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Karolinska Institutet, Stockholm, Sweden

# COMPLICATED PEPTIC ULCER DISEASE – PREVENTION AND TREATMENT

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Stockholm 2017

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Published by Karolinska Institutet.
Printed by E-print AB 2017

ISBN 978-91-7676-626-2

Complicated peptic ulcer disease – prevention and treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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**ABSTRACT**

Peptic ulcer is a common disease worldwide and its complications can cause serious clinical problems. While the incidence of uncomplicated peptic ulcer disease is decreasing, the incidence of more complex ulcer disease is not. The most common complication is bleeding. Endoscopic intervention achieves haemostasis in most patients. The remaining part face a substantial risk of mortality and these patients have typically undergone more or less radical surgery. Transcatheter arterial embolisation (TAE) has emerged as a less invasive alternative to surgery, but there is limited scientific evidence supporting its role. The increased use of gastric bypass surgery for obesity has resulted in an increase in marginal ulcer, a complication of uncertain aetiology which is often difficult to heal. *Helicobacter pylori* (*H. pylori*) is the main risk factor for peptic ulcer, and eradication of this bacterium is an important part of the treatment. Yet, eradication after peptic ulcer is often delayed, with uncertain clinical consequences.

This thesis aimed to help improve the treatment of peptic ulcer bleeding (Study I and II), identify risk factors for marginal ulcer (Study III), and clarify consequences of delayed *H. pylori* eradication after peptic ulcer diagnosis (Study IV).

***Study I*** compared mortality after a more radical with a minimal surgical approach for ulcer bleeding in a population-based cohort study using data from the Swedish Patient Registry in 1987-2008. The overall all-cause 5-year mortality was similar (hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.95-1.16), but was possibly higher following radical surgery from the year 2000 onwards (HR 1.27, 95% CI 0.99-1.63).

***Study II*** compared outcomes after TAE with surgery for ulcer bleeding in a cohort study in Stockholm County in 2000-2014, using data from medical records and the Swedish Patient Registry. Compared to the surgery group, the overall all-cause mortality was decreased in the TAE group (HR 0.66, 95% CI 0.46-0.96) as was the risk of complications (8.3% versus 32.2%), and the median length of hospital stay (8 versus 16 days, adjusted acceleration factor 0.59, 95% CI 0.45-0.77). The risk of re-bleeding (HR 2.48, 95%CI 1.33-4.62) and re-intervention (HR 5.41, 95% CI 2.49-11.76) was higher in the TAE group.

***Study III*** examined potential risk factors for marginal ulcer after gastric bypass surgery in a nationwide population-based cohort study using data from the Swedish Patient Registry in 2006-2011. Diabetes (HR 1.26, 95% CI 1.03-1.55) and peptic ulcer history (2.70, 95% CI 1.81-4.03) were associated with increased risk, while hyperlipidaemia, hypertension and chronic obstructive pulmonary disease were not. Use of aspirin and non-steroid anti-inflammatory drugs (NSAIDs) below the median dose decreased the risk, while use of

aspirin above the median dose entailed increased risk of marginal ulcer. Use of NSAID above the median did not influence the risk of marginal ulcer. Serotonin re-uptake inhibitor use below the median dose was associated with a decreased risk, while use above the median increased this risk.

***Study IV*** tested how various lengths of delays in *H. pylori* eradication after peptic ulcer diagnosis influenced outcomes in a population-based cohort study based on data from nationwide Swedish registries. Delays in eradication time-dependently increased the risk of ulcer recurrence, which was evident already after 8-30 days delay (HR 1.17, 95% CI 1.08-1.25) and so was the risk of complicated ulcer (HR 1.55, 95% CI 1.35-1.78). Longer delays (61-365 days) also seemed to increase gastric cancer risk (HR 3.64, 95%CI 1.55-8.56).

***In conclusion:*** A less radical approach seems sufficient in the surgical treatment of ulcer bleedings. TAE could be recommended as a first-line therapy of peptic ulcer bleeding after failed endoscopic intervention. Diabetes, peptic ulcer history, and higher doses of anti-inflammatory drugs seem to be risk factors for marginal ulcer. Delays in *H. pylori* eradication after peptic ulcer diagnosis must be avoided, since these might time-dependently increase the risk of ulcer recurrence, ulcer complications and gastric cancer.

## LIST OF SCIENTIFIC PAPERS

I. Sverdén E, Sondén A, Leinsköld T, Lagergren J, Lu Y.
**Minimal versus definitive surgery in managing peptic ulcer bleeding: a population-based cohort study**
*Digestive Surgery 2014;31(4-5):276-82*

II. Sverdén E, Mattsson F, Lindström D, Sondén A, Lu Y, Lagergren J.
**Transcatheter arterial embolisation (TAE) compared to surgery for uncontrolled peptic ulcer bleeding**
*Submitted manuscript*

III. Sverdén E, Mattsson F, Sondén A, Leinsköld T, Tao W, Lu Y, Lagergren J.
**Risk factors for marginal ulcer after gastric bypass surgery for obesity: a population-based cohort study**
*Annals of Surgery 2016;263(4):733-7*

IV. Sverdén E, Brusselaers N, Wahlin K, Lagergren J.
**Ulcer and cancer risk following delays in *Helicobacter pylori* eradication in a population-based cohort study**
*Submitted manuscript*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AF | Acceleration factor |
| ATC | Anatomical Therapeutic Chemical |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| COX | Cyclooxygenase |
| CR | The Swedish Cancer Register |
| DR | The Swedish Causes of Death Registry |
| GBP | Gastric bypass |
| H2 | Histamine 2 |
| HCl | Hydrochloric acid |
| HR | Hazard Ratio |
| ICD | International Classification of Disease |
| MU | Marginal ulcer |
| NSAID | Non-steroidal anti-inflammatory drug |
| PPI | Proton pump inhibitor |
| PUB | Peptic ulcer bleeding |
| SSRI | Selective serotonin-uptake inhibitor |
| TAE | Transcatheter arterial embolisation |
| WHO | World Health Organisation |

# INTRODUCTION

Peptic ulcer disease of today is mainly an issue for outpatient routine care. A typical patient is examined and diagnosed (based on endoscopy) in an outpatient setting, receives a short pharmacological treatment – with or without a follow-up examination – and after this, the patient is cured. This uncomplicated peptic ulcer disease is not the clinical issue addressed in this thesis. The scope of this work has instead been to shed some light on more complex forms of peptic ulcer disease. These are less common, but associated with considerable morbidity and mortality, as well as substantial costs for healthcare worldwide. Clinicians regularly face the challenge of quick decision-making in treating life-threatening bleedings from peptic ulcers. They also meet patients presenting with ulcers that arise after obesity surgery, that are difficult to heal, and of unclear aetiology. It is also our responsibility as clinicians to take all measures in order to prevent avoidable ulcer recurrences and further disease development leading to complications of ulcer disease, a task with great impact for the individual as well as for the public health care system. Some of these clinical issues are challenging to scientifically address. The aim of this doctoral project was to add some pieces to the puzzle that will lead to a better knowledge that can improve the treatment of complex ulcer disease.

# BACKGROUND

## HISTORY OF PEPTIC ULCER AND OF PEPTIC ULCER TREATMENT

Peptic ulcer disease and peptic ulcer treatment were first scientifically described in the beginning of the 19$^{th}$ century. The aetiology and cure of this disease has then exercised many minds for the better part of two centuries.

In 1823 it was shown in animal models that gastric acidity was caused by hydrochloric acid (HCl),[1] and it was early recognised that damage was due to impaired resistance of the gastric mucosa to the corrosive properties of this acid. The treatment recommendations for peptic ulcer at this time, besides dietary advice and rest, were different kinds of antacids such as soda, magnesium, and chalk. This regimen persisted far into the 20$^{th}$ century.

In 1938, a report of aspirin causing damage to the gastric mucosa was published.[2] After the introduction of the first non-aspirin non-steroidal inflammatory drug (NSAID) in 1949, reports followed promptly of its association with peptic ulcers.[3 4]

Cimetidine, a histamine 2 (H2) receptor antagonist, was the first effective acid-suppressing drug, invented in 1971 and approved for clinical use in the late 1970s. The even more effective proton pump inhibitors (PPIs) were developed in the 1980s[5] and the first drug in this category for prescription – omeprazole – was introduced in 1988. PPIs irreversibly block the gastric proton pump (the hydrogen/potassium adenosine triphosphatase enzyme system), which is the terminal stage in gastric acid secretion.

In 1982 Warren and Marshall from Australia identified the association between the bacteria *Helicobacter pylori* (*H. pylori*) and peptic ulcer disease[6]. Recommendations that patients with ulcer disease and *H. pylori* infection should be treated with antibiotics came in the middle of the 1990s, which was when the insight that peptic ulcer disease is a curable infectious disease was starting to spread. In 2005, Warren and Marshall were awarded the Nobel Prize in Physiology or Medicine for their important discovery.

Surgery as a means to treat peptic ulcer disease has been reported since the late 19th century. Mikulicz-Radecki was one of the first surgeons to suture a peptic ulcer, and he also developed a precursor to the gastroscope. In 1881 Billroth reported the first successful gastric resection with reconstruction using a gastroduodenostomy for a tumour in pylorus, and the year after, Rydiger performed the first gastric resection for peptic ulcer disease.[7] Gastric resection with Billroth I or Billroth II reconstructions (Figure 1) became standard treatment of ulcer disease in the 1930s, driven by the insight that removing the distal part of the stomach promptly reduced acidity.

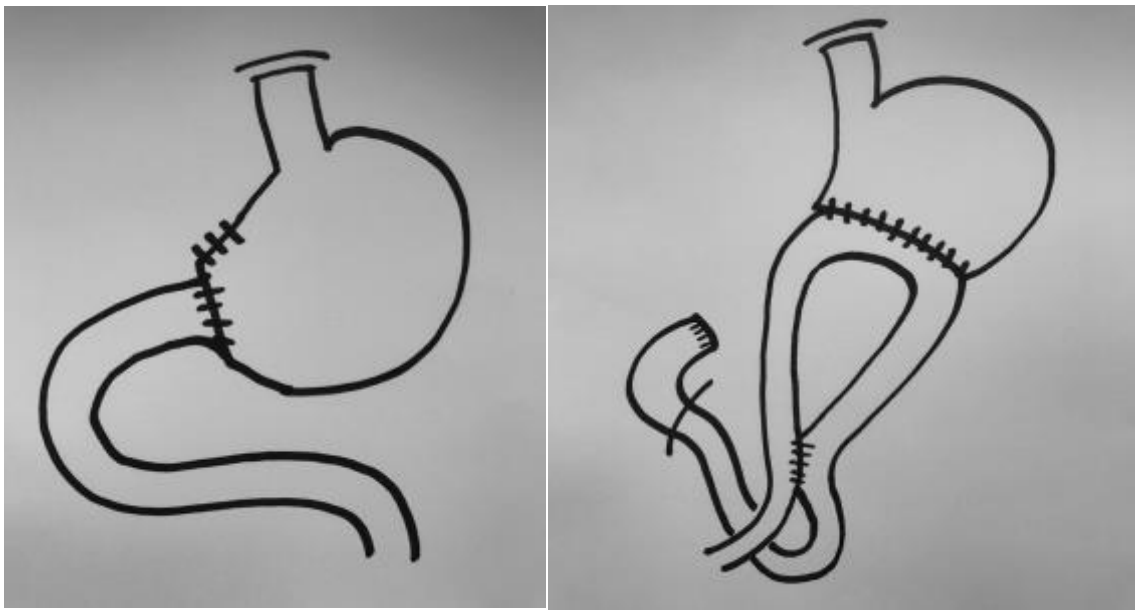

*Figure 1. Billroth I and Billroth II partial gastrectomies*

Common complications following gastric resection were dumping syndrome and anaemia. Dumping syndrome is a constellation of symptoms due to hyperosmolar content emptying into the jejunum, causing for example abdominal pain, nausea, diarrhoea, and vasomotor symptoms such as fatigue, flushing, palpitations, perspiration, tachycardia, hypotension and sometimes syncope.[8] Microcytic anaemia was common due to iron malabsorption caused by achlorhydria, macrocytic anaemia due to loss of parietal cells – leading to deficiency of intrinsic factor and decreased vitamin B12 absorption. There was also a considerable incidence of reported marginal (gastrojejunal) ulcers – up to 33% – that were located close to the anastomosis.[9]

Vagal effects on acid secretion has been known since the beginning of the 20th century, but vagotomy as treatment for peptic ulcer disease was not described until 1946, by Dragstedt.[10] He developed a technique for truncal vagotomy (Figure 2) with remarkably reducing effects on acidic gastric secretion.

