Preventing Complications in Bariatric Surgery
To

Ida - my wife
Tyra and Ellen - my daughters
Hans and Ulla - my parents

There are things known and there are things unknown, and in between are the doors of perception

Aldous Huxley
Örebro Studies in Medicine 147

Erik Stenberg

Preventing complications in bariatric surgery
Abstract


Obesity is a major public health problem. Bariatric surgery is currently the only available treatment that offers sufficient weight-loss and metabolic benefits over time. Although bariatric surgery is considered safe now, serious complications still occur. The aim of this thesis was to identify factors associated with an increased risk for postoperative complication after laparoscopic gastric bypass surgery.

Study I included patients operated with laparoscopic gastric bypass surgery in Sweden from May 2007 until September 2012. The risk for serious complication was low (3.4%). Suffering an intraoperative adverse event or conversion of the operation to open surgery were the strongest risk factors for postoperative complication. The annual operative volume and experience of the procedure at the institution were also important risk factors. Patient-specific risk factors appeared to be less important although age was associated with an increased risk. In Study II, a raised glycated haemoglobin A1c (HbA1c) was evaluated as a risk factor for serious postoperative complications in non-diabetics. A higher incidence of serious postoperative complications was seen with elevated HbA1c values, even at levels classified as “pre-diabetic”.

Study III was a multicentre, randomised clinical trial (RCT). 2507 patients planned for laparoscopic gastric bypass surgery were randomised to either mesenteric defects closure or non-closure. Closure of the mesenteric defects reduced the rate of reoperation for small bowel obstruction from 10.2% to 5.5% at 3 years after surgery. A small increase in the rate of serious postoperative complication within the first 30 days was seen with mesenteric defects closure. This relatively small increase in risk was however outweighed by the marked reduction of later reoperations for small bowel obstruction.

Study IV was a comparison between study III and an observational study on the same population under the same period of time. Although the observational study reached the same conclusion as the RCT, the efficacy of mesenteric defects closure was less pronounced. Observational studies may thus be an alternative to RCTs under situations when RCTs are not feasible. The efficacy may however be underestimated.

Keywords: postoperative complications; bariatric surgery; morbid obesity; risk factor; randomised clinical trial; haemoglobin A1c; prevention

Erik Stenberg, School of Health and Medical Sciences
Örebro University, SE-701 82 Örebro, Sweden
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORIGINAL PAPERS</td>
<td>11</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>12</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>13</td>
</tr>
<tr>
<td>Obesity from a historical perspective</td>
<td>13</td>
</tr>
<tr>
<td>The cause of the obesity epidemic</td>
<td>14</td>
</tr>
<tr>
<td>The consequences of obesity</td>
<td>15</td>
</tr>
<tr>
<td>Treatment of obesity</td>
<td>16</td>
</tr>
<tr>
<td>Change in life-style</td>
<td>16</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>16</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>17</td>
</tr>
<tr>
<td><em>How does bariatric surgery work?</em></td>
<td>22</td>
</tr>
<tr>
<td><em>Effects of bariatric surgery</em></td>
<td>24</td>
</tr>
<tr>
<td><em>The science of bariatric surgery</em></td>
<td>25</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>26</td>
</tr>
<tr>
<td>Complications</td>
<td>28</td>
</tr>
<tr>
<td>Intraoperative adverse events</td>
<td>28</td>
</tr>
<tr>
<td>Early postoperative complications (within 30 days after surgery)</td>
<td>28</td>
</tr>
<tr>
<td><em>Gastrointestinal leakage</em></td>
<td>28</td>
</tr>
<tr>
<td><em>Venous thromboembolism</em></td>
<td>29</td>
</tr>
<tr>
<td><em>Bleeding</em></td>
<td>30</td>
</tr>
<tr>
<td><em>Small bowel obstruction in the early postoperative phase</em></td>
<td>30</td>
</tr>
<tr>
<td><em>Dumping and late hypoglycaemia</em></td>
<td>31</td>
</tr>
<tr>
<td>Late postoperative complications</td>
<td>31</td>
</tr>
<tr>
<td><em>Bowel obstruction</em></td>
<td>31</td>
</tr>
<tr>
<td>Internal hernia</td>
<td>31</td>
</tr>
<tr>
<td>Intussusception</td>
<td>34</td>
</tr>
<tr>
<td>Marginal ulceration</td>
<td>35</td>
</tr>
<tr>
<td>Anastomotic stricture</td>
<td>36</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>36</td>
</tr>
<tr>
<td><em>Nutritional deficiencies</em></td>
<td>37</td>
</tr>
<tr>
<td><em>Gallstone disease</em></td>
<td>38</td>
</tr>
<tr>
<td>Prevention of postoperative complications</td>
<td>38</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>39</td>
</tr>
<tr>
<td>Methodology in surgical studies</td>
<td>40</td>
</tr>
</tbody>
</table>
# AIMS OF THE THESIS

43

# MATERIALS AND METHODS

44

- The Scandinavian Obesity Surgery Registry
- Patients
- Definitions common to all studies in the thesis
  - Definition of comorbid disease
  - Definition of postoperative complications
  - Definition of small bowel obstruction and internal hernia
- Procedure
- Study design
- Ethical considerations
- Paper I
- Statistical analyses
- Paper II
- Statistical analyses
- Paper III
- Randomisation
- Outcomes
- Statistical analyses
- Paper IV
- Outcomes
- Statistical analyses

# RESULTS

52

- Paper I
  - Characteristics of the study group
  - Postoperative complications
  - Patient-specific risk factors
  - Surgery-specific risk factors
  - Multivariate analysis
  - Institutional risk factors
  - Secondary outcomes
- Paper II
  - Secondary Outcomes
- Paper III
  - Adherence to protocol
  - Safety
  - Efficacy
  - Secondary outcomes
Post-hoc multivariate analyses ............................................................ 63
Paper IV .................................................................................................. 63
  Baseline characteristics and follow-up ................................................. 64
  Early postoperative complications – safety outcome ......................... 65
  Reoperation for small bowel obstruction – efficacy outcome .......... 65
  Secondary Outcomes ........................................................................... 66
DISCUSSION .......................................................................................... 67
  General aspects ....................................................................................... 67
  Risk factors for early postoperative complications ............................. 67
  Insulin resistance ..................................................................................... 68
  Prevention of early postoperative complications ............................... 69
  Small bowel obstruction ...................................................................... 70
  Assessment of interventions in surgery ................................................. 72
  The future of bariatric surgery ................................................................. 73
  Limitations .............................................................................................. 74
CONCLUSION ....................................................................................... 76
SWEDISH SUMMARY ........................................................................... 77
ACKNOWLEDGEMENT ....................................................................... 79
REFERENCES ....................................................................................... 80
This thesis is based on four papers, which will be referred to in the text by their Roman numerals (Papers I-IV):

I. Early complications after laparoscopic gastric bypass surgery: results from the Scandinavian Obesity Surgery Registry.


II. Is glycosylated Hemoglobin A1c associated with increased risk for severe early postoperative complications in nondiabetics after laparoscopic gastric bypass?

Stenberg E, Szabo E, Näslund I.  

III. Closure of mesenteric defects in laparoscopic gastric bypass: a multicentre, randomised, parallel, open-label trial.

*Lancet.* 2016;387(10026):1397-404

IV. Laparoscopic gastric bypass: comparison of outcomes from a randomised controlled trial and a concurrent observational study.

Stenberg E, Szabo E, Ottosson J, Näslund I.  
*Submitted manuscript*
ABBREVIATIONS

ADA American Diabetes Association
BMI Body Mass Index (Body weight / Height$^2$)
CPAP Continuous Positive Airway Pressure
CT Computer Tomography
EBMIL Excess BMI-loss ([initial BMI-postoperative BMI] / [initial BMI - 25])
EWL Excess Weight loss ([initial weight-postoperative weight] / [initial weight-weight corresponding to BMI 25 kg/m2])
GLP-1 Glucagon-like peptide-1
HbA1c Glycosylated Haemoglobin A1c
HDL High-Density Lipoprotein
HR Hazard Ration
GBP Gastric bypass
LDL Low-Density Lipoprotein
NIH National Institute of Health
OR Odds Ratio
OS-MRS The Obesity Surgery Mortality Risk Score
PPI Proton Pump Inhibitor
PTH Parathyroid hormone
PYY Peptide YY
RCT Randomised Controlled Trial
RRCT Register-based Randomised Controlled Trial
SF-36 Short Form 36 Health Survey
SG Sleeve gastrectomy
SOReg The Scandinavian Obesity Surgery Registry
SOS Swedish Obese Subjects
VBG Vertical banded gastroplasty
VTE Venous Thromboembolism
Introduction

Obesity from a historical perspective
Shortage of food, starvation, famine and malnutrition have always been part of Man’s history. In this context the ability to retrieve as much energy as possible from food, as well as the ability to store energy as fat, seems to have been an evolutionary advantage. This also reflects the view throughout history of obesity as being beautiful. The Stone Age people believed that gods were obese more than 20 000 years ago, and “fleshy, well-curved women” were considered to be the ideal of beauty in ancient Greece, Egypt and Rome, and during the Middle Ages. This ideal is well exemplified in paintings by Michelangelo and Rubens during the Sixteenth and Seventeenth Centuries. During the Eighteenth Century, attitudes towards obesity began to change, and ironic stereotype characters began to emerge in important literary works such as those by Charles Dickens (Joe in the Posthumous Papers of the Pickwick Club) in the Nineteenth Century and William Golding (Piggy in Lord of the flies) in the 1950s. It was during the Nineteenth Century that the medical consequences of obesity began to be observed, but overweight was still considered a healthy norm. During the Twentieth Century the first alarm reports on the consequences of obesity were published, at about the same time that Freudian theory described an eating disorder as being the consequence of subconscious conflict. Gradually the view of obesity shifted from being a thing of beauty to one of ugliness. During the 1960s medical science began to view obesity as a pathological process and eventually obesity was considered a disease of its own right.

Over the last three decades, overweight (BMI>25) and obesity (BMI>30) have increased dramatically throughout the world, in both developed and developing countries. The worldwide prevalence of overweight has increased from 27.5% in 1980 to 47.1% in 2013, with an estimated 2.1 billion overweight individuals. Although the increase in adult obesity has levelled off in some developed countries over the last decade, no country has seen a significant decline since 1980.
The cause of the obesity epidemic

Although the primary cause of the obesity epidemic is excess calorie intake along with low expenditure of energy \(^4-6\), the development of obesity is a complex process involving political, socio-economic, genetic and environmental factors, as well as the microbial ecology of the gut \(^4,7,8\). The current market-economy system enabling high growth and consumption, along with plentiful food supply and a marketing environment promoting high calorie intake, creates an overconsumption of energy-rich foods \(^7\). Other environmental moderators create an environment where physical activity
and expenditure of energy is low. The modern life-style also promotes a chronic sleep-deprived state that also increases the risk for obesity. Although the choice of whether or not to eat and to exercise are ultimately the choices of each individual, these decisions are usually automatic or subconscious. Furthermore, there are multiple genes linked to increased risk for developing obesity. Individually these genes have only a modest effect on hunger, satiety and food intake, but they may be amplified by environmental factors.

The human gut harbours 10-100 trillion organisms. The obese individual has a profoundly altered composition of gut bacteria, with reduced diversity and altered representation of genes and metabolic pathways. Bacteria in the obese individual’s gut appear to extract more energy from the diet and alter transcription of mediators involved in nutrient absorption, mucosal barrier function, angiogenesis, metabolic function and storage of energy.

---

The consequences of obesity

Obesity is associated with an increased incidence of chronic disease, mainly hypertension, type 2 diabetes mellitus, gallbladder disease, osteoarthritis, hypercholesterolaemia, cataract, depression and cardiovascular disease.
There is also an increased incidence of cancer, mainly colon cancer, oesophageal adenocarcinoma and renal cancer, in both men and women, thyroid cancer in men, and gallbladder cancer, endometrial cancer and postmenopausal breast cancer in women. In addition, an increased risk for obesity-related as well as all-cause mortality associated with obesity, and a reduction in health-related quality-of-life has been reported. A white, American man with a BMI>45 kg/m² can statistically expect a 13-year shorter life than if the same man had a BMI of 24 kg/m². For women with the same background and BMI, the expected number of years of life lost due to obesity is eight.

**Treatment of obesity**

Obesity is a global public health issue that needs to be addressed from several aspects. Despite several attempts to prevent obesity, there are no examples of success through public health campaigns. Effective treatment of obesity at the individual level is thus required.

**Change in life-style**

Life-style changes aiming at promoting a healthier choice of food and avoiding sedentary activity are intriguing methods for losing weight that can be effective in the short term, but results are discouraging when it comes to long-term weight-loss. Even after intensive life-style interventions, the degree of weight-loss is insufficient to reduce the risk for important health-related negative outcomes in morbidly obese persons.

**Pharmacological treatment**

There are limited studies on drug treatment for obesity. Several promising drugs have eventually been removed from the market because of serious toxic effects. The best-studied drugs at present are orlistat, lorcaserin and phentermine/topiramate with reported weight-losses 3-7 kg greater than with placebo, and with a fair chance of losing more than 5% weight over 1 year. They work best if combined with intense lifestyle changes.

Orlistat is an inhibitor of gastrointestinal lipase leading to excretion of approximately 30% of ingested fat. Orlistat is associated with significant improvements in cholesterol and glucose levels and blood pressure. Due to unpleasant gastrointestinal side-effects, however, it is not well tolerated and less than 10% of patients continue treatment more than a year.
Lorcaserin is a selective serotonin 2C receptor agonist with similar weight reducing effects as orlistat and significant effects on blood pressure, cholesterol and triglyceride levels \(^37\). Common side-effects are headache, nausea, fatigue and dizziness. There are also concerns about long-term cardiovascular effects due to an increase in absolute numbers of patients with heart valve problems and hypertension in previous studies \(^38\).

Phentermine/topiramate is an antiepileptic drug that reduces appetite \(^41\). Unfortunately, the drug has teratogenic side-effects and increases the resting pulse with possible risk for cardiovascular events. It has been approved in the US with the requirement that long-term cardiovascular safety must be assessed \(^38\).

In Sweden, only orlistat is currently recommended for prescription. Li raglutide is a GLP-1 agonist available in Sweden for the treatment of type 2 diabetes, but has been approved in the US and parts of the European Union for management of overweight \(^30\). Liraglutide causes an increase in heart rate and there is also concern over the increased risk for thyroid cancer seen in animal studies \(^30\).

**Surgical treatment**

The first attempt to surgically achieve significant weight-loss was performed in Sweden by Viktor Henriksson and reported in a paper in 1952 \(^42\). Dr Henriksson removed 105 cm of small bowel from an obese woman. The results, however, were not promising, with a net weight gain of 2.2 kg after 14 months. In the decades that followed, several different techniques were developed. Based on the results from animal studies, Richard Valasco attempted to bypass parts of the small bowel instead of removing it in a so-called jejuno-ileal bypass in 1953 \(^43\). The method was then used in clinical practice during the 1960s and ‘70s \(^44\). Serious complications were common, mainly in the form of the ”blind loop syndrome” caused by bacterial overgrowth in the isolated bowel resulting in abdominal bloating, migratory ar thralgia and liver problems. As many as 5% developed liver cirrhosis and 1-2% eventually developed liver failure \(^44\). In addition many suffered from diarrhoea and severe malnutrition \(^44\). The jejuno-ileal bypass was abandoned when gastric procedures came onto the scene.

