Faculty of Health Sciences, University of Tromsø – The Arctic University of Norway

The Role of Surgery as a Trigger for Incident Venous Thromboembolism

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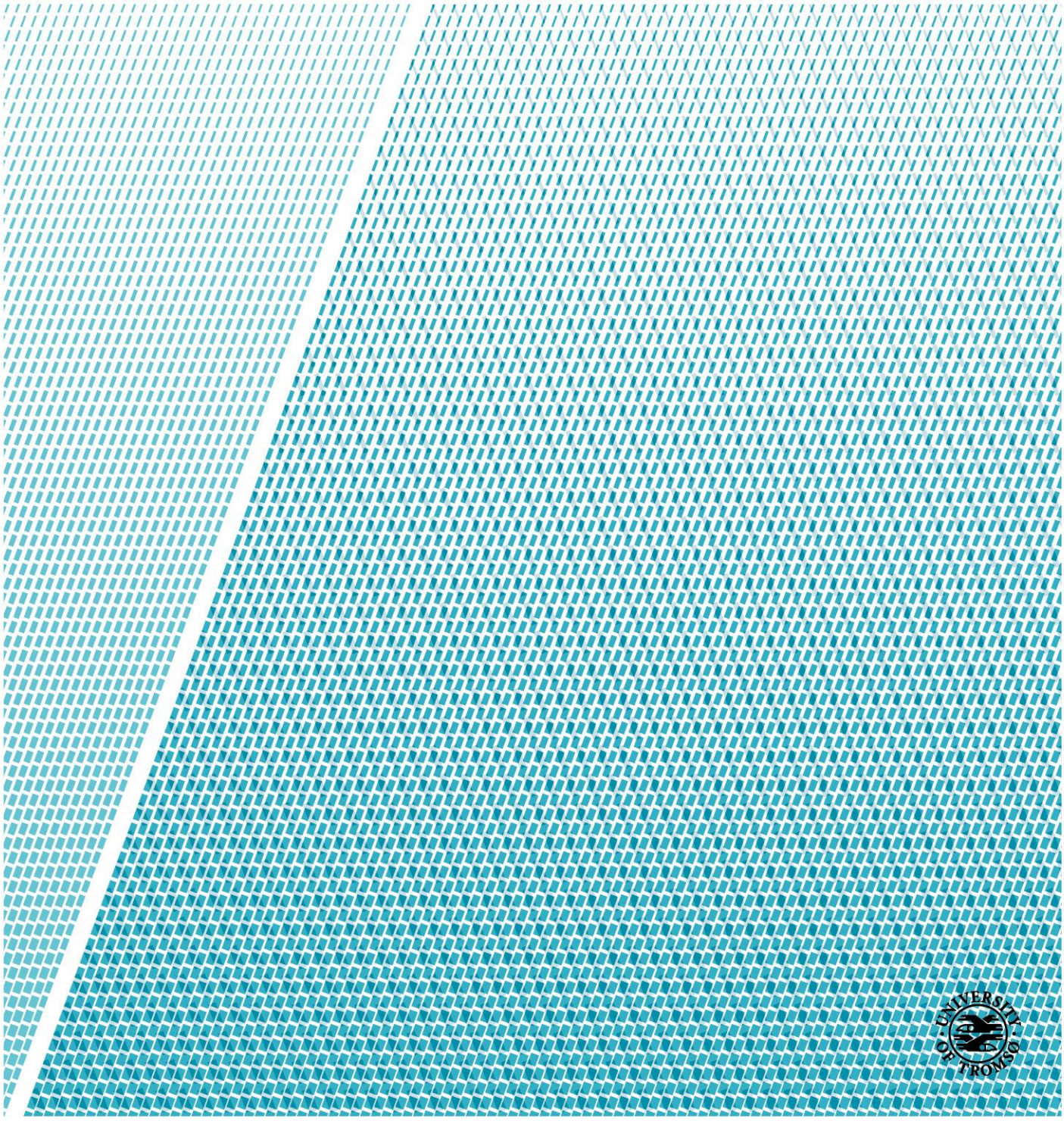

Preface

The aim of this master thesis is to investigate the role of surgery as a trigger for incident venous thromboembolism (VTE) while taking other concomitant VTE triggers into account. I have been a part of K. G. Jebsen – Thrombosis Research and Expertise Center (TREC) since the beginning of 2017, where I have worked with public dissemination. It is through my position at TREC that I have been introduced to the field of thrombosis research. Surgery has been an interest of mine for quite some time, so I have been lucky to be able to conduct my master thesis on both these topics.

The work with this thesis has given me the opportunity to expand my knowledge and has piqued my curiosity, which I am certain will be of great value in my future career. The project was initiated in the fall of 2018 and has been a work in progress until the summer of 2020, when it was concluded. The resources I have used are mainly through the University of Tromsø – The Arctic University of Norway, the University Library and the Tromsø Study. The project was carried out without any funding.

I am immensely thankful to my main supervisor, Vania Morelli, for your academic guidance and for taking the time to share your knowledge with me. I have really appreciated our discussions and your help with finding relevant literature, sculpting and proofreading the thesis. I am also grateful to my co-supervisors, Professor John-Bjarne Hansen and Professor Sigrid Brækkan, for their contributions and for making this project come to life. Additionally, I would like to thank both current and former TREC colleagues for creating such an inspiring and including research environment. I am extremely lucky to know such extraordinary and resourceful people. Being a part of TREC has been a pleasure and a gift.

At last, I am incredibly appreciative to my family for endless support and advice, and for sharing your scientific interest with me. Your achievements and dedication are a great inspiration.

Tromsø, August 2020

Dana Meknas

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Summary

Background: Venous thromboembolism (VTE) is a collective term for deep vein thrombosis and pulmonary embolism. Surgery is a major and well-established transient risk factor (i.e. trigger) for VTE in the general population. However, the impact of major surgery on the risk of VTE has not been thoroughly investigated when other concomitant VTE triggers are also taken into account.

Aim: The aim of this thesis was to investigate the role of major surgery as a trigger for incident VTE using a case-crossover design while adjusting for other VTE triggers.

Methods: A population-based case-crossover study comprising 707 incident VTE cases derived from the Tromsø Study was conducted. Triggers were registered during the 90 days before a VTE event (hazard period) and in four preceding 90-day control periods. Odds ratios (ORs) for VTE was calculated using conditional logistic regression with 95% confidence intervals (CIs) according to the presence of major surgery. A mediation analysis was performed to determine the other VTE triggers' potential to mediate the effect of surgery on VTE risk.

Results: Surgery was registered in 118 (16.7%) of the 707 hazard periods and 88 (3.1%) of the 2828 control periods, yielding an OR for VTE of 6.95 (95% CI: 5.08-9.50). The OR decreased to 2.21 (95% CI: 1.43-3.40) after adjustment for immobilization and infection and was further attenuated to 1.49 (95% CI: 0.92-2.40) when additionally adjusted for trauma, red blood cell transfusion and central venous catheterization. In the mediation analysis, approximately 70% of the total effect of surgery on VTE risk could be mediated through immobilization and infection.

Conclusions: In this case-crossover study, major surgery was a trigger for VTE, but the association between surgery and VTE risk could be largely explained by concomitant factors related to surgery, particularly immobilization and infection.

Abbreviations

ACCP	American College of Chest Physicians
BMI	Body mass index
CI	Confidence interval
CTEPH	Chronic thromboembolic pulmonary hypertension
CVC	Central venous catheter
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
FVL	Factor V Leiden
ICD	International Classification of Diseases
MI	Myocardial infarction
OR	Odds ratio
PE	Pulmonary embolism
PTS	Post-thrombotic syndrome
TF	Tissue factor
VTE	Venous thromboembolism
vWF	von Willebrand factor
WHO	World Health Organization

1 Introduction

1.1 Venous thromboembolism and surgery

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease, after myocardial infarction (MI) and stroke (1). VTE has become a major problem for public health due to its serious short- and long-term complications, including death, recurrence, post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) (2). Despite improved awareness and advances in thromboprophylaxis, time trend studies have shown that the incidence of VTE has slightly increased over the past decades (3-5). It is likely that the incidence of VTE will continue to rise since major risk factors for VTE, such as advancing age, obesity and the incidence of cancer, are increasing in the population (6-8). Surgery is also known to be a major risk factor for VTE (9). Data from several population-based cohort studies have shown that 15-22% of incident VTEs are associated with surgery (4, 10, 11), and the risk of VTE attributed to surgery has increased during the last years (12).

The pathophysiology underlying the VTE risk after surgery is not fully understood and probably involves multiple coexisting mechanisms. For instance, several mechanisms directly related to surgery have been proposed, including vessel wall damage (13), changes in the concentration of hemostatic factors (14, 15), inflammation (16), increased concentration of extracellular vesicles (17) and activation of platelets (18, 19). Additionally, the association between surgery and VTE may be explained by indirect mechanisms, since after surgery patients may be subjected to hospitalization and immobilization, which could in turn increase the risk of VTE (20). It has not been thoroughly examined to what extent surgery serves as a trigger for VTE beyond other well-established VTE triggers. Enhanced knowledge on how surgery affects the VTE risk is clinically relevant since it may provide opportunity for targeted interventions to improve the prevention of VTE after surgery.

The aim of the present thesis was to investigate the role of surgery as a trigger for incident VTE using a case-crossover study while taking other concomitant VTE triggers into account. This study design was chosen because it is suitable for investigating the effects of transient exposures, such as surgery, on acute outcomes, like VTE (21). In the case-crossover study,

participants serve as their own controls, and all potential fixed confounders are largely controlled for through the study design.

1.2 Venous thromboembolism

1.2.1 Epidemiology of venous thromboembolism

VTE, encompassing DVT and PE, is a common disease, occurring in 1-2 per 1000 individuals in the population annually (2). DVT is a condition where a blood clot is formed in the deep veins of the body, most commonly in the large vessels of the legs, as illustrated in Figure 1A, but it can also occur in the upper extremities, cerebral and abdominal veins (22). Common signs and symptoms of DVT include pain, swelling and erythema in the affected limb (23).

PE occurs when parts of the blood clot break away, travel to the lungs, and lodge, such as in Figure 1B, blocking a pulmonary artery, in some cases causing circulatory collapse and death. A PE usually presents with dyspnea, tachypnea, chest pain, tachycardia, cough, hemoptysis, syncope and possibly even death (23, 24). In fact, 25% of all PE cases may present as sudden death (25, 26).

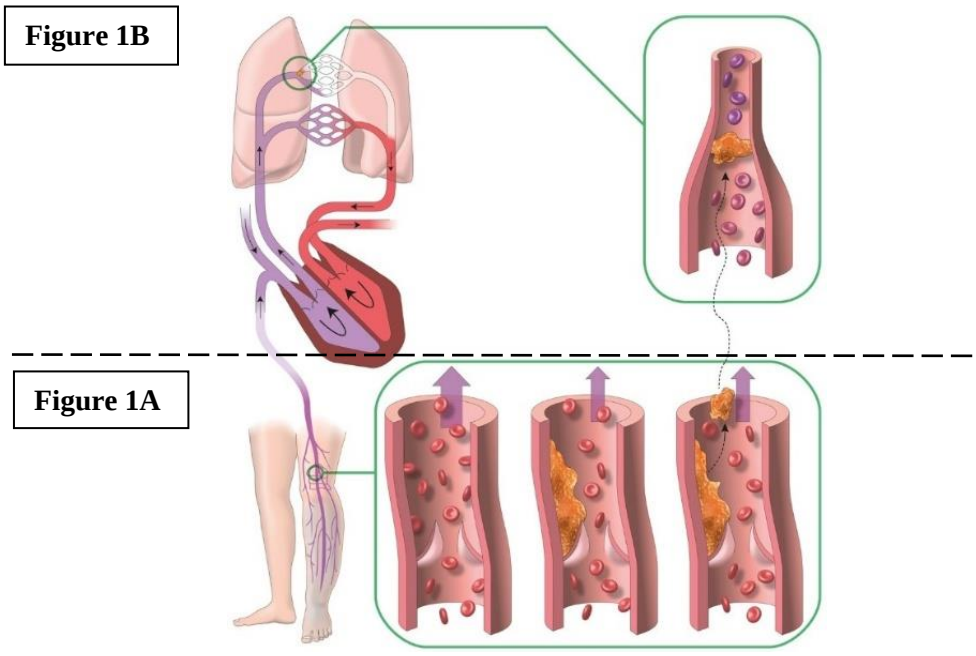

Figure 1A and 1B: Deep vein thrombosis is a condition where a blood clot is formed in the deep veins of the body, most commonly in the large vessels of the legs **(Fig. 1A)**. Pulmonary embolism is a subsequent event of DVT, where embolization causes a part of the original clot to travel to the lungs via the pulmonary circulation (**Fig. 1B)**. Illustration by Roy Lysså.

