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# THROMBOEMBOLISM FOLLOWING ORTHOPAEDIC SURGERY

OUTCOME AND DIAGNOSTIC PROCEDURES  
AFTER PROPHYLAXIS IN LOWER LIMB  
INJURIES

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To my family



# Abstract

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) frequently occur after major orthopaedic surgery. The clinical assessment of DVT and PE is unreliable and most cases are asymptomatic. However, even in asymptomatic DVTs, the risk for a PE is considerable. Low-molecular-weight heparins (LMWHs) have been shown to be safe and effective for this purpose and are used especially in patients undergoing major orthopaedic surgery. Whether prophylaxis is necessary after minor surgery and plaster cast immobilization of the lower limb still remains an issue of debate. Available techniques for the objective diagnosis of DVT include both invasive and non-invasive methods. Technical advances and increased experience have improved the accuracy of non-invasive methods such as colour duplex sonography (CDS).

In an observational study of 30 816 consecutive patients (*Paper I*) undergoing orthopaedic surgery the mortality and incidence of DVT and PE was recorded prospectively during a 6-week follow-up. After major joint surgery of the lower extremity, after spinal surgery and after lower limb fracture surgery, thromboprophylaxis (LMWHs) was administered during 7 to 10 days. The overall DVT and PE incidence was 1.0% and 0.3%, respectively, and the 6-week mortality was 2.3%. The highest incidence of venous thromboembolism (VTE) with the LMWH prophylaxis was seen after pelvic fracture surgery (13.0%) and knee replacement (3.5%). The highest incidence without prophylaxis was found after Achilles tendon repair (7.0%).

The sensitivity and specificity of CDS were compared with that of phlebography in a prospective trial (*Paper II*) with 180 consecutive patients surgically treated for ankle fracture. With a sensitivity of 96% and a negative predictive value of 99%, the results showed that CDS is highly reliable for ruling out DVT for screening purposes.

In a randomized placebo-controlled double-blind study (*Paper III*) on patients surgically treated for an ankle fracture, one week of open-labeled treatment with dalteparin was followed by 5 weeks of dalteparin prophylaxis or placebo. The phlebography verified a DVT incidence of 21% in the dalteparin group and 28% in the placebo group. This difference was not statistically significant and the results do not support the use of prolonged thromboprophylaxis after ankle fracture surgery.

In another randomized placebo-controlled study (*Paper IV*), thromboprophylaxis with dalteparin during 6 weeks was compared with placebo during immobilization after Achilles tendon repair. DVT screening was performed with CDS and all DVTs were confirmed with phlebography. The phlebography verified that the DVT incidence was 34% in the treatment group and 36% in the placebo group. This difference was not statistically significant and thromboprophylaxis after Achilles tendon repair cannot be recommended on the basis of these results.

In summary, despite prophylaxis VTE remains an important cause of morbidity and mortality after orthopaedic surgery. Adequate thromboprophylaxis is essential after major procedures although prolonged prophylaxis after ankle fracture surgery and Achilles tendon repair did not reduce the risk of DVT.

Keywords: Orthopaedic surgery, deep vein thrombosis (DVT), pulmonary embolism (PE), colour duplex sonography, phlebography, fracture surgery, Achilles tendon rupture.

# List of Publications

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This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (Papers I-IV).

- I. Venous thromboembolism following orthopedic surgery. A prospective 6-week follow-up of more than 30 000 consecutive patients surgically treated between years 1996 and 2003.  
*Lapidus L, Ponzer S, Pettersson H, de Bri E.*  
*In manuscript.*
- II. High sensitivity with color duplex sonography in thrombosis screening after ankle fracture surgery.  
*Lapidus L, de Bri E, Ponzer S, Elvin A, Norén A, Rosfors S.*  
*Journal of Thrombosis and Haemostasis 2006; 4:807-12*
- III. Prolonged thromboprophylaxis with dalteparin during immobilization after ankle fracture surgery - a randomized placebo-controlled, double-blinded study.  
*Lapidus L, Ponzer S, Elvin A, Levander C, Lärffars G, Rosfors S, de Bri E.*  
*Accepted for publication in Acta Orthopaedica.*
- IV. Prolonged thromboprophylaxis with dalteparin after surgical treatment of Achilles tendon rupture – a randomized, placebo controlled study.  
*Lapidus L, Rosfors S, Ponzer S, Levander C, Elvin A, Lärffars G, de Bri E.*  
*Journal of Orthopaedic Trauma 2007; 21:52-57.*

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# List of abbreviations

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CDS	Colour duplex sonography
CT	Computed tomography
DVT	Deep vein thrombosis
GCS	Graduated compression stocking
HIT	Heparin-induced-thrombocytopenia
INR	International normalized ratio
IPC	Intermittent pneumatic compression
LMWH	Low-molecular-weight heparin
LR	Likelihood ratio
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PA	Pulmonary angiography
PE	Pulmonary embolism
PPV	Positive predictive value
PTS	Post-thrombotic syndrome
THR	Total hip replacement
TKA	Total knee arthroplasty
VTE	Venous thromboembolism



# Introduction

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## Background

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common causes of morbidity and mortality after orthopaedic surgery.<sup>1, 2</sup> The clinical assessment of these complications is unreliable<sup>3, 4</sup> and the majority of venous thromboembolic events are asymptomatic.<sup>5</sup> Even for an asymptomatic DVT, the risk for PE is considerable.<sup>6</sup> Many DVTs, may however resolve spontaneously without further sequelae.<sup>7, 8</sup> In at least 10% of patients with symptomatic PE the death due to PE occurs within a few hours, before diagnostic and therapeutic action can be taken.<sup>9</sup> Therefore, the prevention of DVT is the most effective approach to preventing death due to PE. Early diagnosis and treatment of DVT may also limit the frequency of PE. Available techniques for the objective diagnosis of DVT include both invasive and non-invasive methods. Technical advances and increased experience have improved the accuracy of non-invasive methods such as colour duplex sonography (CDS).<sup>10</sup> A continuous evaluation of these methods is necessary as they have become interesting diagnostic alternatives.

The development of thromboprophylactic measures has reduced the frequency of venous thromboembolism (VTE) and the use of thromboprophylaxis has become routine after major orthopaedic surgery.<sup>11</sup> However, it still remains an issue for debate as to whether prophylaxis after minor surgery and lower limb immobilization is necessary.<sup>2</sup>

The DVT incidence after different surgical procedures is presented in **Table 1**.

Table 1. Approximate DVT incidence without thromboprophylaxis after different surgical procedures.<sup>1</sup>

Type of surgery	DVT incidence
Lower limb amputation	60–70%
Knee replacement	50–60 %
Hip fracture surgery	40–60%
Hip replacement	45–50%
Abdominal surgery	20–25%
Neurosurgery	20–25%
Gynaecological surgery	15–20%
Transvesicular prostatectomy	40%
Transurethral prostatectomy	10%
Surgical repair of inguinal hernia	5%

## Pathophysiology

A detailed understanding of the pathophysiology of VTE was first published by a German pathologist, Rudolf Virchow (1821–1902), in the 1850s.<sup>12</sup> He presented the cornerstones for clot formation in the veins in the classic “Virchow’s triad”, which includes impaired blood flow (venous stasis), a change in the blood composition resulting in increased coagulability and an endothelial injury in the blood vessel wall acting as a trigger factor for clot formation. By means of autopsy studies, he also described the mechanism of thrombus propagation in the veins followed by embolization to the pulmonary arteries.

## Clinical characteristics of postoperative VTE

The clinical appearance of a VTE is highly unpredictable. The majority of postoperative DVTs and PEs are asymptomatic<sup>5</sup> and therefore the true incidence is unknown. In cases where symptoms of a DVT break through, they can be mistaken for normal postoperative findings and thus remain undiagnosed. The majority of patients with PE symptoms have a DVT although less than 50% of them are symptomatic.<sup>13</sup> It has also been shown that about 50% of patients with a symptomatic proximal DVT have scintigraphic findings indicating a high probability of a PE, although asymptomatic.<sup>14</sup>

The clinical diagnosis of DVT is difficult because the symptoms and signs, such as limb swelling and pain, are unreliable and may be caused by other conditions than the DVT.<sup>3</sup> The accuracy of a clinical diagnosis can be improved if a clinical scoring system is used,<sup>15</sup> although this tool is recommended to be used together with objective tests, such as the CDS.

The clinical diagnosis of PE is also difficult and unreliable due to symptoms with low specificity. In the PIOPED study,<sup>16</sup> the angiographic results confirmed a PE in 68% of patients with a clinically highly suspected PE. When the clinical suspicion was low the PE was confirmed with angiography in 9% of the patients.

## VTE and orthopedic surgery

Orthopaedic surgery is an important risk factor for VTE. After major orthopaedic surgery 40–80% of the patients develop a calf vein thrombosis, 10–20% develop a proximal DVT, and 1–5% suffer a fatal PE in the absence of thromboprophylaxis.<sup>2</sup> Postoperative DVTs also occur in the contra-lateral leg after major joint surgery in approximately 25% of the patients,<sup>17, 18</sup> reflecting the systemic coagulopathy seen after surgery.<sup>19</sup> Cardiovascular disease and venous thromboembolism have been found to be the most common causes of death after major joint surgery.<sup>20, 21</sup>

Some orthopaedic procedures such as hip and knee replacements have therefore become popular models for assessing antithrombotic drugs. The risk of postoperative VTEs remains increased for 2–3 months after major orthopaedic surgery.<sup>22, 23</sup> The majority of thromboembolic events occur, however, during the first post-surgical month.<sup>23</sup> The peak incidence of DVT varies with the surgical procedure. After a TKA 85% of the DVTs diagnosed during the first post-surgical week were detected as early as the first day after surgery.<sup>24</sup> DVTs after THRs seem to occur later, with a peak incidence occurring 4 days after the surgery.<sup>25</sup> Approximately 10–15% of THR patients develop late DVT despite thromboprophylaxis during the first post-surgical week<sup>26, 27</sup> and VTE accounts for 26% of all readmissions after THR.<sup>21</sup>

Not only orthopaedic surgery, but also the trauma itself is an important risk factor for VTEs. Independent risk factors for a VTE after trauma include spinal cord injury, pelvic fracture and lower limb fracture.<sup>28,29</sup> Preoperative DVTs occur frequently. Up to 35–60% of patients with pelvic fractures have been found to have a DVT prior to surgery.<sup>30</sup> Preoperative DVTs are also common after femoral shaft fractures.<sup>31</sup> In patients with hip fractures, the preoperative DVT has been shown to occur in 10% and the risk of DVT tends to increase if hospital admission is delayed more than 2 days.<sup>32</sup>

Patients with hip fractures are at high risk for VTE. Within 3 months fatal PEs occur in 1.4–7% of the patients.<sup>33,34</sup> In an autopsy study fatal PEs accounted for 14% of all deaths after hip fracture surgery, being the 4<sup>th</sup> leading cause of death in this patient group.<sup>35</sup>

A prospective observational study conducted in 1968 by Hjelmstedt et al.<sup>36</sup> evaluated the natural history of VTEs in 79 patients surgically treated for tibial fractures and showed that the overall DVT incidence was 45% and a fatal PE was found at autopsy in one patient.

In another study by Abelseth et al.<sup>31</sup> the incidence of VTE in 102 patients with lower limb fractures was evaluated by phlebography approximately 9 days after surgery. The DVT incidence after a femoral shaft fracture, a proximal tibia fracture, a tibial shaft fracture and a distal tibia fracture was 40%, 43%, 22% and 12%, respectively. Four patients had symptoms indicating a PE but only in one case was the PE confirmed.

The significance of post-traumatic VTE was reported by Tuttle-Newhall et al.,<sup>37</sup> who showed that PE increases the risk for a fatal outcome tenfold, from 2.6% to 26%, after trauma. Advanced age and lower extremity injury were identified as individual risk factors for VTE in this study. Other individual risk factors for VTE are presented in **Table 2**.

Table 2. Risk factors for venous thromboembolism.

