



JUKKA SAARINEN

**Incidence, Risk Associations and
Outcome of Deep Venous Thrombosis
in the Lower Limb**

*University of Tampere
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Incidence, Risk Associations and Outcome of Deep Venous Thrombosis in the Lower Limb

ACADEMIC DISSERTATION

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ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
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*University of Tampere
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LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original communications, which are referred to in the text by their Roman numerals.

I Saarinen J, Sisto T, Laurikka J, Salenius J-P and Tarkka M (1995): Late sequelae after acute deep venous thrombosis: evaluation five and ten years after. *Phlebology* 10: 106-109.

II Saarinen J, Sisto T, Laurikka J, Salenius J-P, Tarkka M and the FINNVASC study group (1995): The incidence of postoperative deep vein thrombosis in vascular procedures. *VASA (Journal of Vascular Diseases)* 24: 126-129.

III Saarinen J, Laurikka J, Sisto T, Tarkka M and Hakama M (1999): The incidence and cardiovascular risk indicators of deep venous thrombosis. *VASA (Journal of Vascular Diseases)* 28: 195-198.

IV Saarinen J, Kallio T, Lehto M, Hiltunen S and Sisto T: The occurrence of the postthrombotic changes after an acute deep venous thrombosis. A prospective two-year follow-up study. *Journal of Cardiovascular Surgery* (accepted).

ABBREVIATIONS

AVP	Ambulatory venous pressure
BMI	Body mass index
CI95%	Confidence interval (95%)
CFDI	Color flow duplex imaging
CVI	Chronic venous insufficiency
CWD	Continuous wave doppler
DVT	Deep venous thrombosis
FINNVASC	Finnish vascular registry
FUT	Fibrinogen uptake test
IPG	Impedance plethysmography
OR	Odds ratio
PTS	Postthrombotic syndrome
RR	Relative risk
VDI	Venous duplex imaging
VRT	Venous refilling time

INTRODUCTION

Deep venous thrombosis (DVT) in the lower limb affects a considerable number of individuals and may lead to acute or chronic complications. Its incidence in the general population has been estimated to be 80-180 per 100000 annually in Western societies (Nordström et al. 1992, Bounameaux et al. 1996, Hansson et al. 1997). In vascular surgical patients, DVT has been found after aortic surgery in 18% (Olin et al. 1993), and postoperative DVT after aortic or lower extremity vascular surgery has been diagnosed in 10% despite adequate prophylaxis with anticoagulants (Fletcher et al. 1997). One of the most feared complications of DVT is pulmonary embolism, which carries a very considerable mortality rate (Lowe 1981, Gillinov et al. 1992); the rate in cardiac surgery patients has been 34% (Gillinov et al. 1992). Another important complication is venous insufficiency, which may cause symptoms in the leg in even 60% of patients (Strandness et al. 1983, Widmer et al. 1985, Heldal et al. 1993, Beyth et al. 1995). On the other hand the rate of venous ulceration reported in the recent literature is low (0-6.5%) (Killewich et al. 1985, Widmer et al. 1985, Lagerstedt et al. 1993, Beyth et al. 1995).

A number of predisposing factors are possibly associated with DVT (Kakkar et al. 1969, Stamatakis et al. 1978, Sikorski et al. 1981, Bergentz 1988, Nicolaides et al. 1992, Bergqvist 1996). In vascular surgery, the range of risk factors for DVT is typically wide (major operation with a long operation time and substantial bleeding, high age, several cardiovascular diseases) but the importance of these factors remains unclear. In addition, the incidence of symptomatic postoperative DVT in these patients is not known. In vascular surgical patients the risk is difficult to predict and this necessitates an individualized risk analysis of patient subgroups (Nicolaides et al. 1992). In the general population, the importance of associated diseases and medical conditions as factors predisposing to DVT has not been established (Carter 1994). The incidence of DVT has been varying and much lower in non-Western societies (Gjöres 1956, Coon et al. 1973, Andersson et al. 1991, Nordström et al. 1992, Nosset et al. 1993, Hansson et al. 1997, White et al. 1998).

The outcome of DVT after an acute thrombotic event has remained unclear (Meissner et al. 1998, Prandoni et al. 1998). Valvular incompetence in the deep venous system seems to be the crucial factor in the development of the postthrombotic syndrome (PTS). Especially the distal venous valves in crural and popliteal veins have an important role in this respect (Killewich et al. 1985, Lindhagen et al. 1985, Moore et al. 1986, Gooley and Sumner 1989, Labropoulos et al. 1996). The factors affecting the outcome, especially in patients with calf DVT, are not known (Browse et al. 1981, Kakkar and Lawrence 1985, Philbrick and Becker 1988, Heldal et al. 1993, Lagerstedt et al. 1993, Monreal et al. 1993, Beyth et al. 1995). It has been observed that recurrent DVTs after the acute period are

surprisingly frequent, their cumulative incidence being 30% during an 8-year follow-up (Prandoni et al. 1996). In addition, propagation of acute thrombosis may occur in 30-38% of patients during anticoagulant therapy (Krupski et al. 1991, Meissner et al. 1995). There is no answer in the literature as to why a distal (calf) DVT is as likely to develop long-term symptoms as a more proximal DVT (Browse et al. 1981, Schulman et al. 1985, Lagerstedt et al. 1993, Beyth et al. 1995).

The aims of the present study were to determine the incidence of DVT in the general population and in vascular surgery. Significance of predisposing factors was studied in both groups. The long-term outcome after an acute DVT was evaluated with special reference to the location of the thrombus either in the calf or in more proximal venous segments. Several questions concerning the risk associations and outcome of DVT have remained unresolved. Such issues constituted the starting point for the present study.

REVIEW OF THE LITERATURE

1. Anatomy and physiology of the venous system in the lower limb

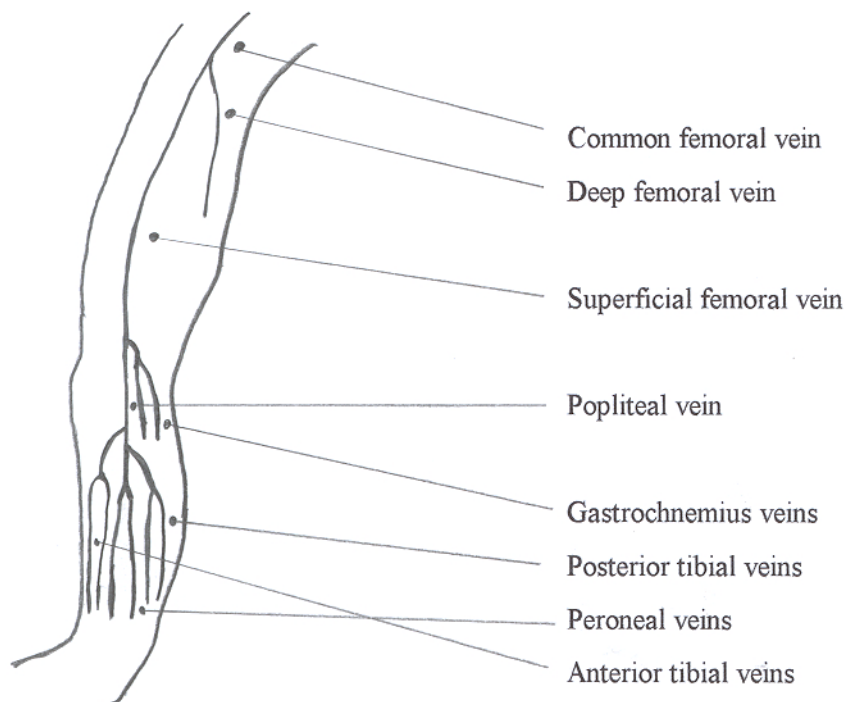
The veins of the lower extremity are divided into a superficial and a deep system, the two groups being connected by perforating veins. The deep veins in the calf consist of three paired stem veins which then unite at different levels to form the popliteal vein. The superficial femoral vein is a continuation of the popliteal vein (Figure 1). The external iliac vein begins at the level of the inguinal ligament and is a direct continuation of the common femoral vein. The external iliac vein joins the internal iliac vein to form the common iliac vein, which then runs to the inferior vena cava (Rabinov and Paulin 1972, Dodd and Cockett 1976, Browse et al. 1988, Barloon et al. 1997). The superficial system in the lower limbs comprises two main trunks, the great and the small saphenous veins. The former courses upward from the dorsomedial aspect of the foot along the medial side of the extremity and terminates at the saphenofemoral junction in the groin, while the latter courses upward from the lateral aspect of the ankle along the posterior side of the calf and ends at the saphenopopliteal junction (Comerota et al. 1985, Dodd and Cockett 1976). The superficial veins lie under the deep fascia and are thin-walled and less muscular (Rabinov and Paulin 1972, Dodd and Cockett 1976, Comerota et al. 1985).

