moreover, the methodological quality was suboptimal in most studies. However, we suggest that clinicians should use the “best available” scores according to performance and quality, which are the Blatchford score to assess the need for re-intervention, and the scores of Villanueva et al. for poor outcome, Guglielmi et al. for rebleeding, and Chiu et al. for mortality risk.

INTRODUCTION

Acute upper and lower gastrointestinal bleeding is a common indication for hospital admission. For upper non-variceal gastrointestinal bleeding, incidence rates of 47.7–102/100 000 persons annually have been reported, with a mortality rate of approximately 15%[1–3]. Although some data suggest a reduction in the incidence, the clinical burden and economic costs of gastrointestinal bleeding remain high[1,4–6].

In order to facilitate risk stratification and clinical triage, various prediction scores have been developed using different outcome measurements, such as mortality, recurrent gastrointestinal bleeding, and the need for clinical intervention. By using demographic, clinical or laboratory findings, prediction scores provide physicians with an algorithm for probability of disease, outcome, and/or response to treatment[7–9]. These scores may assist physicians in medical decision-making and provide information to patients on prognostic items. As gastrointestinal bleeding occurs mostly in an emergency setting in which immediate triage is needed, a prediction score may assist clinical experience and intuition of physicians. Recent international consensus guidelines on the management of patients with gastrointestinal bleeding also recommend stratifying patients into low and high risk groups for rebleeding and mortality based on prediction scores[10]. The consensus panel stated that early identification of high risk patients for rebleeding could allow appropriate intervention and minimize morbidity and mortality.

Two commonly used prediction rules are the Rockall score and the Blatchford score[11,12]. The Rockall score was developed to predict mortality and rebleeding and is based on both clinical and endoscopic variables. In contrast, the Blatchford score identifies the need for clinical intervention, based on pre-endoscopic variables. Both scores are accurate, with the area under the receiver operating characteristic (ROC) curve ranging from 0.61 to 0.81 for the Rockall score in predicting rebleeding and mortality in clinical practice[13,14], and from 0.72 to 0.92 for the Blatchford score in predicting the need for clinical intervention[12,15,16].

However, the predictive power of such scores is not the only indicator of whether the score should be used; methodological quality is also important. The overall number of prediction scores has expanded over the past decade[9]. As one might expect, most studies relate to the development of a particular prediction score, but less attention has been given to the validation of a score and the impact of this score on physician behavior and/or patient outcomes.

We wondered whether currently available prediction scores in gastrointestinal bleeding have been established using high methodological quality standards[8,9]. Many prediction rules were published two decades ago, whereas the treatment of gastrointestinal bleeding has changed considerably over the past 5–10 years. Moreover, several factors associated with gastrointestinal bleeding have also

changed, such as the recognition that *Helicobacter pylori* is involved in peptic ulcer bleeding and can be eradicated[17,18], and the increasing use of non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet therapy[1,19–22]. As a result, new prediction scores have been developed over recent years, and there is now a need for comparison of the currently available prediction scores.

The objective of the current study was to identify all available prediction scores in gastrointestinal bleeding and to evaluate the performance and quality of these scores with regard to the outcome of gastrointestinal bleeding.

METHODS

The methodology and report of the present review is based on the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[23].

Search strategy and study selection

An extensive PubMed literature search was performed up to 1 July 2011. The medical subject headings (MeSH) or keywords used were "gastrointestinal hemorrhage," "prognosis," and "risk factors." In addition, the reference lists of the included studies, reviews or editorials were evaluated.

A study was included when the development of a clinical prediction rule/score was based on data collected from patients with acute upper and/or lower gastrointestinal bleeding. Prediction scores derived only from literature describing previously established predictors or artificial neural networks were excluded as no full quality assessment could be performed. Other exclusion criteria were reviews or comments, papers including only a small subset of cases with gastrointestinal bleeding, such as primarily variceal bleeding, and papers in the non-English language.

Two authors (N.d.G. and J.B.) independently screened all retrieved article titles and abstracts and applied the inclusion and exclusion criteria. The full text was read when flagged as relevant by one of the reviewers. The reviewers were not blinded to journal or authors. Discrepancies were resolved by discussion with a third party arbiter (M.v.O.).

Data extraction and quality assessment

Both reviewers independently read each article and extracted data including population size, study design, input variables, outcome definitions, patient characteristics, and results.

Quality appraisal was performed by using methodological standards as published previously[7,8,24,25]. The assessment items are shown in **Table 1** and **Figure 1**. Two authors (N.d.G. and J.B.) assessed all studies on methodological quality without consideration of the results. Prior to scoring the articles, the interpretations of the methodological standards were defined and agreed. After applying the standards, disagreements were resolved by discussion until consensus was established.

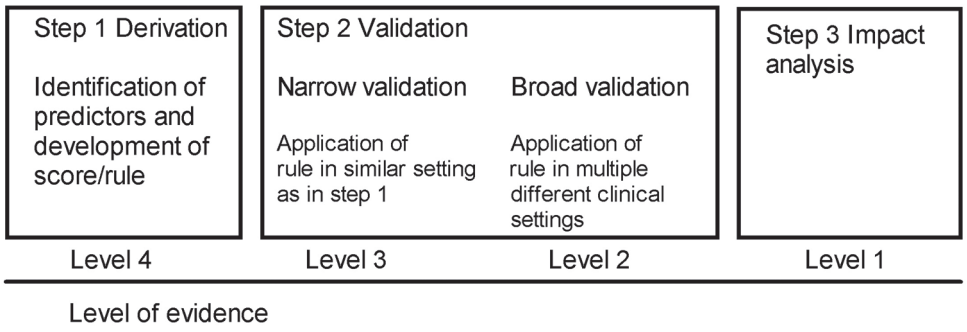

Figure 1 Development of a prediction rule[7]

Table 1 Scoring methodological standards.

	Score
Derivation of the score	
Prospective study design	1
Input variables for score; clinical, laboratory, and endoscopy	1
Clear definition outcome	1
Clinical importance outcome	1
Blind assessment outcome	1
Enough outcome events	1
Identification and definition of predictive variables	1
Blind assessment of predictive variables	1
Important patient characteristics described	1
Study site described	1
Mathematical techniques described; multivariate analysis	1
Results of the rule described	1

	Score
Reproducibility of predictive variables	1
Reproducibility of the rule	1
Clinical sensibility	1
Easy to use	1
Course of action described	1
Validation	
Internal validation by same group	1
External validation by same group	2
Impact analysis	
Evidence that rule changes physician behavior	1
Improves patient outcome	1
Number of patients	
0–500	1
500–1000	2
≥1000	3
Level of evidence	
Level 1	4
Level 2	3
Level 3	2
Level 4	1

RESULTS

A total of 372 articles were identified. After applying the inclusion and exclusion criteria on titles and abstracts, 10 studies were selected. Another 10 studies were found by screening related articles and references, six of which were eligible for analysis. Finally, 16 studies met all inclusion criteria[11,12,14,26–38] (**Figure 2**).

The characteristics of included studies are shown in **Table 2**. A total of 14 studies reported on prediction scores for upper gastrointestinal bleeding, 1 for lower gastrointestinal bleeding, and 1 study reported on both upper and lower gastrointestinal bleeding. Mean ages of patients ranged from 52 to 68 years. Mean mortality rate was 9% (range 2%–18%), and a mean of 16% of patients experienced rebleeding (range 2%–33%).

Table 2 Baseline characteristics and performance.

	Pimpl (36)	Provenzale (37)	Rockall (11)	Marmo (14)	Chiu (38)	Guglielmi (35)	Travis (26)
Year publication	1987	1987	1996	2008	2009	2002	2008
Location of bleed	Upper	Upper	Upper	Upper	Upper	Upper	Upper
Number of patients	193	153	2956	1020	3220	738	236
Mean age, years	57	52	N/A	68	N/A	N/A	67
Mortality rate, %	17.1	17.6	14	4.5	7.1	10	n/a
Rebleeding rate, %	16	N/A	18	33	7.9	13.3	21.6
Outcome	Mortality	Mortality	Mortality	Mortality	Mortality	Rebleeding	Rebleeding
Score	Pre- and post-endoscopic	Pre- endoscopic	Pre- and post-endoscopic	Pre- and post-endoscopic	Pre- and post-endoscopic	Pre- and post-endoscopic	Pre- and post-endoscopic
Results	N/A (only rates per score group)	N/A (only rates per score group)	N/A (only rates per score group)	AUC 0.81	AUC 0.84	Sensitivity and specificity of 76%	AUC 0.71

	Park (32)	Blatchford (12)	Bordley (30)	Villanueva (28)	Kollef (27)	Corley (31)	Strate (29)	Almela (33)	Imperiale (34)
Year Publication	1994	1997	1985	1993	1997	1998	2003	2004	2007
Location of bleed	Upper	Upper	Upper	Upper	Upper and lower	Upper	Lower	Upper	Upper
Number of patients	135	1748	110	233	108	335	252	581	391
Mean age, years	N/A	N/A	54	65	60	58	66	61	63
Mortality rate, %	7	8.1	11.8	5.1	15.7	n/a	2	2	3.1
Rebleeding rate, %	20	n/a	n/a	17	16.7	26	7	1.9	4.6
Outcome	Need for intervention	Need for intervention	Composite endpoint: Good outcome	Composite endpoint: Therapeutic failure	Composite endpoint: Poor outcome	Composite endpoint: Good outcome	Composite endpoint: Poor outcome	Composite endpoint: Good outcome	Composite endpoint: Poor outcome
Score	Pre- and post-endoscopic	Pre-endoscopic	Pre-endoscopic	Pre- and post-endoscopic	Pre-endoscopic	Pre-endoscopic	Pre-endoscopic	Pre- and post-endoscopic	Pre- and post-endoscopic
Results	Correctly predicts laparotomy in 84% of patients	AUC 0.92	NPV 98% PPV 57%	Maximum discrimination point 74%	AUC 0.72	N/A (only rates per score group)	AUC 0.76	C statistic 0.87 Sensitivity 100% Specificity 64%	C statistic 0.81

N/A; Not available
AUC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value.

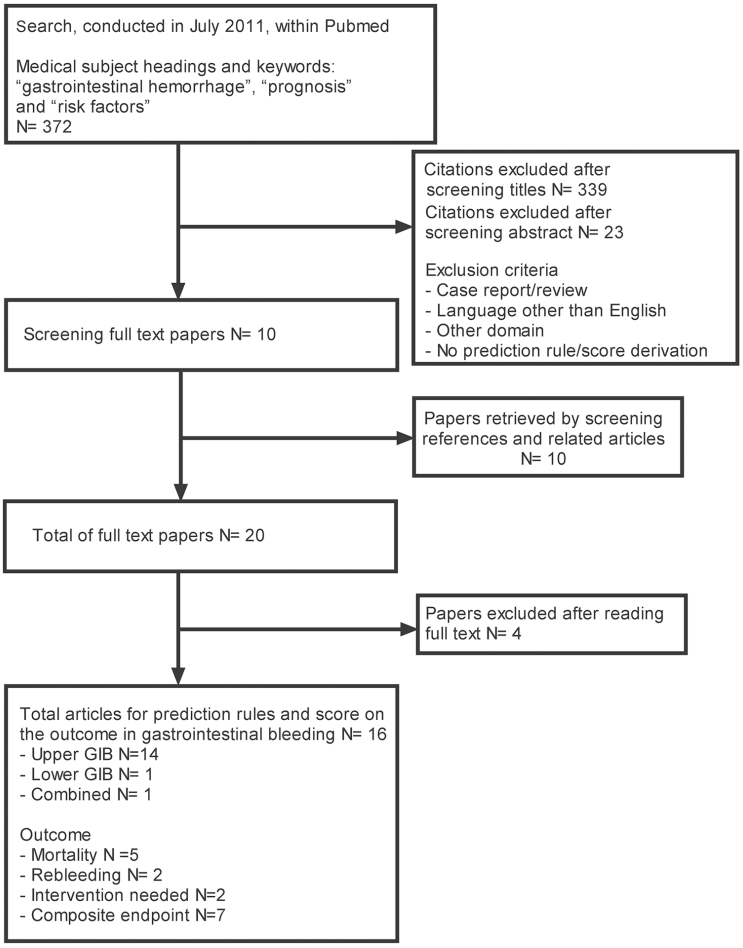

Figure 2 Flowchart of the literature search

Mortality

Mortality was the primary outcome in five studies[11,14,36–38], one of which reported on a score that was developed using pre-endoscopic variables[37]. Pimpl et al.[36], Provenzale et al.[37], and Rockall et al.[11] analyzed the observed mortality rates per risk profile based on their prediction score and found an increasing mortality rate as the risk score increased. Marmo et al.[14] and Chiu et al.[38] developed scores with good predictive power for mortality (AUC 0.81 and 0.84, respectively). Risk factors that were mostly associated with mortality were age, co-morbid disease, time to admission, and blood pressure (**Table 3**).

Rebleeding

Only two scores focused primarily on rebleeding in patients with upper gastrointestinal bleeding[26,35]. Guglielmi et al.[35] developed a risk score for rebleeding in patients with gastric or duodenal ulcer bleeding, whereas Travis et al.[26] developed a score for all non-variceal upper gastrointestinal bleeding. Both scores consisted of pre- and post-endoscopic variables. The predictive power of both scores was reasonable with a sensitivity and specificity of 76% and an AUC of 0.71, respectively. Both scores incorporated liver disease and severity of the bleeding as risk factors for rebleeding (**Table 3**).

Need for intervention

Blatchford et al.[12] and Park et al.[32] developed risk scores to predict the need for an intervention. These were need for blood transfusion or any operative or endoscopic intervention[12], and need for surgery[32], respectively. The prediction score by Blatchford et al.[12] included solely pre-endoscopic variables in the score, and had a high predictive power (AUC 0.92). The prediction score developed by Park et al.[32]showed that the risk score correctly predicted the need for surgery in 84% of the patients. The only consistent predictive variable in both scores was an increased heart rate (**Table 3**).

Composite endpoint

The remaining scores used a composite endpoint mostly described as “good or poor outcome.” Patients with a “good outcome” were defined as those alive, without persisting or recurrent bleeding, and patients who did not need surgery (**Table 2**)[30,31,33]. Consistent variables predicting good outcome included no co-morbid diseases, normal blood pressure, and no fresh blood after performing nasogastric aspiration (**Table 3**). Poor outcome was the primary endpoint in four studies[27–29,34]. Villanueva et al.[28], Almela et al.,[33], and Imperiale et al.[34] developed risk scores for upper gastrointestinal bleeding based on pre- and post-endoscopic variables. Kollef et al.[27] predicted a poor outcome for both upper and lower gastrointestinal bleeding, whereas Strate et al.[29] made a risk score for solely lower gastrointestinal bleeding. A definition of poor outcome was mostly a composite of continued bleeding, rebleeding, need for surgical intervention, and/or mortality. Villanueva et al.[28] found a reasonable predictive power (maximum discrimination point 74%) for predicting therapeutic failure and the risk score of Imperiale et al.[34] had a C statistic of 0.81 for predicting poor outcome. The pre-endoscopic scores of Kollef et al.[27] and Strate et al.[29] (i.e. predicting in-hospital complications, or severe bleeding and rebleeding, respectively) showed similar results (AUC 0.72 and 0.76, respectively). The predictive variables for a poor outcome included co-morbid disease, low blood pressure, and active bleeding (**Table 3**).

Table 3 Independent predictors identified in the prediction scores.

Author article	Mortality	Pimpl (36)	Provenzale (37)	Rockall (11)	Marmo (14)	Chiu (38)	Rebleeding	Guglielmi (35)	Travis (26)	Intervention	Blatchford (12)	Park (32)
Clinical factors												
Age		x		x	x	x						
Co-morbid disease		x	x	x	x	x					x	
Liver disease			x		x			x	x		x	
Obesity												x
ASA class					x							
Time to admission			x		x	x						
In-hospital bleeder												
Recent surgery								x				
Erratic mental status												
Post-procedure heparin									x			
Post-procedure PPI									x			
Aspirin use												
Need for transfusion		x										
Physiological factors												
Blood pressure			x	x		x		x			x	
Heart rate				x							x	x
Syncope											x	
Abdominal examination												
Nasogastric aspiration												
Hematemesis								x				
Melena											x	
Apache score												
Rectal blood loss			x									
Laboratory factors												
Hb level					x						x	
Hematocrit			x		x							
Urea level											x	
Prothrombin time												
Presence of *H. Pylori*						x						
Endoscopic factors												
Active bleeding				x					x			
Rebleeding					x	x						
Forrest class		x						x				
Source bleeding		x		x					x			
Ulcer site		x						x				x
Ulcer size								x				
Epinephrine monotherapy									x			
Failure endoscopic treatment					x	x						

ASA, American Society of Anesthesiologists; PPI, proton pump inhibitor.

Author article	Poor outcome	Bordley (30)	Villanueva (28)	Kollef (27)	Corley (31)	Strate (29)	Almela (33)	Imperiale (34)	Total
Clinical factors									
Age		x							**5**
Co-morbid disease		x	x	x			x	x	**11**
Liver disease					x				**6**
Obesity									**1**
ASA class									**1**
Time to admission						x			**4**
In-hospital bleeder									**1**
Recent surgery									**1**
Erratic mental status				x					**1**
Post-procedure heparin									**1**
Post-procedure PPI									**1**
Aspirin use						x			**1**
Need for transfusion									**1**
Physiological factors									
Blood pressure		x		x	x	x	x		**10**
Heart rate						x	x		**5**
Syncope						x			**2**
Abdominal examination		x				x			**2**
Nasogastric aspiration		x			x				**2**
Hematemesis					x				**2**
Melena									**1**
Apache score								x	**1**
Rectal blood loss									**1**
Laboratory factors									
Hb level									**2**
Hematocrit					x				**3**
Urea level									**1**
Prothrombin time		x		x					**2**
Presence of *H. Pylori*									**1**
Endoscopic factors									
Active bleeding				x			x	x	**5**
Rebleeding									**2**
Forrest class							x		**3**
Source bleeding							x	x	**4**
Ulcer site			x						**4**
Ulcer size			x						**2**
Epinephrine monotherapy									**1**
Failure endoscopic treatment									**2**

Table 4 Quality characteristics and results quantitative appraisal

	Pimpl (36)	Provenzale (37)	Rockall (11)	Marmo (14)	Chiu (38)	Guglielmi (35)	Travis (26)	Park (32)
No. patients	193	153	2956	1020	3220	738	236	135
Study design	+	+	+	+	+	+	–	+
Input variables	–	–	+	+	+	+	+	+
Step 1 Derivation								
Outcome								
Definition	+	+	+	+	+	+	+	–
Clinical importance	+	+	+	+	+	+	+	+
Blind assessment	–	–	–	–	–	–	–	–
Predictive variables								
Identification/ definition	–	+	+	+	+	+	+	+
Blind assessment	+	+	+	+	+	+	–	+
Patient characteristics	–	–	+	+	+	+	+	–
Study site	–	+	+	+	+	+	+	–
Mathematical techniques	–	+	+	+	+	+	+	+
Outcome events	–	–	+	–	+	+	–	–
Results of the rule	–	–	–	+	+	+	+	–
Reproducibility								
Predictive variables	+	+	+	+	+	+	+	+
The rule	+	+	+	+	-	+	+	+
Sensibility								
Clinical sensibility	+	+	+	+	+	+	+	+
Easy to use	–	–	+	–	+	–	+	–
Course of action	–	–	–	–	–	–	–	+
Step 2 Validation								
Internal validation	–	–	–	–	–	+	+	–
External validation	–	+	+	+	+	–	–	–
Step 3 Impact analysis								
Rule changes behavior	–	–	–	–	–	–	–	–
Rule improves patients outcome	–	–	+	–	–	–	–	–
Level of evidence	4	3	2	2	3	3	3	4
Total	9	15	23	21	21	19	16	12

	Blatchford (12)	Bordley (30)	Villanueva (28)	Kollef (27)	Corley (31)	Strate (29)	Almela (33)	Imperiale (34)
No. patients	1748	110	233	108	335	252	581	391
Study design	+	–	+	+	–	–	+	+
Input variables	+	+	+	–	+	–	+	+
Step 1 Derivation								
Outcome								
Definition	+	+	+	+	+	+	+	–
Clinical importance	+	+	+	+	+	+	+	+
Blind assessment	–	–	–	–	–	–	–	–
Predictive variables								
Identification/ definition	+	–	+	+	+	+	–	+
Blind assessment	+	–	+	+	–	–	+	+
Patient characteristics	+	–	–	+	+	+	+	+
Study site	+	+	+	+	+	+	+	+
Mathematical techniques	+	+	+	+	+	+	+	+
Outcome events	+	+	+	+	+	+	–	+
Results of the rule	+	–	+	+	–	+	+	+
Reproducibility								
Predictive variables	+	–	+	+	+	+	+	–
The rule	+	+	+	+	+	+	+	+
Sensibility								
Clinical sensibility	+	+	+	+	+	+	–	+
Easy to use	+	–	+	+	+	-	+	–
Course of action	+	+	–	–	–	–	+	+
Step 2 Validation								
Internal validation	–	–	–	–	–	+	–	+
External validation	+	+	+	+	–	–	–	–
Step 3 Impact analysis								
Rule changes behavior	–	–	–	–	–	–	–	–
Rule improves patients outcome	+	–	–	—	–	–	–	–
Level of evidence	2	3	3	3	4	3	4	3
Total	25	14	19	19	14	15	16	17

Quality appraisal

Figure 3 illustrates the results of the assessment of the included prediction scores according to the applied methodological standards. The mean (±SD) quantitative score was 17.0 ± 4.0 and remained stable over the years of publication. The prediction scores by Rockall[11] and Blatchford[12] were of the highest quality with 23 and 25 points, respectively. Risk scores predicting a composite endpoint had on average the lowest methodological quality score (mean 16.3 ± 2.1) compared with those for mortality (mean 17.8 ± 5.8), rebleeding (mean 17.5 ± 2.1), and need for intervention (mean 18.5 ± 9.2), respectively. Overall, shortcomings were found in several domains (**Table 4**). The studied populations were small with a median population size of 248 (range 108–3220) patients; four studies included more than 1000 patients. Half of the included prediction rules were scored as easy to use, and 5/16 (31%) reported a clinical action based on the results (e.g. performing endoscopy or surgery). Overall, 62.5% of the publications were adequately powered for the number of included independent variables in the search for predictors. Internal and external validation was performed in four (25%) and eight (50%) studies, respectively, with no validation performed in four studies. None of the included prediction scores reported the results of a complete impact analysis.

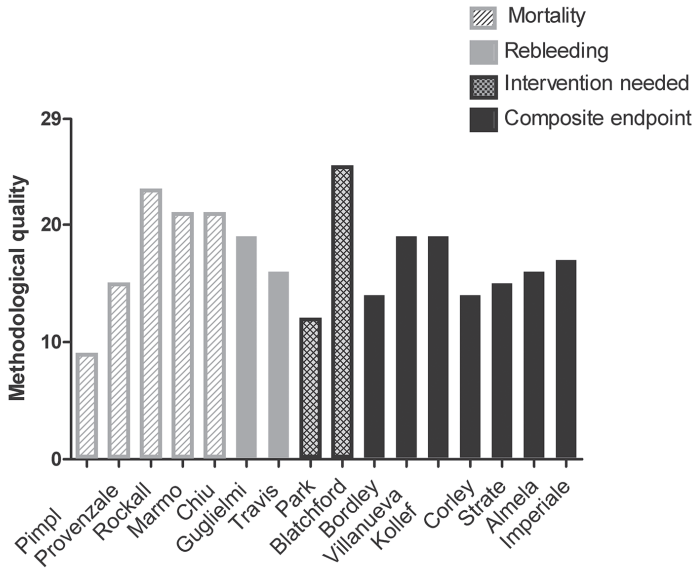

Figure 3 Quantitative appraisal of the different prediction scores

DISCUSSION

Clinical prediction scores have been shown to help physicians in clinical decision-making and have the potential to reduce unnecessary costs. In order to predict the outcome of gastrointestinal bleeding, several prediction scores have been developed over the past 30 years. As these scores are used for triage of clinical care, it is important that these are developed and validated using high methodological standards. By using a systematic review and performing a qualitative and quantitative appraisal, we assessed the existing clinical prediction rules in gastrointestinal bleeding for performance and quality.

A total of 16 prediction rules in gastrointestinal bleeding were included and analyzed. Most scores have been developed for predicting upper gastrointestinal bleeding; however, we also found one score for both upper and lower gastrointestinal bleeding and one primarily for lower gastrointestinal bleeding. Considerable heterogeneity was found for the outcome of the studies. Mortality, rebleeding, and the need for intervention were individually assessed, but a composite of these endpoints was used in the majority of the prediction scores. Furthermore, the way of describing the results differed between studies. Most studies reported an AUC, but some reported sensitivity/specificity, negative and positive predictive values, and incidence rates. These differences make it challenging or even impossible to compare the performance of these prediction scores in daily clinical practice.