Acquired risk factors	Mixed risk factors	Inherited risk factors
History of VTE <sup>38</sup>	Hyperhomocysteinaemia <sup>39</sup>	Antithrombin deficiency <sup>40</sup>
Advanced age <sup>41</sup>	Cardiolipin antibodies <sup>42</sup>	Protein C deficiency <sup>43</sup>
Malignancy <sup>44</sup>	High factor VIII levels <sup>45</sup>	Protein S deficiency <sup>46</sup>
Obesity <sup>47</sup>		Factor V Leiden mutation <sup>48</sup>
Varicose veins <sup>44</sup>		Prothrombin polymorphism <sup>49</sup>
Oral contraceptives <sup>50</sup>		
Pregnancy and puerperium <sup>51</sup>		

Other surgical factors affecting the risk of developing VTE are the type of anaesthesia and the use of a tourniquet. General anaesthesia is associated with a higher risk for VTE compared to spinal and epidural anaesthesia.<sup>52</sup> The use of a tourniquet during lower limb surgery also increases the risk of VTE.<sup>53,54</sup> The deflation of the tourniquet can be a risk factor for PE,<sup>55</sup> and fatal PEs has been reported.<sup>56,57</sup> Surgery with the use of a tourniquet could be a possible risk factor if a preoperative DVT is present.

Another risk factor of importance is lower limb immobilization in a plaster cast, reported as early as 1944.<sup>58</sup> The epidemiology and prevention of VTE after lower extremity injuries have been poorly studied although a few authors have assessed the efficacy of thromboprophylaxis during plaster cast immobilization after lower limb injuries, as presented in **Table 3**.

Table 3. Prevention of VTE during plaster cast immobilization

Author	Year	LMWH	VTEs		P value
			LMWH	Control	
			n/n (%)		
Kujath et al. <sup>59</sup>	1993	Fraxiparine	6/126 (5)	21/127 (17)	<0.01
Kock et al. <sup>60</sup>	1995	Mono-Embolex	0/176 (0)	7/163 (4)	<0.006*
Jørgensen et al. <sup>61</sup>	2002	Tinzaparin	10/99 (10)	18/106 (17)	0.15
Lassen et al. <sup>62</sup>	2002	Reviparin	17/183 (9)	35/188 (19)	0.01

\* one tailed p-value.

Most of the studies are impaired, however, by methodological limitations: e.g., using non-validated screening methods,<sup>59, 60</sup> unblinded treatments<sup>59-61</sup> or an insufficient number of patients.<sup>61</sup> All published studies include mixed non-surgical and surgical patients with fractures and soft-tissue injuries even if in the studies by Jørgensen et al.<sup>61</sup> and Lassen et al.<sup>62</sup> the results for the different subgroups of patients (fractures/soft-tissue injuries) are also presented. In the only randomized and placebo-controlled trial with a phlebographic endpoint by Lassen et al.,<sup>62</sup> the authors demonstrated a significant risk reduction with reviparin during plaster cast immobilization (from 19% to 9%). However, a general consensus regarding thromboprophylaxis during lower limb immobilization does not exist.<sup>2</sup>

## Diagnosis of DVT and PE

Phlebography was introduced in 1923<sup>63</sup> and is considered to be the ‘gold standard’ for the diagnosis of DVT<sup>64</sup> and, if properly conducted, it offers a good visualization of the veins at all levels of the calf and thigh. The technique described by Rabinov and Paulin<sup>65</sup> is well adopted in clinical and scientific practice. The accuracy of DVT diagnosis in symptomatic patients is high<sup>66, 67</sup> even though the reproducibility has been questioned.<sup>68</sup> Other drawbacks with phlebography include the risk of contrast media reactions, the invasive technique and patient discomfort during vein puncture.



Figure 1. Phlebography showing a calf vein thrombosis.

Non-invasive diagnostic methods such as CDS are being used increasingly in clinical practice. Improved experience and technical advances with the introduction of colour Doppler and scanners with high-resolution B-mode imaging have improved the accuracy not only for asymptomatic proximal DVT<sup>69</sup> but also for symptomatic distal DVT.<sup>6</sup> However, the sensitivity of CDS in screening for asymptomatic DVTs, which is the most common form of DVT after surgery, has generally been low so far (38–58%)<sup>70, 71</sup> even though the method has not been sufficiently well validated. Other methods with limited clinical usefulness for DVT diagnosis include impedance plethysmography and fibrinogen uptake tests, which are no longer in use due to the risk of viral transmission. CT and MRI are not widely used for DVT diagnosis, hence are not discussed in this thesis.

Pulmonary angiography (PA) is regarded as the “golden standard” for the diagnosis of PE. Contrast medium is injected through a catheter directly into the pulmonary artery and radiographs are taken. A filling defect in the pulmonary arteries is diagnostic of PE.<sup>72</sup> However, since PA is an invasive examination and is typically not accessible at all hospitals, it is mostly performed when diagnostic uncertainty remains after other examinations such as ventilation/perfusion scintigraphy or CT.

With perfusion scintigraphy, circulation deficits in different lung segments can be detected after intravenous injection of a radioactive isotope. Ventilation defects can be identified after inhaling a gas labelled with radioactive isotope (ventilation scintigraphy). A perfusion defect indicating a PE needs to be matched against a ventilation scintigraphy to rule out other causes of abnormal lung perfusion such as

pneumonia and emphysema. In the evaluation according to the Biello<sup>73</sup> and revised PIOPED criteria, scintigraphic findings can be categorized into a normal, low, intermediate and high probability of PE. A normal perfusion scan essentially rules out the diagnosis of PE.<sup>74, 75</sup> A high probability scintigraphy combined with a high clinical probability of PE corresponds to an accurate PE diagnosis in 87–96%. If a low clinical probability is linked to the high probability scintigraphy, the probability of a PE decreases to 33–56%.<sup>16, 75</sup>

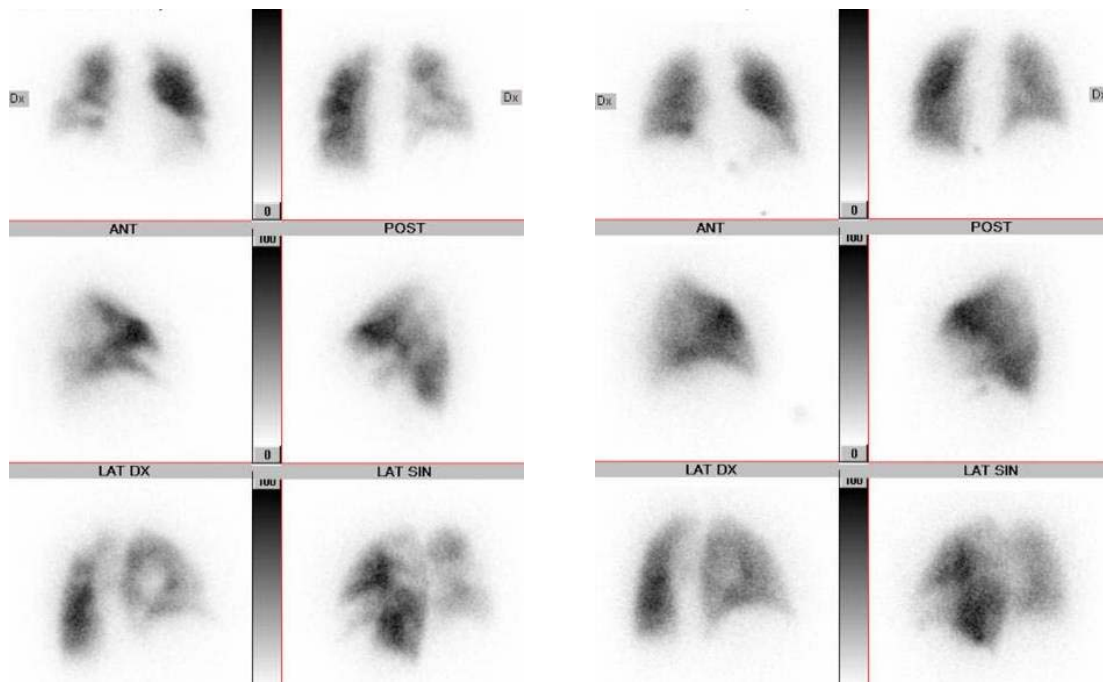


Figure 2. Perfusion scintigraphy (left) and ventilation scintigraphy (right) showing a PE.

Computed tomography (CT) with intravenous contrast has a high accuracy for PE diagnoses although small emboli may remain undetected. Technical advances with the introduction of spiral CT and multi sliced CT have improved the accuracy of the PE diagnosis. Compared to scintigraphy the number of inconclusive examinations is lower and the accuracy of the PE diagnosis and inter-observer reliability are higher.<sup>76, 77</sup>



Figure 3. Multislice CT with intravenous contrast media showing a large PE in the right pulmonary artery.



Magnetic resonance imaging (MRI) may also be used in the VTE diagnosis although this method needs to be further validated.

D-dimer in plasma is composed of cross-linked fibrin, a degradation product of plasmin. The test is available from several manufactures in different settings and each of them needs to be validated separately. D-dimer levels are typically elevated in a patient with VTE although the specificity and the negative predictive value are low since fibrin degradation occurs after several conditions such as wound healing, surgery, trauma, infections and VTE. The negative predictive value is higher, however, and therefore it has been suggested that the D-dimer test should be included in the diagnostic algorithms in patients with a suspected VTE, thus minimizing the need for other examinations.<sup>78</sup>

## **Consequences of a DVT**

The objective of the use of primary prophylaxis in the prevention of VTE is mainly to reduce the risk of PE and post-thrombotic syndrome (PTS). The most severe consequence of an acute PE is obviously sudden death and postoperative fatal PE often occurs in patients with a few other risk factors for sudden death.<sup>79</sup> However, most PEs occurs without symptoms and even symptomatic PEs are often overlooked or misdiagnosed, which could increase the risk of chronic PE and pulmonary hypertension. Both of these diseases are associated with considerable morbidity and mortality. Without thromboprophylaxis the incidence of fatal PE after THR, TKA and hip fracture surgery have been shown to be 0.1–0.4%, 0.2–0.7% and 3.6–12.9%, respectively.<sup>50</sup>

Post-thrombotic syndrome (PTS) is a permanent disability following both symptomatic and asymptomatic DVT.<sup>80</sup> The clinical presentation of PTS varies from mild venous insufficiency with moderate limb swelling to pain and chronic ulceration of the affected limb. The economic consequences for society and the morbidity for the individual can be significant.<sup>81</sup> Epidemiological data on PTS is scarce since the time to clinical presentation of PTS is very long and the initial DVT might never be diagnosed. Prandoni et al.<sup>82</sup> reported that PTS occurred in 20–30% of patients within 5 years of a diagnosed DVT.

The clinical significance of distal DVT is controversial.<sup>83</sup> Even though untreated distal DVTs propagate in 17–28% to proximal DVTs,<sup>84, 85</sup> the majority undergo spontaneous thrombolysis.<sup>7</sup> No clinical or radiological finding can predict, however, the outcome of a single distal DVT and since a DVT is necessary for the development of PE as well as PTS, it is reasonable to believe that even distal DVTs should be prevented and treated.

## **Risk assessment of VTE**

Several consensus conferences have defined risk categories of patients based on clinical criteria and have recommended thromboprophylaxis according to the degree of risk for VTE. The ACCP group (American College of Chest Physicians) have simplified the risk assessment for surgical patients in a model involving four different VTE risk levels based on the type of surgery ( e.g. minor or major), age (e.g., < 40 years, 40 to 60 years and > 60 years) and the presence of additional risk factors (e.g.,

cancer or previous VTE). The incidence of VTE in patients in the various risk categories who did not receive thromboprophylaxis is shown in **Table 4**.

