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Thromboembolic complications after upper abdominal cancer surgery at the University hospital of North Norway

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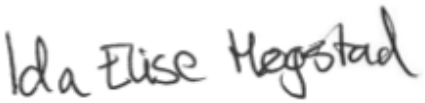
Preface

In the process of finding a project for my master thesis, I asked professor Arthur Revhaug if he had any ideas for a project. Professor Revhaug proposed to investigate the risk of Venous Thromboembolic (VTE) complications associated with short-term antithrombotic prophylaxis, used at University Hospital of North Norway (UNN) between 2013 and 2018, following resections of malignant tumors in the upper part of the abdomen.

This project has been supervised by Professor Arthur Revhaug and Consultant Surgeon Eirik Kjus Aahlin. Professor Revhaug supervised the recording of the data and contributed in the process of defining the project, with inclusion and exclusion criteria. Consultant Surgeon Aahlin supervised the process of organizing the data and writing the thesis. I would like to address a special thanks to the both of them for great support and feedback.



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Abstract

Background: Venous thromboembolism (VTE) is a serious and potentially fatal complication after surgery. Operations for malignancy in the upper abdomen are traditionally regarded as especially prone to such complications. Antithrombotic prophylaxis with low weight molecular heparing (LWMH) before and after surgery has been shown to significantly reduce the risk for VTE complications. Recommended duration of antithrombotic prophylaxis after abdominal cancer surgery is 28 days. Many clinicians argue that antithrombotic prophylaxis until the patient is fully mobilized is sufficient. The primary object of this thesis was to investigate the safety of short-term antithrombotic prophylaxis and the risk of developing VTE after major upper abdominal cancer surgery.

Method: This was a retrospective study of 493 patients undergoing elective surgery for cancer in the eosophagus, stomach, pancreas, liver, gallbladder and biliary tract at University Hospital of North Norway (UNN) Tromsø between 2013 and 2018. Patients which had a VTE while receiving antithrombotic prophylaxis, received antithrombotic prohpylaxis for more than 28 days, died within 90 days, were anticoagulated with vitamin K antagonists, LMWH or new oral anticoagulants before surgery, underwent minor surgery or were transferred to another hospital while still receiving antithrombotic prophylaxis, were excluded. Main outcome was symptomatic VTE diagnosed within 90 days after surgery.

Results: A total of 243 patients were excluded from the main study group. For the remaining 250 patients, five had a non-fatal VTE incident within 90 days of surgery (2%).

Conclusion: Five out of 250 patients (2%) who received antithrombotic profylaxis for less than 28 days suffered from VTE complications within 90 days after surgery. This study highlights the importance of sufficient VTE profylaxis after major upper abdominal cancer surgery.

Abbreviations:

- VTE: Venous thromboembolism
- DVT: Deep venous thrombosis
- PE: Pulmonary embolism
- LMWH: Low molecular weight heparin
- UFH: Unfractionated heparin
- ERAS: Enhanced Recovery After Surgery
- RCT: Randomized controlled trial
- UNN: University Hospital of North Norway
- EHR: Electronic Health Record
- DIPS: Electronic health record software, used at UNN

1 Introduction

1.1 Background

VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), are serious complications after many surgical procedures (1, 2). DVT occurs most often in the lower extremity. PE is an obstruction of the pulmonary artery or its branches by thrombus. The most common source of thrombus in the pulmonary artery is an embolization from the deep veins in the leg (3). PE is one of the most common preventable causes of in-hospital death following surgery. In general, the overall risk of VTE after surgery ranges from 0.5-1.6 % (4). For patients with underlying malignancy the risk is even higher (up to 3.7 %) (4, 5). Patients who undergo surgery for malignancy in the abdominal cavity are traditionally regarded as especially prone to VTE (6-8). Administration of LMWH subcutaneously (sc) before and after the surgical procedure has been shown to significantly reduce the risk of VTE (9).

The guidelines for pre- and postoperative antithrombotic prophylaxis varies significantly depending on baseline risk for VTE. Using the Caprini score (10), patients can be divided into different groups depending on their risk of developing VTE. Modified Caprini risk assessment is illustrated in Figure 1.

- Caprini score 0: Very low risk.
- Caprini score 1-2: Low risk.
- Caprini score 3-4: Moderate risk.
- Caprini score ≥ 5: High risk.

All patients undergoing major abdominal cancer surgery, have a Caprini score ≥ 4 (2 points for major or laparoscopic surgery > 45 mins and 2 points for present malignancy), and thus they are at moderate baseline risk for VTE, even without additional risk factors.

For patients with moderate risk and no contraindications, it is suggested to use pharmacologic prophylaxis rather than mechanical methods, such as compresssion stockings (4). LWMH is generally considered the preferred anticoagulant, based upon randomized trials that report superior or similar efficacy with unfractionated heparin (UFH), while being easier to administer and follow-up (11).

The reason for the increased risk of VTE after surgery is complex, especially in patients with cancer. Individuals with cancer are at risk for thrombotic events due to a hypercoagulate state. The pathogenesis of the hypercoagulable state in malignant diseases involves multiple factors. Some examples are listed below (12):

- Tumor specific factors: some tumor cells express procuagulant activity that can directly induce thrombin.
- Anatomic factors: some tumor increase VTE risk by externally compressing or directly invading large vessels.
- Patient-specific factors: VTE risk is increased in patients with prior VTE, advanced age, obestiy etc.
- Therapy-assosiated factors: Several chemotherapy regiments, bed rest and major abdominal surgery.

A review of 43 808 resections for malignant disease from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database (13), found that the risk of VTE was highest in patients undergoing esophagectomy (6.3%), followed by cystectomy, pancreatectomy, gastrectomy and colectomy. Patients with glucocorticoid steroid medication, advanced age (≥ 60), morbid obesity (BMI ≥ 35), blood tranfusion, reintubation, cardic arrest, postoperative infection complications and prolonged hospitalization were independently associated with increased risk of VTE.

In another review of 44 656 patients from the ACS NSQIP database (14), the following factors were associated with increased risk of VTE:

- Age ≥ 65
- Metastatic disease
- Ascites
- Congestive failure
- BMI ≥ 25 kg/m_2
- Platelet count > 400 × 10_9/L
- Serum albumin < 3 g/dl
- Duration of surgery > 2 hours

In the review, 1/3 of the VTE events occurred after hospital discharge and 30-day mortality was more than six-fold higher in patients with VTE compared to patients without VTE (8.0 vs 1.2 %) (14). VTE is associated with increased morbidity and mortality in cancer patients (15). However, data to support improvement in mortality by using anticoagulation is lacking (12).

A meta-analysis of eight Randomized Controlled Trials (RTCs) with five different preparations of LMWH that included > 48 000 general and abdominal surgery patients found that, compared with no prophylaxis, LWMH reduced the risk of symptomatic VTE by 70 percent, but also caused a two-fold risk of major bleeding and wound hematomas (16).

The optimal duration of postoperative anticoagulation in patients with cancer is unknown, but it is likely to be longer than for patients without cancer (12). Cancer-assosiated VTE is a common condition, but the incidence varies widely depending on multiple factors like patient population, cancer types and stages, patient-related factors and certain cancer therapies. The reported risk varies between 1-8% (17, 18). One RCT investigating the efficacy and safety of four weeks compared to one week administration of antothrombotic prophylaxis following major abdominal surgery, showed significantly reduced rates of VTE with 4 weeks prophylaxis, without increased risk of bleeding (7).

