Novel approaches to upper gastrointestinal conditions: a focus on bleeding and malignancy

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Novel approaches to upper gastrointestinal conditions: a focus on bleeding and malignancy

Nieuwe benadering van bovenste tractus digestivus aandoeningen: een focus op bloeding en maligniteit

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Voor mijn ouders

PART 1

INTRODUCTION

CHAPTER 1.1

GENERAL INTRODUCTION

Gastrointestinal (GI) conditions account for substantial burden and use of healthcare resources. It is estimated that GI conditions are responsible for 15-20% of general practitioner visits, hospital admissions, and drug use. Many of those conditions are related to the upper GI tract, particularly the lower esophagus and stomach. GI endoscopy is the mainstay in diagnosis of these conditions, and plays an important role in the management and treatment of most upper GI symptoms and diseases. In light of the expanding technological abilities, the role of endoscopy will be even more pronounced in the future.[1] This thesis focuses on the prevention and endoscopic management of long-term complications of upper GI conditions, in particular bleeding and premalignant gastric lesions.

The thesis is divided into four parts. The main topics of the thesis are introduced in part I, followed by the aims and outline of the thesis. Part II and III encompass the main body of the thesis. The last part (IV) summarizes and discusses the main findings of the thesis.

CHAPTER 1.2

MANAGEMENT OF ACUTE NONVARICEAL UPPER GASTROINTESTINAL BLEEDING: CURRENT POLICIES AND FUTURE PERSPECTIVES

I. Lisanne Holster, Ernst J. Kuipers

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ABSTRACT

Acute upper gastrointestinal bleeding (UGIB) is a gastroenterological emergency with a mortality of 6–13%. The vast majority of these bleeds are due to peptic ulcers. Non-steroidal anti-inflammatory drugs and *Helicobacter pylori* are the main risk factors for peptic ulcer disease. Endoscopy has become the mainstay for diagnosis and treatment of acute UGIB, and is recommended within 24 h of presentation. Proton pump inhibitor (PPI) administration before endoscopy can downstage the bleeding lesion and reduce the need for endoscopic therapy, but has no effect on rebleeding, mortality and need for surgery. Endoscopic therapy should be undertaken for ulcers with high-risk stigmata, to reduce the risk of rebleeding. This can be done with a variety of modalities. High-dose PPI administration after endoscopy can prevent rebleeding and reduce the need for further intervention and mortality, particularly in patients with high-risk stigmata.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency and has a considerable morbidity and mortality. Management strategies have changed dramatically over recent decades due to the introduction of acid suppressive therapy [histamine-2 receptor antagonists and especially proton pump inhibitors (PPIs)] and endoscopic therapy. This review deals with the current standards and future perspectives in management of acute nonvariceal UGIB.

EPIDEMIOLOGY

The incidence rates of UGIB demonstrate a large geographic variation ranging from 48 to 160 cases per 100 000 population, with consistent reports of higher incidences among men and elderly people.[2-6] Possible explanations for the reported geographic variation in incidence are differences in definition of UGIB in various studies, population characteristics, prevalence of ulcerogenic medication, in particular aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), and *Helicobacter pylori* prevalence. Some but not all time-trend studies have reported a significant decline in incidence of acute UGIB, especially peptic ulcer bleeding, in recent years.[2, 4, 7] This decline is likely due to a combination of factors, including decreasing prevalence of gastric colonization with *H. pylori,*[2] the use of eradication therapy in patients with ulcer disease, and the increased use of PPI therapy, both in general and in patients using aspirin and NSAIDs in particular.

Despite the introduction of therapeutic endoscopy and acid-suppressive therapy, the overall mortality of UGIB has remained stable over recent decades and is still 6–14% in most studies (Table 1).[2, 4-6, 8] The majority of deaths do not directly result from exsanguination, but are related to poorly tolerated blood loss and resultant shock, aspiration, and therapeutic procedures. As such, mortality from UGIB is strongly associated with advanced age and pres-

Table 1. Mortality rates in patients with upper gastrointestinal bleeding in various studies.

	Czernichow[6]	Paspatis[5]	Van Leerdam[4]	Di Fiore[8]	Theocharis[2]	Hearnshaw[11]
Country	France	Greece	The Netherlands	France	Greece	United Kingdom
Year of publication	2000	2000	2003	2005	2008	2010
No. of patients	2133	353	769	453	353	6750
Mortality rate total	14.3%	5.6%	13%	7.2%	6.5%	7.4 %
Varices	22.8%	21.4%	16%	15.2%	9%	15 %
Peptic ulcer	13.3%	2.6%	14%	5%	4.2%	8.7 %

ence of severe comorbidity. The risk of mortality increases with rebleeding, which is thus another major outcome parameter.[6] The incidence of rebleeding in patients with UGIB shows a wide range from 5% to more than 20%, depending on several factors.[4, 5] These firstly include the etiology of the bleeding, with rebleeding being more common in patients with variceal bleeding (25%) and uncommon in patients with small mucosal lesions such as Mallory–Weiss lesions. A second factor that determines the frequency of rebleeding is the timing and use of adequate endoscopic therapy. There is strong evidence that the risk of rebleeding is highest in the initial period of admission, and a 24-h time frame for endoscopic therapy is internationally recommended as the optimal window of opportunity.[9, 10] Mortality amongst those with recurrent bleeding is considerably higher, therefore, rebleeding must be prevented whenever possible.[9]

Peptic ulcer bleeding (PUB) is the most common cause of UGIB, accounting for 31–67% of all cases, followed by erosive disease, variceal bleeding, esophagitis, malignancies and Mallory Weiss tears (Table 2).[2, 4-6, 8, 11] In 2–8% of cases, uncommon causes such as Dieulafoy's lesion, hemobilia, angiodysplasia, vasoenteric fistula, and gastric antral vascular ectasia have been found. In the remainder of this paper, we mainly focus on PUB, yet the approach to and treatment of any patient with nonvariceal UGIB is for the most part comparable. Possible differences will be discussed in the section on endoscopic therapy.

In the subgroup of patients with PUB, bleeding from duodenal ulcers is slightly more frequent than from gastric ulcers.[2, 5] NSAID use and *H. pylori* infection are independent risk factors for UGIB, especially PUB.[9, 12] The prevalence of *H. pylori* infection in PUB patients varies between 43 and 56%,[13-15] and treatment of *H. pylori* significantly reduces the rebleeding rate according to some randomized controlled trials.[16, 17]

Table 2. Causes of upper gastrointestinal bleeding according to recent epidemiological studies.

	%
Peptic ulcer	31-67
Erosive	7-31
Variceal bleeding	4-20
Esophagitis	3-12
Mallory Weiss	4-8
Neoplasm	2-8
Other	2-8
None	3-19

PRE-ENDOSCOPIC MANAGEMENT

Initial resuscitation and risk stratification

Patients with UGIB can present with various symptoms such as hematemesis, hematochezia, melena, or progressive anemia. Immediate evaluation and appropriate resuscitation is of major importance in these patients. Stratification of patients in low- and high-risk categories for rebleeding and mortality can be done using the Blatchford and initial Rockall scores (before endoscopy), or complete Rockall score (after endoscopy) (Table 3).[18, 19] The Blatchford score is more focused on clinical symptoms and laboratory results, whereas the Rockall score considers age as a parameter.

Table 3. Comparison of Blatchford and Rockall risk scoring systems.

Risk factor	Blatchford score		Initial Rockall score	
	Parameter	Score	Parameter	Score
Age (year)	-		60-79	1
			≥80	2
Systolic blood pressure (SBP), mmHg	100-109	1	<100	2
	90-99	2		
	<90	3		
Heart rate, bpm	>100	1	>100 with SBP ≥100	1
Clinical presentation	Melena	1	-	
	Syncope	1		
Comorbidity	Hepatic disease	1	CHF, IHD, major comorbidity	2
	Cardiac failure	1	Renal or liver failure, or disseminated cancer	3
Blood urea, mg/dL (mmol/L)	18.2-22.3 (6.5-7.9)	2	-	
	22.4-27.9 (8-9.9)	3		
	28-69.9 (10-24.9)	4		
	≥70 (≥25)	6		
Hemoglobin, g/dL (mmol/L)	V: 10-11.9 (6.2-7.4) M: 12-12.9 (7.5-8)	1	-	
	M: 10-11.9 (6.2-7.4)	3		
	M/V: <10 (<6.2)	6		
			Complete Rockall score	
Endoscopic diagnosis	-		Non-malignant, non-Mallory-Weiss diagnosis	1
			Upper GI tract malignancy	2
Evidence of bleeding	-		Blood, adherent clot, active bleeding	2

CHF: congestive heart failure, F: female, IHD: ischemic heart disease, GI: gastrointestinal, M: male, SBP: systolic blood pressure.

Resuscitation includes intravenous administration of fluids, and supplemental oxygen, correction of severe coagulopathy, and blood transfusion when needed. The threshold for blood transfusion depends on the underlying condition, rate of bleeding, and vital signs of the patient, but is generally set at a hemoglobin level of ≤ 70 g/l.[20] A recent meta-analysis regarding outcomes following red blood cell transfusion in patients with UGIB, however, suggests that red blood cell transfusion is associated with higher mortality and rebleeding rate. The conclusions of this study were limited by the small size of the studies and the large volume of missing data. In addition, the possibility that patients who present with more severe and active bleeding are more rapidly transfused, acted as a potential major confounder in these analyses.[21] This means that prospective studies need to be done with strict predetermined transfusion protocols, and that for now, the risks and benefits of blood transfusion must be carefully weighed individually.

Pre-endoscopic pharmacotherapy

Administration of PPIs before endoscopy has become common practice in patients suspected with PUB. A strongly acidic environment leads to inhibition of platelet aggregation and plasma coagulation as well as to lysis of already formed clots.[22] PPIs quickly neutralize intraluminal gastric acid, which results in stabilization of blood clots. In the longer term, antisecretory therapy also promotes mucosal healing. A recent systematic review has shown that pre-endoscopic PPI administration significantly reduces high-risk stigmata at index endoscopy (37% *vs*. 46% respectively, OR: 0.67; 95% CI: 0.54–0.84) and need for endoscopic therapy (9% *vs*. 12% respectively, OR: 0.68; 95% CI: 0.50–0.93). However, no effect on clinically important outcome measures such as rebleeding, mortality and need for surgery was seen.[23]

Another pharmacotherapeutic approach includes the use of prokinetics, in particular erythromycin or metoclopramide, before endoscopy. A meta-analysis of five studies assessing a total of 316 patients with acute UGIB has found a significant reduction in the need for repeated endoscopy (OR: 0.55; 95% CI: 0.32–0.94) in the prokinetic treatment group compared to the reference group (placebo or no treatment). The groups did not differ in the need for blood products, hospital stay, and need for surgery.[24] Therefore, prokinetics are not routinely recommended, but can be useful in patients who are suspected of having substantial amounts of blood in the stomach.[10] Administration of PPIs and prokinetics should however not delay endoscopy.

ENDOSCOPY

Time to endoscopy

Endoscopy has become a valuable and indispensable tool for diagnosis and treatment of UGIB.[25, 26] It allows for identification of the bleeding source and application of treatment

in the same session. The optimal timing for endoscopy remains under debate. Emergency endoscopy allows for early hemostasis, but can potentially result in aspiration of blood and oxygen desaturation in insufficiently stabilized patients. In addition, extensive amounts of blood and clots in the stomach can hinder targeted treatment of the bleeding focus, which results in repeated endoscopic procedures. International consensus guidelines recommend early endoscopy within 24 h of presentation, because it significantly reduces the length of hospital stay and improves outcome.[20] Very early endoscopy (< 12 h) has so far not been shown to provide additional benefit in terms of reduction of rebleeding, surgery and mortality, compared with later endoscopy (within 24 h).[27-30] However, emergency endoscopy should be considered in patients with severe bleeding.

Endoscopic therapy for PUB

The aim of therapeutic endoscopy is to stop any ongoing bleeding and prevent rebleeding. Several techniques, including injection therapy, ablative therapy and mechanical therapy have been studied over recent decades.[25, 31, 32] Depending on the appearance of the bleeding focus and the related risk for persistent or recurrent bleeding, a suitable technique should be chosen. In PUB, patients with actively bleeding ulcers or a nonbleeding visible vessel in an ulcer bed are at highest risk of rebleeding and therefore need prompt endoscopic hemostatic therapy (Figures 1 and 2).[33] Patients with low-risk stigmata (a clean-based ulcer or a pigmented spot in an ulcer bed) do not require endoscopic therapy.

The role of endoscopic therapy for ulcers with adherent clots has been a topic of debate.[20] The risk of rebleeding depends on underlying lesions, so that clot removal should be attempted by vigorous irrigation. Stigmata revealed after clot removal are of high risk in about 70% of cases.[34] In a meta-analysis including 240 patients from six different studies, comparing endoscopic versus medical therapy for peptic ulcers with adherent clots, rebleeding was significantly lower in the endoscopic therapy group compared with the control group (8% *vs*. 25%; $P = 0.01$).[35] Another meta-analysis, however, has shown no benefit of endoscopic therapy for bleeding peptic ulcers with adherent clots.[36] These discrepancies could be attributed to inclusion of different studies and heterogeneity in statistical analysis. At present, endoscopic therapy should be considered, although intensive PPI therapy alone might be sufficient in ulcers with adherent clots.[20]

Epinephrine injection therapy promotes initial hemostasis by a combination of vasospasm and local tamponade. This effect declines after 20 min, and requires additional treatment with a more durable technique. In several meta-analyses, no superiority of one specific technique was proven; in particular, hemoclip placement, thermocoagulation (e.g. heater probe), and electrocoagulation (e.g. Gold probe, BICAP probe) all seem equivalent alternatives.[25, 31, 32, 37] Patients with recurrent bleeding can usually be managed by endoscopic therapy. However, emergency surgery or angiographic embolization is required on occasion. There have been no randomized trials that have compared surgery and angiographic embolization.

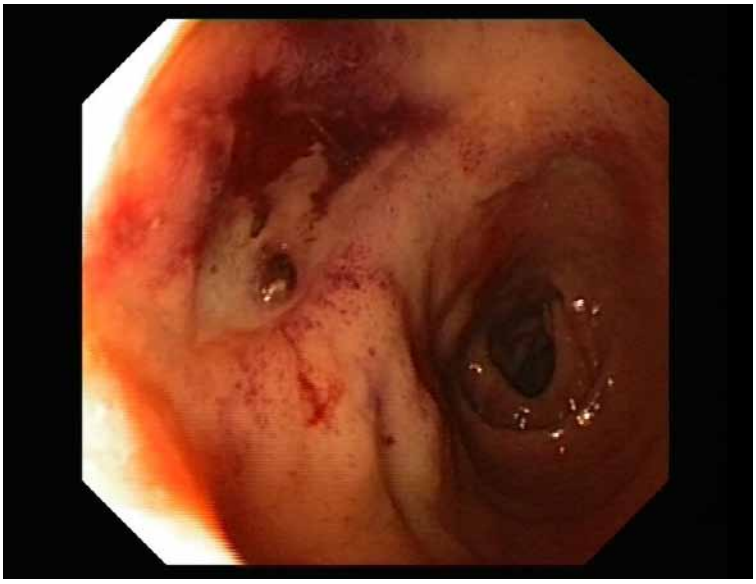

Figure 1. Ulcer with visible vessel.

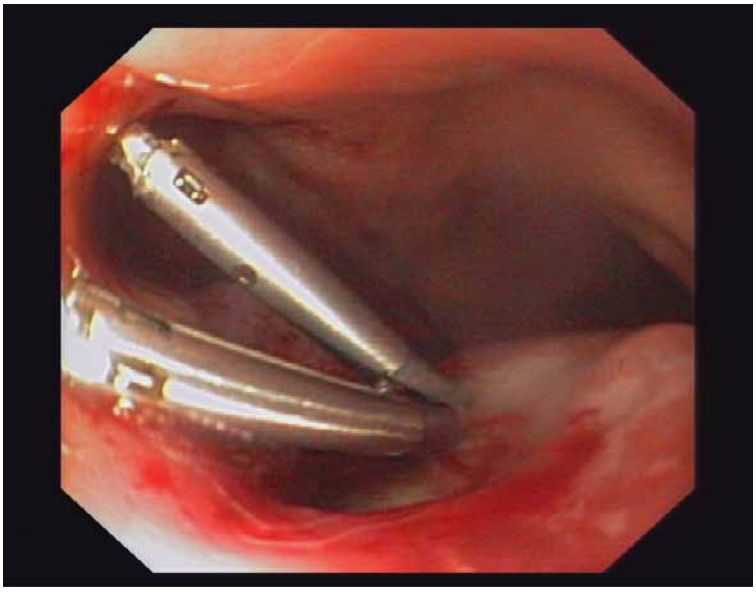

Figure 2. Ulcer with visible vessel after hemoclip placement.

A new promising endoscopic application is the use of a chemical compound which, when sprayed as nanopowder on active bleeding, can lead to immediate hemostasis, with coverage of the bleeding ulcer with a powder layer. In a pilot study of 15 patients with active ulcer bleeding treated with this nanopowder, immediate hemostasis was achieved in 93%, and one patient had recurrent bleeding. No adverse events were reported during the 30-d follow-up.[38] Further studies with this product are ongoing and will elucidate if application is also beneficial for other causes of nonvariceal UGIB.

Endoscopic therapy for other causes of nonvariceal UGIB

Treatment and prevention of (bleeding from) erosions depends upon the cause (e.g. drug-induced, mechanical, or inflammatory). Most cases respond well to PPIs. The offending agent should be discontinued whenever possible and, if present, *H. pylori* should be eradicated. Acute bleeding sometimes needs endoscopic therapy, similar to that for PUB.[39]

Hemorrhage due to neoplastic lesions is often difficult to manage because of the diffuse character of the bleeding and vulnerability of the mucosa. Primary endoscopic therapy is recommended, but additional surgical consultation is sometimes necessary. In cases with diffuse tumor bleeding in a palliative setting, radiotherapy is often the treatment of choice.

Most bleeding from Mallory–Weiss tears stops spontaneously. Patients with stigmata of active bleeding, however, might require interventional endoscopy.[40] Endoscopic therapy is the first choice in bleeding Dieulafoy's lesions and is usually performed with clipping or banding of the lesion.[41]

The current standard for endoscopic treatment of bleeding angiodysplasia consists of coagulation therapy. Sometimes, pharmacological agents such as estrogen and progesterone, octreotide or thalidomide are given, but their effects remain controversial.

Gastric antral vascular ectasia responds best to endoscopic ablation of the lesion.

POSTENDOSCOPIC MANAGEMENT

Antisecretory therapy

Pharmacotherapy plays a second major role in the treatment of UGIB. PPI therapy is superior over histamine-2 receptor antagonists.[20] PPIs can be administered orally or intravenously depending on the rebleeding risk. In a randomized placebo-controlled trial of 767 multiethnic PUB patients treated with endoscopic therapy, because of high-risk stigmata, high-dose intravenous PPI (80 mg esomeprazole bolus, 8 mg/h continuous infusion for 72 h) significantly reduced rebleeding (5.9% *vs*. 10.3%; $P = 0.03$) and the need for endoscopic retreatment.[42] Similar results were found by meta-analysis; high-dose intravenous PPI after endoscopic therapy significantly reduced rebleeding (RR: 0.40; 95% CI: 0.28–0.59), need for surgery (RR: 0.43; 95% CI: 0.24–0.58) and mortality (RR: 0.41; 95% CI: 0.20–0.84) compared with placebo/

no therapy.[36] These data support the guideline recommendation to give high-dose continuous intravenous PPI therapy to patients with PUB with high-risk stigmata.

Additionally, all patients with PUB should be discharged with a prescription for a single-daily-dose oral PPI to reduce the risk of recurrent bleeding. The duration and dose of the PPI depend on the underlying etiology and additional medication use.[20]

H. pylori eradication therapy

Testing for *H. pylori* is recommended in all patients with PUB.[20] This should be followed by eradication therapy for those who are *H. pylori*-positive, with subsequent assessment of the effect of this therapy, and renewed treatment in those in whom eradication fails. The efficacy of eradication therapy and maintenance antisecretory therapy for the prevention of rebleeding has been assessed in a meta-analysis of randomized trials. This revealed a significantly lower risk of rebleeding in the *H. pylori* eradication group, that is, 1.6 *versus* 5.6% within a median follow-up of 12 mo. When only patients with successful *H. pylori* eradication were included, the rebleeding rate was even lower (1%).[15] Therefore, confirmation of eradication is recommended. Diagnostics tests for *H. pylori* have a low negative predictive value in the setting of acute UGIB. This might be due to technical difficulties to collect a sufficient number of representative biopsies, or inaccuracy of the test in a more alkaline environment caused by the blood.[43] Initial negative results on biopsies obtained in the acute setting must therefore be interpreted with caution and repetition of the test during follow-up is recommended.[20]

CONCLUSION

The management of UGIB has changed dramatically over recent decades. Endoscopic therapy and pharmacotherapy have become the mainstay in management. Early endoscopy within 24 h of presentation, or earlier in selected cases with signs of ongoing bleeding, improves outcome and reduces length of hospital stay. Endoscopic epinephrine injection in combination with another endoscopic technique reduces the risk for rebleeding and related mortality in patients with high-risk ulcers. Adequate *H. pylori* eradication and PPI therapy after discharge can bring the rebleeding and mortality rates further down.

Ongoing development is expected especially in the area of development of transfusion policies, and new tools for endoscopic hemostasis. Further studies are needed to clarify the optimal approach for patients with adherent clots. These developments should help to reduce the persistent high mortality rate of UGIB, a disease which nowadays in particular occurs in elderly patients with comorbidity and medication use.

CHAPTER 1.3

UPDATE ON THE ENDOSCOPIC MANAGEMENT OF PEPTIC ULCER BLEEDING

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Current Gastroenterology Reports 2011;13:525-31

ABSTRACT

Upper gastrointestinal bleeding is the most common gastrointestinal emergency, with peptic ulcer as most common cause. Appropriate resuscitation followed by early endoscopy for diagnosis and treatment are of major importance in these patients. Endoscopy is recommended within 24 hours of presentation. Endoscopic therapy is indicated for patients with high-risk stigmata, in particular those with active bleeding and visible vessels. The role of endoscopic therapy for ulcers with adherent clots remains to be elucidated. Ablative or mechanical therapies are superior to epinephrine injection alone in terms of prevention of rebleeding. The application of an ulcer-covering hemospray is a new promising tool. High dose proton pump inhibitors should be administered intravenously for 72 hours after endoscopy in high-risk patients. *Helicobacter pylori* should be tested for in all patients with peptic ulcer bleeding and eradicated if positive. These recommendations have been captured in a recent international guideline.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is the most common gastrointestinal emergency, with peptic ulcer bleeding (PUB) responsible for 31 to 67% of all cases, followed by erosive disease (7 to 31%) and variceal bleeding (4 to 20%). Less frequent causes are esophagitis, Mallory Weiss tears and neoplasm.[2, 4-6, 8, 11] Peptic ulcer bleeding is associated with considerable morbidity and mortality, which in various series range between 5 and 13%.[6] The risk of mortality strongly depends on age, the presence of comorbidity, the severity of the bleed, and the occurrence of rebleeding.[5] Comorbidity as risk determinant explains why in-patients with a bleeding episode have higher mortality rates than out-patients presenting at the emergency unit. Endoscopy and pharmacotherapy have become the mainstay in the management of PUB. Endoscopy allows both identification of the bleeding focus, classification of the risk of rebleeding, and application of treatment in the same session, whereas pharmacotherapy in particular aims at clot stabilization and ulcer healing by profound acid suppression. This review provides an update on the endoscopic management of peptic ulcer bleeding.

RISK ASSESMENT AND PRE-ENDOSCOPIC MANAGEMENT

Pre-endoscopic resuscitation

Immediate evaluation and initiation of appropriate resuscitation by means of administration of iv fluids, oxygen, and blood transfusion when needed are of major importance in patients presenting with UGIB. Red blood cell transfusions are, depending on the underlying condition and clinical presentation generally administered once the hemoglobin level drops below 70 g/l, but the impact of transfusion on rebleeding and mortality is unknown. In a Cochrane meta-analysis the effects of red blood cell transfusions in adults with UGIB were assessed.[44] A total of three randomized or quasi-randomized trials comparing red blood cell transfusion and standard care without red blood cell transfusion included 126 patients. Red blood cell transfusion was in these studies associated with more deaths (5% vs. 0%; 2 studies) and more rebleeds (38% vs. 4%; 1 study). However, the included trials were heterogeneous in treatment regimens and outcome parameters and had several methodological deficiencies, which implied that the results of the meta-analysis can only be used as a stimulus for further studies, but not for firm clinical guidelines. In a large recent UK study, data on 4441 patients with acute UGIB were collected. Patients who received transfusion within 12 hours of presentation had a two-fold increased rate of rebleeding (OR 2.26; 95% CI 1.76-2.90) and a 28% increase in mortality (OR 1.28; 95% CI 0.94-1.74) compared to those not early transfused. These results persisted after correction for the severity of the bleed using Rockall scores and hemoglobin concentrations at presentation, the results may have been biased by persistent differences in case mix between early transfused and non-transfused patients.[45] Prospective

studies with a strict defined transfusion protocol are needed. In the meantime, the risks and benefits of red blood cell transfusion must be carefully weighted individually.

Pharmacotherapy prior to endoscopy

Intravenous administration of high dose proton pump inhibitors (PPIs) prior to endoscopy neutralizes pH and leads to stabilization of blood clots. Investigators from Hong Kong studied the effect of preemptive infusion of omeprazole administered as an 80-mg intravenous bolus followed by an 8-mg infusion per hour before endoscopy in 638 patients with UGIB. They found a significant reduction in the need for endoscopic therapy (19% vs. 28%, p=0.007) with fewer active bleeds during endoscopy (6% vs. 15%, p=0.01) and more ulcers with clean base (64% vs. 47%, p=0.001) in the omeprazole-treated patients.[46] No effect was found on other major outcome parameters as the need for transfusion, rebleeding, and mortality. Therefore, international guidelines remark that pre-endoscopic PPI therapy may be considered to downstage the bleeding site and decrease the need for endoscopic intervention, but that this should not delay endoscopy.[20]

Risk assessment

Early risk assessment is crucial to determine the optimal timing of endoscopy, to define patients at highest risk of rebleeding, and to predict the need for other measures as administration of iv fluids, blood transfusion, and intensive care admission. For this purpose, several risk classification systems have been developed. Two frequently used scoring systems are the Blatchford score and the Rockall score.[16, 19] The latter contains a pre-endoscopic part, as well as a post-endoscopic component including the results of endoscopy. Both the Blatchford and Rockall scoring systems consider vital signs at presentation and comorbidity. The Blatchford score is more focused on symptoms (melena and/or syncope) and laboratory results (hemoglobin and urea) compared to the Rockall score, but does not consider age. A recent prospective cohort study comparing the validity and usefulness of these scoring systems concluded that the Blatchford score, but not the pre-endoscopic Rockall score, is useful for predicting low-risk patients who do not need therapeutic endoscopy and who may be suitable for outpatient management.[17] Disappointingly, the positive predictive value of both scores for the need for endoscopic intervention was low. This supports initiatives to adapt existing scoring systems or develop new, aiming for more precise risk stratification.

Time to endoscopy

International consensus guidelines recommend early endoscopy within 24 hours of presentation for patients with acute upper gastrointestinal bleeding.[20] Data from a nationwide UK survey of 6750 patients seen in 208 hospitals with UGIB show that this recommendation is not widely followed. Of patients deemed at high risk, only 55% received endoscopy within

24 hours.[11] A main reason for delayed endoscopy was the absence in half of the hospitals of a formal out of hours endoscopy rota or service with a consultant available on call.

Early endoscopy is safe and effective for all risk groups, allows timely diagnosis and treatment, reduces use of resources and length of hospital stay, and decreases the need for surgery.[20] So far, no additional benefit from very early or urgent (<12 h) endoscopy was found compared with early endoscopy (<24 h) with respect to rebleeding, surgery, or mortality.[27, 29] However, emergency endoscopy should be performed as soon as possible after hemodynamic stabilization in selective patients who are hemodynamically unstable or have massive hematemeses.

ENDOSCOPIC THERAPY

Endoscopic features and the need for therapy

The endoscopic appearance of peptic ulcers provides important prognostic information and can divide ulcers in those with high versus low risk of rebleeding. Ulcers with signs of active spurting (Figure 1) or oozing hemorrhage (resp. Forrest Ia and Ib) and ulcers with a visible vessel (Forrest IIa) are at high risk of recurrent bleeding with medical therapy alone. In contrast, ulcers with a clean base or flat spot in the ulcer bed (resp. Forrest III and IIc) do only rebleed in 4 to 13% of cases.[33] Ulcers with adherent clots have an intermediate risk of rebleeding (about 25%), depending on the underlying lesion. For that reason, clot removal should be attempted by vigorous irrigation.

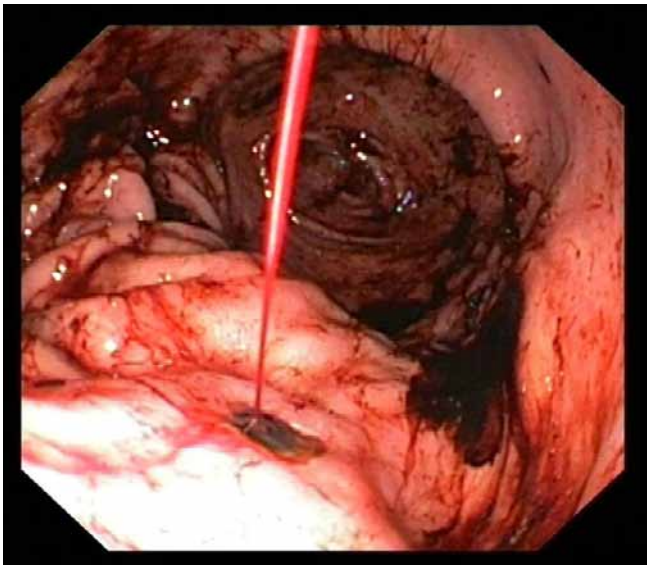

Figure 1. Forrest Ia ulcer bleeding in a small gastric ulcer.

Endoscopic hemostatic therapy is indicated for patients with high risk ulcers, while patients with low-risk stigmata can be treated with pharmacotherapy alone. The optimal management of bleeding peptic ulcers with adherent clot remains controversial. Two meta-analyses have addressed this issue. The first included six studies involving 240 patients from the United States, Southeast Asia, and Europe and found a significantly lower risk of rebleeding in the patients who underwent endoscopic therapy compared with the medical therapy group (8 vs. 25%, p=0.01). The interventions yielded similar results with respect to the need for surgery, transfusion requirement, length of hospital stay and mortality.[35] The validity of this meta-analysis was however questioned since studies with heterogeneous designs were combined and most studies used suboptimal PPI dosage in the control group.[47] A more recent meta-analysis, including 5 trials, comprising 189 patients, found no significant benefit of endoscopic therapy in patients with ulcers with adherent clots.[36] So far, endoscopic therapy should be considered, although intensive PPI therapy may be sufficient among patients with adherent clots resistant to vigorous irrigation.

Injection therapy

Injection therapy with epinephrine is widely used for the treatment of PUB, because it is inexpensive, easy to administer, and effective. Acute hemostasis is achieved by local tamponade, vasospasm, and induction of thrombosis. These effects resolve after about 20 min and it is therefore recommended to combine injection therapy with a more durable endoscopic technique.[20]

Other substances used in addition to or as alternative to epinephrine are sclerosants (e.g. polidocanol, ethanolamine, and ethanol), fibrin sealant, and on some occasions N-butyl cyanoacrylate. However, the use of sclerosants for the treatment of PUB is nowadays limited, because they can cause serious local side-effects and in addition to epinephrine confer minimal additional benefit.[48] Fibrin sealant or glue is a relatively new agent for the treatment of PUB. It was shown to be more effective in preventing rebleeding than injection with polidocanol, but only if repeatedly injected.[49] Also for that reason it is not generally used in clinical practice. N-butyl cyanoacrylate is in particular used for gastric variceal bleeds, but is on rare occasions also applied to bleeding peptic ulcers with massive bleeds as a last resort, with the risk of arterial embolization.[50]

Ablative and mechanical therapies

Several meta-analyses compared the effects of mechanical therapies (e.g. hemoclip placement), ablative therapy (e.g. heater probe and Gold probe), and injection therapy (e.g. epinephrine, fibrin glue, and sclerosants) for hemostasis and prevention of rebleeding in peptic ulcer bleeding (Table 1).[25, 31, 32, 36, 37] This yielded two important messages. The first is that although epinephrine injection is more effective than acid suppressive therapy alone in patients with high risk stigmata, epinephrine monotherapy is inferior to other monothera-

Table 1. Recent meta-analyses comparing endoscopic techniques for treatment of peptic ulcer bleeding.

Author, year	No. trials included	No. patients included	Compared techniques	Conclusion
Marmo, 2007	20	2472	Epinephrine injection + other injection or thermal or mechanical method vs. monotherapy with one of these methods	Dual endoscopic therapy is superior to epinephrine injection alone, but not to thermal or mechanical monotherapy.
Sung, 2007	15	1156	Hemoclips vs. injection/ thermocoagulation	Hemoclip placement is superior to injection alone but comparable to thermocoagulation.
Yuan, 2008	12	699	Hemoclips vs. other endoscopic techniques	Hemoclip placement is not superior to other endoscopic modalities.
Laine, 2009	65	6237	Thermal devices, sclerosants, hemoclips, fibrin glue and epinephrine	Thermal devices, sclerosants, clips and fibrin glue are comparable. Epinephrine monotherapy is inferior to other interventions.
Barkun, 2009	41	4261	Pharmacotherapy, injection, thermocoagulation, clips or combinations	All endoscopic therapies are superior to pharmacotherapy alone. Thermal therapy or clips alone or in combination with injection are comparable.

pies as well as to combination therapy.[25, 31, 36, 37] This means that epinephrine should no longer be applied as monotherapy, but only in combination with other methods. The second major message from the meta-analyses was that none of the ablative or mechanical therapies was superior over the others.

Dual therapy (i.e. epinephrine injection plus other injection or thermal or mechanical method) proved significantly superior to epinephrine injection alone, but had no advantage over thermal or mechanical monotherapy.[37]

In specific situations, e.g. difficult-to-approach or indirectly visualized bleeding sites, heater probe therapy can be superior to hemoclip placement.[51]

Hemospray

A potentially very important new development is the introduction of a hemospray, which can be directly applied via a catheter through the working channel. This nanopowder with clotting abilities has been shown to be highly effective for achieving hemostasis of arterial bleeding in a heparinized animal model. When sprayed on a bleeding site, the powder becomes cohesive and adhesive, and forms a stable mechanical barrier, covering the bleeding site. In a very recent prospective pilot study on 20 adults with confirmed PUB (Forrest Ia or Ib), acute hemostasis was achieved in 95%. Rebleeding occurred in two patients (shown by hemoglobin drop), but no active bleeding was seen during repeat endoscopy in these patients.

No mortality or adverse events were reported during 30-day follow-up.[52] Further studies on the effectiveness of hemospray, also for other causes of UGIB, are ongoing.

Second look endoscopy

Few data support the overall benefit of a routine repeat endoscopy after endoscopic hemostasis. Those studies which did report a benefit from routine second look were in part of older date and did not include the use of PPIs or modern endoscopic hemostatic techniques. Therefore second look endoscopy is not routinely recommended, however it may be beneficial in selected patients at high risk of rebleeding.[18, 20, 24]

POST-ENDOSCOPIC MANAGEMENT

Surgery or angiographic embolization

Although endoscopic therapy is highly effective, sometimes bleeding cannot be stopped or recurs. In case of recurrent bleeding a second attempt at endoscopic treatment is generally recommended.[20] With persistent or renewed bleeding, emergency surgery and selective transcatheter arterial embolization (TAE) of the bleeding artery are rescue modalities.

In a retrospective analysis of 70 cases with refractory PUB, no differences were found between patients treated with TAE versus surgery in the incidence of recurrent bleeding (29% vs. 23.1%), need for additional intervention (16.1% vs. 30.8%), or death (25.8% vs. 20.5). The lack of difference and the fact that the patients in the TAE group were older (75 year vs. 63 year, $p<0.001$) and had more comorbidity, suggests a slight advantage of TAE.[21] There is a pressing need for randomized controlled trials to prospectively compare these two techniques.

Acid suppressive therapy

High dose intravenously administered PPI therapy (80mg bolus, followed by 8mg/hr continuous infusion for 72 h) is recommended to reduce rebleeding in PUB patients with high-risk stigmata at endoscopy. This guideline recommendation is supported by a meta-analysis in which high dose iv PPI therapy significantly improved outcome compared with placebo/no therapy (RR 0.40; 95% CI 0.28-0.59, NNT 12; 95% CI 10-18).[36] In Asian patients, this beneficial effect has been achieved with different PPIs.[53] In Caucasian patients with their on average higher acid output, a significant effect on major outcome parameters such as rebleeding has only been achieved with high-dose continuous esomeprazole infusion.[42] Patients at low risk can be fed within 24 hours and early discharged with oral PPI therapy.

Further measures

In all patients, oral treatment with a PPI is generally recommended for 4 weeks, as this is sufficient to heal nearly all ulcers and address the underlying cause of the bleeding ulcer. *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) are the main risk factors for the development of peptic ulcer disease. Therefore, every patient with a PUB should be tested for *H. pylori* and receive eradication therapy if applicable. Invasive tests obtained in the acute setting may yield false-negative results and should thus be repeated in case they give no evidence of *H. pylori* infection.[20] One month after antimicrobial therapy, patients should be reassessed for successful eradication, as persistent *H. pylori* infection is associated with a more than 50% risk of recurrent ulcer disease within two years, and thus with a significant risk for recurrent ulcer complications including bleeding.[15]

Patients who develop PUB while on NSAID therapy, should be considered for permanent withdrawal of such therapy. If this is not feasible, they should preferentially switch to the combination of a selective COX2-inhibitor together with PPI gastroprotection since a COX2-inhibitor alone, as well as a conventional NSAID with a PPI are both associated with a persistent rebleeding risk.[20, 54] The need for adequate adherence to the gastroprotective PPIs should be stressed, as various studies have now shown that even moderate lack of adherence significantly increases the risk of events.[55, 56]

In patients who develop ulcer bleeding while on low dose aspirin, the need for this therapy should also be reassessed. In many, low dose aspirin is given for secondary prevention of cardiovascular disease. In these patients, continuation of antiplatelet treatment during the bleeding episode may increase rebleeding, but reduces all-cause mortality rates. This was concluded by a recent RCT including 156 low-dose aspirin users for secondary cardiovascular prophylaxis. These patients were after endoscopic treatment for PUB randomly assigned to either continue aspirin or receive placebo, both in combination with 72 hours high dose iv PPI followed by an oral PPI for 8 weeks. The 30-day rebleeding rate was not significantly higher in the aspirin than in the placebo group (10.3 vs. 5.4%; Δ 4.9%, 95% CI -3.6-13.4), but the all-cause mortality (1.3% vs. 12.9%; Δ 11.6 %, 95% CI 3.7-19.5%) and the mortality rates attributable to cardiovascular, cerebrovascular, or gastrointestinal complications (1.3% vs. 10.3%; Δ 9%, 95% CI 1.7-16.3%) were significantly lower in the aspirin group.[57] Till now, no prospective studies have been performed to study shorter intervals of discontinuation of aspirin. The optimal period of discontinuation is thus not yet defined. For now, guidelines recommend to restart aspirin 3 to 5 days after endoscopic therapy, provided that the patients hemodynamic condition is stable.[18]

Patients with idiopathic ulcer disease, i.e. those in whom adequate assessment does not reveal an underlying cause, should also be treated with PPI maintenance therapy as they are at considerable risk for recurrent ulcer formation and bleeding.[58]

FUTURE RESEARCH

In the past two decades, major developments took place in the management of peptic ulcer bleeding. Proton pump inhibitors were introduced, *Helicobacter pylori* was recognized as an important risk factor for the development of peptic ulcers and endoscopic therapy had become the main therapy for the majority of patients with peptic ulcer bleeding. Despite these valuable new discoveries, PUB incidence remained stable an probably will even rise in the near future due to aging of the population accompanied by increasing use of medication and comorbid illness.

Therefore, there is a pressing need for studies to elucidate the optimal time to endoscopy, the optimal approach to patients with adherent clots, the most effective endoscopic techniques, and the best alternative for patients refractory to endoscopic therapy. In addition, development of an appropriate risk stratification scorings system and safe transfusion policy will be important topics for future research.

CONCLUSION

Peptic ulcer bleeding is the most frequent emergency condition in gastroenterology practice. It is associated with significant morbidity and mortality. Endoscopy is the mainstay in the modern management of PUB. Ideally endoscopy should be performed within 24 hours of presentation. Combination therapy of epinephrine injection plus another hemostatic technique or the use of another hemostatic technique alone is more effective than epinephrine alone. Hemospray is a new promising endoscopic therapy. Patients with high-risk stigmata should receive continuous iv PPI administration for 72 hours after endoscopy. After the acute phase, the underlying cause of the ulcer should be verified and treated when possible.

CHAPTER 1.4

PEPTIC ULCER BLEEDING: ENDOSCOPIC DIAGNOSIS, ENDOSCOPIC THERAPY AND PHARMACOTHERAPY

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INTRODUCTION

Endoscopy is the mainstay for diagnosis and treatment of upper gastrointestinal bleeding, the most common gastrointestinal emergency. The importance of endoscopy is fourfold. It firstly allows identification of the bleeding focus. It secondly supports assessment of the underlying cause such as *Helicobacter pylori* infection or a malignancy. It then allows application of treatment, and finally determines the risk of recurrence and mortality, and thus allows dedicated use of resources. These aspects firstly require uniform nomenclature using a few definitions. A peptic ulcer is a mucosal defect in stomach or proximal duodenum with a minimal diameter of 0.5 cm and appreciable depth, mostly defined as penetrating the muscularis mucosae. Lesions of smaller size are defined as erosions. Ulcers are subclassified according to location and endoscopic appearance. Gastric ulcers are mainly located along the smaller curvature, including the angulus, and in the antrum. Ulcers above the transitional zone between corpus and antrum are called proximal ulcers, those at the angulus and below the transitional zone distal ulcers. Duodenal ulcers are mostly located in the bulbus either on the anterior or posterior wall, occasionally at both sites ("kissing" ulcers). As the transitional zone between antral and duodenal type mucosa often lies at the antral side of the pylorus, pyloric ulcers can be considered proximal duodenal ulcers. Postbulbar ulcers are located distal to the duodenal bulb. After a distal gastric resection (Billroth I or II procedure), ulceration may occur at the gastroduodenal anastomosis (anastomotic ulcer), or after a Billroth II reconstruction in the jejunal mucosa at the junction between the afferent and efferent loops (ulcus jejuni pepticum). Peptic ulcers may also develop in metaplastic or heterotopic gastric mucosa, such as in a Meckel's diverticulum, or the rectum. Gastric ulceration can also occur in a large hiatus hernia, usually at the level of the herniation. These ulcers are known as Cameron's ulcers. Dieulafoy ulcers are small mucosal defects over an intramural arteriole. Two thirds of these lesions are found in the stomach, but they can occur in the complete gastrointestinal tract.

Most peptic ulcers develop against a background of chronic mucosal inflammation. Depending on the location, this inflammation is termed gastritis, duodenitis, or bulbitis. With the current high resolution endoscopy equipment, this inflammation can often be recognized by signs of edema, reddening, and swelling of the mucosa. In patients with peptic ulcer disease, the inflammation should be confirmed histologically as this may provide further clues into the etiology of the ulcer, in particular by demonstration of *Helicobacter pylori*.

ENDOSCOPY TIMING AND PREPARATION

Timing of endoscopy

The position of endoscopy in the management of patients with gastrointestinal disorders has changed dramatically over the past 25 years. One of the first areas in which this change

became apparent was upper gastrointestinal bleeding (UGIB). In the 1980s, it was still argued that there was no role for routine endoscopy in patients with upper GI bleeding.[26, 59] It took another ten years to establish that role by showing that endoscopic hemostasis was feasible and could reduce the risk of recurrent bleeding, shorten hospital stay, reduce the need for surgery, and reduce mortality.[60] This was subsequently supported by a large amount of studies, in particular showing that endoscopic hemostasis improves outcome of high-risk cases.[25] The overall magnitude of effect in terms of reduction of rebleeding can amount to above 75%.

These observations led to the search for the optimal timing for endoscopy in patients with UGIB. It was considered that early endoscopy allowed for early hemostasis, but also potentially could lead to complications such as oxygen desaturation and aspiration in insufficiently stabilized patients. Furthermore, the presence of large amounts of blood in stomach and duodenum can hamper adequate endoscopy and require the need for repeat endoscopy. These arguments fed the debate on optimal timing of endoscopy, against a further background that many endoscopy units could not provide 7x24 hour service and thus could not guarantee early endoscopy. In addition, introduction of continuous profound acid suppressive therapy made clinicians falsely confident to delay endoscopy. The need for initial resuscitation or other measures, such as correction of INR in patients using anticoagulants, was often presented as another reason to delay endoscopy. These issues have been adequately settled by further studies which showed that endoscopy within 24 hours of presentation can reduce the need for transfusion and surgery, as well as the length of hospital stay without any major increase in endoscopy-related complications (Table 1).[61, 62] These effects were obtained in the era of profound acid suppressive therapy, and established the position of endoscopy as first-line modality not only for the diagnosis, but also for the treatment of acute upper GI bleeding. This led international guidelines to recommend endoscopy within 24 hours of first presentation in most patients with upper gastrointestinal bleeding, and that initial resuscitation and the need for INR correction should not lengthen this time window.[10 20, 63, 64] The only exception pertains to the minority of patients with very low risk for rebleeding and need for intervention, such as for instance assessed by means of the Blatchford score. The 24-hour time frame, as the most optimal window of opportunity, was further supported by the observation that the risk of rebleeding is the highest in the initial period of admission. This is relevant, as severe and persistent bleeding, as well as rebleeding are all associated with poor outcome. The time-related incidence of rebleeding was illustrated by a large multicenter international trial in which 76 patients with high-risk peptic ulcer bleeding were followed for 30 days after endoscopic hemostasis. A rebleed occurred in 82 (11%) patients, 76% of these rebleeds occurred within the first 72 hours.[42] For these reasons, the 24-hour time frame for endoscopy has been widely accepted and included in international guidelines endorsed by various gastroenterology associations worldwide.[20] This implies that units which cannot guarantee the 24-hour time frame for instance for patients presenting during weekends, should not

Table 1. Outcome of urgent endoscopy for non-variceal upper GI bleeding.

Timing of endoscopy (hours after presentation)	Study, year	Design	Numbers of patients per study arm	Rebleeds (%)	Mortality (%)	Need for blood products (units)	Length of hospital stay (days)
2-3 hours	Lee, 1999	RCT: EEE vs endoscopy <48 h	56 vs 54	3.6 vs 5.6	0 vs 3.7	1.2 vs 1.1	1 vs 2
	Schacher, 2005	Retrospective: EEE vs endoscopy <24 h	43 vs 38	14 vs 15.8	0 vs 0	NR	5.9 vs 5.1
6-8 hours	Bjorkman, 2004	RCT: endoscopy <6 h vs <48 h	47 vs 46	8.5 vs 2.2	0 vs 0	2.1 vs 1.5	4.0 vs 3.3
	Targownik, 2007	Retrospective: endoscopy <6 h vs <24 h	77 vs 92	9 vs 8	8 vs 6	3.3 vs 2.9	4 vs 4
	Tai, 2007	Retrospective: endoscopy <8 h vs <24 h	88 vs 101	3 vs 2	1 vs 6	3.5 vs 3.4	5.1 vs 6.0
<12 hours	Lin, 1996	RCT: endoscopy <12 h vs >12 h	162 vs 163	3.7 vs 4.9	0.6 vs 0.6	450 ml vs 666 ml*	4 vs 14.5*
<24 hours	Cooper, 1998	Observational cohort study: endoscopy <24 h vs >24 h	2240 vs 3247	NR	2.9 vs 2.8	NR	4 vs 6
	Cooper, 1999	Retrospective: endoscopy < 24 h vs > 24 h	583 vs 326	14.2 vs 11.4**	NR	NR	5.0 vs 6.4

EEE: early endoscopy in emergency room, RCT: randomized controlled trial, NR: not reported, Underlined: significant difference ($p < 0.05$)

**: no overall data available, significant benefit was found in a subgroup of patients with a bloody nasogastric aspirate*

***: rebleeding and surgery*

take care of this patient population, and vice versa that all units which accept patients with upper gastrointestinal bleeding have to organize their endoscopy service to be able to meet these emergency demands and perform endoscopy by an experienced team at all times. Unfortunately, many units fail to meet these internationally accepted demands despite the available evidence for their relevance. In a recent survey within the UK in 208 endoscopy units providing emergency care for patients with upper GI bleeding, 6750 patients were included.[11] Only 50% of medium and high-risk patients underwent endoscopy within 24 hours, and the presence of high-risk characteristics did not influence the timing of endoscopy. Units without formal out-of-office hour endoscopy rota more often provided delayed endoscopy services. As this was a survey and not an interventional study, it could not directly assess an effect of delayed endoscopy on outcome. The authors however concluded that their survey showed continuing delays in performance of endoscopy in patients with upper GI bleeding. In a Canadian multicenter observational study, 90% of 1675 patients with upper GI bleeding underwent endoscopy within 48 hours. The proportion undergoing endoscopy within 24 hours of presentation approximated 75%.[65] Presence of an endoscopy-nurse on-call and admission to a hospital unit were predictors for earlier endoscopy, whereas the presence of chest pain, dyspnea, and inpatient status at the onset of bleeding were predictors for delayed endoscopy. The latter is remarkable as these patients almost invariably suffer from comorbidity as recommendation for early endoscopy. Finally, in an observational study from the US among 2592 elderly patients (>65 years) presenting with upper GI bleeding, 71% underwent endoscopy within 24 hours. Early endoscopy was associated with on an on average 2-days shorter hospital stay, and a 63% reduction in the need for surgery, but no significant effect on mortality.[66] All these observational data from various countries confirm the benefit of early endoscopy, and simultaneously show that major further improvements have to be made to ensure early intervention for all eligible patients as 10-50% still fail to be treated according to well-established guidelines.

There have been several studies to determine whether immediate endoscopy within the first 2 to 12 hours after presentation improves outcome in comparison with endoscopy within 24 hours. These studies have not shown that immediate endoscopy has a benefit with respect to the need for transfusion, repeat endoscopy, hospital stay, surgery, and mortality (Table 1). For example, one study assessed in 81 patients whether endoscopy within the first two hours had an effect of outcome. The mean hospital stay was 5.9 days in those who had undergone immediate endoscopy, versus 5.1 days in the controls undergoing regular endoscopy within 24 hours.[27] The timing of endoscopy within the first 24-hour time frame did also not affect rebleeding and complication rates, nor the need for surgery. In a Canadian study in 169 patients, the rebleeding rate was 11.7% in those who had undergone endoscopy within 12 hours, versus 8.7% in those undergoing endoscopy within 24 hours.[29] Similarly, very early endoscopy within 6 hours of presentation did not affect transfusion requirements, length of hospital stay, or any adverse bleeding outcome. Based on these findings, endoscopy is

required within 24 hours, but does not routinely need to be performed within a shorter time interval. Nevertheless, immediate endoscopy should be considered for patients with signs of severe or persistent bleeding, even more so in the presence of comorbidity increasing the risk for poor outcome.

Medical therapy prior to endoscopy

While planning emergency endoscopy, most clinicians will administer high dose proton pump inhibitor (PPI) therapy intravenously. The potential benefit of such an approach firstly depends on the proportion of upper GI bleedings attributable to peptic ulcer disease as the condition which is most likely to benefit from profound acid suppression. In most cases, this proportion will vary between 40 to 60%.[9] In a study from Hong Kong, 638 patients with upper GI bleeding were randomized to receive 80 mg omeprazole or placebo prior to endoscopy.[46] During subsequent endoscopy, 19% of those having received omeprazole versus 28% of those receiving placebo needed a therapeutic intervention because of the presence of high-risk stigmata. This difference was significant, subgroup analysis showed that the difference in endoscopic intervention rate was also significant for patients with peptic ulcer disease, but not for patients with other bleeding causes. On endoscopy, fewer patients in the omeprazole arm had active bleeding ulcers. However, the benefit of iv proton pump inhibitor therapy did not translate in any difference with respect to other relevant parameters, such as need for transfusion, hospital stay, or rebleeding and mortality rates. The result of this study was later confirmed by others.[23] A systematic review of 6 randomized trials including 2223 patients showed that PPI treatment prior to endoscopy reduced the prevalence of stigmata of recent hemorrhage during endoscopy from 46 to 37% (placebo vs PPI treatment, OR 0.67, 95% CI 0.54-0.87). This led to a reduction in the need for endoscopic treatment from 11.7% to 8.7% (placebo vs PPI treatment).[23] Based on these results, the international consensus recommends that pre-endoscopic proton pump inhibitor therapy may be considered to downstage the bleeding lesion and reduce the need for endoscopic therapy.[20] However, because pre-endoscopic PPI therapy has no proven benefit on other clinically relevant outcome parameters such as the need for transfusion, hospital stay, further interventions and mortality, the same guidelines also stress that PPI therapy should not delay endoscopy.[20]

Apart from profound acid suppression, another pharmacotherapeutic approach in UGIB patients is the use of promotility agents, in particular erythromycin and metoclopramide. These drugs have been tested under the assumption that they may clear the stomach and proximal duodenum of blood and thus improve the diagnostic yield of endoscopy and facilitate endoscopic therapy, while simultaneously perhaps decrease the risk of aspiration. This has been assessed in several randomized trials. A meta-analysis of five placebo-controlled trials on erythromycin and metoclopramide in patients who were suspected to have blood in the stomach found that the use of these agents was associated with an almost two-fold reduction in the need for repeat endoscopy (odds ratio 0.51, 95% CI 0.30-0.88), but proki-

netic treatment had no effect on the need for transfusion or any other outcome parameter.[20] Cost-efficacy analysis of the data from the three erythromycin trials showed a cost-effective outcome based on reduction in the need for repeat endoscopy from an average of 1.33 to 1.18 endoscopy per UGIB patient.[67] Based on these data, the international guidelines concluded that promotility agents such as erythromycin or metoclopramide should not routinely be used prior to endoscopy in all patients presenting with UGIB.[20] However, they should be considered in patients who have recently eaten and in those who are suspected to have considerable amounts of blood in the stomach as promotility agents improve visibility, and thus the diagnostic yield and the possibility to apply adequate endoscopic treatment. Both aspects explain the reduction in need for second-look endoscopy.[20]

Gastric lavage prior to endoscopy

Gastric lavage has for long been widely used in patients with UGIB both for diagnostic and therapeutic purposes, the latter for instance under the assumption that cold-water lavage would reduce gastroduodenal blood flow and thus help to stop any ongoing bleeding. This practice dates from the era prior to endoscopy and profound acid suppressive therapy, there is very little place for gastric lavage in the current clinical setting.[68] Lavage is first of all not of any major benefit to clear the stomach and thus improve the yield of endoscopy. In a small randomized trial involving 39 patients comparing pre-endoscopic gastric lavage with up to 15 liters of tap water versus no intervention prior to endoscopy, lavage somewhat improved visualization of the gastric fundus, but not of any other parts of the upper GI tract. It had no effect on identification and treatment of the bleeding source, nor on any other parameter.[69] Secondly, nasogastric aspiration with or without lavage is also not very helpful in identification of the source of bleeding, being in the upper or lower GI tract. Clinical signs give in a large proportion of patients sufficient clues to direct the diagnostic approach without the need for further investigation prior to endoscopy. Furthermore, nasogastric aspiration has been shown to be a poor predictor of the source of bleeding. In a study from the US involving 220 patients presenting with signs of GI bleeding, 23% had positive nasogastric aspiration prior to gastroscopy.[70] The sensitivity of aspiration to detect upper GI bleeding was 42%, the specificity 91%, with positive and negative predictive values of respectively 92% and 64%. The authors concluded that a positive nasogastric aspiration indicates probable upper GI bleeding, but a negative test, seen in almost three quarters of patients, provides little information.[70] Likewise, aspiration is also inadequate to differentiate between persistent and stopped bleeding. In an older study, almost one-fifth of patients with active bleeding had negative aspiration, and almost half of patients without persistent bleeding had a positive aspiration of blood remnants in the stomach.[71] Lavage and aspiration are to some extent helpful in identification of high-risk cases. In a retrospective, Canadian study of 520 patients who underwent nasogastric aspiration and subsequent endoscopy, a bloody aspirate had a specificity of 76% (95%CI 70-80%) for the presence of high-risk lesions. Patients with bloody

aspirates were 2.8-fold (95%CI 1.8-4.3) more likely to have a high-risk lesion than patients with coffee-ground aspirates, and 4.8-fold (2.3-10.1) than those with clear / bile aspirates.[72] With the retrospective design of the study, it remained unclear whether nasogastric aspiration can be used to plan patients for immediate endoscopy. Also, the results of lavage do not predict long-term outcome after endoscopy as shown in an Italian study of 1020 patients, in which patients with bloody or coffee-ground aspirates had a similar mortality as those without.[73] Finally, nasogastric lavage is associated with patient burden, and also with a risk of further bleeds such as from nasal origin, and aspiration and pneumonia. For these reasons, there is nowadays very little place for nasogastric aspiration and lavage in the initial pre-endoscopic management of patients with UGIB.[20, 68]

Other measures prior to endoscopy

Initial resuscitation is of major importance in patients with UGIB and is required prior to endoscopy, yet should not delay the procedure and thus the contact with the endoscopy team. The initial resuscitation includes the administration of intravenous fluids to restore blood pressure and tissue perfusion, transfusion of blood, and correction of marked coagulation disorders. Blood transfusion is generally recommended in patients with a hemoglobin level of 70 g/l or less, aiming for a level between 70 and 90 g/l. The decision for transfusion also depends on the rate of bleeding, medical condition, in particular vital signs, and the presence of co-morbidity. INR correction is required but there are limited data as to the optimal level. Correction should also not delay endoscopy, unless the INR is supratherapeutic.

ENDOSCOPY

Endoscopy team

Endoscopy for acute UGIB not only requires adequate preparation of the patient, but also of the team and equipment. An emergency physician first sees most patients, in-hospital bleeders are seen by a ward doctor. These physicians take care of the initial resuscitation and coordinate the first contacts to other physicians. A gastroenterologist should be available on call at all times, and be able to reach the hospital at short notice. Although there are no direct data that determine an exact time limit, a limit of one hour is generally assumed. The background of this time interval is that it allows ample time to prepare the patient for the procedure and at the same time not unnecessarily delay the procedure in patients with obvious signs of ongoing bleeding and difficult stabilization. Likewise, during office hours an endoscopy unit taking care of UGIB patients should be able to provide an experienced endoscopist for an emergency procedure when needed. The endoscopist should have ample experience with the treatment of acute upper GI bleeding, and be familiar with the equipment at the unit. The team should at all times also consist of an experienced endoscopy nurse

who has full experience with the procedure, is aware of the place of storage and preparation of all equipment that is potentially needed, and experienced in assisting in all diagnostic and therapeutic aspects of the procedure. The team also requires a third person at short hand to monitor the patient, take care of transfusion and medication needs, and assist in any emergency. The endoscopy nurse assisting in the endoscopy procedure itself cannot safely do this. The procedure is for reasons of available equipment preferentially performed at the endoscopy suite if the patient can be transported and adequately monitored, otherwise it should be done at an emergency unit or intensive care. At any location, the endoscopy team should be fully prepared for the procedure. Depending on the severity of the bleed, early involvement of an intensivist is recommended with transfer to an ICU when needed. A full treatment team requires close collaboration with a gastrointestinal surgeon and intervention radiologist for further management in case of failure of endoscopic treatment, either at the first presentation, or during a recurrent bleeding episode. These physicians should have consensus and a local protocol for management of this most common emergency condition in gastroenterology practice. In many cases, the protocol requires early contact with surgeon and/or radiologist even before the endoscopy, in particular in high-risk and unstable patients.

The relevance of having an experienced endoscopy team available 7x24 hours was supported by studies reporting that UGIB patients who were admitted during weekends had worse outcomes than those admitted during weekdays. In an analysis of 237.412 patients admitted with upper GI bleeding in the period of 1993 – 2005 to 3.166 US hospitals, patients admitted on weekends had to wait longer for endoscopy (mean 2.21 vs 2.06 days, $p<0.001$), and were less likely to undergo endoscopy on the day of admission (30 vs 34%, $p<0.001$).[74] This was associated with prolonged hospital stay, in-hospital costs, need for surgery, and mortality (OR 1.12, 95% CI 1.05-1.20). The results of this large study were supported by other studies from the US.[75, 76] Together, these results were likely due to the combination of lack of on-call emergency endoscopy teams, lack of experience of on-call endoscopists, and the tendency to delay interventions in case of weekend admission. This explanation was supported by a large study from Hong Kong which showed that the presence of continuous 24-hour endoscopy service with an experienced team led to similar outcome for patients admitted during weekdays and weekends.[77] These studies support guideline recommendations for 7x24 hour endoscopy rota and endoscopy within 24 hours in all patients except very low risk cases.

Endoscopy kit

The endoscopy unit requires a room with sufficient space for emergency handling by an endoscopy and emergency team if needed. The required equipment needs to be available within the room; this needs to be checked prior to the procedure. The room needs to be equipped with oxygen supply, and patient monitoring equipment, in particular automated registration of blood pressure, pulse, and peripheral oxygen saturation. It is important that

the results of these measurements are stored in the patient charts for retrospective evaluation in case of events and overall safety measurement.

Endoscopy should be performed under continuous monitoring of vital functions, in particular blood pressure, pulse, and saturation. Endoscopy should preferentially be performed with an endoscope with a large diameter working channel, or if available two large working channels. A large diameter working channel improves the ability to remove blood and clots. Two large working channels enable combined removal of fluids and intervention procedures. A side viewing endoscope can be helpful for diagnosis and treatment of duodenal lesions. Equipment for treatment of the cause of the bleed should be directly available in the endoscopy room and the nursing staff should be acquainted with their use. A jet/pump system is helpful for cleansing of the stomach and duodenum in the presence of larger amounts of blood or active bleeding, as well as for removal of adherent clots. A separate suction devise should be directly available for removal of blood from mouth and throat in particular in case patients are not intubated.

Endoscopy procedure

Intubation of the patient prior to the endoscopy can ease the procedure and prevent aspiration of blood, in particular in case of massive bleeding. If the patient is not intubated, some clinicians prefer to administer a benzodiazepine for conscious sedation. This may ease the procedure for the patient, but may also increase the risk of aspiration and potentially impair vital functions in patients at risk. Physicians should monitor vital signs of their patients. If complications occur, the endoscopist should try to determine whether or not these were related to the use or lack of conscious sedation. After introduction of the endoscope, adequate inspection of the full upper GI tract is performed. This should not stop with identification of a bleeding source, as multiple bleeding sources may be present. For adequate inspection, the endoscopist will attempt to remove most of blood remnants if present. This may be more difficult in the presence of large clots, which may block the view and the suction channel of the endoscope, sometimes requiring removal of the endoscope for cleaning. In the presence of massive amounts of bloods and clots, an alternative approach is to try and locate the bleeding source by looking for the presence of fresh rood blood as a flagging sign amongst darker older blood and clots. This should be followed by endoscopic treatment of the bleeding source, after which full inspection can be performed.

Once a peptic ulcer is identified, the endoscopist should assess its appearance and thus determine the risk for persistent or recurrent bleeding, and the need for endoscopic therapy. This is done by determination of signs of active bleeding, either spurting or oozing, and stigmata of recent hemorrhage, in particular a visible vessel or an adherent clot. International consensus guidelines do not indicate endoscopic hemostatic therapy for patients with low-risk stigmata (a clean-based ulcer or a flat pigmented spot in an ulcer bed), because of their low risk of rebleeding (Table 2).[20] In contrast, endoscopic therapy is mandatory in patients

Table 2. Risk of recurrent bleeding in patients with bleeding peptic ulcer after medical therapy alone.

Ulcer characteristics at endoscopy	Incidence (%)	Risk of recurrent bleeding (%)
Active bleeding		
Spurting bleeding	6-10	80-90
Oozing bleeding	4-10	10-30
Signs of recent hemorrhage		
Non-bleeding visible vessel	8-25	39-60
Adherent clot	8-17	22-35
Flat spot	10-23	0-13
Lesions without active bleeding		
Clean ulcer base	35-58	0-12

with high risk lesions, in particular those with signs of active bleeding or a visible vessel (Figure 1-3).[20, 25] The role of endoscopic therapy for ulcers with adherent clots is controversial (see below).[20]

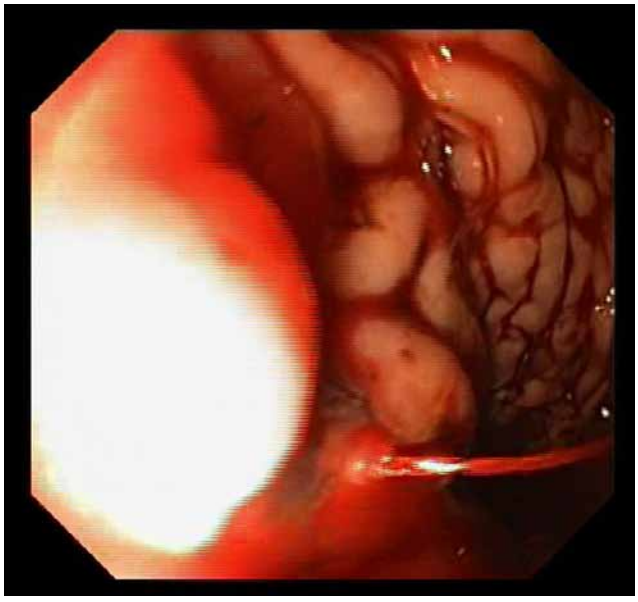

Figure 1. Active ulcer bleeding, with a spurting vessel (Forrest Ia).

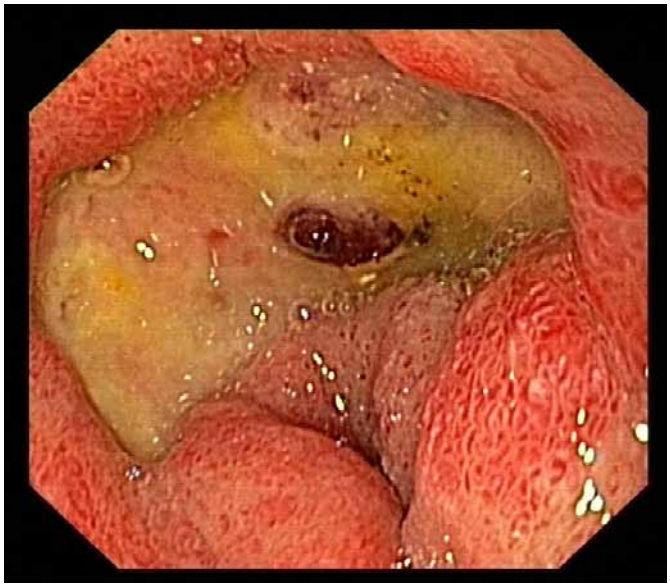

Figure 2. Ulcer with visible vessel (Forrest IIa).

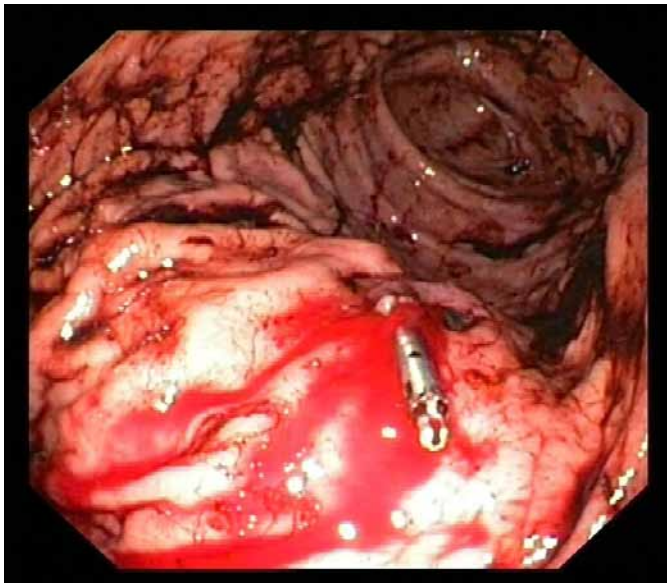

Figure 3. Forrest Ia ulcer after hemoclip treatment.

Different endoscopic treatment options have been widely studied over the last 25 years (Table 3 and 4). These include (a) injection therapy with substances as ephinephrine, normal saline, ethanol, sclerosant, thrombin and fibrin sealant, (b) ablative treatment with techniques as thermocoagulation, electrocoagulation, argon plasma coagulation and laser therapy, and (c) mechanical therapy in particular hemoclips and band ligation. These methods have also been tested in a variety of combination therapies.

Table 3. Endoscopic therapies used for the treatment of bleeding peptic ulcer.

Different endoscopic hemostatic modalities for peptic ulcer bleeding
Injection therapy
·Epinephrine
·Normal saline
·Sclerosant (e.g. polidocanol, ethanolamine, and ethanol)
·Thrombin
·Fibrin sealant
Ablative therapy
·Thermocoagulation (e.g. heater probe)
·Electrocoagulation (e.g. Gold probe, BICAP probe, hemostatis forceps with soft coagulation)
·Argon plasma coagulation
·Laser photocoagulation
Mechanical therapy
·Hemoclip placement
·Band ligation
Combination therapy (injection therapy plus ablative therapy/mechanical therapy)

Table 4. List of randomized controlled trials published over the last 10 years comparing different endoscopic treatments for peptic ulcer bleeding.