Table 4. Risk categories and frequency of VTE

Level of risk	Distal DVT	Proximal DVT	Symptomatic PE	Fatal PE
<b>Low risk</b> # Minor surgery (<30 min) in patients <40 years old with no risk factors	2%	0.4%	0.2%	0.002%
<b>Moderate risk</b> # Any surgery in patients aged 40–60 years with no risk factors # Major surgery (≥30 min) in patients <40 years old with no risk factors # Minor surgery (<30 min) with risk factors	10–20%	2–4%	0.1–2%	0.1–0.4%
<b>High risk</b> # Major surgery in patients >60 years old with no risk factors # Major surgery in patients 40–60 years old with risk factors	20–40%	4–8%	2–4%	0.4–1%
<b>Very high risk</b> # Major surgery in patients ≥40 years old with any of the following: cancer, stroke or spinal cord injury, previous VTE	40–80%	10–20%	4–10%	0.2–5%

Prophylaxis recommended for moderate, high risk and very high risk group patients. Adopted from Geerts et al.<sup>86</sup>

This type of individual approach to thromboprophylaxis has limitations since it is more complex to administer, there is an obvious risk for suboptimal compliance and, finally, the outcome is difficult to evaluate. Hence, the clinical outcome of this protocol has not been validated.

The implementation of group-specific thromboprophylaxis protocols seems more appropriate since they simplify the evaluation of thromboembolic complications, are easier to administer and might also increase the compliance with existing protocols.

## Thromboprophylactic methods

### Pharmacological

The number of trials evaluating the efficacy of different agents in different settings for thromboprophylaxis is immense. The majority of trials involving orthopaedic patients have focused on prophylaxis after THR, TKA or hip fracture surgery. Several different agents are used for thromboprophylaxis in orthopaedic surgery. Each one of

them has limitations in the sense that they need to be injected or require laboratory monitoring.

Low doses (5000 U) of s.c. administered unfractionated heparin every 8 or 12 hours are an effective and safe form of prophylaxis in orthopaedic patients at risk for VTE. In a large analysis including orthopaedic patients by Collins et al., the risk for VTE and fatal PE was reduced by 60%–70%, from 0.8% to 0.3%.<sup>11</sup>

LMWH has a longer plasma half-life, better bioavailability and a more predictable dose response than unfractionated heparin.<sup>87</sup> LMWH has become the anticoagulant of choice for the prevention of VTEs during major orthopaedic surgery and after major trauma. The risk of bleeding with LMWH is small and is comparable to that of low-dose heparins. The risk of heparin-induced thrombocytopenia (HIT) is also lower than that with unfractionated heparin. Compared with placebo, the relative risk reduction for all DVTs, including proximal DVT, is approximately 70% with LMWH. Oral anticoagulants such as warfarin are broadly as effective as heparins but carry the disadvantage of requiring regular laboratory controls (an adjusted dose with target INR [international normalized ratio] 2–3 is recommended).

Aspirin is highly effective in reducing major vascular events in patients with established atherosclerosis. There are however, different opinions as to whether aspirin provides protection against VTE.<sup>88, 89</sup> Nevertheless, warfarins, LMWHs and heparins have all been shown to be more protective against VTE than aspirin.<sup>88</sup>

Several new compounds have also been introduced or are in the pipeline e.g. thrombin inhibitors, factor Xa inhibitors and synthetic pentasaccharides.

The synthetic pentasaccharide fondaparinux was compared with the LMWH enoxaparin in a large trial with hip fracture patients.<sup>90</sup> The verified VTE incidence was significantly reduced from 19.1% to 8.3% with fondaparinux without any increase in major bleeding. The incidence of proximal DVT was also reduced significantly (from 4.3% to 0.9%)

## **Mechanical methods**

Mechanical devices such as different intermittent pneumatic compression (IPC) devices, graduated compression stockings (GCSs) and others have been shown to increase the venous blood flow and reduce venous stasis. The rationale for thromboprophylaxis with these devices is the lack of bleeding complications. The use of both IPC and GCS has been evaluated in several studies and they have been shown to reduce the risk of DVT after both THR and TKA.<sup>91-94</sup> However, their protection against DVT is lower than that of both LMWHs and warfarin. The limited number of randomized studies, patient intolerance and poor compliance reduce the applicability of these devices. The additional benefit of mechanical prophylaxis when the patient has an appropriate pharmacological thromboprophylaxis has not been studied in randomized trials.

Prophylactic placement of vena cava filters in selected trauma patients may reduce the risk of PE, but randomized trials have not been performed and there is still a lack of evidence regarding their efficacy. Indications for vena cava filter insertion include high-risk situations for a PE along with an increased risk of bleeding. Cava filters increase the risk of recurrent VTE.<sup>95</sup>

## Timing and duration of thromboprophylaxis

There has been an ongoing debate regarding the optimal time to start with the first dose of thromboprophylaxis in major orthopaedic surgery. In Europe, the prophylaxis is usually initiated 12 hours preoperatively while North American orthopaedic surgeons have chosen to start the thromboprophylaxis 12 to 24 hours postoperatively out of concern for postoperative bleeding complications. In a metaanalysis,<sup>96</sup> it was shown that a preoperative start with LMWH in THR patients reduced the risk of DVT significantly from 15% to 10% compared to a postoperative start. Also, the risk for major bleeding was reduced significantly from 3.5% to 0.9%. In another review,<sup>97</sup> no significant difference was found between preoperative and postoperative starts of thromboprophylaxis. The differences in efficacy are most likely too small to be clinically relevant and both methods are acceptable.

The optimal duration of thromboprophylaxis is also still under debate. Convincing data show that the coagulation system is activated during at least 4 weeks after a THR.<sup>98, 99</sup> This finding supports the idea that prolonged prophylaxis could reduce the risk for VTE after THR. This issue has been evaluated in several double-blind trials<sup>18, 27, 100-103</sup> in which the efficacy of prolonged LMWH prophylaxis has been compared to placebo or to traditional short-term prophylaxis. In a review of these trials and other ones<sup>104-106</sup> a parallel reduction of both phlebographic DVT and symptomatic DVT was found. While a high (40–60%) relative risk reduction of VTE with prolonged prophylaxis has been demonstrated, the absolute risk reduction is lower. In one review<sup>107</sup> of symptomatic events after THR, the relative risk reduction was approximately 60% but, in terms of absolute risk reduction, it was as low as 1.6% for symptomatic VTE (from 2.7% to 1.1%), 0.4% for symptomatic PE and 0.1% for fatal PE.

## Bleeding complications

It is a well known fact that agents that reduce the incidence of VTE are associated with an increased risk of bleeding in the postoperative period. In general, the more effective a thromboprophylactic agent is in reducing the risk of VTE, the higher the risk of bleeding. Significant bleeding events are reported to range between 1 and 3% in different studies, but the measurement of bleeding complications due to thromboprophylaxis is difficult. Traditional measures such as haemoglobin decline, number of units of blood transfused, wound haematoma and the bleeding index all have limitations and uncertain clinical relevance.

Furthermore, the true risk of significant bleeding may be underestimated in clinical trials since they often exclude by protocol the most fragile patients with a previous bleeding history. Nevertheless, there is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio.

The increased risk of perispinal haematoma after spinal or epidural anaesthesia along with thromboprophylaxis<sup>108, 109</sup> is a major concern for orthopaedic surgeons and anaesthetists. The risk is very small (0.5 to 5.2 in 100 000 spinal or epidural punctions)<sup>110, 111</sup> but the consequences can be severe and result in paraplegia due to the compression and ischaemia in the spinal cord. Most patients that develop spinal haematoma have more than one risk factor for local or systemic bleeding, such as an underlying haemostatic disorder, vascular abnormalities, repeated attempts at spinal puncture, traumatic needle insertion etc.<sup>109, 112</sup> The removal of an epidural catheter in

association with anticoagulation has also been associated with spinal haematoma<sup>109</sup> and it is recommended that the catheter should be removed when the anticoagulation effect is at a minimum level. Prophylaxis should be delayed for at least 2 hours after a spinal puncture. General caution should be undertaken when considering neuraxial anaesthesia together with thromboprophylaxis. Detailed recommendations have been published.<sup>2, 113</sup>

## Aims of the studies

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To assess the incidence of symptomatic DVT and PE during the first six weeks after orthopaedic surgery (Paper I).

To assess the time to VTE diagnosis and the extent of DVT after orthopaedic surgery (Paper I).

To assess postoperative mortality 6 weeks after orthopaedic surgery (Paper I).

To evaluate the sensitivity and the specificity of CDS with those of phlebography in patients surgically treated for an ankle fracture (Paper II).

To evaluate the efficacy of prolonged thromboprophylaxis with dalteparin during immobilization after ankle fracture surgery (Paper III).

To evaluate the efficacy of dalteparin during immobilization after surgical treatment of an Achilles tendon rupture (Paper IV).

# Patients and Methods

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## Paper I

### Patients

All patients over the age of 15 surgically treated at the Department of Orthopaedics at Södersjukhuset between 1 March 1996 and 31 December 2003 were included in the study. Patients participating in clinical trials involving thrombosis screening were excluded (n=388) and 0.6% of the patients were lost to follow-up leaving 30 816 patients in the study population, 13 397 (43.5%) men and 17 419 (56.5%) women, **Table 5**.

The median age of all patients (at the time of their first surgery if operated upon more than once) was 59.9 years (SD 21.9 years, range 15.0–104.6 years). The median age for men and women was 49.3 years (SD 20.8 years) and 70.3 years (SD 20.7 years), respectively. Patients with more than one surgical procedure during a 90-day period were included only once in the analysis of venous thromboembolic events.

Table 5. Summary of patient accountability in Studies I-IV

	Paper I	Paper II	Paper III	Paper IV
Assessed for eligibility	31 458	180	1072	285
Did not meet inclusion criteria	0	-	246	28
Study personnel off-duty	-	-	109	74
Did not sign informed consent	-	-	151	52
Excluded from the study	388	-	294	26
Included	31 070	180	272	105
Lost to follow-up	254	36	44	4
Available for the analysis	30 816	144	228	101
<b>Primary analysis</b>	30 816	116	197	91

### Methods

In order to record the complications related to orthopaedic surgery, a questionnaire was distributed prospectively to all patients before discharge from the hospital. The follow-up time was 6 weeks. A research nurse was responsible for the data collection and for ensuring the follow-up of patients. Mortality within 6 weeks was recorded.

Complications (declared by the patients) were confirmed in medical charts and judged by an orthopaedic surgeon. All DVTs and PEs during the 6-week follow-up were considered to be complications related to the surgical procedure. All

thromboembolic events were symptomatic, diagnosed and treated according to standard hospital protocols.

All data, including surgical information about each patient, were stored in a local database. Before retrieving data for the analysis of venous thromboembolic complications and before the validation process, an extensive review of the register was performed to secure high-quality of data.

In the following validation process the accuracy of the surgical procedure codes in the register was tested for 4586 patients. To validate the completeness of VTE complications, all patients in the register were checked against those treated for DVT and PE at the hospital between the years 1998 and 2003. In addition, all VTEs diagnosed within 90 days after surgery were recorded to estimate the incidence of VTEs occurring on post-surgical days 43–90. Thereafter, a retrospective control of the diagnostic methods for VTE diagnosis was performed and all DVTs were categorized as distal (below the popliteal vein) or proximal (popliteal vein or above).

Incidence rates for VTE and all-cause mortality were analysed for different surgical procedures and correlated with pharmacological and mechanical thromboprophylactic protocols during the study period.

## **Paper II**

### **Patients**

The first 180 consecutive patients randomized to Paper III were included in a prospective study to compare the accuracy of CDS with that of phlebography in DVT diagnostics.

The study population included 83 males and 97 females with a median age of 47 years (range 18-76). All patients were surgically treated for an ankle fracture and immobilized with a plaster cast (n=147) or an orthosis (n=33) for 6 weeks before examination. After patient drop-outs and exclusions, 144 patients were left for analysis.

### **Methods**

Within 24 hours of the removal of the plaster cast or the orthosis, all patients underwent a clinical examination of the injured leg followed by a unilateral CDS and unilateral phlebography, all examinations being evaluated blindly.