Inspired by the weight loss seen after gastric surgery for other reasons, Mason and Ito developed the gastric bypass procedure (GBP) in 1966 \(^45\). Since then the technique has evolved in several steps to become the technique used today \(^46,47\). The first Swedish gastric bypass procedure was performed at Örebro University Hospital in 1975.
In 1971 Printen and Mason performed a horizontal gastroplasty where they divided the upper part of the stomach horizontally leaving a small connection to the lower stomach \(^4^8\). The method later evolved to become the vertical gastroplasty, and eventually the vertical gastroplasty was enforced by a band thus creating the vertical banded gastroplasty (VBG) which became very popular \(^4^9\). To avoid surgery that breaches the gastric wall, the method was further developed into adjustable gastric banding (AGB) where an adjustable band is placed around the fundus of the ventricle without gastroplasty \(^5^0\). All these procedures were based on the original assumption that restriction of the size of the stomach was the most important mechanism behind weight-loss after bariatric surgery \(^5^1\).

![Fig 3. Illustration of a vertical banded gastroplasty (VBG)](image)
In 1979 Scopinaro reported on an operation where the distal stomach was removed along with the jejunum just distal to the ligament of Treitz and reattachment of the proximal end to the lower part of the ileum and the distal end to the gastric remnant. In the Nineties the method was further developed into a vertical gastrectomy with a duodenal switch and later into what is now known as biliopancreatic diversion with duodenal switch. The operation can be performed in two stages the first being a vertical, partial gastrectomy, so-called sleeve gastrectomy (SG). Using this technique many patients lost significant weight after the first stage of the procedure alone, and were able to maintain this weight-loss over time.
In 1986, Geliebter developed a non-invasive technique using an intra-gastric balloon. The balloon technique, however, was associated with erosion of the gastric wall in a significant number of patients and can only be kept in place for a maximum of 6 months $^{60,61}$. Another problem was migration of the balloon causing bowel obstruction. The weight-loss results were disappointing and this method failed to reach widespread use outside private practice and is no longer used in Sweden.

Minimally invasive techniques were developed during the 1990s. In 1993, the first laparoscopic adjustable gastric banding operation was reported $^{62}$ and a few years later laparoscopic gastric bypass was introduced $^{63,64}$. These techniques led to reduction in operation time, postoperative morbidity and complication rates. This together with the increasing prevalence of morbid obesity and many reports on the benefits of bariatric surgery led to a great demand for bariatric surgery. Today the number of procedures performed worldwide has increased dramatically to approximately 500,000 operations each year $^{65}$.

At present, gastric bypass, sleeve gastrectomy, gastric banding and duodenal switch are all commonly performed using minimally invasive technique $^{65}$. Duodenal switch is the most effective bariatric procedure known
Severe nutritional deficiency, however, is a common side-effect and these patients need life-long follow-up. Serious complications limit the widespread use of this procedure.

The two most common procedures worldwide today are gastric bypass and sleeve gastrectomy. Gastric bypass (GBP) seems to be slightly more effective compared to sleeve gastrectomy with an average weight-loss of 70-80% excess weight-loss (EWL) compared to 60-65% EWL for sleeve gastrectomy. Although both methods are effective in improving associated comorbidity, GBP seem to have a better effect on diabetes, hyperlipidaemia and health-related quality-of-life 2 years after surgery. The gastric bypass is reversible, while a large part of the stomach is removed in sleeve gastrectomy (the procedure is thus irreversible). Sleeve gastrectomy (SG) may also significantly worsen symptoms from gastro-oesophageal reflux. On the other hand, there are no anastomoses and no mesenteric defects created, thus eliminating the risk for obstruction and pain originating from the jejunoojejunostomy. The risk for small bowel obstruction is also reduced since the problem of internal herniation is eliminated. Large randomised trials comparing SG and GBP, providing long-term data, are still needed.

The once so popular gastric banding procedure has lately fallen into disrepute because of the disappointing long-term results. There are centres, particularly in Australia and parts of the US, that report good results with gastric banding, but in other parts of the world the results are disheartening with as many as 50% of the bands removed after 15 years.
How does bariatric surgery work?
Traditionally bariatric surgical procedures were viewed as either strictly restrictive, strictly malabsorptive or a combination of the two. With time and research it became evident that restriction was of minor importance for the outcome. Later it became evident that mechanisms other than malabsorption were responsible for the weight-loss. It now appears that the mechanisms behind weight-loss, improvement in glucose homeostasis and resolution of comorbid disease are much more complex than previously believed. The mechanisms seem to depend on reduction in stomach size, rearrangement of the gut anatomy, alterations in bile flow, vagal nerve manipulation and modulation of gut hormones. With Roux-en-Y gastric bypass the food enters a small pouch that, because of intact vagal innervation, mediates early satiety. Although the small pouch to some extent provides restriction, the wide anastomosis is probably more important than the size of the pouch. The wide anastomosis to the small bowel allows the rapid transition of food into the small bowel, generating signals to the brain to reduce the meal size. The consequence of this is a reduction in daily intake.
of calories of between 1200 and 1500 kcal 3-6 weeks after surgery 88,89. Although the daily intake of calories tends to increase over the following years, it remains lower than before surgery 88-90.

Bile enters the gastrointestinal tract via the biliopancreatic limb and this modulation may trigger the gut-brain-liver axis to signal satiety earlier with improved glucose homeostasis after a meal 85. Intact vagal innervation may be necessary for this effect to exist 85. GLP-1 and PYY are peptides released into the small bowel and to some extent the colon as a response to food in the stomach. GLP-1 inhibits gastric emptying in the stomach and promotes insulin sensitivity and secretion. PYY slows gastric emptying and increases the effectiveness of digestion 91. The secretion of both peptides in relation to food increases after surgery 92-94. Ghrelin is another gastric peptide that stimulates appetite 95. Ghrelin levels decrease after GBP 92, but the extent to which this contributes to weight-loss is unclear 91. The altered anatomy following GBP results in undiluted bile acids reaching the distal intestine. This has been proposed to be at least partially responsible for intestinal hypertrophy, secretion of anorexigenic hormones, and changes in the gut microbiota 96. Whether or not this change in gut microbiota contributes to the beneficial effects of bariatric surgery has yet to be established, and for the moment should be viewed as an epiphenomenon 85,96,97.
Effects of bariatric surgery

Besides the obvious effect of weight-loss\textsuperscript{98}, bariatric surgery has several positive effects on health. Hypertension, dyslipidaemia, sleep apnoea and diabetes all improve significantly after bariatric surgery\textsuperscript{99-102}. Remission of diabetes has been reported to be as high as 72-78\% 1-2 years after surgery\textsuperscript{99,103-105}. Although a substantial number of patients experience relapse in their diabetes, as many as 30\% remain free from the disease 15 years after surgery\textsuperscript{99,103,104}. Both macrovascular and microvascular complications are reduced\textsuperscript{104}. Bariatric surgery also prevents new occurrences of diabetes\textsuperscript{106}. The effect on hypertension seems to be less pronounced than the effect on
diabetes. Remission rates of 17-42% have been reported in previous studies, but as many as 63% experience improvement\(^\text{107}\). Triglycerides and LDL are reduced in 67-80% of patients 2 years after surgery, with an equivalent increase in HDL\(^\text{98,99}\). Patients with obstructive sleep apnoea who reduce their weight significantly, and retain this weight-loss, experience significant improvement\(^\text{102,108,109}\).

The risk for cardiovascular events are significantly reduced after bariatric surgery\(^\text{107,110}\), and this is particularly evident in patients with diabetes and obesity\(^\text{111}\). The overall risk for new cancer is also reduced after bariatric surgery. The reduction is mainly seen in women, whereas this effect is not so certain in men\(^\text{112,113}\).

Physical and some aspects of mental quality-of-life improve after bariatric surgery\(^\text{102,114,115}\). This effect is largely related to weight reduction and seems to peak 12-18 months after surgery\(^\text{114}\). A weight-loss of 10% seems to be sufficient for improvement in health-related quality-of-life\(^\text{114}\).

Bariatric surgery reduces mortality from coronary artery disease, diabetes and cancer, but seems to increase mortality from accidents and suicide\(^\text{116}\). All-cause mortality is reduced by 20-40% up to 15 years after surgery\(^\text{116,117}\).

Bariatric surgery is cost-effective when treating patients with a BMI \(\geq 35\) or patients with a BMI \(\geq 30\) with diabetes\(^\text{118}\).

The science of bariatric surgery

Historically, the development of bariatric surgery has followed three periods. Starting with the first bariatric procedure by Victor Henriksson 1952, focus during the first period was on the development of surgical techniques. Although the experimental procedures during this scientific period provided the basis for surgical methods used today, well-designed trials were few. When the adjustable gastric band, vertical banded gastroplasty and the gastric bypass procedures had reached wide acceptance among bariatric surgeons, scientific focus shifted towards assessing the efficacy of bariatric surgery. During this period, larger, more well-designed studies were conducted. However, for many reasons, randomised trials were difficult or impossible to conduct. This was exemplified by the Swedish SOS-study, where the ethics committees disapproved of randomisation due to ethical concerns regarding the safety of bariatric procedures. The scientific reports emerging from the first two periods made way for the dramatic increase in bariatric surgery seen around the beginning of the 21st Century. With this increase in bariatric surgery came a growing concern about complications and side-effects. This led to the third scientific period where focus shifted towards...
safety issues and prevention of short- and long-term complications follow-

**Gastric bypass**

Inspired by the weight-loss seen after gastrectomy with Billroth-II gastro-
jejunostomy for peptic ulcer, Mason and Ito performed the first gastric by-
pass procedure for morbid obesity in 1966 \(^45\). In their original procedure,
the stomach was divided horizontally and anastomosed to the jejunum at
the distal part of the gastric pouch (Fig 9a). The procedure was repeated by
other surgeons, each making small modifications to the original procedure.
Complication rates from leaks and bile reflux were initially rather discour-
gaging. In 1977 Griffen et al reported a gastric bypass procedure where the
bile was diverted from the gastric pouch through a jejunojejunostomy (Fig
9b) \(^47\). During the 1980s the technique shifted towards creating the gastric
pouch on the lesser curve where the blood-supply is better preserved \(^44\).
Since then the technique has largely remained unchanged \(^51\). In 1994 Witt-
grove described the first laparoscopic gastric bypass procedure\(^63\). It took a
further two years before a more technically easily accessible method was
developed \(^64,119\) and the method began to gain a wider acceptance.

With open gastric bypass surgery, wound infection and incisional hernia
were very common complications. After the introduction of the laparo-
scopic technique the incidence rates of these complications were dramati-
cally reduced \(^120-122\). The length of postoperative hospital stay was also sig-
nificantly shorter as was the number of days to return to normal activities
of daily living and work \(^120,121\).
Fig 9a. Illustration of the original gastric bypass procedure described by Mason and Ito
Fig 9b. Illustration of the modified gastric bypass procedure described by Griffen
Fig 9c. Illustration of the Gastric bypass procedure used today
Complications
Although laparoscopic gastric bypass surgery is generally regarded as safe, the large number of operations performed each year means that many individuals will suffer a complication during surgery, in the early postoperative phase (within 30 days after surgery), or at a later stage. The benefits of surgery must always be interpreted in the context of complications suffered. Complication rates must be low in order to motivate the use of surgery for treatment of morbid obesity.

Intraoperative adverse events
As many as 5.5% suffer an intraoperative adverse event 123, the most common being bowel injury, followed by instrument failure, anaesthesia event and revision of anastomosis. Other more infrequent complications include injury to the liver and spleen as well as major vascular injury though this is rare 123,124. Many adverse events are preventable, such as stapling of the nasogastric or orogastric tube, which can easily be prevented by routine retraction of the tube before stapling of the stomach 125. An intraoperative adverse event also seems to increase the risk for postoperative complications 123.

Early postoperative complications (within 30 days after surgery)
Complications occurring within the first 30 days after surgery are generally directly related to the operation or perioperative care. Definitions of what should be counted as a postoperative complication may differ between studies. Between 6.8-9.4% of patients suffer a postoperative complication within 30 days after surgery 126-130. Most complications are easily managed either on the hospital ward or in outpatient facilities. Serious complications are more resource demanding and occur in 3.3 - 4.8% of patients. The definition of serious complication also varies between studies, making direct comparison between studies more difficult. Mortality rates above 1% were common during the 1990s, but with the improvement in surgical technique the 30-day mortality rate has dropped to 0.1-0.2% 127,128,131,132. The most common causes of mortality within 30 days are gastrointestinal leakage, venous thromboembolism and cardiovascular event 126,128,133.

Gastrointestinal leakage
Leakage from the gastric pouch or small bowel after laparoscopic gastric bypass surgery is a very serious complication associated with high morbidity and mortality 126,134. Postoperative leakage seems to occur in 0.8-2.05% of
cases, but if routine postoperative upper gastrointestinal radiology series are performed, the incidence is seen to be as high as 3.4%, although as many as 20% may have subclinical leakage. Leakage can occur at any of the anastomoses or staple lines (i.e. the gastrojejunostomy or the staple lines of the gastric pouch, the gastric remnant, the Roux limb, the jejunal blind stump and the jejunojejunostomy), or from the small bowel where it has been manipulated during surgery. The most common sites of leakage are the gastrojejunostomy or the staple line of the gastric pouch. Many leaks occur early (within the first days after surgery) and are often caused by technical failure. A substantial number of leaks, however, occur after the first few postoperative days and may be due to ischaemia or distal bowel obstruction resulting in high pressure on the staple lines. Higher age, higher BMI, male gender and multiple comorbidities have been reported to increase the risk for postoperative leakage by some authors, but not by others.

Early diagnosis relies on a high index of suspicion. Persistent tachycardia, fever and tachypnoea after the first day following surgery are generally considered early signs of leakage. Abdominal CT with oral soluble contrast is the radiologic procedure of choice, but may prolong the time until reoperation. In cases with severe obesity, for instance, this radiologic procedure may not be available for acute examination due to weight or volume restriction. The sensitivity and specificity of the CT scan is also highly dependent on the radiologist’s experience with postoperative anatomical changes after GBP. The mainstay of treatment is effective drainage. Haemodynamically stable, non-septic patients can sometimes be managed conservatively with antibiotics, percutaneous drainage and fasting with nutritional support. Under other circumstances surgical exploration followed by adequate drainage is required. Sometimes primary repair is possible, but it may not always be feasible due to difficulty in identifying the exact location of the leak and due to severe acute inflammation.