The direction of venous blood flow is controlled by the bicuspid valves, which are oriented to direct flow centrally and to prevent reflux (Cotton 1961, Rabinov and Paulin 1972, Barloon et al. 1997). The valves consist of endothelium and collagen fibres and their structure is mechanically strong (Ackroyd and Browse 1985). The number of valves increases in the distal direction. Only 25 per cent of the common femoral veins are valveless (Powell and Lynn 1951). The supravulvar vein is expanded into the sinus, allowing the valves to open wide without coming into contact with the wall and making rapid closure possible at the beginning of the reverse flow (Cotton 1961). Valves in the communicating veins allow blood to flow only from the superficial to the deep system (Rabinov and Paulin 1972, Barloon et al. 1997). At foot level the communicating veins may be only partly valved and bi-directional flow is possible (Jakobsen 1970). The superficial veins also possess valves, which direct the blood flow towards the heart (Cotton 1961).

The most obvious function of the venous system in the lower extremity is to return blood to the heart from the capillary bed. The position of the body, the function of the venous valves and the function of the calf muscle pump affect pressure conditions in the venous system (Arnoldi 1966, Hjelmsstedt

1968). Strong contractions of the leg muscles when in erect position cause a rapid fall in the venous pressure at the foot level (Hjelmstedt 1968). The muscle pump is the most effective in the calf. Contraction of the calf muscles can produce high venous pressures and compress the intramuscular veins even in standing position (Ludbrook 1966).

Figure 1. Main deep veins of the leg.



2. Pathophysiology of deep venous thrombosis and chronic venous insufficiency

2.1 Acute deep venous thrombosis

A deep venous thrombosis (DVT) is a thrombus which has formed in the veins beneath the deep fascia of the leg. A thrombus is a mass of cellular material bound together with fibrin strands. Venous thrombi are composed mainly of erythrocytes and fibrin (Harker 1986, Browse et al. 1988, Nielsen 1991).

The triad of intimal trauma (wall damage), changes in blood flow (stasis) and blood hypercoagulability have been recognized as a cause of thrombosis since the time of Virchow. DVT usually originate in the calf veins (Gibbs 1957, Sevitt et al. 1961, Nicolaides et al. 1971, Stamatakis et al. 1978a), but may also develop in the iliac, femoral or popliteal veins and be restricted to one or more of these venous segments (Sevitt and Gallagher 1961, Havig 1977, Rollins et al. 1988a). Venous blood flow may be reduced for several reasons. McLachlin et al. (1960) demonstrated that contrast medium can remain for prolonged periods in the valve sinuses if the calf muscles are not used. In experimental venous thrombosis, venous stasis has proved to be an important factor combined with other mechanisms (Wessler 1962). On the other hand, Browse (1962) noted that the calf blood flow reaches its resting level within the first hour of rest. A limb trauma has been associated with DVT in studies with trauma patients, evidencing a role of endothelial damage in the pathogenesis of venous thrombosis (Hjelmstedt et al. 1968, Geerts et al. 1994). Immobilization may further contribute to the development of DVT (Gibbs 1957, Havig 1977). In addition, DVT usually develops to the side of the operated extremity in orthopedic patients (Stamatakis et al. 1978b, Davidson et al. 1996). A hypercoagulable state may be congenital as in patients with deficiencies of antithrombin III, protein C and protein S (Rasi 1995). These disorders increase the risk of DVT by affecting the coagulation system (Thaler and Lechner 1981, Broekmons et al. 1983, Comp et al. 1984). A hypercoagulable state may also prevail in cancer patients, in postpartum or pregnant women, and after surgery (Nielsen 1991). In experimental studies, the role of hypercoagulation in the development of venous thrombosis has been demonstrated (Wessler 1962). In an 8-year follow-up study by Prandoni et al. (1996) a significantly higher recurrence rate of DVT was found in patients with impaired coagulation inhibition. In summary, the etiology of DVT is multifactorial. Estimation of the risk of DVT in individual patients is therefore rather difficult (Wessler 1962, Nielsen 1991, Nicolaides et al. 1992, Porter et al. 1995, Bergqvist 1996).

2.2 Chronic venous insufficiency

Chronic venous insufficiency (CVI) entails an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction (Porter et al. 1995). The term "postthrombotic syndrome" may be used if the patient has experienced an objectively documented previous DVT (Porter et al. 1995). The syndrome may, however, occur without any evidence of a prior episode of DVT (Browse et al. 1980, Lindhagen et al. 1985). Chronic venous insufficiency may likewise be found in legs with no symptoms (Browse et al. 1980, Lindhagen et al. 1985, Porter et al. 1995, Bradbury et al. 1996).

Hjelmstedt (1968) demonstrated differences in the venous pressures in normal legs and in legs with PTS, the differences including a diminished fall in venous pressure and high pressure swings in patients with CVI during exercise. Venous pressure is normally quite low during exercise, under 40 mmHg. In legs with CVI the ambulatory venous pressure remains high, 80-100 mmHg (Hjelmstedt 1968, Nicolaides and Miles 1987, Miller 1995). This hypertension is caused by venous valvular reflux or venous obstruction or both (Strandness et al. 1983, Nicolaides and Christopoulos 1990, Nicolaides et al. 1993, Miller 1995). Nicolaides and colleagues (1993) measured ambulatory venous pressures in patients with or without venous ulcer. No ulcers were detected in legs with venous pressure below 30 mmHg and an increased incidence of ulceration was associated with an increase in venous pressure, a finding also reported by Payne and coworkers (1996). It has been suggested that this high venous pressure is transmitted through communicating veins to the superficial system within the skin and subcutaneous tissues of the calf. According to such a conception venous hypertension leads to venular dilatation and increased capillary permeability, the result being a diffusion barrier formed by fibrin deposits. There is a fibrinolytic activator deficiency in the vein wall and removal of the accumulated fibrin is not possible. The overlying dermis becomes hypoxic because of this barrier (Browse and Burnard 1982, Strandness et al. 1983). The clinical signs and symptoms of PTS are pain, edema, skin changes around the ankle including pigmentation and lipodermatosclerosis, and finally ulceration, all of these manifestations being attributable to venous hypertension.

The development of signs and symptoms of CVI is commonly related to underlying dysfunction of the venous valves (Strandness et al. 1983, Killewich et al. 1985, Lindhagen et al. 1985, Francis et al. 1986, Moore et al. 1986, Gooley et al. 1988, Milne et al. 1994, Myers et al. 1995, Labropoulos et al. 1996, Van Haarst et al. 1996). Edwards and Edwards (1937) demonstrated the effect of thrombosis on the venous valves. The thrombus surrounds the valve cusps or pushes the valvular structures against the venous wall. Eventually this process leads to adhesion of the valves to the venous wall and

fragmentation. By this mechanism valvular function is lost and the vein remains incompetent after the subsequent recanalization.

Edwards and Edwards (1937) first demonstrated the recanalization of veins occluded by a thrombus. If recanalization fails to occur, collateral veins develop around the area of occlusion (Bergvall and Hjelmstedt 1968). Bergvall and Hjelmstedt (1968) examined 24 patients repeatedly by phlebography after an acute DVT and observed the recanalization of the thrombus to be a slow process, usually lasting three to four years. In recent studies in which the ultrasonographic techniques have been used, the time interval for recanalization has been found to be much shorter (Killewich et al. 1989, Meissner et al. 1993, Meissner et al. 1998). Killewich and associates (1989) found a high rate of recanalization (53%) during a three-month observation period. Meissner and colleagues (1993) noted a relatively short median lysis times in different venous segments after an acute DVT (posterior tibial vein 72-80 days, popliteal vein 93-260 days, common femoral vein 111-278 days without or with subsequent venous valvular reflux). A chronic obstruction in the iliofemoral venous segment may lead to venous claudication. Here the patient experiences a sudden pain in the thigh during exercise (Killewich et al. 1984). Raju and Fredericks (1986) found a high rate of severe swelling and ulceration in patients with hemodynamically proven obstruction, but another study revealed no association between the extent and the location of the obstruction and hemodynamic severity (Raju and Fredericks 1991).