We concluded that the overall methodological quality of the prediction scores was suboptimal, with a median of 16.5 of the maximum 29 points. Major shortcomings were found in different methodological domains. First, sample sizes in the included studies were small. In order to extrapolate the results to other patients, one should develop the particular rule in populations of at least 1000 patients. By studying predictors in small sample sizes, the probability of ignoring an independent predictor is increased due to the limited power. Second, thorough external validation, meaning that the rule is being tested for its accuracy, was not performed in half[8/16] of the studies. Predictors found in one study cohort can often not be extrapolated to another group and a different set of predictors may emerge from a different group of patients. In general, it should be evaluated whether a rule derived from one study population can also be applied in another setting and/or another population with gastrointestinal bleeding. Therefore, a prediction rule can only be implemented in clinical care if validated in another study cohort (external validation). Broad external validation was indeed performed for the PNED, Rockall, and Blatchford scores[12,14,15,39–41]. It is even more valuable if the same research group is performing this external validation taking into account the possible variability in application, and the interpretation of the score and the results.

Third, none of the included studies performed an impact analysis to assess the use of the prediction rule and its effect on changing or directing physician behavior and improving patient outcomes or other important parameters, such as length of hospital stay, and reduction of costs. Two commonly used scores – the Rockall score and Blatchford score – have been used in cohorts and randomized controlled trials (RCTs) to assess the outcome of outpatient vs. hospital care of patients with upper gastrointestinal bleeding based on these scoring systems. These studies concluded that the use of these prediction scores reduced healthcare expenses, shortened in-hospital time of patients, and clinical decisions based on these scores were judged as safe[42–44]. The best design for an impact analysis is the RCT, in which centers are randomized to using the prediction score compared with common clinical practice. We are not aware of any other studies that show clearly that a prediction rule had clinical impact on medical decision-making or how often these scores are being used in daily clinical practice.

Based on performance and methodological quality of the prediction scores we recommend the prediction score by Chiu et al.[38] to be used for mortality, as it has a high predictive power and good methodological quality. The preferred risk score for rebleeding is the score developed by Guglielmi et al.[35], which is based on the good methodological quality and equal performance results. The advised score for predicting that an intervention is indicated is actually difficult as outcomes largely differ; however, the Blatchford score[12] had the highest methodological quality and predictive power compared with the other scores. Advice on the preferred prediction score for a good and/or poor outcome is difficult because large differences were seen in outcome, performance, and quality; however, based on the reasonable population size included, the performance of external validation, and average methodological quality we recommend the prediction score of Villanueva et al.[28] (**Table 5**).

Table 5 Overview of the recommended scores.

Outcome	Recommended score	Strengths
Mortality	Chiu et al. (38)	High predictive power Good methodological quality
Rebleeding	Guglielmi et al. (35)	Good predictive power Good methodological quality
Need for intervention	Blatchford et al. (12)	High predictive power High methodological quality
Poor outcome	Villanueva et al. (28)	Reasonable predictive power Good methodological quality Performance of external validation

Large heterogeneity was seen in the predictive variables included in the risk scores. Overall, the most commonly applied variables were pre-endoscopic age, co-morbid diseases, liver disease, blood pressure, post-endoscopic active bleeding, Forrest classification, and ulcer site. Of these, age, co-morbid disease, and blood pressure were most predictive for mortality and the composite endpoints, whereas liver disease and active bleeding were the main predictors for rebleeding. Many scores in gastrointestinal bleeding date back to at least more than a decade ago, and much has changed since. New diagnostic and therapeutic options, such as intravenous proton pump inhibitor therapy, have been implemented, which certainly have increased the number of successful endoscopic treatment procedures. However, medication affecting the gastric mucosa (aspirin and NSAIDs) or increasing the risk of gastrointestinal bleeding (antiplatelet and anticoagulant therapy) are being used increasingly. Despite good recognition of NSAIDs, antiplatelets, and anticoagulants as possible predictive variables, only Travis et al.[26] identified antiplatelet use as a possible predictive variable. Based on these findings, it is unknown whether the use of these medications may have had an impact on the outcomes studied in the studies included in this review. Furthermore, the identification of *H. pylori* as a possible predictive variable in the outcome of upper gastrointestinal bleeding is low in the evaluated prediction scores. Only Chiu et al.[38] identified and incorporated *H. pylori* into the final score. It should be kept in mind, however, that in many countries the role of *H. pylori* in peptic ulcer disease has shown a steady decline in prevalence[45]. This will undoubtedly affect prediction scores as well.

This review has several strengths and some limitations. An explicit and reproducible systematic review was performed to identify all published prediction rules. This is the first quantitative appraisal of prediction rules in gastrointestinal bleeding, enabling a judgment to be made on study quality and making a comparison between the different rules in terms of methodological standards possible. The review reveals a lack of standardization in clinical prediction rules. Moreover, efforts were made to minimize reviewer bias by defining the methodological standards as best as possible through assessing the standards by two authors. Disagreements were resolved by discussion until consensus was established.

Possible limitations of the study include the possibility that studies might have been missed due to the scope of the review and the systematic approach. For example, some familiar prediction scores on the outcome of gastrointestinal bleeding, such as the Baylor score[46] and the Cedars-Sinai score[47] were not included in this review, because these scores were not developed on the basis of a data analysis of a patient cohort. The Cedars-Sinai score was derived from risk factors identified by a literature search, whereas Saeed et al.[46] did not describe clearly how the Baylor score was developed. Second, methodological issues of prediction rules were based on the medical literature. A fair part was extracted

from the publications by Laupacis et al. and Wasson et al.[8,25], in which several methodological standards were described. Additionally, standards identified in studies by McGinn et al.[7,24] were included. All of these standards originate from guidelines, but as no validated instruments are available these are often used to assess the quality of prediction rules[48].

The results of this systematic review emphasize the need for high quality prediction scores in gastrointestinal bleeding. In order to accomplish this, good sensibility, broad validation, and impact analyses of the score to make it applicable in different settings are required. Moreover, a validated instrument for the appraisal of prediction rules is required. Such an instrument will assist not only researchers but also journal editors, clinicians, and policy-makers in the development and appraisal of prediction rules and the translation into clinical practice.

In conclusion, much heterogeneity in outcomes and results of the 16 included prediction scores was seen, of which only two studies included lower gastrointestinal bleeding. Methodological quality was suboptimal. Several factors – that could potentially be remedied – reduced this quality, such as small population size and lack of validation and impact analyses. The results can be used to decide which score to use and to evaluate the quality of prediction rules in gastrointestinal bleeding. As the existing prediction scores may still inform physicians, it is suggested that clinicians use the "best available" scores according to performance and quality until new prediction scores of higher quality have been developed. These include the Blatchford score[12] for predicting whether an intervention for acute gastrointestinal bleeding is required and the scores of Villanueva et al.[28], Guglielmi et al.[35], and Chiu et al.[38] for predicting a poor outcome, rebleeding rate, and mortality, respectively, in patients with acute gastrointestinal bleeding.

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Chapter 6

Prediction scores or gastroenterologist's gut feeling for triaging patients that present with acute upper gastrointestinal bleeding

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Submitted for publication

ABSTRACT

BACKGROUND

Several prediction scores for triaging patients with upper gastrointestinal (GI) bleeding have been developed, yet these scores have never been compared to the current gold standard, which is the clinical evaluation by a gastroenterologist. The aim of this study was to assess the added value of prediction scores to the gastroenterologist's Gut feeling in patients with a suspected upper GI bleeding

METHODS

We prospectively evaluated Gut feeling of senior gastroenterologists and asked them to estimate 1) the risk that a clinical intervention is needed; 2) the risk of rebleeding; and 3) the risk of mortality in patients presenting with suspected upper GI bleeding, subdivided into low, medium or high risk. The predictive value of the gastroenterologist's Gut feeling was compared to the Blatchford and Rockall scores for the various outcomes.

RESULTS

We included 974 patients, of which 667 patients (68.8%) underwent a clinical intervention. During the 30-day follow-up, 140 patients (14.4%) developed recurrent bleeding and 44 patients (4.5%) died. The Gut feeling was independently associated with all studied outcomes, except for the predicted mortality after endoscopy. The predictive power – based on the AUC – of the Blatchford and Rockall prediction scores was higher than the Gut feeling of the gastroenterologists. However combining both the Blatchford and Rockall scores and the Gut feeling yielded the highest predictive power for the need of an intervention (AUC 0.82), rebleeding (AUC 0.73), and mortality (AUC 0.71 predicted before and 0.77 predicted after endoscopy, respectively).

CONCLUSION

The Gut feeling is an independent predictor for the need of a clinical intervention, rebleeding and mortality in patients presenting with upper GI bleeding; however, the Blatchford and Rockall scores are stronger predictors for these outcomes. Combining Gut feeling with the Blatchford and Rockall scores resulted in the most optimal prediction.

INTRODUCTION

There is an increasing role for evidence-based medicine in clinical practice. This is accompanied by the development of prediction scores and their use is increasingly being recommended and adopted in clinical guidelines[1]. A prediction score (or risk score/ decision rule) is a tool for physicians based on several predictors – such as patients' history, physical examination, test results and other disease characteristics – which give an estimation on the probability of a likely diagnosis, prognosis or response to treatment[2]. Such tools can be of added value for the physician in daily clinical practice.

Upper gastrointestinal (GI) bleeding is a common clinical problem and accounts for 25 to 35 hospitalizations per 100,000 person-years[3;4] The severity of the disease may vary from no active bleeding to rapid exsanguinations, and yet the course remains difficult to predict. Almost all patients suspected for upper GI bleeding are therefore admitted to the hospital and endoscopy is being performed within 24 hours after hospitalization[5]. This results in a high pressure on hospital capacity, possibly unnecessary discomfort for the patient and high healthcare costs. Accurate predicting of the course and outcome of upper GI bleeding should ideally facilitate triage into a low and a high-risk group and would thus help clinical management.

Several prediction scores for upper GI bleeding have been developed[6]. The most commonly used scores are the Blatchford and Rockall scores[7;8]. The Blatchford score is a validated score using pre-endoscopic variables, such as clinical and laboratory data, and has the primary goal to predict the need for an intervention, such as an upper endoscopy with a hemostatic procedure. The Rockall score is a validated score based on both clinical and laboratory and endoscopic variables and primarily predicts mortality. Although these scores are validated and recommended by international guidelines[5], gastroenterologists do not always incorporate these scores into clinical practice when taking decisions regarding the management of patients presenting with upper GI bleeding.

It is known that a prediction score is more likely to be implemented if they are easy to use, if recommendations are being made based on the score (instead of just assessment), if they can be incorporated in the normal daily usual workflow and if they are computerized[9]. However, the willingness of a physician to use scores is also important. Reasons of a physician not to use scores may be: the idea that they are difficult to calculate, take time and most importantly that they do not add to their own clinical knowledge or "gut feeling". Moreover, it has been reported that clinical decision-making may be even better than prediction scores in predicting whether patients with upper GI bleeding should be admitted to the intensive care unit[10].

In the current study, we assessed the added value of currently existing prediction scores to the gut feeling of the gastroenterologist in patients with suspected upper GI bleeding presenting to the Accident & Emergency Department (A&E).

METHODS

Patients and Outcomes

All patients of 18 years or older that were admitted to the A&E for suspected upper GI bleeding (i.e. presentation with self-reported melena or hematemesis) between October 2009 and April 2012 were included in eight participating hospitals in the Netherlands, including one tertiary center. Patients were treated according the treatment protocols of the participating centers and no interference was made with regard to patient management. Patients were followed for 30 days after presentation by the study coordinator of the participating hospital.

Upper GI bleeding was defined as 'confirmed' if patients with suspected upper GI bleeding met the criteria shown in **Textbox 1**.

Textbox 1

Diagnostic criteria for upper gastrointestinal bleeding

- Combination of reported signs of melena and/or hematemesis with
  - Anemia (Hb <13.0g/dl for men or <12.0g/dl for women), or
  - Hemodynamic instability (a state requiring pharmacologic or mechanical support to maintain a normal blood pressure or adequate cardiac output), or
  - Discrepant increased urea
- Confirmed bleeding during endoscopy or manifest old/fresh blood

Upper GI bleeding included all hemorrhages of the upper GI tract, including peptic ulcer bleeding, variceal bleeding, Mallory-Weiss lesions, severe reflux esophagitis and gastritis with hemorrhage, Dieulafoy's lesions, neoplastic lesions and angiodysplasia. Data were systematically collected using a dedicated CRF, including demographic features, data from the medical history (presenting signs or symptoms) and physical examination (blood pressure, heart rate), medication use (e.g. non-steroidal anti-inflammatory drugs, proton pump inhibitors and anticoagulants), comorbidities, biochemical (hemoglobin (Hb), platelet count, urea, creatinine and International Normalized Ratio (INR)) and endoscopic findings. Comorbidities included chronic heart disease, liver cirrhosis, previous history of GI haemorrhage, presence of cancer in the GI tract or any other site, lung emphysema,

renal failure (creatinine >200 micromol/L or dialysis), endovascular prosthesis, diabetes mellitus, and ongoing chemotherapy or radiotherapy. Endoscopic findings included location and number of lesions, stigmata of recent hemorrhage and Forrest classification of ulcers. Procedure-related factors included time from presentation to endoscopy, need to perform endoscopic hemostasis as judged by the endoscopist and number of units blood transfused before and after endoscopy.

The primary outcomes were: 1) need for clinical intervention; 2) 30-day mortality (in- and out-hospital); and 3) 30-day rebleeding rate. A clinical intervention was defined as a blood transfusion or any operative, radiological or endoscopic intervention to control the hemorrhage and/or the occurrence of rebleeding or mortality[7]. Mortality was defined as all-cause mortality in- and out-hospital. Rebleeding was defined according to the criteria set by the Peptic Ulcer Bleed study as recurrent hematemesis of fresh blood (>200 ml), active bleeding or fresh blood found during endoscopy, or two of the following: 1) Hb drop >20 g/L within 24 hr, 2) Hb increase <10 g/L after adequate blood transfusion, 3) Systolic RR <90 mm Hg (after being higher initially) or pulse rate >110 /min (after being higher initially) within 30 days after initial stabilization[11].

Gut feeling and prediction scores

Prior to upper endoscopy the treating consultant gastroenterologist filled out a questionnaire with two questions regarding the probability of the patient needing an intervention to control the bleeding and the risk that the patient would die. At this point the gastroenterologist had access to all clinical information, including laboratory results, regarding the patient, however without any endoscopic information. After endoscopy, another two questions were filled out regarding risk of rebleeding and mortality. At this point the gastroenterologist had access to clinical and endoscopic information about the patient. The questions and probabilities are shown in **Textbox 2**. The gastroenterologist estimated whether the patient was at a low, medium or high risk for these endpoints. In this study, we refer to this risk estimation by the gastroenterologist as "gut feeling". Only experienced gastroenterologists were asked to fill out these questionnaires and all participating gastroenterologists had comparable experience with the treatment of upper GI bleeding.

Textbox 2

Questions regarding the Gut feeling of the gastroenterologist

- At presentation at A&E
  - What is the risk for current bleeding requiring endoscopic treatment (or surgery/ angiography) or transfusion in this patient
    - Low risk (<1%)
    - Medium risk (1-10%)
    - High risk (>10%)
  - What is the mortality risk (<30 days) for this patient
    - Low risk (<1%)
    - Medium risk (1-5%)
    - High risk (>5%)
- After upper endoscopy
  - What is the risk for continued bleeding or rebleeding requiring additional endoscopic treatment (or surgery/angiography) or transfusion in this patient
    - Low risk (<1%)
    - Medium risk (1-10%)
    - High risk (>10%)
  - What is the mortality risk (<30 days) for this patient
    - Low risk (<1%)
    - Medium risk (1-5%)
    - High risk (>5%)

The full Rockall score and the Blatchford score were calculated for each patient. The Rockall score consists of both clinical and laboratory variables, and endoscopic findings and the Blatchford score only of clinical and laboratory variables. The Rockall score was used for predicting rebleeding and mortality, the Blatchford score for the need of intervention and mortality. For predicting or excluding an intervention we used a cut-off of < 1 for the Blatchford score as this is the cut-off level mostly used in literature and validation studies[7;12]. For predicting rebleeding and mortality for both scores a cut-off of >2 points was used to compare the performance of the scores with gut feeling. Patients with ≤2 points were classified as low risk and >2 points as medium to high risk[7;8;12;13].

Statistical analysis

Patient characteristics, comorbidities and endoscopic findings were analyzed using standard descriptive statistics. Sensitivity and specificity rates, negative and positive predictive values were calculated for both gut feeling (medium/high risk patients compared to low risk patients and high risk patients compared to low/medium risk patients) and the prediction scores at a cut-off level of < 1 for predicting/excluding the need of an intervention and >2 for predicting rebleeding and mortality. Logistic regression analyses were performed to assess the association between Gut feeling and each individual outcome (need for intervention, rebleeding and mortality predicted before and after endoscopy), as well for the prediction scores and the various outcomes. The area under receiving operating curve (AUC) was calculated to compare the discriminative power of the gut feeling and the prediction scores. Ordinal logistic regression analyses were performed to identify risk factors associated with gut feeling. Statistical analysis was performed with SPSS 14.0 (SPSS Inc. Chicago, IL, USA).

Ethical considerations

This was a prospective observational study, in which patient data were entered anonymously in a central database. The protocol did not include any (additional) interventions and no additional testing was performed. Therefore, the Dutch Law on Medical Research on Humans did not apply here and approval by a medical ethical committee was not required, as agreed by the Medical Ethics Committee of the Sint Antonius Hospital, Nieuwegein, the Netherlands (July 20th, 2009) and the Medical Ethical Boards of the participating centers.

RESULTS

In total, 1001 patients were included, with for 970 patients the gut feeling being completed. The mean age of the studied population was 65 (range 18-99) years and 37% of the patients were female. Other baseline characteristics are shown in **Table 1**.

Table 1 Baseline characteristics for different outcomes

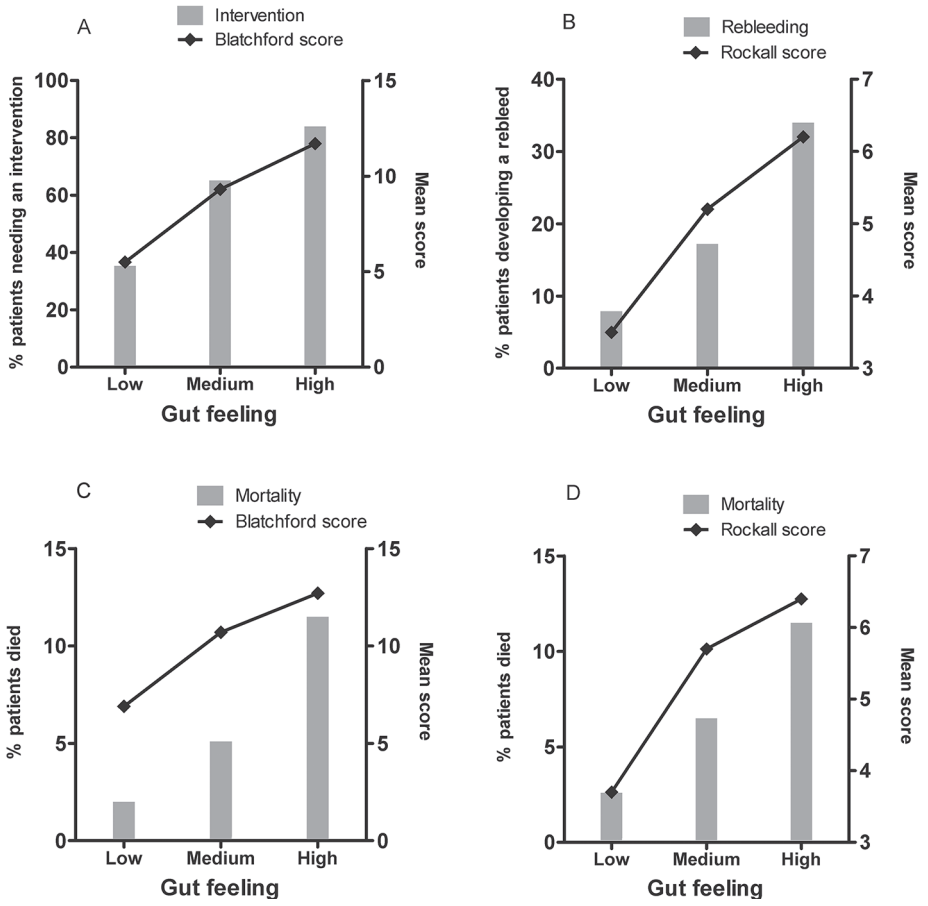
	All Patients N = 970
Age (mean)	66 (range 18-99)
Sex; female	355 (36.5%)
Medical history	
Melaena	614 (63.1%)
Hematemesis	442 (45.4%)
Rectal blood loss	145 (14.9%)
Collapse	153 (15.7%)
Medication use	
oral anti-coagulants	245 (25.2%)
corticosteroids	54 (5.5%)
NSAIDs	103 (10.6%)
Acetylsalicylic acid	309 (31.7%)
Clopidogrel	87 (8.9%)
PPI	330 (33.9%)
SSRIs	42 (4.3%)
Physical examination (mean)	
Systolic RR (mmHG)	127 (SD 25)
Diastolic RR (mmHG)	69 (SD 17)
HR (beats per minute)	90 (SD 19)
Laboratory results (mean)	
Hb level (mmol/L)	6.3 (SD 1.9)
Platelet count (*109)	246 (SD 111)
Creatinine (µmol/L)	108 (SD 80)
Urea (mmol/L)	13.8 (SD 11.0)
INR	1.90 (SD 2.15)
Comorbidities	
Liver cirrhosis	105 (10.8%)
History of upper GI bleeding	214 (22.0%)
Presence of GI-cancer	41 (4.2%)
Chronic heart disease	331 (34.0%)
Lung emphysema	122 (12.5%)
Renal failure	74 (7.6%)
Endovascular prosthesis	92 (9.4%)
Diabetes Mellitus	170 (17.5%)
Active chemo- or radiotherapy	17 (1.7%)
Active cancer on other site than GI-tract	54 (5.5%)

	All Patients N = 970
Endoscopic findings	
Confirmed upper GI bleeding	733 (76.4%)
Variceal bleeding	75 (7.5%)
Causes non-variceal bleeding	
Peptic ulcer bleed	352 (36.1%)
Esophagitis	90 (9.5%)
Malignancy	25 (2.6%)
Other causes	266 (36.3%)
Other	
Admission (median duration in days)	(4 days IR 2-7 days)
Do not resuscitate status	163 (17.0%)
Patients with 1 or more blood transfusions	569 (58.9%)
Patients receiving surgery	16 (1.6%)
Patients receiving angiography	22 (2.3%)

Prediction of need for clinical intervention

In total, 667 patients (69%) underwent a clinical intervention (e.g. blood transfusion, operative or endoscopic procedure to control the hemorrhage). The number of interventions increased significantly with higher estimated risks by the gut feeling, as well as with increasing Blatchford scores (**Figure 1**).

The Blatchford score showed higher sensitivity rates for excluding an intervention while the gut feeling revealed higher specificity rates (**Table 2**). After correcting for the Blatchford score, the gut feeling was still independently associated with the need for an intervention (Odds Ratio (OR) 3.2, 95% confidence interval (CI) 2.2-4.5 for medium risk and OR 15.0 CI 9.6-23.4 for high risk patients). However, the Blatchford score had a better predictive power than the gut feeling of the gastroenterologists (AUC 0.86 versus 0.77, respectively). Combining the gut feeling with the Blatchford score improved the predictive power to 0.88 (**Figure 2**). Regression analyses showed that hemoglobin and urea levels, hematemesis and a history of collapse had the highest effect on the gut feeling of gastroenterologists.



Left Y-axis illustrates the percentage of patients with outcome predicted by the gut feeling. The right Y-axis illustrates the mean prediction score for every group of the gut feeling.