Venous thromboembolism

Venous thromboembolism (VTE) occurs infrequently with an incidence of 0.3-0.5% after laparoscopic gastric bypass surgery. With adequate prophylaxis with low molecular-weight heparin, the risk may be as low as 0.25%. When this complication occurs, however, it is a potentially very serious complication and a common cause of death after laparoscopic gastric bypass surgery. Obesity itself has been described as a risk factor for VTE, although the risk from obesity alone is possibly low.
Morbidly obese patients often have several additional risk factors associated with an increased risk for postoperative VTE, such as mobility limitations and a sedentary lifestyle. High age, high BMI, male gender and previous history of VTE have been described as significant risk factors after bariatric surgery. Together with these risk factors, laparoscopy may also increase the risk due to the effects of general anaesthesia and the increase in intra-abdominal pressure from pneumoperitoneum leading to decreased blood flow in the femoral vein. The use of DVT prophylaxis reduces the incidence of VTE, and is routine in Sweden; adherence, however, may be low.

Bleeding

The incidence of bleeding after laparoscopic gastric bypass has been reported to be 1.9-4.2%. Postoperative bleeding usually occurs in a staple line, the gastrojejunostomy, or the jejunoojjejunostomy. Bleeding occurs intraperitoneally or intraluminally and manifest at an early stage (within 48 h after surgery) or late (after 48 h after surgery). Late bleeding usually presents as melena that is usually the result of previous, but non-active bleeding. Early bleeding can present as haematemesis (if the bleeding originates from the gastrojejunostomy), haematochezia and/or tachycardia or hypotension. The initial management of significant bleeding consists of fluid resuscitation and blood transfusion. When signs of shock are present, reoperation will be necessary. When the bleeding originates from the gastric pouch or gastrojejunostomy, endoscopic therapy may be successful with evacuation of as much blood as possible and haemostasis. With significant bleeding occurring elsewhere, reoperation will be needed with evacuation of blood and control of the source of bleeding, if located. If the source of bleeding cannot be located, all staple lines should be oversewn.

Small bowel obstruction in the early postoperative phase

Small bowel obstruction can occur in the early postoperative phase after laparoscopic gastric bypass surgery, with a reported incidence of 0.8%-1.7%. Obstruction is often located at the site of the jejunojejunalostomy and can be caused by kinking of the jejunojejunalostomy or narrowing of the anastomosis caused by oedema, stenosis, ischaemia, or by a bleeding clot causing obstruction of the lumen. Early obstruction usually requires reoperation with reconstruction of the jejunojejunalostomy and decompression of the gastric remnant if it is significantly dilated.
Dumping and late hypoglycaemia
The classic dumping syndrome occurs 10-30 minutes after a meal when solid food particles rapidly enter the small bowel resulting in a shift of intravascular fluid into the intestinal lumen. The classic symptoms are crampy abdominal pain, nausea and bloating (gastrointestinal symptoms), and fatigue, facial flushing, palpitation, tachycardia, hypotension and syncope (vasomotor symptoms). Although the symptoms of dumping are unpleasant, dumping is considered by many patients to be an important restricting mechanism preventing relapse into food abuse, and they do not see it as a negative complication of the operation.

Symptoms can also occur a while later (1-3 h after a meal) in the form of perspiration, palpitation, hunger, fatigue, confusion, tremor and even aggression and syncope. These late symptoms occur as the result of reactive hypoglycaemia.

Although most patients learn how to regulate food intake in order to avoid dumping, as many as 12% experience dumping 2 years after surgery. Late occurring hypoglycaemic episodes seem to occur less often and can often be avoided with low-carbohydrate diets.

Late postoperative complications

Bowel obstruction
Bowel obstruction commonly occurs after laparoscopic gastric bypass surgery. Incidence rates seem to be as high as 10% , but may be as high as 20% . The most common cause of bowel obstruction after laparoscopic gastric bypass surgery is internal hernia, followed by adhesions, ventral hernia (i.e. incisional hernia and umbilical hernia) and anastomotic stricture. Less common causes are intussusception and bezoars. The various causes are more or less common depending on the surgical technique used. Incisional hernia as the cause of bowel obstruction after laparoscopic gastric bypass surgery, for example, seems to be uncommon if 12 mm ports are used. If 25mm circular staplers are used to create the gastrojejunostomy, incisional hernia seems to be more common.

Internal hernia
The phenomenon of internal herniation was first described by Treitz in 1857. During the 20th Century, internal hernia was viewed as a rare
complication of partial gastrectomy. After the introduction of laparoscopic gastric bypass surgery a drastic increase in the occurrence of this complication was reported, sometimes with severe outcome.

The incidence of symptomatic internal herniation in the literature varies greatly. Many early studies reported quite low incidences, while others found a higher rate. Most of these studies, however, were single-centre, retrospective studies with either short follow-up time or not reported at all. In addition, most studies lack control over loss to follow-up, and follow-up has often been limited to retrospective reviews of patients’ notes at the hospital where the initial operation took place. For this reason, the true incidence of internal herniation is likely to have been underestimated. More recent studies have reported incidence rates as high as 10 - 16%.

When using a retrocolic technique in gastric bypass surgery, there are three potential spaces for the formation of internal hernia. The space associated with the highest incidence of internal hernia is at the site where the small bowel is brought through the mesentery of the colon. Other potential sites for internal herniation are the space beneath the jejunojejunostomy and Petersen’s space. Petersen’s space is the space between the mesentery of the small bowel of the Roux limb and the mesentery of the transverse colon. In the antecolic gastric bypass there are only two potential sites for internal hernia; the space beneath the jejunojejunostomy and Petersen’s space. A much higher risk for internal herniation has thus been reported for retrocolic gastric bypass.

Internal herniation can present in a variety of ways. If the mesenteric defects are not closed during laparoscopic gastric bypass surgery, then the bowel may herniate through these defects. This may occur without causing any symptoms and may be seen at abdominal surgery for other reasons, or on CT-scans. The bowel may however be trapped within a mesenteric defect and cause a wide spectrum of symptoms ranging from vague intermittent abdominal pain to intense, colic abdominal pain that is resistant to analgesics. Abnormal findings at surgery differ along a spectrum from open mesenteric defects without signs of obstruction to incarcerated, ischaemic bowel. With a high level of suspicion, bowel resection is not necessary in most cases. Despite this, there are inevitable deaths related to this complication.

Small bowel obstruction due to internal herniation can develop at any time after the initial operation. Most cases, however, seem to occur 1-2 years after surgery, corresponding to the time when the most
significant weight-loss has occurred\textsuperscript{117}. Rapid loss of mesenteric fat\textsuperscript{189} and lack of adhesions with the laparoscopic technique\textsuperscript{190} have been proposed as contributing factors.

\textbf{Fig 10. Illustration of the potential sites for internal hernia formation after antecolic Roux-en-Y Gastric bypass}

Computer Tomography (CT) with a slice thickness of 5 mm, performed 60-80 s after injection of intravenous iodine contrast (125-150 mL) is held to be the diagnostic method of choice\textsuperscript{164}. Seven classical signs (described in Table 1) have been described as being suggestive of internal herniation\textsuperscript{191}. Using CT with contrast, a diagnostic accuracy of 85\% can be expected. A high level of suspicion must be maintained and the decision to perform diagnostic laparoscopy must be liberal\textsuperscript{188}. If the surgeon operating on a patient with internal herniation has previous experience of bariatric surgery, laparoscopic management is often possible\textsuperscript{188}. For patients with a subacute presentation at night, surgery may often be postponed until the next day to enable optimisation of the surgical team. For patients with acute symptoms and little or no response to analgesics, acute surgery is warranted since the risk for bowel ischaemia is high. An open surgical approach should be the
choice for surgeons with less experience in bariatric surgery, since laparo-
scopic handling of internal herniation, particularly in the presence of incar-
cerated and dilated bowel, is technically demanding, and the anatomy can
be difficult to understand. Concomitant pregnancy can complicate surgery
even more, but in the hands of experts, a laparoscopic approach is feasible
until the 31st week of pregnancy.  

Closure of mesenteric defects may reduce the incidence of small bowel
obstruction after laparoscopic gastric bypass surgery. A reduction in inter-
nal hernia occurrence has been reported in several single-centre, observa-
tional studies. Internal hernia can still develop despite the closure of mes-
enteric defects. There is also concern that closure of a mesenteric de-
fect may itself create other complications such as bleeding, formation of
adhesions and strictures or kinking of the small bowel.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Appearance</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric swirl</td>
<td>swirled appearance of mesenteric fat or vessels at the root of the mesentery</td>
<td>74%</td>
<td>83%</td>
</tr>
<tr>
<td>Mushroom sign</td>
<td>a mushroom shape of the herniated, narrowed mesenteric root with stretching of the mesenteric vessels</td>
<td>46%</td>
<td>93%</td>
</tr>
<tr>
<td>Hurricane eye</td>
<td>a tubular or rounded shape of the distal mesenteric fat closely surrounded by bowel loops</td>
<td>11%</td>
<td>100%</td>
</tr>
<tr>
<td>Small-bowel obstruction</td>
<td>classical signs with dilatated small bowel, with or without fluid-gas levels</td>
<td>26%</td>
<td>89%</td>
</tr>
<tr>
<td>Clustered loops</td>
<td>loops of small bowel clustered small bowel</td>
<td>10%</td>
<td>78%</td>
</tr>
<tr>
<td>Small-bowel behind superior mesenteric artery</td>
<td>small-bowel other than duodenum passing behind the superior mesenteric artery</td>
<td>22%</td>
<td>94%</td>
</tr>
<tr>
<td>Right-sided anastomosis</td>
<td>the jejunoojejunoanastomosis is normally located to the left side of the abdomen, a right-sided location is highly suggestive of internal hernia</td>
<td>8%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1. CT signs of internal hernia. Based on Lockheart et al. Am J Roentgenol. 2007;188(3):744-50

Intussusception
Intussusception has been reported to be a rare postoperative complication
and cause of small bowel obstruction. In more recent studies the incidence
has been reported to be 0.4-1.2%. Due to the retrospective nature of
these trials and the high loss of follow-up, these numbers are probably an underestimation of the true incidence \(^{195}\).

Intussusception usually occurs in a retrograde fashion \(^{195,196}\). In a few cases a leading point, such as the jejunojejunostomy may be the cause of the intussusception, but in most instances a leading point is absent. The most widely accepted hypothesis is that the complication is caused by overactive motility. Bowel motility is coordinated by a pacemaker located in the duodenum. Alteration in the anatomy after gastric bypass, causes the pacemaker function to be disturbed leading to the emergence of ectopic pacemaking zones causing unsynchronized small bowel contractions that predispose to intussusception. This hypothesis is supported by the apparent absence of this complication after the duodenal switch procedure \(^{196}\). Female gender and excessive weight-loss seem to increase the risk for intussusception \(^{194,195}\).

CT-scanning of the abdomen has a high sensitivity and specificity for intussusception \(^{195,196}\).

Approximately one third of all cases present acutely. Acute presentation is associated with leukocytosis and the risk for ischaemia of the intussuscepted bowel is high. Laparoscopic treatment is often possible. If ischaemic bowel or irreversible invagination is discovered, conversion to open surgery is usually indicated, with small bowel resection and anastomosis. Under other circumstances optimal treatment is not so clear. Reposition with or without enteropexi results in a shorter postoperative length of stay \(^{195}\), but resection may result in lower recurrence rates \(^{197}\).

Marginal ulceration

Marginal ulceration is a common complication after laparoscopic gastric bypass surgery with a reported incidence of 1-7\% \(^{198-200}\). In a study where all patients underwent routine endoscopy 1 month after surgery, as many as 12\% had a visible marginal ulceration \(^{201}\). Most marginal ulcers seem to develop soon after the operation \(^{126,201}\). The exact cause is unclear. A larger pouch increases the risk for marginal ulceration \(^{86}\), as does irritation caused by the foreign material \(^{202}\). The use of resorbable sutures for the gastrojejunostomy seem to reduce the incidence when compared with non-resorbable material \(^{202}\). Helicobacter Pylori infection is more common among the patients who develop marginal ulceration after gastric bypass surgery \(^{198}\) and it is thought that damage to the gastric mucosa caused by H.Pylori predisposes to the development of marginal ulceration postoperatively \(^{198}\).
Not all patients develop significant symptoms from a marginal ulcer. When symptoms do occur, the most common is epigastric pain, but ulcers can also present as nausea or vomiting due to stenosis or bleeding. Diagnosis is made by endoscopy. Most wounds heal well with proton-pump inhibitors (PPI). The use of prophylactic PPI after laparoscopic gastric bypass also reduces the risk for marginal ulceration.

**Anastomotic stricture**

High anastomotic stricture rates have been reported in the literature. The surgical technique used to create the gastrojejunostomy seems to have a large impact on the incidence of stricture. The use of circular staplers seems to be associated with a much higher risk than linear staplers or hand-sewn anastomoses. Another important factor contributing to the development of anastomotic strictures is tension or ischaemia in the anastomosis. Recurrent marginal ulceration may heal with fibrosis and thereby the risk of developing stricture of the anastomosis.

Most strictures seem to develop within the first ninety days after surgery and usually present as dysphagia and postprandial vomiting, with or without abdominal pain. Endoscopy is generally considered to be the diagnostic method of choice since this provides the possibility of treatment at the same time. Repeated gentle dilatation is often sufficient, but occasionally surgical revision of the anastomosis is necessary. Endoscopic dilatation carries the risk of perforation of the anastomosis, but with careful dilatation this risk appears to be small.

**Alcohol abuse**

Although the majority of bariatric surgery patients have a low risk alcohol consumption both before and after surgery, dependence on or abuse of alcohol may be as common as 7.6% among bariatric surgery patients before surgery. During the first year after surgery alcohol consumption is slightly reduced, but by two years dependence on or abuse of alcohol rises and has been reported to be as high as 9.6%. Most people, however, do not seem to change their alcohol habit after bariatric surgery. The majority of patients with high alcohol consumption after bariatric surgery have had a high consumption before as well. Gastric bypass is associated with a higher risk for alcohol problems than other methods. This effect may be due to more rapid absorption of alcohol combined with unaltered drinking patterns.
Nutritional deficiencies
Vitamins and minerals are essential factors and cofactors in many biological processes. Deficiencies of these micronutrients are common in obese individuals both before and even more so after gastric bypass surgery. Symptoms are commonly non-specific and late occurring. Absorption of several vitamins occurs in the proximal part of the small bowel and is often facilitated by the acid environment created by hydrochloric acid from the stomach. The absorption of vitamin B12 is also dependent on intrinsic factor produced by parietal cells in the stomach. Intestinal adaption occurs directly after surgery and takes up to three years to reach a maximum. This adaption leads to increased uptake of many micronutrients, but uptake never reaches preoperative levels. With adequate supplementation, fat-soluble vitamin (except vitamin D) and folic acid deficiencies are uncommon. A few vitamins, however, deserve further consideration.