In the development of CVI venous valvular incompetence is a more important mechanism than venous obstruction (Shull et al. 1979, Killewich et al. 1985, McEnroe et al. 1988, Araki et al. 1994, Labropoulos et al. 1996). Especially incompetence in the distal deep veins seems to be crucial (Shull et al. 1979, Strandness et al. 1983, Moore et al. 1986, Gooley and Sumner 1988, Labropoulos et al. 1996). Strandness and colleagues (1983) found an association between incompetence of the distal deep valves and postthrombotic symptoms and signs, measurements being made by continuous wave Doppler (CWD). Lindhagen et al. (1985) also using CWD, noted an association between the incompetence in the popliteal vein and leg symptoms. The severity of postthrombotic symptoms was higher in patients with incompetence in the distal deep veins. The above-mentioned study by Moore and group (1986) involved a total of 122 patients and the diagnostic method was CWD. Shull et al. (1979) demonstrated that the most important factor in determining ambulatory venous pressure (AVP) and ulceration in legs with PTS was the status of the popliteal valves. The popliteal measurements were here too made by CWD. The same phenomenon was registered by photoplethysmographic methods measuring the venous refilling time (VRT). Pathologic VRT was associated with distal valvular incompetence as detected by CWD (Gooley and Sumner 1988).

The pathophysiology of CVI has been further evaluated by more advanced ultrasonographic methods. In recent studies measurements have been made using venous duplex imaging (VDI) or color flow duplex imaging (CFDI) (Van Bemmelen et al. 1990, Hanharan et al. 1991, Lees and Lambert 1993, Myers et al. 1995, Bradbury et al. 1996, Labropoulos et al. 1996, Haenen et al. 1999). In many cases, a combination of venous reflux in the superficial, deep and communicating veins has been evinced. Hanharan and colleagues (1991) studied 95 extremities with a venous ulcer and observed multisystem incompetence in 66% of them, at least two venous systems being affected. Myers et al (1995) demonstrated that superficial reflux with or without deep venous reflux occurred in most limbs with more severe symptoms and signs. Lees and Lambert (1993) reported superficial reflux in 57% of patients with CVI and Labropoulos and associates (1996) demonstrated a high proportion (80%) of distal deep reflux in symptomatic legs.

Recent follow-up studies have revealed valvular incompetence of the deep veins to be the most common in venous segments previously affected by a thrombus (Markel et al. 1992, Van Haarst et al. 1996, Janssen et al. 1998). Such incompetence can occur in a venous segment with no previous evidence of DVT (Caps et al. 1995). The role of recurrent DVTs and propagation of the thrombus into new venous segments is not clearly understood, but these events may be of crucial significance for the outcome (Krupski et al. 1991, Lohr et al. 1991, Beyth et al. 1995, Prandoni et al. 1996). The rate of propagation in patients with calf DVT was 28% in a prospective study involving 192 patients, but in a subgroup of 23 treated with unfractionated heparin propagation occurred in only 3 cases (Lohr et al. 1995). Other reports have given similar (23-32%) frequencies of propagation (Kakkar et al. 1969, Lohr et al. 1991). Meissner and colleagues (1995) investigated further thrombotic events after an initial DVT. In serial VDI measurements a propagation to new venous segments was seen in 30% of patients despite treatment with anticoagulants. Krupski's group (1991) found a high rate of propagation (38%) after acute DVT treated with anticoagulants. An objectively diagnosed recurrent thromboembolic event was relatively rare (15%) in a long-term cohort study involving 124 patients (Beyth et al. 1995). In a two-year follow-up Prandoni et al. (1992) recorded a recurrent DVT in 16% of patients, but the rate of recurrences was higher in patients with cancer. Prandoni and associates (1996) made similar findings during an 8-year follow-up period. Lagerstedt and colleagues (1993) found a clearly higher rate of recurrence (28%) in a 4-6-year follow-up study.

3. Diagnostic means of detecting acute deep venous thrombosis and chronic venous insufficiency

3.1 Acute deep venous thrombosis

3.1.1 Clinical examination

Typical symptoms of an acute DVT are leg pain, edema, tenderness and discoloration (Lohr et al. 1995). Diagnosis on the basis of clinical signs of DVT is however inadequate (Nicolaidis et al. 1971, Simpson et al. 1980, Sandler et al. 1984). An acute DVT may even be asymptomatic (Kakkar et al. 1969, Olin et al. 1993, Davidson et al. 1996). In 50 patients with suspected DVT physical examination was the least accurate method, whereas ascending contrast phlebography attained an accuracy of 90% (Sandler et al. 1984).

3.1.2 Phlebography

Ascending contrast phlebography has been generally accepted as the most reliable method in the diagnosis of an acute DVT (Williams 1973, Lea Thomas et al. 1977, Browse 1978, Sandler et al. 1984). When contrast medium is injected into a dorsal vein of the foot, the entire deep venous system of the leg can be visualized. Criteria for the diagnosis of DVT include a constant filling defect intraluminally, abrupt termination of the column of contrast material or repeated nonfilling of a segment in a deep vein (Rabinov 1972). Ascending phlebography is an invasive method attended by appreciable morbidity (Albrechtsson et al. 1976, Bettmann et al. 1987), but this approach yields reliable information as to the location and extent of the thrombus (Lea Thomas 1972, Lea Thomas et al. 1977, Browse 1978).

3.1.3 Ultrasonography

In Doppler ultrasound the detector emits an audible signal which changes with the velocity of blood flow. It is a "blind" and subjective method and differentiation of the vessels is thus rather difficult (Matzdorff and Green 1992). In venous duplex imaging (VDI) the vessels of the leg are visualized in B-mode. Measurement of blood flow is made by combining Doppler ultrasound to the system. If this

latter is then converted into a color signal (CFDI), flow disturbances can be visualized (Rose et al. 1990, Mattos et al. 1992, Matzdorff and Green 1992).

Venous duplex imaging combined with color has been shown to determine the anatomic extent of an acute DVT in a consensus statement (Porter et al. 1995). Compared with other means of detecting DVT the accuracy of VDI has been widely demonstrated (Appelman et al. 1987, Rollins et al. 1988b, Comerota et al. 1990, Foley et al. 1990, Prandoni et al. 1993, Poppiti et al. 1995). Appelman and associates (1987) compared VDI with ascending contrast phlebography and established 100% sensitivity of VDI in detecting proximal DVTs. In studies involving distal DVTs sensitivity has been 89-91% and specificity 95-100% (Cronan et al. 1987, Lensing et al. 1989, Wright et al. 1990), which would indicate that the accuracy of VDI is lower in detecting calf DVTs. In patients with symptomatic DVT, Mattos and colleagues (1992) demonstrated 100% sensitivity and 98% specificity of CFDI compared with phlebography in detecting proximal DVT. However, below-knee sensitivity was 94% and specificity 75%. As a screening test the reliability of VDI is not clearly established; it has been shown to be less sensitive among asymptomatic patients with DVT (Barnes et al. 1990, Mattos et al. 1992, Jongbloets et al. 1994, Wells et al. 1995). In patients screened after total hip replacement sensitivity compared to phlebography was only 55% in detecting calf DVT (Mattos et al. 1992).

3.1.4 Other methods

A number of plethysmographic methods can be used to detect an acute DVT, including impedance plethysmography (IPG), air-cuff plethysmography, strain-gauge plethysmography and phleborheography (Sandler et al. 1984, Hull et al. 1985, Heijboer 1991, Matzdorff and Green 1992). These methods are based on changes in blood volume in the leg. An acute DVT occludes the major veins of the leg, reduces venous compliance and increases venous outflow resistance (Heijboer 1991). IPG has been demonstrated to be fairly sensitive (83-88%) in the diagnosis of proximal DVTs (Hull et al. 1985, Comerota et al. 1988), but sensitivity is lower in materials including both proximal and distal DVTs (63-71%), the technique being relatively insensitive in detecting calf DVT and small non-occlusive DVTs (Hull et al. 1985, Comerota et al. 1988).

In the ¹²⁵I-fibrinogen uptake test (FUT) surface radioactivity is measured over several points on both legs. Radiolabeled fibrinogen incorporates itself into a forming clot and the phenomenon can be detected (Kakkar 1972, Comerota et al. 1985). FUT has been widely used as a screening method for detecting postoperative DVT (Kakkar et al. 1969, Kakkar 1972, Bergentz 1988). It has, however, proved less sensitive (44-49%) as a screening method after hip surgery (Harris et al. 1985, Cruickshank et al. 1989). Paiement and colleagues (1988) reported a relatively low sensitivity (59%)

in patients with calf DVT when FUT was compared with phlebography in asymptomatic patients. The sensitivity of FUT was particularly low (14%) in detecting proximal DVT. Scintigraphic methods have also been used in detecting DVT in the leg, but these methods involve a number of limitations. These methods are unreliable in the calf and the accuracy decreases in patients with previous thromboembolism (Knight 1993, Barloon et al. 1997).