For most patients where antithrombotic prophylaxis is indicated, experts agree that pharmacological agents should ideally commence within 2-12 hours preoperatively (4). Generally, anticoagulation is continued daily for 10 to 12 days. 28 days is often considered reasonable for patients undergoing major abdominal or pelvic surgery (19). International and national guidelines generally recommend that postoperative administration of LMWH should last for 28 days after cancer operations in the abdomen (20-22).

Over the last years, important changes have been implemented in perioperative protocols which may lower the incidence of postoperative VTE after abdominal cancer surgery. Two of the most important factors are the introduction of Enhanced Recovery After Surgery (ERAS) protocols and the introduction of minimally invasive techniques (23, 24). These factors may reduce the thrombogenic insult, as the recovery of patients becomes faster and procedures are less invasive.

VTE prophylaxis guidelines used today are mostly based on studies from before ERAS and minimally invasive techniques were implemented. Thus, many clinicians argue that these factors reduce the probability of developing clinically significant VTE, and hence administer LMWH prophylaxis routinely for 5-7 days or until the patients are fully mobilized and ambulatory, on their way home. Even though this practice may seem logical, it has not been studied in more than one RCT, to our knowledge (25).

Randomized trials (7, 8, 25) have shown that four weeks duration antithrombotic prophylaxis with LWMH, decrease the risk of asymptomatic DVT by 50-60% without increasing the risk of postoperative bleeding compared to short-term prophylaxis. None of the studies disclosed a reduction in symptomatic DVT, symptomatic PE or VTE-related death.

One large cohort study from Denmark has recently shown administration of short-term antithrombotic prophylaxis seems safe for colo/rectal cancer surgery when the patients follow the ERAS programme (24). This study showed that the risk of symptomatic VTE after uncomplicated, elective surgery for colon cancer with ERAS seemed negligible. However, a recent large retrospective review of the NSQIP database (2005-2013) focusing on patients with gastric, colorectal, pancreatic, and gynecologic malignancies still argue that there are several conditions of abdominal operations that seems to benefit from prolonged prophylaxis (26).

A review of seven RCTs comparing prolonged thromboseprophylaxis (≥ fourteen days) with any LWMH agent with placebo or thromboseprophylaxis during admission only, found the incidence of overall VTE after major abdominal or pelvic surgery was 13.2% in the control group compared to 5.3% in the patients receiving out-of-hospital LMWH (27). The incidence of symptomatic VTE was 1% and 0,1% respectively.

The efficacy of prolonged antithrombotic prophylaxis (four weeks) with LWMH in patients undergoing hip or knee replacement, have been documented by meta analysis (28). These patients are arguably more immobilized after surgery, and application to a different population is questionable.

1.2 Aim

Traditional practice at UNN has been prolonged LMWH prophylaxis for 28 days after elective abdominal cancer surgery. For several years (including 2013-2018), patients undergoing abdominal cancer surgery at UNN received the first dose of LMWH the night before surgery and prophylaxis was generally continued until full mobilization or discharge (short duration).

The amount of research on prolonged antithrombotic prophylaxis is limited, especially in terms of number of randomized controlled trials (RCTs). The primary objective of this thesis was to thoroughly investigate the effect of short duration LMWH prophylaxis on the risk of developing VTE after major abdominal cancer surgery. The primary outcome was symptomatic VTE confirmed by ultrasound or CT within 90 days after surgery.

2 Method

The investigation was a retrospective cohort study of patients who underwent major abdominal cancer surgery in the upper abdomen at the Gastrointestinal Surgery Department at UNN, in the period from 2013 to 2018.

Major cancer surgery in the upper abdomen includes esophageal, gastric, pancreatic and major hepatobiliary cancer surgery (thus excluding colorectal cancers). Hence, patients who underwent a gastrointestinal surgical procedure corresponding to the following NCSP NCMP: JCC, JDC, JDD, JJB4, JJB5, JJB6, JJB1, JJB2, JJB3, JJB7, JJB9, JJB00, JJB01, JLC0, JLC1, JLC2, JLC3, JLC4, JLW96, JLW97 and ICD-10 codes C15, C16, C17, C22, C23, C24, C25, C78 were included. Only elective resections were included.

UNN has allocated resources for retrieving, pre-processing, and making available electronic health record (EHR) data from the Department of Gastrointestinal Surgery for the years 2004-2018 via the research project entitled *QUAKE: Quality control of medical performance with unstructured EMR data* (HST1194-14). This huge, longitudinal data set is referred to as the QUAKE database. The 493 patients included in this cohort were identified using the QUAKE

database. In order to adress the objective, the investigator used the electronic health record system for UNN (DIPS) to investigate the patients in the cohort.

For all patients, the following data were collected: diagnosis and procedure code, use of antithrombotic medications before the surgery, number of days receiving antithrombotic prophylaxis, and number of days being hospitalized. In this process, patients that were diagnosed with VTE using standard methods, were identified. Standard methods include e.g. diagnosing symptomatic DVT by Doppler ultrasound or PE by CT pulmonary angiography. In addition, reoperation and deaths were recorded. A qualitative assessment was performed for the patients that had a VTE incident within 90 days of surgery.

All of the UNN hospitals have a manual system for handling and documenting the patient´s in-hospital medication. Therefore, to register the number of days each patient received Dalteparin or other LWMH, handwritten and scanned medication lists used by the nurses in the ward, had to be examined.

Out of 493 patiens, a total of 243 patients were excluded from the study. These patients were excluded due to the following criteria's (Figure 2):

1. Patients that had a VTE incident within 28 days of surgery, while receiving antithrombotic prophylaxis. There were five patients in this group.
2. Patients that were transferred to a hospital outside the UNN system while still receiving antithrombotic prophylactic treatment. There were 120 patients in this group.
3. Patients receiving antithrombotic prophylaxis for more than 28 days. There were 41 patients in this group. Most of these patients had a complicated postoperative course and were immobilized for longer than 28 days or had multiple established risk factors for VTE.
4. Patients that died within 90 days after surgery. There were 8 patients in this group. None of these died from VTE related complications.
5. Patients already being treated with Vitamin K antagonist, LWMH or new oral anticoagulants before surgery and with continued treatment afterwards. Patients that started using these drugs in the postoperative course due to non-VTE related complications were also excluded. There were 38 patients in this group.

6. Patients that did not undergo major abdominal surgery, but minor procedures like placement of central venous catheter or needle biopsy. There were 25 patients in this group.

Also, six patients were excluded because the list of medication while hospitalized was not scanned into their medical records.

Patients who used platelet aggregation inhibitors, such as aspirin or clopidogrel, were not excluded because VTE prophylaxis is not an indication for these drugs (24).

Ultimately the study group included patients that underwent major cancer surgery in the upper abdomen at UNN Tromsø between 2013 and 2018, that were discharged or transferred to a local hospital within 28 days without prolonged antithormbotic prophylaxis (n = 250).

Use of the QUAKE-database for quality control is granted by REK (2012/2127) and The Norwegian Center for Research Data (NSD). The Data Protection Official at UNN HF granted permission for this internal control and quality assesment after Helsepersonelloven §26 and informed consent was not be required for this work.