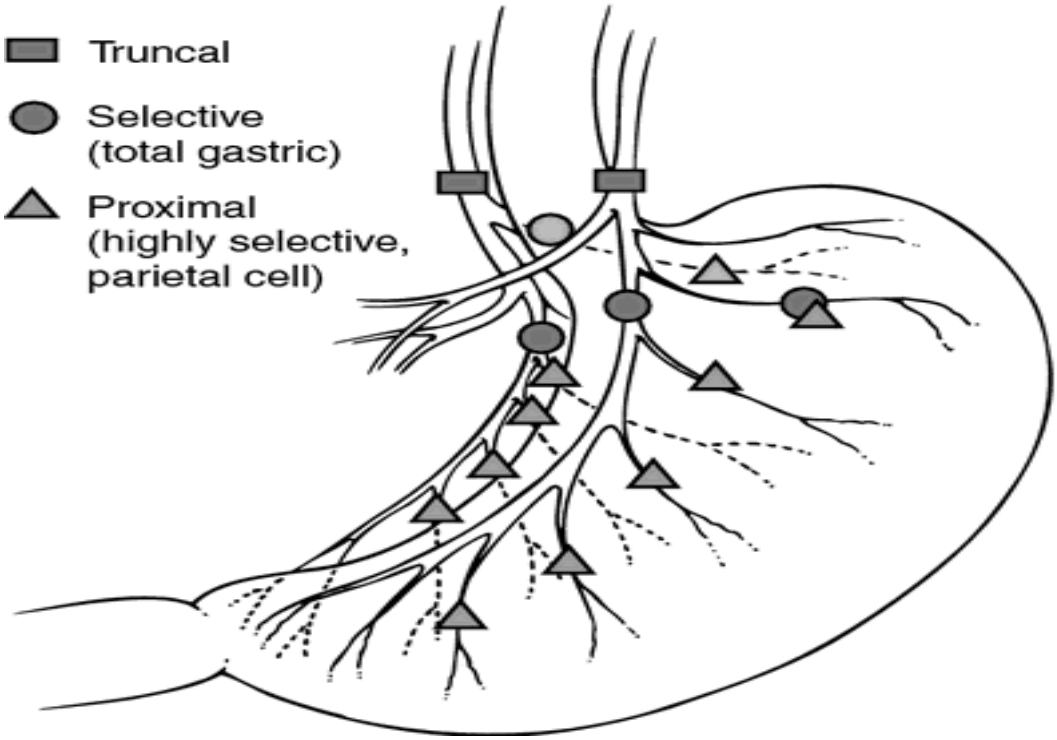


*Figure 2. Truncal, selective and highly selective vagotomy*

Unfortunately, truncal vagotomy also caused hypotonicity of the stomach in more than 50% of the patients, leading to gastric outlet problems. This is the reason why Dragstedt later added the construction of a gastrojejunostomy to the procedure. A little more than 10% of

the patients had ulcer recurrence after truncal vagotomy.[7] Later, developments of the method altered the gastrojejunostomy to a pyloroplasty, with the intention of avoiding gastric outlet problems while maintaining normal food pathway. Another adverse effect of vagotomy was diarrhoea, which was thought to be caused by denervation of the small bowel. In an attempt to reduce this problem, Frankson and Jackson 1948 suggested the use of selective vagotomy, saving branches to the celiac ganglion and anterior vagal nerve to the liver.[11] Later, animal models showed that food and mechanical distention of the antrum caused increased gastric secretion. This effect was inhibited by a low pH, as a regulatory mechanism. In the end of the 1940s, vagotomies were therefore combined with antral resections, conserving 56-60% of the proximal stomach. Rates of ulcer recurrence were fairly low, and the method remained widely used until the end of the 20$^{th}$ century. An even more selective method, "parietal cell vagotomy" or "highly selective vagotomy" was introduced in the 1970s. It was technically more challenging, as it demanded careful removal of vagal fibres from the oesophagus. It denervated the parietal cell mass, but left the antrum innervated (Figure 2).

Gastro-oesophageal endoscopy as a diagnostic tool was introduced in the early 1960s, when a student in physics and a gastroenterology trainee, Curtiss and Hirschowitz, developed the flexible fibre-optic endoscope.[12] Techniques for endoscopic haemostatic intervention for bleeding peptic ulcers were described in the 1970s,[13] and it became common clinical practice in the 1980s, defining a paradigm shift. Endoscopy is since then a mainstay in the treatment of bleeding peptic ulcers.

In the 1990s, simply underrunning the ulcer became an option in emergency surgical treatment of peptic ulcer, combined with acid-supressing therapy and eradication of *H. pylori.* The need for planned peptic ulcer surgery was dramatically decreased after the introduction of effective medical treatment – H2-blockers, PPI and *H. pylori* eradication – and the evolution of endoscopic intervention. Emergency surgery for complications such as perforation and bleeding remained however, and has come to constitute the majority of all peptic ulcer surgery procedures.

Treating peptic ulcer bleeding with interventional radiology started in the 1970s.[14] Transcatheter arterial embolisation (TAE) has gradually gained increased acceptance as an alternative to surgery in peptic ulcers with severe bleeding, and is currently widely used in clinical practice, at least in some centres. Figure 3 depicts frequencies of TAE and surgery

for peptic ulcer bleedings in Stockholm between 2000 and 2014. The introduction of an ambulatory 24-hour radiologic intervention service, is reflected in the increasing incidence of TAE in Stockholm from 2007 and onwards.

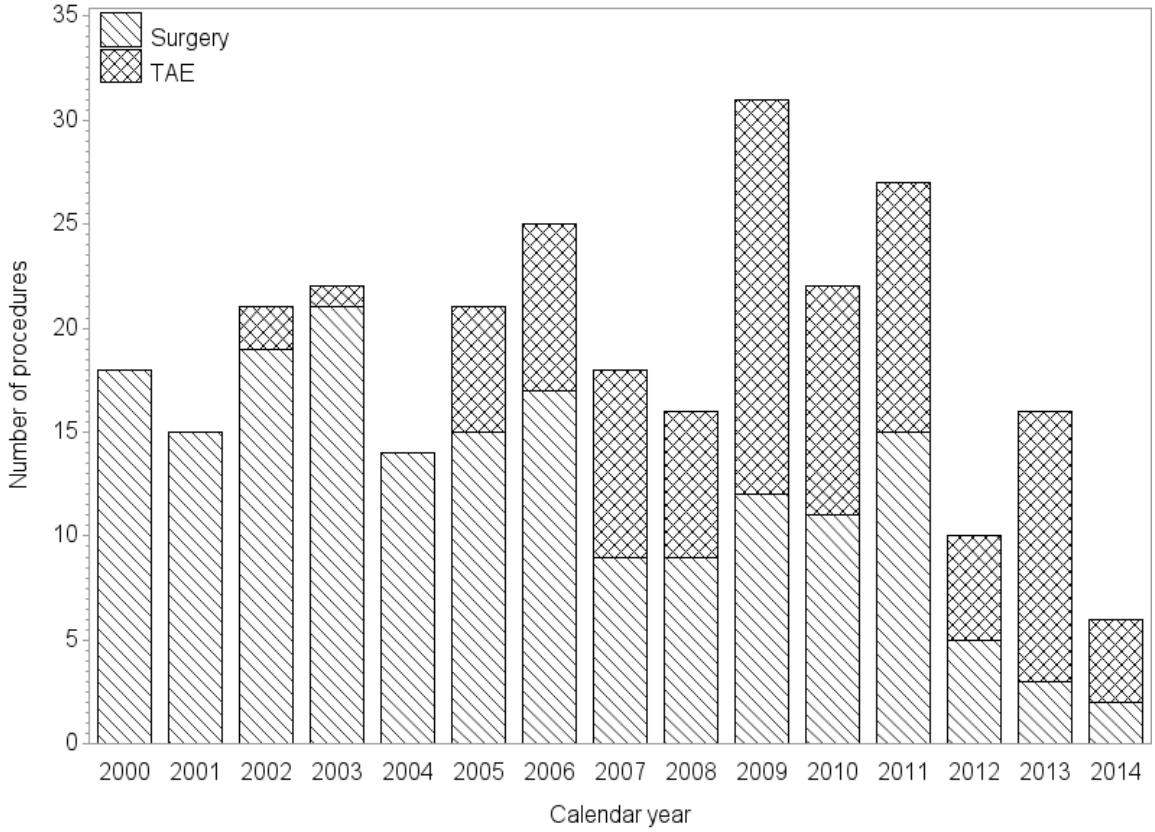


*Figure 3. Changes in the use of surgery versus TAE for peptic ulcer bleeding between 2000 and 2014 in Stockholm County*

## ANATOMY AND PHYSIOLOGY OF THE STOMACH AND THE DUODENUM

### Anatomy

The stomach can be divided into the cardia, fundus, corpus, antrum, and pylorus (Figure 4). The **cardia** is the proximal area where the oesophagus and the stomach connect. To the left of the cardia is the **fundus**. Below the fundus is the **corpus**, which is the largest part of the stomach. The greater curvature, or major side, is the convex left part of the stomach. The lesser curvature, or minor side, is the right concave part. The **antrum** is a more distal part of the stomach. The **pylorus** is an opening with a smooth muscle sphincter that connects the stomach to the duodenum.

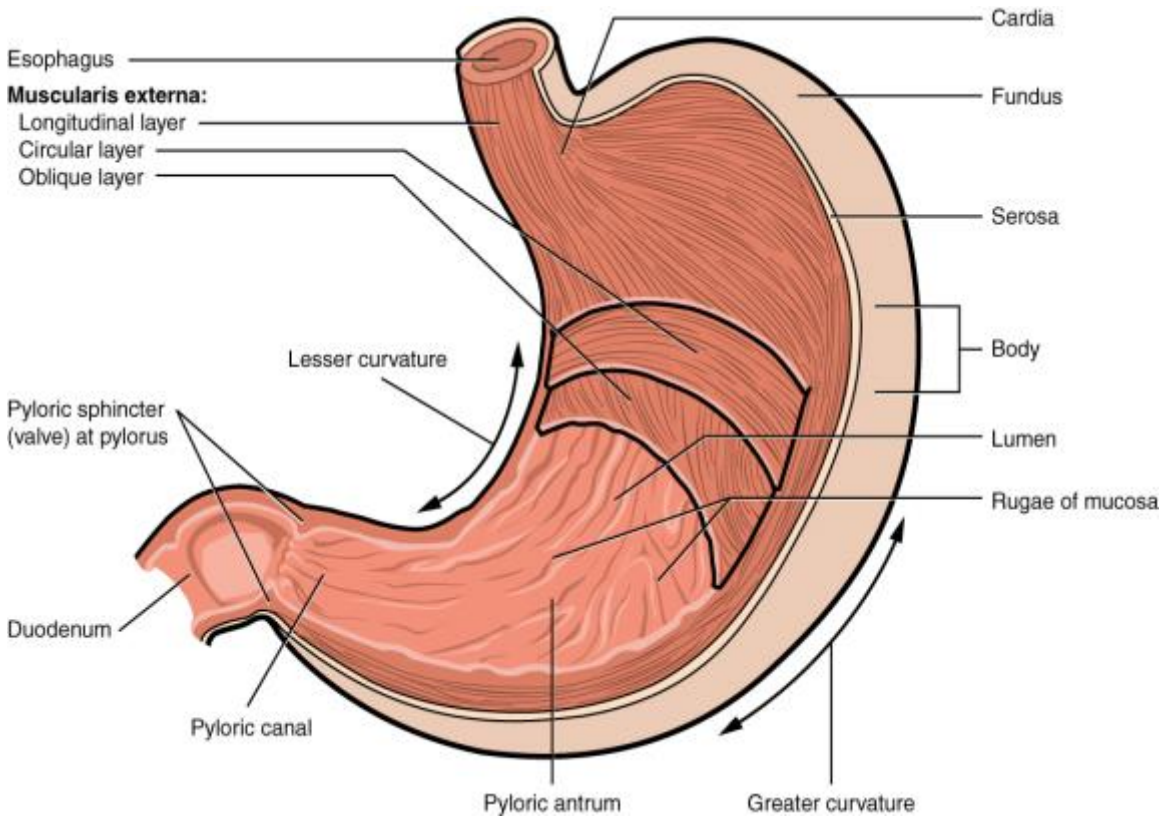


*Figure 4. Anatomy of the stomach* [15]