Magnetic resonance imaging is able to detect filling defects in the deep venous system of the lower limb. This also includes calf and especially pelvic veins (Erdman et al. 1990, Evans et al. 1993, Barloon et al. 1997). However, MRI is considered to be highly operator-dependent and is expensive (Barloon et al. 1997).

3.1.5 Evaluation of the current methods

The most important diagnostic means of detecting an acute DVT are ascending phlebography and ultrasonography (VDI or CFDI). In the consensus statement (Porter et al. 1995) both methods are considered to be acceptable in determining the anatomic extent of an acute DVT.

3.2 Chronic venous insufficiency

3.2.1 Clinical evaluation

Clinical symptoms and signs of chronic venous insufficiency (CVI) consist in leg pain, edema and skin changes. In the consensus statement CVI is graded in seven classes. Class 0 represents a situation with no signs of venous disease and in class 6 there is active ulceration with skin changes in the affected leg (Porter et al. 1995).

3.2.2 Ambulatory venous pressure

Assessment of ambulatory venous pressure (AVP) is the basic method in gauging the status of the deep venous system in the leg (Ackroyd and Browse 1986, Nicolaides and Zukovski 1986, Nicolaides

and Christopoulos 1990). Venous pressure is measured by inserting a needle into a vein on the dorsum of the foot. The needle is connected through a pressure transducer and an amplifier to a potentiometric pen recorder and changes in venous pressure registered during rest and standard exercise (Nicolaidis and Zukovski 1986). AVP tends to fall rapidly under 40 mmHg during exercise if the venous system is functioning normally (Nicolaidis and Zukovski 1986, Nicolaidis et al. 1993, Payne et al. 1996). There is an association between the incidence of ulceration and AVP (Nicolaidis et al. 1993). A pneumatic cuff may be used to distinguish between superficial and deep incompetence. AVP is an invasive method and its use as a screening test or in repeated testings is thus restricted (Nicolaidis and Zukovski 1986).

3.2.3 Phlebography

Ascending phlebography affords a means of studying the anatomy of the venous system in the leg. The procedure has been described elsewhere. It allows detection of an obstruction in the outflow tract, likewise recanalization changes and the collateral veins (Ackroyd and Browse 1986, Nicolaidis and Christopoulos 1990). Ascending phlebography is a basic mode for patients with CVI (Lehtola et al. 1997). Descending phlebography is used, for its part, to demonstrate the presence of deep vein valve cusps and the degree of venous reflux (Herman et al. 1980, Kistner et al. 1986, Ackroyd et al. 1986). It is performed by inserting a needle into the common femoral vein. Contrast medium is injected during provocation (the Valsalva manoeuvre) and the degree of reflux is estimated. In most severe cases the reflux continues below the knee (Ackroyd and Browse 1986, Ackroyd et al. 1986). The approach is useful in selected patients and of considerable value when planning surgical procedures (Ackroyd et al. 1986). Baker and associates (1993) observed, however, that descending phlebography underestimates venous reflux in the leg compared to venous duplex imaging.

3.2.4 Ultrasonography

Continuous wave Doppler ultrasound (CWD) can be used to detect reflux or obstruction in the venous system of the leg. This is a subjective and qualitative method, and is therefore not currently recommended in the evaluation of CVI (Porter et al. 1995). Venous duplex imaging allows identification of the individual venous segments, quantification of reflux and detection of total or partial obstruction (Szendro et al. 1986, Van Bemmelen et al. 1989, Vasdekis et al. 1989, Markel et al. 1992, Araki et al. 1993, Prandoni et al. 1993, Van Ramshorts et al. 1994). The patient is studied in standing or supine position. Venous reflux in a certain segment is measured after sudden release of a cuff or by means of manual compression. Venous reflux longer than 0.5 seconds is usually rated abnormal (Szendro et al. 1986, Van Bemmelen et al. 1989). Araki and coworkers (1993) found a

mean reverse flow duration of 0.3 seconds in normal legs. Szendro et al. (1986) used VDI in patients with normal veins and in patients with CVI and compared the results against AVP measurements. The sensitivity of VDI was 84% and specificity 88%. Araki and coworkers (1993) studied both VDI and CFDI in documenting venous valvular reflux in the popliteal vein. The highest sensitivity and specificity (91% and 100%) were reached using standing position and distal cuff compression. When distal cuff compression was used in supine position, the corresponding figures were 73% and 100%. Both supine and upright positions have been widely used in follow-up studies in detecting venous valvular reflux (Killewich et al. 1989, Markel et al. 1992, Meissner et al. 1993, Caps et al. 1995, Meissner et al. 1995, Van Haarst et al. 1996).

3.2.5 Plethysmography

Several plethysmographic methods are available for measurements of CVI. Strain-gauge plethysmography and air-plethysmography detect volume changes in the calf and can be used to estimate the presence and degree of venous obstruction (Ackroyd and Browse 1986, Christopoulos et al. 1987, Christopoulos et al. 1989). Photoplethysmography detects differences in skin blood volume. Venous refilling time (VRT) is measured after standard exercise; It comprises the time in seconds from the end of exercise to the point of resting level of blood volume (Nicolaidis and Miles 1987). A short venous refilling time indicates an incompetence in the venous valves. If superficial veins are occluded with a cuff, an abnormal VRT can be taken to describe deep venous reflux (Abramowitz et al. 1979, Killewich et al. 1985, Ackroyd and Browse 1986, Browse 1986, Nicolaidis and Miles 1987, Nicolaidis and Christopoulos 1990). Foot volumetry has also been used for the functional assessment of the veins in the leg. This approach is based on water displacement, which measures volume changes in the foot (Lawrence and Kakkar 1980).

The value of these plethysmographic methods is mainly qualitative. Patients can be divided into those with normal and those with abnormal test results. This may help to select the patients who need further investigations (Browse 1986).

3.2.6 Evaluation of current methods

Venous duplex imaging is the best-documented noninvasive means of quantifying venous reflux (Porter et al. 1995). The role of ascending phlebography is important in defining of areas of

obstruction, recanalization and collaterals. Plethysmographic studies mirror measurements of leg vein pressure. Absolute measurements are of no great value, but the qualitative information may be important for the diagnosis of CVI (Browse 1986, Ackroyd and Browse 1986, Porter et al. 1995).

4. Epidemiology of deep venous thrombosis

4.1 Risk associations

Deep venous thrombosis is a disease of multifactorial etiology. The main etiologic factors underlying thrombus formation have been discussed in earlier sections. The overall number of risk factors determined to predispose venous thromboembolism is high. Risk associations of DVT according to the U.S. consensus statement are collected in Table 1.

4.1.1 Age and Gender

Advancing age is a component with well-demonstrated statistical correlation to DVT (Gjöres 1956, Kakkar et al. 1970, Coon et al. 1973, Sikorski et al. 1981, Andersson et al. 1991, Franks et al. 1992, Nordström et al. 1992, Davidsson et al. 1996, Hansson et al. 1997). In surgical patients, Kakkar and associates (1970) observed an increased incidence of postoperative DVT. Similarly, Davidson et al. (1996) found age to be an independent risk factor for DVT after major orthopedic surgery. Community-oriented studies have shown a sharp increase in the risk of DVT during the fifth decade (Anderson et al. 1991, Nordström et al. 1992). The same phenomenon has been seen in autopsy studies (Sevitt and Gallagher 1961, Havig 1977).

The significance of gender as a risk factor underlying DVT remains controversial. In older community-oriented studies the life-time prevalence of DVT was slightly higher in women (Gjöres 1956, Coon et al. 1973). The incidence was the same in both sexes in recent community-oriented studies (Andersson et al. 1991, Nordström et al. 1992). Silverstein et al. (1998) noted a higher incidence of venous thromboembolism (130 versus 110 per 100000 per year) in men. Female gender was an independent risk factor for DVT in a community-oriented study in London (Franks et al.

1992), while in surgical patients, Davidson's group (1996) found an increased risk to be associated with male gender. In conclusion it would appear that male or female gender cannot be cited as a risk factor implicated in DVT.

There are nonetheless certain important risk associations related to female gender. A link between DVT and oral contraceptive pills has been demonstrated in several studies (Vessey et al. 1968, Sartwell et al. 1969), a finding confirmed in more recent multicentre trials (Farley et al. 1995, Poulter et al. 1995, Daly et al. 1996, Grodstein et al. 1996, Jick et al. 1996). Obesity may involve an additional risk of DVT among the patients using contraceptive pills (Vessey et al. 1968). The risk of DVT was seen to be increased during pregnancy and the postpartum period in the Tecumseh community study (Coon et al. 1973).