DVT accounts for around two-thirds of the VTE cases, and PE for one third (27), even though more recent data using sensitive imaging modalities for PE detection point towards an equal distribution of DVT and PE (28). There is over one million VTE events annually in Europe and 540,000 VTE-related deaths, with sudden fatal PE causing 34% of all VTE-related deaths (2). VTE affects both men and women at all ages, even though the incidence increases exponentially with age (4, 10, 29). Ethnicity also seems to play a role in the incidence of VTE, where Caucasians and African-Americans have a particularly elevated risk of VTE compared to Hispanics and Asian-Pacific Islanders (27, 30). Moreover, African-Americans have been reported to be at the highest risk of VTE of all ethnicities (30-32), also in regard to postoperative VTE (33, 34).

VTE is a major public health concern, not only because of the rates of death, but also due to its long-term complications (35). Several studies have been conducted on the recurrence of VTE, showing a cumulative incidence of recurrence around 30% after 10 years (36-38), which is considered a high risk. Studies have consistently shown that patients whose first VTE event is not triggered by transient factors such as surgery, are at a higher risk of recurrence (37).

PTS is another common complication of VTE. This is a collective term for clinical signs and symptoms that occur due to chronic venous insufficiency following a DVT (39). In a Canadian prospective, multicenter cohort study approximately 40% of the patients experienced PTS during the two year-period after a DVT (40). Other studies with similar follow up-time have estimated the frequency to be 20-50% (41, 42). In addition to being an economical burden for the society, the patient may suffer from pain, swelling, heaviness and ulcers from the affected limb, ultimately leading to a reduced quality of life (39).

CTEPH is a complication seen after PE. A meta-analysis revealed a pooled incidence of CTEPH of 0.56% during a follow-up of 2-3 years, increasing to 3.2% within eight years of follow-up (43). Although the incidence of CTEPH is relatively low, a substantial proportion of patients suffer from shortness of breath and attenuated physical capacity (44).

1.2.2 Pathophysiology of venous thromboembolism

It is essential to be familiar with Virchow's triad (Figure 2) in order to understand the pathogenesis behind the formation of venous thrombosis (45). The three factors in the triad are stasis, hypercoagulability and vessel wall changes, representing the systems that are disturbed, leading to a VTE (13). Stasis indicates a change in blood flow and hypercoagulability is a

change in blood composition. Vessel wall changes occur in the endothelium of the vessel wall. The endothelium remains intact but is converted from a surface with anticoagulant properties to one with procoagulant properties.

Figure 2

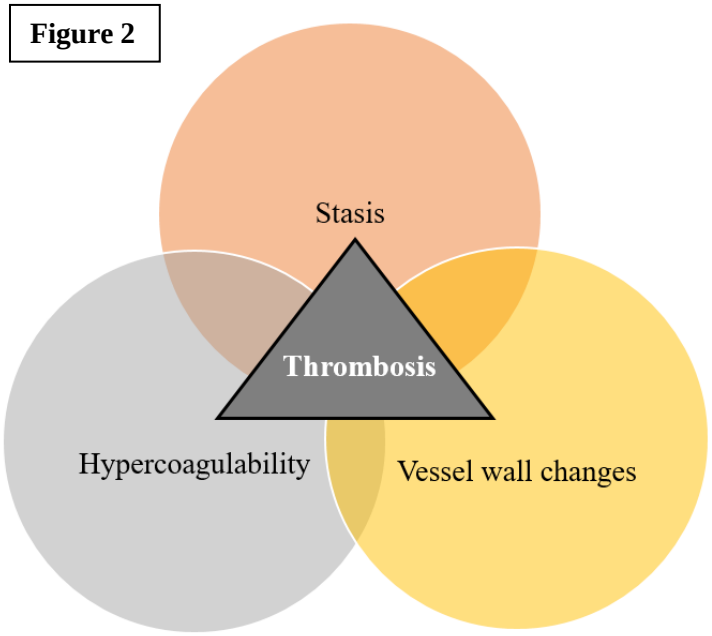

Figure 2: Virchow's triad is comprised of three factors: Stasis, hypercoagulability and vessel wall changes. The triad is essential in order to understand the pathogenesis behind the formation of a thrombus.

The venous thrombus most often arises in relation to the valvular sinuses, where the blood flow is characterized by a vortical pattern with low oxygen tension (46). This is illustrated in Figure 3. This hypoxic condition triggers the activation of endothelial cells and shifts the environment in the vein into a proinflammatory and procoagulant state (13).

Figure 3

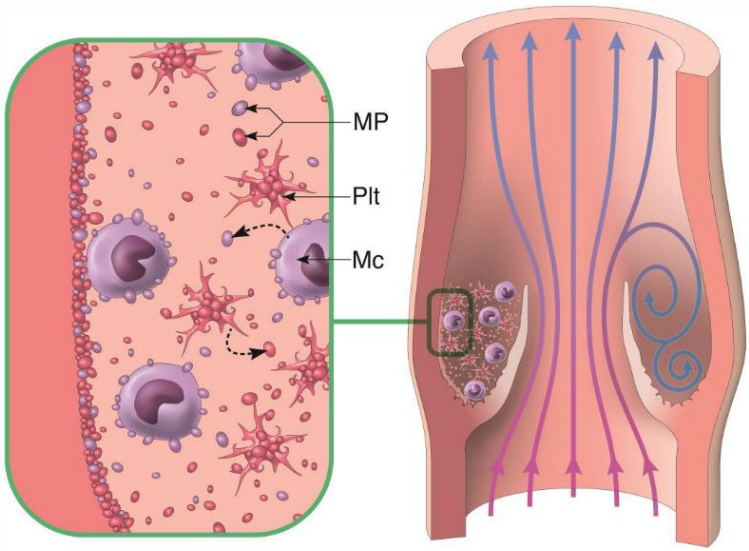

Figure 3: Proposed mechanism of thrombus formation. Hypoxic conditions due to vortical blood flow in the valvular sinuses trigger the activation of endothelial cells. Leukocytes, such as monocytes (Mc), and platelets (Plt) are recruited. These cells shed microparticles (MP) that are tissue factor-positive. This process may lead to the formation of a thrombus. Illustration by Roy Lyså.

1.2.3 Risk factors for venous thromboembolism

Until the 1990s, VTE was mainly considered a complication of major surgery (47). Today we know that VTE is a complex, multifactorial disease with many established risk factors (48, 49). These are usually split into two groups: acquired risk factors and genetic risk factors. A risk factor is a characteristic, in the presence of which, the probability of developing disease is higher than in its absence (50). Risk factors can be genetic, acquired or a mixture of such origins. When the factor is transient, increasing the risk of disease in the short-term, it can be called a trigger. Table 1 sums up the most relevant risk factors known for VTE (48, 50).

Surgery, and more specifically, **major surgery,** is one of the acknowledged risk factors for VTE and will be discussed in detail in section 1.3.

Table 1: Risk factors for venous thromboembolism

Acquired	Genetic	Mixed
Age	Antithrombin deficiency	Elevated levels of von Willebrand factor
Obesity	Protein C deficiency	Elevated levels of factor VIII
Acute medical conditions (MI, stroke, infections)	Protein S deficiency	Elevated levels of factor IX
Cancer	ABO (non-O blood type)	Elevated levels of factor XI
Antiphospholipid syndrome	Factor V Leiden	
Surgery	Prothrombin G20210A	
Immobilization	Fibrinogen gamma gene (FGG) – C10034T	
Central venous catheter		
Blood transfusion		
Trauma		
Pregnancy/puerperium		
Hormone therapy (oral contraceptives, hormone replacement therapy)		

Abbreviations: MI, myocardial infarction.

Adapted from Rosendaal FR (48).

Acquired risk factors

Many risk factors for VTE have been acknowledged through the years, such as age, obesity, cancer, acute medical illness (infection, cardiovascular disease, etc.), major surgery, immobilization, pregnancy and oral contraceptives (48, 50-52). Some of these, like surgery, are considered provoking factors, whilst others, like age, are not (53). An unprovoked VTE is one that is not caused by an important transient factor (e.g. surgery and trauma) or a persistent provoking factor (e.g. cancer). Whether a VTE is provoked or not has important clinical implications related to risk of recurrence and treatment duration with anticoagulants (54).

Age is known to be among of the strongest risk factors for VTE, and with increasing age, the incidence of thrombosis increases exponentially (4, 10, 51, 55). Studies have shown that age as a risk factor is responsible for 70-90% of all VTE events in the population (12, 56). Many explanations for this have been postulated, including increased hypercoagulability (56), body mass index (BMI) (57), immobilization (58) and co-morbidity (57). Data from the Tromsø Study suggest that this increased risk cannot, however, be explained by a higher incidence of cancer in the elderly (59).

Obesity is an important risk factor for many diseases, including VTE. The World Health Organization (WHO) defines obesity as a BMI of 30 kg/m^2 or more (60). It has been shown that obese subjects have a 2- to 3-fold increased risk of VTE compared with normal weight subjects, and that the risk increases linearly with BMI (61, 62). Obesity was reported to account for about 30% of the unprovoked VTE cases in the community (12). Different measurements of obesity that reflect both central obesity (waist circumference and waist-hip ratio) and peripheral obesity (hip circumference) are associated with VTE (63). In particular, waist circumference has been shown to be the measure yielding the highest risk estimates for VTE and identifying the most patients at risk of VTE (64).

Cancer has repeatedly been proven to be strongly associated with VTE, and as much as 20-30% of all first VTE events are associated with cancer (65). In fact, thrombosis can be the first sign that cancer is present (65). Researchers have found that cancer patients have a 4- to 7-fold increased risk of thromboembolic disease, and that they have an increased risk of recurrent thrombosis. The cancer types that are more strongly associated with VTE risk are brain cancer, pancreatic cancer, lung cancer and hematological malignancies (66).

Acute medical conditions, such as myocardial infarction (MI), ischemic stroke, respiratory disease and infections, are also known to increase the risk of VTE by different mechanisms (20, 67-70). In some cases, the association is partly mediated through immobilization, which is another recognized risk factor for VTE (20, 55). Other established risk factors associated with medical illness and hospitalization are **central venous catheters (CVCs)** and **blood transfusions** (71). Patients who are admitted because of **trauma** are also at an increased risk of VTE, and the incidence of thrombosis increases with the severity of the injury (72).

Pregnancy, **puerperium**, **oral contraceptives** and **hormone replacement therapy** are all established risk factors for VTE in women (51, 71, 73, 74).

Genetic risk factors

As already stated, VTE is a multicausal disease in which both acquired and genetic risk factors play important roles (52). A large Swedish sibling-study conducted by Zoller et al. reported 40-47% heritability for VTE (75). Other studies have shown variations in heritability ranging from 35 to 60% (76). Until 2015, researchers have identified 17 genetic variants that are particularly relevant to the VTE risk (77). The genetic risk factors can be classified as strong, moderate or weak according to the strength of their association with VTE (78). The risk factors that are considered strong increase the VTE risk 5-10-fold, and examples of these are deficiencies of **antithrombin**, **protein C** and **protein S** (78), which are natural anticoagulants of the hemostatic system. Moderately strong risk factors increase the risk 2-5-fold and include **non-O blood type** and single nucleotide polymorphisms (SNPs) in genes encoding coagulation factors, like **Factor V Leiden (*F5*, G1691A)**, **prothrombin G20210A *(F2)*** and the **C10034T SNP** in the **fibrinogen gamma gene (*FGG*)** (78). There are several weak risk factors which increase the risk maximum 1.5-fold (78).

The most common genetic risk factor for VTE in the Caucasian general population is the non-O blood type, with a prevalence of 50-60% (76, 79). For the other genetic risk factors, the prevalence in the population varies from less than 1%, as in the deficiencies of antithrombin, protein C and protein S (78), to 5 and 6% for the Factor V Leiden (76) and the *FGG* C10034T (78), respectively. The prevalence of prothrombin G20210A varies largely based on ethnicity, as it occurs in 1-8% in a healthy, Caucasian population, but it is more rare in Northern European countries and almost absent in non-Caucasians (Asian, African, American, Australian) (80).

Some risk factors have both acquired and genetic determinants and can be placed in the category "mixed", as demonstrated in Table 1. An example is elevated levels of the coagulation factors, which may be the result of subtle changes in their concentration due to genetic factors (52). Concurrently, acquired factors may also affect the concentration of these factors (52). This includes the **von Willebrand factor** (vWF), **factor VIII** (FVIII), **factor IX** (FIX) and **factor XI** (FXI) (78, 81-83). High levels of one of these factors can lead to a tendency of thrombosis (78, 81-83). A recent study found that out of all the coagulation factors, vWF and FVIII were associated with the highest VTE risk (84). Elevation of one or more of these procoagulant factors due to surgery might be a possible explanation of the mechanism behind surgery-related thrombosis. A more detailed description of this mechanism can be found in section 1.3.5.

Even though several risk factors for VTE have been identified, 25-50% of all VTE events have no identifiable risk factor and are considered idiopathic (27). Further research is therefore necessary to discover novel factors in order to improve treatment and prevention of VTE.