Figure 1 Association gut feeling and prediction scores with the outcome
A prediction of a clinical intervention B prediction of a rebleeding C prediction mortality before endoscopy D prediction after endoscopy

Table 2 Sensitivity and specificity rates of the Gut feeling and the prediction scores for the various outcomes

	Gut feeling Low risk (vs medium/high risk)	Gut feeling High risk (vs low/medium)	Prediction score
Intervention needed N= 667 (68.8%)			**Blatchford score Cut-off < 1**
Sensitivity	551/667 (82.6%)	345/667 (51.7%)	663/667 (99,4%)
Specificity	181/303 (59.7%)	273/303 (90.5%)	41/262 (13,5%)
NPV	181/297 (60.9%)	273/595 (45.9%)	41/45 (91,1%)
PPV	551/673 (81.9%)	345/375 (92.0%)	663/925 (71,7%)
Rebleeding N = 140 (14.4%)			**Rockall score Cut-off < 2**
Sensitivity	99/140 (70.7%)	54/140 (38.6%)	133/140 (95.0%)
Specificity	479/801 (59.8%)	696/801 (86.9%)	190/816 (23.3%)
NPV	479/520 (92.1%)	696/782 (89.0%)	190/197 (96.4%)
PPV	99/421 (23.5%)	54/159 (34.0%)	133/759 (17.5%)
Mortality predicted before endoscopy N = 44 (4.5%)			**Blatchford score Cut-off < 2**
Sensitivity	34/44 (77.3%)	18/44 (40.9%)	41/43 (95.3%)
Specificity	488/924 (52.8%)	785/924 (85.0%)	121/900 (13.4%)
NPV	488/498 (98.0%)	785/811 (96.8%)	121/123 (98.4%)
PPV	34/470 (7.2%)	18/157 (11.5%)	41/820 (5.0%)
Mortality predicted after endoscopy			**Rockall score Cut-off < 2**
Sensitivity	25/41 (61.0%)	11/41 (26.8%)	43/44 (97.7%)
Specificity	611/896 (68.2%)	811/896 (90.5%)	196/908 (21.6%)
NPV	611/627 (97.4%)	811/841 (96.4%)	196/197 (99.5%)
PPV	25/310 (8.1%)	11/96 (11.5%)	43/ 755 (5.7%)

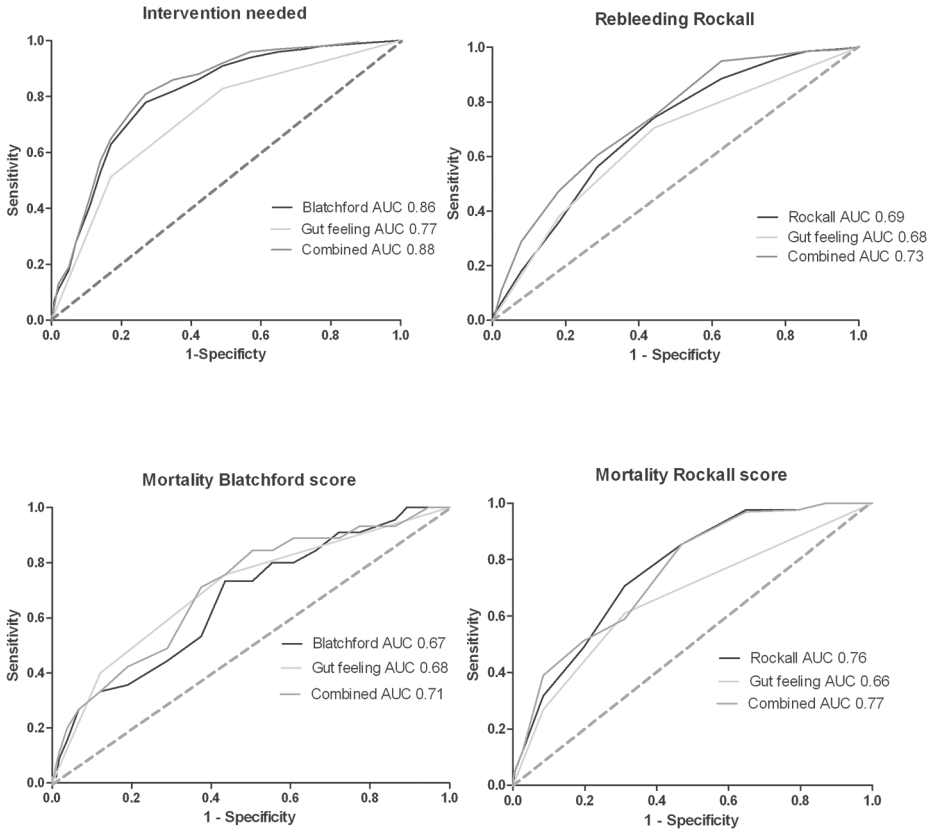


Figure 2 ROC curves for various outcomes

Prediction of Rebleeding

In total, 140 patients (14.4%) developed a rebleeding. The rebleeding rate and the mean Rockall score increased significantly with higher estimated risks by the gut feeling (**Figure 1**). Sensitivity rates were highest for the Rockall score, while specificity rates where highest for the gut feeling (**Table 2**). The gut feeling was independently of the Rockall score associated with rebleeding (OR 1.7 CI 1.1-2.7 for medium risk and OR 3.4 CI 2.1-5.7 for high risk patients). Rebleeding was slightly better predicted by the Rockall score compared to the gut feeling, but both predict rebleeding only to a moderate degree (AUC 0.69 vs. AUC 0.68). Combining the Rockall score and the gut feeling improved the predictive power to an AUC of 0.73 (**Figure 2**). An intervention and to a lesser extent hematemesis and a history of a collapse had the highest effect on the gut feeling of gastroenterologists.

Prediction of Mortality

Forty-four patients (4.5%) died. The intra-observer agreement between the gut feeling before and after endoscopy was low with a kappa of 0.41, suggesting that the results of endoscopy significantly changed the gastroenterologists view on the patient's prognosis. Mortality rates increased with higher gut feeling risk estimations before and after endoscopy (**Figure 1**). The sensitivity of the gut feeling was highest before endoscopy, while the specificity was highest after endoscopy. Both Blatchford and Rockall scores showed high sensitivity rates (95.6% and 95.7%, respectively) (**Table 2**). A high gut feeling risk estimation before endoscopy was a significant predictor for mortality, also after adjustment for the risk scores (OR 1.8 CI 0.8-4.1 for medium risk and OR 3.3 CI 1.4-8.0 for high risk patients); however, the gut feeling after endoscopy was no predictor after correcting for the Rockall score (OR 1.4 CI 0.6-3.0 for medium risk and OR 2.0 CI 0.8-4.7 for high risk patients). The predictive power of the gut feeling and the risk scores are shown in **Figure 2**. The Rockall score combined with the gut feeling provided the most optimal prediction for mortality (AUC 0.77). The gut feeling before endoscopy was mostly affected by hemoglobin level, liver disease, hematemesis and a Do Not Resuscitate (DNR) status of the patient. The gut feeling after endoscopy was mostly affected by a DNR status, liver disease and whether an intervention was performed.

DISCUSSION

We found that the gut feeling of gastroenterologists was a good predictor for the need of a clinical intervention, rebleeding and mortality in patients presenting with upper GI bleeding; however, the Blatchford and Rockall prediction scores had overall higher predictive values. Prediction scores had a higher sensitivity, and thus performed better in excluding an unfavorable outcome, while the gut feeling showed a higher specificity and thus had a better performance in predicting an unfavorable outcome.

We observed an overall tendency in gastroenterologists to overestimate the risk of an adverse outcome (positive predictive value), especially for the risk of rebleeding and mortality. An explanation could be that the estimation of gastroenterologists of the risk of rebleeding and mortality is based on older literature citing high rebleeding and mortality rates while a considerable reduction in rebleeding and mortality has been observed over the last decade as a result of better acid suppression, advanced endoscopy hemostatic techniques and improvement of radiological hemostatic interventions[22;23]. With regard to the outcomes in this study, both the gut feeling and the prediction scores performed well in excluding mortality and rebleeding as high negative predictive values were

observed for those endpoints. For predicting the need of a clinical intervention, high positive predictive values were observed, especially for the gut feeling, meaning that gastroenterologists were able to predict the need for an intervention. The high sensitivity rates of the Blatchford and Rockall scores can be used to select patients who need closer monitoring. A high specificity – such as we found for the gut feeling – is however also of clinical importance because hospital admission and endoscopy are both a burden to patients, but to some extent also to the hospital and a decision to do so should be based on well-established risk factors.

These risk factors used in the prediction scores and the risk factors gastroenterologists based their gut feeling on are different for the various outcomes. For predicting the need of a clinical intervention, gastroenterologists mainly based their gut feeling on low hemoglobin levels, and presentation with hematemesis and collapse. In the Blatchford score, a collapse and hemoglobin levels also play an important role, but, other parameters used in this score, such as blood urea levels, tachycardia and blood pressure were not used to a large extent by gastroenterologists[7]. A recent systematic review by Srygley et al. identified tachycardia and hemoglobin level as important predictors for a clinical intervention, while they also identified a history of cirrhosis, malignancy and nasogastric lavage with red blood as risk factors[14]. For rebleeding the most important predictors identified in the literature are age, comorbidities, active bleeding and location of the bleeding[15-17]. The gut feeling of gastroenterologists was however mainly based on whether an intervention was performed (which might be a reflection of active bleeding), and to a smaller extent on hematemesis and collapse. And lastly, important predictors of mortality found in literature are age, comorbidities and hemodynamic instability[8;18-21]. Gastroenterologists found hemoglobin level, liver disease, hematemesis and a Do Not Resuscitate (DNR) status the most important indicators for mortality, which partly overlap with the predictors known from the literature.

This study has several strengths and limitations. This is the first study that shows that prediction scores are better than clinical estimation of experienced gastroenterologists in risk classification of patients with upper GI bleeding. Secondly, not only patients with an established upper GI bleeding, but also patients with a suspected upper GI bleeding were included, as this is clearly a better reflection of the population actually presenting to the A&E and requiring risk classification. Moreover, the predictive power of the Blatchford and Rockall scores may increase somewhat after excluding variceal bleeding as these scores were originally developed for patients with non-variceal bleeding, resulting in a larger difference with the gut feeling. A limitation of this study was that due to the prospective design, we were unable to compare the gut feeling to other more recently developed risk scores (e.g. AIM65, PNED score[19;21]) as we did not include variables such as time from onset of symptoms to admission and albumin.

Retrospective collection of these parameters would likely have resulted in missing values and bias.

The results of our study may have important implications for clinical practice. We have shown that the use of prediction scores increases the predictive power for all clinical relevant outcomes of upper GI bleeding over gut feeling. The use of these scores will therefore lead to a better prediction. The prediction scores were superior to the clinical estimation of experienced gastroenterologists and given that A&Es are usually manned by less experienced registrars and junior house officers there is definitely a reason for incorporation of these scores in clinical practice. Especially in patients who are triaged at low risk by the gut feeling, a prediction score should be used to prevent that patients are being sent home or triaged wrongly. The combination of the gut feeling and prediction scores may well emphasize that (experienced) gastroenterologists should always be included in clinical decision making and triaging of patients presenting with upper gastrointestinal bleeding. Based on our results, we propose to combine gut feeling and the established prediction scores; However, this needs to be confirmed in a prospective follow-up study.

In conclusion, this is the first study in which the added value of prediction scores was compared to the gut feeling of gastroenterologists in predicting rebleeding, mortality and the need for a clinical intervention in patients with upper GI bleeding. We found that gut feeling is an independent predictor for adverse outcome of patients presenting with a suspected upper GI bleeding. However, prediction scores have a higher sensitivity and a better predictive power compared to the gut feeling. The combination of these scores and gut feeling results in the best prediction of adverse outcome. We therefore suggest using prediction scores in combination with the gut feeling of gastroenterologists in making clinical decisions regarding treatment and monitoring of patients with upper GI bleeding.

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Chapter 7

Admission time is associated with outcome of upper gastrointestinal bleeding; results of a multicenter prospective cohort study

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Accepted for publication in Alimentary Pharmacology and Therapeutics

ABSTRACT

BACKGROUND

It has been suggested that patients presenting with upper gastrointestinal bleeding (UGIB) during the weekend have a worse outcome compared to weekdays, with an increased risk of recurrent bleeding and mortality. The aim of this study was to investigate the association between timing of admission and adverse outcome after UGIB.

METHODS

We prospectively collected data from patients presenting with symptoms suggestive of UGIB to the emergency room of 8 participating hospitals. Using standard descriptive statistics and logistic regression analyses, differences in 30-day mortality, rebleeding rate, and need for angiography and surgical intervention were assessed for week- and weekend admissions and time of admission. Moreover, patient- and procedure-related factors were identified that could influence outcome.

RESULTS

In total, 571 patients were included with suspected UGIB. Patient admitted during the weekend had a higher mortality rate than patients admitted during the week (9% vs.3%; adjusted odds ratio 2.68 (95%CI 1.07-6.72)). Weekend admissions were not associated with other adverse outcomes. Patients admitted during the weekend presented more often with bleeding and had a significantly lower systolic and diastolic blood pressure. No differences were found in procedure related factors. Time of admission was not associated with an adverse outcome; although patients admitted during the evening had a significantly longer time to endoscopy (15, 22 and 16 hours for day, evening and night admissions, respectively, $p<0.01$).

CONCLUSION

Although quality of care did not appear to differ among week/weekend admissions, patients with suspected UGIB admitted during the weekend were at higher risk of an adverse outcome. This might be due to the fact that these patients have more severe bleedings.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common indication for hospital admission. Although incidence rates for hospitalization have decreased, still around 40/100.000 patients with UGIB are being admitted each year[1,2]. More importantly, mortality rates remain high (6-8%) despite more advanced pharmacological and endoscopic treatment modalities available[3-5]. Because of the acute and potential critical presentation of UGIB, early diagnosis and treatment through endoscopic risk stratification and intervention is needed.

Although at least as many patients are being hospitalized for UGIB during a weekend day as during a weekday[6,7], staffing levels are lower during weekends. It has been previously reported that hospital admission in the weekend was associated with a higher mortality rate and longer length of stay for several acute illnesses[8-11]. Beside changes in hospital staffing, it may also be so that fewer urgent procedures are performed in emergently hospitalized patients in the weekend explaining this "weekend effect"[12]. For UGIB only limited data exist for the "weekend effect"[7,13,14]. Although three large cohort studies were performed with increased weekend mortality ranging from 3.4% to 3.8%, the data used was derived from healthcare databases. This indicates limitations in available clinical, biochemical and endoscopic data of included patients, with consequent high residual confounding. In contrast to the results of these studies, a recent prospective cohort study showed that patients admitted during the weekend were more critically ill (presented more often with shock and received more often blood transfusion); however, this did not result in higher mortality rates compared to weekday admission[6].

It therefore remains to be established whether patients admitted during the weekend have higher risks of an adverse outcome and whether patient-related factors (e.g. more severe bleedings during the weekend) and/or procedure-related factors (e.g. delayed endoscopy) account for this possible higher risk of an adverse outcome. Early endoscopy (i.e. endoscopy within 24 hours) is nowadays recommended by international guidelines[15]. A systematic review on early versus delayed endoscopy reported that early endoscopy is indeed safe and effective[16]. However, whether early endoscopy also results in a better prognosis for the individual is still unknown[17-21]. In addition, no distinction has been made between day and night time admissions while this could be equally important as week day versus weekend effects.

We conducted a prospective cohort study to investigate whether 1) rebleeding and mortality rates differ between weekday or weekend admission; 2) time of the day is associated with rebleeding or mortality outcomes; 3) patient- or procedure-related factors could be identified that are responsible for a potential out-of-hours effect.

METHODS

Data collection and patient population

Data were prospectively collected using a dedicated case report form in eight participating hospitals in the Netherlands. All adult patients admitted to the Emergency Unit for suspected UGIB (i.e. presentation with self-reported melaena or hematemesis) between October 2009 and September 2011 were included. UGIB was defined as 'confirmed' if patients with suspected UGIB met the criteria shown in Textbox 1. UGIB included all bleedings of the upper gastrointestinal tract (i.e. peptic ulcer bleeding, variceal bleeding, Mallory-Weiss lesions, severe reflux oesophagitis and gastritis with bleeding, Dieulafoy's lesions, neoplastic lesions and angiodysplasia). Patients were treated according to the treatment protocols of the participating centers and no interference was made on patient management. During and after hospitalization, patients were followed-up for 30 days by the study coordinator of the particular hospital.

Textbox 1

Diagnostic criteria for upper gastrointestinal bleeding

- Combination of reported signs of melaena and/or hematemesis with
  - Anaemia (Hb <13.0g/dl for men or <12.0g/dl for women), or
  - Hemodynamic instability (systolic blood pressure <100 mmHg and heart rate > 100 beats per minute), or
  - Abnormal blood urea/ creatinine ratio
- Confirmed bleeding during endoscopy or manifest old/fresh blood

Study variables and outcomes

Time of admission was recorded, defining day/evening/night as 8:00 am to 4:59 pm/ 5:00 pm to 10:59 pm/11:00 pm to 7:59 am, respectively, and weekend as Friday from 11:00 pm to 7:59 am on Monday. Hospital admissions on (official) holidays were also recorded as weekend admissions. Patient-related factors included demographic features, data from the medical history (presenting signs or symptoms) and physical examination (blood pressure, heart rate), medication use (e.g. non-steroidal anti-inflammatory drugs, proton pump inhibitors and anticoagulants), comorbidities, biochemical (haemoglobin (Hb), platelet count, urea, creatinine and International Normalized Ratio (INR)) and endoscopic findings. Comorbidities included chronic heart disease, liver cirrhosis, history of GI bleeding, presence of GI cancer, lung emphysema, renal failure (creatinine >200 micromol/L or dialysis), endovascular prosthesis, diabetes mellitus, active chemotherapy or radiotherapy and active cancer at any other site than the GI tract. Endoscopic

findings included location and number of lesions, stigmata of recent bleeding and Forrest classification, if appropriate. Procedure-related factors included time to endoscopy, need to perform endoscopic hemostasis and number of units blood transfused.

The primary outcome was 30-day mortality (in- and out-hospital) and 30-day rebleeding rates. Rebleeding was defined according to the criteria defined by the Peptic Ulcer Bleed study as recurrent hematemesis of fresh blood (>200 ml), active bleeding or fresh blood found during endoscopy, or two of the following: 1) Hb drop > 20 g/L within 24 hr, 2) Hb increase < 10 g/L after adequate blood transfusion, 3) Systolic blood pressure (RR) < 90 mm Hg (after being higher initially) or pulse rate > 110 /min (after being higher initially) within 30 days after initial stabilization[22]. Secondary outcomes were the need for a surgical or radiological intervention to control the bleeding (defined as the need for abdominal surgery or angiography with embolization).

Data analyses

Chi-square test, t-test, and one-way anova were performed to identify differences in patient characteristics, comorbidities and endoscopic findings associated with the day and time of admission. Logistic regression analyses were performed to determine the association between outcome and week versus weekend, and day versus evening versus night admission. Possible important prognostic predictors of the outcome were entered in a model to adjust for confounding. Differences in outcome were expressed in odds ratios (OR) with 95% confidence intervals (CI), where appropriate. Statistical analysis was performed with SPSS 14.0 (SPSS Inc. Chicago, IL, USA).

Ethics

This is a prospective observational study, in which patient data are entered anonymously in a central database. The protocol did not include any (extra) interventions and no additional testing was performed. Therefore, the law on medical research on humans did not apply here and approval by a medical ethical committee is not required in The Netherlands. Nonetheless, the protocol was approved by the Medical Ethics Committee of the Sint Antonius Hospital, Nieuwegein, the Netherlands on July 20th, 2009.

RESULTS

A total of 571 patients were included. Of these, 71% was admitted during the week and 29% during the weekend. More patients were admitted during daytime (57%) compared to evening (23%) or night (18%). The frequency of admissions over the different days of the week was equally distributed (**Figure 1**). No statistical significant differences were found for the number of admissions during daytime, evening and night between week and weekend admissions.

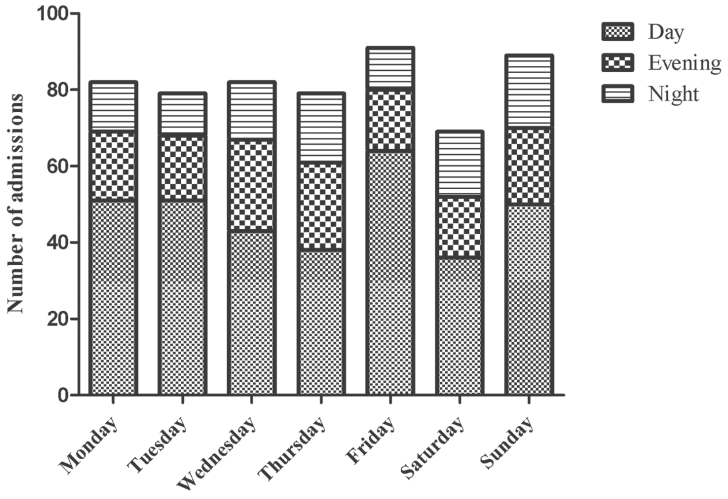


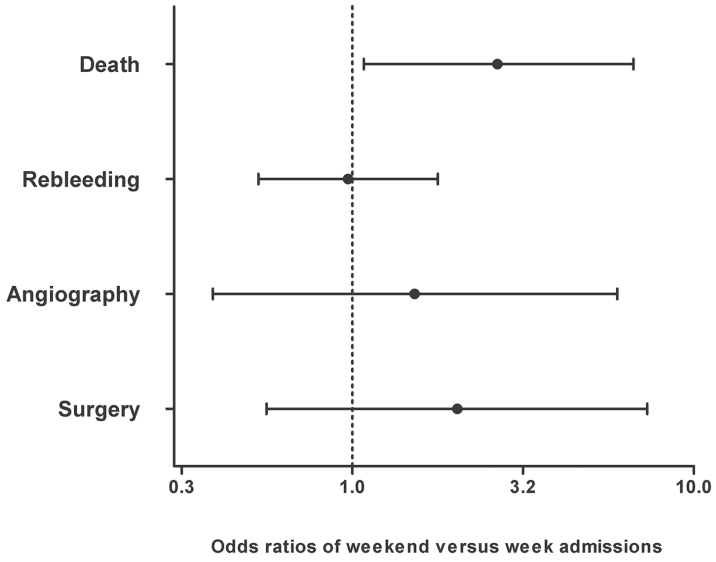
Figure 1 Number of admissions per day of the week and time of admission

Weekday versus Weekend admissions

A total of 27/571 (5%) patients died within 30 days of admission. Patient admitted during the weekend had a higher mortality rate compared to patients admitted during the week (9% versus 3%, $p<0.01$). After adjusting for age, presence of GI cancer, diabetes mellitus, rectal blood loss, collapse, systolic blood pressure, diastolic blood pressure, hemoglobin, urea, whether an intervention was needed and need for pre- and post-endoscopic blood transfusion, weekend admission was still associated with a higher risk of death (OR 2.68; 95% CI 1.07-6.72) (**Figure 2**). Patients admitted during the weekend also tended to have a higher need for surgery and angiography, although not statistically significant (**Table 1, Figure 2**).

Table 1 Unadjusted outcomes of patients suspected for UGIB

Outcome	Week (%)	Weekend (%)	P value	Day (%)	Evening (%)	Night (%)	P value
Death	3.0	9.0	0.002	4.6	3.1	7.8	0.24
Rebleeding	14.9	17.4	0.46	16.2	13.7	16.5	0.78
Angiography	1.7	3.6	0.18	1.8	2.3	3.9	0.48
Surgery	1.7	4.2	0.08	2.4	0.8	4.9	0.14



Adjusted for: age, GI cancer, DM, rectal blood loss, collapse, systolic blood pressure, diastolic blood pressure, hemoglobin, urea, intervention needed, pre- and post-endoscopic blood transfusion

Figure 2 Adjusted odds ratios of the outcome of week versus weekend admissions

Looking at patient related factors, patients admitted during the weekend had a significantly lower systolic and diastolic blood pressure compared to patients admitted during the week ($p<0.01$ and $p=0.05$, respectively) (**Table 2**).