4.1.2 Trauma

Limb trauma has been envisaged as a risk factor for DVT in a consensus statement (Porter et al. 1995). A number of studies have shown such an association between limb trauma and DVT. Hjelmstedt and associates (1968) demonstrated a high (54%) incidence of DVT in patients with tibial fractures in age groups 25-74 years; Geerts et al. (1994) found a high incidence of DVT (58%) in 349 patients with major trauma, 18% of their patients having the thrombus located proximally. Furthermore, fractures of femur or tibia and spinal cord injury emerged as independent risk factors. In hip surgery postoperative DVT has been shown to develop at the site of operation, which would suggest that a direct surgical trauma to the tissue might predispose to DVT formation (Stamatakis et al. 1978b).

4.1.3 Malignancy

An association between malignancy and DVT has been demonstrated in several studies. Kakkar and associates (1970) found a link between DVT and cancer in surgical patients. A follow-up study revealed significantly higher cancer rates in patients with DVT (Goldberg et al. 1987). Another study showed an increased cancer rate during follow-up after an idiopathic DVT (Prandoni et al. 1992). Bastounis et al. (1996) found a high cancer rate (25%) in patients with an idiopathic DVT. The risk of recurrent episodes of DVT proved significantly higher in cancer patients in a prospective cohort study (Prandoni et al. 1996).

4.1.4 Coagulation abnormalities

A number of coagulation and fibrinolysis disorders predispose to abnormal clotting, among them venous thrombosis (Conard et al. 1988, Porter et al. 1995). Antithrombin III, protein C and protein S deficiencies are congenital. They work as coagulation inhibitors and a deficiency induces typically venous thromboses (Thaler and Lehner 1981, Broekmans et al. 1983, Comp et al. 1984). The most common genetic disorder is resistance to activated protein C, a disorder arising from a mutation in factor V (Rasi 1995). Resistance to activated protein C (APC resistance) was associated with a relative risk of 5.0 in elective hip or knee replacement surgery (Lindahl et al. 1999). Dysfibrinogenemias and disorders of the fibrinolytic system are likewise associated with DVT (Lottenberg et al. 1985, Samana et al. 1987, Conard et al. 1988), while lupus anticoagulants have been shown to be the most common acquired disorder predisposing to DVT (Mueh et al. 1980, Rasi 1995).

4.1.5 Cardiac disease

An association between myocardial infarction and DVT was observed by Simmons and colleagues (1973). They found that 27% of patients had DVT after myocardial infarction. The relationship between congestive heart failure and DVT has not been clearly established (Carter 1994). However, congestive heart failure and other medical conditions which cause stasis have been identified as risk factors for DVT in consensus statements in Europe and in U.S (Roberts et al. 1986, Nicolaides et al. 1992). Cardiac disease emerged as the most significant predisposing factor for venous thromboembolism in a retrospective study in Boston (Byrne 1955). Hypertension has proved to be significantly associated with pulmonary embolism in women in the U.S (Goldhaber et al. 1997). In contrast, Franks and coworkers (1992) found no association between DVT and hypertension in their community-oriented study.

4.1.6 Other risk associations

A previous thromboembolic event has been seen to increase the risk of DVT after surgery (Kakkar et al. 1970). Previous thromboembolism proved to be an independent risk factor for DVT in patients who had undergone an abdominal operation (Flordal et al. 1995). The role of immobilization was assessed in an autopsy study, prolonged bed rest being clearly implicated in DVT (Havig 1977); Gibbs (1957) likewise demonstrated that a longer duration of bed rest (over two weeks) increased the

risk of DVT. Stroke involved a high rate of DVT (more than 50%) on the paralytic side (Warlow et al. 1972). Obesity may be associated with DVT, but results on this are not clear. Kakkar et al. (1970) showed such an association in surgical patients. As mentioned above, the use of contraceptives may associate with an increased risk of DVT in obese women (Vessey et al. 1968). Goldhaber et al. (1997) noted a significant risk of pulmonary embolism in obese women, their multivariate relative risk being 2.9 when body mass index (BMI) was more than 29 Kg/m².

Table 1. Risk associations of DVT according to a consensus statement from the U.S (Roberts et al. 1986).

Inherited risk factors

Antithrombin III deficiency
 Dysfibrinogenemia
 Disorders of plasminogen and plasminogen activation
 Protein C deficiency
 Protein S deficiency

Acquired risk factors

Advancing age
 Cancer
 Estrogen therapy
 Immobilization
 Inflammatory bowel disease
 Lupus anticoagulant
 Nephrotic syndrome
 Obesity
 Paroxysmal nocturnal hemoglobinuria
 Polysythemia rubra vera
 Prior thromboembolism
 Sepsis
 Stroke
 Stasis - Congestive heart failure, Myocardial infarction, Cardiomyopathy, Constrictive pericarditis

4.2 Incidence and prevalence in the general population

The incidence and prevalence of a symptomatic DVT vary considerably. Study designs also differ in that in some the data are collected from hospital discharges (Anderson et al. 1991, Bounameaux et al. 1996, Silverstein et al. 1998, White et al. 1998). In community-oriented studies the method of detecting DVT varies. Nordström and associates (1992) used phlebography in the diagnosis, whereas Franks et al. (1992) employed a self-administered questionnaire in the collection of data. Hansson's group (1997) followed up prospectively 855 men from the age of 50 years to the age of 80, diagnosis being again by phlebography.

The incidence of DVT was 160 per 100000 per year in a community-oriented study employing phlebographic examinations (Nordström et al. 1992). Similarly, in a cohort-study by Hansson's group (1997), the incidence was 182 per 100000 per year. The life-time prevalence of DVT and pulmonary embolism was 6% in a community-oriented questionnaire study involving 2103 persons (Franks et al. 1992). Gjörres (1956) found the life-time prevalence of DVT to be 2.2% in a certain district in Sweden. In the Tecumseh health study the life-time prevalence was 3.6% in women and 1.0% in men (Coon et al. 1973), but methods of diagnosis were not consistent and in most cases an objective diagnostic method was lacking.

An extensive retrospective study in Worcester showed that the incidence of DVT was 48 per 100000 annually (Anderson et al. 1991). The study design was based on data obtained from hospital discharges. Bounameaux et al. (1996) made a retrospective study likewise based on hospital discharges. The incidence of DVT was 80 per 100000 per year. Silverstein et al. (1998) reported on a retrospective study based on discharge data and gave the annual incidence of DVT as 48 per 100000.

The incidence of DVT is thought to be higher among white people (Burkitt 1972, Carter 1994). Dodd (1964) reported that in a large hospital material in Africa this disease was seen only in sporadic cases. Nosset et al. (1993) studied a black Caribbean population and the incidence of DVT was particularly low, only 11 per 100000 annually. Recently, White et al. (1998) studied the incidence of DVT based on hospital records among ethnic groups in the U.S. They reported a low annual incidence of DVT (60 per 100000) in Asians and Pacific Islanders; the incidence was very significantly higher (230 per 100000) among white persons.

The most reliable estimates of the incidence of DVT are probably those based on the community studies by Nordström's (1992) and Hansson's groups (1997). The first-mentioned was made in a

clearly defined area and in all cases the diagnosis was based on phlebography. Similarly, Hansson et al. (1997) followed up a cohort of men and in all cases the objective (phlebography) diagnosis of DVT was checked from medical records.

4.3 Surgical patients

4.3.1 Factors affecting the risk

Patients undergoing surgical procedures are known to be at risk of postoperative DVT (Kakkar et al. 1969, Cohen et al. 1973, Walsh et al. 1974, Sikorski et al. 1981). The type of surgery involved is an important factor in this respect (Nicolaidis et al. 1992, Bergqvist 1996). The incidence of DVT is highest in orthopedic surgery, but rates are also high in surgery involving the urogenital and abdominal region, especially in patients with cancer (Mayo et al. 1971, Cohes et al. 1974, Sikorski et al. 1981, Bergqvist and Lindblad 1988, Reasbeck et al. 1988, Nicolaidis et al. 1992). The importance of the duration of surgery is controversial. Flordal et al. (1995) found long duration of an operation to constitute an independent risk factor for postoperative DVT. Davidson et al. (1996) report that postoperative DVT is more common in patients receiving general anesthesia, but the duration of anesthesia was not predictive. The increased risk of DVT after surgery may last longer than previously suggested. Planes and coworkers (1996) demonstrated that the risk of postoperative DVT was marked for at least a 35-day period after orthopedic surgery. Sikorski et al. (1981) noted that the peak incidence of postoperative DVT in orthopedic patients occurred one week after operation. On the other hand, prolonged thromboprophylaxis appears to have no significant effect on the incidence of DVT after general surgery (Lausen et al. 1998). In one consensus statement (Nicolaidis et al. 1992) surgical patients were divided into three risk categories. The highest risk of venous thromboembolism was estimated to obtain in major orthopedic surgery, extensive pelvic or abdominal surgery for malignancy and general or urologic surgery in patients over 40 years with a previous history of thromboembolism.