1.3 Surgery

1.3.1 Historical aspects

Surgery has existed among humans for hundreds and thousands of years. Already 5000 years BCE there is evidence of human skulls which were exposed to trepanation – modern day burr holes (85). The reason for this procedure is unknown. Some assume it was for ritual purposes, others that it might have had medical benefits. Nevertheless, it is presumed that many of the first procedures performed in the early days were religiously or culturally motivated, and they were associated with high rates of complications, such as infections, bleeding and death (85). Medicine has come a long way since then. In 1735, Claudius Amyand performed the first successful appendectomy, and almost 200 years later, in 1925, the first open heart surgery was performed by Henry Souttar (86, 87). Even though the many learned lessons along the way have led to massive progression, there are still many challenges when it comes to surgery. The development of other areas within the medical field, such as the introduction of imaging modalities and the use of antibiotics as antisepsis measurements, have also been crucial for advances within the surgical field (88, 89).

1.3.2 Definition of major surgery in the literature

Surgery is the use of operative techniques for exploratory (diagnostic) or therapeutic purposes, and can be elective, i.e. planned, or urgent, as in an acute setting. Surgery can further be defined as either minor or major. The present thesis is focused on major surgery, since VTE risk is mainly associated with major procedures, although studies have shown that some minor surgeries can also be associated with an increased risk of VTE (53).

There is *per se* no clear-cut definition or well-defined criteria for major surgery. Although the term is frequently used, it is poorly defined. Already in 1917, Dr. Robert Earl highlighted the issue and raised the question of what the term "major surgery" actually included (90). The reply he got from the editor of *Annals of Surgery* at the time stated that his understanding of the definition included "all work requiring general anesthesia, operations involving openings into the great cavities of the body, procedures running a risk of severe hemorrhage, conditions where the life of the patient is at stake or which require special anatomical knowledge and manipulative skill" – although he admitted that this was a rather general statement (90).

In 1965, Small and Witt conducted a survey among surgeons in America in order to define criteria of major surgery (91). They included twelve variables that could be scored from 1-5, where a higher score indicated a larger surgery, and all procedures >25 points were considered major surgery. The scale included mortality and potential morbidity, amount of trauma, extent of dissection, duration of operation, type of anesthesia, patient status and expertise needed, among other variables (91).

The John Hopkins surgery risk classification system was published in 1996, when R. Pasternak developed a risk assessment system (92). It was originally meant as an aid in the preanesthetic evaluation of the surgical patient, independent of the patient's preoperative medical conditions and type of anesthesia. The classification split operations into five categories (1-5) based on the invasiveness of the surgical procedure and physiologic factors. A modified version of this classification system also exists (93). There have not been published any attempts of definitions or criteria since.

However, at the beginning of 2020, the European Surgical Association (ESA) Members published an article where they aimed to reach consensus on a definition of major surgery (94). They found that severe comorbidity was repetitively agreed upon as a patient-related factor linked to major surgery. Of the procedure-related factors, vascular clampage or organ ischemia,

high intraoperative blood loss, intraoperative vasopressor support, perioperative blood transfusion and long operative time were the parameters that reached consensus. No cut-off could be defined for procedure duration required for it to be classified as a major procedure. Long hospital stay was agreed upon as a criterion by half of the experts and did not reach consensus. Among factors related to the postoperative period, morbidity, mortality and the need for intensive or intermediate care were the most important factors related to major surgery (94).

A reason why it might be so challenging to classify a procedure as major or minor could be due to the fact that there are several factors apart from the procedure itself which determine its complexity. Such factors could be patient characteristics or peri- and postoperative complications, as previously exemplified.

1.3.3 Attempt to narrow the definition of major surgery

Since the definition of major surgery is not well established, it is necessary to look to different individual studies and guidelines in order to evaluate their included surgical procedures when describing major surgery (95). Alternatively, it is possible to look to consensus-based definitions. **In general, major surgery is defined as surgery associated with significant fluid loss (96) and typically, at least one night in the hospital (92).** Experts are divided in their opinion on the volume of blood loss required for the procedure to be categorized as a major surgery, ranging from >500 mL to >1000 mL (94), or even >1500 (93). This is also true for the length of the hospital stay (97). The duration of the surgery is an important parameter when defining its complexity. **With this regard, a major surgery is any intra-abdominal surgery or other major surgical procedure lasting >45 minutes (98), although some authors define it as procedures requiring general anesthesia for more than 30 minutes (47, 53, 54).** Several procedures within orthopedic surgery, vascular surgery, neurosurgery and cardiothoracic surgery are included in the definition of major surgery (see Table 2 for a more detailed description). Some procedures within gastrointestinal surgery, urology, gynecology and plastic surgery are also included in this definition (99). Major surgery is generally considered a strong risk factor for VTE (47). Procedures such as arthroscopic knee surgery, on the other hand, are considered moderate risk factors, and some laparoscopic procedures are even regarded weak risk factors (47, 100). It is noteworthy that for orthopedic procedures, even minor procedures such as arthroscopy affect the VTE risk to some degree (48). Additionally, some argue that even though lower than for open procedures, some degree of hypercoagulability is still observed

in laparoscopy, hence there is an ongoing debate on the definition of this particular type of surgery (47, 100-103). Finally, cancer surgery is somewhat different because cancer patients have an overall increased risk of VTE, so the procedure risk is affected by the disease (99, 104).

Table 2: Classification of major and minor surgery by surgical specialty with examples of procedures

Surgical specialty	Minor surgery	Major surgery
Orthopedic surgery	Arthroscopy (105, 106)	Hip arthroplasty (99, 105-107)
		Knee arthroplasty (99, 105-107)
		Hip fracture surgery (99, 105-107)
Vascular surgery	Varicose vein excision (99)	Abdominal aorta aneurism repair (open or endovascular) (94, 99, 108)
		Amputation (99)
		Placement of peripheral vascular shunt (99)
		Bypass of the aorta, femoral or popliteal arteries (99)
Neurosurgery	Spinal surgery with no additional risk factors (97)	Craniotomy (97), intracranial surgery
		Spinal surgery if malignancy or combined anterior-posterior approach (109)
Cardiothoracic surgery	Bronchoscopy (93)	Coronary artery bypass (47, 108)
		Pulmonary lobectomy (94), pulmonary resection (109)
Gastrointestinal surgery	Small bowel resection (94)	Low anterior rectal resection (94)
	Rectopexy (94)	
	Stoma closure (94)	Bariatric surgery (109)
	Laparoscopic cholecystectomy (99, 103)	
Urology	Transurethral surgery (110, 111)	Kidney transplantation (94)
	Laparoscopic procedures (110)	Radial cystectomy (110)
Gynecology	Vaginal resection (106)	Hysterectomy (111)
	Benign laparoscopic surgery (112)	
	Tubal ligation (111)	
Head and neck	Thyroid or parathyroid surgery (94, 99)	Maxillary or mandibular osteotomy (113)
	Sinus surgery (99)	

1.3.4 Epidemiology of surgery-related VTE

In the general population, around 1-2 per 1000 individuals suffer from VTE every year (2). However, this incidence can increase up to 8 per 1000 individuals in surgical patients (16). Data from the Tromsø study, a Norwegian population-based cohort, revealed that approximately

15% of the incident VTE events are related to surgery (4). Another community-based study showed that institutionalization (i.e. hospitalization or nursing home confinement) accounts for a large portion of incident VTE cases, and that in fact 24% of these VTE events could be attributed to surgery (74). A recent study involving a population-based cohort in the United States suggests that the increasing prevalence of surgical procedures, in addition to cancer and obesity, could partly explain the persistent incidence of VTE in the community (12). In a study by Samama et al., it has been shown that recent surgery is among the clinical situations associated with the highest risk of VTE, together with medical conditions (e.g. myocardial infarction, congestive heart failure and chronic obstructive pulmonary disease), immobilization and cancer (114). The estimated risk of VTE can be up to 22-fold increased in patients undergoing major surgery (114, 115). Factors that have been shown to increase the risk of VTE in the surgical setting include open procedures, malignancy, increased age, general anesthesia and duration of the procedure (116).

The VTE incidence varies with the different kinds of surgical procedures (99, 117). Table 3 shows the incidence proportion of VTE according to several surgical specialties. As presented in the table, orthopedic surgery is associated with an especially high risk of VTE during the 91-day period after surgery in comparison to other types of surgery (e.g. gastrointestinal, urologic and gynecological procedures). Therefore, separate guidelines for thromboprophylaxis have been developed when it comes to orthopedic surgery (105).

In a prospective cohort study comprising middle aged women in the United Kingdom (Million Women Study), Sweetland et al. reported that compared with not having surgery, women were 70 times more likely to be admitted with a VTE in the first six weeks after an inpatient surgery (9). The same study showed that the risk of VTE was lower, but still substantially increased 7-12 weeks after surgery. Such findings highlight that patients undergoing a surgical procedure can still be at risk of VTE after hospital discharge. Another study showed that approximately two-thirds of VTEs occurred in the outpatient setting, and that 23% of these patients had undergone surgery during the preceding 90 days (118).

Table 3: Incidence proportion of venous thromboembolism by surgical specialty during the 91-day period after surgery

Surgical specialty	Incidence proportion (%)
Orthopedic	1.2
Vascular	1.1
Neurosurgery	0.8
Cardiothoracic	0.7
Gastrointestinal	0.4
Urology	0.3
Gynecology	0.3
Head and neck	0.1

Adapted from White et al. (99).

Surgery and thromboprophylaxis

Thromboprophylaxis is used in patients at risk for thrombosis and mainly consists of anticoagulation. Heparin (low-molecular-weight heparin and unfractionated heparin) and, more recently, the DOACs (Directs Oral Anticoagulants) (105, 109) are among the most commonly used anticoagulant medications for thromboprophylaxis. When pharmacological measures are not sufficient or contraindicated, mechanical prophylaxis, such as elastic compression stockings, intermittent pneumatic compression or sequential compression device, may be used (105, 109). In addition to type of surgery and duration, postoperative complications and bleeding risk are also factors taken into account when considering the use of thromboprophylaxis after surgery. For instance, intracranial surgery can be a relative contraindication to anticoagulants due to the increased bleeding risk (47), and in this case, mechanical prophylaxis with intermittent compression can be indicated.

Older studies comparing patient groups at risk for VTE show that there is a clear difference in the occurrence of VTE in patients who receive thromboprophylaxis versus the ones who do not (48, 119-121). Rosendaal summarized the risk of VTE after surgery taking into account studies published in the 1970s and 1980s. The author reported that in this period, the risk of VTE in the absence of prophylaxis ranged from 30-50% among different specialties (48). A prospective, double-blinded, randomized trial in surgical patients revealed a frequency of VTE of only 8% in the group of patients receiving heparin versus 42% in the control group receiving

placebo, a difference which was statistically significant (119). Similar results have been found in clinical trials investigating the frequency of PE and PE as a cause of death in surgical patients (120). A review of 70 randomized trials including 16,000 patients undergoing general, orthopedic or urologic surgery concluded that the use of perioperative pharmacological prophylaxis (subcutaneous heparin) significantly reduced the risk of VTE (121). In fact, it was demonstrated that the use of prophylaxis could reduce half of all the PE events and two-thirds of the DVTs, in addition to a significant reduction in total mortality (121). These studies, among others, have led to the development of recommendations for routine thromboprophylaxis in surgical patients. The American College of Chest Physicians (ACCP) published their first set of guidelines in 1992 (122) and since then the ACCP has published nine editions of the guideline. Other guidelines and recommendations for perioperative thromboprophylaxis have also been developed and updated throughout the years (97, 108, 113, 123-126). It is noteworthy that most of the guidelines are coherent on the postoperative use of thromboprophylaxis immediately after surgery and as long as the patient is exposed to reduced mobility (typically 3-7 days). However, the evidence for extended thromboprophylaxis duration beyond this is variable, and sometimes weak, with some guidelines recommending prophylaxis up to 35 days after surgery or after discharge of surgical patients (113, 125, 127).

In summary, it has been shown that the use of thromboprophylaxis can reduce the relative risk of postoperative DVT by up to 75% (128). Even though the findings are so convincing, data from the ENDORSE survey (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) reported that globally more than 40% of patients admitted to surgical wards, who are at risk of developing DVT, do not receive ACCP-recommended VTE prophylaxis (128, 129). This is in line with the findings of other studies (107, 130-132), supporting the need of improvement in this field.

The current underuse of thromboprophylaxis by clinicians could be due to bleeding risk concern. In order to guide clinicians in their decision-making on thromboprophylaxis (e.g. decisions on type, duration and dosage of pharmacological prophylaxis), risk assessment models for VTE risk have been developed. The Modified Caprini Risk Assessment Model is a prediction model developed for stratifying VTE risk in surgical patients (Table 4) (109). The model takes into account comorbidities, demographics and even genetic factors, as well as recent surgery and trauma. When interpreting the score, a score of 1-2 points represents a low risk, a score of 3-4 points represents a moderate risk, and ≥5 points is associated with a high

VTE risk (109). There are other risk assessment models for VTE, such as the Padua Prediction Score (133), which was designed to assess VTE risk in hospitalized medical patients.

