From Department of Clinical Science, Intervention and Technology (CLINTEC)

Karolinska Institutet, Stockholm, Sweden

HAEMORRHAGIC AND THROMBOEMBOLIC COMPLICATIONS FOLLOWING CHOLECYSTECTOMY

Jonas Strömberg

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Institutionen för klinisk vetenskap, Intervention och teknik (CLINTEC), Enheten för kirurgi

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Huvudhandledare:

Docent Gabriel Sandblom
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik (CLINTEC),
Enheten för kirurgi

Bihandledare:

Docent Folke Hammarqvist
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik (CLINTEC),
Enheten för kirurgi

Associate Professor Omid Sadr-Azodi
Karolinska Institutet
Institutionen för miljömedicin,
Enheten för epidemiologi

Fackultets opponent:

Docent Kevin Mani
Uppsala Universitet
Institutionen för kirurgiska vetenskaper,
Enheten för kärlkirurgi

Betygsnämnd:

Docent Markku Haapamäki
Umeå Universitet
Institutionen för kirurgisk och perioperativ,
vetenskap,
Enheten för kirurgi

Docent Lisa Strömmer
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik (CLINTEC),
Enheten för kirurgi

Docent Mikael Wirén
Linköping Universitet
Institutionen för klinisk och experimentell medicin
Avdelningen för kirurgi, ortopedi och onkologi

To Clara, Mira, Joen and Maje

The only weapon with which the unconscious patient can immediately retaliate upon the incompetent surgeon is haemorrhage.

W. S. Halsted (1852-1922)

ABSTRACT

Laparoscopic cholecystectomy for gallstone disease is one of the most common procedures in the Western world. The overall complication rate is 10%. Whereas most complications are easily managed, bile duct injuries may have devastating consequences. However, less described are haemorrhagic complications that cause morbidity and, in some cases, mortality. In addition, the use of thromboembolism prophylaxis (TP) is still questioned although in some institutions used routinely to prevent venous thromboembolism (VTE). The aims of this thesis were to evaluate the need for TP administration in patients undergoing cholecystectomy, and to determine the incidence and risk factors associated with haemorrhagic and thromboembolic complications in gallstone surgery.

In Paper I, we included 48,010 patients from the Swedish Register for Gallstone Surgery and ERCP (GallRiks). The aim of the study was to evaluate the impact of TP on haemorrhagic complications in cholecystectomy. We found that the cumulative incidence of perioperative haemorrhagic complications doubled and that postoperative bleeding increased by 50% in patients receiving TP. Furthermore, in multivariable analysis, TP significantly predicted the risk for haemorrhage.

In Paper II, data from GallRiks were cross-matched with the Swedish National Patient Register (NPR) to determine the incidence and risk factors for postoperative venous thromboembolism (VTE). The incidence of VTE in the cohort of 62,488 patients was 0.25%. A previous VTE event was the predominant risk factor for developing a thromboembolic complication following cholecystectomy.

In Paper III, data from GallRiks were linked with the NPR to extract information regarding patients with liver cirrhosis (n=77) undergoing cholecystectomy. In our study we found that, compared to non-cirrhotic patients, those with liver cirrhosis were older and more often had complicated gallstone disease (cholecystitis or pancreatitis) at the time of surgery. Furthermore, patients with cirrhosis were more likely to receive a blood transfusion, and the number of postoperative complications was significantly higher than in non-cirrhotic patients.

Paper IV assessed the impact of comorbidity and prescription drugs on haemorrhagic complications in cholecystectomy. A total of 94,557 patients were included from GallRiks and cross-matched with the NPR for data on comorbidity. In the second part of the study, data were cross-matched with the Swedish Prescribed Drug Register (PDR) for information regarding drugs prescribed within 90 days prior to surgery. We found that renal disease, previous myocardial infarction, heart failure, cerebrovascular disease and obesity were associated with an increased risk for haemorrhagic complications. Furthermore, perioperative haemorrhage increased the risk for bile duct injury/leakage as well as mortality.

In conclusion, TP increases the risk for haemorrhagic complications in cholecystectomy. The incidence of VTE following cholecystectomy is low and TP should only be considered in patients with risk factors for VTE. Furthermore, patients with liver cirrhosis have a higher risk for developing perioperative complications. Finally, comorbidity must be considered when assessing the risk for haemorrhagic complications in patients undergoing cholecystectomy.

LIST OF PUBLICATIONS

I. G. Persson, J. Strömberg, B. Svennblad, G. Sandblom. Risk of bleeding associated with use of systemic thromboembolic prophylaxis during laparoscopic cholecystectomy. Br J Surg 2012; 99: 976-986.

II. J. Strömberg, O. Sadr-Azodi, P. Videhult, F. Hammarqvist, G. Sandblom. Incidence and risk factors for symptomatic venous thromboembolism following cholecystectomy. Langenbecks Arch Surg 2015; 400(4): 463-469.

III. J. Strömberg, F. Hammarqvist, O. Sadr-Azodi, G. Sandblom. Cholecystectomy in patients with liver cirrhosis. Gastroenterol Res Pract 2015; 2015: 783823

IV. J. Strömberg, G. Sandblom. Impact of comorbidity and prescription drugs on haemorrhage in cholecystectomy. World J Surg. 2017 Mar 6. doi: 10.1007/s00268-017-3961-3. (Epub ahead of print).

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ASA	American Society of Anesthesiologists
BMI	Body mass index
CBD	Common bile duct
CI	Confidence interval
CTP	Child-Turcotte-Pugh score
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
ERCP	Endoscopic retrograde cholangiopancreaticography
GD	Gallstone disease
HR	Hazard ratio
INR	International normalised ratio
LC	Laparoscopic cholecystectomy
LDUH	Low-dose unfractionated Heparin
LMWH	Low molecular weight heparin
LRYGB	Laparoscopic Roux-en-Y gastric bypass
MELD	Model for end-stage liver disease
MRA	Multivariable regression analysis
MRCP	Magnetic resonance cholangiopancreaticography
NBHW	National Board of Health and Welfare
NPR	National Patient Register
NRN	National Registration Number
OC	Open cholecystectomy
OR	Odds ratio
PDR	Prescribed Drug Register
PC	Percutaneous cholecystostomy
PE	Pulmonary embolism
PVT	Portal vein thrombosis
SIR	Standardised incidence ratio
TCA	Tricyclic antidepressants
TCP	Thrombocytopenia
TF	Tissue factor
TF-MP	Tissue factor micro particle
TP	Thromboembolism prophylaxis
TPO	Thrombopoeitin
US	Ultrasonography
VTE	Venous thromboembolism
VWF	Von Willebrands factor

CONTENTS

1 INTRODUCTION

In Sweden, approximately 12,000 cholecystectomies for gallstone disease are performed each year. Laparoscopic cholecystectomy (LC) is one of the most frequently performed general surgical procedures[1]. This high rate of surgery reflects the great impact of gallstone disease (GD) on public health. Gallstones are common in the Western world with a prevalence of up to 15%. In the US, 600,000 patients undergo cholecystectomy each year at an estimated annual cost of $ 5 billion[2]. Being the most common disease of the digestive system leading to hospitalisation in the Western world, GD represents a major healthcare problem and poses a considerable financial burden on society[3].

In the introduction of this thesis, GD is described with underlying history, natural history, pathogenesis and common complications. Hence, the description of gallstone pathology provides a framework for the latter discussion of complex alterations in haemostasis that occur in patients with comorbidity (e.g. liver cirrhosis) and medication (e.g. thromboembolism prophylaxis) when undergoing cholecystectomy. Changes in haemostasis may have profound effects on surgical outcome and thromboembolic as well as haemorrhagic complications may be life threatening. The aim for this thesis is to assess complications that may occur when the intricate balance of haemostasis is offset by factors inherent to specific patients or by the surgical procedure.

1.1 GALLSTONE DISEASE

1.1.1 History

One of the earliest recordings of gallstone disease was the finding of gallstones in the mummified body of princess Amenen from Thebes (1500BC)[4]. In ancient Rome, the anatomist Galen suggested that small "seeds" could obstruct the bile ducts, leading to jaundice[5]. The Italian professor Gentile da Foligno was the first to describe the finding of a gallstone at a human autopsy in 1348[6]. The composition of gallstones was extensively analysed during the late eighteenth century in a work by Fourcroy and Thenard[7]. However, treatment options were lacking until 1867, when the American John Stugh Bobbs pioneered removal of a gallstone (with the gallbladder left *in situ*) in a patient with a painful right upper quadrant mass[8]. In the years following, surgeons were preoccupied with procedures creating a fistula to relieve the gallbladder from its stones. However, concomitant animal studies had suggested that the gallbladder was not essential for life, and this was extrapolated to humans in 1882 by the Berlin surgeon Carl Langenbuch who successfully performed the first cholecystectomy in a patient with gallstone colic[9]. In 1910, inspired by Georg Kelling's animal experiments, the Swedish internist Hans Christian Jacobaeus drained ascites in 17 patients using a "Stille trocar", thereby performing first clinical laparoscopic procedure in 1910[10].The first person to perform laparoscopic cholecystectomy (LC) was Professor Erich Mühe in 1985 [11]. Since its introduction in 1985, LC has proven superior to open cholecystectomy (OC) as regards early ambulation, short hospital stay and rapid convalescence [12]. An increasing number of procedures are today performed using the minimally invasive laparoscopic technique. In 2015, the Swedish Register for Gallstone Surgery and ERCP (GallRiks) reported that 95 % of elective and 83% of acute cholecystectomies were performed laparoscopically [13].

1.1.2 Aetiology

Bile fluid is produced by hepatocytes in the liver. It is mainly composed of water (>90%), phospholipids, cholesterol and bile salts [14]. Gallstones are solid deposits of crystallised bile fluid and are predominantly found in the gallbladder. As regards their chemical composition, gallstones are divided into three categories: cholesterol stones; black pigment ("bilirubin") stones; and brown stones (associated with

infection). In the Western world, cholesterol accounts for 80% of gallstones found at cholecystectomy[15, 16].The pathogenesis of cholesterol gallstone disease is the precipitation and formation of crystals in bile supersaturated by cholesterol. The crystallisation of bile in the gallbladder is a normal process where microscopic crystals form and are flushed out into the duodenum by postprandial gallbladder contraction[17]. However, in patients who tend to develop gallstones, factors such as biliary proteins found in gallbladder mucin, and bilirubinate (calcium salt) accelerate the crystallisation process[16, 18]. The precipitation of gallstones is further facilitated by gallbladder dyskinesia and bile stasis[19].

1.1.3 Risk factors

There are several factors that increase the risk for developing gallstones such as female gender, oestrogen therapy, parity, high age, ethnicity, obesity and rapid weight loss[20, 21]. Oestrogen promotes the excretion of cholesterol from hepatocytes, which explains why women are twice as likely to develop gallstones as men[22]. Obesity and rapid weight loss are both associated with cholesterol supersaturation. Obese individuals have a five times greater risk for gallstone disease than the rest of the population[20]. Liver cirrhosis is also a known risk factor for developing black gallstones rich in bilirubin, referred to as pigment stones[23]. The reason for increased lithogenesis in liver cirrhosis is partly due to a fibrotic gallbladder leading to dysmobility and bile stasis[24]. Furthermore, increased haemolysis (hypersplenism) produces an excess of unconjugated bilirubin facilitating nucleation in supersaturated bile[23].

1.1.4 Epidemiology

Gallstones are highly prevalent in the Western world. However, epidemiological studies have shown that great ethnic differences in prevalence exist. The highest prevalence of gallstones has been reported in Pima indians living in Arizona. In this population 64% of women (older than 47 years) develop gallstones[25]. There are also reports of a high prevalence of gallstone disease amongst Mapuche indians (35%), a finding that has been attributed to "lithogenic" genes in the South American native population[26]. In contrast, the lowest prevalences are found in

Africa where gallstones in the Masi and Bantu tribes are virtually non-existent[27]. Several studies have reported similar age-related prevalence rates in the US and Europe. A large epidemiological survey in the US based on ultrasonography showed that the overall prevalence of gallstones was 8% among men and 17% among women with a progressive increase after 20 years of age[28]. A multicentre study in Italy, showed gallstone prevalences of 1.9% in men aged 30-34 and 12.4% in men aged 65-69 years. In the same study, women had higher age-related prevalences (30-34 years: 4.9%, and 65-69 years: 17.2%)[29]. An ultrasonographic screening programme in Sweden, including 556 men and women aged 40 and 60 years, respectively, showed a prevalence of gallbladder stones in 4-15% of men and 11-24% of women[30]. Gallstones are virtually non-existent in children. In a screening study on 1,570 children and adolescents aged 6-19 years, Palascino et al reported finding only two subjects with gallstones (0.13%).

1.1.5 Natural history and symptoms

Eighty per cent of patients with gallstones remain asymptomatic with only a 1-2% risk per year of developing pain or complications[31]. However, gallstones may cause severe problems ranging from sporadic episodes of biliary pain to complications such as cholecystitis, gallstone-induced pancreatitis or, in rare cases, gallbladder cancer[32]. Gallstones become symptomatic when they obstruct the cystic duct or papilla Vateri leading to pressure elevation in the gallbladder and/or biliary tract. The pain is mediated through visceral nerves[33]. The typical presentation of symptomatic "uncomplicated" gallstone disease is the sudden onset of pain in the right upper quadrant (gallstone "colic") with or without referred pain to the right shoulder or back (Collins sign)[34]. The pain usually reaches a peak within one hour and then resolves over a period of 1-5 hours. Persisting pain should raise suspicion of secondary gallstone complications such as cholecystitis or biliary pancreatitis. Patients often recall having biliary pain 30-60 min after a fatty meal or waking up with pain. Though most attacks are postprandial, Diehl et al, in a study on 122 patients with known gallstone disease, reported 32% having "attacks" of abdominal pain that had no relation to dietary intake[33].

1.1.6 Diagnostics

Serum bilirubin and alkaline phosphatase are an important part of the clinical work-up in the evaluation of patients with suspected gallstone disease. However, gallstones are best confirmed with ultrasonography (US), a non-invasive, cheap and readily available technique with high sensitivity (84%) and specificity (99%) [35]. Furthermore, ultrasonography provides information on liver and pancreatic parenchyma, and the thickness of the gallbladder wall in patients suspected of having cholecystitis. In a meta-analysis by Shea et al, the sensitivity and specificity of US in diagnosing cholecystitis was 88% and 80% respectively[35]. Since only about 10% of all gallstones are calcified, computed tomography (CT) has poorer sensitivity for diagnosing gallstones[35]. Magnetic resonance cholagiopancreaticography (MRCP) is another technique that provides detailed depiction of the gallbladder and biliary tract. It is used for preoperative imaging and may be used with liver-specific gadolinium-based contrast medium such as Primovist® to detect postoperative complications such as bile duct injury or leakage[36].

1.1.7 Indication for surgery, and gallstone-related secondary complications

1.1.7.1 Biliary pain (colic)

Patients with recurring attacks of biliary pain may be advised cholecystectomy unless there is significant comorbidity (cardiopulmonary) that could contraindicate general anaesthesia[37] or pose other contraindications (see below). Gallstone complications such as cholecystitis and gallstone pancreatitis, on the other hand, are strong indications for surgery.