The CDS examination was performed by experienced personnel using modern equipment. In summary, all proximal (in and above the popliteal vein) and distal (below the popliteal vein) veins were evaluated except the anterior tibial vein and muscular veins. The examinations were classified as positive for DVT, negative or inconclusive. The DVT diagnosis was based on a compression test of the affected blood vessel, which was visualized by means of colour Doppler flow.

Phlebography was performed after the CDS examination, using a modified form of the Rabinov and Paulin technique.<sup>65</sup> The phlebographic findings were considered to be the reference method in the comparison between the two diagnostic methods. Only a constant intraluminal filling defect seen in at least two projections was regarded as DVT.

Results were presented with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the likelihood ratio (LR).



## Paper III

### Patients

Two hundred and seventy-two patients with an acute ankle fracture were randomized to a prospective, double-blind study to evaluate the efficacy of prolonged thromboprophylaxis with dalteparin. The mean age of the study population was 48 (18-76) years, and 148 (54 %) of the patients were female.

The inclusion criteria were defined as patients 18-75 years of age admitted to the hospital with an acute (0-72 h) ankle fracture and accepted for surgery. Exclusion criteria are presented in **Table 6**.

Table 6. Exclusion criteria for Studies III and IV

Exclusion criteria for Studies III and IV
Inability or refusal to sign informed consent for participation in the studies, ongoing treatment with anticoagulant therapy, known allergy to contrast media, planned follow-up at another hospital, inability to comply with the study instructions (due to, for example, drug or alcohol abuse, cognitive dysfunction, etc.), known kidney disorder, nephrectomy or kidney transplantation, a recent thromboembolic event (within 3 months), recent surgery (within 1 month), known malignancy, a current bleeding disorder, pregnancy, treatment with high doses of acetylsalicylic acid (325 mg) or other platelet inhibitors, and multitrauma (injuries involving more than one organ system in addition to the musculoskeletal system, or patients with multiple fractures).

Of the 272 patients (**Table 5**) 136 were randomized to treatment with dalteparin and 136 were randomized to placebo, 197 patients (72%) were included in the primary analysis of efficacy and 75 patients were lost to follow-up (n=71) or excluded from the analysis (n=4).

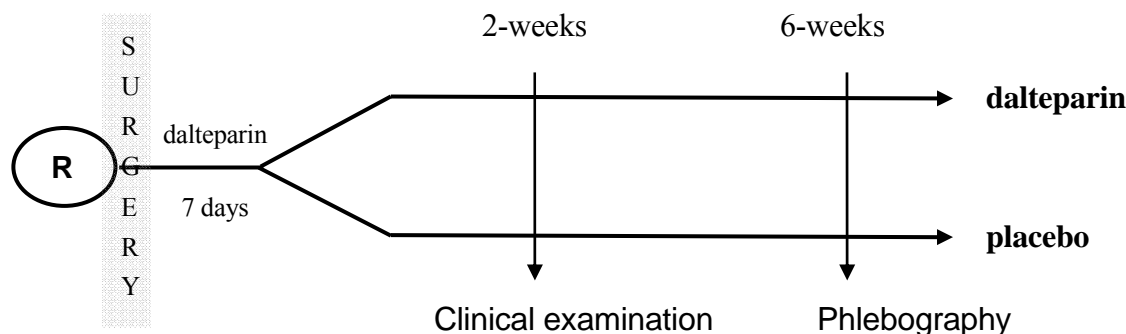
### Methods

After surgical treatment of the ankle fracture, all patients were immobilized with a plaster cast or orthosis for 44 days (+/- 2 days). Study medication was started after a 7-day open treatment with dalteparin and continued during the immobilization. Clinical examinations of the injured leg were done at 2 weeks and at 6 weeks postoperatively. Unilateral phlebography was performed when the cast was removed (+ 1 day). CDS was used in cases where the phlebography failed, most often due to difficulties in establishing a venous access (**Figure 4**).

The primary efficacy was assessed in terms of the number of patients in each treatment group with phlebographically verified distal and/or proximal DVT and/or PE. The primary endpoint analysis was performed according to the “intention-to-treat” (ITT) principle and patients receiving at least 1 dose of the study medication were included if assessable phlebography was obtained at the end of the study. An additional per-protocol analysis was carried out in patients with a compliance of more than 86% with the study medication (i.e. they had missed fewer than 6 syringes during the study period).

Secondary efficacy (secondary endpoints) included the incidence of phlebography or CDS-verified distal and/or proximal DVT and/or PE and the DVT incidence when using different types of immobilization (i.e. plaster cast or orthosis).

Figure 4. Design of Study III.



## Paper IV

### Patients

One hundred and five patients (83 men, 79%) with a mean age of 40 years were randomized to a prospective, double-blind study to evaluate the efficacy of prolonged thromboprophylaxis with dalteparin after surgical repair of an Achilles tendon rupture.

The inclusion criteria were: patients 18-75 years of age with an acute (0-72 h) Achilles tendon rupture accepted for surgery.

The exclusion criteria were the same as in Study III, presented in **Table 6**.

A total of 285 patients with an Achilles tendon rupture were assessed during the study period. Of these, 257 fulfilled the inclusion criteria and 105 were included in the study (**Table 5**). Fifty-two patients were randomized to treatment with dalteparin and 53 to treatment with placebo. In total, 91 patients (87%) were included in the primary analysis of efficacy performed according to the intention-to-treat principle. Fourteen patients were lost to follow-up or had inconclusive examinations.

### Methods

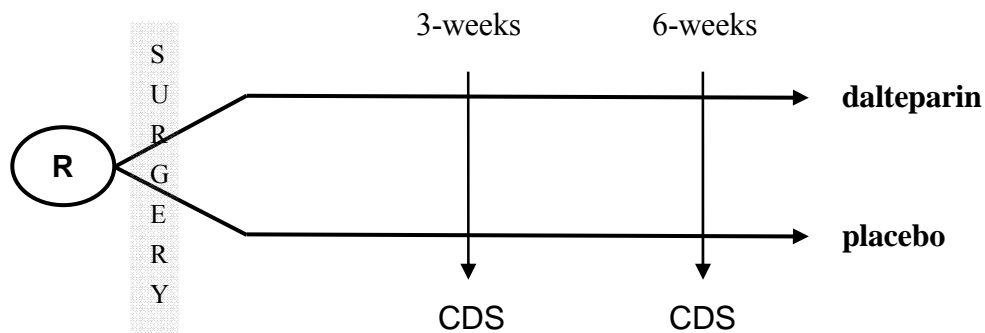
The surgical repair of the ruptured Achilles tendon was performed on average, 2 days after the trauma. Over 90% of the operations were performed under local anaesthesia. After a short medially placed skin incision, the tendon was repaired with an end-to-end suture, most frequently using a modified Kessler technique.

After surgery a below-knee plaster cast or an orthosis was applied with the ankle in the equinus position. The study medication was initiated a few hours after surgery, before discharge from the outpatient surgical ward and was continued during the immobilization.

Outpatient visits took place three weeks (when the plaster cast was replaced to allow full weight bearing) and six weeks (end of study) after surgery. At both visits a clinical examination was followed by screening for thrombosis with CDS (**Figure 5**).

DVTs diagnosed with CDS were confirmed with unilateral phlebography and the phlebographic results were used in the primary analysis of efficacy. In the secondary analysis of efficacy (n=96), CDS was accepted as the endpoint for patients with multiple distal DVTs or a proximal DVT.

Figure 5. Design of Study IV.



### Randomization

The randomization in Papers III and IV were performed with numbered, sealed envelopes and the randomization order was computer-generated and the block size was known only to the statistical co-ordinator.

Randomization was not performed in Paper I. In Paper II the first 180 patients from Paper III were examined.

### Study drug administration

The study drug used in Papers III and IV was prefilled in identical syringes to a volume of 0.2 ml and consisted of either placebo (9% (w/v) sodium chloride) or 5000 U dalteparin (Fragmin®, Pharmacia & Upjohn/Pfizer Inc.). In both studies, the study drug was administered subcutaneously once daily and all patients were trained in self-injection techniques by a study nurse before leaving the hospital.

In Paper III the administration of the study drug was started on day 8 after surgery, following a 7-day long open-labelled treatment with dalteparin. The initial dalteparin prophylaxis started in the evening after surgery or the evening before surgery in case of delayed surgery (more than one day after admission). The patients received the study drug during the remaining period of immobilization (35 days, +/- 2 days).

In Paper IV, the study medication was started a few hours after surgery, before discharge from the outpatient surgical ward and was continued throughout the immobilization (43 days, SD 2 days).

## **Patient safety and treatment of VTE**

In Papers III and IV, all patients were encouraged to report all kinds of unexpected events (including bleeding events) during and after the follow-up. All adverse events were recorded and judged by the investigator.

In Paper III a minor bleed occurred in 2 patients (1 in the dalteparin group and 1 in the placebo group) and the study treatment was stopped at the patients request due to discomfort. In Paper IV a minor bleed occurred in one patient (in the dalteparin group) and, due to discomfort, the treatment was stopped. No major bleeding occurred in any of the studies and other adverse events were of a technical nature.

For patients diagnosed with a DVT in Papers II-IV, anticoagulant treatment with warfarin (WARAN®, Nycomed AB, Stockholm, Sweden) was initiated according to standard protocols at the Department of Internal Medicine. This secondary prophylaxis was given for three months to patients with a DVT. To patients with symptomatic muscle vein thrombosis, secondary prophylaxis was given for three to six weeks, in some cases using subcutaneous dalteparin 200 U/kg/day instead of warfarin.

## **Phlebographic examinations**

In Papers II-IV the phlebographic examinations were performed with the patients examined standing without bearing any weight on the examined leg. Tourniquets were avoided when a contrast agent (100 ml of Omnipaque®, 240 mgI/ml) was administered intravenously as peripherally as possible. Several injections were given when necessary. Images of the calf were taken in three projections (anterior posterior (AP), lateral and AP with internal rotation). Images from the popliteal vein to the pelvis were taken in at least two projections (AP and lateral).

The criterion for diagnosing a DVT was a constant intraluminal filling defect seen in at least two projections. The DVT was considered to be proximal when it was located in or above the popliteal vein. The study radiologist made an individual interpretation of the examination in cases for which there was a short isolated inadequate vascular segment, classifying the result as positive, negative or inconclusive. For clinical purposes, a preliminary evaluation of the examination was made by the radiologist on duty. A standardized secondary evaluation was then performed by a blinded independent reader unaware of previous imaging findings. If the interpretation of the phlebographic findings differed between the preliminary and the secondary evaluations, a third blinded independent reader examined the phlebographic findings to reach a consensus statement.

## **Colour duplex sonography**

For Papers II-IV, a Siemens Acuson Sequoia (C512 Mountain View, Ca, USA) duplex imager was used in all CDS examinations. The examination was performed by experienced personnel. A standard procedure was used that included evaluation of the following venous segments in all patients: external iliac (distal part), common femoral, superficial femoral, popliteal, tibiofibular trunc, posterior tibial and peroneal veins. The proximal veins were examined with the patient in the supine position, and the popliteal vein and calf veins were examined with the patient in the sitting position with the leg hanging down.

If a vascular segment shorter than 2 cm could not be seen, but no other signs of DVT were present (i.e. the flow signals immediately above and below this short segment were normal), the case was classified as negative.<sup>114</sup> Anterior tibial veins and soleal veins, although readily accessible with CDS, were not included in the study protocol in Paper II since, according to our experience, they are not consistently demonstrated phlebographically and thus are of minor interest for the comparison between these diagnostic modalities.

DVT was diagnosed based on the criterion of abnormal wall compressibility in the transversal plane. Prior to this, the vessels were visualized by means of colour flow Doppler, which is especially important in the calf in order to identify the multiple vein segments. If a vascular segment measuring 2 cm or longer could not be seen, but no definite DVT was diagnosed since compressibility results could not be obtained, the result was classified as inconclusive. All positive or inconclusive studies and all other examinations

considered to be technically difficult were reviewed by a specially trained vascular physician before ending the examination. This physician classified the result as negative, positive or inconclusive.