Patients with adequate supplementation after gastric bypass surgery have normal thiamine (vitamin B1) concentrations, and thiamine deficiency is considered to be uncommon in this group of patients. Thiamine supplies, however, are small and under certain conditions deficiency does occur. Most cases of thiamine deficiency occur after a longer period of vomiting, often caused by anastomotic stricture. In the absence of vomiting, rapid weight loss, loss of appetite or non-adherence to vitamin supplementation all seem to be precipitating factors. The majority of cases seem to develop within the first 6 months after surgery. Symptoms can be quite drastic with signs of neuropathy progressing to Wernicke’s encephalopathy in up to 35% of severe cases. Although most instances of thiamine deficiency do not progress to Wernicke’s encephalopathy, many patients develop peripheral neuropathy with neurological impairment that may remain despite treatment.

The absorption of vitamin B12 is dependent on intrinsic factor from the stomach and an acid environment to facilitate release of the vitamin from dietary protein. Without adequate substitution, B12 deficiency commonly occurs and manifests itself as megaloblastic anaemia, polyneuropathy and paraesthesia.

Iron deficiency is not uncommon. Symptoms are rarely dramatic and usually present as anaemia. Without supplementation iron deficiency is particularly common in menstruating women and adolescents after gastric bypass surgery.

The absorption of Calcium and vitamin D is reduced after gastric bypass surgery. Low calcium levels stimulate parathyroid hormone (PTH) secretion.
and can lead to secondary hyperparathyroidism. PTH increases the production of active vitamin D from the liver and kidney increasing absorption of calcium from the bowel but also, in the absence of sufficient calcium absorption, resorption of calcium from bone and preservation of calcium in the kidneys. If secondary hyperparathyroidism is left untreated for longer periods of time, bone resorption may result in osteopenia and osteoporosis, and increase the risk for fractures. Without supplementation of calcium and vitamin D, secondary hyperparathyroidism may be as common as 69% after surgery. Vitamin D + calcium supplementation should thus be prescribed after gastric bypass surgery. The optimal dose, however, is not known and remains a matter of debate.

Postoperative diet supplementation with multivitamins, vitamin D + Calcium and vitamin B12, along with monitoring of calcium, vitamin B12, ferritin, folate and iron each year, has been recommended. Furthermore, iron supplementation is recommended for menstruating women and adolescents. Adherence to supplementation has been reported to be 52-83% 5 years after surgery.

Gallstone disease
The prevalence of gallstones in the obese population may be as high as 25%. Following gastric bypass surgery, rapid weight-loss and decreased emptying of the gallbladder lead to increased risk for gallstone formation and thus cholecystectomy. Following gastric bypass surgery, access to the choledochus in the case of choledocholithiasis is much more difficult. In order to prevent problems related to gallstones, some authors advocate prophylactic cholecystectomy. This can either be done as a separate operation before, or at the time of bariatric surgery. Mortality and complication rates, however, seem to be higher if both procedures are performed at the same time. Given the fact that few asymptomatic stones develop to become symptomatic, other authors advocate a “wait and see” approach.

Prevention of postoperative complications
Prevention of postoperative complications requires the identification of factors associated with increased risk for complications as well as methods to modify these risk factors. Age, male gender, BMI >50, hypertension, obesity hypoventilation syndrome, previous venous thromboembolism and low surgical volume have all been linked to increased postoperative mortality. Although it is imperative that postoperative mortality be reduced to a minimum,
the low mortality rates seen after bariatric surgery today has caused a shift in focus towards prevention of serious postoperative complications.

In previous studies, mobility limitations, previous history of venous thromboembolism, coronary artery disease or previous history of stroke, hypertension, obstructive sleep apnoea, diabetes, age more than 50 years, BMI in the extremes, male gender and history of smoking have all been reported as factors associated with a higher risk for serious postoperative complications. Suffering an intraoperative complication has also been associated with a higher risk for a serious postoperative complication. During the process of establishing a new surgical procedure, complication rates are always higher. The effect of the learning-curve is, to a large extent, linked to the complexity of the intervention. Distribution of a pill, for example, is hardly associated with a learning-curve effect. For laparoscopic gastric bypass surgery it has been described that 100 cases are required for completion of the learning-curve, although this figure could be less with significant previous experience of advanced laparoscopic surgery. Low surgical volume as a risk factor is a matter of debate. In bariatric surgery both the annual volume of the hospital, and that of the surgeon have been linked with complication and mortality rates.

Besides optimisation of comorbid disease, many risk factors are unavoidable. They do, however, alert personnel to the increased postoperative risk and for the need to optimise the team working around the patient. A few additional measures have been reported to improve outcome. A preoperative weight-loss of at least 5% of the total bodyweight, reduces both the risk for postoperative complications and is associated with better postoperative weight-loss. Preoperative weight-loss improves exposure during surgery due to both a significant decrease in liver volume and intrahepatic fat. Participation of senior colleagues during the learning-curve period also reduces complication rates.

**Insulin resistance**

As a response to stress, the body initiates powerful metabolic changes to make available rapid energy and the building blocks for acute phase proteins and tissue healing. Insulin resistance is an important part of this physiologic response. Surgical trauma also stimulates this change in metabolism resulting in glucose production and impairment of glucose utilisation. The degree of impact depends on the magnitude of surgical trauma. A large fall in insulin sensitivity is associated with increased risk for a postoperative complication.
Haemoglobin A1c (HbA1c) measures long-term glycaemic exposure and can be used in the diagnosis of diabetes \(^{252}\). Based on the risk for microvascular complications, a HbA1c value \(\geq 6.5\%\) has been defined as the cut-off point for a diagnosis of diabetes \(^{252,253}\). There is, however, a HbA1c continuum ranging from 5.5 to 6.4\% where the risk for future development of diabetes is high and the risk for cardiovascular and microvascular complications is raised \(^{252}\). Given this background, the American Diabetes Association (ADA) recognizes HbA1c levels of 5.7-6.4\% as “prediabetic” \(^{254}\).

HbA1c reflects intraoperative insulin sensitivity and has prognosticative value for postoperative complication after major cardiovascular and colorectal surgery \(^{250,252,256-258}\). Obesity is also associated with decreased insulin sensitivity \(^{250}\). Previous studies performed in patients with cardiovascular disease or colorectal cancer undergoing major open surgery may, however, not be representative of the obese patient undergoing minimally invasive bariatric surgery.

**Methodology in surgical studies**

Despite the many advances that have been made in surgery over the last century, the introduction of novel surgical interventions has traditionally been slow, sporadic and non-standardised \(^{259}\). Optimally the development of a new surgical technique follows the same stages as the development of new pharmaceutical drugs \(^{260,261}\). Ideally the first step (Stage 1) is the innovation of a new solution to a clinical problem, its clinical implementation and eventual publication as a case report \(^{261}\). Under most circumstances this stage should be preceded by testing in a pre-clinical environment. In the second step (Stage 2a) the novel intervention is developed as part of a study on a small group of patients. This step is often traditionally reported in the form of a retrospective case series, a practise that has been criticised \(^{262}\). Ideally, this second step should be designed as a prospective development study with meticulous recording of all technical modifications \(^{261}\). Once the technique has been developed it needs to be explored (Stage 2b). Technically complex interventions have a learning-curve until competence is achieved \(^{242,263}\). Ideally a prospective non-controlled clinical trial with a large number of patients is performed before starting a randomised controlled trial (RCT). The focus at this stage should be on evaluation of the learning-curve and adverse outcomes \(^{261}\). This stage could be immediately incorporated in a randomised controlled trial, but this must be incorporated in both the design and interpretation of the study \(^{259}\). After the first two stages of development the intervention needs to be fully evaluated. The “gold standard”
for evaluation at this stage (Stage 3) is the RCT evaluating efficacy and safety outcomes, patient-centred outcomes, and cost-effectiveness. Finally, long-term effects and evaluation of rare, but severe side-effects must be followed up (Stage 4). Usually this requires a large set of patients and a long follow-up period. For practical purposes, well-designed register studies are often used.

In most circumstances the RCT is the best study design that is practical for evaluating the third stage of development of a surgical intervention. Due to ethical or pragmatic reasons the RCT may not always be feasible. An observational study design is then an alternative. Furthermore, construction of a RCT can be challenging, and aspects of the design can affect generalisability of the results to a defined group of individuals outside of the trial (i.e. the external validity of the trial). Even if a RCT is possible, further observational studies may serve as complements to improve understanding and evaluation of the intervention.

Observational studies follow treatment protocols used in clinical practise and have the potential to have high external validity, simply because they are performed in a non-experimental setting and include the effects of the doctor-patient relationship and patient preference. However, observational studies cannot fully be adjusted for confounding factors, and are thus generally viewed as an adjunct rather than an alternative. Well-designed RCTs have a very high internal validity, but are often criticised due to lack of external validity. There is also a risk that RCTs overestimate the benefits of a new intervention. This is particularly true if the study is performed in a single-centre setting, uses strict inclusion and exclusion criteria and surrogate end-points, and follows up study patients more meticulously after the intervention than would otherwise have been the case.

There are several important aspects of study design that have been reported to affect the external validity in RCTs. First the choice of the setting for the trial is important. The health-care system in the country where the study takes place can have an important influence on both diagnosis of disease and implications of treatment. This difference is particularly true when results from studies in the developed world are generalised to the developing world, and vice versa. The surgical centre and clinicians participating in the study affect the outcome and generalisability of the study. Single-centre studies, often performed at expert centres, tend to overestimate the effects of treatment.
The study population is also of great importance, and may be strongly selected and thus not truly represent the population in which the treatment is to be used. In many trials, patients available for randomisation are not considered (this is often not adequately reported). The use of highly selective inclusion and exclusion criteria, along with the loss of patients who decline randomisation, can result in a study group that represents a very small part of the intended study group. The proportion of patients that are finally considered for randomisation can be as low as 1% or less.

Finally, outcome measures can be constructed in a way that they lack clinical relevance. In some RCTs the treatment method or the protocol might differ significantly from the protocol being used in clinical practice. Thus, an important and real problem with RCTs is their external validity. Other factors such as how the randomisation is performed, if the study is blinded to both the patient and the surgeon (in our case) or not, can affect the outcome.
Aims of the thesis

The overall objective of this thesis was to identify preventable factors that increase the risk for a serious postoperative complication after laparoscopic gastric bypass surgery.

The specific aims of each study (represented by roman numerals) was:

1. To review the incidence of early complications in a prospective material from the SOReg database and to identify preoperative and intraoperative factors predisposing to postoperative complications.

2. To assess whether an association exists between preoperative HbA1c and severe postoperative adverse outcome in patients without medical treatment for diabetes.

3. To assess if closure of mesenteric defects in laparoscopic gastric bypass surgery can reduce the incidence of surgery for subsequent small bowel obstruction, and if closure of the mesenteric defects can be performed at an acceptable price in terms of serious early postoperative complications.

4. To evaluate a large multicentre register-based RCT when compared with the population it is meant to represent, and to see if the results from the RCT differ from observational data in the setting of a complex surgical intervention.
Materials and methods

The Scandinavian Obesity Surgery Registry

The Scandinavian Obesity Surgery Registry (SOReg) is a national quality and research register. After a pilot study in 2005, the SOReg started in 2007. At present there are 43 centres performing bariatric surgery in Sweden. All of these centres report to the register, and the current inclusion rate is 99.1% of all procedures performed in Sweden. Some variables in the SOReg are mandatory and have a 100% completion rate, other variables are optional resulting in an average completion rate of 67% for those variables277. Data are prospectively collected starting with base-line data, including blood-chemistry and anthropometric data, approximately 1 month before surgery. The register contains data from the operation concerning technical aspects, operation time and intraoperative complications. Follow-up data are recorded after 6 weeks (for Days 0-30) and 1, 2, and 5 years after surgery. Follow-up data contain anthropometric data, information on complications and quality-of-life estimated using the SF-36 and Obesity Problems Scale.

The register is cross-matched monthly with the Swedish Population Register so as to cover all mortality. The register is also validated in several ways. Different variables are scanned for non-logical or improbable values, and in such cases compared with the patient’s records. Regular audit is performed by a visiting independent observer who checks values that are outside a predetermined level for length of hospital stay and random sampling. So far the register has been shown to have a very high validity277. All studies in this thesis are based on SOReg data.

Patients

All patients in this thesis were operated with laparoscopic gastric bypass surgery in Sweden and registered in the SOReg. All patients met the international and national criteria for bariatric surgery based on the 1991 NIH Consensus Statement (i.e. BMI ≥35 kg/m²)278.
Definitions common to all studies in the thesis

Definition of comorbid disease
Comorbidity is defined as a condition needing active pharmacological or continuous airway pressure (CPAP) treatment. Comorbid diseases are specified as hypertension, diabetes, dyslipidaemia, diarrhoea, depression, sleep apnoea or other specified condition. Previous history of deep venous thrombosis or pulmonary embolism and smoking were registered from May 1\textsuperscript{st}, 2010. OS-MRS \textsuperscript{237}, a risk score for mortality, was also calculated after this date.

Definition of postoperative complications
Using the Swedish Population Register, follow-up regarding mortality is close to 100%. Today, however, death resulting from a bariatric surgery complication is a rare event making mortality unsuitable for use in the study of adverse outcome after bariatric surgery. A postoperative complication can affect the patient over a long period of time and result in profound health-care costs. It thus seems more reasonable to consider postoperative complications, in particular serious postoperative complications, when assessing adverse outcomes.

Complications must be standardised in a way that allows reproducibility between centres and studies over time. One widely accepted way to classify complications is to use the Clavien-Dindo classification \textsuperscript{279}. In the Clavien-Dindo classification complications are graded from 1-5 based on the seriousness of the complication (Table 2). Any deviance from a normal postoperative course, is considered a postoperative complication. We considered complications classified as Clavien-Dindo Grades 3b-5 to be serious complications. This classification system was introduced into the SOReg in 2010.
Grade | Definition |
--- | --- |
Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions |
Grade II | Requiring pharmacological treatment, blood transfusion or total parenteral nutrition |
Grade III | Requiring surgical, endoscopic or radiological intervention |
Grade IIIa | Intervention not under general anaesthesia |
Grade IIIb | Intervention under general anaesthesia |
Grade IV | Life-threatening complication requiring IC/ICU management |
Grade IVa | Single organ dysfunction |
Grade IVb | Multiorgan dysfunction |
Grade V | Death of a patient |

IC = intermediate care; ICU = intensive care unit

Table 2. The Clavien-Dindo classification of postoperative complications

Besides grading the severity of postoperative complications in this thesis, we have categorised them as: leakage or deep intra-abdominal infection; bleeding; gastrointestinal obstruction or ileus; port-related complications; wound dehiscence; other wound complication (mainly superficial wound infection); anastomotic stricture; marginal ulcer; cardiovascular event; pulmonary complication (other than pulmonary embolism); deep venous thrombosis or pulmonary embolism; urinary tract infection; and other (in this case specified) complication.