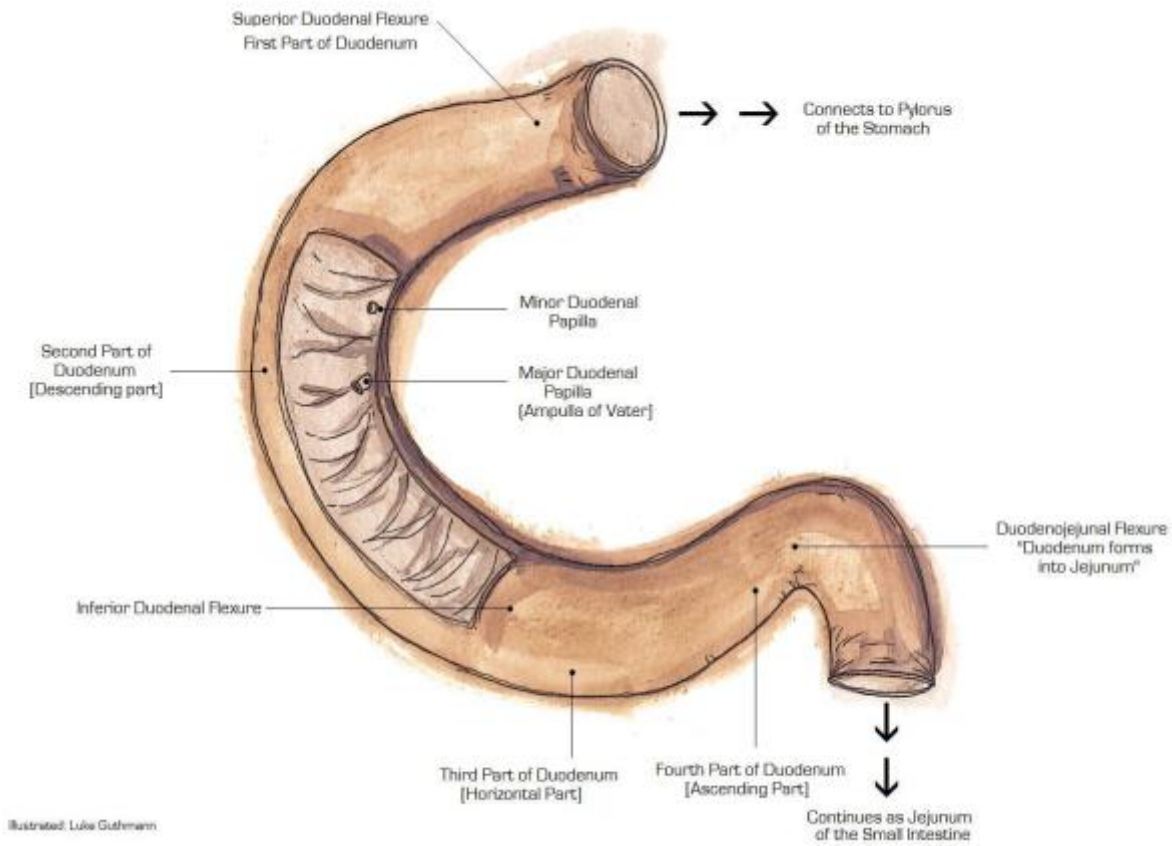


*Figure 5. Anatomy of the duodenum*[15]

Figure 5 depicts the first part of the small intestine – the duodenum. The duodenum starts at the pylorus and reaches to the ligament of Treitz, and it can be divided into four parts. The **superior part,** measuring approximately 5 centimetres, begins at the pylorus, and its first part of 2-3 centimetres is called the **duodenal bulb.** The superior part then passes beneath the liver, becoming the **descending part** of the duodenum. The descending part takes a curve and goes downwards along the pancreatic head. This is the part where the common bile duct and the pancreatic duct enter the medial side of the duodenum, at the major papilla (papilla Vateri). The duodenum then turns medially again and becomes the **horizontal part**, passing across the spinal column while inclining upward for about 5–8 centimetres. The **ascending part** begins to the left of the spinal column. It ascends on the left side of the aorta for another couple of centimetres, and then it reaches **the ligament of Treitz,** where the jejunum starts.

**Blood supply**

The stomach is well supplied with blood flow from various large vessels that communicate with each other (Figure 6), which makes the organ easy to resect with secured oxygenation. The major side is supplied with blood from the left and right gastroepiploic arteries. The upper portion of the major side and the fundus also receives blood from the short gastric arteries. The minor side is supplied from the left gastric artery – which also supplies the cardiac region – and from the right gastric artery. The gastroduodenal artery supplies blood to the distal part of the pylorus and to the proximal duodenum, and to the major side of the stomach. There is also a branch from the superior mesenteric artery supplying the duodenum, the inferior pancreaticoduodenal artery.

**Histology**

The stomach and the duodenum consist of four layers (Figure 7):

1. The **mucosa** is the inner lining, containing epithelial cells, lamina propria (loose connective tissue) and muscularis mucosae (very thin muscular layer).
2. The **submucosa**, consisting of connective tissue with blood vessels, lymph vessels, and nerve cells.
3. The **muscularis externa** (or muscularis propria) consists of 3 different layers of muscle in the stomach.
4. The **serosa** is a fibrous membrane, covering the outside of the stomach and the duodenum.

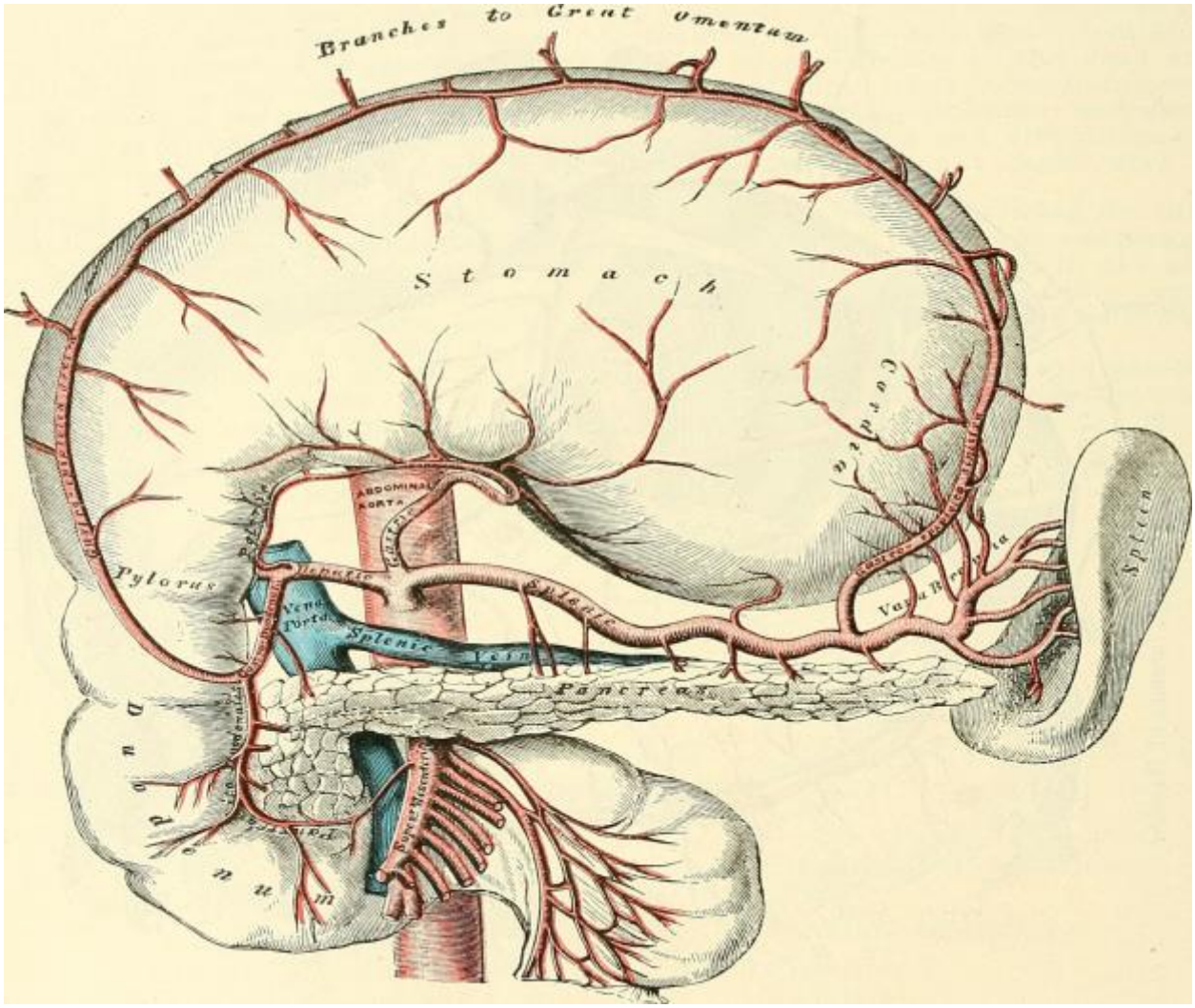


*Figure 6. Blood supply of the stomach and the duodenum*

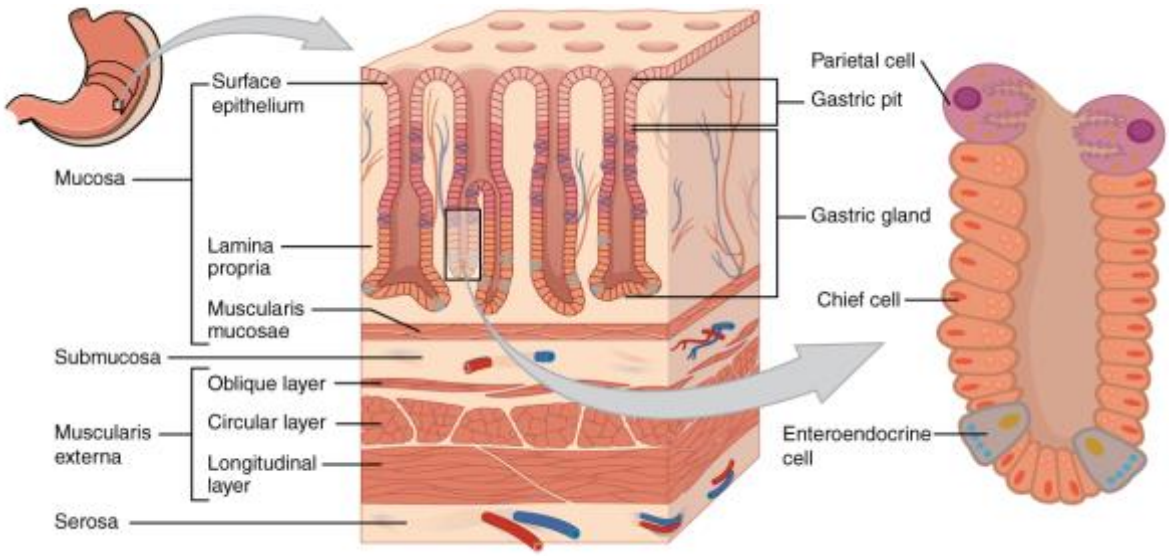


*Figure 7. Histology of the stomach*[15]

**Physiology**

There are several cell types in the stomach (Figure 7). In the cardia, the glands secrete mainly mucus and bicarbonate. The parietal-, chief-, enterochromaffin-like-, and D-cells reside mainly in the fundus and corpus. The majority of parietal cells are localised in the corpus. The antrum contains mostly G cells and D cells, which are so called enteroendocrine cells.[16] **Parietal cells** are highly differentiated epithelial cells that produce hydrochloric acid (**HCl**), responsible for the high acidity (pH 1.5 - 3.5) of the stomach. HCl is also needed to activate **pepsin**, which is an enzyme needed for protein digestion. In addition, HCl has anti-bacterial effects. The parietal cells also produce **intrinsic factor**, a protein that is necessary for the absorption of **vitamin B12** in the small intestine. **Chief cells** secrete **pepsinogen**, the inactive form of pepsin. **Enterochromaffin-like cell**s synthesise and secrete histamine. **Enteroendocrine cells** secrete various hormones, including **gastrin**, which is released mainly by **G cells,** and **somatostatin** produced by **D-cells**.

HCl secretion from parietal cells is under hormonal and nervous control. The major stimulus of acid secretion is gastrin, which mediates the so called **gastric phase** of secretion. Gastrin probably does not stimulate the parietal cells directly, but acts to mobilise histamine from the enterochromaffin-like cells in the mucosa.[17] Histamine then stimulates the parietal cells to secrete HCl. Parietal cells can also produce HCl in response to acetylcholine stimulation from the vagal nerve, protein ingestion, and distension of the stomach. The primary transporter responsible for the acidity of the stomach is the H+/K+ ATPase, also called the **proton pump**, which is located on the surface of the cell. Parietal cells secrete a proton (H+) into the lumen of the stomach in exchange of a potassium ion (K+). There is also a negative regulation of secretion, mediated by somatostatin. A low pH in the antrum stimulates release of somatostatin from the D cells, which exert inhibitory control of gastrin release from the G cells.

The acidic environment in the stomach functions as protection against microbes. The gastric mucosa is protected from the acid by high turnover, tight junctions, mucus, and bicarbonate secretion. If the protective mechanisms of the mucosa are overwhelmed by the damaging effects of gastric acid and pepsin, ulcer formation and other pathology can occur. It has been shown that a low intragastric pH activates pepsin, which can dissolve clots at a site of mucosal damage. The acidic environment also inhibits platelet function.[18]

The duodenum has a villous mucosa, which increases the surface area and facilitates absorption of nutrients. Brunner´s glands in the duodenal mucosa secrete mucus with a high concentration of alkaline bicarbonate that neutralises the acid from the stomach. In response to stimuli from acid and fat-containing food, neural reflexes and prostaglandin production mediate both an increase in alkaline secretion from cells in duodenum, and the release of cholecystokinin and secretin. These hormones stimulate the secretion of bile and pancreatic enzymes into the intestinal lumen.