Author, year	Forrest classification of included patients	Treatment per study arm (n)		Primary hemostasis (%)		Rebleeding (%)		Surgery (%)		Bleeding related mortality (%)	
Cipolletta, 2001	Ia + Ib + IIa	hemoclips (56)	heater probe (57)	86	89	1.8	21	3.6	7	3.6	3.5
Lin, 2002	Ia + Ib + IIa	hemoclips (40)	heater probe (40)	85	100	8.8	5	5	2.5	5	2.5
Lin, 2002	Ia + Ib + IIa	fibrin sealant (26)	epi (25)	100	100	15	56	8	8	0	0
Laine, 2002	Ia + Ib + IIa	saline injection (48)	bipolar (52)	71	88	NR		4.2	1.9	6	2
Pescatore, 2002	Ia + Ib + IIa + IIb	Epi (70)	epi + fibrin sealant (65)	100	100	24.3	21.5	10	6	3	3
Gevers, 2002	Ia + Ib + IIa	epi + poli (34) hemoclips (35)	hemoclips + epi + poli (32)	80 86	91	15 37	25	NR		0 0	9.3
Chau, 2003	Ia + Ib + IIa + IIb	heater probe + epi (97)	argon plasma + epi (88)	95.9	97.7	21.6	17	9.3	4.5	6.2	5.7
Soon, 2003	Ia + Ib + IIa + IIb	monopolar (56)	heater probe + epi (43)	96.4	76.7	0	14	0	0	0	0
Lin, 2003	Ia + Ib + IIa	hemoclips (46)	heater probe + epi (47)	95.1	100	10.3	6.4	0	4.7	0	0
Chou, 2003	Ia + Ib + IIa	hemoclips (39)	distilled water (40)	100	97.5	10.3	28.2	5.1	12.5	2.6	5.0
Church, 2003	Ia + Ib + IIa	heater probe + thrombin (127)	heater probe (120)	97	97	15	15	13	11	6	12
Shimoda, 2003	Ia + Ib + IIa	etha (42) hemoclips (42)	hemoclips + etha (42)	85.7 90.5	92.9	14.3 9.5	7.1	0 0	0	2.4 7.1	2.4
Skok, 2004	Ia + Ib + IIa + IIb	argon plasma (50)	epi + poli (50)	94	90	14	18	6	8	8	10
LJubicic, 2004	Ia + Ib	hemoclips + epi (31)	poli + epi (30)	96.8	96.7	6.5	13.3	3.2	3.3	3.2	0
Bianco, 2004	Ia + Ib + IIa	bipolar + epi (58)	bipolar (56)	100	68.4	8.2	14.3	1.8	7.1	1.7	5.3
Park, 2004	Ia + Ib + IIa	hemoclips/ band ligatie + epi (45)	epi (45)	97.8	97.8	4.5	20.5	0	2.2	0	2.2
Saltzman, 2005	Ia + Ib + IIa + IIb	hemoclips (26)	bipolar + epi (21)	100	95.2	15.4	23.8	11.5	4.8	0	9.5
Lo, 2006	Ia + Ib + IIa + IIb	hemoclips + epi (52)	epi (53)	98	92	3.8	21	0	9	2	0
Taghavi, 2009	Ia + Ib + IIa + IIb	argon plasma + epi (89)	hemoclips + epi (83)	96.6	98.8	11.2	4.8	2.2	0	2.2	1.2
Arima, 2010	Ia + Ib + IIa	hemostatic forceps (48)	hemoclips (48)	85	79	2	10	0	0	2	0

epi: epinephrine, etha: ethanol, poli: polidocanol, NR: Not reported, Underlined: significant difference ($p < 0.05$)

Injection therapy

Injection therapy with epinephrine is one of the most widely used methods for initial treatment of bleeding peptic ulcers, because it is effective, relatively inexpensive and easy to administer. It promotes hemostasis by a combination of local tamponade, vasospasm and induction of thrombosis and accordingly produces a cleaner field permitting further targeted treatment of the bleeding focus. Injection is performed with a standard sclerotherapy needle, introducing it tangentially into the submucosa. Injection is started in quadrants around the bleeding site, followed by central injection. When injecting in the right plane, local swelling occurs with whitening of the surrounding mucosa. Epinephrine typically reduces or stops bleeding initially, but rebleeding may recur from 20 minutes after injection when epinephrine is absorbed and a permanent clot has not yet been formed. Therefore, epinephrine injection therapy should be combined with a more durable hemostatic technique.[33] The optimal injection volume of epinephrine for endoscopic treatment of an actively bleeding ulcer is still a matter of debate. In a Chinese study of 228 patients with actively bleeding ulcers (spurting or oozing), injection with either 20, 30 or 40 mL diluted epinephrine (1:10.000) was equally effective for initial hemostasis, but 30 mL injection was more effective in preventing rebleeding than 20 mL, and gave rise to fewer perforations than 40 mL.[78] In another study of 72 patients with actively bleeding ulcer or non-bleeding visible vessel, 35-45 mL diluted epinephrine (1:10.000) was more effective than injection of 15-25 mL of the same solution for prevention of recurrent bleeding.[79] A similar observation was done in a trial in 156 patients randomized to 1:10.000 epinephrine injection in a volume of either 5-10 mL or 13-20 mL.[80] The higher volume reduced rebleeding rates from 31 to 15%. Although these observations support the recommendation to use higher volume epinephrine injection, they are insufficient evidence for routine use of large volume injection, in particular because epinephrine injection should preferentially be combined with a second treatment modality for durable hemostasis.[20, 81] Furthermore, larger volumes of injected epinephrine may result in tachycardia, cardiac arrhythmias and hypertension and can potentially produce angina in patients at risk, in particular in the presence of anemia and hypotension. This risk may be reduced by further dilution of epinephrine to 1:20.000 in high risk cases. Normal saline is safer in use for patients with severe coronary artery disease, although it has been suggested that it is less effective in achieving initial hemostasis, because it only causes mechanical tamponade but no vasospasm or platelet aggregation.[82] Sclerosants (e.g. polidocanol, ethanolamine, and ethanol) are used as addition or alternative to ephinephrine. They produce local tissue inflammation, acute chemical fixation and edema, resulting in tamponade of the bleeding and promotion of the thrombogenesis.[33] However, the use of sclerosants for the treatment of peptic ulcer bleeding is nowadays limited, since local side effects are considerable and the benefit over epinephrine is marginal.[48, 83-85] Sclerosants may in particular induce enlargement of the ulcer, leading to impaired healing, recurrent bleeding, and in some eventually marked scarring or even perforation. An alternative is formed by thrombin injection, which has been

experimentally used for the treatment of bleeding ulcers, both as monotherapy and as accessory agent, however without impressive results. An Italian study compared polidocanol versus thrombin injection in 82 consecutive patients with recent or ongoing ulcer hemorrhage. The rebleeding rate of patients treated with thrombin did not significantly differ from those treated with polidocanol (14.6% vs 9.1%).[86] In a randomized trial of 247 patients in the United Kingdom, the combination of thrombin and heater probe treatment did not confer an additional benefit over heater probe and placebo for the treatment of bleeding peptic ulcer.[87] Fibrin sealant or glue is a two-component system which promotes thrombogenesis by mixing thrombin and fibrin locally at the site of bleeding after injection. In one randomized controlled trial of 51 patients with ulcer bleeding, fibrin sealant was equally effective as epinephrine in attaining primary hemostasis, but more effective in preventing rebleeding (15% vs. 56%).[88] Another randomized trial compared the use of fibrin sealant (single application and daily repeated doses) with the use of polidocanol 1% in 854 patients with actively bleeding ulcers or ulcers with a visible vessel. Repeated injection with fibrin sealant was significantly more effective in preventing rebleeding than injection with polidocanol.[49] Nevertheless, repeated injections are uncomfortable for the patient, costly and increase workload. Therefore fibrin sealant is not generally used in clinical practice. Several recent meta-analyses compared the results of various endoscopic therapies. Although the use of epinephrine injection alone was more effective than medical therapy alone in patients with high risk lesions, monotherapy with epinephrine was significantly inferior in prevention of rebleeding compared with other monotherapies, as well as epinephrine followed by another modality. Therefore, epinephrine should be used in combination with another method.[25, 31, 36, 37, 81] According to a Cochrane review, additional endoscopic treatment after epinephrine injection significantly reduced rebleeding from 18.8% to 10.4% (OR, 0.51, 95% CI 0.39-0.66), need for emergency surgery (10.8% to 7.1%; OR 0.63, 95% CI 0.45-0.89), and mortality (5% to 2.5%; OR 0.50, 95% CI 0.30-0.82) in patients with bleeding peptic ulcer. This risk reduction was regardless of which second procedure was applied.[81]

Ablative therapy

Ablative therapies can be divided into contact methods (e.g. thermocoagulation and electrocoagulation) and non-contact methods (e.g. argon plasma coagulation and laser photocoagulation). Hemostasis is promoted by the delivery of intense energy, which causes coagulation of tissue proteins, edema and vasoconstriction. It also activates thrombocoagulation and destroys tissue.[33] Contact devices require placement of the probe directly to the bleeding focus for optimal effect and minimal scatter injury. Widely used devices for thermocoagulation are the heater probe and for electrocoagulation the Gold and BICAP probes. In a comparative study of 80 patients with bleeding peptic ulcer or non-bleeding visible vessel, heater probe treatment was significantly better in achieving ultimate hemostasis than endoscopic hemoclip placement (97.5% vs 77.5%). This result was especially seen in a

subgroup of 21 patients with a difficult-to-approach bleeding focus such as in the posterior duodenal bulb. Nine patients (82%) in the heater probe group and three patients (30%) in the hemoclip group eventually achieved hemostasis.[88] An alternative approach comes from the new developments in endoscopic mucosal resection and submucosal dissection, techniques which are associated with frequent bleeds. These are often treated by means of coagulation via grasping forceps. Recent studies show promising results for the use of this same forceps technique with soft coagulation in active gastrointestinal bleeding. Soft coagulation was as effective and safe as hemoclip placement, according one randomized trial and two retrospective studies.[89-91]

Argon plasma coagulation offers fairly controlled, non-contact electrocoagulation. This technique uses monopolar electrocoagulation to ionize argon gas into a plasma that coagulates tissue nearest to the catheter tip. Argon plasma coagulation has some advantages; it is safe and has lower cost compared to laser, it can be learned easily, is repeatable and induces limited tissue destruction. Furthermore, it can be used for tangentially located or indirectly visualized bleeding sites.[33] On the other hand, the depth of injury is unpredictable; it may be too shallow to produce sufficient hemostasis or too deep resulting in the risk of perforation.[92] The risk of gastrointestinal perforation is about 0.5% or lower.[93] In a series of 2193 sessions in 1062 patients with gastric vascular ectasia, the risk of perforation was 0.2%.[94] Argon plasma coagulation was previously shown effective for the treatment of angiodysplasia, gastric antral vascular ectasia and radiation proctitis. A few published studies confirm this efficacy for bleeding peptic ulcers.[92, 95, 96] However, newer techniques which allow more targeted, dosed treatment such as heater prober and clips are more efficient and have replaced the use of argon plasma coagulation for bleeding peptic ulcer. Likewise, laser photocoagulation has also become obsolete, because the relatively high risk of gastrointestinal perforation (approximately 3%), the high kit cost, and the inferiority in achieving hemostasis compared to other therapies.[33] In a meta-analysis, with a subgroup-analysis of four trials comparing hemoclips versus thermocoagulation with or without injections, initial hemostasis was significantly different between hemoclips (88.7%) and thermocoagulation (94.5%). Definitive hemostasis, rebleeding rate, the need for surgery and all-cause mortality were similar.[31] According to another meta-analysis, a significant decrease in rebleeding attributable to clips compared with thermal therapy was noted (OR 0.24, 95% CI 0.06-0.95). No differences were seen for surgery or mortality.[25]

Mechanical therapy

Mechanical therapies compress the bleeding source by placement of a device (e.g. a clip or a rubber band). The device achieves hemostasis in a manner similar to surgical ligation. A study on 100 patients with peptic ulcer bleeding compared the effect of hemoclip placement with triclip (a novel clipping device with three prongs over the distal end) placement. Hemoclip placement was superior in obtaining primary hemostasis (94% vs. 76%) and was

easier to place in difficult-to-approach sites. Rebleeding rates, volume of blood transfusion and mortality rate did not significantly differ.[97] Metallic hemoclips or endoclips are currently the most popular mechanical therapy. They immediately and securely occlude the bleeding vessel, arresting the bleeding. Side-effects are seldom reported. The clips may also seal small gastrointestinal tears or perforations caused by other endoscopic techniques. Proper hemoclip placement, however, can be challenging and requires a highly skilled endoscopist. Furthermore, application of the clips can be difficult in tangentially located bleeding sites or when massive hemorrhage obscures the visual field.[33] Hemoclips normally fall off 7 to 14 days after application, when the lesion has partly healed. Rebleeding at that time is unlikely. Sometimes clips dislodge prematurely, giving rise to a recurrent bleeding. An Iranian randomized trial compared the effect of argon plasma coagulation plus epinephrine injection with hemoclip placement plus epinephrine injection in 172 patients with major stigmata of peptic ulcer bleeding. The investigators found no significant difference in initial and definitive hemostasis and rebleeding rate between the two groups.[92] Endoscopic band ligation is the most popular method for the treatment of esophageal varices, but it is incidentally used to treat bleeding peptic ulcers. In a study of patients with upper gastrointestinal hemorrhage from peptic ulcer in whom at least two attempts to control bleeding by injection therapy failed, definitive hemostasis could be performed in all eleven patients.[98] A meta-analysis of 9 studies including 699 patients, compared endoscopic clipping with heater probe alone, thermal therapy plus injection, and injection therapy alone for the treatment of peptic ulcer bleeding. The rate of initial hemostasis was not significantly different between the hemoclip group and the controls (92% vs 96%, OR 0.58, 95% CI 0.19-1.75, p=0.33). The rebleeding rate was nonsignificantly decreased with hemoclips compared to controls (8.5% vs 15.5%, OR 0.56, 95% CI 0.30-1.05, p=0.07). Emergency surgery and mortality rates showed no significant differences. A subgroup analysis comparing hemoclips with injection monotherapy showed similar results.[32] In a similar designed meta-analysis of 15 studies including 1156 patients, however, definitive hemostasis was higher with hemoclips (86.5%), than injection therapy alone (75.4%). In line with the previously mentioned meta-analysis, no significant differences between the hemoclip placement and thermocoagulation were found with respect to definitive hemostasis, rebleeding, need for surgery, and mortality.[31]

Combination therapy

It is generally accepted that epinephrine injection alone is inferior to mechanical or ablative therapy for definitive hemostasis and prevention of rebleeding and should be used in combination with another endoscopic therapy, especially in high risk ulcers.[20, 37, 81, 99, 100] The most suitable (combination of) therapies, however, has not yet been defined. In a meta-analysis of 20 randomized clinical trials encompassing 2472 patients with recent bleeding from peptic ulcers with high-risk lesions, dual endoscopic therapy was significantly superior to epinephrine injection alone, but had no advantage over thermal or mechanical monotherapy.[37]

Another recent meta-analysis concluded that all endoscopic treatments were superior to pharmacotherapy alone. Thermal therapy or clips, either alone or in combination with other methods, showed similar effects with respect to rebleeding, surgery and mortality.[25] Data fail to demonstrate any superiority of dual therapies over ablative therapy or hemoclip placement alone. It is hypothesized, that different subgroups of patients (e.g. large visible vessel, or tangentially located site) benefit from specific therapies. In a subgroup of patients with difficult-to-approach bleedings, heater probe was superior to hemoclip placement.[80] Larger trials need to be done to confirm this hypothesis. Clinicians may choose the method based on their own experience, availability of equipment and ulcer and patient characteristics. In addition, new developments may add to the current mono and combination treatments. One potentially very important new development is the introduction of nanopowder spray to seal the bleeding lesion and induce hemostasis. This technique was highly effective in a first proof-of-principle study.[38]

Treatment of adherent clots

The risk of rebleeding of ulcers with adherent clots depends on finding a vessel underlying the clot and treatment of that vessel can reduce the risk of rebleeding.[35] For that reasons, there is international consensus that clot removal should be attempted by vigorous irrigation.[20] This leads to removal of the adherent clot in some 26 to 43% of cases.[34, 101] In a study of 46 patients with peptic ulcer bleeding and an adherent clot, vigorous irrigation for 5 minutes led to removal of the clot in 43%, revealing in almost equal frequency oozing bleeding, a visible vessel, or flat pigmented spots, and only in rare cases either a spurting bleed or a clean ulcer.[34] If vigorous irrigation does not lead to removal of the clot, further endoscopic management can be considered. This is generally done by epinephrine injection at the base of the clot, followed by cold snaring, leaving the clot pedicle intact. This approach leads to higher clot removal rates. In an international study on 764 patients with peptic ulcer bleeding and stigmata of active or recent hemorrhage, 22% of patients had adherent clots.[42] More than half of these clots were successfully removed by a combination of irrigation and snaring if needed, again in particular revealing oozing bleeds and visible vessels. These data together, show that some 70% of cases with adherent clots have high-risk lesions underneath. The rebleeding risk of irremovable clots varied in different studies between 0 to 35%.[101-104] A systematic review on endoscopic therapy for adherent clots reported that endoscopic management is not associated with increased risk.[37] Several systematic reviews suggested that endoscopic therapy for adherent clots reduced the risk of rebleeding (relative risks for rebleeding ranging from 0.30 to 0.45), although most of these results did not reach statistical significance given the limited patient numbers included in the analysis.[35, 37, 47] Independent risk factors for a higher chance of rebleeding are comorbid illness, shock, and initial hemoglobin level of ≤ 10 gm/dL.[101]

PHARMACOTHERAPY

Introduction

Pharmacotherapy plays a second, major role after endoscopic therapy, together they form the mainstay of treatment for patients with peptic ulcer bleeding. While endoscopic therapy is only applied in patients with high-risk stigmata, pharmacotherapy is relevant for both patients with and without these stigmata. In the absence of high-risk stigmata (active bleeding, visible vessel, or adherent clot), endoscopic therapy is not required and pharmacotherapy can be the sole treatment option. In the presence of high risk stigmata, the current standard of care is endoscopic treatment followed by profound acid suppressive therapy. Already since 1953, it is known that a strongly acidic environment may lead to clot lysis.[105] Further studies demonstrated that lowering of environmental pH below 6.0 leads to inhibition of platelet aggregation,[106] and lowering the pH below 5.0 inhibits plasma coagulation.[22, 107] These data led to the hypothesis that acid inhibition and the consequent increase of intragastric pH could contribute to the treatment of patients with peptic ulcer bleeding. Therefore, histamine H2 receptor antagonists, somatostatin and octreotide were used and studied as treatment options for peptic ulcer bleeding. Although all these agents inhibit acid secretion by receptor blockage, no studies provided convincing evidence for the beneficial effect of any of these drugs.[108] The introduction of proton pump inhibitors (PPIs) allowed more effective suppression of acid secretion. PPIs directly and irreversibly block the acid pump instead of the receptor and have a higher anti-secretory potential than the previously mentioned agents.[104, 109-116]

Proton pump inhibitors

PPIs inhibit gastric hydrochloric secretion by irreversible binding to the H^+, K^+-ATPase proton pump, which blocks the final step in acid production.[117-119] This block is maintained during the lifetime of the proton pump, which lies around 3 days.[120] As binding of the PPI to the acid pump requires activation of the drug by protonation, a single dose of PPIs only leads to blocking of active pumps, and thus not to a total blocking of acid secretion.[110]

Omeprazole was the first PPI to be developed and since then several other PPIs have emerged on the market, in particular pantoprazole, lansoprazole, rabeprazole and esomeprazole. Omeprazole is the most widely studied PPI.[113, 121-123] Several studies demonstrated that omeprazole is more effective than placebo in the treatment of peptic ulcer bleeding in high risk patients in terms of bleeding recurrence, hospital days, and the need for transfusion.[42, 111, 115, 124-127] Other studies demonstrated a positive effect of omeprazole on rebleeding, surgery, hospital stay and death in patients with low risk peptic ulcer bleeding.[122, 128] Differences between the different PPIs lie in pharmacokinetic characteristics and metabolization, and, in the case of esomeprazole, in consisting only of the active isomer. Several meta-analyses concluded that high dose PPIs were effective in consistently increasing intragastric pH to 6.0 and above and decreasing the rebleeding rates.[109, 129] This conclusion was based on stud-

ies giving the PPI as a bolus followed by continuous infusion for 72 hours, after which the drug was continued as once daily oral dose. However, these conclusions were in particular based on the results of studies in Asian populations, with fewer, non-conclusive data from Western populations. This difference is relevant as Asian subjects often have lower acid output than Caucasians and African-Americans. Furthermore, they usually have higher *H. pylori* prevalence rates, in particular of *cagA*-positive strains, which is associated with active gastritis which further impairs acid production. Finally, Asian populations have a higher prevalence of low-metabolizing CYP2C19 polymorphisms, which is associated with a smaller first-pass effect of most PPIs, and thus a higher efficacy of a given dose of PPIs. Taking all these effects together explains why high dose PPI therapy has more pronounced acid suppressive effect in Asians than in European and US populations. [111, 112, 126, 130] Based on these discrepancies and the lack of a convincing effect in non-Asian populations of high-dose iv treatment with the first generation PPIs on outcome of peptic ulcer bleeding, no PPI was until recently registered for this indication. However, this changed recently when the results of a large multicenter, international trial became available. This trial was conducted in a multiethnic population with high risk peptic ulcer bleeding. Study subjects were randomized to either intravenous esomeprazole given as 80 mg bolus followed by continuous infusion of 8 mg/h or placebo for 72 hours after adequate hemostatic endoscopic therapy. In this study a significant difference was found between both treatments with respect to the rates of recurrent bleeding, being 5.9 vs 10.3% (p=0.026) and the need for endoscopic retreatment (6.4 vs 11.63%; p=0.01).[42] A further cost-effectiveness study showed that high dose intravenous administration of esomeprazole after successful endoscopic therapy improves patient outcomes at a modest increase of costs (Table 5).[131]

Table 5. Literature PPI in peptic ulcer bleeding.

Study (year)	Area	Study design	Patients	(n)	Treatment	Results	Study period
Jensen *et al.* (2006)	US	RCT	Peptic ulcer bleeding (high risk)	153	Endoscopic treatment and PPI iv 80 + 8mg/h (72h) or H_2RA 50 mg + 6.25 mg/h (72h) After 72h po PPI 20 mg for 30 days.	Stopped early because slow enrolment Rebleeding 6.9% vs. 14.3%, mortality 4% vs. 4%. No significant differences.	30 days
Sung *et al.* (2003)	Asia	RCT	Peptic ulcer bleeding (high risk)	156	Endoscopic therapy+ PPI iv 80 mg + 8 mg/h (72h) or only PPI iv 80 + 8 mg/h (72h) After 72h both groups PPI 20 mg po	Rebleeding 1.1% vs. 11.6% (p=0.009) Mortality 2.6% vs. 5.1%. Endoscopic therapy important	30 days
Zargar *et al.* (2006)	Asia	RCT	Peptic ulcer bleeding (high risk)	203	Endoscopic therapy + PPI iv 80mg + 8mg/h (72h) or placebo (72h) After 72h all PPI 40 mg po 6 weeks	Rebleeding 7.8% vs. 19.8% (p=0.01), fewer transfusions (p=0.003), fewer days in hospital (p=0.0003)	30 days
Lau *et al.* (2000)	Asia	RCT	Peptic ulcer bleeding (high risk)	240	Endoscopic therapy + PPI 80 mg + 8 mg/h or placebo for 72h. After 72h all PPI 20 mg po 2 months	Rebleeding 6.7% vs. 22.5% (HR 3.9), mortality 4.2% vs. 10%	30 days
Kaviani *et al.* (2003)	Middle East	RCT	Peptic ulcer bleeding (high risk)	160	Endoscopic therapy + PPI 20 mg/6h or placebo	Mean hospital stay 62.8 ± 28.6 vs. 75 ± 35h (p=0.032), mean transfusion 1.13 ± 1.36 vs. 1.68 ± 1.68 bags (p=0.029) rebleeding 12 vs.26 cases (p=0.022)	3 weeks
Schaffalitzky de Muckadell *et al.* (1997)	Europe	RCT	Peptic ulcer bleeding (high risk)	274	Endoscopic therapy + PPI 80 mg + 8 mg/h iv or placebo After 72h both PPI 20 mg po till day 21	Overall outcome score difference in favor of omeprazole (p=0.004), less blood transfusions (p=0.01), shorter degree and duration of bleeding (p=0.02) and less surgery (p=0.003) or additional endoscopic therapy (p= 0.04)	21 days

Table 5. *(Continued)*

Study (year)	Area	Study design	Patients	(n)	Treatment	Results	Study period
Khuroo *et al.* (1997)	Asia	RCT	Peptic ulcer bleeding (high risk)	220	PPI 40 mg BID for 5 days or placebo	Further bleeding/rebleeding 10.9% vs. 36.45 (p <0.001) surgery 8 vs. 26 cases (p< 0.001) Mortality 2 vs. 6 pts. Transfusions 29.1% vs. 70.9% (p< 0.001) Significant reduction in ulcers with NBVB and adherent clots, no significant reduction in oozing or arterial spurting ulcers	30 days
Lin *et al.* (2006)	Asia	RCT	Peptic ulcer bleeding (high risk)	200	Endoscopic therapy + PPI iv 40 mg/6h or PPI iv 40 mg/12h or H_2RA 400 mg/12h. After 72h both PPI 20 mg po 2 months	Rebleeding omeprazole 40 mg/6h 9% vs. 32.8% in cimetidine (p<0.01).Volume of transfusion less in OME mg/6h than OME 40mg/12h and CIM (p<0.001) No statistical difference: hospital stay, surgery and mortality	14 days
Lin *et al.* (1998)	Asia	RCT	Peptic ulcer bleeding (high risk)	100	Endoscopic therapy + PPI iv 40 mg + 160 mg/24h or H_2RA Cimetidine iv 300 mg + 1200mg/24h If necessary second look and therapy and after 72h all PPI 20 mg po 2 weeks	Intragastric pH >6 84.4% ± 22.9% vs. 53.5% ± 32.3% (p<0.001) Rebleeding 4% vs. 24% (p=0.004), less transfusion median 0 (0-2500ml) vs. median 0 (0-5000ml) (p=0.08). No difference in mortality, hospital stay or surgery rate	14 days

Table 5. *(Continued)*

Study (year)	Area	Study design	Patients	(n)	Treatment	Results	Study period
Hasselgren *et al.* (1997)	Europe	RCT	Peptic ulcer bleeding	333	Endoscopic therapy+ PPI iv 80 mg + 8 mg/h or placebo. After 72h groups PPI 20 mg po 2 weeks	Overall outcome (scale) omeprazole better (p=0.017) Need for surgery omeprazole vs. placebo (p=0.003), degree of bleeding (p=0.003) and treatment failure (p=0.0009). Mortality identical. Subgroup oozing: outcome omeprazole better (p=0.01)	21 days
Sung *et al.* (2009)	Worldwide	RCT	Peptic ulcer bleeding (high risk)	767	Endoscopic therapy+ PPI iv 80 mg + 8 mg/h or placebo for 72 h. After 72h all PPI po 40 mg for 27 days	Recurrent bleeding 5.9% vs. 10.3% (p=0.026), retreatment 6.4% vs. 11.6% (p=0.012), surgery 2.7% vs. 5.4% and all-cause mortality 0.8% vs. 2.1% (last 2 not significant)	30 days
Li *et al.* (2000)	Asia	Retrospective	Peptic ulcer bleeding (excl. arterial spurt)	607	Endoscopic therapy in oozing bleeding H_2RA 400 mg bolus bid for 5 days or PPI iv 40 mg for 5 days	Surgery 3.8% vs. 9.28% (p <0.05) mortality rate 1.49% vs. 2.66% not significant. Transfusion not significantly different in number and volume.	30 days

Bid: twice daily, H2RA: histamine H2 receptor antagonist, iv: intravenous, po: per os, PPI: proton pump inhibitor, RCT: randomized controlled trial.

Administration method

PPIs can be administered orally as well as intravenously. Most indications for PPI therapy, e.g. GERD, can be treated with oral administration of a low daily dose of PPI. In the case of peptic ulcer bleeding the preferred administration method differs between high risk and low risk bleeders. In case of low risk peptic ulcer bleeding, the highest concern is to induce re-epithelialization of the ulcer and treatment of the underlying cause. The risk of rebleeding is however low and therapy therefore aims at maintaining a pH above 4. Oral and intravenous administration of PPI are both effective in reaching this goal, and thus low-risk patients can be adequately managed by oral PPI therapy with early discharge.[20]

In high risk peptic ulcer bleeding the first concern is the prevention of rebleeding and thus rapid increase of intragastric pH. Several administration methods and schemes have been studied and current guidelines recommend treatment with an intravenous bolus followed by continuous infusion of PPI in patients with high-risk stigmata who have undergone successful endoscopic therapy.[20] Because the proton pumps are continuously being regenerated and the bio-availability of a PPI in the circulation is short, the rationale for this regimen is to first inactivate all actively secreting proton pumps with a bolus injection, then prevent further activation of remaining proton pumps with the continuous infusion.[132]

Dosage

In patients without high-risk stigmata, treating in particular aims at re-epithelialization of the ulcer. For this purpose, a daily PPI dosage to 20-40 mg omeprazole is sufficient. In patients with high-risk stigmata, treatment also aims at maintaining hemostasis. For this purpose, continuous high-dose intravenous PPI therapy is needed. A double blind cross-over study in *H. pylori*-positive healthy volunteers measured the intragastric pH during intravenous treatment with 80 mg omeprazole given as a bolus followed by continuous infusion with either 2, 4, or 8 mg/h. The 8 mg/h infusion led to higher mean pH levels than the other treatment regimens.[133] Another study evaluated the intragastric pH in bleeding peptic ulcer patients during intravenous treatment with pantoprazole 80 mg bolus followed by either 6 or 8 mg/h intravenously. Again, the 8 mg/h regimen showed a lower intra-individual variability of the intragastric pH and a greater proportion of time with an intragastric pH above 6.[134]

Current practice

The current standard of care for patients with low-risk ulcers consists of standard dose oral PPI treatment for a period determined by the underlying cause of peptic ulcer disease. No head to head studies have been conducted comparing the different PPI agents in the treatment of high risk peptic ulcer bleeding. In patients with a high risk for rebleeding, the first 3 days after endoscopic therapy are crucial since most recurrent bleeding occurs within 72 hours. It is generally accepted based on the literature mentioned earlier that the aim for these patients is to maintain the intragastric pH > 6 during those initial 3 days. This goal can be ap-

proached by continuous high dose iv esomeprazole treatment, starting with a bolus of 80 mg followed by 8 mg/h continuously, as was decided in the latest guidelines.[20, 42] Esomeprazole iv has recently been the first PPI to be approved in the EU and other markets for the short-term maintenance of hemostasis and prevention of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. Earlier, no such approval existed for any PPI anywhere in the world.

Follow-up

Management of peptic ulcer bleeding consists not only of acute therapy, but should also include diagnosis and treatment of the underlying cause. The most common causes of peptic ulcers are *H. pylori* infection and use of NSAIDs (non-steroidal anti-inflammatory drugs) and low dose acetylsalicylic acid (ASA) use. In the case of underlying *H. pylori* infection, eradication of *H. pylori* is mandatory. *H. pylori* eradication does not affect the early rebleeding rates, eradication therapy can thus be scheduled after discharge.[135, 136] In fact, some studies have demonstrated a faster and higher increase of intragastric pH in *H. pylori*-positive patients during PPI treatment, related to the fact that *H. pylori* gastritis augments the acid-suppressive effect of the PPI. Once the acute episode has passed, *H. pylori* eradication should be prescribed as it is the most efficient strategy, also better than maintenance acid suppressive treatment, to prevent renewed bleeding from recurrent ulcers.[58] In determining whether a bleeding ulcer is related to *H. pylori*, it is of importance to note that active bleeding as well as PPI therapy can cause false negative outcomes in *H. pylori* testing.[43] For this reason, guidelines recommend to retest patients with a negative *H. pylori* test-result obtained in the acute setting.[20] Eradication therapy can consist of several medication combinations from the standard triple therapy (PPI and 2 different kinds of antibiotics), quadruple therapy (containing a PPI, bismuth, and 2 antibiotics or a PPI and 3 antibiotics), to sequential therapy or the more recent hybrid sequential therapy, with treatments schedules varying from 7 to 14 days (Table 6). The more extensive therapies such as quadruple therapy are more effective, in particular in patients with strains carrying antimicrobial resistance.[55] The effect of eradication therapy should be assessed at least 4 weeks after the end of therapy, as patients in whom eradication treatment failed have a significant risk for recurrent ulcer bleeding.

In the case of NSAIDs or low dose ASA use the important question is whether or not the medication can be permanently withdrawn. This is not possible in the majority of patients receiving low dose ASA, as they use this medication for secondary cardiovascular prophylaxis. In fact, a study from Hong Kong showed that low dose aspirin should be restarted as soon as possible in these patients despite their bleeding ulcer, to prevent early occurrence of cardiovascular events.[45] For secondary prophylaxis of bleeding during ongoing low dose aspirin treatment, *H. pylori*-negative patients required PPI maintenance treatment in a dose equivalent to 20 mg omeprazole once daily. In *H. pylori*–positive patients, PPI maintenance treatment and *H. pylori* eradication are equally effective to prevent rebleeding.[56] Replacing

Table 6. Overview of antibiotics used for *H. pylori* eradication.

Drug class	Drug	Triple therapy[1]	Quadruple therapy[2,3]	Quadruple therapy[2]	Sequential therapy[4]	Sequential-hybrid[5]
		Dose	Dose	Dose	Dose	Dose
Acid suppression	proton pump inhibitor	20-40 mg bid[6]	20-40 mg bid[6]	20-40 mg bid[6]	20-40 mg bid[6]	20-40 mg bid[6]
Standard antimicrobials	bismuth compound[7]	2 tablets bid	2 tablets bid			
	Amoxicillin	1 g bid		1 g bid	1 g bid	1 g bid
	Metronidazole[8]	500 mg bid	500 mg tid	500 mg tid	500 mg bid	500 mg bid
	Clarithromycin	500 mg bid		500 mg bid	500 mg bid	500 mg bid
	Tetracycline		500 mg qid			
Salvage antimicrobials	Levofloxacin	300 mg bid				
	Rifabutin	150 mg bid				
	Furazolidone	100 mg bid				

[1] Triple therapy consists of a PPI or bismuth compound, together with two of the listed antibiotics, usually given for 7 – 14 days. [2] Quadruple therapy consists of a PPI plus bismuth compound with two antibiotics as listed given for 4 – 10 days **or** *PPI plus three antibiotics as listed given for 4 – 10 days. [3] Bismuth, metronidazole and tetracycline can be administered in a single capsule 1 times daily (Pylera ®). [4]Sequential therapy consists of 10 days of treatment with a PPI, plus amoxicillin for the first 5 days and a combination of clarithromycin and metronidazole for the second 5 days. [5] Sequential Hybrid consists of 14 days of PPI and amoxicillin during the last 7 days combined with clarithromycin and metronidazole (malfertheiner 2010). [6] PPI dose equivalent to omeprazole 20 mg bid. [7] Bismuth subsalicylate or subcitrate.[8]Alternative = tinidazole 500 mg bid.*

aspirin by clopidogrel is an inferior strategy to prevent rebleeding.[137] A considerable proportion of patients who present with peptic ulcer bleeding during NSAID therapy, this medication can be stopped. This is sufficient prophylaxis for rebleeding, unless subjects are also infected with *H. pylori*. In that case, additional *H. pylori* eradication is recommended. Patients who need to continue NSAIDs, should be preferentially treated with a combination of a COX-2 inhibitor and a PPI in a dose equivalent to omeprazole 20 mg once daily, as alternative strategies of a COX-2 inhibitor alone or a PPI with a conventional NSAID are still associated with a significant risk of rebleeding.[20, 54, 138]

Patients with non-NSAID non-*H. pylori* idiopathic ulcer disease require maintenance treatment with a PPI in a dose equivalent to 20 mg omeprazole once daily. They further need to be assessed for the underlying cause of the ulcer.[53] Once identified, the underlying cause should be treated if possible. Finally, patients with gastric ulcer disease need to adequately assessed for the possibility that the ulcer is due to underlying gastric malignancy.[139, 140]

CONCLUSION

The management of peptic ulcer bleeding has changed dramatically over the past 20 years. Early endoscopy is crucial for initial diagnosis and risk assessment. For cases with high-risk stigmata, in particular active bleeding, visible vessel or adherent clot, endoscopic treatment is the mainstay in management. Endoscopic treatment primarily consists of clips placement or thermal coagulation, alone or in combination with epinephrine injection. After adequate hemostasis, high risk cases should receive profound acid suppressive therapy, for the first 72 hours given as continuous infusion. Recurrent bleedings can usually firstly be managed again by endoscopic treatment. Failures should either undergo surgery or trans-arterial embolization. During follow-up, adequate attention should be given to identify and manage the underlying cause of the bleeding ulcer. With this multistep approach, the outcome of bleeding has strongly improved over the years.

CHAPTER 1.5

OTHER CAUSES OF UPPER GI BLEEDING

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INTRODUCTION

Upper gastrointestinal bleeding can be classified into several different categories, according to etiology and pathophysiology. The commonest causes of upper gastrointestinal (GI) bleeding, as reported in several endoscopic studies, are variceal bleeding and peptic ulcer bleeding.[4, 6, 141] These two main causes have been discussed in the previous chapters, yet the list of differential diagnoses of bleeding of the upper gastrointestinal tract is much longer (Table 1). Although less common than variceal and peptic ulcer bleeding, these other causes are met frequently. A retrospective study from Sweden reported that the incidence of peptic ulcer bleeding had decreased over a 20 year period from 62 to 32 per 100.000 per year, the incidence of non-ulcer, non-variceal upper gastrointestinal bleeding had remained stable at 30 per 100.000 per year.[142] These data are in line with the results of a UK study on 5004 patients presenting with upper GI bleeding. Peptic ulcer and varices were present in 36 and 11% patients; the remainder of bleeds was related to other causes.[11] In a similar Dutch study on 769 patients with upper GI bleeding, 47% had non-ulcer non-variceal bleeding.[4] The main causes of non-ulcer, non-variceal bleeding are gastroduodenal erosions and esophagitis. This chapter deals with the spectrum and variety of causes of non-variceal non-ulcer upper GI bleeding.

Table 1. Etiology of non-variceal, non-peptic ulcer upper gastrointestinal bleeding.

Non-variceal non-peptic ulcer causes of upper GI bleeding	
EROSIVE	**TRAUMATIC OR IATROGENIC**
·Toxic (drugs-induced)	·Mallory Weiss tear
·Inflammatory (esophagitis / gastritis / duodenitis)	·Intramural hematoma
·Mechanic (e.g. Cameron lesion)	·Boerhaave's syndrome
VASCULAR	·Foreign body / toxic substance ingestion
·Angiodysplasia	·Post-endoscopy intervention
·Dieulafoy lesion	·Post-surgical intervention
·Vasoenteric fistula	**MISCELLANEOUS**
·Portal hypertensive gastropathy	·Hemobilia
·Gastric antral vascular ectasia	·Hemosuccus pancreaticus
·Vasculitides and systemic disorders	·Bleeding diathesis
·Hereditary vascular anomalies	·Nasopharyngeal lesion
·Sudden venous outflow obstruction	·Metastatic tumor
NEOPLASTIC	
·Polyp (adenomatous / hyperplastic / fundic gland / hamartomatous)	
·Adeno-/squamous cell carcinoma	
·Lymphoma	
·Mesenchymal neoplasm	
·Kaposi's sarcoma	
·Melanoma	
·Neuroendocrine tumor	
·Metastatic tumor	

EROSIVE CAUSES OF UPPER GASTROINTESTINAL BLEEDING

An erosion is a breach of the epithelial surface that does not extend beyond the muscularis mucosa and has a diameter ≤5 mm. Erosions can occur throughout the gastrointestinal tract. Causes of upper gastrointestinal erosions can be divided into direct toxic, mechanic, and inflammatory etiology.

Erosions are a common finding during upper endoscopy. In a random sample of the adult population of two Swedish municipalities, 1001 subjects underwent upper endoscopy. Esophageal erosions were found in 16% of the population.[143] Based on a validated questionnaire, two thirds of subjects with esophageal erosions reported gastrointestinal symptoms. The erosions were often seen in combination with gastro-esophageal reflux disease. In a similarly designed study in Italy, endoscopic abnormalities were found in 23% of the subjects. Esophagitis was found in 11.8% and peptic ulcer in 5.9% of individuals, whereas 5.3% had gastroduodenal erosions.[144] A large population-based study in China among 1022 randomly selected volunteers who underwent a gastroscopy, reported a much higher prevalence of gastroduodenal erosions (49.9%).[145] The majority (77.3%) of these individuals with erosive lesions were asymptomatic. Duodenal erosions were more prevalent among men.

Drug induced erosion

Mucosal erosions caused by direct toxic effects of drugs are more frequently seen, since aging populations are naturally burdened with chronic diseases and polypharmacy. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are considered the main cause of erosive disease in Western patients.[146] NSAIDs can produce a spectrum of mucosal damage. Intramucosal petechial hemorrhage can occur within 2 hours of initial ingestion. Superficial and hemorrhagic erosions, gastroduodenitis, and ulceration may develop with continued exposure.[147] In an endoscopic study of 187 patients using low dose aspirin for at least 3 months without gastroprotective agents, erosions were found in 63% of subjects.[148] A similar study in asymptomatic patients using aspirin with gastroprotective agents reported the presence of erosions in 34%.[149]

Other notorious mucosal damage causing drugs are selective serotonin reuptake inhibitors (SSRIs), and corticosteroids. Both classes of drugs are associated with peptic ulcer bleeds as well as non-ulcer, non-variceal bleeds. In a large case-control study from Sweden, current use of SSRIs was associated with an odds ratio of 1.67 (95% CI 1.46-1.92) for upper gastrointestinal bleeding.[150] These bleeds are related both to overt ulcer disease, as well as gastroduodenal erosions.

Nitrogen-containing bisphosphonates, mainly used for the treatment of osteoporosis, can also cause mucosal irritation of the upper GI tract and even ulceration, bleeding and perforation. A review on the adverse effect of bisphosphonates showed little or no increased risk of gastrointestinal complications if bisphosphonates were administered properly and

discontinued promptly if esophageal symptoms developed.[151] However, proper administration requires that bisophosphonate tablets are taken in the morning with sufficient water and the patient remaining upright and fasting for at least 30 minutes after bisphosponate intake. These precautions are often not adhered to. Other classes of drugs, which can lead to erosions and ulceration are potassium tablets, some antibiotics (e.g. erythromycin, nalidixin acid, sulfonamides and derivatives), and chemotherapy, as well as radiation therapy.[147]

Mechanical erosions

A common cause of mechanical erosive disease is hiatal hernia. Larger hiatal hernia can give rise to development of linear erosions and ulcers or so-called Cameron lesions within the stomach at the impression of the diaphragm (Figure 1a and b).[152] They predominantly occur along the smaller curvature, and their exact etiology is unknown. They most likely occur as a result of the combination of chronic mechanical trauma (e.g. rubbing of the mucosal folds at the level of the diaphragm during respiratory excursions) and acid injury. Local ischemia has been suggested to contribute to this process, *H. pylori* does not appear to play a role.

Cameron lesions are found in about 5% of the patients with hiatal hernia undergoing upper endoscopy, two thirds of these patients have multiple lesions.[153] Their prevalence rises with the size of the hernia. They have been reported to occur in 10-20% of patients with a hernia $\geq$5 cm.[154] Usually they are seen accidentally, although they may cause acute or chronic gastrointestinal bleeding and iron deficiency anemia. This was already illustrated by the first description of lesions in 1986 by Cameron and Higgins.[152] They reported on 109 patients with hiatal hernia, half of whom had anemia. Cameron lesions were found in 24% of those anemic patients. Since then, Cameron lesions have been associated with chronic bleeding leading to anemia, but also with acute bleeding. The treatment of choice is acid suppression, generally with excellent outcome. Acute bleeds sometimes require endoscopic treatment such as of

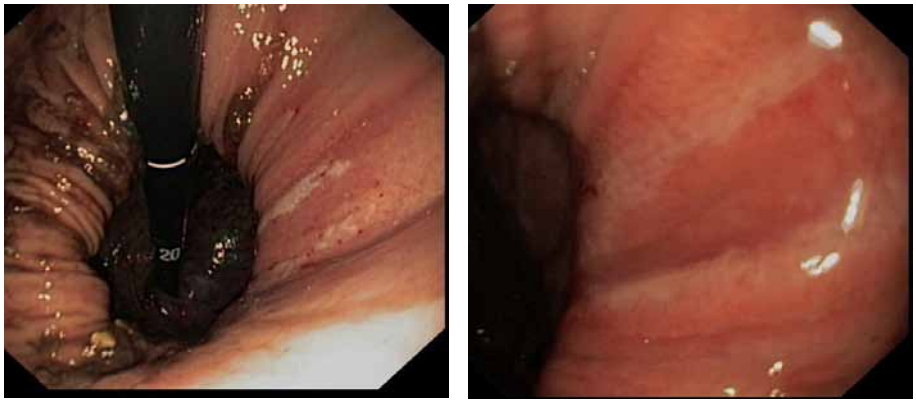

Figure 1a and b. Cameron lesions showing as white mucosal breaks at the 1 to 3 o'clock position in a large hiatal hernia with the endoscope in retroflexion. Some red spots indicate minor bleeding.

a visible vessel, for which the treatment is similar to the approach of other gastroduodenal ulcers. Cameron lesions are a well-known cause of missed diagnoses in patients with upper GI bleeding undergoing endoscopy. Patients with larger hiatal hernia and signs of anemia or bleeding should therefore be adequately inspected including endoscopy in retroversion to optimize the inspection of the hernia.

Inflammatory erosions

Erosive esophago-gastro-duodenitis, an acute or chronic inflammation of the lining of the esophagus, stomach and/or duodenum, has many possible causes. Acute causes are associated with excessive alcohol consumption and the use of drugs (see before).[155] Chronic causes include gastro-esophageal reflux disease and *H. pylori* infection (Figure 2).[39, 156] Infection with *H. pylori* causes chronic inflammation of the gastric mucosa, which may slowly progress via atrophic gastritis, intestinal metaplasia, and dysplasia to gastric adenocarcinoma.[157]

In most cross-sectional studies of patients with upper gastrointestinal bleeding, erosive disease is reported as underlying cause in 8% to 34% percent of cases (Table 2).[2, 4-6, 8]

However, in a 17 year follow-up study of 117 patients with gastric erosions without peptic ulcer disease, no clinical history of gastrointestinal bleeding during the follow-up and no difference in hemoglobin level compared with the group patients without erosions was seen.[39] This indicates that gastroduodenal erosions infrequently cause clinically significant blood loss. This is supported for instance by data from cohort studies of long-term aspirin users, showing the common occurrence of gastroduodenal erosions, but a low incidence of clinically overt bleeding. A systematic review of literature data reported an annual incidence of any major bleeding in 1 per 769 low-dose aspirin users.[158]

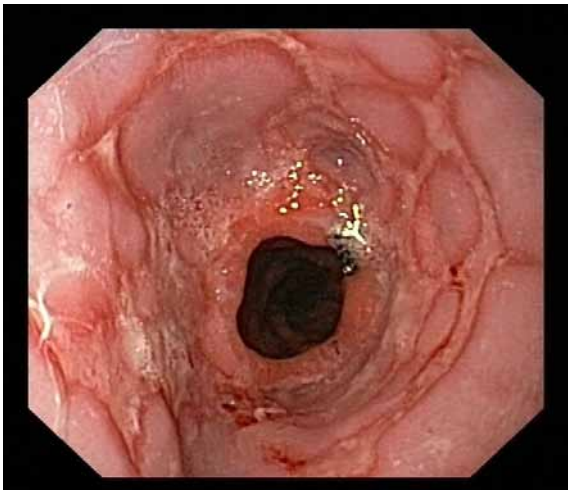

Figure 2. Reflux esophagitis in the presence of hiatal herniation.

Table 2. Proportional distribution of causes of upper gastrointestinal bleeding in various studies.

	Czernichow	Paspatis	Van Leerdam	Di Fiore	Theocharis
Country	France	Greece	The Netherlands	France	Greece
Year of report	1996	1998-1999	2000	2000	2005
No. of patients	2133	353	769	453	353
Peptic Ulcer	37	49	46	31	67
Gastric	NR	21	NR	NR	32
Duodenal	NR	27	NR	NR	33
Erosive disease	12	31	20*	16**	8***
Esophagitis	12	3	NR	11	NR
Esophageal / gastric varices	14	4	7	20	6
Mallory Weiss tear	7	NR	NR	8	4
Malignancy	3	3	5	2	8
Other diagnosis	7	3	8	NR	2
No cause identified	8	7	14	11	5

*NR: not reported. *: Including esophageal ulcers, esophagitis, gastritis, bulbitis and erosions. **: Including gastritis. ***: Gastroduodenitis.*

Treatment and prevention of (bleeding from) erosions depends upon the cause. Most cases respond well to proton pump inhibitor (PPI) therapy, leading to healing of erosions and normalization of hemoglobin levels. The offending agent should be discontinued whenever possible and, if present, *H. pylori* should be eradicated. Some patients require surgical therapy, such as correction of a hiatal hernia for recurrent bleeding from Cameron lesions.[154]

VASCULAR ANOMALIES

Angiodysplasia

Angiodysplasia is defined as a sharply delineated vascular lesion within the mucosa, with a typical red appearance, with flat or slightly raised surface (Figure 3). The lesions are often multiple and frequently seen in the colon, but may also involve the upper gastrointestinal tract and small bowel. They are generally believed to be acquired, since the peak of diagnosis lies in the fifth and sixth decade of life. The exact causes of angiodysplasia are unknown.[159] Associations with renal insufficiency and cardiac valve disease have been reported, but it is unknown whether these associations are in any way causal.[160, 161] An explanation is that the lesions are actually not more common in patients with renal and cardiac disease, but are instead detected more frequently because of the increased risk of bleeding in these patients.

Patients with angiodysplasia can present with chronic anemia, as well as with acute gastrointestinal bleeding with melena and seldom hematemesis. In a study from the US evaluat-

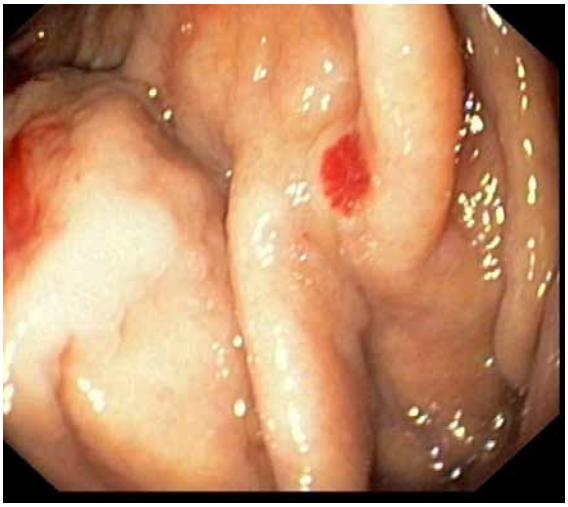

Figure 3. Angiodysplasias of the gastric corpus, presenting as marked red spots within the mucosa.

ing 727 patients with end-stage renal disease and acute upper gastrointestinal bleeding, 1.3% bled from an angiodysplastic lesion.[162] The current standard of endoscopic treatment of bleeding angiodysplasias consists of coagulation therapy. Although this is associated with a high success rate for treatment of individual lesions, patients may during follow-up often present with recurrent anemia or overt bleeding due to incomplete treatment of multiple lesions, or due to occurrence of renewed lesions. This may require repeat endoscopy, often also including colonoscopy and sometimes enteroscopy.

In a Dutch study of 132 patients who underwent balloon-assisted enteroscopy for reasons of recurrent or persistent anemia without a focus on gastroduodenoscopy and ileocolonoscopy, angiodysplasia or vascular malformation was found in 40 patients (30%). Twenty-two percent of patients initially treated for angiodysplasia suffered from rebleeding after initial improvement. In all but one patient, persistent angiodysplasias and/or vessel malformations were seen, requiring repeated therapy. This repeated therapy resulted in improvement in 58%.[163]

In this context, systemic medical therapy may play an adjuvant or even primary role [164]. The best studied pharmacological agents are estrogen and progesterone, but their effects remain controversial. A Spanish multicenter, randomized controlled trial compared ethinylestradiol (0.01mg) plus norethisterone (2mg) with placebo for a minimum period of one year. No difference in bleeding episodes and transfusion requirements was found between both treatment arms.[165]

Another potential effective drug is somatostatin analogues such as octreotide. A recent meta-analysis including a total of 62 patients of three studies showed a beneficial effect of octreotide on the need for transfusion in patients with angiodysplastic lesions.[166] The weighted mean difference in transfusion requirements before starting therapy and after

treatment initiation was -2.2 (95% CI -3.9 to -0.5). Although less widely studied, thalidomide may be a promising drug where other therapies failed to stop the bleeding.[167, 168] In a pilot study, seven patients with chronic angiodysplastic bleeding were treated with thalidomide in a starting dose of 50mg/day, increased if tolerated with 50mg/day every week up to 200mg daily. Therapy was then continued for six months. Four patients discontinued treatment within 3-8 weeks because of side effects and required the same amount of blood transfusions as pre-study. In contrast the other three patients did not require any transfusion during the six months of therapy.[169]

Dieulafoy lesion

A Dieulafoy lesion consists of a dilated tortuous artery with a diameter up to 3 mm that protrudes through the mucosa (Figure 4a and b). These lesions most commonly occur in the proximal stomach along the lesser curve, but they are incidentally seen in the esophagus,[170] small intestine and colon.[171] Dieulafoy lesions may cause massive gastrointestinal hemorrhage by rupture of the artery, accounting for 1-6% of cases of acute non-variceal upper gastrointestinal bleeding.[41] Rupture occurs probably by a combination of factors like straining of the vascular wall during peristalsis, morphologic changes of the artery, and peptic digestion.[41, 172] The high prevalence of co-morbidity (90%) and correlated drug-use in patients with Dieulafoy lesions is likely to play an additional role in the process of vessel rupture.[41]

Dieulafoy lesions can easily be missed during endoscopy, because the mucosal break is usually minor, may be hidden from view due to blood remnants, and because the bleed can be intermittent. This may give rise to a typical pattern of repeated acute severe bleeding with shock, yet failure to identify the source of the bleed during endoscopy. This requires adequate full inspection of the gastric mucosa, with removal of blood remnants if necessary, combined with proper insufflation and sometimes change in position of the patient if needed for a full view, in particular in the presence of large clots. In rare cases, endoscopic ultrasound may help to identify the lesion. Endoscopic treatment is the first choice in bleeding Dieulafoy

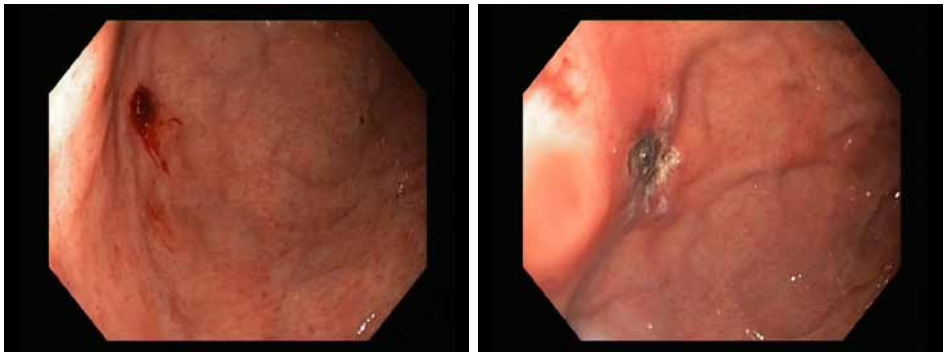

Figure 4a and b. Dieulafoy lesion in the fundus before and after treatment with argon plasma coagulation.

lesions[173] and is able to achieve hemostasis in more than 90% of cases.[41] Treatment is usually performed with clipping or banding of the lesion. Overall mortality rates due to bleeding Dieulafoy lesions are up to 20%[41] and associated with advanced age and co-morbidity rather than directly to exsanguination.[172]

Vasoenteric fistula

A fistula developing between an abdominal vessel and the gastrointestinal tract is an uncommon but severe, life threatening cause of gastrointestinal bleeding. The diagnosis can be difficult, as bleeding may occur intermittently and the actual lesion is often small. Most lesions arise from the aorta, in particular in the presence of an aneurysm (so-called primary fistulas) or an aortic prosthesis (secondary fistula). Secondary aortoduodenal fistulas are far more frequent. Primary aortoduodenal fistulas are most frequently caused by infrarenal aneurysms of the abdominal aorta. Other reported causes are the primary or metastatic tumors, ingested foreign bodies puncturing the luminal wall into a major adjacent artery, radiation therapy, diverticulitis, and perforating ulcers.[174] About three-quarters of aortoenteric fistulas communicate with the duodenum, usually the horizontal part. In rare cases, a duodenocaval fistula may occur, of which some 40 cases have been described in the literature, among others after ingestion of a fish bone and after surgery.[175] Fistulas to vascular bypasses or prostheses, such as a mesocaval shunt may also give rise to bleeding (Figure 5). An early contrast-enhanced computed tomography is indicated in cases suspected of vasoenteric fistula, rather than an endoscopy, which is inferior in detecting these lesions. However, endoscopy is relevant for exclusion of other causes of acute gastrointestinal hemorrhage.[176] Without operative management the mortality rate of bleeding due to vasoenteric fistula is nearly 100%. Open

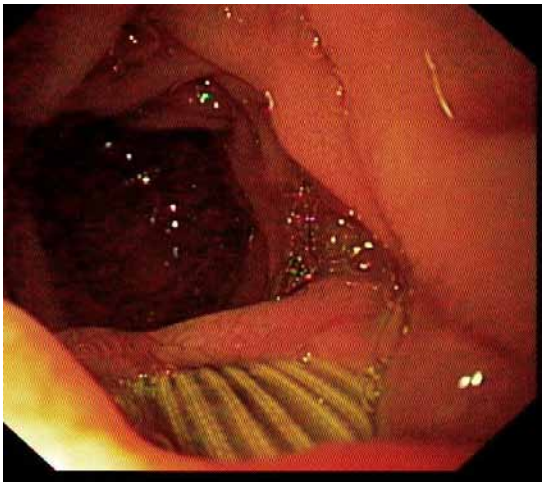

Figure 5. Appearance of a mesocaval shunt eroding into the duodenum in a patient presenting with intermittent severe upper GI bleeding 27 years after bypass surgery for reasons of portal hypertension.

surgery is the option of choice in most patients. Endovascular aortic repair (EVAR) may be an option in fragile patients and can be used as a bridging procedure to definitive repair.[174, 177, 178]

Portal hypertensive gastropathy

Portal hypertensive gastropathy or congestive gastropathy refers to changes in the gastric mucosa in patients with portal hypertension. Gastroscopy classically reveals a mosaic like pattern of the mucosa, resembling a snake-skin (Figure 6).[179] These endoscopic findings correspond to dilated mucosal capillaries without inflammation. Similar mucosal changes can be seen in the small bowel and colon of patients with portal hypertension, named portal hypertensive enteropathy[180] and portal hypertensive colopathy,[181] respectively. Bleeding from these conditions usually occurs as slow, diffuse oozing, but it may also be acute (and even) massive.

A recent review reported prevalence of portal hypertensive gastropathy ranging from 20% to 98% in various series of patients with cirrhosis.[182] This wide range in prevalence was likely related to a combination of factors including patient selection, absence of uniform diagnostic criteria and classification, and differences in inter- and intra-observer interpretation of endoscopic lesions.

Portal hypertensive gastropathy is often seen in the presence of esophageal or gastric varices. The degree of portal hypertension needed for development of portal hypertensive gastropathy remains controversial.[182] *Helicobacter pylori* infection is unlikely to be involved in the pathogenesis.[183]

As portal hypertension is a key factor in etiology, treatment in portal hypertensive gastropathy aims to reduce portal venous pressure. This may be accomplished by a variety of

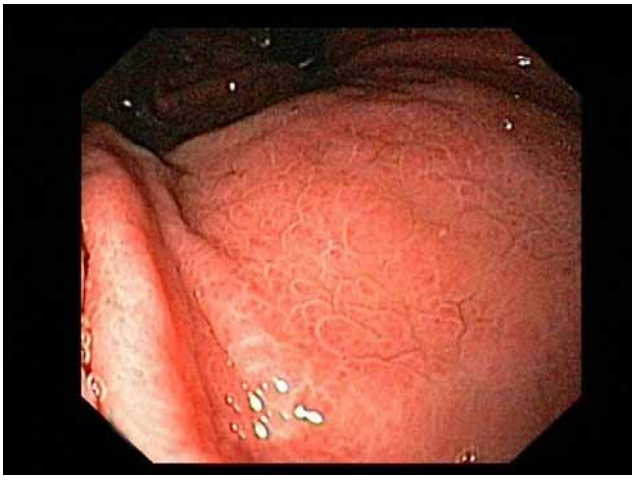

Figure 6. Portal hypertensive gastropathy.

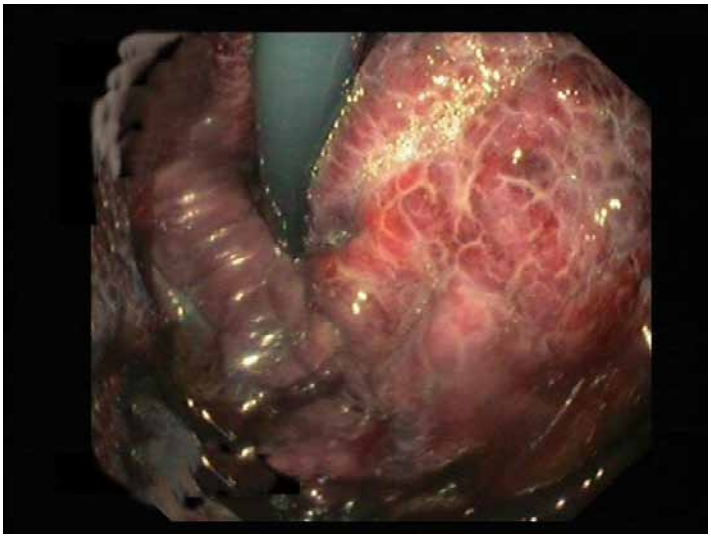

Figure 7. Severe acute portal hypertensive gastropathy after TIPS closure.

measures including non-selective β-blockers, somatostatin and octreotide, surgical portocaval shunts, and TIPS.[184]

A similar pattern of vascular disease can in rare cases be observed when there is acute, severe venous outflow obstruction of stomach and/or duodenum, for instance due to a severe right-sided cardiac decompensation, or in case of thrombosis (Figure 7).

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE) is often confused with portal hypertensive gastropathy. Although GAVE is closely related to portal hypertension, it can also appear in the absence of portal hypertension. It is also called "Watermelon Stomach" because of linear red stripes, separated by normal mucosa, giving the appearance of a watermelon (Figure 8a and b).

GAVE have been associated with several auto-immune diseases (e.g. Sjögren's syndrome, Addison's disease, and systemic sclerosis), renal failure, and bone marrow transplantation.[185-188] GAVE generally does not respond to treatments which reduce portal pressure. The first-line treatment of actively bleeding GAVE as well as recurrent bleeding from GAVE therefore is endoscopic ablation of the lesion.[184] This is usually done by means of argon plasma coagulation. In a series of 20 patients with GAVE-related bleeding and liver cirrhosis treated with argon plasma coagulation, GAVE eradication was achieved after a median of 3 sessions per patient. Thirty percent of patients had relapse of GAVE after a mean of 7.7 months. These patients were successfully retreated with argon plasma coagulation.[189]

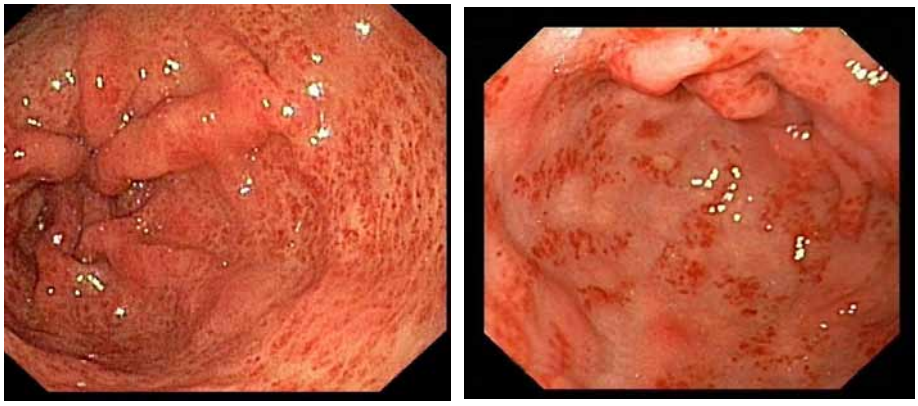

Figure 8a and b. Gastric antral vascular ectasia.

Hereditary vascular anomalies

A wide variety of hereditary and congenital vascular anomalies can cause upper gastrointestinal bleeding. These include hereditary hemorrhagic telangiectasia,[190] pseudoxanthoma elasticum,[191] Ehlers-Danlos syndrome,[192] and blue rubber bleb nevus syndrome (Table 3).[193, 194] Together, these syndromes are rare causes of upper gastrointestinal bleeding.

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome is an autosomal dominant disorder of the fibrovascular tissue. It is characterized by teleangiectasias and arteriovenous malformations of skin, mucosa (Figure 9) and viscera. There are two different phenotypes, HHT1 and HHT2 with respectively mutations of endoglin and Activin A receptor like kinase-1 genes.[195] In a study on 25 patients with HHT, teleangiec-

Table 3. Hereditary vascular anomalies related to gastrointestinal bleeding.

Disease	Original reporter(s)	Prevalence	Heredity	Pathophysiology	Gastrointestinal manifestations
Hereditary hemorrhagic telangiectasia	Osler-Weber-Rendu	1:5000-8000	Autosomal dominant	Diverse, depending on the mutation	Iron deficiency anemia or acute bleeding
Pseudoxanthoma elasticum	Grönblad-Strandberg	1:25.000-100.000	Autosomal recessive (80%) also autosomal dominant and sporadic	Progressive calcification and fragmentation of elastic fibers	Gastrointestinal bleeding
Cutis hyperelastica	Ehlers-Danlos	1:5000-10.000	Autosomal dominant or recessive depending on type	Defect in the synthesis of collagen	Perforation and massive bleeding
Blue rubber bleb nevus syndrome	Bean	Extremely rare	Usually sporadic, seldom autosomal dominant	Venous malformations	Massive or occult hemorrhage and iron deficiency anemia

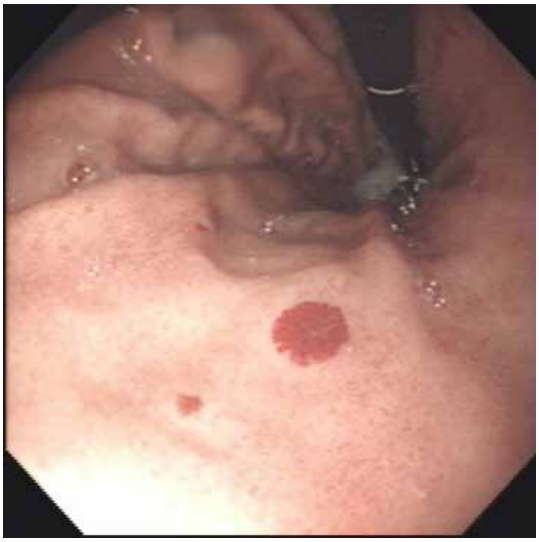

Figure 9. Vascular anomaly in the stomach of a patient with Osler-Weber-Rendu syndrome.

tasias were found in 92% of the patients throughout the gastrointestinal tract, with lesions observed in 67% of patients at gastroduodenoscopy, in 76% at videocapsule endoscopy, and in 32% at colonoscopy. Large teleangiectasias in small intestine and colon appear to occur predominantly in HHT1. Hepatic arteriovenous malformations are mainly found in HHT2.[195] Recurrent gastro-intestinal bleeding occurs in up to one third of the patients. This bleeding can be severe. A study of hereditary hemorrhagic teleangiectasia families in Denmark documented that 25% of patients of 60 years and older suffered from severe gastrointestinal bleeding, defined as requiring at least 6 units of blood within 6 months.[196] Curative options are limited. The use of photocoagulation using bipolar electrocoagulation, argon plasma coagulation, or laser techniques is useful for control of bleeding in the short term. Medical treatment with progesterone and estrogen has shown to be beneficial in reducing the incidence of rebleeding.[197]

Pseudoxanthoma elasticum (Grönblad–Strandberg syndrome) is an autosomal recessive disease characterized by progressive calcification and fragmentation of elastic fibers.[198] Patients typically develop ocular, cutaneous and cardiovascular manifestations, but the gastrointestinal tract may also be affected. The principal symptom is gastrointestinal bleeding.[191] Ehlers-Danlos syndrome is also a hereditary connective tissue disorder. The classic manifestations are skin hyper-extensibility and generalized joint hypermobility. Less known is the fact that these patients are also prone to gastrointestinal catastrophes such as perforation and massive bleeding.[192]

Blue rubber bleb nevus syndrome is a very rare vascular anomaly syndrome consisting of multifocal venous malformations. The venous malformations can occur in any tissue. However, lesions of the gastrointestinal tract appear to be more clinically relevant than

skin or soft tissue lesions, since chronic continuous bleeding, leading to anemia or massive sudden hemorrhage can occur. Therapies are not widely studied. Anti-angiogenetic agents, octreotide, argon photo coagulation, and endoscopic band ligation have not shown durable beneficial effect. Serious chronic bleedings can be effectively treated by aggressive resection of the venous malformations.[199]

Vasculitides and systemic disorders

In rare cases, upper gastrointestinal bleeding is caused by vasculitis, in particular as part of Henoch-Schönlein purpura, Behçet's disease, polyarteritis nodosa, Churg-Strauss syndrome, Wegener granulomatosis, or microscopic polyangiitis.[200-203] Furthermore, gastrointestinal vasculitis has also been described in giant cell arteritis, Takayasu's disease, Buerger's disease, lupus vasculitis, mixed connective tissue disease, and rheumatoid arthritis.[203, 204] Bleeding lesions due to these vascular conditions may occur from the upper nasopharynx throughout the gastrointestinal tract, even in rare cases giving rise to bleeding from other sites such as hemobilia, when vasculitis affects the bile ducts or gall bladder.[204] The bleeding focus can usually be diagnosed by gastroduodenoscopy, in some cases additional procedures such as enteroscopy or ERCP are required. Lesions may typically be very topical, affecting sharply demarcated areas, yet arising at multiple sites. With transmural involvement of the bowel such as in Churg-Strauss vasculitis, lesions may not only give rise to bleeding, but also to perforation. Endoscopic biopsy specimens of the affected area may reveal ulceration and inflammation, but are often insufficient to demonstrate the underlying vasculitis. This is more likely to be found in full thickness biopsy specimens, such as can be obtained when surgery is needed for complicated disease. Diagnosis of the underlying disease is more adequately done by full assessment for systemic disease, including targeted auto-immune serology, urine sediment and measurement of renal function, thorax X-ray, and others. Treatment mostly starts with corticosteroids and immune suppressives, together with PPIs in patients with upper GI lesions.

Ischemia of the digestive tract

Acute gastric ischemia (Figure 10) is uncommon because of the stomach's rich vascular supply. Nevertheless it's important to recognize, since progression to necrosis can lead to perforation and sepsis. Cases reported in the literature include arterial thrombosis of mesenteric vessels, gastric volvulus or hiatus hernia's, acute necrotizing gastritis, ingestion of caustic substances, therapeutic embolizations, postoperative complications and acute gastric dilatation related to eating disorders, trauma, acute pancreatitis, and diabetic ketoacidosis.[205, 206] It may also occur in case of stenosis of the celiac trunk and insufficient collateral circulation.[207] Gastrointestinal bleeding due to ischemia has been described in a few case reports.[208, 209]

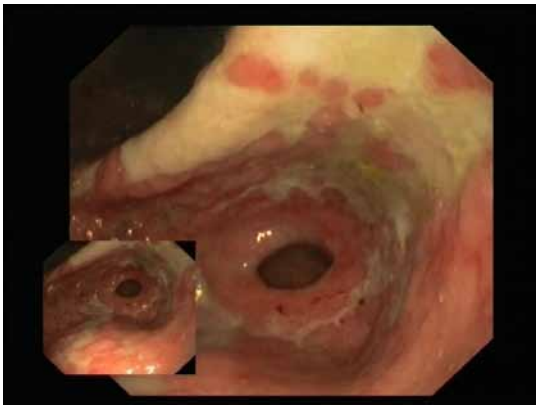

Figure 10. Gastric ulceration due to ischemia in the presence of severe stenosis of the celiac trunk and upper mesenteric artery.

NEOPLASTIC LESIONS

Neoplastic lesions of the upper GI tract account for 2 to 8% of the cases of gastrointestinal bleeding (Table 2).[2, 4-6, 8] These lesions include benign polyps as well as malignancies, among which gastric adenocarcinomas are the most prevalent among patients presenting with upper GI bleeding.

Polyps

Polyps of the GI tract can be either sporadic or arise as part of a hereditary polyposis syndrome. In the upper GI tract, the stomach and proximal duodenum are the most frequently affected sites. Most of these polyps are asymptomatic, but some may give rise to bleeding, typically occult. This in particular occurs from larger or ulcerated polyps.[210] In a large endoscopic study of 987 patients with anemia, hyperplastic polyps of the stomach were found in 1.4% of cases.[211]

Polyps can be grossly divided into fundic gland polyps, hyperplastic polyps (Figure 11), adenomatous polyps, and hamartomas.[212] Fundic gland polyps are typically affecting the acid secreting proximal compartment of the stomach. They either occur as part of a hereditary syndrome, in particular familial adenomatous polyposis, or sporadic. The vast majority, if not all sporadic fundic gland polyps occur in long-term users of proton pump inhibitors. This is thought to be due to a blocking of the glandular flow by swelling and intraluminal protrusion of parietal cells with blocked secretory function. This explains why these lesions only arise in the corpus, have a somewhat transparent, soft fluid-filled appearance, and can show regression after withdrawal of PPI therapy. They usually are discovered by chance, and do not require therapy. In some cases however, the polyps may become large (> 1-2 cm) and may give rise to blood loss. In those cases, the only existing therapies are endoscopic removal of

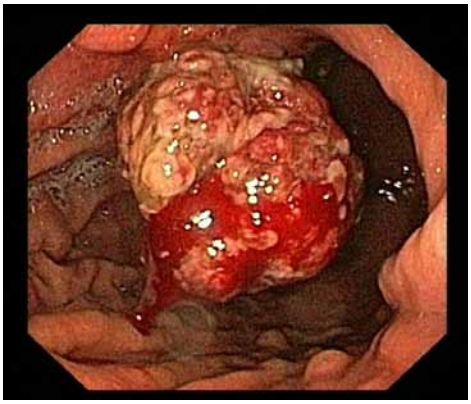

Figure 11. Hyperplastic polyp of the gastric body, with signs of bleeding.

the largest polyps. The clinical indication for PPI therapy should then also be reconsidered, but routine withdrawal of PPI therapy is not indicated. Malignant degeneration of these PPI-associated sporadic fundic gland polyps has hardly ever been described. There is therefore no evidence that these patients require any surveillance. This does not pertain to patients with familial adenomatous polyposis (FAP), when diagnosed with PPI-unrelated fundic gland polyps. These fundic gland polyps do have malignant potential and should be surveyed together with other polypoid lesions which may arise in stomach and duodenum of these patients.[213]

Hyperplastic polyps in particular occur sporadically. Gastroduodenal adenomas can also occur sporadically, as well as against a background of a familial polyp syndrome, in particular including FAP, and to a lesser extent Lynch syndrome, and Peutz-Jeghers syndrome.[214] In FAP, the adenomas in particular arise in the proximal duodenum. In Lynch and Peutz-Jeghers syndrome, there may be predominance for gastric lesions. Sporadic adenomas of the duodenum are associated with a risk for coexistent colorectal adenomas. In a study on 49 cases (M/F 27/22, mean age 63 years, range 29-88) with sporadic duodenal adenoma, 47% was found to have colorectal adenoma on colonoscopy.[215] The discovery of all these upper gastrointestinal polyps lies in the identification of hereditary cancer syndromes, surveillance and early detection of progression to malignancy, and treatment of complications such as bleeding. Bleeding lesions are best treated by endoscopic removal of the polypoid lesion.

Adeno- and squamous cell carcinoma

Gastric and esophageal cancer are the second and sixth leading cause of cancer mortality worldwide respectively.[216] Most gastric cancers are adenocarcinomas. In the esophagus, squamous cell carcinoma is still the most common type worldwide, although the incidence of esophageal adenocarcinomas has risen rapidly in the past three decades and has become the predominant esophageal malignancy in the United States and northern Europe. Major

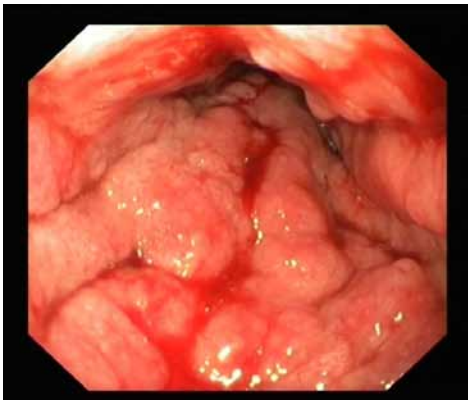

Figure 12. Invasive gastric adenocarcinoma circumferentially affecting the stomach wall, and giving rise to diffuse bleeding.

risk factors for esophageal adenocarcinoma are obesity, gastroesophageal reflux and it's resultant Barrett's esophagus.[217]

Most patients with esophageal cancer have complaints of dysphagia (74%) or odynophagia (17%) at time of diagnosis. Weight loss is common, and (if more than 10% of body weight) associated with poor prognosis.[218] Bleeding is an infrequent first presentation of esophageal cancer, but is more common during the course of disease if curative surgery cannot be performed. Adenocarcinomas of the stomach (Figure 12) more often bleed as initial presentation.[219] A North American study of 42 patients with severe upper GIB due to upper gastrointestinal cancer showed that most presented at an advanced stage presumably with larger ulcerating tumor masses.[219] Bleeding was the initial presentation of the tumor in half of the cases. Endoscopic hemostasis was initially effective in all cases. However, severe bleeding from gastrointestinal tumors was correlated with a poor one-year survival. In contrast to the success of endoscopic therapy in this case series, endoscopy offers little treatment options in case of diffusely bleeding cancers. Surgery is the mainstay of therapy for cure of gastroesophageal carcinomas, nowadays mostly combined with perioperative chemotherapy or chemoradiation.[220] In patients with bleeding cancers for whom surgery is no option, short-term radiotherapy or angiography with embolization of the supplying vessel are alternative treatment options. In a retrospective study of 30 patients with gastric cancer bleeding, 73% responded to radiotherapy, with a 3-month rebleeding rate of 60%. Twelve patients received concurrent chemoradiotherapy and had a significant lower rebleeding rate (17.5%).[221] In another retrospective study, 23 patients with gastric cancer bleeding underwent transcatheter arterial embolization. The overall clinical success rate was 52%, with a one-month rebleeding rate of 8%.[222] Bleeding of the cancer or surrounding mucosa may also occur as a result of the radio- and/or chemotherapy. These bleeding episodes are often difficult to manage because of their diffuse character and vulnerability of the mucosa, and primarily require supportive measures and temporary or permanent withdrawal of therapy.