Table 4: Modified Caprini Risk Assessment Model

Risk score			
1 point	**2 points**	**3 points**	**5 points**
Age 41 to 60 years	Age 61 to 74 years	Age >75 years	Stroke (<1 month)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m2	Major open surgery (>45 minutes)	Family history of VTE	Hip, pelvis or leg fracture
Swollen legs	Malignancy	Factor V Leiden	Acute spinal cord injury (<1 month)
Varicose veins	Confined to bed (>72 hours)	Prothrombin 20210A	
Pregnancy or postpartum	Immobilizing plaster cast	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Central venous access	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement		Elevated serum homocysteine	
Sepsis (<1 month)		Heparin-induced thrombocytopenia	
Serous lung disease, including pneumonia (<1 month)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (<1 month)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Abbreviations: BMI, body mass index.

Adapted from Gould MK et al. (109).

1.3.5 Mechanisms of VTE by surgery

Even though the association between surgery and VTE is well-established, the mechanisms underlying the association are not fully elucidated. Several mechanisms have been proposed in

order to explain the association between surgery and VTE. This can be through both direct and indirect mechanisms (Figure 4). Direct mechanisms can be regarded as those mechanisms directly related to the surgical procedures, such as tissue damage and vessel wall trauma. Indirect mechanisms can be seen as complications related to the surgery (e.g. acute infection and immobilization) that have the potential to increase the risk of VTE, thereby acting as mediators of the VTE risk in surgical patients (Figure 4).

Figure 4

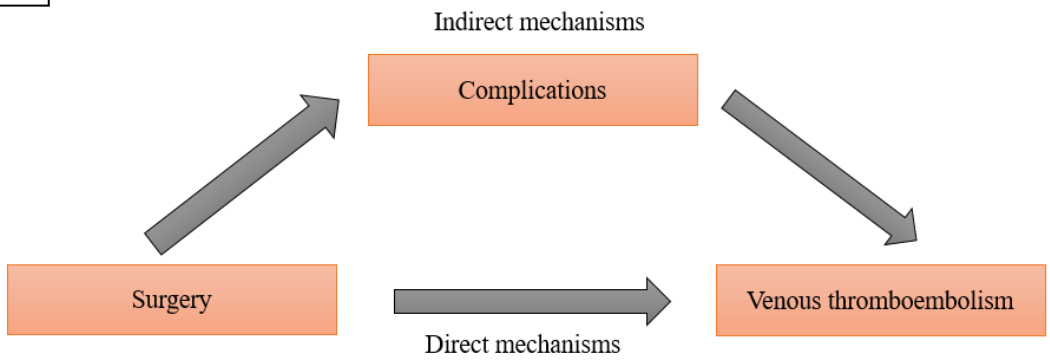

Figure 4: The potential association between surgery and venous thromboembolism can be through direct mechanisms, which are a direct consequence of the surgical procedure, or indirect mechanisms, i.e. complications related to the surgery.

Potential direct mechanisms

The surgery itself is traumatic for the tissue and could lead to VTE due to vessel wall changes, one of the factors in Virchow's triad (see Figure 2). In some types of surgery, like hip and knee surgery, damage to the veins, and also stasis, are considered major contributors to the VTE occurrence (134). In the case of surgery or trauma, the endothelium is disrupted, leading to exposure of tissue factor (TF). TF is the main trigger of blood coagulation *in vivo* (135), and its exposure to the blood may lead to venous thrombus formation (135). Researchers have found that TF is increased after both tumor removal surgery and total knee arthroplasty (14, 136), leading to hypercoagulability.

Hypercoagulability due to increased levels of procoagulant factors can be another direct mechanism of VTE by surgery. It is known that surgery is associated with an increased activation of the coagulation system postoperatively (15). Platelet activity and levels of coagulation factor VIII, vWF and fibrinogen are reported to significantly increase after surgery

(19, 137). Researchers have also found a postoperative change in the level of coagulation factor VII, as well as in products of activation of blood coagulation and fibrinolysis, such as prothrombin fragment 1 + 2, thrombin-antithrombin complexes and D-dimer (15, 138).

Exposure of TF is related to the activation of the coagulation cascade (135). TF can be exposed through inflammatory cells (e.g. monocytes) when stimulated by proinflammatory cytokines, linking inflammation to coagulation (135). Inflammation as a consequence of surgery can be a plausible mechanism explaining surgery-related thrombosis. Manipulation of the tissues, such as done in surgery, can trigger both local and systemic inflammation, which in turn might lead to endothelial dysfunction, upregulation of TF, activation of the coagulation system and a hypercoagulable state (16), such as described in Virchow's triad.

Interestingly, several cytokines related to thrombosis in epidemiological studies are markedly increased after surgical procedures (16). A systematic review, mainly based on case-control studies, suggests that elevated plasma levels of **interleukin 6 (IL-6), interleukin 8 (IL-8), Monocyte Chemoattractant Protein-1 (MCP-1)** and **tumor necrosis factor a (TNFa)** are associated with an increased risk of VTE (139). Some of these proinflammatory cytokines, including **IL-6, IL-8 and TNFa**, have been reported to increase postoperatively, and researchers have even described this as a cytokine "storm" following surgery (16). Another proposed mechanism for VTE risk in surgery is the generation of microparticles carrying TF (16, 18). It has been shown that monocytes, which shed microparticles that are TF-positive, are recruited and activated in the postoperative setting (14). Microparticles and their procoagulant effect have been studied and found to be increased in patients undergoing surgery (17, 140).

Potential indirect mechanisms

Regarding the indirect mechanisms, these are mechanisms related to the hospitalization, immobilization and medical complications after surgery, such as infections. Hospitalization itself seems to increase the risk of VTE. As demonstrated in a study from Heit et al., the incidence of in-hospital VTE is about 100 times greater than community acquired VTE, and one third of the VTE cases in the community occurred in recently hospitalized patients (141). A case-control study showed that hospitalization increased the risk of VTE by 8-fold and was an independent and important risk factor for VTE (115). Bjøri et al., using a population-based case-crossover study derived from the Tromsø study, have recently demonstrated that hospitalization is a major trigger for VTE, especially in the presence of immobilization (142),

which is also a well-established risk factor for VTE. Immobilization may lead to venous stasis and reduced blood flow, which is one of the proposed mechanisms for venous thrombus formation, as described in Virchow's triad presented in Figure 2 (13, 46).

Medical complications can arise after surgery, and infection stands out as one of the most problematic postoperative complications. Clinical practice guidelines for antimicrobial prophylaxis in surgery have been developed to combat this issue (143). Yet, this is still a major concern (144). Infection is associated with an increased risk of VTE in epidemiological studies (20, 71, 145-148). Using a case-crossover study derived from the Tromsø Study, Grimnes et al. showed that the risk of VTE after acute infection was 24-fold increased, and the risk remained substantially elevated even after adjustment for immobilization (20). Studies investigating VTE risk in surgical patients report that both infection and immobilization increase the risk significantly. Some claim that postoperative infection is one of the strongest positive predictors of VTE (149, 150). Wound infection, surgical site infection, pneumonia, urinary tract infections and other infections are among the postoperative complications associated with an increased VTE risk (151-154). Immobility is also among the clinical factors that predict the incidence and risk of VTE after different surgical procedures (155-157). One cohort analysis found that length of hospital stay for 5 days or more after surgery was a risk factor for VTE, increasing the risk more than 3-fold (158). A risk assessment study concluded that immobility was among the top two most common risk factors for VTE in all surgical patients, together with anesthesia >45 minutes (159). Researchers discourage extended postoperative immobilization and protocols recommend early mobilization as a measure of VTE prophylaxis postoperatively (160-162).

1.4 Aim of the thesis

Even though the relationship between surgery and VTE has been thoroughly evaluated in the literature, there is still a need for further investigation on the contribution of surgery to the VTE risk when other potential concomitant VTE triggers are taken into account. The aim of this thesis was therefore to investigate the impact of major surgery as a trigger for incident VTE and to explore the effect of immobilization, infection and other VTE triggers on the relationship between major surgery and VTE. To accomplish this aim, a population-based case-crossover study of VTE patients derived from the Tromsø study was used. The case-crossover design allows to largely control for potential fixed confounders because participants serve as their own controls.

2 Materials and methods

2.1 Study population

The study participants were recruited from the Tromsø Study, which is a single-center, population-based, prospective cohort study with repeated health surveys of the inhabitants of Tromsø, Norway. Until today, seven surveys have been conducted, details of which can be found elsewhere (163, 164). The fourth survey (Tromsø 4) conducted in 1994/1995 was used, where 27,158 subjects aged ≥25 years participated, corresponding to 77% of the eligible population who was invited to take part in Tromsø 4. The participants were followed from study inclusion (1994-1995) until December 31, 2012. All potential first lifetime VTE events occurring during follow-up were identified using the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry from the University Hospital of North Norway (UNN), which is the only hospital in the Tromsø region (165). Validation of each VTE event was performed by trained personnel through an extensive review of medical records, as previously described (165). An episode of VTE was confirmed if there were signs and symptoms of DVT or PE in combination with objective confirmation by radiological methods, resulting in treatment initiation (165). A total of 707 individuals experienced an incident VTE event during the follow-up period (1994-2012). Information on transient risk factors or VTE triggers was obtained by trained medical personnel through a detailed review of the hospital medical records (20). All participants gave their written consent, and the study was approved by the Regional Committee of Research Medical and Health Ethics (REK Nord).

2.2 Study design

A case-crossover study was carried out, as this is a suitable design for the present study aimed at investigating the association between surgery, a transient exposure, and VTE, an acute outcome (21). In this design, study participants serve as their own controls (21). Therefore, fixed confounders are largely controlled for by the study design since each individual is compared to herself/himself. Examples of potential fixed confounders are comorbidities, chronic conditions and genetic risk factors. In the case-crossover study, only individuals who have experienced the outcome of interest are included (21). This way, the study population consisted of all the incident VTE cases (n=707) occurring in the study period (1994-2012). The 90 days preceding the date of the incident VTE was defined as the hazard period (i.e. risk

period), as previously described (20, 68, 70). Exposures during the hazard period were compared with exposures occurring during the four previous 90-day control periods (Figure 5). The rationale behind the use of 90-day periods is based on a pre-existing definition of provoking factors for VTE (53). In order to avoid carry-over effects, a 90-day washout period was introduced between the control periods and the hazard period.

Trained medical personnel systematically evaluated the hospital medical records for each VTE case and recorded potential VTE triggers, in addition to diagnostic procedures, surgical and medical treatment, laboratory tests and diagnoses occurring during hospital admissions, day care and outpatient visits in any of the control or hazard periods. It is important to point out that in this study there was no access to records from general practice (20, 68, 70).

Figure 5

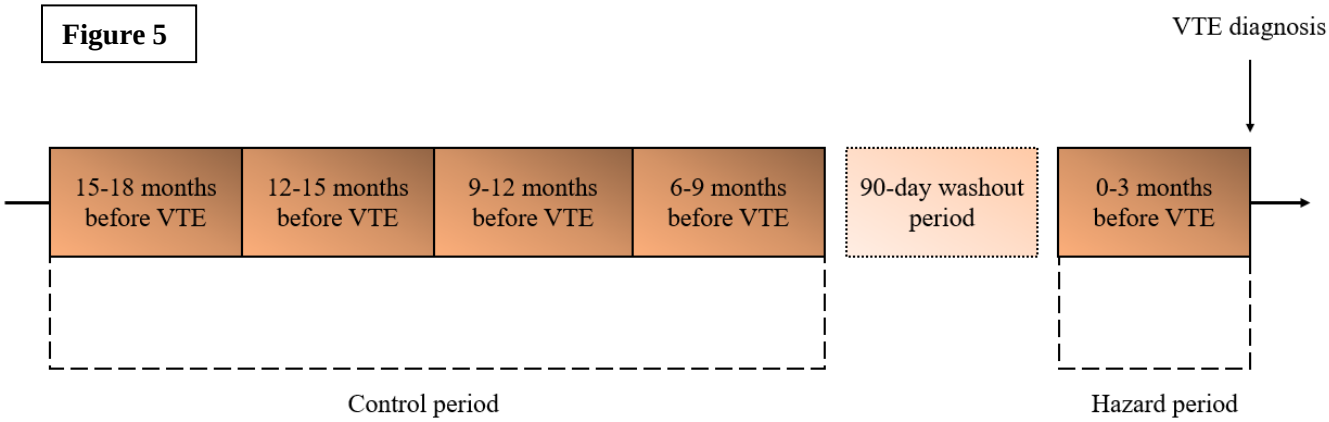

Figure 5: Case-crossover study design. The hazard period was defined as the 90-day period prior to the VTE event. Exposures occurring in the hazard period were compared with exposures occurring during the four previous 90-day control periods. In order to avoid carry-over effects, a 90-day washout period was introduced between the control periods and the hazard period.