## PEPTIC ULCERS, DEFINITION AND AETIOLOGY

A peptic ulcer is endoscopically usually defined as a mucosal break in the stomach or duodenum, more than 3mm (some would argue 5mm) in diameter, with a visible depth. Histologically, an ulcer is defined as a break through the muscularis mucosae. If it breaches only through the lamina propria mucosae, or if it is smaller than 3-5 mm, it is instead called an erosion.[19] Complications of peptic ulcer include bleeding, perforation, penetration (to another organ), and obstruction (from stricturing). Bleeding from a peptic ulcer occurs when an ulcer erodes an underlying vessel. Perforation or penetration of a peptic ulcer means that the entire wall of the stomach and duodenum is breached. Obstruction with fibrotic strictures occurs mainly in the pyloric region, often due to chronic ulceration and inflammation.

Acid is no longer regarded dominant in the causal chain of peptic ulcer formation. Instead, it is a well-established fact that the two most common causes of peptic ulcer are infection with the bacteria *H. pylori*, and the use of NSAIDs. [20] [21] Smoking is another well-established risk factor,[22] whereas psychological stress is probably not an important risk factor, even though some researchers have found a weak association.[23] “Stress ulcerations” refer to ulcers that occur during physiological stress such as trauma, major operative procedures, injury of the central nervous system, and during critical illness. Alcohol and coffee seem not to be causal risk factors.[24] Among uncommon causes of peptic ulcers are the Zollinger-Ellison syndrome with excessive hydrochloric acid production due to gastrin secretion, infections, and certain systemic diseases. Cameron ulcers are ulcers in a hiatal hernia where the stomach passes through the diaphragm. Marginal ulcers can appear after gastric resection, or after bypass surgery. These ulcers are usually situated on the jejunal side of the anastomosis.

**Peptic ulcer and *Helicobacter pylori***

*H. pylori* is a spiral-shaped gram-negative bacterium, which colonises the stomach of about 50% of the people in the world. In some countries, the prevalence is well over 70%.[25] Intra-familial oral transmission is considered common.[26] *H. pylori* invades the mucosa, and is considered to be responsible for more than 90% of duodenal ulcers and more than 70% of all gastric ulcers. *H. pylori* is diagnosed by histological test at endoscopy, breath test, serology, or by stool-antigen test. The sensitivity and specificity of the tests vary, as depicted in Table 1.

**Table 1. Different tests to identify *H. Pylori* [27]**

| Test | Indication | Comments | Sensi-tivity (%) | Speci-ficity (%) | Reference |
|---|---|---|---|---|---|
| ***Non-invasive tests*** | | | | | |
| **Urea breath test** | Primary diagnosis, eradication control | Accurate, practical, available | 95 | 98 | Leodolter [28] |
| **Monoclonal stool antigen** | Primary diagnosis, eradication control | Available, requires refrigeration of samples | 94 | 97 | Gisbert[29] |
| **Polyclonal stool antigen** | Primary diagnosis, eradication control | Available, requires refrigeration of samples | 91 | 93 | Gisbert[30] |
| **Serological testing** | Not after treatment | Available, inexpensive, good negative predictive values | 85 | 79 | Loy[31] |
| **Office based blood test** | Not advised | Low accuracy | 71 | 88 | Vaira[32] |
| ***Biopsy-based tests*** | | | | | |
| **Histology** | Additional information on gastritis, atrophy, dysplasia | Expensive, requires trained staff | 93 | 99 | Cutler[33] |
| **Rapid urease test** | Primary diagnosis if endoscopy required | Inexpensive; rapid | 90 | 95 | Vaira[32] |
| **Culture** | Antibiotic susceptibility testing | Excellent specificity, expensive, limited availability, slow growth | 73 | 100 | Grove[34] |

The Maastricht V Consensus Report from 2012 recommended the rapid urease test (RUT) at endoscopy as the first choice to identify *H. pylori*.[35] It has been shown that ulcer bleeding makes *H. pylori* diagnosis more difficult to detect. A prospective study from South Korea found that bleeding decreased the sensitivity of the rapid urease test from 96% to 85%.[36] Use of proton pump inhibitors can make the bacteria go into a coccoid form, which can give false negative test results. For that reason, it is recommended to withdraw such medication two weeks before testing. New techniques for diagnosis are under development, including different kinds of enhanced endoscopic imaging techniques.

*H. pylori* infection is also a well-established risk factor for gastric cancer.[37] In 2014, the World Health Organisation (WHO) reported a strategy of preventing gastric cancer through eradication of *H. pylori*. The report stated that gastric cancer was the third leading cause of cancer deaths worldwide, and that 80% of the 1 million new cases each year were caused by *H. pylori*.[38] A presumed mechanism for this is that the release of pro-inflammatory and acid-suppressive cytokines from the parietal cells induce gastritis, mobilisation of suppressor cells, dysplasia and cancer. The cancer risk is more strongly associated with gastric ulcers than with ulcers of the duodenum.[39 40] There is also a substantial variability regarding the strength of the association between *H. pylori* and gastric cancer between different populations, which could be due to factors that influence the interaction between the bacteria and host, i.e. human genetic polymorphisms, environmental factors and the high genomic diversity of *H. pylori.*

Peptic ulcer disease is associated with histologically proven gastritis. In patients with duodenal ulcers, studies show that the gastritis is localised primarily to the antrum,[41] which differs from the pattern in patients with gastric ulcer or in patients with gastritis, but no ulcer. In gastric ulcer patients, there is a gradual extension of the gastritis from the antrum into the corpus, which eventually leads to loss of parietal cells and development of atrophy. The gradual increase of gastritis leads to decreased acid secretion. When it was discovered that vagotomy was associated with a rather rapid extension of gastritis into the corpus, it was concluded that acid secretion could be responsible for protecting the corpus from atrophic gastritis, possibly by inhibiting the effect of *H. pylori* on further extension of gastritis. A conclusion was that also pharmacological acid suppression could lead to accelerated corpus gastritis caused by *H. pylori*.[42] Development of atrophic gastritis and potentially gastric cancer can thus be enhanced by profound acid suppression in the presence of *H. pylori*.[43]

There is convincing evidence that eradication of *H. pylori* after a peptic ulcer bleeding significantly decreases risk of recurrence.[44] Studies have also shown that such eradication promotes duodenal ulcer healing and prevents recurrence of duodenal ulcers in general[45] and that it decreases recurrence rate for gastric ulcers.[46] The treatment recommendations for *H. pylori* differ between countries, mainly depending on the status of local antibiotic resistance. In Sweden, the first line treatment is presently clarithromycin plus metronidazole for one week in combination with a proton pump inhibitor. Follow-up tests, for example with urea breath test, is not routinely recommended in Sweden today, due to the low incidence of antibiotic resistance.

**Peptic ulcer and non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs in the world, used because of their analgetic and anti-inflammatory effects.[47] Aspirin is often discussed as an entity of its own, but is sometimes also included in this group of drugs. NSAIDs, as well as aspirin, suppress the production of prostaglandins by inhibiting cyclooxygenase (COX), an enzyme required for prostaglandin biosynthesis. Prostaglandins mediate inflammation, and can also inhibit gastric acid secretion, stimulate mucus and bicarbonate secretion, as well as increase mucosal blood flow.[48] Aspirin also has pronounced antiplatelet properties, which is the reason for its widespread use in primary and secondary prevention of cardiovascular disease. Aspirin use is more common among men, while there is a female predominance among NSAID users. The use of aspirin and NSAIDs has increased during the last decades. In 2010, the use of aspirin and NSAIDs in the United States had increased by 57% and 43%, respectively, over a 5-year period, and 46% of all adults over 70 years reported using aspirin regularly.[47]

NSAID-users have an increased incidence of both duodenal and gastric ulcers, occurring in approximately 10% and 14%, respectively, and the incidence is even higher among long-term users.[49 50] Cyklo-oxygenase (Cox)-2 selective NSAIDs are associated with a lower degree of ulcer formation compared to non-selective NSAIDs,[51] but they are associated with an increased risk of cardiovascular disease.

## OCCURRENCE OF PEPTIC ULCER

### Incidence of peptic ulcers, and of peptic ulcer bleeding

The overall incidence of uncomplicated peptic ulcer disease has been decreasing in recent years. A systematic review from 2009 examining the incidence in western countries, reported an annual incidence of 0.10-0.19%.[52] A corresponding decrease in the incidence of complicated peptic ulcer disease, as well as of mortality, could be expected, but these outcomes do not seem to decrease at the same pace. Published data on incidence and mortality for complicated peptic ulcer disease show contradictory results, and there is substantial variability between different countries.[53] The most frequent complication of peptic ulcers is bleeding. The reported annual incidence rate of peptic ulcer bleeding in the general population ranged from 19 to 57 cases per 100,000 individuals (0.02-0.06%) in a systematic review from 2011, based mainly on studies from Europe.[54] In Sweden, the incidence rate of peptic ulcer bleeding was reported to be 38 per 100,000 individuals in 2005 (0.04%).[55]

### Incidence of marginal ulcer

Obesity is one of the leading public health concerns in the world today. WHO reported in 2014 that 13% of adults worldwide – about 600 million people – were obese (BMI >30), and the prevalence has more than doubled in 30 years.[56] Surgery has proven to be an effective treatment for severe obesity with subsequent remission of several obesity-related comorbidities, and improved quality of life and survival.[57] The estimated number of surgical procedures for obesity worldwide was 468,609 in 2013, and the most common procedure was gastric bypass (45%), usually performed with a laparoscopic approach (Figure 8).[58] Furthermore, it is estimated that only <1% of eligible people with severe obesity are undergoing surgery today, which indicates that the use of these procedures might further increase within the foreseeable future.

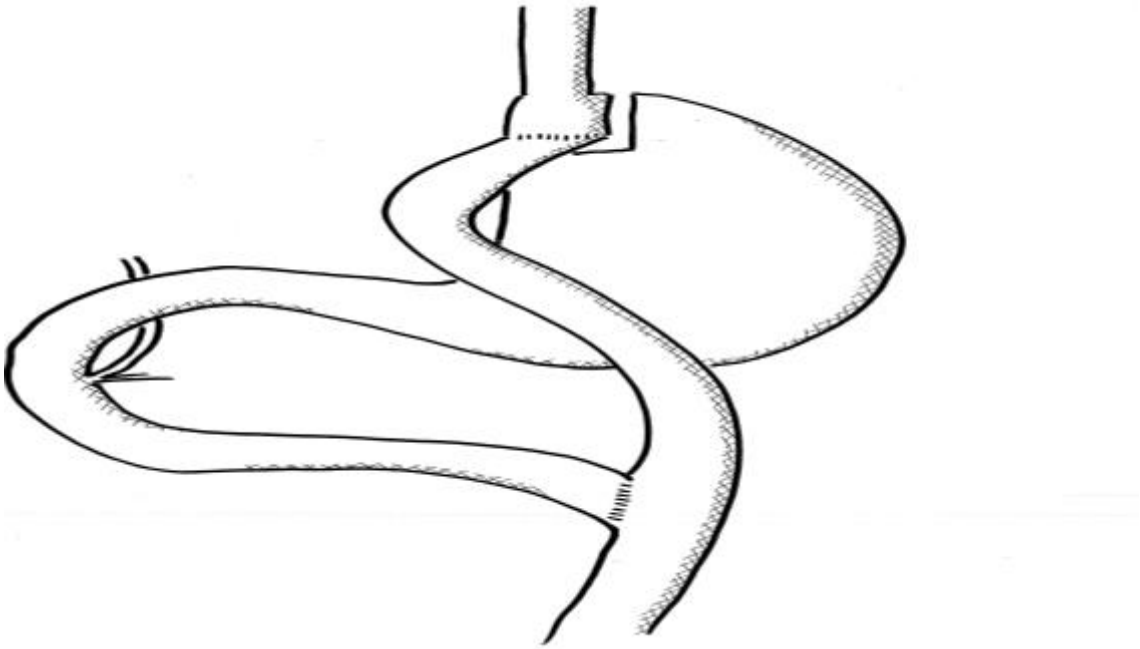

*Figure 8. Gastric bypass (illustration by Rebecka Zacharias)*

One of the most common complications of gastric bypass surgery is a marginal ulcer, which has been estimated to occur in around 5% of patients.[59] These ulcers are almost always located on the jejunal side of the anastomosis. The underlying mechanisms are unclear, but impaired microcirculation and different inflammatory mechanisms have been suggested. Efforts have been made to prevent marginal ulcer by screening for *H. pylori* and treat all who test positive with eradication therapy in combination with prophylactic PPI-treatment for several months. Even with these precautions, 2.3% of the patients developed marginal ulcer after a mean follow-up time of 15 months.[60] Of these, 44.1% required surgical intervention.

## CURRENT TREATMENT

### Treatment of peptic ulcer disease

All patients diagnosed with peptic ulcers should be tested for *H. pylori*. If positive, eradication therapy is indicated.[44] In Sweden however, guidelines usually recommend eradication therapy to all duodenal ulcers without prior testing, since >90% of these ulcers are considered to be caused by *H. pylori.* If the patient has received eradication therapy previously, a diagnostic test is advised to confirm the diagnosis. The eradication therapy consists of a combination of at least two antibiotics and one PPI, the latter is used to accelerate the healing process. For uncomplicated duodenal ulcers, there is no need for continued PPI after the eradication therapy. For gastric ulcers, PPI treatment should last for up to 8 weeks, due to the slower healing of these ulcers.[61] Gastric ulcers should also be

followed up with repeat endoscopies until healed, mainly because some of these ulcers could be misdiagnosed gastric cancers.