Lymphoma

Upper gastrointestinal lymphomas in particular occur in the stomach. They are almost invariably associated with *H. pylori*. Most are low-grade, marginal zone B-cell lymphomas confined to the mucosa and submucosa (stage IE) (Figure 13a and b). Fifty-five to 78% of these lesions show partial or complete remission after *H. pylori* eradication as monotherapy.[223] The recognition of the association between these lymphomas and *H. pylori*, the increased use of diagnostic upper GI endoscopy, and improved knowledge on the appearance and biology of these lymphomas led a decade ago first to a rise in gastric lymphoma incidence. This incidence is now decreasing as a result of decreasing *H. pylori* prevalence.[224] Nevertheless, gastric lymphomas still make up for 30% or more of all primary gastrointestinal lymphomas. Some 5% of all GI lymphomas are small bowel lymphomas, in particular T-cell lymphomas associated with long-existing celiac disease.[225, 226]

Data on the incidence of bleeding of these tumors are scarce. In a small study of 14 patients with primary gastrointestinal NK-/T-cell lymphoma, gastrointestinal bleeding was the most frequent presenting symptom (42% of cases). Unfortunately, the disease was at an advanced stage at the time of diagnosis in all cases.[227] Likewise, gastric marginal zone lymphomas may present as ulcerative disease giving rise to bleeding, either acute or chronic. In these cases, endoscopic treatment may be feasible if the bleeding is focal. Successful endoscopic treatment should be followed by PPI therapy, and full workup of the lesion followed by individualized therapy depending on the histology and transmural depth of the lesion, and the presence of extragastric local or distant disease. Therapeutic options primarily consist of *H. pylori* eradication. For more advanced and high-grade lesions as well as those which do not respond adequately to *H. pylori* eradication, CHOP chemotherapy and radiotherapy, as well as surgery all form alternatives. *H. pylori* eradication as monotherapy is in particular indicated for low-grade lesions confined to the (sub-)mucosa, stage IE. More advanced lesions usually require additional therapy. This is also true for lesions which carry a specific chromosomal rearrangement, the API2-MALT mutation as the presence of this mutation is a predictor for poor response to *H. pylori* eradication. In a systematic review of 1408 cases, only 22% of patients

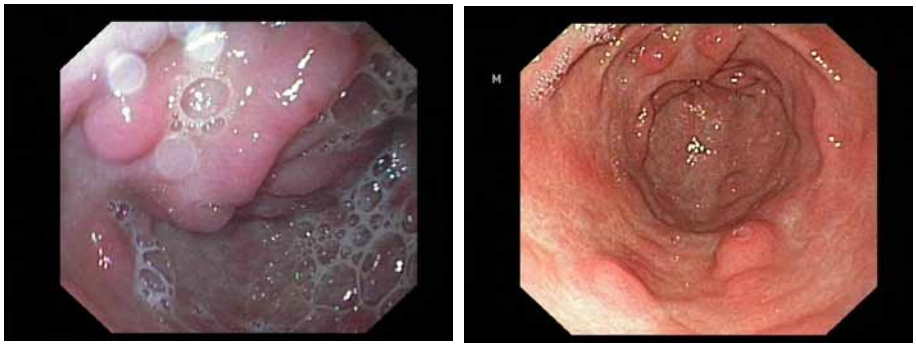

Figure 13a and b. Marginal zone B-cell (MALT) lymphoma.

with this mutation responded to *H. pylori* eradication.[223] Other gastrointestinal lymphomas such as small bowel T-cell lymphomas are primarily treated with chemotherapy.

Mesenchymal tumors

Like many other organ systems, the gastrointestinal tract is the origin of a wide range of mesenchymal or stromal neoplasms. The most common group consists of neoplasms that are collectively referred to as gastrointestinal stromal tumors (GISTs) (Figure 14, 15). Less frequent mesenchymal neoplasms include leiomyomas/leiomyosarcomas, lipomas/liposarcomas, Schwannomas and peripheral nerve sheath tumors. They are classified upon their morphologic and immunophenotypic profile.

GISTs are most frequent observed in the stomach, although they are estimated to account only for 1 to 3 percent of all gastric neoplasms.[228] They are characterized by the presence of KIT mutations as well as mutations in platelet-derived growth factor receptor alpha tyrosine kinases.[229] The most common presentation of GISTs is gastrointestinal bleeding, which may be either acute or chronic. Patients can also present with abdominal pain caused by tumor rupture, internal bleeding, or gastrointestinal obstruction. Smaller GISTs are often coincidentally found during endoscopy. About 20 to 25% of gastric and 40 to 50% of small intestinal GISTs are malignant. Common metastatic sites are the abdominal cavity and liver, but bones, soft tissues, skin and seldom lymph nodes and lungs may also be affected. Long-term clinical follow-up is needed since metastases can occur more than 15 years after initial diagnosis.[230]

Leiomyoma is the most common esophageal mesenchymal tumor.[231] They are slowly growing benign intramural tumors. Most patients are asymptomatic and lesions are often found accidentally during endoscopy. However, with increasing size of the lesion, symptoms like dysphagia, retrosternal pain and regurgitation can occur. Ulcerated leiomyomas may occasionally present with bleeding. Although smaller lesions are often followed by means

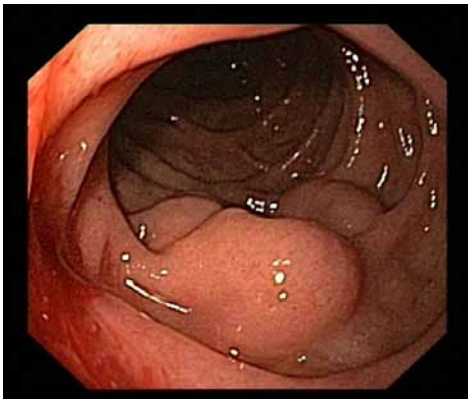

Figure 14. Duodenal gastrointestinal stromal tumor (GIST).

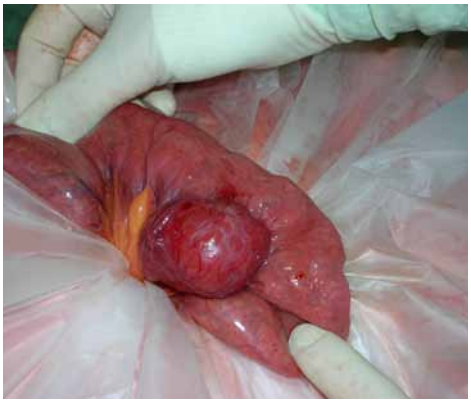

Figure 15. Peroperative view of a jejunal GIST in a patient presenting with repeated episodes of melena.

of endoscopy with endoscopic ultrasound, bleeding lesions require treatment both because of the bleeding and the risk of malignant degeneration which increases with size. Treatment usually consists of surgical or endoscopic resection. The latter is done by means of endoscopic submucosal dissection. Malignant transformation is extremely rare in leiomyoma. Malignant leiomyosarcomas grow much faster and occur at older age.[232]

Gastrointestinal lipomas account for 4% of benign gastrointestinal tumors.[233] The majority are located in the colon (60-75%), followed by small bowel (20-25%) and stomach (5%). They are usually asymptomatic, but can cause the same symptoms as leiomyomas. Larger lesions most frequently present with gastrointestinal hemorrhage (in over 50% of cases).[234]

Liposarcomas are extremely rare in the gastrointestinal tract. Less than 20 cases, mainly esophageal liposarcomas (Figure 16), have been reported in the world literature.[235] Treatment of bleeding lesions is the same as for leiomyomas and GISTs.

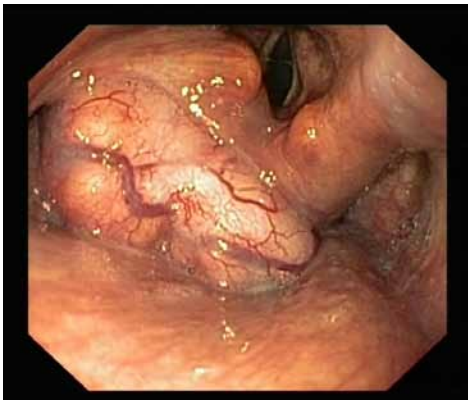

Figure 16. Liposarcoma of the esophagus.

Kaposi's sarcoma

Kaposi's sarcoma is a low grade vascular tumor associated with human herpesvirus-8 infection (Figure 17). It is the most common HIV-related gastrointestinal tumor and seen in about 40% of AIDS patients. The incidence of Kaposi sarcoma has decreased significantly since the availability of HAART therapy. Kaposi sarcomas are usually asymptomatic, but gastrointestinal hemorrhage has been reported.[210] Possible therapies for bleeding from Kaposi's sarcomas are injection therapy, heat coagulation, sclerotherapy, radiotherapy, systemic chemotherapy, surgical excision and angiographic embolization.[236]

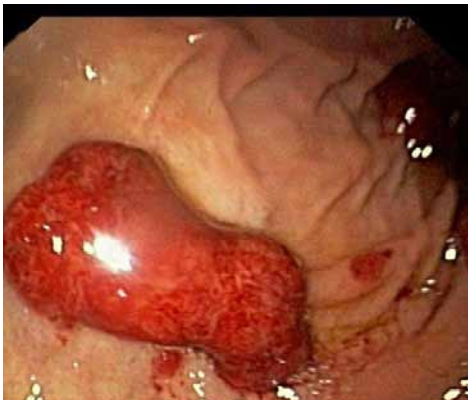

Figure 17. Kaposi's sarcoma in a HIV positive patient.

Primary malignant melanoma

Although most malignant melanomas of the gastrointestinal tract are of metastatic origin, primary malignant melanomas do occur in the gastrointestinal tract, in particular in the esophagus, small bowel, rectum and anus. They tend to be more aggressive and are associated with worse outcome than metastatic melanoma lesions of the gastrointestinal tract.[237] Initial presentation with gastrointestinal bleed is rare and has only been described in case reports.[238, 239] Treatment of bleeding depends on the location and situation of the tumor, angiographic embolization is like for other malignant bleeding lesions one of the treatment options of first choice.

Neuroendocrine tumor

The gastrointestinal tract is the largest neuroendocrine system in the body. The majority of neuroendocrine tumors (NET) arise from the gastrointestinal and pulmonary system.[240] NETs comprised 0.8% of all gastrointestinal tumors in an English population based cancer registry between 1971 and 2006. Their incidence is rising. Of primary gastrointestinal NETs 38% arose in the appendix, 29% in the small intestine, 13% in the colon, 12% in the stomach and 8% in the rectum.[241] NETs can occur sporadically or as part of a syndrome (e.g. Zollinger-Ellison and

multiple endocrine neoplasia type 1 (MEN1)). Most gastroentero-pancreatic neuroendocrine tumors are asymptomatic and discovered coincidentally upon imaging or surgery for unrelated reasons. About 10% of neuroendocrine tumors secrete excessive levels of hormones, most notably serotonin, causing flushing, wheezing, diarrhea, abdominal cramping and peripheral edema. In rare cases, hemorrhage is the presenting symptom.[242] Like for other malignant tumors, primary diagnosis and treatment for bleeding lesions consists of endoscopy, if needed followed by secondary intervention, in particular angiographic embolization.

Metastatic tumor

Metastatic tumors to the gastrointestinal tract are very rare in comparison to primary malignancies. Malignancies which are known to metastasize to the gastrointestinal tract are malignant melanoma, breast, lung, and renal cancer. Disseminated lymphoma can also affect the gastrointestinal tract. Furthermore, primary gastrointestinal malignancies such as esophageal cancers may sometimes also give rise to metastases elsewhere in the tract, although local transmural growth such as from airways and mediastinum to the esophagus, and from the colon to the stomach is more common. The relative frequencies of these tumors are not well defined, given the fact that the reported series are small. For instance, two series from the United States and Japan on respectively 67 and 389 cases with metastatic tumors in the stomach found a range of primary tumors, mostly coming the lungs, skin (melanoma), and breast.[243, 244]

A typical sign both on radiological and endoscopic imaging of metastatic disease is the so-called bull's eyes sign, corresponding to the clinical appearance of a submucosal tumor with central ulceration (Figure 18). Another characteristic is the presence of multiple lesions, present in about 35% of cases.[244] Bleeding from the ulcerative lesion may be the first presenting sign; these bleeds are often diffuse from vulnerable tissue and thus offer limited options for endoscopic treatment. Endoscopy remains the first tool in management, to assess the

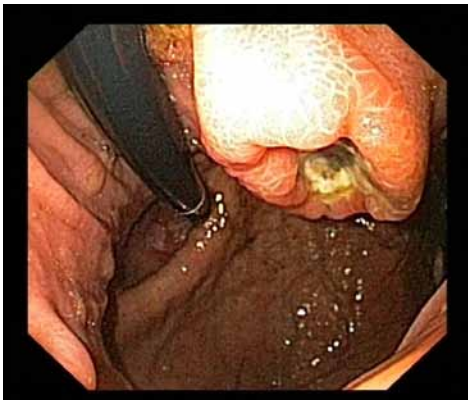

Figure 18. Metastasis of malignant melanoma in the stomach with central ulceration (bull's eyes sign).

source of the bleed and look for treatment options. The appearance of the lesion is typical for malignant disease. In patients with a known primary tumor, the association is usually readily made. In patients with an unknown primary, further investigation has to reveal the source of the metastasis. In both cases, histology may be needed to confirm the source or to guide further evaluation. Depending on the severity of the bleed, histology is either obtained at the first endoscopy, or postponed till a more severe bleed is adequately managed.

TRAUMATIC OR IATROGENIC BLEEDING

Mallory Weiss tear

A Mallory Weiss tear is a mucosal laceration at the gastroesophageal junction or gastric cardia usually caused by retching or forceful vomiting (Figure 19a and b). This condition was first described in 1929 by G. K. Mallory and S. Weiss.[245] A typical presentation is with the occurrence of hematemesis after first having vomited without blood. Mallory Weiss lesions are a common cause of upper GI bleeding, several epidemiological studies reported these lesions as the bleeding source in 2% to 8% of patients presenting with acute upper gastrointestinal bleeding.[2, 6, 8, 11, 246] In a large UK audit including 5004 patients undergoing endoscopy for upper GI bleeding, Mallory Weiss lesions were the only bleeding source in 2.1% of cases, and were overall present in 4.3% of cases.[11] Many factors have been associated with the development of Mallory Weiss lesions, including alcohol use, use of aspirin and coumarines, paroxysms of coughing, pregnancy, heavy lifting, straining, seizure, blunt abdominal trauma, colonic lavage, and cardiopulmonary resuscitation.[40] It is best diagnosed with upper endoscopy, but is also reported as a complication in <0.1% of diagnostic endoscopies.[247] The amount of blood loss is usually mild. In a retrospective study in the USA of 73 patients with Mallory Weiss lesions, 20% needed blood transfusion of >6 units, 11% had further bleeding, 3% underwent surgery and 3% died.[248] The management of Mallory Weiss lesions is thus mostly

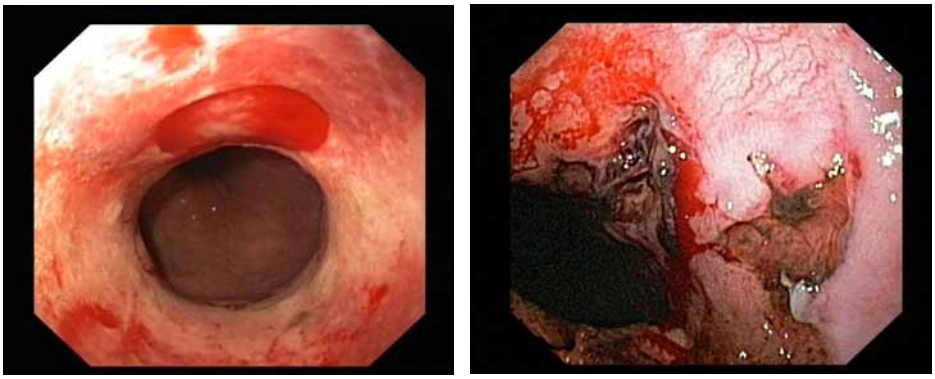

Figure 19a and b. Mallory Weis tear.

Table 5. Treatment of Mallory Weiss lesions in randomised controlled trials.

	Llach		Huang		Park		Cho		Lecleire	
Year of publication	2001		2002		2004		2008		2009	
Treatment options	EEI*	NET	EHP	EEI	EBL	EEI	EBL	EHP	EBL	EHP + EEI
Patients per arm	32	31	18	17	17	17	20	21	29	27
Primary haemostasis	100%	NR	100%	100%	100%	94.1%	100%	100%	100%	100%
Rebleeding	6.2%	25.8%	6%	6%	0%	0%	10%	6%	0%	18%

*NR: not reported, EBL: Endoscopic band ligation, EEI: Endoscopic epinephrine injection, EHP: Endoscopic hemoclip placement, NET: No endoscopic therapy. * and polidocanol.*

supportive because about 90% of lesions spontaneously stop bleeding.[246, 248] A minority of cases requires endoscopic treatment. In a French series of 218 patients with Mallory Weiss bleeding, 56 (26%) had active bleeding on endoscopy. In other series, this proportion ranged from 5 to 44%.[246, 249] Various studies have looked at optimal endoscopic treatment (Table 5). In a series of randomized controlled trials, rebleeding rates after only supportive therapy were much higher than after any form of endoscopic therapy. Endoscopic epinephrine injection, endoscopic hemoclip placement, and endoscopic band ligation were equivalent for primary hemostasis. Rebleeding rates after band ligation and hemoclip placement were similar in a randomized Korean trial, but significantly lower after band ligation in a French trial.[249-253] It is unknown whether prescription of a proton pump inhibitor accelerates healing.

Intramural hematoma

Intramural hematoma of the upper GI tract can occur spontaneously, or on minor or larger trauma, such as improper swallowing of pills, food impaction, strained vomiting, or endoscopic intervention including endoscopic biopsy, esophageal dilatation, and variceal injection therapy.[254] Conditions that impair hemostasis, such as use of coumarins, are considered risk factors. It typically appears as a bulging, purplish lesion with a smooth, normal overlying mucosa, occupying most of the lumen (Figure 20).[40] The condition predominantly occurs in the esophagus, where it is considered an intermediate stage in the spectrum from Mallory-Weiss tear to Boerhaave's syndrome. It may however also affect other parts of the gastrointestinal tract such as the duodenum. Most lesions resolve completely within a few weeks, with conservative treatment,[255] in some cases the hematoma may break through to the lumen, giving rise to overt blood loss (Figure 21).

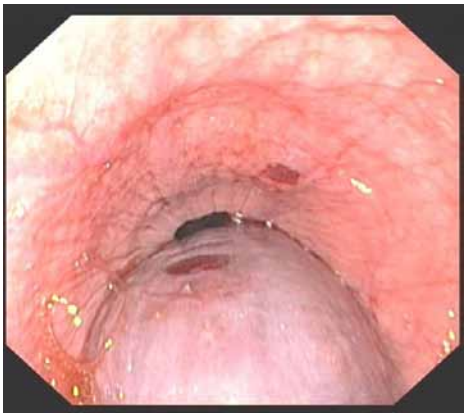

Figure 20. Endoscopic view of esophageal hematoma appearing as purplish lesion bulging into the lumen.

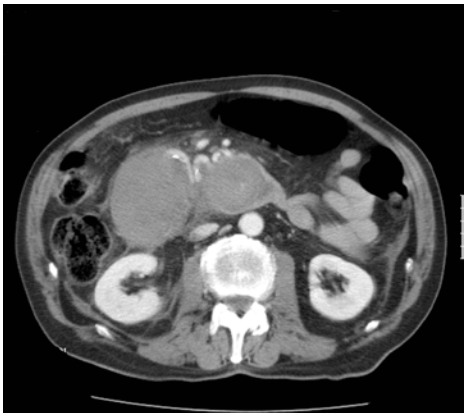

Figure 21. Abdominal computed tomography scan of the abdomen revealing a large hematoma in the duodenal wall. This patient developed melena, 3 days after presentation with signs of gastric outlet syndrome, due to ruptured hematoma.

Boerhaave's syndrome and other causes of transmural perforation

Boerhaave's syndrome is a rupture of the esophagus caused by a rapid rise in intraluminal pressure in the distal esophagus combined with negative intrathoracic pressure caused by straining or vomiting. Other causes of benign esophageal perforation include endoscopic and surgical handling and foreign body impaction.[256] A diagnosis of esophageal perforation is usually readily made by chest X-ray and thorax CT showing signs of mediastinal air and fluid, and often pleural effusion, with leakage of contrast. In some cases, bleeding may be an accompanying symptom. Endoscopy has a role in the diagnosis of small lesions, as well as in the treatment of bleeding and closure of the perforation. This can be done by means

of placement of a self-expandable metal stent, which is appearing as a good alternative to conventional surgical therapy.[256]

Foreign body and toxic substance ingestion

Ingestion of foreign bodies and toxic substance can be both accidental and intentional. They are mainly seen in children and persons attempting suicide. Caustic injury can be caused by a range of alkaline (e.g. NaOH, KOH, NH_3), as well acidic agents (e.g. HCl, H_2SO_4), and by neutral substances such as phenol, formaldehyde, iodine, and concentrated hydrogen peroxide. The ingestion of strong alkali results in liquefaction necrosis, which is associated with deep tissue penetration and may result in perforation.[257] Acidic agents cause more superficial coagulation necrosis with scarring that may limit the extent of the injury.[258] Induction of emesis and caustic neutralization with acids are both contraindicated, and empiric use of antibiotics has no proven benefit. Early prophylactic esophageal stenting is under investigation.[259] Bleeding may occur as a result of widespread ulceration. Endoscopy has a role in evaluation of tissue damage, but often has little to offer in terms of treatment of bleeding. More severe bleeding is however rare.

Upper gastrointestinal mucosal injury is also seen after foreign body ingestion. In children, these often include toy particles, coins, and other smaller things. Potentially more harmful are batteries, and magnets. The former can lead to local toxic effects in case of leakage, while swallowing of two or more magnets (present in toys as well as for instance in certain

Table 4. Frequently ingested foreign bodies associated with gastrointestinal hemorrhage.

Ingested foreign bodies
Metallic
· Coins
· Batteries
· Magnets
· Wires
· Needles
Indigestible food parts
· Fish bones
· Other animal bones
Liquids
· Alkalis (e.g. NaOH, KOH, NH_3)
· Acids (e.g. HCl, H_2SO_4)
· Other caustics (e.g. phenol, formaldehyde, iodine, concentrated hydrogen peroxide)
· Alcohol
Other
· Denture/dental bridges
· Toothpicks

children's jewelry, such as earrings) can lead to local adhesion with gut wall in-between. Both leakage and pressure adhesion can lead to local ulceration, bleeding and perforation.[260] In adults, foreign bodies often include partial dentures, toothpicks, needles, and indigestible parts of the meal, like fish and other animal bones (Table 4). Hemorrhage is the second most frequent complication after foreign body ingestion.[261] It can occur as a result of local pressure, or puncture of the mucosa with sometimes fistula formation to a larger vessel.[262] Endoscopy has a role in removal of the foreign body if needed, and in diagnosis and treatment of the source of a bleed.

Post-endoscopy bleeding

Bleeding is one of the most common complications of upper gastrointestinal endoscopy, in particular intervention endoscopy. Higher risk procedures include endoscopic mucosal resection (EMR) and submucosal dissection (ESD), as well as endoscopic polypectomy.

In a series of 273 gastric low-grade dysplastic lesions removed by EMR, bleeding rate was 6.2%.[263] In a large study of 468 subjects with gastric non-invasive adenocarcinoma, post-ESD bleeding occurred in 5.5% of cases.[264] Bleeding reported after endoscopic gastroduodenal polypectomy occurred in less than 1%.[265, 266] Most of these bleeds occur during the initial procedure and can be dealt directly. Polypectomy bleeds are often clipped, whereas mucosal resection bleeds can be well treated by treatment of the small bleeding vessels by means of brief grasping and coagulation with a hot biopsy forceps. Lower risk interventions include dilation with balloon, boogies, or needle knife.[267, 268] In a series of 985 balloon dilations for achalasia, only 2 episodes of bleeding were noted.[267]

Post-surgery bleeding

Gastrointestinal bleeding is an infrequent well-known major complication of abdominal surgery. Notorious surgical procedures are esophagectomy, (partial or total) gastrectomy, pancreaticoduodenectomy, and bariatric surgery.[269] Bariatric procedures at risk include: gastric band placement, sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion. Immediate postoperative bleeding is usually from staple lines, from the site of the anastomosis, or from poor hemostasis at the time of surgery. Late bleeding can occur due to erosions and ulcerations in the gastric remnant, at the site of the gastric band and at anastomoses.[270]

MISCELLANEOUS CAUSES OF BLEEDING

Hemobilia

Hemobilia or bleeding from the hepatobiliary tract is a rare cause of gastrointestinal bleeding. It either occurs as a result of an intrabiliary lesion, or when there is a fistula between

a vessel of the splanchnic circulation and the intrahepatic or extrahepatic biliary system. The causes include iatrogenic and accidental trauma (e.g. liver biopsy,[271] percutaneous transhepatic cholangiography, cholecystectomy, TIPS, endoscopic biliary biopsies/stenting, angioembolization, and blunt abdominal trauma), gallstones, cholecystitis, hepatic or bile duct tumors, hepatic artery aneurysms and hepatic abscesses. In an older series of 196 with hemobilia, 137 were secondary to accidental trauma, and 59 cases resulted from iatrogenic causes.[272] Since then, the incidence of iatrogenic hemobilia has increased with the rise of percutaneous liver procedures. In a more recent review on 222 cases with hemobilia, 65% was iatrogenic, while accidental trauma accounted for only 6%. Other causes were inflammation (13%), vascular malformations (9%), malignancy (7%) and other (1%).[273] In rare cases, bleeding may occur due to a fistula to the portal system or a hepatic vein, either due to trauma, malignancy, endoscopy or surgery. In most cases, these bleeds are self-limiting and do not require intervention other than preventing biliary obstruction due to clots. In rare cases, a connection between the biliary ducts and a hepatic vein can lead to rapid onset of extreme jaundice.[274]

Symptoms of hemobilia can be diverse. The classic triad of jaundice, biliary colic and upper gastrointestinal bleeding was in the most recent series only observed in 22% of the patients.[273] Endoscopic retrograde cholangiography (ERCP) is helpful to confirm diagnosis and the underlying cause, and can also be of help in clearance of the biliary tree, with stenting if necessary to reduce the risk of renewed obstruction (Figure 22a and b). Most bleeds are self-limiting. In the previously mentioned review 43% of cases were managed conservatively, whereas 36% were treated by transarterial embolization (TAE). Surgery was indicated when laparotomy was performed for other reasons and after failure of TAE.[273]

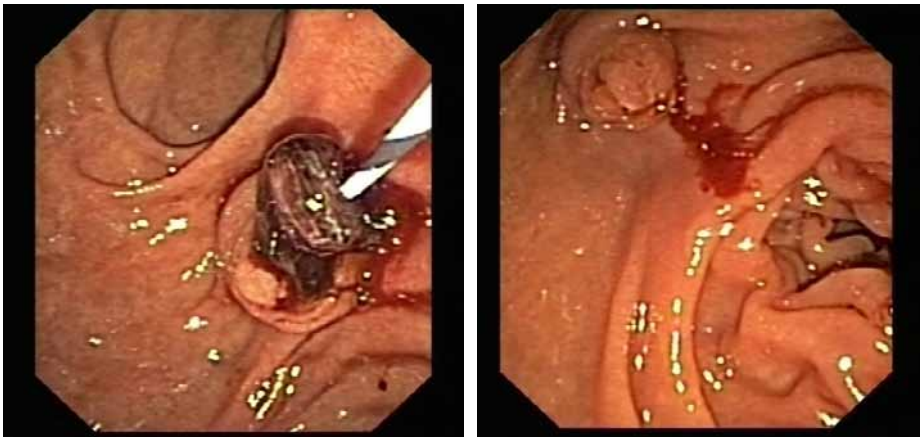

Figure 22a and b. Hemobilia due to an aneurysm of the right hepatic artery in a patient with primary sclerosing cholangitis.

Hemosuccus pancreaticus

Hemosuccus pancreaticus, previously known as Wirsungorrhage, is caused by a bleeding source in the pancreas, pancreatic duct or adjacent structures, such as the splenic artery connecting to the pancreatic duct.[275] It is another rare cause of upper gastrointestinal bleeding and has been estimated to occur in about 1 per 500-1500 cases of upper GI bleeding. Hemosuccus pancreaticus predominantly occurs in men (sex ratio: 7:1),[276, 277] and is most often due to pancreatic pseudoaneurysms resulting of acute or chronic pancreatitis.[276-278] It is also reported sporadically caused by pancreatic tumors,[279] true splenic artery aneurysms,[280] and after therapeutic endoscopy of the pancreas or pancreatic duct, including pancreatic stone removal, pseudocyst drainage, pancreatic duct sphincterotomy, or pancreatic duct stenting (Figure 23).[281] Pseudoaneurysms can occur as a complication of pancreatitis, when a pseudocyst erodes a neighboring artery, resulting in hemorrhage into the pancreatic duct.

In two retrospective studies, including a total of 40 patients, the most frequent complaints at presentation were melena, hematochezia, hematemesis, and epigastric pain. Less reported was presence of a pulsating epigastric mass with a thrill at auscultation.[276, 277] Patients may also develop symptoms of nausea and vomiting, weight loss and jaundice (when the bleed also leads to obstruction of the common bile duct).

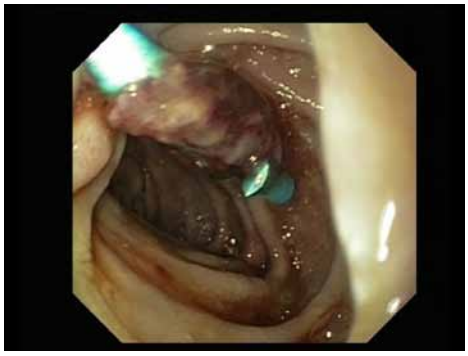

Figure 23. Hemosuccus pancreaticus (here seen in the form of an adhered clot on the endoprosthesis in the pancreatic duct) in a patient with chronic pancreatitis.

In a recent report including 31 patients with hemosuccus pancreaticus, the presence of duodenal blood was observed during upper GI endoscopy in only half of the patients.[277] This underlines that the diagnosis is not always easy to establish, mainly due to the hidden and intermittent nature of the bleeding. A side-viewing duodenoscope can be helpful to localize the bleeding. Other diagnostic tools are abdominal ultrasonography and abdominal computed tomography and CT-angiography. Conventional angiography may be used to visualize the celiac axis, and in particular the gastroduodenal and splenic arteries to determine the bleeding focus. This technique may also be used to terminate the bleeding. Selective arterial embolization is successful in 50% of the patients, while surgery is often necessary in

emergency situations or after failure to control the bleeding by arterial embolization.[277] Surgical procedures include distal pancreatectomy and splenectomy, central pancreatectomy, intracystic ligation of blood vessel and aneurysmal ligation of bypass graft, depending on the nature of the bleeding.

Bleeding diathesis

Bleeding diathesis is an unusual susceptibility to bleeding mostly due to a coagulopathy (e.g. von Willebrand disease, and hemophilia). Bleeding diathesis as a cause of upper gastrointestinal bleeding should be considered in presence of other relating symptoms of prolonged bleeding and rebleeding. Bleeding can occur from minute lesions, and may often require repeated endoscopy in the acute setting to determine the source of the bleed and treat accordingly. Further treatment primarily consists of correction of coagulopathy if possible.

Bleeding from the posterior nasopharynx

Bleeding from the posterior nasopharynx can sometimes be mistaken for a gastrointestinal bleeding. Presentation can be similar with melena and/or hematemesis. In the absence of another bleeding focus, this diagnosis should be anticipated and should lead to a careful examination of the nose and nasopharynx.[282]

CONCLUSION

Peptic ulcers and gastroesophageal varices are by far the most common causes of severe upper gastrointestinal bleeding. Nevertheless, 27 to 49 percent of upper GI bleeds is due to other causes, which include a range of conditions.[2, 4-6, 8] Upper gastrointestinal endoscopy is like for peptic ulcer and varices the mainstay for diagnosis and treatment. The medical history with focus on items such as symptoms, timing of onset of the bleed in relation to other parameters such as a meal or vomiting, drug use, and previous interventions provide important clues for a diagnosis and therapeutic approach.

CHAPTER 1.6

HELICOBACTER PYLORI INFECTION AND ASSOCIATED DISEASES

HELICOBACTER PYLORI

The presence of spiral Gram-negative bacteria on the human gastric mucosa was already recognized in the late 19th century, although it took until 1982 before *Helicobacter pylori* was first successfully cultured from a gastric biopsy sample by Warren and Marshall.[283] They were awarded the Nobel Prize in Medicine in 2005 for this discovery. *H. pylori* has evolved intricate mechanisms to avoid the bactericidal acid in the gastric lumen and to colonize and persist in the gastric mucosa (Figure 1). *H. pylori* is acquired by human-to-human transmission through oral-oral, vomitus-oral, or fecal-oral spread, although the exact mechanism is not yet entirely clarified.[284] The bacterium is mainly acquired during early childhood, with maternal infection supposed as the most important risk factor.[285] Once colonized with *H. pylori*, it generally persists throughout life unless treated with targeted antibiotics. In the elderly, however, *H. pylori* can disappear as the gastric mucosa becomes increasingly atrophic and therefore inhospitable to colonization.

It is estimated that more than half of the world's population has been colonized with *H. pylori*, although its prevalence is highly variable between and within countries. In developing countries and among first-generation immigrants living in the Western world, the prevalence of *H. pylori* gastritis is high (often >80%) in all age groups, including children. In Western countries, the prevalence of *H. pylori* gastritis has decreased steadily over the past decades, showing a birth-cohort specific decline. In elderly persons the prevalence is still between 40-60%, while in young adults it is currently often less than 20% and in children <10 years even below 10%.[286] Factors involved in the decreasing infection rate in subsequent generations are decreased family size, widespread use of antibiotics, and improved hygiene and housing conditions. The pathogenicity of *H. pylori* is increased in strains harboring the virulence factor cytotoxin-associated gene A (CagA). Bacterial strains that express *CagA* are

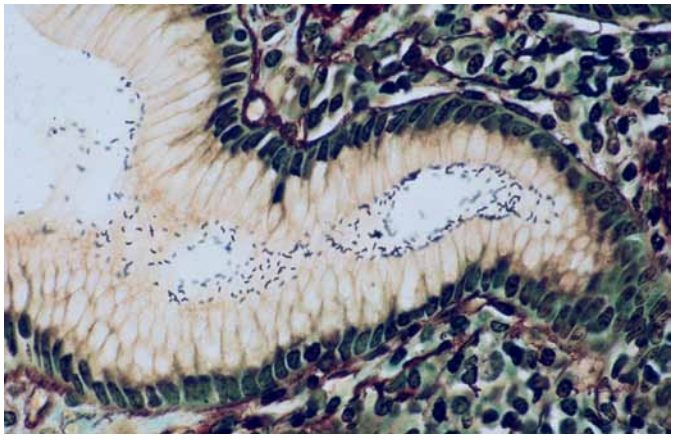

Figure 1. *H. pylori* on gastric mucosa (Steiner staining).

more interactive with the gastric epithelium and as a result cause more severe gastritis, which is associated with an increased risk for both gastroduodenal ulceration and gastric cancer.

BENEFICIAL EFFECTS OF *H. PYLORI*

H. pylori is suggested to have not only pathogenic properties. The close and longstanding interaction with the gastric mucosa is thought to influence the maturation of the immune system, as the stomach has adaptive immunological activity in terms of both T and B-cell function. In this context and in line with the "disappearing microbiota" hypothesis, the decline in prevalence of *H. pylori* (a member of the ancient indigenous microflora) has been suggested to contribute to the simultaneous increase in childhood asthma and atopy. Although some studies have indicated an inverse association between *H. pylori* and asthma, especially for CagA+ strains in relation to early onset asthma and allergic rhinitis, other studies have reported no association.[287] Large prospective studies in children are needed to definitively conclude on this hypothesis. Such studies are ongoing within the Rotterdam Generation R study.[288]

H. PYLORI AND PEPTIC ULCER DISEASE

Colonization induces chronic active gastritis in virtually all infected subjects. In most people this colonization is asymptomatic, but *H. pylori* carriers do have an increased risk of developing peptic ulcer disease (PUD). The pattern and distribution of gastritis correlate strongly with the resultant clinical conditions. Patients with antral-predominant gastritis are predisposed to duodenal ulcers, whereas patients with corpus predominant gastritis and multifocal atrophy are more likely to have gastric ulcers.[284] In Western countries, duodenal ulcers occur more frequently than gastric ulcers. The predominant age at which duodenal ulcers occur is between 20 and 50 years, whereas gastric ulcers mostly occur in patients above 40 years. The prevalence of *H. pylori* in patients with PUD ranges from 36 to 73% depending on ethnicity, geographic and socioeconomic factors.[285] The other frequent cause of gastroduodenal ulcers is the use of aspirin and NSAIDs. Together they account for 80 to 95% of the ulcer disease cases. Hemorrhage is one of the major complications of PUD and occurs in about one out of six patients with ulcers over the course of their ulcer activity. There is a synergistic effect for the development of bleeding when *H. pylori* and ulcerogenic medication are both present. In addition to endoscopic and acid suppressive therapy, a test-and-treat strategy for *H. pylori* is recommended in all patients with PUB. Tests for *H. pylori* can be divided in invasive (i.e. requiring endoscopy) and noninvasive methods. In case of suspected peptic ulcer (bleeding) or other indication for endoscopy, gastric biopsy samples can be taken and stained or cultured

for *H. pylori*. In other cases, noninvasive methods including stool antigen test, urease breath test, and serology are preferred. Treatment requires a combination of antibiotics to eradicate the bacteria and acid suppressive medications to ensure their effectiveness in the stomach. The choice for antibiotics should be based on local resistance patters. In general, novel triple, quadruple and sequential therapy are considered superior to standard triple therapy.[289] After successful eradication of *H. pylori* and withdrawal of NSAIDs, peptic ulcer rebleeding is virtually reduced to null, even without maintenance antisecretory therapy.[290]

GASTRIC CANCER AND ITS PRECURSOR CONDITIONS

Gastric cancer is a world health burden, ranging as the fourth most common cancer and second cause of cancer related death worldwide. Although the incidence of gastric cancer is declining, the absolute number of new cases per year is increasing, due to aging of the world's population and expansion of high incidence populations. In its early stages, stomach cancer is often either asymptomatic, or it may cause only nonspecific symptoms. By the time of diagnosis, the cancer has often reached an advanced stage, with limited therapeutic options (Figure 2). Consequently, gastric cancer carries a poor prognosis, with overall five-year survival of less than 20 percent. Gastric cancers are predominantly adenocarcinomas (90%). Histologically, there are two major types of gastric adenocarcinoma: intestinal type (60%) and diffuse type (30%). Based on large epidemiological studies, there is very strong evidence that *H. pylori* increases the risk of either type adenocarcinoma.[291] Therefore, *H. pylori* has been classified as a type I (definite) carcinogen by the World Health Organization. After *H. pylori* infection, several stages of precursor conditions progress along a multistep cascade to cancer. These precancerous lesions comprise atrophic gastritis, intestinal metaplasia and

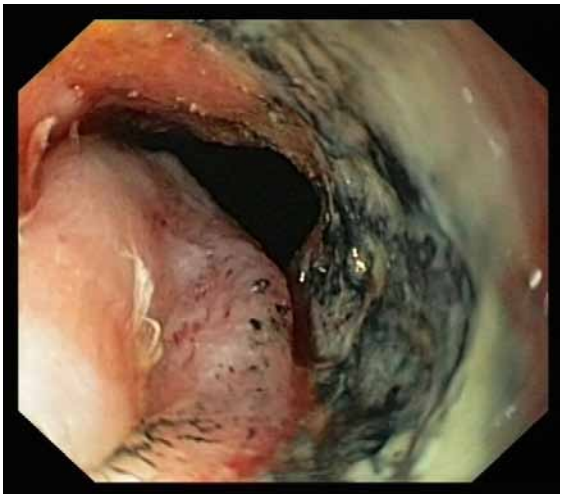

Figure 2. Ulcerative gastric cancer.

dysplasia.[292] Given the fact that gastric cancer is difficult to cure unless it is found in an early stage, increasing emphasis is put on the management and surveillance of these precancerous gastric conditions. A recent guideline recommends surveillance for patients with extensive atrophic gastritis, intestinal metaplasia, or dysplasia.[293] However, there is little evidence whether screening of all these patients is beneficial, and whether there might be additional risk factors that justify screening in individuals with less extensive premalignant conditions.

CHAPTER 1.7

AIMS AND OUTLINE OF THE THESIS

This thesis starts with an overview of what is currently known about upper gastrointestinal bleeding, *Helicobacter pylori* and premalignant gastric lesions **(PART I)**.

In **PART II**, we further focus on upper gastrointestinal bleeding (UGIB). Well-known ulcerogenic drugs that increase the risk of UGIB are NSAIDs and aspirin. In **Chapter 2.1**, we aim to assess the use of a new generation of oral anticoagulants (nOACs: factor IIa and Xa inhibitors) as potential risk factor for the occurrence of gastrointestinal bleeding. **Chapter 2.3** addresses the (endoscopic) management, when facing a suspected nOAC-associated gastrointestinal hemorrhage based on the current available literature.

At present available hemostatic techniques include injection therapy, hemoclips, thermocoagulation, and band ligation. They are highly effective, but can be technically demanding, difficult to deploy due to the position of the bleeding, or may provoke more severe bleeding. Therefore, novel endoscopic hemostatic modalities should be evaluated to overcome these problems. Two of the most promising emerging devices are Hemospray and self-expandable metal stents. In **Chapter 3**, we expand our knowledge on the application of Hemospray, a novel hemostatic powder registered for the treatment of non-variceal UGIB. We investigate the effects on coagulation and thrombus formation of Hemospray in vitro, in a porcine model with an arterial bleeding, and by means of electronic microscopy **(Chapter 3.1).** Our first *in vivo* experiences with Hemospray for the treatment of non-variceal upper GI bleeding, lower GI bleeding, and variceal bleeding are described in **Chapters 3.2-3.4** respectively. In **Chapter 4**, we describe our experiences with another novel hemostatic device: self-expandable metal stents for the treatment of esophageal variceal bleeding. Besides management of acute bleeding, prevention of rebleeding is another important aspect of therapy, especially in patients with variceal bleeding, as it is associated with increased mortality. Secondary prevention strategies include endoscopic therapy in combination with β-blocker treatment or transjugular intrahepatic portosystemic shunt (TIPS) placement. So far, the evidence supporting the use of early covered-TIPS over endoscopic treatment, focuses on the survival benefit of high risk populations, but leaves clinicians uncertain regarding non-high risk patients. We aim to compare these strategies in a randomized setting in unselected cirrhotic patients with a first or second variceal bleeding **(Chapter 5)**.

In **PART III**, we focus on *Helicobacter pylori* and related conditions. In **Chapter 6**, we define *H. pylori* prevalence as well as risk groups for colonization in a cohort of young women living in Rotterdam, a city with a multi-ethnic population. Prevention of asthma and atopic disorders is one of the suggested beneficial effects of *H. pylori* colonization. We aim to assess the impact of *H. pylori* colonization on atopic disorders in a cohort of Dutch children **(Chapter 7)**. As described before, *H. pylori* is the initial step in the cascade from chronic gastritis to intestinal type gastric cancer via the premalignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia. If *H. pylori* is eradicated at an early stage (i.e. before premalignant lesions occur), the chance of developing gastric cancer is dramatically reduced. It is however unknown whether this also holds for different stages in the premalignant process, or that these lesions

have passed a point of no return. We aim to investigate this in a Cochrane review in **Chapter 8**. So far, no clear guidelines for the follow-up of premalignant lesions exist. To identify the role of distribution, extent and severity of premalignant lesions in risk to progression, we set up a prospective cohort of patients with premalignant lesions using a well-known scoring system and extensive biopsy protocol. The first results of this study are described in **Chapter 9**. Resulting from the cohort-specific decrease in *H. pylori* acquisition, a further decline in gastric cancer incidence in young persons would be expected. Contradictory, recent incidence trend studies in the US report an increasing incidence of gastric cancer in younger persons. In **chapter 10**, we closely analyze gastric cancer incidence trends by age, sex, subsite, and stage in the Netherlands to provide essential information for the understanding of recent patterns and to anticipate future trends and guide etiological investigations.

In the fourth part, the conclusions of this thesis and future perspectives are discussed **(Chapter 11)**.

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PART II

UPPER GASTROINTESTINAL BLEEDING

CHAPTER 2.1

NEW ORAL ANTICOAGULANTS INCREASE RISK FOR GASTROINTESTINAL BLEEDING – A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background & Aims: A new generation of oral anticoagulants (nOAC), which includes thrombin and factor Xa inhibitors, has shown to be effective, but little is known about whether these drugs increase patients' risk for gastrointestinal bleeding (GIB). Patients who require OAC therapy frequently have significant comorbidities and also take aspirin and/or thienopyridines. We performed a systematic review and meta-analysis of the risk of GIB and clinically relevant bleeding in patient taking nOAC.

Methods: We queried MEDLINE, EMbase, and the Cochrane library (through July 2012) without language restrictions. We analyzed data from 43 randomized controlled trials (151,578 patients) that compared nOAC (regardless of indication) with standard care for risk of bleeding (19 trials on GIB). Odds ratios (ORs) were estimated using a random-effects model. Heterogeneity was assessed with the Cochran Q test and Higgins I^2 test.

Results: The overall OR for GIB among patients taking nOAC was 1.45 (95% confidence interval [CI], 1.07–1.97), but there was substantial heterogeneity among studies (I_2 61%). Subgroup analyses showed that the OR for atrial fibrillation was 1.21 (95% CI, 0.91–1.61), for thromboprophylaxis after orthopedic surgery the OR was 0.78 (95% CI, 0.31–1.96), for treatment of venous thrombosis the OR was 1.59 (95% CI, 1.03–2.44), and for acute coronary syndrome the OR was 5.21 (95% CI, 2.58–10.53). Among the drugs studied, the OR for apixaban was 1.23 (95% CI, 0.56–2.73), the OR for dabigatran was 1.58 (95% CI, 1.29–1.93), the OR for edoxaban was 0.31 (95% CI, 0.01–7.69), and the OR for rivaroxaban was 1.48 (95% CI, 1.21–1.82). The overall OR for clinically relevant bleeding in patients taking nOAC was 1.16 (95% CI, 1.00–1.34), with similar trends among subgroups.

Conclusions: Studies on treatment of venous thrombosis or acute coronary syndrome have shown that patients treated with nOAC have an increased risk of GIB, compared with those who receive standard care. Better reporting of GIB events in future trials could allow stratification of patients for therapy with gastroprotective agents.

BACKGROUND

Gastrointestinal bleeding (GIB) is a serious medical condition that causes considerable morbidity and mortality (5 to 15%) and poses an enormous burden on global health care use.[1] The mean hospital costs are reported to range from $2,500 to $7,300 for upper GIB, $ 4,800 for lower GIB, and around $ 40,000 for small bowel bleeding.[2] The expanding indications and increasingly intensive treatment with antithrombotic agents have increased the burden of GIB related to these agents.[3] Antiplatelet agents (e.g. aspirin and thienopyridine derivatives) can give rise to GIB by producing ulcers and erosions throughout the gastrointestinal tract. Anticoagulants (i.e., vitamin K antagonists [VKA]) and heparins might precipitate bleeding from pre-existing lesions.[4] The relative risk of GIB varies from 1.5 for low-dose aspirin compared with nonuse[5] and more than 5 for the combination of aspirin and VKA.[3] In light of their efficacy, the increased risk of bleeding induced by the therapy is acceptable. Two important limitations of the traditional antithrombotic agents comprise the need for international normalized ratio monitoring with tailored VKA dosing, or subcutaneous administration of low-molecular-weight heparins (LMWH).

Novel oral anticoagulants (nOAC) (e.g. factor IIa [thrombin] or factor Xa inhibitors) have been developed and theoretically lack these limitations.[6-8] These drugs are as effective compared with current therapy. Some randomized controlled trials reported an isolated higher GIB risk,[9, 10] which is potentially fatal, costly, and avoidable. It is therefore important to carefully review the literature on GIB risk attributable to use of nOAC. This is particularly relevant because patients on nOAC often use concomitant low dose aspirin and/or thienopyridines, which may add substantially to the as yet unknown GIB risk. Furthermore, in contrast with the traditional OAC, no clinically tested antidote is currently available for the novel agents, hampering therapeutic options in case of GIB.[11] For these reasons, we conducted a systematic review focusing on the risk of GIB of all nOAC. Because not all trials separately reported GIB risk, we also reviewed the evidence on risk of clinically relevant bleeding associated with nOAC use.

METHODS

Study definitions

The exposure of interest was defined as the (approximated) indication-specific recommended daily dose of the nOAC either by the European Medicines Agency[12] or the Food and Drug Administration[13] for registered nOAC. When nOAC was not registered for the indication it was studied in, the indication-specific daily dose was defined according to the pharmaceutical manufacturer.

Table 1. Definitions of bleeding

Endpoint	Sub endpoint	Definition
Clinically relevant bleeding	Major bleeding	Acute, clinically overt bleeding accompanied by one or more of the following events: a decrease in the hemoglobin level of 2 g/dL or more within a 24-hour period; a transfusion of 2 or more units of packed red cells; bleeding at a critical site (i.e., intracranial, intraspinal, intraocular, pericardial or retroperitoneal bleeding); bleeding into the operated joint (for the studies regarding thrombophrophylaxis after surgery), requiring an additional operation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding.[15, 16] In addition to the above: when major bleeding occurred in the gastrointestinal tract (defined by at least one episode of clinically apparent hematemesis, melena, spontaneous rectal bleeding) or when a major bleeding was confirmed by endoscopy, it was defined as (major) gastrointestinal bleeding (GIB).[14]
	Clinically relevant non-major bleeding	Acute, clinically overt bleeding, such as excessive wound hematoma, bruising or ecchymosis (>25 cm^2), gastrointestinal bleeding, hemoptysis, macroscopic hematuria, gingival bleeding (>5 min), epistaxis (>5 min), or any bleeding leading to hospital admission or discontinuation of the study medication, unscheduled contact with a physician, or discomfort or impairment of activities of daily life, that did not meet the other criteria for major bleeding.

Standard care was either defined as low-molecular-weight heparin, vitamin K antagonist, antiplatelet therapy, or no (additional) therapy/placebo, depending on the (inter)national guidelines regarding antithrombotic therapy for the concerning indication.

The primary outcome of this systematic review was the risk of GIB. GIB was considered as at least one episode of clinically apparent hematemesis (frank blood or coffee ground material that tested positive for blood), melena, or spontaneous rectal bleeding (if more than a few spots) or endoscopically confirmed bleeding, and was judged as major or clinically relevant nonmajor depending on the severity.[14]

The secondary outcome was the risk of clinically relevant bleeding (encompassing both major bleeding and clinically relevant nonmajor bleeding).

Major bleeding and clinically relevant nonmajor bleeding in the included studies were defined by (1) the International Society on Thrombosis and Haemostasis (ISTH),[15, 16] (2) the Thrombolysis In Myocardial Infarction (TIMI),[17] or (3) an adjustment of the ISTH definition (see Table 1 for exact definitions).

Data sources and searches

A comprehensive literature search was conducted to identify randomized controlled trials (RCTs) reporting GIB or clinically relevant bleeding in patients receiving nOAC compared with standard treatment. MEDLINE with PubMed as interface, EMbase, and the Cochrane Central Register of Controlled Trials were searched from inception to July 2012. Medical subject heading terms and keywords used to identify RCTs included: "apixaban", "rivaroxaban", "dabi-

gatran", "edoxaban", "betrixaban", "humans", and "randomized controlled trial". No language restrictions were applied. The electronic search strategy was complemented by manual review of reference lists of included articles. References of recent reviews on nOAC also were examined.[11, 18-23]

Study selection

Search results were combined and duplicates were removed. Studies were first screened based on title and abstract for relevance, after which the full-text was reviewed. This was independently done by two reviewers (I.L.H. and V.E.V.). Inter-rater agreement was assessed using kappa statistic. Any discrepancies were resolved by consensus, contacting a third author (E.T.T.L.T.). Studies had to meet the following inclusion criteria: 1) the study compared nOAC with the current standard care in a randomized setting; 2) results included bleeding events as safety outcome; 3) the study was conducted in the target population of the drug and not in healthy volunteers; and 4) it was published as full-text article. If any of the four criteria were not met, the study was excluded. If data from the same study were published in multiple languages, data from the English article were extracted. In case of suspicion of double reporting of the same patient populations, data from the main publication were extracted.

Data extraction

The included studies were divided by clinical indication of anticoagulant therapy into the following indication groups: 1) prevention of stroke and systemic embolism in patients with atrial fibrillation (AF); 2) prevention of venous thromboembolism following orthopedic surgery (OS); 3) prevention of venous thromboembolism in medically ill patients; 4) treatment of acute deep vein thrombosis (DVT) or pulmonary embolism (PE); and 5) treatment of acute coronary syndrome (ACS). For each included study, we recorded the number of trial participants, follow-up period, and number of patients who developed the primary safety endpoints for both treatment arms. The mean age at baseline and percentage of males were assessed, as well as other characteristics of the study population such as relevant concomitant medication that may affect bleeding risk. This was done independently by two authors (I.L.H. and V.E.V.). Finally, we contacted the main investigator for missing data. Furthermore, given the heterogeneity of the studies, an individual patient data analysis was attempted. All authors were contacted and requested for individual patient data. We received response from 7 of 23 authors (covering 12 of 43 studies). Unfortunately, no one agreed to share this information.

Quality assessment

The quality of included studies was assessed according to the Cochrane Reviewers' Handbook.[24] Both manuscript and protocol, if available online, were scanned for relevant information on quality.

Data synthesis and analysis

Odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated for each RCT and were the bases for the meta-analyses. To include studies with null events in either active treatment arm or standard care arm, 0.5 events were added to all cells with study results. In case of null events in both arms, no OR was calculated. To quantify how many patients needed to be exposed to nOAC therapy to cause one additional (GI) bleeding compared with standard care the number needed to harm (NNH) was assessed.

To explore between-study variability the Cochran Q test and Higgins I^2 test for heterogeneity were used. Significant heterogeneity was assumed when Cochran's Q p-value was less than 0.10 and the I^2 was greater than 50%. To reduce the impact of heterogeneity, we used a random-effects model in these cases.

To account for possible sources of heterogeneity, we performed prespecified subgroup analyses according to type of nOAC and indication. Heterogeneity between subgroups was further evaluated by a post-hoc meta-regression analysis by indication, type of nOAC, and comparator. Comprehensive meta-analysis v2.0 (Biostat, Englewood NJ, USA) was used to perform the meta-analysis. Meta-regression was performed using PASW statistics 20.0 for Windows (SPSS, IBM, Armonk, New York, USA).

Sensitivity analysis was performed to exclude studies that compared the bleeding risk of nOAC use with the use of placebo as standard care because this intervention is unlikely to increase bleeding risk. Because we only included published data, publication bias was quantified with Egger's regression test and Begg's test, with the results considered to indicate publication bias when the p-value was less than 0.10. Additionally, funnel plots were examined for asymmetry.

RESULTS

Studies

Our initial search identified 375 records (Figure 1a). A total of 42 studies were eligible for inclusion. The agreement between reviewers for trial inclusion was excellent (κ=0.94) The clinical indication comprised AF in 8 studies,[9, 10, 25-30] OS in 21 studies,[31-51] medically ill patients in 2 studies,[52, 53] DVT/PE in 6 studies (reporting on 7 trials), [54-59] and ACS in 5 studies (Figure 1b).[60-64]

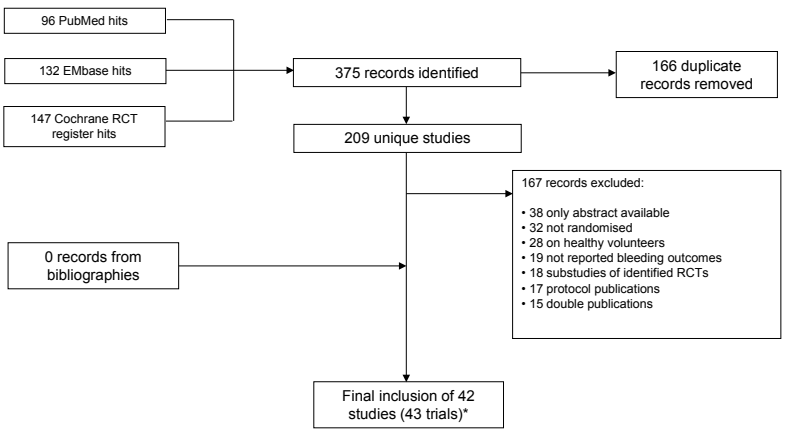

Figure 1a. Flow-chart of included studies.

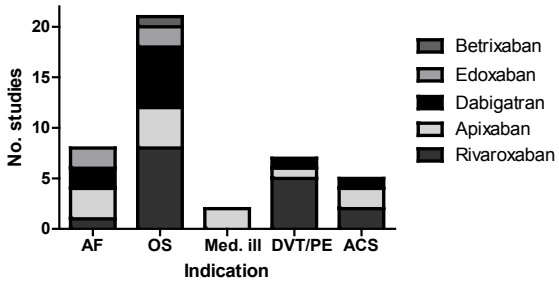

Figure 1b. Indications of included studies split by drug.

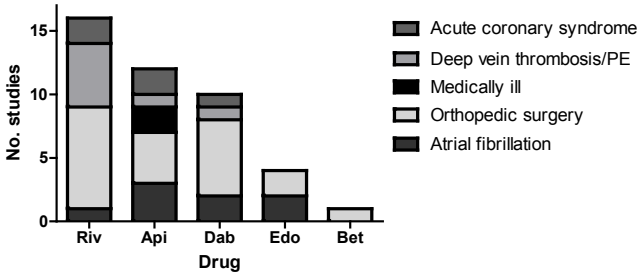

Figure 1c. Drugs of included studies split by indication.

** One of these studies describes 2 subsequent trials, and is therefore mentioned twice in the data-extraction. ACS: acute coronary syndrome, AF: atrial fibrillation, api: apixaban, bet: betrixaban, dab: dabigatran, DVT: deep vein thrombosis, edo: edoxaban, OS: orthopedic surgery, PE: pulmonary embolism, RCT: randomized controlled trial, riv: rivaroxaban.*

To gain insight into the performance per drug, the information on bleeding risk was summarized per individual drug (Figure 1c). Rivaroxaban was most frequently studied (15 studies reporting on 16 trials),[10, 32-35, 39-41, 44, 54, 55, 58, 59, 61, 63] followed by apixaban (12 trials),[28-30, 38, 45, 48, 49, 52, 53, 56, 60, 62] dabigatran (10 trials),[9, 25, 31, 36, 37, 42, 46, 51, 57, 64] edoxaban (4 trials),[26, 27, 47, 50] and betrixaban (1 trial).[43] The main characteristics of the 43 included trials are summarized in Supplementary Tables 1-5.

Study characteristics

A total of 151,578 patients were included in the 43 trials. Duration of follow-up ranged from 3 weeks to 31 months, with shorter durations of follow-up evaluation for the OS studies and longer durations for AF studies. Patients with a recent history of peptic ulcer disease or patients with an otherwise increased risk of GIB (e.g., patients with a thrombocytopenia or coagulation disorder) were excluded in all 43 trials. Concomitant use of any co-medication affecting coagulation was prohibited in 19% of trials, only low-dose aspirin (<160 mg) was allowed in 14%, only short-acting non-steroidal anti-inflammatory drugs (NSAIDs) (<17 hours) were allowed in 16%, short-acting NSAIDS/cyclooxygenase-2 inhibitors and/or low-dose aspirin and/or thienopyridines was allowed in 44%, mostly with the addition that it was discouraged. Information on the allowance of antithrombotic co-medication was absent in 7% of trials (Supplementary Tables 1-5).

Study exposure

First, the risk estimates from each study were pooled by indication as the registered/recommended dose for each individual nOAC differs per indication (Supplementary Table 6). A total of 125,354 patients (83%) were enrolled in the therapeutic arms relevant to this review. Of the 8 trials on AF, 7 trials compared one of the novel agents with dose-adjusted warfarin. Of the 21 trials on thromboprophylaxis after OS, 19 compared a nOAC with LMWH (Supplementary Tables 1-5). All trials, except one trial[58] on DVT/PE treatment, compared a nOAC with LMWH followed by VKA. The trials on treatment of ACS compared nOAC with placebo, in addition to standard (double) antiplatelet therapy.

Publication bias

The result of the Egger regression test for publication bias was not significant (intercept 0.7, 95% CI –0.4, 1.7, P=0.20) and no funnel plot asymmetry was observed (Supplementary Figure 1), indicating no evidence of publication bias.

Methodological quality of included studies

Supplementary Table 7 presents an overview of the methodological quality of included RCTs. The majority of trials mentioned the employed method for randomization (93%) and

adequate concealment of allocation (72%). Seventy percent of studies applied a double blind design, 23% had a single-blind design, and 7% followed an open-label design. An independent blinded committee identified all suspected outcome events in each study. Ninety-three percent of studies used an intention-to-treat analysis at least for the safety analysis. The number of patients lost to follow-up evaluation varied between 0.1% and 2.5%, but were reported in only 53% of studies.

Gastrointestinal bleeding

Nineteen trials (44%) reported separate data on GIB.[9, 10, 27-30, 33, 35, 38, 39, 41, 45, 48, 49, 53, 57, 58, 60, 64] Two small trials yielded null events in both groups and were therefore excluded from the GIB analyses.[35, 38] A total of 1,101 GIB events in 75,081 patients were reported (1.4%) (Supplementary Table 8). These GIBs were predominantly major bleeds (89%). The percentage of GI bleeds per trial in the nOAC group was low in the trials on OS (nOAC 0.1% vs. control 0.2%), intermediate in the trials on AF (nOAC 2.1% vs. control 1.6%) and DVT/PE (nOAC 3.0% vs. control 1.9%), and high in the trials on ACS (nOAC 5.3% vs. control 1.0%). The number needed to harm (NNH) was 500 (95% CI -10.000-200), meaning that if 1000 patients were treated with the nOAC instead of standard care, this would result in 2 additional GIBs.

Four of 17 studies showed an increased risk, 12 a comparable and 1 a lower risk of GIB when the nOAC was administered compared with the standard care. After pooling the results of 17 RTCs, the nOAC were found to be associated with a higher risk of GIB compared to standard care (pooled OR 1.45, 95% CI: 1.07-1.97), but with substantial heterogeneity (I^2 61%). First, a considerable part of the increased risk could be attributed to the 2 trials on ACS (pooled OR 5.21, 95% CI 2.58-10.53, I^2 0%). To illustrate, the NNH was 24 (95% CI 17- 42), meaning that per 24 patients treated with the nOAC on top of standard care for ACS one extra GIB would occur. Second, the risk of GIB with nOAC was increased for the two trials on DVT/PE (pooled OR 1.59, 95% CI 1.03-2.44, I^2 27%), but not for other indications for nOAC. The calculated OR (95% CI) of each trial is shown in Figure 2a and 2b. With post-hoc meta-regression, we studied the effect of indication of use (therapeutic use of nOAC vs. prophylactic use). This showed no difference between therapeutic or prophylactic use when adjusted for comparator (placebo vs. antithrombotic agent).

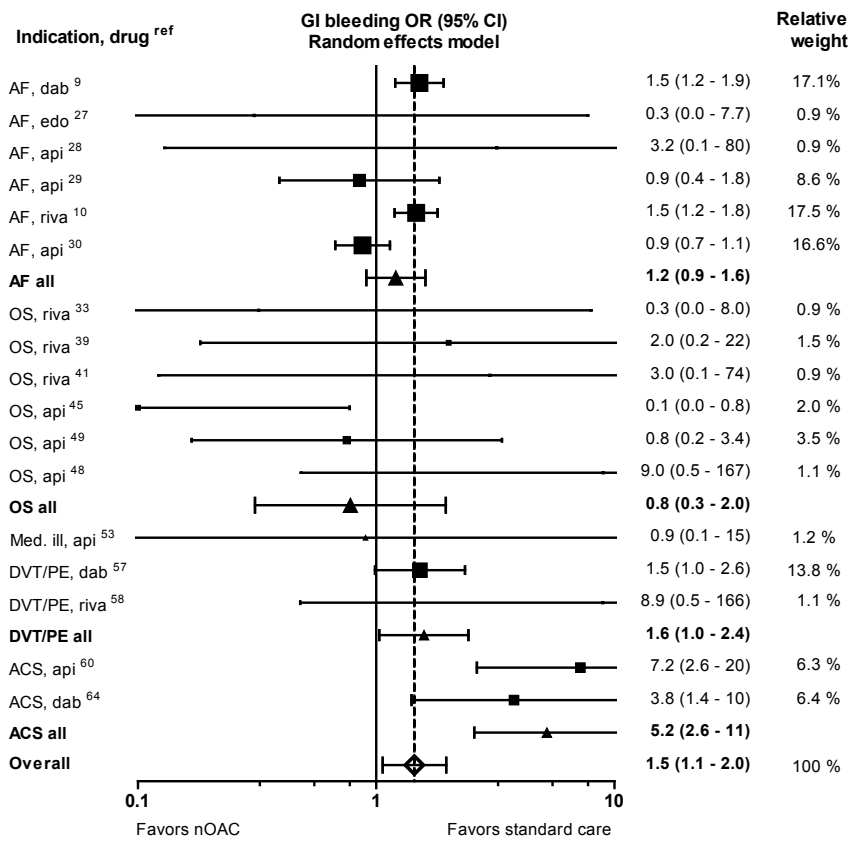

Figure 2a. Forrest plot of gastrointestinal bleeding with subgroup analysis by indication.
Data are presented as odds ratios (OR, 95% CI) using a random effects model and I2 test for heterogeneity. ACS: acute coronary syndrome, AF: atrial fibrillation, api: apixaban, bet: betrixaban, dab: dabigatran, DVT: deep vein thrombosis, edo: edoxaban, OS: orthopedic surgery, PE: pulmonary embolism, RCT: randomized controlled trial, riv: rivaroxaban.

In a subgroup analysis of individual drugs, dabigatran (3 studies[9, 57, 64]; I^2 36%), and rivaroxaban (5 studies[10, 33, 39, 41, 58]; I^2 0%) were associated with a significant increase in risk of GIB, whereas apixaban (8 studies[28-30, 38, 45, 48, 49, 53, 60]; I^2 0%) and edoxaban (1 study[27]) were not. The pooled OR of GIB associated with dabigatran use was 1.58 (95% CI 1.29-1.93) (Figure 2b). Expressed in terms of NNH: per 83 patients treated with dabigatran compared to standard care one additional GIB would occur (95% CI 59-143). The GIB risk associated with use of rivaroxaban was OR 1.48 (95% CI 1.21-1.82). When adjusting for indication of use (therapeu-

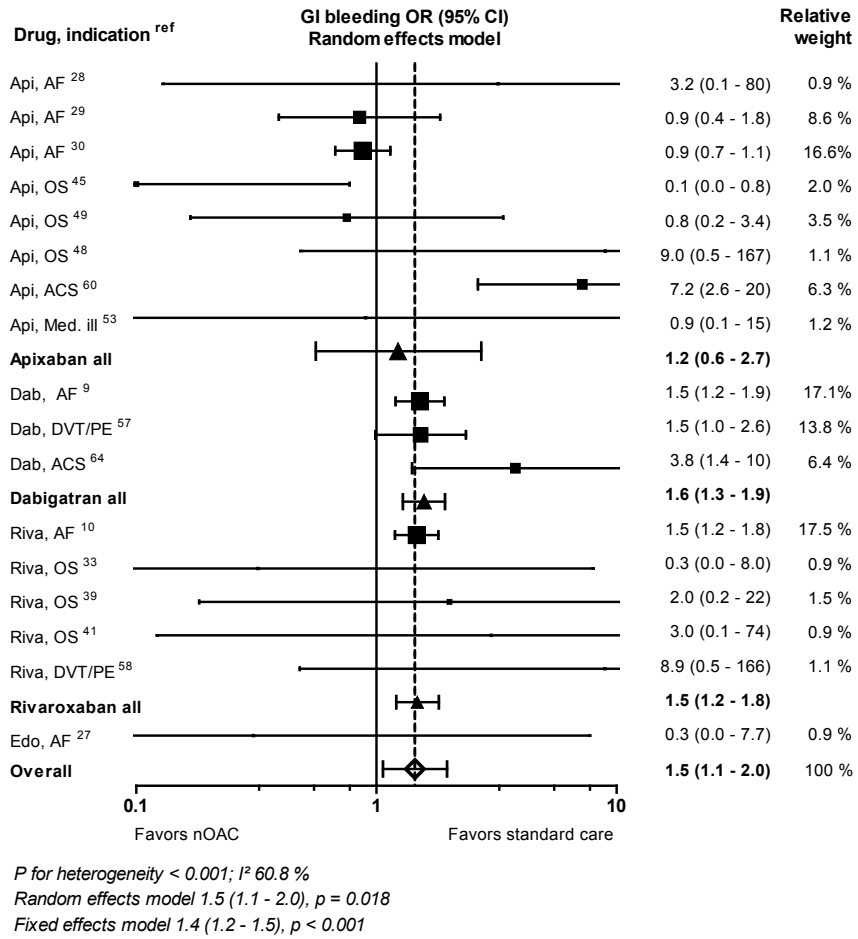

Figure 2b. Forrest plot of gastrointestinal bleeding with subgroup analysis by drug.
Data are presented as odds ratios (OR, 95% CI) using a random effects model and I2 test for heterogeneity. ACS: acute coronary syndrome, AF: atrial fibrillation, api: apixaban, bet: betrixaban, dab: dabigatran, DVT: deep vein thrombosis, edo: edoxaban, OS: orthopedic surgery, PE: pulmonary embolism, RCT: randomized controlled trial, riv: rivaroxaban.

tic versus prophylactic), the risk of rivaroxaban remained significantly higher than that of apixaban (OR 1.77, 95% CI 1.32-2.38). Analysis by comparator, adjusted for indication of use, revealed no significant differences between different comparators.

In the sensitivity analysis, we excluded studies that compared nOAC with placebo therapy. No major deviations were seen, expect for the risk of GIB during DVT/PE treatment, which

reduced and became inconclusive (OR 1.53, 95% CI 0.99-2.36). Complete results of this sensitivity analysis are shown in Supplementary Table 8.

Clinically relevant bleeding

Because GIB is a substantial component of clinically relevant bleeding, we also included this in our analysis. All 43 trials reported on clinically relevant bleeding. The overall risk of clinically relevant bleeding was significantly higher with the use of nOAC compared with standard care (OR 1.16, 95% CI 1.00-1.34). Considerable overall heterogeneity, however, was observed (I^2 83%).

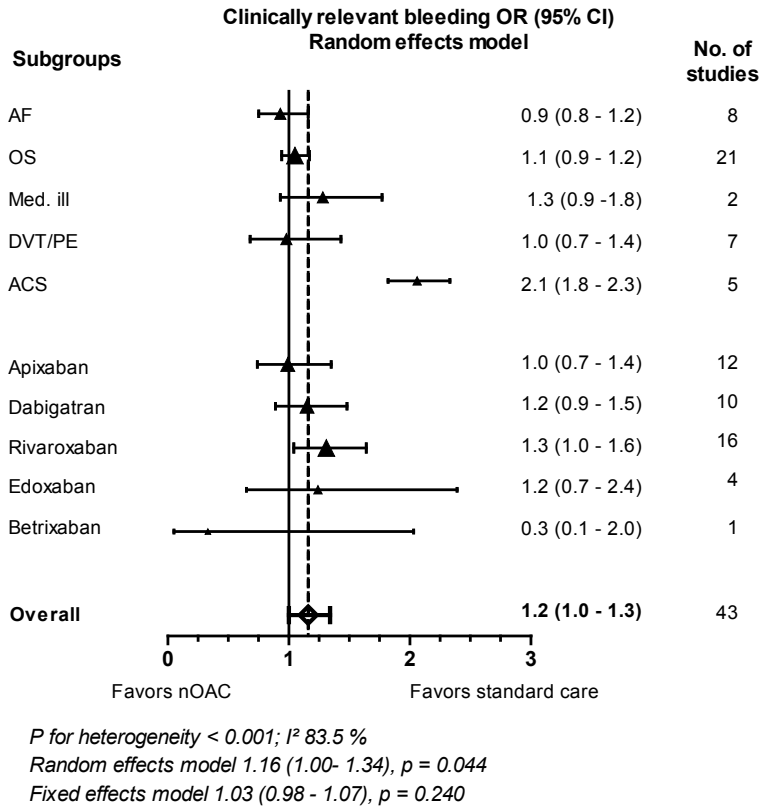

Figure 3. Forrest plot of clinically relevant bleeding summarized by indication and by drug.
Data are presented as odds ratios (OR, 95% CI) using a random effects model and I2 test for heterogeneity. ACS: acute coronary syndrome, AF: atrial fibrillation, DVT: deep vein thrombosis, OS: orthopedic surgery, PE: pulmonary embolism, RCT: randomized controlled trial.

In a subgroup analysis in which different indications for nOAC therapy were considered, we found that patients treated for ACS have an increased risk of bleeding (OR 2.06; I^2 22%) in contrast to patients receiving thromboprophylaxis during OS (OR 1.05; I^2 36%). The other indications did not show a significantly increased risk, but this may be hampered by the substantial heterogeneity. Subgroup analysis by individual drug showed a slightly increased risk of rivaroxaban compared with standard care (OR 1.31, 95% CI 1.04-1.64), but likewise was marked by heterogeneity (I^2 85%), limiting a solid conclusion on the risk of clinically relevant bleeding (Figure 3 and Supplementary Table 8). The risk of clinically relevant bleeding did not differ by drug when adjusted for indication of use.