Gallstones are often found incidentally when undergoing radiological examination. Prophylactic cholecystectomy is not recommended in asymptomatic patients because of the low risk of developing biliary pain, complications (e.g. cholecystitis) or gallbladder cancer[38-40]. However, due to the risk of developing a malignant condition, prophylactic cholecystectomy may be considered in patients with a "porcelain" gallbladder or large gallbladder polyps (≥5 mm)[41, 42]. Prophylactic cholecystectomy has also been suggested in patients undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB) for morbid obesity. These patients experience

rapid weight-loss and there is an increased risk (32-42%) for developing gallstones following LRYGB[43]. Another concern is that the rearranged gastrointestinal anatomy in LRYGB patients complicates the use of ERCP in the event that gallstones in the common bile duct (CBD) need to be extracted. There is no consensus on prophylactic cholecystectomy concomitant with LRYGB[43-45] and some institutions have adopted their own protocol[46].

1.1.7.2 Cholecystitis

Cholecystitis is the most common complication of gallstone disease and accounts for about 15% of the overall complication rate[47, 48]. Due to oedema and inflammation in the wall of the gallbladder and surrounding tissues, LC for cholecystitis is converted to open surgery in 15-20% of all cases[49, 50]. Patients with cholecystitis should undergo either early surgery within 24-78 hours after onset of symptoms or conservative management (with antibiotics) and delayed surgery (within 6-8 weeks)[51, 52]. Early surgery has been shown to be safe and superior to delayed surgery with shorter hospital stay, economic benefits and avoidance of further complications during the conservative management period[53, 54]. Furthermore, a recent randomised trial showed that early surgery in patients with up to seven days of symptoms of cholecystitis was associated with lower overall morbidity compared to delayed surgery [55].

1.1.7.3 Biliary pancreatitis

The incidence of acute pancreatitis due to gallstones in Sweden is 6-8/100,000 per year[56]. Acute pancreatitis is often a benign and self-limiting disease. However, severe pancreatitis with devastating complications such as multi-organ failure and/or necrotising pancreatitis may develop in as many as 20 % of patients [57]. Severe pancreatis is associated with high mortality rates that may reach 27% depending on the aetiology [58]. It is advocated that patients with severe biliary pancreatitis with cholangitis or dilated CBD undergo emergency ERCP within 48 hours to decompress the CBD and pancreatic duct[59]. This potentially life-saving procedure should be followed by intensive care until the condition of the patient permits cholecystectomy as final treatment[60]. In contrast to those with severe pancreatitis, patients with mild biliary pancreatitis often recover spontaneously with supportive care.

The timing of cholecystectomy in the case of mild biliary pancreatitis has been a matter of discussion and is still not resolved[60-66]. Despite guidelines recommending that cholecystectomy should be performed during the same admission[59], many patients with biliary pancreatitis are readmitted 6-8 weeks later for final surgical treatment[62, 67]. Failure to comply with guidelines is probably due to the fear of increased complication rates[66]. However, evidence is mounting that mild biliary pancreatitis should be intervened upon within first admission[68]. A small randomised trial (n=50) reported that early surgery (within 48 hours of admission) was not associated with more difficult dissection or increase in perioperative complications compared to delayed surgery[61]. In further support of early intervention, Bakker et al reported that patients planned for delayed surgery have a 10 % risk recurrence of biliary pancreatitis before surgery takes place[62].

1.1.8 Special indications

1.1.8.1 Pregnancy

As mentioned, oestrogen increases cholesterol production. Furthermore, elevated progesterone levels during pregnancy reduce bile acid secretion and inhibit gallbladder emptying[69]. Pregnancy is thus a prolithogenic state and complications from gallstone disease is the second most common non-obstetric condition after appendicitis that requires surgical treatment during pregnancy[70]. , LC has previously been considered a contraindication due concerns regarding harm to the enlarged uterus, and that pneumoperitoneum could reduce uterine blood flow and venous return to the heart[71]. However, with the exception of technical difficulties such as a limited laparoscopic view, which may lead to conversion to open surgery, increasing evidence has shown that LC in pregnant women is as safe as open surgery[69, 70, 72]. Another concern with performing surgery on pregnant women is the increased risk for venous thromboembolism. Pregnant women have a five times higher risk for developing venous thromboembolism (VTE) than non-pregnant women[73]. This is largely explained by venous congestion caused by compression of veins by the gravid uterus[73]. Furthermore, pregnancy is a hypercoagulable state with decreased fibrinolysis and it is known that the risk for VTE is as equally abundant throughout the entire gestation period[74]. The Society of Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines from 2007 recommend that intermittent pneumatic leg

compression devices should be used as thromboembolism prophylaxis in pregnant women undergoing LC, and that early ambulation should be encouraged[75].

1.1.8.2 Liver cirrhosis

Liver cirrhosis is a characterised by fibrous transformation of liver parenchyma due to chronic inflammation, usually caused by excessive alcohol consumption or hepatitis[76]. Cirrhosis may be complicated by ascites, encephalopathy, portal hypertension, oesophageal varices[77] and hepatorenal failure[78]. The disease may gradually progress into liver failure and in some cases cause hepatocellular carcinoma[79]. The severity of disease is defined by scoring systems such as the Child-Turcotte-Pugh (CTP) score taking into account INR, bilirubin, albumin as well as grade of encephalopathy and ascites[80]. The Model for End-Stage Liver Disease (MELD), used for the prediction of survival and need for transplantation, is based on bilirubin, creatinine and INR[76]. High MELD and CTP scores are known risk factors for morbidity and mortality rates after surgery [81].

Gallstones are twice as common in cirrhotic patients. A combination of poor gallbladder emptying and increased haemolysis predisposes cirrhotic patients to developing gallstones, 80% of which are black pigment "bilirubin" stones [82]. The stones are formed in bile supersaturated with bilirubin caused by increased secretion or haemolysis[23]. Symptomatic gallstones are found in 7.5% of patients with liver cirrhosis[82] and GD is associated with higher morbidity and mortality rates than in non-cirrhotic patients[81]. Historically, liver cirrhosis has been considered a contraindication to LC due to the risk for haemorrhagic complications[83]. However, as laparoscopic techniques have evolved, a number of studies have reported LC to be a safe intervention in selected patients with liver cirrhosis[24, 81, 83, 84], and today cholecystectomy is the most frequently performed surgical procedure in patients with liver cirrhosis[85].

Neovascularisation and dilation of intra-abdominal veins associated with portal hypertension in patients with liver cirrhosis increase the risk for haemorrhage during surgical procedures[86]. Furthermore, liver dysfunction associated with cirrhosis causes major disturbances in the haemostatic and fibrinolytic systems. Haemostatic disturbances in patients with liver cirrhosis (see separate topic below) include abnormalities in primary haemostasis, impaired synthesis of clotting factors[87-91], disturbed fibrinolysis[90, 92, 93] and thrombocytopenia (TCP)[94-98].

1.1.9 Treatment

Laparoscopic cholecystectomy is the gold standard procedure for the removal of the gallbladder in the patients with symptomatic gallstone disease (i.e. colic and/or gallstone complications) [99]. Approximately 7% of all procedures are converted to open surgery because of poor vision, "hostile abdomen" (adhesions), or failure to achieve the "critical view" of the anatomy in the triangle of Calot [100]. The most feared complication of cholecystectomy is iatrogenic bile duct injury, with a rate of 0.5-1% for LC[101-103] and 0-0.4% for OC[103, 104]. However, in a Swedish study on over 51, 000 cholecystectomies where postoperative bile leak was also included, a higher rate (1.5%) was reported [102]. In LC, the overall complication rate is 2-11%[104, 105] and mortality has been reported to be in the range of 0.04-0.5%[101, 104].

1.1.9.1 Alternative management

Some patients with cholecystitis are considered unfit for surgery because of sepsis, comorbidity or high age. In this patient group, percutaneous cholecystostomy (PC) plus broad-spectrum antibiotics is a possible bridging therapy to definitive surgery. Cholecystostomy is a percutaneous drain usually inserted transhepatically with the aid of ultrasound. PC alleviates the ischaemia and inflammation associated with increased pressure in the gallbladder[106], and in cases where bacteria are present in the bile, drainage also deviates the source of infection. The gallbladder may also be decompressed through ultrasound-guided aspiration[107].

1.1.10 Contraindications to LC

In 1992, the NIH consensus statement on gallstone disease and laparoscopic cholecystectomy suggested a number of conditions where LC is less appropriate. Among the relative contraindications are severe pancreatitis, generalised peritonitis, septic shock due to cholangitis, untreated coagulopathy, end-stage cirrhosis with liver failure, previous abdominal surgery and expected "hostile abdomen", and patients with suspected gallbladder cancer[37].

1.2 HAEMOSTASIS AND THROMBOSIS

1.2.1 Primary haemostasis

An understanding of the mechanisms of haemostasis and thrombosis is essential in the management of patients undergoing surgical procedures. Haemostasis is a complex and tightly regulated process initiated by a response to vascular damage and haemorrhage.

To simplify, this response can be divided into two main phases; the primary (cellular) and secondary (humoral) phases[108]. The primary phase of haemostasis is initiated by an immediate vasoconstriction due to the release of substances such as endothelin from endothelial cells[109]. Smooth muscle cells lining the vessel contract and blood loss is restricted. The effect of vasoconstriction is further augmented by pressure exerted on the vessel due to accumulation of blood in the surrounding tissues[110]. Vasoconstricition is followed by the formation of a platelet plug. In this process, circulating von Willebrands factor (VWF) binds to tissue factor (TF) expressed on cell surfaces in the subendothelial matrix at the site of injury[111]. Platelets adhere to VWF via the GP1b receptor and begin to secrete granules containing platelet-recruiting factors such as adenosine diphosphate, fibrinogen and serotonin[112, 113]. Activated platelets change form and secrete thromboxane A2, further augmenting platelet recruitment and vasoconstriction[112]. A soft haemostatic "plug" of aggregated platelets that bind to each other via GP IIb/IIIa receptors and fibrinogen is formed[111].

1.2.2 Secondary haemostasis

During secondary haemostasis, fibrin is enzymatically cleaved from fibrinogen converting the plug to an insoluble clot[110]. In a modern cell-based model, coagulation can be divided into a initiation, amplification and propagation phase[114]. The process is initiated when TF-bearing cells such as fibroblasts are exposed to blood at the site of injury. TF bound to factor VII (TF-VIIa complex) catalyses the activation of factors X and IX[114]. During the amplification phase, platelets are recruited and a small amount of thrombin generated near TF-bearing cells triggers full activation of platelets and coagulation factors V, VIII and XI on the platelet surface[115].
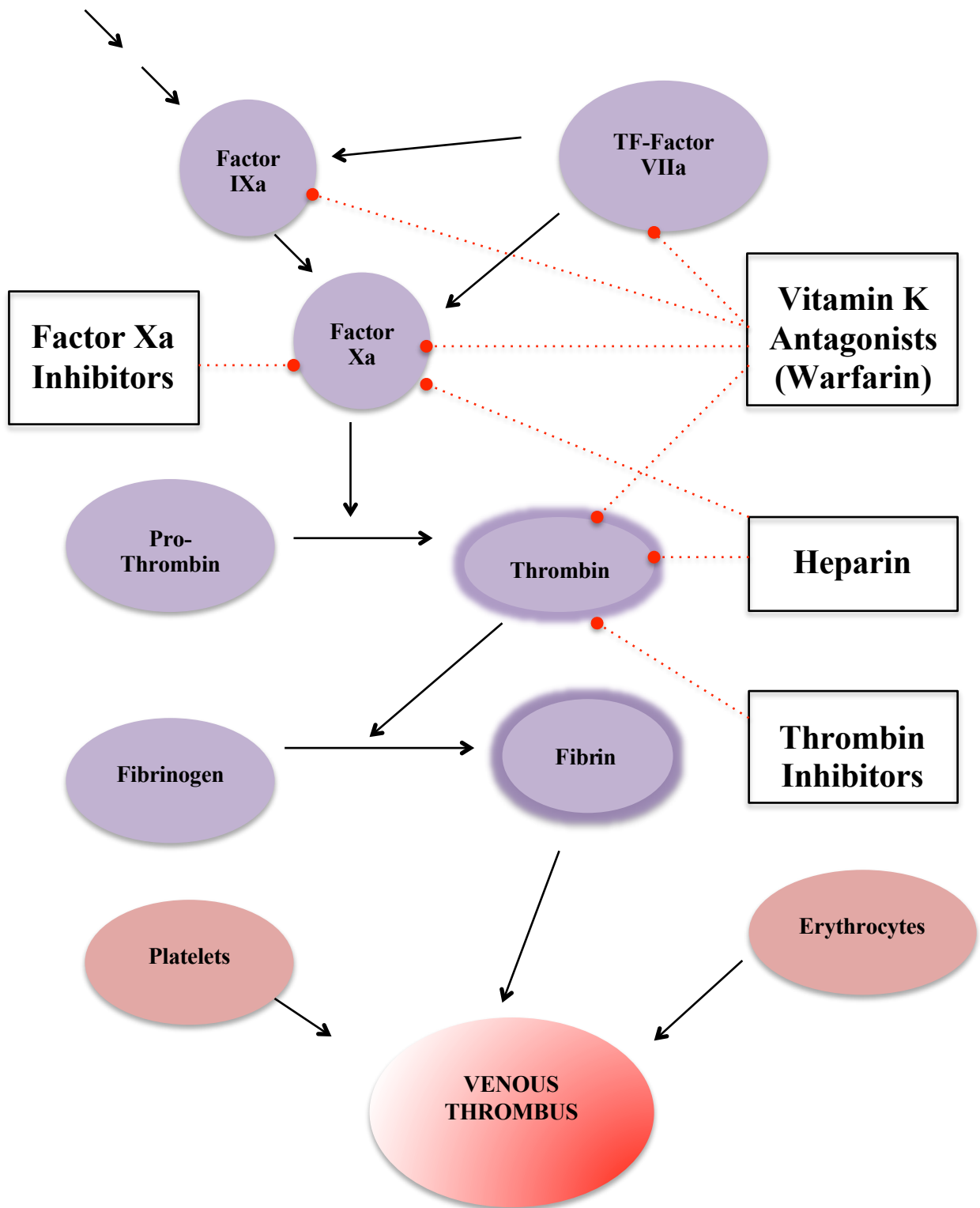
Figure 1: The coagulation cascade modified from Wolberg et al[114]. TF-VIIa complex initiates coagulation. The venous thrombus, i.e. "red clot", has a high content of erythrocytes and less amount of platelets than seen in arterial "white" thrombi. In addition to traditional anticoagulants (heparin, vitamin K antagonists), two classes of direct oral anticoagulants (DOACs) have recently been developed. DOACs inhibits factor Xa (dabigatran; Pradaxa®) or thrombin (rivaroxaban; Xarelto®, apixaban; Eliquis®, edoxaban; Lixiana®) respectively.

This process has been shown to be stimulated by serotonin (released by activated platelets)[116]. The full-blown coagulation response is then generated during the propagation phase, where factors IX and X are activated together with factors V and VIII[117]. This occurs on activated platelets and generates a thrombin "burst" [118]. Subsequently thrombin facilitates the transformation of fibrinogen into fibrin, which stabilises the thrombus into a clot.

To prevent haemostasis from becoming overwhelming and only occur at the injured site, the clot is regulated by anti-coagulation mechanisms. In this context, the vitamin K-dependent Protein C and its co-factor protein S are important factors. Coagulation is hampered by the formation of a protein C-S complex that subsequently degrades factor VIIIa and Va respectively[117].

1.2.3 Fibrinolysis

Upon healing of the injured vessel, the clot is broken down in a process called fibrinolysis. Fibrin is degraded by plasmin that becomes active when transformed from plasminogen by tissue plasminogen activator (t-PA) and urokinase[119]. The lysis of the haemostatic clot produces small protein fragments such as D-dimer that are detectable in whole blood. In clinical practice, a normal D-dimer level excludes thrombosis or embolism[120].