The modern modes of prophylaxis have markedly reduced the incidence of DVT in surgical practice (Borow and Goldson 1983, Glagett and Reisch 1988, Collins et al. 1988). The incidence after abdominal surgery was 7-13% in 2070 patients with prophylaxis of low-molecular-weight heparin (Bergqvist et al. 1995). In patients operated for abdominal or pelvic cancer the proportion was 15%, prophylaxis here too being with low-molecular-weight heparin (Bergqvist et al. 1997).

4.3.2 Incidence in vascular surgery

The incidence of DVT in vascular surgery has varied between 8 and 43% in studies in which no specific prophylactic treatment was given (Hamer 1972, Myhre et al. 1974, Angelides et al. 1977, Olin et al. 1993). Both numbers of patients and study designs differed considerably, which would explain such variability. The incidence of postoperative DVT was 20% among 88 patients who had undergone elective aorto-iliac reconstruction, surgery of abdominal aortic aneurysms resulting in a higher rate of DVT (33% versus 12%) than surgery for occlusive aorto-iliac disease (Angelides et al. 1977). Hamer (1972) found a high rate of postoperative DVT (43%) among patients undergoing femoro-popliteal bypass, while a notably lower rate (8%) was presented by Myhre et al. (1974). Despite the use of unfractionated heparin, 10% of patients have been found to have postoperative DVT after vascular surgery in the aortic or lower extremity region (Fletcher et al. 1997). The incidence of postoperative DVT in patients operated for varicose veins is not known, although there are studies this disorder and DVT (Kakkar et al. 1970, Crandon et al. 1980, Sue-Ling et al. 1986).

4.3.3 Incidence in other fields of surgery

In general surgical patients the incidence of DVT was 25% in a large meta-analysis comprising 54 studies. The diagnosis of postoperative DVT was based on FUT. When the diagnosis was confirmed by phlebography, the incidence was 19% (Clagett and Reisch 1988). In addition, pooled results showed a higher (30% versus 16%) incidence of DVT in European than in North American studies (Clagett and Reisch 1988).

The occurrence of postoperative DVT has been rather frequent following major abdominal, urological or gynaecological surgery. There is some evidence to suggest that the use of the laparoscopic technique may reduce the incidence (Caprini et al. 1994). In urology, transurethral prostatectomy seems to have a similar effect compared to open surgery (Mayo et al. 1971, Nicolaidis et al. 1972). The frequency of postoperative DVT has been reported to reach 70% among patients undergoing an orthopedic operation in the lower limb (Bergqvist et al. 1976, Sikorski et al. 1981, Suomalainen et al. 1983, Hull et al. 1986). Among other types of orthopedic surgery, such as spinal and scoliosis surgery, the incidence of postoperative DVT has been fairly low, approximately 0.5-6% (Uden 1979, Ferree et al. 1993a, Ferree et al. 1993b). In arthroscopic knee surgery the recorded incidence is likewise low, about 8% (Schippering et al. 1998). Similarly, a low incidence (0.22%) has been found in foot and ankle surgery (Mizel et al. 1999). Examples of studies concerning the incidence of postoperative DVT are shown in Table 2.

Table 2. Postoperative DVT in abdominal, urological, gynecological and orthopedic surgery. A sample of previous studies.

Source and year	Number of patients	Operation	DVT(%)	Diagnosis	Prophylaxis
Reasbeck et al. 1988	152	abdominal	24%	Phlebo/FUT	none
Törngren and Engström 1991	30	abdominal	37%	FUT	lmw-heparin
Caprini et al. 1994	100	laparoscopic cholecystectomy	1%	VDI	compression
Walsh et al. 1974	100	vaginal hysterectomy	7%	Phlebo	none
Walsh et al. 1974	22	gynecological carcinoma	45%	Phlebo	none
Mayo et al. 1971	41	open prostatectomy	51%	FUT	none
Mayo et al. 1971	20	transurethral resection of prostate	10%	FUT	none
Cohen et al. 1973	35	knee surgery	56%	Phlebo	none
Sikorski et al. 1981	223	hip replacement	48%	Phlebo+FUT	none
Suomalainen et al. 1983	108	hip surgery	43%	Phlebo	warfarin
Schippinger et al. 1998	101	knee arthroscopy	8%	Phlebo	lmw-heparin
Mizel et al 1998	2733	foot/ankle surgery	0.22%	VDI	none

5. Outcome of deep venous thrombosis

5.1 Incidence of chronic venous insufficiency

The predictability of postthrombotic symptoms and signs remains to be assessed (Meissner et al. 1988, Prandoni et al. 1998). The incidence of postthrombotic sequelae varies markedly as shown in Tables 3 and 4. A typical finding in most studies is a somewhat high rate of leg symptoms while the rate of ulceration has been low (Tables 3 and 4).

Bauer (1942) noted an extremely high rate of late sequelae of DVT in patients with previous major DVT. In most cases the initial diagnosis was based on ascending contrast phlebography. Ulceration

was found in 78% of patients if the follow-up period was more than five years. Strandness and colleagues(1983) demonstrated a high frequency of pain and edema, but only few cases of ulceration in a prospective three-year follow-up. A retrospective study with 67 patients revealed that 33% of legs which had suffered major DVT evinced no symptoms (Browse et al. 1980). Halstuk et al. (1984) record all five patients with a previous iliofemoral DVT as showing clinical evidence of PTS. Raju and Fredericks (1986) studied 29 legs in 19 patients with a previous DVT documented by ascending contrast phlebography; only two limbs were free of hemodynamic abnormalities and the rate of subjective symptoms was high. In a long-term follow-up study the rate of asymptomatic patients was 27% about 4.5 years after an acute DVT (Meissner et al.1998). Franzeck et al. (1996) followed 39 patients up to 12 years and noted a high proportion (64%) of asymptomatic patients. Monreal et al. (1993) found no physical evidence of CVI in 44% of their patients three years after DVT. There are also follow-up studies in which the initial diagnosis of an acute DVT was based on FUT; the incidence of symptoms and signs of CVI varies in them between 16-24% (Browse et al.1974, Mudge and Hughes 1978, Lindhagen et al. 1983).

The long-term outcome of an isolated calf DVT has remained a matter of controversy (Philbrick and Becker 1988). According to some follow-up studies the outcome seems to be fairly benign (Widmer et al. 1985, Franzeck et al 1996, Masuda et al. 1998). Other studies, however, have revealed a high rate of late sequelae in the leg (Schulman et al. 1986, Heldal et al. 1993, Lagerstedt et al. 1993, Meissner et al. 1997). A typical finding in follow up studies is also a poor association between the initial extent of an acute DVT and the outcome (Lagestedt et al. 1993, Meissner et al. 1998, Prandoni et al.1998). Schulman et al. (1986) followed 36 patients with a phlebographically proven calf DVT and found signs or symptoms of CVI in 37%. Lindhagen and associates (1985) in their retrospective study noted that there was no difference between calf and more proximal DVTs after a follow-up period of 5-8 years. Lagerstedt et al. (1993) report similar findings in a 6-year follow-up with 39 patients. Heldal et al. (1993) also found no difference in outcome between proximal and distal DVTs. Widmer's group (1985) demonstrated a low rate of late symptoms and signs in patients with previous calf DVT, and Franzeck et al. (1996) followed 13 patients prospectively up to 12 years and recorded a high rate of asymptomatic patients (85%). An asymptomatic postoperative DVT may lead to impaired venous function, as demonstrated in several studies (Francis et al. 1986 and Andersen and Wille-Jorgensen 1991). The results from trials focusing on the outcome of calf DVT are shown in Table 5.