In the sensitivity analysis, excluding studies comparing with placebo, the overall clinically relevant bleeding risk was not elevated (OR 0.98, 95% CI 0.88-1.10, I^2 65%) (Supplementary Table 8).

DISCUSSION

This systematic review and meta-analysis on 43 trials shows that the novel oral anticoagulants (nOAC) are associated with a modest, but significantly higher, risk of gastrointestinal bleeding (GIB) compared with current standard care. This risk is the highest in patients treated for thrombosis (ACS and DVT/PE). In ACS, nOAC were administered on top of other antithrombotic medication, increasing the well-known cumulative risk on GIB.[5] The risk on GIB in patients treated for DVT/PE or receiving thromboprophylaxis for AF is higher than in patients receiving thromboprophylaxis after OS, this might suggest a dose- and/or duration-effect on top of difference in risk caused by patient characteristics in the different indication groups. However, within the subgroup of AF patients, only patients treated with dabigatran and rivaroxaban carry a higher GIB risk, but not with apixaban. Because head to head studies between nOAC in AF have not been performed, it is not possible to conclude on drugs with lowest GIB risk in AF without applying statistical indirect comparisons. A network meta-analysis on overall safety was conducted by others on OS patients and showed no significant differences.[65]

The major strength of this meta-analysis was its focus on GIB. We provide a complete review of 43 trials with a total of 151,578 patients. Given the implementation of nOAC on a large scale, all currently available types of nOAC and all present indications were included because GI physicians will have to deal with GIB complications, irrespective of drug or indication. The data conveyed are corroborated by two small meta-analyses with GIB as a secondary safety outcome and in which in total only 3 studies for AF were reviewed.[66, 67] For optimal clinical relevance, we included only data obtained with the indication-specific registered/recommended dose per drug, instead of combining all levels of dosages per trial, which was performed in meta-analyses assessing overall risk/benefit of thromboprophylaxis after OS.[8, 65]

Two limitations of the current study need to be addressed: (1) study design and GIB report of included studies, and (2) heterogeneity between studies. First, all included studies have been designed for showing non-inferior or superior efficacy of nOAC versus current standard care. As a consequence, GIB is not reported as safety outcome in majority of studies and will have to be assessed by future studies or by critical assessment of published studies. A large number of enrolled studies report only on the composite endpoint of bleeding outcomes in general. Although the use of this endpoint has the advantage of increased power, a difference in GIB risk therefore cannot be investigated. However, when studies separately reported on GIB, this was performed for major bleedings, but mostly not for clinically relevant nonmajor bleedings. This led to an underestimation of the risk of all clinically relevant GIBs (i.e., composed of both major and clinically relevant nonmajor GIB). In addition, for GIB there was no standard definition according to a scientific commission, but most trials reported used a uniform definition to identify GIB. Regarding heterogeneity, which is inevitable with current available data, we applied a random-effects model and excluded observational cohorts, healthy volunteer studies, nonregistered drugs and unpublished data.

Furthermore, we addressed all perceived sources of heterogeneity by prespecified subgroup analysis and meta-regression by indication, type of nOAC and comparator. Analysis by concomitant use of antiplatelet therapy was not feasible due to lack of stratification of outcome by use of antiplatelet therapy.

Some statistical issues merit clarification. First, we calculated risk estimates per study by means of odds ratios (ORs). Although it would have been preferable to calculate hazard ratios, the rationale to compute ORs was that the mean follow-up time until bleeding was not reported per treatment-arm for all studies. The OR can be interpreted as an estimate of the relative risk since the overall reported GIB is rare (1.5%). Second, for the analysis on GIB, following standard practice, we excluded two studies which had no events in both arms. This exclusion was done because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect, while exclusion of the two trials would thus not affect the point estimate. Both studies were of relatively small size (and thus had a low weight in the meta-analyses, together equalling approximately 2%).

As evidence on superior efficacy of nOAC accumulates,[8, 65, 67] it is important to consider two crucial issues. First, most trials used extensive exclusion criteria to enroll only those patients with a presumed low risk of (GI) bleeding complications attributable to anticoagulants. It is estimated that when these drugs are marketed for daily clinical practice, almost 25 to 40% of future users are high-risk patients and the risk of hemorrhage can be as much as 3 to15-fold increased.[68] It is tempting to speculate that the balance between efficacy and safety will shift unfavorably in these patients because the bleeding risk increases to a much greater extent than the risk of thromboembolisms. Second, data on concomitant proton pump inhibitors (PPIs) use was not available, except for one trial.[62] A recent consensus guideline states that PPIs should be considered in any person with risk factor for GIB receiving any type

of antithrombotic agent,[69] since PPIs have proven to reduce the risk of upper GIB among both traditional NSAIDs, low-dose aspirin users, and among patients taking clopidogrel.[70] Future trials, investigating whether gastroprotective agents could increase NNH in patients on nOAC, are warranted. This is of importance because many patients may use these drugs for considerable duration of time and mostly have significant comorbidity.

In conclusion, we have shown that the gastrointestinal bleeding risk associated with nOAC use might be higher compared with standard care. The current evidence, however, is based on a highly selected patient group with a low bleeding risk, disallowing a true reflection of future patients in daily clinical practice. We recommend that future studies specifically report on the gastrointestinal bleeding risk to further elucidate the true incidence and associated risk. Subsequently, co-administration of gastroprotective agents could be beneficial and warrants further investigations.

SUPPLEMENTARY TABLES AND FIGURES

Table S1. RCTs studying new oral anticoagulants for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents (% study /% control)	Median use of study medication	Median Follow-up	Mean $CHADS_2$ score study/ control [71,72]	Major bleeding HR, RR (95% CI) or % study/% control Definition of major bleeding*	Clinically relevant bleeding HR, RR (95% CI) or % study/% control Definition of CRB**	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control	INR within therapeutic range in warfarin group, median time ‡
Ezekowitz, PETRO, 2007 [25]	AF with coronary artery disease plus ≥1 of the following: HT, DM, symptomatic heart failure, LVEF <40%, previous stroke/TIA, or age >75 y	Major hemorrhage in the past 6 months, any contraindication to anticoagulant therapy	Dabigatran 50 mg bid (59/21/27), 150 mg bid (100/36/33) or 300 mg bid (105/34/30) without aspirin or with aspirin 81 or 325 mg qd vs. warfarin INR 2-3 (70)	70 y, 82%	ASA: 40.7/0	Not reported	Not reported, total follow-up 3 mo	Not reported	6.3% in dabigatran 300 mg bid + aspirin, no major bleeding in other groups ($p<0.02$)# ISTH	1.9%/ 7.7% /10.1% /5.7% Standard definition	Not reported	57.2%
Connolly, RE-LY 2009 [9]	AF and at least one of the following: previous stroke/ TIA, LVEF <40%, congestive heart failure, age ≥75 y, or age 65-74 plus DM or HT or coronary artery disease	Conditions that increased the risk of hemorrhage	Dabigatran 110 mg bid (6015) or 150 mg bid (6076) vs. warfarin INR 2-3 (6022)	72 y, 64%	Aspirin (<100mg/ day) permitted (21.1/19.6/20.8) during treatment period. Also other antiplatelet agents	Not reported	2.0 y	2.1/2.2/2.1	RR 0.80 (0.69-0.93) (110 mg) RR 0.93 (0.81-1.07) (150 mg) vs. control group ISTH	Not reported	RR 1.1 (0.86-1.41) (110 mg) RR 1.5 (1.19-1.89) (150 mg)# vs. control group	64% mean
Weitz, not reported, 2010 [26]	AF and age 18-85 and $CHADS_2$ ≥1	Bleeding disorder or recent major bleeding	Edoxaban 30 mg qd (235) or 30 mg bid (244), or 60 mg qd (234) or 60 mg bid (180) vs. dose-adjusted warfarin (INR 2-3) (250)	65 y, 62%	Not reported	Not reported	84 days	% $CHADS_2$ score of 2 is 63.3%	0/2/0.4/3.3/0.4 P=0.023 for 60 mg bid vs warfarin# ISTH	3.0/7.8/3.8/10.6/3.2 P=0.029 for 30 mg bid vs warfarin P=0.002 for 60 mg bid vs warfarin# The edoxaban 60mg bid arm was prematurely terminated because of an excess of bleeding Standard definition	Not reported	49.7%

Table S1. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents (% study /% control)	Median use of study medication	Median Follow-up	Mean $CHADS_2$ score study/ control [71, 72]	Major bleeding HR, RR (95% CI) or % study/% control Definition of major bleeding*	Clinically relevant bleeding HR, RR (95% CI) or % study/% control Definition of CRB**	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control	INR within therapeutic range in warfarin group, median time ‡
Chung, not reported, 2011 [27]	NVAF, age 18-80 y and $CHADS_2 \geq 1$	Known bleeding disorders and conditions associated with high risk of bleeding	Edoxaban 30 mg qd (79) or 60 mg (80) qd vs. dose-adjusted warfarin (INR 2-3) (75)	65 y, 65%	Ongoing treatment with antiplatelet agents not allowed during study	Not reported	Not reported, total follow-up 12 wk	2.0/1.9/1.8	0.0/0.0/2.7 ISTH	0.0/7.5/6.7 Standard definition	0.0/0.0/1.3 (only major GI bleeding reported)	45.1% mean
Ogawa, ARISTOTLE-J, 2011 [28]	NVAF and age ≥20 y and at least one of the following: age ≥75 , previous stroke/TIA, LVEF ≤40%, DM, HT	Contraindications for warfarin use (e.g. peptic ulcer), current thrombocytopenia, known or suspected hereditary bleeding tendencies	Apixaban 2.5 mg bid (74), Apixaban 5 mg bid (74) vs. dose-adjusted warfarin (INR 2-3 or 2-2.6 if age > 69) (74)	Mean age 70 y, 61%	Concomitant ASA use during study allowed (20.8/28.2/25.3)	85 days/85 days/84 days	Not reported	Mean $CHADS_2$ 1.8/2.1/1.9	0.0/0.0/1.3 ISTH	1.4/1.4/5.3 Standard definition	0.0/1.4/0.0	>60% of patients had INR within range for 60% of the treatment period
Connolly, AVERROES, 2011 [29]	AF, ≥50 y and at least one of the following: prior stroke/TIA, age ≥75 y, HT, DM, heart failure, LVEF <35%, peripheral artery disease and for whom vitamin K antagonist therapy was expected unsuitable	A serious bleeding event in the previous 6 months or a high risk of bleeding. Conditions other than AF that required anticoagulation	Apixaban 5 mg bid and aspirin placebo (2808) vs. aspirin 81-324 mg qd and apixaban placebo (2791)	70 y, 59%	Thienopyridine could be prescribed during the study if an indication emerged; (1%/2%), non-study aspirin use was discouraged but was taken in 9% of patients >50% of study time	Not reported	1.1 y	2.0/2.1	HR 1.13 (0.74-1.75) ISTH	5.0/4.4 Definition not reported	HR 0.86 (0.40-1.86)	Not applicable

Table S1. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents (% study /% control)	Median use of study medication	Median Follow-up	Mean $CHADS_2$ score study/ control [71, 72]	Major bleeding HR, RR (95% CI) or % study/% control Definition of major bleeding*	Clinically relevant bleeding HR, RR (95% CI) or % study/% control Definition of CRB**	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control	INR within therapeutic range in warfarin group, median time ‡
Patel, ROCKET-AF, 2011[10]	NVAF and history of stroke/ TIA/Systemic embolism or at least two of the following: heart failure or LVEF <35%, HT, age ≥75 y or DM	History or condition associated with an increased risk of bleeding	Rivaroxaban 20 mg qd and warfarin placebo (7131) vs. dose-adjusted warfarin (INR 2-3) and rivaroxaban placebo (7133)	73 y, 60 %	Aspirin (≤100 mg/ day) (34.9/36.2) or thienopyridine allowed	590 days	707 days	3.5/3.5	HR 1.04 (0.90-1.20) ISTH	HR 1.03 (0.96-1.11) Standard definition	3.2/ 2.2 # (only major GI bleeds)	58%, mean 55%
Granger, ARISTOTLE, 2011[30]	AF and at least one of the following: age>74 y, previous stroke/ TIA/systemic embolism, symptomatic heart failure or LVEF <40%, DM, HT	Conditions other than AF that required anticoagulation, a need for aspirin at a dose of >165 mg a day or for both aspirin and clopidogrel	Apixaban 5 mg bid and warfarin placebo (9120) vs. dose-adjusted warfarin (INR 2-3) and apixaban placebo (9081)	70 y, 65%	Aspirin <165 mg/ day or clopidogrel allowed	Not reported	1.8 y	2.1/2.1	HR 0.69 (0.60-0.80) ISTH	HR 0.68 (0.61-0.75) Standard definition	HR 0.89 (0.70-1.15) (only major GI bleeds)	66%, mean 62.2%

** according to the ISTH (International Society on Thrombosis and Haemostasis) criteria[16]/TIMI (thrombolysis in myocardial infarction) criteria,[17] or adjusted criteria, **according to the standard definition as reported in the method section, or adjusted definition, ‡ using the method of Rosendaal, #= significant difference.*
Abbreviations: AF: atrial fibrillation, bid: twice daily, $CHADS_2$: scoring system used to identify patients in need of anticoagulation (congestive heart failure, hypertension, age, diabetes, previous stroke), CI: confidence interval, DM: diabetes mellitus, HR: hazard ratio, HT: hypertension, INR: international normalized ratio, LVEF: left ventricular ejection fraction, qd: once daily, NVAF: non-valvular AF, RR: relative risk, TIA: transient ischemic attack.

Table S2. RCTs studying new oral anticoagulants for the prevention of venous thromboembolism following orthopedic surgery.

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Eriksson, BISTRO II, 2005 [31]	Age ≥18 y and ≥ 40 kg and scheduled for primary elective THR or TKR	Any bleeding diathesis, coagulation disorders, gastrointestinal bleeding within the last year	Dabigatran 50 mg bid (389) or 150 mg bid (390), 300 mg qd (385) or 225 mg bid (393) and matching placebo vs. enoxaparin 40 mg sc qd and matching placebo (392)	66 y, 39 %	Short acting NSAIDS with half-lives of less than 12 h, low-dose aspirin and COX-2 inhibitors were allowed	7 days	Not reported, total study time 4-6 wk	68% THR, 32% TKR, 1.4 h	0.3/4.1/4.7/3.8/2.0^ ISTH	2.6/8.2/8.3/8.4/4.6^ Standard definition	Not reported
Turpie, ODIXa-KNEE, 2005 [32]	Male patients age ≥ 18 y or postmenopausal females scheduled for elective TKR	Any bleeding disorder	Rivaroxaban 2.5 mg bid (100), 5 mg bid (102), 10 mg bid (103), 20 mg bid (98) or 30 mg bid (106) and matching placebo vs.enoxaparin 30 mg bid sc (104) and matching placebo	67 y, 39 %	Anticoagulants, platelet aggregation inhibitors or any other drug influencing coagulation prohibited at inclusion. NSAIDS with half-life <17 h allowed	Mean 7.3 days	Not reported, total FU 30-60 days	100% TKR, 89 min	1.0/0.0/1.9/3.1/7.5/1.9^ ISTH	3.0/2.9/2.9/8.2/14.2/4.8^ Standard definition	Not reported
Eriksson, ODIXa-HIP I 2006 [33]	Male patients age ≥ 18 y or postmenopausal females scheduled for elective THR	Any bleeding disorder	Rivaroxaban 2.5 mg (135) bid, 5 mg bid (139), 10 mg bid (138), 20 mg bid (137) or 30 mg bid (37) and matching placebo vs. enoxaparin 40 mg qd sc (136) and matching placebo	65 y, 40 %	Anticoagulants, platelet aggregation inhibitors or any other drug influencing coagulation prohibited at inclusion. NSAIDS with half-life <17 h allowed	Mean 8.3 days	Not reported, total FU 30-60 days	100% THR, 85 min	0.8/2.2/2.3/4.5/5.4/1.5^ ISTH	2.3/8.0/4.5/9.0/8.1/1.5^ Standard definition	Major: 0.0/0.0/0.0/0.0/0.0/0.8

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Eriksson, ODIXa-HIP II, 2006 [34]	Men aged >17 y and postmenopausal women scheduled for elective, primary THR	Gastrointestinal bleeding in the previous 6 months	Rivaroxaban 5 mg qd (128),10 mg qd (142), 20 mg qd (140, 30 mg qd (143) or 40 mg (142) qd plus matching placebo vs. enoxaparin 40 mg sc qd plus matching placebo (157)	65 y, 41 %	Only NSAIDS with a half-life <17 h allowed	7/8 days	Not reported, total FU 30-60 days	100% THR, 87 min	2.3/0.7/4.3/4.9/5.1/1.9^ ISTH	3.9/2.8/5.0/7.0/8.0/5.1^ Standard definition	Not reported
Eriksson, not reported, 2007 [35]	Men aged ≥18 y and postmenopausal women scheduled for elective, primary THR	No statement about exclusion of patients with higher risk of bleeding	Rivaroxaban 2.5 mg bid (77), 5 mg bid (84), 10 mg bid (68), 30 mg qd (91), 20 mg bid (79), 30 mg bid (80) vs. enoxaparin 40 mg sc qd (162)	65 y, 41 %	Only NSAIDS with a half-life <17 h allowed	7/8 days	Not reported, total FU 30-60 days	100% THR, duration ns	0/2.5/2.9/4.5/6.5/10.8 ^ ISTH	2.6/3.8/7.3/11.3/11.7/20.3/1.9^ Standard definition	0.0/0.0/0.0/1.1/0.0/0.0/0.0^
Eriksson, RE-MODEL, 2007 [36]	Patients ≥18 y and >40,g, scheduled for primary elective unilateral TKR	Any bleeding diathesis, GI bleeding or ulcer disease within the past 6 months	Dabigatran etexilate 150 mg qd (679) or 220 mg qd (703) and matching placebo vs. enoxaparin 40 mg sc qd (694) and matching placebo	68 y, 34 %	Concomitant treatment with low-dose aspirin (<160 mg) and selective COX2-inhibitors was allowed	8/7 days	Not reported	100% TKR, 91 min	1.3/1.5/1.3^ ISTH	6.8/5.9/5.3^ Standard definition	Not reported

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Lassen, APROPOS, 2007 [38]	Patients 18-90 y scheduled for TKR	Bleeding/ coagulation disorder, GI bleeding within 90 days of surgery or ulcer disease within 30 days before surgery	Apixaban 2.5 mg bid (153), 5 mg qd (157), 5 mg bid (157), 10 mg qd (156), 10 mg bid (154), 20 mg qd (156) and enoxaparin placebo vs. warfarin (INR 1.8-3.0) (153) or Enoxaparin 30 mg sc bid (152) and apixaban placebo	67 y, 37 %	No co-use of medications affecting coagulation/ platelet function allowed	Not reported	Not reported, final evaluation on day 42	100% TKR, 1.56 h	0/2.6/2.6/0.6/2.6/3.3/0/0^ ISTH	Major and potentially significant non-overt: 0/2.6/2.6/1.2/2.6/3.3/0/1.3^ Adjusted definition	Major bleeding: 0/0/0/0/0.6/0/0/0^
Eriksson, RE-NOVATE, 2007 [37]	Patients ≥18 y and >40 kg scheduled for elective unilateral THR	Bleeding diathesis, history of GI bleeding or ulcer disease in the past 6 months	Dabigatran etexilate 150 mg qd (1163) or 220 mg qd (1146) and matching placebo vs. enoxaparin 40 mg sc qd (1154) and matching placebo	64 y, 44 %	Concomitant administration of low-dose aspirin (<160mg) and selective COX-2 inhibitors or short acting NSAIDs were allowed	33 days	94 days	100% THR, 86 min	1.3/2.0/1.6^ ISTH	6.0/6.2/5.1^ Standard definition	1 Fatal event in 150 mg group with septicaemia and GI bleeding
Eriksson, RECORD-I 2008 [39]	Patients ≥18 y and scheduled for elective THR	Active bleeding or high risk of bleeding	Rivaroxaban 10 mg qd (2266) and matching placebo vs. enoxaparin 40 mg sc qd (2275) and matching placebo	63 y, 45%	Other anticoagulant therapy prohibited at inclusion	33.4/33.7 days	FU visit 30-35 days after last study drug	100% THR, 91 min	0.3/0.1^ p=0.18 ISTH	3.2/2.5^ No definition reported	0.1/<0.1^
Lassen, RECORD III, 2008 [40]	Patients ≥18 y and scheduled for TKR	Active bleeding or high risk of bleeding that contraindicated the use of LMWH	Rivaroxaban 10 mg qd (1220) and matching placebo vs. enoxaparin 40 mg sc qd (1239) and matching placebo	68 y, 32%	Other anticoagulant therapy prohibited at inclusion	11.9/12.5 days	FU visit 30-35 days after last study drug	100% TKR, 97 min	0.6/0.5^ ISTH	3.3/2.7^ No definition reported	Not reported

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Kakkar, RECORD II, 2008 [41]	Patients ≥18 y and scheduled for elective THR	Active bleeding or high risk of bleeding that contraindicated the use of LMWH	Rivaroxaban 10 mg qd (1228) and matching placebo vs. enoxaparin 40 mg sc qd (1229) and matching placebo	62 y, 46%	Other anticoagulant therapy prohibited at inclusion	33.5/12.4 days	FU visit 30-35 days after last study drug	100% THR, 94 min	<0.1/<0.1^ ISTH	3.3/2.8^ No definition reported	<0.1/0.0^
Ginsberg, RE-MOBILIZE, 2009 [42]	Patients ≥18 y and >40 kg scheduled for primary elective unilateral TKR	Clinically significant bleeding disorder, GI bleeding or ulcer disease within the last 6 months	Dabigatran etexilate 150 mg qd (877) or 220 mg qd (862) and matching placebo vs. enoxaparin 30 mg sc bid (876) and matching placebo	66 y, 42 %	Concomitant administration of low-dose aspirin (<160mg) and selective COX-2 inhibitors or short acting NSAIDs were allowed	14 days	Not reported, 94% was followed 3 mo	100% TKR, 91 min	0.8/0.7/1.4^ ISTH	3.6/4.0/4.1^ Standard definition	Not reported
Turpie, EXPERT, 2009 [43]	Patients 18-75 y and 50-120 kg scheduled for primary elective unilateral TKR	Bleeding disorders, a recent episode of internal bleeding or at high risk of bleeding	Betrixaban 15 mg bid (87) or 40 mg bid (84) vs. enoxaparin 30 mg sc bid (43)	64 y, 40 %	Use of thrombolytic agents and anticoagulants was prohibited within 7 days prior to surgery and throughout the treatment period; use of aspirin <325 mg and NSAIDs were allowed but discouraged	11/10.3 days	Not reported	100% TKR, duration not reported	0.0/0.0/2.3^ Modified ISTH	0.0/2.4/7.0^ No definition reported	Not reported

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Turpie, RECORD IV, 2009 [44]	Patients ≥18 y and scheduled for elective TKR	Active bleeding or high risk of bleeding that contraindicated the use of LMWH	Rivaroxaban 10 mg qd (1584) and matching placebo vs. enoxaparin 30 mg sc bid (1564) and matching placebo	65 y, 35%	Not reported	11.7/11.0 days	Patients were followed up for 30-35 days after the last dose	100% TKR, 100 min	0.7/0.3^ p=0.11 ISTH	3.0 /2.3^ Standard definition	1 fatal UGIB in rivaroxaban arm
Lassen, ADVANCE I, 2009 [45]	Patients ≥18 y and scheduled for elective TKR or revision	Bleeding or coagulation disorder, active bleeding or high risk of bleeding, ongoing need for oral anticoagulant therapy	Apixaban 2.5 mg bid (1599) and matching placebo vs. enoxaparin 30 mg sc bid (1596) and matching placebo	66 y, 38%	Only NSAIDS with a half-life <17 hours allowed	11.7/11.6 days	Follow-up at 30 and 60 days after last dose	100% TKR, 1.54 h	0.7/1.4^ p=0.053 ISTH	2.9/4.3^ p=0.03 Standard definition	<0.1/0.6^
Fuji, not reported, 2010 [46]	Patients >19 y and at least 40 kg scheduled for primary unilateral elective total knee replacement	Any bleeding diathesis, clinically relevant bleeding or ulcer bleeding within the last 6 mo	Dabigatran etexilate 110 mg qd (133), 150 mg qd (126) or 220 mg qd (129) vs. placebo (124) LMWH not yet registered in Japan at this time	72 y, 17%	The concomitant use of anticoagulants and antiplatelet agents was prohibited	13 days	Follow-up 7-10 days after last dose	100% TKR, 109 min	0.8/0.0/2.3/0.8^ ISTH	0.8/0.8/3.9/3.2^ Standard definition	Not reported
Lassen, ADVANCE II, 2010 [49]	Patients scheduled for elective TKR	Active bleeding or needed continuing anticoagulant or anti-platelet treatment	Apixaban 2.5 mg bid (1528) and matching placebo vs. enoxaparin 40 mg sc qd (1529) and matching placebo	67 y, 38 %	Other anticoagulant or anti-platelet therapy prohibited at inclusion	12.1/12.1 days	Follow-up at 30 and 60 days after last dose	100% TKR, 1.58 h	0.6/0.9^ ISTH	3.5/4.8^ Standard definition	0.2/0.3^

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Raskob, not reported, 2010 [50]	Patients ≥18 y and scheduled for elective THR	Known or suspected bleeding or coagulation disorder or GI bleeding or peptic ulcer within the past 3 months	Edoxaban 15 mg qd (193), 30 mg qd (171), 60 mg qd (187) or 90 mg qd (177) and matching placebo vs. dalteparin 5000 IU sc qd (175) and matching placebo	58 y /40%	Only aspirin <100 mg qd allowed	Not reported	Follow-up at 30 and 60 days after last dose	100% THR, 1.38 h	0.5/0.6/0.5/1.1/0.0^ ISTH	1.6/1.8/2.2/2.3/0.0^ Standard definition	Not reported
Fuji, not reported, 2010 [47]	Patients 20-84 y and scheduled for primary elective TKR	History of GI bleeding or peptic ulcer	Edoxaban 5 mg qd (105), 15 mg qd (106), 30 mg qd (104), 60 mg qd (106) vs. placebo (102) LMWH not yet registered in Japan at this time	71 y, 21 %	Other anticoagulant or anti-platelet therapy prohibited at inclusion. Use of dextran was allowed	Not reported	Follow-up 25-35 days after last dose	100% TKR, 1.50 h	0.0/0.0/0.0/0.9/0.0^ ISTH	1.9/3.8/3.9/4.7/3.9^ Adjusted definition	Not reported
Lassen, ADVANCE III, 2010 [48]	Patients scheduled for elective THR or revision	Bleeding or coagulation disorder, active bleeding or high risk of bleeding, ongoing need for oral anticoagulant therapy	Apixaban 2.5 mg bid (2708) and matching placebo vs. enoxaparin 40 mg sc qd (2699) and matching placebo	61 y, 47 %	Only NSAIDS with a half-life <17 h allowed	34.0/33.9 days	Follow-up 65 and 95 days after last dose	100% THR, 1.49 h	0.8/0.7 ^ ISTH	4.8/5.0^ Standard definition	0.1/0.0^

Table S2. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants (% study /% control)	Median use of study medication	Median Follow-up, year	Type of surgery, mean duration	Major bleeding, % study/ % control ‡ Definition of major bleeding*	Clinically relevant bleeding, % study/ % control ‡ Definition of CRB**	Gastrointestinal bleeding, % study/ % control
Eriksson, RE-NOVATE-II 2011 [51]	Patients ≥18 y and scheduled for elective THR	Clinically significant bleeding disorder, GI bleeding or ulcer disease within the last 6 months	Dabigatran 220mg qd (1036) and matching placebo vs. Enoxaparin 40 mg sc qd (1019) and matching placebo	62 y, 48 %	No co-use of medications affecting coagulation/ platelet function allowed Concomitant administration of low-dose aspirin (<160mg) and selective COX-2 inhibitors or short acting NSAIDs were allowed	32 days	92 days	100% THR, 80 min	1.4/0.9^ ISTH	3.7/2.9^ Adjusted definition	Not reported

** according to the ISTH (International Society on Thrombosis and Haemostasis) criteria [16]/TIMI (thrombolysis in myocardial infarction) criteria,[17] or adjusted criteria, **according to the standard definition as reported in the method section, or adjusted definition,, # p< 0.05, ‡ major postoperative bleeding: starting after the first postoperative dose of study drug, but not >2days after the last administration of study drug, ^ during treatment period, not during follow-up.*

Abbreviations: bid: twice daily, CHF: congestive heart failure, CI: confidence interval, COX-2: cyclooxygenase 2, FU: follow-up, GI gastrointestinal, HR: hazard ratio, IBD: inflammatory bowel disease, LMWH: low-molecular-weight-heparin, qd: once daily, NSAIDs: non-steroidal anti-inflammatory drugs, RR: relative risk, THR: total hip replacement, TKR: total knee replacement, sc: subcutaneously, UGIB: upper gastrointestinal bleeding.

Table S3. RCTs studying new oral anticoagulants for the prevention of venous thromboembolism in medically ill patients.

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Median use of study medication	Median Follow-up, year	Major bleeding, RR (95% CI) or % study/ % control ‡ Definition of major bleeding *	Clinically relevant bleeding RR (95% CI) or % study/% control ‡ Definition of CRB **	Gastrointestinal bleeding, % study/ % control
Goldhaber, ADOPT, 2011[52]	Patients age ≥40 y hospitalized for CHF, acute respiratory failure or for infection, acute rheumatic disorder, IBD and at least 1 additional risk factor for VTE and an expected hospital stay of at least 3 days and moderately or severely restricted in mobility	A disease requiring ongoing treatment with parenteral or oral anticoagulant agent, thrombocytopenia, actively bleeding or at high risk for bleeding	Apixaban 2.5 mg bid and placebo (3255) vs. enoxaparin sc 40mg qd and placebo (3273)	68 y, 49 %	Patients with 2 or more antiplatelet agents or aspirin at a dose >165 mg/day were excluded	Mean 24.9/7.3 days	Not reported	Relative risk 2.58 (1.02-7.24) ISTH	Relative risk 1.28 (0.93-1.76) Standard definition	Not reported
Levine, not reported, 2012[53]	Patients >18 y receiving first-line or second-line chemotherapy for advanced or metastatic lung, breast, GI, bladder, cancer of unknown origin, ovarian or prostate cancer, myeloma or selected lymphomas and if the expected course of chemotherapy was ≥90 days	Active bleeding or high risk for bleeding, presence of a coagulopathy, requiring long-term oral anticoagulant therapy	Apixaban 5mg qd (32), 10 mg qd (30), 20 mg qd (33) vs. placebo (30)	60 y, 50%	Aspirin in a dose ≤ 165 mg allowed, clopidogrel, cilostazol or aspirin-dipyridamole prohibited	Mean 79.2/76.0/ 73.6/69.9 days	Total 12 weeks, completed by 78%/80%/76%/ 63%	0.0/0.0/6.3/3.4ISTH	3.1/3.4/ 12.5/3.4 Adjusted definition	3.1/0/3.1/3.4

** according to the ISTH (International Society on Thrombosis and Haemostasis) criteria[16]/TIMI (thrombolysis in myocardial infarction) criteria,[17] or adjusted criteria,*
***according to the standard definition as reported in the method section, or adjusted definition, # p< 0.05, ‡ major postoperative bleeding: starting after the first postoperative dose of study drug, but not >2days after the last administration of study drug.*
Abbreviations: bid: twice daily, CHF: chronic heart failure, GI: gastrointestinal, IBD: inflammatory bowel disease, qd: once daily, sc: subcutaneously, RR: risk ratio, VTE: venous thromboembolism.

Table S4. RCTs studying new oral anticoagulants for the treatment of acute symptomatic deep vein thrombosis or pulmonary embolism.

Author, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Mean use of study medication	Median Follow-up	INR within therapeutic range in control group, median time ‡	Major bleeding % study/ % control Definition of major bleeding *	Clinically relevant bleeding HR, RR (95% CI) or % study/ % control Definition of CRB **	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control
Agnelli, ODIXa-DVT, 2007 [54]	Patients with symptomatic acute thrombosis of the popliteal or more proximal veins and age≥18 and no symptoms of PE	Intracerebral or gastrointestinal bleeding within the past 6 months, an active peptic ulcer or known bleeding disorder	Rivaroxaban 10 mg bid (119), 20 mg bid (117), 30 mg bid (121), 40 mg qd (121) vs. enoxaparin^ and a VKA for 12 wk (126)	59 y, 61 %	Thrombolytic therapy or treatment with antiplatelet agents, NSAIDs with a half-life >17 h are prohibited, short term analgesia with ASA 500 mg/d permitted	Not reported	Not reported, total study time 12 wk	60 %	1.7/1.7/3.3/1.7/0.0 ISTH	Not reported	Not reported
Buller, BOTTICELLI 2008 [56]	Patients with acute symptomatic proximal DVT or extensive calf vein thrombosis and no symptoms of PE	Active bleeding or high risk of bleeding	Apixaban 5 mg bid (130), 10 mg bid (134), or 20 mg qd (128) vs. tinzaparin, enoxaparin or fondaparinux^ and a VKA (128)	59 y, 62 %	Acetylsalicylic acid <165 mg/day allowed	80/81/77/80/82	Not reported, total study time 12 wk	57%	0.8/0.0/1.6/0.0 ISTH	8.6/4.5/8.9/7.9 Standard definition	Not reported
Buller, EINSTEIN-DVT, 2008 [55]	Patients with acute symptomatic proximal DVT or extensive calf vein thrombosis and no symptoms of PE	Active bleeding or high risk of bleeding	Rivaroxaban 20 mg qd (135), 30 mg qd (134) or 40 mg qd (136) vs. unfractioned heparin^, tinzaparin or enoxaparin (137) and VKA	58 y, 51%	Use of NSAIDs and antiplatelet agents was discouraged. If indicated, aspirin (up to 100 mg/day), clopidogrel (75 mg/day), or both were allowed	Median 85 days/not reported	Not reported, end of study 84 days	50.3	0.7/1.5/0/1.5 ISTH	5.9/6.0/2.2/8.8 Standard definition	Not reported

Table S4. *(Continued)*

Author, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Mean use of study medication	Median Follow-up	INR within therapeutic range in control group, median time ‡	Major bleeding % study/ % control Definition of major bleeding *	Clinically relevant bleeding HR, RR (95% CI) or % study/ %control Definition of CRB **	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control
Schulman, RE-COVER, 2009 [57]	Patients ≥18 y with acute, symptomatic, DVT of the legs or PE	High risk of bleeding	Dabigatran 150 mg bid (1273) and matching placebo vs. parenteral anticoagulation^ and warfarin (1266) and matching placebo	56 y, 58 %	Not reported	163.4/163.9 days	Not reported, total study time 6 mo	59.9	HR 0.82 (0.45-1.48) ISTH	HR 0.63 (0.47-0.84)# Adjusted definition	4.2/2.8
Bauersachs, EINSTEIN-ACUTE DVT, 2010 [58] †	Legal age for consent symptomatic DVT, without symptomatic PE	Active bleeding or high risk of bleeding	Rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg qd (1731) vs. enoxaparin^ and VKA (INR 2.0-3.0) (1718)	Mean age: 56 y, 57%	Use of NSAIDs and antiplatelet agents was discouraged. If indicated, aspirin (up to 100 mg/day), clopidogrel (75 mg/day), or both were allowed	Not reported, total: 3-12 mo based on intended treatment duration	Not reported, total study time 3, 6, or 12 mo	Overall the INR was in the therapeutic range for 57.7% of the time	HR 0.65 (0.33-1.30) ISTH	8.1/8.1 Standard definition	Not reported
Bauersachs, EINSTEIN-EXTENSION, 2010 [58] †	DVT or PE and treated for 6-12 months with a VKA or rivaroxaban	Active bleeding or high risk of bleeding	Rivaroxaban 20 mg qd (602) vs. placebo (595)	Mean 58 y, 58%	Use of NSAIDs and antiplatelet agents was discouraged. If indicated, aspirin (up to 100 mg/day), clopidogrel (75 mg/day), or both were allowed	Not reported, total 6 to 12 mo	Not reported, total study time 6-12 mo	Not applicable	0.7/0.0 ISTH	HR 5.19 (2.3–11.7)# Standard definition	0.7/0.0

Table S4. *(Continued)*

Author, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Mean use of study medication	Median Follow-up	INR within therapeutic range in control group, median time ‡	Major bleeding % study/ % control Definition of major bleeding *	Clinically relevant bleeding HR, RR (95% CI) or % study/ % control Definition of CRB **	Gastrointestinal bleeding HR, RR (95% CI) or % study/ % control
Buller, EINSTEIN-PE, 2012[59] †	Acute symptomatic PE, with or without DVT	Active bleeding or high risk of bleeding contraindicating anticoagulant treatment	Rivaroxaban 15 mg bid first 3 weeks, followed by 20 mg qd (2419) vs. enoxaparin and VKA (INR 2.0-3.0) (2413)^	Mean 58 y, 53%	The use of NSAIDs and antiplatelet agents was discouraged. Aspirin <100 mg per day and clopidogrel at a dose of 75 mg per day were allowed	214/216 days	268/263 days	62.7%	1.1/2.2 ISTH	10.5/11.9 Standard definition	Not reported

** according to the ISTH (International Society on Thrombosis and Haemostasis) criteria[16]/TIMI (thrombolysis in myocardial infarction) criteria,[17] or adjusted criteria, **according to the standard definition as reported in the method section, or adjusted definition, ^ for at least 5 days until INR 2-3 for 2 consecutive days, ‡ using the method of Rosendaal, † This paper consists of two trials; one for the treatment of acute DVT, and one for continued treatment in patients who have received treatment for acute DVT or PE, # significant difference.*

Abbreviations: ASA: acetyl salicylic acid, bid: twice daily, CI: confidence interval, DVT: deep vein thrombosis, HR: hazard ratio, INR: international normalized ration, NSAIDs: non-steroidal anti-inflammatory drugs, PE: pulmonary embolism, qd: once daily, RR: risk ratio, VKA: vitamin K antagonist.

Table S5. RCTs studying new oral anticoagulants for the treatment of acute coronary syndrome.

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Median use of study medication	Median follow-up	Major bleeding, % study/ % control Definition of major bleeding *	Clinically relevant bleeding, RR or HR (95% CI) or % study/% control Definition of clinically relevant bleeding **	Gastrointestinal bleeding HR, RR or % study/ % control
Appraise investigator, APPRAISE, 2009 [60]	Patients 18-90 y with a recent ACS, and at least 1 additional risk factor for recurrent ischemic events	Coagulopathy, active bleeding or high risk of bleeding	Phase A: Apixaban 2.5 mg bid (179), 10 mg qd (184) Phase B: Apixaban 2.5 mg bid (138), 10 mg qd (134), 10 mg bid (248) or 20 mg qd (221) vs. Phase A: placebo (184), Phase B: placebo (427)	61 y, 76%	All patients were to receive aspirin < 165 mg/day (99.7/99.7/100/100/100). The use of clopidogrel was left to the discretion of the treating physician >75% received dual antiplatelet therapy	22.1/21.5/12.7/10.9/ 21.7/ wk	Not reported, total follow-up of study 6 mo	Phase A and B: 2.5 mg bid en 10 mg qd: 1.6/1.9/0.8 The 2 higher dose apixaban arms were discontinued because of excess total bleeding Phase B: 0.8/0.0/2.9/4.1/0.0 ISTH	Phase A and B: 2.5 mg bid en 10 mg qd: 5.7/7.9/3.0 HR 2.5 mg bid: 1.78 (0.91-3.48) HR 10 mg qd: 2.45 (1.31-4.61)# Phase B: 5.0/5.6/7.8/7.3/0.8 Standard definition	Phase A and B: 2.5 mg bid en 10 mg qd 5.7/2.5/0.8
Mega, ATLAS ACS-TIMI 46, 2009 [61]	Patients >17 y with a ACS and at least one extra risk factor	A hemoglobin concentration <100 g/L, a platelet count <90 000 per ul of blood, or a history of any intracranial hemorrhage	Rivaroxaban 5 mg qd (231), 10 mg qd (294), 20 mg qd (236) with aspirin only or 5 mg qd (228), 10 mg qd (1288), 15 mg qd (534), 20 mg qd (680) with aspirin and thienopyridine vs. placebo (1160)	57 y, 77%	Warfarin prohibited at inclusion. Aspirin: ASA/ ASA+thienopyridine/ placebo: 99.2/98.9/99.0 Thienopyridine: 80.8 (baseline)	Not reported	Not reported, total follow-up of study 6 mo	With aspirin only: 0.0/2.2/0.0/0.0 With aspirin+ thienopyridine:0.7/1.5/1.8/1.8/0.1 TIMI	5 mg: HR 2.21 (1.25-3.91)# 10 mg: HR: 3.35 (2.31-4.87)# 15 mg: HR 3.60 (2.32-5.58)# 20 mg: HR 5.06 (3.45-7.42)# TIMI clinically significant	0.8/1.2 needed colonoscopy or upper endoscopy because of bleeding

Table S5. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Median use of study medication	Median follow-up	Major bleeding, % study/ % control Definition of major bleeding *	Clinically relevant bleeding, RR or HR (95% CI) or % study/% control Definition of clinically relevant bleeding **	Gastrointestinal bleeding HR, RR or % study/ % control
Alexander, APPRAISE-II, 2011 [62]	Patients with a recent ACS and at least 2 additional high risk characteristics	Coagulopathy, active bleeding or high risk of bleeding	Apixaban 5 mg bid (3705) vs. placebo (3687)	67 y, 68%	Parenteral or oral anticoagulants or high dose aspirin (>325mg/ day) prohibited at inclusion. The use, choice and duration of antiplatelet therapy and other medical therapy were left to the discretion of the treating physician.	175/185 days	240/242 days	2.7/1.1 HR 2.48 (1.72-3.58)# After recruitment of about 7000 patients the trial was stopped, owing to an excess of clinically important bleeding events with apixaban in the absence of a counterbalancing reduction in ischemic events ISTH	3.2/1.2 HR 2.64 (1.87-3.72)# Standard definition	Not reported
Oldgren, RE-DEEM, 2011 [64]	Patients ≥ 18 y hospitalized with MI within the last 14 days receiving dual antiplatelet therapy and at least one risk factor for subsequent cardiovascular complications	Ongoing or planned treatment with VKA, conditions associated with an increased risk of bleeding such as history of severe bleeding, GI hemorrhage within the past year, PUD in the previous 30 days	Dabigatran 50 mg bid (372), 75 mg bid (371), 110 mg bid (411) or 150 mg bid (351) vs. placebo (373)	Mean 62 y, 76%	The daily aspirin dose was strongly advised to be ≤ 100 mg, but higher doses were permitted according to local practice. The recommended daily dose clopidogrel was 75 mg although loading doses of 300-600 mg were allowed for PCI procedures (aspirin and clopidogel at randomization 99.2%, aspirin only 0.4%, aspirin and clopidogrel at 26 wk 83.8, aspirin only 14.2%	Range 158.9-164.4 days for the dabigatran groups and 164.7 days for the placebo group	Total 28 wk	0.8/0.3/2.0/1.2/0.5 ISTH	50 mg: HR 1.77 (0.70-4.50), 75 mg: HR 2.17 (0.88-5.31), 110 mg: HR 3.92 (1.72-8.95), 150 mg: 4.27 (1.86-9.81)# Standard definition	2.4/3.0/4.9/ 3.2/1.3

Table S5. *(Continued)*

Author, trial name, year	Baseline condition	Exclusion criteria, specified on bleeding risk	Study group (n) vs. control group (n)	Median age, % men	Concomitant use of antiplatelet agents or other anticoagulants, % study /% control	Median use of study medication	Median follow-up	Major bleeding, % study/ % control Definition of major bleeding *	Clinically relevant bleeding, RR or HR (95% CI) or % study/% control Definition of clinically relevant bleeding **	Gastrointestinal bleeding HR, RR or % study/ % control
Mega, ATLAS ACS 2-TIMI 51, 2012 [63]	Patients ≥ 18 y with MI or unstable angina. Patients <55 y had in addition either DM or a previous MI	Clinically significant GI bleeding within 12 months before randomization	Rivaroxaban 2.5 mg qd (5174), 5 mg qd (5176) vs. placebo (5176)	Mean 62 y, 75%	All patients were to receive low-dose aspirin; they were to receive a thienopyridine according to the national guidelines	13.1 mo	Not reported, maximum 31 mo	1.8/2.4/0.6 TIMI	11.5/15.0/6.3 TIMI clinically significant	Not reported

** according to the ISTH (International Society on Thrombosis and Haemostasis) criteria[16]/TIMI (thrombolysis in myocardial infarction) criteria,[17] or adjusted criteria,*
***according to the standard definition as reported in the method section, or adjusted definition, # statistically significant.*
Abbreviations: ACS: acute coronary syndrome, ASA: acetylsalicylic acid, bid: twice daily, CI: confidence interval, HR: hazard ratio, GI: gastrointestinal MI: myocardial infarction, PCI: percutaneous coronary intervention, PUD: peptic ulcer disease, RR: relative risk, VKA: vitamin K antagonist.

Table S6. Registered/recommended dose per indication.

	Rivaroxaban	Apixaban	Dabigatran	Edoxaban	Betrixaban
AF	20 mg qd[a,b 10]	5 mg bid[b,c 28-30]	150 mg bid[a,b 9, 25]	60 mg qd[c 26, 27]	-
OS	10 mg qd[a,b 34, 39-41, 44] or 5 mg bid[d 32, 33, 35]	2.5 mg bid[a 38, 45, 48, 49]	220 mg qd[a 36, 37, 42, 46, 51] or 300 mg qd[d 31]	30 mg qd[c 47, 50]	40 mg bid[d 43]
ACS	5 mg[d 61, 63]	5 mg bid[d 60] or 2.5 mg bid[d 62]	110 mg bid[d 64]	-	-
DVT/PE	15 mg bid 3 weeks followed by 20 mg qd[a,b 58, 59] 10 mg bid[d 54], or 30 mg qd[d 55]	10 mg bid[c 56]	150 mg bid[d 57]	-	-
Medically ill	-	5 mg qd[d 53] or 2.5 mg bid[d 52]	-	-	-

Source: [a] registered dose at the European Medicines Agency, b registered dose at the Food and Drug Administration, [c] on request of the pharmaceutical company, [d] the lowest studied effective dose or dose most comparable with registered dose.

Abbreviations: ACS: acute coronary syndrome, AF: atrial fibrillation, bid: twice daily, DVT: deep vein thrombosis, OS: orthopedic surgery, PE: pulmonary embolism, qd: once daily.

Table S7. Methodological quality* of included studies according to the Cochrane Reviewers' Handbook.

Author, year, trial	Method of randomization (A/B/C)	Concealment of allocation (A/B/C)	Blinding for treatment (A/B/C/D)	Independent clinical end-point committee (A/B/C)	Lost to follow-up of total study population (%)	Intention to treat analysis (A/B/C/D)
Ezekowitz, 2007 PETRO [25]	C	C	B	A	Not reported	C
Connolly, 2009 RELY [9, 73]	A	A	B	A	20/18113 = 0.1%	A
Weitz, 2010 [26]	A	A	B	A	3/1146= 0.3%	A
Chung, 2011 [27]	A	A	B	A	2/235=0.9%	A
Ogawa, 2011 [28]	A	C	B	A	4/222=1.8%	A
Connolly, 2011 AVERROES [29, 74]	A	A	A	A	Not reported	A
Patel, 2011 ROCKET AF [10, 75]	A	A	A	A	32/14264=0.2%	A
Granger, 2011 ARISTOTLE [30, 76]	A	C	A	A	69/18201 = 0.4%	A
Eriksson, 2005, BISTRO II [31]	A	C	A	A	12/1969 = 0.6%	A
Turpie, 2005, ODIXa-KNEE [32]	A	A	A	A	3/621=0.5%	A
Eriksson, 2006, ODIXa-HIP I [33]	C	C	A	A	Not reported	A
Eriksson, 2006, ODIXa-HIP II [34]	C	C	A	A	Not reported	A
Eriksson, 2007 [35]	A	C	C	A	Not reported	A
Eriksson, 2007, RE-MODEL [36]	A	A	A	A	Not reported	A
Lassen, 2007, APROPOS [38]	A	A	B	A	Not reported	A
Eriksson, 2007, RE-NOVATE [37]	A	A	A	A	Not reported	A
Eriksson, 2008, RECORD1 [39]	A	A	A	A	Not reported	A
Lassen, 2008, RECORD3 [40]	A	A	A	A	Not reported	A
Kakkar, 2008, RECORD2 [41]	A	A	A	A	Not reported	A
Ginsberg, 2009, RE-MOBILIZE [42]	A	A	A	A	Not reported	A
Turpie, 2009, EXPERT [43]	A	A	B	A	1/215 = 0.4%	A
Turpie, 2009, RECORD4 [44]	A	A	A	A	Not reported	A

Table S7. *(Continued)*

Author, year, trial	Method of randomization (A/B/C)	Concealment of allocation (A/B/C)	Blinding for treatment (A/B/C/D)	Independent clinical end-point committee (A/B/C)	Lost to follow-up of total study population (%)	Intention to treat analysis (A/B/C/D)
Lassen, 2009, ADVANCE-1 [45]	A	C	A	A	79/3195 = 2.5%	A
Fuji, 2010 [46]	A	C	A	A	Not reported	A
Lassen, 2010, ADVANCE-2 [49]	A	A	A	A	Not reported	A
Raskob, 2010 [50]	A	A	A	A	Not reported	A
Fuji, 2010 [47]	A	C	A	A	Not reported	A
Lassen, 2010, ADVANCE-3 [48]	A	A	A	A	Not reported	A
Eriksson, 2011, RE-NOVATE II [51]	A	A	A	A	2/2055 = 0.1%	A
Goldhaber, 2011 ADOPT [52]	A	A	A	A	Not reported	A
Levine, 2012 [53]	A	A	A	A	0/125=0%	A
Agnelli, 2007 [54]	A	A	B	A	1/613 = 0.2%	A
Buller, 2008, BOTTICELLI [56]	A	A	B	A	Not reported	A
Buller, 2008 Einstein-DVT [55]	A	A	B	A	1/542 = 0.2%	A
Schulman, 2009 RE-COVER [57]	A	A	A	A	15/2564 = 0.6%	B
Bauersachs, 2010 EINSTEIN-ACUTE DVT [58]	A	A	C	A	33/3449= 1.0%	B
Bauersachs, 2010 EINSTEIN-ExTENSION [58]	A	A	A	A	2/1196 = 0.2 %.	A
Buller, 2012, EINSTEIN-PE [59]	A	A	C	A	18/4832 = 0.4%	A
Appraise investigators, 2009, APPRAISE [60]	A	A	A	A	25/1715 = 1.5%	A
Mega, 2009 ATLAS ACS-TIMI 46 [61]	A	C	A	A	22/3491=0.6%	A
Alexander, 2011, APPRAISE-2 [62]	A	A	A	A	50/7392 = 0.7%	A
Oldgren, 2011, RE-DEEM [64]	A	A	A	A	12/1878 = 0.6%	A
Mega, 2012, ATLAS ACS 2-TIMI 51 [63]	A	C	A	A	0.3%	A

*Legend: * The quality of included studies was assessed according to the Cochrane Reviewers' Handbook. The quality assessment criteria include: 1. Method of randomization: A. Truly random: computer generated random numbers, coin toss etc., B. Quasi random: birth-date, patient registration-number etc., C. Not stated/unclear; 2. Allocation concealment: A. Adequate: trialist unaware of each participant's allocation, by for instance central randomization systems or serially numbered opaque envelopes etc., B. Inadequate: trialist aware of allocations at recruitment, C. Not stated/ unclear; 3. Blinding for treatment: A. Double blind, B. Double blind for dose of NOAC, but not for NOAC vs. control, C. Unblinded, D. Not stated/unclear; 4. Blinding of outcome assessment: A. Blinded, B. Unblinded, C. Not stated/unclear. 5. Participant flow: Loss to follow-up of total study population described; 6. Intention to treat analysis (all subjects who received at least one dose are considered to be part of the trial, regardless of completion of treatment): A. Yes at least for safety analysis, B. Only for efficacy analysis, C. No, D. Not stated/unclear.*

Table S8. Gastrointestinal and clinically relevant bleeding by indication and by drug including sensitivity analysis.

Subgroups	No of studies*	N events/N total nOAC	N events/ N total control	OR (95% CI)	P for hetero-geneity	I^2 (%)
GIB, all studies	17	631/37201	470/37335	1.45 (1.07-1.97)	0.001	61
By indication						
Atrial fibrillation	6	524/25234	408/25140	1.21 (0.91-1.61)	0.017	64
Orthopedic surgery	6	11/9343	16/9340	0.78 (0.31-1.96)	0.149	39
Medically ill	1	1/32	1/29	0.91 (0.05-15.13)	1.000	0
Deep vein thrombosis/ pulmonary embolism	2	57/1871	35/1856	1.59 (1.03-2.44)	0.241	27
Acute coronary syndrome	2	38/721	10/970	5.21 (2.58-10.53)	0.372	0
By drug						
Apixaban	8	145/18084	153/18301	1.23 (0.56-2.73)	0.001	70
Betrixaban	0	-	-	-	-	-
Dabigatran	3	255/7755	160/7659	1.58 (1.29-1.93)	0.208	36
Edoxaban	1	0/80	1/75	0.31 (0.01-7.69)	1.000	0
Rivaroxaban	5	231/11282	156/11300	1.48 (1.21-1.82)	0.631	0
Sensitivity analysis of GIB	13 (-4)	588/35850	459/35746	1.29 (1.14-1.46)	0.022	49
By indication						
Atrial fibrillation	6 (idem)	524/25234	408/25140	1.21 (0.91-1.61)	0.017	64
Orthopedic surgery	6 (idem)	11/9343	16/9340	0.78 (0.31-1.96)	0.149	39
Medically ill	(-1)	-	-	-	-	-
Deep vein thrombosis/ pulmonary embolism	1 (-1)	53/1273	35/1266	1.53 (0.99-2.36)	1.000	0
Acute coronary syndrome	(-2)	-	-	-	-	-
By drug						
Apixaban	6 (-2)	126/17737	147/17673	0.87 (0.68-1.10)	0.192	32
Betrixaban	0	-	-	-	-	-
Dabigatran	2 (-1)	235/7349	155/7288	1.52 (1.24-1.87)	0.981	0
Edoxaban	1 (idem)	0/80	1/75	0.31 (0.01-7.69)	1.000	0
Rivaroxaban	4 (-1)	227/10684	156/10710	1.47 (1.20-1.81)	0.772	0
Clinically relevant bleeding, all studies	43	4690/62186	4582/63168	1.16 (1.00-1.34)	<0.001	78
By indication						
Atrial fibrillation	8	2632/25637	2867/25460	0.93 (0.75-1.16)	<0.001	84
Orthopedic surgery	21	681/17130	652/17211	1.05 (0.94-1.17)	0.052	36
Medically ill	2	86/3216	68/3246	1.28 (0.93-1.77)	0.806	0
Deep vein thrombosis/ pulmonary embolism	7	517/6387	566/6361	0.98 (0.68-1.43)	<0.001	78
Acute coronary syndrome	5	774/9816	429/10890	2.06 (1.82-2.33)	0.396	22
By drug						
Apixaban	12	1211/25228	1426/25435	0.99 (0.74-1.35)	<0.001	87
Betrixaban	1	2/84	3/43	0.33 (0.05-2.03)	1.000	0
Dabigatran	10	714/12130	708/11964	1.15 (0.89-1.48)	0.001	70

Table S8. *(Continued)*

Subgroups	No of studies*	N events/N total nOAC	N events/ N total control	OR (95% CI)	P for hetero-geneity	I^2 (%)
Edoxaban	4	22/587	17/599	1.24 (0.65-2.39)	0.690	0
Rivaroxaban	16	2741/24157	2428/25127	1.31 (1.04-1.64)	<0.001	85
Sensitivity analysis of clinically relevant bleeding	34 (-9)	3870/51508	4137/51433	0.98 (0.88-1.10)	<0.001	65
By indication						
Atrial fibrillation	8 (idem)	2632/25637	2867/25460	0.93 (0.75-1.16)	<0.001	84
Orthopedic surgery	19 (-2)	672/16898	644/16985	1.05 (0.94-1.17)	0.027	42
Medically ill	1 (-1)	85/3184	67/3217	1.29 (0.93-1.78)	1.000	0
Deep vein thrombosis/ pulmonary embolism	6 (-1)	481/5789	559/5771	0.85 (0.74-0.96)	0.135	41
Acute coronarysyndrome	(-5)	-	-	-	-	-
By drug						
Apixaban	9 (-3)	1075/21208	1362/21165	0.84 (0.67-1.06)	<0.001	74
Betrixaban	1	2/84	3/43	0.33 (0.05-2.03)	1.000	0
Dabigatran	8 (-2)	677/11595	696/11469	1.03 (0.83-1.28)	0.014	60
Edoxaban	3 (-1)	18/484	13/497	1.32 (0.63-2.76)	0.511	0
Rivaroxaban	13 (-3)	2098/18137	2063/18259	1.04 (0.93-1.18)	0.173	27

** Between brackets number of excluded studies in sensitivity analysis*
In case of I^2>50% significant heterogeneity was assumed and a random effects model was used.

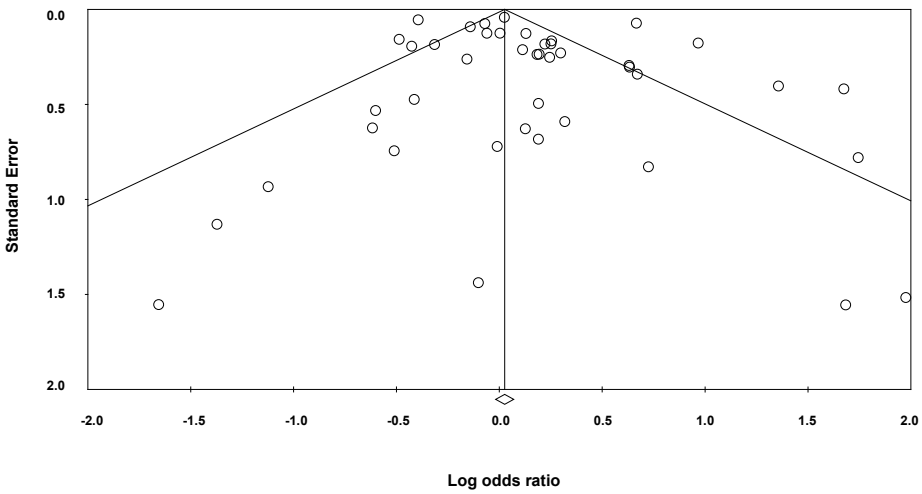

Figure S1. Funnel plot of publication bias.

CHAPTER 2.2

REPLY: OVERCOMING PROBLEMS OF A META-ANALYSIS

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We are grateful to Beyer-Westendorf et al as well as Brouwer and colleagues for emphasizing the importance of research on new oral anticoagulant (nOAC) safety.

Advantages of a meta-analysis, by design, are that an overall effect size can be estimated, inconsistency of results across studies can be analyzed and quantified, moderators can be included to explain variation between studies, and the presence of reporting and publication bias can be investigated. In our recent meta-analysis on the risk of gastrointestinal bleeding (GIB) with nOAC use,[71] we included all indications and all currently available nOAC , but with careful prespecified subgroup analyses. GI physicians will eventually be confronted with complications of these drugs regardless of indication for which they were given.

For reasons of quality, we only included randomized controlled trials in our meta-analysis. The high quality of included trials was further specified according to the Cochrane guidelines for systematic reviews. We attempted an individual patient data analysis, for which we contacted the authors of all 43 original studies included in our analysis. Because of the lack of any positive response, such an analysis was not feasible.

We further applied all measures common to a well-performed meta-analysis to deal with heterogeneity among studies. First, we performed subgroup analyses by indication and drug, using a random effects model as most conservative option. Second, we performed a sensitivity analysis excluding the placebo-controlled studies. After exclusion of these four trials, the GIB risk still remained significantly greater (OR 1.29; 95%CI 1.14-1.46) with nOAC use compared with active comparator, which is slightly lower than the primary analysis (OR 1.45; 95%CI 1.07-1.97; see Supplementary Table 8). The risk thus remains significantly increased, instead of "vanished" as was suggested by Beyer-Westendorf. Third, we performed a meta-regression analysis by comparator correcting for the indication of use. This confirmed that there were no significant differences between the different comparators.

We only included the officially European Medicines Agency and/or US Food and Drug Administration-approved dosages per nOAC per study. Brouwer et al. suggest to also incorporate dabigatran 110 mg bid in our analysis. Although this is a valid suggestion, the 110 mg bid dose is only registered for selected high-risk patients.[12] We did not perform such analysis, as this would require detailed information on these individuals. For the nonregistered indication acute coronary syndrome, we took the lowest effective dose of nOAC, providing only the most conservative bleeding risk. Moreover, we note that this dose was even lower than for any other indication. Higher nOAC doses were associated with an excess of clinically important bleeding events leading to preliminary study termination.[60, 62] Two randomized, phase II, dose-escalating studies with supra-therapeutic dosages, lacking data on GIB, were only included in the clinically relevant bleeding (CRB) analysis. When excluding these trials from the CRB analysis, no significant impact was observed on the OR, as could be expected based on their minimal weight (~4%).

To speculate on the reasons behind the higher estimated OR of nOAC-related GIB in studies on therapeutic use in venous thromboembolism compared with studies on stroke

prevention in atrial fibrillation, would be a misinterpretation of a meta-analysis. The differences observed are indeed not explained by older age or co-medication but, as suggested by Beyer-Westendorf, by increasing dosages of anticoagulants. Rivaroxaban and apixaban were prescribed in higher dosages when used for therapeutic indication instead of prophylactic indication. In addition, it is noticed that stricter inclusion criteria were used for some atrial fibrillation trials, selecting patients at lower GIB risk at baseline.

We deliberately excluded nonrandomized post-marketing observational studies, such as referred to by Beyer- Westendorf, because of they are likely influenced by channelling bias, as a result of patient selection.[72]

To validate the findings of our study, future trials on nOAC should separately report gastrointestinal bleeding events. We hope to encourage not only Beyer-Westendorf, Brouwer and other co-investigators of the included trials, but also the sponsors of these studies to share the individual patient data in order to assess the true risk-benefit ratio at patient level. In observational studies, important patient characteristics need to be collected and corrected for. To study the difference in performance of various nOAC, head-to-head studies between different nOAC are eagerly awaited. For now, clinicians need to be aware the nOAC-associated GIB risk and weigh it per individual patient against its advantages.[73]

CHAPTER 2.3

ON THE TREATMENT OF NEW ORAL ANTICOAGULANT-ASSOCIATED GASTROINTESTINAL HEMORRHAGE

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ABSTRACT

The recently introduced new oral anticoagulants (nOAC) carry a higher gastrointestinal bleeding risk compared with traditional antithrombotic therapy. Current diagnostic coagulation tests are not accurate enough to determine the level of coagulopathy. Besides that, the lack of a specific antidote leaves the endoscopist unsure how to achieve hemostasis during gastrointestinal hemorrhage. In this brief report, we address the (endoscopic) management, when facing a suspected nOAC-associated gastrointestinal hemorrhage. We recommend that specific coagulation tests such as diluted thrombin time and anti-Xa measurement should be made available. Furthermore, nOAC should be stopped. Finally, correcting coagulopathy with administration of prothrombin complex concentrate, recombinant factor VIIa and even hemodialysis should be considered, whereas fresh frozen plasma and vitamin K have no place. The generalizability of these recommendations needs to be confirmed in future studies.

INTRODUCTION

With the advent of the new oral anticoagulants (nOAC), endoscopists face a novel and potent adversary. NOAC are increasingly being considered to replace standard treatment for indications such as thromboprophylaxis during orthopedic surgery, prevention of thromboembolic complications in patients with atrial fibrillation, but also treatment for pulmonary embolism (PE) and deep vein thrombosis (DVT).[19] In addition to their equal or even improved efficacy over current drugs such as vitamin K antagonists (VKA) and low-molecular-weight heparin (LMWH), a possible advantage of nOAC includes the lack of repetitive blood testing to dose within therapeutic levels.[19] Currently, three nOAC have reached phase IV clinical trials, i.e. dabigatran (Pradaxa® Boehringer-Ingelheim Pharma GmbH, Germany), rivaroxaban (Xarelto® Johnson&Johnson / Bayer HealthCare, Germany) and apixaban (Eliquis® Bristol Myers Squibb/ Pfizer, UK).[19] Dabigatran is a direct thrombin (factor IIa) inhibitor, whereas the latter two are factor Xa-inhibitors. As these drugs have novel targets within the coagulation cascade, current coagulation tests such as international normalized ratio (INR) are not accurate enough and, moreover, no antidote is available thus hampering proper management in case of bleeding. Furthermore, drug-drug interactions and renal impairment may lead to increased blood levels of these drugs, resulting in a higher bleeding risk.

This brief report addresses the (endoscopic) management, when facing a suspected nOAC-associated gastrointestinal (GI) hemorrhage.

EPIDEMIOLOGY OF NOAC-ASSOCIATED GI HEMORRHAGE

The impact of nOAC on gastrointestinal hemorrhage is yet unknown, but substantial evidence for an increased risk can be derived from reviewing the current available data of the phase II/ III studies covering more than 150,000 patients.[74] The incidence of upper GI bleeding in the general population is relatively low, counting 1 per 1000 person-years.[75] The use of nOAC compared with standard anticoagulant therapy leads to a 30% increase in GI hemorrhage on top of the 2 to 3-fold increased GI bleeding risk compared with non-use.[75, 76] More than ten million persons in Europe and North-America are estimated to require anticoagulant therapy and may switch to nOAC in the near future.[77] Therefore, a small but significant absolute risk excess will have major implications for the overall GI bleeding incidence.

INITIAL MANAGEMENT OF SUSPECTED NOAC-ASSOCIATED GI HEMORRHAGE

As a recent international consensus on the management of gastrointestinal bleeding recommends, no time should be lost correcting VKA-induced coagulopathy before starting early

endoscopy.[69] However, it is not known if the use of nOAC, in contrast to VKA, predisposes to prolonged bleeding or rebleeding. Standard coagulation tests such as activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) are used as a screening tool.[78] However, endoscopists should realize that these routine coagulation tests are highly reagent dependent and that normal INR and APTT results do not rule out the presence of therapeutic anticoagulant levels. Each laboratory should test the sensitivity of their assays to nOAC.[79] Specific tests such as diluted thrombin time (dTT) for dabigatran and anti-Xa measurement for rivaroxaban and apixaban can measure accurately the level of anticoagulation (i.e. level of concentration in blood).[80] The availability of these tests varies between laboratories and this should be checked in advance. Though, no reports have yet been published on the exact nOAC concentration range and the risk on GI hemorrhage.

ENDOSCOPIC AND PHARMACOLOGICAL MANAGEMENT OF NOAC-ASSOCIATED GI HEMORRHAGE

Concerning endoscopic management, no data are available regarding other endoscopic strategies than currently used. Antithrombotic agents may precipitate and prolong bleeding from pre-existing lesions despite current hemostatic techniques.[76] Novel endoscopic modalities such as hemostatic powder may thus prove a welcome alternative when dealing with nOAC-associated bleedings.[81]

No data on the protective effect of proton pump inhibitors (PPIs) during nOAC use are currently available. However, in case of nOAC-associated upper GI bleeding, intravenous administration of high dose PPIs is presumably beneficial, as it neutralizes pH which leads to stabilization of the blood clot.[69]

CORRECTING COAGULOPATHY DURING NOAC-ASSOCIATED GI HEMORRHAGE

Supratherapeutical ranges of drug induced coagulopathy during GI bleeding are associated with increased mortality.[82] Correcting nOAC-induced coagulopathy should thus be the goal; however, no specific antidote against dabigatran or rivaroxaban and apixaban is available. The current available measures to restore coagulation have not been tested in bleeding patients on nOAC in a controlled experimental setting. Some recommendations can be made based on limited clinical experience and studies in healthy volunteers and animals (Table 1).

Stopping the nOAC. This can be considered for every patient experiencing GI hemorrhage while using nOAC. The decision to discontinue nOAC therapy in the setting of acute bleeding should be made on an individual basis, carefully weighing the thromboembolic and gastrointestinal risks.[69] The nOAC-induced coagulopathy is quickly recovered after stopping ($t_{1/2}$

Table 1. Summary of recommendations for managing significant nOAC-associated gastrointestinal hemorrhage.

	Recommendations
1	Supportive care such as restrictive blood transfusions
2	Determine level of coagulopathy
3	Stop nOAC, and consider switch to VKA after hemostasis
4	Endoscopy: as commonly performed, consider i.v. PPI
5	In severe bleeding: consider PCC (also DDAVP, tranexamic acid)
6	In uncontrollable bleeding: consider recombinant factor VIIa, hemodialysis

DDAVP: desmopressin, nOAC: new oral anticoagulants, PCC: prothrombin complex concentrate, VKA: vitamin K antagonist.

9-14 h depending on renal clearance). In addition, within 2-4 hours after restarting nOAC, the therapeutic effect is restored. The latter is of importance given the increased mortality when stopping anticoagulants compared to continuation after GI hemorrhage.[83] Switching to VKA therapy in these patients might be a safer option and should be considered.

Prothrombin complex concentrate (PCC). Some evidence exists that administration of PCC may act as reversal agents in healthy humans using nOAC.[84, 85] Whether the recovery of coagulopathy is also paralleled by hemostasis remains to be observed. Nevertheless, administration of PCC (25-50 IU FIX/kg i.v.) is to be considered in case of severe nOAC-associated GI hemorrhage.

Fresh frozen plasma. Although commonly used, no data exists in humans taking nOAC. Scant data in animal models argue against recommendation.[86]

Recombinant factor VIIa. Its use has not been studied in humans for reversal of nOAC and the results in animal models are inconclusive.[86] In case of severe nOAC-associated GI hemorrhage, the benefit-to-costs-and-risks-balance should be weighted per person. No experimental evidence is available for desmopressin (DDAVP) and antifibrinolytic agents such as tranexamic acid. A raised concern for the possibility of a tromboembolic event was recently waived after a Cochrane review showing no increased risk on myocardial infarction, stroke, DVT or PE.[87]

Hemodialysis or hemoperfusion. Whereas rivaroxaban and apixaban are too highly protein bound to be effectively removed by these methods, dabigatran is the only appropriate candidate.[88] Unfortunately, performing this in a bleeding patient in a hypovolemic shock may be, at least, challenging.

CONCLUSION

In light of absence of reports on outcome of nOAC-associated GI bleedings, endoscopists should be prepared to deal with such bleeds given the increased risk of hemorrhage. Ac-

curate determination of coagulopathy by specific coagulation tests such as dTT and anti-Xa measurement, stopping nOAC, considering PPI administration and achieving hemostasis with products such as PCC will have to be included in the endoscopist's toolkit. Careful surveying and reporting on nOAC-associated GI hemorrhage will clarify the remaining areas of uncertainty.

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CHAPTER 3.1

EFFECTS OF THE HEMOSTATIC POWDER HEMOSPRAY ON COAGULATION AND CLOT FORMATION

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Submitted

ABSTRACT

Background and aims: Hemospray is a novel hemostatic powder for gastrointestinal use, that is thought to achieve hemostasis by concentrating clotting factors and forming a mechanical plug on the injured blood vessel. However, no detailed studies on the underlying mechanism of hemostasis have been performed. In this study, we examined the working mechanism of Hemospray *in vitro* and *in vivo*.

Methods: Recalcification time, thromboelastometry using EXTEM and INTEM assays, and plasma coagulation tests (APTT and PT) were performed with blood samples mixed with Hemospray and compared with talcum powder (negative control), and kaolin (positive control) at 0.1 to 10 mg/ml. Scanning electron microscopy (SEM) and light microscopy were performed on *in vitro* thrombi and on gastric thrombi from an animal model of GI hemorrhage treated with Hemospray.

Results: Median recalcification time of whole blood was 187.5 sec. Addition of 1mg/ml and 10mg/ml Hemospray significantly shortened this time (median 60 and 45 sec resp., $p<0.05$). The median clotting time (CT) measured using the INTEM assay with whole blood (160 sec, IQR 159-176.5) significantly reduced with Hemospray (91 sec, IQR 84-102, $p=0.005$). Plasma PT was 11.6 sec and significantly shortened with addition of Hemospray to 9.5 sec ($p=0.011$). SEM of *in vivo* clots demonstrated that Hemospray rapidly interacted with whole blood, forming one confluent mass over the bleeding site. In sufficient amounts, Hemospray was able to deform and pack erythrocytes.

Conclusion: Hemospray covers the bleeding site, shortens coagulation time and eases clot formation in vitro. Implementing these unique properties in daily practice may optimize future hemostatic endoscopic treatment with Hemospray.

INTRODUCTION

Achieving durable hemostasis in gastrointestinal (GI) hemorrhage remains a challenge. This is reflected by the relative high incidence of rebleeding and associated mortality.[1] Hemospray (formerly known as TC-325) is a CE-marked mineral blend powder (Cook Medical, Winston-Salem, North Carolina, USA) developed specifically for endoscopic hemostasis. It is metabolically inert, contains neither human or animal proteins nor botanicals and has no known allergens.[2]

In animal models with upper GI bleeding, initial hemostasis reached with Hemospray was almost complete and there were no powder-related complications.[2, 3] Furthermore, no post-procedural systemic coagulation effects (in terms of prothrombin time and partial thromboplastin time) were observed.[3] It has been speculated that when Hemospray comes in contact with an actively bleeding site, the powder absorbs water, then acts both cohesively and adhesively, forming a mechanical barrier over the bleeding site. However, data supporting this hypothesis are lacking.

Hemospray has been shown to be safe and effective in achieving hemostasis in both upper and lower GI bleeding.[4-8] Hemospray was equally effective in users and non-users of systemic antithrombotic therapy , suggesting local hemostatic properties.[4] It is unknown if Hemospray has an effect on the local coagulation cascade. Understanding of the working mechanism may help to improve the efficacy of Hemospray treatment. We therefore performed coagulation experiments in the presence of Hemospray to reflect hemostasis on-site. We furthermore studied the formation of the blood clot *in vitro* as well as in an animal model. In this study, we thus provide a unique insight into the working mechanism of this promising hemostatic agent.