**Definition of small bowel obstruction and internal hernia**

In Papers III and IV, reoperation for small bowel obstruction was used as primary outcome variable. Small bowel obstruction was defined as acute presentation of symptoms (i.e. abdominal pain or vomiting) with hallmarks of bowel obstruction found during surgery for this presumed complication. We considered dilatation of the small bowel or gastric remnant, mesenteric lymphoedema, or incarcerated bowel with or without signs of ischaemia to be hallmarks of bowel obstruction. Internal hernia was considered to be the cause of the bowel obstruction if the bowel was herniated at the time of surgery, with signs of small bowel obstruction as defined above.
Procedure

The surgical technique for laparoscopic gastric bypass is well standardised in Sweden. All gastric bypass procedures are performed with a Roux-en-Y technique, with more than 99% being performed with the antecolic, antegastric technique described by Lönroth and Olbers 119. The gastrojejunostomy was constructed using a single linear stapler together with hand-sewn closure of the remaining defect in 98.5% of cases. All patients routinely receive prophylaxis against deep venous thrombosis.

All patients in Papers III and IV were operated with the technique described by Lönroth and Olbers with construction of both the gastrojejunostomy and the jejunojejunostomy using a single linear stapler together with hand-sewn closure of the remaining defects. When randomised to mesenteric defects closure in Paper III, a running, braided, non-absorbable suture was used. The defect beneath the jejunojejunostomy was then closed continuously in two layers. Petersen’s space was closed in one layer either continuously or as a purse string. When the mesenteric defects were closed in Paper IV, they were closed with either sutures or clips according to the preference of the surgeon.

Study design

Papers I and II were observational cohort studies based on prospectively collected data. Paper III was a parallel, open-label, superiority, randomised clinical trial. Paper IV was a comparison between two parallel studies; a randomised clinical trial and an observational cohort study.

Ethical considerations

All studies were conducted in accordance with the ethical standards of the Helsinki Declaration 6th revision and were approved by the Uppsala/Örebro Regional Ethics Committee. Trial registrations are available at clinicaltrials.gov, identifiers: NCT01862159 (Papers I and II), NCT01137201 (Paper III), NCT02763501 (Paper IV).

Paper I

Paper I included all patients operated from May 1st, 2007 until September 30th, 2012 in Sweden who were registered in the SOReg. Patients operated with bariatric procedures other than laparoscopic gastric bypass, had had previous bariatric surgery, or were planned for open gastric bypass surgery were excluded.
The main outcome was serious postoperative complications within 30 days after surgery. Secondary outcomes were overall and specified postoperative complications as listed above.

Annual surgical volume was calculated by dividing the number of operations during the 6-month period when the operation took place plus the preceding 12-months, by 1.5. Information on operations performed prior to registration in the SOReg was retrieved from the Swedish National Patient Register.

**Statistical analyses**
Categorical data were analysed using unadjusted logistic regression. Continuous data were analysed with unadjusted linear regression. Odds ratios (OR) with 95% confidence intervals (CI) were calculated and presented as measures of association. Patient-specific risk factors with a p<0.10 were entered into a multivariate analysis using stepwise, forward, logistic regression. Significant risk factors were then entered into a multiple regression analysis with significant surgical risk factors.

Data were analysed using SPSS Statistics (IBM Corporation, Armonk, New York, USA) version 20.

**Paper II**
**Paper II** included all patients without pharmacological treatment for diabetes, operated with a primary laparoscopic gastric bypass procedure in Sweden between January 1\(^{st}\) 2010 and September 30\(^{th}\) 2012 who were registered in the SOReg. In cases where documentation of preoperative HbA1c-level was missing, the patient was excluded.

The main outcome was serious postoperative complication within 30 days after surgery. Secondary outcomes were overall and specified postoperative complications as listed above.

**Statistical analyses**
Categorical data were analysed using unadjusted logistic regression. Continuous data were analysed with unadjusted linear regression. Odds ratios (OR) with 95% confidence intervals (CI) were calculated and presented as measures of association. Comorbidities, age, gender, BMI and HbA1c were entered into a multivariate, logistic regression analysis.

Data were analysed using SPSS Statistics (IBM Corporation, Armonk, New York, USA) version 21.
Paper III
Patients operated with laparoscopic gastric bypass surgery between May 1\textsuperscript{st}, 2010 and November 14\textsuperscript{th}, 2011 at any of the 12 centres participating in the study were available for inclusion. Exclusion criteria were: previous bariatric surgery; planned open procedure or early conversion to open surgery (before randomisation); or inability to understand the concept of the trial.

Randomisation
The patients in Paper III were randomised in a 1:1 ratio, with permuted blocks of different sizes, stratified by centre. Patients were randomised once abdominal access had been achieved and the surgeon had decided to proceed with a laparoscopic procedure. A sealed envelope, with randomisation to either mesenteric defects closure or non-closure, was opened. According to the decision of the Regional Ethics Committee, the study was conducted as open-label after the operation.

Outcomes
The primary endpoints were serious complications within 30 days after surgery (safety) and surgery for small bowel obstruction (efficacy). Secondary endpoints were overall and specified complications within 30 days, operation time, and length of postoperative hospital stay. In Paper IV, weight-loss 2 years after surgery was also specified as a secondary outcome. Excess BMI-loss ($\%EBMIL = 100 \times \frac{\text{initial BMI-postoperative BMI}}{\text{initial BMI-BMI 25 kg/m}^2}$) was used as measurement of postoperative weight-loss.

Statistical analyses
Based on the incidence of bowel obstruction after laparoscopic gastric bypass surgery reported at the time of planning Study III, a power calculation was made based on the assumption of a reduction in reoperation for bowel obstruction from 5\% to 2.5\% within 3 years after the initial operation. To detect a difference with a power of 80\% at the 5\% significance level, a minimum of 906 patients were needed in each group. Since varying incidence rates were reported in previous studies, we decided to include at least 1200 patients in each group.

Continuous variables were analysed using Student’s t-test, categorical data with $\chi^2$ test, or Fisher’s test when appropriate. When analysing safety outcome, logistic regression was used to calculate OR with 95\%CI. Efficacy outcome was estimated with the Kaplan-Meier method and visualised as
cumulative probability (1-Kaplan-Meier estimate). All patients were followed until surgery for small bowel obstruction, and censored if lost to follow-up, at death, if the mesenteric defects were closed during any operation, or after 3 years of follow-up or at Dec 31st, 2013, whichever came first. When analysing efficacy outcome, Cox regression was used to calculate hazard ratios (HR) with 95% CI as measures of association. Because of non-proportional hazards, as shown by Schoenfeld residuals, time-dependent analyses were performed for Days 0-30 and more than 30 days. To assess potential risk factors for internal hernia with small bowel obstruction, univariate and multivariate Cox regression analyses were performed with the variables comorbid disease (as specified previously), sex, age, BMI, previous abdominal surgery, handling of mesenteric defects and %EBMIL at 30 days. Numbers needed to treat was estimated using the Kaplan-Meier method at 3 years of follow-up. The Bonferroni-Holm method was used to address the issue of multiple comparisons with two primary end-points. All data were analysed on an intention-to-treat basis.

We considered p<0.05 to be statistically significant.

Data were analysed using SPSS Statistics (IBM Corporation, Armonk, New York, USA) version 22. STATA version 11 was used for the time-dependent analyses in Paper III.

**Paper IV**

Patients operated in Sweden with primary laparoscopic gastric bypass surgery between May 1st, 2010 and Nov 14th, 2011, were included in the study. Patients previously operated with a bariatric procedure, with missing information on how the mesenteric defects were handled, or those operated with a primary open procedure or with a retrocolic gastric bypass procedure were excluded.

**Outcomes**

Primary endpoints were serious complication within 30 days after surgery (safety) and surgery for small bowel obstruction (efficacy). Secondary endpoints were overall and specified complications within 30 days, operation time, and length of postoperative hospital stay. In Paper IV, weight-loss 2 years after surgery was also specified as a secondary outcome.

Excess BMI-loss (%EBMIL) was used as measurement of postoperative weight-loss.
Statistical analyses
In Paper IV, continuous variables were analysed using Student’s t-test, categorical variables with $\chi^2$ test or Fisher’s test when appropriate. When analysing safety outcome, logistic regression was used to evaluate risk, with OR with 95% CI as measures of association. For efficacy outcome, Cox regression was used, with HR and 95% CI as measures of association. Additional adjusted logistic regression and Cox regression analyses were made with stratification for comorbid diseases, age, sex and preoperative BMI. Patients were followed until first operation for small bowel obstruction, and censored if lost to follow-up, at death, if the mesenteric defects were closed at any reoperation, revisional surgery, or 4 years after the operation or on Dec 31st, 2014, whichever came first.

Data were analysed using SPSS Statistics (IBM Corporation, Armonk, New York, USA) version 23
We considered $p<0.05$ to represent statistical significance.
Results

Paper I
All patients operated from May 1st, 2007 until September 30th, 2012, and registered in the SOReg, were assessed for eligibility. We identified 29,288 patients operated with bariatric surgery. After exclusion for procedures other than laparoscopic gastric bypass, previous bariatric surgery and planned open gastric bypass surgery, 26,173 patients remained in the study. Follow-up at Day 30 was 95.7% (n=25,038).

Characteristics of the study group
The majority of patients in the study were women (76.0%). Mean body mass index (BMI) was $42.7 \pm 5.43$ kg/m$^2$. Using our definition of comorbid disease, 48.0% of all patients had at least one comorbid condition.

Postoperative complications
A postoperative complication occurred after 8.7% (2,170 / 25,038) of all operations. A serious complication occurred after 3.4% (630 / 18,737) of operations performed after Jan 1st, 2010. The 90-day mortality rate was 0.04% (11 / 25,038).

<table>
<thead>
<tr>
<th>Specified complication</th>
<th>Incidence n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leakage or abscesses</td>
<td>449 (1.8%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>522 (2.1%)</td>
</tr>
<tr>
<td>Wound dishesence</td>
<td>15 (0.1%)</td>
</tr>
<tr>
<td>Port-related complication</td>
<td>140 (0.6%)</td>
</tr>
<tr>
<td>Other wound complication</td>
<td>266 (1.1%)</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>241 (1.0%)</td>
</tr>
<tr>
<td>Stricture</td>
<td>59 (0.2%)</td>
</tr>
<tr>
<td>Marginal ulcer</td>
<td>116 (0.5%)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>27 (0.1%)</td>
</tr>
<tr>
<td>Cardiovascular complication</td>
<td>56 (0.2%)</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>183 (0.7%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>107 (0.4%)</td>
</tr>
</tbody>
</table>

Table 3. Postoperative, specified complications within 30 days after surgery
**Patient-specific risk factors**

Age, sleep apnoea and depression increased the risk for serious complication (Table 4). After adjustment for patient-specific variables only age remained a significant risk factor (adjusted OR 30-40 yrs. 1.08; CI 0.82-1.41, p=0.585; 40-50 yrs. OR 1.34, CI 1.04-1.72, p=0.025, 50-60 yrs. OR 1.40, 1.06-1.84, p=0.016; >60 yrs. OR 1.48, CI 0.99-2.20, p=0.054)

Male gender, age, and any of the listed comorbid diseases (sleep apnoea, hypertension, diabetes, dyslipidaemia, depression and previous VTE) increased the risk for postoperative complication regardless of severity.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n</th>
<th>Incidence n (%)</th>
<th>OR (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>3087</td>
<td>85 (2.8%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>30-40</td>
<td>5098</td>
<td>151 (3.0%)</td>
<td>1.08 (0.82-1.41)</td>
<td>0.585</td>
</tr>
<tr>
<td>40-50</td>
<td>6062</td>
<td>221 (3.6%)</td>
<td>1.34 (1.04-1.72)</td>
<td>0.025</td>
</tr>
<tr>
<td>50-60</td>
<td>3593</td>
<td>137 (3.8%)</td>
<td>1.40 (1.06-1.84)</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt;60</td>
<td>897</td>
<td>36 (4.0%)</td>
<td>1.48 (0.99-2.20)</td>
<td>0.054</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>1987</td>
<td>82 (4.1%)</td>
<td>1.27 (1.00-1.61)</td>
<td>0.046</td>
</tr>
<tr>
<td>Depression</td>
<td>2674</td>
<td>107 (4.0%)</td>
<td>1.24 (1.00-1.53)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Based on univariate, logistic regression analyses

*Table 4. Significant patient-specific risk factors for severe postoperative complications within 30 days after surgery*

**Surgery-specific risk factors**

The conversion rate was 1.1%. Conversion to open surgery was associated with an increased risk for serious postoperative complication (OR 4.12, CI 2.47-6.89; p<0.001). No significant difference was seen between different causes for conversion.

An intraoperative adverse event occurred in 2.8% of all operations (712 / 25 038). An intraoperative adverse event increased the risk for a serious postoperative complication (OR 2.63, CI 1.89-3.66; p<0.001). Submucosal stapling or unintentional malrotation (10.6% suffered from a serious complication) resulted in the highest risk for serious complication, followed by unintentional bowel injury (9.0 %), bleeding (7.6 %) and instrument failure...
The risk was not significantly increased after stapling of the nasogastric tube (4.2%) or for other reasons (3.1%).

If an additional operation was done at the same time as the laparoscopic gastric bypass procedure, the risk for serious complication was increased (OR 1.50, CI 1.04-2.18; p=0.030).

**Multivariate analysis**

When age and surgery-specific risk factors were entered into multiple regression analyses, conversion to open surgery (adjusted OR 3.12; 1.83 – 5.30; p<0.001), intraoperative adverse event (adjusted OR 2.31, CI 1.65 – 3.24; p<0.001) and age (30-40 yrs. adjusted OR 1.06, CI 0.81 – 1.67, p=0.664; 40-50 yrs. adjusted OR 1.30, CI 1.00 – 1.67, p=0.046; 50-60 yrs. adjusted OR 1.33, CI 1.01 – 1.75, p=0.044; >60 yrs. adjusted OR 1.33, CI 0.89 – 1.99, p=0.159) remained as statistically significant risk factors. Other procedure at the time of gastric bypass did not remain significant (adjusted OR 1.31, CI 0.90 – 1.91, p=0.152).

**Institutional risk factors**

Annual gastric bypass surgery volume at the hospital was inversely correlated to the risk for serious complication (Fig 11). The incidence of serious postoperative complications was significantly higher up until annual volumes of 200 operations.

Serious postoperative complications were more common following the first 400 operations performed at the hospital (Fig 12).

![Fig 11. Incidence of serious postoperative complications with annual operative volume](image1)

![Fig 12. Incidence of serious postoperative complications with total number of previous laparoscopic gastric bypass procedures](image2)
Secondary outcomes
The greater the waist circumference, the higher the risk was for leakage/deep infection ($p=0.005$) and other wound complications ($p=0.032$). Higher age was associated with increased risk for leakage/deep infection ($p<0.001$), bleeding ($p<0.001$), anastomotic strictures ($p=0.003$) and other wound complications ($p<0.001$). Male gender increased the risk for leakage/deep infection, bleeding and port-related complications, but was associated with a lower risk for intestinal obstruction or ileus. Table 5 lists specific risk for each postoperative complication according to comorbidity and sex.

Conversion to open surgery was specifically associated with an increased risk for leakage/deep infection (OR 5.98; CI 3.92 – 9.13; $p<0.001$), bleeding (OR 2.06; CI 1.12 – 3.78; $p=0.021$), venous thromboembolism (OR 11.81; CI 3.53 – 39.45; $p<0.001$) and other wound complications, mainly wound infection (OR 15.57; CI 10.62 – 22.82; $p<0.001$).