3 Results

In the study group, 124 patients underwent laparoscopic resections. The median length of antithrombotic prophylactic treatment amongst these patients was seven days. 126 patients underwent open resections. The median length of antithrombotic prophylactic treatment amongst these patients was 12 days. Most of the patients received Dalteparin 5000 IU sc, but a few patients received Enoksaparin 40 mg sc.

The dispersion of tumor localization in the study group was as following:

- Esophagus: 24.
- Stomach: 59.
- Liver metastasis, mostly from colorectal cancer: 85.
- Primary liver tumor: 21.
- Biliary tract and gall bladder: 9.

- Pancreas: 41.
- Unspecified: 11.

Five patients that were discharged within 28 days of surgery without prolonged prophylaxis had a symptomatic VTE within 90 days. None of the incidents were fatal. All of these patients except one underwent open surgery. All of the patients were treated with anticoagulants for a minimum of 3 months after being diagnosed with VTE. Three of the patients had a PE (1,2%)

Qualitative assessment of these patients:

- Patient 1: 73 years old female, no prior history with VTE, no known cardiovascular disease. She underwent a laparoscopic resection of multiple lever segments after being diagnosed with metastatic colon cancer. The surgery was uncomplicated. Postoperative she had episodes with dyspnea, desaturation and low pO2. She went through a CT angiogram while hospitalized, but no PE was discovered. She received Dalteparin 5000 IU sc for a total of five days, starting the night before surgery. Six weeks after the surgery, she started adjuvant chemotherapy. Approximately two months after the surgery, she had repeated episodes of chest pain and dyspnea. She was hospitalized for an ultrasound of the heart that revealed cor pulmonale. CT did not show any sign of present PE, but she was diagnosed from the clinical picture and echocardiographic findings.
- Patient 2: 75 years old female. No prior history of VTE. Medically treated for hypertension, otherwise no known cardiovascular disease. Used Albyl-E 75 mg once daily prior to the surgery, uncertain indication. She underwent an open transhiatal esophagectomy. The surgery was uncomplicated. Postoperative she got atrial fibrillation and was treatet for three days in the intensive care unit with Cordarone. She also had a therapeutic thorascentesis due to symptomatic pleural effusion. She received Dalteparin 5000 IU sc for 16 days, starting the night before surgery. She was fully mobilized at the postoperative day seven. She was readmitted to the hospital 23 days after surgery with dyspnea and hypoxia and was diagnosed with bilateral PE using CT angiogram.
- Patient 3: 53 years old male. No prior history of VTE. No cardiovascular disease. He used Albyl-E before the surgery, the indication was uncertain. He underwent an open transthoracic esophagectomy removing a distal tumor in the esophagus. The surgery

was uncomplicated, but the tumor was bigger than expected and they had to do a total gastrectomy and cholecycstectomy. Postoperative the patients had a lot of pain, but otherwise the postoperative course was relatively uncomplicated. He received Dalteparin 5000 IU sc for 11 days, starting the night before surgery. He was diagnosed with a PE using CT angiogram 28 days after surgery.

- Patient 4: 55 years old male. No prior history of VTE. He used antihypertensive medication, otherwise no known cardiovascular disease. He underwent an open pancreatectomy and resection of the stomach. The procedure and postoperative course were uncomplicated. He received Dalteparin 5000 IU sc for 8 days, starting the night before the surgery. More than two months after the surgery he was admitted with stomach pain. CT scans from approximately 1,5 months after the surgery showed a thrombose in the portal vein and new CT scans showed an even bigger thrombus that involved the mesenteric veins.
- Patient 5: 71 years old female. No know cardiovascular disease, no prior history of VTE. She underwent an open resection of a tumor in the lever, suspected to be recurrence of previously treated HCC. The procedure and the postoperative course were uncomplicated. She received Daltaparin 5000 IU sc for three days, starting the night before the surgery. She experienced swelling and pain in her right foot 35 days after the surgery, and CT venography revealed thrombosis from the vene cava inferior, to vena tibialis posterior.

Four patients had a VTE incident while being hospitalized and still receiving antithrombotic prophylaxis. These patients were excluded from the study group, but the assessment of these patients is described below as it highlights the complexity of thromboembolic complications. Two of these patients had esophageal cancer, one had metastatic colon/rectal cancer, one had Hepatocellular carcinoma (HCC) and one had pancreatic cancer. These patients were treated according to national guidelines in regards of antithrombotic profylaxis and received treatment for the VTE with higher doses of anticuagulants after diagnosis.

Qualitative assessment of these patients:

- Patient 6: 56 years old male. No prior history of VTE. Known COPD. He had neoadjuvant chemotherapy before the surgery. He used Albyl-E 75 mg daily before the surgery after having a cerebrovascular incident three months before surgery. He

underwent transhiatal esophagectomy for an adenocarsinoma in the gastroesophageal junction (GEJ). He had a reoperation five days postoperative for wound dehiscence. He was intubated for several days. He received Dalteparin 5000 IU sc until he was diagnosed with PE on day 15 postoperative.

- Patient 7: 68 years old male. No prior history of VTE. Hypertension and diabetes mellitus type II. He underwent an open surgery for a pancreatic tumor that had locally advanced into the portal vein. He got multiple GoreTex grafts perioperative. He received Dalteparin 5000 IU sc x 2 daily. Six days after the surgery, he was reoperated due to abdominal pain and the GoreTex graft was occluded. A trombus was also discovered above the graft in the portal vein.
- Patient 8: 54 years old male with cancer coli with metastasis to the lever. He underwent an open lever segment resection. The procedure was uncomplicated, but postoperative he had a pneumothorax. The second day after the surgery his lactate levels were rising. He had a CT angiogram, but no PE was confirmed. He received Dalteparin 5000 IU sc daily. Day six postoperativ he had another CT angiogram that confirmed a suspected PE.
- Patient 9: 68 years old male with cancer sigmoideum with liver metastasis. He underwent an open lever segment resection. He received Dalteparin 5000 IU sc for five days, then Enoksaparin 40 mg sc for 21 days. He was diagnosed with DVT two and a half months after the surgery.

In addition, three patients that were anticuagulated with Vitamin K antagonists, LWMH or new oral anticoagulants prior to the cancer diagnosis and thus were excluded from the study group, had a VTE incident while hospitalized. Two of these patients had prior history of PE. They were given Dalteparin 5000 IU sc daily as antithrombotic prophylaxis until they were diagnosed with PE. The last patient was anticoagulated with 100 mg Enosaparin x 2 daily before the surgery and received Dalteparin 5000 IU once daily while hospitalized. He was diagnosed with a thrombus in v. jugularis interna 13 days postoperative.

Two patients that underwent minor surgery and thus were not included in the study group, had VTE complications within 90 days. One patient had a symptomatic DVT 26 days after an ERCP. The other patient had a symptomatic DVT 4 days after a needle biopsy in the liver. Both of these patients had hepatocellular carsinoma.

In this study group 8% of the patients that underwent a resection of the esophagus, 1% of the patients that underwent a liver segment resection for metastatic colorectal cancer, 5% of the patients that underwent a pancreatectomy and 2% of the patients that underwent a liver segment resection for HCC had a VTE incident within 90 days of surgery (Table 1).

4 Discussion

In this retrospective cohort study of elective surgery for cancer in the upper abdomen with antithrombotic prophylaxis for 28 days or less, VTE occurred in two percent of the 250 patients. These five incidents occurred in patients that received prophylaxis for 3-15 days after surgery. None of these patients had prior history of VTE or other established risk factors for VTE, other than age, present cancer and major surgery.