Table 2 Baseline patient characteristics of patients presenting with a suspected UGIB during the week vs. weekend and day vs. evening and night

Patient characteristics	Week 404 (%)	Weekend 167 (%)	P value	Day 333(%)	Evening 134(%)	Night 104(%)	P value
Age (mean)	66	66	0.99	67	65	63	0.16
Sex; female	35.6	32.3	0.60	35.7	36.6	30.1	0.23
Medical history							
Melaena	65.3	57.5	0.08	68.9	61.8	45.6	<0.01
Hematemesis	44.3	55.1	0.01	41.5	48.9	65.0	<0.01
Rectal blood loss	14.6	15.6	0.77	14.0	14.5	18.4	0.54
Collapse	14.6	18.6	0.24	13.7	15.3	22.3	0.11
Medication use							
oral anti-coagulants	23.5	23.4	0.97	25.6	23.7	17.5	0.24
corticosteroids	5.9	3.0	0.15	5.2	5.3	3.9	0.85
NSAIDs	12.9	7.2	0.05	11.6	9.9	9.7	0.80
Acetylsalicylicacid	30.2	34.1	0.36	29.6	35.9	31.1	0.42
Clopidogrel	7.7	8.4	0.78	7.3	9.9	7.8	0.65
PPI	34.2	31.7	0.58	34.1	36.6	26.2	0.21
SSRIs	3.5	6.6	0.09	4.0	6.9	2.9	0.28
Physical examination							
Systolic RR	129	121	<0.01	128	126	124	0.27
Diastolic RR	70	67	0.05	69	69	68	0.88
HR	89	92	0.09	90	88	93	0.19
Laboratory results							
Hb level (mean)	6.3	6.4	0.33	6.3	6.3	6.4	0.59
Platelet count	240	250	0.33	242	251	233	0.47
Creatinine	112	102	0.78	108	112	111	0.83
Urea	14.1	15.0	0.45	12.5	13.7	17.1	0.53
INR	3.9	3.1	0.73	4.0	3.3	3.2	0.58
Comorbidities							
Liver cirrhosis	13.6	8.4	0.08	11.3	7.6	17.5	0.06
History of UGIB	23.8	19.8	0.30	21.6	23.7	23.3	0.87
Presence of GI-cancer	3.2	6.6	0.07	4.6	3.8	3.9	0.92
Chronic heart disease	35.9	32.9	0.50	36.6	36.6	29.1	0.36
Lung emphysema	11.6	10.2	0.62	11.3	13.7	6.8	0.24
Renal failure	9.2	4.2	0.04	7.6	6.9	9.7	0.71
Endovascular prosthesis	7.4	11.4	0.13	7.9	9.2	10.7	0.67
Diabetes Mellitus	16.3	13.2	0.34	15.9	12.2	18.4	0.41
Active chemo- or radiotherapy	1.5	3.6	0.11	2.4	0.8	2.9	0.44

Patient characteristics	Week 404 (%)	Weekend 167 (%)	P value	Day 333(%)	Evening 134(%)	Night 104(%)	P value
Active cancer on other site than GI-tract	6.4	6.0	0.84	6.4	6.9	4.9	0.80
Endoscopic findings							
Confirmed UGIB	74.9	81.3	0.11	79.1	72.4	75.0	0.28
Intervention performed	37.0	38.0	0.84	37.7	33.9	40.6	0.59
Variceal bleeding	10.5	12.3	0.58	9.7	13.2	10.7	0.67
Forrest classification			0.66				0.63
Ia	7.1	6.0		4.6	8.3	12.5	
Ib	16.3	14.0		13.8	13.9	25.0	
IIa	18.4	26.0		20.7	22.2	16.7	
IIb	12.2	8.0		12.6	13.9	0.0	
IIc	11.2	18.0		14.9	8.3	16.7	
III	34.7	28.0		33.3	33.3	29.2	

During the weekend, patients presented more often with hematemesis (55% vs. 44%, p=0.01) and less frequently with melaena (58% vs. 65%, p=0.08). Furthermore, patients admitted during the weekend tended to have more often a history of active GI cancer (7% vs 3% p=0.07) and suspected UGIB tended to be more often confirmed as a true bleeding in patients admitted during the weekend (81% vs 75% p=0.11). Patients admitted during the week had more often renal failure (9% vs. 4%, p= 0.04). Time between admission and endoscopy was not significantly different during the weekend than during the week (15.9 hrs vs 17.6 hrs). The need for endoscopic intervention was not different between the two groups (**Table 3**). In addition, patients with suspected UGIB were also not more frequently admitted to the hospital or stayed longer as in-patients. The number of units blood transfused was comparable between week and weekend admissions, both before and after endoscopy (**Table 3**).

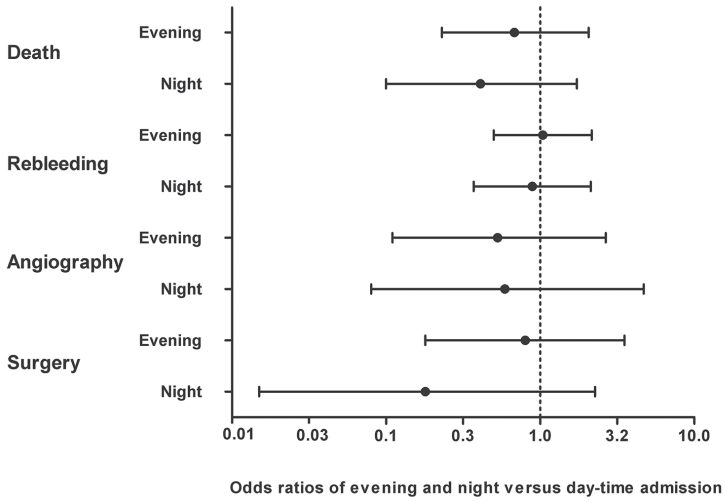
Table 3 Baseline procedure-related characteristics of patients presenting with a suspected UGIB during the week vs. weekend and day vs. evening and night

Procedure characteristics	Week	Weekend	P value	Day	Evening	Night	P value
Admission (%)	90.1	93.9	0.14	90.8	90.1	94.1	0.51
Time to endoscopy (hours)	17.6	15.9	0.50	15.3	22.4	15.8	<0.01
Performance of second endoscopy	22.8	28.1	0.19	26.5	20.8	22.3	0.37
Length of hospital stay (days)	6.6	7.6	0.18	7.4	5.6	7.4	0.47
Units blood transfused Pre-endoscopy	0.88	0.92	0.73	0.82	0.96	1.02	0.61
Units blood transfused Post-endoscopy	1.41	1.67	0.21	1.47	1.53	1.56	0.67

Daytime versus evening and night admissions

Time of admission to the hospital had no effect on the prognosis of patients (**Table 1 and Figure 3**). In addition, subgroup analyses with patients admitted during week or weekend did not reveal significant different outcomes for time of admission.

Patients admitted during the evening and night were slightly younger than those admitted during the day and presented more often with hematemesis (42%, 49% and 65% respectively, p<0.01) and less frequently with melaena (69% vs 62% and 46%, p<0.01) (**Table 2**). In addition, patients admitted during the night tended to present more often with a collapse (22% vs 14% during the day). Comorbidities were not significantly different between the three groups, but patients admitted during the night tended to be more often known with liver cirrhosis (p=0.06). Patients admitted during the evening had a significantly longer time to endoscopy compared to patients admitted during daytime and night (15, 22 and 16 hours respectively for day, evening and night, p<0.01). The proportion of patients admitted to the hospital for suspected UGIB, length of hospital stay and units of blood transfused was not significantly different between the three groups (**Table 3**).



Adjusted for: age, GI cancer, DM, rectal blood loss, collapse, systolic blood pressure, diastolic blood pressure, hemoglobin, urea, intervention needed, pre- and post-endoscopic blood transfusion

Figure 3 Adjusted odds ratio of the outcome of time of admission

DISCUSSION

In this large prospective observational study of patients admitted to the Emergency Unit with a suspected UGIB, we found that patients admitted during the weekend had a higher 30-day mortality risk than those admitted during the week and this effect persisted after adjusting for various prognostic variables. Our data suggests that the higher mortality rate during the weekend can be explained by patient-related factors. Patients admitted during the weekend more often presented with hematemesis and collapse and more often had a lower systolic and diastolic blood pressure and tachycardia at presentation. Rates for rebleeding and need for angiographic and surgical interventions were also higher in patients admitted during the weekend.

It is possible that besides patient-related factors also procedure- or hospital/physician-related factors may have accounted for the higher mortality rate during the weekend. Lower staffing levels and the presence of relatively young and inexperienced staff during the weekend could potentially contribute to a worse outcome. As these factors are related to 'off hours', evening and night admission could potentially also be associated a worse outcome. However, we found that time of admission during the day did not influence the prognosis of patients presenting with suspected UGIB and patients admitted during the night did not do worse that those admitted during the day. This suggests that physician-related factors are not predominant. Furthermore, we did not identify procedure-related factors that could have explained the inferior outcome during the weekend. We even found that time to endoscopy tended to be shorter during off hours (nights and weekends). Based on our results, procedure- and hospital-related factors are therefore unlikely to explain the higher mortality rate in patients admitted during the weekend. In addition, several studies assessing the effect of early endoscopy on mortality have previously confirmed that early endoscopy is not associated with lower mortality rates[16-21].

Our results confirm the studies performed by Shaheen et al[7], Dorn et al[13] and Ananthakrishnan et al,[14] which all found higher mortality rates in patients admitted during the weekend. In addition, Shaheen et al. reported that patients with suspected UGIB underwent also more frequently a surgical intervention when admitted during the weekend. However, a limitation of these studies was that they were derived from healthcare databases and therefore not able to identify reasons for the 'weekend effect' as important clinical, biochemical and endoscopic data were not available and the obtained data could therefore not be adjusted for these factors. A study by Jairath et al. showed that patients admitted during the weekend were more critically ill and had a greater delay in time to endoscopy, however this did not result in a worse outcome in these patients[6]. A possible explanation for

this different outcome compared to our findings could be the differences in length of follow-up as we followed all patients for 30-days during and after admission. In addition, we looked at both in- and out-hospital mortality, while Jairath et al. focused on hospital records for mortality.

In our study, detailed information was available on patient characteristics including clinical, laboratory and endoscopy data. We also had data available on the exact time of endoscopy and rebleeding rates. This made it possible to adjust for important prognostic variables. We also incorporated time of admission in our analyses, while previous studies only focused on day of admission. After correcting for covariates, we were able to exclude a procedure-related effect for the observed increased mortality during the weekend. An inexperienced physician effect as explanation for the increased mortality in the weekend was also much less likely because this was not seen during evening and nights. Furthermore, we assessed both in- and out-hospital mortality, while most studies only focused on in-hospital mortality.

A potential limitation of this study could be that treatment of patients was not standardized and could potentially differ between centers and physicians. On the other hand, the outcome of the study was corrected for various co-variables including treatment modalities and therefore this effect is likely to be minimal. Secondly, we assessed all-cause mortality of patients. GI-bleeding related mortality would have been a better primary endpoint, however this endpoint was difficult to define. For example, a subgroup of patients has died as a result of cardiovascular diseases (myocardial infarction, stroke and heart failure), these conditions could potentially have been triggered by the GI bleed.

Our results may have implications for risk assessment of patients presenting with suspected UGIB by creating more awareness of higher mortality rates in patients presenting during the weekend. It could be argued that patients admitted during the weekend should receive closer monitoring compared to week admissions based on these results.

In conclusion, patients admitted to the Emergency Unit during the weekend with a suspicion of UGIB are at increased risk of mortality compared to those admitted during the week. This might be explained by the observation that the patients that present during the weekend are more often critically ill. No procedure related factors could be identified associated with an adverse outcome. Evening or night-time admission was not associated with an adverse outcome in these patients, even though time to endoscopy was significantly longer in patients admitted during evening-time.

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Chapter 8

Prediction of peptic ulcer rebleeding and mortality using the Forrest classification four decades after its establishment: can it be simplified?

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Accepted for publication in Endoscopy

ABSTRACT

BACKGROUND

We aimed to reassess whether the Forrest classification could still be used for the prediction of rebleeding and mortality of peptic ulcer bleedings and, based on this, whether this classification could be simplified.

METHODS

Using a prospective registry we collected and categorized peptic ulcer bleedings according to the Forrest classification. The primary outcome was 30-day rebleeding and all-cause mortality rates. We used ROC curves to test whether simplification of the Forrest classification into a high risk (Forrest Ia), a increased risk (Forrest Ib-IIc) and a low risk (Forrest III) class could be an alternative for the original classification.

RESULTS

In total 397 patients were included, with 18 bleedings (4.5%) being classified as Forrest Ia, 73 (18%) as Forrest Ib, 86 (22%) as Forrest IIa, 32 (8%) as Forrest IIb, 59 (15%) as Forrest IIc and 129 (33%) as Forrest III. Rebleeding occurred in 74 patients (19%). Rebleeding rates were highest in Forrest Ia peptic ulcers (59%). The odds ratios for rebleedings in patients with Forrest Ib-IIc were almost comparable. In subgroup analysis, predicting rebleeding using the Forrest classification was more reliable for gastric ulcers than for duodenal ulcers. The simplified Forrest classification had similar test characteristics compared to the original Forrest classification.

CONCLUSION

We found that the Forrest classification still has predictive value for rebleeding of peptic ulcers, especially for gastric ulcers; however, it does not predict mortality. Based on our results, we suggest a simplified Forrest classification. Nonetheless, further studies are needed to validate these findings.

INTRODUCTION

Upper gastrointestinal (GI) bleeding is a common cause of hospital admission. Although the incidence rate is slightly declining, still 61 to 134 bleeds occur per 100,000 patients per year[1;2] and the mortality remains considerable. The most common cause of upper GI bleeding is peptic ulcer bleeding[3], with *H. Pylori* infections and/or the use of non-steroidal anti-inflammatory drugs (NSAIDs) including low-dose aspirin as most important risk factors[4;5].

Rebleeding is an frequently observed complication of peptic ulcer bleeds and the potential occurrence of rebleeding often prevents early discharge[6]. Patients classified as being at a high risk for rebleeding or mortality are often closely monitored or admitted to the intensive care unit (ICU). Reliable prediction of rebleeding and/or mortality is difficult. Several risk scores based on clinical input parameters have been developed over the last decades for predicting the outcomes of peptic ulcer bleeding[7;8]. Yet how often these scores are implemented in clinical practice remains unknown and gastroenterologists seem to rely more on their own clinical intuition or on simple classifications such as the Forrest classification.

The Forrest classification was developed almost four decades ago[9]. The purpose of this classification was initially to uniformly describe lesions that are or have been bleeding. However, the Forrest classification (or at least stigmata of bleeding) is nowadays mostly used to identify patients at an increased risk for rebleeding and mortality[8;10;11]. The Forrest classification differentiates ulcers with a spurting hemorrhage (Forrest Ia), an oozing hemorrhage (Forrest Ib), with a visible vessel (Forrest IIa), an adherent clot (Forrest IIb), hematin on the ulcer base (Forrest IIc) and a clean ulcer base (Forrest III), and rebleeding rates reported in the literature vary between 90% for a Forrest Ia lesion and 5% for a Forrest III lesion.

These rebleeding rates for different Forrest classes were reported many years ago and much has changed over the last decades regarding not only the etiology but also the treatment of peptic ulcer bleeding. Regarding the latter, the use of intravenous proton pump inhibitors (PPI) and the development of endoscopic treatment has improved the outcome of peptic ulcer bleeding considerably[12]. The aim of this study was therefore to reassess the Forrest classification in predicting the outcome of peptic ulcer bleeding. More specifically, we tested whether the Forrest classification had better test characteristics in gastric than in duodenal ulcers, and whether a simplified Forrest classification could be an alternative for the original classification.

METHODS

Patients and Outcomes

All adult patients with upper GI bleeding due to a gastric or duodenal ulcer between October 2009 and April 2012 were prospectively included in eight participating hospitals in the Netherlands. Patients were treated according to the protocols of each participating center and no interference was made with patient management. Patients were followed for 30 days after presentation by the study coordinator of that particular hospital.

All peptic ulcer bleeds were categorized by the endoscopist according to the Forrest classification in Ia Spurting hemorrhages, Ib Oozing hemorrhages, IIa Visible vessel, IIb Adherent clot, IIc Hematin on ulcer base, III Clean base ulcer (**Figure 1**). Data were systematically collected using a dedicated CRF and included demographics, medical history (presenting signs or symptoms), physical examination (blood pressure, heart rate), medication use (e.g. non-steroidal anti-inflammatory drugs, proton pump inhibitors and anticoagulants), comorbidities, biochemical data (hemoglobin (Hb), platelet count, urea, creatinine and International Normalized Ratio (INR)) and endoscopic findings. The endoscopic findings were extracted from the endoscopy reports. Procedure-related factors included the need to perform endoscopic hemostasis as determined by the endoscopist, need for angiography or surgery to control the bleeding and number of units blood transfused pre- and post-endoscopy. All patients with peptic ulcer bleeding were treated with high dose PPI intravenously.

The primary outcomes were 30-day rebleeding rate and 30-day all-cause mortality rate. The definition of rebleeding was derived from the Peptic Ulcer Bleed (PUB) study as; recurrent haematemesis of fresh blood (>200 ml), active bleeding or fresh blood found during endoscopy, or two of the following: 1) Hb drop > 20 g/L within 24 hr, 2) Hb increase < 10 g/L after adequate blood transfusion, 3) Systolic RR < 90 mm Hg (after being higher initially) or pulse rate > 110 /min (after being higher initially) within 30 days after initial stabilization[13]. Mortality was defined as all-cause mortality in- and out-hospital.

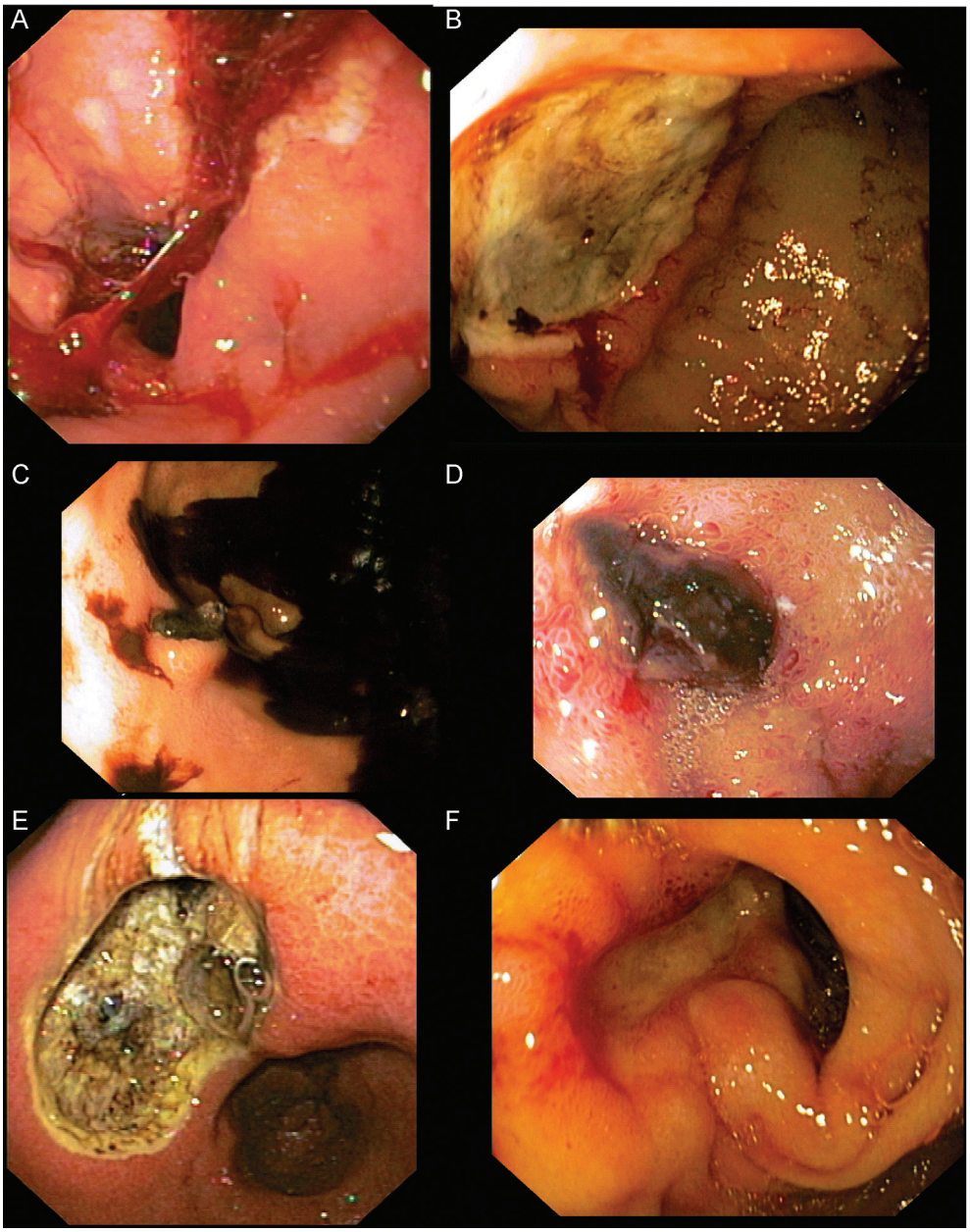

Figure 1 Forrest classification
A Forrest Ia, B Forrest Ib, C Forrest IIa, D Forrest IIb, E Forrest IIc, F Forrest III

Statistical analysis

Standard descriptive statistics were used to study baseline characteristics. The chi-square test, t-test and Mann-Whitney U test were performed to identify differences in patient characteristics, comorbidities and endoscopic findings between gastric and duodenal ulcers, as appropriate. Logistic regression analyses were performed to assess the association between the Forrest classification and outcome. Subgroup analyses were performed to assess the predictive value of the Forrest classification for gastric and duodenal ulcers separately for the primary endpoints.

We calculated the area under the receiving operating characteristics (ROC) curve (AUC) for both the original Forrest classification, and a simplified version of the Forrest classification. The simplified version consists of three categories: a high risk (Forrest Ia), an increased risk (Forrest Ib-IIc) and a low risk (Forrest III) class. Statistical analysis was performed with SPSS 14.0 (SPSS Inc. Chicago, IL, USA).

Ethical considerations

This is a prospective observational study, in which patient data are entered anonymously in a central database. The protocol did not include any (extra) interventions and no additional testing was performed. Therefore, the Dutch Law on Medical Research on Humans did not apply here and approval by a medical ethical committee was not required. The Medical Ethics Committee of the Sint Antonius Hospital, Nieuwegein, the Netherlands agreed on this approach on July 20, 2009, as well as the medical ethics boards of the other participating centers.

RESULTS

Patient characteristics

In total 431 patients had an upper GI bleeding with a confirmed gastric or duodenal ulcer. For 397 patients (92%) the Forrest classification was reported. Eighteen patients (4.5%) were classified with a Forrest Ia, 73 (18.4%) with a Forrest Ib, 86 (21.7%) with a Forrest IIa, 32 (8.1%) with a Forrest IIb, 59 (14.9%) with a Forrest IIc and 129 (32.5%) with a Forrest III bleeding. Mean age was 67 (SD17) years and 31.7% of patients were female. Other baseline characteristics and differences between gastric and duodenal ulcers are shown in **Table 1**.

Table 1 Baseline characteristics and differences between gastric and duodenal ulcers

	All peptic ulcer bleeds N= 397	Gastric ulcer bleeds N= 216	Duodenal ulcer bleeds N=181	P value
Age (mean)	67 (SD 17)	70	65	< 0.01
Sex (female)	126 (31.7%)	73 (33.8%)	53 (29.3%)	0.20
Rebleeding	73 (19,4%)	38 (17,7%)	36 (20.0%)	0.32
Medical history				
Melaena	301 (75.8%)	160 (74,1%)	141 (77,9%)	0.22
Hematemesis	153 (38.5%)	99 (45,8%)	54 (29,8%)	< 0.01
Rectal blood loss	64 (16.1%)	25 (11.6%)	39 (21.5%)	< 0.01
Collapse	83 (20.9%)	47 (21,8%)	36 (19.9%)	0.37
≥1 comorbidities	263 (66.2%)	151 (74.8%)	105 (59.7%)	< 0.01
Concomitant drug use				
Anticoagulants	95 (23,9%)	56 (25,9%)	39 (21,5%)	0,19
Low-dose aspirin	150 (37,8%)	89 (41,2%)	61 (33,7%)	0,08
Other antiplatelet therapy	40 (10,1%)	26 (12,0%)	14 (7,7%)	0,10
NSAIDs	50 (12,6%)	28 (13,0%)	22 (12,2%)	0,47
Corticosteroids	26 (6,5%)	12 (5,6%)	14 (7,7%)	0,25
SSRIs	15 (3,8%)	9 (4,2%)	6 (3,3%)	0,43
PPIs	70 (17,6%)	37 (17,1%)	33 (18,2%)	0,44
Physical examination				
Systolic RR (mean) (mmHg)	123 (SD 23)	123	122	0.74
Diastolic RR (mean) (mmHg)	67 (SD 16)	67	68	0.71
HR (mean) (beats per minute)	91 (SD 19)	90	92	0.38
Laboratory results				
Hb level (mean) (mmol/L)	6.0 (SD 2.0)	5,9	6,0	0.97
Platelet count (*109)	269 (SD 112)	264	277	0.25
Creatinine (µmol/L)	108 (SD 81)	111	105	0.48
Urea (mmol/L)	16 (SD 10)	17	15	0.03
INR	1.9 (SD 2.3)	2.1	1.7	0.18
Admission (median duration in days)	6	6	6	0.91
Do not resuscitate status	56 (14.3%)	35 (16,4%)	21 (11.8%)	0.122
Patients with ≥ 1 blood transfusions	266 (67.0%)	138 (70.1%)	119 (70.0%)	1.0
Need for endoscopic intervention	213 (53.8%)	104 (48,4%)	109 (60.2%)	0.01
Patients receiving surgery	5 (1.3%)	3 (1.4%)	2 (1.1%)	1.0
Patients receiving angiography	15 (3.8%)	3 (1.4%)	12 (6.6%)	< 0.01
Mortality	15 (3,8%)	9 (4,2%)	6 (3,3%)	0,43

Endoscopic data

Table 2 illustrates the number of patients receiving endoscopic intervention, the type of intervention used and whether hemostasis was reached. Up to Forrest IIb, the far majority of the patients was treated endoscopically. Most patient received dual combination therapy (range 70.6%-73.9%), however a fair number of the patients also received monotherapy (range 21.2%-23.5%). Forrest IIc ulcers were treated in 25.4% of the cases with monotherapy (42.9%) or dual combination therapy (50.0%). If Forrest III were treated endoscopically, it was with monotherapy (88.9%). In Forrest Ia ulcers most often no hemostasis was reached, in Forrest Ib-IIc this was almost comparable.