Adapted from Morelli et al. (68) and Sejrup et al. (70).

2.3 Definition of risk factors

A transient risk factor, or trigger, was defined as a risk factor present in the hazard period, i.e. in the 90 days prior to the VTE event, or in any of the four control periods. If an exposure occurred over several days, it was considered to have occurred if any of the days of the exposure fell within the specified 90-day period (20, 68, 70). In this case-crossover study, major surgery was registered for operations on organs within the chest, abdomen, pelvic cavity and cranium, and also for hip and knee operations. Minor surgeries were not included and were defined as

procedures requiring less than 30 minutes of general anesthesia (54). Other triggers were recorded as previously described (20, 68, 70). In short, immobilization was defined if one of the following factors were present: bedrest for three days or more, ECOG (Eastern Cooperative Oncology Group) score of four or other immobilizing factors (confinement to wheelchair, cast immobilization, etc.). If an acute infection was noted in the medical records by a physician, infection was recorded. This included hospital-acquired infections, but also community-acquired infections leading to hospital admission. Respiratory tract infection (RTI), urinary tract infection (UTI) and other infections were included. Since symptoms of RTIs and PEs may present similarly, some PE patients could initially have been diagnosed with RTI. Therefore, all cases with RTIs and PEs were thoroughly re-evaluated by a specialist in infectious diseases. Diagnoses of RTIs that were probably incorrect were recoded as "no RTI" (n=8). Trauma, red blood cell transfusion and use of CVC were recorded if noted in the medical record.

2.4 Statistical analysis

Statistical analyses were carried out using STATA version 16.1 (Stata Corporation, College Station, Texas, United States). Conditional logistic regression was used to calculate odds ratios (ORs) for VTE with 95% confidence intervals (CIs) according to the presence of major surgery in hazard and control periods. In a first model, the crude association between surgery and VTE was assessed. In a second model, the association was adjusted for immobilization and acute infection. In a third model, the association was further adjusted for the presence of other VTE triggers (i.e. red blood cell transfusion, trauma and central venous catheter).

Under the assumption that immobilization and infection are consequences of surgery, a mediation analysis was performed in order to determine to what extent these two triggers have the potential to mediate the effect of surgery on VTE risk. This was done using the method developed by Karlson, Holm, and Breen (KHB method), which has been described in detail elsewhere (166, 167). Briefly, the method estimates direct, indirect and total effects on the same scale, and the coefficients in conditional logistic regression models are not influenced by rescaling, especially when the total effect is decomposed into direct and indirect effects. This enables a comparison of the coefficients without any issues with scale identification. Furthermore, the KHB method is able to deal with more than one mediator simultaneously, which is an important property. The KHB method also allows decomposing the contribution from different mediators while performing adjustment for other factors.

In addition to the overall analyses, a subgroup analysis was performed, stratified by the localization of the thromboembolic event, i.e. DVT and PE with or without concomitant DVT. For sensitivity purposes, analyses for overall VTE were conducted where subjects with active cancer at the time of VTE diagnosis (n=176) were excluded.

2.5 Literature search for the thesis and the grading

In this thesis, the PubMed database was used to perform the literature review on surgery and VTE. The PubMed database was searched for publications on surgery and VTE by using combinations of several terms, including “surgery”, “surgical procedure”, “major surgery”, “venous thrombosis”, “venous thromboembolism”, “deep vein thrombosis”, and “pulmonary embolism”. To address topics of interest related to surgery and VTE (e.g. study design, thromboprophylaxis, type of surgical procedure), other terms were added to the literature search, such as “thromboprophylaxis” and “case-crossover”. Medical subject headings (MeSH-terms) were used, but a free-text search was also conducted to identify all the relevant articles. A test-search was done where the terms were combined to see if preselected key articles would be identified as an indication of the quality of the search. Only studies reported in English consisting of an adult population (≥18 years old) were included. Relevant publications were also identified by cross-referencing from the reference lists of the retrieved papers.

Guideline developers rate the quality of evidence and the strength of recommendations using a variety of different systems. The GRADE system (Grading of Recommendations, Assessment, Development and Evaluations) is a framework which is increasingly being implemented by organizations worldwide (168). It classifies evidence in four categories: High quality, moderate quality, low quality or very low quality, based on a range of factors (169). Furthermore, there are two levels of recommendation: Strong or weak. Here, the GRADE method was applied to the most relevant articles (n=6) in order to assess the quality of evidence. The articles were chosen in collaboration with my supervisor and they were part of the literature review that was carried out to conceive this thesis. Since the included studies for grading were not on therapeutic intervention, it was not relevant to consider the level of recommendation (168).

3 Results

3.1 Baseline characteristics and occurrence of VTE triggers

Among the 707 VTE cases, there were 408 DVTs (57.7%) and 299 PEs (42.3%). The median age at VTE diagnosis was 71 years and 53.6% of the participants were women. The baseline characteristics are presented in Table 5.

Table 5: Baseline characteristics of study participants

Characteristics at time of VTE diagnosis (n=707)	
Median age, years ± SD	71 ± 14
Female sex, n (%)	379 (53.6)
Deep vein thrombosis, n (%)	408 (57.7)
Pulmonary embolism*, n (%)	299 (42.3)

Abbreviations: SD, standard deviation; VTE, venous thromboembolism.

*Pulmonary embolism with or without concomitant deep vein thrombosis.

Table 6 shows the distribution of transient risk factors (i.e. triggers) for VTE in the hazard and control periods. All triggers of interest occurred more frequently in the hazard period than in the control periods. This was also true for major surgery, which occurred in 118 of the 707 hazard periods (16.7%) and only in 88 of the 2828 control periods (3.1%). Immobilization occurred in 222 of the hazard periods (31.4%) in comparison to 57 of the control periods (2.0%). The most common VTE trigger in this study population was acute infection. There were 267 infections diagnosed in the hazard period (37.8%) and 107 in the control periods (3.8%).

Thromboprophylaxis with low-molecular weight heparin (LMWH) was prescribed more often in the hazard period than in the control periods. In total, thromboprophylaxis was found in 138 of the 707 hazard periods (19.5%) and 78 of the 2828 control periods (2.8%).

Table 6: Distribution of VTE triggers for venous thromboembolism in the hazard and control periods

VTE triggers	Hazard period (n=707)	Control periods (n=2828)
Major surgery, n (%)	118 (16.7)	88 (3.1)
Immobilization*, n (%)	222 (31.4)	57 (2.0)
Infection, n (%)	267 (37.8)	107 (3.8)
Red blood cell transfusion, n (%)	82 (11.6)	28 (1.0)
Trauma (e.g. fracture), n (%)	71 (10.0)	25 (0.9)
Central venous catheter, n (%)	56 (7.9)	17 (0.6)

Abbreviations: VTE, venous thromboembolism; ECOG, Eastern Cooperative Oncology Group.

*Defined as bed rest >3 days, ECOG 4, and other immobilizing factors specifically recorded.

3.2 Risk of venous thromboembolism by major surgery

The frequency of major surgery in the hazard and control periods is displayed in Table 7 with corresponding ORs for VTE, DVT and PE. In an unadjusted model, the estimated risk of VTE was considerably high after major surgery, with an OR of 6.95 (95% CI: 5.08-9.50). With adjustment for immobilization and infection, the OR for VTE by surgery was attenuated to 2.21 (95% CI: 1.43-3.40), as shown in model 2. The OR further decreased to 1.49 (95% CI: 0.92-2.40) when adjusted for red blood cell transfusion, trauma and central venous catheter in addition to immobilization and infection, as seen in model 3.

Subgroup analyses were performed in order to stratify the risk of DVT and PE by surgery. The crude ORs for DVT and PE were 7.52 (95% CI: 4.88-11.58) and 6.36 (95% CI: 4.04-10.01), respectively. After adjustment for immobilization and infection in model 2, the ORs were attenuated for DVT (OR 2.84, 95% CI: 1.59-5.07), and particularly for PE (OR 1.63, 95% CI: 0.85-3.14). With further adjustment for the other triggers in model 3, the OR for DVT was only slightly attenuated (OR 2.28, 95% CI: 1.21-4.30), whereas the association between major surgery and PE disappeared, with an OR of 0.92 (95% CI: 0.43-1.98).

Appendix tables 1-3 describe the association of major surgery with overall VTE, DVT and PE with a stepwise adjustment for the other VTE triggers. It is noteworthy that when immobilization and infection were added separately to the regression models, the effect of major surgery on the risk of VTE (Appendix table 1) was attenuated to a similar extent when adjusted for immobilization only (OR 4.09, 95% CI: 2.81-5.96) or infection only (OR 3.51,

95% CI: 2.41-5.10). The effect of major surgery on the risk of DVT and PE was also attenuated to a similar extent when adjusted only for immobilization or infection (Appendix tables 2 and 3).

Table 7: Distribution of major surgery in the hazard and control periods and odds ratio for overall venous thromboembolism, deep vein thrombosis and pulmonary embolism

	Hazard period n (%)	Control periods n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
VTE	n=707	n=2828			
Major surgery	118 (16.7)	88 (3.1)	6.95 (5.08-9.50)	2.21 (1.43-3.40)	1.49 (0.92-2.40)
DVT	n=408	n=1632			
Major surgery	66 (16.2)	49 (3.0)	7.52 (4.88-11.58)	2.84 (1.59-5.07)	2.28 (1.21-4.30)
PE	n=299	n=1196			
Major surgery	52 (17.4)	39 (3.3)	6.36 (4.04-10.01)	1.63 (0.85-3.14)	0.92 (0.43-1.98)

Abbreviations: CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

Model 1: Unadjusted OR.

Model 2: Adjusted for immobilization and infection.

Model 3: Adjusted for immobilization, infection, trauma, red blood cell transfusion and central venous catheter.

In a sensitivity analysis, patients with active cancer at the time of VTE diagnosis (in the hazard period) were excluded (n=176), and the results are presented in Appendix tables 4-6. After excluding cancer patients, the association between surgery and VTE was somewhat more pronounced in comparison to the main analysis, yielding a crude OR for VTE of 11.40 (95% CI: 7.40-17.50). Of note, the risk of VTE remained considerably high even with adjustment for immobilization and infection (OR 4.10, 95% CI: 2.40-6.94), and after adding all the other triggers to the regression model, with an OR of 3.31 (95% CI: 1.83 -5.96). With the exclusion of cancer patients, the association of major surgery with DVT and PE was also more pronounced compared to the main analysis in crude and adjusted models (Appendix tables 5 and 6).

3.3 Mediating effects by immobilization and infection

In order to analyze the magnitude of the potential mediating effects of immobilization and infection on the relationship between surgery and overall VTE, the KHB mediation analysis was applied. The mediation analysis was adjusted for red blood cell transfusion, trauma and central venous catheterization. The results, which are summarized in Table 8, show that 72.6% of the association between surgery and VTE risk was due to a mediating effect (i.e. indirect effect), acting via immobilization and infection. In relation to the mediating effect, 52% was attributable to immobilization and 48% to infection. Figure 6 illustrates the relationship between surgery and VTE taking into account the potential mediators.

Table 8: The KHB mediation analysis and decomposition results for the association between major surgery and venous thromboembolism

Conditional logistic regression			
	Coefficient	**SE**	**Mediation percentage**
Coefficients			
Total effect	1.46	0.25	-
Direct effect	0.40	0.25	-
Mediating effect*	1.06	0.18	72.6
Through			
Infection	0.51	0.10	48.0
Immobilization	0.55	0.14	52.0

Abbreviations: KHB, Karlson, Holm and Breen; SE, standard error.

*p <0.005.

Figure 6

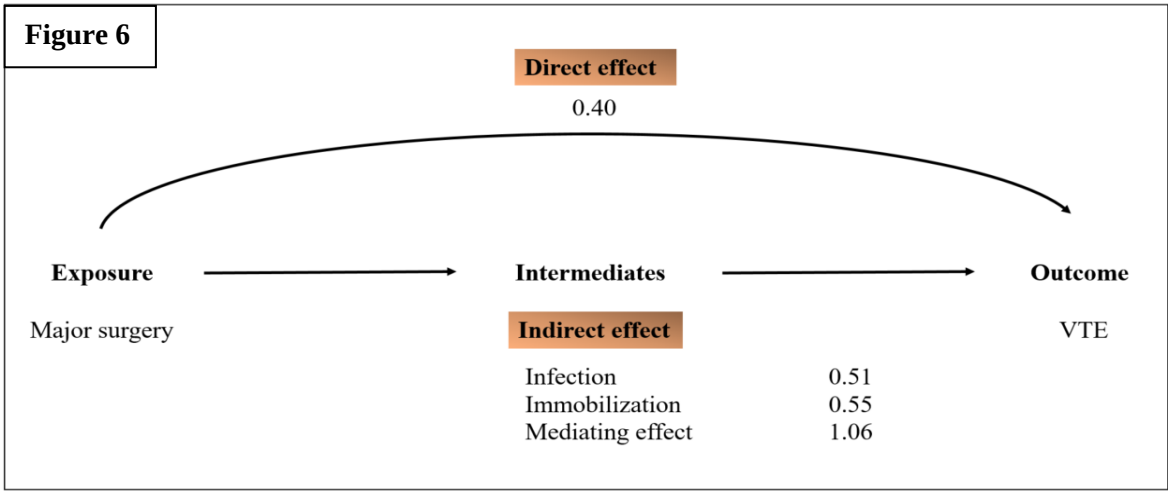

Figure 6: Potential relationship between major surgery and subsequent risk of venous thromboembolism. The effect of surgery that acts through the intermediates is the indirect effect, and the effect that is not explained by the intermediates investigated is the direct effect.