1.2.4 Venous thromboembolism

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and is the third leading cause of cardiovascular death in the world[120]. Known genetic risk factors for VTE are deficiencies in antithrombin, protein C, protein S and mutated factor V (Leiden) as well as activated protein C resistance. In addition, among acquired risk factors are high age, surgery, obesity, pregnancy, hormone based contraceptives, hormone replacement, acute infection and immobilization[121]. VTE is most commonly manifested as DVT in the leg, where the majority of thrombus formation occurs in distal veins (e.g. peroneal vein) with only 10 % affecting the proximal veins (e.g. ileo-femoral) [122].

DVT causes local inflammation and pain at the site of thrombus and is treated with anticoagulant medication. Spontaneous recanalisation occurs in up to 90% of cases (depending upon venous segment)[123]. However, 30-50 % of patients with DVT develop chronic swelling of the leg and lower extremity venous incompetence[124]. This condition is known post-thrombotic syndrome and has been attributed to inadequate recanalisation[125], lesions of the venous valves, or both[124]. Pulmonary embolism may occur as the DVT propagates and parts of the thrombus become dislodged and migrate to the pulmonary circulation. Proximal DVTs are more likely to cause PE, compared to the calf vein thrombosis[126]. In contrast to DVT, PE is a far more serious condition that may cause pulmonary hypertension, right ventricle failure, and in some cases death[127].

1.2.4.1 Pathophysiology

In contrast to a haemostatic clot formation as a response to haemorrhage, venous thrombosis occurs in veins with an intact endothelium. The pathophysiological process of thrombus formation in veins was originally described in 1856 by Rudolf Virchow as dependent upon, altered blood flow (stasis), increased blood coagulation and endothelial dysfunction[128]. In line with the "triad of Virchow", the origin of a DVT usually lies in the region of reduced blood flow or stasis behind a venous valve (i.e. valve pocket)[120, 121, 129]. The physiological function of venous valves is to facilitate the transport of blood back to the heart by opposing the downward force of gravity. In healthy vessels, the shear force (stress) exerted by laminar blood flow on endothelial cells generates a genetic upregulation of antithrombotic substances such as thrombomodulin on the endothelial surface.[130]. Conversely, in conditions of stasis or turbulence, local hypoxia and loss of shear stress from laminar flow reduces expression of antithrombotic gene proteins[120]. Thereby, converting the endothelium from an anticoagulant to a procoagulant surface. Furthermore, it has been suggested that a reduction in blood flow in valve pockets may lead to accumulation of prothrombotic substances such as circulating microparticles containing tissue factor (TF), known as TF-MPs[131]

This concept of "blood borne thrombosis" is tempting since as already mentioned, it is known that TF plays an important role during clot formation in haemostasis. TF-MPs are small membrane vesicles (<1µm) that are released from activated or apoptotic cells (e.g platelets)[132]. The release of TF-MPs is stimulated by hypoxia[133]. This may partly explain the pathophysiology behind thrombus formation in the

absence of vessel wall damage. Furthermore, it has been suggested that the increased incidence of VTE seen in patients with cancer is attributed to the release of tumour derived TF-MPs[134].

1.2.4.2 *VTE and surgical trauma*

Surgical trauma elicits an inflammatory response orchestrated by pro-inflammatory cytokines such as IL-1β, and IL-6[135]. Cytokines are small proteins derived from monocytes and leukocytes, acting as intercellular signals. Elevated concentrations of IL-1β, and IL-6 are almost immediately detectable in blood following surgical procedures[136]. The cytokine surge is proportional to the magnitude of trauma inflicted. Consequently, following major surgery, the cytokine concentration in blood is higher than in patients undergoing minor surgical procedures[137, 138]. Cytokines promote coagulation[136, 139] by stimulating monocytes to release TF-MPs that bind to activated platelets at the wound site[135], and by inhibiting the anticoagulant effect of protein C[140]

It has been shown that there is an immediate significant increase in fibrin degradation products in blood following laparoscopic cholecystectomy [141]. D-dimer concentration is also elevated 24-72 hours postoperatively[141, 142]. The immediate inflammatory response to surgery (activating coagulation) constitutes the rationale for preoperative administration of medical thromboembolism prophylaxis.

1.2.5 Thromboembolism prophylaxis

Surgical trauma is a risk factor for VTE, and in the absence of prophylaxis the incidence of objectively confirmed VTE is 10-40% after general surgery and 40-60% after orthopaedic surgery[143].

VTE increases postoperative morbidity and mortality[143-145], and PE is the most preventable cause of death among hospitalised patients[146]. Patients undergoing surgical procedures often receive thromboembolism prophylaxis (TP) in order to reduce the risk of venous thrombosis. The most commonly used TP in Sweden is low molecular weight heparin (LMWH)[147]. The anticoagulant effect of LMWH is mediated through activation of antithrombin[148], which inhibits factors Xa, IXa, XIa and thrombin[149] (Figure 1).

It has been reported that prophylaxis reduces the relative risk of fatal PE and symptomatic VTE by about 70% compared to no prophylaxis[150]. VTE risk-scoring systems have been developed to guide TP administration (Table 1)

AT9 Category	Caprini Score	VTE risk (%)	Bleeding Risk	Prophylaxis	Grade*
Very low	0	< 0.5	-	Early ambulation	1B
Low	1 - 2	0.5 - 1.5	-	IPC	2C
Moderate	3 - 4	1.5 - 3.0	low	LMWH or UFH	2B
Moderate	3 - 4	1.5 - 3.0	high	LMWH or UFH	2B
High	≥ 5	3.0 - 6.0	low	LMWH or UFH	1B
High	≥ 5	3.0 - 6.0	High	IPC	2C
High*	≥ 5	3.0 - 6.0	low	Low-dose aspirin or fondaparinux	2C

Table 1: Risk stratification of VTE in general surgery patients modified from: VTE in non-orthopedic surgery patients. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians (ACCP), Evidence-Based Clinical Practice Guidelines 2012 (AT9)[151]. IPC – Intermittent pneumatic compression. LMWH – Low Molecular Weight heparin. LDUH - Low-dose Unfractionated Heparin. *Patients with contraindication for LMWH or LDUH. *Grade of recommendation; Grade 1B: Strong recommendation, evidence from Randomised control studies (RC) with limitations. Grade 2B: Weak recommendation, evidence from RC-trials with important limitations. Grade 2C. Very weak recommendation, evidence from observational studies or RC trials with serious flaws.

1.2.6   Haemostatic disturbances in liver cirrhosis

1.2.6.1   Thrombocytopenia

Defined as a platelet count below 140 x 10^9/L, TCP is found in >76% of all patients with liver cirrhosis[95]. Severe TCP (platelets < 50 x 10^9) is found in only 1% of patients[95] and due to an increased risk for haemorrhagic complications, often mandates prophylactic platelet transfusion prior to surgical procedures[152]. The pathogenesis of TCP in liver cirrhosis is not fully understood, but suppression of bone marrow has been proposed as one underlying factor. Megacaryocytes reside in bone marrow and produce platelets by "budding off" cytoplasmic vesicles[153]. This

process is stimulated by thrombopoeitin (TPO), which is produced by hepatocytes[98]. Low levels of serum TPO have been detected in patients with liver cirrhosis, which normalises following liver transplantation[153].

1.2.6.2 Hypersplenism

Another factor contributing to TCP is hypersplenism. In patients with liver cirrhosis, portal hypertension redirects blood flow to the spleen, causing its enlargement[96]. Subsequently, platelets are trapped and broken down in the hypertrophic spleen[98]. Sequestered platelets in the spleen also consume TPO, which further reduces TPO-levels in serum[154]. Platelet-binding antibodies[97] (making them more susceptible to removal from circulation) and low- grade disseminated intravascular coagulation[155], have also been suggested as reasons for platelet consumption in patients with liver cirrhosis.

1.2.6.3 Coagulopathy

Patients with liver cirrhosis have an increased tendency to bleed due to a reduction in coagulation factors produced in the liver. When treating patients with cirrhosis, coagulation ability is evaluated by testing the capacity of the blood to form clots. One such clotting parameter is the prothrombin time, and cirrhotic patients often have a "spontaneously" increased prothrombin time due to deficit of the pro-coagulant factors II, V, VII, IX, X, XI and fibrinogen[90]. Liver disease is also associated with vitamin K deficiency resulting from a reduction in uptake in the gastro-intestinal system due to reduced secretion of bile salts in the liver[156]. Vitamin K is an important activator of several coagulation factors and vitamin K deficiency is well-known to be pro-haemorrhagic. The International Normalised Ratio (INR) is a standard value for expressing the prothrombin time (i.e. clotting tendency) of the patient and reflects liver-produced coagulation factor levels. However, it has long been known that the INR is not reliable when evaluating the coagulation status of patients with liver disease[90, 157]. This has been explained by the fact that a decreased production of pro-coagulation factors is "balanced" by a parallel reduction in anticoagulation factors such as protein C[87]. Elevated levels of factor VIII (pro-thrombotic) are also seen in patients with liver cirrhosis[158, 159]. This paradox has been explained by a reduction in the clearance of factor VIII, associated with high levels of von Willebrand factor (VWF) that binds factor VIII in plasma[159]. The increase in VWF has been attributed to low-grade disseminated intravascular coagulation (DIC)[159] and possibly bacterial

infection[158]. Both factors VIII and VWF are intricately involved in haemostasis and add on to the pro-thrombotic state. In this context, the traditional view of cirrhotic patients being "naturally anticoagulated" and thereby protected against VTE is not correct [88, 89, 91]. Indeed, these complex alterations in coagulation are known to cause VTE-events in cirrhotic patients.

1.2.6.4 Thrombosis

Portal Vein Thrombosis (PVT) is a common complication of liver cirrhosis. This is partly explained by the increase in resistance to blood flow in the fibrotic liver leading to stagnation in the portal system[160 160]. PVT is mostly associated with hepatic cellular cancer and is clinically important since it is considered a relative contraindication to liver transplantation[161]. PVT in non-malignant liver cirrhosis is less frequent, and the prevalence of PVT determined by ultrasonography screening has been reported to be 16% in patients with liver cirrhosis [162].

Besides PVT, other VTE events such as PE or DVT have been reported in cirrhotic patients. In a retrospective study on 21,000 hospitalised patients with cirrhosis, Northup et al reported that 113 (0,5%) were diagnosed with VTE[88]. The authors concluded that even if the prevalence of VTE in cirrhotic patients was lower than VTE rates seen in general medical patients (0.9-4.5)[163-165], clinicians should "maintain a high level clinical suspicion as VTE events do occur in these patients"[88]. In a study based on data from the Danish National Register of Patients including 99,444 patients hospitalised for VTE versus a reference group of 496,872 patients, Sogaard et al reported a two-fold increase in unprovoked VTE among patients with cirrhosis compared to the general public[166]. Furthermore, Dabbagh and colleagues reported a VTE incidence of 6.3 % in large case-control study including 190 cirrhotic patients. Over a seven-year period, 50% of VTE occurred in patients with INR > 1.6 and the risk for VTE persisted in patients with INR>2.2[157].

2 AIMS

The aim of this thesis was to determine the incidence and risk factors for haemorrhagic and thromboembolic complications in patients undergoing cholecystectomy. The aims of each study were:

- **Study I:** To evaluate the need for thromboembolism prophylaxis (TP) and assess the influence of TP on haemorrhagic complications following cholecystectomy.

- **Study II:** To determine the rate of and risk factors for symptomatic venous thromboembolism (VTE) following cholecystectomy. To determine which patient groups are at greatest risk developing VTE.

- **Study III:** To evaluate whether or not cholecystectomy is a safe procedure in patients with liver cirrhosis. To evaluate if patients with cirrhosis have a higher incidence of peri- and/or postoperative complications than non-cirrhotic patients when undergoing cholecystectomy. To determine the characteristics of liver cirrhotic patients at the time of surgery. To analyse outcomes after open and laparoscopic cholecystectomy in patients with liver cirrhosis.

- **Study IV:** To study the rate of and risk factors for haemorrhagic complications requiring intervention in cholecystectomy. To analyse the impact of comorbidity and/or prescribed medication on the occurrence of haemorrhagic complications. To determine whether there is a relationship between perioperative haemorrhage and bile duct injury and/or leakage.

3 METHODS

3.1 DATA SOURCES

3.1.1 GallRiks

The Swedish Register of Gallstone Surgery and ERCP (GallRiks)[13] is an internet-based register that prospectively collects data regarding patient characteristics, indication for surgery, surgical approach, operation time and postoperative complications for patients that undergo cholecystectomy or ERCP in Sweden. The GallRiks register was started in 2005 and by 2011 had grown to reach full national coverage (>90%) of all cholecystectomies (open and laparoscopic) performed in Sweden[167]. GallRiks is approved by the Swedish National Board of Health and Welfare[168], and by the Swedish Surgical Society.

All procedures and perioperative complications are registered on-line by the surgeon performing the cholecystectomy or the ERCP. The web-based questionnaire constitutes mainly of yes/no dichotomous questions but there is also a box in which text regarding complications or procedures that deviate from standard cholecystectomy may be entered. The use of thromboembolism prophylaxis, for instance, is registered as a dichotomous yes/no answer. The register does not provide information regarding type of drug, dose or interval of administration. Postoperative complications (within 30 days) are registered by a specially trained local coordinator at each participating hospital.

During follow-up, the coordinator reviews all in- and outpatient records to check for further admissions or emergency department visits where postoperative complications may have been detected and recorded. Besides serving as an instrument for the validation and safety of gallstone surgery in Sweden, GallRiks acts as a source of research data. In addition, each participating hospital and surgeon can extract updated on-demand reports providing information that enables comparison of their outcome data with data from the rest of the country.

A rigorous continuous validation programme assures the quality of data in GallRiks. Specially appointed members of the GallRiks register organisation regularly visit each participating hospital to check the accuracy of all data registered. The visits

serve to ensure that adequate resources have been assigned for registration and follow-up. Furthermore, a blinded re-registration of about 25 patient records is then performed and matched with GallRiks registered data. Previous reviews have resulted in an matches between patient records and GallRiks registrations of up to 98.2% [169].

3.1.2 National Patient Register

The Swedish National Patient Register (NPR)[170] was established in 1964 under the administration of the Swedish National Board of Health and Welfare (NBHW) . Among variables collected in the register are age, gender, county, municipality, hospital, date of admission/discharge and primary/additional diagnosis. The register provides data on prevalence and incidence of diseases in different geographical regions and enables the safety assessment of medical interventions, including all surgical procedures. Since 1987, the coverage of somatic diagnoses is almost 100%[171]. From 1997 and onwards all daycare surgical procedures are included and since 2001, the register also includes information on all hospital-based outpatient care[171]. However the coverage for outpatient care is lower (80%) since private outpatient caregivers are missing. Furthermore, the NPR does not include diagnoses from primary health care facilities[170]. In a validation by Ludwigson et al, the positive predictive value (PPV) is generally 85-95% for most diagnoses in the NPR.

3.1.3 Prescribed Drug Register

The Swedish Prescribed Drug Register (PDR) has collected data regarding dispensed medication since July 2005. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. All dispensations at Swedish pharmacies are registered in the PDR. Information on substance, brand name, dosage, expenditure, patient data (age/gender/residence), date of prescription), and dispensation are collected and matched to each patient's individual national registration number (NRN). However, the PDR does not register drugs administered at hospitals or heath care facilities during inpatient care. Furthermore, there is no information on sales or distribution of over-the-counter

drugs (without prescription) or on drugs administered in the day-care (outpatient) setting. As an indication of coverage, the PDR has been reported to register 84% of the nation's total consumption of drugs and 77% of the total expenditure[172].