Table 2 Endoscopic intervention and outcome

Forrest classification	Endoscopic intervention	Type endoscopic intervention	Patients with no hemostasis reached
Forrest Ia (18, 4.5%)	17 (94.4%)	Monotherapy 4 (23.5%) Combination therapy (dual) 12 (70.6%) Combination therapy (triple) 1 (5.9%)	3 (16.7%)
Forrest Ib (73, 18.4%)	68 (93.2%)	Monotherapy 15 (22.7%) Combination therapy (dual) 47 (71.2%) Combination therapy (triple) 4 (6.1%)	4 (5.5%)
Forrest IIa (85, 21.5%)	81 (95.3%)	Monotherapy 17 (21.2%) Combination therapy (dual) 57 (71.2%) Combination therapy (triple) 6 (7.5%)	4 (4.7%)
Forrest IIb (32 (8.1%)	23 (71.9%)	Monotherapy 5 (21.7%) Combination therapy (dual) 17 (73.9%) Combination therapy (triple) 1 (4.3%)	1 (3.1%)
Forrest IIc (59, 14.9%)	15 (25.4%)	Monotherapy 6 (42.9%) Combination therapy (dual) 7 (50.0%) Combination therapy (triple) 1 (7.1%)	2 (3.4%)
Forrest III (129, 32.6%)	9 (7.0%)	Monotherapy 8 (88.9%) Combination therapy (dual) 0 Combination therapy (triple) 1 (11.1%)	0 (0.0%)

Predictive value of the Forrest classification

Rebleeding

In total 74 patients (18.6%) had a rebleeding. Rebleeding rates were highest for Forrest Ia peptic ulcer bleeds (58.8%), but comparable for Forrest Ib, IIa and IIb ulcers (26.0%, 21.2% and 31.2% respectively). Forrest IIc and III showed lower rates for rebleeding (15.6% and 6.5% respectively). We found that patients with Forrest Ia ulcers were at very high risk (Odds ratio (OR) 17.0; 95% Confidence Interval (CI) 5.3-54.3) for rebleeding compared to Forrest III ulcers. A more or less

similarly increased rebleeding risk was found for patients with Forrest Ib, IIa, IIb ulcers (OR 4.2; 95% (CI) 1.8-9.6 for Forrest Ib, OR 3.2; 95% CI 1.4-7.3 for Forrest IIa and OR 5.4; 95% (CI) 2.0-14.5 for Forrest IIb) (**Figure 2**).

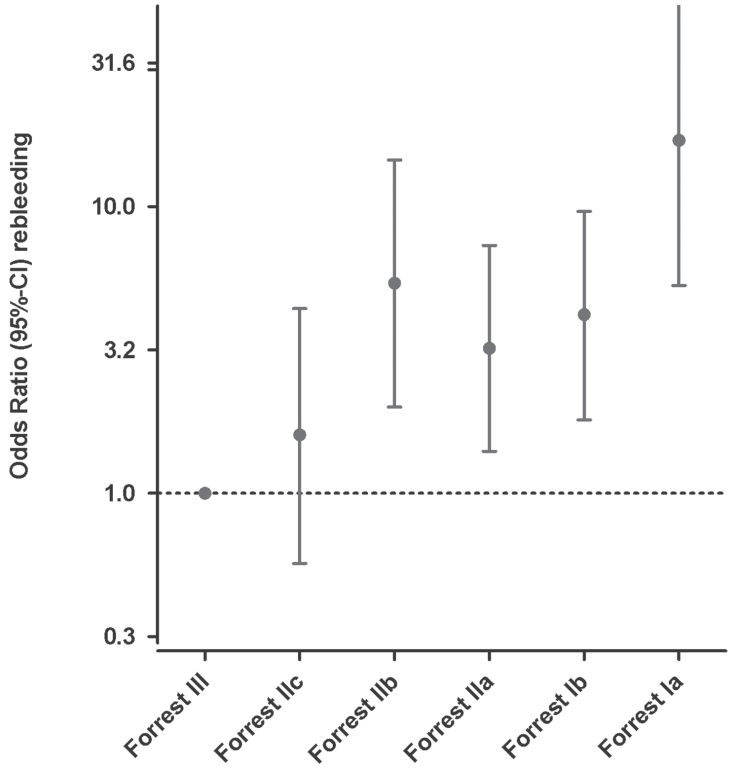

Figure 2 Association between Forrest classification and rebleeding

The association between Forrest classification and rebleeding was higher in gastric ulcers compared to duodenal ulcers (**Figure 3**). The AUC for Forrest classification and rebleeding was 0.68. Simplification into high, medium and low risk resulted in an AUC of 0.65 (**Figure 4**).

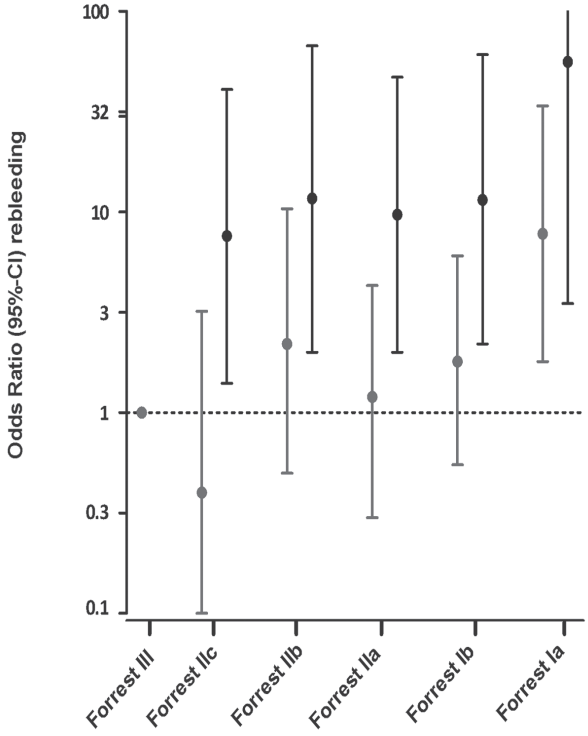

Figure 3 Results subgroup analyses. Association between Forrest classification and rebleeding in gastric (black stacks) and duodenal ulcers (grey stacks).

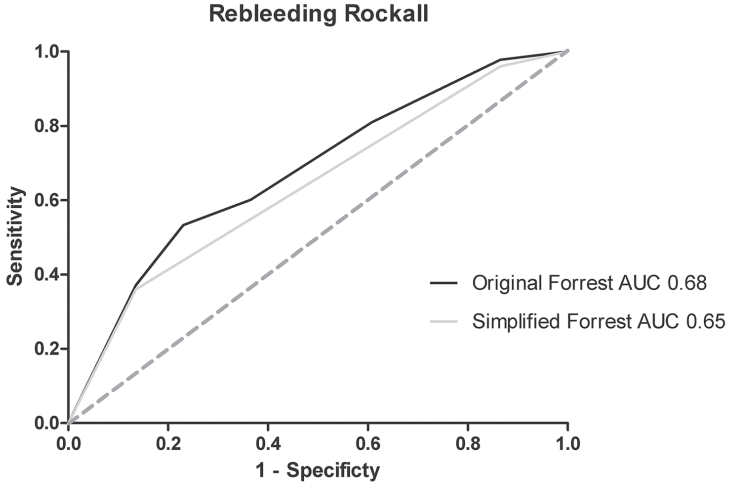

Figure 4 Receiving operating characteristics (ROC) curve for Forrest classification and the simplified Forrest classification in predicting rebleeding

Mortality

In total 15 patients (3.8%) died. Most patients died from non-GI bleeding related causes, which included malignancy (one patient), cardiovascular disease (three patients), pulmonary disease (three patients) and unknown causes (two patients). In the 14 patients with a Forrest Ia ulcer bleed, no deaths occurred. The mortality rates in the other Forrest classifications were fluctuating; 5.5% in the Forrest Ib group, 3.4% in the Forrest IIa group, 3.1% in Forrest IIb group, 1.7% in Forrest IIc group and 4.7% in the Forrest III group. **Figure 5** shows the odds ratios for mortality for different Forrest classes compared to Forrest III ulcers (OR for Forrest Ib ulcers 1.2; 95% CI 0.3-4.4, for IIa OR 0.8; CI 0.2-3.1, for IIb OR 0.7; CI 0.1-5.7 and for IIc: 0.4; 95% CI 0.1-3.0). No odds ratio was calculated for Forrest Ia ulcers as no deaths occurred in this group. Subgroup analyses for gastric and duodenal ulcers or Forrest simplification were not performed due to limited power.

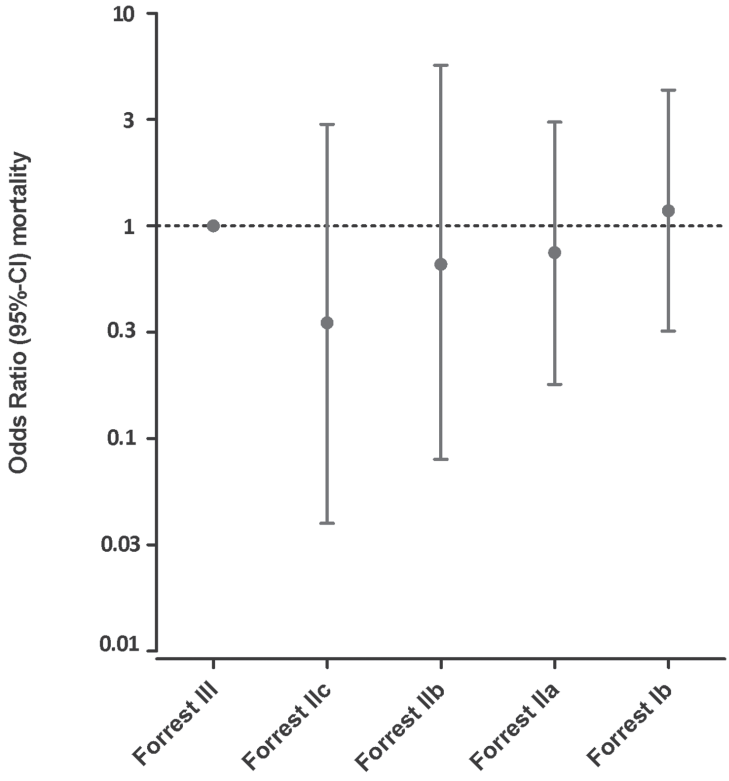

Figure 5 Association between Forrest classification and mortality.

DISCUSSION

In this study, we reassessed the current predictive value of the Forrest classification in predicting rebleeding and mortality and found that the Forrest classification can still be used as a predictor for the occurrence of rebleeding. The association was stronger for gastric ulcers than for duodenal ulcers. We also found that Forrest Ia ulcers are a different risk category compared to other Forrest categories. This emphasizes the importance of separating spurting and oozing hemorrhages, which was also recommended in the recently developed clinical guideline for peptic ulcer bleeding by Laine et al.[6]. Finally, simplification of the Forrest classification (**Table 3**) resulted in similar test characteristics and could therefore be an alternative to use in daily clinical practice.

Table 3 Reclassification and simplification of Forrest classification

Low risk	Patients with a clean base ulcer (FIII)
Increased risk	Patients with oozing haemorrhages or ulcers with stigmata of recent haemorrhage (FIIc-FIb)
High risk	Patients with spurting haemorrhages (FIa)

The risk of rebleeding among Forrest classification Ib, IIa, IIb and IIc ulcers turned out not to differ considerably and was found to be almost comparable. In clinical practice, these ulcers are often treated similarly with intravenous PPI and endoscopic combination therapy, which we also found in our cohort and which may well be the explanation for the observed similar prognosis after treatment. Clinical guidelines also recommend intravenous PPI and combination therapy for all ulcers. However, Forrest IIc and Forrest III ulcers are recommended not to be treated endoscopically[6]. These recommendations are based on the risk of rebleeding within the various Forrest classification groups. It can be postulated however that based on our results, Forrest IIc ulcers should also be treated endoscopically. This will probably imply overtreatment of patients instead of undertreatment. Yet, the rationale is to better treating too often than having a preventable rebleed.

An alternative explanation for the comparable risk estimations may be the moderate interobserver agreement of the Forrest classification. Both Bour et al. and Mondardini et al. have shown that gastroenterologists often disagree on bleeding stigmata[14;15]. Particularly, lesions with stigmata of recent hemorrhage revealed suboptimal kappa values varying from 0.44 to 0.49. Based on our findings, we propose to reclassify and simplify the Forrest classification with patients with a Forrest III ulcer being classified at a low risk, patients with oozing hemorrhages or ulcers with stigmata of recent hemorrhage (Forrest Ib-IIc) at an increased risk

and patients with a spurting hemorrhage (Forrest Ia) at a high risk of rebleeding. Simplifying the Forrest classification has also been advocated by Bour et al.[14] Based on the above-mentioned low interobserver agreement for certain subcategories of the Forrest classification, these authors concluded that the Forrest classification should have fewer categories.

We observed differences in the prognostic significance of the Forrest classification for gastric and duodenal ulcers. The association between type of lesion characterized with the Forrest classification and the rebleeding risk was better for gastric ulcers compared to duodenal ulcers, as has also been reported previously[16]. Gastric ulcers are better visible during endoscopy allowing a better classification compared to duodenal ulcers. Secondly, the endoscopic treatment of duodenal ulcers can be more difficult compared to gastric ulcers, especially when located at the posterior wall of the duodenal bulb.

The risks of rebleeding with the different Forrest categories of ulcers were found to be not very different from the risks of rebleeding reported in the 1970's. It was confirmed that spurting hemorrhages (Forrest Ia ulcers) represent the highest risk factor for rebleeding, followed by oozing ulcers (Forrest Ib) and ulcers with stigmata of bleeding (Forrest IIa-IIc). Mortality was not associated with the Forrest classification. The observation that the prediction of rebleeding risk of the Forrest classification has not changed considerably is surprising in the light of various changes in the etiology and treatment of peptic ulcer bleeds over the last 40 years. With regard to the latter, endoscopic advancements such as injection therapy, bipolar coagulation and endoscopic clip placement have changed the management of peptic ulcer bleeds considerably[6;18]. Perhaps the most significant improvement has been suggested to come from the use of (intravenous) PPI[12]. Nonetheless, despite all these changes, our results are in line with studies from over two decades ago[19-21], with the only exception being the rebleeding rates for Forrest Ia/active bleeding, which have declined compared to older studies (from 50-90% to 60%). Perhaps without these therapies, the rebleeding rates would have even been higher[12;17].

We found that mortality was not associated with type of ulcer according to the Forrest classification. This is in contrast to the literature, in which both the presence of bleeding stigmata and the Forrest classification were shown to be associated with mortality[10;22]. An explanation for this could be that the all-cause mortality in our study was low (3.8%), which may have resulted in an insufficient power to detect an association between ulcer type and mortality. This mortality rate clearly differed from previously reported mortality rates associated with peptic ulcer bleeds that ranged from 10-15%[7;8]. Moreover, the majority (9/15 (60%)) of patients in our study died from other, non-GI bleeding related, causes. Patients with a lower Forrest classification – due to their known higher risk of rebleeding or

mortality – possibly were under closer monitoring resulting in a lower mortality rate. In fact, we found that none of the patients with a Forrest Ia bleeding died although these patients more often developed a rebleeding. This likely highlights the fact that these patients are probably closely monitored whenever a spurting bleeding is seen during endoscopy.

Our study has limitations as well. First, we relied on endoscopy reports for the classification of the ulcers and did not collect the pictures on all cases. Pictures may have added information to the endoscopy report. However in the selection of the pictures we used for this manuscript we experienced that interpretation of pictures made by another subject also is difficult to interpret and subjective as well. Second, in our database we found that there was still heterogeneity within the treatment of the different Forrest classifications. International standardised protocols are required for the endoscopic treatment of GI ulcers and may prevent both under- and overtreatment. In addition, we also did not validate the simplified Forrest classification in another cohort of patients with peptic ulcer bleeding.

In conclusion, the Forrest classification is still a clinically useful tool to identify patients who are at increased risk of rebleeding, with the highest prognostic significance for gastric ulcers. In addition, we suggest to re-classify and simplify the Forrest classification with patients with a Forrest III ulcer being classified at a low risk, patients with oozing hemorrhages or ulcers with stigmata of recent hemorrhage (Forrest Ib-IIc Forrest) at an medium risk and patient with spurting hemorrhages (Forrest Ia) at a high risk of rebleeding. Future research should focus on how this simplified Forrest classification can be implemented in clinical practice and perhaps endoscopic therapy should be adjusted to this new classification.

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Chapter 9

Predicting the need for hospital admission in patients suspected of upper gastrointestinal bleeding: the RASTA score

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Submitted for publication

ABSTRACT

Background

It has been shown that prediction scores can be helpful to identify high and low risk patients with suspected upper gastrointestinal (GI) bleeding. These scores are composed of clinical and laboratory parameters, but clinical judgment of the treating physician is not taken into account. The aim of this study is to develop a score for predicting the need for hospital admission in which the clinical judgment of the physician is also incorporated.

Methods

Consecutive patients presenting to the emergency room in 8 participating hospitals (RASTA study) with suspected GI bleeding were included between October 2009 and August 2012. The primary outcome was the need for hospital admission, defined as the need for a clinical intervention. Treating gastroenterologists were asked to estimate the probability that the patient would need an intervention to control the bleeding (gut feeling). Logistic regression analysis was performed to assess the association between patient risk factors and the need for intervention. The discriminatory power of the prediction score was assessed with an area-under-the-curve (AUC) of a receiver operating characteristic (ROC) curve.

Results

In total 1,134 patients were prospectively included, of which 783 (69%) had a clinical intervention. Independent predictors for the need of a clinical intervention were aspirin use, presence of endovascular prosthesis, hemoglobin level <7 g/dl, urea level >9 mmol/L and a estimated medium or high probability for an intervention as determined by the gut feeling of the gastroenterologist. Using these predictors, the RASTA prediction score was developed. The discriminative power of the score was excellent with an AUC of 0.88 (95% confidence interval 0.86-0.90). Internal validation by bootstrap analyses showed an AUC of 0.87.

Conclusion

In this Dutch population of patients presenting to the emergency room with suspected GI bleeding, the RASTA score, that includes the gastroenterologist's gut feeling, has a high predictive power for the need of hospital admission, but prospective studies are needed to validate it.

INTRODUCTION

Upper gastrointestinal (GI) bleeding is an emergency situation that often leads to hospital admission[1]. Although case fatality seems to be declining, mortality rates are still reported to be as high as 10%, as is the case for rebleeding rates[1-3]. Due to a relatively high morbidity and mortality risk as well as the poor prediction of these outcomes, almost all patients are being admitted to the hospital and are recommended to undergo endoscopy within 24-hours. This leads to a high demand on hospital wards and endoscopy units and results in significant healthcare costs[4]. In order to reduce unnecessary admissions and health care costs it is important to predict which patients require a clinical intervention within 30 days after presentation and those who definitely do not.

Various prediction models have been developed over the past few decades[5]. The Blatchford score and the Rockall score are probably the most commonly used scores. The Blatchford score has been designed to predict the need for an intervention requiring admission such as a blood transfusion, endoscopic treatment, or a surgical or radiological intervention This score was validated and adopted several times over the years[6-8]. A disadvantage of the Blatchford score is that it was developed in a population with confirmed upper GI bleeds. However, a significant part of the patients presenting to the emergency room (ER) with a suspected upper GI bleed do not have a confirmed bleeding which makes this score less suitable to extrapolate to all patients presenting to the ER.

In previous work we found that, besides these prediction models, clinical judgment (gut feeling) of experienced gastroenterologists was found to be a good predictor for outcome of patients presenting with suspected upper GI bleeding[9], although prediction scores yielded a higher predictive power. Combining prediction scores and gut feeling led to the most optimal predictive performance.

The aim of this study was to develop a novel prediction score for predicting the need of a clinical intervention – and thus the need for admission – in which the clinical risk estimation of the physician was incorporated.

METHODS

Patients and Outcomes

Consecutive patients, 18 years or older, that were admitted to the ER for suspected upper GI bleeding (i.e. presentation with self-reported melena or hematemesis) between October 2009 and August 2012 were included in the 'Risk ASsessment and Triage of Acute bleeding (RASTA) study'. This study was performed in eight participating hospitals in the Netherlands. Patients were treated according to the

Dutch guideline and no interference was made with regard to patient management. Patients were followed for 30 days after presentation by the study coordinator of each participating hospital.

Upper GI bleeding was defined as 'confirmed' if patients with suspected upper GI bleeding met the criteria shown in **Textbox 1**.

Textbox 1

Diagnostic criteria for upper gastrointestinal bleeding

- Combination of reported signs of melena and/or hematemesis with
  - Anemia (Hb <13.0g/dl for men or <12.0g/dl for women), or
  - Hemodynamic instability (a state requiring pharmacologic or mechanical support to maintain a normal blood pressure or adequate cardiac output), or
  - Discrepant increased urea
- Confirmed bleeding during endoscopy or manifest old/fresh blood

Upper GI bleeding included all hemorrhages of the upper GI tract, including peptic ulcer bleeding, variceal bleeding, Mallory-Weiss lesions, severe reflux esophagitis, gastritis with hemorrhage, Dieulafoy's lesions, neoplastic lesions and angiodysplasias. Data were systematically collected using a dedicated CRF, including demographic features, medical history (presenting signs or symptoms) and physical examination (blood pressure, heart rate), medication use (e.g. non-steroidal anti-inflammatory drugs, aspirin, proton pump inhibitors and anticoagulants), comorbidities, biochemical results (haemoglobin (Hb), platelet count, urea, creatinine and International Normalized Ratio (INR)) and endoscopic findings. Comorbidities included chronic heart disease, liver cirrhosis, history of GI hemorrhage, presence of cancer in the GI tract or any other site, lung emphysema, renal failure (creatinine >200 micromol/L including patients having dialysis), endovascular prosthesis, diabetes mellitus, and ongoing chemotherapy or radiotherapy. Endoscopic findings included location and number of lesions, stigmata of recent hemorrhage and Forrest classification of ulcers. Procedure-related factors included time from presentation to endoscopy, need to perform endoscopic hemostasis as judged by the endoscopist and number of units of blood transfused before and after endoscopy.

After evaluation on the ER and prior to upper endoscopy the treating gastroenterologist had to fill out a questionnaire regarding his/her judgment whether the patient would require an intervention to control the bleeding. The questions and probabilities are shown in **Textbox 2**. The gastroenterologist estimated whether the patient was at a low, medium or high risk for these endpoints. In this study, we refer to this risk estimation by the gastroenterologist as "gut feeling".

Textbox 2

Questions regarding the Gut feeling of the gastroenterologist

- At presentation at A&E
  - o What is the risk for current bleeding requiring endoscopic treatment (or surgery/ angiography) or transfusion in this patient
    - – Low risk (<1%)
    - – Medium risk (1-10%)
    - – High risk (>10%)

The primary outcome was the need for clinical intervention. Patients at very low risk for the need of a clinical intervention can probably be discharged after presentation to the ER. A clinical intervention was a composite endpoint consisting of a blood transfusion or any surgical, radiological or endoscopic intervention to control the hemorrhage and/or the occurrence of rebleeding or mortality, as defined by Blatchford[6]. Mortality was defined as all-cause mortality in- and out-of-hospital. Rebleeding was defined according to the criteria set by the Peptic Ulcer Bleed study[10] as recurrent hematemesis of fresh blood (>200 ml), active bleeding or fresh blood found during endoscopy, or two of the following: 1) Hb drop >20 g/L within 24 hr, 2) Hb increase <10 g/L after adequate blood transfusion, 3) Systolic RR <90 mm Hg (after being higher initially) or 4) Pulse rate >110 /min (after being higher initially) within 30 days after initial stabilization.