The time interval in which the symptoms and signs of CVI occur after the acute episode has not been established. Recent studies demonstrate that the development of venous valvular incompetence may begin during the first months after DVT (Killewich et al. 1989, Markel et al. 1992). The rate of recanalization may also be relatively rapid (Markel et al. 1992). Killewich et al. (1989) found venous valvular incompetence in 62% of 21 patients 270 days after an acute DVT. Markel et al. (1992)

showed that two thirds of patients developed venous valvular incompetence during a one-year period after an acute DVT, and Meissner et al. (1997) observed valvular incompetence in 24% of patients at one year. Brandjes and coworkers (1997) demonstrated that over 60% of patients with a proximal DVT develop CVI within a two-year follow up. However, a long-term follow up of 24 patients revealed significant progression in deep venous valvular incompetence (from 48% to 60%) when subjects were examined approximately three and seven years after DVT (Van Haarst et al. 1996).

Although previous DVT predisposes to CVI, this may also occur without a previous thrombotic event (Browse et al. 1980, Scott et al. 1995). Mudge and Hughes (1978) followed 564 patients for three years after abdominal surgery, and they found 12 new patients with a symptomatic CVI. A high proportion of these patients (50%) evinced no evidence of postoperative DVT in screening studies with FUT after the operation. Browse et al. (1980) found that 32% of legs with no previous history of DVT had symptoms, while Francis and coworkers. (1986) observed no difference in leg symptoms when patients with a previous DVT were compared to controls (27% versus 37%). Lindhagen et al. (1985) found that more than one third of patients with no evidence of previous DVT yielded subjective and objective findings of CVI. In contrast, Haldal et al. (1993) found no symptoms or objective signs of CVI in control legs when they restudied 25 patients who had had DVT seven years earlier. Lindhagen et al. (1986) concurred in this observation, too. The prevalence of deep popliteal reflux in the general population was found to be approximately 10% when the criterion for abnormal venous reflux was 0.5 seconds or more (Evans et al. 1998).

Table 3. The incidence of subjective symptoms after phlebographically confirmed deep venous thrombosis. n=number of patients, y=range in the follow-up time in years.

Source	Patients (n)	Follow-up (y)	Subjective symptom		
			Pain	Edema	Ulcer
Bauer (1942)	12	5-10	--	100%	58%
Killewich et al. (1985)	32	0.8-12	49%	29%	3%
Widmer et al. (1985)	341	3.4-6.4	29%	59%	6.5%
Bergqvist et al. (1990)	95	7-27	38%	55%	4%
Andersen et al. (1991)	25	3.4-8	21%	48%	0%
Lagerstedt et al (1993)	39	3.8-7.2	23%	36%	0%
Beyth et al. (1995)	52	6-8	15%	35%	0%
Meissner et al. (1998)	68	1.5-9.1	18%	34%	2.7%

Table 4. The incidence of chronic venous insufficiency after phlebographically confirmed DVT (physical signs=chronic venous insufficiency estimated after physical examination. Instrumental=Chronic venous insufficiency diagnosed by plethysmographic methods, Doppler ultrasound or venous duplex imaging. n=number of patients, y=range in the follow-up time in years).

Source	Patients (n)	Diagnostic method		
		Follow-up (y)	Physical signs	Instrumental
Browse et. al (1980)	67	5-10	30%	--
Strandness et al. (1983)	61	0.1-12	67%	60%
Halstuk et al. (1984)	15	0.5-4.5	67%	--
Lindhagen et al. (1985)	85	5-8	44%	49%
Killewich et al. (1985)	32	0.8-12	58%	74%
Widmer et al. (1985)	341	3.4-6.4	21%	--
Francis et al. (1986)	16	4.2	58%	74%
Lindhagen et al. (1986)	23	3-10	35%	65%
Schulman et al. (1986)	36	5	37%	26%
Raju et al. (1986)	19	2-13	79%	93%
Heldal et al. (1993)	25	6.6-8.5	42%	68%
Monreal et al. (1993)	79	3	56%	--
Eichlisberger et al. (1994)	123	11.6-14.4	39%	--
Milne et al. (1994)	107	1-34	72%	--
Johnson et al. (1995)	78	1-6	41%	--
Franzeck et al. (1996)	39	11-12.4	36%	69%
Van Haarst et al. (1996)	24	6.1-8.7	--	60%
Brandjes et al. (1997)	98	5-8	68%	--

Table 5. The incidence of chronic venous insufficiency in patients with phlebographically/venous duplex imaging confirmed calf deep venous thrombosis (physical signs=chronic venous insufficiency estimated after a physical examination. Instrumental=chronic venous insufficiency diagnosed by plethysmographic methods, Doppler ultrasound or venous duplex imaging). n=number of patients, y=range in the follow-up time.

Source	Patients (n)	Diagnostic method		
		Follow-up (y)	Physical signs	Instrumental
Kakkar et al. (1985)	73	2	22%	66%
Widmer et al. (1985)	37	3.4-6.4	0%	--
Francis et al. (1986)	8	4.2	50%	50%
Lindhagen et al. (1986)	7	3-10	43%	71%
Schulman et al. (1986)	36	5	37%	26%
Heldal et al. (1993)	10	6.6-8.5	42%	60%
Lagerstedt et al. (1993)	20	3.8-6	35%	--
Eichlisberger et al. (1994)	28	11.6-14.4	4%	--
Franzeck et al. (1996)	13	11-12.4	15%	46%
Masuda et al. (1998)	23	1-6	5%	27

5.2 Possibilities of influencing the outcome of deep venous thrombosis

Efforts to prevent the postthrombotic syndrome may be made before or after an episode of DVT. The prevention of DVT is the most important procedure in preventing PTS. The current modes of prophylaxis are rather effective in this respect. The effect of prophylactic methods in surgery has been discussed earlier in chapter 4.3.

5.2.1 The use of heparin and warfarin

The long-term sequelae of an acute DVT have been investigated in patients receiving the traditional treatment with iv-heparin and peroral warfarin during the acute phase. Although the rate of late symptoms has been variable, it has tended to be high (Strandness et al. 1983, Halstuk et al. 1984, Kakkar and Lawrence 1985, Bergqvist et al. 1990, Heldal et al. 1993, Eichlisberger et al. 1994, Beyth et al. 1995, Meissner et al. 1998). Meissner and associates (1993) demonstrated that early recanalization may preserve venous valve integrity when they followed patients after DVT with repeated VDI studies. The results remained controversial, however, in that some of the patients developed valvular incompetence despite this early lysis of the thrombus and some venous segments remained competent despite late spontaneous lysis. Caprini et al. (1999) showed an association between the level of oral anticoagulation therapy achieved by warfarin and the resolution of DVT.

5.2.2 Thrombolytic management

Thrombolysis has been used to preserve valvular function (Rogers and Lutchter 1990, Turpie et al. 1990, Pietilä 1993, Miller 1995, Partch 1996). Rogers and Lutchter reviewed 13 studies which had compared heparin and streptokinase in the treatment of an acute DVT. According to this review, the incidence of PTS was lower in patients treated with streptokinase. However, when Kakkar and Lawrence (1985) undertook a 2-year follow-up study after an acute DVT, they found no difference between heparin and streptokinase (54% versus 72%) in hemodynamic grading by foot volumetry. Eichlisberger et al. (1994) reported the results of their long-term (13 years) follow-up after DVT. One hundred patients were initially treated with streptokinase and 123 with anticoagulants. The incidence of PTS was 23% in the former and 39% in the latter group. In a six-year follow-up the proportion of asymptomatic patients was 76% in a group with thrombolysis and 33% in a group initially treated with anticoagulants (Arnesen et al. 1982). Schulman et al. (1985) found no difference in late sequelae between these methods in patients with calf DVT. Turpie et al. (1990) reported that thrombolysis

with tissue plasminogen activator therapy in the acute phase of DVT resulted in a smaller number of symptomatic patients in a three-year follow-up. Martelli and coworkers (1998) studied the difference between thrombolysis and thrombectomy in experimental DVT, and concluded that thrombolysis may preserve vein function better than thrombectomy.