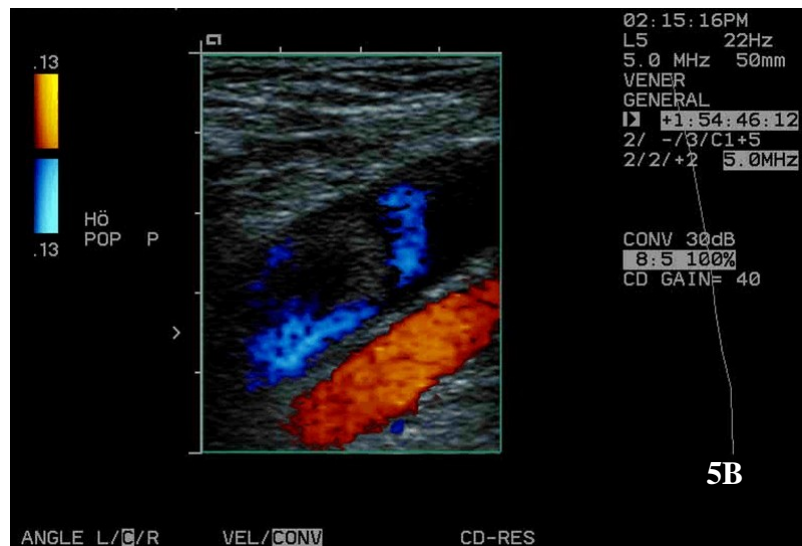


Figure 5. (A and B) CDS showing a DVT in the popliteal vein.

### Statistical methods

Differences between groups were assessed using Student's *t*-test for continuous variables and the *chi*-squared test or Fisher's exact test for categorical variables. An  $\alpha$ -level of less than 0.05, two-tailed, was considered significant in all tests.

In Paper II, the diagnostic performance of CDS is presented with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) along with 95% confidence intervals. The phlebographic outcome was used as the reference method. In addition, likelihood ratios (LRs) with 95% confidence intervals were calculated for CDS results.<sup>115</sup> The LR indicates how much the CDS result will raise or lower the probability of DVT. Likelihood ratios greater than 1 increase the probability and LRs less than 1 decrease the probability of DVT. In general, an LR >10 or <0.1 generates large and, most often, clinically important changes from pretest to posttest

probability, whereas LR<sub>s</sub> of 1-2 and 0.5-1 alter probability to a small and clinically unimportant degree.

All primary analyses of efficacy in Papers III and IV were performed according to the “intention-to-treat” (ITT) principle, and patients receiving at least one dose of study medication were included if an assessable endpoint analysis was achieved at the end of the studies. In Paper III, a per-protocol analysis was carried out for patients whose compliance with the study medication was more than 86% and who had an assessable phlebography at the end of the study. In Paper IV, DVTs were excluded with a normal CDS examination and the phlebographically verified incidence of DVT was used in the primary analysis of efficacy. In the secondary analysis of efficacy, CDS was accepted as the endpoint for patients with multiple distal DVTs or proximal DVT.

The power analysis in Papers III and IV was based on the work of Kujath et al.<sup>59</sup> For Papers I and II no power analysis was performed.

The data were analysed using the SPSS statistical software. For Studies II-IV, version 11.0.0, SPSS Inc., Chicago IL, was used, for Study I, version 13.0.0, SPSS Inc., Chicago IL. For all studies the design, data entry, editing and analyses were carried out by the investigators.

## **Ethics**

All the studies were approved by the Ethics Committee South of the Karolinska Institute and conducted according to the Helsinki Declaration. The informed consent of all patients in Papers II-IV was obtained. Paper I was also judged by the Ethics Committee and was considered to be a quality assurance project.

# Results

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## Paper I

There was 99% (4564/4586) agreement in the coding of femoral fractures between the discharge register and our register. In 90% the code was identical and in 9% the code was comparable at 3 or more levels (out of 5), meaning that only the type of femoral osteosynthesis was coded differently. In our register 0.3% (n=14) of the patients in the discharge register were missing. One patient had an incorrect code.

We found 12 more unregistered VTEs in the retrospective control during the years 1998–2003, which were thus missed in our registration process. For one patient, registered with a postoperative PE, the diagnosis was subsequently withdrawn.

During the same years another 38 patients suffered a VTE (30 with DVT and 8 with PE) during postoperative period days 43–90, after our follow-up time. These late VTEs, diagnosed after our 6-week follow-up period, represented 11% (38/350) of postoperative VTEs during the years 1998–2003.

During the 6 post-surgical weeks, 2.3% (n=719) of the 30 816 patients deceased. The overall incidence of DVT and PE was 1.0% (n=312) and 0.3% (n=98), respectively. In total, 1.3% of the patients (n=392) suffered a VTE during the 6-week follow-up. The median age of patients diagnosed with DVT and PE was 58.4 years (SD 19, range 15–95 years) and 78.1 years (SD 16, range 19–100 years), respectively.

The median time to DVT diagnosis was 16 days and 82% (n=257) were diagnosed after hospital discharge. Phlebography was the most common diagnostic method for DVT and approximately a third of the DVTs were located in proximal veins.

The median time to the PE diagnosis was 17 days and 71% (n=76) were diagnosed after discharge from the hospital. CT and ventilation/perfusion scintigraphy were the most common diagnostic methods although 17% (n=17) of the PEs were diagnosed at autopsy. Thirty-four percent (n=33) of the PEs were recorded as fatal. Autopsy was performed in 4.3% (n=31) of patients deceased during the 6-week follow-up.

An overview of the mortality and the incidence of VTE after different surgical procedures is presented in **Table 7**.

For surgical procedures performed without thromboprophylaxis, the highest VTE incidence was found after Achilles tendon rupture (7%). A low incidence of VTE was registered after other procedures done without thromboprophylaxis: knee arthroscopy (0.5%); foot surgery (0.5%); upper extremity surgery (0.2%) and other minor procedures (0.4%).

The mortality and the incidence of VTE after hip replacement varies with the indication for surgery. The incidence of DVT and PE after THR following degenerative hip disorders was 1.6% and 0.9%, respectively. Hip prosthesis surgery after proximal femur fracture is presented in **Table 8** together with other lower limb fractures treated with osteosynthesis. The highest incidence of VTE despite thromboprophylaxis was found after pelvic fracture surgery (13%). Highest mortality was found in proximal femur fracture patients. No VTEs were recorded after patella fracture.

Table 7. VTE and all cause mortality following orthopaedic surgery

	Mortality	PE	DVT
	- n (%)	- n (%)	- n (%)
Hip replacement * (all indications) (n=3196)	91(2.8)	24 (0.8)	38 (1.2)
Knee replacement * (all indications) (n=1078)	1 (0.1)	2 (0.2)	37 (3.4)
Spinal surgery * (all indications) (n=1115)	8 (0.7)	3 (0.3)	0
Lower limb amputation * (at or above ankle) (n=776)	110 (14.2)	7 (0.9)	2 (0.3)
Pelvic and lower limb fracture * - all osteosyntheses (n=10395)	524 (5.0)	51 (0.5)	111 (1.1)
Knee arthroscopy (n=5450)	2 (0.04)	2 (0.04)	24 (0.4)
Anterior cruciate ligament reconstruction * (n=547)	0	0	3 (0.5)
Achilles tendon ruptures (n=668)	0	0	47 (7.0)
Foot surgery (n=2461)	11 (0.4)	1 (0.04)	12 (0.5)
Upper extremity surgery (n=7249)	30 (0.4)	4 (0.06)	8 (0.1)
Miscellaneous procedures in the lower limb □ (n=915)	18 (2.0)	2 (0.2)	12 (1.3)
Minor surgery (n=4696)	63 (1.3)	2 (0.06)	17 (0.4)

\* Protocol for thromboprophylaxis during 7–10 days

□ Thromboprophylaxis practice differs



Table 8. VTE and all-cause mortality following lower extremity fracture

Fracture location	Median Age (25 <sup>th</sup> -75 <sup>th</sup> percentile)	Mortality – n (%)	PE – n (%)	DVT – n (%)
Pelvis (n=46)	45.1 (31–57)	1 (2.2)	3 (6.5)	3 (6.5)
Acetabulum, THR (n=22)	74.4 (68–81)	2 (9.1)	0	1 (4.5)
Proximal femur fracture osteosynthesis (n=6914)	83.1 (77–88)	492 (7.1)	32 (0.5)	41 (0.6)
Proximal femur fracture, THR (n=271)	78.3 (72–83)	7 (2.6) <sup>□</sup>	5 (1.8)	2 (0.7)
Proximal femur fracture, hemiarthroplasty (n=430)	84.6 (80–89)	47 (10.9)	4 (0.9)	1 (0.2)
Femur (diaphysis and distal) (n=519)	76.7 (62–86)	25 (4.8)	1 (0.2)	6 (1.2)
Patella (n=133)	63.2 (48–75)	0	0	0
Proximal tibia (n=308)	52.3 (38–67)	0	3 (1.0)	11 (3.6)
Diaphyseal tibia/fibula (n=416)	46.6 (33–58)	1 (0.2)	2 (0.5)	5 (1.2)
Distal tibia/fibula (n=136)	47.9 (36–62)	0	1 (0.7)	1 (0.7)
Ankle fracture (n=1923)	51.2 (37–63)	5 (0.3)	9 (0.5)	44 (2.3)
Foot fracture (n=239)	38.7 (26–51)	0	0	1 (0.4)

□ Including 3 fatal PEs, 2 verified at autopsy and one by an with undefined diagnostic method

## Paper II

Diagnostic tests that could be evaluated according to the study protocol were available for a total of 116 patients. Thus 28 examinations were regarded as inconclusive or technical failures. The DVT incidence was 21% (24/116) by phlebography and 31% (36/116) by CDS. With phlebography, proximal DVT was diagnosed in 6 out of 24 DVTs (5% of the population).

Compared to phlebography, the CDS result was false negative in one case and false positive in 13 cases. The remaining 102 examinations were correctly assessed as positive or negative. This result corresponds to a sensitivity of 96% (CI: 88%–100%) and a specificity of 86% (CI: 79%–93%). The positive and negative predictive values were 64% (CI: 48%–80%) and 99% (CI: 96%–100%), respectively. Negative CDS examination corresponded to a very low LR for DVT, 0.05 (CI: 0.01–0.33).

The corresponding results for distal DVTs are presented in **Table 9**. From this table, an LR of 7.1 (4.2–12.0) for a positive CDS and an LR of 0.06 (0.01–0.43) for a negative CDS were calculated.

Finally, the correlation for findings in different vein segments was very high between CDS and phlebography, 97–100% in the proximal veins and 85–90% in the distal veins.

Table 9. Accuracy of CDS in detecting distal DVT after ankle fracture surgery.

<u>CDS</u>	<u>Phlebography</u>		
	DVT	No DVT	
DVT	17	13	30
No DVT	1	85	86
	18	98	116

Distal DVTs:

Sensitivity: (17/18) 94% (CI: 84%–100%)

Specificity: (85/98) 87% (CI: 80%–93%)

Positive predictive value: (17/30) 57% (CI: 39%–74%)

Negative predictive value: (85/86) 99% (CI: 92%–100%)

## Paper III

In the primary analysis of efficacy (ITT analysis), the phlebography-verified DVT incidence was 21% (21/101, CI, 13–29%) in the dalteparin group and 28% (27/96, CI, 19–37%) in the placebo group ( $p = 0.25$ ), OR=0.7 (0.4–1.3), **Table 10**. Proximal DVT was diagnosed in 4% (4/101, CI, 0–8%) of the patients in the dalteparin group and 3% (3/96, CI, 0–6%) in the placebo group. No patient presented clinical signs of PE.