Statistical analysis

Differences in patient characteristics, comorbidities and endoscopic findings associated with the need for an intervention were analyzed using the chi-square test, Student t-test or Mann-Whitney U test when appropriate. Predictors with a p-value below 0.10 were included in the multivariate analyses. Logistic regression analysis was performed to assess the association between candidate risk factors and the need for an intervention. Statistical significance was considered if $p<0.05$.

In order to develop an easy to use score, we identified the most important risk factors through backward stepwise selection using likelihood ratios. Risk factors were assigned an integer point based on a common denominator across all beta coefficients of the risk factors. Continuous variables were both studied as predictor in a continuous setting and were also dichotomized using the optimal cutoff point (based on the AUC) or using existing medical literature where appropriate. We quantified the discriminatory value of the prediction score with an area-under-curve (AUC), with an AUC of 0.5 indicating no discrimination, and a value of 1.0, indicating perfect discrimination between high and low risk patients. Calibration of the scores was assessed with a Hosmer-Lemeshow goodness-of-fit test in which

the agreement between observed and predicted outcomes is studied. To account for optimism and to achieve a bias-corrected, more accurate estimate of the predictive power of the model a bootstrap analysis was performed. One thousand random bootstrap samples were drawn, with replacement, from the original cohort. Finally, we calculated the Blatchford score for all patients and compared the AUC of the Blatchford score to that of our developed score. This score has been validated and patients with a score of 0 are assumed save to be discharged.

Ethical considerations

This was a prospective observational study, in which patient data were entered anonymously in a central database. The protocol did not include any (additional) interventions and no additional testing was performed. Therefore, the Dutch Law on Medical Research on Humans does not apply here and approval by a medical ethical committee was not required. This was confirmed by the Medical Ethics Committee of the Sint Antonius Hospital, Nieuwegein, the Netherlands (July 20th, 2009).

RESULTS

Baseline results

In total 1,134 patients were included, of which 783 (69%) had a clinical intervention (blood transfusion or any operative, radiological or endoscopic intervention to control the hemorrhage and/or the occurrence of rebleeding or mortality). Mean age of patients was 66 years (range 18-99 years), with the majority being male (63.5%). In total, 170 patients (15%) developed a rebleeding and 55 patients (4.9%) died. The type of clinical interventions are shown in **Table 1**. The gut feeling of the gastroenterologist was recorded in 1,131 patients, of which 344 were classified at a low risk, 352 at a medium risk and 435 patients at a high risk for the need of an intervention. Blood transfusion was determined to be required in 656 patients (57,8%) (mean of 0.9 units before endoscopy and 1.4 units after endoscopy). A surgical and/or radiological intervention to stop the bleeding was performed in 19 (1.7%) and 28 (2.5%) patients, respectively.

Table 1 Distribution clinical interventions within the cohort

	N = 1134
Any intervention	783 (69,0%)
Endoscopic Intervention	468 (41.3%)
Radiological intervention	28 (2.5%)
Surgical intervention	19 (1.7%)
Blood transfusion	656 (57.8%)

Prediction score for the need of a clinical intervention

The result of the univariate and multivariate analyses of clinical parameters is shown in **Table 2**. Independent predictors for the need of a clinical intervention were low-dose aspirin use, an endovascular prosthesis, hemoglobin level <7 g/dl, urea level >9 mmol/L and an estimated medium or high risk for an intervention by the gut feeling of the gastroenterologist (**Table 3**). Hemoglobin level and an estimated high risk for the need of an intervention by the gastroenterologist's gut feeling were the strongest predictors of an intervention. The prediction score was developed based on the beta coefficients. Using this, patients could be qualified based on a score between 0 and 14 points, with a higher score increasing the risk of having a clinical intervention.

Table 2 Results of univariate and multivariate logistic regression analyses of the predictors for the need of a clinical intervention in patients suspected for upper GI bleeding

	Patients with need for an intervention N=783	Patients without need for an intervention N=351	P value	Adjusted Odds ratio (95% Confidence interval)
Age (mean)	69 (SD 16)	59 (SD 19)	< 0.01	0.99 (0.98-1.07)
Cut-off > 65 years				1.10 (0.73-1.68)
Sex; female	283 (36.1)	130 (37.1)	0.40	
Medical history				
Melaena	532 (67.9)	176 (50.3)	< 0.01	0.96 (0.63-1.47)
Hematemesis	328 (41.9)	192 (54.9)	< 0.01	0.95 (0.63-1.45)
Rectal blood loss	119 (15.2)	47 (13.4)	0.25	
Collapse	154 (19.7)	25 (7.1)	< 0.01	1.25 (0.71-2.22)
Medication use				
oral anti-coagulants	229 (29.2)	50 (14.2)	< 0.01	1.42 (0.83-2.44)
corticosteroids	53 (6.8)	14 (4.0)	0.04	1.09 (0.47-2.51)
NSAIDs	67 (8.6)	53 (15.1)	< 0.01	0.77 (0.45-1.34)
Acetylsalicylic acid	295 (37.7)	81 (23.1)	< 0.01	**1.79 (1.12-2.84)**

	Patients with need for an intervention N=783	Patients without need for an intervention N=351	P value	Adjusted Odds ratio (95% Confidence interval)
Clopidogrel	86 (11.0)	17 (4.8)	< 0.01	1.16 (0.56-2.42)
PPI	279 (35.6)	115 (32.8)	0.19	
SSRIs	31 (4.0)	20 (5.7)	0.13	
Physical examination (mean)				
Systolic RR	122 (SD 25)	136 (SD 24)	< 0.01	1.00 (0.99-1.01)
Cut-off < 100 mmHg				1.61 (0.74-3.53)
Diastolic RR	65 (SD 16)	78 (SD 16)	< 0.01	0.98 (0.97-1.01)
Cut-off < 70 mmHg				1.14 (0.76-1.72)
Heart rate	90 (SD 19)	87 (SD 17)	0.02	1.01 (1.00-1.02)
Cut-off > 100/min				**2.13 (1.40-3.21)**
Laboratory results (mean)				
Hb level (mean)	5.5 (SD 1.9)	7.9 (SD 1.4)	< 0.01	0.50 (0.43-0.57)
Cut-off <7.0 mmol/L				**8.51 (5.75-12.60)**
Platelet count	250 (SD 118)	239 (SD 89)	0.33	
Creatinine	116 (SD 84)	91 (SD 58)	< 0.01	0.99 (0.99-1.00)
Cut-off > 100 umol/L				0.77 (0.49-1.21)
Urea	16 (SD 11)	9.4 (SD 8)	< 0.01	1.02 (0.99-1.04)
Cut-off > 9 mmol/L				**1.88 (1.24-2.85)**
INR	2.1 (SD 2.4)	1.5 (SD 1.5)	< 0.01	High correlation anticoagulant use
Comorbidities				
Liver cirrhosis	94 (12.0)	25 (7.1)	0.01	1,88 (0,98-3,58)
History of UGIB	183(23.4)	71 (20.2)	0.26	
Presence of GI-related malignancy	33 (4.2)	14 (4,0)	1,0	
Chronic heart disease	320 (40.9)	75 (21.4)	< 0.01	1.11 (0.65-1.88)
COPD	108 (13.8)	36 (10.3)	0.06	0,92 (0.48-1.76)
Renal failure	73 (9.3)	12 (3.4)	< 0.01	0.90 (0.40-2.02)
Endovascular prosthesis	94 (12,0)	10 (2.8)	< 0.01	**3.04 (1.22-7.56)**
Diabetes Mellitus	157 (20.1)	46 (13.1)	< 0.01	0.89 (0.54-1.50)
Ongoing chemo- or radiotherapy	16 (2.0)	4 (1.1)	0.34	
Presence of malignancy outside GI tract	54 (6.9)	16 (4.6)	0.11	
Number of comorbidities (mean)	0.9 (SD 1.0)	1.3 (SD 1.1)	< 0.01	0.81 (0.62-1.07)
Cut-off > 2 comorbidities				0.75 (0.45-1.24)
Gut feeling for need for intervention			< 0.01	
Low	139 (17.8)	205 (58.6)		Reference
Medium	240 (30.7)	112 (32.0)		**1.68 (1.13-2.51)**
High	402 (51.5)	33 (9.4)		**7.07 (4.25-11.79)**

Table 3 Independent predictors for the need of an intervention based on the multivariate logistic regression analysis and derivation of prediction score

Predictor	Adjusted OR	Beta coefficient	Score point
Low-dose aspirin use	1.55	0.44	1
Endovascular prosthesis	2.98	1.09	2
Heart rate > 100 beats/min	2.12	0.75	1
Hemoglobin < 7 g/dl	8.60	2.15	4
Urea > 9	1.93	0.66	1
Gut feeling: medium risk	1.80	0.59	1
Gut feeling: high risk	8.23	2.11	4
Total			14 points

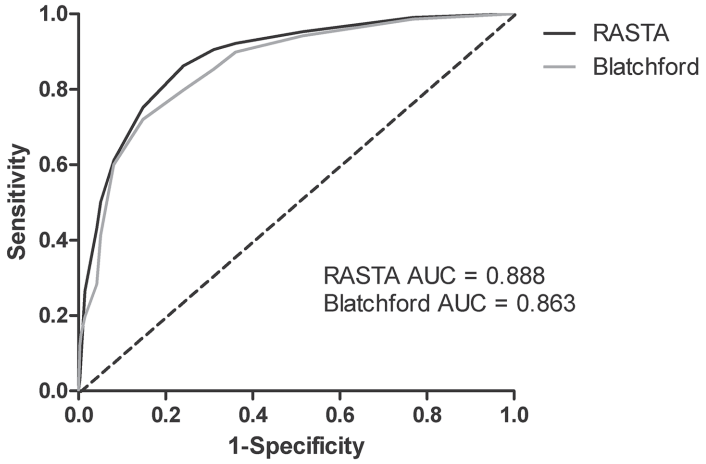

Figure 1 Illustrates the distribution of the risk of having an intervention based on this risk score compared with the Blatchford score.

Performance of the RASTA prediction score

The RASTA score calibrated well with a p=0.34. The discriminative power of the score was good with an AUC of 0.88 (95% confidence interval (CI) 0.86-0.90) (**Figure 1**). Internal validation of the RASTA score by bootstrap analysis showed an AUC of 0.87. The Blatchford score yielded a discriminative power in the same range with an AUC of 0.86 (95% CI 0.83-0.88).

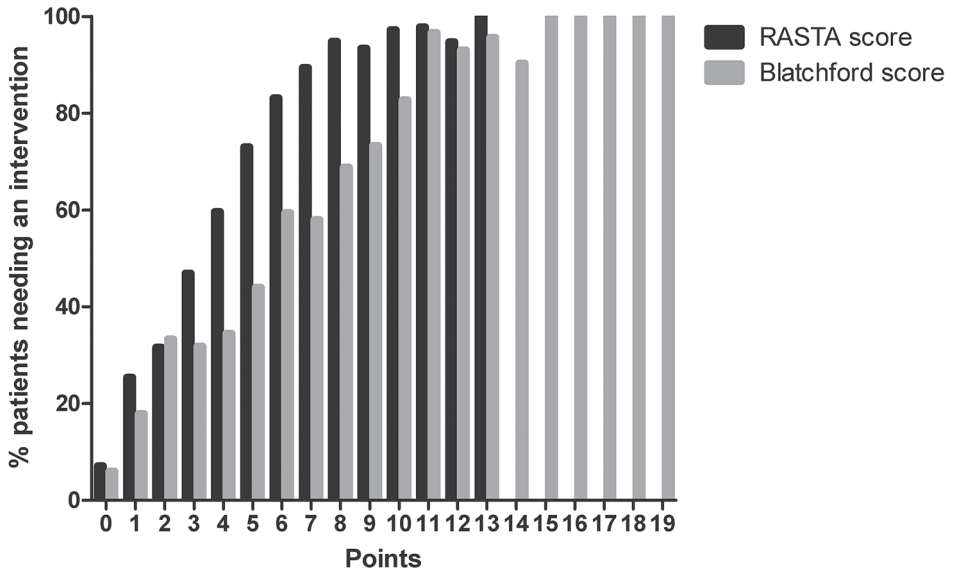

Figure 2 Distribution of the patients needing an intervention for the different score groups of the RASTA and Blatchford score

For both the RASTA and the Blatchford score a steep increase in the risk of a clinical intervention was seen between 0 and 1 points (**Figure 2**). With a score of 0, both scores have a sensitivity of 99% for excluding patients who need an intervention, which drops to 96.2% and 98.7% at a score of 1 for the RASTA and Blatchford score, respectively. Therefor the cut-off of the RASTA score for excluding the need of an intervention was set at 0 points. Yet still 6 (7,1%) patients with 0 points (**Figure 1**) underwent an intervention in the RASTA cohort; three patients had an endoscopic intervention, two patients a blood transfusion while one patient developed a rebleed. In the group of patients with a Blatchford score of 0 points, three patients required an intervention (6.0%); 1 patient had an endoscopic intervention and two a blood transfusion. The specificity of the RASTA score of 0 was 23.2% while this was 13.4% for the Blatchford scor%.

DISCUSSION

In this study we developed an easy to use prediction score for hospital admission, the RASTA score, in which clinical patient demographics and the gastroenterologist's gut feeling were incorporated. This score was based on a large prospectively

collected multicenter database including patients presenting to the emergency room with a suspected upper gastrointestinal (GI) bleeding. We found that the RASTA score performed well and showed a predictive power that was slightly better than that of the Blatchford score.

Our RASTA score overlaps significantly with the Blatchford score with respect to the input of data (i.e. pre-endoscopic predictors) and predicted outcome (i.e. the need for an intervention). Moreover, hemoglobin and urea levels, and increased heart rate were found to be predictors for a clinical intervention in both the RASTA and Blatchford score. The difference with the Blatchford score is that in the RASTA score the gut feeling of experienced gastroenterologists was included. Furthermore, use of low-dose aspirin and having an endovascular prosthesis were found to be predictors for the need of an intervention.

Until now, only one study has identified low-dose aspirin use as a predictor of poor outcome in patients with suspected upper GI bleeding[11], whereas the presence of an endovascular prosthesis was never identified as a risk factors for a poor outcome[2;12-14]. The discrepancy between the observed effect of low dose aspirin use and most literature reports could be due to the fact that in most countries low-dose aspirin is available over the counter and thus difficult to register in studies while in the Netherlands nearly all users do this on a prescription base. In addition, the presence of an endovascular prosthesis could well be a proxy for patients with an overall poor health state, and therefore a predictor for poor outcome. These patients usually have a higher age, vascular disease and use one or more anticoagulant or antithrombotic drugs.

We found that the gut feeling of a gastroenterologist was one of the most powerful predictors for the need of an intervention, which is our view an important observation. The last few years quite a few scores have been developed that predict the outcome of patients with upper GI bleeding. These scores suggest that they improve clinical decision making and reduce unnecessary health care costs[15]. For upper GI bleeding, guidelines recommend using risk stratification tools such as the Blatchford score and the Rockall score[6;16]. However, as is shown in this study, physicians should not rely solely on prediction scores as clinical experience may well add significant information which can not easily be captured in an “objective” score. We indeed were able to show that gut feeling is an independent predictor of the outcome after adjustment for various clinical parameters. This finding is in line with the observed importance of clinical intuition of physicians for the estimation of severity of other diseases. For example, disease activity in patients with ulcerative colitis is measured with the Ulcerative Colitis Disease Activity Index (UCDAI) in which a physician’s global assessment is included[17]. The same is true for rheumatoid arthritis and psoriasis for which physician assessments are included in prediction scores as well[18;19].

Although the RASTA score showed a high predictive power, we found that the decision not to admit a patient based on the RASTA score (at a cut-off of 0 points), would likely result in a readmission rate of 7% of the cases. Similarly, a Blatchford score of 0 in our population, would probably have resulted in a readmission rate of 6%. It is therefore questionable whether these scores can be used to discharge patients with a score of 0 points. On the other hand, when using either of both scores, the *a priori* likelihood of the need of a clinical intervention can be lowered considerably, from 69% to 7%. Furthermore, patients with high scores in both the RASTA score and the Blatchford score almost all required an intervention, which means that gastroenterologists can anticipate on this in determining the urgency of upper endoscopy, i.e, whether patients require upper endoscopy within 24 hours, or should be admitted to a medium or high care unit.

This study has several strengths and limitations. To our knowledge this is the only study that developed a prediction score, based on a cohort in which all patients with a suspected upper GI bleeding were included. Most prediction scores are based on cohorts of patients with confirmed upper GI bleeding. However, the RASTA score can be used in patients presenting to the ER with suspected upper GI bleeding. In our opinion, the previously developed prediction scores can therefore not always be used in daily clinical practice. Second, by incorporating gut feeling of gastroenterologists we speculate that this may increase the specificity of the score and perhaps will increase the willingness of physicians to use this score. Third, we performed a large prospective cohort study in 8 large Dutch hospitals representing with full coverage of the Dutch population. By performing internal validation we adjusted for over-optimism and were able to show that the results of the RASTA score can be extrapolated

On the other hand, our study is limited by the fact that no external validation was performed. Moreover, an impact analysis should have been conducted to assess incorporation of the score in clinical practice and to evaluate whether implementation results in better prediction of the outcome of patients with upper GI bleeding. Furthermore, when comparing the intervention rates in the participating hospitals in our study to those observed in cohorts of the Blatchford study, more patients underwent an intervention in our study. While in the Blatchford score validation studies, intervention rates varied between 40 and 50%[8;20;21] in our study this was 69%. This was mainly due to a high percentage of patients receiving blood transfusions. A likely explanation for this could be a difference in severity of the bleeding for which the patients presented. However, insufficient data for rebleeding and mortality rates, hemoglobin levels and anti-coagulant use were provided in these studies to conclude this. It is therefore not easy to find an explanation for the differences in intervention rates between these and our studies. Based on the recent findings on the prognostic influence of blood transfusion in patients with

GI bleeding, it can suspected however that fewer patients would have received a blood transfusion when the results of this study would have been known earlier[22].

In conclusion, we developed a prediction score, the RASTA score, for predicting the need for a clinical intervention and therefore the need for hospital admission in patients presenting with a suspected upper GI bleeding to the ER. The score showed a high predictive power, comparable to the Blatchford score. This is the first score in which the gut feeling of the gastroenterologist is incorporated and this was found to be highly predictive. Nonetheless, further improvement and validation of this score as well as the Blatchford score is required particularly for the group of patients with low scores as discharging them from the ER without further evaluation carries the risk that they need to be readmitted.

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PART

Summary and Discussion

Chapter 10

Summary / Samenvatting

Part I

Several national and international guidelines have been developed that present recommendations for groups of NSAID and low-dose aspirin users that should receive gastroprotection in order to reduce the risk of upper gastrointestinal (GI) bleeding. These recommendations are based on several publications on risk factors for upper GI bleeding. However, the risk stratification tools incorporated in the guidelines have not been tested for their sensitivity and specificity in predicting upper GI bleeding and the tools are based on consensus recommendations. We therefore developed a novel prediction score for predicting upper GI bleeding in both NSAID and low-dose aspirin users, which is described in **Chapter 2**. By using data from two large anonymized health insurance databases, we defined a development and validation cohort with NSAID and low-dose aspirin users, which were followed-up for the occurrence of upper GI bleeding. In total, 421 cases of upper GI bleeding were identified in the development cohort of 784,263 NSAID users (incidence rate 54.2 per 10,000 person-years), while 1295 cases of upper GI bleeding were identified in 235,531 low-dose aspirin users (incidence rate 37.9 per 10,000 person-years). Both for NSAIDs and low-dose aspirin use risk scores were developed by identifying the five most dominant predictors. The risk of upper GI bleeding increased with a higher risk score in both groups. For NSAID users the score included age, male gender, anemia and concomitant use of low-dose aspirin or anticoagulants. For low-dose aspirin users, age, anemia, diabetes and concomitant use of antiplatelet drugs or anticoagulants were included in the risk score. The predictive power of the scores was only moderate, but sensitivity and specificity were higher compared to scores recommended by international guidelines.

Patients at increased risk for upper GI bleeding should receive gastroprotection to prevent upper GI complications. However, in the era in which PPI costs have decreased dramatically due to generic availability and new combination tablets (i.e. NSAID/low-dose aspirin combined with gastroprotection in one pill) were developed, the cost-effectiveness of this recommendation may have changed. We therefore studied the cost-effectiveness of various gastroprotective strategies in both NSAID and low-dose aspirin users in **Chapter 3 and 4**. As several publications have appeared the last years about suboptimal compliance to gastroprotection, we also included compliance in the models. We performed two cost-utility analyses. Estimates for outcomes and costs were derived from the literature. Primary outcome was incremental cost per quality adjusted life year gained. In the NSAID model we compared eight gastroprotective strategies including NSAIDs, cyclooxygenase (COX)-2 inhibitors, proton pump inhibitors (PPIs), histamine-2 receptor antagonists, misoprostol, and single tablet formulations. NSAID+PPI co-therapy was found to be the most cost-effective strategy in all chronic arthritis patients irrespective of

their risk for GI complications. For patients with increased GI risk, the NSAID/PPI single tablet formulation was also a cost-effective treatment option. In the low-dose aspirin model we found that PPI co-therapy was cost-effective in all patients taking low dose aspirin for primary and secondary prevention of acute coronary syndrome. In secondary prevention, a single tablet formulation of low-dose aspirin and PPI was another cost-effective option in patients with increased risk for upper GI bleeding or in those with moderate to low PPI compliance.

Part II

To assess whether there was need for a prediction score such as the one we developed in chapter 2, we performed a systematic review of literature available. We however found that no prediction scores is currently available for the prediction of upper GI bleeding in NSAID and/or low-dose aspirin users, while we concluded that various prediction scores have been developed for predicting the outcome (i.e. rebleeding, mortality and need for intervention) in patients with GI bleeding. In **Chapter 5** we identified all published prediction scores and appraised them based on their predictive power and methodological quality. Substantial heterogeneity in endpoints and results was seen in the 16 identified prediction scores. Moreover, the methodological quality was suboptimal in most studies. Major shortcomings were found in the lack of validation of the prediction scores. Half of the developed prediction scores were not validated internally or externally. Furthermore, there was no complete impact analysis performed for any of the 16 scores. We suggested that clinicians should use the “best available” scores according to performance and quality.

The recommendation to use these scores was further underlined in the study that we performed in **Chapter 6**. Here we assessed how the clinical intuition (or gut feeling) of experienced gastroenterologists performs in predicting the prognosis of patients with gastrointestinal bleeding. We found that the recommended prediction scores had a higher predictive power than the gut feeling, while combining the two led to an even better prediction of the outcomes.

As the various prediction scores were mostly limited to inclusion of clinical or patient-related factors to predict the outcome of upper GI bleeding, hospital- or procedure-related factors may also play an important role in the outcomes after a bleeding. In the past few years several studies have been performed assessing the influence of day and time of admission on the outcome of patients with upper GI bleeding, but with conflicting results. We therefore studied the effect of weekend admission on the outcome in our prospective cohort of patients referred for suspected upper GI bleeding. Additionally, we assessed the association between time of admission and outcome. In **Chapter 7** we report the results of this large multicenter cohort study, including 1137 patients suspected for upper GI bleeding.

We concluded that patients admitted to the Emergency Unit during the weekend with suspected upper GI bleeding were at increased risk of mortality compared to those admitted during the week. No procedure related factors were associated with an adverse outcome. Evening or nighttime admission was not associated with an adverse outcome compared to daytime, even though time to endoscopy was significantly longer in patients admitted during the evening.

An important predictor for the outcome after upper GI bleeding due to peptic ulcers is the Forrest classification, in which ulcers are categorized based on the presence of endoscopically visible bleeding stigmata. Although this classification was only designed to classify ulcers, it is often used as a prognostic classification. Since the development of the Forrest classification, its prognostic value may have changed over time parallel to changes in the etiology and treatment of peptic ulcers. In **Chapter 8** we found that the Forrest classification was still a good univariate predictor for rebleeding, although the predictive power was higher for gastric ulcers compared to duodenal ulcers. The Forrest classification did not predict mortality. Based on our results, we concluded that the Forrest classification could be simplified, as ulcers with a Forrest Ib to Forrest IIc were comparable in their risk of rebleeding.