3.1.4 Cause of Death Register

The Swedish Cause of Death Register was founded in 1952 and comprises the causes of death (according ICD-10) of all Swedish citizens dying in Sweden or abroad. The register has a high coverage with cause of death registered in up to 98.7% of all deaths[173]. The register is managed by the NBHW and updated annually along with a publication regarding causes of death in the Swedish population. The use of the NRN, allows cross-matching causes of death with other data registers. This enables, for example, the estimation of mortality following a surgical procedure.

3.2 STUDY DESIGN, DEFINITIONS AND STATISTICS

3.2.1 Study I

All cholecystectomies that were registered in GallRiks 2005-2010 were included in the study. Patients were excluded if they had undergone cholecystectomy as part of another major procedure or if registered at participating hospitals with a volume of less than 50 procedures *per annum*. Registrations with incomplete data concerning follow-up or gender were also excluded. The principal end-points of this study were perioperative and postoperative haemorrhage (within 30-days). No quantitative estimation of blood loss was made. Perioperative haemorrhage was registered by the operating surgeon and defined as a bleed that could not be controlled by ordinary surgical measures (diathermy, clipping or suturing), but required other actions, such as conversion to open surgery or perioperative blood transfusion.

Postoperative haemorrhage was registered as a complication at the 30-day follow-up. The registration was carried out by the local coordinator at each participating hospital, and defined as a bleed that mandated a postoperative blood transfusion, or re-operation. The operating surgeon registered the use of thromboembolism prophylaxis (TP) in the on-line patient specific document of GallRiks. However, there is no information about drug, dose, timing or interval of administration.

Univariate logistic regression provided Odds Ratios (ORs) with 95% confidence intervals for each predictor, including hospital volume, patient characteristics TP, and type of surgery (approach/duration). In addition, multivariable regression was used to obtain adjusted ORs, which included and controlled for all the non-dependent variables included in the study. In order to relate haemorrhage to type of surgical approach, sub-group analysis (univariable and multivariable) were performed on patients undergoing open cholecystectomy, mini-laparotomy, and primary laparoscopic cholecystectomy including conversion to open surgery. The appropriateness of these analyses was assessed by a logistic regression interaction test. All analyses were performed with R statistics version 2.12[174].

3.2.2 Study II

In Study II, all patients that underwent open or laparoscopic cholecystectomy 2006-2011 were included. By using the Swedish National Registration Number (NRN)[175], data from GallRiks were cross-matched with data from the NPR to investigate rates of and risk factors for deep venous thrombosis (DVT), pulmonary embolism (PE) and VTE (DVT and/or PE), occurring within 30 days after cholecystectomy. The diagnosis of VTE was obtained from patient records. There was, however, no information as to whether or not the thromboembolic event was confirmed by radiological imaging or ultrasonography. The diagnosis codes used were based on the International Statistical Classification of Diseases and Related Health Problems 10:th edition (PE: I26.9, I26.0, DVT: I80.1, I80.2, I80.3, I80.8, I80.9, I82.9, O22.3, O87.1). Since GallRiks lacks detailed information with respect to what kind of VTE event occurred, we used the NPR to determine the frequencies of DVT and PE respectively. Cause of death was established by cross-matching data from GallRiks with the Swedish Cause of Death Register.

The standardised incidence ratio (SIR) was calculated by dividing the observed DVT and PE rates with rates expected in an age- and gender matched background population according to information obtained from the Swedish National Board of Health and Welfare (Socialstyrelsen)[168].[168]. Multivariable regression analysis (including and controlling for all but the variable in question) determined the impact of independent variables (gender, age, operative indication, surgical approach, operation time, body mass index (BMI), TP, ERCP, and previous history of venous

thromboembolism) on the risk for VTE within 30 days following cholecystectomy. All statistical analyses were performed using IBM® SPSS® statistics 21 programme.

3.2.3 Study III

In Study III, all open and laparoscopic cholecystectomies registered 2006-2011 in GallRiks were included. Data from GallRiks were cross-matched with the NPR in order to identify patients with a diagnosis of liver cirrhosis at the time of surgery. The following ICD-codes (ICD-10) were used to defined a patients with liver cirrhosis: B18.0E, B18.0G, B18.1E, B18.2E, B18.1G, B18.8E, B18.2G, B18.8G, B18.9E, B18.9G, K70.3, K71.7, K74.3, K74.4, K74.5, K74.6 and decompensated liver cirrhosis (oesophageal varices, ascites, encephalopathy): G92.9, G93.4, I85.0, I85.9, I98.2, K70.3, K76.7, R18.9. Patient characteristics and perioperative complications were obtained from GallRiks. Postoperative complications within 30 days following cholecystectomy were assessed using data from both GallRiks and the NPR.

If the cholecystectomy was as part of another major procedure or if any of the variables "gender" or "surgical approach" was missing, the registratrion was excluded. Furthermore, in the analysis of individual variables, patients were excluded if the variable was missing (i.e missing data). Numbers of missing data are shown in Table 2: gender (n=1); age (n=2); American Society of Anesthesiologists (ASA) grade (n=619); operation time (n=1,239); surgical approach (n=1,354); and thromboembolism prophylaxis (n=1,387) and in Table 3: pancreatitis (n=2,209); bile duct obstruction (n=2,216); cholangitis (n=2,209); blood transfusion (n=2,238); abscess (n=2,210); bile leak (n=2,213); and bleeding (n=2,210).

In the statistical analysis, Chi-Square test was used for comparison of base-line characteristics and multivariable analysis for determining the Odds Ratios for cirrhotic versus non-cirrhotic patients undergoing cholecystectomy. IBM®, SPSS Statistics version 22.0 was used for all statistical analyses.

3.2.4 Study IV

In Study IV, all patients registered in GallRiks having undergone laparoscopic or open cholecystectomy 2006-2015 were included. As mentioned previously, each citizen in Sweden has a unique National Registration Number (NRN), which allows for cross-matching of data from GallRiks with data from other registers. In this study we cross-linked data from GallRiks with the National Patient Register (to obtain comorbidity) and to the Swedish Prescribed Drug Register (PDR)[176] for information on drugs prescribed within 90 days prior to cholecystectomy. There was, however, no information on compliance, dose, timing or discontinuation of drugs prior to surgery in the PDR. Furthermore, patient NRNs were used to cross-match data from GallRiks to the Swedish Cause of Death Register[177] using ICD-10 codes to identify cause of death. Mortality was only considered to be procedure-related if a complication was registered on the death certificate as the primary or contributing cause.

We used the same definition for haemorrhage as in study I, i.e., a bleeding complication that occurred during cholecystectomy and required an intervention. This implied that the haemorrhage could not be controlled with conventional techniques (diathermy, clipping, suturing) but led to conversion to open surgery (in LC-cases), and/or required perioperative blood transfusion or other intervention not routinely used in gallstone surgery. Postoperative haemorrhage was defined as a bleed occurring within 30 days of cholecystectomy requiring blood transfusion or reoperation. The total rate of postoperative haemorrhage was obtained by combining aggregate data from GallRiks and the NPR.

The ICD-10 codes used to identify haemorrhagic complications in the NPR were T81.0 and T81.7. The overall incidence of haemorrhagic complications was defined as a bleed in the peri- and/or postoperative period. Body Mass Index (BMI) was assessed for correlation with haemorrhagic complications in univariate analysis where BMI values were divided dichotomously (BMI < 25 and BMI ≥ 25). Bile duct injury was defined as injury and/or clinically significant leakage from the bile ducts, detected in the peri- and/or postoperative period.
Chi-square test and univariate regression analyses were performed to compare patient characteristics and identify risk factors for peri- and postoperative haemorrhage respectively. The risk for haemorrhage was estimated using Odds

Ratios (ORs). The impact of prescribed drugs (with known anticoagulant or antiaggregant effect) on peri- and/or postoperative, and total number of haemorrhagic complications was assessed by Chi-Square test and univariate regression analysis. This analysis was then subjected to a Bonferroni correction[178] to rule out mass significance. In this analysis the p-value was to rule out mass significance. In this analysis, the chosen p-value was divided by the number of independent variables (drugs tested). Accordingly, when testing 28 different drugs, data were considered significant at the 95% level if the p-value was less than 0.05/28 =0.018. The association between comorbidity and overall haemorrhagic complications was determined by univariate and multivariable analyses adjusting for gender, age, indication, surgical approach, ASA-classification, anticoagulant/aggregant drugs.

Multivariable analysis was used to assess the correlation between perioperative haemorrhage and bile duct injury and/or leakage. The impact of perioperative bleeding on survival was assessed with a Kaplan-Meier plot followed by a Cox-regression analysis estimating Hazard ratio (HR) and adjusted HR (controlling for the above-mentioned independent variables). All statistical analyses were performed using SPSS, IBM® (version 23.0.0.0).

4 RESULTS

4.1 Study I

A total of 51,621 procedures were registered in GallRiks between 2005 and 2010. After exclusion based on the criteria named previously, 48,010 patients remained in the study group. In this group, 21,259 (44.3 %) patients received thromboembolism prophylaxis (TP). In the patients given TP, perioperative haemorrhage occurred in 400 (1.9%) and postoperative in 296 (1.4%) of all procedures. In comparison, of the 26,751 patients not receiving TP, 189 (0.7%) and 195 (0.7%) were reported as having peri- and postoperative haemorrhage respectively.

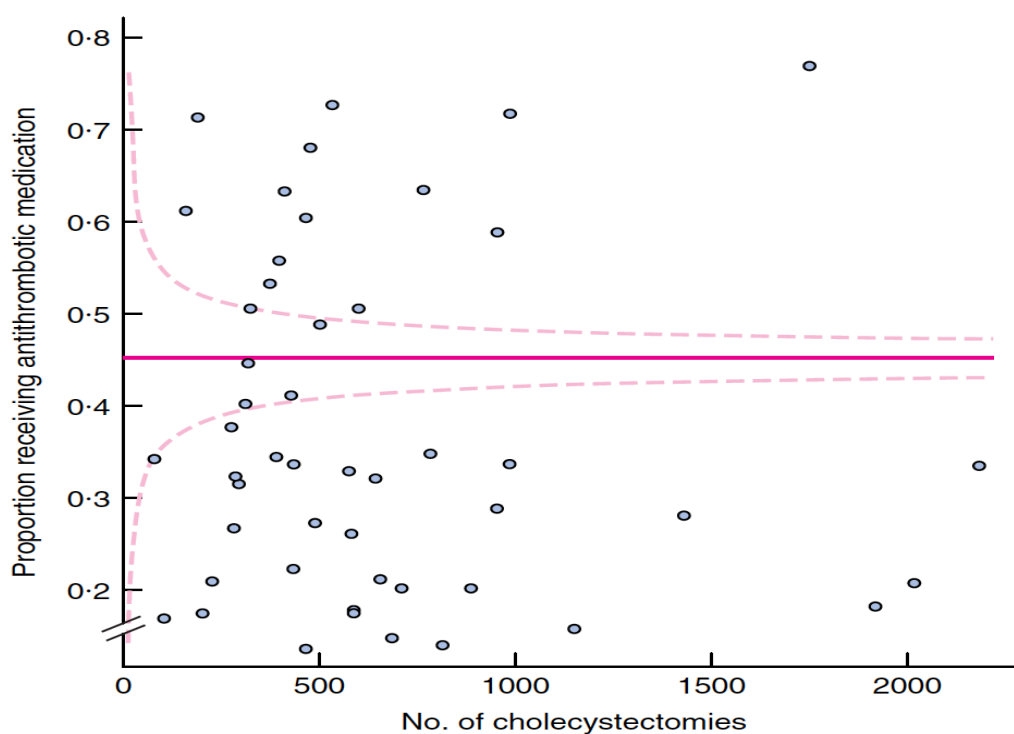**Figure 2:** Each dot in the funnel-plot represents a hospital participating in GallRiks registrations. The graph displays the proportion of patients receiving thromboembolism prophylaxis (TP) as a function of the number of cholecystectomies performed at each unit. The overall proportion of patients receiving TP is shown by the solid line, with the dashed lines representing the 95% confidence interval.

A bleeding complication was registered in (n=666, 3.1%) of the 21,259 patients receiving antithrombotic medication. In this group, 400 (1.9%) bleedings occurred perioperatively and 296 (1.4%) postoperatively. Of the 26,751 patients not receiving antithrombotic medication 365 patients (1.4%) had a haemorrhagic complication. In this group, 189 bleedings (0.7%) occurred perioperatively and 195 (0.7%) postoperatively.

In univariate analysis (Figure 3), an increased risk for haemorrhage was seen in men, older patients, patients with ASA>2, after emergency surgery, for patients with complicated gallstone disease, in procedures with long operation time and for patients receiving thromboembolism prophylaxis (TP).
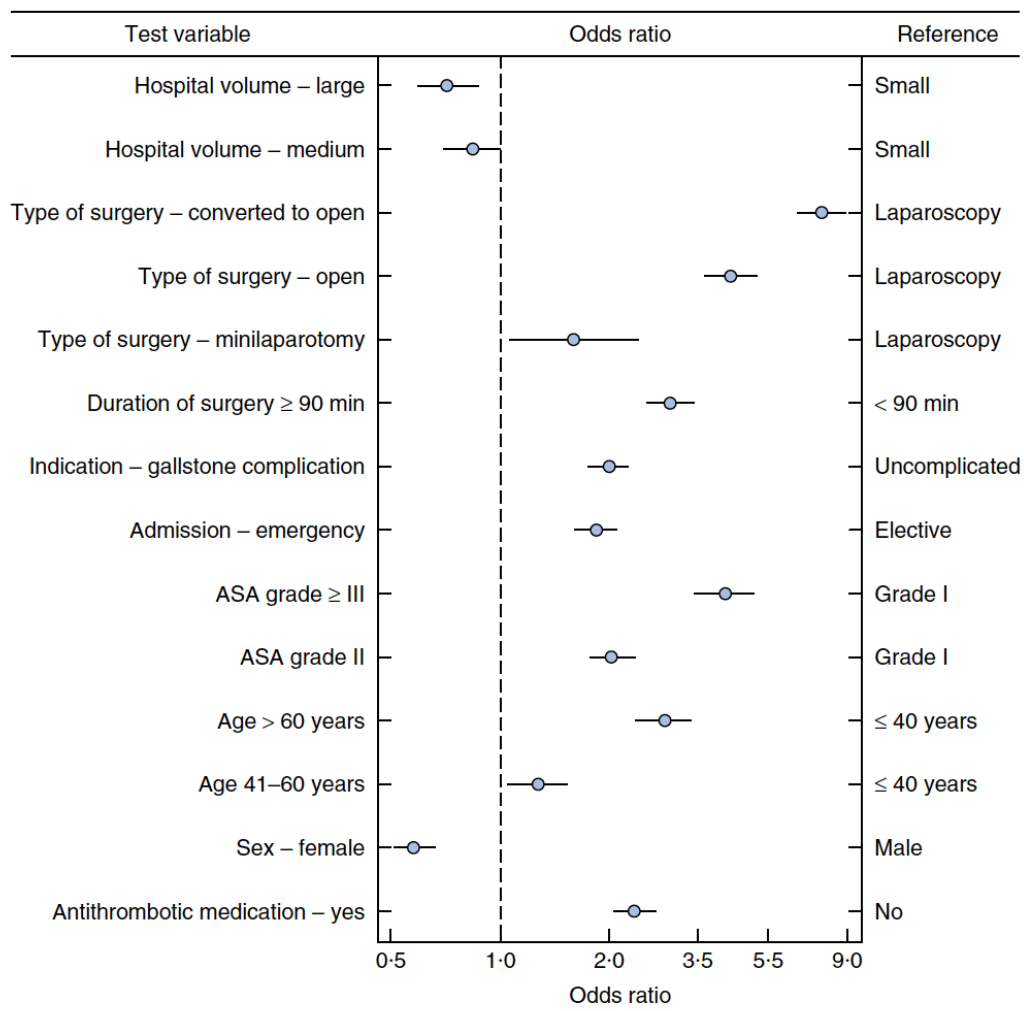

Figure 3: Univariate regression analysis of independent variables and the risk for overall bleeding complications (peri per- and/or postoperative) as defined by Odds Ratio.