4 Discussion

4.1.1 Discussion of main results

In this thesis, the impact of major surgery as a transient risk factor (i.e. trigger) for incident VTE was assessed using a case-crossover design comprised of 707 VTE patients recruited from a general population. Major surgery was associated with a substantially increased risk of VTE, with an OR of 6.95 (95% CI: 5.08-9.50). However, the association between surgery and VTE was largely attenuated after adjustments for immobilization and acute infection (OR 2.21, 95% CI: 1.43-3.40). When all the VTE triggers studied were taken into account in the regression analyses (i.e. immobilization, infection, red blood cell transfusion, trauma and central venous catheter), risk estimates were further attenuated to 1.49 (95% CI: 0.92-2.40). In the mediation analysis, almost 73% of the effect of surgery on the risk of overall VTE could be mediated by immobilization and infection. In the subgroups, the impact of major surgery on the risk of DVT and PE was similar to the impact observed for overall VTE. However, after adjustment for all the other VTE triggers, the relationship between surgery and PE disappeared (OR 0.92, 95% CI: 0.43-1.98), whereas the OR for DVT remained somewhat high (OR 2.28, 95% CI: 1.21-4.30). In the sensitivity analysis, all patients with a cancer diagnosis at the time of the VTE event were excluded. Interestingly, the relationship between surgery and VTE was more pronounced in this analysis compared to the main analysis, even after adjustment for all transient risk factors. The findings of this case-crossover study indicate that major surgery is a trigger for incident VTE, but other VTE triggers, particularly immobilization and infection, seem to have an important effect on the association between surgery and VTE risk.

Surgery is a well-known and major transient risk factor for VTE (9, 11, 71, 99). However, the mechanisms underlying the association between surgery and VTE are not fully elucidated. Furthermore, a clear definition of major surgery is lacking, and not so many studies have been able to categorize procedures by specialty as major or minor (94, 99, 110, 112). In line with prior studies (9, 71), major surgery was a transient risk factor for VTE when occurring within the first 90 days before the thrombotic event in this case-crossover study. Nevertheless, immobilization and acute infection seemed to play an important role in the risk of VTE conferred by surgery, explaining more than two-thirds of the total effect of surgery on the risk of VTE.

To the best of our knowledge, this is the largest case-crossover study that has been conceived to date aimed to investigate the role of major surgery as a VTE trigger while taking other concomitant VTE triggers into account. It is also the only study investigating the relationship between surgery and VTE using a case-crossover design derived from a general population. Thus far, only a few case-crossover studies on surgery and VTE have been reported. The first case-crossover study was conducted in the US by Rogers et al. (71), which involved subjects aged ≥51 years who were beneficiaries of the Medicare Service. In the aforementioned study, comprised of 399 VTE events identified by the use of International Classification of Diseases (ICD) codes, major surgery, including cardiovascular and orthopedic procedures, was a trigger for VTE. Similarly to the present findings, the association between surgery and VTE was attenuated after adjustment for other triggers, such as immobilization, infection, blood transfusion and central venous catheterization, among others.

Recently, Caron et al. published a case-crossover study investigating the duration and magnitude of PE risk among cancer-free middle-aged patients in France (170). The patients were 45-64 years of age and admitted to the hospital for PE between 2009 and 2014. PE was identified by ICD codes using data from the French national inpatient database. According to the authors, DVT is routinely treated in an outpatient setting and was therefore not included in the study. In total, 60,703 patients with a diagnosis of a first PE were included in the analysis. Authors found that the risk of PE postoperatively was elevated for at least 12 weeks after all types of surgery. However, the risk was clearly higher during the first 1-6 weeks after surgery. The analysis was stratified by the type of surgical specialty: vascular surgery, gynecological surgery, gastrointestinal surgery, hip or knee replacement, fracture surgery and other orthopedic operations. Fracture surgery (OR 8.34, 95% CI: 6.07-11.45) and gynecological surgery (OR 8.17, 95% CI: 5.19-12.86) yielded the highest risk estimates for PE within the first six weeks postoperatively. Orthopedic procedures, encompassing fracture surgery (OR 4.23, 95% CI: 3.01-5.92) and hip or knee replacement (OR 3.64, 95% CI: 2.66-4.99), were associated with the largest risk 7-12 weeks postoperatively. There are some epidemiological aspects of the study by Caron et al. that are worthwhile to mention (170). The study only gives the crude estimate of PE risk – not adjusting for other VTE triggers and their possible impact on the risk. Additionally, it is important to keep in mind that the inclusion of only middle-aged patients, with the exclusion of those with cancer, might limit the generalizability (i.e. external validity) of the study findings, and that only PEs identified by ICD codes were included. On the other

hand, this is a large study, and the sample size made it possible to stratify the risk of PE by surgery type.

Regarding the other VTE triggers assessed in this study, immobilization is a well-established risk factor for VTE (20, 71, 142, 171), and according to the results of the present study, it has the potential to mediate a large portion of the VTE risk in surgical patients. A study that investigated the influence of immobilization and surgery on PE patients found that 43% of patients dying from PE had recent immobilization and 6.7% had recent surgery, suggesting that many of these deaths could have been prevented (171). Sebastian et al. investigated risk factors for VTE in surgical patients and that found length of hospital stay (>5 days), reflecting immobilization, was associated with an increased risk of VTE (158). The authors also found that paralysis (complete or incomplete quadriplegia) was an independent risk factor (158). Surgical patients are exposed to immobilization not only during the surgical procedure, but mainly in the period following surgery, and a careful assessment of thromboprophylaxis use and its duration should be done in these patients.

Infection can be the reason for a surgical procedure, such as in the case of necrotizing fasciitis, which needs surgical debridement and in some cases amputation of the affected limb (172). Some patient groups, like diabetic patients, are more prone to infections that may ultimately lead to major surgical intervention (i.e. amputation) (173). This way, infection may act as a confounder in the relationship between surgery and VTE because of its association with both the exposure (surgery) (172, 173) and the outcome (VTE) (20, 145-147). On the other hand, acute infection is also a common complication after surgery (174), having the potential to mediate, at least in part, the relationship between surgery and VTE. A recently published study including over 90,000 patients undergoing elective surgery found that postoperative surgical site infections occurred in 1.4% of the patients and urinary tract infections in 1.3%, making infection the most common complication after surgery (175). Such findings are in line with the Annual Epidemiological Report on Communicable Diseases, in which surgical site infections are reported to be the most common healthcare-associated infections (174). These postoperative infections are associated with a prolonged hospital stay, additional surgical procedures, treatment in intensive care units and higher mortality (174, 176).

In the current study, the mediation analysis suggested that infection substantially contributed to the VTE risk in surgical patients, with 48% of the indirect effect of surgery on VTE risk being

attributable to infection. Using data from the same case-crossover study, Grimnes et al. found that there was a high VTE risk related to infection, and the combination of infection and immobilization was suggested to have a synergistic effect on the VTE risk (20). More specifically, Monn et al. investigated the association of infection (i.e. urinary tract infection, pneumonia, superficial or deep surgical site infection and wound dehiscence) with VTE in surgical patients. Authors found that almost 50% of the VTE patients had at least one postoperative infectious complication. The development of any infection was associated with a 2.8-fold increased risk of VTE, and the risk of postoperative VTE was especially pronounced for pneumonia (149). A possible explanation for the increased risk of VTE after acute postoperative infection would be an increased inflammatory response, which in turn could lead to a prothrombotic state (16, 135).

It is noteworthy that even after adjustment for all VTE triggers, surgery was associated with a 50% increased risk of VTE (OR 1.49, 95% CI: 0.92-2.40). Caution is needed for the interpretation of this result because the confidence intervals of the risk estimate are wide and included unity. Still, surgery seemed to be associated with an increased risk of VTE after an extensive adjustment for other VTE triggers. In a case-crossover study, all fixed confounders are controlled for through the design and are therefore unlikely to influence the results (21). It might be speculated that the remaining VTE risk is due to those factors that can be a direct consequence of the surgical procedure (for details, see section 1.3.5 in the introduction), such as hypercoagulability and/or an increased inflammatory response (13, 15, 16).

The results of this study may have some clinical implications. Evidence-based guidelines on antithrombotic and thrombolytic therapy have been published for both surgical and medical patients by the ACCP (109). Authors separate surgical patients in different risk groups based on type of operation and known patient risk factors, and they strongly recommend thromboprophylaxis for patients who are at high risk of developing a VTE. The guidelines for surgical thromboprophylaxis specifically mention bedrest ≥4 days, prolonged hospital stays, infections (urinary tract infections and pneumonia) and sepsis as factors that increase the risk of VTE in surgical patients (109). The current findings showing that immobilization and acute infection have the potential to mediate in great part the VTE risk in surgical patients underscore the need for a careful assessment of not only the use of thromboprophylaxis, but also its duration, in patients exposed to infection and prolonged immobilization after a major surgery.

It is important to address that the association between surgery and VTE was attenuated also after adjustment for red blood cell transfusion, trauma and CVC, which are VTE triggers that, like immobilization and infection, can often coexist with surgical procedures. The finding of the impact of other VTE triggers on the association between surgery and VTE risk implies that paying more attention to them can help reduce the surgery-associated VTE risk. For instance, it is possible to increase efforts to avoid unnecessary blood transfusions and CVCs, encourage early mobilization and take measures to prevent or to mitigate the risk of infections in the postoperative setting.

In the subgroup analysis, the influence of the other VTE triggers was more important for the association between surgery and PE than for the association between surgery and DVT. Indeed, adjustment for immobilization, acute infection, trauma, red blood cell transfusion and central venous catheter resulted in a larger attenuation of the association of major surgery with PE than with DVT. This could be due to the fact that PE patients as compared with DVT patients would be more likely to have been exposed to more VTE triggers, thus contributing to a larger impact of the other triggers on the risk of PE conferred by surgery (20, 177). Interestingly, when excluding patients with cancer at the hazard period, the impact of major surgery was more pronounced compared to the main analysis for overall VTE, DVT and PE in crude and adjusted models. Of note, the frequency of exposure to major surgery was slightly lower in the control period after excluding cancer patients (1.8%) in comparison to the main analysis (3.1%) for overall VTE and subgroups. This might explain the greater impact of major surgery on VTE in cancer-free patients. However, the statistical power in the subgroups and in the sensitivity analysis is limited due to a lower sample size, and the aforementioned results should therefore be interpreted with caution.

4.1.2 Methodological considerations

The case-crossover design allows for investigating the effects of transient exposures, such as surgery, on acute outcomes, like VTE (21). This particular study design enables to focus on transient risk factors while controlling for potential fixed confounders because participants serve as their own controls. Even if fixed confounders are essentially controlled for through the study design, residual confounding cannot be completely ruled out due to unmeasured or unknown transient risk factors that could have influenced the association between surgery and VTE.

When conducting epidemiological studies, generalizability is important in order to make sure the results are applicable to the general population. The attendance rate of the Tromsø Study is high compared to other population-based prospective cohort studies. The fourth Tromsø Survey, which was used to conceive the present case-crossover study, is the largest one, with an attendance of 77% (163).

In this study, thromboprophylaxis with LMWH was prescribed more often in the hazard period (19.5%) than in the control periods (2.8%). Confounding by indication is likely to be the reason for the higher proportion of thromboprophylaxis use in the hazard period, i.e. patients regarded to be at a high risk of developing VTE during the hazard period by doctors were those who most likely had the indication of thromboprophylaxis. This is important to keep in mind when interpreting the results on thromboprophylaxis in this case-crossover study.

The hazard period was defined as the 90 days preceding the date of the incident VTE event, as previous studies have done (20, 68, 70, 118). The impact of surgery on the VTE risk is likely to have been even higher if the hazard period was comprised of a shorter interval, as other studies have demonstrated that the VTE risk is highest in the first 1-6 weeks postoperatively (9, 170).

4.1.3 Strengths and weaknesses

The strengths of the present study are the high attendance rate in the Tromsø Study where the cases were recruited from. Differently from the two previous case-crossover studies in which assessment of the VTE events was carried out by ICD codes (71, 170), all VTE events in this study were validated by trained personnel using objective criteria. Moreover, this case-crossover study was derived from the general population, in which both DVT and PE were evaluated as outcomes, not only PE, as Caron et al. did (170). There are some limitations that need to be addressed. Information on exposure to VTE triggers during the last 90 days before each admission was obtained, but without assessing the temporal sequence between them. In this study, analyses were conducted under the assumption that surgery was present before immobilization, infection and the other VTE triggers. It is unlikely, but not impossible, that in some cases, surgery may have taken place after exposure to the other VTE triggers. Therefore, caution is needed when interpreting the results, particularly the mediation analysis. A prospective cohort of surgical patients would be valuable to confirm the current findings from

the mediation analysis, in which a temporal sequence between exposure, intermediate and outcome is established through the design.