METHODS

Study subjects and materials

Blood and/or plasma samples of ten healthy controls (mean age 34 years, 60% female) were collected in 3.2% sodium citrate vacuum tubes (4.5 ml) at room temperature and were processed within four hours after sampling. Use of anticoagulants within the last 72 hours prior to inclusion was a contraindication.

Hemospray was obtained directly from the manufacturer (Cook Medical). For the various experiments, blood or plasma was tested in the presence or absence of Hemospray at 0.1, 1, and 10 mg/ml (final concentration). All tests were performed in duplicate. As positive control, we included the known hemostatic clay mineral kaolin ($Al_2Si_2O_5(OH)_4$ (BHD, Poole, England)).[9] Talcum powder (Mentho10 pure talcum powder, Galvastore BV, Bladel, the Netherlands) served as negative control.

Coagulation assays

Unless stated otherwise, we focussed on the use of whole blood instead of plasma in the coagulation experiments to reflect the *in vivo* situation.

For the blood recalcification time, 50 µl 0.2 M $CaCl_2$ was added to 1 ml of whole blood in the presence or absence of Hemospray, kaolin and talcum powder (all 37°C, 1 and 10 mg/ml) and the time needed for formation of a clot was measured.

Fully-automated rotational thromboelastometry assays (INTEM, EXTEM, FIBTEM; ROTEM®, Tem innovations GmbH, Munich, Germany) were performed in the presence or absence of Hemospray. The thromboelastometry parameters measured include clotting time (CT: latency time from addition of the start reagent to blood until first clot formation); clot formation time (CFT: the time from CT until reach of a clot firmness of 20 mm point); angle ([alpha], the kinetics of clot formation); and maximum clot firmness (MCF: the maximum strength or firmness of the developed clot).

Platelet function (in seconds) was tested in 1 ml of citrated blood in the presence or absence of Hemospray using a platelet function assay (PFA-100®, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

Activated partial thromboplastin time (APTT) was measured using ActinFS (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) and prothrombin time (PT) was measured using Thromborel S (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) as described by the manufacturer in the presence or absence of Hemospray using a semi-automated coagulation analyzer (KC4 Delta™, Sigma Amelung, Lemgo, Germany).

Scanning electron microscopy of clots

The animal study was approved by the Johns Hopkins Animal Care and Use Committee and complied with the Guide for the Care and Use of Laboratory Animals and the US Animal Welfare Act

First, scanning electron microscopy (SEM: Jeol JSM6610LV at 5KV) on dry particles of Hemospray, kaolin and talcum powder was performed. Next, we analyzed blood clots in the presence of liberally sprayed Hemospray onto a small bleeding skin lesion (i.e. needle puncture), fixed after 1, 3, 5 and 10 minutes. Furthermore, we analyzed clots derived by recalcification of whole blood with a low dose of Hemospray and clots from an animal model of upper GI hemorrhage treated with Hemospray. All Hemospray-blood clots were washed in buffer, fixed in EM-fixative (2% glutaraldehyde + 4% buffered paraformaldehyde) and stored in cacodylate solution until further preparation. Samples were segmented and mid thrombus sections were dehydrated in graded ethanol series and dried using hexamethyl disilazane. Then, the samples were sputtered with gold (Agar auto sputter coater (B7341), Agar Scientific, Essex, UK), prior to further SEM examination.

In domestic swine (Yorkshire-landrace swine), a gastrointestinal bleeding was created as described before.[2] Shortly, a major gastric artery was dissected, inserted through the wall

of the stomach, and positioned in such a way that it was exposed to the gastric lumen. Gastroscopy was performed, and the exposed vessel was incised with a needle knife until spurting bleeding resulted. Hemospray was sprayed liberally onto the bleeding site until durable hemostasis. Three animals were treated and sacrificed after 15 minutes, 2 hours, and 6 hours after treatment. None of the animals was heparinized or had systemic anticoagulation. At the conclusion of the respective time points, the animals were euthanized according to facility practices. Hemospray treated sites were isolated from the stomach and pinned flat. Specimens were immersion fixed in EM-fixative in preparation for SEM as described above.

Light microscopy of clots

Tissues adjacent to segments studied by SEM were prepared for light microscopy by embedding in paraffin. Sections were stained by hematoxylin-eosin as a routine stain, and resorcin fuchsin as a collagen and elastin stain. Sections were digitized by Clemex vision PE (Clemex Technologies Inc., Longueuil, Quebec, Canada).

Statistical analysis

Results were reported as median and interquartile range (IQR). We used non-parametric Wilcoxon signed-rank tests to compare powders. Data were analyzed using PASW statistics 21.0 for Windows (SPSS, IBM, Armonk, New York, USA). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

First, we established the optimal concentration of Hemospray to perform all experiments with. In doses <1 mg/ml no effect was seen, while at >10 mg/ml flow obstructions or sludge/sediments occurred, hampering adequate measurements. We therefore performed the in-vitro experiments at a Hemospray concentration of 1 and 10 mg/ml. The concentration of the controls kaolin and talcum powder were equal to the Hemospray concentration. For the animal experiments, Hemospray was liberally sprayed onto the bleeding site.

Coagulation assays

In order to assess general clot formation *ex vivo*, we performed recalcification tests. Median recalcification time of whole blood was 187.5 sec (IQR 176.3-202.5). Addition of 1 mg/ml and 10 mg/ml Hemospray (median 60 sec, IQR 45-63.8 / 45 sec, IQR 41.3-48.8), kaolin (median 75 sec, IQR 60-78.8 / 45 sec, IQR 41.3-48.8), or talcum powder (median 105 sec, IQR 101.3-108.8 / 82.5 sec, IQR 75-90) significantly shortened this time (all p-values<0.05) (Figure 1).

Thromboelastometry provides a reaction curve (thrombogram) that shows clot elasticity over time during formation. Representative thrombograms in the absence or presence

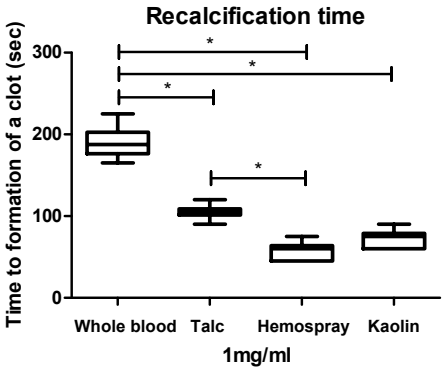

Figure 1. Boxplot of recalcification time with different powders compared with plain blood.
** p<0.05, ** p<0.01, ***p<0.001*

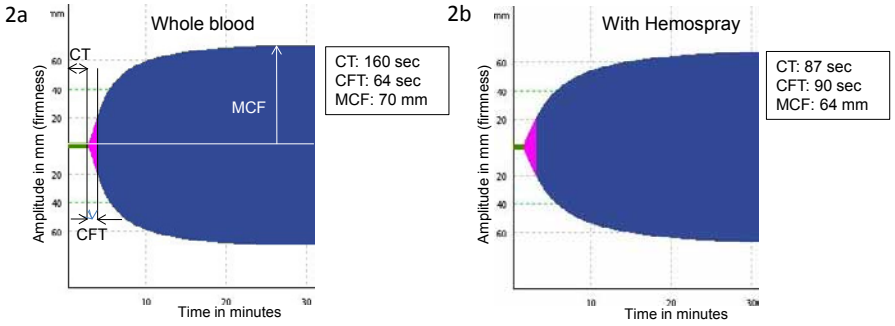

Figure 2. A representative INTEM thrombogram of an untreated whole blood sample (A) and after addition of 1mg/ml Hemospray (B).
In the ROTEM system, a blood sample is placed into a cuvette and a rotating cylindrical pin is immersed. As long as the blood is liquid the rotation of the pin is unrestricted. As soon as the blood clots, the clot restricts the rotation of the pin increasingly with rising clot firmness. The curve is plotted two-sided and the amplitude is expressed in mm. The green line (CT) represents thrombin formation and start of the clot polymerisation (initiation phase). The pink part (CFT) represents fibrin polymerisation and stabilization of the clot with thrombocytes and FXIII (amplification phase). CFT ends when a clot firmness of 20 mm is detected. During the dark blue phase, the clot is further stabilized by thrombocytes, FXII, as well as fibrin (propagation phase). The maximal amplitude represents the MCF.
CT: clotting time, CFT: clot formation time, MCF: maximum clot firmness

of 1mg/ml Hemospray are shown in Figures 2A and 2B resp. The median clotting time (CT) with the INTEM assay with whole blood was 160 sec (IQR 159-176.5) and was significantly shortened with Hemospray and kaolin (91 and 93 sec resp., both p<0.05) (Figure 3A). Clot formation time (CFT) was longer with Hemospray (101.5 sec) compared with whole blood (65.5 sec, p=0.022). Also, addition of kaolin (93 sec, p=0.009) and talcum powder (88.5 sec,

p=0.017) prolonged CFT compared with whole blood. Median maximal clot firmness (MCF) values were slightly lower for Hemospray (59.5 mm, p=0.005), kaolin (62 mm, p=0.048), and talcum powder (62 mm, p=0.011) compared with whole blood (63 mm). EXTEM showed a decreased CT after addition of both Hemospray (CT 48 sec, IQR 44.5-56, p=0.012) and kaolin (CT 54.5 sec, IQR 45-57, p=0.029), but not after addition of talcum powder (CT 59 sec, IQR 50.8-68.3, p=0.759) compared with whole blood (CT 57 sec, IQR 51.5-65) (Figure 3B). EXTEM CFT did not differ between whole blood with and without addition of Hemospray (p=0.066). MCF was lower with all three powders (Hemospray 57 mm, p=0.005; kaolin 57.5 mm, p=0.007; and talcum powder 59.5 mm, p=0.007) compared with whole blood (62 mm). FIBTEM assays showed similar results as EXTEM assays (data not shown).

Next, we assessed the intrinsic and extrinsic pathway of the coagulation cascade by performing standard activated partial thromboplastin time (APTT) and prothrombin time (PT)

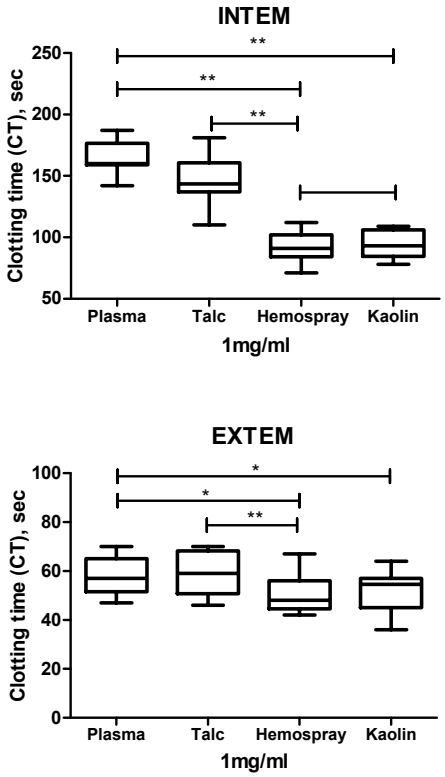

Figure 3. Boxplot of INTEM (A) and EXTEM (B) clotting time (CT) with different powders compared with whole blood.

** p<0.05, ** p<0.01, ***p<0.001*

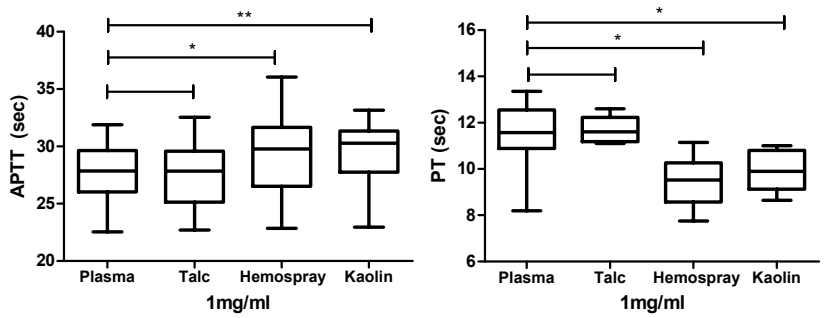

Figure 4. Boxplot of APTT (A) and PT (B) with different powders compared with plasma.
** p<0.05, ** p<0.01, ***p<0.001*
APTT: activated partial thromboplastin time, PT: prothrombin time

testing in plasma in the presence or absence of Hemospray. APTT was 27.9 sec (IQR 26.0-29.6) in plasma and was prolonged with Hemospray (29.8 sec, IQR 26.5-31.7) or kaolin (30.3 sec, IQR 27.8-31.3), but did not alter with the addition of talcum powder (Figure 4A). Data on APTT and PT were obtained with 1 mg/ml, Hemospray, kaolin or talcum powder as technical limitations occurred at 10 mg/ml. PT was 11.6 sec (IQR 10.9-12.6) and showed a significant shortening of 16.4% after addition of Hemospray (9.5 sec, IQR 8.6-10.3, p=0.011) and of 12.1% after addition of kaolin (9.9 sec, IQR 9.1-10.8, p=0.022). Talcum powder did not influence the PT (11.6 sec, IQR 11.2-12.2, p=0.683) (Figure 4B).

Scanning electron microscopy of clots

In order to identify Hemospray in the clots, we first examined dry Hemospray particles. These had a somewhat flaked appearance and varied considerably in size; ranging from 5x5µm for the smallest particles to 120x50µm for the largest ones (Figure 5A). The surface of kaolin particles appeared rougher than Hemospray particles and they were generally smaller, ranging from 1x2µm to 45x21µm (Figure 5B). Talcum powder particles appeared similar to Hemospray, but were more homogenous in size, with the smallest particles around 7x9µm and the largest 33x13µm (Figure 5C).

In the clots from the Hemospray treated finger puncture lesion, Hemospray (now recognizable as the porous material) formed one confluent mass in the presence of blood. Only a few individual particles could still be identified (Figure 5D). Erythrocytes (identified as the oval shaped cells with a diameter of 6-8µm) changed shape, turning them into a layer of crystal shaped or cobble stone-shaped cells (Figure 6A and B).

The clots from the recalcified blood, containing a relatively low amount of Hemospray (1 to 10 mg/ml), showed a clearly visible fibrin network with mostly normal shaped erythrocytes and Hemospray particles (Figure 6C). Red-cell aggregation and formation of a fibrin matrix was already noted 1 minute after whole blood was exposed to the product.

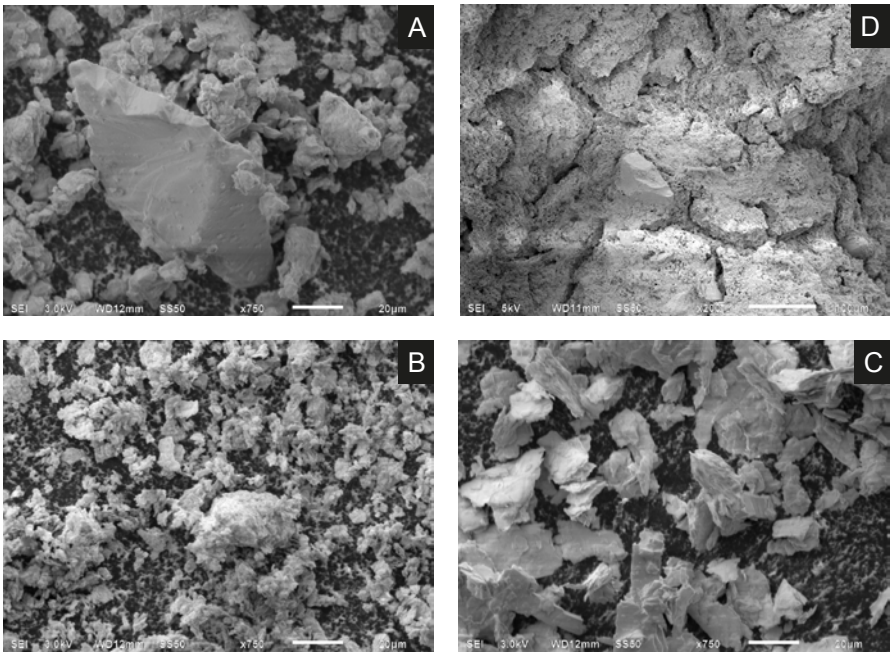

Figure 5. Scanning electron micrograph (SEM) of dry Hemospray (A), kaolin (B), and talcum powder (C) particles showing a range in particle sizes and rugged shape (magnification 750x), D) Surface of a Hemospray-blood clot from a skin lesion fixed after 10 minutes with in the middle intact Hemospray particles and around a confluent mass without individual recognizable particles (magnification 200x).

In the animal experiments, slices from the gastric thrombus 15 minutes, 2 hours and 6 hours after treatment with Hemospray were analyzed. Hemospray was best identified after 15 minutes. The powder formed a cohesive layer covering the induced arterial gastric bleeding and a substantial part of the gastric epithelium, no individual particles were seen anymore. Residual plant material, as part of the test animals diet, could be identified in the Hemospray layer (Figure 7A-C).

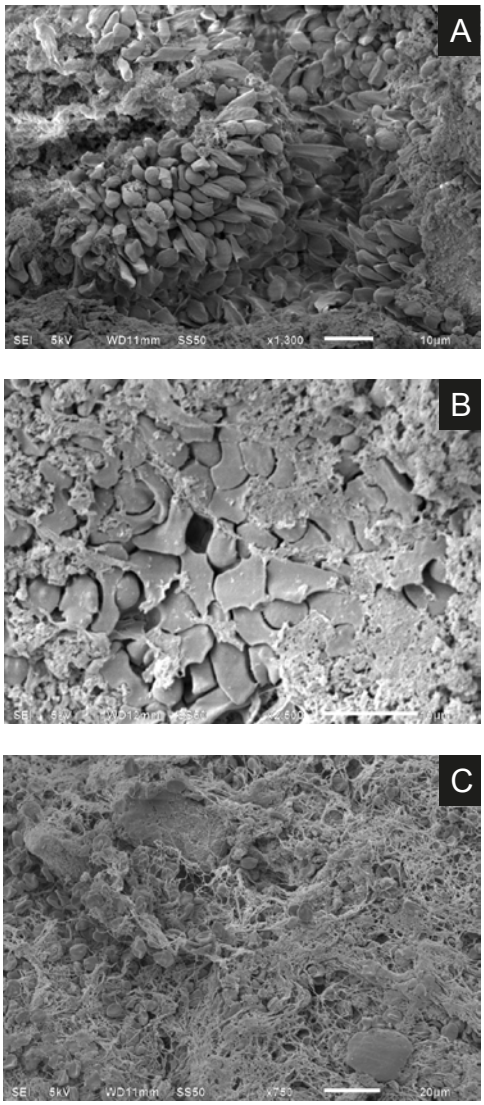

Figure 6. A) Detail of a Hemospray-blood clot from a skin lesion fixed 5 minutes after Hemospray application, showing interaction of Hemospray with whole blood. Erythrocytes (identified as the oval shaped cells with a diameter of 6-8µm) have a changed, crystal-like shape (magnification 1300x), B) Detail of the same clot: erythrocytes have a distorted and packed appearance, like cobblestones and are surrounded by Hemospray (magnification 2500x), C) SEM of a clot from the recalcification experiments (Hemospray 1 mg/ml) shows formation of a clearly visible fibrin matrix with aggregated erythrocytes (most normally shaped) and some pieces of Hemospray interacting with the fibrin network (magnification 750x).

Light microscopy

Light microscopy of the gastric bleeding site after 15 minutes, 2 hours and 6 hours showed Hemospray on top of the bleeding spot with a similar appearance at the different time points. Hemospray did not infiltrate or interfere with the gastric epithelial cells (Figure 7D, E, and F). The powder did not appear to be toxic for the epithelium, as no eosinophils, morphological changes, or cell damage were observed.

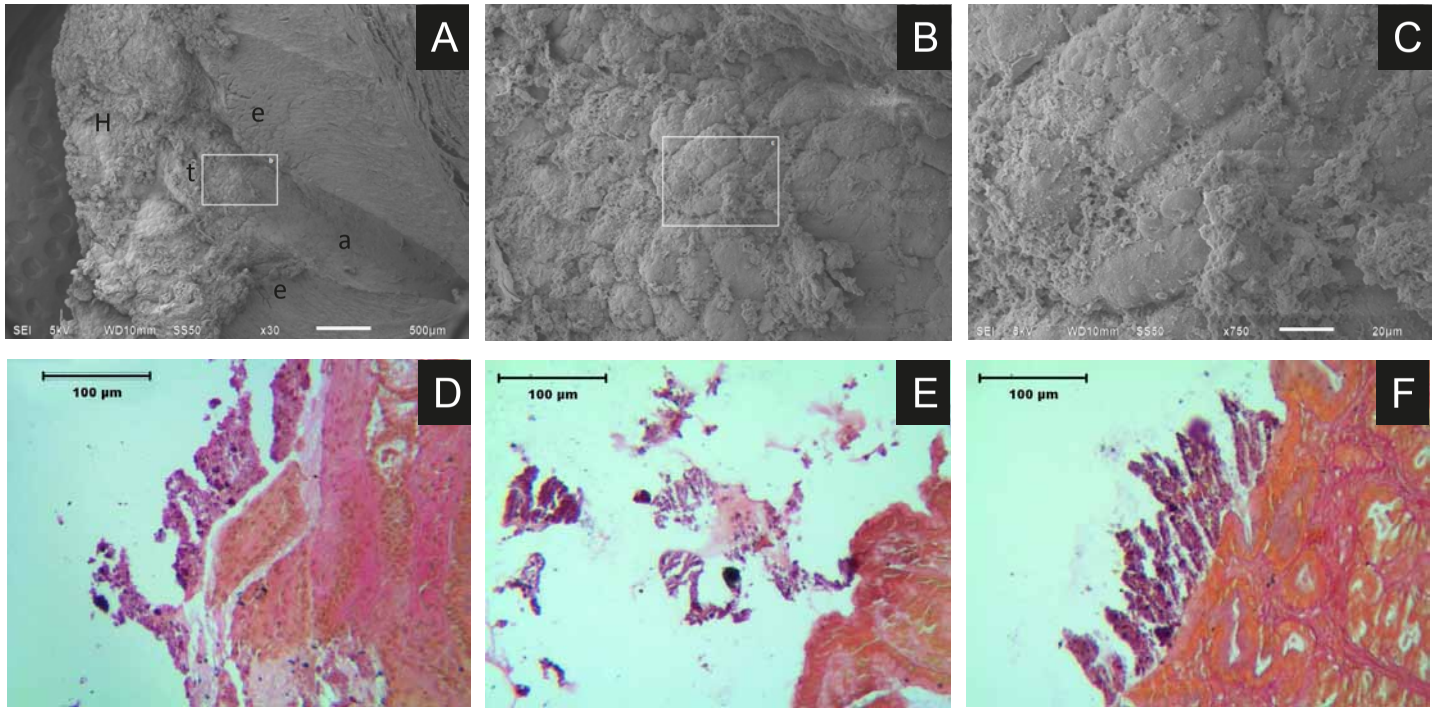

Figure 7. A) Overview of a gastric bleeding site in a swine model, with at the right side gastric epithelium (e) with crypts and mucus producing cells and the cut artery (a), in the middle the thrombus (t) and at the left side a confluent Hemospray layer (H) covering the thrombus. Some dietary fiber-like material was identifiable at the lumen side (magnification 30x), B) Detail of A: Hemospray forms one mass overlaying the gastric epithelium (magnification 200x), C) Detail of B, showing the epithelium covered by a porous fibrin network and some Hemospray particles (magnification 750x), D-F) Light microscopy pictures of a gastric bleeding site in a swine 15 minutes (D), 2 hours (E), and 6 hours (F) after treatment with Hemospray showing the presence of Hemospray (purple) on top of the bleeding spot with a similar appearance at the different time points (resorcin fuchsin stain, magnification 20x).

DISCUSSION

Over the last decades, many hemostatic agents to stop life-threatening hemorrhage in a rapid and secure fashion have been developed in the military combat environment.[10] The different powders, dressings, and impregnated gauzes consist of a variety of hemostatic products, including chitosan, zeolite, kaolin, fibrin, and smectite. Following promising results, the use of some of these agents has been expanded and they are now being utilized in in-hospital setting.[11, 12] One of these agents is Hemospray, a proprietary mineral blend that has been specifically designed for the endoscopic treatment of gastrointestinal bleeding. In this study, we examined the effect of Hemospray on coagulation and clot formation *in vitro* and *in vivo*.

We show that recalcification time and clotting time dose-dependently shortened in whole blood in the presence of Hemospray. This is most evident with the INTEM assay. Both INTEM assay and the recalcification test enable isolated analysis of the intrinsic cascade.[13] Theoretically, via the common pathway, the extrinsic cascade will finally be activated as well, but the testing time is too short to allow this. Indeed, the EXTEM assay also demonstrated shortening of clotting time in the presence of Hemospray.

In addition, the plasma coagulation tests showed a shortened prothrombin time (PT) after addition of Hemospray. Given the comparable, however less pronounced, effect of kaolin in the recalcification and INTEM tests, Hemospray could act in a similar manner as kaolin. Kaolin is a clay mineral, known for its ability to initiate the intrinsic cascade by its negative charge.[14, 15] Interestingly, the PT shortened, while the APTT did not shorten after addition of Hemospray. Apparently, plasma behaves differently than whole blood in the presence of Hemospray.

Clot formation time, a ROTEM parameter for clot amplification, did not shorten. This suggests that the effect of Hemospray is limited to the initiation phase of clot formation.[16] The maximal firmness of the clot was slightly less in the presence of Hemospray, which is in contrast to a study that tested blood with combat gauze impregnated with kaolin, demonstrating increased clot firmness.[15] As these tests were performed with traditional thromboelastrometry, it may be attributable to a technical difference between traditional thromboelastometry and ROTEM.

The powder substance itself may also ease clotting. This would explain why talcum powder, lacking known coagulation-activating properties, also shortened the recalcification time. Powder absorbs fluids, which might facilitate agglomeration of cells and factors necessary for clot formation. This is confirmed by the scanning electronic microscopy of *in vivo* clots demonstrating that Hemospray rapidly interacted with whole blood, forming one confluent mass over the bleeding site. In sufficient amounts, Hemospray was able to deform and pack erythrocytes. We thus hypothesize that this is by extraction of fluids from the erythrocytes.

The major pitfall of demonstrating effects of any hemostatic agent on coagulation is the artificial modelling of a complex physiological process of anti- and procoagulation, but

also adhesive and inflammatory factors, using the outcome of in vitro tests as substitute. Interpreting data from *in vitro* tests such as the plasma-bound PT and APTT is thus limited and should only carefully be extrapolated to the *in vivo* mechanism of action. In line with this, the traditional model of 2 separate (intrinsic and extrinsic) coagulation pathways has been changed,[16] recognizing the intricate interplay of the aforementioned factors and the major role of tissue factor in the initiation of coagulation. This problem is only partially overcome with the use of the whole-blood assays such as ROTEM.

There are a few other issues to be addressed. First, Hemospray is a proprietary compound. No exact data on, for instance, the electrochemical composition have been published, limiting further insight into its effects on coagulation and clot formation. Second, ROTEM has proven its benefit in major blood loss situations, not to measure "hyperactivity" of the clotting system. Therefore, the values of the blood-powder tests, could not be compared with reference values. Furthermore, the concentration of Hemospray tested in the *in vitro* experiments (up to 10 mg/ml blood) are much lower than the amounts used in clinical bleeding, suggesting that the effects on coagulation may be lesser important than the effects observed in the *in vivo* experiments. Obviously at higher concentrations *in vitro*, the used automates are not equipped to measure such blood-powder mixtures and led to technical problems. Also, flow of the platelet function assay obstructed, hampering adequate measurement even in the lowest concentrations of Hemospray. Interestingly, FIBTEM results were similar to EXTEM, suggesting that platelet function is unaltered in presence of Hemospray.

Implementing these findings in daily endoscopic practice would be of particular relevance in massive blood loss due to spurting arterial bleeds, in which Hemospray treatment currently results in lower rates of primary hemostasis than in non-massive bleeds.[6, 8] One should most probably deploy substantial amounts of Hemospray concordant to the amount of blood, allowing both clot formation and forming of a mechanical barrier to result in effective and durable hemostasis.

In conclusion, Hemospray shortens coagulation times *in vitro* and eases clotting formation *in vivo*. Future studies should elaborate on the extended implications of the demonstrated effects of Hemospray.

Disclosures

ETT has received an unrestricted educational grant from Cook Medical Ireland.

CHAPTER 3.2

HEMOSPRAY IN THE TREATMENT OF UPPER GASTROINTESTINAL HEMORRHAGE IN PATIENTS ON ANTITHROMBOTIC THERAPY

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Endoscopy 2013;45:63-6

ABSTRACT

Patients on antithrombotic therapy (ATT) have the highest risk of ongoing bleeding and mortality. Hemospray (Cook Medical, Winston-Salem, North Carolina, USA) is a novel hemostatic agent for the treatment of upper gastrointestinal bleeding (UGIB). Initial reports on its use appear promising in terms of initial hemostasis and rebleeding rates. It is unknown whether this also pertains to patients on ATT. The aim of the current study therefore was to evaluate the efficacy of Hemospray in the treatment of UGIB in patients taking ATTs. A total of 16 unselected consecutive patients with UGIB who were treated with Hemospray were analyzed (eight taking ATT for various indications and eight not on ATT). Initial hemostasis was achieved after Hemospray application in 5/8 patients on ATT (63%) and in all eight patients not on therapy (p=0.20). Rebleeding rates were similar in both groups. These preliminary data on the use of Hemospray in the management of UGIB are promising in both patients with and without ATT, however, caution should be exercised for its use in patients on ATT with spurting arterial bleeding.

INTRODUCTION

Antithrombotic therapy (ATT) includes antiplatelet therapy (e.g. aspirin and clopidogrel) and anticoagulants (e.g. warfarin) and potentially can give rise to life-threatening gastrointestinal hemorrhage. Whereas the use of ATT is reported in most major studies on the management of acute upper gastrointestinal bleeding (UGIB), outcome of endoscopic treatment is typically not specified by subgroup.[17, 18] Nevertheless, antithrombotic agents may precipitate and prolong bleeding from pre-existing lesions,[19] suggesting impaired clot formation and disrupted coagulation. As a result, patients on antiplatelet agents may have a higher risk of ongoing bleeding and are thus difficult to manage endoscopically. Furthermore, vitamin K antagonist (VKA)-induced elevation of international normalized ratio (INR) >1.5 significantly predicts mortality.[20] Therefore, UGIB in patients on ATT can be hard to treat with current endoscopic modalities and novel approaches should be evaluated to overcome this.

Hemospray (Cook Medical, Winston-Salem, North Carolina, USA) is a hemostatic agent recently introduced for the management of UGIB. Its efficacy has been shown in peptic ulcer bleeding (PUB),[21] as well as in cancer-related UGIB.[5] When applied to the bleeding site endoscopically, this inorganic hemostatic powder becomes cohesive and adhesive, and forms a stable mechanical barrier that covers the bleeding source (Figure 1 and 2). Currently, an ongoing multicentre European initiative on the use of Hemospray for non-variceal UGIB is prospectively collecting data to assess Hemospray in daily practice.[22] In a small study reporting on the effectiveness of Hemospray in UGIB, patients on ATT were excluded.[21] We describe the first eight cases of Hemospray application for UGIB in patients on ATT.

PATIENTS AND METHODS

Patients

From June 2011 to May 2012, unselected and consecutive patients who were evaluated endoscopically for suspected UGIB were treated with Hemospray for active bleeding of various origins. Data on sex, age, medication use, procedural details, and outcome were collected prospectively, anonymized, and analysed retrospectively. Approval was obtained by the Institutional Review Board of the Erasmus MC University Medical Centre.

Methods

Endoscopic hemostatic interventions (using an Olympus Q180-1T scope; Olympus, Tokyo, Japan) were performed exclusively by expert endoscopists who were experienced in therapeutic endoscopy for UGIB and were specifically trained in Hemospray application. The training consisted of a theoretical part and hands-on training on a model. Hemospray (maximum 20 g) was applied onto the active bleeding site through a 10Fr catheter (Cook Medical) in

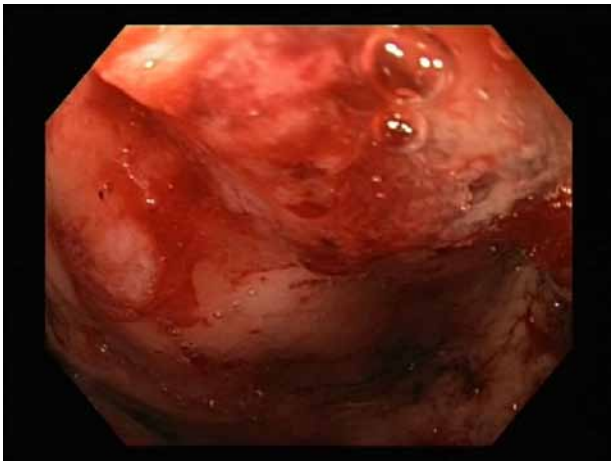

Figure 1. Oozing tumor bleeding after injection with epinephrine.

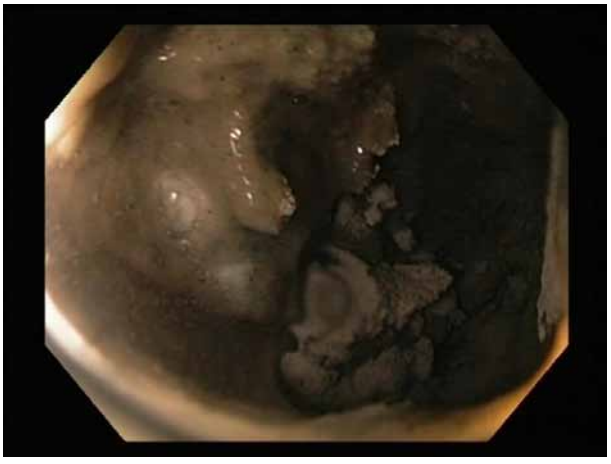

Figure 2. Complete hemostasis after application of Hemospray.

short bursts of a CO_2-propelled canister until hemostasis was confirmed. Successful initial hemostasis was defined when Hemospray application led to hemostasis after 5 minutes of visual inspection. Hemospray was used either as monotherapy or as salvage therapy at the discretion of the endoscopist and depending on the origin of UGIB. Salvage therapy was defined as application of Hemospray after failure of one or more other endoscopic modalities. Failed initial hemostasis was defined as the need for a subsequent modality for cessation of bleeding after application of 20g of Hemospray. No standard scheduled second-look endos-

copy was carried out unless clinical signs of rebleeding were present, including tachycardia, hypotension, and a drop in hemoglobin concentration.

Statistical analysis

Fisher's exact test and Mann-Whitney U test were used to compare patients on ATT (ATT+group) with those not receiving ATT (non-ATT group). All analyses were performed using PASW statistics 17.0 for Windows (SPSS, IBM, Amonk, New York, USA). A two-sided p-value of <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

A total of 16 patients (median age 69.5 years, range 47-88 years, 75% male) with UGIB were treated with Hemospray during the study period (Table 1).

Eight patients were on ATT at the time of bleeding: three on antiplatelet therapy, one on a combination of antiplatelet therapy and non-steroidal anti-inflammatory drugs (NSAIDs), one with chronic use of NSAIDs, two on VKA (INR 5.1) or heparin (activated partial thromboplastin time 38 seconds at time of the bleed), and one on a combination of NSAIDs and VKA (INR 1.4). In the ATT+ group, prophylactic proton pump inhibitor co-therapy was also being used by four patients. Interestingly, none of the patients receiving gastroprotective co-therapy bled from a peptic ulcer.

Bleeding characteristics

The origin of the bleeding was a peptic ulcer in 9/16 patients (56%), tumor bleeding in 2/16 (13%), and other (e.g. Dieulafoy lesion, variceal bleeding, anastomotic bleeding) in 5/16 (31%).

Treatment success

As our center is a tertiary referral center, a substantial number of the included patients were referred from other hospitals where prior endoscopic treatment had failed 5/16 patients (31%) (Table 2). In the analysis, this prior endoscopic therapy did not count as the first modality. The first treatment of the bleed at our center, which was a rebleed in these five patients, was considered the first modality. This percentage was slightly higher in the patients on ATT+ (3/8: 38%) compared with the non-ATT group (2/8: 25%).

Successful initial hemostasis was achieved by Hemospray in 5/8 ATT+ patients (63%) and in all cases (8/8) of the non-ATT group (p=0.20). In these successful cases, Hemospray was used as monotherapy in three ATT+ patients (38%) and five non-ATT patients (63%). Hemo-

Table 1. Patient characteristics.

Case no.	Sex	Age, years	Antithrombotic therapy at time of bleeding	PPI co-therapy, mg	Previously treated site	Hemospray as first modality	Immediate hemostasis after HS	Subsequent modalities used	7-day rebleed. (time of rebleed); alternative therapy	Origin of bleeding	Location
1	F	88	ASA	40	No	Yes	No	TAE	No	Diverticula	Duodenum (D3)
2	M	79	VKA, INR 1.4 NSAID	-	Epinephrine	Yes	Yes	No	Yes (<48 hours); goldprobe	Forrest Ia ulcer (MALT-lymphoma)	Angulus
3	M	85	VKA, INR: 5.1	-	No	Yes	No	Clips, epinephrine	No	Forrest Ia ulcer	Duodenum
4	M	72	Heparin	40	No	Yes	Yes	No	No	Arterial bleeding	Cyst-gastrostomy (chronic pancreatitis)
5	M	47	NSAIDs, clopidogrel, ASA	40	No	No, clips	Yes	No	Yes (<48 hours); surgery	Dieulafoy lesion	Lesser curvature
6	M	82	ASA	20	Epinephrine, biopsy forceps, TAE	Yes	No	Clips	Yes (>72 hours); TAE	Arterial bleeding after resection of ampullary adenoma	Ampulla
7	F	71	ASA, dipyridamol	-	Epinephrine, clips	Yes	Yes	No	No	Forrest Ib ulcer	Duodenum (D2)
8	M	47	NSAIDs	-	No	No, epinephrine	Yes	No	No	Forrest Ia ulcer	Duodenum
9	M	50	No	+	No	Yes	Yes	No	No	Forrest Ib ulcer	Esophagus (GEJ)
10	M	76	No	-	No	Yes	Yes	No	No	Forrest Ib ulcer	Gastro-jejunostomy
11	M	65	No	-	Epinephrine, clips, goldprobe, etoxysclerol, TAE	Yes	Yes	No	No	Forrest Ib ulcer	Bulbus
12	M	57	No	-	Epinephrine, clips	Yes	Yes	No	Yes (<48 hours); TAE	Forrest Ia ulcer	Lesser curvature
13	M	71	No	40	No	No, epinephrine, clips, goldprobe	Yes	No	Yes (<48 hours); TAE	Forrest Ia ulcer	Bulbus
14	F	79	No	40	No	No, histo-acryl lipiodol	Yes	No	No	Variceal bleeding	Fundus
15	F	68	No	-	No	Yes	Yes	No	No	Diffuse tumor bleed	Esophago-gastrostomy
16	M	51	No	-	No	No, epinephrine	Yes	No	No	Arterial tumor bleed	Lesser curvature

ASA: acetylsalicylic acid, GEJ: gastroesophageal junction, INR: international normalized ratio, MALT: mucosa-associated lymphoid tissue, NSAIDs: non-steroidal anti-inflammatory drugs, TAE: transarterial embolization.

Table 2. Treatment outcome in patients on antithrombotic therapy compared with patients not receiving such treatment at time of gastrointestinal bleeding.

	Total n=16	ATT+ n=8	Non-ATT n=8	P value[1]
Ulcer bleedings, n (%)	9 (56)	4 (50)	5 (63)	1.0
Previously treated site, n (%)	5 (31)	3 (38)	2 (25)	1.0
Blatchford score, mean	9.5	9.3	9.6	0.94
Successful initial hemostasis after Hemospray[2], n (%)	13 (81)	5(63)	8 (100)	0.2
- Monotherapy	8 (50)	3 (38)	5 (63)	
- Salvage therapy	5 (31)	2 (25)	3 (38)	
Failed initial hemostasis after Hemospray[3], n (%)	3 (19)	3 (38)	0 (0)	0.2
Rebleed (7 days), n (%)	5 (31)	3 (38)	2 (25)	1.0
Mortality (7 days), n (%)	0 (0)	0 (0)	0 (0)	-

ATT: antithrombotic therapy.

[1] Fisher's exact test and Mann-Whitney U test.

[2] Hemospray was applied as last modality before hemostasis was reached. This could either be as monotherapy or as salvage therapy.

[3] A subsequent modality had to be used for hemostasis after application of Hemospray.

spray as part of salvage therapy was used in two ATT+ patients and three non-ATT patients. In all cases, a maximum of 20g of Hemospray was used.

Of the three ATT+ patients in whom Hemospray failed to achieve hemostasis, two had a spurting arterial bleed, which could be controlled by additional clipping. In the third patient, radiological intervention by means of angiography with coiling of the bleeding vessel was necessary to achieve hemostasis.

Rebleeding within 7 days occurred in five patients in total: 3/8 patients (38%) in the ATT+ group and in 2/8 patients (25%) in the non-ATT group (p=1.0). In two of the three cases in the ATT+ group, Hemospray was applied to arterial spurting bleeding (postampullary adenoma resection and Forrest Ia ulcer in a mucosa-associated lymphoid tissue lymphoma). In both rebleeding cases in the non-ATT group, Hemospray was used for a PUB-related arterial bleed. No deaths occurred within 7 days and 30 days after Hemospray application.

DISCUSSION

In this patient series, the outcomes are presented of 16 consecutive patients with UGIB who were treated with Hemospray in a high-volume tertiary care referral center. In expert hands, Hemospray was very effective in reaching initial hemostasis of UGIB in patients without ATT (non-ATT group). In addition, a majority of patients on ATT also reached initial hemostasis after treatment with Hemospray. However, the reported success rate cannot be compared

directly with other series because outcome of endoscopy in patients taking ATT is often not reported.[20, 21, 23, 24] Failed initial hemostasis and rebleeding in the ATT+ group was almost exclusively observed when Hemospray was applied to arterial spurting bleeds, suggesting limited effectiveness of Hemospray in a selection of patients on ATT.

This series is the first to describe the successful use of Hemospray in patients on ATT. The use of AT results in impaired activation and aggregation of thrombocytes or distortion of the direct and indirect coagulation cascade, which might prevent formation of a thrombin-mediated clot on the bleeding site.[25] The current data suggest that endoscopic hemostasis by Hemospray is not hampered by the effects of systemic ATT. As Hemospray was also successfully applied as salvage therapy, this may even suggest beneficial effects on clot formation which cannot be achieved by current endoscopic hemostatic modalities such as clipping. More research is needed to further elucidate the role of Hemospray in clot formation both *in vitro* and *in vivo*.

The current case series is limited by the small number of patients and the high proportion of spurting bleeds (50%). This may be explained by the tertiary care setting and the use of Hemospray as salvage therapy and treatment for high-risk cases. Further studies are required to confirm the efficacy of Hemospray in daily endoscopic practice in less-selected cases.

CONCLUSIONS

Effectiveness of Hemospray in the management of UGIB is promising in a small series of patients, both those with and those without ATT but caution is advised in using Hemospray in patients on ATT with a spurting arterial bleeding. The inclusion of these patients in future trials is recommended to increase the generalizability of the results.

Acknowledgments

Material support was provided by Cook Medical (Winston-Salem, North Carolina, USA).

CHAPTER 3.3

HEMOSPRAY TREATMENT IS EFFECTIVE FOR LOWER GASTROINTESTINAL BLEEDING

I. Lisanne Holster, Enric Brullet, Ernst J. Kuipers, Rafel Campo, Alberto Fernández-Atutxa, Eric T.T.L. Tjwa

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ABSTRACT

Acute lower gastrointestinal bleeding (LGIB) is diverse in origin and can be substantial, requiring urgent hemostasis. Hemospray is a promising novel hemostatic agent for upper gastrointestinal bleeding (UGIB). It has been claimed in a small series that the use of Hemospray is also feasible in LGIB. We aimed to expand our knowledge of the application of Hemospray for the treatment of LGIB in a wider range of conditions to further define the optimal patient population for this new therapeutic modality.

We analyzed the outcomes of 9 unselected consecutive patients with active LGIB treated with Hemospray in two major hospitals in Europe. Initial hemostasis was achieved after Hemospray application in all patients. Rebleeding occurred in 2 patients (22%) who were on acetyl salicylic acid and presented with spurting bleeds. These preliminary data show that Hemospray can be effective in the management of LGIB, but suggest cautious use for patients on antithrombotic therapy and spurting bleeds.

INTRODUCTION

Lower gastrointestinal bleeding (LGIB) accounts for 20 to 40% of acute gastrointestinal bleeding and its incidence is rising.[26, 27] Acute LGIB may be massive and associated with hemodynamic instability, so requires prompt, reliable and durable hemostasis. Frequently used treatment modalities are hemoclips, over-the-scope clips (OTSCs) and thermal coagulation. However, placement of clips is not suitable for diffusely bleeding lesions and can be difficult when massive hemorrhage obscures the bleeding focus or in tangentially located bleeding sites. The latter also applies to injection therapy. Thermocoagulation is suitable for large bleeding surfaces such as diffuse angiodysplasia, but its in-depth application may result in complications in the thin-walled parts of the colon. Hemospray (Cook Medical, Winston-Salem, North Carolina, USA) is an easy applicable hemostatic powder that has been shown to be effective in both focused and diffusely bleeding lesions in the upper gastrointestinal tract, without side effects.[21, 28] Evidence on the efficacy of this endoscopic therapy in LGIB is very limited, based on extrapolations of what happens in UGIB and in small series of patients.[29] In Europe, Hemospray is not registered for use in the lower gastrointestinal tract so its use for lower gastrointestinal bleeding is currently off-label. It is therefore unlikely in the short term that randomized trials on the use of Hemospray in LGIB, both major and clinically relevant non-major, and with concomitant use of antithrombotic medications will be performed. We present our case series considering these aspects in patients with LGIB treated with Hemospray at two large European university hospitals, adding to the increasing experience with this promising treatment modality.

PATIENTS AND METHODS

Patients

From October 2011 to April 2013, all patients who were treated endoscopically with Hemospray for active LGIB in Sabadell Hospital, Spain and Erasmus Medical Center, University Hospital, Rotterdam, the Netherlands were identified. Data on sex, age, comorbidity, clinical presentation, medication use, procedural details and outcome were prospectively collected, anonymized, and analyzed. Approval for this study was obtained from the Institutional Review Board of the participating centers.

Methods

Endoscopic hemostatic interventions were exclusively performed by registered endoscopists experienced in therapeutic colonoscopy and specifically trained in Hemospray application. The training consisted of both theory and hands-on training on an animal model. Hemospray was deployed onto the active bleeding site through a 10-Fr catheter (Cook Medical, USA)

Figure 1. The Hemospray device (version 2.0) inserted into a colonoscope (CF-Q180AL).

propelled by short bursts of carbon dioxide from a canister until hemostasis was confirmed (Figure 1). A burst on average contains 1-5 g of powder. Successful initial hemostasis was defined as persistent hemostasis after 3-5 minutes of visual inspection following Hemospray application (Figure 2). Hemospray was used either as monotherapy or as salvage therapy at the discretion of the endoscopist and depending on the origin of bleeding. Salvage therapy was defined as the use of Hemospray after failure of one or more other endoscopic modalities. Failed initial hemostasis was defined as the requirement for a subsequent treatment modality to achieve cessation of the bleeding after the application of Hemospray. A scheduled second-look endoscopy was not performed unless clinical signs of rebleeding were present, including tachycardia, hypotension, or a significant drop in hemoglobin.

RESULTS

Patient characteristics

A total of nine patients (five men, four women; median age 63, range 22-79) with active LGIB were treated with Hemospray (5-30g) during the study period (Table 1). Four patients were on antithrombotic therapy at time of bleeding (acetyl salicylic acid, n=2; thienopyridine, n=1; low-molecular-weight heparin, n=1). One patient had chemotherapy-induced thrombocytopenia ($21*10^9$/L). The clinical presentation was hematochezia in five patients, and hypovolemic shock (blood pressure 60/20 mmHg, heart rate 124) in one patient. In the remaining three patients, the bleeding occurred directly after polypectomy. Of the nine patients, three patients experienced major bleeding (defined as a decrease in the hemoglobin level of 2 g/dL

Figure 2. Endoscopic images showing: a) a post-polypectomy bleed in the descending colon with the Hemospray catheter in situ, b) a bleeding point in the rectum post-polypectomy after an initial burst of Hemospray has been applied (patient #7), c) sustained hemostasis after multiple bursts of Hemospray have been applied (patient #7).

or more within a 24-hour period or transfusion of two or more units of packed red cells) and six had non-major clinically relevant bleeding (defined as any bleeding leading to hospital admission, unscheduled contact with a physician, or discomfort or impairment of activities of daily life that did not meet the criteria for major bleeding) according to the International Society of Thrombosis and Hemostasis.[30] The median volume of red blood cells transfused per patient was two units (range 0-8 units).

Bleeding characteristics

LGIB occurred spontaneously in five patients from: a colorectal anastomosis, a rectal ulcer, a colonic diverticulum, a cecal adenocarcinoma, and proctitis with coexistent chemotherapy-induced thrombocytopenia (one patient each). Post-polypectomy bleeding occurred in four patients, either immediately following polypectomy (n=3) or 24 hours after polypectomy (n=1). The bleeding was located in the rectum (n=2), transverse colon (n=1), and ascending colon (n=1). Polypectomy was performed with standard snares and using EndoCut (Vio 300D; Erbe, Tübingen, Germany).

Table 1. Patient characteristics.

Case no.	Sex	Age	Origin of bleeding	Severity of bleeding	Antithrombotic therapy use	Hemospray as first modality	Immediate hemostasis after Hemospray	7-day rebleed (time of rebleed)-> alternative therapy	Adverse effects
1	F	70	Oozing immediate polypectomy bleeding (pedunculated polyp >20 mm) rectum	Clinically relevant	-	No, clips and epinephrine	Yes	No	Abdominal pain after each burst of powder
2	F	62	Pulsatile anastomotic bleeding colorectal anastomosis	Major	Thienopyridine	Yes	Yes	No	-
3	F	45	Oozing rectal ulcer	Clinically relevant	-	Yes	Yes	No	-
4	M	77	Pulsatile immediate polypectomy bleeding (sessile polyp 10 mm) transverse colon	Clinically relevant	ASA	No, clips	Yes	Yes (after 24 h) -> TAE	-
5	M	75	Pulsatile diverticulum bleeding descending colon	Major	ASA	Yes	Yes	Yes (after 24 h) -> clips*	-
6	M	79	Diffuse bleeding from adenocarcinoma cecum	Clinically relevant	-	Yes	Yes	No	-
7	M	55	Oozing immediate polypectomy bleeding (sessile polyp 40 mm) rectum	Clinically relevant	-	No, epinephrine	Yes	No	-
8	F	63	Pulsatile post-polypectomy-ulcer bleeding ascending colon	Major	-	Yes	Yes	No	-
9	M	22	Diffuse oozing leucocytopenic proctitis	Clinically relevant	LMWH	Yes	Yes	No	-

**: One point Hb drop within 24 h, a non-bleeding visible vessel at re-colonoscopy was seen, which was clipped, ASA: acetyl salicylic acid, LMWH: low-molecular-weight heparin, TAE: transcatheter arterial embolization.*

Treatment success

In all patients, successful initial hemostasis was obtained with the use of Hemospray. In the majority of patients (n=6), Hemospray was used as monotherapy. In three patients, all of whom had post-polypectomy bleeding, Hemospray was successfully used as salvage therapy (after failed hemostasis with hemoclips and/or epinephrine). Rebleeding within 7 days occurred in 2/9 patients (22%) in the form of a diverticular bleed in the descending colon (patient #5) and a post-polypectomy bleed in the transverse colon (patient #4). In the former, Hemospray had been used as monotherapy and hemoclip placement resulted in definitive hemostasis. In the latter, Hemospray had already been used as salvage therapy, so radiological embolization was required. Both patients were on antithrombotic therapy (acetyl salicylic acid). None of the nine patients experienced rebleeding after 30 days.

Safety outcome

One female patient experienced significant abdominal cramps after each burst of Hemospray onto the post-polypectomy site in the rectum. This pain subsided directly after application. Perforation, symptomatic systemic embolism, and bowel obstruction were not observed during 30-day follow-up period.

DISCUSSION

LGIB is currently treated with variable success by epinephrine injection, hemoclip placement, and/or thermal treatment modalities. Hemospray is a highly effective endoscopic hemostatic alternative in LGIB. Initial hemostasis was achieved in all nine cases, being used as the first modality in six patients. Rebleeding was observed in two patients, both of whom were on antithrombotic therapy.

One possible major advantage over current endoscopic modalities may be the ability to control diffuse bleeding from a larger area, for which hemoclip placement is not feasible. Argon plasma coagulation (APC) may overcome this problem, but this treatment is associated with a delicate technical balance between achieving durable hemostasis and risk of perforation. The risk of perforation induced by the application of Hemospray is as yet unknown, but it is expected to be much lower than with APC. Both major and non-major clinical relevant bleeding can be treated with Hemospray, which allows the endoscopist to optimize the efficacy of the colonoscopy as one modality is suitable for all levels of bleeding. In line with our earlier report in UGIB,[4] Hemospray in LGIB may not result in sustained hemostasis in patients on antithrombotic therapy with a spurting arterial bleed.

A few issues need to be addressed. First, our series is limited by its small size and the diversity of indications for therapy, although patients were included from both a tertiary and non-tertiary centre, providing a representative sample of LGIB patients, Second, treatment of LGIB may be challenging to treat because of the often angled position of the endoscope and sometimes the presence of bloody stools. It is therefore important to optimize application of Hemospray, limiting technical complications such as obstruction of the catheter. From previous experience in UGIB, it is known that endoscopists can be easily trained.[28] The decision to use Hemospray, was left to the discretion of the endoscopist. This was a subjective decision and may not be reproducible.

Third, in terms of complications, one patient experienced abdominal pain after each application of Hemospray. We have observed a similar side effect in the treatment of a patient with UGIB (data not shown). One can speculate this may the consequence of the carbon dioxide burst when deploying Hemospray. No other reports in the literature have so far mentioned this complication.

Finally, the use of OTSCs has been advocated for hemostasis of severe post-polypectomy bleeds, but high costs and technical issues may make endoscopists reluctant to go down this route.

In conclusion, Hemospray is a welcome alternative in the management of colorectal bleeding. It can be used instead of the current treatment modalities, but also as rescue therapy when injection and clips have failed to achieve hemostasis or in large diffuse bleeds when otherwise only thermal therapy would be possible. The true merit and generalizability of the data presented need to be confirmed in larger cohorts of patients.

Acknowledgments

Material support was provided by Cook Medical, Winston-Salem, North Carolina, USA.

Competing interests

Eric Tjwa, Enric Brullet, and Rafel Campo have received an unrestricted educational grant from Cook Medical Ireland. In Europe, the use of Hemospray for lower gastrointestinal bleeding is currently off-label.

CHAPTER 3.4

CONTROLLING GASTRIC VARICEAL BLEEDING WITH ENDOSCOPICALLY APPLIED HEMOSTATIC POWDER (HEMOSPRAY)

I. Lisanne Holster, Jan-Werner Poley, Ernst J. Kuipers, Eric T.T.L. Tjwa

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TO THE EDITOR

Gastric variceal bleeding tends to be more severe (2.9 vs. 4.8 transfusion units per patient) and is associated with a higher mortality (30% vs. 45%) than bleeding from esophageal varices.[31-33]

Failure of endoscopic therapy commonly requires rescue placement of a transjugular intrahepatic portosystemic shunt (TIPS),[34] but this option is costly and not always feasible.

Hemospray is a novel hemostatic spray recently introduced for the management of non-variceal upper gastrointestinal bleeding.[21]

We describe the first case of variceal bleeding refractory to standard endoscopic therapy, successfully treated with Hemospray, obviating the need for TIPS.

A 79-year-old woman presented to the emergency department with a 3-day history of melena. Her previous medical history included idiopathic myelofibrosis with hepatosplenomegaly due to extramedullary hematopoiesis. This was complicated by portal hypertension and ascites. Furthermore, she suffered from a severe hypertension-related pre-existent dilated cardiomyopathy. Previous upper endoscopy did not show the presence of varices.

At presentation she had a blood pressure of 80/40 mmHg with a pulse rate of 90 bpm with peripheral cyanosis. On rectal examination, black stools were noticed. Laboratory test results showed a hemoglobin 4.8 mmol/L, urea 27 mmol/L, creatinine 68 mmol/L, INR 1.4, and normal transaminases and bilirubin.

In anticipation of a variceal hemorrhage, standard administration of an antibiotic (norfloxacin 400 mg twice daily) and vasopressor drugs (octreotide) was initiated. Fluid and packed cell administration was restricted to stabilize vital signs. The patient was meanwhile transferred to the intensive care unit.

Upper gastrointestinal endoscopy was performed using an Olympus Q180-1T scope (Olympus, Japan). In the distal esophagus, small varices without bleeding stigmata were seen, but in the gastric fundus a profusely bleeding varix of 8 mm (GOV2 [32]) was observed. Next, in three consecutive injections, a total volume of 2.6 ml Histoacryl with lipiodol was injected. However, hemostasis could not be achieved and hemodynamic instability ensued. Rescue treatment with TIPS was considered, but not pursued given her cardiac condition. Instead of injecting more Histoacryl, we decided to apply Hemospray (Cook Medical, USA). For this, we sprayed approximately 10 g of Hemospray covering the entire bleeding varix. Persistent hemostasis was confirmed after 5 minutes of visual inspection.

The patient received standard post-endoscopic care and went home. No rebleeding occurred at follow-up at day 7 and 30. We did not perform a second-look endoscopy given the absence of signs of rebleeding.

Gastric variceal hemorrhage is an acute life-threatening condition in which the endoscopist is challenged to act swift in a technically demanding retroflexed position. Endoscopic management involves single or multiple injection(s) of cyanoacrylate glue into the varix

resulting in the formation of a polymeric plug. Despite its relative high initial hemostasis rate (87-100%),[31] injection carries distinct risks. First, polymerisation of acrylate beyond the bleeding site may result in thromboembolic events.[31] Second, needle obstruction frequently occurs necessitating retrieval. This means loss of precious time. Third, ulceration of the bleeding site after injection is commonly seen, and may result in secondary bleeding.[31]

When hemostatic treatment with cyanoacrylate glue fails, urgent TIPS is not always feasible due to local unavailability, when the patient condition is too unstable or, as in this case, when there are clear contraindications such as cardiomyopathy.[35]

Hemospray is a novel proprietary hemostatic spray recently introduced for the management of non-variceal upper gastrointestinal bleeding. Its safety and efficacy has been shown in peptic ulcer bleeding,[21] as well as in cancer-related upper gastrointestinal bleeding.[5] Upon application, this inorganic hemostatic powder becomes cohesive and adhesive, and forms a stable mechanical barrier that covers the bleeding site. We report on the first case in literature in which Hemospray is successfully applied in initially failed endoscopic hemostasis of a variceal bleeding.

There are few concerns that need to be addressed. Hemospray is applied by a CO_2-propelled canister with a positive outflow pressure. Hypothetically, particles may enter the vascular system and give rise to venous thromboembolisation. However, the outflow pressure at the catheter tip is less than the known intravariceal venous pressures (often exceeding 15 mmHg) [36] at a distance of 1-2 cm from the mucosa. Also, data from an ongoing multicentre European initiative on the use of Hemospray for non-variceal upper gastrointestinal bleeding does not report incidence of thromboembolism (*unpublished data*). Another concern involves the effects of Hemospray on coagulation. This is of importance since most gastric varices occur in cirrhotic patients with frequent unbalance of pro- and anti-coagulatory factors.[37] More research needs to be performed to elucidate this issue, but preliminary data show only minor effects *in vitro* of Hemospray on coagulation parameters.[38]

In conclusion, Hemospray may offer a simple and welcome alternative in durably controlling bleeding (gastric) varices. However, we need to await its use in controlled trials to determine the true added value.

Conflict of interest

Jan-Werner Poley is consultant for Cook Medical.

Other disclosures

The use of Hemospray for variceal bleeding is currently not an indicated use in the device labelling.

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CHAPTER 4

SELF-EXPANDABLE METAL STENTS AS DEFINITIVE TREATMENT FOR ESOPHAGEAL VARICEAL BLEEDING

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ABSTRACT

The use of self-expandable metal stents (SEMS) has occasionally been described for the treatment of uncontrollable esophageal variceal bleeding (EVB) as a bridge to an alternative treatment option (i.e. transjugular intrahepatic portosystemic shunt [TIPS]). It is currently not known whether SEMS placement is appropriate for more than temporary hemostasis. This case series report describes five patients in whom EVB could not be controlled with variceal band ligation and who were not suitable to undergo a TIPS procedure at the time of bleeding. SEMS were placed in these patients with the intent of definitive treatment. Successful initial hemostasis was achieved in all five patients, and sustained hemostasis occurred in four. Stents were removed from two patients after >14 days and remained in situ until death in three other patients (range 6–214 days). No complications related to this longer duration were observed. In one case, TIPS could be performed at a later stage. SEMS could be a definitive treatment for uncontrollable esophageal bleeding in patients with a limited life expectancy or those unsuitable for TIPS at the time of bleeding.

INTRODUCTION

Acute esophageal variceal bleeding (EVB) is a life-threatening condition. Standard pharmacological therapy in combination with endoscopic variceal band ligation (VBL) fails to control bleeding in 10%–20% of cases.[1] The use of self-expandable metal stents (SEMS) for the treatment of acute EVB has been reported in small patient cohorts over the past decade.[2, 3] These fully covered SEMS have a substantial diameter, and achieve durable hemostasis in 70%–100% of cases and reduce the risk of rebleeding (Figure 1).[4] SEMS placement is intended to serve as a bridge to further treatment.[5] During this interval, management aims include patient stabilization with reduction of portal pressure. Transjugular intrahepatic portosystemic shunt (TIPS) has a proven efficacy for secondary prophylaxis in patients at high risk of treatment failure.[6] In the literature, the SEMS is usually removed after 1 week to avoid possible severe adverse events such as pressure-induced perforation. However, some case studies have reported slightly longer durations of up to 14 days.[2, 7]

It is currently not known whether SEMS can serve as more than a temporary hemostatic method prior to TIPS. SEMS for EVB could provide a most welcome alternative for individual patients, as well as for centers that are unable to place TIPS. In this report we describe five cases of uncontrollable EVB, in which SEMS was placed with the intent of definitive treatment rather than a bridge to further treatment.

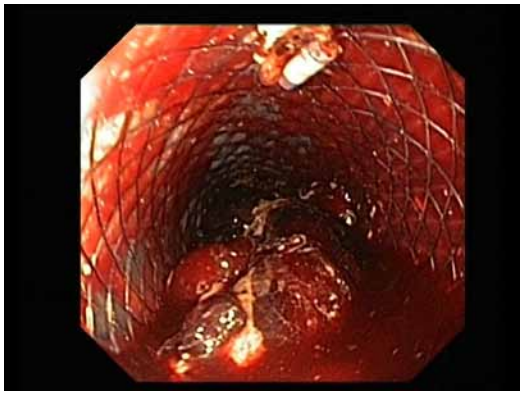

Figure 1. Self-expandable metal stent after placement, showing a clot in the lumen of the stent.

CASE SERIES

Patients

The current study analyzed all patients who received a SEMS for acute EVB following failed endoscopic variceal band ligation (VBL) between February 2012 and October 2012. The treating physician decided whether a patient was fit for TIPS or eligible for SEMS placement.

For patients in whom clinical condition was a limiting factor for TIPS placement, the acute physiology and chronic health evaluation (APACHE) II score, the Emory score, and the Bonn TIPS early mortality (BOTEM) score were reported[8] in order to predict the risk of early mortality if TIPS had been placed.

Data on sex, age, procedural details, rebleeding, and clinical course were collected prospectively, anonymized, and then analyzed. The study was performed in agreement with the local ethical committee.

Methods

Endoscopic interventions (using an Olympus Q180-1T scope; Olympus, Tokyo, Japan) were exclusively performed by endoscopists experienced in therapeutic hemostatic interventions. VBL using a 6-Shooter Saeed Multi-band Ligator (Cook Medical, Winston-Salem, North Carolina, USA) was the principal modality to obtain hemostasis. Insertion of the SEMS (Sx-Ella Danis, fully covered, Ø 30/25/30 ´ 135 mm; ELLA-CS, Hradec Králové, Czech Republic) was considered if at least one previous attempt at endoscopic hemostasis had failed and if the patient was not considered to be a candidate for TIPS at the time. Stents were inserted and removed according to the manufacturers' instructions, as previously described.[2]

In addition to endoscopic therapy, all patients received standard supportive care by means of fluid resuscitation, red blood cell transfusion (if necessary), prophylactic antibiotics (norfloxacin or ceftriaxone), and vasoactive drugs (e.g. octreotide 50 µg bolus, followed by 50 µg/hour for at least 3 days).

RESULTS

The following results describe five consecutive patients who underwent stent placement for uncontrollable variceal bleeding and failed VBL. The median age was 58 years (range 48–78 years); three of the patients (60%) were male (Table 1).

Case 1

A 57-year-old man presented with hematemesis. He had experienced two similar episodes in the previous 4 weeks for which he had undergone VBL of large bleeding esophageal varices as a consequence of non-cirrhotic portal hypertension due to liver metastasis of colon cancer. TIPS placement was considered but was not carried out due to the metastasized disease. At presentation, the patient was pale, had a heart rate of 107 bpm and a systolic blood pressure of 130/64 mmHg. There was marked ascites without signs of spontaneous bacterial peritonitis. His laboratory results revealed mixed cholestatic and hepatocellular injury with a total bilirubin of 51 mmol/L and an international normalized ratio (INR) of 1.1. The hemoglobin count was 4.4 mmol/L. Radiological imaging of the liver revealed extensive hepatic

Table 1. Summary of cases.

Patient	Age, years	Sex	Variceal bleeding	SEMS in situ	Stent complications	Rebleeding 1/6 months	Clinical course
1	57	M	NCPHT due to liver metastases	Until death: 214 days	None	No/No	Died after 7 months from progressive disease
2	62	F	Acute on chronic liver failure (auto-immune cirrhosis)	14 days	SEMS migration to the stomach	No/No	Liver transplantation a few hours later
3	78	F	PHT due to alcoholic cirrhosis	Until death: 11 days	None	N/A	Died after 11 days from progressive liver disease
4	48	M	PHT due to alcoholic cirrhosis	Until death: 6 days	None	Yes/N/A	Coiling of coronary veins, died 6 days thereafter due to progressive liver disease
5	58	M	PHT due to alcoholic cirrhosis	17 days	None	No/No	TIPS after 15 days

F: female, M: male, N/A: not applicable, NCPHT: non-cirrhotic portal hypertension, PHT: portal hypertension, SEMS: self-expandable metal stent, TIPS, transjugular intrahepatic portosystemic shunt.

metastasized disease without portal vein thrombosis. Gastroscopy showed a large profusely bleeding esophageal varix and several non-bleeding stigmata of recent ligations, including fibrotic scarring. An attempt was made to place a rubber band onto the fibrotic esophageal tissue, but this did not lead to optimal hemostasis. In the absence of any endoscopic alternatives, a SEMS was subsequently placed with successful hemostasis. The patient experienced post-procedural retrosternal pain that was relieved by paracetamol. Given the poor overall prognosis, it was decided to leave the stent in situ and refrain from further endoscopic treatment. No rebleeding episodes occurred during follow-up. The patient died 7 months later from progressive disease.

Case 2

A 62-year-old woman was admitted due to acute liver failure with unknown etiology. She had an unremarkable medical history, except for depression for which she used paroxetine. Her model for end-stage liver disease (MELD) score was 27 and she met the King's College criteria for urgent liver transplantation. Radiological imaging showed collapsed liver parenchyma suggestive of massive necrosis, but also splenomegaly. In combination with mild thrombocytopenia (123 ´ 10^9/L), longstanding portal hypertension was suspected. A few hours prior to transplantation, hematemesis occurred. The patient was tachycardic (130 bpm), with

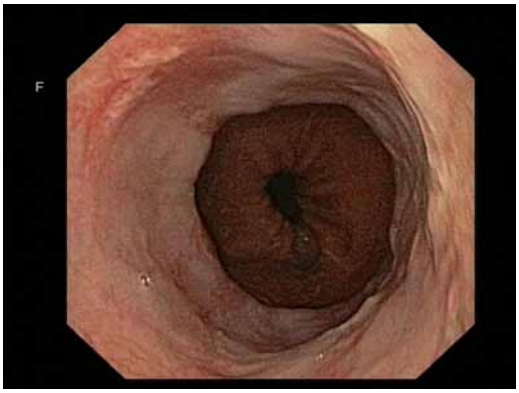

Figure 2. Esophagus wall after removal of self-expandable metal stent: a healing ulcer with reflux esophagitis grade B (previously grade D) and obliterated varices are shown.

a marked drop in blood pressure to 100/60 mmHg. The INR was 2.7 and the hemoglobin level was 4.5 mmol/L. At gastroscopy, severe reflux esophagitis (Los Angeles classification grade D) and a bleeding esophageal ulcer on top of middle-sized varices were noted. After VBL, the ulcer was still oozing. TIPS placement was not considered given the pending liver transplantation. A SEMS was placed resulting in definitive hemostasis. She underwent an uncomplicated liver transplantation. The explanted liver showed auto-immune cirrhosis, suggesting pre-existing liver failure in this patient. At gastroscopy for stent removal 2 weeks later, the SEMS had migrated to the stomach, probably due to blind placement of a gastric tube (14 Fr, 4.7 mm x 122 cm). A healing ulcer with reflux esophagitis grade B and obliterated varices were observed (Figure 2). No rebleeding occurred during 6 months of follow-up.

Case 3

A 78-year-old female with a history of abdominal hysterectomy and alcoholic cirrhosis complicated by ascites and a spontaneous bacterial peritonitis was admitted for a strangulated incisional hernia. At 6 days after surgery hematemesis occurred. She was hemodynamically unstable (blood pressure 80/50 mmHg; heart rate 103 bpm), and her hemoglobin dropped 1.2 points to 4.3 mmol/L. The MELD score was 14 with a Child–Pugh score of B-9. Gastroscopy showed large and profusely bleeding esophageal varices. Placement of multiple rubber bands did not result in initial hemostasis. Due to the patients' age, (decompensated) liver function, and poor medical and postsurgical condition, TIPS placement was considered to carry a very high risk for complications. The predicted risk of early mortality if TIPS had been placed was indeed intermediate to high (APACHE II 18, Emory 2, BOTEM 6). Subsequently, a SEMS was placed. The course was complicated by further deterioration of the liver function with hepatic encephalopathy due to spontaneous bacterial peritonitis with multi-resistant bacteria. Further management was restricted to supportive care and the patient died 11 days after SEMS placement. No rebleeding episodes had occurred.

Case 4

A 48-year-old man with a medical history of alcohol abuse was transferred to the intensive care unit because of hemorrhagic shock due to uncontrollable EVB. Vasopressive support was necessary to maintain proper blood pressure. He was initially admitted for decompensated cirrhosis (MELD score 28, Child–Pugh score C-12) due to a *Staphylococcus aureus* sepsis. The referring physician had not been able to manage the bleed endoscopically. For that reason, a Sengstaken–Blakemore tube had been placed. Abdominal imaging revealed a complete portal vein thrombosis and massive ascites. Gastroscopy was performed after removing the Sengstaken–Blakemore tube, showing large esophageal varices with all stigmata of pending and recent bleeding (cherry red spots, white nipples, and red wale signs). VBL was performed resulting in initial hemostasis. His medical course was further complicated by spontaneous bacterial peritonitis and deteriorating renal function. At 8 days after the initial bleed, melena re-occurred. A second gastroscopy showed recurrent active bleeding esophageal varices. Despite several attempts, no hemostasis could be achieved using VBL. Ultimately, a SEMS was placed leading to immediate hemostasis. TIPS placement was not possible due to the patient's severe medical condition and the presence of complete portal vein thrombosis. The predicted risk of early mortality associated with TIPS was high (APACHE II 21, Emory 4, BOTEM 8). Rebleeding occurred 7 days after SEMS placement. The third gastroscopy revealed a bleeding varix above the SEMS, which was well positioned. The proximal flare of the SEMS was not fully thrusted against the esophageal wall resulting in unsuccessful wall pressure (Figure 3). The SEMS was positioned more proximally to control the bleeding leaving the gastroesophageal junction exposed without signs of recurrent varices. As further endoscopic therapeutic options were not available and TIPS was not feasible, an urgent selective radiological embolization of the coronary veins radiating to the distal esophagus was performed

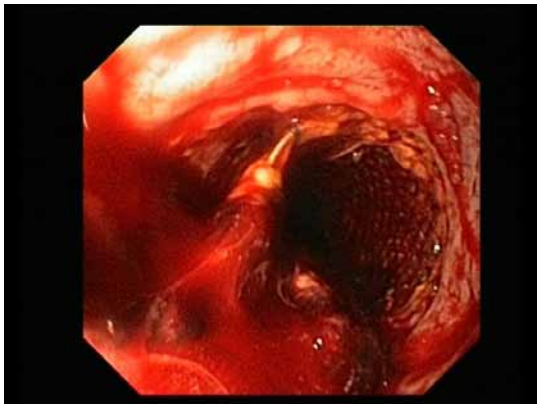

Figure 3. Variceal rebleeding with self-expandable metal stent (SEMS) in situ due to incomplete thrust of the proximal flare of the SEMS against the esophageal wall, resulting in unsuccessful wall pressure.

resulting in definite hemostasis. Unfortunately, the patient died 6 days later due to progressive liver and renal failure.

Case 5

A 58-year-old man presented with melena and hematemesis. His past medical history included alcoholic cirrhosis, complicated by a hepatic hydrothorax resolved by diuretics 2 years earlier. At physical examination he was hemodynamically stable. The initial hemoglobin count was 5.0 mmol/L. The MELD score was 11; the Child–Pugh score was A-6. At gastroscopy a medium-sized actively bleeding esophageal varix was observed. VBL was performed and initial hemostasis was achieved. However, his clinical condition deteriorated 12 hours later as he became hypotensive with recurrent profuse hematemesis, including a hemoglobin count of 3.7 mmol/L. A second gastroscopy showed active bleeding at the ligation site. Additional ligation was not feasible due to lack of variceal base below the level of the existing rubber band. Removing the previously placed band or emergency TIPS was considered but not pursued given the poor hemodynamic condition in the presence of an ongoing bleed. The predicted risk of early mortality if TIPS was placed was intermediate to high (APACHE II 17, Emory 2, BOTEM 6). A SEMS was placed followed by immediate and persistent hemostasis after 5 minutes of visual inspection. No recurrent bleeding occurred, allowing full recovery and elective TIPS placement after 15 days. The SEMS was removed 2 days later showing complete obliteration of varices and an intact esophageal mucosa. No rebleeding occurred during 6 months of follow-up.