In the last chapter (**Chapter 9**) we combined all knowledge that is currently available so far and developed a novel prediction score, the RASTA score, to predict the need for a clinical intervention. This RASTA score included hemoglobin and urea levels and heart rate, which are known predictors for outcome. We also included the gut feeling of experienced gastroenterologists, as was the use of low-dose aspirin and presence of an endovascular prosthesis. It was found that the score performed well and showed an even higher predictive power compared to the Blatchford score.

SAMENVATTING

Deel I

Verschillende nationale en internationale richtlijnen zijn ontwikkeld om te voorspellen welke patiënten met NSAID en/of lage dosis aspirine gebruik, een verhoogd risico hebben op een gastrointestinale bloeding. Op basis van risicostratificatie worden aanbevelingen gedaan met betrekking tot het voorschrijven van gastroprotectieve medicatie. Echter deze risicostratificatie – vaak door middel van een predictie score – is tot nu toe alleen gebaseerd op consensus. Om deze reden ontwikkelden wij een predictie score op basis van patiënten data. Dit wordt beschreven in **Hoofdstuk 2**. We maakten gebruik van twee grote datasets van Nederlandse zorgverzekeraars. In de ene dataset werden de scores ontwikkeld en in de andere dataset werden de ontwikkelde scores gevalideerd. Voor zowel NSAID als lage dosis aspirine gebruikers werd een score ontwikkeld op basis van de 5 meest voorspellende variabelen voor gastrointestinale bloedingen. We zagen dat het risico op een gastrointestinale bloeding toenam, naarmate de score toenam. Voorspellers voor het ontstaan van een bloeding waren voor zowel NSAID als lage dosis aspirine gebruikers respectievelijk leeftijd, anemie en het gelijktijdig gebruik van trombocytenaggregatieremmers en anticoagulantia. Daarnaast vonden we dat bij NSAID gebruikers mannen een hoger risico hadden en bij lage dosis aspirine gebruikers was dit een diagnose van diabetes mellitus. Deze scores presteerden qua sensitiviteit en specificiteit beter dan de richtlijnen, echter de voorspellende waarde was nog steeds laag.

Wanneer patiënten met een verhoogd risico op gastrointestinale bloedingen kunnen worden geïdentificeerd, kunnen preventieve maatregelen zoals het voorschrijven van gastroprotectieve medicatie adequaat genomen worden. De kosten voor gastroprotectie en met name voor proton pomp remmers (PPIs) zijn recent sterk gedaald door generieke beschikbaarheid van deze groep medicijnen. Het zou kunnen zijn dat door deze prijsdaling gastroprotectie niet alleen kosteneffectief is voor mensen met een verhoogd risico op bloedingen, maar ook voor mensen met een normaal risico. Daarnaast zijn er verschillende combinatiepreparaten van NSAIDs/aspirine met gastroprotectie op de markt gekomen, omdat patiënten niet optimaal compliant blijken voor hun gastroprotectieve medicatie. Om te kijken welke strategie we het beste kunnen voorschrijven werden een tweetal kosteneffectiviteitsanalyses verricht, zoals beschreven in **Hoofdstuk 3 en 4**. Voor zowel NSAID en aspirine gebruikers bleek dat bij alle patiënten (dus ook diegene met een normaal risico op bloedingen) het voorschrijven van PPIs kosteneffectief is. Een combinatiepreparaat zoals hierboven beschreven was vanwege de hogere kosten alleen kosteneffectief voor patiënten met een verhoogd risico op bloedingen.

Deel II

Alvorens de predictie score uit hoofdstuk 2 werd ontwikkeld, is gekeken of er niet reeds dergelijke scores bestaan. Een uitgebreid literatuur onderzoek liet zien dat er inderdaad enkele predictie scores bestaan voor de prognose na een bloeding. In **Hoofdstuk 5** werden alle 16 beschikbare scores op een rijtje gezet en met elkaar vergeleken ten aanzien van voorspellende waarde en methodologische kwaliteit. Er werd een aanzienlijke heterogeniteit gevonden tussen de verschillende scores, zowel op gebied van eindpunten als qua resultaten. Daarnaast bleek de methodologische kwaliteit suboptimaal. De voornaamste tekortkomingen van de scores was het gebrek aan validatie. Daarnaast bleek dat onvoldoende gekeken was naar de impact van de scores op de klinische praktijk en de prognose van de patiënten. Gezien het ontbreken van een perfecte score blijft de aanbeveling om de beste huidige scores te gebruiken.

Dat deze scores gebruikt dienen te worden, bleek ook uit onze studie in **Hoofdstuk 6** waarin deze predictie scores werden vergeleken met de klinische intuïtie van maag-, darm- leverartsen. We vonden dat de scores een betere voorspellende waarde hadden dan de klinische intuitie, echter de twee gecombineerd (predictiescores en klinische intuïtie) leidde tot de beste voorspelling van de prognose.

Naast het feit dat patiënt gerelateerde factoren de prognose van een patiënt met een gastrointestinale bloeding kunnen voorspellen (zoals vaak gedaan werd in de predictie scores) kunnen procedure- en ziekenhuis gerelateerde factoren ook de prognose beïnvloeden. Veel onderzoek is de laatste tijd verricht naar het zogenaamde ‘weekend effect’ waarbij het mogelijk zo is dat patiënten die opgenomen worden gedurende het weekend een slechtere prognose hebben dan patiënten die doordeweeks worden opgenomen. De resultaten van deze studies zijn tegenstrijdig. In een groot landelijk prospectief cohort werd dit mogelijke verband bestudeerd en vonden we dat patiënten die in het weekend opgenomen worden inderdaad een significant hoger risico hadden op mortaliteit (**Hoofdstuk 7**).

Vervolgens werd gekeken in welke mate een bijna 40 jaar oude endoscopische classificatie, de Forrest classificatie, nog een goede voorspeller is voor de prognose bij patiënten met een gastrointestinale bloeding als gevolg van een ulcus pepticum. In **Hoofdstuk 8** beschreven we het resultaat van dit onderzoek, en het bleek dat deze classificatie nog een steeds een goede voorspeller is voor het krijgen een recidief bloeding en dan voornamelijk van belang kan zijn bij het classificeren van ulcera in de maag en minder in het duodenum. De classificatie was geen goede voorspeller voor mortaliteit. Tevens bleek dat de classificatie gesimplificeerd kon worden tot 3 categorieën in plaats van 6.

Tenslotte trachtten we in **Hoofdstuk 9** om zowel klinische voorspellers als de klinische intuïtie van de arts te verwerken in een nieuwe predictiescore. Als eindpunt hebben we gekozen om te voorspellen welke patiënten een klinische interventie nodig zullen hebben en daarom dienen te worden opgenomen in een ziekenhuis. Deze RASTA score bleek een goede voorspellende waarde te hebben voor de noodzaak tot interventie, en lijkt zelfs beter vergeleken met de Blatchford score die ook voor dit doel ontwikkeld en gevalideerd is.

Chapter 11

General discussion

Predicting whether a disease will occur or, predicting what the course of the disease will be, enables to anticipate on this situation and sometimes even prevent certain events from happening. In the first part of this thesis we studied several aspects in the prediction and prevention of gastrointestinal (GI) complications in NSAID and low-dose aspirin users and we focused on the prediction of the outcomes in patients with GI complications in the second part of this thesis.

PART I

Predicting upper gastrointestinal bleeding in NSAID and low-dose aspirin users

Many studies have been performed to identify risk factors for upper GI complications in NSAID and low-dose aspirin users. Important predictors are a previous upper GI bleed, a history of (un)complicated peptic ulcer disease, increasing age and concomitant use of antiplatelet drugs, anticoagulants, corticosteroids and SSRIs[1;2]. In order to give physicians a tool to stratify patients into those with a low and a high risk for GI complications, these risk factors should be incorporated in a validated prediction score. We developed such a risk stratification tool. Our tool partly overlaps with the tools proposed by the current guidelines. Yet, the predictors that we incorporated in our prediction scores are somewhat different to those that are often reported. The most important predictor, a history of upper GI bleeding, was not incorporated in our score. This was due to the fact that we excluded patients with upper GI bleeding in the year prior to starting NSAID and/or low-dose aspirin. For these patients preventive strategies have already been recommended by the current guidelines[3;4] and inclusion of these patient groups was therefore decided to be of limited added value. A history of uncomplicated peptic ulcers was however recorded, and although we expected that this predictor would be one of the five most important predictors, this was in fact not the case. This is in contrast with the literature and current guidelines which often classify a previous uncomplicated peptic ulcer as an important predictor[5;6]. An explanation could be that uncomplicated ulcers remain often unnoticed and we therefore found a low incidence of a history of an uncomplicated ulcer in our dataset. On the contrary, anemia was found to be an important predictor, while this is not known from literature. Possibly, these patients with anemia already had blood loss in the upper GI tract, which may well be aggravated by NSAID and/or low-dose aspirin use. Other predictors as dual antiplatelet therapy, anticoagulants and increasing age are known risk factors and these were also identified as such in our cohort. We found that our score

had a higher sensitivity compared to the risk stratification tools recommended in the guidelines. Identification of patients that were at increased risk for upper GI bleeding was only to a moderate extent possible. In part, this could reflect the limitations of our study as we used a health insurance database, with residual confounding and no excess to primary care information. However an alternative explanation could be that predicting upper GI bleeding in such a heterogeneous population is not possible with a high predictive power. For example, patients using NSAIDs are using this drug for various indications, for different time periods and also vary in age and comorbidity status.

Implications of this study are that patients with an increased risk profile should receive gastroprotection and/or physicians should re-evaluate the indication for NSAID and/or low-dose aspirin use. Future research should focus on improving the proposed prediction score or on improving the quality of data for this purpose. Ideally, a comparable study should be performed in a large prospective long-term cohort with both data from primary care, secondary care and pharmacy data. We also suggest that guidelines include a well-validated risk stratification tool, derived from individual patient data, which should perform well in identifying high risk patients.

Prevention of upper GI complications in NSAID and low-dose aspirin users

Several studies have focussed on the cost-effectiveness of different gastroprotective strategies in NSAID and low-dose aspirin users. So far most studies concluded that PPI co-therapy is cost-effective in patients with an increased risk profile for gastrointestinal complications[7-10]. However, due to generic availability the prices of PPIs dropped dramatically the last years. Furthermore several new combination tablets have been developed[11;12]. In our cost-effectiveness analyses we incorporated these changes in the model and we also included compliance of patients for gastroprotective strategies in the model. We found that PPI co-therapy is cost-effective regardless of the risk profile of the patient. Compliance to drug use was found to affect the outcome, which made that use of misoprostol, with a suboptimal compliance, was less cost-effective. The frequently occurring side effects result in a low compliance. The single tablet formulation of NSAID or low-dose aspirin with PPI was found to be cost-effective however in patients with low compliance to PPIs and/or at high risk for complications. Based on these results we suggest that all patients using NSAID or low-dose aspirin should receive PPI co-therapy. This recommendation is also made by the British guidelines (NICE) for patients with osteoarthritis[13]. However, our study is the first to show that these results can be applied to a general population.

PART II

Developed prediction scores for GI bleeding

Several prediction scores for the outcome of upper GI bleeding have been developed in the last decades. However, the most recent guidelines still recommend the Blatchford score and the full Rockall score[3;4]. We concluded that these two scores were indeed of reasonable quality and particularly the Blatchford score performed well. Although much effort has been taken to validate these scores and to develop new prediction scores, the implementation of these scores in clinical practice tends to be low[14;15]. No data are available on how often physicians use prediction scores at this moment or how these scores change their management and improve patient outcome. Besides improving prediction of the outcome of upper GI bleeding, future research should also focus on the implementation of the scores in clinical practice. This can be achieved by studying the effects of implementation on patients' outcome by performing trials comparing with application and non-application of the prediction score on the one hand and by developing and providing tools that are easily able to calculate these scores, such as smartphone applications. Implementation of risk score calculations in quality indicators can also help stimulating their use.

Predictors for the outcome of upper GI bleeding

The different prediction scores are also composed of various predictors. In this thesis we identified new predictors and updated the Forrest classification. We found that patients admitted during the weekend are at a higher risk for an adverse outcome than those admitted during the week. Several other studies also focused on this 'weekend effect'; however, the results remained conflicting. Furthermore, most studies were performed on data from healthcare databases which contained limited information on clinical and endoscopic parameters[16-18]. As explanation we postulated that patients wait longer during the weekend before they present to the hospital and therefore are more likely to be critically ill. We could not detect any procedure-related factor that could have accounted for this effect, but we were not able to adjust for all hospital-related factors such as the availability of experienced gastroenterologists/endoscopists during the weekends. Future studies may aim to look into these hospital-related factors and their possible association with outcomes of patients presenting with upper GI bleeding.

The Forrest classification is a well-known predictor for rebleeding in patients with peptic ulcer bleeding. Although this classification was developed almost 40 years ago and with the purpose to only classify ulcers, this classification is still often used as prognostic indicator[19]. Much has however changed in the etiology and treatment of peptic ulcers and we therefore updated the Forrest classification.

We found that the Forrest classification still has the ability to predict rebleeding, especially in gastric ulcers. The latter may be due to the often better visibility of ulcers in the stomach compared to the duodenum which makes it easier to classify gastric ulcers. That the classification is probably too complicated in clinical practice can be concluded from our results that Forrest Ib and IIc were almost comparable in rebleeding risk. This can be explained by the known low interobserver agreement within the classification[20]. We therefore propose to use a simplified Forrest classification and perhaps the type of endoscopic treatment should be adjusted to this classification.

Gut feeling for predicting the outcome of upper GI bleeding

We further studied whether we anyhow would need a prediction score. Physicians seem often to rely on their own clinical intuition (gut feeling), and it is often thought that the scores do not add to this. However, we found that the prediction scores had a higher predictive power compared to the gut feeling of experienced gastroenterologists. Combining the two led to the best prediction however. This implies that in an emergency situation an inexperienced or non-specialized physician should use the recommended scores to perform risk stratification, but also consult a gastroenterologist to incorporate his gut feeling about the patient in the work-up. This combination of objective predictors with the gut feeling of gastroenterologists was used to develop a novel prediction score. We aimed to predict whether patients would need a clinical intervention and therefore hospital admission. This is to our opinion the most meaningful endpoint, as it will enable discharging a fair part of the patients presenting thereby reducing unnecessary burden to the patients, pressure on hospital wards and healthcare costs. Patients with low scores may be discharged before endoscopic evaluation, or even at the emergency room before being admitted to the hospital. We would like to emphasize that both the Blatchford and our RASTA score need to be validated externally in a large prospective cohort for this specific purpose before we can start using this strategy. Furthermore, future research should focus on implementing the scores in clinical practice, perhaps by performing a randomized controlled trial aiming to evaluate whether use of the scores leads to better outcome of patients and lower healthcare costs. Only when this is done, the RASTA score can be applied in clinical practice.

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PART

Appendices

IV

Technical appendix chapter 4

Input parameters

We performed a structured search using PubMed and Embase databases limiting our results to English language and using combinations of relevant entry terms *(aspirin, proton pump inhibitor, gastrointestinal, acute coronary syndrome, prevention, compliance, adherence, incidence, risk, relative risk, cost-effectiveness)*. Where available, we used meta-analyses or systematic reviews reporting intention-to-treat summary estimates. In order to derive annual transition probabilities, we multiplied placebo risks (on the development of ACS, upper GI bleeding and dyspepsia) by the relative risks of aspirin and, if necessary, PPI. In case placebo risks were unknown, we divided the risk with aspirin monotherapy by the relative risk of aspirin. Utility values of the combined health states for which no data was available (e.g. Post ACS + dyspepsia) were derived by multiplying the separate utilities of the involved health states (**eTable1**).

Model assumptions

1) A patient who develops dyspepsia visited his/her primary care provider and received a four week trial of PPI therapy (omeprazole 20 mg daily). Patients previously treated with PPIs were assumed to be given a dose of 40 mg/day. Should this be ineffective (approximately 45% of patients), the patient is referred to a gastroenterologist. The patient receives diagnostic endoscopy including a *H.pylori* test. *H.Pylori* eradication therapy is given if appropriate, and eradication is confirmed by a breath test. Patients receive another eight weeks of PPI therapy and are assumed to visit their primary care provider a total of three times per year.
2) All patients with persistent dyspepsia receive PPI therapy. Patients who were allocated to *no medication* or *aspirin monotherapy* receive 20 mg PPI daily during the complete cycle, whereas patients who were allocated *aspirin+PPI* or a *single tablet formulation* receive additional PPI (40 mg omeprazole daily in total). All patients are assumed to visit their primary care provider annually.
3) Patients who develop an upper GI bleeding are admitted to the hospital after reporting to the emergency department. Sixty percent of patients need a blood transfusion and all receive endoscopic therapy, intravenous PPI, *H.pylori* testing and *H.pylori* eradication therapy plus breath test confirmation if necessary. A second therapeutic endoscopy is performed in case of therapy failure, followed by percutaneous embolization if therapeutic endoscopy remains unsuccessful. A second look endoscopy is performed in patients with an ulcus ventriculi. The average duration of hospitalization is 10 days. At discharge all patients receive PPI therapy for the remainder of the time horizon: 20 mg omeprazole in case

the patient was allocated to *no medication* or *aspirin monotherapy* and 40 mg omeprazole in case the patients was allocated *aspirin+PPI* or a *single tablet formulation*. Patients allocated to the *single tablet formulation* continue their assigned medication and are prescribed an additional 20 mg PPI (instead of changing to 40 mg PPI concomitant to low-dose aspirin). In case of primary prevention of ACS, low-dose aspirin therapy is interrupted for one year. Patients are assumed to visit the outpatient clinic once in the following year. During the first year, 6.7% of patients experiences a rebleeding.

4) Patients experiencing an ACS report to the emergency department where an ECG is made and cardiac marker levels (including troponin) are determined. We assumed that coronary angiography is performed in 90% of patients, whereas 70% of patients receive an additional percutaneous intervention and 5% of patients require coronary artery bypass grafting surgery. In hospital, all patients receive low-dose aspirin and β-blockers, and some patients receive clopidogrel (60%), ACE-inhibitors (55%), nitroglycerin (70%) and heparin (35%). The average duration of hospitalization is 5 days. At discharge, all patients receive low-dose aspirin. In addition, patients receive β-blockers, statins and ACE-inhibitors for the remainder of the time horizon, whereas 80% also receive clopidogrel for one year. During the first year rehospitalization is necessary in 30% of patients. Patients are assumed to visit the outpatient clinic four times during the first year and once annually thereafter

Appendix Table 1

Derivation of health state utilities

Health state	Percentage of patients	Utility	Duration (days)	Disutility*
Dyspepsia	55%	0,88	28	0.005
	45%	1	337	0
	45%	0.88	365	0.054
				0.059
Dyspepsia persist	100%	0.88	365	0.12
GI bleeding	100%	0.49	31	0.043
	100%	0.98	334	0.019
				0.062
Post GIB	100%	0.98	365	0.02
ACS	100%	0.49	31	0.043
	100%	0.90	334	0.092
				0.135
Post ACS	100%	0.90	365	0.1

† Duration of events were based on assumptions

* Disutility = Percentage · (1-utility) · duration ÷ 365

Appendix Table 2

Health care costs

Activities	Costs (€)	Source
GP consult	28	Health Care Insurance Board
GP home visit	43	Health Care Insurance Board
Accident and emergency department visit	151	Health Care Insurance Board
Day In hospital (normal)	457	Health Care Insurance Board
Day In hospital (IC)	2183	Health Care Insurance Board
Blood transfusion	204,35	Sanquin blood bank
Endoscopy (diagnostics)	397,86	Dutch Healthcare Authority
Endoscopy + intervention	850	Hospital tariff
Surgical/radiological intervention after GIB	1329,47	Dutch Healthcare Authority
H.Pylori diagnostics (biopsy)	3,5	Dutch Healthcare Authority
H.Pylori diagnostics (breathtest)	63,92	Dutch Healthcare Authority
H.Pylori eradication	11,39	Medicijnkosten.nl
ECG	19,02	Dutch Healthcare Authority
Biomarkers (troponin)	8,03	Dutch Healthcare Authority
PCI	4246,32	Dutch Healthcare Authority
CABG	11429	Dutch Healthcare Authority
Angiocardiography	348,6	Dutch Healthcare Authority
Stress test	38,2	Hospital tariff
Outpatient visit	72	Health Care Insurance Board
Trombolysis	209,06	Medicijnkosten.nl

Appendix Table 3

Annual Costs per health state

Health state	Costs* (€)
No complications	37.89
Dyspepsia	356.77
Dyspepsia persist	104.36
GI bleed	6389.11
Post GI bleed	84.39
ACS	8836.95
Post ACS	174.57

* Costs include medication costs. Costs displayed are from the treatment strategy “aspirin monotherapy”

Appendix Table 4

Distributions of the probabilistic sensitivity analyses

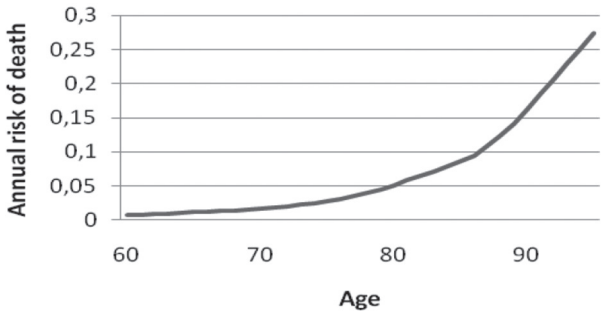
Variable	Base case estimate	Distribution	Input	
Baseline probabilities			**Alpha**	**Beta**
Probability of recurrent dyspepsia	0.62	Beta	897.22	549.91
Probability of recurrent dyspepsia on ASA	0.55	Beta	212.87	174.17
Probability of recurrent dyspepsia in ASA and PPI	0.7	Beta	229.77	98.47
Probability of ACS postACS	0.031	Beta	5.72	178.66
Probability of death after an ACS	0.09	Beta	21.16	214.00
Probability of death after GIB	0.08	Beta	8.97	103.13
Probability of dyspepsia after an ACS	0.25	Beta	17.76	53.27
Probability of dyspepsia on ASA	0.19	Beta	11.04	47.08
Probability of GIB after an ACS	0.015	Beta	7.02	461.07
Probability of GIB postACS	0.007	Beta	15.25	2163.58
Probability of GIB postGIB after an ACS	0.063	Beta	15.81	235.16
Probability of GIB postGIB on ASA	0.048	Beta	9.31	184.74
Relative risks			**Log mean**	**SE**
ASA; dyspepsia	1.09	Log normal	0.09	0.04
ASA; GIB	2.07	Log normal	0.73	0.12
ASA; ACS		Log normal	-0.22	0.10
Primary prevention	0.80			
Secondary prevention	0.78			
PPI; dyspepsia	0.58	Log normal	-0.54	0.18
PPI; GIB	0.32	Log normal	-1.14	0.40
Costs			**Alpha**	**Beta**
Dyspepsia	€ 313.00	Gamma	25	0.08
Dyspepsia persist	€28.00	Gamma	25	0.89
GIB	€6.168.00	Gamma	25	0.004
Post GIB	€ -	Gamma		
Post GIB + dyspepsia	€594.00	Gamma	25	0.04
Post GIB + dyspepsia persist	€28.00	Gamma	25	0.89
Post GIB + ACS	€8.799.00	Gamma	25	0.003
ACS	€8.799.00	Gamma	25	0.003
Dyspepsia persist + ACS	€8.827.00	Gamma	25	0.003
Post GIB + dyspepsia persist + ACS	€8.827.00	Gamma	25	0.003
Post ACS	€137.00	Gamma	25	0.18
Post ACS + dyspepsia	€450.00	Gamma	25	0.06
Post ACS + dyspepsia persist	€165.00	Gamma	25	0.15
Post ACS + GIB	€6.305.00	Gamma	25	0.004
Post ACS + Post GIB	€137.00	Gamma	25	0.18
Post ACS + Post GIB + Dyspepsia	€730.00	Gamma	25	0.03
Post ACS + Post GIB + dyspepsia pers	€165.00		25	0.15

Variable	Base case estimate	Distribution	Input	
Annual utilities			**Alpha**	**Beta**
Dyspepsia	0.94	Beta	55.14	8.98
Dyspepsia persist	0.88	Beta	23.06	1.47
GI bleeding	0.94	Beta	47.12	6.43
Post GIB	0.98	Beta	23.06	1.47
ACS	0.86	Beta	39.10	4.34
Post ACS	0.90	Beta	21.24	0.43