One percent of the patients in the study group that underwent laparoscopic surgery had a VTE incident (1/124) and three percent of the patients that underwent an open surgery had a VTE incident (4/126). The numbers in this study group are small. Still, this might indicate that there is a difference in risk of VTE for open and laparoscopic surgery. A significant difference has been reported in multiple larger studies (29-32).

The median duration of prophylaxis in this cohort was 12 days. Two percent of the patients that received short-term antithrombotic prophylaxis had a symptomatic VTE incdence within 90 days of surgery. In comparison, the Cochrane review found an incidence of 1% of VTE complications within 30 days in patients that received short-term antithrombotic prophylaxis (27).

The period of follow-up in was 90 days in this study. The longer the follow-up, the higher the risk of other factors contributing (e.g. chemotherapy). At least one of the patients which had an VTE incident within, 90 days received adjuvant chemotherapy in this period. The long follow-up period might contribute to a higher incidence of symptomatic VTE than in the Cochrane review. 0,8 percent of the patients in this study, had a VTE incident within 30 days of surgery.

The incident of VTE after major abdominal surgery found in studies varies greatly. Vendler et. al. found an incident of 0,2% of VTE in patients that underwent colorectal cancer surgery and receiving antithrombotic prophylaxis until discharge and following the ERAS programme (24). Vedovati et al. found VTE in 9,27% of the patients receiving antithrombotic prophylaxis for only one week after laparoscopic colorectal cancer surgery (25). Rasmussen et al. found the incidence of VTE to be 16,3% in patients that underwent open abdominal surgery (7). Both Vedovatis and Rasmussens studies also disclosed asymptomatic DVT, thus giving a higher incident than other studies. Henke et al. found an overall VTE risk of 2,2% within 30 days for patients undergoing colectomy (6).

All the patients with an VTE incident in the study group, underwent either esophagectomy, pancreatectomy or liver segment resection. Non of the patients that underwent resection of the stomach or tumors in the biliary tract/gallbladder had a VTE incident. This might indicate that esophagal cancer, pancreatic cancer and liver metastasis from colorectal cancer might be associated to a higher risk of VTE compared to stomach, gallbladder and biliary tract cancer. Due to the small numbers in the study group, the correlation might also be a coincidence and is not significant. More studies are required to affirm a significant correlation.

Some factors contributing to this variation might be related to the different surgical techniques used for different localization, difference in tumor characteristics etc. Removal of tumors in the pancreas and esophagus are complicated procedures that are usually preformed as open surgery, while e.g. removal of the stomach is more often done laparoscopic. Metastatic disease is known to increases the risk of VTE (13, 14).

This study has several limitations. As a result of the retrospective design, some cases of VTE might have been missed. In Norway, all acute cases of suspected VTE is usually diagnosed and treated at the public hospitals. In the study group, a number of the patients have a different hospital than UNN as their local hospital. When the VTE incident is believed to be a complication of the surgery, this is registered in the patient's health record. There is still a possibility that some patients had a VTE within 90 days and this was not reported as a complication to the surgery directly.

Since there is not yet an electronic system for handling everday in-hospital medications at UNN, the number of days patients received LWMH might be inaccurate. The scanned lists of given medication were from the nurses at the ward. Some days it was not registrered that a patient received LWMH. It is impossible to know if the nurses forgot to give the patient LWMH or if they forgot to sign the medication list. Hence, the number of days registrered might not be correct in some patients.

There have been several RCTs comparing 4 weeks duration of antithrombotic prophylaxis to 1 week (7, 24, 25), but all of these disclosed asymptomatic VTE incidents. The morbidity and mortality related to asymptomatic VTEs is not fully certain, but one mortality risk analysis of patients with metastatic colorectal cancer found a longer survival for patients with asymptomatic VTE than in patients without VTE (33). This suggest that the significance of asymptomatic VTE is small. Therefore, it would be valuable to do an RCT comparing four weeks versus one week of antithrombotic prophylaxis in patients having major abdominal cancer surgery where end point is symptomatic VTE. Ideally, such an RCT should be stratified on open and laparoscopic surgery.

In 2019, the Gastrointestinal Surgery Department at UNN changed the duration of antithrombotic prophylaxis. Today, all patients undergoing surgery for malignancy in the abdomen, receive a minimum of 14 days of antithrombotic prophylaxis.

5 Conclusion

Out of 250 patients that received short-term antithrombotic prophylaxis after cancer surgery in the upper part of the abdomen at UNN Tromsø between 2013 and 2018, two percent had a VTE incident within 90 days after surgery. In this study group, the overall risk of VTE was highest for patients that underwent esophagectomy. This study highlights the importance of sufficient length of VTE prophylaxis and is in accordance with other major studies

6 References

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7 Figures

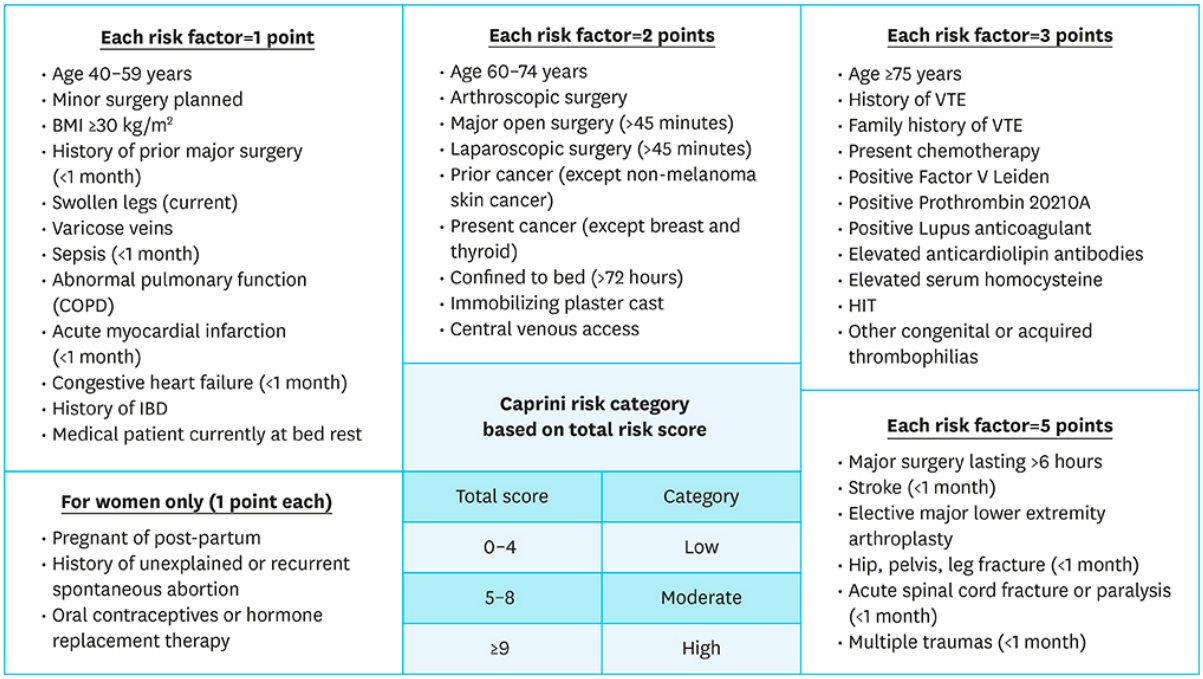

Figure 1: Caprini risk assessment model (34)