DISCUSSION

EVB remains a difficult challenge to even the most experienced endoscopists. VBL has been proven to be an effective method of controlling bleeding, but VBL requires accurate placement onto the bleeding site. This exact placement can be difficult during profuse active bleeding.[9] In cases of VBL failure, TIPS is the preferred alternative, as it is highly effective in controlling bleeding.[8] The cost-effectiveness of TIPS needs to be considered, because life expectancy of patients experiencing EVB is often severely compromised.[10] EVB frequently occurs in patients with decompensated liver disease, revealing latent cardiopulmonary and renal dysfunction. TIPS might be very effective in achieving immediate hemostasis in stabilized Child–Pugh B/C patients;[6] however, the urgency of TIPS (i.e. for uncontrolled bleeding) is an independent predictor for early mortality.[11] In addition to hemostasis, intensive medical support is thus mandatory to treat these patients. In this respect, mortality within 6 weeks after EVB is high (30%).[1]

The use of SEMS for acute EVB as a bridge to further therapeutic intervention (i.e. TIPS) has been described.[12] However, it is unclear whether SEMS is also a treatment option in patients

who cannot undergo subsequent TIPS. The current case series reports on five patients in whom EVB could not be controlled with VBL and who were not considered suitable candidates for TIPS at the time of bleeding. In these patients, a SEMS was placed with the intent of definitive treatment. Successful initial hemostasis was demonstrated in all five patients, and sustained hemostasis was achieved in four of them. The first two cases described above illustrate the dilemmas endoscopists are confronted with when dealing with uncontrollable EVB in rare presentations such as hepatic metastasis or immediately prior to liver transplantation. In these cases, TIPS was not expected to remain in situ for any considerable time. The other three cases show that SEMS can serve as a definitive treatment modality when patients are unfit for TIPS. If these patients had undergone TIPS at the time of bleeding, the risk of early death after TIPS would have been very high, approaching 60%.[8] The fact that two out of the three cases died within 2 weeks from progressive liver disease emphasizes the importance of reconsidering emergency TIPS placement in high risk patients with uncontrollable EVB.

The current policy is that SEMS should be removed after approximately 1 week to avoid complications. Indeed, in the previously published cohorts, SEMS were removed after a median of 5–9 days.[2,7] In the current series, however, stents were removed from two patients after >14 days and remained in situ until death in three other patients (range 6–214 days). No complications related to this longer duration (e.g. esophageal tears or mucosal injury) were observed. Without additional TIPS, rebleeding rates after SEMS removal of up to 60% have been reported.[10] However, no case of rebleeding with the SEMS in situ has been reported previously and we can only speculate that this occurrence in the current series (case 4) was due to suboptimal wall pressure of the SEMS at the level of the gastroesophageal junction.

The current case series is limited by its small size, but the cases reflect daily encountered clinical dilemmas. Further studies are needed to confirm the efficacy of SEMS as a definitive treatment for uncontrollable EVB.

In conclusion, SEMS placement has been shown to be a definitive treatment for acute EVB in patients with a limited life expectancy and in those who at the time are unsuitable to undergo TIPS. Inclusion of such patients in future trials on the applicability of SEMS for variceal bleeding is recommended to increase the generalizability of results.

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CHAPTER 5

TIPS VS ENDOSCOPY AS STANDARD THERAPY FOR PREVENTION OF VARICEAL REBLEEDING

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Submitted

ABSTRACT

Background: Transjugular intrahepatic portosystemic shunting (TIPS) with covered stents reduces variceal rebleeding compared with endoscopic therapy in combination with β-blockers. This improves survival in selected cirrhotic high-risk patients. It is unknown whether this benefit also pertains to other cirrhotic patients. The study was to compare the efficacy and safety of these treatments in unselected cirrhotic patients.

Methods: In this multicenter randomized trial, long-term endoscopic variceal ligation (EVL) + β-blocker treatment was compared with TIPS placement in 72 patients with a first or second episode of gastroesophageal variceal bleeding, following sustained endoscopic hemostasis and hemodynamic stabilization. Randomization was stratified according to Child-Pugh score. Kaplan-Meier (event free) survival estimates were used for the endpoints rebleeding, death, treatment failure and hepatic encephalopathy.

Results: During a median follow-up of 23 months, 10 (29%) of 35 patients in the endoscopy group as compared with 0 of 37 (0%) patients in the TIPS group developed variceal rebleeding (p=0.001). Mortality (TIPS 32% vs. endoscopy 26%, p=0.418) and treatment failure (TIPS 38% vs. endoscopy 34%, p=0.685) did not differ between groups. Early hepatic encephalopathy (within 1-year) was significantly more frequent in the TIPS group (35% vs. 14%, p=0.035), but during long-term follow-up this difference diminished (p=0.121).

Conclusions: In unselected cirrhotic patients, covered TIPS was superior to EVL + β-blocker for reduction of variceal rebleeding, but did not improve survival. TIPS was associated with higher rates of early hepatic encephalopathy.

Dutch trial register: NTR973

INTRODUCTION

Gastroesophageal variceal bleeding (GEVB) is a severe complication of portal hypertension. Rebleeding is associated with increased mortality and hospitalization costs ranging between $6,600 and $23,000 in the USA. Therefore, management should be directed at its prevention.[1, 2] Secondary prevention is firstly achieved by endoscopic treatment (endoscopic variceal ligation [EVL] for esophageal varices and N-butyl cyanoacrylate for gastric varices) in combination with β-blocker therapy. Transjugular intrahepatic portosystemic shunt (TIPS) placement forms an alternative.[3] EVL requires multiple sessions to achieve successful eradication of varices and is associated with frequent rebleeding from varices or banding ulcers. TIPS on the other hand is an expensive procedure that carries a risk, albeit low, of severe complications including bleeding, liver injury, and heart failure. It is associated with a relatively high risk of hepatic encephalopathy.[4, 5] Currently, the combination of EVL and β-blockers is the standard of care. TIPS is recommended in patients who fail endoscopic and pharmacological therapy and is considered in those at high-risk of treatment failure.[3]

In cirrhotic patients with GEVB, TIPS with uncovered stents proved more effective than endoscopic therapy in reducing variceal rebleeding, but did not improve survival. This was paralleled by an increment of TIPS-related hepatic encephalopathy.[6]

Uncovered stents have been increasingly replaced by polytetrafluorethylene (PTFE)-covered stents.[7-9] Recent data suggest that early placement (i.e. within 24 hours) of covered TIPS reduces rebleeding, but also improves survival in selected high-risk patients without increasing the risk of encephalopathy.[10] It is unknown if these results also pertain to unselected patients and patients treated at later time points. This is a relevant issue, particularly since TIPS is a technically demanding treatment option that is only available in a limited number of specialized centers.

We compared the efficacy and safety of elective TIPS using PTFE-covered stents with endoscopic therapy + β-blocker for the secondary prevention of GEVB in unselected cirrhotic patients presenting with a first or second variceal bleeding.

METHODS

Study population

Patients were eligible for the study if they were between 18-75 years and presented with a first or second episode of esophageal or gastric variceal bleeding, as documented by endoscopic criteria for variceal bleeding.[11] Following stabilization, patients were randomly assigned to receive long-term endoscopic therapy (EVL or injection therapy) plus β-blocker or TIPS placement.

Exclusion criteria included: a history of serious or refractory hepatic encephalopathy unrelated to gastrointestinal bleeding; a history of significant heart failure (New York Heart Association class III & IV); portal hypertension due to other causes than liver disease (e.g. portal or splenic vein thrombosis); previous TIPS placement; advanced hepatocellular carcinoma; a Child-Pugh score >13; sepsis and/or multi-organ failure; and inability or unwillingness to give informed consent.

The trial was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The institutional review board at each center approved the protocol, and written informed consent was obtained from all patients before randomization. The trial protocol including data analysis plan is available online with the full text of this article. All authors contributed to the writing of the manuscript, had full access to all the data and analyses, and vouch for the accuracy and completeness of the data reported.

Study design

Randomization was performed after hemodynamic stabilization and sustained endoscopic hemostasis, preferably within 1-2 days after admission. Patients were randomly assigned through a permanently available central telephone system to receive further endoscopic therapy in combination with β-blocker therapy (standard of care) or TIPS placement. The randomization sequence was computer generated with the use of a concealed block size of four, stratified by Child-Pugh class.

Treatment

Initial stabilization in all patients included broad-spectrum antibiotics, vasoactive drugs, fluid and packed cell administration, and endoscopic treatment according to international consensus guidelines.[3] Vasoactive drugs (octreotide 50 µg bolus followed by 50 µg/h, terlipressin 6-12 mg iv/day, or somatostatin 250 µg bolus followed by 250 µg/h) were started at admission for 5 days. Endoscopic treatment of esophageal varices consisted of EVL (6-Shooter Saeed Multi-band Ligator®, Cook Medical, Winston-Salem, North Carolina, USA). Gastric varices were injected with cyanoacrylate glue (HistoAcryl™, B. Braun, Germany) with lipiodol (Lipiodol®, Guerbet, France).

In the endoscopic arm, a non-selective β-blocker (preferably slow release propranolol, titrated to the maximum tolerated dose aiming to decrease the heart rate in rest by 25%, with a lower limit of 50 bpm) was started at day 5 after the index bleeding, unless a contraindication was present (severe arrhythmia, severe obstructive COPD or known intolerance). Elective EVL sessions started 2 weeks after the index bleeding and were performed every 2-4 weeks thereafter until eradication of varices, and every 6-12 months thereafter.

In patients allocated by randomization to endoscopic treatment, further endoscopic management occurred on site by gastroenterologists with large experience in interventional

endoscopy including variceal ligation. Patients assigned to TIPS placement were transferred to one of the four main trial centers (i.e. university hospitals experienced in TIPS procedures).

All TIPS procedures were performed by an intervention radiologist experienced with TIPS placement. Antibiotic prophylaxis was given by means of a cephalosporin. TIPS placement was performed under general anesthesia after transhepatic portography. PTFE-covered stents (Viatorr, W.L. Gore and Associates, Flagstaff, AZ, USA) were used with initial balloon dilatation to 8 mm, aiming for a decrease in portal-venous pressure gradient to less than 12 mm Hg. If necessary, additional dilatation to 10 mm was performed. Embolization of the coronary vein or other collaterals was considered when there was evidence of active variceal bleeding during the procedure, and when portography showed marked collateral filling despite an otherwise successful procedure in terms of the portal-venous pressure gradient. Post-TIPS monitoring of shunt patency and function was done according to local guidelines.

Outcomes and follow-up

The primary outcome of the study was clinically significant variceal rebleeding. This was defined as recurrent melena or hematemesis resulting in either hospital admission, blood transfusion, drop in haemoglobin of at least 3 gram/liter, or death within six weeks after rebleeding. Variceal rebleeding was further divided into failure to control bleeding (within 120 hours after index endoscopic treatment), or failure of secondary prophylaxis (after 120 hours) and defined according to the Baveno Guidelines.[3]

Secondary outcomes were occurrence of treatment failure (either switch to other therapy or death), bleeding related mortality, liver transplantation, and hepatic encephalopathy based on clinical parameters.[12] All outcomes were scored by two physicians (ILH, ETTLT) independently and discussed with a third person (HRB) in case no consensus could be reached.

All patients were followed from inclusion until study termination at September 1, 2013. Outcomes were reported after 2 years and after total follow-up. The first year after inclusion, patients were followed with 3-monthly intervals and thereafter every 6 months.

Statistical analysis

Initial sample size was determined at 124 patients, with an alpha level of 0.05 and a power of 80%. However, during the course of this study the results of a trial suggested more benefit from early TIPS in terms of the primary endpoint rebleeding than expected.[10] It was decided to recalculate the sample size, resulting in a required population of 72 patients.

Intention to treat analyses were based on all randomized patients. Patients were censored at the time of liver transplantation, loss-to-follow-up, or last outpatient visit before study closure. In the "as-treated" analysis, patients were analyzed according to the treatment regimen that they received.

Independent sample t-tests were used for continuous variables and chi-square tests for categorical variables. Kaplan-Meier (event free) survival analyses with log-rank tests and Cox proportional hazard analyses were performed for the endpoints rebleeding, treatment failure, death, and hepatic encephalopathy. In case of zero events in one arm, likelihood ratio test with Firth's correction and 95% hazard ratio profile with likelihood confidence limits were used.[13] Data were analyzed using PASW statistics 21.0 for Windows (SPSS, IBM, Armonk, New York, USA) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

This trial was registered with trialregister.nl: number NTR973.

RESULTS

Patients, recruitment, and follow-up

Between July, 2007 and June, 2013, 174 patients were screened in 12 centers in the Netherlands and, of these, 72 patients were randomly assigned treatment (Figure 1). Thirty-five were assigned to receive endoscopic therapy plus a β-blocker, 37 to receive TIPS (intention to treat population).The mean age was 55 years (range 30-75 years) and 57% was male. Eighty-five percent was Caucasian. Alcohol was the most common cause of cirrhosis (Table 1). Median follow-up was 23.4 months (IQR 5.9-30.7 months). Six patients (8%) (4 in the endoscopy arm, 2 in the TIPS arm) were lost-to-follow-up after a median of 22.5 months (IQR 4.2-34.3). Twelve (17%) patients underwent liver transplantation (7 endoscopic arm vs. 5 TIPS arm, p=0.627) after a median of 19.9 months (IQR 6.9-38.5).

Six (16%) of the 37 patients randomized to TIPS crossed over to the EVL group. Four of them were not treated with TIPS placement for reasons of advanced hepatocellular carcinoma diagnosed after randomization (n=2), technical infeasibility, and per-procedural resuscitation. Two patients with TIPS developed severe untreatable hepatic encephalopathy, for which the only alternative finally proved to be TIPS closure. Six (17%) of the 35 patients randomized to EVL switched to TIPS during the course of the study; five because of recurrent/uncontrollable variceal rebleeding and one because of refractory ascites.

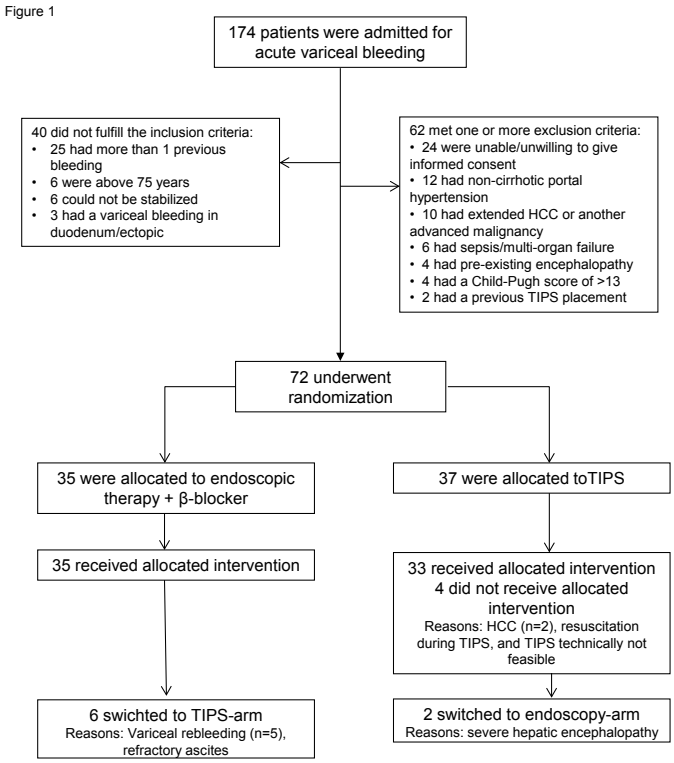

Figure 1. Participant flow.
HCC: hepatocellular carcinoma, TIPS transjugular intrahepatic portosystemic shunt.

Table 1. Baseline characteristics*.

	Overall N=72	Endoscopic + β-blocker group N=35	TIPS group N=37
Age (yr), mean (range)	55 (30-75)	54 (30-71)	56 (37-75)
Male sex	41 (57)	23 (49)	18 (66)
Cause of cirrhosis			
Alcohol	31 (43)	18 (51)	13 (35)
Hepatitis B/C	8 (11)	1 (3)	7 (19)
Alcohol and hepatitis B/C	6 (8)	3 (8)	3 (8)
Auto-immune liver/ biliary disease**	18 (25)	9 (26)	9 (24)
Other	9 (13)	4 (11)	5 (14)
Child-Pugh classification			
A (5-6)	26 (36)	13 (37)	13 (35)
B (7-9)	37 (51)	18 (51)	19 (51)
C (10-13)	9 (13)	4 (11)	5 (14)

Table 1. (Continued)

	Overall N=72	Endoscopic + β-blocker group N=35	TIPS group N=37
Child-Pugh score ¥	7.4±2.0	7.3±.9	7.5±2.0
MELD score$	13.1±5.2	12.7±3.8	13.5±6.3
MELD-Na score$	14.4±5.6	13.8±4.2	14.9±6.6
Albumin (g/l)	30.6±6.1	30.9±6.9	30.4±5.2
Bilirubin (mg/dl)	3.3±4.0	2.7±2.2	3.8±5.2
Creatinine (mg/dl)	0.8±0.2	0.8±0.2	0.8±0.2
INR	1.4±0.5	1.4±0.3	1.5±0.6
Thrombocytes (*10^9/L)	112.7±64.2	107.0±49.6	118.1±75.9
Ascites	28 (39)	13 (37)	15 (41)
Previous variceal bleeding***	14 (19)	9 (26)	5 (14)
β-blocker prophylaxis before index-bleed	11 (15)	5 (14)	6 (16)
Endoscopic prophylaxis ± β-blocker before index-bleed	17 (24)	11 (31)	6 (16)
Active bleeding at index gastroscopy	32 (44)	16 (46)	16 (43)
Location of varices at index gastroscopy			
Esophageal varices only	59 (82)	30 (86)	29 (78)
Gastric varices only	4 (6)	2 (6)	2 (5)
Esophageal and gastric varices	9 (13)	3 (9)	6 (16)
Endoscopic therapy at index bleed			
Endoscopic band ligation	59 (82)	26 (74)	33 (89)
Injection sclerotherapy	5 (7)	5 (14)	0 (0)
Injection Histoacryl-lipiodol	6 (8)	4 (11)	2 (5)
Hemoglobin at admission (mmol/L)	6.2±0.9	6.3±1.0	6.1±0.9
Previous episode of HE	2 (3)	2 (6)∞	0 (0)

***** *Intention to treat population. Plus-minus values are means ±SD, other values are no. (%). There were no significant differences between the two study groups. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4.* ****** *Includes primary biliary cirrhosis, primary sclerosing cholangitis and auto-immune hepatitis.* ******* *According to the inclusion criteria, patients could have had max. 1 previous variceal bleeding.* **¥** *The Child-Pugh score ranges from 5 to 15, class A (5 to 6 points) indicates the least severe disease, class B (7 to 9 points) moderately severe disease, and class C (10 to 15 points) the most severe disease. Patients with a Child-Pugh score of >13 were not included in the study.* **$** *The Model for End-Stage Liver Disease (MELD) and MELD-Na scores range from 6 to 40, with higher scores indicating more severe disease.* **∞** *One patient with grade1 and one patient with grade 2 hepatic encephalopathy.*

HE: hepatic encephalopathy, INR: international normalized ration, NASH: non-alcoholic steato-hepatitis, TIPS: transjugular intrahepatic portosystemic shunt.

Treatments

In the endoscopy arm, a total of 103 upper endoscopies (mean 2.9±2.4 per patient) were performed in the first year after randomization. The majority (56%) of procedures included EVL with placement of a mean 4.3 bands per procedure, 5% included injection therapy, and in 38% no treatment was considered necessary. All except one patient used beta-blockers, titrated on heart rate and/or tolerance.

In the TIPS group, 31 patients received one stent, and 2 patients two stents. Median time from bleeding to TIPS was 6 days (IQR 3-9 days). The mean portal pressure gradient dropped from 13.4±3.3 mmHg before the procedure to 4.4±2.1 mmHg after the procedure. For this, the shunt was balloon-dilated to 8 mm in 21 patients and to 10 mm in 10 patients. Embolization of collaterals was performed in 8 (24%) patients. The two-year patency rate was 94%; two patients underwent a successful revision of the TIPS for partial/complete occlusion.

Primary endpoint: Rebleeding

During long-term follow-up, 10 (29%) patients in the endoscopy arm experienced a total of 15 rebleeds compared with none of the patients in the TIPS arm (p=0.001) (Figure 2A). Endoscopic hemostasis was achieved in all cases; 5 patients switched to TIPS and remained free

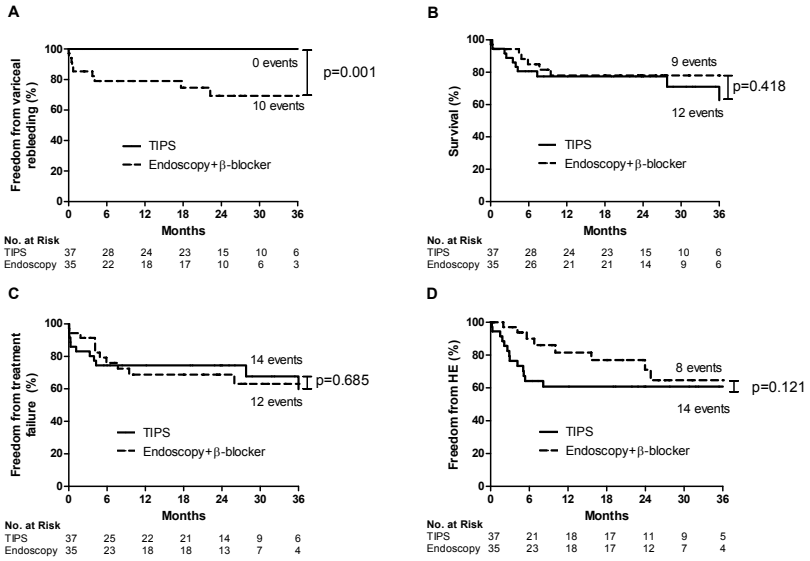

Figure 2. Kaplan-Meier analysis of freedom of variceal rebleeding, survival, treatment failure and hepatic encephalopathy.

Panel A shows the probability of remaining free from significant variceal rebleeding. Panel B shows the probability of survival. Panel C shows the probability of remaining free from treatment failure. Panel D shows the probability of remaining free from hepatic encephalopathy.

TIPS: transjugular intrahepatic portosystemic shunt.

from rebleeding thereafter. Nine out of 10 rebleeds occurred within 2 years of follow-up; two met the criteria of failure to control bleeding and eight had failure of secondary prophylaxis. Additionally, 6 non-variceal upper GI bleeds, mostly post-EVL ulcer bleeds, occurred during 2-year follow-up (Table 2). In the as-treated analysis, 10 (26%) patients treated with endoscopy experienced a rebleed compared with none of the patients treated with TIPS (p=0.002) (Figure S1A). In the univariate Cox regression analysis, active bleeding at index gastroscopy (HR 2.99, 95% CI 0.77-11.59, p=0.11), Child-Pugh C (HR 4.08, 95% CI 0.86-19.41, p=0.08), previous variceal bleeding (HR 2.68, 95% CI 0.73-9.82, p=0.14), randomization to endoscopy (HR

Table 2. Summary of outcome measurements after 2 years of follow-up.

	Endoscopic + β-blocker group N=35	TIPS group N=37	p-value
Total upper gastrointestinal bleeding	13 (37)	2 (5)	0.001
Significant variceal rebleeding	9 (26)	0 (0)	0.001
Failure to control bleeding (<120 h)	2	0	
Failure of secondary prophylaxis (>120 h)	7	0	
Other significant upper GI rebleeding	4 (11)	2 (5)	
Portal hypertensive gastropathy	1	1	
Post-EVL ulcer	2	1	
Peptic ulcer	1	0	
Treatment failure **	10 (29)	10 (27)	0.976
Liver transplantation	3 (9)	4 (11)	0.760
Encephalopathy	7 (20)	13 (35)	0.117
Grade 1-2	3	5	
Grade 3-4	4	8	
Death	7 (20)	8 (22)	0.818
Hepatocellular or cholangiocarcinoma	2	2	
Liver failure~	0	3	
Sepsis/pneumonia	0	2	
Peptic ulcer bleeding	1	0	
Intra-abdominal bleeding	2^	0	
Other∞	2	1	
Bleed to TIPS time, median (IQR)	NA	6 (3-9)	
Transfusion of RBC during index admission	2.8±2.8	2.6±3.5	0.73
Time in hospital during index admision, days	8.8±5.4	12.4±.11.2	0.095

** Intention to treat population. Plus-minus values are means ±SD, other values are no. (%).** combination of switch to other therapy or death. ~ All deaths occurred within 4 months after TIPS placement. ^ One intra-abdominal bleeding from an intra-abdominal varix, one from a laceration of the hepatic artery duringTIPS placement (after switch from endoscopic arm to TIPS for reasons of variceal rebleeding). ∞ Cerebrovascular accident, myocardial infarction, and respiratory insufficiency.*
EVL: endoscopic variceal ligation, NA: not applicable.

24.13, 95% CI 3.11-infinitive, p<0.001), and baseline thrombocytes <100*10^9/l (HR 2.59, 95% CI 0.67-10.03, p=0.17) showed a trend towards more variceal rebleeding. In the multivariate analysis, endoscopic treatment was the only parameter that was significantly associated with rebleeding (p=0.036).

Mortality and treatment failure

Nine (26%) patients in the endoscopy arm died, compared with 12 (32%) patients in the TIPS arm (p=0.418) (Figure 2B). None of the patients in either group died from a gastroesophageal variceal rebleeding, but in the endoscopy group one patient died from an intra-abdominal variceal bleeding. Two-year survival was 92% in the patients with Child-Pugh A, 76% in Child-Pugh B, and 56% in Child-Pugh C (p=0.049). Most common causes of death were: hepatocellular- or cholangiocarcinoma, liver failure, and systemic infection/sepsis (Table 2). In the univariate analysis, Model for End-Stage Liver Disease (MELD) score (HR 1.14, 95% CI 1.05-1.24, p=0.002), Child-Pugh score (HR 1.26, 95% CI 1.03-1.53, p=0.022), and thrombocytes <100*10^9/l (HR 1.90, 95%CI 0.76-4.76, p=0.169) were associated with mortality. In the multivariate analysis, only MELD score was a significant predictor for mortality (HR1.15, 95% CI 1.06-1.25, p=0.001).

The composite endpoint treatment failure did not differ between treatment groups (EVL 34% vs. TIPS 38%, p=0.685). Mortality and treatment failure did also not significantly differ in the as-treated population (Figure S1B and C).

Hepatic encephalopathy

Hepatic encephalopathy occurred in 22 patients (31%) in total; 14 in the TIPS group compared with 8 in the endoscopy group (Figure 2D). Early hepatic encephalopathy (within 1-year) was significantly more frequent in the TIPS group (35% vs. 14%, p=0.035), but during long-term follow-up this difference disappeared (p=0.121). Among those cases with encephalopathy, 64% of the cases in TIPS group and 50% of the cases in endoscopy group developed severe encephalopathy (grade 3 or 4). Treatment consisted of lactulose (n=17) or rifaximin (n=2). In one patient no treatment was necessary and in 2 patients TIPS revision/closure was inevitable for reasons of refractory encephalopathy. In the as-treated analysis, we found a significantly higher proportion of encephalopathy in the TIPS group both after one year as well as during long-term follow-up (p=0.002 and p=0.017 resp.) (Figure S1D). Univariate proportional hazard analysis showed that the risk of newly developing encephalopathy was higher in males (HR 4.23, 95% CI 1.43-12.54, p=0.009). In the multivariate analysis, male gender (p=0.004) and treatment with TIPS (p=0.033) were independent predictors of encephalopathy.

Separate analysis by MELD score revealed that the higher risk of early encephalopathy was confined to patients with a MELD score <10 points (endoscopy 0/8 (0%), TIPS 5/11 (45%); HR 11.59, 95% CI 1.30-infinity, p=0.002). In those with a higher MELD score, there was no significant difference in newly developing encephalopathy between the treatment arms

Table 3. Adverse events.

	Endoscopy-group < 2years	TIPS-group < 2years	Endoscopy-group >2 years until end follow-up	TIPS-group >2 years until end follow-up
	No. of events (no. of patients)			
SEVERE ADVERSE EVENTS				
Bleeding complications				
Variceal rebleeding	14 (9)		1	
Bleeding from banding ulcer	2 (2)	1		
Bleeding from portal hypertensive gastropathy	1	1		1
Other upper GI bleeding	1			1
Intra-abdominal bleeding from collaterals	1			
Laceration hepatic artery (during TIPS placement)	1			
OTHER COMPLICATIONS				
Hepatic encephalopathy	6 (6)	18 (12)	2 (2)	2 (2)
Ascites	11 (6)	4 (3)	2 (2)	1
Spontaneous bacterial peritonitis	3 (2)			2 (2)
Hepatorenal syndrome			1	
Hepatocellular or cholangiocarcinoma	3 (3)	2 (2)	1	
Acute on chronic liver failure	2 (1)	3 (3)	1	1
spontaneous TIPS occlusion		2 (2)		1
Cholangitis	2 (2)			6 (3)
Alcoholic hepatitis	2 (2)			1
Sepsis/systemic infection	1	3 (2)		1
Cardiac events (ventricular fibrillation, third degree AV block after start β-blocker, myocardial infarction)	2 (2)	1	1	
Neurological disorders (delirium tremens, Korsakoff syndrome, cerebellar ataxia)	2 (2)		1	1
Other (allergic reaction, peripheral edema, diabetes mellitus, erysipelas, gastroenteritis, incarcerated hernia inguinalis	2 (2)	2 (2)	1	1
NON-SERIOUS ADVERSE EVENTS				
Severe itching	1	1		
Hepatic encephalopathy	1			
Gynecomastia		1		

AV: atrioventricular, GI: gastrointestinal, TIPS: transjugular intrahepatic portosystemic shunt.

(MELD-score 10-14: endoscopy 13% vs TIPS 23%, MELD-score >14: endoscopy 27% vs TIPS 42%).

Other events

Overall, 24 (69%) patients in the endoscopy arm and 24 (65%) patients in the TIPS arm experienced at least one severe adverse event (p-value=0.74). There were no significant differences in the number of patients who experienced a specific adverse event between both arms (Table 3).

DISCUSSION

The importance of secondary prophylaxis (i.e. the prevention of variceal rebleeding) has been extensively acknowledged, yet the method most successful in achieving less mortality has been of much debate.[3] This randomized controlled clinical trial showed that placement of covered TIPS, in comparison with endoscopic therapy plus propranolol, significantly decreased variceal rebleeding rates in unselected patients presenting with a first or second episode of EGVB. This was however not associated with increased survival.

Preventing variceal rebleeding may be a substitute outcome of survival.[14] It has been shown that TIPS effectively lowers portal pressure and thus the driving force behind variceal (re)bleeding.[15] Indeed, early TIPS in selected high-risk patients resulted in a significant drop in mortality due to rebleeding.[8-10] In this study, we now show that TIPS did not confer a survival benefit. This warrants careful appreciation of the data. Rebleeding is associated with increased risk of mortality,[3] but in the current study mortality was exclusively from causes as progressive liver disease, infection, and malignancy rather than from rebleeding. This could be the result of patient characteristics such as etiology of liver disease (of note: this study included a relatively high proportion of patients with primary sclerosing cholangitis, primary biliary cirrhosis, and auto-immune hepatitis) or, more important, Child-Pugh score. In the present study, unselected patients with respect to Child-Pugh score and presence of active bleeding at the index endoscopy were included, in contrast to the patients in the trials showing benefit.[8-10] This suggests that a survival benefit associated with TIPS is only manifest in a population carrying a high mortality risk directly related to portal hypertension. Apparently, the selection criteria and the design of the present study did not identify such a population. This is further illustrated by the finding that none of the patients treated with EVL + propranolol died from variceal rebleeding. However, when we applied the high-risk selection criteria used in previous trials [8,9] in a post-hoc analysis, we still were not able to detect a survival difference (Figure S2). The ability of the Child- Pugh score to distinguish subjects by their mortality risk is, however, rather crude due to the lack of precision in the absence

of interval scale properties.[16] Patient with the same Child-Pugh score may have a different mortality risk depending on what combination of scores in variables led to that score.

Additionally, timing of TIPS placement may influence survival. The interval between bleeding and TIPS allows selection between those with and without progression to liver failure and/or death. In our cohort, the mean time to TIPS was approximately 1 week while this was 1-2 days in the aforementioned trials.[8-10] This reflects daily practice where clinicians face the dilemma between EVL and TIPS when opting for secondary prophylaxis. The first encompasses repetitive endoscopic sessions and the latter a demanding (both financial and logistical) but definite portal pressure lowering procedure.

In line with earlier studies on bare-metal TIPS,[6] we found a higher proportion of early hepatic encephalopathy in the TIPS group. Remarkably, the difference in encephalopathy between treatment groups was the largest in the first year and in patients with the lowest MELD scores. The portal pressure gradient, both before and after TIPS placement, was lower than expected. We found however no association between the risk of encephalopathy and the portal pressure gradient, nor the post-dilatation diameter of the stent.

In conclusion, covered TIPS is clearly superior to endoscopic therapy in combination with pharmacotherapy for the prevention of variceal rebleeding, but does not result in early or late survival benefit in unselected cirrhotic patients. Rebleeding may not be a good predictor for mortality, as prognosis is also linked to factors other than rebleeding. For now, the debate on secondary prophylaxis deepens. Studies on cost-effectiveness, quality of life, and randomization between early and elective TIPS placement should be performed to elucidate this issue further.

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SUPPLEMENTARY FIGURES

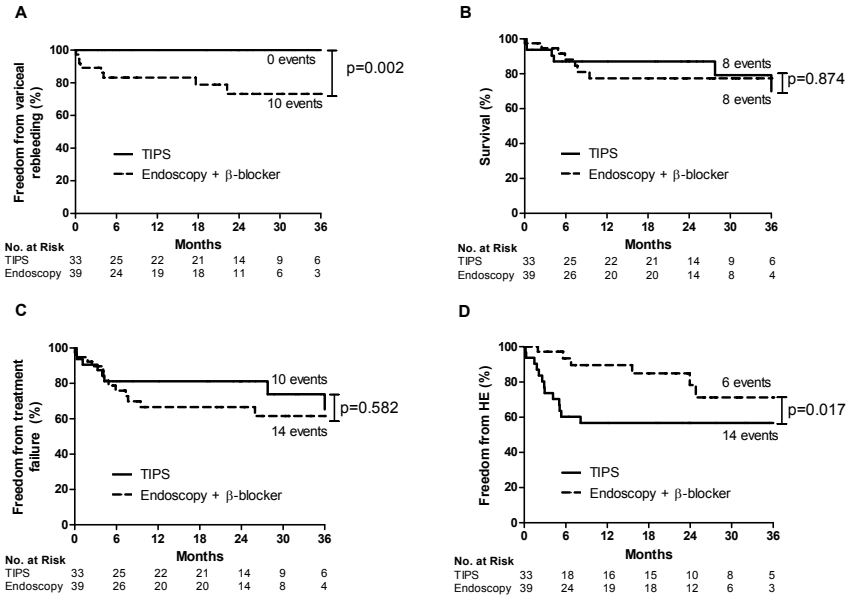

Figure S1. Kaplan-Meier analysis of freedom of variceal rebleeding, survival, treatment failure and hepatic encephalopathy for the "as treated" population.
Panel A shows the probability of remaining free from significant variceal rebleeding. Panel B shows the probability of survival. Panel C shows the probability of remaining free from treatment failure. Panel D shows the probability of remaining free from hepatic encephalopathy.
TIPS: transjugular intrahepatic portosystemic shunt.

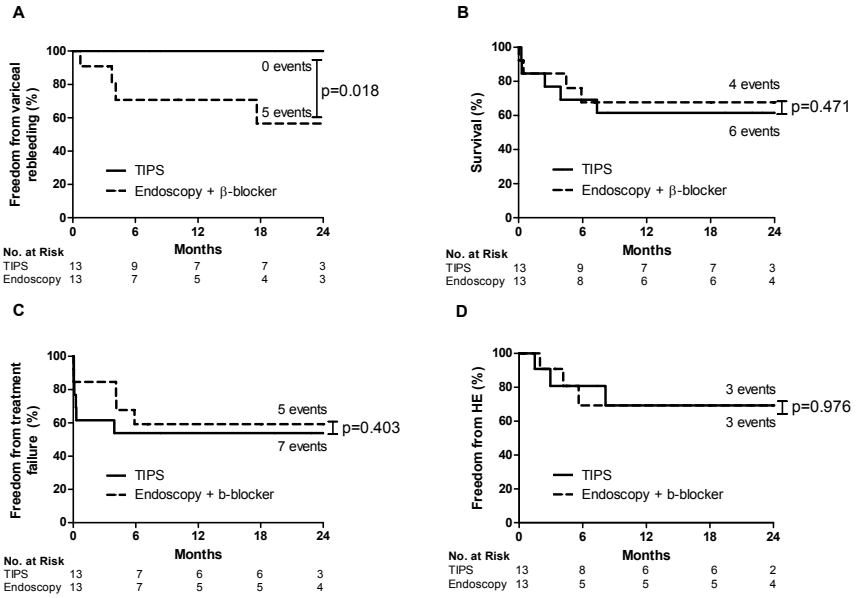

Figure S2. Kaplan-Meier analysis of freedom of variceal rebleeding, survival, treatment failure and hepatic encephalopathy for a selection of high-risk patients (Child-Pugh B with active bleeding or Child-Pugh C).[9] *Panel A shows the probability of remaining free from significant variceal rebleeding. Panel B shows the probability of survival. Panel C shows the probability of remaining free from treatment failure. Panel D shows the probability of remaining free from hepatic encephalopathy.*
TIPS: transjugular intrahepatic portosystemic shunt.

PART III

HELICOBACTER PYLORI AND PREMALIGNANT GASTRIC LESIONS

CHAPTER 6

ETHNICITY IS A STRONG PREDICTOR FOR *HELICOBACTER PYLORI* INFECTION IN YOUNG WOMEN IN A MULTI-ETHNIC EUROPEAN CITY

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ABSTRACT

Background: At the same time that *H. pylori* prevalence is declining in Western countries, immigrants from developing countries with high *H. pylori* prevalence have settled in Western urban areas. Actual epidemiologic data on *H. pylori* in a migrant community may help in realizing a more selective approach to assess *H. pylori*-related diseases. We aimed to define *H. pylori* prevalence as well as risk groups for *H. pylori* in a cohort of young women living in a multi-ethnic European city.

Material and methods: We measured immunoglobulin G (IgG) anti-*H. pylori* and CagA-antibodies in serum of pregnant women included in a population-based prospective cohort study, the Generation R study. Information on demographics, and socioeconomic status was collected by questionnaires. Chi-square and logistic regression were used.

Results: In total, 3146 (46%) of the 6837 tested women (mean age 29.7 ± 5.3) were *H. pylori*-positive and 1110 (35%) of them were CagA-positive. The *H. pylori* prevalence in women of Dutch origin was 24%, which was significantly lower than in non-Dutch women (64%; p<0.001). In particular, *H. pylori* positivity was found in 92% of Moroccan (odds ratio 19.2; 95% confidence interval 11.8-32.0), 80% of Cape Verdean (7.6; 5.0-11.5), 81% of Turkish (9.0; 6.7-12.1), 60% of Dutch Antillean (3.3; 2.3-4.7), and 58% of Surinamese women (3.0; 2.3-3.8). Among *H. pylori*-positive Dutch subjects, 19% were CagA-positive compared with 40% of the non-Dutch subjects (p<0.001).

Conclusion: Despite a general trend of declining prevalence in Western countries, *H. pylori* remains highly prevalent in migrant communities, which may constitute target groups for screening and eradication to prevent *H. pylori*-related diseases.

INTRODUCTION

Isolation and identification of *Helicobacter pylori* in 1982 led to better understanding of gastric pathophysiology. This Gram-negative bacterium is an important risk factor for peptic ulcer disease, gastric adenocarcinoma, and mucosa associated lymphoid tissue (MALT)-lymphoma.[1] The prevalence of *H. pylori* widely varies geographically and is highest in developing countries. In Western countries, however, prevalences have declined over recent decades to below 40%, in part as a result of improved hygiene and sanitation as well as the active elimination by antibiotics.[1] In parallel to the declining *H. pylori* prevalence, incidences of certain *H. pylori*-related diseases are decreasing as well.[2, 3]

These trends in Western populations call for risk group identification, as test-and-treat strategies for *H. pylori* both on population as well as individual level are unlikely to be cost-effective in low-prevalence countries.[4] Knowledge about specific risk groups may permit assessment of disease risk, and will offer opportunities for targeted interventions. The *H. pylori* colonization rate is associated with factors such as age, socioeconomic status, childhood crowding, and non-western ethnicity.[5] During past decades, many immigrants from developing countries with high *H. pylori* prevalence have settled in Western urban areas. In Rotterdam, a large Western city, more than 50% of the urban population is originating from outside The Netherlands. The largest non-Dutch ethnic groups consist of people from Morocco, Turkey, Suriname, Dutch Antilles, and Cape Verde. Previous studies indicated that *H. pylori* colonization rates in immigrants are higher compared to native Western populations.[6-8] Some of these migrant communities have a high risk of gastric cancer,[9, 10] in which *H. pylori* is involved as the major causative agent. Especially, CagA-positive *H. pylori* strains are known to be more interactive with higher risk of peptic ulcer disease, atrophic gastritis, and gastric cancer,[11, 12] and lower risk of gastro esophageal reflux disease, Barrett's esophagus, adenocarcinoma of the gastroesophageal junction, and childhood-onset asthma.[13, 14]

In this study, we aimed to obtain actual epidemiologic data on *H. pylori* prevalence in different ethnic groups living in a Western urban area. Moreover, we also measured anti-CagA-antibodies. As mothers are considered to be a source for transmission to their children, this study was performed in a cohort of pregnant women living in Rotterdam, a multi-ethnic European city.

METHODS

Setting and participants

This study was embedded in the Generation R Study, a population-based cohort study from fetal life until young adulthood in Rotterdam, with a multi-ethnic community, and the second

largest city in the Netherlands. The background, design and aims of this study have been reported in detail.[15]

Briefly, 8880 pregnant women were enrolled in the study between April 2002 and January 2006. Medical data were collected by physical examination and by questionnaires, and information on age, ethnicity, educational level, life style, and household income was obtained by questionnaires.[15]

The Generation R Study was approved by the Medical Ethical Committee of the Erasmus University Medical Center. All participants gave written informed consent.

Sociodemographic determinants

The cohort comprises various ethnic groups, reflecting the urban population of Rotterdam. The largest ethnic groups consist of Dutch, Surinamese, Turkish, Moroccan, Dutch-Antilles and Cape Verdean mothers. Ethnicity was determined by country of birth of the pregnant mother and her parents. A participating mother was considered of non-Dutch ethnic origin if one of her parents was born abroad (according to the definition of Statistics Netherlands).[16] If both parents were born in different countries other than the Netherlands, the country of the mother prevailed. Subjects of non-Dutch origin and born abroad were defined as first-generation immigrants. A participant of non-Dutch origin but born in the Netherlands was defined as a second-generation immigrant. People of Dutch origin were considered as the native population. According to the definitions of Statistics Netherlands,[16] participants with other ethnic background as mentioned above were grouped as 'other Western' for European (n=493), North American (n=24), Oceanean (n=9), Japanese (n=7) and Indonesian (n=194), and as 'other non-Western' for African (n=123), Asia (n=189) and South and Central American (n=91). The division into 'Western' and 'non-Western' is based on differences in socioeconomic and cultural situation. Participants from Indonesian were classified as 'Western', since they are originating from former Dutch-East Indies. Educational level was classified into four educational levels on the basis of the highest completed education: high (university or higher vocational training), high-secondary (general secondary school or intermediate vocational training), low-secondary (intermediate general school or lower vocational training), and low (primary school or no education). Educational level served as proxy for the socioeconomic status. Household income, defined by the total net monthly income of the family, was categorized as < € 1200, € 1200-2000, and > € 2000. Data on possible confounders like age, smoking habits, and alcohol use were obtained from the questionnaires.

Serologic determinants

Mid-pregnancy serum samples of 7185 mothers were available for analysis (Figure 1). Mothers included more than once (because of more than one pregnancy within inclusion period) were excluded (n=348), which left a total study population of 6837 pregnant women. Procedures for collection and storage of the sera samples have been described in detail

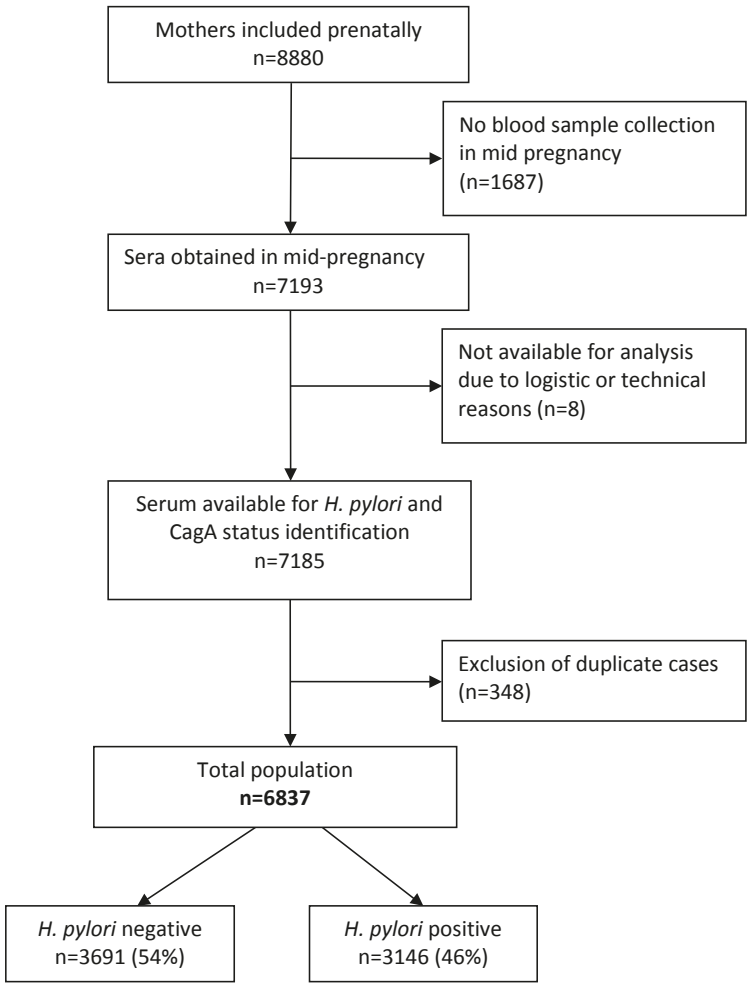

Figure 1. Flowchart of the study.

previously.[17] Samples were examined for *H. pylori* immunoglobulin G (IgG) antibody levels by enzyme-linked immunosorbent assay (ELISA), using whole cell antigens.[18] A separate ELISA was performed to determine serum IgG antibodies against a specific recombinant truncated CagA protein, as described.[19] All samples were measured in duplicate. For each sample, the optical density ratio (ODR) was calculated by dividing the optical density (OD) by the mean OD of the positive controls. *H. pylori* positivity was defined as either an ODR ≥ 1 or CagA positivity. The cut-off for CagA positivity was an ODR value ≥ 0.35. Both ELISAs were validated locally.

Statistical analysis

Chi-square tests (categorical variables) and t-tests (continuous variables) were used to compare different variables in relation to *H. pylori* status. Univariate analysis was performed to assess determinants associated with the presence of *H. pylori*. To study the individual effect of each potential determinant, each was separately tested, followed by a multivariate analysis corrected for all other determinants. In addition, a stratified analysis according to ethnicity was performed. Subjects with missing data on any of above-mentioned covariates were excluded from the multivariate analysis; this left a total of 4605 evaluable subjects.

A two sided p-value <0.05 was considered to be statistically significant. All analyses were performed using PASW Statistics 20.0 (SPSS, IBM, New York, USA).

RESULTS

Presence of *H. pylori*

In total, the serum samples of 6837 women were analyzed. Their mean age was 29.7 (± 5.3) years. Subjects of Dutch origin were older (mean age 31.4 years) than non-Dutch participants (mean age 28.4 years) ($p<0.001$). Table 1 shows the general characteristics and *H. pylori* status: 3146 (46%) subjects were *H. pylori*-positive, and 3691 (54%) subjects *H. pylori*-negative. Data on ethnicity were available for 6389 women: 3166 (50%) subjects were of Dutch ethnicity, 597 (9%) of Turkish, 577 (9%) of Surinamese, 408 (6%) of Moroccan, 275 (4%) of Cape Verdean, 237 (4%) of Dutch Antilles, 726 (11%) of other Western and 403 (6%) of other non-Western origin. The *H. pylori* positivity rate was highest among Moroccan women (92%), followed by Cape Verdean (80%), Turkish (81%), Dutch Antillean (60%), and Surinamese subjects (58%) (Figure 2). In contrast, the prevalence in women of Dutch origin was 24% ($p<0.001$).

The overall CagA-prevalence rate was 16.2%. Among *H. pylori*-positives, 1110 women (35.2%) were colonized with a CagA-positive strain, which however varied widely between ethnicities (Figure 2). Only 64 subjects were CagA-positive but *H. pylori*-negative (6%). Colonization with a CagA-positive *H. pylori* strain was most common in Surinamese (56%) mothers, followed by subjects of other non-Western (46%), Dutch Antillean (46%), Turkish (39%), Cape Verdean (34%), Moroccan (34%), other Western (29%), and Dutch (19%) origin ($p<0.001$).

Table 1. Baseline characteristics of study population, distribution by *H. pylori* status, and univariate analysis.

	Study population (n)	*H. pylori* - (n=3,691)	*H. pylori* + (n=3,146)	OR Univariate	95% CI
Age, mean (SD)	6,837 (100)	30.7 (4.9)	28.7 (5.4)	0.93	0.92-0.94
Dutch population (%)	3,166 (46)	31.5 (4.4)	31.0 (4.9)	0.98	0.96-1.0
Non-Dutch	3,223 (47)	29.2 (5.5)	27.9 (5.4)	0.96	0.94-0.97
Parity (%)					
Nulli parity	3,746 (55)	2,173 (58)	1,573 (42)	1.0	
Multi parity	3,025 (45)	1,496 (50)	1,529 (51)	1.4	
Missing	*66 (1)*				1.3-1.6
Ethnicity (%)					
Dutch	3,166 (50)	2,415 (76)	751 (24)	1.0	
Other Western	726 (11)	467 (64)	259 (36)	1.8	1.5-2.1
Turkish	597 (9)	116 (19)	481 (81)	13.3	10.7-16.6
Surinamese	577 (9)	244 (42)	333 (58)	4.3	3.7-5.3
Moroccan	408 (6)	32 (8)	376 (92)	37.8	26.0-54.7
Cape Verdean	275 (4)	54 (20)	221 (80)	13.2	9.7-17.9
Dutch Antilles	237 (4)	94 (40)	143 (60)	4.9	3.7-6.4
Other non-Western	403 (6)	154 (38)	249 (62)	5.2	4.2-6.5
Missing	*448 (7)*				
Dutch + Western	3,892 (61)	2,882 (74)	1,010 (26)	1.0	
Non-Western	2,497 (39)	694 (28)	1,803 (72)	7.4	6.6-8.3
Immigrant generation (%)					
Native	3,115 (49)	2,376 (76)	739 (24)	1.0	
1st generation	2,225 (35)	688 (31)	1,537 (69)	7.2	6.4-8.1
2nd generation	1,046 (16)	510 (49)	536 (51)	3.4	2.9-3.9
Missing	*451 (7)*				
Education (%)					
Low	719 (11)	199 (28)	520 (72)	6.6	5.5-8.0
Low secondary	980 (16)	451 (46)	529 (54)	3.0	2.6-3.5
High secondary	1,971 (31)	1,026 (52)	945 (48)	2.3	2.1-2.6
High	2,613 (42)	1,873 (72)	740 (28)	1.0	
Missing	*554 (8)*				
Household income (%)					
<1200 Euro	1,101 (21)	354 (32)	747 (68)	5.2	4.5-6.0
1200-2000 Euro	992 (19)	489 (49)	503 (51)	2.5	2.2-2.9
>2000	3,182 (60)	2,264 (71)	918 (29)	1.0	
Missing	*1,562 (23)*				
Alcohol (%)					
Yes	3,005 (51)	2,027 (68)	978 (32)	0.4	0.3-0.4
No	2,948 (49)	1,296 (44)	1,652 (56)	1.0	
Missing	*884 (13)*				
Smoking (%)					
Yes	1,688 (28)	930 (55)	758 (45)	1.0	0.9-1.2
No	4,348 (72)	2,430 (56)	1,918 (44)	1.0	
Missing	*801 (12)*				

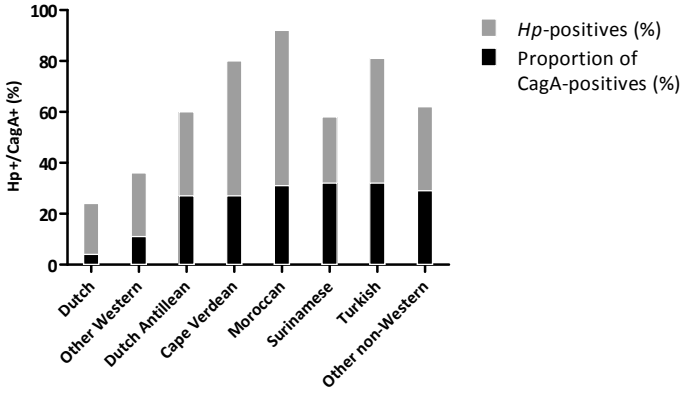

Figure 2. Proportion of CagA-positive and *H. pylori*-positive subjects.

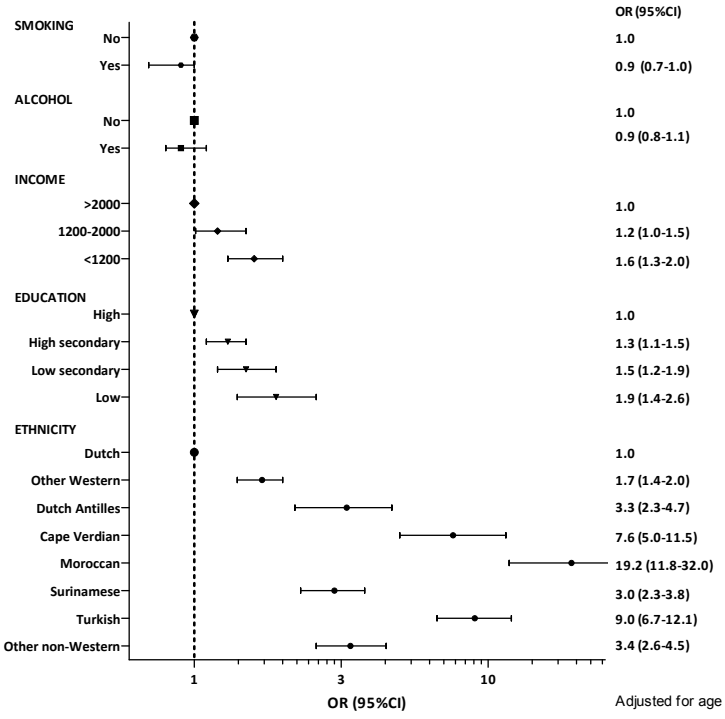

Figure 3. Multivariate analysis of determinants associated with *H. pylori* colonization in one model. Odds ratios (ORs) and 95% confidence intervals are adjusted for age.

Determinants of *H. pylori* colonization

Univariate logistic regression revealed that non-Dutch ethnicity was an independent risk factor for *H. pylori* positivity (Table 1). Furthermore, lower educational level, first generation immigrant, and lower household income were significantly associated with *H. pylori* infection. However, alcohol use was inversely associated with *H. pylori* presence.

The following variables were entered into the multivariate logistic regression model: age, ethnicity, education level, household income, smoking, and alcohol use. This analysis continued to reveal ethnicity as the most important independent risk factor for *H. pylori* (Figure 3). Compared with Dutch ethnicity, highest risk was found for Moroccan women (odds ratio 19.4; 95% confidence interval 11.8-32.0), followed by Turkish (9.0; 6.7-12.1), Cape Verdean (7.6; 5.0-11.5), other non-Western (3.4; 2.6-4.5), Dutch Antillean (3.3; 2.3-4.7), Surinamese (3.0; 2.3-3.8), and other Western (1.7; 1.4-2.0) subjects. In addition to ethnicity, the following independent risk factors were found: low education level compared with high education level (1.9; 1.4-2.5), and low income compared with high income (1.5; 1.2-1.9).

After stratification by ethnicity, multivariate analysis showed within all non-Dutch ethnicities that subjects born abroad (first generation immigrants) had a significantly higher risk to be colonized with *H. pylori* compared with second-generation immigrants ($p<0.05$ for Turkish, Surinamese, Moroccan, Cape Verdean, and Dutch Antillean subjects) (Table 2). Within the different ethnicities, age, smoking, and alcohol use were not associated with *H. pylori* colonization. Except for the Turkish and Cape Verdean subjects, low socio-economic status was an independent risk factor for *H. pylori* colonization. Dividing the whole population into either Western or non-Western showed in both groups first generation immigrants, subjects with low education level, and low household income to be more at risk for *H. pylori* colonization (Table 3).

Table 2. Multivariate analysis of *H. pylori* stratified to ethnicity.

	Dutch n=2,545	Other Western n=574	Turkish n=376	Surinamese n=355	Moroccan n=196	Cape Verdean n=149	Dutch Antillean n=154	Other non-Western n=254
Age	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (0.9-1.0)	1.0 (1.0-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (1.0-1.1)
Education								
Low	2.0 (1.1-3.4)	2.2 (0.9-5.3)	0.5 (0.2-1.4)	1.4 (0.6-3.6)	3.7 (0.5-24.7)	--	1.7 (0.4-6.9)	10.3 (2.7-38.6)
Low secondary	1.4 (1.0-1.9)	1.5 (0.7-3.2)	0.8 (0.3-2.3)	1.7 (0.8-3.7)	3.1 (0.5-17.7)	--	3.0 (0.8-10.8)	2.0 (0.7-5.7)
High secondary	1.2 (0.9-1.5)	1.5 (1.0-2.1)	1.0 (0.4-2.4)	1.5 (0.8-2.8)	1.1 (0.3-5.0)	--	1.2 (0.4-3.4)	1.6 (0.8-3.0)
High	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Generation								
Native	1.0	N.A	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
1st generation	N.A.	1.4 (1.0-2.1)	2.9 (1.6-5-3)	1.8 (1.1-3.0)	4.3 (1.4-13.3)	4.6 (1.6-13.4)	4.9 (1.9-12.7)	1.8 (0.8-3.8)
2nd generation	N.A.	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Household income								
<1200 Euro	1.7 (1.2-2.5)	1.6 (0.9-3.1)	1.3 (0.6-2.8)	2.0 (1.1-3.7)	0.8 (0.2-2.7)	0.3 (0.1-1.8)	0.7 (0.2-1.8)	1.6 (0.8-3.3)
1200-2000 Euro	1.0 (0.8-1.4)	1.4 (0.9-2.2)	1.0 (0.5-2.1)	1.6 (0.9-2.8)	3.1 (0.7-15.1)	0.1 (0.0-0.8)	0.4 (0.1-1.3)	1.4 (0.6-3.1)
>2000 Euro	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Alcohol								
Yes	0.9 (0.7-1.1)	0.7 (0.5-1.1)	0.7 (0.3-1.5)	1.0 (0.6-1.6)	3.6 (0.3-43.7)	1.2 (0.5-2.9)	0.8 (0.4-1.7)	0.9 (0.5-1.7)
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Smoking								
Yes	1.1 (0.9-1.3)	1.0 (0.6-1.5)	0.8 (0.4-1.3)	0.6 (0.4-1.1)	0.6 (0.1-3.0)	0.5 (0.2-1.3)	1.0 (0.5-2.4)	1.0 (0.4-2.1)
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

-- No output due to too small numbers.

Numbers are displayed as Odds Ratio (95% Confidence Interval). Reference categories are put as 1.0. All listed variables were entered into the multivariate analysis

N.A.: not applicable.

Table 3. Multivariate analysis stratified to ethnicity (Western vs. non-Western).

	All Western n=3,119	All non-Western n=1,484
Age	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Education		
Low	2.0 (1.3-3.2)	2.1(1.4-3.2)
Low secondary	1.4 (1.1-1.9)	2.0 (1.4-3.0)
High secondary	1.2 (1.0-1.5)	1.4 (1.0-1.9)
High	1.0	1.0
Generation		
Native	1.0	N.A.
1st generation	1.8 (1.4-2.3)	2.0 (1.5-2.6)
2nd generation	1.4 (1.1-1.8)	1.0
Household income		
<1200 Euro	1.7 (1.2-2.4)	1.4 (1.1-2.0)
1200-2000 Euro	1.1 (0.9-1.4)	1.4 (1.0-1.9)
>2000 Euro	1.0	1.0
Alcohol		
Yes	0.9 (0.7-1.0)	0.6 (0.5-0.8)
No	1.0	1.0
Smoking		
Yes	1.0 (0.8-1.3)	0.8 (0.6-1.1)
No	1.0	1.0

Numbers are displayed as Odds Ratio (95% Confidence Interval). Reference categories are put as 1.0. All listed variables were entered into the multivariate analysis.
N.A.: not applicable.

DISCUSSION

This population-based study demonstrates that *H. pylori* colonization is still common in a Western society, in particular in migrant communities. Among women of non-Dutch ethnicity, first generation immigrants were more at risk for *H. pylori* colonization then second-generation immigrants. Although others have focused on risk group identification as well, both the cohort size and design of this study are unique, and results reflect the actual epidemiologic data on *H. pylori* colonization in a Western urban area.

The relatively high prevalence of *H. pylori* and CagA-positive strains found in ethnic minority groups indicates that the health risks imposed by *H. pylori* remain a significant concern. Studies comparing first and second-generation immigrants with the native population have demonstrated a higher risk for non-cardia gastric cancer in first-generation immigrants.[20, 21] Childhood colonization with *H. pylori* could be a possible cause.[22, 23] Our results support this explanation, since *H. pylori* colonization among second-generation immigrants was signifi-

cantly lower compared with first-generation immigrants, but still higher than in the native population.

Based on estimates of the incidence of gastric cancer in different regions all around the world, study participants originating from Surinam, Caribbean, and Turkey are expected to have a higher gastric cancer risk compared with subjects from Western Europe.[24] Indeed, studies from Sweden have indicated a higher gastric cancer incidence ratio in immigrants born in high risk countries and living in Sweden.[20] Hence, those migrant communities could be an appropriate focus for considering the health advantages of *H. pylori* eradication. The latter is found effective for gastric cancer prevention in patients without precancerous lesions.[25, 26]

We tested for *H. pylori* antibodies in pregnant women, about to give birth. Close family members like mothers and siblings are considered to be the major transmission sources for *H. pylori* acquisition during the first years of life.[1] Hence, a high prevalence in mothers may be considered predictive for a high colonization rate in their children. Moreover, via day care attendance these children may also be a source for transmission to other children.[27, 28] Our finding indicates that *H. pylori* will remain to be prevalent for the coming decades, even in Western societies.

The observed *H. pylori* colonization rate in the Dutch study subjects was consistent with a previous study in subjects of the same age.[29] Studies evaluating *H. pylori* colonization in immigrant groups all showed higher infection prevalence than in native populations.[8, 29-33] A previous study of 288 adults in Rotterdam showed nearly similar positivity rates among different immigrant groups, however, higher prevalence in subjects of Dutch origin (46%) than we observed.[8] This may have been due to both the relative higher age and the small number of Dutch patients in that study.

The geographical variance of *H. pylori* strains was confirmed by this study. *H. pylori* strains colonizing Western subjects were least often CagA-positive.[34] In a Finnish population, CagA-positive *H. pylori* strains declined faster than CagA-negative *H. pylori* strains, especially among subjects less than 45 years old.[35] The low CagA prevalence among Dutch and other Western subjects is consistent with those observations. Nevertheless, overall prevalence of CagA-positive strains was lower than expected, especially in subjects born abroad.

This study is limited by the inclusion of young women in a limited age range which restricted the possibility of extrapolating our finding to older age cohorts. Owing to the well-described birth cohort effect for *H. pylori,*[27] we expect *H. pylori* to be more prevalent in older age cohort. However, whether this is true for all various ethnic groups remain unclear. Second, the population in our study may not have been reflective of the general population of Rotterdam owing to overrepresentation of more highly educated women in this cohort.[36]

In conclusion, in a multi-ethnic population, ethnicity is the strongest predictor of *H. pylori* colonization in young women. In particular, migrant communities constitute target groups

for screening of *H. pylori* to minimize *H. pylori*-related diseases. Additional knowledge of *H. pylori* biological cost, and details on implementation require further research.

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CHAPTER 7

THE IMPACT OF *HELICOBACTER PYLORI* ON ATOPIC DISORDERS IN CHILDHOOD

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ABSTRACT

Background: The prevalence of *Helicobacter pylori* in Western populations has steadily decreased. This has been suggested as one of the factors involved in the recent increase of asthma and allergy. Some studies have reported a negative association between *H. pylori* and asthma and allergy, but data are inconsistent and there are a few studies in children.

Aim: We investigated whether the prevalence of *H. pylori* was associated with asthma symptoms, allergic rhinitis, and atopic dermatitis in childhood.

Methods: We determined IgG anti-*H. pylori* and CagA antibodies in serum of Dutch children, who took part in the PIAMA birth cohort study. Serum was collected from 545 children, aged 7-9 years (Dutch ethnicity 91.5%). Symptoms of asthma and atopy were assessed by yearly questionnaires. Chi-square tests and logistic regression were used.

Results: We found 9% *H. pylori* and 0.9% CagA seropositivity. Twelve (5.9%) children with reported wheezing ever were *H. pylori* positive, compared to 37 (10.9%) of the non-wheezers (p=0.05). No significant differences in *H. pylori* prevalence were found between children with or without allergic rhinitis (8.5% vs. 9.5%), atopic dermatitis (8.7% vs. 9.2%), and physician-diagnosed asthma (7.1% vs. 9.4%). Multivariate analysis showed no significant associations between *H. pylori* seropositivity and wheezing (OR 0.52; 95% CI 0.25-1.06), allergic rhinitis (OR 0.96; 95% CI 0.51-1.81), atopic dermatitis (OR 1.05; 95% CI 0.56-1.98) or physician-diagnosed asthma (OR 0.87; 95% CI 0.37-2.08).

Conclusion: We found a borderline significantly lower *H. pylori* seropositivity in children with wheezing compared to non-wheezers, but no association between *H.pylori* serum-antibody status and allergic rhinitis, atopic dermatitis, or asthma.

INTRODUCTION

Helicobacter pylori, a Gram-negative bacterium, colonizes the stomach of more than half of the human population. Colonization invariably leads to chronic gastritis, which can give rise to other conditions, in particular peptic ulceration and gastric adenocarcinoma.[1] The prevalence of *H. pylori* has decreased steadily in Western populations over the past decades and has now reached low levels in children (<10% in children aged <10 years).[2-5] Possible contributors to the disappearance of *H. pylori* are the widespread use of antibiotics, improved hygiene and decreased family size.[6]

While this has occurred, the prevalence of atopic disorders such as allergic rhinitis, asthma, and atopic dermatitis has risen dramatically.[7] Numerous environmental causes including air pollution, exposure to tobacco smoke, exogenous infections, microbial substances in the environment, ownership of furry pets, and obesity have been proposed to explain this phenomenon.[8, 9]

In addition to these exogenous factors, a change in our indigenous microflora may have led to the rise in atopic disorders. According to the "disappearing microbiota hypothesis", ecological changes affecting our ancient indigenous microbiota may have contributed to the increased prevalence of asthma and allergy.[10] Changes in the overall pattern of commensals and pathogens in the gastrointestinal tract could be particularly relevant to this mechanism, as the gut associated lymphoid tissue is critical for normal maturation of our immune system, possibly preventing the later development of atopic conditions.[11] In line with this hypothesis, a negative association has been observed between *H. pylori* colonization, the dominant member of the gastric microflora, and the occurrence of asthma or allergy.[10, 12] However, data are inconsistent and few studies have been performed in children so far. [4, 13]

Therefore, the objective of the present study was to test whether the prevalence of *H. pylori* is indeed inversely related to the prevalence of asthma symptoms, allergic rhinitis and atopic dermatitis in a cohort of Dutch children.

METHODS

Study population

The study population consisted of a subsample of Dutch children who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study; details of this study have been published.[14] Expectant mothers were recruited from 52 prenatal health care clinics. Children born between the summer of 1996 and the late fall of 1997 were followed prospectively from birth until the age of 8 years.

The study protocol was approved by the Institutional Review Boards of the participating institutions. The parents of all participants gave written informed consent.

Questionnaires

Questionnaires for parental completion were sent at the third trimester of pregnancy, at 3 months after birth, at the age of one year and yearly thereafter, up to the age of 8 years.[15] In these questionnaires, information on wheezing symptoms, allergic rhinitis, atopic dermatitis, physician-diagnosed asthma, and asthma medication use was collected, using questions based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires. Furthermore, data on socio-economic status, demographics, and a wide range of possible risk factors for asthma and allergies were collected.

Definitions

Wheezing was assessed with the question: "Has your child had wheezing or whistling in the chest in the last 12 months?". Allergic rhinitis was assessed with the question: "Has your child had runny nose or sneezing without having a cold in the last 12 months?". Atopic dermatitis was defined as positive if parents reported the presence of an itchy rash which was intermittent in the prior 12 months on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles). 'Current physician-diagnosed asthma' was defined as a positive response to both the questions: "Did a physician ever diagnose asthma in your child?" and "Has your child had asthma in the last 12 months?". Data on prescription of inhalation corticosteroids was collected from pharmacies for children above the age of 2 years.

Unless stated otherwise, all outcome measures refer to the composed outcome 'ever', defined as the presence at any point in the first 8 years of life, e.g. wheezing ever was defined as the presence of wheeze at any point in the first 8 years of life. For wheezing, we also examined the effect at each year of age separately (allowing ascertainment of time-trends).

Laboratory tests

Blood samples were collected at a physical examination at the age of 7-9 years. Serum anti-*H. pylori* IgG antibody levels were determined by enzyme-linked immunosorbent assay (ELISA), using whole cell antigens.[16] CagA status was determined by a separate ELISA, based on the presence of serum IgG antibodies against a specific recombinant truncated CagA protein, as described.[16, 17] Both ELISAs have been validated in adults and children,[18] including Dutch adults but not Dutch children. They have been used in previous studies in Dutch children.[5] All samples were at least tested in duplicate. The optical density (OD) was determined spectrometrically at 405 nm for each specimen. For each sample, the optical density ratio (ODR) was calculated by dividing the OD of the sample by the mean OD of the positive controls. Specimens were considered positive for *H. pylori* if the ODR was ≥1.0. The cut-off for CagA positivity was a value of ODR >0.35 based on previous validation.

Statistical analysis

Chi-square tests (for categorical variables) and t-tests (for continuous variables) were used to compare the distribution of socio-economic, demographic, and lifestyle variables in relation to *H. pylori* status. Univariate and multiple logistic regression was performed to assess a relationship between *H. pylori* positivity and atopic symptoms. We performed an incomplete case analysis to minimize the risk of selection bias and compared the results with a complete case analysis. Results of both analyses did not differ, so we opted to use the incomplete case analysis to gain statistical power. In the multivariate analysis, odds ratios (ORs) were adjusted for potential confounders, including gender, ethnicity, exposure to indoor smoking, breastfeeding and educational attainment of parents. Children with missing data on any of these covariates were excluded from the multivariate analysis.

A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using PASW Statistics 17.0 for Windows (SPSS, IBM, New York, United States).

RESULTS

In total, 545 children were studied. Their general characteristics are shown in Table 1. The population consisted of more boys than girls (M/F: 300/245) and children were predominantly of Dutch ethnicity (91.5%).

Children included in the final analyses were less likely to have an atopic mother than children in the original PIAMA population (7% vs. 31%), but they were comparable with respect to ethnicity, percentage having been breastfed, parental socio-economic status, and exposure to indoor smoking with children in the original PIAMA population.

The overall prevalence of *H. pylori* seropositivity was 9% (95% CI 6.6-11.4%) (n=49) and the prevalence of anti-CagA antibodies was 0.9% (n=5), of which 4 were also *H. pylori* positive. *H. pylori*-positive children were significantly more often exposed to indoor smoking (> 1 cigarette/week) (27% vs. 12%, P=0.006), less often received breastfeeding (73% vs. 86%, p=0.03), and their parents had a lower educational attainment (43% vs. 29%, p=0.04) compared to children with negative *H. pylori* serology.

In the univariate analysis, the prevalence of *H. pylori* in children with 'wheezing ever' was 5.9% (n=12) while the *H. pylori* prevalence in those without wheezing ever was 10.9% (n=37). This difference was borderline significant (p=0.05). When including the one CagA positive *H. pylori* negative child, the p-value became 0.08. Analysis of the association between *H. pylori* prevalence and wheezing at separate ages showed a consistent inverse trend from age 1 to 8 years, but this trend did not reach statistical significance (Figure 1). No significant differences in *H. pylori* seropositivity were found between children with or without allergic rhinitis (8.5% vs. 9.5%), atopic dermatitis (8.7% vs. 9.2%), physician-diagnosed asthma (7.1% vs. 9.4%), and use of inhaled corticosteroids (8.4% vs. 9.1%).

Table 1. Baseline characteristics of study population, according to *Helicobacter pylori* status.