The information on some exposures might be biased as doctors could be more aware of risk factors for VTE (e.g. immobilization) when this diagnosis is suspected in a patient in the hazard period than during hospital admissions for other conditions in the control periods. Additionally, some of the risk estimates should be interpreted with caution due to limited statistical power, particularly in the subgroups and in the sensitivity analysis. Unfortunately, the sample size was a limitation for conducting procedure-specific analyses in this case-crossover study, although it has been shown that some specialties, like orthopedic surgery, have an especially high risk of VTE (9, 99). Information on exposure to major surgery was based on review of medical records by trained medical personnel, without further validation defining whether the surgical procedure was major or minor by an independent end-point committee. Still, misclassification would be unlikely due to predefined criteria that were taken into account to define a surgical procedure as major.

4.1.4 Final remarks and future perspectives

The review of literature has revealed a considerable variance in the categorization of surgical procedures as minor or major, and an inconsistency in the usage of the terms. While the classification of orthopedic procedures seems rather clear in terms of what is considered major surgery, it is not specified and there is no consensus around other surgical specialties. This is an issue, as it makes it difficult to perform standardized, reproducible and comparable research since the included procedures may vary based on the chosen definition.

The development of minimally invasive surgeries continues to expand and is changing the surgical field. What will this mean for the VTE risk in the future? Arthroscopic and laparoscopic surgeries have been shown to yield a low incidence of postoperative VTE, lower than for open surgery (100, 128, 178-180), and arthroscopy and some types of laparoscopy are by definition minor surgeries. Guidelines state that patients undergoing arthroscopy or laparoscopic procedures without additional risk factors for VTE are not recommended any pharmacological VTE prophylaxis (107, 109). This may mean that the continued development of minimally invasive procedures might influence the VTE incidence. For now, it is still necessary to continue conducting research on the topic as PE remains the most common cause of preventable death among surgical complications (106).

5 Conclusion

In conclusion, major surgery was a trigger for VTE in this case-crossover study. The present findings suggest that the association between major surgery and subsequent VTE may be largely explained by concomitant factors related to surgery, particularly immobilization and infection. There is potential for improvement in the field and further studies investigating the topic should be conducted.

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Appendix

GRADE tables

<table>
<tr><td colspan="3">Reference: Caron A, Depas Nm Chazard E, Yelnik C, Jeanpierre E, Paris C, Beuscart JP, Ficheur G. Risk of pulmonary embolism more than 6 weeks after surgery among cancer-free middle-aged patiens. JAMA Surg 2019; 154(12):1126-1132.</td><td>GRADE
Quality of evidence: Moderate
Recommendations: None</td></tr>
<tr><td>Aim
To assess the duration and magnitude of the late postoperative risk of pulmonary embolism (PE) among cancer-free middle-aged patients by the type of surgery.

Conclusion
The risk of postoperative PE is elevated beyond 6 weeks after surgery regardless of type of procedure.

Country
France.
Year data collection
2007-2014.</td><td>Study design: Case-crossover.
Data foundation: French national inpatient database.
Exclusion criteria: History of thrombosis, myocardial infarction, ischemic stroke and cancer.
Data material: Cancer-free subjects aged 45-64 years.
Data collection: Registry based.
Exposure: Surgery (vascular, gynecological, gastrointestinal, hip or knee replacement, fractures and other orthopedic operations).
Outcome: Diagnosis of a first PE.
Validation of exposure and outcome: International Classification of Diseases (ICD) codes and national procedure-grouping codes.
Statistical methods: The odds ratio (OR) for PE was calculated according to surgery type comparing the case and control periods.</td><td>A total of 60,703 patients were included. The risk of postoperative PE was elevated for at least 12 weeks after all types of surgery, but it was highest within the first 6 weeks (early postoperative risk).

Early postoperative (1-6 weeks after surgery) PE risk estimates (OR):
• Fracture surgery: 8.34 (95% CI: 6.07-11.45)
• Gynecological surgery: 8.17 (95% CI: 5.19-12.86)
• Gastrointestinal surgery: 5.51 (95% CI: 4.45-6.82)
• Other orthopedic procedures: 5.46 (95% CI: 4.40-6.78)
• Vascular surgery: 5.24 (95% CI: 3.91-7.01)

Late postoperative (7-12 weeks after surgery) PE risk estimates (OR):
• Fracture surgery: 4.23 (95% CI: 3.01-5.92)
• Hip/knee replacement: 3.64 (95% CI: 2.66-4.99)
• Vascular surgery: 3.15 (95% CI: 2.25-4.41)
• Other orthopedic procedures: 2.82 (95% CI: 2.20-3.61)
• Gastrointestinal surgery: 2.26 (95% CI: 1.81-2.82)</td><td>The study adds important data on the topic of prolonged PE risk after surgery and underscores the need for assessing extended thromboprophylaxis.
Strengths
- Large number of patients included.
- Suitable study design for the aim.
- The results are in line with previously published studies.
- Few previous studies on the topic with an extended observation time have been published.
Limitations
- Only PE was studied, not DVT.
- Excluding part of the population due to age selection.
- Concomitant risk factors, which may have influenced the PE risk, were not taken into account or adjusted for.
- A broad range of procedures were studied, including some minor procedures with the major surgeries.
- Lack of knowledge regarding the use of oral medications and thromboprophylaxis, so the observed incidence reflects the risk associated with the hospitalization, the use of medications which may trigger VTE (e.g. hormone replacement therapy) and the use or non-use of thromboprophylaxis.
- Use of administrative data (i.e., ICD coding) to define the outcome, which without validation can lead to misclassification.</td></tr>
</table>

Reference: Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of Hospitalization for Venous Thromboembolism. Circulation 2012; 125:2092-2099.			**GRADE**
			Quality of evidence: Moderate
			Recommendations: None
Aim	**Material and methods**	**Results (main findings)**	**Discussion/comments**
To evaluate triggers of hospitalization for venous thromboembolism (VTE). **Conclusion** Infection was the most common trigger of hospitalization for VTE. Other common triggers were erythropoiesis-stimulating agents and blood transfusions. **Country** USA. **Year data collection** 1991-2007.	**Study design:** Case-crossover. **Data foundation:** The Health and Retirement Study. **Exclusion criteria:** Surgical hospitalizations, <1.5 years of observation, VTE diagnosis at a date previous to index hospitalization. **Data material:** 16,781 patients in a linked database between 1991-2007. **Data collection:** Registries, medical records, ICD classification. **Exposure:** Infection, erythropoiesis-stimulating agents, blood transfusion, chemotherapy, antipsychotics, injuries, surgery, central venous catheter, immobility. **Outcome:** Hospitalization for venous thromboembolism (VTE). **Validation of exposure and outcome:** Healthcare Common Procedure Coding System codes, International Classification of Diseases (ICD) codes. **Statistical methods**: Exposures occurring in the 90-day period before hospitalization for VTE (risk period) were compared to exposures in the four 90-day control periods.	Among the 16,781 patients in the linked database, 399 patients hospitalized for VTE were included. DVT accounted for 58.6% of admissions, PE for 41.4%. Infection was the most common trigger of hospitalization for VTE, occurring in 52.4% of the risk periods before hospitalization. Adjusted incidence rate ratios were 2.9 (95% CI: 2.13-3.94) for all infections, 2.63 (1.90-3.63) for infection without a previous hospital or skilled nursing facility stay and 6.92 (4.46-10.72) for infection with a previous hospital or skilled nursing facility stay. Respiratory tract infections (RTIs) occurred in 21.8% and non-respiratory tract infections in 26.8% of the risk periods. RTIs were more strongly related to hospitalization. Cardiovascular, orthopedic and other major surgeries in the 90 days before hospitalization were significant, independent VTE triggers. Other predictors were erythropoiesis-stimulating agents, blood transfusion, fractures, immobility and chemotherapy. These predictors accounted for 69.7% of exposures before VTE hospitalization (35.3% in the comparison periods). Similar results were found when excluding the patient group with cancer.	The authors argue that the case-crossover design is suitable for evaluating the VTE predictors. In the case-crossover, participants serve as their own controls, and all potential fixed confounders are largely controlled for through the study design. This makes it suitable for investigating the effects of transient exposures, such as the assessed VTE triggers, on acute outcomes, like VTE. A reevaluation of current risk algorithms for VTE is suggested, where infection, erythropoiesis-stimulating agents and blood transfusion are included. **Strengths** - Suitable study design for the aim. - Consistent results with previously published studies. **Limitations** - Limited number of included cases, thereby limited statistical power. - A follow-up time of 1.5 years means changes in vascular health could have occurred without being recorded in medical records. - Lack of knowledge regarding the use of oral medications and thromboprophylaxis, so the observed incidence reflects the risk associated with the hospitalization, the use of medications which may trigger VTE (e.g. hormone replacement therapy) and the use or non-use of thromboprophylaxis. - Use of administrative data (i.e., ICD coding) to define the outcome, which without validation can lead to misclassification.

Reference: White RH, Hong Z, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost 2003; 90(03): 446-455.			**GRADE**
			Quality of evidence: Moderate
			Recommendations: None
Aim	**Material and methods**	**Results (main findings)**	**Discussion/comments**
To determine the incidence of symptomatic venous thromboembolism (VTE) within a 3-month period after commonly performed surgical procedures. **Conclusion** Total hip arthroplasty, vascular procedures, invasive neurosurgery and radical cystectomy were associated with the highest incidence of VTE. Fifty-six percent of all VTE events were diagnosed after hospital discharge. **Country** USA. **Year data collection** 1992-1996.	**Study design:** Cohort study. **Data foundation:** The California Patient Discharge Data Set. **Exclusion criteria:** Upper extremity venous thrombosis, and a VTE event occurring within the 182-day period before the index hospitalization. **Data material:** 1,653,275 cases (age ≥18 years) who underwent one of 76 selected surgical procedures between 1992-1996. **Data collection:** Registries. **Exposure:** Urgent or elective surgical procedures. **Outcome:** Venous thrombosis or pulmonary embolism. **Validation of exposure and outcome:** Discharge diagnosis registry, International Classification of Diseases (ICD) codes. **Statistical methods:** The crude 91-day VTE incidence was calculated according to surgical procedures. Logistic regression was used to investigate potential VTE predictors.	Among the 1,653,275 cases, 13,533 were diagnosed with VTE, yielding an overall incidence of 0.8% (95% CI 0.7-0.9%). Among the 13,533 cases, 56% (n = 7528) had a VTE diagnosis after hospital discharge within a period of 91 days of surgery. In cases without malignancy, procedures associated with the highest incidence of VTE (in the range of 2-3%) were embolectomy or endarterectomy, invasive neurosurgery and total or partial hip arthroplasty. In cases with malignancy, the highest incidence of VTE (in the range of 3-4%) was noted after radical cystectomy, nephrostomy, invasive neurosurgery and total hip replacement. Variables associated with an increased odds ratio for VTE in the multivariate analysis - predictors of VTE: • Advancing age (per 5-year increment in age): OR 1.1 (95% CI: 1.1-1.1) • Malignancy: OR 1.7 (95% CI: 1.6-1.8) • Prior VTE: OR 6.2 (95% CI: 5.5-7.0) • African-American ethnicity (*versus* Caucasian): OR 1.2 (95% CI: 1.1-1.3) • Charlson Comorbidity score ≥1: OR 1.1 (95% CI: 1.0-1.1)	The results may help physicians estimate the risk of VTE associated with various surgical procedures, and highlight the factors associated with an increased risk of VTE after surgery. The authors explain the high proportion of VTE events diagnosed after discharge by two factors: the fall in average length of hospital stay following surgery during the last 30 years, and extended thromboprophylaxis after a short period of hospitalization being an uncommon practice. The results of this study underscore the need for further studies of extended thromboprophylaxis after surgery. **Strengths** - Large number of patients. -The main results of the present study are consistent with previously published studies. **Limitations** - Lack of knowledge regarding the use of thromboprophylaxis. As a result, the observed incidence reflected the combination of the risk associated with the surgery, patient specific risk factors and the use or non-use of thromboprophylaxis. - Use of administrative data (i.e., ICD coding) to define the outcome. Registry-based information without validation can lead to misclassification, as ICD codes in hospitals may be subjected to errors.