ASA = low-dose aspirin; PPI = Proton Pump Inhibitor; GIB = (upper) Gastrointestinal bleeding; ACS = Acute coronary syndrome; GI = gastrointestinal

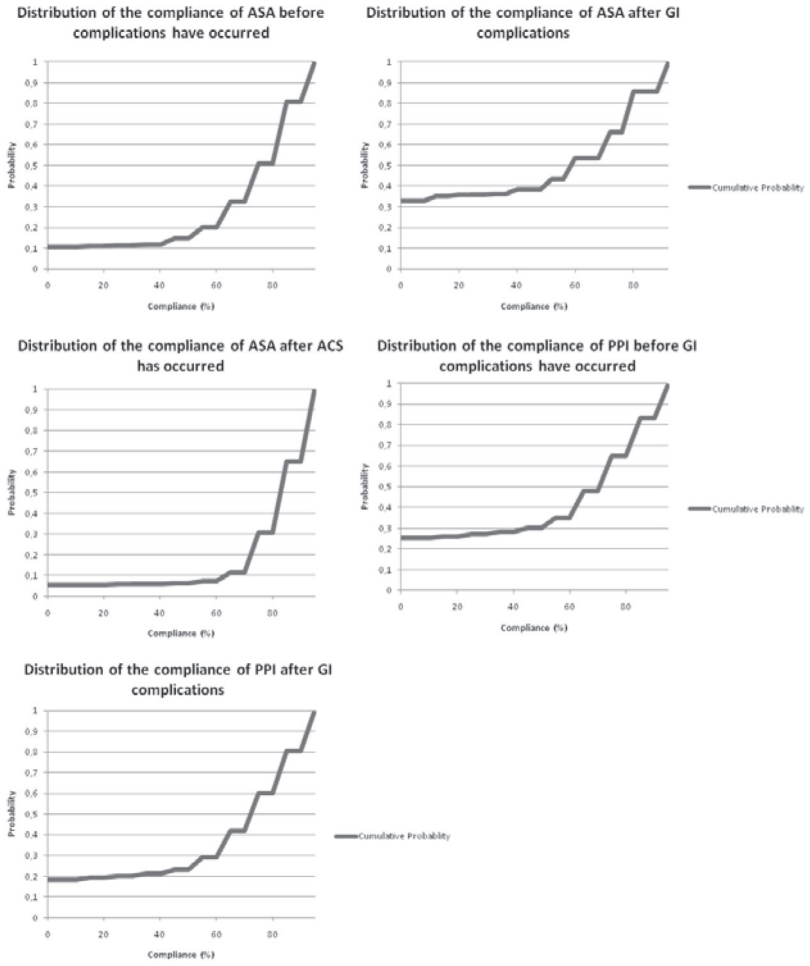
Appendix Figure 1

(Risk of death all causes) by age



Appendix Figure 2

Probability distributions of compliance



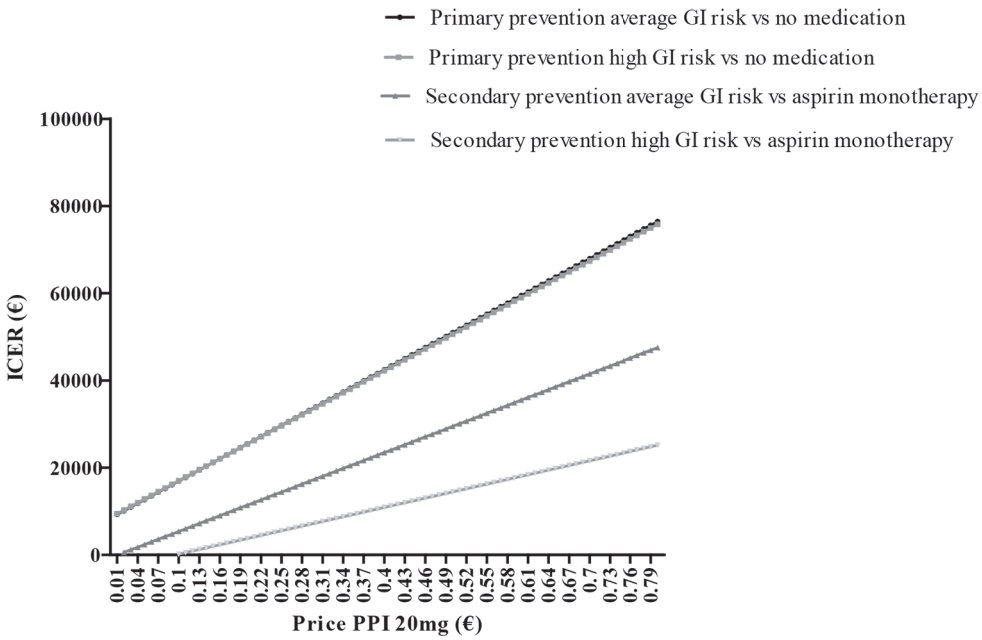
N.B.

The compliance to the single tablet formulation before complications have occurred, was assumed to equal the compliance to aspirin before complications have occurred.

The compliance to the single tablet formulation after ACS or GI complications, was assumed to equal the compliance to aspirin after an ACS.

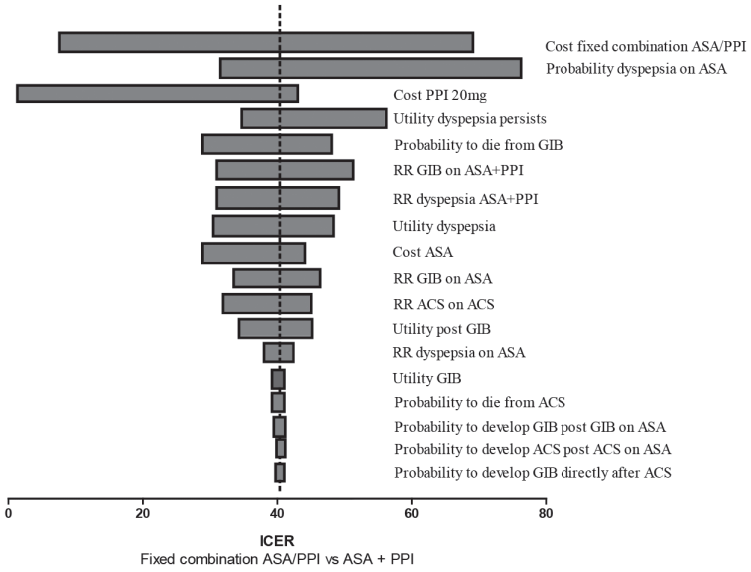
Appendix Figure 3

Cost-effectiveness of PPI co-therapy for a range of PPI prices



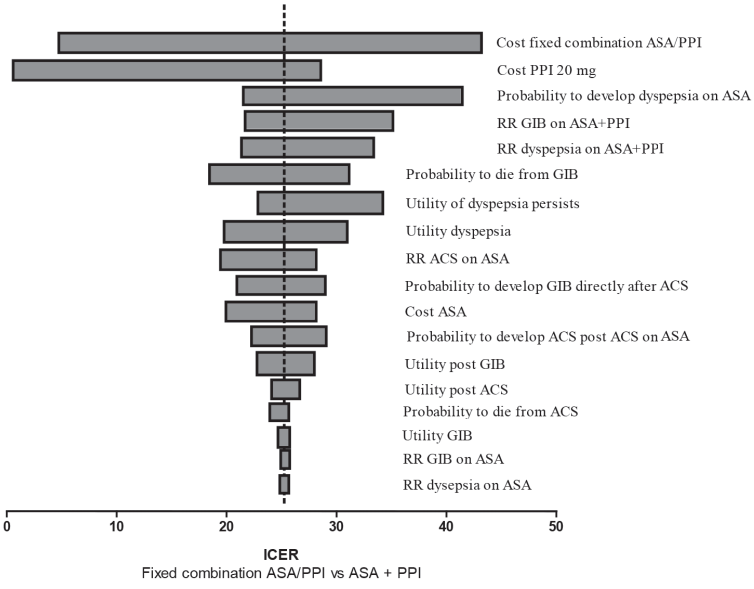
Appendix Figure 4

Tornado diagram of one way sensitivity analyses comparing the fixed combination with ASA+PPI co-therapy for average risk patients using aspirin for primary prevention



Appendix Figure 5

Tornado diagram of one way sensitivity analyses comparing the fixed combination with ASA+PPI co-therapy for average risk patients using aspirin for secondary prevention



PhD Portfolio

OPLEIDING

2011 Cursus Master program Epidemiology
Introduction to Epidemiology
Clinical Epidemiology

2011 Young Investigator Meeting UEGW Stockholm
How to present and write an abstract

WERKERVARING

2010 – heden Promotieonderzoek Universitair Medisch Centrum Utrecht
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Promotor: Prof. Dr. P.D. Siersema
Co-promotor: Dr. M.G.H. van Oijen
PhD; Prediction and prevention of upper gastrointestinal bleeding
Sept 2011 en mei 2012; onderzoeksstages bij UCLA, Los Angeles.
Onderzoeksbeurs ontvangen van AstraZeneca

WETENSCHAPPELIJKE ERVARING

Publicaties

- N.L. de Groot, J.S. Burgerhart, P.C. van de Meeberg, D.R. de Vries, A.J.P.M. Smout, P.D.Siersema. Systematic review: Effect of conservative and surgical treatment of obesity on gastroesophageal reflux. Aliment Pharmacol Ther. 2009 Dec 1;30(11-12):1091-102
- N.L. de Groot, J.H. Bosman, P.D. Siersema, M.G.H. van Oijen. *Prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal.* Endoscopy 2012; 44(8):731-9
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- N.L. de Groot, JH Bosman, PD Siersema, MGH van Oijen, A J Bredenoord, on behalf of the RASTA study group*. Admission time is associated with outcome of upper gastrointestinal bleeding; results of a multicenter prospective cohort study*. Aliment Phramacol Ther 2012;36(5):477-84
- N.L. de Groot, M.G.H. van Oijen, K. Kessels, M. Hemmink, B.L.A.M. Weusten, R. Timmer, W.L. Hazen, N. van Lelyveld, J.R. Vermeijden, W.L. Curvers, L.C. Baak, R. Verburg, J.H. Bosman, L.R.H. de Wijkerslooth, J de Rooij, N.G. Venneman, M. Pennings, K. van Hee, R.C.H. Scheffer, R.L. van Eijk, R. Meiland, P.D. Siersema, A.J. Bredenoord. *Prediction of peptic ulcer rebleeding and mortality using the Forrest classification four decades after its establishment: can it be simplified?* Accepted for publication in Endoscopy
- N.L. de Groot, M.G.H. van Oijen, K. Kessels, M. Hemmink, B.L.A.M. Weusten, R. Timmer, W.L. Hazen, N. van Lelyveld, J.R. Vermeijden, W.L. Curvers, L.C. Baak, R. Verburg, J.H. Bosman, L.R.H. de Wijkerslooth, J de Rooij, N.G. Venneman, M. Pennings, K. van Hee, R.C.H. Scheffer, R.L. van Eijk, R. Meiland, P.D. Siersema, A.J. Bredenoord. *Prediction scores or gastroenterologist's Gut feeling for triaging patients that present with acute upper gastrointestinal bleeding.* Submitted for publication
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Voordrachten

Digestive Disease week 2012, San Diego, USA

'Risk factors for upper gastrointestinal bleeding in short and long term NSAID users'; oral Presentation.

'Gastroprotective strategies in chronic NSAID users: a cost-effectiveness analysis comparing single tablet formulations with individual components'; poster presentation (Nominee Top Poster Prize).

'Time to upper gastrointestinal bleeding in NSAID and low-dose aspirin users; results of a prospective cohort study'; poster presentation

'Adverse cardiovascular outcome after gastrointestinal bleeding; incidence and risk fac tors'; poster presentation.

Voorjaarsvergadering NVGE 2012, Veldhoven, Nederland
'Potential Benefits of Proton Pump Inhibitor Use on Acute Coronary Syndromes: Results of a Decision Analysis'; mondelinge presentatie

United European Gastroenterology Week 2011, Stockholm, Sweden
'Weekend admission is associated with an adverse outcome, irrespective of time of admission and patient-related factors in patients with suspected upper gastrointestinal bleeding'; poster presentation (Nominee Top Poster Prize). 'Gastroprotective strategies in chronic NSAID users: a cost-effectiveness analysis comparing a single tablet formulation with individual component strategies'; poster presentation. 'All low dose aspirin users benefit from gastroprotection; results of a cost-utility analysis of competing strategies'; poster presentatie

Najaarsvergadering NVGE 2011, Veldhoven, Nederland
'Weekend admission is associated with an adverse outcome, irrespective of time of admission and patient-related factors in patients with suspected upper gastrointestinal bleeding'; mondelinge presentatie. 'Gastroprotective strategies in chronic NSAID users: a cost-effectiveness analysis comparing a single tablet formulation with individual component strategies'; mondelinge presentatie.

Digestive Disease week 2011, Chicago, USA
'The quality of prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal'; poster presentation

Voorjaarsvergadering NVGE 2011, Veldhoven, Nederland
'The quality of prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal'; mondelinge presentatie

Dankwoord

Bij het gebruik van richtlijnen – of zoals in dit proefschrift ontwikkelde predictiescores – wordt wel eens in negatieve zin gesproken over ‘kookboek geneeskunde’. Eenieder die wel eens een poging tot koken gedaan heeft, weet echter hoe een kookboek gebruikt wordt: als leidraad of als basis. Tijdens mijn promotie had ik een fantastisch kookboek tot mijn beschikking.

********* Starter / Voorgerecht ***********

“Voorgerecht is de smaakmaker van de maaltijd”

Beste prof. dr. P.D. Siersema, u bent daadwerkelijk de starter van mijn proefschrift. In mijn vierde jaar van mijn geneeskunde studie liep ik, met een licht verhoogde hartslag en wat klamme handjes, voor het eerst uw kamer binnen. Nu, zeven jaar later, zit ik daar nog steeds met enige regelmaat, maar gelukkig heel wat meer ontspannen. U heeft mij door deze jaren heen geënthousiasmeerd, niet alleen voor het vak MDL-arts, maar ook voor de wetenschap an sich. Dit is richtinggevend geweest voor de afgelopen jaren en mijn toekomst. Ik wil u graag bedanken voor de tijd en energie die u in mijn proefschrift heeft gestoken en voor uw kritische blik die mijn werk net dat beetje extra gaf.

********* Hoofdgerecht *********

“Geen maaltijd zonder hoofdgerecht. En voor veel gerechten geldt: maak een grotere hoeveelheid dan je nodig hebt, dan kun je er meerdere keren van genieten”

Dr. M.G.H. van Oijen, beste Martijn, waar de ’Jamie in 30-minuten’ gerechten vaak toch nog bijna een uur duren, heeft jouw ‘Martijn in 2-jaar promoveren’ traject behoorlijk goed stand gehouden. Vanaf het begin heeft jouw enthousiasme aanstekelijk gewerkt op mij. Modellen bouwen bleek leuker dan ik van tevoren had gedacht! Mede dankzij jou heb ik optimaal kunnen genieten van mijn promotietraject: mooie congressen bezocht, leuke praatjes gegeven en buitenlandse tripjes gemaakt naar het zonnige LA. Lastiger werd het toen je de kans aangreep om bij UCLA te gaan werken en zodoende naar Amerika vertrok, maar zelfs via skype/facetime waren onze wekelijkse meetings leuk en leerzaam. Dank dat je mij, nu bijna 3 jaar geleden, zover hebt gekregen om dit proefschrift te gaan schrijven. Ik had het voor geen goud willen missen.

Dr. A.J. Bredenoord, extra veel van het hoofdgerecht heb ik gemaakt dankzij jou Arjan. Nadat ik al van start was gegaan met het eerste deel van mijn proefschrift, kruisten onze wegen en bleek jij een start te hebben gemaakt met een studie die perfect aansloot op mijn onderwerp. En je was gelukkig ook nog op zoek naar iemand om de RASTA-kar te trekken. Wat een fantastische kans! Ik kende jou alleen als 'de arts-assistent in het St Antonius ziekenhuis die al 69 publicaties op zijn naam had staan'. De kans om met jou samen te werken heb ik dan ook met beide handen aangegrepen. Ook al blijft het publiceren van onze stukken nog een klein beetje uit, mijn 'gut feeling' zegt dat we een ontzettend goede database hebben opgebouwd! Bedankt dat ik op jouw rijdende trein mocht springen en daardoor toch wat meer klinische input heb kunnen geven aan mijn proefschrift.

Beste Matthijs, heel wat uurtjes heb ik naast jou gezeten en zitten staren naar de abracadabra die je intypte in het programma SAS. Waar de termen 'data', 'proc' en 'run' in eerste instantie mij helemaal niets zeiden, begon ik het op het laatst toch een beetje te begrijpen. Met een databestand waar serieus mijn computer van ging roken, hebben we toch iets moois en overzichtelijks gemaakt. Zonder jouw hulp en expertise had ik hoofdstuk 2 nooit op papier kunnen krijgen. Bedankt voor je geduld, het bleef namelijk helaas niet bij één keer dat ik de analyses toch wat anders wilde waardoor we weer bij het begin moesten beginnen.

Beste Heleen, het gebeurt denk ik niet vaak dat een 'stagiair' een begeleider zoveel leert zoals jij dat hebt gedaan bij mij. Daar waar ik input vanuit klinisch oogpunt kon geven, maakte jij in een mum van tijd een kosten-effectiviteitsmodel waar mijn hoofd nog steeds van gaat tollen. Ik vond onze samenwerking ontzettend leuk, ik wens je heel veel succes met je eigen promotie, maar daar heb ik alle vertrouwen in.

RASTA team. Ik wil jullie bedanken voor jullie inzet om de RASTA studie tot een goed einde te brengen. Ongetwijfeld werden jullie wel eens moe als ik weer een mailtje stuurde met de vraag of de inclusie nog een beetje liep, maar ik hoop dat we binnenkort de vruchten kunnen gaan plukken van dit mooie cohort. Daarnaast ook dank voor de input en gezelligheid die jullie boden tijdens de RASTA meetings.

Daarnaast wil ik graag alle leden van de beoordelingscommissie, te weten Prof. Dr. A.C.G. Egberts, Prof. Dr. Y. van der Graaf, Prof. Dr. A.I.M. Hoepelman, Prof. Dr. M.M.E. Schneider en Prof. Dr. N.J. de Wit bedanken voor het beoordelen van dit proefschrift.

Tenslotte, Andrea en Els, dank voor de mogelijkheid die jullie mij hebben geboden om deze promotie uit te voeren. Jullie enthousiasme en betrokkenheid was super.

********* Bijgerecht *********

"Zeker in deze Hollandse cultuur doet de aardappel niet onder voor het stukje vlees"

Linda en Ada, dank voor jullie ondersteuning de afgelopen jaren. Maar ook alvast dank voor de aankomende jaren, ik zal ongetwijfeld nog meerdere malen jullie kamer binnenlopen voor het inplannen van afspraken of opleidingszaken. Fijn dat jullie deur altijd open staat.

Alle stafleden en arts-assistenten van het UMCU, dank voor jullie input de afgelopen jaren tijdens de researchmeetings. Daarnaast natuurlijk ook voor de gezelligheid op de borrels en de wintersportuitjes. Ik kijk uit naar de samenwerking aankomende jaren.

********* 'Voor bij de Borrel' *********

"Inspiratie voor het verrichten van onderzoek biedt zich eerder aan onder het genot van een biertje dan achter het bureau op de werkplek"

Lieve onderzoeks-collegaatjes. Dankzij jullie is het hele promotietraject nog zoveel leuker geworden! In het bijzonder de 'eetclub meiden', ik hoop dat we nog heel veel gezellige avondjes hebben met elkaar. Lieve Fiona, toch wel de opper-onderzoeker van onze groep en dan ook nog binnen tien minuten het coecum bereiken de eerste keer dat je een endoscoop in je hand had! Ik heb genoten van je droge humor en scherpe opmerkingen! Mirthe, jouw tomeloze energie, ongelooflijk! De afdeling is heel wat hechter geworden dankzij jouw inspanningen (borrels, wintersport, sinterklaas, promotie-filmpjes). Lieve Meike, de telefoontjes met 'heb even een vraagje' waren altijd een leuke afleiding, hopelijk volgen er nog veel gezellige momentjes nu je ook in de mooiste straat van Utrecht woont! Lieve Romy, een echte levensgenieter ben je, fantastisch! Je haalt echt alles uit het leven, heerlijk om altijd jouw verhalen aan te horen. Daisy, ondanks dat je wat verder weg zat, hebben onze kamerplanten het dankzij jou de afgelopen twee jaar overleefd. En jouw lach, aanstekelijk! Lieve Lot, twee jaar naast elkaar dag in dag uit, ik persoonlijkheidstype A, jij type B, maar eigenlijk een super goede match. Ik vind het super dat we nu samen zo naar onze promotie toewerken! Nog een maand en dan zal ik een super trotse paranimf voor je zijn!

En dan de mannen. Jullie nemen het langzaam over op de afdeling, maar wat heb ik met jullie gelachen. Ik bewaar bijzondere herinneringen aan jullie opmerkingen over mijn 'Zalando-analyses', balletjes overgooien, dumpert filmpjes kijken en de flauwe opmerkingen (waar ik dan als enige om moest lachen). De dagen achter de computer werden zoveel aangenamer door jullie, onwijs bedankt daarvoor!

Collega's van de Interne geneeskunde in het UMC Utrecht, nu alvast dank voor de gezelligheid van de afgelopen maanden en ik kijk uit naar het komende anderhalf jaar!

********* Dessert *********

"Een mooi nagerecht maakt een diner helemaal af. Een goed dessert kan met terugwerkende kracht zelfs de maaltijd upgraden"

Lieve vrienden, dank voor alle leuke en gezellige middagen, avonden en nachten die jullie hebben gebracht. Ontspanning is de helft van de prestatie. Hopelijk schept de Nederlandse samenvatting wat duidelijkheid in wat ik nou eigenlijk de afgelopen drie jaar heb gedaan…! Lieve Sher, Suus en Han, jullie zijn absolute toppers, zo fijn dat ik altijd bij jullie terecht kan. Greetje, ik vind het heel bijzonder dat je mijn paranimf wilt zijn. Samen hebben wij de studie geneeskunde doorlopen en heel even had ik de hoop dat ook jij werd aangestoken door het 'MDL-virus', maar ik denk dat je een super goede keus hebt gemaakt en dat je een fantastische huisarts gaat worden.

Lieve Fred, mijn kleine grote zus. Vroeger misschien af en toe wat haren-getrek tussen ons, nu ben ik super blij met je! Altijd heb je wel even tijd voor wat wijze woorden en zelfs je 'de Groot humor' kan ik waarderen. Samen met Jaap en Mats zijn jullie een heerlijk stel.

Lieve pap en mam, dankzij jullie liefde, steun, vertrouwen en af en toe dat zetje in de goede richting is dit boekje tot stand gekomen. Mam, ik koester onze dagelijkse telefoontjes, ik op de fiets op weg naar huis, jij thuis wachtend op pap. Ze zorgen er altijd voor dat ik de beslommeringen van de dag even kan vergeten. Dank dat je er altijd voor me bent! Pap, ik vind het zo bijzonder dat jij nu, bijna 30 jaar na je eigen promotie, hier achter mij staat als paranimf. Je bent mijn grote voorbeeld.

Lieve Eddy, mijn rots in de branding. Jouw vermogen tot relativeren, je humor en natuurlijk je liefde zorgt ervoor dat elke dag samen een feestje is. Bedankt dat je er altijd voor me bent.

Curriculum Vitae

Nicolette de Groot werd geboren op 28 augustus 1984 in Beverwijk en groeide op in Castricum. Na het voltooien van het VWO in 2002 en het behalen van deelcertificaten voor natuurkunde, scheikunde en wiskunde B op het James Boswell Instituut, is zij in 2003 gestart met de opleiding geneeskunde in Utrecht. Tijdens het 4de, 5de en 6de studiejaar heeft Nicolette zich zowel op klinisch als wetenschappelijk gebied verdiept in de Maag-, Darm- en Leverziekten. Na haar afstuderen heeft zij eerst klinische ervaring opgedaan als arts-assistent Interne geneeskunde in het St Antonius ziekenhuis te Nieuwegein om vervolgens in 2010 te starten met haar promotietraject onder begeleiding van Prof. Dr. P.D. Siersema, Dr. M.G.H. van Oijen en Dr. A.J. Bredenoord. Tijdens haar promotie heeft zij tot tweemaal toe enkele weken onderzoek gedaan aan de University of California Los Angeles (UCLA). In januari 2013 is Nicolette gestart met de opleiding tot Maag-, Darm- en Leverarts.