An intraoperative adverse event increased the risk for a postoperative complication (OR 2.36, CI 1.93-2.87; $p<0.001$). The risk was specifically increased for leakage/deep infection (OR 3.79; 2.74 – 5.23, $p<0.001$), bleeding (OR 2.05; 1.40 – 3.01; $p<0.001$), pulmonary complications (OR 3.56; 2.15 – 5.90; $p<0.001$), marginal ulcer (OR 2.55; 1.24 – 5.25; $p=0.011$), port-related complication (OR 2.08; 1.02 – 4.27; $p=0.045$) and other wound complication (OR 2.83; 1.78 – 4.49; $p<0.001$).

Operation time and length of hospital stay became shorter with increasing annual volume up to 300 operations/year. At the individual hospital level, operation time and length of hospital stay became increasingly shorter up to a total of 500 operations indicating the effect of increasing experience.
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Postoperative complication</th>
<th>OR (CI)</th>
<th>P-value</th>
<th>Corrected P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>bleeding</td>
<td>1.78 (1.48-2.12)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>cardiovascular complication</td>
<td>4.27 (2.50-7.27)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>pulmonary complication</td>
<td>1.60 (1.18-2.17)</td>
<td>0.003</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>leakage / deep infection</td>
<td>1.32 (1.08-1.62)</td>
<td>0.007</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>bowel obstruction / ileus</td>
<td>0.72 (0.52-0.98)</td>
<td>0.040</td>
<td>N.S</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>leakage / deep infection</td>
<td>1.67 (1.28-2.17)</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
<td>1.49 (1.16-1.92)</td>
<td>0.002</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>cardiovascular complication</td>
<td>2.53 (1.33-4.79)</td>
<td>0.004</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>marginal ulcer</td>
<td>1.82 (1.11-2.98)</td>
<td>0.018</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>venous thromboembolism</td>
<td>2.64 (1.07-6.56)</td>
<td>0.036</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>other wound complication</td>
<td>1.45 (1.02-2.07)</td>
<td>0.038</td>
<td>N.S</td>
</tr>
<tr>
<td>Diabetes</td>
<td>bleeding</td>
<td>1.71 (1.39-2.11)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>leakage / deep infection</td>
<td>1.64 (1.31-2.05)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>cardiovascular complication</td>
<td>3.41 (1.98-5.86)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>pulmonary complication</td>
<td>1.80 (1.28-2.53)</td>
<td>0.001</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>other wound complication</td>
<td>1.59 (1.18-2.13)</td>
<td>0.002</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>marginal ulcer</td>
<td>1.81 (1.18-2.77)</td>
<td>0.007</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>bowel obstruction / ileus</td>
<td>0.65 (0.43-0.99)</td>
<td>0.044</td>
<td>N.S</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>bleeding</td>
<td>1.82 (1.45-2.30)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>cardiovascular complication</td>
<td>2.17 (1.12-4.20)</td>
<td>0.021</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>pulmonary complication</td>
<td>1.54 (1.02-2.32)</td>
<td>0.040</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>venous thromboembolism</td>
<td>2.53 (1.02-6.28)</td>
<td>0.045</td>
<td>N.S</td>
</tr>
<tr>
<td>Depression</td>
<td>pulmonary complication</td>
<td>1.81 (1.28-2.57)</td>
<td>0.001</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
<td>1.38 (1.10-1.73)</td>
<td>0.005</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>marginal ulcer</td>
<td>1.72 (1.10-2.69)</td>
<td>0.016</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>leakage / deep infection</td>
<td>1.30 (1.01-1.67)</td>
<td>0.038</td>
<td>N.S</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>anastomotic stricture</td>
<td>5.86 (2.11-16.28)</td>
<td>0.006</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>venous thromboembolism</td>
<td>6.42 (1.51-27.21)</td>
<td>0.012</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
<td>1.91 (1.07-3.43)</td>
<td>0.030</td>
<td>N.S</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>venous thromboembolism</td>
<td>11.24 (3.65-34.63)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>port-related complication</td>
<td>3.33 (1.43-7.72)</td>
<td>0.005</td>
<td>N.S</td>
</tr>
<tr>
<td>Smoking</td>
<td>urinary tract infection</td>
<td>1.92 (1.19-3.11)</td>
<td>0.007</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>other wound complication</td>
<td>1.47 (1.02-2.12)</td>
<td>0.040</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td>pulmonary complication</td>
<td>1.53 (1.01-2.30)</td>
<td>0.042</td>
<td>N.S</td>
</tr>
<tr>
<td>Male gender</td>
<td>bleeding</td>
<td>1.60 (1.33-1.92)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>leakage / deep infection</td>
<td>1.60 (1.31-1.95)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>bowel obstruction / ileus</td>
<td>0.54 (0.37-0.76)</td>
<td>0.001</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>port-related complication</td>
<td>1.65 (1.09-2.21)</td>
<td>0.015</td>
<td>N.S</td>
</tr>
</tbody>
</table>

1Calculated by means of Bonferoni-Holm method.

Table 5. Risk factors for specific postoperative complication
## Table 6. Annual operative volume and operating time and hospital stay

<table>
<thead>
<tr>
<th>Operations/year</th>
<th>Length of operation, min</th>
<th>P-value</th>
<th>Length of hospital stay, days</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>110.3 (47.83)</td>
<td>&lt;0.001</td>
<td>3.0 (4.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100-149</td>
<td>89.3 (34.24)</td>
<td>&lt;0.001</td>
<td>2.6 (2.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>150-199</td>
<td>78.2 (29.82)</td>
<td>&lt;0.001</td>
<td>2.3 (2.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>200-249</td>
<td>77.3 (30.37)</td>
<td>&lt;0.001</td>
<td>2.4 (3.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>250-299</td>
<td>67.1 (27.67)</td>
<td>&lt;0.001</td>
<td>2.2 (3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;300</td>
<td>56.8 (22.70)</td>
<td>Ref</td>
<td>1.7 (2.24)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

## Table 7. Learning curve and operating time and hospital stay

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Length of operation, min</th>
<th>P-value</th>
<th>Length of hospital stay, days</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>115.1 (51.90)</td>
<td>&lt;0.001</td>
<td>3.0 (4.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100-199</td>
<td>99.2 (45.63)</td>
<td>&lt;0.001</td>
<td>2.8 (4.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>200-299</td>
<td>94.2 (41.12)</td>
<td>&lt;0.001</td>
<td>2.8 (3.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300-399</td>
<td>78.6 (37.50)</td>
<td>&lt;0.001</td>
<td>2.2 (2.39)</td>
<td>0.002</td>
</tr>
<tr>
<td>400-499</td>
<td>77.7 (31.55)</td>
<td>&lt;0.001</td>
<td>2.3 (2.38)</td>
<td>0.003</td>
</tr>
<tr>
<td>&gt;500</td>
<td>66.2 (28.52)</td>
<td>Ref</td>
<td>2.0 (2.71)</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Preventing Complications in Bariatric Surgery

Paper II

A total of 19,448 patients were operated with laparoscopic gastric bypass surgery from January 1st, 2010 until September 30th, 2012. A preoperative HbA1c-level was documented for 15,828 patients. Follow-up at Day 30 was 96.6% (n=15,297). After exclusion for diabetes (n=2,447), a study group of 12,850 patients without preoperative medical treatment for diabetes remained. Based on preoperative HbA1c-levels, the patients were divided into 3 categories according to recommendations of the American Diabetes Association [254]. Patients with higher HbA1c were older, and had a higher BMI and waist circumference. They were also more often males, and more often had comorbid diseases (Table 8).

<table>
<thead>
<tr>
<th>HbA1c &lt;5.7%</th>
<th>HbA1c 5.7-6.49%</th>
<th>HbA1c ≥6.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) or mean ± SD</td>
<td>N (%) or mean ± SD</td>
<td>P</td>
</tr>
<tr>
<td>Individuals</td>
<td>8040</td>
<td>4204</td>
</tr>
<tr>
<td>Female gender</td>
<td>6513 (81.0%)</td>
<td>3186 (75.8%)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>125 ± 13.9</td>
<td>129 ± 13.4</td>
</tr>
<tr>
<td>Age</td>
<td>37 ± 10.1</td>
<td>44 ± 10.3</td>
</tr>
<tr>
<td>BMI</td>
<td>42.2 ± 5.14</td>
<td>43.1 ± 5.50</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>3104 (38.6%)</td>
<td>2363 (75.8%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1966 (29.9%)</td>
<td>1167 (32.7%)</td>
</tr>
</tbody>
</table>

Table 8. Baseline characteristics in Study II

A preoperative HbA1c-value higher than 5.7% (39 mmol/mol) was associated with an increased risk for a serious postoperative complication (Table 9). After adjusting for sex, age, BMI, sleep apnoea, hypertension, dyslipidaemia and depression, HbA1c was still significantly correlated to an increased risk for a serious postoperative complication (HbA1c 5.7-6.49%, adjusted OR 1.26, CI 1.01-1.59, p=0.042; HbA1c ≥6.5%, adjusted OR 1.65, CI 1.08-2.51, p=0.021)

58  ERIK STENBERG  Preventing Complications in Bariatric Surgery
Table 9. Risk for serious complication stratified by HbA1c value, categorised as HbA1c <5.7% (<39 mmol/mol), HbA1c 5.7-6.49% (39-47.9 mmol/mol), and HbA1c ≥6.5% (>48 mmol/mol)

### Secondary Outcomes
Higher HbA1c levels were associated with a higher incidence of postoperative complications, specifically leakage/deep infection, bleeding, small bowel obstruction, pulmonary complications and cardiovascular complications (Table 10).

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Serious Complication</th>
<th>n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.7%</td>
<td>Reference</td>
<td>216 (2.7%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5.7 – 6.49%</td>
<td>146 (3.5%)</td>
<td>1.30 (1.05 – 1.61)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>≥ 6.5%</td>
<td>27 (4.5%)</td>
<td>1.69 (1.12 – 2.54)</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Significant specified complications in relation to HbA1c value, categorised as HbA1c < 5.7% (<39 mmol/mol), HbA1c 5.7-6.49% (39-47.9 mmol/mol), and HbA1c ≥6.5% (>48 mmol/mol)
Paper III

From May 1st, 2010 until Nov 14th, 2011, 2,519 patients operated at any of the 12 participating centres, consented to participate in the study. Ten patients were excluded due to either early conversion to open surgery or termination of the operation due to unexpected findings at surgery. Two patients were mistakenly offered inclusion, but since they were planned for open gastric bypass surgery they were excluded. The remaining 2,507 patients became the basis for our study. Follow-up at Day 30 was 2,503 (99.8%), at 1 year 2,439 (97%), and at 2 years 2,245 (90%). With additional data from The Swedish National Patient Register, follow-up for re-operation for small bowel obstruction covered 2,482 patients (99%).

Fig 13. CONSORT-diagram

Adherence to protocol

Of all patients randomised to mesenteric defects closure, 60 patients did not receive their allocated intervention: 32 patients had none of their mesenteric defects closed (19 for technical reasons, 4 due to adhesions, 4 suffered from an intraoperative complication, 3 because of anticipated risk for bleeding,
2 for protocol violation or unknown reason). For technical reasons, 22 patients had only one of the mesenteric defects closed (19 only the defect beneath the jejunojejunostomy and 3 only Petersen’s space), and 6 patients were converted to open surgery after randomisation. Of all patients randomised to non-closure, the mesenteric defects were closed in 5 patients for unknown reasons, and 4 patients were converted to open surgery after randomisation. All patients who underwent randomisation were included in the study on an intention-to-treat basis.

**Safety**

A severe postoperative complication occurred after 3.6% of all operations. Severe complications were more common during the first 30 days after surgery when the mesenteric defects were closed (54 (4.3%) with closure vs. 35 (2.8%) with non-closure, OR 1.55, CI 1.01-2.39, p=0.044).

**Efficacy**

Closure of the mesenteric defects was associated with lower risk for reoperation due to small bowel obstruction (5.5% with closure, vs 10.2% with non-closure, HR 0.56, CI 0.41-0.76). As shown in Figure 14, a time-dependent difference existed between the groups. During the early postoperative phase, reoperation for small bowel obstruction was more common when the mesenteric defects were open than when the mesenteric defects were closed (HR for closed vs. open defects day 0-30, HR 2.62, CI 1.16-5.90, p=0.021). Subsequently, more patients with non-closure of the mesenteric defects underwent reoperation due to small bowel obstruction (HR for closed vs. open defects after day 30, HR 0.40, CI 0.28-0.58, p<0.001). The most common cause for small bowel obstruction was internal hernia.
Secondary outcomes

A postoperative complication occurred during the first 30 days after 7.8% of all operations. The risk was increased for pulmonary compilation (10 (0.8%) with closure vs. 2 (0.2%) with non-closure, p=0.038) and for bowel obstruction/paralysis (26 (2.1%) with closure vs. 9 (0.7%) with non-closure, p=0.004). The main cause for small bowel obstruction in the early postoperative phase was kinking of the jejunojejunalostomy (Table 11).

The mean operation time was 69.9 ± 27.7 min without mesenteric defects closure and 83.3 ± 29.7 min with mesenteric defects closure (p<0.001). No significant difference was seen in the length of hospital stay postoperatively (2.2 ± 2.1 days with closure vs. 2.1 ± 1.5 days with non-closure, p=0.107).
Days 0-30

<table>
<thead>
<tr>
<th>Condition</th>
<th>Open defects</th>
<th>Closed defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinking of jejunojejunostomy</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Internal hernia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Beneath jejunojejunostomy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Petersen’s space</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combined/undefined</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adhesions</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Intussusception</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

After day 30

<table>
<thead>
<tr>
<th>Condition</th>
<th>Open defects</th>
<th>Closed defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinking of jejunojejunostomy</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Internal hernia</td>
<td>89</td>
<td>27</td>
</tr>
<tr>
<td>Beneath jejunojejunostomy</td>
<td>58</td>
<td>18</td>
</tr>
<tr>
<td>Petersen’s space</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Combined/undefined</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Adhesions</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intussusception</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 11. Causes for small bowel obstruction

Post-hoc multivariate analyses

In unadjusted, univariate Cox-regression analyses, previous anti-reflux surgery (HR 4.16, CI 1.32-13.10, p=0.015), non-closure of mesenteric defects (HR 3.39, CI 2.22 – 5.17, p<0.001) and percentage excess BMI-loss at 30 days (HR 1.01, CI 1.00-1.03, per % EBMIL, p=0.032) were significant risk factors for reoperation for small bowel obstruction, while increased age (HR 0.97, CI 0.96-0.99 per year, p=0.002) and hypertension (HR 0.70, CI 0.55-0.91, p=0.006) were significantly associated with reduced risk. In the multivariate analyses previous anti-reflux surgery (HR 4.19, CI 1.32-13.27, p=0.015), non-closure of mesenteric defects (HR 3.33, CI 2.18-5.09, p<0.001), percentage excess BMI-loss at 30 days (HR 1.02, CI 1.00-1.03, p=0.017) remained as significant risk factors while increased age (HR 0.98, CI 0.96-1.00 per year, p=0.023) was associated with reduced risk.