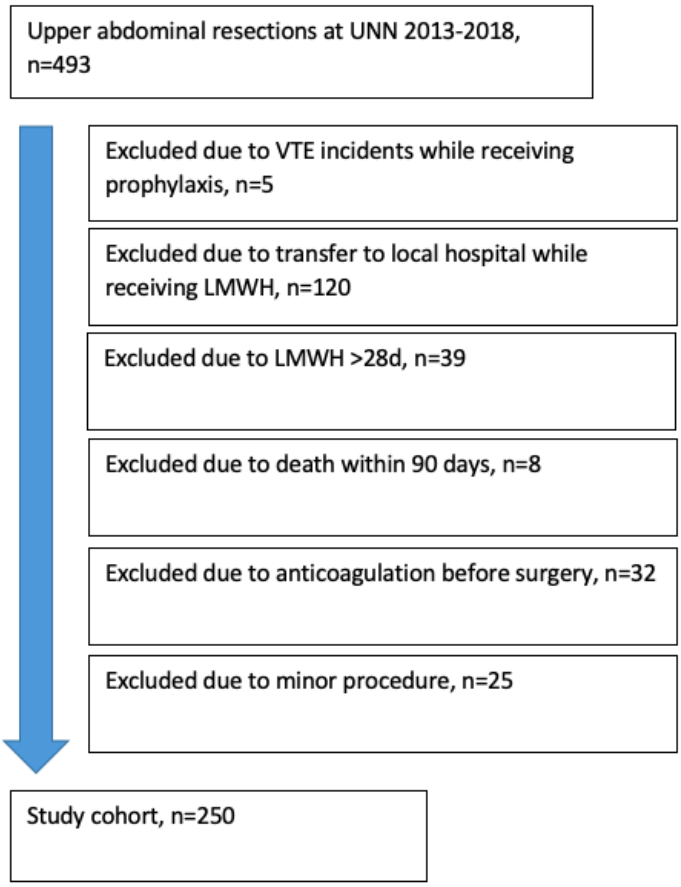

Figure 2: Patients excluded from the study group

8 Tables

Type of resection (n)	**VTE n (%)**
Esophagus (24)	2 (8)
Stomach (59)	0 (0)
Hepatic metastasis (85)	1 (1)
Primary hepatic tumor (21)	1 (5)
Biliary tract and gallbladder (9)	0 (0)
Pancreatic (41)	1 (2)
Unspesified (11)	0 (0)

Table 1: List of VTE incidents sorted by type of resection

9 Grade

Referanse: Rasmussen MS JL, Wille-Jørgensen P, Nielsen JD, Horn A, Mohn AC, et al. . Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. Journal of thrombosis and haemostasis. 2006;4(11):2384-90.			Studiedesign: **RCT** **Grade - kvalitet** Strong
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To evaluate the efficacy and safety of antithrombotic prophylaxis with LMWH, administered for 28 days after major abdominal surgery compared to 7 days treatment. **Konklusjon** Four-week administration of dalteparin, 5000 IU once daily, after major abdominal surgery significantly reduces the rate of VTE, without increasing the risk of bleeding, compared with 1 week of thromboprophylaxis. **Land** Denmark, Norway **År data innsamling** January 1997 – June 2003	**Inklusjons-/eksklusjonskrit.** Patients were eligible for inclusion in the study provided they were hospitalized for major abdominal surgery, gave written informed consent to participate in the study, and were over 18 years old. Major surgery was defined as an open abdominal surgical intervention in the gastric tract, the biliary system, pancreas, or intestine, as well as explorative laparotomy. The duration of the planned surgical procedure was more than 1 h. The exclusion criteria were severe peripheral arterial insufficiency (absence of a palpable pulsation in the dorsalis pedis artery), pregnancy, allergy to radiographic contrast medium, acid sulfite or LMWH, hepatic insufficiency, acute stroke within the last 3 months, gastrointestinal bleeding within the last month, hemorrhagic diathesis, anticoagula- tion treatment (including heparin, and vitamin K antago- nists, but not antiplatelet treatment), treatment with dextran, psychosis or severe dementia, simultaneous participation in another clinical study, or previous participation in the present study. **Datagrunnlaget** 590 patients were recruited, 427 patients were randomized and 343 patients reach an evaluable endpoint. 222 were randomized to short-term thromboprophylaxis and 205 to prolonged thromboprophylaxis. All patients received standard thromboprophylaxis with once-daily s.c. dalteparin, 5000 IU, and wore graduated compression stockings for 7 days. Patients scheduled for abdominal surgery were enrolled in the study and randomly assigned to receive either no further treatment after day 7 (short-term thromboprophylaxis group) or prolonged administration of once-daily dalteparin, 5000 IU s.c., for a further 21 days (prolonged thrombo-prophylaxis group). **Utfall (outcome) validering** The primary efficacy endpoint was objectively verified VTE occuring between 7 and 28 days after surgery. All patients underwent bilateral venography at day 28. **Eksponeringsvariabler (validert/ikke validert)** **Viktige konfunderende faktorer** The patients in the two treatment arms were well matched for age, sex, weight, previous VTE, and previous cancer (Table 1). The types of surgical procedure were similar in the two groups, colorectal resection being the most common. **Statistiske metoder** The chi-squared test was used for comparing binominal data, and the Mann–Whitney U-test for continuous data. The level of significance was taken as less than 0.05. For the estimation and interpretation of differences between the two groups in rates of VTE, 95% confidence intervals (CIs) were calculated. The statistical software used was SPSS for Win- dows, version 8.0 (SPSS Inc., Chicago, IL, USA). The occurrence of VTE was analyzed on an intention- to-treat (ITT) basis.	**Hovedfunn** The cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (29/178 patients) to 7.3% after prolonged thromboprophylaxis (12/ 165). The number that needed to be treated to prevent one case of VTE was 12 (95% confidence interval 7–44). Bleeding events were not increased with prolonged compared withshort-termthromboprophylaxis. **Hvor stor er «intervensjons-effekten»?** Relative risk reduction for overall VTE with 4 weeks prophylaxis was 55% (95% confidence interval 15–76; p 0.012). Relative risk reduction for DVT with 4 weeks prophylaxis was 51% (95% conficence iterval 6-74; p 0.027). **Bifunn – andre viktige endepunkter** Major and minor bleeding events were not increased in the prolonged vs. the short-term thromboprophylaxis group. Major bleeding occurred in four (1.8%) patients in the short- term group and in one (0.5%) patient in the prolonged thromboprophylaxis group.	**Sjekkliste:** • **Er formålet klart formulert?** YES • **Var gruppene like ved starten?** YES. • **Hvem er inkludert/ekskludert?** Both patients with cancer and with non-malignant surgeries were included. • **Randomiseringsprosedyre?** Computer-generated random allocation in blocks of 10, stratified by center. • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** Partly. The radiologist performing the venography was blinded. The patients either administrered Dalteparin for 1 or 4 weeks and thus were not blinded. • **Ble gruppene behandlet likt utover «intervensjonen»?** YES • **Primære endepunktet – validert? (Classificatin bias?)** YES. • **Ble deltakernne gjort rede for på slutten av studien? (attrition/follow-up bias)** YES. Patients were followed up for a period of minimum 2 months after venography. • **Kan resultatene overføres til praksis?** YES • **Ble alle utfallsmål vurdert?** YES • **Er fordelene verdt ulemper/kostnader?** YES • **Annen litteratur som styrker resultatene?** YES **Styrke:** - The robustness of the study was tested by an analysis that included randomized patients without a sound VTE endpoint. This analysis also showed a highly significant reduction in VTE with prolonged thromboprophylaxis. - Wide inclusion criteria to limit selection bias. **Svakhet:** - Preliminary results were published and might be source of bias. **Har resultatene plausible forklaringer?** YES