	H. pylori - (n=496)	*H. pylori* + (n=49)	p-value
Male gender, n (%)	274 (55)	26 (53)	0.442
Age, mean (SD), y *	7.9 (0.6)	7.9 (0.6)	0.683
Race/ethnicity, n (%)			0.456
Dutch	459 (93)	45 (92)	
Non-Dutch Caucasian	13 (3)	1 (2)	
Non-Caucasian	14 (3)	3 (6)	
Low education of parents, n (%) ¥	144 (29)	21 (43)	0.039
Atopy in mother, n (%)	36 (7)	1 (2)	0.166
Atopy in father, n (%)	156 (31)	15 (31)	0.904
Number of older siblings, mean (SD)	0.86 (1.1)	0.96 (1.0)	0.563
Mother smoking during pregnancy, n (%)	54 (11)	7 (14)	0.472
Breastfeeding, n (%)	428 (86)	36 (73)	0.032
Day care attendance before age 5, n (%) †	392 (80)	35 (71)	0.207
Exposure to indoor smoke, n (%) ‡	61 (12)	13 (27)	0.006

** Age at time of blood sample collection*
¥ Defined as at least one parent with low educational attainment
† Defined as at least 4 hours per week in a day-care centre with other children (under 12 year of age) present
‡ Defined as >1 cigarette/week.

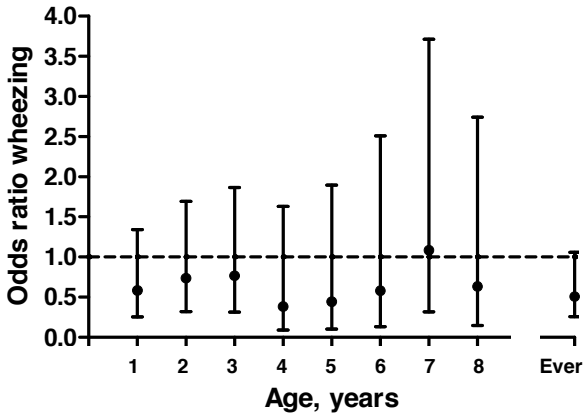

Figure 1. Odds ratios (ORs) and confidence intervals for the inverse association between *Helicobacter pylori* and wheezing. ORs given for the overall effect and for each year of age, separately.

Table 2. Association between *Helicobacter pylori* status and asthma, asthmatic symptoms, allergic rhinitis, and atopic dermatitis.

	H. pylori – (n=496)	*H. pylori* + (n=49)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)*	P-value
Wheezing			0.51 (0.26-1.01)	0.05	0.52 (0.25-1.06)	0.07
No	304	37				
Yes	192	12				
Allergic rhinitis			0.88 (0.49-1.58)	0.67	0.96 (0.51-1.81)	0.89
No	227	24				
Yes	269	25				
Atopic dermatitis			0.94 (0.52-1.70)	0.84	1.05 (0.56-1.98)	0.88
No	276	28				
Yes	220	21				
Physician-diagnosed asthma			0.74 (0.32-1.70)	0.48	0.87 (0.37-2.08)	0.76
No	405	42				
Yes	91	7				
Inhaled corticosteroid use			0.92 (0.40-2.13)	0.85	1.00 (0.42-2.40)	1.00
No	420	42				
Yes	76	7				

CI: confidence interval, OR: odds ratio.
OR and 95% CI correspond to the ratio of the odds of outcome in H. pylori positivity vs. the odds of outcome in H. pylori negativity.
** OR adjusted for gender, ethnicity, exposure to indoor smoking, breastfeeding and educational attainment of parents, excluding participants with unknown data for one of the covariates (n=40).*

In the multivariate analyses the inverse association between *H. pylori* prevalence and wheezing ever remained borderline significant (OR 0.52; 95% CI 0.25-1.06; p=0.07). No significant associations were found with allergic rhinitis (OR 0.96; 95% CI 0.51-1.81), atopic dermatitis (OR 1.05; 0.56-1.98), physician-diagnosed asthma (OR 0.87; 95% CI 0.37-2.08), or inhaled corticosteroid use (OR 1.00; 95% CI 0.42-2.40) (Table 2). The seropositivity rate for CagA was too low for statistical analysis.

DISCUSSION

This study shows an inverse trend in children between colonization with *H. pylori* and wheezing

The present observations to some extent support the "disappearing microbiota hypothesis".[10] According to this hypothesis, the disappearance of our ancestral indigenous microbiota is proposed to contribute to the rise in prevalence of asthma and other atopic conditions. *H. pylori*, the ancient dominant member of the gastric niche, is one of these disappearing mi-

croorganisms in the Western world. Although probably not exclusively responsible, *H. pylori* can be considered as a model to study this hypothesis. One reason is that colonization with *H. pylori* is mostly persistent and stable over time. *H. pylori* status can easily and reliably be assessed with non-invasive methods, such as serology and stool antigen detection.

One of the suggested underlying molecular mechanisms of this possible preventive effect of *H. pylori* is that the neutrophil-activating protein of *H. pylori* (HP-NAP) not only plays a key role in driving T-helper type 1 (Th1) inflammation, but is also able to inhibit T-helper type 2 (Th2)-mediated bronchial inflammation of allergic bronchial asthma.[19] More details come from a recent mouse model study, in which models of allergic airway disease were experimentally infected with *H. pylori*. Mice infected neonatally were found to exhibit significantly less tissue inflammation and goblet cell metaplasia than uninfected controls. Their bronchoalveolar inflammation, eosinophilia, and IL-5 and IL-13 secretion were clearly reduced and the pulmonary infiltration of Th2 and Th17 cells were diminished in infected animals. Asthma protection was further associated with impaired maturation of lung-infiltrating dendritic cells and the induction of regulatory T cells.[20]

Several large cross-sectional and case-control studies demonstrate an inverse relationship between asthma and *H. pylori* especially for CagA+ strains and early onset asthma and allergic rhinitis.[4, 12, 13, 21, 22] Others have reported no associations [23-25] or, in line with our findings, weak inverse associations.[22]

To our knowledge, this is the first study with longitudinal data on asthma and atopy in relation to *H. pylori* status. There was no risk of recall bias, since parents were not aware of *H. pylori* status of their child at the time of completion of the questionnaires. Furthermore, we achieved a very high participation grade on repeated questionnaires. Only 1.5% to 6.2% of the yearly questionnaires were (partly) missing.

In an observational study, it is not possible to firmly demonstrate causality, as correlations may be explained by other mechanisms.[8] A crucial requirement for causality is that the *H. pylori* infection precedes the start of symptoms. Since there are reliable data that *H. pylori* is acquired almost exclusively in childhood, and usually persists for life if not eliminated by antibiotics, it might be speculated that *H. pylori* precedes the diagnosis of asthma.[26, 27] However, asthma commonly has its onset early in life as well. In the present study, questionnaires were collected from very young age; however *H. pylori* was only tested at 8 years of age. Therefore, temporality of wheezing symptoms and *H. pylori* infection could not be examined in this study.

In the absence of specific data on antibiotic use, one can speculate that the use of antibiotics is a potential confounder, since children with asthma may receive antibiotic treatment for respiratory infection. However elimination of *H. pylori* by antimicrobial monotherapy is infrequent, which likely limited the effect of this potential confounder.[28] Furthermore, successful removal of *H. pylori* cannot be detected for many months after eradication as IgG titres fall with about 50% per 6-12 months.[29] Arguments against a substantial confounding

effect of antibiotics come from studies in which a specific inverse association was found between *H. pylori* and early onset asthma, but not late onset asthma.[12] If antibiotic therapy would act as a notable confounder, the effect would be expected to increase with age similar to the increased cumulative exposure to antibiotics.

Asthma is difficult to diagnose in infants and young children for whom testing of reversible airway obstruction is technically difficult. Therefore, wheezing is often used as a proxy for asthma in children in epidemiologic studies. Especially in the first years of life this could lead to considerable misclassification, due to the high prevalence of transient wheezing symptoms during common respiratory infections.[30] The specificity of wheezing as a proxy for asthma increases with age. We found an inverse trend between wheezing and *H. pylori*, which was consistent over age. In fact, the association at the age of 4-6 years was somewhat stronger than at 1-3 years. The inverse association between *H. pylori* and asthma (OR 0.87) was not significant, possibly due to the low numbers of children with a physician-diagnosis of asthma.

The current study has some potential limitations. First, we largely relied on self-reported data on asthmatic symptoms and atopic conditions. This may have led to some (non-differential) misclassification and thereby to bias toward the null. This would indicate that the true association may be larger than observed. Second, our data do not allow conclusions on the exact age of *H. pylori* acquisition, because children were tested only once at the age of 8 years. Third, it is possible that the observed inverse association between wheezing and *H. pylori* arose by chance, as multiple associations were examined. This is less likely, considering that we found a very consistent trend over time and over the different parameters defining atopy. A plausible explanation is that our study was not adequately powered to detect a moderate inverse association. Finally, although both ELISAs have been validated in adults and children, including Dutch adults, and have been used in previous studies in Dutch children,[5] they have not been separately validated in Dutch children specifically.

Identification of similar prevalences in larger groups will allow more solid conclusions to be drawn. If we gain better understandings of not only the relations between *H. pylori* and atopy, but also the mechanisms underlying the possibly protective effects of *H. pylori* for atopic disorders, we could investigate whether there are disease contexts in which gastric carriage of *H. pylori* in early life could yield benefits.[31]

Acknowledgements

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CHAPTER 8

HELICOBACTER PYLORI ERADICATION FOR PREMALIGNANT LESIONS OF THE GASTRIC MUCOSA

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Submitted to Cochrane Database of Systematic Reviews

ABSTRACT

Background: *Helicobacter pylori* infection is a major risk factor for gastric cancer development. However, the effect of *H. pylori* eradication for prevention of gastric cancer is still controversial, in particular in patients with premalignant gastric lesions.

Objectives: To assess the effect of *H. pylori* eradication therapy on different stages of premalignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia.

Search methods: Trials were identified through electronic searches of the Cochrane Library, MEDLINE and EMBASE databases, using appropriate subject headings and keywords.

Selection criteria: All randomized controlled trials comparing *H. pylori* eradication therapy with either placebo, no treatment or symptomatic treatment in patients with premalignant gastric lesions.

Data collection and analysis: Data were collected on histological changes of the gastric mucosa and functional parameters of gastric mucosal condition.

Main results: Seventeen randomized controlled trials were included (describing a total of 2,890 patients, range n = 20 to 587 per study). These trials compared *H. pylori* eradication therapy with either placebo, no treatment or acid suppressive medication, and evaluated the effect on gastric mucosal changes after 8 weeks to 6 years follow-up. The majority of trials observed that *H. pylori* eradication had a preventive effect on the progression of atrophic gastritis, especially in trials with a study population of over 100 subjects and follow-up of more than 1 year. The observed effects of *H. pylori* eradication on the progression of intestinal metaplasia were however contradictory, and data on progression of dysplasia were limited. Since outcome measures varied largely between trials and were based on non-interchangeable parameters, quantification of outcomes was not feasible.

Authors' conclusions: This systematic review supports the concept that *H. pylori* eradication prevents disease progression in patients with atrophic gastritis, whereas the evidence in patients with intestinal metaplasia and dysplasia is inconclusive.

BACKGROUND

Description of the condition

Gastric cancer is the fourth most common cancer and second leading cause of cancer related death worldwide. Although the incidence of gastric cancer is declining, the absolute number of new cases per year is increasing, due to ageing of the world population and expansion of high incidence populations. As symptoms are often absent or non-specific, gastric cancer is frequently diagnosed at an advanced stage, with limited therapeutic options. Consequently, gastric cancer carries a poor prognosis, with overall five-year survival of less than 20 percent.[1]

Intestinal type adenocarcinomas account for approximately 60% of gastric cancers, whereas 30% of the adenocarcinomas are of the diffuse type.[2] In contrast to diffuse-type carcinomas, intestinal-type carcinomas have recognizable precursors, which are thought to mark subsequent stages in gastric carcinogenesis. These are defined as atrophic gastritis, intestinal metaplasia, and gastric dysplasia.[3]

Colonization with *Helicobacter pylori* is considered to be an important initial step in this multi-step cascade of gastric carcinogenesis, and may even be a prerequisite for cancer development. However, its role during further progression along the carcinogenic cascade is unknown, and thus also the effect of *H. pylori* eradication on premalignant gastric conditions.

Description of the intervention

H. pylori eradication treatment regimens commonly consist of a combination of antibiotics and acid suppressive medication (see Types of interventions).

How the intervention might work

H. pylori causes chronic inflammation of the gastric mucosa, which can slowly progress through the premalignant stages of atrophic gastritis, intestinal metaplasia, dysplasia to gastric adenocarcinoma. Given its pivotal role in gastric carcinogenesis, eradication of *H. pylori* seems a logical step in the prevention of gastric cancer. Eradication leads to healing of gastritis, which may stop further progression of the cancer cascade.

Why it is important to do this review

Several clinical studies have been published on the potential of *H. pylori* eradication to prevent gastric cancer, and meta-analyses have demonstrated that eradication in *H. pylori*–induced chronic active gastritis significantly reduces gastric cancer risk.[4, 5] In addition, several studies have shown that eradication of *H. pylori* could be cost-effective for gastric cancer prevention.[6, 7] It is unclear whether such intervention would benefit all *H. pylori*-positive subjects irrespective of the condition of their gastric mucosa, or whether patients with premalignant conditions have passed a point of no return. Despite a considerable number of clinical trials, controversy remains whether *H. pylori* eradication benefits patients with premalignant gastric

lesions, i.e. whether *H. pylori* eradication halts the progression and/or causes the regression of premalignant lesions.

Objectives

To assess the effect of *Helicobacter pylori* eradication therapy on different premalignant conditions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria: randomized controlled trials, blinded or unblinded. Studies evaluating the effect of *H. pylori* eradication on premalignant gastric lesions either as a primary or secondary outcome measure were included. Abstracts and unpublished studies were included, provided that a protocol and sufficient data on study design, intervention and outcome were available or could be obtained.

Exclusion criteria: clinical trials without randomization, cross-over studies. We excluded studies in which *H. pylori* eradication was part of a treatment comparison containing additional variables that could not be evaluated separately.

Types of participants

H. pylori-positive subjects with premalignant gastric lesions (atrophic gastritis, intestinal metaplasia, dysplasia) were included. From studies that comprised a mixture of participants, with and without premalignant gastric lesions, we extracted the data concerning participants with premalignant gastric lesions. The *H. pylori* status was considered positive when assessed by any one of the following methods: histology, rapid urease test, culture (from antral/ body biopsies obtained during endoscopy), serology or urea breath test.

Types of interventions

We compared *H. pylori* eradication versus no treatment or placebo, and *H. pylori* eradication versus symptomatic treatment (in particular acid suppressive medication). The *H. pylori* eradication regimen needed to be acknowledged for achieving at least a 50% eradication rate and to consist of one of the following regimens given for at least one week:

1. Proton pump inhibitor (PPI) dual therapy (PPI plus either amoxicillin or clarithromycin) or PPI triple therapy (PPI plus 2 of the following; amoxicillin, macrolide, nitroimidazole)
2. H2-receptor antagonist triple therapy (H2-receptor antagonist plus 2 of the following; amoxicillin, macrolide, nitroimidazole)
3. Bismuth triple therapy (Bismuth salt and nitroimidazole with either amoxicillin or tetracycline)
4. Bismuth quadruple therapy (as bismuth triple therapy, but PPI in addition)
5. Ranitidine bismuth citrate dual/triple therapy (as for PPI)

Types of outcome measures

Primary outcomes: improvement of premalignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia based on repeated histological assessment.

Secondary outcomes: deterioration of premalignant lesions of the gastric mucosa. Other secondary outcomes were functional parameters of gastric mucosal condition (in particular serum pepsinogen level, serum gastrin level, vitamin B12 level, acid secretion), and adverse effects of therapy.

The effect of PPIs on the progression of premalignant gastric lesions is beyond the scope of this review, and will be assessed in the Cochrane Review by Eslami et al.

Search methods for identification of studies

A search was conducted to identify all published and unpublished randomized controlled trials.

Electronic searches

Trials were identified by a search of the following electronic databases - The Cochrane Library, MEDLINE and EMBASE. The electronic search strategy was complemented by manual review of the reference lists of included articles. No language restrictions were applied. Published abstracts from the most recent edition of the following conference proceedings 1) United European Gastroenterology Week (published in Gut), 2) Digestive Disease Week (published in Gastroenterology), 3) European *Helicobacter Pylori* Study Group (abstracts published in Helicobacter), 4) International Gastric Cancer Congress (abstract book) were also manually reviewed. The search strategy for this review was constructed by using a combination of MESH subject headings and text words relating to the use of *H. pylori* eradication therapies in the treatment of premalignant lesions of the gastric mucosa.

To identify randomized controlled trials, the search was combined with the Cochrane highly sensitive search strategy phases one, two, and three as contained in the Reviewer's Handbook (Clarke 2000).

Searching other resources

In addition members of the Cochrane UGPD Group and experts in the field were contacted and asked to provide details of ongoing clinical trials and any relevant unpublished materials.

Data collection and analysis

Selection of studies

The title and abstract of all retrieved references was scanned. The full-text of relevant, eligible studies was collected and further assessed. This was done independently by two reviewers (ACV and ILH). Any discrepancies were resolved by a third reviewer (EJK) and consensus discussion.

Data extraction and management

The following data were extracted:

- General information: title, authors, source, year of publication, full text/ abstract, published/ unpublished, language
- Trial characteristics: RCT, blinding, duration (follow-up), setting
- Study population: in- and exclusion criteria (in particular coexisting gastro-esophageal diseases), number of patients, baseline characteristics, similarity of groups at baseline, region (Asian/ non-Asian)
- Intervention: *H. pylori* eradication method, therapy after eradication failure, treatment of control group (no eradication/ placebo/ symptomatic treatment)
- Outcome measurement: method of assessment of gastric mucosa (histology, endoscopy, functional parameters), method of diagnosing *H. pylori* infection, method of diagnosing *H. pylori* eradication, number and timing of follow-up gastroscopies, number and site of biopsies per gastroscopy
- Outcomes:1) Improvement of premalignant lesions of the gastric mucosa, 2) Deterioration of premalignant lesions of the gastric mucosa, 3) Change in functional parameters of gastric mucosal condition (pepsinogens, gastrin, vitamin B12, acid secretion), and 4) Adverse effects of *H. pylori* eradication therapy

Assessment of risk of bias in included studies

The risk of bias tool as described in the Cochrane Reviewer's handbook was used to assess the methodological quality and risk of bias in the included studies. This involved consideration of six items: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. For each feature the risk of bias was scored into the categories "Low risk", "High risk", or "Unclear risk". This judgement was explained by a description of the design, conduct or observations. The assessment of each study was summarized in the "risk of bias" table.

Measures of treatment effect

A plan for data synthesis was described in the originally published Cochrane Protocol. We planned to calculate improvement as the number of patients in whom histology improved versus the number in whom histology did not change or deteriorated in a fixed-effects meta-analysis. As a secondary outcome, deterioration was planned to be calculated as number of patients in whom histology deteriorated versus in whom histology did not change or improved. Unfortunately, due to reasons described later in this Review the analyses could not be performed.

Alternatively, the results of the trials were reported in a table and discussed in the review. In order to investigate whether the effect of Helicobacter pylori eradication varies according to premalignant stage, subgroup assessment was performed for the different stages of premalignant lesions separately: atrophic gastritis, intestinal metaplasia and dysplasia. In addition, subgroup assessment of studies was performed according to study size (up to 100 randomized participants; over 100 participants), and length of follow-up (follow-up up to 1 year; 1 to 2 years, over 2 years of follow-up).

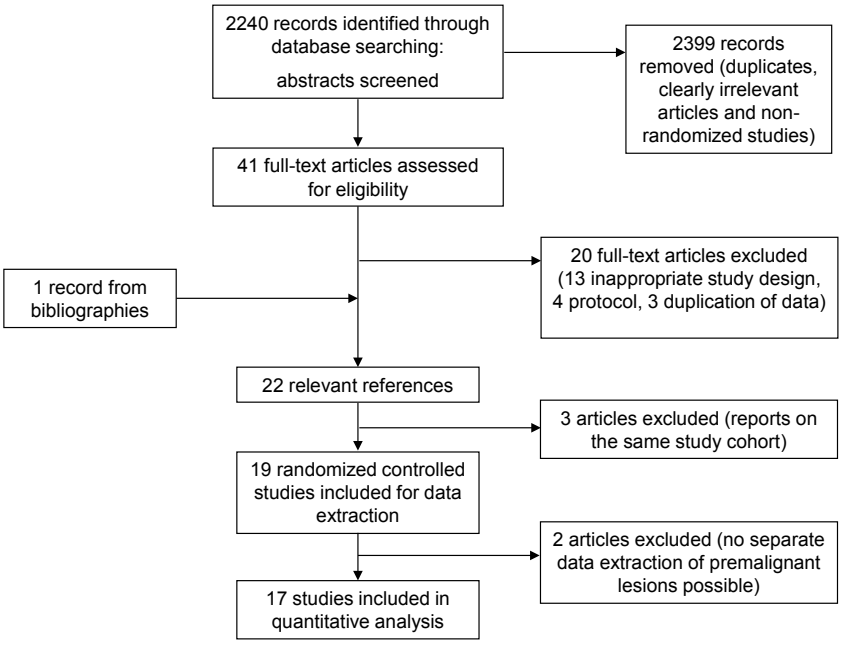

Figure 1. Flowchart of search strategy.

MAIN RESULTS

Description of studies

Results of the search

A total of 2440 references were identified by the search strategy. The results of the electronic database search are described in Figure 1. We excluded 2399 clearly irrelevant references, non-randomized studies, and duplicate references through reading abstracts. Accordingly, 41 references were retrieved in full-text for further assessment.

After further assessment, a total of 20 articles were excluded. Thirteen articles were excluded for reasons of inappropriate study design for this review: 6 had a non-randomized study design[8-13] in five articles the primary outcome measure (histology) could not be evaluated due to missing data at baseline or follow-up;[14-18] and in two studies no appropriate control group was included.[19, 20] Three articles were excluded because they duplicated data of other references.[21-23] Four additional references described the study design of three ongoing or unpublished trials, and were excluded as no data were reported.[24-27] The article describing the results of the protocol published by Stolte was already retrieved for assessment and excluded.[15] The results of the other two unpublished trials could not be retrieved.

After this evaluation of the full-text articles, 21 articles identified by the electronic search fulfilled the inclusion criteria and were assessed in this review.[17, 21, 28-47] One additional reference was identified through handsearching the reference lists of the identified randomized trials and relevant reviews.[48] Therefore, a total of 22 articles were further assessed.

Included studies

From the total of 22 references, five publications described results after different periods of follow-up of two original study cohorts.[21, 30, 37, 41, 44] This rendered a total of 19 randomized controlled trials with unique cohorts for assessment. After assessment, three articles[17, 41, 45] were excluded for reasons described in the section Excluded studies; this resulted in exclusion of only two randomized controlled trials as the article by Mera et al. describes the same study cohort as the included article by Correa.[30] The articles form Sung[44], Leung [37], and Zhou[21] were first assessed separately for data extraction, and thereafter combined as one randomized controlled trial for qualitative assessment.

Finally, a total of 17 randomized studies were included in this review for further qualitative assessment. Details of the included trials are shown in Table 1; Characteristics of included studies. A total of 2890 patients were randomized; 1.493 patients were randomized to receive *H. pylori* eradication treatment and 1.285 patients were randomized to a control group; in one article the results of randomization were not reported for 92 patients.[28] The study size varied from 20[36] to 587.[44] The year of publication of the articles ranged from 1997 to 2010. Ten trials were performed in European countries (1325 patients), 5 trials were performed in Asian

Table 1. Characteristics of included studies.

Author	Region	Baseline condition	Hp diagnosis	Hp eradication confirmation	Intervention			Total N randomized (treatment/ control group)	Age (mean) Men (%) Overall (treatment/ control group)	N with premalignant lesions (treatment/ control group) (worst diagnosis)	Follow-up endoscopy	Biopsy scheme (histological evaluation)	Hp eradication rate in treatment group (overall)
					Treatment group	Length of treatment	Control group						
Arkkila 2006	Finland	Peptic ulcer and AG	Rapid urease test and histology	Rapid urease test, histology and culture (all negative)	Bismuth quadruple therapy; PPI triple therapy; PPI dual therapy	2 wks	Placebo +PPI	92	58 y 66% men	92 IM	8, 52 wks	2 A, 2 C	97%
Ley 2004	Mexico	General population, antibodies to CagA and gastrin levels ≥25 µg/ml	Histology	Histology	PPI triple therapy	1 wk	Placebo	161/155	51/52 y 36%/ 37% men	14/10 AG, 59/63 IM, 2/2 DYS	6 wk and 1 y	3 A, 1 Ang, 3 C	79%
Befrits 2004	Sweden	Gastric ulcer	Culture or Histology	Culture and histology	PPI triple therapy	1 wk	Placebo + omeprazole	64/61	63/62 y 51%/56% men	NS	6, 12, 24 mo	2 A, 2 C	88%
Kuipers 2004	Western-Europe and Australia	GORD	Culture/ Histology	Culture and histology	PPI triple therapy	1 wk	Omeprazole	111/120	61/62 y 49%/ 60% men	NS	1, 2 y	NS	88%
Kamada 2003	Japan	Dyspepsia and atrophic gastritis	Histology, serology and/or UBT	Histology and UBT	PPI triple therapy	1 wk	Placebo	45/45	56/56 y 51%/53% men	45/45 AG	1, 2, 3 y	2 A, 2 C	82%
Correa 2000	Colombia	AG, IM, DYS	Histology	Histology and UBT	Bismuth triple therapy	2 wks	No treatment	120/117	51 y 46% men	NS	3, 6 y	3A, 1C	74%
Sung 2000	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 wk	Placebo	295/292	NS	NS	1 y	2 A, 2 C	89%
Zhou 2003	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 wk	Placebo	276/276	NS	NS	2, 5 y	2 A, 2 C	89%
Leung 2004	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 wk	Placebo	295/292	52 y 48% men	4 AG, 194 IM	1, 5 y	2 A, 2 C	75%

Table 1. *(Continued)*

Author	Region	Baseline condition	Hp diagnosis	Hp eradication confirmation	Intervention			Total N randomized (treatment/ control group)	Age (mean) Men (%) Overall (treatment/ control group)	N with premalignant lesions (treatment/ control group) (worst diagnosis)	Follow-up endoscopy	Biopsy scheme (histological evaluation)	Hp eradication rate in treatment group (overall)
					Treatment group	Length of treatment	Control group						
Monés 2001	Spain	Duodenal ulcer	UBT, rapid urease test and/or histology	UBT	PPI triple therapy	1 wk	Placebo + omeprazole	42/43	NS 79%/76% men	32 IM	5 wks and 12 mo	2 A, 2 C	78%
Schenk 2000	the Netherlands	GORD	Culture or both histology and rapid urease test	Culture and histology (in case indecisive: serology)	PPI triple therapy	1 wk	Placebo + omeprazole	NS (in analysis: 27/30)	NS NS	NS	3, 12 mo	3 A, 4 C	85%
Miwa 2000	Japan	Dyspepsia	Histology or UBT	Histology or UBT	PPI triple therapy	1 wk	Placebo + omeprazole	50/40	53/ 49 y 52%/41% men	NS	3 mo	1 A, 1 C	85%
Gisbert 2000	Spain	Duodenal ulcer	Rapid urease test and Histology, or Culture	Culture and histology	H2-receptor antagonist triple therapy/ Bismuth triple therapy	2 wks	Ranitidine	45/45/45	NS NS	NS (46 AG, 18 IM)	3, 6, 12, 18 mo	2 A	48%
Moayyedi 2000	United Kingdom	Moderate oesophagitis	UBT and Rapid urease test/ Culture/ Histology	UBT	PPI triple therapy	1 wk	Placebo + omeprazole	21/20	NS 78%/58% men	NS	2, 12 mo	2 A, 2 C	78%
Leri 1999	Italy	Dyspepsia and AG	Serology positive, Histology negative	Serology	PPI triple therapy	2 wks	No treatment	10/10	57 y 60%/50% men	10/10 AG (IM NS)	8 wks	2 A, 1 C	86%
Ohkusa 1998	Japan	Hyperplastic gastric polyp	Culture, Histology, UBT, Rapid urease test (2/4 tests positive)	Culture, histology, UBT, rapid urease test (all negative)	PPI triple or dual therapy	NS	No treatment	17/18	55/ 57 y 53%/56% men	17/18 AG (IM NS)	1-3, 7-9, 12-15 mo	NS	88%
Lazzaroni 1997	Italy	Gastric ulcer	Rapid urease test and histology	Histology	PPI dual therapy	2 wks	Placebo + omeprazole	29/30	53/54 y 76%/67% men	NS	2 y	2 A, 3 C	62%

Table 1. *(Continued)*

Author	Region	Baseline condition	Hp diagnosis	Hp eradication confirmation	Intervention			Total N randomized (treatment/ control group)	Age (mean) Men (%) Overall (treatment/ control group)	N with premalignant lesions (treatment/ control group) (worst diagnosis)	Follow-up endoscopy	Biopsy scheme (histological evaluation)	Hp eradication rate in treatment group (overall)
					Treatment group	Length of treatment	Control group						
Tulassay 2010	Hungary	Gastric ulcer	Rapid urease test and 2/3 positive: UBT and/ or histology and/ or culture	UBT and histology	PPI triple therapy*	1 wk	Placebo + PPI	316/ 164	NS NS	NS	4 wks, 6 and 12 mo	2 A, 2C	82% 77%
Yang 2009	Taiwan	GORD	UBT and/or histology	Hp-specific stool antigen	PPI triple therapy	1 wk	ODT or continuous PPI	105/105	43/44 y 57%/63% men	33/27 IM (AG NS)	1, 2 y	2 A, 3 C	90%

A: antrum, AG: atrophic gastritis, Ang: angulus C: corpus, GORD: gastro-esophageal reflux disease, Hp: H. pylori, IM: intestinal metaplasia, NS: not stated, ODT: on-demand therapy PPI: proton pump inhibitor, UBT: urea breath test.

countries (1012 patients), 1 trial in South America (237 patients), and 1 trial in North America (316 patients). Details on sex and age distribution are reported in Table 1. From the total of 1.295 controls, 492 (38%) patients received placebo, no treatment was given to 145 patients (11%), and 658 (51%) patients received treatment with PPI or H2-receptor antagonist (with or without placebo antibiotics).

A histologic diagnosis of atrophic gastritis at baseline was recorded in 219 patients, intestinal metaplasia in 522 patients and dysplasia in 4 patients. However, true numbers of randomized patients with these diagnoses were most likely significantly higher, as these numbers on most advanced premalignant stage were not stated in several articles (Table 1). The most important explanation for these missing data is probably that only five studies aimed to evaluate the effect of *H. pylori* on premalignant gastric lesions as a primary outcome measure and selectively included patients with such a condition,[28, 30, 32, 36, 38] whereas the other trials were either population-based studies [21, 37, 44] or included patients with various gastrointestinal conditions at baseline, including peptic ulcer disease in 6 trials,[28, 29, 31, 34, 40, 43] gastro-oesophageal reflux disease,[33, 35, 42, 49] or other.[39, 48] (Table 1).

Twelve trials used PPI triple therapy to eradicate *H. pylori*, 1 used PPI dual therapy, 1 bismuth triple therapy and 3 diverse regimens. These regimens resulted in eradication rates in the individual studies ranging from 48%[31] treatment with H2-receptor antagonist triple therapy or bismuth triple therapy for 2 weeks) to 97% [28] (PPI triple therapy for 2 weeks). The methods used to diagnose *H. pylori* infection and confirm eradication varied substantially across the trials, details are mentioned in Table 1.

The effect of *H. pylori* eradication on premalignant changes of the gastric mucosa was assessed by endoscopy with biopsy sampling. The interval between *H. pylori* eradication and follow-up endoscopy varied from 8 weeks[36] to a maximum of 6 years.[30] In all trials, antrum biopsies as well as corpus biopsies were obtained, except for the trial of Gisbert[31] in which only antrum biopsies were obtained. In one trial additional biopsies from the angular incisure were obtained.[38] The number of gastric biopsies varied from two[31, 39] to seven[33, 38, 42] (Table 1).

To express the effect of *H. pylori* eradication on premalignant lesions, nine trials reported on histology scores.[21, 28-30, 33, 35, 37, 42-44, 49] These were expressed in various ways: the publications by Sung,[44] Leung,[37] and Zhou[21] expressed the effect of eradication per patient as well as per category of premalignant lesions. Five trials reported on the most advanced histologic lesion in terms of numbers of patients affected at baseline and follow-up.[28, 33, 35, 43, 49] Three trials only recorded percentages of patients with premalignant lesions at baseline and follow-up, without exact number of patients.[29, 30, 42] Two trials expressed the proportion of patients affected by premalignant lesions according to *H. pylori* status at follow-up,[28, 42] whereas seven trials reported proportions in accordance with an intention to treat principle according to assigned treatment group.[21, 29, 30, 33, 35, 37, 43, 44, 50]

Twelve publications reported the effect of *H. pylori* eradication as an overall histological score.[28, 31, 32, 34, 36, 38-40, 42-44, 48] The score that these trials used was often based on the Sydney

System to grade gastritis, including the parameters atrophic gastritis and intestinal metaplasia into the grades "absent", "mild", "moderate" or "severe", [28, 32, 34, 36, 39, 40, 42, 43, 48] although variant scores were developed by others.[31, 38, 44, 49] In addition to the histologic evaluation of premalignant lesions, two trials used pepsinogen or gastrin serology to evaluate the effect of *H. pylori* eradication on the gastric mucosa,[32, 48] and one of these studies reported details on the effect of *H. pylori* eradication on gastric acid secretion.[32]

Excluded studies

The publication by Mera was excluded, as all patients in the control group received *H. pylori* eradication treatment after a follow-up of 6 years, and data before this intervention duplicated the publication by Correa.[30, 41]

The publication by Wong was excluded as no histologic data on premalignant lesions at follow-up were reported, although the methods section mentioned histologic evaluation of lesions at baseline and follow-up.[49]

In addition, the article written by You et al. was excluded as *H. pylori* eradication could not be evaluated separately. In this article, the effect of *H. pylori* eradication could not be differentiated from the effect of a combination of *H. pylori* eradication with vitamin or garlic supplements.[45]

Risk of bias in included studies

An overview of the assessment of the methodological quality of included randomized controlled trials is provided in Table 2 'Methodological quality of included studies'. Overall, 2 trials scored a maximum score on five predefined major criteria[35, 38], and 3 trials scored a maximum score on four out of five criteria.[21, 37, 39, 43, 44, 51] Participant flow was reported by 15 of 17 included randomized trials; with according to these reports a loss to follow-up varying from 0% to 54%. (See below: Incomplete outcome data).

Allocation (selection bias)

A total of nine trials (53%) were considered "truly random" as they mentioned details on randomization, including the method used to generate a random sequence; eight trials (47%) used a computer generated sequence [21, 28, 30, 33-35, 37, 40, 43, 44] , and one trial used a coin method.[38] (See section Methods, subheading Assessment of risk of bias in included studies). Concealment of allocation of patients after randomization was described in five trials, all used sealed envelopes, and this was considered "adequate" according to the predefined criteria.

Blinding (performance bias and detection bias)

Ten trials (59%) had a double-blind design, although details on the method of blinding were not provided. In the trial of Arkkila,[28] patients were blinded by use of placebos, however, details on blinding of the treating physician were not reported. Six trials (35%) did not men-

Table 2. Methodological quality of included studies.

Author	Method of randomization (A/B/C)*	Concealment of allocation (A/B/C)*	Blinding (A/B/C)*	Blinding of pathologist to treatment (A/B/C)*	Participant flow (n lost to follow-up of total study population) (%)	Intention to treat analysis
Arkkila 2006	A	C	B	A	16/92 (17%)	No
Ley 2004	A	A	A	A	68/316 (22%)	Yes
Befrits 2004	C	C	A	A	2/125 (2%)	No
Kuipers 2004	A	C	C	A	NS	Yes
Kamada 2003	C	C	A	A	0 (0%)	No
Correa 2000	A	C	C	A	345/976 (35%)	NS
Sung 2000	A	A	A	A	72/587 (12%)	No
Zhou 2003	A	A	A	A	90/552 (16%)	No
Leung 2004	A	A	A	A	152/587 (26%)	Yes
Monés 2001	A	A	A	C	2/85 (2%)	No
Schenk 2009	C	C	A	A	17/100 (17%)	No
Miwa 2000	C	A	A	A	5/90 (6%)	Yes
Gisbert 2000	C	C	C	A	13/135 (10%)	No
Moayyedi 2000	A	A	A	A	22/41(54%)	Yes
Leri 1999	C	C	C	C	0 (0%)	Yes
Ohkusa 1998	C	C	C	A	0 (0%)	Yes
Lazzaroni 1997	A	C	A	C	NS	No
Tulassay 2010	A	C	A	A	140/480 (29%)	Yes
Yang 2009	C	A	C	A	34/210 (16%)	Yes

** A/B/C-coding as described in Quality assessment. NS: not stated.*

tion any details on blinding of patients or treating physicians.[30, 31, 33, 36, 48, 49] In 15 trials (88%) the pathologist was blinded to the treatment allocation when assessing the outcome measures.

Incomplete outcome data (attrition bias)

Details on loss to follow-up were available in 15 trials (88%). The loss to follow-up varied from 0% after eight weeks to three years follow-up [32, 36, 48] to 54% after 6 years follow-up.[35] Nine trials (53%) performed an intention to treat analysis.

Selective reporting (reporting bias)

It is unclear whether a prespecified plan was available for histological evaluation and analysis of the effect of treatment on premalignant gastric lesions in the vast majority of manuscripts. Only the manuscript by Yang et al. reported data on histologic changes of premalignant gastric lesions as expected.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

The outcomes measures that were used in the randomized controlled trials and the way of reporting the results were highly heterogeneous. Therefore, no quantitative meta-analysis could be performed with available data. The effect of intervention is described in the following paragraphs.

Atrophic gastritis

The effect of *H. pylori* eradication on atrophic gastritis was reported in 16 publications, in one publication only an overall gastritis severity score was reported.[38] A preventive effect of *H. pylori* eradication on the progression of atrophic gastritis, defined as either no change or regression, was reported by 9 trials (total number of included patients n = 1670), whereas 7 trials (total n = 904) showed no preventive effect of *H. pylori* eradication in comparison to the control group (studies showing a preventive effect; [28-30, 32, 33, 35, 42, 44, 49] studies showing no preventive effect.[31, 34, 36, 39, 40, 43, 48] In addition, a preventive effect was in particular reported in studies with larger study populations. Four of the 9 trials with a study population of up to 100 patients reported a preventive effect, as compared to 5 of 7 trials with more than 100 randomized patients. Similarly, the proportion of trials demonstrating a preventive effect increased with longer periods of follow-up. A preventive effect was demonstrated in none of two trials with histologic follow-up up to 3 months[36, 39]; in 3 [28, 35, 44] of 6 available trials with follow-up from 3 months to 1 year; in 3 [29, 33, 49] of 5 available trials with a follow-up of 1 to 2 years; in 2 [30, 32] of 3 trials with longer follow-up (up to 6 years). In the reports of Sung[44], Leung[37], and Zhou[46] a preventive effect of *H. pylori* eradication on progression of atrophic

gastritis was reported after 1 year, however, after 5 years the effect was no longer observed. In trials that prescribed no treatment or placebo to the included control group, a preventive effect was observed in 3 of 4 trials, as compared to 5 of 12 trials in which a PPI or H2-receptor antagonist was prescribed to the control group. Trials with a low risk of bias (i.e. score 4 or 5 A's according to the methodological quality assessment) reported a preventive effect in 2 of 5 trials.

Intestinal metaplasia

The effect of *H. pylori* eradication on intestinal metaplasia was reported in 13 publications. A preventive effect, defined as either no change or regression, was reported in 4 trials (total number of included patients n = 1119),[30, 37, 40, 44, 46, 49] whereas 9 trials (total n = 1255) reported no beneficial effect.[28, 29, 31, 33-35, 42, 43, 48] Larger study size and increased length of follow-up were not clearly associated with reports of a preventive effect of eradication. One of 6 trials with a study population of up to 100 patients reported a preventive effect, as compared to 3 of 7 trials with more than 100 randomized patients. One of 6 trials with histologic follow-up up to 1 year showed a preventive effect,[40] 1 of 5 trials[49] with a follow-up of 1 to 2 years, yet both trials[30, 37, 44, 46] trials with longer follow-up demonstrated a preventive effect. In trials that prescribed no treatment or placebo to the included control group, a preventive effect was observed in 2 of 3 trials, as compared to 2 of 10 trials in which a PPI or H2-receptor antagonist was prescribed in the control group. Trials with a low risk of bias reported a preventive effect in 2 of 3 trials.

Dysplasia

The included trials were not designed to investigate the effect of *H. pylori* eradication on the progression of gastric dysplasia. Only two trials included patients with dysplasia at baseline, however, the number of included patients is unclear from the available publications. Both trials reported no preventive effect after respectively 5 and 6 years of follow-up.[30, 37, 44, 46]

Functional parameters of gastric mucosal condition

Details on functional parameters of gastric mucosal condition were only available from two trials[32, 48] which included relatively small study populations (respectively 37 and 35 patients). Both studies observed a significant decrease in serum gastrin levels after eradication therapy. Kamada et al.[32] also observed an increase in pepsinogen I/II ratio and intragastric pH.

DISCUSSION

Eradication of *H. pylori* is a frequently prescribed therapy in both primary and secondary care, due to the high prevalence of *H. pylori* infection worldwide and its important role in the

etiology of a range of gastric conditions. In respect to this frequent use, beneficial effects of eradication need to unmistakably outweigh associated disadvantages, such as side effects and costs. Eradication of *H. pylori* is commonly accepted as a strategy to prevent gastric cancer,[52] as *H. pylori* infection is an essential step in initiating the gastric cancer cascade. Nevertheless, the role of *H. pylori* may decline during progression of premalignant lesions towards gastric cancer, as indicated by frequent loss of *H. pylori* colonization in the presence of premalignant lesions. This systematic review addresses the issue whether eradication of *H. pylori* halts progression of premalignant gastric lesions.

A total of 17 randomized studies, with a total number of 2890 participants were included in this review. *H. pylori* eradication prevents the progression of atrophic gastritis, defined as either no change or regression of the condition. This finding was reported by the majority of trials, and is further supported by the fact that it was in particular reported by studies with large study populations and long follow-up, i.e. study cohort over 100 participants and/ or with a follow-up of more than one year. In contrast, the reported effects on intestinal metaplasia were conflicting. Only a minority of studies showed a preventive effect, however, both trials with a follow-up longer than 2 years indeed demonstrated a preventive effect. No preventive effect was reported in case of gastric dysplasia, however, only few cases were included in the available studies.

In this review, systematic and quantitative evaluation of available studies was largely hindered. Although planned according to the previously published Review Protocol, the change in proportion of patients affected by premalignant gastric lesions at the end of follow-up could not be evaluated in an overall quantitative analysis. The most important impediment to conducting a systematic and quantitative evaluation is the large variety of outcome measures used in individual studies. These measures are often non-interchangeable, such as prevalence changes and transition percentages, reported either according to treatment allocation or to *H. pylori* status at the end of follow-up (see Included studies and Results). In addition, several trials used an overall score to describe the severity of premalignant conditions and to analyze data, this score was often based on the Sydney System to grade gastritis. The Sydney System is a visual, qualitative score to help the pathologist express the severity of gastritis. The trials used this score as a linear score to quantify the severity of gastritis and perform statistical calculations. However, a linear relation between the grades of gastritis and gastric cancer risk has not been substantiated, and seems highly unlikely as hazard rates show no linear incline with increasing severity of premalignant lesions.[51] Attempts to grade gastritis according to gastric cancer risk have resulted in the development of the OLGA and OLGIM staging systems, according to which the severity and intragastric extent of atrophic gastritis or intestinal metaplasia are combined to evaluate gastric cancer risk.[46, 50] Yet, unless validation studies become available, both gastritis scores and gastritis grades cannot be used as linear scores in statistical calculations.

A second factor that greatly hindered the systematic evaluation of trials was the generally low, and frequently even unclear number of included patients with premalignant lesions in the randomized controlled trials (see Table 1). Therefore, a significant proportion of trials may have been underpowered to demonstrate a beneficial effect of *H. pylori* eradication.

Several factors have interfered with the observations of this review. Firstly, baseline conditions of included patients varied greatly, and may have reflected a different baseline gastric cancer risk, as differences in underlying gastritis pattern may bring about significant differences in cancer risks. For instance, the pangastritis pattern commonly observed in gastric ulcer patients is associated with significantly higher gastric cancer risk, as compared to the antrum-predominant gastritis pattern commonly observed in duodenal ulcer patients.[47] Secondly, follow-up in most studies was relatively short to investigate progression of premalignant lesions (with a maximum follow-up up to 6 years), as progression of premalignant lesions towards gastric cancer generally takes decades. Thirdly, the number of biopsies obtained in individual patients was generally low, potentially leading to imprecise results as a consequence of sampling errors. Fourthly, according to the reported details on methodological quality of the trials, the majority of trials was of mediocre quality according to current standards, as information on important methodological details was not mentioned. The effect of the methodological quality to reach a positive or negative result on the preventive effect of *H. pylori* eradication is uncertain, however, it may certainly blur the results.

SUMMARY OF MAIN RESULTS

A total of 17 randomized controlled trials with a total of 2890 participants were included. These trials showed that *H. pylori* eradication halts the progression of atrophic gastritis, in particular when considering trials with more than 100 participants and/ or with a follow-up of more than one year. The results with respect to the effect of *H. pylori* eradication on intestinal metaplasia were conflicting, with only a minority of studies showing a beneficial effect. *H. pylori* eradication did not prevent progression of gastric dysplasia, however, only few patients were included in the available studies. The effect of *H. pylori* eradication on the progression of premalignant gastric lesions could not be quantified due to the heterogeneity of outcome measures.

Overall completeness and applicability of evidence

Unfortunately, the identified studies use a large variety of outcome measures, as mentioned previously. This hinders an overall quantitative conclusion on the magnitidude of the effect of *H. pylori* eradication on premalignant gastric lesions.

Quality of the evidence

A total of 17 randomized studies, with a total number of 2890 participants were included in this review. The methodological quality of the studies was generally adequate for the method of randomization, blinding of patients, doctors and assessment of the outcome (mostly pathologists). However, details on concealment of allocation, and loss to follow-up were insufficiently provided by the majority of studies. Overall, the majority of trials was of mediocre quality according to current standards.

Potential biases in the review process

In this review, it was attempted to identify all relevant studies, through a search of large databases, without language restriction. However, it is possible that ongoing trials were insufficiently recognized. Therefore, updates will be provided in case new publications are available.

AUTHORS' CONCLUSIONS

Implications for practice

H. pylori eradication harbors great potential for prevention of gastric cancer. Clinical evidence for the prevention of carcinogenic progression in patients with atrophic gastritis is highly suggestive, whereas the evidence in patients with intestinal metaplasia is contradictory. The evidence on dysplasia is scarce, although available evidence shows no preventive effect. Possibly, frequent loss of *H. pylori* colonization in patients with intestinal metaplasia and dysplasia indicates limited benefit from *H. pylori* eradication. At this moment, we advise to consider *H. pylori* eradication for prevention of gastric cancer at the earliest stage of gastric carcinogenesis. However, it must be realized that *H. pylori* eradication may be insufficient to halt gastric carcinogenesis in patients with intestinal metaplasia and dysplasia.

Implications for research

As in many cancers, gastric cancer has a multifactorial pathogenesis. Factors involved in the continuation of carcinogenesis, beyond initiation of the cascade by *H. pylori* infection, need further exploration, in which both clinical research and research on pathogenic molecular pathways is essential. In addition, long-term follow-up data on the effect of *H. pylori* eradication, preferably including data on large numbers of subjects with intestinal metaplasia and dysplasia, are eagerly awaited.

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CHAPTER 9

FOLLOW-UP OF PREMALIGNANT LESIONS IN PATIENTS AT RISK FOR PROGRESSION TO GASTRIC CANCER

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ABSTRACT

Background and study aims: A recent international guideline recommends surveillance of premalignant gastric lesions for patients at risk of progression to gastric cancer. The aim of this study was to identify the role of the distribution and severity of premalignant lesions in risk categorization.

Patients and methods: Patients with a previous diagnosis of atrophic gastritis, intestinal metaplasia, or low grade dysplasia were invited for surveillance endoscopy with non-targeted biopsy sampling. Biopsy specimens were evaluated by pathologists (four general and one expert) using the Sydney and the operative link for gastric intestinal metaplasia (OLGIM) systems, and scores were compared using kappa statistics.

Results: 140 patients were included. In 37% (95% confidence interval [CI] 29%-45%) the severity of premalignant lesions was less than at baseline, while 6% (95% CI 2%-10%) showed progression to more severe lesions. Intestinal metaplasia in the corpus was most likely to progress to more than one location (57%; 95% CI 36%-76%). The proportion of patients with multilocated premalignant lesions increased from 24% at baseline to 31% at surveillance ($P = 0.014$). Intestinal metaplasia was the premalignant lesion most frequently identified in subsequent endoscopies. Intestinal metaplasia regressed in 27% compared with 44% for atrophic gastritis and 100% for low grade dysplasia. Interobserver agreement was excellent for intestinal metaplasia ($k = 0.81$), moderate for dysplasia ($k = 0.42$), and poor for atrophic gastritis ($k < 0$).

Conclusions: Premalignant gastric lesions found in the corpus have the highest risk of progression, especially intestinal metaplasia, which has excellent interobserver agreement. This supports the importance of intestinal metaplasia as marker for follow-up in patients with premalignant gastric lesions.

INTRODUCTION

Gastric cancer is the second leading cause of cancer-related mortality worldwide. This disease has its highest incidences in eastern Asia, eastern Europe and South America. Even though the incidence is declining in various regions, partly because of the decline in *Helicobacter pylori* prevalence, more cases occur every year because of expansion and aging of the world population. The majority of gastric cancers are diagnosed late, leading to a 5-year survival of no more than 25%.[1] This late-stage diagnosis and the resulting low survival, as well as the fact that the majority of gastric cancers are preceded by clearly recognizable precursors has led to many studies on the possibility of screening and surveillance.

Several issues are relevant for the applicability of a screening or surveillance program for gastric cancer. Firstly, it is important to recognize that the majority of patients with *H. pylori* infection and premalignant lesions do not develop gastric cancer. This is in line with a range of other premalignant conditions of the gastrointestinal tract, such as Barrett's esophagus and colorectal adenoma. Therefore, the identification of lower grades of premalignant lesions does not seem to justify surveillance, even though this could lead to early detection and treatment of advanced lesions and early gastric carcinomas.[2-4] Recent guidelines therefore recommend surveillance for those patients who have extensive atrophic gastritis, intestinal metaplasia, or dysplasia.[5] However, even in those patients some may show disease progression, while others remain stable or show regression that may be either true regression, or pseudo regression related to sampling and interobserver variation in histological grading.[6-9]

Secondly, the location, severity, and extent of any precancerous lesions, especially of intestinal metaplasia, are indicators of the risk of developing gastric carcinoma. Previous studies have shown that these factors reflect the chances of either progression or regression of premalignant gastric lesions.[10-14] For example, atrophic gastritis and intestinal metaplasia are diagnosed more often in the antrum than in the corpus, and the lesser curvature is more often affected than the greater curvature.[15-17] Premalignant lesions found in the corpus, however, may be more likely to progress to gastric cancer.[18] Furthermore, individuals with premalignant lesions at multiple locations have a higher risk of progression than those with lesions found in only one location. In addition, precursor lesions extend in a proximal direction, which is more significant along the lesser than along the greater curvature. Because of the gradual progression of these lesions in the presence of persistent *H. pylori* colonization,[19] their prevalence increases with age.[10, 14, 18]

The extent of intestinal metaplasia found in biopsies further indicates the risk of malignant progression. For example, one study reported that the presence of intestinal metaplasia in over 20% of a biopsy specimen is associated with a significant increase in the risk of developing gastric cancer. Furthermore, the risk of gastric cancer is least in patients with sporadic intestinal metaplasia, is higher in patients with more widespread intestinal metaplasia in the antrum or along the lesser curvature, and highest in patients with diffuse intestinal metapla-

sia.[20] The character of the premalignant lesions is a further indication of the risk of malignant progression. In a previous large cohort study, we observed that the risk of progression to cancer within 10 years was 0.8% for individuals with atrophic gastritis, 1.8% for those with intestinal metaplasia and 3.9% for those with low grade dysplasia.[2, 21] However, if the severity, location, and extent of premalignant gastric lesions are to be used as reliable indicators, a uniform biopsy sampling protocol and a uniform, reproducible histological grading system must be applied. Most published studies on the location, severity, and/or extent of precancerous lesions and their possible use as risk indicators have used different biopsy protocols and are not uniformly comparable.[14, 16, 20-23] In most studies, the histopathology scoring has been done by an expert pathologist using established classifications and scores. In routine practice, even when the same biopsy protocol is applied, the scoring results from general pathologists are likely to be less consistent and less stringent.[24-28] All these factors influence the potential benefit of surveillance of patients with premalignant gastric lesions.

The primary aim of this study was to identify the locations, severity, and extent of premalignant lesions in a group of patients previously diagnosed with atrophic gastritis, intestinal metaplasia, or low grade dysplasia, applying a well-known classification and scoring system and extensive biopsy protocol. The secondary aim was to compare the diagnoses of an expert pathologist with those of general pathologists.

PATIENTS AND METHODS

Patient selection

This study was performed in the Erasmus MC University Medical Center in Rotterdam, the Deventer Hospital in Deventer, and the Rijnstate Hospital in Arnhem, all in the Netherlands.

Patients were eligible for inclusion if they were over 18 years of age and had a previous diagnosis of a premalignant lesion within the last 10 years. They were identified in the histopathology database of each hospital. All patients were assessed by two clinical reviewers. Patients with a medical history of upper gastrointestinal cancer, esophageal or gastric surgery, treatment with chemotherapy, age above 82 years, or life expectancy of less than 2 years were not invited to participate in the study. Eligible patients were invited by mail to undergo a surveillance endoscopy at the hospital of first diagnosis.

Patients responding to our invitation letter underwent a surveillance endoscopy between September 2009 and June 2011. Written informed consent was obtained from all patients before the endoscopy. The institutional review boards of all participating hospitals approved this study.

Baseline data collection

Before the upper gastrointestinal endoscopy, patients were asked to complete a structured questionnaire with items on lifestyle factors, medication use, medical history, and family history of gastric cancer.

In addition, information with regard to macroscopic lesions and histopathology from the baseline endoscopy were retrieved from the endoscopy and histopathology reports.

Baseline and surveillance endoscopies

All patients underwent a conventional upper gastrointestinal endoscopy using a standard forward-viewing videogastroscope (Olympus). At the baseline endoscopy, biopsies had been taken using the local protocol, with non-targeted biopsies in the antrum and corpus and targeted biopsies of visible lesions.

At the surveillance endoscopy, biopsies were taken from five standardized intragastric locations for histological assessment according to a previously determined protocol for optimal assessment of the severity and distribution of premalignant gastric lesions (Figure 1).[29] Four biopsy specimens were taken from the antrum, being one from each quadrant (2-3 cm proximal to the pylorus), two from the angulus, two from the corpus lesser curvature, two

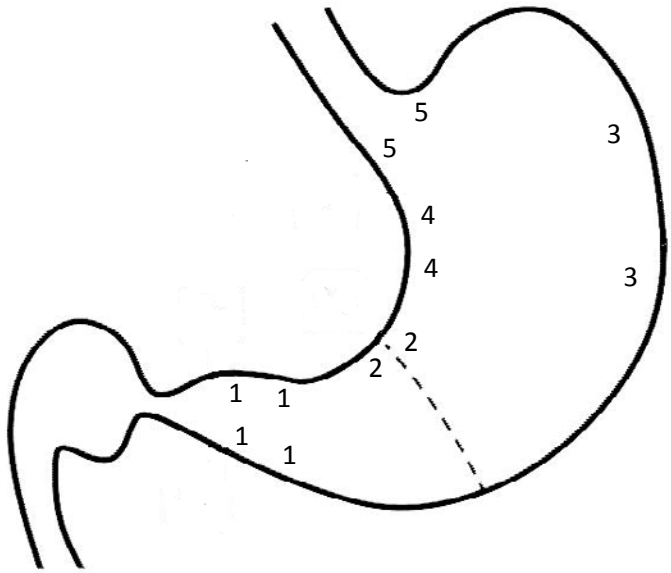

Figure 1. Biopsies were taken from five standardized intragastric locations for histological assessment according to a previously determined protocol for optimal assessment of the severity and distribution of premalignant gastric lesions.[29] 1: antrum (four quadrants), 2: incisura angularis, 3: corpus greater curvature, 4: corpus lesser curvature, 5: cardia.

from the corpus greater curvature, and two from the cardia. In the case of endoscopic abnormalities or visible lesions in the stomach, further targeted biopsy specimens were obtained.

Histological assessment from the surveillance endoscopy

The histopathological protocols were the same in all three hospitals. The biopsy specimens from separate locations were put in separate containers, fixed in buffered formalin and embedded in paraffin. Three sections were scored per biopsy specimen Each block per gastric biopsy was cut at three levels, 30%, 50% and 70%, which corresponds to 1.3,1.0, and 0.7 mm, with each biopsy being 2 mm thickness. Slide sections were stained with hematoxylin and eosin.

The biopsy specimens were assessed for each intragastric location by the local pathologist and scored for the presence of *H. pylori*, atrophic gastritis, intestinal metaplasia, and dysplasia. All specimens were then reassessed by an expert pathologist (K.B.) who was blinded to patient data, endoscopic findings, and the baseline and follow-up histological diagnoses of the general pathologist.

Scoring was done according to the updated Sydney classification system.[25] *H. pylori* density, acute inflammation (neutrophil infiltration), chronic inflammation (mononuclear infiltration), atrophic gastritis, and intestinal metaplasia were scored separately from 0 (absent) to 1 (mild), 2 (moderate), and 3 (marked). In addition the Vienna system was used to score dysplasia, from low grade to high grade and neoplasia.[26]

Subsequently, the severity and distribution of intestinal metaplasia was evaluated using the operative link on gastric intestinal metaplasia (OLGIM) system and classified into four stages (I to IV; Table 1).[24] The OLGIM scores were calculated for patients with a diagnosis of intestinal metaplasia in at least one biopsy. The antral OLGIM score was calculated by using the average score (mild, moderate, or marked) of the antrum and angulus, whereas the corpus OLGIM score was based on the average score of the corpus lesser and greater curvature.

Table 1. The operative link on gastritis assessment with intestinal metaplasia (OLGIM) staging system. (Adapted from Capelle et al. Gastrointest Endosc 2010[24]).

	Corpus intestinal metaplasia score			
	No (score 0)	Mild (score 1)	Moderate (score 2)	Severe (score 3)
Antrum intestinal metaplasia score				
No (score 0)	Stage 0	Stage I	Stage II	Stage II
Mild (score 1)	Stage I	Stage I	Stage II	Stage III
Moderate (score 2)	Stage II	Stage II	Stage III	Stage IV
Severe (score 3)	Stage III	Stage III	Stage IV	Stage IV

For the calculations, we took into account the most severe premalignant lesion. Patients with atrophic gastritis and evidence of intestinal metaplasia were included in the group with intestinal metaplasia.

Statistical analyses

Continuous variables were reported as mean and standard deviation (SD) or median and 25th to 75th percentiles, whereas categorical variables were reported as counts and percentages.

Chi-squared tests and *t* tests were applied to evaluate clinical, macroscopic and histological parameters in patients with different OLGIM stages and different Sydney scores. Furthermore chi-squared and *t* tests were used for univariate analysis of possible risk factors for the locations and extent of the premalignant lesions. Logistic regression was then applied to the possible risk factors and differences between patient groups with a p-value <0.05 in the univariate analysis. A two-sided p-value <0.05 was considered to be statistically significant. Interobserver agreement was determined by using kappa statistics.[30] Kappa statistics were evaluated for the occurrence of atrophic gastritis, intestinal metaplasia, and low-grade dysplasia in the non-targeted and targeted biopsies. Analyses were performed using SPSS software, version 15 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Evaluation of the electronic data records of the three participating hospitals revealed 344 patients with premalignant lesions, of whom 76 were excluded because of a previous malignancy of the upper gastrointestinal tract (n=36) or an estimated life expectancy of less than 2 years (n=40). The remaining 268 patients met the inclusion criteria and were approached by means of an information letter only or by the treating physician and an information letter. Eventually 140 patients (52%) consented and were included (72 men, 68 women; median age 64 years, interquartile range [IQR] 50–80).

Of the patients, 113 (79%) were of Caucasian descent (Table 2). A total of 41 patients (29%) reported a previous ulcer, and 65 (46%) *H. pylori* infection with 91% of these having received treatment. Proton pump inhibitors (PPIs) were used at least daily by 54%, while 25% used non-steroidal anti-inflammatory drugs (NSAIDs) regularly.

At initial endoscopy, 7% of patients had been diagnosed with atrophic gastritis, 80% with intestinal metaplasia, and 13% with low grade dysplasia as the most severe premalignant lesion. The median age at baseline diagnosis of the premalignant gastric lesion had been 58.6 years (IQR 43-74). The premalignant lesions at baseline had been confined to the antrum in 59%, and to the corpus in 16%, whereas the remaining 24% had lesions located both in antrum and corpus.

Table 2. Baseline characteristics in 140 patients with previously diagnosed gastric lesions who underwent a surveillance endoscopy.

	Overall N=140*
Gender n (%)	
Male	72 (51%)
Female	68 (49%)
Age, years	
Mean (SD)	63.0 (10.7)
Range	31.8–81.3
Age at diagnosis of premalignant lesion, years	
Mean (SD)	57.7 (10.8)
Range	29.3–77.7
Most severe premalignant lesion, n (%)	
Atrophic gastritis, n (%)	10 (7%)
Intestinal metaplasia	112 (80%)
Low grade dysplasia	18 (13%)
Ethnicity, n (%)	
Caucasian	113 (81%)
African	21 (15%)
Other	6 (4%)
BMI, kg/m^2 (135 patients)	
Mean (range)	26.0 (16.2–45.3)
Patients, n (%)	
<20	7 (5%)
20–25	53 (39%)
25–30	53 (39%)
>30	21 (16%)
Smoking (132 patients)†	
Never	45 (33%)
<10 pack-years	15 (12%)
10–20 pack-years	14 (11%)
>20 pack-years	58 (44%)
Alcohol consumption, n (%)	
0–1 units/day	86 (62%)
2–3 units/day	21 (15%)
>3 units/day	33 (23%)
NSAID, n (%)	
<1/week	104 (74%)
1 daily	32 (23%)
>1/day	4 (3%)

Table 2. (Continued)

	Overall N=140*
PPI, n (%) (138 patients)	
<1/week	63 (46%)
1 daily	60 (44%)
>1/day	15 (10%)
History of *Helicobacter pylori*, n (%)	
Yes	65 (46%)
No	75 (54%)
History of gastric ulcer	
Yes	41 (29%)
No	99 (71%)
Family history of gastric cancer	
Yes	39 (29%)
No	100 1%)

** Data of 140 patients or otherwise stated. †One pack-year is defined as 20 manufactured cigarettes (one pack) smoked per day for 1 year.*
SD: standard deviation, BMI: body mass index, NSAID: non-steroidal anti-inflammatory drug, PPI: proton pump inhibitor.

Surveillance endoscopy

The surveillance endoscopy was performed a mean 3.3 years (SD 2.8) after the baseline diagnosis of a premalignant change of the gastric mucosa. Evidence of persistent *H. pylori* infection was found in 27 patients (19%).

Table 3 presents data on the most advanced premalignant lesions found during surveillance endoscopy, as assessed by the expert pathologist. In the majority of patients (90/140) intestinal metaplasia was diagnosed as the most severe lesion. High grade dysplasia and gastric cancer were diagnosed in one patient each. The latter patient had a diffuse gastric carcinoma identified in the biopsies of both the lesser and greater curvature and was sched-

Table 3. Most severe premalignant lesion found by histopathology of biopsies taken at surveillance endoscopy in 140 patients previously diagnosed with premalignant gastric lesions.

	Patients	
	n	%
No premalignant lesions	38	27
Atrophic gastritis	3	2
Intestinal metaplasia	90	65
Low grade dysplasia	7	5
High grade dysplasia/gastric cancer	2	1

uled for surgery. The patient with high grade dysplasia was scheduled for stringent follow-up endoscopy in the absence of any macroscopic lesion.

In addition to the non-targeted biopsies, in 17 patients (12%) targeted biopsies were obtained from visible lesions or suspect areas of macroscopic intestinal metaplasia. The histopathology of these targeted biopsies was scored as severe intestinal metaplasia in 12 patients. In four patients only gastritis was diagnosed and in one patient low grade dysplasia was diagnosed together with severe intestinal metaplasia.

Intragastric locations and extent of intestinal metaplasia

The median Sydney score for intestinal metaplasia was highest at the lesser curvature of the corpus (2); the median Sydney score for atrophy was highest in the biopsies taken from the lesser and greater curvature of the corpus and the cardia (2) (Table 4).

Of the patients with intestinal metaplasia, 47% had intestinal metaplasia only in the antrum or angulus; 10% had intestinal metaplasia restricted to the corpus or cardia; 16% had intestinal metaplasia in two locations; and 28% had intestinal metaplasia in more than two locations.

Table 4. Histopathology findings at surveillance endoscopy using the modified Sydney classification: distribution of gastritis and premalignant lesions, presented as median Sydney System scores, where: 0, none; >0 to 1, mild; >1 to 2, moderate; >2 to 3 severe.

	Helicobacter pylori (n = 25)	Neutrophils (n = 25)	Monocytes (n = 135)	Atrophy (n = 37)	Intestinal metaplasia (n = 99)
Antrum	1.5	0.5	1	1	0.75
Angulus	2	1	1	1	1.5
Corpus: lesser curvature	1	1	1	2	2
Corpus: greater curvature	1	1	1	2	1.5
Cardia	1	1	1	2	1

The OLGIM scores were calculated for patients with a diagnosis of intestinal metaplasia in at least one biopsy, i.e., 99 patients. The majority of patients were categorized as OLGIM stage I or II; 48% and 33% respectively, and 19% of patients scored OLGIM stage III or IV (Figure 2). Of the patients with an OLGIM stage III or IV, 94% had intestinal metaplasia as baseline diagnosis of whom 33% had baseline intestinal metaplasia in more than one location.

Surveillance endoscopy compared with baseline endoscopy

Regression and progression of premalignant gastric lesions were scored both in terms of severity as well as extent. Table 5 presents progression and regression in terms of disease severity compared to baseline, defined as most advanced stage in the histological cascade towards cancer. The patients with intestinal metaplasia at baseline showed least regression

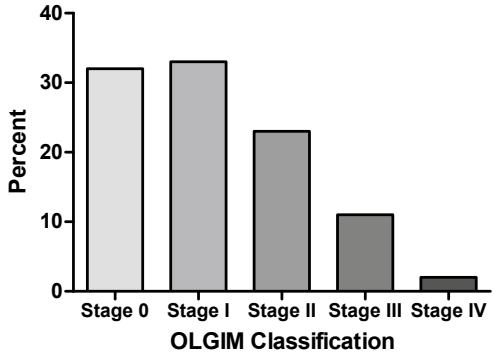

Figure 2. Intestinal metaplasia at follow-up surveillance endoscopy. Operative link on gastritis assessment with intestinal metaplasia (OLGIM) stages[24] for all patients. As a uniform biopsy protocol is needed for application of the OLGIM system, this scoring could be done only at the surveillance endoscopy.

and a small number of patients (2.7%) showed progression to low grade dysplasia, high grade dysplasia, or carcinoma. In 37% (95% confidence interval [CI] 29%-45%) the severity of premalignant lesions was less than at baseline, while 6% (95% CI 2%-10%) showed progression to more severe lesions (can be calculated from table 5).

Table 6 demonstrates the progression and regression of the extent of intestinal metaplasia. By comparing the histopathological findings at the different biopsy sites at baseline endoscopy with that at surveillance endoscopy we could compare the intragastric extent of premalignant lesions at baseline with that at surveillance endoscopy. At inclusion 76% of patients had intestinal metaplasia in one location, 59% in the antrum and 17% in the corpus, while at surveillance the numbers of patients with intestinal metaplasia in one location was 69%. A third of the patients with intestinal metaplasia found at baseline only in the antrum, showed no intestinal metaplasia at all at surveillance and spread to more than one location in 24% (Table 6). The patients with intestinal metaplasia found at baseline only in the corpus, showed no intestinal metaplasia in 4%, while 57% showed progression to more than

Table 5. Progression or regression of premalignant gastric lesions in terms of most severe lesion.

	Surveillance endoscopy					
	Normal	Gastritis	Atrophic gastritis	Intestinal metaplasia	LGD	HGD/ carcinoma
Baseline endoscopy						
Atrophic gastritis (n=9)	0	44.4% (4)	0	55.6% (5)	0	0
Intestinal metaplasia (n = 113)	4.4% (5)	20.3% (23)	1.8% (2)	70.8% (80)	0.9% (1)	1.8% (2)
LGD (n = 18)	5.6% (1)	22.2% (4)	5.6% (1)	66.6% (12)	0	0

LGD: low grade dysplasia, HGD: high grade dysplasia.

Table 6. Progression and regression of the intragastric extent of intestinal metaplasia as seen at a surveillance endoscopy in 140 patients with a previously diagnosed malignant lesion. Actual numbers are shown in parentheses.

	Surveillance endoscopy						Change from baseline	
	None	Antrum only	Corpus only	Cardia only	2 locations	>2 locations	Progression (to>1 location) (*>2 locations)	Regression
Baseline endoscopy								
Antrum only 59% (83/140)	36% (30)	39% (32)	1% (1)	1% (1)	8% (6)	16% (13)	24%	36%
Corpus only 17% (23/140)	4% (1)	26% (6)	9% (2)	4% (1)	22% (5)	35% (8)	57%	4%
>1 location 24% (34/140)	20% (7)	30% (10)	8% (3)	6% (2)	15% (5)	21% (7)	21%*	64%
Total	27% (38)	34% (48)	4% (6)	3% (9)	11% (6)	20% (28)		

one location. Table 6 shows that the premalignant lesions had spread to significantly more locations in the surveillance endoscopy than at inclusion. At inclusion multifocal intestinal metaplasia was identified in 24%, this proportion increased to 31% found at surveillance endoscopy (p=0.014).

OLGIM stage

None of the patients with an OLGIM stage of III and IV progressed to dysplasia or cancer. The majority of these patients however did show greater extent of intestinal metaplasia. In 67% of them, intestinal metaplasia was observed in more biopsies from different areas than at baseline, in 28% it remained constant, and in 5.6% the intragastric extent was less than diagnosed at baseline. The differences between the intragastric extent at baseline and at follow-up were not significant (p=0.22).

Risk factors

We analyzed possible risk factors for progression of severity and extent of premalignant lesions. No correlations were found between sex, age, body mass index (BMI) and an OLGIM stage of III or IV. Patients with an active or previous *H. pylori* infection less often had an OLGIM stage of III or IV, than patients who had never been diagnosed with *H. pylori* infection (33% vs. 62%, p=0.09). A previous or active *H. pylori* infection were both significantly correlated (p=0.05) with progression of disease severity (Table 7). This observation, combined with the

Table 7. Possible risk factors for most severe lesion at surveillance endoscopy. Data analyzed from 140 patients with previously diagnosed gastric lesion.

Risk factor	*P* value
Sex	0.608
Ethnicity	0.327
Smoking > 20 pack years*	0.373
Alcohol >2 units a day	0.318
Family history positive for gastric cancer	0.966
BMI > 25 kg/m^2	0.05
Current or past *Helicobacter pylori* infection	0.05

** One pack-year is defined as 20 manufactured cigarettes (one pack) smoked per day for 1 year.*

lower *H. pylori* prevalence among OLGIM III and IV individuals, is compatible with previous observations that individuals tend to lose signs of *H. pylori* colonization once they develop severe, widespread atrophy and metaplasia.[19] No other risk factors for disease progression were identified. Only the inclusion diagnosis correlated significantly ($p < 0.001$) with progression or regression during surveillance endoscopy. Patients with low grade dysplasia at inclusion more often showed regression (94%) than those with atrophic gastritis at baseline (44%) or intestinal metaplasia at baseline (24%).

Interobserver agreement

We compared the diagnoses of the single expert pathologist with the four general pathologists using the biopsy specimen of 140 patients. Overall, agreement between the pathologists was poor for atrophic gastritis ($k < 0$), almost perfect for intestinal metaplasia ($k = 0.81$), and moderate for dysplasia ($k = 0.42$). Table 8 presents the agreement for the overall diagnosis, as well as the agreement for each intragastric location based on non-targeted biopsies.

Table 8. Interobserver agreement (kappa values), for the overall diagnoses and according to intragastric location, among one expert and four general pathologists. Biopsy samples were taken from 140 patients (see text for details).

	Overall	Antrum	Angulus	Corpus greater curvature	Corpus lesser curvature	Cardia
Atrophic gastritis	–0.007	–0.061	0.036	–0.036	–0.027	–0.041
Intestinal metaplasia	0.805	0.686	0.755	0.669	0.587	0.602
Dysplasia	0.478	0.229	1.0	*	0.663	*
LGD	0.421	0.319	1.0	*	*	*
HGD	0.663	*	*	*	0.663	*

** No measurement of agreement can be computed since at least one variable is a constant. LGD: low grade dysplasia, HGD: high grade dysplasia.*

DISCUSSION

This study focuses on several important issues in the field of premalignant gastric lesions. Firstly, we have demonstrated that a previous diagnosis of atrophic gastritis, intestinal metaplasia, and low grade dysplasia, obtained without the use of extensive biopsy protocol, is inadequate for provision of reliable data on severity and extent of any premalignant lesions. Histopathologic assessment according to the protocol as applied in this study provides an overview of the true spread and severity of the premalignant lesions. Moreover, the use of the OLGIM scoring is then helpful for disease classification and selection of patients at highest risk for progression to high-grade dysplasia and cancer. This helps to identify that small proportion of patients for whom surveillance is appropriate.[1] In our population, this consisted of 13% of patients, namely those with an OLGIM stage of III or IV. Secondly, the interobserver agreement between the general pathologists and the expert pathologist varies greatly with regard to each type of premalignant lesion, but excellent agreement was seen for intestinal metaplasia. This confirms the importance of using intestinal metaplasia as a primary histopathology parameter.