Paper IV

From the SOReg we identified 11 931 patients operated with gastric bypass surgery between May 1st, 2010 and Nov 14th, 2011. After exclusion for primary open procedure (n=148) and previous bariatric surgery (n=375), 11 408 patients remained in the study.

All patients in Paper III were included in the RCT-group. After exclusion for retrocolic gastric bypass surgery (n=37) and missing data on handling
of the mesenteric defects (n=369), 8 485 patients remained in the non-RCT group.

Baseline characteristics and follow-up
The distribution of gender was similar in the RCT and in the non-RCT groups (76.1% of female gender in the RCT vs. 74.3% in the non-RCT, p=0.067). Mean BMI was slightly lower in the non-RCT group (42.7 ± 5.3 vs. 42.4 ± 5.04, p=0.002), with a slightly lower age (41.7 ± 10.7 vs. 41.0 ± 11.1, p<0.001). The patients in the non-RCT group more often had associated comorbid disease (50.0% vs 55.0%, p<0.001).

Follow-up as registered in the SOReg was 99.8% (n=2 503) at 30 days (safety outcome) in the RCT-group and 99.3% (n=8 427) in the non-RCT group. Follow-up at 2 years (weight-loss) was 89.5% (n=2 245) in the RCT-group and 63.0% (n=5 342) in the non-RCT-group. With additional data from the Swedish National Patient Register, follow-up for operation for small bowel obstruction by December 31st, 2014, was 99.0% (n=2 481) in the RCT group and 98.8% (n=8 485) in the non-RCT-group. Five individuals in the RCT and 21 individuals in the non-RCT group did not have an address in Sweden at that time, and were considered lost to follow-up after their last
recorded follow-up visit. In the RCT-group 21 individuals (0.8%) died during the follow-up period, and 79 individuals (0.9%) in the non-RCT group.

**Early postoperative complications – safety outcome**
In the RCT group, 196 patients suffered from a postoperative complication (7.8%) compared to 665 patients (7.9%) in the non-RCT group. No difference was seen between the non-RCT and the RCT groups regarding serious postoperative complications (3.6% in the RCT group vs. 3.1% in the non-RCT group, p=0.253). No statistically significant difference was seen between the RCT and the non-RCT groups when the defects were not closed (OR 0.94, 0.64-1.36, p=0.728) or when the defects were closed (OR 1.34, CI 0.96-1.86, p=0.087). However, when stratified for age, BMI, sex and comorbid diseases, the risk for early serious complication was significantly higher in the RCT compared to the non-RCT group when the defects were closed (adjusted OR for open defects 0.89, CI 0.61 – 1.30, p=0.559; adjusted OR for closed defects 1.47, CI 1.03 – 2.09, p=0.032)

**Reoperation for small bowel obstruction – efficacy outcome**
Over the study period the risk for small bowel obstruction was lower in both groups when the mesenteric defects were closed (HR_{RCT} 0.50, CI 0.38-0.68, p<0.001; HR_{non-RCT} 0.75, CI 0.63-0.87, p<0.001). The relative risk for small bowel obstruction with non-closure compared to closure of the mesenteric defects was 1.91 in the RCT group and 1.39 in the non-RCT group. No significant difference was seen between the RCT and the non-RCT group when the defects were closed (cumulative incidence in RCT 5.7%, non-RCT 7.0%; HR 0.82, CI 0.62-1.07, p=0.137; adjusted HR stratified for sex, BMI, age and co-morbid diseases 0.86, CI 0.65-1.14, p=0.297). However, during the first 30 days, reoperation for small bowel obstruction was more common in the RCT group (OR 2.14, CI 1.22 – 3.75, p=0.008). No significant difference was seen between the two groups when the mesenteric defects were not closed (cumulative incidence in the RCT group 10.9%, in the non-RCT group 9.4%; HR 1.20, CI 0.99-1.46, p=0.065; adjusted HR stratified for sex, BMI, age and comorbid disease 1.21, CI 1.00-1.47, p=0.053).

When the groups were compared according to received treatment, no difference was seen whether the defects were closed (HR 0.81, CI 0.62 – 1.06, p=0.128; adjusted HR stratified for sex, BMI, age and comorbid disease 0.85, CI 0.64-1.13, p=0.266), or not closed (HR 1.19, CI 0.98 – 1.45, p=0.074; adjusted HR stratified for sex, BMI, age and comorbid disease 1.21, CI 1.00-1.47, p=0.056).
Secondary Outcomes

The operation time was shorter in the RCT group compared to the non-RCT group when the mesenteric defects were left open (69.9 ± 27.7 min vs. 81.0 ± 37.5 min, p < 0.001). With mesenteric defects closure, operation time was longer in the RCT group (83.3 ± 29.7 min vs 57.4 ± 27.2 min, p < 0.001). Length of hospital stay was longer in the RCT group compared to the non-RCT group when the mesenteric defects were closed (2.2 ± 2.1 days vs. 1.8 ± 2.9 days, p < 0.001) whereas no difference was seen when mesenteric defects were not closed (2.1 ± 1.5 days vs. 2.2 ± 2.6 days, p = 0.169).

No difference was seen between the RCT and the non-RCT group with respect to weight loss (%EBMIL 2 years after surgery in the RCT-group 81.8% vs. 81.8% in the non-RCT group, p = 0.966). Three individuals in the non-RCT group underwent revision surgery during the first two years after surgery compared to one individual in the RCT group (p = 1.000).
Discussion

General aspects

Obesity is a major public health problem today. With the lack of effective public health interventions and medical treatment, bariatric surgery has become the mainstay of treatment for morbidly obese individuals. Previous important scientific contributions have provided us with at least three effective surgical techniques with proven benefits for these patients. The focus of bariatric surgical science is now shifting towards the prevalence and prevention of side-effects and adverse outcomes after surgery. It is in the interest of both patients and tax-payers to keep postoperative complications at a minimum.

The focus of this thesis has been to identify potential risk factors for early postoperative complication after laparoscopic gastric bypass surgery and in a randomised clinical trial evaluate an intervention (mesenteric defects closure) to see if this can reduce the occurrence of a specific major adverse outcome (small bowel obstruction).

Risk factors for early postoperative complications

Operating on morbidly obese patients have previously been considered high risk surgery\textsuperscript{236}. With improvements in surgical technique, perioperative care as well as specific training of new bariatric surgeons, complication rates have fallen with time\textsuperscript{149}. Today bariatric surgery is considered to be safe. In Study I the mortality rate was seen to be as as low as 0.04\%. Complication rates were also low. In our material a serious complication occurred after 3.4\% of all laparoscopic gastric bypass procedures. However, given the high number of operations performed annually, a fairly high number of patients will still suffer a complication resulting in long-term consequences for the individual as well as a great impact upon healthcare economy. In previous studies, several patient-specific risk factors have been reported. In our study only sleep apnoea, depression and age were significant patient-specific risk factors associated with serious postoperative complication. The most important of these seemed to be age, which was the only patient-specific risk factor to remain in the adjusted analyses. This result has been verified in a recent Dutch study\textsuperscript{281}. BMI did not affect the risk for serious complication in our trial. In a previous work by Gupta\textsuperscript{143}, BMI in the extremes were associated with increased complication rates. Although the same tendency
was seen in our study, it failed to reach significance, indicating that BMI alone is a poor predictor of risk for serious postoperative complication.

Although patient-specific risk factors may be used for preoperative selection and optimisation prior to surgery, surgical and centre-related risk factors seem to have a more profound impact on outcome. Low annual operative volume and previous operative experience at the institution are both risk factors for serious postoperative complication. These complications decrease with increasing annual operative volume, at least up to 200 operations per year. In our study we could not address the experience of individual surgeons, but rather the total experience at the centre. A learning-curve of around 400 cases seems to be the case when introducing laparoscopic gastric bypass surgery at a new centre.

The most important factors affecting risk for adverse outcome is what happens during surgery and the perioperative period. This are affected by experience of bariatric surgery at each hospital. In a previous study, suffering an intraoperative adverse event, even when detected and managed during surgery, increased the risk for a postoperative complication. An intraoperative adverse event was an important risk factor for serious postoperative complication in our study as well. The risk was particularly high after unintentional bowel injury, submucosal stapling or malrotation of the small bowel and in the case of surgical instrument failure. What these complications have in common is that they lead to unnecessary breach of the bowel wall with potential spilling of small bowel contents. An increased risk was also seen with intraoperative bleeding. Conversion to open surgery markedly increased the risk for serious postoperative complication. The complication rates in this group was much higher than previously described for primary open gastric bypass surgery. This, of course, may well be explained by the fact that conversion was due to a complicated laparoscopic procedure which itself increases the risk.

Patient-related risk factors, particularly age, can be identified prior to surgery. However, intraoperative adverse event and conversion to open surgery are the strongest risk factors for serious postoperative complication after laparoscopic gastric bypass surgery. Annual operative volume and experience at the centre are also important for the outcome.

**Insulin resistance**

Insulin resistance and type 2 diabetes mellitus are common in the general population with estimated prevalence of 9.8% in men and 9.2% in women. Diabetes is even more common among patients undergoing bariatric
surgery, with incidence rates of up to 25% in Europe and 33% in North America \textsuperscript{127,132}. Insulin resistance occurs after both elective and acute surgery, and the magnitude largely depends on the extent of surgery \textsuperscript{251}. Insulin resistance appears to be an important mechanism by which several postoperative complications are triggered \textsuperscript{249}. HbA1c has previously been reported to correspond to intraoperative insulin sensitivity and postoperative complications after major surgery. In paper II we report an association between HbA1c and serious postoperative complication after a minimally invasive procedure on non-diabetic obese subjects. This association was already seen at HbA1c values defined by the American Diabetic Association as “pre-diabetic”. Raised HbA1c values were associated with higher age, increased presence of comorbid disease and BMI. However, after adjustment for these factors, a high HbA1c value still remained a significant risk factor for serious postoperative complication. It is likely that patients with higher preoperative HbA1c values experience a more significant loss in insulin sensitivity as a response to the surgical trauma. Although surgical trauma is less pronounced after laparoscopic gastric bypass surgery compared to major colorectal and cardiovascular surgery, it still seems to be an important consideration. Further studies are necessary to evaluate preventive measures that can be undertaken to reduce the risk associated with elevated HbA1c values and to further identify subgroups of individuals in the “pre-diabetes group” who develop more profound insulin resistance in response to surgical trauma.

**Prevention of early postoperative complications**

Although it is important to strive for low postoperative complication rates, it is unlikely that we will ever be able to completely prevent all complications from occurring. There are, however, some complications after laparoscopic gastric bypass surgery that are preventable, and others that may be anticipated. We have identified age, intraoperative adverse event and conversion to open surgery as factors associated with increased risk for serious postoperative complication. Age is a factor that cannot be modified, but it can be taken into consideration in the preoperative assessment prior to bariatric surgery. One must bear in mind, however, that an elderly morbidly obese patient stands to benefit significantly from the operation \textsuperscript{283} and should not be excluded on a general basis.

The incidence of intraoperative adverse events tends to fall with time \textsuperscript{149}. Increased surgical quality, standardisation of technique, and presence of ex-
Experienced surgeons during the learning-curve period are all factors that contribute to a reduction of such events. Conversion to open surgery in some instances may be anticipated, while other conversions occur due to unexpected findings or events during surgery. We need to address specific intraoperative complications in future studies in order to identify modifiable risk factors associated with these events.

With this knowledge we can identify patients at high risk for a serious postoperative complication. With a high level of suspicion, a serious complication can be identified and treated at an early stage thus reducing morbidity and mortality. Based on the results from our Paper I, it may be advisable to avoid operating on patients with high age or with increased risk for intraoperative adverse event, or those with a high risk for conversion to open surgery at centres performing relatively few operations per year or while still in the learning-curve period (i.e. the first 400 cases).

Insulin resistance appear to be an important mechanism for the development of a substantial number of postoperative complications. HbA1c values correlate to the occurrence of intraoperative insulin resistance and has some predictive value. Further studies are needed to evaluate how this information can be used to optimise patients preoperatively, but based on the findings from Study II along with previous findings from major colorectal and cardiovascular surgery, HbA1c should be a part of patient assessment prior to bariatric surgery.

**Small bowel obstruction**

Ever since the introduction of laparoscopic gastric bypass surgery, small bowel obstruction caused by internal herniation, has been a growing concern. Prior to our study (Paper III), there was a lack of high quality evidence to support preventive measures to reduce the incidence of small bowel obstruction. In Study III we were able to show that by closing the mesenteric defects in laparoscopic gastric bypass surgery, the risk for small bowel obstruction is markedly reduced. However, this comes at a price since the additional closure of the mesenteric defects increases operation time, which could account for the small increase in pulmonary complications seen in our study. Closure of the mesenteric defects also increases the risk for small bowel obstruction in the early postoperative phase, mainly due to kinking of the jejunojejunostomy. The incidence of this complication falls with increased experience of mesenteric defects closure, as suggested by the lower incidence reported in Paper IV. Other methods have been suggested that might also reduce the incidence of kinking of the jejunojejunostomy, such
as an anti-obstructive stitch \(^{285}\), wide division of the mesentery, and the creation of a wide jejunojejunostomy by the use of two linear staplers. The evidence to support these various preventive measures, however, is weak and further studies addressing the issue of kinking of the jejunojejunostomy are needed.

In Study III, the mesenteric defects were closed with running, non-absorbable sutures. This is now the technique that has the best scientific support. Given the fact that the incidence of internal herniation with small bowel obstruction increases with time, non-absorbable sutures are preferred to absorbable materials. There are, however, methods other than suturing available, such as glue or clips. Sutures have the highest tensile strength \(^{286}\), but clips have been tested with promising results \(^{154,187}\). Further studies assessing the best way to close the mesenteric defects are needed.

When interpreting the incidence of small bowel obstruction in general and internal herniation in particular, a problem is how does one define symptomatic internal hernia? \(^{287}\) Differing definitions may account for the divergent results from previous studies. To allow better comparison between studies, a uniform classification of internal hernia resembling the classification of postoperative complications described by Clavien and Dindo \(^{279,288}\) is needed. Such a classification must be relevant both from a scientific point of view and its application to clinical practice. In a recent paper, symptoms and findings consistent with internal herniation, with full remission of symptoms three months after reoperation in the absence of other pathology found at reoperation was proposed as a definition of internal hernia \(^{187}\). The problem with such a definition, however, is that in the population without signs of bowel obstruction, with or without herniation at the time of surgery, some patients may have symptomatic internal herniation, others may not. In Study III we tried to overcome this problem by looking at cases of small bowel obstruction and not those with presumed internal herniation. Although the definition “small bowel obstruction” miss patients with intermittent abdominal pain that may be caused by intermittent herniation, it does give a clearer picture of the more severe cases suffering from bowel obstruction.