In the additional per-protocol analysis the incidence of phlebography-verified DVT was 17% (13/75, CI, 10–25%) in the Dalteparin group and 26% (17/65, CI, 18–35%) in the placebo group. This difference was not statistically significant ( $p=0.2$ ).

In a separate analysis of the efficacy the phlebography-verified DVT incidence in patients treated with plaster cast immobilization (all patients with orthosis excluded) was 21% (18/86, CI, 13–29%) in the Dalteparin group and 36% (27/75, CI, 27–45%) in the placebo group.

The incidence of phlebography-verified DVT in the orthosis group was 3/36 (8%) and 45/161 (28%) in the plaster cast group.

During the study 18 patients had clinically suspected DVT and therefore underwent acute phlebography or CDS. Five of these phlebographies and 2 of the CDSs were positive for DVT (1 proximal DVT and 6 distal DVTs), and 1 CDS was positive for muscle vein thrombosis (3% of the study population). Two of these patients were in the dalteparin group and 6 were in the placebo group. None of these patients was immobilized with an orthosis.

Table 10. Study III, thromboembolic events, intention-to-treat analysis (ITT), and per-protocol analysis (PP)

	Dalteparin	Placebo	<i>p</i> -value
	<i>n/N (%)</i>	<i>n/N (%)</i>	
<i>All patients</i>			
Phlebography, ITT analysis	21/101 (21)	27/96 (28)	0.2
Phlebography + CDS, ITT analysis	24/117 (21)	34/109 (31)	0.07
Phlebography, PP analysis	13/75 (17)	17/65 (26)	0.2
<i>Patients immobilized only in plaster cast</i>			
Phlebography, ITT analysis	18/86 (21)	27/75 (36)	0.04
Phlebography + CDS, ITT analysis	21/99 (21)	33/86 (38)	0.02

CDS = Colour duplex sonography

## Paper IV

The results from Study IV are summarized in **Table 11**. The (ITT) sample (n=91) included all patients with a negative CDS and all patients with a DVT verified by phlebography. In this primary analysis the DVT incidence was 34% (16/47) in the Dalteparin group and 36% (16/44) in the placebo group. The difference between the two groups was not significant ( $p=0.8$ ). The difference remained insignificant even when accepting CDS as the endpoint analysis for patients with multiple distal DVT or proximal DVT. This increases the ITT sample to 96 patients (secondary analysis of efficacy). The incidences of DVT in this secondary analysis was 37% (18/49) in the dalteparin group and 40% (19/47) in the placebo group ( $p=0.8$ ).

Proximal DVT occurred in four patients, one (2%) in the dalteparin group and three (6%) in the placebo group ( $p=0.6$ ). Two of these were confirmed by phlebography. One of the proximal DVTs propagated from an asymptomatic muscle vein thrombosis, which had been detected by CDS 3 weeks after surgery. No patient presented clinical signs of pulmonary embolism.

Table 11. Study IV, thromboembolic events, intention-to-treat analysis

Primary analysis of efficacy	Dalteparin (n=47)	Placebo (n=44)	<i>p</i> -value
Thromboembolic events – no. (%)	16 (34%)	16 (36%)	0.8
<i>Secondary analysis of efficacy</i>			
	Dalteparin (n=49)	Placebo (n=47)	
Thromboembolic events – no. (%)	18 (37%)	19 (40%)	0.8
No. of patients with both CDS exams negative	25	23	
Proximal DVT – no. (%)	1 (2%)	3 (6%)	0.6
Mean time to DVT diagnosis, days (SD)	30 (12)	26 (10)	
No. of patients treated for DVT (%)	20 (40%)	23 (43%)	

# Discussion

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Thromboprophylaxis is widely used after major orthopaedic surgery. It is commonly prescribed for 7–10 days although the optimal duration of prophylaxis after, for example, major joint surgery is an issue of debate. In several studies a significant risk reduction of all VTEs has been demonstrated with prolonged thromboprophylaxis (up to 35 days) after THR and after hip fracture surgery.<sup>18, 27, 90, 100-102</sup>

After minor orthopaedic procedures the risk of VTE due to the surgery is lower. On the other hand, other risk factors, such as preceding trauma or lower limb immobilization, are often present. The use of thromboprophylaxis during plaster cast immobilization of the lower limb is an issue of debate, practice varies<sup>116</sup> and no consensus has been reached in this matter.<sup>2</sup>

The studies in this thesis assess the mortality and the incidence of VTE after different orthopaedic procedures (Paper I). It also evaluates CDS as an alternative to phlebography in the diagnosis of DVT (Paper II) and the efficacy of dalteparin prophylaxis during immobilization after ankle fracture surgery and Achilles tendon repair (Papers III and IV).

## DVT screening

Over the years, the majority of thromboprophylaxis trials have used DVT, detected by different screening methods, as the primary efficacy outcome. In early VTE screening studies fibrinogen uptake test were used to detect asymptomatic DVT<sup>117</sup> although both the sensitivity and specificity of this test were poor.<sup>118, 119</sup> With the introduction of phlebography the sensitivity and specificity for DVT increased and for a long period of time phlebography has been the reference method for DVT diagnosis. In later years phlebography has been challenged by CDS, but the accuracy for this method in diagnosing asymptomatic DVT in clinical trials has been questioned. Each of the two methods has its own limitations.<sup>120</sup> Phlebography is an invasive method with a 20-40% rate of failure or inconclusive examinations. The interpretation of the findings has a moderate inter-observer reliability<sup>68, 121-123</sup> and there is also a risk for contrast media reactions. Furthermore, it is more or less a non-recurrent test since patients hardly accept repeated examinations due to painful or unpleasant venous puncture. On the other hand, CDS is highly operator-dependent and therefore the accuracy varies.<sup>124</sup> The sensitivity for asymptomatic DVT has previously been low<sup>125, 126</sup> and, although technical advances have increased the sensitivity, the accuracy is still less validated than that of phlebography. Moreover, the assessment of the findings by a second observer is difficult, especially in clinical trials using a central adjudication committee to evaluate the screening results.

Regardless of the choice of method, there have been controversies about the appropriate endpoint in clinical studies evaluating different thromboprophylactic methods.<sup>120, 123</sup> Some argue for phlebographic screening of all patients in order to detect both symptomatic and asymptomatic DVTs since the risk reduction for asymptomatic DVT is strongly correlated with the risk reduction of clinically important symptomatic VTE.<sup>104, 106, 127</sup> Others propose that the efficacy should be based on the reduction of all-cause mortality. Both of these suggestions have limitations. Screening of all patients

results in the finding of asymptomatic DVTs, regarded by some authors as not being clinically significant. Furthermore, treatment of these asymptomatic DVTs reduces the risk of symptomatic events, and therefore the true rate of symptomatic VTE in clinical trials may be underestimated.

To use a reduction in all-cause mortality or fatal PE as the primary objective in a thromboprophylaxis trial is also problematic. Such studies would require thousands of patients and, with low autopsy rates, the diagnosis of fatal PE would be difficult. Furthermore, there is a significant morbidity also after non-fatal VTE, such as PTS and pulmonary hypertension. These consequences are also important to address in the prevention strategies for VTE.

A combination of these two approaches has been suggested,<sup>2, 120, 123, 128</sup> i.e. detection of all DVTs in phase II and some phase III clinical trials as a test of the biological efficacy of a new intervention, followed by large clinical trials using clinically more important VTE as the endpoint, such as verified symptomatic DVT or PE, or asymptomatic proximal DVT.

This suggestion seems reasonable. However when including patients with lower limb injuries in a clinical trial it is possible that the screening should include distal DVTs as well since the symptoms of such DVTs could be masked by normal postoperative findings. Even if most asymptomatic distal DVTs seem to resolve spontaneously<sup>7</sup> and some authors have also demonstrated a very low risk for symptomatic VTE,<sup>129, 130</sup> a proximal extension of distal DVTs is not uncommon.<sup>84</sup> It seems pertinent at least to follow the course of a distal DVT until the risk of propagation is ruled out. CDS in proper hands is excellent in this situation since it is repeatable and noninvasive. As a result of improvements in the accuracy of CDS, one would expect an increasing number of DVT screening studies utilizing CDS outcomes. However, the standardization of the CDS technique is critical in reducing the risk for the false-positive test results reported in some trials.

## **Paper I, symptomatic VTE following orthopaedic surgery**

Patients undergoing major orthopaedic surgery face a very high risk of VTE without thromboprophylaxis. The overall DVT incidence is 40%–60% after major orthopaedic surgery. The incidence of proximal DVT ranges between 10% and 30%,<sup>86, 131</sup> symptomatic DVT between 1% and 10% and the incidence of fatal PE is 1% to 5%.

Due to this high risk of thromboembolic complications, it is widely accepted that all patients should receive adequate thromboprophylaxis after major surgery. LMWHs have been shown to be safe and effective for this purpose and are used worldwide.

Data from Paper I show that the overall rates of DVT and PE were low with the present protocol for thromboprophylaxis. DVT and PE were diagnosed in 1.0% and 0.3% of the patients, respectively. On average, this corresponds to one event per week during the study at our department. This indicates that the diagnosis of postoperative VTE is an incidental finding for a single orthopaedic surgeon. Since most of these VTEs were diagnosed after discharge from hospital, often by other physicians than the surgeon, a systematic feedback of postoperative VTE is essential for complication awareness and quality control after surgery.

It is widely recognized that the majority of postoperative VTEs are asymptomatic and never identified. Poor clinical awareness of thromboembolic complications as well as difficulties in distinguishing VTE from normal postoperative findings could

contribute to underestimation of the VTE rate in our study. In addition, many patients with a fatal PE remained undiagnosed in our study since the course of this condition is often very rapid and results in sudden death before resuscitation.<sup>9, 132</sup> In a retrospective review of autopsy reports, Sandler et al.<sup>132</sup> found that 83% of patients with fatal PE had concomitant DVT determined at autopsy. Even if 19% of these patients had had symptoms indicating DVT, only 5 out of these 38 patients (13%) had been examined for suspected DVT. This indicates that also symptomatic DVTs remain undiagnosed to a great extent. In our study, only 15% of the patients with a PE had a concomitant symptomatic DVT. Thus, the majority of PEs were caused by asymptomatic DVT. This reflects the relevance of using asymptomatic DVT as an endpoint in clinical trials.

There are several methods of thromboprophylaxis that have been proved safe and effective in orthopaedic surgery. With a few modifications, we used a single protocol for thromboprophylaxis with dalteparin for selected procedures during the study period. The prophylaxis was prescribed for 7 to 10 days and prolonged prophylaxis was not used by routine. Although this protocol was well acknowledged by colleagues, it is not unlikely that prophylaxis was individualized for some patients. Furthermore, patients discharged to rehabilitation units might have been entered in other thromboprophylactic protocols without our knowledge.

In general, the incidence of VTE after different procedures was as expected although some interesting findings are worth noting.

After osteosynthesis of pelvic fractures the VTE incidence (13%) was unexpectedly high even if this is a known high-risk situation for VTE.<sup>28, 30</sup> Out of 46 cases, 3 patients were diagnosed with DVT and 3 with PE. The small number of patients limits the interpretation of these findings. Nevertheless, it is noted that all VTEs were diagnosed by phlebography and CT, all 6 patients had isolated injuries (4 in the acetabulum and 2 in the pelvic ring), they had a slightly higher median age (54 years) than patients without VTE (45 years), and in all 6 patients the VTE diagnosis was established after 7–10 days of dalteparin prophylaxis (all unpublished data). Despite the limitations, it is clear that this VTE outcome after pelvic fracture surgery is unacceptable high. Obviously there is a need for improved thromboprophylaxis and a prolonged duration seems most appropriate even if this has not been tested in a clinical trial for this population of patients.

Below-knee fractures also carried a significant risk for both DVT and PE, especially proximal tibia fractures (4.2%) and ankle fractures (2.7%). Foot fractures appear to be the only lower limb fracture mediating a low VTE risk even without routine prophylaxis (0.4%). However, no detailed analysis was performed comparing forefoot and hind foot injuries and it is possible that thromboprophylaxis was used in selected cases.