After adjusting for all other variables in a multivariable logistic regression model, the

combined endpoint (any bleeding complication) in patients receiving TP was OR=1.35 (95% CI: 1.17-1.55). Furthermore, when endpoints where analysed separately, a significant increase was seen for both peri- and postoperative bleeding complications OR=1,40 (CI: 1,16-1,69) and OR=1,21 (CI, 0,99-1,47) respectively.

An interaction test indicated open and laparoscopic cholecystectomy to be appropriate for subgroup analysis. There was no significant increase in bleeding complications in the subgroup undergoing open cholecystectomy with TP. However, in the laparoscopic group of 42271 patients (including 3768 converted to open surgery) the Odds Ratio were 2.07 (CI: 1.70-2.51) and 1.35 (CI: 1.08-1.68) for peri- and postoperative haemorrhage respectively.

In the whole cohort of 48,010 patients, the symptomatic venous thromboembolism (VTE, [deep venous thrombosis and/or pulmonary embolism]) rate was 0.2%. In the patient group receiving TP, 43 (0.2%) developed VTE, compared to 31 (0.1%) of patients not receiving TP. Univariate analysis indicated that patients receiving TP were at higher risk for developing VTE (OR=1.75, CI: 1.10-2.77).

4.2 Study II

In total, 62,488 patients undergoing laparoscopic and open cholecystectomy were registered in GallRiks 2006-2011, forming the study population. The overall VTE rate, derived from both GallRiks and NPR was 0.25% (n=154). The rate of VTE after 60 and 90 days was 0.12% (n=77) and 0.14% (n=87) respectively. The number of symptomatic deep venous thromboses (DVT) within 30 days after cholecystectomy registered in the NPR was 0.06% (n=36) and the number of pulmonary emboli (PE) 0.04% (n=25). The age- and sex-standardised incidence ratio for venous thromboembolism (VTE) was 22.2 (95% CI 13.1-31.3) and for pulmonary embolism 5.6 (95% CI 2.3-8.9). Data from GallRiks showed that, 26,217 (43%) patients received thromboembolism prophylaxis (TP).

	VTE[a]		DVT[b]		PE[b]	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
Gender						
Male	1	Ref	1	Ref	1	Ref
Female	1.13	0.80–1.61	1.07	0.51–2.28	0.93	0.39–2.22
Age (years)						
≤50	1	Ref	1	Ref	1	Ref
50–70	1.55	1.04–2.32	1.60	0.69–3.70	3.22	0.87–11.86
≥70	2.69	1.68–4.30	1.22	0.41–3.61	6.49	1.62–26.00
BMI (kg/m^2)						
<18.5	1	Ref	1	Ref	1	Ref
18.5–25	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
>25	1.20	0.59–2.47	3.77	0.63–22.6	N.S.	N.S.
Operative indication						
Gallstone colic	1	Ref	1	Ref	1	Ref
Acute cholecystitis	1.69	1.18–2.42	1.80	0.87–3.73	1.86	0.78–4.45
Acute gallstone pancreatitis	1.31	0.54–3.21	1.11	0.15–8.10	N.S.	N.S.
Surgical approach						
Laparoscopic or conversion	1	Ref	1	Ref	1	Ref
Open	1.95	1.31–2.92	2.26	0.996–5.11	2.18	0.84–5.63
Operation time						
<120	1	Ref	1	Ref	1	Ref
≥120	1.66	1.18–2.35	1.56	0.74–3.27	2.07	0.88–4.91
TP						
No	1	Ref	1	Ref	1	Ref
Yes	1.05	0.74–1.50	1.30	0.60–2.82	1.22	0.48–3.07
Previous VTE						
No	1	Ref	1	Ref	1	Ref
Yes	50.5	27.3–92.8	183	77.6–431.2	51.8	14.5–185
ERCP treatment[c]						
No	1	Ref	1	Ref	1	Ref
Yes	12.2	7.61–19.6	3.0	0.78–12.2	2.1	0.28–15.6

Table 2: Multivariable analysis of the risk for pulmonary embolism (PE), deep venous thrombosis (DVT) and venous thromboembolism (VTE) within 30-days following cholecystectomy. OR; Odds Ratio. CI; Confidence Interval. [1] Total VTE risk calculated from GallRiks and/or NPR. [2] Risk for DVT and/or PE derived from NPR. Patients treated with ERCP within 30 days after cholecystectomy. Ref=reference, N.S=not significant.

In this cohort, 80 (0.31%) of all patients developed VTE. In comparison, 34,884 (57%) patients did not receive TP and in this group 65 (0.19%) patients developed VTE within 30 days following cholecystectomy (P>0.05).

The 30-day mortality rate following cholecystectomy was 0.2% (n=127) of which 2 patients died from pulmonary embolism. In multivariable logistic regression,

controlled for all other independent variables included in Table 2, patients with a previous history of venous thromboembolism were 183 times more likely to develop postoperative DVT (OR=183, 95% CI 77.6-431.2). Age, gender, BMI, operative indication, surgical approach, operation time, and TP were not associated with postoperative DVT.

Age was found to be a risk factor for postoperative VTE in patients aged over 50 years (OR=1.55, 95% CI 1.04-2.32) and those aged over 70 years (OR=2.69, 95% CI 1.04-2.32). Furthermore, patients aged over seventy years had a significantly elevated risk for developing postoperative PE (OR=6.49, 95% CI 1.62-26.00). Gender, indication, surgical approach, operation time and the use of TP were not associated with a significant change in the PE rate. However, open surgery (OR=1.95, 95% CI 1.31-2.92) and prolonged operation time (OR=1.66, 95% CI 1.18-2.35) both predicted an increased risk for VTE. Patients undergoing ERCP at the same time as cholecystectomy were at higher risk of developing VTE (OR=12.2, 95% CI 7.61-19.6). Finally, no significant increase or decrease in VTE frequency was observed in patients receiving TP when undergoing cholecystectomy.

4.3 Study III

Of the 62,488 individuals included in the study, 77 patients (0.12%) were diagnosed with liver cirrhosis. In this subgroup, 29 (37.7%) patients had symptomatic cirrhosis in the form of oesophageal varices, ascites or hepatic encephalopathy.

Patient characteristics are shown in Table 3. Patients with cirrhosis were older (age >50 years, p<0.001) compared to non-cirrhotic patients. Patients with liver cirrhosis more often had gallstone complications such as cholecystitis or pancreatitis at the time of surgery (p<0.05). Operation time was more often >90 minutes and open cholecystectomy was more frequently adopted in cirrhotic patients (p<0.001). Finally, patients with liver cirrhosis had a higher rate of conversion to open surgery and received TP more often than non-cirrhotic patients (p<0.001).

	Number of data available	Cirrhosis N = 77 (%)	Noncirrhosis N = 62,411 (%)	P*
Gender	62487			<0.05
Male		38 (49.4)	20590 (33.0)	
Female		39 (50.6)	41820 (67.0)	
Age (years)	62486			<0.001
<50		10 (13.0)	29666 (47.5)	
50–70		50 (64.9)	25089 (40.2)	
>70		17 (22.1)	7654 (12.3)	
ASA grade	61869			<0.001
1		15 (20.0)	33666 (54.5)	
2		31 (41.3)	23678 (38.3)	
>2		29 (38.7)	4450 (7.2)	
Operative indication	62488			<0.05
Gallstone colic		38 (49.4)	39110 (62.7)	
Gallstone complication[1]		39 (50.6)	23301 (37.3)	
Operation time (min)	61249			<0.001
<90		23 (31.1)	30309 (49.5)	
>90		51 (68.9)	30863 (50.5)	
Operative approach	61134			<0.001
Laparoscopic		44 (59.5)	49093 (80.4)	
Open		19 (25.7)	5502 (9.0)	
Conversion		10 (13.5)	4778 (7.8)	
Thromboembolism prophylaxis	61101			<0.001
Yes		46 (62.2)	26171 (42.9)	
No		28 (37.8)	34856 (57.1)	

Table 3: Baseline characteristics of cirrhotic versus non-cirrhotic patients undergoing cholecystectomy. [1]Gallstone complication: cholecystitis, pancreatitis, or obstructive jaundice. ASA: American Society of Anesthesiologists. Lap: laparoscopic. *Pearsons Chi-Square test.

Thromboembolism prophylaxis was given to 62% and 42% of patients in the cirrhosis and non-cirrhosis groups respectively. None of the patients with cirrhosis developed a postoperative cardiovascular complication (acute myocardial infarct, DVT, PE, stroke) within 30 days after cholecystectomy. Furthermore, none of the patients in the cirrhosis group developed acute liver failure or died within 30 days after surgery. Four patients (5.2%) with liver cirrhosis and 2,203 patients (3.5%) without cirrhosis suffered perioperative complications (data not shown) but no statistically significant difference was detected p=0.43). Two liver cirrhotic patients received blood transfusion following cholecystectomy, which was a higher rate than in non-cirrhotic patients (p<0.05). In addition, a significantly higher number of patients with liver cirrhosis received antibiotic treatment > 1 day (11.4%) compared to non-cirrhotic patients (5.3%, p< 0.05).

	Number of data available	Cirrhosis N = 77 (%)	Noncirrhosis N = 62,411 (%)	P
Gallstone complications				
Pancreatitis	60279	1 (1.3)	374 (0.6)	n.s
Bile duct obstruction	60272	1 (1.3)	589 (0.94)	n.s
Cholangitis	60279	0 (0)	129 (0.21)	n.s
Cardiovascular complications				
Acute myocardial infarct	62488	0 (0)	75 (0.12)	n.s
DVT	62488	0 (0)	36 (0.06)	n.s
PE	62488	0 (0)	25 (0.04)	n.s
Stroke	62488	0 (0)	92 (0.15)	n.s
Surgical complications				
Antibiotic compl.[2]	60251	8 (11.4)	3174 (5.3)	<0.05
Blood transfusion	60250	2 (2.9)	402 (0.67)	<0.05
Liver failure	62430	0 (0)	5 (0.01)	n.s
Wound infection	62488	1 (1.3)	153 (0.25)	n.s
Abscess	60278	2 (2.6)	834 (1.3)	n.s
Sepsis	62430	1 (1.3)	49 (0.07)	n.s
Bile leak	60275	0 (0)	804 (1.3)	n.s
Wound dehiscence	62488	0 (0)	15 (0.02)	n.s
Bleeding	60278	0 (0)	498 (0.83)	n.s
Perforation	62488	0 (0)	2	n.s
Reoperation	62488	0 (0)	34 (0.05)	n.s
Mortality	62488	0 (0)	127 (0.20)	n.s
Other complications	62488	3 (3.9)	2,099 (3.3)	n.s

Table 4: [1]Postoperative complications from GallRiks and/or NPR. n.s = non-significant.
[2]Patients with postoperative infection requiring antibiotic treatment >1 day.

In subgroup-analyses based on surgical approach, univariate regression failed to detect any significant differences between cirrhotic and non-cirrhotic patients. However, in univariate analysis patients with liver cirrhosis were found to have a significantly higher risk of having a blood transfusion (OR = 4.4, 95% CI 1.08–18.0) or prolonged antibiotic treatment (OR =2.3, 95% CI 1.11–4.84) following cholecystectomy. Furthermore, in multivariable analysis the overall post-operative complication rate was higher in cirrhotic (16.9%) compared to non-cirrhotic patients (9.2%, p=0.02). Finally, there were no deaths and none of the patients with liver cirrhosis developed postoperative liver failure within the first 30 days after cholecystectomy.

4.4 Study IV

In total, 94,557 patients undergoing cholecystectomy (open and laparoscopic) 2005-2015 and registered in GallRiks were included. Perioperative haemorrhage was registered in 799 patients (0.8%) and 1192 patents (1.3%) developed postoperative bleeding complications. By combining peri- and/or postoperative bleeding figures, the overall haemorrhagic complication rate was 2.0%. Haemorrhagic shock was registered in 10 patients (0.01%).

As observed in Study I, risk factors for haemorrhagic complications were: male gender; age>40 years; ASA>1; gallstone complications (i.e. cholecystitis and/or pancreatitis); acalculous cholecystitis; open cholecystectomy; thromboembolism prophylaxis; conversion to open surgery; and prolonged surgery (>120 min). Due to large numbers of missing data, Body Mass Index (BMI) was assessed separately in a sub-group analysis of 36,797 patients. However, univariate regression did not show a significant association between BMI and haemorrhagic complication (OR= 1.04, CI 1.10-1.56).
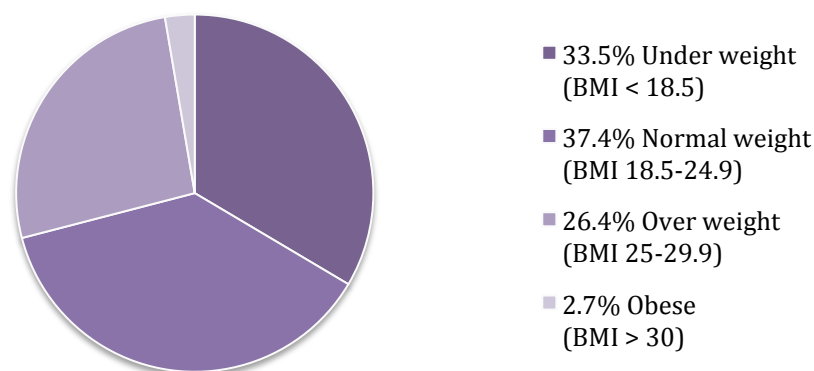

- 33.5% Under weight (BMI < 18.5)
- 37.4% Normal weight (BMI 18.5-24.9)
- 26.4% Over weight (BMI 25-29.9)
- 2.7% Obese (BMI > 30)

Figure 4: Distribution of BMI among patients undergoing cholecystectomy 2005-2015.

univariate analysis, dipyridamole (n = 252, OR = 2.39, CI 0.98–5.81) and tricyclic antidepressants (TCA, n = 1151. OR = 1.78, CI 1.10–2.89) were associated with significantly elevated risk for perioperative haemorrhage. However, when performing a Bonferroni analysis, the correlation was disregarded as a finding of mass significance.

In multivariable analysis of comorbidity (Table 5), cerebrovascular disease (OR = 1.96, CI 1.64–2.34), previous myocardial infarction (OR = 1.94, CI 1.56–2.40), renal disease (OR = 1.93; CI 1.41–2.63), heart failure (OR = 1.73, CI 1.37–2.18), diabetes (OR = 1.49, CI 1.27–1.74), peripheral vascular disease (OR = 1.49, CI 1.13–1.95), and obesity (OR = 1.27, CI 1.08–1.51) predicted an increased risk for haemorrhagic complication. The overall incidence of bile duct injury and/or leakage was 1.6%. Between 2005-2016, 236 of 6857 (3.4%) open cholecystectomies and 837 out of 78814 (1.6%) LCs (including conversions) resulted in a bile duct injury (p<0.05). Patients with perioperative haemorrhage had a significantly higher incidence of bile duct injury (5.4%, p<0.05). In addition, multivariable regression significantly predicted perioperative haemorrhage as a risk factor for bile duct injury and/or leakage (OR=2.45, CI 1.79-3.37).