Referanse: Vedovati M BC, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. . A Randomized Study on 1-Week Versus 4-Week Prophylaxis for Venous Thromboembolism After Laparoscopic Surgery for Colorectal Cancer. Annals of Surgery. 2014;259(4):665-9.			Studiedesign: **RCT** **Grade - kvalitet**
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To compare the efficacy and safety of antithrombotic prophylaxis given for 1 week or 4 weeks in patients undergoing laporascopic surgery for colorectal cancer. **Konklusjon** VTE occurred in 11 of 113 patients randomized to short and in none of 112 patients randomized to extended prophylaxis. The rate of bleeding complications was similar in the txo groups. **Land** Italy **År data innsamling** 2010-2012	**Rekruttering deltakere** Consecutive patients who had undergone elective laparoscopic surgery for colorectal cancer in 5 hospitals in Italy were considered for inclusion. **Inklusjons-/eksklusjonskrit.** Patients with no evidence of VTE of the lower limbs after being examined with ultrasound 8± 2 days of antithrombotic prophylaxis were randomized. Patients were excluded in case of age < 18 years, noncancer surgery, anticipated duration of surgery < 45 minutes, conversion from laporascopic to open surgery, other indications for anticoagulant treatment, major postsurgery complications leading to reoperation or bleeding before randomization, renal or hepatic failure, known cerebral metastasis, bleeding disorders, intracranial hemorhage or neurosurgery within the previous 6 months, known hypersensitivity for LMWH, previous heparininduced thrombocytopeni, pregnancy or lactation or refusal to participate **Datagrunnlaget** 301 patients were evaluated for inclusion in the study and 225 were randomized. Study patients received antithrombotic prophylaxis for 8 ± 2 days starting on the evening before surgery. A complete compression ultrasonography of the venous system of the lower limbs was performed at day 8 ± 2 after surgery. Patients with no evidence of VTE were randomized to short (heparin withdrawal) or to extended (heparin continued for 3 additional weeks) prophylaxis in an open fashion. **Utfall (outcome) validering** The primary efficacy outcome was symptomatic VTE (deep vein thrombosis or pulmonary embolism) or deep vein thrombosis diagnosed at complete compression ultrasonography at day 28 ± 2 from surgery. Computed tomography or pulmonary angiography or ventilation/perfusion lung scanning was done to confirm the clinical suspicion of pulmonary embolism. **Statistiske metoder** Data were reported as frequencies or means ± SD according to variables. Continuous data were compared with the use of the *t* test. Categorical data were compared with use of either a χ 2 test or a Fisher exact test. The reported *P* values are based on 2-sided tests. To assess differences in the rates of VTE between the 2 treatment groups, the relative risk reduction and 95% confidence intervals (CIs) were calculated. Proportional hazards were calculated according to Cox regression statistics.	**Hovedfunn** VTE occurred in 11 of 225 patients (4.9%, 95% CI: 2.8%– 8.5%) from randomization to day 28 ± 2. All these events occurred in patients randomized to short heparin prophylaxis (11 of 113; 9.7%, 95% CI: 5.5%–16.6%); no episode occurred in patients randomized to extended heparin prophylaxis (95% CI: 0%–3.3%) (*P* = 0.001). The study was interrupted after the results of the interim analysis were available and showed a reduction in the rate of VTE in patients assigned to extended heparin prophylaxis (*P* < 0.01). VTE was proximal or symptomatic deep vein thrombosis in 2 patients, both presenting with signs and symptoms suggestive of VTE before the scheduled day 28 ± 2 examination (Table 2). The remaining 9 venous thromboembolic events were asymptomatic distal deep vein thrombosis. No episodes of pulmunary embolism was observed. During the 3-month follow-up period, VTE was suspected in 1 patient randomized to extended prophylaxis and in none of those randomized to short prophylaxis. The overall 3-month incidence of VTE was 5.3% (12 events out of 225 patients; 95% CI: 3.1%–9.1%) and, in particular, 9.7% (11 events out of 113 patients; 95% CI: 5.5%–16.6%) in patients randomized to short heparin prophylaxis and 0.9% (1 out of 112; 95% CI: 0.2%–4.9%) in patients randomized to extended heparin prophylaxis (relative risk reduction: 91%, 95% CI: 30%–99%; *P* = 0.005). None of the patients complained for signs or symptoms suggestive of pulmonary embolism during the 3-month follow-up. **Bifunn** At univariable analysis, age more than 70 years was a predictor of VTE (hazard ratio: 3.89, 95% CI: 1.17–12.93; *P* = 0.02), and advanced cancer (stage IV according to TNM Classification of Malignant Tumours [TNM]) was associated with a higher but not statistically significant risk of VTE (hazard ratio: 3.2, 95% CI: 0.42–24.90; *P* = 0.26). Age more than 70 years was confirmed to be an independent predictor of VTE at multivariable analysis (hazard ratio: 3.77, 95% CI: 1.13–12.55; *P* = 0.03). One patient randomized to short heparin prophylaxis experienced a major bleeding (intestinal bleeding with a blood loss of >20 g/L and requiring transfusions), and 1 patient randomized to extended prophylaxis experienced a clinically relevant nonmajor bleeding (rectal bleeding requiring heparin withdrawal) from randomization to day 28. The rate of major or clinically relevant nonmajor bleed- ing was 0.9% in each group (95% CI: 0.2%–4.8%).	**Sjekkliste:** • **Er formålet klart formulert?** YES • **Hvem er inkludert/ekskludert?** Only cancer patients included. • **Var gruppene like ved starten?** Demographic features, risk factors for VTE, type and stage of cancer, and duration of surgery were similar in the 2 study groups. • **Randomiseringsprosedyre?** A central randomization (1:1 short vs extended prophylaxis, in permuted blocks of 4, stratified according to study center) was used. • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** The patients were not blinded, but the assessor was. • **Ble gruppene behandlet likt utover «intervensjonen»?** YES • **Primære endepunktet – validert? (Classificatin bias?)** YES • **Ble deltakernne gjort rede for på slutten av studien? (attrition/follow-up bias)** YES • **Hva er resultatene? Presisjon?** Prolonged prophylaxis reduces the risk of VTE. • **Kan resultatene overføres til praksis?** YES • **Ble alle utfallsmål vurdert?** YES • **Er fordelene verdt ulemper/kostnader?** YES • **Annen litteratur som styrker resultatene?** YES **Hva diskuterer forfatterne som:** **-styrke** **-svakhet** - This was a study with an open design; however, randomization was central and the operator who performed ultrasonography was blinded to treatment assignment. - The suboptimal sensitivity of ultrasonography as screening test for deep vein thrombosis could have underestimated the event rates. - The study was that patients received different types of LMWH for prophylaxis of VTE. All types and doses of LMWH used in this study were val- idated in the extended prophylaxis of VTE after major orthopedic surgery. **Har resultatene plausible forklaringer?** YES