**Treatment of peptic ulcer bleeding**

In patients who present with upper gastrointestinal bleeding, the first action is resuscitation. Volume replacement should mainly be obtained by crystalloids[62]. A restrictive transfusion strategy is recommended, with a target haemoglobin (Hb) level of 70-90 g/L.[63] For patients with ischemic heart disease, a higher target Hb could be considered. The European Society of Gastrointestinal Endoscopy (ESGE) recommends prompt injection with high-dose intravenous PPI, followed by infusion for 3 days in cases of substantial bleeding. A Cochrane meta-analysis has shown a significant decrease in bleeding stigmata and need for endoscopic intervention following early intravenous treatment with PPI, even if no significant differences in re-bleeding or mortality could be detected.[64] The issue of continuous PPI-infusion after endoscopy is under debate. A recent re-assessment of a randomised multi-centre trial found low re-bleeding rates among Forrest Ib ulcers after endoscopic treatment, irrespective of PPI or placebo treatment.[65] There is no evidence to support the use of Tranexamic acid.[66 67] There is also uncertainty whether Tranexamic acid could increase the risk of cardiovascular or thromboembolic, since many of these patients have a history of cardiovascular disease and stroke.[68]. Intravenous erythromycin is recommended as a single dose in order to promote gastric emptying and improve endoscopic visualisation.[69] It is recommended to use a scoring system for risk stratification, preferably the Glasgow-Blatchford Score.[70] Early endoscopy (within 24 hours of in-hospitalisation) is recommended.[71] If the patient is unstable despite resuscitation, endoscopy should be performed without delay.

**Table 2. Forrest classification in relation to risk of re-bleeding after endoscopy**

| | Forrest grade | Prevalence* | Re-bleeding* | Surgery* | Mortality* |
|---|---|---|---|---|---|
| Spurting bleed | Forrest Ia | 18% | 55% | 35% | 11% |
| Oozing bleed | Forrest Ib | | | | |
| Non-bleeding visible vessel | Forrest IIa | 17% | 43% | 34% | 11% |
| Adherent clot | Forrest IIb | 17% | 22% | 10% | 7% |
| Flat haematin spot | Forrest IIc | 20% | 10% | 6% | 3% |
| Fibrin-covered clean base | Forrest III | 42% | 5% | 0.5% | 2% |

*All data from prospective trials where no patients received endoscopic therapy[72]

At endoscopy, peptic ulcers should be classified according to the Forrest classification, as a means of deciding whether there is an indication for endoscopic intervention (Table 2).[72] Ulcers with ongoing bleeding or high risk features of re-bleeding (Forrest grade Ia, Ib and IIa), are qualified for intervention due to their substantial risk of recurrent bleeding, as shown in Table 2. Regarding adherent clots (Forrest grade IIb), it is usually suggested to remove the clot if possible[73], since many of these ulcers then can be re-classified to Forrest IIa. Whether to treat a clot that is not removable, is under debate.[74] Endoscopic intervention should consist of a dual therapy with epinephrine injection in combination with either clips, a thermal method or an injection method.[75 76] Novel methods exist, for example haemostatic powder, but these need further evaluation.[77] Second-look endoscopy after initial haemostasis following endoscopy is not recommended,[78] unless the patient shows clinical signs of re-bleeding. Patients with Forrest grade Ia-IIa ulcers, as well as IIb ulcers that have not received endoscopic treatment, should have continuous PPI-infusion for 72 hours. If the patient re-bleeds, a second attempt of endoscopy is recommended. If the bleeding persists, the ESGE recommends transcatheter angiographic embolisation (TAE) or surgery. Bleeding ulcer patients should be tested for *H. pylori*. If the test is negative in the acute setting, re-testing should be performed. Aspirin as secondary prophylaxis for cardiovascular disease should not be discontinued in patients with Forrest grade IIc-III. Patients with Forrest grade Ia-IIb are recommended to resume aspirin 3 days after haemostasis.[63] NSAID-treatment should be withdrawn if possible. If not, treatment with a COX-2 inhibitor seems as effective as combining a regular NSAID with PPI, with respect to the prevention of recurrent bleeding.[79]

**Treatment of marginal ulcer**

Since the incidence of marginal ulcer has been shown to be 27-36% in symptomatic patients after gastric bypass,[80] early endoscopy is recommendable for all patients with symptoms like epigastric pain, nausea, vomiting, or dysphagia. There is no treatment tailored for marginal ulcer. It is recommended to eliminate plausible risk factors, such as tobacco smoking, and to initiate PPI-treatment. There is no consensus or real evidence regarding dosage of PPI, but a high-dose regimen is usually recommended until healing is obtained.[81] These patients should be followed with repeat endoscopies until the ulcer is healed. There is no well-established strategy for secondary prevention after treatment for marginal ulcer.

# AIMS OF THE THESIS

The overall aim of this thesis was to compare treatment options for complicated peptic ulcer, to find risk factors for marginal ulcers after gastric bypass surgery, and to investigate the consequences of non-adherence to follow-up recommendations regarding *H. pylori* eradication after peptic ulcer disease.

The specific aims were:

- To compare mortality after more and less extensive surgery for peptic ulcer bleeding
- To compare mortality, risk of re-bleeding, length of hospital stay and complication rates after transcatheter arterial embolisation with surgery for peptic ulcer bleeding when endoscopic intervention fails to stop the bleeding
- To evaluate risk of marginal ulcer after gastric bypass surgery in relation to diabetes, hyperlipidaemia, hypertension, chronic obstructive pulmonary disease (COPD), ulcer history, use of proton pump inhibitors (PPIs), aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs)
- To test how various lengths of time delays in *H. pylori* eradication following peptic ulcer diagnosis influence the risk of recurrent ulcer, ulcer complications, and gastric cancer

# METHODS

## STUDY OVERVIEW

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| **Short title** | Minimal versus definitive surgery for peptic ulcer bleeding | Transcatheter arterial embolisation versus surgery for uncontrolled peptic ulcer bleeding | Risk factors for marginal ulcer after gastric bypass surgery for obesity | Ulcer and cancer risk following delays in *H. pylori* eradication |
| **Study design** | Population-based cohort study | Population-based cohort study | Population-based cohort study | Population-based cohort study |
| **Data sources** | Swedish Patient Registry, Swedish Causes of Death Registry, Registry of the Total Population | Swedish Patient Registry, Local Hospital Registries, Medical records | Swedish Patient Registry, Swedish Prescribed Drug Registry, Registry of the Total Population | Swedish Patient Registry, Swedish Prescribed Drug Registry, Swedish Cancer Registry |
| **Source population** | All adults in Sweden undergoing surgery for bleeding peptic ulcer during the study period | All adults in Stockholm county undergoing TAE or surgery for bleeding peptic ulcer during the study period | All adults in Sweden undergoing gastric bypass surgery during the study period | All adults in Sweden receiving prescription for *H. pylori* eradication after peptic ulcer diagnosis during the study period |
| **Study period** | 1987 - 2008 | 2000 - 2014 | 2006 - 2011 | 2005 - 2013 |
| **Sample size** | 4131 individuals | 282 individuals | 20,294 individuals | 29,032 individuals |
| **Exposure** | Minimal or definitive surgery for peptic ulcer bleeding | TAE or surgery for peptic ulcer bleeding | Diabetes, hyperlipidaemia, hypertension, COPD, ulcer history, PPI, aspirin, NSAID, SSRI | Predefined delays of *H. pylori* eradication: ≤7d, 31-60d, >365d |
| **Outcome** | Risk of all-cause overall mortality, and all-cause mortality within 30 days, 90 days, 1y, and 5 y of surgery | 1. All-cause mortality, 30d, 90d, 1y, and 5y<br>2. In-hospital re-bleeding<br>3. Duration of hospital stay | Marginal ulcer after gastric bypass surgery | 1. Recurrence of peptic ulcer<br>2. Peptic ulcer complication<br>3. Gastric cancer |
| **Main statistical methods** | Multivariable Cox regression, propensity score model | Multivariable Cox regression, parametric accelerated failure time models | Multivariable Cox regression | Multivariable Cox regression |

## DATA SOURCES

Study I, III and IV are based entirely on data from Swedish national healthcare registries. Study II also uses local hospital registries, and on medical records. Linkage between registries, and between registries and medical records, was possible by using the Swedish personal 10-digit identity number, which uniquely identifies all Swedish residents.[82]

### The Swedish Patient Registry

*The Patient Registry* was established in 1964, and contains complete nationwide data of in-hospital care in Sweden since 1987.[83] Since 2001, the registry also contains complete data of specialist outpatient care and day surgery, including both private and public caregivers. Diagnosis codes at discharge, codes of surgical procedures and hospitalisation dates are among the data that can be obtained. Validation studies have shown that 85-95% of diagnoses are valid,[84] and codes representing upper gastrointestinal surgery have been shown to have up to 99.6% positive predictive value.[85] The diagnoses are coded according to the International Classification of Diseases (ICD) versions 9 and 10.

### The Swedish Cancer Registry

The Cancer Registry was established in 1958. It has 98% complete registration of type and date of gastric cancer diagnoses in Sweden according to a validation study from our group.[86]

### The Swedish Causes of Death Registry

The Causes of Death Registry was established in 1961 in its current shape. It collects information about all deaths among Swedish residents and is believed to have a 99% coverage.[87]

### The Swedish Prescribed Drug Registry

The Prescribed Drug Registry records all prescribed and dispensed drugs in Sweden since 1st July 2005.[88] The registry contains information on names of prescribed drug substances according to the anatomical therapeutic chemical classification (ATC).[88] It also contains information about dose and amount of each prescribed drug.

### The Swedish Registry of the Total Population

This Registry of the Total Population was established in 1968 and provides complete information on dates of birth, death, and migration in Sweden.

## STUDY DESIGN AND METHODS

All studies included in this thesis were population-based cohort studies in design.

### Study I

To compare mortality after less and more extensive surgery for peptic ulcer bleeding, Study I used data from the Swedish Patient Registry to identify all adult patients undergoing surgery for peptic ulcer bleeding between 1987 and 2008. We used the International Classification of Diseases (ICD) version 9 and 10 codes for peptic ulcer bleeding, and the Nordic Medico-Statistical Committee (NOMESCO) codes for identifying the relevant surgical procedures. Less extensive surgery was defined as under-running of the ulcer through a gastrotomy or duodenotomy with or without ligation of the major source artery and/or local excision of the ulcer. More extensive surgery was defined as resection of a part of the stomach or duodenum, with or without vagotomy. The Swedish Patient Registry was also used to identify comorbidities, and to identify if the hospital was a high volume, medium volume, or low volume centre for these procedures. Calendar period was taken into account by dividing the cohort into an early and a late period, analysed separately. Outcomes were all-cause overall mortality, and 30-day, 90-day, 1-year, and 5-year all-cause mortality.

### Study II

To compare key outcomes following transcatheter arterial embolisation (TAE) with conventional surgery for uncontrolled peptic ulcer bleeding, study IV identified patients undergoing TAE or surgery for peptic ulcer bleeding in Stockholm County between the years 2000 and 2014. Patients undergoing TAE were further evaluated through local hospital registries at the radiology departments. This procedure does not have an established code in the Patient Registry. The registries used were the administrative sources on which the radiology departments get economic compensation for their examinations and interventions. All the departments used digitalised recording and patients have to be registered in the system with their personal identity number in order to initiate an examination or intervention. These individuals were then linked to the Patient Registry to identify those who had a peptic ulcer diagnosis at the same hospitalisation. All medical records for patients having undergone abdominal angiography at the time of hospitalisation for peptic ulcer were scrutinised by the author of this thesis, and patients with other indications for angiography than peptic ulcer bleeding were excluded. Patients undergoing

surgery were identified through the Patient Registry. In patients who underwent both TAE and surgery, the first intervention after endoscopy was assigned to the individual. The primary outcome was all-cause mortality, occurring within 30 days, 90 days, 1 year, and 5 years after the intervention. Secondary outcomes were in-hospital re-bleeding, re-intervention, duration of hospitalisation, and complications.

**Study III**

To assess risk factors for marginal ulcer after gastric bypass surgery, study II used the Patient Registry to identify all adult patients who underwent gastric bypass in Sweden between 2006 and 2011. The Patient Registry and the Prescribed Drug Registry were then used to identify the presence of any of 9 potential risk factors that were under study: diabetes, hyperlipidaemia, hypertension, chronic obstructive pulmonary disease, ulcer history, and use of proton pump inhibitors (PPIs), aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin re-uptake inhibitors (SSRIs). The study outcome was the development of marginal ulcer.