Condition	N (%)	Bleed (%)	Univariate			Multivariate		
			p	OR	CI	p	OR	CI
Cerebrovascular disease	3283 (3.48)	151 (4.60)	0.001	2.52	2.12–2.98	0.001	1.96	1.64–2.34
Diabetes	5396 (5.71)	197 (3.65)	0.001	1.99	1.71–2.31	0.001	1.49	1.27–1.74
Heart failure	1797 (1.90)	103 (5.73)	0.001	3.14	2.56–3.85	0.001	1.73	1.37–2.18
Kidney disease	788 (0.83)	48 (6.10)	0.001	3.28	2.44–4.41	0.001	1.93	1.41–2.63
Liver cirrhosis	345 (0.37)	14 (4.10)	0.005	2.11	1.23–3.61	0.053	1.71	0.99–2.94
Lung disease	8750 (9.27)	181 (2.10)	0.51	1.05	0.90–1.23	0.363	0.930	0.79–1.09
Obesity	6173 (6.54)	157 (2.54)	0.01	1.32	1.12–1.56	0.005	1.27	1.08–1.51
Peripheral vascular disease	1314 (1.40)	64 (4.87)	0.001	2.60	2.01–3.35	0.004	1.49	1.13–1.95

Table 5: Overall haemorrhagic complications for different comorbidities assessed by univariate and multivariable regression analyses with 95% confidence intervals (CIs). The multivariable analysis calculated Odds Ratios (ORs) as measurement of risk for haemorrhage and was adjusted for: gender, age, indication, surgical approach, ASA-classification and anticoagulant/aggregant drugs.

In total, 223 patients (0,24%) died within 30 days following cholecystectomy. When reviewing data from the Swedish Cause of Death Register, 25 patients died from procedure-related causes, of which 48% had a perioperative haemorrhage registered prior to death. Furthermore, perioperative haemorrhage significantly increased mortality not only within 30 days, but also during the first postoperative

year (Figure 5). Perioperative haemorrhage was associated with HR = 4.9 (CI 3.52-6.93) and an adjusted HR of 1.8 (CI 1.28-2.53). Finally, in performing a sub-group analysis, the risk of death remained significant when the first 30 days were excluded from the analysis (p<0.05).
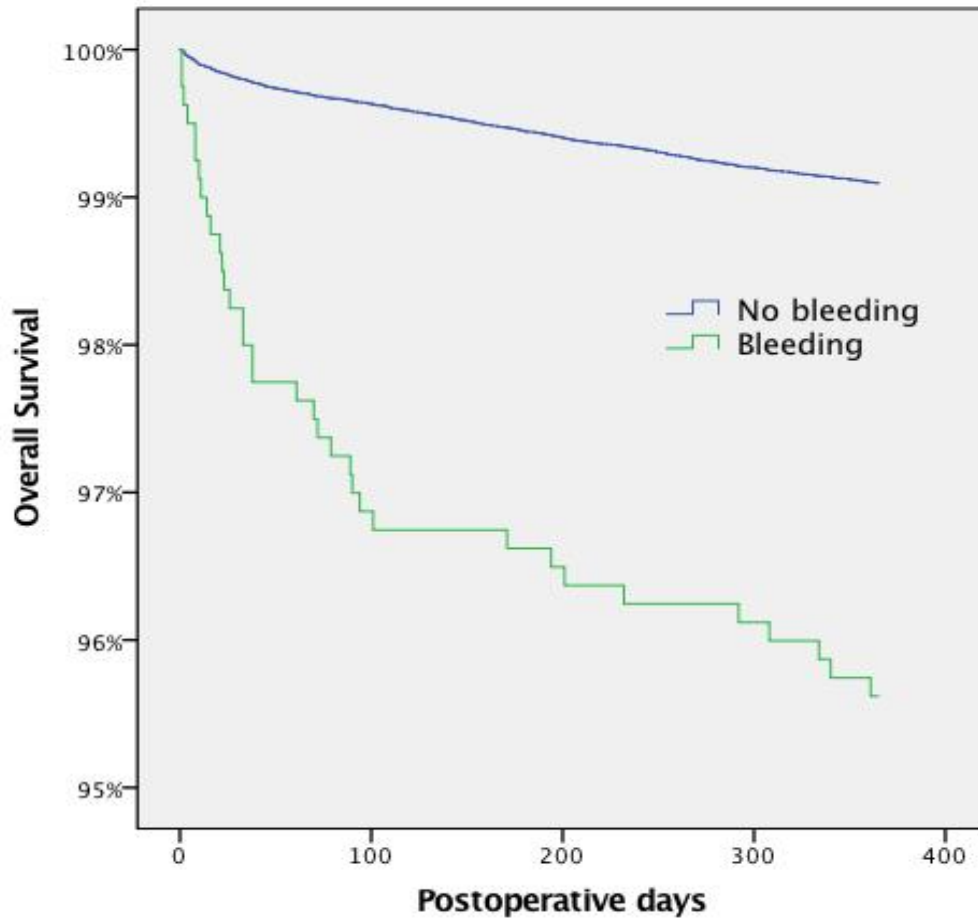

Figure 5: Kaplan-Meier analysis of survival following perioperative bleeding in cholecystectomy.

5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 Hypothesis testing

In modern research it is of great importance to carefully construct a hypothesis prior to beginning a project. A hypothesis test evaluates two mutually exclusive statements about a population in order to determine which statement is best supported by sample data. The hypothesis is often impossible to prove and it is therefore common practice to attempt to disprove a hypothesis instead. Consequently, a hypothesis is usually constructed as a "negative" statement (e.g. no effect or no difference). This hypothesis is referred to as the "null hypothesis". By disproving (rejecting) the null hypothesis the alternative hypothesis (often a negation of the null hypothesis) is accepted. When comparing two study groups, an assumption of no difference between groups is made if the null hypothesis is true. If the null hypothesis can be rejected the assumption is that there is a difference between groups. This may be exemplified with the use of the odds ratio (OR). If the OR equals one there is no difference between groups and the null hypothesis cannot be rejected. The probability of rejecting a null hypothesis is set at different arbitrary significance levels such as 95 % or 99 %. This implies a 5% or 1% "risk" of incorrectly rejecting (due to chance) a true null hypothesis. This is known as a Type 1 error. A Type 2 error is defined as failure to reject a null hypothesis that is untrue. Type 2 errors may occur if the study is too small or if bias is present. Bias is a form of systematic error and is explained below.

5.1.2 Error

When analysing research data, it is important to consider the possibility of error that might influence the results. There are two types of errors referred to as systematic and random error. Systematic error is usually considered be due to confounding and bias. Random error opposes systematic error in being uncontrolled and due to chance alone. This section briefly explains each type of error.

5.1.3 Confounding

Epidemiology is the study of patterns, causes and effects of health and disease in defined populations. In epidemiological research, a common approach is to assess how an event or exposure affects the study population (outcome). This relationship can further be described as an outcome that varies due to influence of the exposure. Accordingly, the exposure can be seen as an independent variable with an impact on the population that may be regarded as a dependent variable (outcome). A type of systematic error is the presence of a variable that affects both independent and dependent variables; defined as a confounding factor.
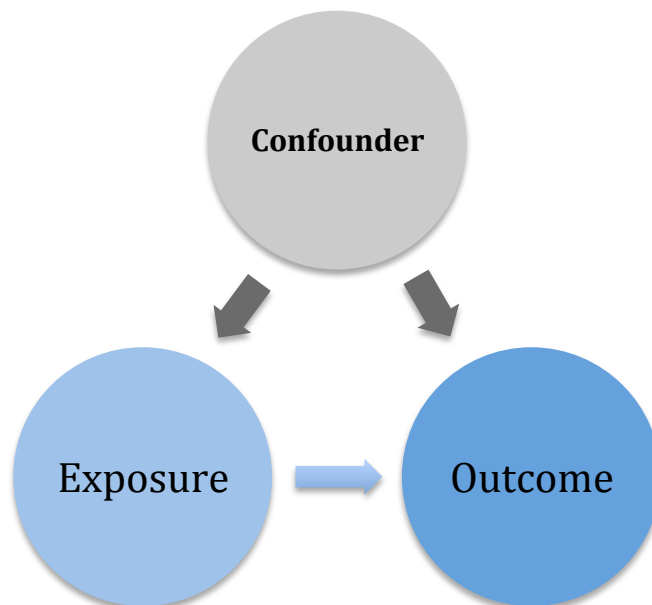
Figure 6: A confounding factor is able to influence both exposure and outcome.

The confounding effect is related to the independent as well as the dependent variables and may increase or decrease the exposure or outcome. If the confounding variable is not identified or controlled for, it may result in a false estimate of the correlation between exposure and outcome. An example could be when two operative modalities, say open versus laparoscopic surgery, are to be compared regarding haemorrhagic complications. Since open surgery inflicts a more profound inflammatory response and activation of the coagulation system, surgeons will be more prone to give thromboembolism prophylaxis (TP) to patients undergoing open surgical procedures than those operated laparoscopically. Failure

to identify TP as a potential confounding factor for haemorrhagic complications could incorrectly lead to the conclusion that open surgery is associated with more bleeding complications than laparoscopic surgery.

Failure to control for confounding variables undermines the credibility and internal validity of the study. Effort to identify and control for confounding variables is often made in study design before the study is performed (restriction, randomisation or matching). However, in large study populations, there are restrictions in how a study cay be designed and confounding must be controlled statistically. In this thesis, when collecting data from GallRiks, all efforts have been made to include as many relevant variables as possible that could affect the outcome of cholecystectomy. In this respect, age, gender, ASA-classification, surgical approach, operative indication were co-variables with a potential confounding effect that needed to be taken into account.

In large study populations with many covariables, confounding can be checked for by multivariable regression analysis (MRA). In contrast to simple logistic regression (dealing with only one dependent and independent variable), MRA calculates the effect of multiple independent factors on the dependent study variable. In addition, the effect of one independent variable can be studied as the other covariables (confounders) are fixed and controlled. In logistic regression, Odds Ratio (OR) represents the odds that an outcome will occur given a particular exposure. In MRA, the OR is the coefficient that predicts the "risk" or possible impact of an exposure on the outcome variable. OR is often presented as a correlation or association between independent and dependent variables and should not be interpreted as a factor of causative relationship. This is also one of the drawbacks with register studies (dealing with large study groups) as results merely are presented as associations. The association, represented by a significant OR, could be the result of a failure to identify unknown confounding factors.

5.1.4 Bias

The value of register-based studies depends heavily upon the study design. If confounding factors that could influence both treatment selection and outcome are not recognised, the study is flawed. Furthermore, when analysing data obtained from a register it is important to ascertain the number of missing data for the

various study variables. Missing data might influence outcome, rendering it susceptible to selection bias. The term "bias" can be explained as systematic favoritism in the collection of data, generating skewed or misleading results. Another factor distinguishing a high-quality register study is the coverage of the population that is studied. High coverage naturally reflects a more reliable result or outcome and reduces the effects of selection bias. Register studies are limited by reporting and observer bias. For example, healthcare providers responsible for a procedure with unsatisfactory outcome are more likely to neglect an objective report, even when earnestly striving to provide the best possible care for the patient.

Complications are reported in GallRiks, by each participating hospital as well as by the surgeon performing the registration. In this setting, observation bias may be a problem due to the fact that complications and poor results reflect directly upon the individual surgeon or institution. When assessing the quality of a register it is also of great importance to make sure that register data are thoroughly validated.

5.1.5 Random Error

Besides systematic error, there is always a chance (risk) that an observation is the result of random error. Random error can be dealt with by introducing confidence intervals and p-values to ascertain that the alternative hypothesis, i.e. the difference between groups, is "significant". A P-value is defined as the probability of obtaining a sample more extreme than the ones observed in the population, assuming that the null hypothesis is true. Hence, p-values may be interpreted as the probability of making a Type 1 error.

A 95% confidence interval may also be used to reject a null hypothesis. The CI has the benefit of being able to present the point estimate ("best estimate" of the unknown population parameter) with a display of the precision of the estimate.

A wide confidence interval is associated with low precision, whereas the opposite is true for a narrow CI. A 95% CI may be defined as a number of random observations from a population where 95% of all estimates (e.g haemorrhage rate) include the true rate in the study population.

5.1.6 Strengths and limitations of GallRiks

Register-based research is an important compliment to other study designs, such as randomised control trials, in that they cover a large number of individuals and in many cases generate results that may be generalisable to the population as a whole. Register studies can therefore provide information about the safety and efficacy of a treatment or intervention in a large number of patients.

A strength of studies originating from GallRiks, is the use of an unselected population-based national register designed for quality assurance of gallstone surgery. Moreover, the database is continuously validated by experienced surgeons who review the medical records of patients included in the register. The inter-observer reliability has been found to be over 95%. Nevertheless, in self-reported registers there is a risk of selection bias. As mentioned, a falsely low complication rate could be generated since the surgeon reporting might be less prone to register a negative outcome of the surgical procedure than an objective observer. However, this possibility is minimised since registrations are double-checked by assigned specially trained local coordinators at each participating hospital.

An obvious limitation of register-based studies is that interpretation of adverse events is highly dependent upon the objectivity of the physician or healthcare provider responsible for registration. In GallRiks, a haemorrhagic complication is defined as blood loss during the procedure that could not be controlled with measures (clipping, diathermy or suturing) routinely used in gallstone surgery. Upon registration in the internet module of GallRiks, information regarding the aforementioned definition of perioperative haemorrhage is provided in an information box (Figure 7). However, this information could be missed, which may lead to a biased registration. For instance, the surgeon may have perceived the operation as difficult due to minor bleedings and therefore "tick in" the dichotomous yes/no box for haemorrhagic complication without paying attention to the GallRiks definition of haemorrhage. This could presumably cause an erroneously high incidence of haemorrhagic complications.

Figure 7: GallRiks internet module. Circled rings indicate the boxes for answering dichotomous questions regarding complications (left) and the information box regarding the definition of intervention demanding haemorrhage in GallRiks (right).

Another limitation of register-based studies is the difficulty in assessing the impact of other factors not included in the register such as drugs that could influence outcome. In Study IV, data from GallRiks was cross-matched with the Swedish Prescribed Drug Register in order to obtain merged data on anticoagulant and antiaggregant medication prescribed to the patient. Confounding due to medication was therefore reduced.

In the 30-day follow-up, the local coordinator at each participating hospital reviews the local hospital medical records to answer the dichotomous questions in the GallRiks module. Patient records from other hospitals or from primary healthcare facilities are not available for review, enabling postoperative complications recorded at other health care institutions to possibly go unnoticed. Furthermore, a possible reporting bias resulting in missed registrations could be expected in that the local coordinator is presumably "off guard" regarding rare complications such as pulmonary embolism.