After lower limb fracture surgery a difference in DVT location was also noticed. Typically, the percentage of proximal DVTs was highest for proximal lower limb fractures, 58–67% after femoral and pelvic fractures, compared to 20–40% after below-knee fractures. This difference in the relation between proximal and distal DVTs has also been demonstrated regarding DVTs after THR and TKA,<sup>23</sup> and similar results were also found in our study. After THR, 62% of the categorized DVTs were located in proximal veins and, after TKA, the corresponding rate was 29%. The higher percentage of proximal DVTs after THR has been assigned to a local injury to the femoral vein occurring when the leg is flexed and rotated during the surgery.<sup>133-135</sup> Since the level of DVT seems to correlate with the fracture site, it is likely that a local vascular injury also

plays an important role in the formation of DVT after lower limb injury, as previously postulated by Virchow.<sup>12</sup>

The breakthrough of symptomatic VTE despite prophylaxis occurred after several procedures. After elective THR (degenerative hip) and TKA the VTE incidence was 2.2% and 3.4%, respectively. Previous studies have shown incidence rates of 2-5%<sup>2</sup> after THR and 1.6%-2.1% after TKA<sup>22,23</sup> which is in accord with our findings.

The time to the VTE diagnosis also differed between THR and TKA. After THR the median time to the VTE diagnosis was 19 days and 93% of the cases were diagnosed after discharge from the hospital. After TKA the median time to diagnosis was 5 days and 66% of the VTEs were diagnosed during the initial hospital stay. Similar differences have been reported previously.<sup>22, 26</sup> Reasonable mechanisms for late-occurring VTE have been related to prolonged activation of the coagulation system.<sup>19,98</sup> A prolonged reduction in venous outflow has also been described, persisting for 6 weeks after THR<sup>136, 137</sup> but normalizing during the first week after TKA.<sup>138</sup> It is possible that elderly people, who are well mobilized during hospitalization, become more or less bedridden at home after discharge and are therefore at increased risk for late VTE.<sup>139</sup>

After most of the surgical procedures performed without routine thromboprophylaxis, such as knee arthroscopy, foot surgery and upper extremity surgery, the VTE incidence was less than 0.5% and therefore routine thromboprophylaxis does not seem justified. These results are comparable with previous reports.<sup>26, 140, 141</sup> However, after Achilles tendon repair, the incidence of DVT was high (7.0%).

Only a few conclusions regarding the cause of death can be drawn from the mortality data due to the low autopsy rate and selection bias. The overall mortality at 6 weeks was 2.3% (n=719). An autopsy was performed in only 4.3% and in half of these cases a PE was found to have either contributed to death or was the major cause of death. However, it is obvious that the true rate of fatal PE is highly underestimated in our study. The highest 6-week mortality was seen after lower limb amputation (14%), hip hemiarthroplasty (11%) and osteosynthesis of proximal femoral fractures (7%). These patient groups also had the highest median ages of 80 years, 85 years and 83 years, respectively.

Based on the validity control, we believe that the overall data quality in our register is highly valid with a high accuracy in coding and few missing cases.

## **Paper II, accuracy of CDS**

Paper II was designed to challenge the diagnostic performance of CDS. Since previous results have confirmed that a similar technique is highly sensitive and specific for symptomatic proximal DVT<sup>142</sup> and symptomatic distal DVT<sup>143, 144</sup> but lower for asymptomatic DVT,<sup>126</sup> we chose to conduct this study on patients with an expectedly high incidence of asymptomatic DVT. These DVTs are considered to be more difficult to diagnose with CDS as they are often non-occlusive and located in distal veins.<sup>5, 145, 146</sup> The methodology was optimized for this aim and we used modern high-resolution equipment together with experienced personnel for the examinations. To achieve reliable results, a predefined protocol for the CDS examination was used together with predefined criteria for normal, pathologic and inconclusive examinations.<sup>114</sup> The positioning of the patient during the examination was considered important, especially



when the distal veins were examined (sitting position with the leg hanging down). All positive, inconclusive or technically difficult examinations were reviewed by an experienced physician who also classified the findings.

The phlebographic examination was performed using a modified form of the Rabinov and Paulin technique,<sup>65</sup> a common recommended method.<sup>2</sup> The interpretation of the findings was performed in 2 independent and blinded sessions (one for clinical purposes and one for study purposes) and only direct criteria for the DVT diagnosis were accepted.<sup>147</sup> Nevertheless, in 10 out of 144 examinations there was disagreement in the 2 evaluations reflecting the difficulties with the reference method for DVT diagnosis. Observer variation should be considered in approximately 10% with phlebography.<sup>148</sup>

For both methods, the number of excluded and inconclusive examinations was at an acceptable level. Phlebography was unfeasible in 10% of the patients, mainly due to the inability to establish adequate venous access. For CDS 8% of the examinations were inconclusive, mainly due to the difficulties in visualizing the full length of the calf veins. In most of the cases DVT was suspected using CDS but a firm diagnosis was not possible. Subsequent phlebography showed DVT in 5 of the 12 inconclusive segments and in 5 cases the initial assessment differed from the secondary assessment. LR for an inconclusive CDS was 2.8. Thus, in our hands, it is slightly more probable that the phlebography is positive than negative in a patient with an inconclusive CDS.

In this comparative study CDS had a high sensitivity and a very high negative predictive value. Only in one patient was the CDS result negative while subsequent phlebography diagnosed a small DVT in a fibular vein, corresponding to a sensitivity of 96% and a negative predictive value of 99%. This suggests that CDS can be used to screen even for asymptomatic distal DVT in clinical trials.

In 13 cases, the CDS diagnosed a false positive distal DVT compared to phlebography. However, in many of these there was also disagreement between the different phlebographic evaluations. Nevertheless, in asymptomatic patients with small distal DVTs on CDS, confirmatory phlebography could be helpful to avoid false positive findings and unnecessary antithrombotic therapy.

The difficulties in interpreting the phlebographic findings show that phlebography also has its limitations and call into question the status of phlebography as the reference method for DVT diagnosis.

We believe that duplex sonography can be used for DVT screening and that, in the future, it may replace phlebography as a screening method in clinical trials.

### **Paper III, VTE after ankle fracture surgery**

The attitude to thromboprophylaxis during plaster cast immobilization varies world wide. Some argue for prophylaxis during the entire immobilization period while others prefer not to use prophylaxis at all. We have used dalteparin for thromboprophylaxis after ankle fracture surgery since the early 90s. Prophylaxis for 7 to 10 days has been considered appropriate. Despite prophylaxis for 7 days, we found in the review of 1923 surgically treated ankle fractures (Study I), an incidence of symptomatic DVT and PE of 2.3% and 0.5%, respectively. Although the majority of the DVTs were located in distal veins, a significant number (20%) were proximal. Five patients (0.3%) deceased during the 6-week follow-up. An autopsy was performed on and confirmed a fatal PE

in one of these patients. The other 4 did not undergo autopsy and therefore the true incidence of fatal PE in this study is not known.

The above results confirm that there is a small but not negligible risk for symptomatic VTE during immobilization after ankle fracture surgery. Even fatal PE occurs, despite thromboprophylaxis during 7-10 days.

In Paper III prolonged prophylaxis with dalteparin was compared with our standard regimen of 7 days of dalteparin prophylaxis. All patients were screened for DVT with unilateral phlebography at the time of cast removal. In this study no significant difference was found between prolonged and short-term prophylaxis. In the intention-to-treat analysis, the overall DVT incidence was high, 21% in the treatment group and 28% in the control group. The majority of DVTs were located in distal veins although 4% of the DVTs were proximal. None of the patients presented clinical signs of PE.

The discrepancy between the DVT incidence in Papers I and III is explained by the high proportion of asymptomatic DVTs diagnosed by phlebography in Paper III. The clinical relevance of these mainly distal, asymptomatic DVTs is debatable. Even if the majority of these DVTs resolve spontaneously,<sup>7</sup> it is suggested that they are associated with an increased risk of late development of PTS.<sup>83</sup>

The lack of significant risk reduction with prolonged thromboprophylaxis was unexpected. An incorrect sample size could be one reason for this, even though we carried out a power analysis prior to the study to ensure a sufficient number of patients. Another reason for the non-significant results could be that the long-lasting immobilization *per se* is such a strong risk factor for local thrombosis that thromboprophylaxis in the standard dosage is insufficient. It is also possible that the 7 days of dalteparin prophylaxis prior to the study medication equalized the effect in the 2 treatment groups. This study design was necessary as we considered it unethical to deviate from the standard prophylactic regimen in the control group.

In previous prospective studies, the phlebography-verified DVT incidence without thromboprophylaxis during plaster cast immobilization has ranged from 17% to 19%.<sup>61, 62</sup> Despite one week with thromboprophylaxis in our control group, we found a higher DVT incidence than previously reported. One reason for this could be that all our patients underwent surgery, which was not the case in the comparable studies.<sup>61, 62</sup> Also the immobilisation time was longer in our study. Another explanation for a higher DVT incidence could be a different interpretation of the phlebographic findings although we used the same diagnostic criteria for DVT.<sup>147</sup> Also, the compliance with the study medication was considered acceptable in our study and should not affect the results as compared to previous reports.

One limitation of the study that needs to be addressed separately is the lack of stratification into different types of immobilization (i.e. below knee orthosis or below knee plaster cast). We found that patients immobilized with plaster cast had a higher incidence of DVT than patients immobilized in an orthosis (28% vs. 8%). The risk of DVT was also reduced by dalteparin in the plaster-cast group (21% vs. 36%). However, there is an obvious risk that a selection bias was introduced as the study protocol did not allow stratification or randomization between these groups. Therefore, no conclusions can be drawn from these results. It should also be noted that patients with other conditions that could increase the risk for DVT or bleeding were excluded from the study. Furthermore, only 33% of the eligible patients were actually included in the study, although less than 20% were excluded because they did not consent to participate.

In conclusion, our results did not support prolonged thromboprophylaxis with dalteparin after ankle fracture surgery.

## **Paper IV, VTE after Achilles tendon repair**

Our review of the 668 patients surgically treated for Achilles tendon ruptures during an almost 8-year period (Paper I) showed that the incidence of symptomatic DVT without thromboprophylaxis was 7% during a 6-week follow-up. The majority of the DVTs were located in distal veins, although 1.2% of the patients were diagnosed with a proximal DVT. No patient was diagnosed with a PE.

We have considered the risk for a diagnostic suspicion bias as a contributory cause of the high DVT incidence in Study I. The fact that the patients were operated on and immobilized for this injury might have triggered the search for a DVT. With a 30-40% risk for DVT (symptomatic or asymptomatic) the chance of a positive finding is high if a CDS or a phlebography is performed. However, the DVT incidence was consistent in our audit during all years 1996–2003 (unpublished data) contradicting a biased result.

In Paper IV, dalteparin was compared with placebo during the 6-week period of immobilization after surgery. All patients were screened for DVT with CDS at 3 and 6 weeks and, in the primary analysis, all DVTs were confirmed by phlebography. In this study no significant difference was shown between the 2 study groups. The DVT incidence was 34% in the dalteparin group and 36% in the placebo group. Proximal DVT occurred in 4 patients (4.4%), one in the dalteparin group and 3 in the placebo group.

The discrepancy between the incidences of DVTs in Papers I and IV emphasizes that the majority of the postoperative DVTs are asymptomatic. However, the true rate of symptomatic DVT in Paper IV could not be determined due to difficulties in the clinical assessment. Hence, DVT symptoms could not be distinguished from normal postoperative findings, and even without disturbing postoperative findings the clinical diagnosis of DVT is unreliable.<sup>3</sup>

The high DVT incidence after Achilles tendon repair in Paper IV was expected. Even if the cause of VTE is multifactorial, it is not likely that the minor injury causing the tendon to rupture or the limited surgical trauma contributes to the increased risk of DVT to any greater extent. The subsequent long-lasting immobilization seems to be a more important risk factor for DVT, especially since all patients were non-weight bearing for the first 3 weeks.