The mesenteric defects should thus be closed in laparoscopic gastric bypass surgery in order to reduce the incidence of small bowel obstruction. Despite the marked effect of this preventive measure, small bowel obstruction due to internal herniation still occurs. All surgeons working with emergency surgery must be aware of this complication. With less acute symptoms, CT-scanning can aid the diagnostic work-up, and in cases presenting at night,
surgical evaluation should be postponed until the day after when a bariatric surgeon can be present. If the patient presents with acute symptoms, particularly if they are resistant to analgesics, acute exploration, with or without a bariatric surgeon present, is necessary. If the reoperation is performed by a surgeon with limited experience of bariatric surgery, open surgery is advisable. Laparoscopic exploration may be possible if the surgeon is highly experienced in bariatric surgery.

**Assessment of interventions in surgery**

Large, well-designed randomised controlled trials (RCTs) are considered to be the “gold standard” to assess efficacy and safety of new medical innovations. RCTs are however time-consuming and very expensive to conduct. The net cost for a phase III RCT varies from 0.7 - 64 million USD. Furthermore, they may not always be feasible, for practical or ethical considerations. Although gains for the healthcare system from these trials are considered to be large and cost-effective, it is becoming increasingly more difficult to undertake extremely expensive trials. This is particularly true in the field of surgery, where RCTs are scarce, and other study designs are needed to evaluate the effectiveness and safety of new surgical innovations. One such method is the observational study. The observational study is conducted in the “real clinical world” and provide high external validity, but it can never be fully standardised for the many potential confounding factors, and is generally not considered a real alternative to the RCT.

In paper IV we compared the results of the register-based RCT in Paper III with observational data from virtually the entire population of bariatric surgery patients in Sweden over the same period of time. Our results show that an observational study comparing mesenteric defects closure with non-closure, performed at the same time, reached the same conclusion as the RCT. The importance of this finding is that it seems to justify the use of observational studies both as a supplement to RCT (further addressing issues of external validity) and as an option when a RCT, for some reason, is not possible. In our study, however, the treatment effect of mesenteric defects closure was smaller in the observational study than in the RCT. There are several possible reasons for this. In Study III, a meticulous review of all reoperations for suspected small bowel obstruction was performed. This was not possible in the non-RCT group and this could explain the lower incidence rate seen among patients with non-closure of the mesenteric defects. In addition, different techniques were used to close the mesenteric defects in the non-RCT group. Although both sutures (Paper III) and clips
154,187 seem to be effective methods for mesenteric defects closure, they may not be equally so. The technique for mesenteric defects closure was well standardised in the RCT, but less so in the non-RCT group. These differences in technique could contribute to the higher small bowel obstruction incidence rate seen in the non-RCT group with mesenteric defects closure. One of the limitations, but also strengths, of observational studies is this lack of standardisation of technique, thus representing to a greater extent the way in which the new technique is applied in clinical practice. One of the benefits of introducing a novel surgical innovation using a RCT is the standardised introduction of the technique to the surgical profession 261.

Another alternative to the traditional RCT is the register-based RCT. By using existing, high-quality clinical registers to monitor and follow-up patients in the trial, a register-based RCT has the strength of having a high number of patients over a short time period with accurate follow-up, at a much lower cost and effort than the traditional RCT 259,290,293. The price of our trial can be estimated to be less than 50 000 USD, or 20 USD/patient which is much lower than the cost of standard phase III RCTs 289. Apart from a previous register-based RCT in cardiology 293, to our knowledge, Study III in this thesis is the first large register-based RCT to be performed. The register-based RCT may be regarded as a new paradigm offering the potential to conduct RCTs easily and frequently and without the disadvantage of poor external validity commonly seen in traditional RCTs 290. However, the quality of a register-based RCT will never be better than the quality of the register itself, introducing new fundamental challenges that need to be overcome in order to fully allow the wide use of register-based RCTs 290.

The future of bariatric surgery

It is unlikely that we will see a pharmacological alternative that can replace bariatric surgery in the near future. However, there may well be pharmacological interventions that in combination with life-style interventions enable weight-losses of around 10% of the total body weight. Given the fact that many of the metabolic benefits from weight-loss are already seen at a loss of 10% of the total body weight, this could be an alternative for patients with a BMI of 35-40 without severe comorbidity such as diabetes, hypertension and obstructive sleep apnoea. For other morbidly obese persons, future studies will hopefully provide us with scientific evidence supporting the choice of a particular surgical method based on which provides the maximum benefit for the individual patient. Given what we know today, the choice is likely to be either sleeve gastrectomy or gastric bypass. Perhaps the
recommendation will be to perform sleeve gastrectomy in patients with a BMI of less than 45 and without severe comorbidity or gastro-oesophageal reflux disease, and gastric bypass for other patients. Well-conducted research and better adherence to the results, rather than following the opinions of experts would provide a better base for selection of patients for bariatric surgery, with a sharper focus on technique, results and further development. The introduction of a novel surgical intervention takes a long time to reach clinical practice. It is possible that the widespread use of register-based RCTs will provide the foundation for more standardised introduction of novel interventions, with less concern about the external validity of traditional RCTs thus enhancing the acceptance of these trials among clinicians. One such study is being conducted in Sweden at present, in association with a standardised introduction of laparoscopic sleeve gastrectomy (NCT02767505).

Limitations
The four studies in this thesis are based on data registered in the Scandinavian Obesity Surgery Registry. The use of a high-quality register for observational and register-based RCTs offers the possibility to retrieve data for a large number of patients at a limited cost. The data obtained, however, will never be better than the accuracy of registration in the clinical register. By using a clinical register, we are also obliged to use parameters and outcome measures defined in advance by the structure of the register. One major limitation in the Studies I and II of this thesis was that it was not mandatory to register cardiovascular comorbidity. Cardiovascular comorbidity has previously been reported to increase the risk for postoperative complications after bariatric surgery, but we could not evaluate this as a risk factor in this thesis. However, only a minority of patients undergoing bariatric surgery suffer from severe cardiovascular disease and this variable may not be well suited to predict risk for severe postoperative complication among bariatric surgery patients. The registration of a previous history of deep venous thrombosis and pulmonary embolism, and smoking was introduced into the SOReg at a later stage making the statistical power of these variables less robust.

No information on insulin resistance was available in Study II. Although HbA1c value has been linked to intraoperative insulin resistance in other surgical fields, this has not been evaluated in the bariatric surgery population.

Paper III reports a multicentre randomised trial including university hospitals, county hospitals, district hospitals and one private clinic. Although
this may be viewed as a strength (better external validity), it also complicates the study. With several centres enrolling patients into the trial, the risk of faulty randomisation increases. A few patients, for instance, had their mesenteric defects closed at a later operation performed for reasons other than a complication (such as cholecystectomy). Symptoms from gallstone disease can resemble intermittent non-acute internal herniation, and some of these patients may well have eventually presented with small bowel obstruction due to internal hernia. Whatever the situation, the surgeon must put the well-being of his/her patient before any on-going trial. This is a dilemma that can only be controlled by careful registration of such procedures and of subsequent adverse outcome. In Study III the effect of this would be a slight underestimation of adverse outcome. All surgeons participating in Study III were beyond their learning-curve for laparoscopic gastric bypass surgery, but not necessarily so for mesenteric defects closure. This could in part account for the increased risk for kinking of the jejunoojejunostomy reported in Paper III, which is supported by the results in Paper IV. In accordance with the decision of the Ethics committee, randomisation in Study III became open-label after the operation. Knowledge of how the mesenteric defects were treated could have affected the interpretation of abdominal pain by both patient and surgeon. To overcome this issue, we carefully reviewed all reoperations for potential small bowel obstruction to ensure that a uniform definition was used.

In Study IV, there was a difference in follow-up rates between the RCT and the observational study (non-RCT) groups in the SOReg 2 years after the operation. To overcome this issue and to add information concerning reoperation for small bowel obstruction of up to 4 years after surgery, additional data were collected from the Swedish National Patient Register. With the combined data from these registers, we were able to achieve a very high follow-up rate. All reoperations for suspected small bowel obstruction were meticulously reviewed in the RCT group. This, however, was not possible in the non-RCT group. The implication of this has been discussed previously. In Study IV, we compared a standardised method for closure of the mesenteric defect in the RCT group with the varied, less standardised techniques employed in the non-RCT group. However, this is one of the main differences between a RCT and an observational study, and highlights one of the major benefits of introducing a novel technique through a large, multicentre RCT.
Conclusion

Intraoperative adverse events and conversion to open surgery are the strongest risk factors for serious postoperative complications after laparoscopic gastric bypass surgery. Annual operative volume and total institutional experience are important for the outcome. Patient-related factors, in particular age, also increase the risk for complications but to a lesser extent.

An elevated preoperative HbA1c value, even at levels regarded as “prediabetic” is associated with an increased risk for serious postoperative complication after laparoscopic gastric bypass surgery.

Closure of the mesenteric defects in laparoscopic gastric bypass surgery significantly reduces the rate of reoperation for small bowel obstruction and should be considered a standard part of the procedure.

An observational study may be an option for the assessment of efficacy of a surgical intervention when a RCT is not feasible. The observational study may, however, underestimate the treatment effect of a complex surgical intervention.
Swedish summary


I den första studien analyserade vi data för tidig postoperativ komplikation hos individer som opererats med laparoskopisk gastric bypass i Sverige till och med september 2012. Vi fann att risken för allvarlig komplikation var relativt sett låg (3.4%). Att drabbas av en komplikation under operationen samt om operationen konverterades till öppen operation var de starkaste riskfaktorerna för att drabbas av allvarlig postoperativ komplikation. Den årliga operationsvolymen, liksom erfarenheten av operationen vid sjukhuset var också viktiga. Patientrelaterade faktorer framstod som mindre viktiga, även om ffa ålder också innebär en ökad risk.


Den tredje studien utgjordes av en registerbaserad, randomiserad multicenter studie (RCT) där individer som opererats vid 12 centra i Sverige randomiserades till förslutning av de mesenteriella defekterna i samband med operationen, alternativt till att de lämnades öppna. Vi analyserade tidig komplikation (inom 30 dagar) som ett säkerhetsmått samt reoperation pga tarmvred (inom 3 år) som effektmått. Förslutning av de mesenteriella defekterna minskade risken för reoperation pga tarmvred från 10.2% till 5.5% vid 3 år efter operationen. En liten risk ökning sågs för tidig allvarlig komplikation vid förslutning. Denna riskökning förklaras huvudsakligen av en knickbildning vid enteroanastomosen. Denna relativt lilla riskökning vägdes dock helt upp av den senare riskminskningen för tarmvred.
Acknowledgement

This thesis was made possible by a number of friends and colleagues to whom I wish to convey my gratitude

Ingmar Näslund, my main tutor. For always taking my small steps towards understanding medical science with great seriousness and for the ability to always identify what’s important in science and in life

Eva Szabo, my co-tutor, for solid support, in particularly during hard times of the work on the thesis

Johan Ottosson, co-worker on Studies I, III and IV, for the many interesting intellectual discussions concerning bariatric surgery and science

Anders Magnusson, for providing excellent guidance and teaching in medical statistics

All friends and colleagues at the departments of surgery at Lindesbergs Hospital and Örebro University Hospital

All co-workers of Paper I and the steering committee of the SOReg, for the collaboration and support

All co-workers at the 12 centres participating in Paper III, those named as co-authors of the manuscript and those not named, for making this work possible. I would particularly like to thank Anders Thorell for the excellent support during the work on this paper.

All co-workers from the SOReg for making excellent work with the register. I would particularly like to thank Monica Johansson and Niclas Björnfot for quick, solid and professional support.

Tina Galmén for excellent collaboration and support related to the SOReg.

Peter Cox for quick, high quality guidance and review of the English language through the entire work of this thesis.

Thore Wikström for introducing me into the field of medical science and teaching me the value of never giving up despite repeated misfortunes of experiments.

Ulla Stenberg, my mother, for among many things teaching me to never give up hope until the final signal has sounded and also to continuously question facts.

Hans Ljungberg, my father, for among many things teaching me the value of standing on my own feet.

Tyra and Ellen Lagstam, my daughters, for being just the persons you are and thus enlightening my life.

Ida Lagstam, my wife, for love, friendship and patience with me when my attention has been to occupied with work.
References


68. Prachand VN, Davee RT, Alverdy JC. Duodenal switch provides superior weight loss in the super-obese (BMI \( \geq 50 \) kg/m\(^2\)) compared with gastric bypass. *Ann Surg.* 2006;244(4):611-619.


142. Hamilton EC, Sims TL, Hamilton TT, Mullican MA, Jones DB, Provost DA. Clinical predictors of leak after laparoscopic Roux-


222. Pournaras DJ, le Roux CW. After bariatric surgery, what vitamins should be measured and what supplements should be given? *Clin Endocrinol (Oxf).* 2009;71(3):322-325.


266. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet.* 2005;365(9453):82-93.


Gastric surgery interpreted by Tyra Lagstam
Publications in the series

Örebro Studies in Medicine


35. Söderqvist, Fredrik (2009). Health symptoms and potential effects on the blood-brain and blood-cerebrospinal fluid barriers associated with use of wireless telephones.


41. Gustafsson, Sanna Aila (2010). The importance of being thin – Perceived expectations from self and others and the effect on self-evaluation in girls with disordered eating.

42. Johansson, Bengt (2010). Long-term outcome research on PDR brachytherapy with focus on breast, base of tongue and lip cancer.

43. Tina, Elisabet (2010). Biological markers in breast cancer and acute leukaemia with focus on drug resistance.


46. de Leon, Alex (2010). Effects of Anesthesia on Esophageal Sphincters in Obese Patients.


52. Loiske, Karin (2011). Echocardiographic measurements of the heart. With focus on the right ventricle.


64. Nordin Olsson, Inger (2012). Rational drug treatment in the elderly: "To treat or not to treat".


67. Thuresson, Marie (2012). The Initial Phase of an Acute Coronary Syndrome. Symptoms, patients’ response to symptoms and opportunity to reduce time to seek care and to increase ambulance use.


75. Gustavsson, Anders (2012): Therapy in Inflammatory Bowel Disease.


83. Lönn, Johanna (2013): The role of periodontitis and hepatocyte growth factor in systemic inflammation.


96. Sundh, Josefin (2013): Quality of life, mortality and exacerbations in COPD.


98. Palmetun Ekbäck, Maria (2013): Hirsutism and Quality of Life with Aspects on Social Support, Anxiety and Depression.


101. Jildenstål, Pether (2014): Influence of depth of anaesthesia on post-operative cognitive dysfunction (POCD) and inflammatory marker.

102. Söderström, Ulf (2014): Type 1 diabetes in children with non-Swedish background – epidemiology and clinical outcome

103. Wilhelmsson Göstas, Mona (2014): Psychotherapy patients in mental health care: Attachment styles, interpersonal problems and therapy experiences


109. Törös, Bianca (2014): Genome-based characterization of Neisseria meningitidis with focus on the emergent serogroup Y disease


120. Pelto-Piri, Veikko (2015): Ethical considerations in psychiatric inpatient care. The ethical landscape in everyday practice as described by staff.


140. Östlund Lagerström, Lina (2016): ”The gut matters” - an interdisciplinary approach to health and gut function in older adults.