5.2 GENERAL DISCUSSION

This thesis used the high quality Swedish Register for Gallstone Surgery and ERCP (GallRiks) to explore haemorrhagic and thromboembolic complications following cholecystectomy. We found that thromboembolism prophylaxis (TP) increases the haemorrhagic complication and conclude that TP administration should be guided by patient risk factors (Studies I and II) rather than routinely. The metabolic and anatomic changes in patients with liver cirrhosis increase the risk for complications during surgical procedures. In Study III we found that patients with liver cirrhosis were older and had a higher frequency of complicated gallstone disease at the time of surgery. The postoperative complication rate was higher than in non-cirrhotic patients, and 25% of patients with cirrhosis were treated with open cholecystectomy. In Study IV we found that male gender, age>40 years, ASA>1, gallstone complications (i.e. cholecystitis and/or pancreatitis), acalculous cholecystitis, open cholecystectomy, TP and prolonged surgery (>120 min) were associated with a higher haemorrhagic complication rate. Furthermore, commonly prescribed drugs do not need to be discontinued prior to surgery in order to reduce the risk for haemorrhage. Finally, we suggest that perioperative haemorrhage is an independent risk factor for bile duct injury and/or leakage.

5.2.1 Study I

In this population-based register study we found that patients receiving TP had a 50% increase in the frequency of both peri- and postoperative bleeding. After adjusting for all variables included in the study in a multivariable regression analysis, TP increased the risk for overall bleeding by OR=1.35 (95% CI: 1.17-1.55). In the present study, a postoperative haemorrhagic complication was defined as a surgical site bleed that required reoperation or blood transfusion. It could be argued that a more stringent way of reporting haemorrhage would have been to estimate the volume of blood lost. However, our definition of major haemorrhage is well in line with that used in many other surgical studies[179]. TP is registered in GallRiks, as a dichotomous yes/no answer, and there is no information regarding dose, type of pharmacological prophylaxis, timing or duration of administration. This makes interpretation of the impact of TP on perioperative bleeding difficult. In clinical practice, hospitalised patients with complicated gallstone disease (e.g. cholecystitis

and/or pancreatitis) may receive TP prior to surgery. In contrast, elective patients (outpatients) usually receive TP after the intervention. It could thus be argued the results regarding the impact of TP on perioperative haemorrhage in this study are inconclusive.

Studies on bleeding complications following TP use in cholecystectomy are scarce in the literature. Incidences of 0.5%-25%[180-182] have been reported, though these studies had small sample sizes and differed widely regarding the criteria used to define haemorrhage. A recent retrospective study from Turkey, that had a similar design to Study I, showed no increase in bleeding complications following the use of TP in patients undergoing cholecystectomy[183]. In the Turkish study, 1,485 patients undergoing cholecystectomy were included, and of these 1,178 patients received LMWH of varying duration depending on VTE risk. Patients with known comorbidity predictive of bleeding complications or acute cholecystitis, where the procedure lasted >90 minutes, or where "operative technical errors" due to bleeding led to conversion, were excluded. As well as the rather small control group, a problem with this study was the vast number of exclusion criteria used, resulting in a study cohort not representative of the general population undergoing cholecystectomy.

Bleeding complications arising from inadvertent trauma to a major vessel (e.g. cystic artery) can hardly be attributed to the pharmacological effect of TP. However, TP may give rise to minor capillary bleeding that hampers the visualisation of major vascular structures, thereby increasing the risk for inadvertent damage to larger vessels. Subsequently, we believe that in the evaluation of haemorrhage associated with TP use, the exclusion of patients being converted due to major bleeding results in selection bias.

In a meta-analysis of eight randomised trials of patients undergoing general and abdominal surgery, Mismetti et al reported that LMWH was associated with a two-fold increase in risk for major haemorrhage (OR=2.05, 95% CI 1.37-3.01) compared to patients not receiving prophylaxis[144]. Another meta-analysis recently investigated the frequency of bleeding complications and VTE events in patients undergoing surgical procedures with or without TP[184]. Pooled data from 13 studies comprising 14,776 patients with varying VTE risk levels according to the Caprini risk stratification score[185], were analysed . As in many previous studies on bleeding complications, definitions of bleeding used in the studies included varied. Nevertheless, the use of TP was associated with an increased overall risk for "clinically relevant" bleeding

complications following surgical procedures (OR=1.69, 95% CI 1.16-2.45). Furthermore, the use of TP only reduced the postoperative VTE risk in patients with a Caprini score 7-8 (OR= 0.60, 95% CI 0.37-0.97) or Caprini score >8 (OR= 0.41, 95% CI 0.26-0.65)[184]. In conclusion, given the pharmacological effect of thromboembolism prophylaxis, it is reasonable to believe that TP not only reduces the risk of fatal PE[186] but also increases the risk of bleeding in all patients undergoing major surgical procedures.

In 1986, Erich Muhe was met with scepticism when trying to introduce LC[11]. Today, the technique is widespread and established as the treatment of choice for symptomatic gallstone disease. The American College of Chest Physicians (ACCP) states in guidelines from 2012 that laparoscopic cholecystectomy may be regarded as a procedure with low risk for developing postoperative VTE[151]. Despite guidelines and well-proven risk assessment models[185], the use of TP in laparoscopic cholecystectomy is still a matter of debate. Supplement data provided (Appendix) show the administration of pharmacologic TP to patients undergoing cholecystectomy in Sweden. Over the period 2006-2014 the use of TP use has gradually decreased (Appendix, Figure 8). However, a number of hospitals still administer TP to more than 50 % of all patients undergoing cholecystectomy (see results, Study I, Figure 2). Furthermore, overall administration rate is 45% and 20% of all in- and outpatients respectively (Appendix, Figure 9). The wide variety in TP routines has been discussed previously[147, 187, 188], implying that the issue of TP in cholecystectomy is far from being settled, and continues to be subject to the individual surgeon's preference or routine of the institution. Indeed, a more selective approach to TP administration is warranted rather than routine prophylaxis to large numbers of patients undergoing cholecystectomy. The challenge lies in balancing the risk for haemorrhage against the risk for thrombosis. The preoperative identification of individual risk factors for both bleeding and thromboembolism is of uttermost importance if we are to minimise haemorrhagic complications at the same time as preventing VTE.

5.2.2 Study II

The overall VTE rate within 30 days following cholecystectomy was 0.25%. The risk for VTE persisted through 60 days (0.14%) and 90 days (0.14%). A low

frequency of VTE following cholecystectomy has previously been reported (0-0.2%)[180, 189-192]. In Study II, the diagnosis of venous thromboembolism (i.e. deep venous thromboembolism and/or pulmonary embolism) was determined using ICD-codes. Accordingly there is no information on whether VTE events were diagnosed using radiographic imaging or ultrasonography, or whether the diagnosis was based on clinical examination alone. More precise data on the incidence of postoperative DVT would have been gained by routine US screening of all patients with postoperative symptoms of thrombosis. When screening with US a high frequency of non-symptomatic DVT in calf veins (2.0-11.4)[142, 191] has been reported after surgery. However, it is not clear as to what extent these thrombi are clinically significant and ultimately lead to pulmonary embolism[150, 193].

In the early years of laparoscopic surgery, concern was raised over the possibility of the reversed Trendelenburg position and pneumoperitoneum causing venous stasis in the iliac veins, predisposing to the development of thrombi [194]. However, LC enables early ambulation and trauma to the abdominal wall is less. As in previous studies[142, 195, 196], we found that VTE is more common following open cholecystectomy than after laparoscopic cholecystectomy (OR=1.95, CI 1.31-2.92). This observation has been verified in studies on perioperative changes in haemostasis, where OC leads to higher levels of soluble fibrin degradation products and D-dimer[141, 197] compared to LC. In addition, the postoperative coagulation response has been shown to be greater in older patients[198]. This may partly explain the observation in Study II, where patient age >70 years predicted an increased risk for postoperative VTE (OR=2.69, CI 1.68-4.30).

Study II showed that the risk for VTE is about 20 times higher in patients undergoing cholecystectomy than in an age- and gender-matched general population. This may partly be explained by the immobilisation associated with surgical recovery but it is also known that surgical trauma induces a pro-coagulant response[141]. In view of the fact that cholecystectomy leads to a "hypercoaguable state"[142], it is important to consider adequate TP in selected cases. As mentioned above, the ACCP recognises laparoscopic cholecystectomy as being a "low risk" procedure with a Caprini risk score (CS) of 2 (at baseline) for all patients and recommends pneumatic intermittent compression as prophylaxis[151]. According to

ACCP guidelines, patient-specific risk factors generate a higher CS and the operating surgeon should consider pharmacological TP in patients with a score ≥ 3[151].

The results of Study II indicate a higher VTE risk in patients with a previous VTE event, age>50 years, open surgery, acute cholecystitis, operation time exceeding 120 minutes and concomitant ERCP intervention. Based on the Caprini risk stratification, all patients undergoing cholecystectomy already have a CS of 2 at baseline (without other risk factors). Any additional VTE risk factor automatically yields a CS of ≥ 3. Hence, if following ACCP guidelines, the conclusion that must be drawn from the findings of Study II is that any patient undergoing cholecystectomy with one or more of the risk factors evaluated (Table 2), should be considered for TP. However, it should be noted that there may be other risk factors for the development of VTE in surgical patients as previously described [185].

5.2.3 Study III

In Study III, a higher frequency of postoperative complications was found in cirrhotic patients (16.9%), compared to non-cirrhotic patients undergoing cholecystectomy (9.2%, p=0.02). Furthermore, multivariable analysis showed an increased risk for postoperative complications in patients with liver cirrhosis compared to non-cirrhotic patients (OR = 2.0, 95% CI 1.11–3.65). There was no significant difference in perioperative complication rate between cirrhotic (5.2%) and non-cirrhotic (3.5%) patients (p=0.43). None of the cirrhotic patients died within 30 days after surgery.

In the literature, patients with cirrhosis are reported to be at greater risk for complications in during surgery due to the metabolic and anatomic changes associated with liver dysfunction and portal hypertension[85, 199]. A wide range of morbidity (6.6-42%) and mortality (0.9-4%) rates has been reported for patients with liver cirrhosis undergoing cholecystectomy[24, 83, 200-202]. Furthermore, it is well known that surgical complications are correlated to the severity of liver disease as determined by the CTP or MELD scoring systems[201]. This is an obvious weakness of Study III, where the severity of liver disease was simply classified as "decompensated". Using this definition, 29 patients had decompensated cirrhosis (ascites, oesophageal varices and/or hepatic encephalopathy) with there was no

significant difference in postoperative complication rate between these patients and those with compensated cirrhosis (p=0.9). The inability to detect significant differences in postoperative complications between these patient groups may be the result small sample sizes, and brings into question the validity of our definition of "decompensated" cirrhosis. Furthermore, there wwas no information regarding patient optimisation prior to surgery, such as thrombocyte transfusion to reduce the risk of haemorrhage[201] or laparocentesis to relieve symptoms of ascites. Finally, no information was provided regarding the level of hospital care and treatment. It is reasonable to believe that fewer complications occur when a patient is treated at a specialised tertiary centre, compared to a small county hospital.

In Study III, rates of postoperative blood transfusion and infectious complications necessitating antibiotic treatment for more than one day were significantly higher in cirrhotic compared to non-cirrhotic patients (p<0.05). However, the increased rate of blood transfusion is questionable since the observation is only correlated to two patients in the cirrhosis group. Furthermore, any conclusion in drawn from the results of Study III regarding length of antibiotic "treatment" must be interpreted with caution This can be explained by the fact that antibiotic treatment is regarded as a postoperative complication in the GallRiks register. In the Internet-module, the coordinator answers the dichotomous (yes/no) question as to "if the postoperative complication was treated with antibiotics". There is no certainty to whether the treatment is actually correlated to a postoperative infection or merely represents a prolonged antibiotic prophylaxis.

The present results indicate that, compared to non-cirrhotics, patients with liver cirrhosis are older at the time for surgery. Furthermore, that cholecystectomy in liver cirrhotic patients is more often indicated by gallstone complications (i.e. cholecystitis and/or pancreatitis). Cholecystitis is a known risk factor for perioperative morbidity in cirrhotic patients[81, 203]. However, Study III provided no assessment of the impact of cholecystitis on perioperative morbidity. Consequently, as an attempt to clarify the significance of cholecystitis regarding haemorrhagic complications, a previously unpublished subgroup analysis (based on the prospectively collected data in GallRiks) is provided in in the Appendix of this thesis (Table 6). In this analysis of 345 patients with liver cirrhosis, 76 suffered from cholecystitis at the time of cholecystectomy, of whom 5 patients (6.6%) with cholecystitis and 1 patient (0.4%) without cholecystitis developed perioperative

bleeding. In multivariable analysis, adjusted for gender, age, ASA-classification, surgical approach, operation time and anticoagulant/aggregant drugs, cholecystitis was a strong risk factor for perioperative haemorrhage (OR=12.8, CI1.29-126.34) in patients with liver cirrhosis. The increased complexity of cholecystectomy has been recognised in this patient group and some authors have suggested percutaneous cholecystostomy[81] or subtotal cholecystectomy[203] as being more suitable treatment options.

Several publications debate the preferred surgical approach to perform cholecystectomy in liver cirrhotic patients [81, 84, 204, 205]. In a meta-analysis by De Goede et al, 234 patients with liver cirrhosis from four randomised controlled trials were pooled to compare outcome in LC versus OC[81]. The authors concluded that LC was associated with a lower overall complication rate (Risk ratio 0.52, CI 0.29-0.92), a shorter hospital stay (mean difference −3.05 days, p < 0.001) and earlier return to normal diet (mean difference −27.48 hours, p < 0.001). The analysis was limited by few patients with Child-Turcotte- Pugh (CTP) Grade C included, and the fact that surgery was mainly indicated by biliary pain. In the absence of evidence, Grade C patients may best be treated with conservative cholecystostomy (drain) or subtotal cholecystectomy[106, 203]. For Grades A and B liver cirrhosis patients, the study by Goede et al provides evidence that the laparoscopic approach is preferable to open cholecystectomy. With this in mind, it is difficult to explain the high frequency of open cholecystectomy seen in Study III, where an open approach was used in 25.7% of patients with cirrhosis compared to 9% of non-cirrhotic patients (p<0.001). Accepting the above-mentioned limitations of Study III, we conclude that cholecystectomy is reasonably safe in patients with liver cirrhosis. Furthermore, cholecystitis is a strong risk factor for haemorrhagic complications in cirrhosis patients (Appendix, Table 6). Furthermore, the fact that patients with liver cirrhosis are often older and have more complicated gallstone disease at the time of surgery, leads us to conclude that surgery should not be delayed thereby giving less time for complications to occur.

5.2.4 Study IV

The administration of thromboembolism prophylaxis at the time of a surgical procedure requires assessment of the haemorrhage risk in each patient. We

therefore conducted a study focusing on the incidence and risk factors for haemorrhagic complications in patients undergoing cholecystectomy. As a secondary endpoint the impact of prescription drugs on haemorrhage rate was assessed.

Major haemorrhage due to injury to a large blood vessel is considered a rare complication in LC[104, 206, 207]. Minor haemorrhage is more frequent, arising from the abdominal wall (during trocar insertion) or from the liver bed during dissection. In order to avoid the wide variation in the definition of major haemorrhage, we used a clinically significant definition of major haemorrhage in line with the definition proposed by the International Society of Thrombosis and Haemostasis (ISTH)[179]. In Study IV, the overall rate of intervention-demanding haemorrhagic complications was 2.0%. Previous studies report similar bleeding rates (0.25-4.1%)[103-105, 208]. In our study, haemorrhage was eight and fifty times more frequent than VTE and PE respectively. Whereas PE is a potentially lethal complication, haemorrhage is usually easily managed surgically. However, in Study IV we showed that a perioperative bleeding is associated with a five-fold increase in postoperative mortality following cholecystectomy (HR = 4.9 (CI 3.52-6.93).