**Study IV**

To test how various lengths of delays in *H. pylori* eradication influence the risk of recurrent peptic ulcer, ulcer complications (bleeding or perforation) and gastric cancer, Study IV used the Patient Registry and the Prescribed Drugs Registry to identify all adults in Sweden that were diagnosed with peptic ulcer *and* who were prescribed eradication therapy for *H. pylori* between the years 2005 and 2013. Pre-defined time latency intervals between peptic ulcer diagnosis and *H. pylori* eradication were analysed in relation to the study outcomes.

## STATISTICAL ANALYSES

Associations between exposures and outcomes in all studies were estimated using multivariable Cox proportional hazard regression models, which provided hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for pre-selected potential confounders. In Study I, an additional propensity score matched analysis was conducted since the hazards assumptions were not entirely met. In study II additional parametric accelerated failure time models were used to estimate the association between TAE or surgery and the outcome length of hospital stay, expressed as acceleration factor (AF) and 95% CI.

## ETHICAL CONSIDERATIONS

All studies in this thesis were approved by the Regional Ethical Review Board in Stockholm. Study I, III and IV are strictly register-based, with study subject being anonymous to the researcher. Study II included manual review of medical records, but data were analysed and presented at a group level. Data storage, management and analyses have been performed on firewall- and password protected servers at Karolinska Institutet. Discs were stored in locked safes located in constantly locked offices, accessed only by a personal key card with password.

## RESULTS AND CONCLUSIONS

### Study I

Among 4163 patients having undergone surgery for peptic ulcer during the study period, 2132 (51.2%) underwent less extensive surgery and 2031 (48.8%) underwent more extensive surgery for peptic ulcer bleeding. When comparing these groups, no differences in all-cause overall mortality were identified. Using the less extensive surgery group as the reference, the HRs for mortality in the more extensive surgery group within 30 days, 90 days, 1 year, and 5 years were 0.87 (95% CI 0.72-1.05), 0.93 (0.80-1.09), 1.00 (95% CI 0.87-1.14), and 1.05 (95% CI 0.95-1.16), respectively. No statistically significant differences in mortality were found when analysing the calendar period before and after year 2000 separately, but a trend towards better survival for minimal surgery was indicated in the late period (Table 3). In the later calendar period, using the less extensive surgery group as the reference, the HRs for death in the more extensive surgery group within 30 days, 90 days, 1 year, and 5 years were 1.05 (95% CI 0.65-1.69), 1.18 (95% CI 0.81-1.73), 1.17 (0.84-1.62), and 1.27 (95% CI 0.99-1.63), respectively. The estimates of the propensity score model were similar.

Thus, a minimal approach is probably sufficient in most cases of peptic ulcer bleedings requiring surgery.

**Table 3. Risk of all-cause mortality after surgery for peptic ulcer bleeding before and after year 2000, expressed as hazard ratios with 95% confidence intervals**

| | *Regression model** | | | | *Propensity score model*** | | | |
|---|---|---|---|---|---|---|---|---|
| | Minimal surgery | | Definitive surgery | | Minimal surgery | | Definitive surgery | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| **Before year 2000** | | | | | | | | |
| 30-day | 1.00 (Reference) | | 0.84 | (0.69 -1.02) | 1.00 (Reference) | | 0.92 | (0.74-1.14) |
| 90-day | 1.00 (Reference) | | 0.90 | (0.76 -1.06) | 1.00 (Reference) | | 0.94 | (0.78-1.12) |
| 1-year | 1.00 (Reference) | | 0.97 | (0.84 -1.12) | 1.00 (Reference) | | 1.02 | (0.87-1.20) |
| 5-year | 1.00 (Reference) | | 1.03 | (0.92 -1.14) | 1.00 (Reference) | | 1.04 | (0.93-1.18) |
| **After year 2000** | | | | | | | | |
| 30-day | 1.00 (Reference) | | 1.05 | (0.65-1.69) | 1.00 (Reference) | | 1.21 | (0.65-2.27) |
| 90-day | 1.00 (Reference) | | 1.18 | (0.81-1.73) | 1.00 (Reference) | | 1.27 | (0.76-2.11) |
| 1-year | 1.00 (Reference) | | 1.17 | (0.84-1.62) | 1.00 (Reference) | | 1.22 | (0.79-1.88) |
| 5-year | 1.00 (Reference) | | 1.27 | (0.99-1.63) | 1.00 (Reference) | | 1.22 | (0.88-1.70) |

*Adjusted for age, sex, comorbidities, hospital volume, endoscopic intervention and ulcer history

**Adjusted for propensity score, matched for age, sex, comorbidities, hospital volume, endoscopic intervention and ulcer history

**Study II**

Study II included 282 patients with bleeding ulcer. Of these, 97 (34.4%) patients were assigned to the TAE group and 185 (65.6%) patients to the surgery group. Compared to the surgery group, the overall all-cause mortality was decreased in the TAE group (adjusted HR 0.66, 95% CI 0.46-0.96). The corresponding HRs for all-cause mortality within 30 days, 90 days, 1 year and 5 years were 0.70 (95% CI 0.37-1.35), 0.69 (95% CI 0.38-1.26), 0.88 (95% CI 0.53-1.47) and 0.67 (95% CI 0.59-1.00), respectively (Table 4a). The risk of re-bleeding was higher in the TAE group compared to the surgery group (HR 2.48, 95% CI 1.33-4.62) (Table 4b). The median length of hospital stay was shorter in the TAE group compared to the surgery group (8 versus 16 days), and the acceleration factor (AF) comparing median hospital stay in the TAE-group and the surgery group adjusted for confounders was 0.59 (95% CI 0.45-0.77) (Table 4c). The frequency of complications was lower in the TAE-group (8.3% versus 32.2%).

Taken together, this study indicated that TAE compares favourably with surgery for refractory peptic ulcer bleeding. A better prognosis, shorter length of hospital stay and fewer complications outweigh the higher risk of re-bleeding. Thus, TAE could be recommended as first-line treatment for many peptic ulcer patients.

**Table 4a. Surgery or transcatheter arterial embolisation (TAE) for refractory peptic ulcer bleeding and risk of all-cause mortality, expressed as hazard ratios (HR) and confidence intervals (CI).**

| | Surgery group | TAE group |
|---|---|---|
| | Adjusted HR* (95% CI) | Adjusted HR* (95% CI) |
| Overall mortality | 1.00 (reference) | 0.66 (0.46-0.96) |
| 30 day mortality | 1.00 (reference) | 0.70 (0.37-1.35) |
| 90 day mortality | 1.00 (reference) | 0.69 (0.38-1.26) |
| 1 year mortality | 1.00 (reference) | 0.88 (0.53-1.47) |
| 5 year mortality | 1.00 (reference) | 0.67 (0.45-1.00) |

**Table 4 b. Surgery or transcatheter arterial embolisation (TAE) for peptic ulcer bleeding and risk of re-bleeding and re-intervention, expressed as HR and CI.**

| | Surgery group | TAE group |
|---|---|---|
| | Adjusted HR* (95% CI) | Adjusted HR* (95% CI) |
| Re-bleeding | 1.00 (reference) | 2.48 (1.33-4.62) |
| Re-intervention | 1.00 (reference) | 5.41 (2.49-11.76) |

* Adjusted for age, sex, former ulcer history, comorbidity (Charlson Index) and calendar period.

**Table 4 c.**
**Surgery or TAE for peptic ulcer bleeding and duration of hospital stay after the procedure, expressed as acceleration factor (AF) and CI.**

| | Surgery group | TAE group |
|---|---|---|
| | Adjusted AF (95% CI) | Adjusted AF (95% CI) |
| Duration of hospital stay | 1.00 (reference) | 0.59 (0.45-0.77) |

* Adjusted for age, sex, former ulcer history, comorbidity (Charlson Index) and calendar period.

**Study III**

This study included 20,294 gastric bypass patients. Diabetes and peptic ulcer history were associated with increased risks of marginal ulcer (HR 1.26, 95% CI 1.03-1.55 and HR 2.70, 95% CI 1.81-4.03 respectively), while hyperlipidaemia, hypertension and chronic obstructive pulmonary disease were not. PPI users had an increased risk of marginal ulcer (HR 1.37, 95% CI 1.17-1.60) (Table 5). Aspirin and NSAID consumption below or equal to the median level was followed by decreased risk of marginal ulcer (HR 0.56, 95% CI 0.37-0.86 and HR 0.30, 95% CI 0.24-0.38), while aspirin and NSAID use above the median level had an increased risk and no association with marginal ulcer, respectively (HR 1.90, 95% CI 1.41-2.58 and HR 0.90, 95% CI 0.76-1.87). Selective serotonin re-uptake inhibitor use below or equal to median level had decreased risk of marginal ulcer (HR 0.50, 95% CI 0.37-0.67), while use above the median entailed increased HR (HR 1.26, 95% CI 1.01-1.56).

Taken together, diabetes and peptic ulcer history seem to be risk factors for marginal ulcer, but not hyperlipidaemia, hypertension, or chronic obstructive pulmonary disease. Lower doses of aspirin, NSAIDs and selective serotonin re-uptake inhibitors might not increase the risk, while higher doses of aspirin might. The association with PPI is likely to be due to confounding by indication.

**Table 5. Risk of developing marginal ulcer after gastric bypass surgery for obesity in Sweden 2006-2011, expressed as hazard ratios (HR) and confidence intervals (CI)**

| | HR* | 95% CI |
|---|---|---|
| Diabetes | 1.26 | (1.03-1.55) |
| Hyperlipidaemia | 1.23 | (0.95-1.59) |
| Hypertension | 1.17 | (0.97-1.43) |
| Chronic obstructive pulmonary disease | 0.55 | (0.26-1.17) |
| Ulcer history | 2.70 | (1.81-4.03) |
| Proton pump inhibitor use | 1.37 | (1.17-1.60) |
| Aspirin use | 1.11 | (0.86-1.44) |
| Non-steroid anti-inflammatory drug use | 0.56 | (0.48-0.66) |
| Selective serotonin re-uptake inhibitor use | 0.83 | (0.69-1.00) |

*Adjusted for sex, age, diabetes, hyperlipidaemia, hypertension, chronic obstructive pulmonary disease and ulcer history when applicable

**Study IV**

Study IV included 29 032 patients with peptic ulcer who had had *H. pylori* eradication. Delays in *H. pylori* eradication after peptic ulcer diagnosis time-dependently increased the risk of recurrent ulcer, and even more so for complicated ulcer, starting from delays of 8-30 days (Table 6). Longer delays (61-365 days) also seemed to increase gastric cancer risk. Compared to eradication within 7 days of peptic ulcer diagnosis, eradication within 31-60 days had a HR of recurrent ulcer of 2.37 (95% CI 2.16-2.59), and a HR of complicated ulcer of 3.19 (95% CI 2.69-3.78). Regarding gastric cancer, a delay of 61-365 days corresponded with a HR of 3.64 (95% CI 1.55-8.56).

These findings emphasise the relevance of implementing well-working strategies to expedite *H. pylori* eradication.

**Table 6. Latency intervals between peptic ulcer and Helicobacter pylori eradication in relation to risk of recurrent peptic ulcer, ulcer complicated by bleeding or perforation and gastric cancer, expressed as hazard ratios (HR) and confidence intervals (CI)**

| | Recurrent ulcer | Complicated ulcer | Gastric cancer |
|---|---|---|---|
| **Latency interval** | **Adjusted HR* (95% CI)** | **Adjusted HR* (95% CI)** | **Adjusted HR* (95% CI)** |
| **≤ 7 days** | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| **8-30 days** | 1.17 (1.08-1.25) | 1.55 (1.35-1.78) | 0.85 (0.32-2.23) |
| **31-60 days** | 2.37 (2.16-2.59) | 3.19 (2.69-3.78) | 1.31 (0.31-5.54) |
| **61-365 days** | 2.96 (2.76-3.16) | 4.00 (3.51-4.55) | 3.64 (1.55-8.56) |
| **>365 days** | 3.55 (3.33-3.79) | 6.14 (5.47-6.89) | 4.71 (2.36-9.38) |

* Adjusted for age, sex, comorbidity, history of ulcer disease, use of ulcerogenic drugs and use of proton pump inhibitors.

## METHODOLOGICAL CONSIDERATIONS

Potential errors affecting the results in any direction need to be considered in any research. These errors can be **systematic** or **random**. The systematic errors, also called bias, can distort the results. There are multiple sources of bias. **Information bias** occurs when data are collected or assessed, for example when there is a misclassification of the study exposures or outcomes. The studies of this thesis are all register-based, and the registries used are well-validated. Regarding Study I-III, the Swedish Patient Registry has been validated to have a high sensitivity and specificity for the surgical procedures, which are study exposures. The registry can be expected to have somewhat lower sensitivity regarding less dramatic diagnoses such as for example diabetes, hypertension, hyperlipidaemia, and chronic pulmonary disease, which are used to define the exposure in Study III. It is reasonable to think that more severe forms of these conditions are registered, while less severe form could tend not to be. For example, the specificity of diabetes in the registry has been shown to be high in validation studies, while the sensitivity for the same diagnosis is lower [84]. This can lead to an underestimation and misclassification of the exposure status. However, this misclassification would probably be **non-differential**, i.e., all study subjects would have the same probability of being misclassified, regardless of group assignment. As opposed to **differential** misclassification, non-differential misclassification does not explain associations, but instead dilutes them.