The lack of efficacy with dalteparin was unexpected. The continuous local thrombogenic stimulus caused by the plaster cast could be too strong to be inhibited by dalteparin in the present dosage. Compliance with the study treatment was judged to be very high and the patients showed a very high acceptance of the study protocol, as reflected by a low drop-out rate.

A few other studies<sup>59-62</sup> have addressed the issue of VTE and lower limb immobilization. Even if a reduction of VTE was found in 3 of the studies,<sup>59, 60, 62</sup> no consensus has been reached about the necessity of thromboprophylaxis during cast immobilization. Approximately 60% of the eligible patients were included in Study IV, thus the risk for selection bias is low. We believe that the results are applicable to all patients surgically treated for Achilles tendon rupture, without other obvious risk factors for VTE. Therefore, routine thromboprophylaxis with dalteparin cannot be recommended after Achilles tendon repair.

## Limitations

Since the risk for VTE after orthopedic surgery can be increased up to 2–3 months,<sup>23</sup> it is obviously a limitation that our follow-up was restricted to 6 weeks in Paper I. The majority of VTEs occur, however, during the first post-surgical month.<sup>22, 23</sup> This was also confirmed in our retrospective analysis with 11% late-occurring VTEs during post-surgical days 43 to 90. In all outcome studies with symptomatic VTE, there are several sources of error, not least the underestimation of fatal PE and the limitations of the diagnostic methods used. Nevertheless, we believe that our results provide valuable information about VTE after orthopaedic surgery.

Another limitation that needs to be addressed separately is the lack of stratification into different types of immobilization (i.e. below-knee orthosis or below-knee plaster cast) in Papers III and IV. Compared to other risk factors for VTE (trauma, injury and surgery), we considered the risk for VTE to be equal irrespective of the type of immobilization, especially since the absolute majority of the orthoses were applied after the 2-week postoperative control. Therefore, stratification was not performed and no conclusions can be drawn about the DVT incidence and the efficacy of dalteparin with different types of immobilization.

## Summary of findings

### Paper I.

The highest incidence of VTE in patients receiving routine thromboprophylaxis was seen after pelvic fracture surgery (13%, 6/46) and TKA (3.5%, 38/1078). After THR following degenerative joint disease, the incidence of PE and DVT was 0.9% (12/1408) and 1.6% (22/1408), respectively.

Without thromboprophylaxis a high DVT incidence was found after Achilles tendon repair (7%, 47/668). A low incidence of VTE was recorded after other procedures performed without thromboprophylaxis (knee arthroscopy [0.5%, 25/5450], foot surgery [0.5%, 13/2461] and upper extremity surgery [0.2%, 11/7249]).

The overall mortality at 6 weeks was 2.3% (n=719). The highest mortality was seen after lower limb amputation (14%, 110/776) and after hip hemiarthroplasty and osteosynthesis of proximal femoral fractures (11%, 47/430) and (7%, 545/7619), respectively.

### Paper II.

The DVT incidence with phlebography and CDS was 21% (24/116) and 31% (36/116), respectively. The CDS result was false negative in one case and false positive in 13 cases. The remaining 102 examinations were correctly assessed as positive or negative. This result corresponds to a sensitivity of 96% (88%–100%) and a specificity of 86% (79%–93%). The positive and negative predictive values were 64% (48%–80%) and 99% (96%–100%), respectively.

### Paper III.

The DVT incidence was 21% in the treatment group and 28% in the placebo group (p=0.3). The incidence of proximal DVT was 4% and 3%, respectively. No PE or major bleeding occurred in either of the groups.

#### **Paper IV.**

The DVT incidence was 34% in the treatment group and 36% in the placebo group ( $p=0.8$ ). Proximal DVT was diagnosed in one patient (2%) in the dalteparin group and in three patients (6%) in the placebo group ( $p=0.6$ ). No PE or major bleeding occurred in either of the groups.

## Conclusions

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With thromboprophylaxis (dalteparin) during 7 to 10 days following major joint surgery, spinal surgery and fracture surgery in the lower limb, the overall risk for symptomatic venous thromboembolism was generally low at the 6-week follow-up and the majority of all DVTs and PEs were diagnosed after discharge from hospital. Patients surgically treated for pelvic fracture run the highest risk of late symptomatic VTE despite thromboprophylaxis. After Achilles tendon repair, without routine thromboprophylaxis, the incidence of symptomatic DVT was unexpectedly high. The highest mortality was found after amputations of the lower limb and after proximal femur fracture (Paper I).

Colour duplex sonography (CDS) can be used for DVT screening after ankle fracture surgery. With a high sensitivity and a high negative predictive value, CDS can rule out even asymptomatic distal DVTs. Experienced personnel and well defined diagnostic criteria are, however, essential to achieve high accuracy (Paper II).

DVTs were common during immobilization after ankle fracture surgery. The majority of DVTs were asymptomatic and located in distal veins. Prolonged thromboprophylaxis with daily subcutaneous injections of dalteparin (5000 U) during 6 weeks did not reduce the risk of DVT compared to one week of prophylactic treatment. Our results do not support prolonged thromboprophylaxis with dalteparin after ankle fracture surgery (Paper III).

Asymptomatic distal DVTs occurred frequently during immobilization after Achilles tendon repair. Daily subcutaneous administration of 5000 U of dalteparin during the 6 week immobilization period did not affect the incidence of DVT as compared to placebo. Our results do not support this prophylaxis regimen after Achilles tendon repair (Paper IV).

## Implications for future research

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Despite thromboprophylaxis venous thromboembolism remains a significant cause of morbidity and mortality after orthopaedic surgery. Not only PE but also PTS are important to consider when discussing DVT prevention strategies. The risk for asymptomatic DVT is high after lower limb surgery. Little is known about the consequences of these sub-clinical DVTs, especially regarding the long-term effects. Many patients with ankle fractures and Achilles tendon ruptures that need surgery are young and PTS symptoms might affect the patients for several years. Since the efficacy of thromboprophylaxis is suboptimal for these patients and the long-term benefit of this prophylaxis is poorly validated, there is a need for further studies in order to:

- Identify patients at risk of developing late occurring symptomatic VTE and consequently to find and evaluate adequate thromboprophylaxis regimens
- Evaluate the long-term consequences of both asymptomatic and symptomatic DVT after Achilles tendon repair and ankle fracture surgery
- Evaluate the significance of different types of immobilization devices for the DVT incidence after lower limb injury

## Abstract in swedish

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Djup ventrombos (DVT) och lungembolism (PE) är mycket vanligt förekommande efter ortopedisk kirurgi och utgör olika manifestationer av venös tromboembolism (VTE). Majoriteten av dessa tromboser ger inga symptom och den kliniska bedömningen är svår. Utfallet är oförutsägbart, de flesta djupa ventromboser löses upp spontant medan andra ökar i storlek, progredierar till proximala vener och emboliserar till lungorna. Utan trombosprofylax drabbas 40-60% av patienterna av DVT efter större höft- eller knä kirurgi. Endast 1-10% diagnostiseras till följd av kliniska symptom medan övriga förblir oupptäckta. I upptill 1-5% inträffar PE med dödlig utgång.

Som en konsekvens av den höga risken för VTE används sedan 20 år tillbaka trombosprofylax rutinmässigt efter större operationer. Olika typer av preparat reducerar risken för VTE inkl hepariner, warfarin och lågmolekylära hepariner (LMWH). LMWH har bättre effekt och är enklare att administrera än både warfarin och hepariner och har därför kommit att användas rutinmässigt som trombosprofylax efter kirurgi i stora delar av världen. Vanligen ges denna förebyggande behandling i 7-10 dagar efter operationen. På senare tid har flera studier framhållit värdet av förlängd trombosprofylax, upp till 35 dagar efter total höftledsplastik. Endast ett fåtal studier har undersökt effekten av trombosprofylax i anslutning till extremitetsskador som kräver efterföljande gipsbehandling, vilket i sig är en riskfaktor för VTE. Konsensus om behovet saknas och det föreligger stora variationer i praxis.

Diagnostiken av DVT har ur ett historiskt perspektiv dominerats av flebografi och undersökningen har utgjort en referensmetod för korrekt DVT diagnostik. En teknisk utveckling och ökade erfarenheter har emellertid gjort att bildgivande flödesmätning med ultraljud (färgduplex) blivit en allt mer använd metod som kommit att ersätta flebografi som förstahandsmetod vid diagnostik av symptomgivande DVT. Denna icke-invasiva undersökning har flera fördelar jämfört med flebografi. Tidigare studier har dock visat att sensitiviteten är låg för att påvisa asymptomatisk DVT som oftast har mycket begränsad utbredning (icke ockluderande) och oftast förekommer isolerat i vadens vener. Kontinuerlig metodutvecklingen kräver regelbunden validering av den diagnostiska säkerheten.

I detta avhandlingsarbete har vi i *Studie I* prospektivt kartlagt mortalitet och incidens av DVT och PE de första 6 veckorna efter ortopedisk kirurgi. Studien omfattar 30816 patienter som opererades på Ortopediska kliniken, Södersjukhuset mellan 1996-03-01 och 2003-12-31. Den totala mortaliteten var 2.3%. Incidensen av DVT och PE var 1.0% respektive 0.3%. Trots trombosprofylax sågs en hög andel VTE efter bland annat frakturkirurgi i bäckenet (13%) och efter knäproteskirurgi (3.5%). Utan rutinmässig profylax var DVT-incidensen 7% efter hälseneruptur medan risken var mindre än 0.5% efter övre extremitetskirurgi, fotkirurgi och artroskopi av knäleden. Sammanfattningsvis fann vi en oväntat hög risk för VTE efter frakturkirurgi i bäckenet och efter hälseneruptur.

I *Studie II* inkluderades 180 patienter opererade för fotledsfraktur för en validering av den diagnostiska säkerheten för färgduplex jämfört med flebografi. Efter förväntat bortfall kvarstod 116 undersökningar för analys. DVT incidensen var 21% med flebografi och 31% med färgduplex. Färgduplex var falskt positiv för 13



undersökningar, falskt negativ för en undersökning och korrekt bedömd för 102 undersökningar. Resultatet motsvarar en sensitivitet på 96% och ett negativt prediktivt värde på 99% för färgduplex. Vår konklusion är att metoden är mycket användbar vid screening för DVT då risken att missa en trombos är liten.

*Studie III* utgjordes av en prospektiv, dubbel-blind, randomiserad och placebokontrollerad studie där 272 patienter som opererats för fotledsfraktur inkluderades till öppen behandling med dalteparin under 7 dagar efter operationen följt av dalteparin eller placebo under resterande immobiliseringstid (5 veckor). Vid avgipsning gjordes flebografi på samtliga patienter. Efter bortfall kvarstod 197 patienter för analys. DVT incidensen var 21 % i dalteparin gruppen och 28 % i placebogruppen. Skillnaden var ej signifikant ( $p=0.3$ ). Vi konkluderade att förlängd trombosprofylax inte kan rekommenderas efter operation av fotledsfraktur.

*Studie IV* var en prospektiv, dubbel-blind, randomiserad och placebokontrollerad studie där effekten av dalteparin utvärderades efter hälseneruptur. 105 patienter som opererats för hälseneruptur randomiserades till dalteparin eller placebo givet under 6 veckors immobilisering. Efter 3 och 6 veckor utfördes DVT screening med färgduplex och funna trombosor verifierades med flebografi. Vi fann ingen signifikant skillnad i DVT incidensen mellan grupperna, 34 % i dalteparingruppen och 36 % i placebogruppen ( $p=0.8$ ). Vi konkluderade att DVT är vanligt efter operativ behandling av hälseneruptur. Profylax med dalteparin minskade dock inte risken för DVT och kan därför inte generellt rekommenderas.

Keywords: Orthopaedic surgery, deep vein thrombosis (DVT), pulmonary embolism (PE), colour duplex sonography, phlebography, fracture surgery, Achilles tendon rupture.

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## Original publications (I-IV)

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