Referanse: Bergqvist D AG, Cohen A T, Eldor A, Nilsson P E, Moigne-Amrani A L, et al. . Duration of prophylaxis against venous thromboembolism with Enoxaparin after surgery for cancer. New English Medical Journal of Medicin. 2002;346(13):975-80.			Studiedesign: **RCT** **Grade - kvalitet** Strong
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To compare the efficacy of Enoksaparin to placebo for 21 days extended antithrombotic prophylaxis. **Konklusjon** Enoxaparin prophylaxis for four weeks after surgery for abdominal or pelvic cancer is safe and significantly reduces the incidence of venograph- ically demonstrated thrombosis, as compared with enoxaparin prophylaxis for one week. **Land** Denmark, France, Greece, Isreal, Italy, Sweden, Switzerland and the United Kingdom. **År data innsamling** 1998-2000	**Inklusjons-/eksklusjonskrit.** Eligible patients were 40 years of age or older, with a life expectancy of at least six months, and were scheduled to undergo open, elective, curative surgery for a malignant tumor of the gastrointestinal tract (other than the esophagus), genitourinary tract, or female reproductive organs. Procedures were performed with the patient under general anesthesia and with a planned duration of surgery of more than 45 minutes. The exclusion criteria were renal or hepatic insufficiency; known hypersensitivity to low-molecular-weight heparin or radiographic contrast medium; cerebral thrombosis, cerebral hemorrhage, or neurosurgery within the previous six months; known cerebral metastases, generalized bleeding disorders, endo- carditis, or active peptic ulcer; venous thromboembolism within the previous three months; uncontrolled arterial hypertension; treatment with heparin compounds or oral anticoagulant agents within five days before surgery; and pregnancy or lactation. **Datagrunnlaget** **Utfall (outcome) validering** The primary efficacy end point was deep-vein thrombosis verified by venograms read by a central committee that was unaware of the patients' treatment assignments, symptomatic pulmonary em- bolism confirmed by ventilation–perfusion lung scanning or pulmonary angiography, or both. Venography was performed routinely between days 25 and 31. A clinical suspicion of venous thrombo- embolism before that time required objective testing and adjudi- cation by a central committee. The secondary efficacy end point was death from thromboembolic disease before three months, with sep- arate analyses of mortality during the three-week double-blind period and the two-month follow-up period. The venographic results were evaluated and agreed on by the venography reading committee (consisting of three radiologists) before the investigators were unblinded. The primary safety end point was the occurrence of hemorrhage during the period of double-blind treatment. **Eksponeringsvariabler (validert/ikke validert)** **Viktige konfunderende faktorer** **Statistiske metoder** Categorical data were compared with use of either a chi-square test or Fisher's exact test. The reported P values are based on two- sided tests. For the estimation and interpretation of differences be- tween the groups in the rates of venous thromboembolism, 95 per- cent confidence intervals were calculated.	**Hovedfunn** During the double-blind period, the overall inci- dence of venous thromboembolism was 8.4 percent (28 of 332). In the group given one week of prophy- laxis (placebo group), the incidence was 12.0 percent (20 of 167); in the group given four weeks of prophy- laxis, it was 4.8 percent (8 of 165) (P=0.02). This corresponds to a reduction in risk of 60 percent (95 per- cent confidence interval, 10 to 82 percent). Proximal deep-vein thrombosis was identified in three patients in the placebo group and one in the enoxaparin group **Bifunn – andre viktige endepunkter** There were no significant differences between the groups in the incidence of major or minor bleeding during the double-blind period or the two-month follow-up period. There were no cases of thrombocytopenia	**Sjekkliste:** • **Er formålet klart formulert?** YES • **Hvem er inkludert/ekskludert?** Patients with cancer were included. • **Var gruppene like ved starten?** The patients in the two groups were well matched at baseline with regard to demographic variables, risk factors, and the type and duration of surgery • **Randomiseringsprosedyre?** Randomization was stratified according to the country where the institution was located. All patients randomly assigned to enoxaparin or placebo after the first week of therapy. • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** YES • **Ble gruppene behandlet likt utover «intervensjonen»?** YES • **Primære endepunktet – validert? (Classificatin bias?)** YES • **Ble deltakernne gjort rede for på slutten av studien? (attrition/follow-up bias)** YES • **Hva er resultatene? Presisjon?** Prolonged prophylaxis reduces the risk of VTE. • **Kan resultatene overføres til praksis?** YES. For cancer patients only. • **Ble alle utfallsmål vurdert?** YES • **Er fordelene verdt ulemper/kostnader?** YES. NNT 14. • **Annen litteratur som styrker resultatene?** YES **Hva diskuterer forfatterne som:** **-styrke** **-svakhet** Approximately one third of the patients did not undergovenography or had an uninterpretable venogram. **Har resultatene plausible forklaringer?** YES

Referanse:
Vendler MM I HT, Waage JE, Kleif J, Kristensen B, Gögenur I, et al. Incidence of venous thromboembolic events in enhanced recovery after surgery for colon cancer: a retrospective, population-based cohort study. Colorectal Disease. 2017;19(11).

Studiedesign: Population based study

Grade - kvalitet | Moderate

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To describe the risk of venous thromboembolism (VTE) and estimate the cost of preventing one case of VTE by prolonged thromboseprofylaxis (PT) under Enhanced Recovery After Surgery (ERAS). **Konklusjon** The risk of symptomatic VTE after uncomplicated, elective surgery for colon cancer with ERAS seems negligible and the cost-effectiveness of PT to prevent one symptomatic VTE seems questionable. **Land** Denmark **År data innsamling** 2008-2013	**Populasjon:** Patients undergoing elective surgery for colon cancer Stage I-III in the Capital Region of Denmark, 1 June 2008 to 31 December 2013. Patients not eligible for prolonged low-dose LMWH VTE prophylaxis were excluded according to the fol- lowing criteria: - Group 1. Patients, who died before discharge from hospital or were discharged at postoperative day 28 or later. These patients received LMWH until the time of death or discharge and are not relevant according to the guidelines in question. - Group 2. Patients already on prophylaxis with vita- min K antagonists (VKA), LMWH or new oral anti- coagulants (NOAC) before surgery and with continued prophylaxis afterwards were excluded from the analyses. This concurrent use was considered equivalent to, or more effective than, the prolonged low-dose LMWH VTE prophylaxis recommended in the guidelines. As such, patients were not included if they had a VTE less than 3 months before the resec- tion, as they were treated with one of the drugs men- tioned above. **Hovedutfall:** Primary outcome was the incidence of symptomatic VTE within 60 days after surgery. The secondary outcome was the cost of prolonged thromboprophylaxis with LMWH to prevent one symptomatic VTE. A sen- sitivity analysis of the primary outcome was performed, with deaths of unknown causes assumed to be VTE-related. **Statistiske metoder** Continuous data are presented as median [interquartile range (IQR)] values, and categorical data are presented as n (%). All statistical analyses were carried out using R statistical software, version 3.3.1	**Hovedfunn** In the study group, four (0.21%; 95% CI: 0.07– 0.58) of 1893 patients discharged within 28 days of surgery and without prolonged VTE prophylaxis had a symptomatic VTE diagnosed during the first 60 postoperative days of colon resection. As a result of the small number of VTEs, identification of risk factors using a multivariable logistic regression analysis was not plausible. **Bifunn** If we assume that the risk is equivalently reduced for symptomatic and asymptomatic VTEs and that the effect of prolonged VTE prophylaxis is a 60% reduction of the risk of VTE, the number needed to treat can be calculated. The number of VTE events in 1893 patients would decrease from 4 to 1.6 and the number needed to treat would be 789. If the three deaths from unknown causes within 90 days of surgery were caused by VTE, the number needed to treat is reduced to 451. The cost of each VTE prevented is estimated to be 517 660– 954 890 kr (Danish kroner), equivalent to £63 709– 111 455 at the time of writing.	**Sjekkliste:** • **Er formålet klart formulert?** YES • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** YES • **Var inklusjonskriteriene klart definert?** YES • **Var alle pasientene i samme stadium av sykdommen?** NO • **Var responseraten høy nok? Frafallsanal.?** YES • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** YES • **Er prognostiske/konfunderende faktorer beskrevet tatt hensyn til i design/anal?** YES • **Var registreringen prospektiv?** NO, retrospecitve. • **Var oppfølgningen lang nok?** Maybe. The longer the follow-up, the bigger the risk for other risk factor to contribute. • **Var oppfølgningen tilstrekkelig for å nå endepunktene?** YES • **Stoler du på resultatene?** YES • **Kan resultatene overføres til praksis?** YES • **Annen litteratur som støtter resultatene?** YES **Hva diskuterer forfatterne som:** **Styrke:** Population-based studies might be biased by misclassification if the data on medication are based on diagnoses or on prescriptions drawn from registers. To strengthen our study, we reviewed the medical records of all patients regarding anticoagulant defined as VKA, NOAC or LMWH. This enabled us to decrease the potential risk of selection bias by excluding only patients receiving VKA, NOAC or LMWH. This review also increased the validity of the outcome (i.e. symptomatic VTE). **Svakhet:** As a result of the retrospective design, some symp- tomatic VTEs may potentially have been missed, but because treatment of all acute cases of VTE in Denmark is managed within the public health system, the risk is very low. The minor differences in the ERAS protocols between the participating centres are a limitation, but the effect seems to be negligible because of the low risk of VTE found in the present study. Another limitation is that the end point is symptomatic VTEs only. **Har resultatene plausible biologiske forklaringer?** YES