The updated Sydney System is a widely applied biopsy protocol. However, some studies have demonstrated that this protocol does not reflect the actual presence of intestinal metaplasia.[11, 29] Therefore we have chosen to apply a more extensive protocol that reflects all gastric regions known to be involved in the development of premalignant gastric lesions and possible malignant degeneration. Detection of premalignant gastric lesions might be difficult because they represent mostly an incidental finding in patients who undergo diagnostic endoscopy using an appropriate gastric mapping protocol with biopsy sampling. Since most low-incidence countries do not so far apply surveillance for patients with these lesions, a large proportion of patients will never be re-evaluated. With our study, we therefore tried to demonstrate the consequence of this practice. In our patients we see that the initial findings do not reliably predict the location, severity, and extent of the premalignant lesions. Most striking is the fact that an inclusion diagnosis of low grade dysplasia showed regression in 67% to intestinal metaplasia and in the rest to atrophic gastritis and even normal mucosa during surveillance endoscopy.

Our data show that the course of premalignant lesions seen during clinical surveillance shows both progression and regression. This is also known from previous cohort studies on *H. pylori* gastritis.[19] In several studies some evidence on possible regression of intestinal metaplasia is reported. However, it seems a contradiction to describe the regression of low grade dysplasia. The apparent regression of lesions can either true regression or the result of misclassification (interobserver variability). The fact remains that, even with an extensive biopsy protocol, in a majority of cases the most advanced diagnosis may become less severe with further surveillance. This may be a favorable prognostic factor for such patients compared with those patients diagnosed repetitively with premalignant lesions.

We demonstrated that the intraobserver and interobserver agreement for atrophic gastritis is poor. Therefore, an alternative risk score system using intestinal metaplasia instead of atrophic gastritis was developed, namely the OLGIM staging system.[24] This scoring system is easily applicable as a risk indicator for future malignant progression of intestinal metaplasia. Our results demonstrate that intestinal metaplasia is the most identified premalignant lesion in subsequent endoscopies, which can be explained by the uniformity in scoring this lesion and the more easy identification of this lesion. Since we expected no significant change in the interobserver variability over time, we expect the findings at surveillance endoscopy in interobserver variability to reflect those at baseline. In our study, we applied the OLGIM scoring and identified the 19% of patients (n=27) at highest risk for progression to high-grade dysplasia and cancer. Longer follow-up is necessary to conclude whether this system can be used as the sole selection tool to identify patients for surveillance. The mean follow-up period in our study was 3.3 years. This period was in line with the recommendations in the recent guidelines on the management of premalignant gastric lesions. Our study therefore offers an insight into the changes that occur during such an interval as recommended by the recent guideline.

One limitation of this study is the fact that the baseline and surveillance endoscopy used different biopsy protocols, with the routine approach at baseline, and the more extensive study protocol at follow-up. This implies that data on disease progression and regression may have been biased by this confounder. Most importantly however, this does not preclude the further use of the standard protocol in daily clinical practice, and simultaneously confirms the usefulness of the extensive protocol for surveillance assessment. A second limitation of our study is that we used regular white-light endoscopy both at baseline and at surveillance. Recent guidelines recommend considering the use of narrow-band imaging for assessment of premalignant gastric lesions.[5] However, this is not routine practice in most countries, including the Netherlands. Since it was our goal to reflect daily practice, we deliberately used white-light endoscopy at surveillance also. Adherence to the guideline recommendation,[5] with wider availability of narrow-band imaging will likely improve the delineation and surveillance of atrophy and intestinal metaplasia of the stomach.

Moreover, we chose not to apply special stains for subtyping of intestinal metaplasia, since it has not been convincingly shown that this has clinical relevance. This is in accordance with the guidelines that note that specific staining is of no proven clinical benefit.[5]

It is striking in our study that the majority of patients had intestinal metaplasia as the most severe premalignant lesion (76%). This might seem to limit the power of our study. However, as has been demonstrated in earlier studies, the majority of patients fulfilling our inclusion criteria show intestinal metaplasia in their biopsies and we therefore believe that this is not a limitation of our study but a representation of the true numbers.[31]

Even though we have seen a decline in the incidence and prevalence of gastric cancer (at least in the Western world), to date the disease still occurs as frequently in Western

countries as other important gastrointestinal cancers such as esophageal adenocarcinoma and pancreatic cancer. From a global perspective, the disease is even in the top three of the most common gastrointestinal malignancies, together with colorectal and liver cancer. Despite significant attempts to improve treatment, the prognosis of gastric cancer is poor and prevention or early diagnosis can help to reduce considerably the morbidity and mortality of gastric cancer. This underlines the importance and clinical significance of these data. Moreover recent studies have demonstrated that the decline in *H. pylori* infection has not continued in the last 15 years; consequently we expect to see a stabilization of the incidence of premalignant gastric lesions and gastric cancer.[32, 33]

In conclusion, this study demonstrates that surveillance endoscopy with more extensive biopsy sampling provides adequate assessment of the locations and intragastric extent of premalignant gastric lesions. It further shows that regression of premalignant lesions is common during surveillance of these patients, and that use of the OLGIM system allows identification of a small subgroup at highest risk for progression to high grade dysplasia and cancer. Future prospective studies will need to further reveal the impact and burden of surveillance, as well as the optimal surveillance intervals.

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CHAPTER 10

TREND BREAKS IN INCIDENCE OF NON-CARDIA GASTRIC CANCER IN THE NETHERLANDS

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ABSTRACT

Introduction: The incidence of gastric cancer declined over the past decades. Recently, unfavorable trend breaks (i.e. rise in incidence) were seen for non-cardia cancer in younger age groups in the US. It is unclear whether these also occur in other Western countries. We aimed to analyze the gastric cancer incidence trends by age, sex, subsite and stage in the Netherlands.

Methods: Data on all patients with gastric adenocarcinoma diagnosed from 1973-2011 (n=9,093) were obtained from the population-based Eindhoven cancer registry. Incidence time trends (European Standardized Rates per 100,000) were separately analyzed by sex, age group (<60, 60-74, and >75 years), subsite, and pathological stage. Joinpoint analyses were performed to discern trend breaks, age-period-cohort analyses to examine the influence of longitudinal and cross-sectional changes.

Results: The incidence of non-cardia cancer declined annually by 3.5% (95%CI -3.8; -3.3). However, in males <60 years, the incidence flattened since 2006, and tended to rise in those >74 years. This pertained to corpus cancers. The incidence of cardia cancer peaked in 1985 and decreased subsequently by 2.4% (95%CI -3.2; -1.5) yearly. The absolute incidence of stage IV disease at first diagnosis initially decreased, but then remained stable over the past 15-20 years.

Conclusions: The incidence of non-cardia cancer declined over the past four decades in the Netherlands, but now seems to be stabilizing particularly in males. Unfavorable trend breaks are seen for corpus cancer in younger and older males. The trend breaks in the Netherlands are however not similar to those observed in the US.

INTRODUCTION

Gastric cancer remains the second leading cause of death from cancer worldwide, although the incidence has steadily declined over the past sixty years.[1-3] This may reflect the simultaneous cohort-specific decrease in *Helicobacter pylori* acquisition, its most important carcinogen.[4] Consequently, a further decline in gastric cancer incidence in young persons would be expected.

Recent incidence trend studies, however, reveal an unfavorable trend break. The incidence of non-cardia gastric cancers in younger age groups (< 50 years) has stabilized or even started to rise again in the United States since 1977.[5, 6] Furthermore, the incidence of cardia cancer has increased over the past decades in Asia.[5, 7, 8] The cause and extent of these discrepant trends are unknown.

We therefore aimed to closely analyze the gastric cancer incidence trends by age, sex, subsite and stage in the Netherlands, to find out whether the observed trends in the US are taking place in Western European countries as well. Detailed trend studies provide essential information for the understanding of recent patterns and are necessary to anticipate future trends and guide etiological investigations.

METHODS

Study population

For our analyses we used data from the Eindhoven Cancer Registry, which has prospectively collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955.[9] Until 1988, the registry area covered 1.0 million inhabitants. In both 1988 and 2001 the region has been expanded and covers nowadays a population of 2.4 million inhabitants (~15% of the Dutch population). The area offers good access to specialized medical care in 10 general public hospitals and is served by 6 regional pathology laboratories. Trained registry personnel actively collect data on diagnosis, stage, treatment and survival from the medical records after notification by pathologists and medical registration offices. Tumors were registered according to the ICD-O (International Classification of Diseases for Oncology) edition of the respective period.[10]

In this study, we included all patients newly diagnosed with gastric cancer between 1973 and 2011. Only adenocarcinomas were included (morphology codes 8010, 8012, 8020, 8021, 8140, 8141, 8142, 8143, 8144, 8145, 8200, 8201, 8210, 8211, 8221, 8230, 8255, 8260, 8261, 8263, 8310, 8440, 8453, 8470, 8480, 8481, 8490, 8500, 8512, 8560, 8570, 8574, 8890). This included 95% of the total number of gastric carcinomas. We defined the following subsite categories: 1) cardia, 2) fundus, 3) corpus (including lesser and greater curvature), 4) antrum,

5) pylorus, 6) overlapping sites, and 7) unspecified subsite (NOS). Because of changing coding rules, incidence rates of the subsites are shown from 1985 to 2011.

Stage at diagnosis was primarily based on the pathologists' report, using the TNM classification according to the edition of the respective period,[11] or when missing, complemented by the clinical stage. Incidence rates are shown from 1975-2011, because stage was included in the registry from 1975.

Statistics

Incidence rates were calculated for the period 1973–2011. Age-adjustment was performed by direct standardization according to the European Standard Population (European Standardized Rates [ESR], per 100,000 person-years). Results are presented as 3-year moving averages (for 1973 and 2011 as 2-year moving averages). Incidence rates were calculated by subsite, sex, age group (<60, 60-74 and 75 and older), and stage.

Temporal changes in incidence rate were evaluated by calculating the annual percentage change (APC) and the corresponding 95% confidence interval (CI) using joinpoint software. Joinpoint is statistical software for the analysis of trends using joinpoint models, that is models where several different lines are connected together at the "joinpoints". A regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and x = calendar year; then $APC = 100 * (e^a - 1)$). Joinpoint regression analyses were performed to discern significant changes in the trend which we defined as trend breaks, and, if present, when they occurred.[12] In case a trend break was observed after a period of decreasing incidence, we defined this as an unfavorable trend break as the incidence then started to flatten or even increase.

Age-period-cohort analyses were performed to jointly examine the influence of longitudinal and cross-sectional changes.[13, 14] Patients aged younger than 20 (0.01% of all cases) and 90 or older (1%) were excluded from these analyses because of the small number of cases in these groups. The population was divided into 5-year age groups (i.e. 20-24, …, 85-89), 5-year calendar periods (except the first and last period: 1973-1980, 1981-1985, …, 2001-2005, 2006-2011) and matching 10-year birth cohorts (except the first and last cohorts due to longer periods of diagnosis: e.g. the oldest group in the first period (1973-1980) was born 1883-1895, …, youngest group in last period (2006-2011) was born 1981-1991). The GENMOD procedure of the SAS package was used to fit a series of Poisson regression models, to estimate the separate effects of age, time of diagnosis and birth cohort on the trend in incidence, according to the models described by Clayton and Schifflers.[13, 14] To test the goodness-of-fit of the models with the observed incidence rates and to test the models against one another, deviances and differences between the deviances with appropriate degrees of freedom were used. The following models were fitted: the age, age-drift, age-period, age-cohort, and age-period-cohort model. Drift is a linear component of the overall rate of change in the

incidence rate with time that describes models for which the age-period and age-cohort parameters fit the data equally well. Such a model thus serves as an estimate of the rate of change of a regular trend.[14] Trends in incidence were evaluated according to gender and subsite (cardia versus non-cardia).

Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, U.S.A.). P-values were two-sided and values <0.05 were considered significant. The software for the joinpoint analyses was the Joinpoint Regression Program, version 3.5.4 of the National Cancer Institute.

RESULTS

Overall trends

Between 1973 and 2011 a total of 9,093 gastric adenocarcinoma cases were registered in the Eindhoven Cancer Registry (Table 1). In total, 49,707,736 person years were accumulated in the cohort. The age-adjusted incidence rates of non-cardia gastric cancer declined by 3.5% (95% CI -3.8; -3.3) per year from 50 to 12 per 100,000 person years. In males, the incidence of non-cardia gastric cancer appeared to stabilize in recent years, although not yet confirmed by trend breaks. The age-adjusted incidence rate of cardia cancer increased by 8.0% (95% CI 5.1; 11.1) per year from 1973 to 1985 and decreased subsequently by 2.4% (95% CI -3.2; -1.5) per year. These patterns were similar in both sexes (Figure 1), although in women the

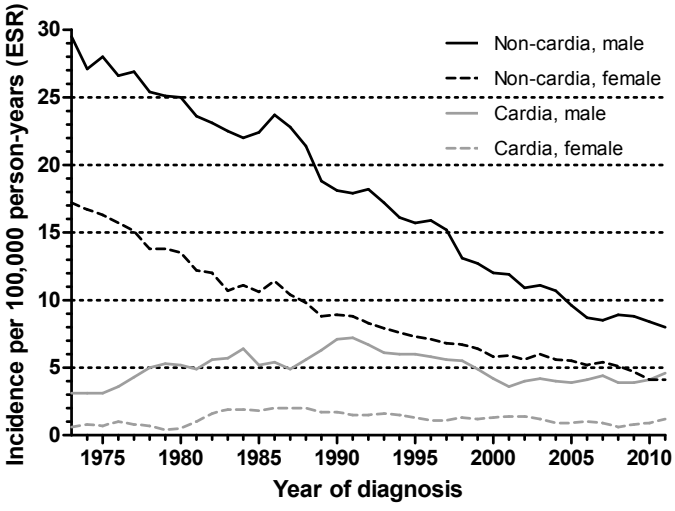

Figure 1. Incidence of gastric cancer per 100,000 person-years in the South of the Netherlands, according to sex and subsite (European Standardized Rate (ESR), 3-year moving averages).

Table 1. Patient characteristics of stomach cancer patients (adenocarcinoma only) in the Southern Netherlands according to period of diagnosis.

	1973-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2011	Total	p-value X^2-test
Number of patients	1182	791	1258	1539	1406	1331	1586	9093	
% males	62	63	62	63	65	63	64	62	0.7
Age (%)									
<60 y	25	25	21	20	21	21	18	25	<.0001
60-74 y	47	44	43	44	46	44	40	47	
>75 y	28	31	36	36	34	36	41	28	
Subsite (%)									<.0001
Cardia	10	18	21	23	23	22	27	21	
Non-cardia									
Fundus	1	1	2	1	2	2	2	2	
Corpus, incl. lesser and greater curvature	6	21	20	21	21	20	18	18	
Antrum	7	18	20	20	22	20	20	19	
Pylorus	5	7	6	6	6	7	6	6	
Overlapping lesion of stomach	15	22	26	25	22	23	21	22	
Not otherwise specified	57	13	5	3	4	7	6	12	
TNM stage distribution (%)*									
1	3	8	14	18	17	15	13	13	<.0001
2	11	21	12	14	15	14	11	14	
3	8	20	19	14	14	14	13	14	
4	38	41	32	32	31	39	44	37	
X	41	10	23	22	22	18	18	22	

** primarily referring to pathological stage, supplemented with clinical stage in case pathological stage is missing.*

decrease in cardia cancer started slightly earlier (1983 vs. 1990). The overall sex ratio (M:F) was 1.7 (non-cardia 1.5, cardia 3.2). No significant changes in sex ratio over time occurred (p=0.9).

Age-period-cohort analyses

The fits of the different models are presented in Table 2a. Comparing the models separately (Table 2b), showed that the age-drift model was the best model to describe the incidence for males and females with non-cardia cancer. For cardia cancer, the age-period-cohort model gave the best fit in females. In males, the age-period model best described the data (Figure 2), with increasing and decreasing relative risks over time (range relative risks 0.9-1.6 compared to the last period).

Table 2a. Deviations of age-period-cohort modeling for stomach cancer incidence in southern Netherlands, diagnosed between 1973 and 2011.

Model		Non-cardia		Cardia	
		M	F	M	F
	Df	Deviance	Deviance	Deviance	Deviance
Age	84	747.16**	502.39**	153.521**	124.41**
Age-drift	83	113.54*	83.82	136.74**	117.04**
Age-period	78	104.81*	79.96	94.10	83.26
Age-cohort	65	86.24*	66.16	108.95**	91.03*
Age-period-cohort	59	59.14	54.42	71.98	51.41

Df: degrees of freedom, M: male, F: female.
*** goodness-of-fit test p<0.01, * goodness-of-fit test p<0.05.*

Table 2b. Difference in deviation of the comparison of models in the age-period-cohort analyses for stomach cancer incidence in southern Netherlands, diagnosed between 1973 and 2011.

Models to compare		Non-cardia		Cardia	
		M	F	M	F
	Δ Df	**Δ** deviances	**Δ** deviances	**Δ** deviances	**Δ** deviances
Age vs age-drift	1	663.62**	418.57**	16.78*	7.37**
Age-drift vs age-period	5	8.73	3.86	42.64*	41.16**
Age-drift vs age-cohort	18	27.3	17.66	27.79	33.38*
Age-period vs age-period-cohort	19			22.12	31.85*
Age-cohort vs age-period-cohort	6				39.62**
Best fit		*age-drift*	*age-drift*	*age-period*	*age-period-cohort*

Δ Df: difference in degrees of freedom between the models to compare, M: male, F: female.
*** p<0.01, * p<0.05.*

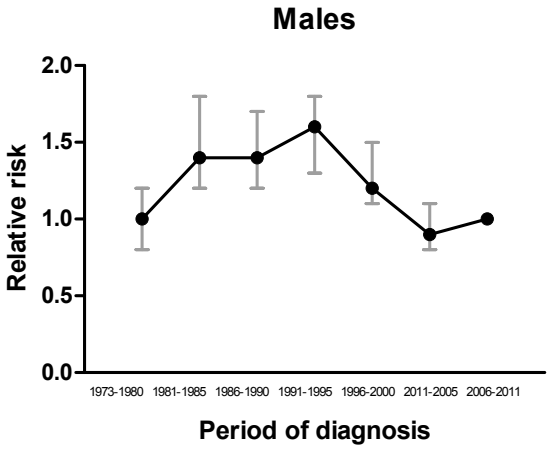

Figure 2. Relative risk for males of developing cardia cancer according to period in the Southern Netherlands.

Age-related trends

When stratified by age groups, the incidence of non-cardia gastric cancer significantly decreased in all groups (Figure 3a-3c). The declining incidence was most pronounced in those aged 60-74 (males: APC -3.6%, 95% CI -4.1; -3.1, females: -3.9%, 95% CI -4.5; -3.3) (Figure 3b). In contrast, in males <60 years, the incidence flattened since 2006, and even tended to rise in those >74 years although no trend changes were found by Joinpoint analyses yet (Figure 3a and 3c).

For cardia cancer, a significant increase in incidence among females <74 years was seen since 1973 (APC <60: 37.6%, 95% CI 20.4; 57.1, APC 65-74: 13.3%, 95% CI 1.1; 26.9). Among men aged 60-74, the decline in incidence started from 1993 with an annual decrease of 3.8% (95% CI -5.8; -1.8).

Anatomical subsite – non-cardia

In terms of anatomical location, 21% of the cancers were located in the cardia, 19% in the antrum, 18% in the corpus, 6% in the pylorus, 2% in the fundus, and 22% affected multiple sites (Table 1). In the remaining 12%, the location was unspecified. Tumors of an unspecified subsite decreased until early 1990s and afterwards remained stable over time (APC 2.6%, 95% CI -0.2; 5.6). Focusing on non-cardia subsites, the incidence of tumors of fundus, corpus, antrum, pylorus, and overlapping lesions declined significantly with 3.0 to 4.4% per year since the late eighties (Figure 4a and 4b). In most recent years a flattening of the incidence of adenocarcinomas of the corpus and pylorus was observed, although not supported by changes in linear trends as analyzed with joinpoint.

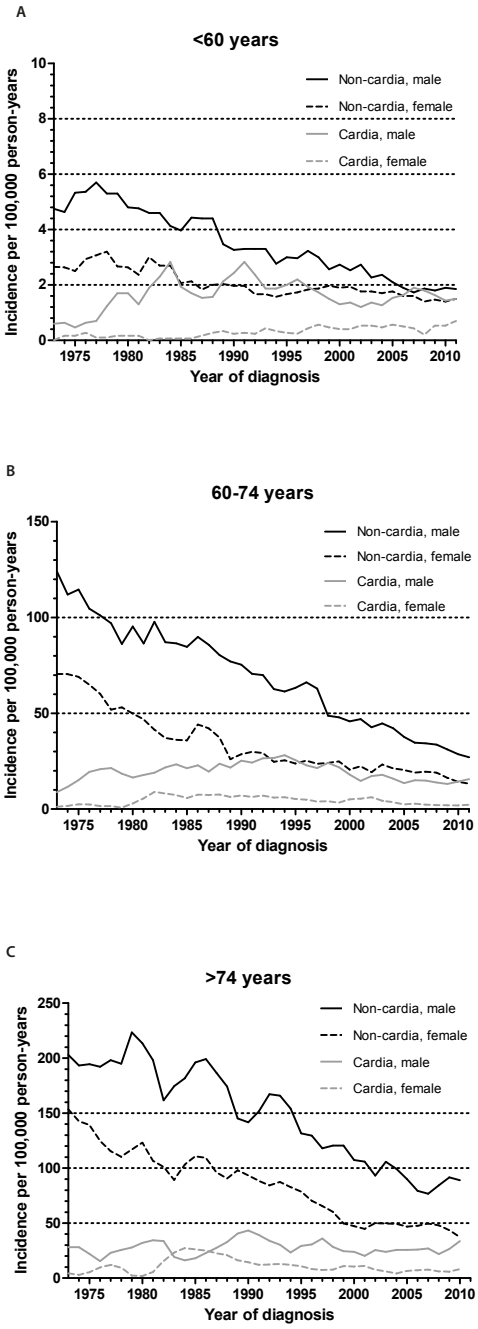

Figure 3a-c. Age-specific incidence rates of cardia and non-cardia gastric cancer among men and women between 1973 and 2011.

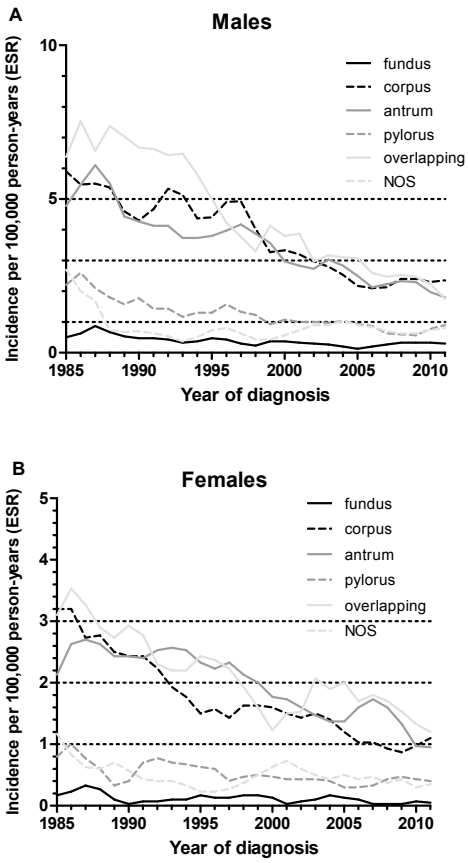

Figure 4a-b. Sex-specific incidence trends for non-cardia subsites, 3-year moving averages.

Patterns were similar between both sexes (Figure 4a and 4b). In general, specific age groups showed similar trends, except for a trend break in corpus cancer of those aged 75 and over. Here, an increase since 2006 was seen (Figure 4c-4e).

Pathological stage

For non-cardia gastric cancer, the incidence of stage IV decreased with 5.4% per year from 1973 to 1997 and remained stable thereafter (APC -0.6, 95% CI -3.1; 1.9), whereas the incidence of stages I, II, III and unknown continued to decrease with 6.1 to 6.5% per year after 1997 (Figure 5a). These trends were seen for both sexes.

The incidence of stage IV cardia gastric cancer similarly stabilized from 1990 onwards (APC 0.4, 95% CI -1.2; 2.0), while the incidence of stage I, II, III and unknown non-significantly decreased (Figure 5b). Here, the trends were more pronounced in males.

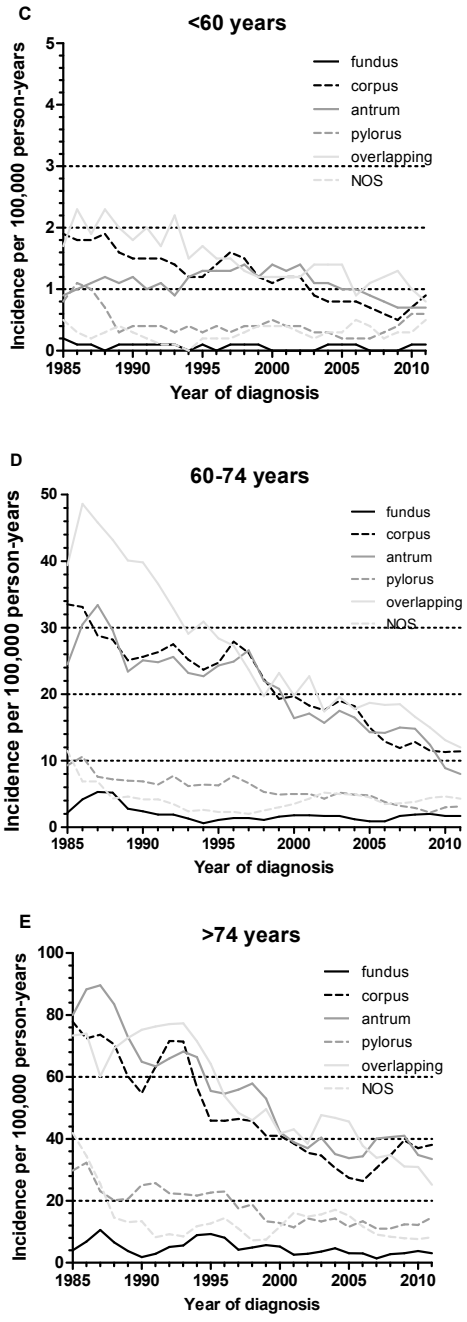

Figure 4c-e. Age-specific incidence trends for non-cardia subsites, 3-year moving averages. NOS: not otherwise specified.

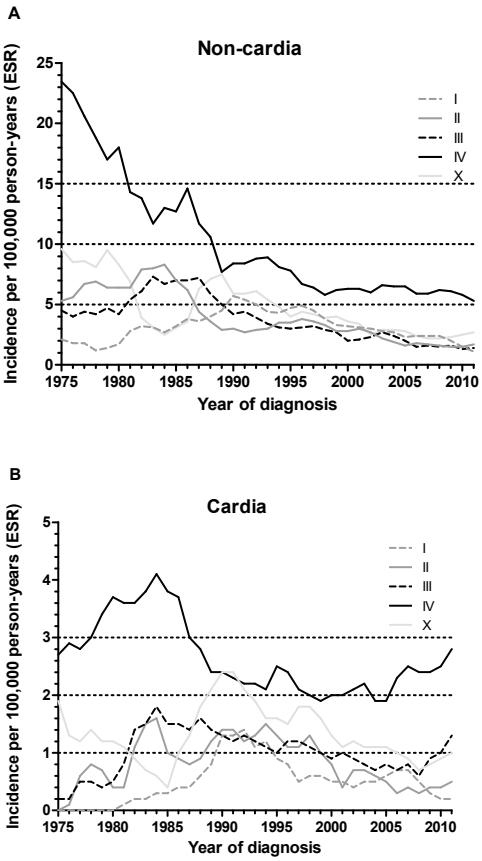

Figure 5a-b. Stage distribution for non-cardia and cardia cancer.
Stage X: unknown stage, (partly) missing information.

DISCUSSION

In the Southern Netherlands, the incidence rates of non-cardia gastric cancer declined over the past four decades, with this decline being most pronounced in the age group 60-74. However, in recent years, unfavorable trend breaks were seen in males <60 and >74 years. The incidence of cardia cancer also decreased for both sexes and all age groups, except for females <60 years.

Cardia and non-cardia gastric cancer show different epidemiological behavior owing to distinct etiologies. *Helicobacter pylori* plays a major role in the development of non-cardia gastric cancer.[15] Decreasing non-cardia gastric cancer rates, as also reported by others,[6, 16] may predominantly reflect a birth-cohort specific decline in *H. pylori* acquisition.[17] However, our analyses (showing discrepant trends for males <60 and >74 years compared to those

aged 60-74) did not point to such a birth-cohort effect. Since we calculated crude incidence rates for the age groups (i.e. not age adjusted), hypothetically, an improved life expectancy and a decrease in cardiovascular causes of death may play a role in the recent increasing incidence in elderly males. It is also possible that due to better performance status and improved diagnostic modalities, physicians tend to search more aggressively for a diagnosis in these elderly. Another potential explanation lies in the fact that these men were teenagers and young adults around World War II, a period which was characterized by severely affected life conditions, often with poorer hygiene and thus increased risk of *H. pylori* acquisition, as well as poor nutritional status. Such an effect might have been indicated by the age-period-cohort analyses, as we observed that an age-drift model best described the patterns in males with non-cardia stomach cancer. That means that there must be some temporal variation over time, which does not distinguish between period and cohort influences. We have previously described a similar phenomenon in the changes in incidence of atrophic gastritis and intestinal metaplasia in the Dutch population.[18] In our study, poor hygienic conditions including infection with *H. pylori* during World War II might have led to a period effect, and different exposures in different generations to carcinogens such as *H. pylori* (cohort effect) might have affected the trends in incidence. In women, similar effects might have been present, since an age-drift model also best fitted the trends in incidence.

Our observed age-specific non-cardia trends are in contrast with those found in the United States, although these studies used slightly different categorizations for age and subsite. These revealed an increasing incidence among whites <40 years from 1977-2006,[6] while in our study the incidence in the younger age groups flattened from 2007, but did so far not increase. Analysis by anatomical subsite in the US revealed decreasing rates for all non-cardia subsites, except for corpus cancer and antral cancer in young and middle-aged.[5] We similarly showed an isolated increase in corpus and pylorus cancer although only in the highest age group. Several hypotheses have been postulated. Theoretically, emergence of new gastric carcinogens following the disappearance of *H. pylori* may play a role. Furthermore, the possible role of long-term gastric acid inhibitory therapy as modulating factor should be considered. Other possible explanations relate to the role of diet. Although those hypotheses were only able to capture part of the observed trends.[5, 6]

In contrast to non-cardia gastric cancer, the etiology of cardia tumors is to a greater extent multifactorial. It may be related to obesity, gastro-esophageal reflux (more prevalent in the absence of *H. pylori* and presence of abdominal obesity), and tobacco smoking.[19] Furthermore, nutritional exposures and physical activity have been implicated as factors influencing the risk.[20] Besides these behavioral and environmental factors, host-related factors as genetic polymorphisms may also play a role. Due to this multifactorial origin, trends are more difficult to address. We found a declining incidence of cardia cancer after the peak in 1985, except for a significant increase in incidence among females <60 years since 1973. The prevalence of tobacco smoking in the Netherlands dropped from 60% in 1958 to 25% in 2011, but

peaked in the early seventies among young females.[21] In the same period, the prevalence of (abdominal) obesity increased dramatically.[22] Given the (long) period to develop cancer, both these behaviors might have contributed to the incidence trends. Another explanation for the declining incidence of cardia cancer is reclassification (i.e. a change in how diagnostic terminology is applied). Adenocarcinomas of the gastro-esophageal junction are vulnerable to misclassification, as there are no clear morphologic differences that distinguish adenocarcinomas of the lower esophagus from those of the cardia. This phenomenon may have led to a shift from cardia cancer towards distal esophageal cancer.[23, 24]

Our analyses showed that the trend in incidence of cardia adenocarcinoma among males is best described with an age-period model. That suggests that there is a period effect which changes incidence in all age groups at the same time, e.g. due to exposure to the above mentioned factors. Given the changing prevalence of smoking, it seems that increasing prevalence of e.g. obesity or reflux still leads to increasing risk of cardia cancer, regardless of age. However, for women we found that trends in cardia cancer were best described by an age-period-cohort model. It is therefore impossible to disentangle the effects of age, period and cohort.

To our knowledge, this is the first population-based study in Europe reporting on recent incidence trends in gastric cancer by age and subsite. The study included a significant time span (38 years) and the collected data were estimated to have a high level of accuracy [25] and completeness (>95%).[26]

Our study has limitations. First, a significant decrease in tumors in an unspecified subsite was observed from 1985. This is most likely explained by improvement in diagnostics over time and does not reflect a real decrease. We therefore analyzed subsite trends only from 1985 onwards. Second, we found a relative increase in stage IV compared to less advanced stage groups for both types of gastric cancer. This may partly be explained by "stage migration". Due to improved imaging modalities, metastases are found more frequently. This results in an increase in patients classified in a more advanced stage group. Furthermore, for correct interpretation of the pathological stage trends, the reclassification of TNM stage over time has to be taken into consideration (as we did). Third, sub classification might lead to small numbers of patients. Especially in the younger age groups, the numbers were relatively small, hampering further subdivision of age groups <60 years.

In conclusion, the trend breaks in gastric cancer incidence seen in the US do not likewise occur in this Western European population. However, since the end of the 2000s the incidence of adenocarcinomas of the corpus and pylorus appears to flatten, which may be the announcement of changing trends in incidence of non-cardia carcinoma in the forthcoming years. Observed discrepancies in time trends for age, sex and subsite are mainly attributable to a heterogeneous distribution of risk factors. Further studies are needed to confirm our findings and to unravel the potential causes.

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PART IV

DISCUSSION

CHAPTER 11

GENERAL DISCUSSION AND CONCLUSIONS

SUMMARY

This thesis dealt with the prevention and endoscopic management of upper gastrointestinal bleeding and premalignant gastric lesions and was divided in four parts. The first part provided an introductory summary on gastrointestinal bleeding, *Helicobacter pylori*, and premalignant gastric lesions, followed by the aims and outline of this thesis.

In part two of this thesis, we showed that new oral anticoagulants (nOAC) are associated with a modestly increased risk of GIB in comparison to standard care. This risk is highest in patients treated for thrombosis compared with patients where nOAC were given as prophylaxis. Hemospray is a valuable alternative in the treatment of both upper and lower GIB, as it can fill several gaps, where the currently available modalities have difficulties to reach hemostasis. Self-expandable metal stents can be a definitive treatment for acute esophageal variceal bleeding in patients with a limited life-expectancy, and those unsuitable to undergo transjugular intrahepatic portosystemic shunt (TIPS). In unselected cirrhotic patients, covered TIPS is superior to endoscopic variceal ligation plus β-blocker in prevention of variceal rebleeding, but does not improve survival and increases the risk of early hepatic encephalopathy.

In part three, we showed that ethnicity is the strongest predictor for *Helicobacter pylori* colonization in young women. As such, *H. pylori* infection will remain prevalent for the coming decades in multi-ethnic Western societies. Colonization with *H. pylori* is inversely associated with childhood wheezing and might thus be beneficial in childhood. Later in life, it can give rise to premalignant lesions. In these cases, eradication should be considered, but may be insufficient as single management. Additional endoscopic surveillance is recommended in patients with extensive premalignant lesions at risk of progression to gastric cancer.

This final part discusses the novel insights obtained from our research projects and directions for future research.

GASTROINTESTINAL BLEEDING (PART II)

In the field of gastroenterology, upper gastrointestinal bleeding is the most common emergency and causes significant morbidity and mortality. While trying to optimize endoscopic treatment and to reduce rebleeding, we are at the same time confronted with new potential risk factors for gastrointestinal bleeding (GIB).[1] Within this context, the focus of this thesis was to investigate the GIB risk of a new generation of oral anticoagulants and the efficacy and safety of emerging technologies for endoscopic hemostasis, including Hemospray and self-expandable metal stents. Moreover, in patients who already experienced an episode of variceal bleeding, we studied two treatment strategies for prevention of rebleeding.

New oral anticoagulants

A substantial part of gastrointestinal bleeding is caused by antithrombotic agents.[2] The expanding indications and increasingly intensive treatment might even increase this burden in the future.[3] We conducted a systematic review and meta-analysis on the GIB risk of a new generation of oral anticoagulants (nOAC) **(Chapter 2.1)**. These drugs represent landmark advancements in anticoagulant care as they overcome some of the important limitations of warfarin and low-molecular-weight heparin. However, it was at the start of this review, based on 43 randomized controlled trials including over 150,000 patients, not clear whether these new agents could increase the risk of gastrointestinal bleeding. We found that the overall odds ratio for GIB was 1.45, although not all indications and all nOAC seemed to confer the same increased GIB risk. The first might suggest a dose and/or duration effect on top of difference in risk caused by patient characteristics in the different indication groups. For the latter it has been proposed that differences in bioavailability and therefore varying amounts of active anticoagulant effect along or within the gastric mucosa may play a role.[4] An important issue was that only 44% of included trials reported separate data on GIB and that even in these studies, data about the origin of the bleeding and the endoscopic treatment, as well as information about ulcerogenic co-medication and gastroprotective agents were lacking. This hampered a detailed prediction of which patients were at highest risk. We therefore recommend that future studies on nOAC specifically report the number, severity, location and origin of GIB, to further elucidate the true incidence of GIB. Individual patient data in terms of demographic characteristics, comorbidities and co-medication, are necessary to test whether known risk factors for aspirin- and warfarin-induced GIB also apply to nOAC-users.[5] Next, intersectional thinking and collaboration between cardiologists, hematologists and gastroenterologists will contributes to develop a more comprehensive risk prediction tool, both including the risk of a thromboembolic event as well as the risk of gastrointestinal bleeding. Moreover, co-administration of gastroprotective agents could protect high-risk patients and warrants further investigations.

As these drugs have novel targets within the coagulation cascade, current coagulation tests are not accurate and, more alarming, no clinically tested antidote is available.[6] Specific reversal agents are in development, but need further time. In **Chapter 2.3**, we recommend, based on a review of the currently available literature, that specific coagulations tests such as diluted thrombin time (for thrombin inhibitors) and anti-Xa (for factor Xa inhibitors) measurements should be made available in every hospital. In case of acute severe GIB in a patient on these agents, nOAC should be stopped and coagulopathy should be corrected. Administration of prothrombin complex concentrate or recombinant factor VIIa may be helpful.[7, 8] However, it is important to recognize that most urgent management recommendations are derived from limited nonclinical data and require further validation. For the near future, it is essential to develop clear guidelines to support the management of acute GIB in patients using nOAC.

Hemospray

Hemospray (Cook Medical, Winston-Salem, North Carolina, USA) is a novel hemostatic powder specifically developed for the treatment of gastrointestinal bleeding, following promising results of similar agents in the combat environment.[9, 10] It is a non-organic mineral blend powder that is thought to work via absorption of liquid at the bleeding site, forming an adhesive and cohesive mechanical barrier over the bleeding site. However, data supporting this hypothesis was lacking. In **Chapter 3.1**, we investigated the working mechanism of Hemospray. We performed coagulation experiments in the presence of Hemospray. Furthermore, we studied the formation of the blood clot *in vitro* and also by microscopic imaging of the bleeding site in an animal model. We concluded that Hemospray stimulates clot formation presumably by activation of the intrinsic pathway. Whether negative charge or other factors are responsible for this activation requires further research. Additionally, the powdery substance itself may ease clotting. In contact with blood, Hemospray particles form one confluent mass on top of the bleeding focus, packing and deforming erythrocytes. These unique properties distinguish Hemospray from other endoscopic hemostatic modalities. Next, we aimed to find out to what extent this would be of additional value in patients with acute gastrointestinal bleeding.

At the start of our clinical research, evidence on the efficacy and safety of Hemospray was, besides animal experiments, limited to the very promising results of a prospective study on patients with active peptic ulcer bleeding.[11, 12] We analyzed efficacy and safety in two cohorts of Hemospray-treated patients with upper or lower GIB of diverse origin including peptic ulcer, tumor, Dieulafoy lesion, anastomosis, post-polypectomy, and diverticulum **(Chapter 3.2 and 3.3)**. Hemospray was successful in reaching hemostasis both as monotherapy and as rescue therapy even in patients on antithrombotic therapy. However, in the combination of antithrombotic therapy and spurting bleeding, it was, similar to experiences with other endoscopic modalities, more difficult to reach hemostasis. Besides in non-variceal bleeds**,** we

showed that Hemospray could also be successfully used in a patient with refractory gastric variceal bleeding **(Chapter 3.4)**. This was confirmed by another group, who applied Hemospray in patients with portal hypertensive bleeds.[13, 14] For this type of bleeds, Hemospray should be seen as a tool to halt these otherwise difficult to stop active bleeds. Since, it has no effect on portal pressure, neither does it eradicate the underlying varices, more definitive treatment such as β-blocker therapy or transjugular portosystemic shunt (TIPS) placement should be instituted after stabilization.

With these case series, we and others showed that Hemospray is a valuable alternative in the management of gastrointestinal bleeding. It can overcome some of the limitations of other treatment modalities, as it is easy and safe in use and can be applied on large bleeding areas or when the exact bleeding focus cannot be visualized.

To increase the generalizability, future trials on Hemospray should also include patients on antithrombotic therapy, as this category of patients is especially at risk of GIB. The true merit of Hemospray should be confirmed in larger cohorts or randomized controlled trials comparing Hemospray with other treatment modalities.

Variceal bleeding

Active esophageal variceal bleeding, often in an hemodynamically instable patient, remains a challenge for endoscopists. Endoscopic variceal ligation (EVL) has been proven effective in controlling bleeding, but the bands can be difficult to place in an area of profuse bleeding.[15] In these situations, balloon tamponade (using the Sengstaken tube) is an effective way to achieve short-term hemostasis, but due to the high complication risk, this device is unpopular among endoscopists. Recently, self-expandable metal stents (SEMS) have been introduced for temporary control of bleeding.[16, 17] An ongoing trial compares the efficacy of self-expandable metal stents with balloon tamponade in patients with variceal bleeding refractory to medical and endoscopic therapy.[18] In **Chapter 4**, we showed that SEMS can also be definitive treatment rather than a bridge to further treatment. In the described patients, esophageal variceal bleeding could not be controlled with EVL and patients were unfit for TIPS placement at the time of bleeding. To further conclude on the hypothesis that self-expandable metal stents can be a definitive treatment of acute esophageal variceal bleeding, a well-designed randomized controlled trial comparing endoscopic variceal ligation and SEMS placement is eagerly awaited.

Besides controlling of acute variceal bleeding, secondary prophylaxis (i.e. the prevention of variceal rebleeding) is a cornerstone of therapy in cirrhotic patients, as preventing rebleeding is seen as a substitute outcome of survival. Yet, the method most successful in achieving less mortality has been of much debate. In **Chapter 5**, we presented the results of our multicenter randomized controlled trial, in which we compared EVL plus β-blocker treatment with TIPS placement in 72 patients with a first or second gastroesophageal variceal bleeding. In unselected cirrhotic patients, covered TIPS was superior to EVL + β-blocker for reduction

of variceal rebleeding, but did not improve survival. This was paralleled by an increment of early TIPS-related hepatic encephalopathy. These results shed new light on the debate on the optimal strategy for prevention of variceal rebleeding. Particularly, since TIPS is a technical demanding procedure only reserved for expert centers, associated with high initial costs that only may pay off over time. As TIPS in our study did not result in a survival benefit in unselected cirrhotic patients compared with endoscopic treatment, other arguments may influence the decision to choose for one of both secondary preventions strategies. Studies on cost-effectiveness, quality of life, and randomization between early and elective TIPS placement should be performed to elucidate this issue further.

H. PYLORI AND PREMALIGNANT GASTRIC LESIONS (PART III)

Epidemiology

H. pylori infection is mostly acquired in the first years of life.[19, 20] Close family members like mothers and siblings are seen as the major transmission source for *H. pylori* acquisition.[21, 22] Therefore, *H. pylori* prevalence in pregnant women can be considered predictive for prevalence in the next generation. Up to now, the effect of ethnic distribution of a population on the *H. pylori* colonization is largely unknown. In **Chapter 6**, we defined *H. pylori* prevalence in a multi-ethnic cohort of pregnant women living in Rotterdam (Generation R study). Overall, 46% of the more than 6800 tested women was *H. pylori* positive, although the prevalence varied widely from 24% in Dutch women to 92% in Moroccan women. The proportion of CagA-positive strains was also higher among women of non-Dutch origin. Overall colonization rates in this young multi-ethnic population were higher than expected. A plausible explanation is the altered composition of western communities, as a result of immigration from countries where *H. pylori* is frequently endemic.

Our results indicate that, even in western cities, the health risks imposed by *H. pylori* remain a significant concern for the coming decades, especially in ethnic subgroups. Therefore, these migrant communities may be suitable for targeted screening and intervention. Yield and cost-effectiveness of screening and details on implementation require further research.

In addition to the mothers of the Generation R cohort, their children are currently tested for *H. pylori* as well. This will allow us, to closely study the transmission route and to investigate the association between *H. pylori*-associated diseases on population level.

H. pylori and atopic disorders

Besides pathogenic properties, some studies have suggested a beneficial effect of *H. pylori* on the development of childhood asthma and allergy.[23-25] According to the "disappearing microbiota" hypothesis, the decline in prevalence of our ancient indigenous microflora, with *H. pylori* as a dominant member, is thought to have fuelled the simultaneous rise in childhood

asthma and atopy.[23] We assessed the impact *of H. pylori* colonization on atopic disorders in a cohort of 545 Dutch children **(Chapter 7)**. An inverse trend between colonization with *H. pylori* and wheezing was seen (OR 0.52, 95% CI 0.25-1.06). However, no inverse relationship between *H. pylori* and physician diagnosed asthma, eczema or allergic rhinitis was found. The sample size of this pilot study might not have been large enough to detect moderate inverse associations. Therefore, the same research question is currently studied in the 10-times larger Generation R cohort. Additionally, the effect of CagA-positive strains will be investigated, as these strains have the closest interaction with the immune system and consequently might have the strongest protective effect.

To definitely conclude on causality between the absence of *H. pylori* and atopic disorders, long-term prospective studies are indispensable with repeated assessment of *H. pylori* status and presence of asthmatic symptoms.[26, 27]

Premalignant gastric lesions and gastric cancer

Given its pivotal role in gastric carcinogenesis, eradication of *H. pylori* seems a logical step in the prevention of gastric cancer. Eradication leads to healing of gastritis, which may stop further progression of the cancer cascade. Some systematic reviews have demonstrated that eradication in *H. pylori*–induced chronic active gastritis significantly reduces gastric cancer risk.[28, 29] In our Cochrane review in **Chapter 8**, we investigated the preventive effect of *H. pylori* eradication for patients who already developed precancerous gastric lesions. We included 17 randomized controlled trials (2890 patients) that compared *H. pylori* eradication therapy with either placebo, no treatment, or acid suppressive medication and evaluated the effect on the gastric mucosa after 8 weeks to 6 years. We concluded that treatment of *H. pylori* infection has a preventive effect on progression of atrophic gastritis, whereas the effect on intestinal metaplasia and dysplasia remains inconclusive. Quantification of the results was hampered by the fact that the outcome measures and the way of reporting the results were highly heterogeneous amongst studies. To generate homogenous and clinically useful outcomes, we recommend future trials on this topic, to use a standardized biopsy scheme with both non-targeted and targeted biopsies. Non-targeted biopsies should be taken from at least antrum, angulus and corpus. Additionally, targeted biopsies should be obtained from macroscopic lesions (if any).[30] Moreover, histological scoring of biopsies should be based on the updated Sydney System en Vienna system.[31, 32] Reporting should ideally be done per location, to allow OLGA and OLGIM scoring, and as most severe lesion overall.[33, 34]

With the knowledge derived from our review, *H. pylori* eradication may be insufficient as single management modality in patients with premalignant gastric lesions and should be combined with long-term endoscopic surveillance.[35]

In **Chapter 9**, the first results of our prospective study on surveillance of patients with premalignant lesions were presented. Premalignant lesions restricted to the corpus had the highest risk of extent to more than one location during follow-up. We found a relatively high

number of patients that showed regression (i.e. severity of premalignant lesions was less at follow-up than at baseline). Whether this is either true regression, or pseudo-regression related to inevitable sampling error and interobserver variation in histological grading, will be elucidated during follow-up gastroscopy. Indeed, the interobserver agreement between general and expert pathologist was low for atrophic gastritis and low grade dysplasia, but very high for intestinal metaplasia. We therefore recommend to use intestinal metaplasia as most important histopathologic scoring tool. Additional staining, as is currently available and performed in case of uncertain premalignant diagnosis, can distinguish active gastritis from "indefinite for dysplasia".

Together with the decreasing *H. pylori* prevalence, the incidence of gastric cancer has steadily declined over the past six decades. Until recent studies showed a trend break for non-cardia gastric cancer in younger age groups.[36, 37] To study the extent and possible cause of these discrepant trends, we closely analyzed the gastric cancer incidence trends by age, sex, subsite, and stage **(Chapter 10)**. We found a stabilizing incidence for corpus cancer in males. Hypothetically, there may be a role for emergence of new gastric carcinogens, influence of sustained profound acid suppression by means of long-term proton pump inhibitor use, or diet. Future studies should confirm this trend break and investigate to what extent our postulated hypotheses contribute to the observed trends.

CONCLUSIONS

Management of gastrointestinal bleeding is a rapidly moving field. In this thesis, we showed updates in the area of risk factors, endoscopic treatment and secondary prevention strategies. Novel oral anticoagulants are a possible new threat for the gastroenterologists. Hemospray and self-expandable metal stents are a welcome addition to the armamentarium against gastrointestinal bleeding. TIPS, on the other hand, might remain restricted to high risk patients.

H. pylori infection will remain prevalent for the coming decades in multi-ethnic Western societies It is possible that for most individuals, *H. pylori* is beneficial in childhood and more deleterious later in life. Premalignant gastric lesions should be both managed with *H. pylori* eradication as well as endoscopic follow-up to reduce the incidence of gastric cancer. Since the end of the 2000s the incidence of adenocarcinomas of the corpus in males appears to flatten, which may be the announcement of changing trends in incidence of non-cardia carcinoma in the forthcoming years.

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APPENDICES

- **SUMMARY IN DUTCH**
- **ABBREVIATIONS**
- **CONTRIBUTING AUTHORS**
- **LIST OF PUBLICATIONS**
- **PHD PORTFOLIO**
- **ACKNOWLEDGEMENTS**
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SUMMARY IN DUTCH

Aandoeningen aan het maag-darmkanaal zijn een veelvoorkomend probleem. Deze zijn verantwoordelijk voor 15-20% van alle huisartsenbezoeken, ziekenhuisopnames en medicatiegebruik. Veel van deze aandoeningen zijn gerelateerd aan het bovenste gedeelte van het spijsverteringskanaal, namelijk de slokdarm en de maag. Dit proefschrift richt zich op de preventie en behandeling van twee lange termijn complicaties: bloedingen **(PART II)** en maagkanker **(PART III)**.

In het eerste deel **(PART I)** wordt een uitgebreid overzicht gegeven van wat er tot nu toe bekend is over deze onderwerpen en worden de doelstellingen van het proefschrift beschreven.

In het tweede deel **(PART II)** wordt dieper ingegaan op bloedingen van de maag en slokdarm. Verreweg het grootste gedeelte van de bloedingen in het bovenste deel van het maag-darm kanaal wordt veroorzaakt door een zweer. Deze zweren ontstaan meestal niet door stress, zoals vroeger gedacht werd, maar door een maagbacterie, genaamd *Helicobacter pylori*. *H. pylori* is de enige bacterie die langdurig in het zure milieu van de maag kan overleven. Bij de meeste mensen geeft de bacterie geen aanleiding tot klachten, maar bij een kleine groep veroorzaakt hij maagpijn en/of maag-darmzweren. Als deze groot of diep worden, kunnen ze een bloeding of perforatie veroorzaken. Een andere belangrijke oorzaak voor het ontstaan van een zweer is het gebruik van aspirine of pijnstillers behorend tot de groep van NSAIDs (zoals ibuprofen, diclofenac en naproxen). Sinds kort is er een nieuwe generatie bloedverdunners op de markt. Deze bloedverdunners zijn gebruiksvriendelijker dan de middelen van de trombosedienst, die ze naar verwachting deels zullen gaan vervangen. Bovendien werken ze krachtiger tegen het ontstaan van tromboses. Een mogelijk nadeel is dat de bijwerkingen (bloedingen) ook ernstiger zijn. Het was tot nu toe niet uitgezocht of deze nieuwe middelen een hoger risico hebben op maag-darmbloedingen dan de huidige bloedverdunners. In **hoofdstuk 2.1** hebben we een zogenaamde meta-analyse gedaan, waarbij we alle studies die één van deze nieuwe bloedverdunners hebben bestudeerd, bij elkaar optelden. Uit deze analyse bleek dat het gebruik van deze nieuwe generatie bloedverdunners een iets verhoogd risico op maag-darmbloedingen met zich meebracht. Het risico was afhankelijk van de reden voor gebruik en het soort middel. In **hoofdstuk 2.3** geven we adviezen over hoe te handelen in het geval van een door deze nieuwe bloedverdunners veroorzaakte maag-darmbloeding.

De belangrijkste pijlers van de behandeling van een bloeding van het bovenste gedeelte van het maag-darm kanaal zijn het toedienen van maagzuurremmers via een infuus en het doen van een maagonderzoek (gastroscopie) met behulp van een endoscoop (een slang met een camera aan het uiteinde). Tijdens deze gastroscopie kan gekeken worden naar de oorzaak van de bloeding en er kan ook meteen een behandeling plaatsvinden. Meestal wordt

de bloeding dichtgebrand of worden er klipjes op het bloedende vat geplaatst. In sommige gevallen is dit door de locatie of aard van de bloeding niet goed mogelijk. Daarom was er behoefte aan aanvullende methoden om bloedingen te kunnen stoppen. In **hoofdstuk 3.1-3.4** testten we de werkzaamheid van een bloedstelpend poeder, zowel in het laboratorium als bij patiënten. Een variant van dit poeder wordt al jaren in oorlogsgebieden gebruikt om grote uitwendige bloedingen bij gewonde soldaten te stelpen. Recent is dit bloedstelpende poeder doorontwikkeld, zodat het nu via de endoscoop op een bloeding in het maag-darmkanaal kan worden gesprayd. De eerste resultaten van de door ons behandelde patiënten met dit poeder zijn veelbelovend.

Spataderen zijn een andere oorzaak van een slokdarm- of maagbloeding. Deze spataderen zijn verwijde aderen in de wand van de slokdarm. Ze kunnen ontstaan als de lever verlittekend is (levercirrose) en niet meer in staat is het bloed uit de poortader (een grote ader waardoor bloed van de darm naar de lever stroomt) te verwerken. Dit bloed stuwt dan en zoekt een andere route om terug naar het hart te stromen. Die route bestaat uit een netwerk van bestaande, maar door het lichaam normaal niet veel gebruikte aderen die rond de slokdarm en maag lopen. Deze kunnen in het geval van levercirrose verwijd raken en noemt men dan slokdarmspataderen. De druk in deze spataderen is relatief hoog en de wand is kwetsbaar, waardoor ze gemakkelijk kunnen gaan bloeden. Deze bloedingen zijn heel verraderlijk, omdat de patiënt van een dergelijke bloeding, net als bij andere oorzaken van maagbloedingen, aanvankelijk niets merkt. Na enkele uren kan misselijkheid en bloedbraken optreden. De patiënt kan ook buiten bewustzijn raken, omdat de bloeddruk te veel zakt. Verder kan er na 1 à 2 dagen zwarte, stinkende ontlasting optreden. In **hoofdstuk 4** hebben wij gekeken naar een speciaal type stent (kippengaasbuisje bekleed met plastic) dat in de slokdarm kan worden geplaatst tijdens een slokdarmspataderbloeding om de spatader dicht te drukken en zo te zorgen dat de bloeding stopt. Dit bleek erg effectief en het hoopvolle was dat deze stents enige tijd konden blijven zitten zonder klachten te geven. Behalve het stoppen van de bloeding in de acute situatie, is het ook van belang te voorkómen dat er opnieuw een bloeding optreedt. Nu is de standaard behandeling een combinatie van een β-blokker (dit verlaagt de druk in de spatader) en rubberbandligatie. Dit laatste is een techniek waarbij tijdens een gastroscopie rubberen elastiekjes om de spataderen worden geschoten, zodat deze als het ware worden afgebonden en afsterven. Het nadeel van deze methode is dat dit meerdere keren moet gebeuren voordat alle spataderen weg zijn. Daarbij is de kans op het ontstaan van een bloeding tijdens deze behandeling vrij groot. Een nog relatief nieuwe behandeling is het plaatsen van een stent door de verlittekende lever. Via deze stent wordt er een kunstmatige verbinding gemaakt tussen twee bloedvaten, zodat het bloed via deze verbinding terug naar het hart kan stromen. Deze methode heet ook wel TIPS plaatsing. In **hoofdstuk 5** hebben we rubberbandligatie vergeleken met TIPS plaatsing bij patiënten die al een spataderbloeding hadden gehad. De resultaten van onze studie lieten zien dat de TIPS behandeling effectiever was in het voorkómen van hernieuwde bloedingen, maar dat dit

de overlevingskans niet verbeterde. In beide groepen kwamen namelijk evenveel mensen te overlijden, maar dat kwam vooral door de onderliggende leverziekte en niet door de bloeding zelf. In de groep patiënten die met een TIPS plaatsing behandeld waren, kwam wel iets vaker verwardheid voor.

In het derde deel **(PART III)** gaan we dieper in op de bacterie *H. pylori*, op voorloperafwijkingen van maagkanker en op het vóórkomen van maagkanker.

Ongeveer de helft van de wereldbevolking is besmet met *H. pylori*, maar er zijn grote verschillen in besmettingsgraad tussen ontwikkelingslanden (tot 90%) en westerse landen (20-60%). Hygiëne, gezinsgrootte en antibioticagebruik spelen hierbij een rol. De bacterie wordt meestal opgelopen op kinderleeftijd, waarbij familieleden (voornamelijk de moeder) de belangrijkste bron zijn. Eenmaal besmet, dan blijft men de bacterie vaak het hele leven bij zich dragen, tenzij deze gericht behandeld wordt. Bij de meeste mensen geeft hij geen aanleiding tot klachten of ziekteverschijnselen, maar bij een kleine groep wel. Behalve de al eerder genoemde maagzweren, wordt *H. pylori* ook in verband gebracht met de ontwikkeling van maagkanker. In **Hoofdstuk 6** hebben we gekeken naar het vóórkomen van *H. pylori* in een grote groep zwangere vrouwen in Rotterdam. Hieruit bleek dat *H. pylori* in een multiculturele stad als Rotterdam nog veel voorkomt, met name onder niet-westerse immigranten.

Naast ongunstige eigenschappen, zou *H. pylori* mogelijk ook gunstige eigenschappen bezitten. Het zou beschermend kunnen werken tegen astma en allergieën door een betere rijping van het immuunsysteem. Wij hebben bij ruim 500 kinderen gekeken of astma en allergische aandoeningen minder vaak voor kwamen bij kinderen die besmet waren met *H. pylori* **(Hoofdstuk 7)**. Dit bleek inderdaad het geval, al was het verschil niet zo heel groot.

In sommige gevallen is het nodig om de bacterie te behandelen. Dit is onder andere het geval wanneer iemand een maagzweer heeft (gehad), wanneer iemand specifieke maagklachten heeft of wanneer er voorloperafwijkingen van maagkanker gevonden zijn. De behandeling bestaat uit een combinatie van antibiotica en maagzuurremmers. Wij hebben gekeken of deze behandeling de progressie van voorloperafwijkingen kan stoppen bij patienten die al voorloperafwijkingen van maagkanker hadden op het moment van behandelen. Dit was het geval bij de mildste afwijkingen, maar bij de wat verder tot vergevorderde stadia van voorloperafwijkingen leek het behandelen van *H. pylori* alléén onvoldoende **(Hoofdstuk 8)**. Aanvullend wordt geadviseerd dat deze patiënten onder controle blijven en geregeld een gastroscopie ondergaan, waarbij biopten (kleine hapjes weefsel) worden genomen. We hebben een grote groep patiënten, bij wie deze voorloperafwijkingen toevallig tijdens een maagonderzoek ontdekt zijn, gevolgd om het eventuele ontstaan van maagkanker in een veel vroeger stadium te ontdekken **(Hoofdstuk 9)**. In **Hoofdstuk 10** hebben we gekeken naar de trends in het vóórkomen van maagkanker vanaf de jaren 70 tot heden. We zagen dat maagkanker over het algemeen, samen met het afnemen van *H. pylori* de meest bekende risicofactor, steeds minder voorkomt, De laatste jaren lijkt er echter sprake te zijn van stagnatie

of zelfs van een kleine toename van kanker, met name van bepaalde locaties in de maag bij mannen in bepaalde leeftijdsgroepen. Toekomstig onderzoek moet deze trend bevestigen en zich richten op de mogelijke oorzaken van deze trendbreuk.

In het afsluitende deel **(PART IV)** worden de belangrijkste bevindingen uit de voorgaande hoofdstukken samengevat en in een bredere context geplaatst en worden toekomstige richtingen voor vervolgonderzoek beschreven.

ABBREVIATIONS

ACS:	acute coronary syndrome,
AF:	atrial fibrillation,
APACHE:	acute physiology and chronic health evaluation,
APC:	annual percentage change,
APC:	argon plasma coagulation,
APTT:	activated partial thromboplastin time,
ASA:	acetyl salicylic acid,
ATT:	antithrombotic therapy,
bid:	twice daily,
BMI:	body mass index,
BOTEM:	Bonn TIPS early mortality,
CagA:	cytotoxin-associated gene A,
CFT:	clot formation time,
CI:	confidence interval,
COX-2:	cyclooxygenase-2,
CT:	clotting time,
DDAVP:	desmopressin,
DM:	diabetes mellitus,
dTT:	diluted thrombin time,
DVT:	deep vein thrombosis,
ELISA:	enzyme-linked immunosorbent assay,
EMR:	endoscopic mucosal resection,
ERCP:	endoscopic retrograde cholangiography,
ESD:	endoscopic submucosal dissection,
ESR:	European Standardized Rates,
EVB:	esophageal variceal bleeding,
EVL:	endoscopic variceal ligation,
FAP:	familial adenomatous polyposis,
GAVE:	gastric antral vascular ectasia,
GERD:	gastroesophageal reflux disease,
GEVB:	gastroesophageal variceal bleeding,
GI:	gastrointestinal,
GIB:	gastrointestinal bleeding,
GIST:	gastrointestinal stromal tumor,
HHT:	hereditary hemorrhagic telangiectasia,
HT:	hypertension,
IBD:	inflammatory bowel disease,

ICD-O: International Classification of Diseases for Oncology,
INR: international normalized ratio,
IQR: interquartile range,
ISAAC: international study of asthma and allergies in childhood,
ISTH: International Society on Thrombosis and Haemostasis,
iv: intravenous,
LGIB: lower gastrointestinal bleeding,
LMWH: low-molecular-weight heparin,
LVEF: left ventricular ejection fraction,
MCF: maximal clot firmness,
MELD: model for end-stage liver disease,
MEN1: multiple endocrine neoplasia type 1,
NASH: non-alcoholic steato-hepatitis,
NET: neuroendocrine tumor,
NNH: number needed to harm,
NNT: number needed to treat,
nOAC: new oral anticoagulants,
NOS: not otherwise specified,
NSAIDs: non-steroidal anti-inflammatory drugs,
OD: optical density,
ODR: optical density ratio,
OLGA: operative link for gastric assessment,
OLGIM: operative link for gastric intestinal metaplasia,
OR: odds ratio,
OS: orthopedic surgery,
OTSC: over-the-scope clip,
PCC: prothrombin complex concentrate,
PE: pulmonary embolism,
PIAMA: prevention and incidence of asthma and mite allergy,
PPI: proton pump inhibitor,
PT: prothrombin time,
PTFE: polytetrafluorethylene,
PUB: peptic ulcer bleeding,
PUD: peptic ulcer disease,
qd: once daily,
RCT: randomized controlled trial,
RR: relative risk,
sc: subcutaneous,
SD: standard deviation,

SEM: scanning electronic microscopy,
SEMS: self-expandable metal stents,
SSRI: selective serotonin reuptake inhibitor,
TAE: transcatheter arterial embolization,
TIA: transient ischemic attack,
TIMI: Thrombolysis in Myocardial Infarction,
TIPS: transjugular intrahepatic portosystemic shunt,
TT: thrombin time,
UGIB: upper gastrointestinal bleeding,
VBL: variceal band ligation,
VKA: vitamin K antagonist,
VTE: venous thromboembolism.

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LIST OF PUBLICATIONS

Publications based on studies described in this thesis

1. **I.L. Holster**, H.M.M. van Beusekom, E.J. Kuipers, F.W.G. Leebeek, M.P.M. de Maat, E.T.T.L. Tjwa. Effects of the hemostatic powder Hemospray on coagulation and clot formation. *Submitted.*
2. A.C. de Vries, **I.L. Holster**, E.J. Kuipers. *Helicobacter pylori* eradication for premalignant lesions of the gastric mucosa. *Submitted.*
3. **I.L. Holster**, E.T.T.L. Tjwa, A. Moelker, A. Wils, B.E. Hansen, J.R. Vermeijden, P. Scholten, B. van Hoek, J.J. Nicolai, E.J. Kuipers, P.M.T. Pattynama, H.R. van Buuren. TIPS vs endoscopy as standard therapy for prevention of variceal rebleeding. *Submitted.*
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17. **I.L. Holster**, E.J. Kuipers. Update on the endoscopic management of peptic ulcer bleeding. *Curr Gastroenterol Rep.* 2011 Dec;13(6):525-31.

Other publications

18. C.M. den Hoed, A.J. Vila, **I.L. Holster**, G.I. Perez-Perez, M.J. Blaser, J.C. de Jongste, E.J. Kuipers. *Helicobacter pylori* and the birth cohort effect: evidence for stabilized colonization rates in childhood. *Helicobacter*. 2011 Oct;16(5):405-9.
19. **I.L. Holster**, L.J. Hoeve, M.H. Wieringa, R.M.S. Willis-Lorrier, H.H.W. de Gier. Evaluation of hearing loss after failed neonatal hearing screening. *J Pediatr.* 2009 Nov;155(5):646-50.

Book chapters

20. Gastro-intestinaal bloedverlies. I.L. Holster, E.J. Kuipers, *Leerboek maag-, darm- en leverziekten*, door E.J. Kuipers, De tijdstroom, 2014 *in press.*
21. Een patiënte met acute pijn in de buik. E.T.T.L. Tjwa, I.L. Holster. *Probleemgeoriënteerd denken in levensbedreigende situaties*, door M.J. Schultz, A.B.J. Groeneveld, P.E. Spronk, De tijdstroom, 2013. ISBN: 9789058982414
22. Een patiënt met bloedbraken. I.L. Holster, E.T.T.L. Tjwa, E.J. Kuipers. *Probleemgeoriënteerd denken in levensbedreigende situaties*, door M.J. Schultz, A.B.J. Groeneveld, P.E. Spronk, De tijdstroom, 2013. ISBN: 9789058982414
23. Peptisch ulcuslijden. I.L. Holster, E.J. Kuipers. *Het gastro-enterologie formularium: een praktische leidraad, 3e editie*, door E.M.H Mathus-Vliegen en M.E. Numans. Bohn Stafleu van Loghum, 2013. ISBN 9789031350926
24. Peptic ulcer bleeding: Endoscopic diagnosis, endoscopic therapy, pharmacotherapy. I.L. Holster, C.M. den Hoed, E.J. Kuipers. *Gastrointestinal bleeding, second edition* by J.J. Sung, E.J. Kuipers, A.N. Barkun. Blackwell Publishing Ltd, 2012. ISBN: 9781405195553
25. Other causes of upper gastrointestinal bleeding. I.L. Holster, E.J. Kuipers *Gastrointestinal bleeding, second edition* by J.J. Sung, E.J. Kuipers, A.N. Barkun. Blackwell Publishing Ltd, 2012. ISBN: 9781405195553

PHD PORTFOLIO

Name: Ingrid Lisanne Holster **PhD period**: October 2010 - April 2014
Promotor: Prof. dr. E.J. Kuipers **Co-promotor**: Dr. E.T.T.L. Tjwa
Affiliation: Erasmus MC University Medical Center Rotterdam
Department: Gastroenterology and Hepatology

PHD TRAINING

General academic skills

Scientific English writing course
Erasmus MC Rotterdam, 2011

Research Integrity: BROK-course
Consultatiecentrum Patiëntgebonden Onderzoek (CPO), Erasmus MC Rotterdam, 2011

Research skills

Biostatistics for clinicians
Netherlands Institute for Health Sciences (NIHES), Erasmus University Rotterdam, 2011

Regression analysis for clinicians
Netherlands Institute for Health Sciences (NIHES), Erasmus University Rotterdam, 2011

Topics in Meta-analysis
Netherlands Institute for Health Sciences (NIHES), Erasmus University Rotterdam, 2011

Presentations at international conferences

Evidence for inverse association between *Helicobacter pylori* and wheezing in childhood
Oral presentation, Digestive Disease Week, Chicago, USA, 2011
Poster presentation, United European Gastroenterology Week, Stockholm, 2011; shortlisted for the 'Top Poster Prize'

A cost study of covered transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic treatment for secondary prevention of gastro-esophageal variceal bleeding
Oral presentation, Nederlandse vereniging van gastro-enterologie, Veldhoven 2012
Poster presentation, Digestive Disease Week, San Diego, USA, 2012
Poster presentation, United European Gastroenterology Week, Amsterdam, 2012

In vitro examination of the effects of the hemostatic powder (Hemospray) on coagulation and thrombus formation in humans
Poster presentation, Digestive Disease Week, San Diego, USA, 2012

New oral anticoagulants and the risk of gastrointestinal bleeding – a systematic review
Poster presentation, Digestive Disease Week, San Diego, USA, 2012

Increased risk of gastrointestinal bleeding with use of new oral anticoagulants – a meta-analysis
Oral presentation, United European Gastroenterology Week, Amsterdam, 2012; awarded an 'Oral Free Paper Prize' in the Free Paper Session: NSAIDS and upper GI bleeding

Self-expandable metal stents as definitive treatment for esophageal variceal bleeding.
Oral presentation, Nederlandse vereniging van gastro-enterologie, Veldhoven 2013
Poster presentation, International Liver Congress (EASL), Amsterdam 2013
Poster presentation, Digestive Disease Week, Orlando, USA, 2013

The end of the decreasing incidence of non-cardia gastric cancer?
Poster presentation, Digestive Disease Week, Orlando, USA, 2013

Metaplasia in a biopsy – What to follow-up? UEG/ESP Joint Symposium: Pathology meets Endoscopy – Metaplasia in the gastrointestinal tract.
European Congress of Pathology, Lisbon, Portugal, 2013

Early transjugular intrahepatic portosystemic shunt (TIPS) as compared to endoscopic treatment reduces rebleeding but not mortality in cirrhotic patients with a 1st or 2nd episode of variceal bleeding: a multicentre randomized controlled trial
Oral presentation, United European Gastroenterology Week, Berlin, 2013; awarded an 'Oral Free Paper Prize' in the Free Paper Session: Complications of cirrhosis

Hemospray treatment is effective for lower gastrointestinal bleeding
Poster presentation, United European Gastroenterology Week, Berlin, 2013

Presentations at national conferences and symposia

Clinical and microbiological evaluation of liver abscesses: 15-year single-centre experience in the Netherlands
Wetenschapsdag Sint Franciscus Gasthuis, Rotterdam, 2011

Rationale and design of the PROREGAL study: a prospective cohort study on the progression and regression of premalignant lesions
Dutch colorectal cancer group (DCCG) Day, Utrecht, 2011

Hoge tractus digestivus bloedingen: een oud probleem met nieuwe oplossingen
Topics in Intensive Care, Lunteren, 2012

Why do we need systematic reviews and meta-analyses?
PhD day Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, 2012

Transcatheter arterial embolization and surgery for the treatment of upper gastrointestinal bleeding.
Regio avond thema bloedingen, Novotel brainpark, Rotterdam, 2013

State of the art lecture: Gastro-intestinale bloedingen, risicofactoren en therapie.
Nascholingsavond, MDL opleiding Radboud UMC, studiecentrum Soeterbeeck, 2014

Membership

Dutch Society of Gastroenterology, 2010

Peer review activities

Alimentary Pharmacology and Therapeutics
BMC Gastroenterology
Expert Reviews Gastroenterology and Hepatology
Gut
Helicobacter
Thrombosis Research

TEACHING ACTIVITIES

Lecturing

Bloedingen na plaatjesremmers en NSAID's, nascholing apothekers, HARM-wrestling cyclus Mediq, Aristo, Utrecht, 2012

Gastro-intestinale bloedingen, curriculum spoedeisende hulp en intensive care verpleegkundigen i.o. Zorgacademie, Erasmus MC, Rotterdam, 2011-2013

Supervising graduation project

Frances van Deurzen, microbiological analyst in training, Zadkine college, Rotterdam
Helicobacter pylori infection in de Rotterdamse populatie: het Generation R cohort. Graduation thesis, 2011-2012

Simon Bac, medical student, Erasmus University Rotterdam
The predictive value of liver disease scoring systems on mortality, treatment failure and hepatic encephalopathy after TIPS. Master's thesis, 2012-2013

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Lisanne
Rotterdam, april 2014

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ABOUT THE AUTHOR

Ingrid Lisanne Holster was born on November 4th 1983 in Dordrecht, the Netherlands. She attended the Johan de Witt Gymnasium in Dordrecht, where she graduated in 2002. In the same year, she started Medical School at the Erasmus University in Rotterdam. As part of this education, she did two rotations abroad in Hospital Vall d'Hebron, Barcelona, Spain and in Royal Victoria Teaching Hospital, Banjul, the Gambia. In 2008, she obtained her qualification as a Medical Doctor with cum laude honors. Before starting a research career, she worked as a resident not in training (ANIOS) at the Emergency Department of the Vlietland Hospital Schiedam and Erasmus MC University Medical Center Rotterdam for one year, and as a resident at the Internal Medicine department of the Sint Franciscus Gasthuis Rotterdam for one year. In October 2010, she started her PhD trajectory as described in this thesis at the department of Gastroenterology and Hepatology of the Erasmus MC University Medical Center under supervision of prof. dr. E.J. Kuipers and dr. E.T.T.L. Tjwa. As of April 2014, she started the Internal Medicine part (Albert Schweitzer Hospital, Dordrecht, programme director: dr. E.F.H. van Bommel) of the formal postgraduate training in Gastroenterology and Hepatology (cluster Erasmus MC, Rotterdam, programme director: dr. R.A. de Man), after which she will continue with the first 2 years of her training in Gastroenterology and Hepatology in the same hospital (programme director: dr. R. Beukers).

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