In surgical patients, the risk for haemorrhagic complications is dependent upon type of operation, patient-specific risk factors and drugs that may disturb haemostasis. Furthermore, the cause of bleeding in elderly patients with several comorbidities is often multifactorial and may be related to medication[209]. In this study we found several comorbidities (cerebrovascular disease, previous myocardial infarction, renal disease, heart failure, diabetes, peripheral vascular disease, obesity) to be associated with an increased bleeding risk. Furthermore, in multivariable analysis, male gender, age>40 years, ASA>1, gallstone complication (i.e. cholecystitis and/or pancreatitis), acalculous cholecystitis, open cholecystectomy and TP predicted the risk for haemorrhagic complications in patients undergoing cholecystectomy. Prolonged operation time (>120 min) and conversion to open surgery also predicted an increased risk of haemorrhage. However, this association is highly unreliable since haemorrhage may increase operation time as well as be the cause of conversion to open surgery.

In the literature, data is scarce regarding surgical patient specific risk factors for haemorrhagic complications[210] and definitions of major haemorrhage vary. However, it may be assumed that currently available risk scoring systems based on spontaneous bleeding in medical patients also apply to surgical patients in the perioperative setting[210]. In a register study by Ducrocq et al, 64,589 medical outpatients with known atherosclerotic disease were assessed for spontaneous bleeding. The authors concluded that high age, peripheral arterial disease, diabetes, hypertension, anticoagulant and antiplatelet therapy were risk factors for "serious haemorrhage"[211]. Furthermore, Decousus and coworkers reported from the multinational observational IMPROVE study on 15,516 hospitalised medical patients, that active gastroduodenal ulcer, age>85 years, renal failure, rheumatic disease, male gender and a history of previous bleeding predicted "clinically significant bleeding"[212].

Study IV has limitations regarding the assessment of prescription drugs on haemorrhagic complications. Our data provide no information on drug compliance or possible discontinuation in the perioperative period. However, from a clinical perspective it is unlikely to believe that medication other than anticoagulant (or in some cases antiplatelet drugs) may have been discontinued prior to surgery. We found that dipyramidole and tricyclic antidepressants (TCA) were associated with an increase in haemorrhagic complications but this correlation did not withstand Bonferroni correction for mass-significance. In recognizing a limited interpretation of our results, we conclude that commonly prescribed drugs are not associated with an increased risk of haemorrhage and therefore do not need to discontinued prior to cholecystectomy.

The field of bile duct injury has been extensively investigated[101, 104, 213-215]. However, the association between perioperative haemorrhage and bile duct injury has not been recognised previously. In the early years of LC, the incidence of bile duct injury was reported to be twice as common as in open cholecystectomy[216]. Today, LC is performed in 95% of all elective cases and surgical residents are rarely taught the art of OC[217]. In study IV when comparing the incidence of bile duct injury and/or leakage following cholecystectomy, we found that OC was associated with a higher incidence of bile duct injury than LC. This could be explained by the fact that surgeons are less familiar with the open surgical technique resulting in a higher

complication rate. It could also be argued that selection bias towards open approach, in cases with a predicted difficult operation, might explain a higher incidence of bile duct injury in OC patients. In study IV, after adjusting for ASA classification, age, gender, indication, and operative approach, we found peri-operative haemorrhage to be associated with an increased risk for bile duct injury and/or leakage (OR=2.45, CI 1.79-3.37).

It is known that bleeding distorts visualization during dissection and thereby increases the risk for bile duct injury[213, 218]. However, to the best of our knowledge this is the first time that perioperative bleeding has been shown to be a risk factor for bile duct injury and/or leakage in gallstone surgery. Therefore, upon encountering perioperative haemorrhage, we recommend to judiciously consider conversion to open surgery.

6 CONCLUSIONS

- Thromboembolism prophylaxis (TP) increases the risk for haemorrhage in patients undergoing cholecystectomy.

- VTE is a rare complication following cholecystectomy (0.25%) and the administration of TP should be guided by the presence of risk factors for venous thromboembolism (VTE). Risk factors for postoperative VTE are age>50 years, open surgery, acute cholecystitis, operation time exceeding 120 minutes and concomitant ERCP intervention.

- Cholecystectomy is relatively safe in patients with liver cirrhosis. However, cirrhotic patients have a higher frequency of postoperative complications compared to non-cirrhotic patients. Cholecystitis is a strong risk factor for perioperative haemorrhage in patients with liver cirrhosis (OR=12.8, CI1.29-126.34).

- Male gender, age>40 years, ASA>1, gallstone complication (i.e. cholecystitis and/or pancreatitis), acalculous cholecystitis, open cholecystectomy, TP and prolonged surgery (>120 min) are independent risk factors for haemorrhage in cholecystectomy.

- Comorbidity is associated with increased risk for haemorrhage. These include cerebrovascular disease, previous myocardial infarction, renal disease, heart failure, diabetes, peripheral vascular disease, and obesity.

- Prescription drugs need not be discontinued in the perioperative period solely to reduce the risk of haemorrhage during cholecystectomy.

- Perioperative haemorrhage is associated with an increased risk for bile duct injury/leakage.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Gallsten är vanligt förekommande i Sverige och västvärlden (15%). För c:a 80 % av patienterna förblir gallstenssjukdomen utan symptom (80%), men kan också vara förenad med komplikationer såsom gallstenssmärta, gallsten i djupa gallgången samt medföra inflammation av gallblåsa (kolecystit) och bukspottskörtel (pankreatit). Kirurgisk borttagning av gallblåsan (kolecystektomi) är en av våra vanligaste allmänkirurgiska operationer i Sverige. Av c:a 12,000 operationer/år utförs merparten (95%) med titthålskirurgi (laparoskopi). Alla kirurgiska ingrepp medför en ökad risk för blodproppsbildning (trombos) men nyttan i användandet av blodproppsförebyggande läkemedel (trombosprofylax) i samband med gallstenskirurgi är inte helt klarlagt.

I de fyra studierna som utgör denna avhandling har vi använt oss av det svenska kvalitetsregistret för gallstenskirurgi och ERCP (GallRiks) för att studera frekvens och riskfaktorer för blödning och blodproppsbildning (trombos) efter gallstenskirurgi. I studie I, framkom att det föreligger stora nationella skillnader i användandet av trombosprofylax (TP) och att detta läkemedel medför en ökad risk för blödning i samband med gallstenskirurgi. Då TP medför ökad risk för blödning är det viktigt att identifiera och selektivt behandla patienter med ökad risk för trombosutveckling. I studie II, länkades data från GallRiks med det Svenska Patientregistret för att kartlägga förekomst av trombos i benen (djup ventrombos) och lungorna (lungemboli). Vi fann att den generella förekomsten av trombos är låg (0.25%) efter kolecystektomi samt att patienter över 50 år, med förlängd operations tid (>120 min), efter öppen kirurgi, med pågående kolecystit eller tidigare genomgången trombos löpte störst risk för blodproppsbildning efter gallstenskirurgi.

Det är känt att patienter med skrumplever (lever cirros) har metabola och anatomiska förändringar sekundärt till sin grundsjukdom som medför en ökad risk för komplikationer vid kirurgiska ingrepp. I studie III, fann vi att patienter med cirros inte bara hade en generell högre andel komplikationer, utan också erhöll blodtransfusion efter operationen i större utsträckning än patienter utan cirrhos. I studie IV undersöktes huruvida samsjuklighet (komorbiditet) och/eller förskrivna läkemedel påverkar frekvens av blödningskomplikationer i samband med gallstenskirurgi. Vi fann att cerebrovaskulär sjukdom, tidigare hjärtinfarkt, njursjukdom, hjärtsvikt, diabetes, perifier kärlsjukdom och obesitas var förknippade med ökad risk för blödning. Slutligen, att vanligt föreskrivna läkemedel inte behövs sättas ut innan operationen, då de inte påverkar blödningsrisken.

8 ACKNOWLEDGEMENTS

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10 APPENDIX

In the following results section we present a brief overview (data not previously published) of the use of thromboembolism prophylaxis in Sweden between 2006-2014. TP use over time is shown as well as administration according to type of healthcare service and indication. Finally, we provide a subgroup analysis on the risk for haemorrhage in patients with liver cirrhosis and cholecystitis at the time of surgery.
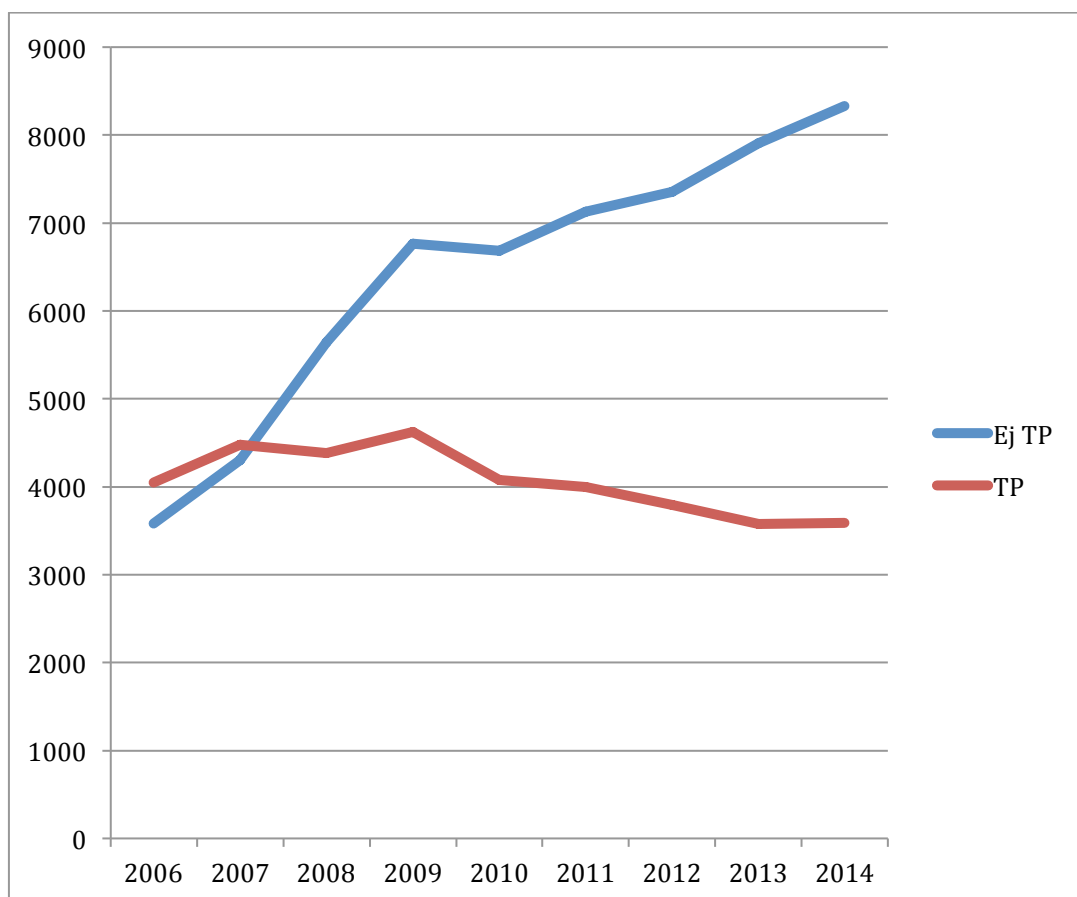
Thromboembolism prophylaxis in Sweden

Figure 8: Number of patients receiving pharmacological thromboembolism prophylaxis (TP) when undergoing cholecystectomy in Sweden 2006-2014.

Thromboembolism prophylaxis according to type of healthcare service and indication

Inpatient

- No TP
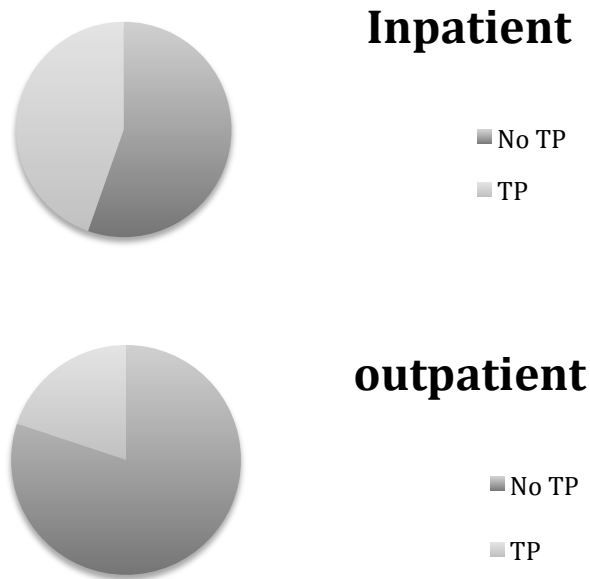- TP

outpatient

- No TP
- TP

Figure 9: Thromboembolism prophylaxis (TP) administered according to healthcare service. Between 2005-2014, 45% of inpatients and 20% of ambulatory patients (outpatient service) received thromboembolism prophylaxis when undergoing cholecystectomy.
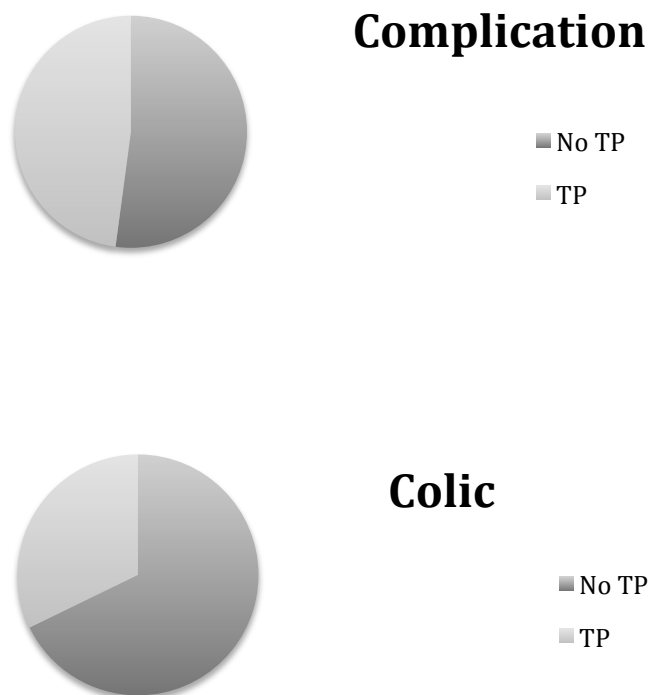
Complication

- No TP
- TP

Colic

- No TP
- TP

Figure 10: Thromboembolism prophylaxis (TP) according to indication. Between 2005-2014, 48% of patients with complicated gallstone disease (e.g. cholecystitis,pancreatitis, jaundice) and 32% of patients with gallstone colic received TP when undergoing cholecystectomy.

Haemorrhagic complications in patients with liver cirrhosis and cholecystitis

Haemorrhage	No CC (n=269) (%)	CC (n=76) (%)	OR	CI	p	OR*	CI	p
Peri-operative	1 (0.4)	5 (6.6)	18.9	2.17-164.13	<0.05	12.8	1.29-126.34	<0.05
Post-operative	5 (1.9)	3 (3.9)	2.2	0.51-9.29	0.25	1.28	0.25-6.52	0.77
Total bleeding	6 (2.2)	8 (10.5)	5.2	1.73-15.36	<0.05	3.25	0.96-11.0	0.058

Table 6: Subanalysis of patient with liver cirrhosis (n=345) and with cholecystitis (n=76).
*Adjusted for gender, age, ASA-classification, surgical approach, operation time and anticoagulant/aggregant drugs, CC-Cholecystitis, CI-Confidence Interval, P-p-value, OR-Odds Ratio.