Referanse:
Nguyen NT HM, Fayad C, Valera E, Konyalian V, Stamos MJ, et al. . Laparoscopic Surgery Is Associated With a Lower Incidence of Venous Thromboembolism Compared With Open Surgery. Annals of Surgery. 2007;246(6):1021-7.

Studiedesign: Retrospective Cohort

Grade - kvalitet Low

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
To compare the incidence of VTE after laparoscopic and open surgery over a 5-year period. **Konklusjon** Within the context of this large administrative clinical data set, the frequency of perioperative VTE is lower after laparo-scopic compared with open surgery. **Land** United States **År data innsamling** 2002-2006	**Populasjon** Patients from the University Health System Consortium (UCH) database who were 18 years or older and who underwent 1 of 4 commonly performed gastrointestinal procedures - appendectomy, cholecystectomy, antireflux surgery, and Roux- en-Y gastric bypass. These 4 procedures were selected because they have both the laparoscopic and open ICD-9 procedural codes for their respective procedures. **Kohorter** Patients that underwent laparoscopic compared with open appendectomy, cholecystectomy, antireflux surgery, and Roux-en-Y gastric bypass. **Hovedutfall** The principal outcome measure was the incidence of venous thrombosis or pulmonary embolism occurring during the initial hospitalization after laparoscopic and open surgery. The diagnosis of venous thrombosis and PE during the hospitalization for laparoscopic and open surgery was based on the presence of a secondary diagnosis of an ICD-9 CM code for venous thrombosis and/or PE. **Viktige konfunderende faktorer** **Statistiske metoder** Data was expressed as mean ± SD. Differences in patient characteristics and VTE between laparoscopic versus open group were analyzed using Fisher exact test or the Pearson's X^2 test. Univariate analysis was performed and the 95% confidence interval (CI) of the odds ratio (OR) was obtained. Continuous variables were compared using Student *t* tests. Statistical analysis was performed using Epi Info statistical software, version 3.3.2 (CDC, Atlanta, GA). A *P* value of less than 0.05 was considered significant.	**Hovedfunn** Overall, VTE was diagnosed during the index hospitalization in 259 of 92,490 (0.28%) laparoscopic cases and 271 of 46,105 (0.59%) open cases. Univariate analysis showed that open surgery was a significant factor for development of VTE even when stratified according to different level of severity of illness; for minor/moderate severity of illness level the OR was 1.83 (95% CI: 1.32–2.54) and for major/extreme severity of illness level the OR was 1.31 (95% CI: 1.06 –1.62). Laparoscopic appendectomy was associated with a lower rate of VTE compared with open appendectomy (0.11% vs. 0.28%, $P < 0.01$). Laparoscopic cholecystectomy was associated with a lower rate of VTE compared with open cholecystectomy (0.36% vs. 1.03%, $P < 0.01$) and persisted when stratified according to different severity of illness level; for minor/moderate severity of illness level the OR was 1.99 (95% CI: 1.20–3.27) and for major/extreme severity of illness level the OR was 1.35 (95% CI: 1.04– 1.74). Laparoscopic antireflux surgery was associated with a lower rate of VTE com- pared with open antireflux surgery (0.09% vs. 1.1%, $P < 0.01$) and persisted when stratified according to minor/mod- erate severity of illness level with an OR of 24.66 (95% CI: 2.61–580.87). Laparoscopic gastric bypass was associated with a lower rate of VTE compared with open gastric bypass (0.30% vs. 0.78%, $P < 0.01$) and persisted when stratified according to minor/moderate severity of illness level with an OR of 3.37 (95% CI: 1.76–6.45).	**Sjekkliste:** • **Formålet klart formulert?** YES • **Er gruppene rekruttert fra samme populasjon/befolkningsgruppe?** YES • **Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)** No. There was difference in the severity of illness between the 2 groups. • **Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?** NO • **Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene?** YES. • **Er den som vurderte resultatene (endepunktene) blindet for gruppetilhørighet?** No. • **Var studien prospektiv?** The study was retrospective. • **Ble mange nok personer i kohorten fulgt opp?** YES • **Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall?** NO. Only in-hospital data. • **Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?** NO. • **Tror du på resultatene?** YES • **Kan resultatene overføres til den generelle befolkningen?** NO • **Annen litteratur som styrker/svekker resultatene?** YES • **Hva betyr resultatene for endring av praksis?** The study is not good enough to change practice. **Hva diskuterer forfatterne som:** **Svakhet:** A weakness in comparing the outcome of laparoscopic versus open procedure is the limited use of risk-adjustment in most databases. An argument against the validity of the results in this study is that open procedures were performed in higher risk patients with more comorbidity. There is no information available on the use or nonuse of thromboprophylaxis or about the type (mechanical or antithrombotics) and duration of prophylaxis. Another limitation is that the data used in this study were obtained from an administrative database that does not have any information concerning the use or nonuse of thromboprophylaxis or the type and duration of the prophylaxis. There is also lack of information about the physiologic status of the patient and history for venous thrombosis or PE, and lack of body mass index for risk stratification in the morbidly obese patients. Additionally, the UHC database is compiled from discharge abstract data and is limited to in-hospital morbidity only without follow-up data. Therefore, VTE arising after discharge would not be captured in this database and we do not know the true incidence of VTE at follow-up for both groups.