In Study II, besides the well-validated Swedish Patient Registry, non-validated registries kept by the hospital radiology departments were used to identify the TAE-exposure. To minimise the risk of missing patients with an inaccurate registration in these registries, all patients with any code of abdominal angiography were included for further evaluation, regardless of what abdominal vessel, and regardless of registered intervention or not. This assured a high sensitivity. Since all medical records for these patients were scrutinised, and patients with other indications were excluded, the specificity for the exposure definition was close to 100%.

**Selection bias** can occur in the sampling of study participants, and although mainly a problem for case-control studies, this can also be a problem in cohort studies, for example due to differential levels of loss to follow-up between exposure groups. This specifically is not a substantial problem in the present studies, since the loss to follow-up is negligible thanks to the completeness of the registries used. A related problem however, is the issue of competing risk. This can be a problem especially for other outcomes than death, since there is a risk that individuals are lost to follow-up in the sense that they die before the event of

interest occurs, which could be a problem if the mortality differs between the comparison groups. In study II, where the study individuals in general were old with several comorbidities, and where the mortality of the studied disease was considerable, the **competing risk** of death was taken into account when hazard ratios for in-hospital re-bleeding, re-intervention and duration of hospital stay were assessed.

**Confounding** is a bias that needs to be considered in all study designs, not the least in register-based cohort studies. A confounding factor is associated with both the exposure and the outcome, without being a link in the causal pathway between the two. An example is confounding by indication, which means that the characteristics of the comparison groups differ systematically because of the outcome under study. This is a limitation of Study I-II. Some of the known confounding factors are possible to adjust for in the statistical analyses of cohort studies, e.g. by multivariable regression, matching or restrictions, but there will always be a risk of confounding from known or unknown factors that might influence the results in one direction or the other, often referred to as **residual confounding**. In Study I, the additional propensity score analysis was used in an effort to handle the issue of confounding. The ideal study design for comparing two different treatment options and their relation to one or several outcomes is the experimental setting with a large **randomised clinical trial (RCT).** By randomly assigning very many patients one or the other treatment, you can theoretically avoid confounding. However, many exposures are not suitable for randomisation, as is true for many surgical procedures, due to practical or ethical considerations. Moreover, even with a randomised design, there can be a problem with **random errors**, since the number of included individuals is usually a problem in an RCT. Random errors are the errors that prevail even if all systematic errors have been accounted for. These errors are decreased with increased study size, as opposed to the systematic errors.

If a study is well-designed and measures have been taken to avoid as many errors as possible, the **internal validity** can be considered to be high. That means that the study actually measures what it was intended to measure and that you can trust the result to be correct. The next question will be if also the **external validity** is satisfactory, i.e. if the study results can be generalised for people not included in the study. Since the studies of this thesis are population-based, the external validity in general might be considered to be good. Study I, II, and IV are based on the entire Swedish population, which facilitates generalisability. Study II, however, is based on the population of Stockholm County only,

where TAE is probably more readily available compared to some rural areas. Thus, the results might not be generalisable for all of Sweden (or all other populations).

In all included studies of this thesis, Cox proportional hazard regression models were used to estimate hazard ratios. The Cox model is a popular way of analysing survival data, a key reason is that it does not rely on distributional assumptions for the outcome, and it is a robust model - the results will closely approximate the results for the correct model. A parametric model relies on assumptions that the survival time follows a known distribution. If the assumption is correct, the estimate of the regression coefficients will gain accuracy compared to semi-parametric or non-parametric models. A non-parametric model makes no assumptions of distributions. The Cox model is often referred to as semi-parametric, because the baseline hazard is an unspecified function. The Cox proportional hazard model assumes that the hazard for one individual is proportional to the hazard for any other individual, and that the proportionality constant is independent of time. The estimate is a measure of the extent to which a variable multiplicatively increases or decreases an event rate. There are several methods to evaluate if the proportional hazards assumption is fulfilled, for example graphically - through Kaplan-Meier survival curves - or by calculating the correlations between Schoenfelds residuals for a particular covariate and the ranking of individual failure time. In study II, III, and IV the proportional hazards assumption was evaluated and not violated.

In Study I, the Cox proportional hazards assumption was evaluated, both by examining the "log-log"-plots and by calculating the correlation between Schoenfelds residuals for a covariate, and the ranking of individual failure time. Most variables met the assumption, but not all. When addressing the issue of a non-fitting model, there are different options. One option is to abandon the model in favour of another. Another option is to fit the non-proportional variable in a stratified model. In Study I, an additional propensity score model was planned a priori, to take the issue of confounding by indication into account. This model was adjusted for all variables included in the regression model. The propensity score model showed similar results as did the Cox proportional hazards model. Different survival time periods were analysed in both models, and the different calendar periods were analysed separately in a stratified model.

In Study II, parametric accelerated failure time (AFT) models were used to estimate the association between TAE or surgery and the outcome length of hospital stay. In the AFT

model, the effect of a covariate is to accelerate or decelerate the course of an event by some constant (the acceleration factor, AF), in this case the length of hospital stay. Whereas the Cox models compared hazards, the AFT-model compared median survival time.

In Study IV, calculations of the attributable risk were performed. Although such estimations assume causality, which cannot be claimed, this can be used to indicate the proportion of outcomes that theoretically could be avoided by eliminating the specific exposure.

# GENERAL DISCUSSION

## Study I and II

The results of this thesis suggest that there are no major differences in survival in relation to operation method in patients that undergo surgery for peptic ulcer bleeding. The results indicate better survival after TAE compared to surgery in these patients.

A major limitation of both studies is the risk of confounding. It is reasonable to think that clinicians are more prone to allocate older patients with several comorbidities to the seemingly less traumatic treatment option, i.e., less extensive surgery rather than more extensive surgery, and similarly to radiologic intervention (TAE) rather than surgery. This is supported by the distribution of co-morbidities. In the statistical models, age and co-morbidity were therefore adjusted for along with other relevant clinical factors, and in study I we also added a propensity score analysis in an effort to reduce confounding. Residual confounding can of course not be excluded. Another limitation of study I is the lack of TAE-data, which is a possible confounder. The resulting error is more likely be a type II error, by diluting the risk estimates.

Strengths of Study I and II are the population-based design which makes them generalisable, and the completeness of follow-up. The sample size of both studies also exceeds other published studies within the same topic. In both studies, the two emergency treatment alternatives for peptic ulcer bleeding that were compared can roughly be described as one less extensive/invasive with higher risk of re-bleeding and one that is more extensive/invasive with lower risk of re-bleeding. Since both short-term and long-term mortality among these patients usually is not re-bleeding, but rather respiratory or cardiovascular events,[89] it seems reasonable to advocate the less extensive approaches in most patients.

## Study III

The results of this study support some earlier suggestions about the aetiology of marginal ulcer. Earlier literature showed contradictory results regarding diabetes, but this study of over 20 000 patients undergoing gastric bypass for obesity suggests that it actually is a risk factor for developing marginal ulcer. The increased risk in patients with a history of peptic ulcer was also reasonably convincing. However, it is unclear whether this is related to *H. pylori* or some other, endogenous factor. The findings indicating that low doses of NSAIDs and SSRIs could have some protective effect were rather new, and this could be an interesting area for further research in order to understand the mechanisms behind the development of this common surgical complication.

A limitation of Study III is the risk of misclassification of exposure or outcome. Regarding the exposures of different drugs, patient compliance to prescriptions is not known, and over-the–counter use of NSAIDs could not be accounted for. Most smokers do not have a chronic obstructive pulmonary disease, at least not until later in life, so this proxy probably includes the most severe cases of tobacco use, but far from all smokers. The coding of marginal ulcer after gastric bypass surgery in the Swedish Patient Registry has not been validated. However, in our sensitivity analyses, the estimates were similar. Nevertheless, these sources of error should be random and would thus dilute the associations, and not explain them. There is also a small risk of confounding of indication regarding the analgesic anti-inflammatory drugs, but since only prescribed drugs are included this is probably not a big problem. A difficulty in drawing conclusions regarding NSAID use is that the doses are not studied in any detail. Therefore, we cannot draw any conclusions about thresholds for risk-usage of these drugs.

Strengths of the study include the population-based design, the very large sample-size and the completeness of follow-up. Moreover, several potential confounding factors were considered and adjusted for.

**Study IV – Delays in *H. pylori* eradication**

The results of Study IV show that even a rather short delay of *H. pylori* eradication therapy significantly increases the risk of ulcer recurrence and ulcer complications. The fact that eradication of *H. pylori* decreases risk of ulcer recurrence and gastric cancer was suggested in some previous research. However, in practise many patients do not receive eradication therapy in close proximity to the ulcer diagnosis. The new findings of this study show how even limited delays have major impact for the patient and thus for healthcare. Even if follow-up time was short for gastric cancer evaluation, a statistically significant increase in risk could be seen for delays of 60-365 days. Considering that approximately 70% of stomach ulcers and >90% of duodenal ulcers in Sweden are considered to be caused by *H. pylori* and that only 40% have received eradication therapy within 90 days[55] after hospitalisation for bleeding peptic ulcer, a clinical problem obviously exists. This, in a country with rather cheap and available common healthcare for all citizens and subsidies on prescribed drugs. An international multi-centre study from 2012 compared adherence to guidelines for peptic ulcer bleedings in different European countries. In that study, only 18-45% of patients hospitalised for peptic ulcer bleeding were tested for *H. pylori.*[90]

A limitation of this study is the risk of misclassification of the exposure. The *H. pylori* status of all individuals in the study is based on the fact that they are diagnosed with peptic

ulcer and have received eradication therapy. The definition of eradication therapy was based on the treatment recommendations in Sweden, and on the assumption that these antibiotics in combination with a PPI prescription are not commonly used for other indications than *H. pylori* eradication. The misclassification would probably be non-differential and thus dilute the results, instead of explaining them.

Another limitation is that we had no data on medication before start of the Prescribed Drugs Registry in 2005, and we therefore do not know whether there have been earlier attempts to treat *H. pylori* in these individuals, which could be considered a potential confounding factor. Information on smoking habits was not available, but chronic obstructive pulmonary diseases and cardiovascular diseases were included in the models as comorbid conditions, which should reduce any confounding effect. There is a possibility that some ulcer diagnoses in the Swedish Patient Registry within short time from the index ulcer represent physicians referring to the index diagnosis. This potential misclassification would probably also be non-differential – or possibly more common among the patients receiving early treatment, since several visits to doctors with the ulcer being considered, would theoretically increase the chance of remembering the eradication therapy. In both cases, estimates would be diluted instead of enhanced.

The reasons for delays of *H. pylori* eradication therapy could be several. One reason can be false negative test results. False negative tests for *H. pylori* is especially a risk with ongoing bleeding – which has been shown in studies. Another reason for a negative test result could be that some patients have been using PPI prior to the test. It is also possible that physicians simply forget to test and/or treat *H. pylori,* and also that the patient for some reason choose not to collect the prescribed medication. In Sweden, both surgeons and gastroenterologists perform gastrointestinal endoscopy, surgeons mostly in an emergency setting. If an *H. pylori* test has not been performed at the emergency endoscopy in the surgery clinic, patients are sometimes referred for this, and general follow-up, at the gastroenterology outpatient clinic, which can also be a reason for eradication delays. It seems urgent to develop better strategies for *H. pylori* eradication therapy that assures that all patients promptly get tested and treated, regardless of setting at diagnosis.

## CONCLUSIONS

- In patients diagnosed with of peptic ulcer bleeding where surgery is the remaining treatment, less radical surgery with over-sewing of the ulcer is probably sufficient in most patients, and more radical surgery with resection might not be required.
- In patients diagnosed with peptic ulcer bleeding where endoscopic intervention fails to achieve haemostasis, transcatheter arterial embolisation (TAE) can be a first-line treatment at centres with experience of this procedure.
- Diabetes and former ulcer history seem to be risk factors for marginal ulcer after gastric bypass surgery for obesity, while hyperlipidaemia, hypertension and chronic obstructive pulmonary disease might not be associated with this complication.
- Use of aspirin and other non-steroidal anti-inflammatory drugs (NSAID) below the median dose might decrease the risk of marginal ulcer, while aspirin and NSAID use above the median might increase the risk and not be associated with marginal ulcer, respectively.
- Use of serotonin re-uptake inhibitor below the median dose might decrease the risk of marginal ulcer, while use above the median dose might increase this risk.
- Delays in *H. pylori* eradication after peptic ulcer diagnosis seem to increase the risk of recurrent ulcer and, even more so, of ulcer complications in a time-dependant manner.
- Delays of 3 months to 1 year in *H. pylori* eradication after peptic ulcer diagnosis might also increase the risk of gastric cancer.

## CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Clinical decision-making in a situation with massive bleeding from a peptic ulcer will continue to be a challenge for physicians. With modern resuscitation, pharmacological peptic ulcer treatment, effective endoscopic interventions and the addition of TAE, our findings support the "as little as possible" regimen. This doctoral thesis implies that TAE is better than surgery for patients who cannot be managed with endoscopic intervention. A randomised multicentre trial comparing TAE and surgery would be desirable, but practical and ethical aspects make this very difficult in practice. Since it seems safe to conclude that TAE is an important tool in these cases, a 24-hour availability of this intervention can be recommended, which can be accomplished for example by an ambulatory service between hospitals. An interesting topic for future studies is to assess the value of prophylactic TAE in selected cases after endoscopy, preferably in in a randomised multicentre study. Efforts have been made to study this, but not in a larger scale.

Regarding aetiology and treatment of marginal ulcer after gastric bypass surgery, many questions remain to be answered. The role of *H. pylori* is for example unclear, and endogenous patient factors are not well studied. Our findings regarding a potential protective effect of drugs affecting inflammation and coagulation is an interesting topic for further studies examining potential mechanisms.

Evidence-based guidelines recommend testing and treating for *H. pylori* in patients with peptic ulcer disease. However, the adherence to these recommendations seem to be poor, and the findings of this thesis emphasise the clinical consequences of this. Actions need to be taken to improve the compliance to guidelines, including clinical routines, ensuring the quality of tests and monitoring of antibiotic resistance of *H. pylori*.
Finally, it would be desirable to combine the power of nationwide registries with the availability of detailed clinical data by establishing a Swedish quality registry for endoscopy, with prospective data collection. This would facilitate future studies and eventually improve the management of peptic ulcer disease.

## POPULÄRVETENSKAPLIG SAMMANFATTNING

Magsår definieras som ett sår i magsäckens eller tolvfingertarmens slemhinna som är mer än 3-5 millimeter i diameter och sträcker sig ned till muskellagret i väggen. Kunskapen om, och behandlingen av magsår har närmast revolutionerats under de senaste 30 åren. Från att man har ansett att magsår berodde på för mycket magsyra och psykisk stress, vet vi nu att ungefär 70 % av såren i magsäcken och 90 % av såren i tolvfingertarmen beror på en bakterieinfektion som är fullt behandlingsbar med antibiotika tillsammans med medicin mot magsyra. Denna så kallade ”magsårsbakterie” kallas *Helicobacter pylori* (*H. pylori*) och förekommer i magsäcken hos ungefär hälften av världens befolkning även om den inte hos alla orsakar magsår. Den näst vanligaste orsaken till magsår är användandet av vissa vanligt förekommande läkemedel mot inflammation eller smärta eller som blodförtunnande, t.ex. acetylsalicylsyra.

Behandling av magsår består vanligen av en veckas kur med två antibiotika mot *H.* Pylori i kombination med en magsyrahämmande medicin. På så sätt blir de allra flesta patienter av med bakterien. I de fall där läkemedel har orsakat magsåret, ska man om möjligt avbryta den läkemedelsbehandlingen. Om det inte är möjligt bör medicinen bytas mot något mindre skadligt och/eller kompletteras med magsårsskyddande läkemedel. De allra flesta fall av magsår behandlas i öppenvård, men ibland leder magsår till komplikationer, som blödning (vanligast) eller att det går hål (brustet magsår). Trots att insjuknandet i magsår minskat under senare år, har antalet komplikationer till magsår inte minskat, åtminstone inte i samma takt. Detta beror sannolikt på att de patienter som löper störst risk att insjukna ofta är äldre och har flera andra samtidiga sjukdomar.

Vid blödande magsår görs i första hand åtgärder i samband med gastroskopiundersökning, via en lång böjlig slang med kamera och kanaler för olika tillbehör. Detta stoppar blödningen i mer än 9 av 10 fall. Hos resterande patienter har länge det enda återstående alternativet varit operation. Men dödligheten är hög i samband med den belastning kirurgi för blödande magsår innebär i denna akuta situation. Det har saknats studier som jämför resultaten efter olika omfattning av det kirurgiska ingreppet. De studier som finns genomfördes dessutom innan den moderna magsårsbehandlingen gjort sitt inträde, när kirurgi fortfarande var en del i behandling av själva magsårssjukdomen – inte bara av den akuta blödningen. I ***Studie I*** ville vi därför undersöka om det är någon skillnad i överlevnad hos de patienter där man tar bort delar av magsäck och tolvfingertarm (mer omfattande operation) jämfört med dem där man bara sätter stygn över själva blödningen (mindre

omfattande operation). Vi använde information från Socialstyrelsens patientregister för åren 1987-2008 och kunde inkludera 4163 patienter som opererats för blödande magsår och sedan jämföra de två operationsmetoderna. Ingen skillnad i 5-årsöverlevnad kunde ses över hela studieperioden, men dödligheten var antytt högre efter mer omfattande operation jämfört med mindre omfattande operation under den senare halvan av studieperioden (relativ risk [HR] 1.27, 95 % konfidensintervall [CI] 0.99-1.63).

Ett alternativ till kirurgisk behandling av blödande magsår, som använts i ökande utsträckning under de senaste 20 åren, är att stoppa blodflödet till magsåret via en kateter införd i ett större blodkärl, så kallad transarteriell kateter embolisering (TAE). Det går till så att man sticker in i en röntgenkateter via en pulsåder i ljumsken och för katetern uppåt via kroppspulsådern och ut till det blödande kärlet i anslutning till magsåret. Sedan pluggas det blodkärlet igen så att flödet till magsåret förhoppningsvis upphör. Det har dock saknats större studier på hur väl den här metoden står sig i jämförelse med den mer beprövade operationen. I ***Studie II*** ville vi därför jämföra överlevnad, komplikationer, risk för ny blödning och vårdtid på sjukhus för de patienter som behandlades med TAE jämfört med kirurgi. Vi använde information från patientregistret, register på röntgenavdelningar, samt medicinska journaler för att identifiera och jämföra patienter som genomgått TAE (97 individer) eller kirurgi (185 individer) för blödande magsår i Stockholms län under åren 2000-2014. Jämfört med kirurgi var TAE associerat med en 34 % lägre dödlighet (HR 0.66, 95 % CI 0,46–0,96) och med ett lägre antal komplikationer (8,3% jämfört med 32,2%). Vårdtiden var också kortare vid TAE (mediantid 8 jämfört med 16 dygn), men risken för förnyad blödning var klart högre (HR 2.48, 95 % CI 1,33–4,62).

En annan typ av svårbehandlat magsår är det som kan uppkomma efter kirurgi för behandling av fetma. Den ökande förekomsten av fetma och de positiva långvariga effekter som påvisats av kirurgi mot fetma avseende följdsjukdomar och dödlighet, gör att denna behandling ökat snabbt. Det vanligaste ingreppet är en förbikoppling av magsäcken, så kallad gastric bypass, där maten dirigeras förbi stora delar av magsäcken och hela tolvfingertarmen (bild 1, sida 2). En av de vanligaste komplikationerna till detta ingrepp är en särskild variant av magsår som kallas marginalsår. Dessa uppstår intill kopplingen mellan den nyskapade mindre magsäcksfickan och tunntarmen, nästan alltid på tunntarmssidan. Såren är ofta mer svårläkta än vanliga magsår. Orsakerna till varför såren uppstår är till stora delar okända. Tidigare har detta studerats endast i mindre studier från enskilda kirurgiska centra. I ***Studie III*** ville vi identifiera riskfaktorer för marginalsår efter

gastric bypass kirurgi genom att studera en stor grupp opererade patienter från hela Sverige. Vi använde svenska patientregistret och fann 20 294 personer som genomgått gastric bypass kirurgi för fetma mellan åren 2006 och 2011 Genom patientregistret och läkemedelsregistret kunde vi undersöka om vissa på förhand möjliga riskfaktorer verkade påverka risken för marginalsår. Diabetes (HR 1,26, 95 % CI 1,03–1,55) och tidigare magsårssjukdom (HR 2,70, 95 % CI 1,81–4,03) ökade risken, medan höga blodfetter, högt blodtryck och kronisk lungsjukdom (som ofta drabbar rökare) inte medförde ökad risk. Användning av acetylsalicylsyra och antiinflammatoriska smärtstillande läkemedel verkade ge något lägre risk för marginalsår i låga doser, medan högre doser istället gav ökad eller ingen skillnad i risk.

Trots att *H. pylori* kan orsaka magsår och även öka risken för cancer i magsäcken och är en viktig behandling av magsår, så har studier visat att många patienter av någon anledning inte behandlas mot infektionen i nära anslutning till att de vårdats för blödande magsår. Det är oklart om denna fördröjning medför risker, varför vi i ***Studie IV*** undersökte om fördröjning i behandlingen av *H. pylori* med olika tidsintervall efter magsårsdiagnos påverkar risk för återfall i magsår, magsårskomplikationer och magsäckscancer. Vi använde information från patientregistret och läkemedelsregistret och kunde finna 29 032 personer som fått diagnosen magsår och erhållit behandling mot *H. pylori* under åren 2005–2013. Sedan användes patientregistret och cancerregistret för att se hur risken för att få nytt magsår, komplikationer till magsår, eller magsäckscancer påverkades av olika grader av försenad behandling. Vi kunde se att risken för nytt magsår (HR 1,17, 95 % CI 1,08–1,25) och ännu mer dess komplikationer (HR 1,55, 95 % CI 1,35–1,78), ökade redan vid 8-30 dagars försening av behandling. Ju längre fördröjning, desto högre risker. Dessutom fann vi att längre försening (61–365 dagar) även verkade öka risken för magsäckscancer (HR 3,64, 95% CI 1,55–8,56).

**Slutsatser vid dragit av studieresultaten:**

**I:** Mindre omfattande operation tycks ge minst lika bra överlevnad som mer omfattande kirurgi för blödande magsår där åtgärder vid gastroskopi inte kunnat stoppa blödningen, varför den förstnämnda metoden kan rekommenderas.

**II:** TAE tycks vara bättre än kirurgi i behandlingen av blödande magsår. Även om patienter som behandlats med TAE har större risk för ny blödning, så var överlevnaden bättre med färre allvarliga komplikationer och kortare vårdtid efter TAE jämfört med kirurgi.

**III:** Diabetes och tidigare magsår verkar öka risken för marginalsår efter fetmakirurgi med gastric bypass, medan högt blodtryck, höga blodfetter och kronisk lungsjukdom inte tycks öka denna risk. Användning av lägre doser antiinflammatoriska läkemedel tycks inte öka risken, men högre doser verkar göra det.

**IV:** Att fördröja behandling för *H. pylori* ökar risken att återinsjukna i magsår och ännu mer för att få komplikationer som blödning eller brustet magsår på ett tidsberoende sätt. Om behandlingen skjuts upp till intervallet mellan 2 månader och 1 år efter magsårsdiagnosen, verkar även risken för cancer i magsäcken öka.

# ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to a number of people that have contributed very much to the making of this thesis.

**Jesper Lagergren**, my principal supervisor. Thank you for your energy, your patience and your instant e-mail responses around the clock. Thank you also for your inspirational and professional leadership of our research group, of which I am proud to have been a part of.

**Yunxia Lu**, my co-supervisor. Thank you for teaching an ignorant surgeon about epidemiology and biostatistics.

**Anders Sondén**, my co-supervisor. Thanks for moral support and input along the way.

**Urban Arnelo**, my mentor. Thank you for clinical guidance and occasional pep-talks.

**Fredrik Mattsson,** statistician in the research group**.** Thanks for being my tutor in statistics, with endless patience. Thank you also for never letting any details slip away unnoticed.

**Hanna Johans,** the rock upon which our research group rests. Thank you for answering questions I didn't know I had.

**Karl Wahlin,** statistician in the research group. Thank you for enthusiastic work with Study IV and for your pedagogic skills.

My dear present and former colleagues at the department of upper gastrointestinal surgery: **Camilla, Hans, Lennart, Per, Rebecka, Tora, and Totte**. Thank you for covering for me during research weeks and for the fun and support during clinical weeks. I am proud to be a part of our team.

**Ted Leinsköld**, head of upper GI surgery at Södersjukhuset. Thank you for your general support, and for giving me research time when I needed it. I also want to thank you for being a modern leader of our department and for not giving me the sack when I insult you.

**Magdalena Plecka Östlund** my roomie, friend and colleague. Thank you for the support and entertainment. And for your foul mouth.

**The surgical endoscopy team** at Södersjukhuset. Thank you for your professionalism, expertise and support – and for patience and laughter during long procedures dressed in lead.

**Lennart Boström**, head of surgery at Södersjukhuset. Thank you for letting me attend research school with support from the surgery department.

**Agneta Lind** chief secretary at the department of surgery. Thank you for patience with my confused e-mails and for your support during the years.

**Martin Dahlberg**, sometimes apprentice, sometimes tutor. Thank you for helping out with revisions.

**Present and former colleagues in the research unit.** Thank you for interesting discussions and input throughout the years, it has been a true pleasure.

**Eva och Bo Sverdén**, my dear parents. For endless and unconditional love and support all my life, not the least the last few years as a mother of three. I owe you the world!

**Friends and family,** for happy times and moral support.

*Last but certainly not least – my beloved husband **Marcus**. For being my best friend and my better half. Always supportive, always believing in me. I med- och i motgång är du min livboj. Jag älskar dig.*

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