Reference: Sweetland S, Green J, Liu B, Berrington de González A, Canonico M, Reeves G, Beral V, Million Women Study collaborators. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009;339:b4583.			**GRADE**
			Quality of evidence: Moderate
			Recommendations: None
Aim	**Material and methods**	**Results (main findings)**	**Discussion/comments**
To examine the duration and magnitude of increased risk of venous thromboembolism (VTE) after different types of surgery. **Conclusion** The risk of VTE is significantly increased the first three months postoperatively and varies by the type of surgery. Hip or knee replacement and cancer surgery yielded the highest risk of VTE. **Country** United Kingdom (UK). **Year data collection** 1996-2001.	**Study design:** Prospective cohort. **Data foundation:** Million Women Study. **Exclusion criteria:** History of VTE diagnosis or cancer, previous surgery in the year before follow-up, more than one operation during follow-up. **Data material:** 947,454 middle aged women in the UK. **Data collection:** Hospital admission records, questionnaire data from the Million Women Study linked with hospital admission/death records. **Exposure:** Surgical procedures. **Outcome:** Hospital admission or death from VTE by type of surgery. **Validation of exposure and outcome:** International Classification of Diseases codes. **Statistical methods**: The relative risk of VTE in relation to time since surgery and surgery type was estimated. The risk estimate was adjusted for potential confounders (BMI, hormone replacement therapy, oral contraceptives, smoking and medical conditions).	A total of 947,454 women were included in the main analyses, and 239,614 women (25%) had an operation. Among these, 90,259 were inpatient and 149,355 were day case. A total of 5419 women were admitted to hospital with VTE, and 270 had a first diagnosis of VTE at death. More than one third of VTE events were diagnosed among the 25% of women who had surgery. The risk of VTE remained substantially elevated in the first 12 weeks postoperatively. Incidence rates for VTE were over 100 times the rates without surgery. Day case surgery yielded a lower risk of VTE than inpatient surgery. • Joint replacement was the procedure related with the greatest relative risk (220.6, 95% CI: 187.8-259.2). The risk was also substantially increased after surgery for cancer (relative risk 91.6, 95% CI 73.9-113.4), fracture (89, 95% CI: 65.5-121.0) and vascular conditions (87,0, 95% CI: 67.2-112.5). • The relative risk related to other orthopedic procedures and gastrointestinal surgery were also high (57.3, 95% CI: 42.3-77.7 and 56.3, 95% CI: 39.4-80.4).	The findings suggest that the risk of VTE is greater and lasts for longer than previously thought. The risk peaks about three weeks after surgery but is substantially increased up to 12 weeks postoperatively. Also, even though the risk is greater after inpatient surgery than after day case surgery, the risk is still substantially elevated in day case surgery. The magnitude of the increased relative risk might be underestimated and in fact be even higher due to lack of information about thromboprophylaxis. The results may affect the recommendations of thromboprophylaxis when it comes to length after surgery. **Strengths** - Large number of patients. - Longer follow-up time than other studies. - Access to information on several confounders, which were adjusted for. - Comparison between inpatient and day case surgery, which few others have done. **Limitations** - Different end of follow-up in the countries within the UK. - Only women included. - Lack of knowledge regarding the use of thromboprophylaxis, so the observed incidence reflects the risk associated with the surgery, patient specific risk factors and the use or non-use of thromboprophylaxis. - Lack of information on certain VTE triggers that are also confounders (e.g. immobilization).

Reference: Heit JA, Ashrani A, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thromb Haemost 2017; 117(2):390-400.			**GRADE**	
			Quality of evidence	Moderate
			Recommendations	None
Aim	**Material and methods**	**Results (main findings)**	**Discussion/comments**	
To determine VTE incidence trends and risk factor prevalence, and estimate population attributable risk (PAR) trends for each risk factor. **Conclusion** Almost 80% of incident VTE events are attributable to known major VTE risk factors, and one-third of incident idiopathic VTE events are attributable to obesity. Increasing surgery PAR suggests that concurrent efforts to prevent VTE may have been insufficient. **Country** USA. **Year data collection** 1981-2010.	**Study design:** Population-based cohort study. **Data foundation:** Rochester Epidemiology Project (REP). **Exclusion criteria:** None. **Data material:** Medical records-linkage system. **Data collection:** Registries, medical records, International Classification of Diseases (ICD) codes. **Exposure:** Established risk factors for VTE. **Outcome:** Venous thromboembolism (VTE). **Validation of exposure and outcome:** ICD codes. **Statistical methods**: Trends in annual prevalence of major VTE risk factors were estimated through linear regression. The population attributable risk was derived from the Olmsted County population.	Between 1981 and 2010, 3293 residents developed a first lifetime VTE. VTE incidence in this period did not change significantly. The increasing prevalence of obesity, cancer and surgery accounted, in part, for the persistent VTE incidence. The prevalence of hospitalization, trauma/fracture, nursing home placement and number of pregnancies decreased. Patient age, hospitalization, surgery, cancer, trauma, leg paresis and nursing home confinement jointly accounted for 79% of incident VTE. Obesity accounted for 33% of incident idiopathic VTE. Active cancer, surgery, trauma/fracture and leg paresis showed an increased VTE risk of 3.3-, 3.2-, 2.1- and 2.2-fold, respectively. Increasing surgery population-attributable risk (21.5%) suggests that concurrent efforts to prevent VTE may have been insufficient.	The authors discuss that reasons for persistent incidence of VTE over time may include exposure to new and unrecognized factors, an increase in prevalence of known VTE risk factors, incorrect or underuse of effective prophylaxis and prophylaxis failure. The need for better risk assessment tools to identify the individual at risk is promoted, especially individuals with active cancer and undergoing surgery. **Strengths** - Based on a large, population-based study (REP). - Results of the present study are consistent with previously published studies. **Limitations** - The data are relatively old, meaning it may not be applicable to the present and routines nowadays. - Large administrative datasets are usually assembled from data originally intended for billing purposes. Many diagnostic procedures may therefore be underreported. - Lack of knowledge regarding the use of oral medications and thromboprophylaxis. As a result, the observed incidence reflected the combination of the risk associated with the hospitalization, the use of medications which may trigger VTE (e.g. as hormone replacement therapy) and the use or non-use of thromboprophylaxis. - Use of administrative data (i.e., ICD coding) to define the outcome. Registry-based information without validation can lead to misclassification, as ICD codes in hospitals may be subjected to errors.	

Reference: Assareh H, Chen J, Ou L, Hollis SJ, Hillman K, Flabouris A. Rate of venous thromboembolism among surgical patients in Australian hospitals: a multientre retrospective cohort study. BMJ Open 2014; 4(10):e005502.			**GRADE**	
			Quality of evidence	Low
			Recommendations	None
Aim	**Material and methods**	**Results (main findings)**	**Discussion/comments**	
To explore venous thromboembolism (VTE) and subsequent mortality rates, trends and variations in surgical patients across Australian acute public hospitals. **Conclusion** VTE incidence is increasing among surgical patients and there is a large variation between-hospital and within-hospital peer groups. This suggests room for improvement in the prevention and treatment of postoperative VTE. **Country** Australia. **Year data collection** 2002-2009.	**Study design:** Retrospective cohort study. **Data foundation:** Records from New South Wales Admitted Patient Data Collection database. **Exclusion criteria:** Children, urgent/emergency surgery (not elective surgery), transfer to another acute care facility. **Data material:** 4,362,624 patients in 82 hospitals between 2002-2009. **Data collection:** Registries, medical records, ICD classification. **Exposure:** Surgery. **Outcome:** Postoperative venous thromboembolism (VTE). **Validation of exposure and outcome:** ICD codes. **Statistical methods**: Adjusted incidence rates and rate ratios were calculated. The association of hospital performances between VTE and post-VTE deaths was assessed.	In total, 4,362,624 patients were included. 2/1000 patients developed postoperative VTE among the elective surgical admissions. Total knee replacement, abdominal aortic aneurism repair and total hip replacement were the surgeries with the highest risk of VTE. Over the study period, VTE increased by 30%, from 1.77/1000 patients in 2002 to 2.3 in 2009. The differences between hospitals with the highest and lowest rates of VTE were significant. The smaller hospitals had the lowest overall VTE rates exhibited a greater increase overtime and greater between-hospital variations compared to the larger hospitals. Mortality among patients with VTE after surgery was 8% and remained stable over time. The mortality rate after postoperative VTE was lower among orthopedic patients compared to other procedures.	The authors discuss that the variation in the application of VTE prevention guidelines may have contributed to the differences in outcomes among hospitals. Contrary to other studies, this study showed that smaller hospitals had a lower VTE risk compared to bigger hospitals. The proposed explanation for this is more high-risk patients and more complex surgeries in the bigger hospitals. **Strengths** - It is the first population-based observational study across all acute public hospitals within one health region. - A standardized measure was used, allowing for international comparisons. - Some of the results are consistent with previous studies. **Limitations** - Geographical variations in coding and underreporting of VTE due to miscoding may have led to differences in incidence between hospitals and underreporting of VTE. - Only elective surgical patients were studied, which does not necessarily represent the whole inpatient population. - Data were retrospectively collected. - Lack of knowledge regarding the use of oral medications and thromboprophylaxis. The observed incidence reflects the risk associated with the hospitalization, the use of medications which may trigger VTE (e.g. hormone replacement therapy) and the use or non-use of thromboprophylaxis.	

Appendix tables

Appendix table 1: Distribution of major surgery in the hazard and control periods and odds ratios for venous thromboembolism

	Hazard period (n=707) n (%)	Control periods (n=2828) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	118 (16.7)	88 (3.1)	6.95 (5.08-9.50)	4.09 (2.81-5.96)	3.51 (2.41-5.10)	2.21 (1.43-3.40)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	118 (16.7)	88 (3.1)	1.88 (1.21-2.93)	2.01 (1.28-3.15)	1.85 (1.16-2.94)	1.49 (0.92-2.40)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.

Appendix table 2: Distribution of major surgery in the hazard and control periods and odds ratios for deep vein thrombosis

	Hazard period (n=408) n (%)	Control periods (n=1632) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	66 (16.2)	49 (3.0)	7.52 (4.88-11.58)	4.61 (2.73-7.78)	4.01 (2.43-6.66)	2.84 (1.59-5.07)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	66 (16.2)	49 (3.0)	2.70 (1.49-4.91)	2.75 (1.53-4.95)	2.57 (1.40-4.73)	2.28 (1.21-4.30)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.

Appendix table 3: Distribution of major surgery in the hazard and control periods and odds ratios for pulmonary embolism

	Hazard period (n=299) n (%)	Control periods (n=1196) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	52 (17.4)	39 (3.3)	6.36 (4.04-10.01)	3.61 (2.10-6.21)	2.98 (1.71-5.18)	1.63 (0.85-3.14)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	52 (17.4)	39 (3.3)	1.37 (0.70-2.69)	1.25 (0.60-2.60)	1.17 (0.57-2.41)	0.92 (0.43-1.98)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.

Appendix table 4: Distribution of major surgery in the hazard and control periods and odds ratio for venous thromboembolism after excluding patients with active cancer at the time of the thrombotic event

	Hazard period (n=531) n (%)	Control periods (n=2124) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	85 (16.0)	38 (1.8)	11.40 (7.40-17.50)	6.11 (3.75-9.94)	7.27 (4.51-11.74)	4.10 (2.40-6.94)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	85 (16.0)	38 (1.8)	3.50 (2.03-6.03)	4.16 (2.39-7.23)	3.87 (2.21-6.77)	3.31 (1.83-5.96)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.

Appendix table 5: Distribution of major surgery in the hazard and control periods and odds ratio for deep vein thrombosis after excluding patients with active cancer at the time of the thrombotic event

	Hazard period (n=302) n (%)	Control periods (n=1208) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	51 (16.9)	21 (1.7)	13.54 (7.47-24.53)	7.01 (3.62-13.58)	8.87 (4.63-17.01)	5.26 (2.60-10.67)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	51 (16.9)	21 (1.7)	5.12 (2.49-10.51)	6.50 (3.12-13.55)	5.57 (2.64-11.75)	5.41 (2.49-11.76)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.

Appendix table 6: Distribution of major surgery in the hazard and control periods and odds ratio for pulmonary embolism after excluding patients with active cancer at the time of the thrombotic event

	Hazard period (n=229) n (%)	Control periods (n=916) n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Major surgery	34 (14.8)	17 (1.9)	9.25 (4.95-17.28)	5.13 (2.48-10.61)	5.65 (2.77-11.50)	2.89 (1.27-6.57)
			Model 5 OR (95% CI)	**Model 6 OR (95% CI)**	**Model 7 OR (95% CI)**	**Model 8 OR (95% CI)**
Major surgery	34 (14.8)	17 (1.9)	2.32 (1.00-5.41)	2.16 (0.89-5.28)	2.37 (0.99-5.63)	1.55 (0.61-3.96)

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 1: Unadjusted OR.

Model 2: Adjusted immobilization.

Model 3: Adjusted for infection.

Model 4: Adjusted immobilization and infection.

Model 5: Adjusted for immobilization, infection and trauma.

Model 6: Adjusted for immobilization, infection and central venous catheter.

Model 7: Adjusted for immobilization, infection and red blood cell transfusion.

Model 8: Adjusted for immobilization, infection, red blood cell transfusion, trauma, central venous catheter.