5.2.3 The role of recurrent events

The incidence of recurrent thrombosis following therapy with streptokinase has not been ascertained. It has been estimated that rethrombosis could occur in 9-22% of patients treated with streptokinase and anticoagulants (Rogers and Lucher 1990). Recurrence rate of 14-28% has been recorded in patients treated with anticoagulants (Schulman et al. 1985, Lagerstedt et al. 1993, Beyth et al. 1995). The benefit of long-term anticoagulation in prevention is not established. Schulman et al. (1985) found no difference in a 2-year follow-up between patients treated for different periods (1.5-3 months, 3-6 months, 6-12 months) with anticoagulant therapy. Hull et al. (1979) found warfarin to be significantly better than low-dose subcutaneous heparin in preventing recurrences during a 12-week period after an acute DVT. Theoretically, new thrombotic events may aggravate the risk of PTS by causing further damage to the venous system. This includes a rethrombosis in a recanalized segment, propagation of a thrombus to new segments and a rethrombosis in a new segment. This may lead to more severe venous valvular damage or obstruction (Meissner et al. 1995, Miller 1995, Partch 1996). Hull and colleagues (1997) observed in a 3-month follow up a correlation between the time needed to achieve the lower limit of the activated partial thromboplastin time (APTT) during heparin therapy and recurrent DVT

.The effect of compression

The benefits of compression stockings have quite recently gained recognition. Early application may reduce transcapillary filtration and increase the venous flow (Brakkee and Kuiper 1988). Christopoulos et al. (1987) assessed legs by air-plethysmography and observed that elastic stockings reduced reflux and improved calf muscle ejection during exercise. Brandjes et al. (1997) demonstrated the effect of compression stockings in a randomized study with 194 patients having a proximal DVT. Two years' follow up revealed a significant reduction in the incidence of PTS in the group regularly using stockings. The use of stockings had no effect on the rate of recurrent DVTs (13.3% in the stocking group versus 14.1% in the control group). Evers and Wuppermann (1999) showed that compression stockings reduce the reflux velocity in patients with postthrombotic syndrome.

5.2.5 The basis of prevention

It would appear that the duration of anticoagulant therapy does not clearly influence the outcome of DVT. The prevention of recurrences and other new DVT events is of great importance; and there is evidence to suggest that prompt initial treatment with heparin may reduce this risk (Hull et al. 1997). An effective level of anticoagulant therapy may be associated with better resolution (Caprini et al. 1999), and it can be estimated that the adequate use of current treatment with unfractionated heparin and warfarin has positive effects on the outcome. In addition, compression stockings should be used at least after a proximal DVT (Brandjes et al. 1997). The role of low-molecular-weight heparins remains unresolved.

PURPOSES OF THE STUDY

The aims of the present study were:

1. To ascertain the incidence and prevalence of symptomatic deep venous thrombosis in the general population and in patients undergoing vascular surgery (studies II and III).
2. To analyze the risk associations of DVT in these populations (studies II and III).
3. To establish the incidence of postthrombotic leg symptoms, development of recanalization, venous valvular incompetence and obstruction after an acute DVT, with special reference to the location of the initial thrombus (studies I and IV).

PATIENTS AND METHODS

1. Late sequelae five and ten years after an acute DVT (study I)

The design of the study was retrospective and involved two groups of patients with a previous DVT confirmed by phlebography. The patients in the first group had had DVT five years earlier (1985) and those in the second group had been diagnosed ten years earlier (1980). The extent of the initial DVT was assessed from the original phlebograms. Only patients in whom the extent of the DVT could be assessed were accepted for the study. On the basis of the phlebograms two groups were formed: DVT in the calf veins (thrombus not extended into popliteal vein) and DVT in more proximal veins (thrombus detected in proximal, including popliteal, femoral and/or iliac veins).

A total of 86 patients fulfilled the diagnostic criteria and 70 (81%) (30 men and 40 women) agreed to participate and answered the questionnaire. The mean age at the time of the diagnosis of an acute DVT was 54 years (range 21-87). Group I comprised 47 patients (DVT 5 years earlier) and 23 patients formed group II (DVT 10 years earlier). The standard treatment of DVT with intravenous heparin and peroral warfarin was given in 94% of the patients. In the remainder the treatment comprised warfarin alone as the DVT was considered to be relatively old (1-2 weeks). The duration of the intravenous heparin treatment was 6-8 days and that with warfarin 3-6 months.

The questionnaire, sent in 1991, sought information on specific symptoms (pain, edema, pigmentation, ulceration) in the leg with a previous DVT. Patients were asked to estimate the degree of the symptoms in the leg (no symptoms, moderate symptoms, severe symptoms). In addition, the number of visits to medical care centres because of the symptoms in the leg was asked. The use of compression stockings after an acute DVT was also recorded.

Main limitations of the study were the retrospective design and the use of questionnaires. Two groups were formed on the basis of the initial phlebographic examination. The evaluation of the late sequelae was made by means of a questionnaire. Thus, the results show the subjective symptoms in legs with a previous DVT.

2. Incidence of postoperative DVT in vascular surgery (study II)

This registry-based study consisted of 7533 patients undergoing aortic and peripheral vascular procedures during a time interval of 23 months in 1991-1992. The material was collected from the nationwide Finnish vascular registry (FINNVASC). The register embraces a total of 5.0 million inhabitants and covers the major part of the country.

Of the overall total 4759 (63%) of the patients were men. The mean age was 65 years (range 10-93). All vascular operations were registered, including endovascular procedures. Surgery for varicose veins and primary amputations were not considered. The collected data included patient identification, gender, age, procedure indication, other diseases, operation code with identification of anatomical site and possible graft materials and clinical status at discharge and during a 30-day follow up. The use of thromboprophylaxis was not registered.

Symptomatic postoperative DVTs were recorded as reported by the participating centres. The distribution of vascular procedures in the subgroup of postoperative DVT was analysed and compared to the rest of the patients subjected to the same procedure.

The use of a registry-based material has some shortcomings associated with the validity of the data. This study was conducted during years 1991-1992. Kantonen and colleagues (1997) assessed the validity of the FINNVASC-registry during 1991-1994. Rate of missing registrations was 19%. The difference was 3% in nonsurgical complications when variables in primary data were compared to positive alternatives in refilled forms. Therefore, these problems should be considered when conclusions are drawn. In addition, the register is mainly concentrated to arterial disorders and this limits the possibilities to assess some risk associations.

3. Incidence of DVT in general population (study III)

This population-based follow-up study initially involved 5568 patients (2467 men and 3101 women). The first questionnaire was sent to all residents born 1929, 1939 and 1949 in the city of Tampere in 1989 and the second five years later, in 1994. The number of respondents was 4903 (2043 men and 2854 women) in the second survey. The participation rates were 83% (1989) and 88% (1994). One reminder was sent to those who did not reply to the first questionnaire.

The questionnaire included questions related to circulation in the lower extremities. The year of the DVT and the affected extremity were asked. In addition, superficial thrombophlebitis was asked separately. The question on DVT was answered by 71% of the participants. The questionnaire sought information on age, weight, height, gender, smoking and previously diagnosed diseases. Data on other diseases concentrated on diseases related to circulatory disturbances, for example cardiovascular and respiratory diseases, diabetes and diseases affecting the lower extremities.

The study design allowed estimation of the incidence of symptomatic DVT during the 5-year follow-up period. Data on concomitant diseases were collected from the first questionnaire, and it was possible to study the association between DVT and other reported medical conditions. The prevalence of DVT in relation to age and sex was calculated (Table 6).

Table 6. Study design.

First questionnaire		Second questionnaire	
Prevalence of DVT		Incidence of DVT	
Concomitant diseases and medical conditions			
1989	-----	TIME	----- 1994

The study was based on data recorded from self-administered questionnaires. The accuracy of data has been shown to be fairly high in epidemiological studies (Samet 1978, Harlow and Linet 1989). The number of new DVT cases is quite small which may reduce validity of multivariate analysis and cause variation. On the other hand, study design was planned in the direction of causality. Another problem is related to events during a 5-year follow-up, while data about pre-existing diseases and

medical conditions was collected from the first questionnaire. Furthermore, recall errors and drop-out may affect results.

4. Late sequelae two years after an acute DVT (study IV)

In the prospective study the 2-year follow-up was complete in 26 cases and 31 patients entered the study at the onset. Three patients were lost (two deaths not connected with DVT and one patient unwilling to participate). Two patients participated in only the first examination. The patients entered the study in Tampere University hospital and in the Valkeakoski District hospital.

The starting-point was an acute unilateral DVT in the lower leg diagnosed by phlebography. Its extent was assessed from the phlebograms in the acute phase. No patients had a history of a previous DVT in the affected leg; two had suffered a previous DVT in the contralateral leg. All were treated with low-molecular-weight heparin followed by warfarin.

The follow-up design included two control examinations after the acute DVT and two questionnaires. The flowchart of the study is shown in Table 7. In the acute phase the patients filled in a questionnaire which sought information on age, gender, height, weight, smoking habits and medical history. Previous symptoms such as varices, pain, edema, ulcer, pigmentation in the lower legs was recorded. In the first control examination after a mean time of 7.5 months (range 5-12 months) the leg with DVT was examined by ascending phlebography and color-flow duplex imaging (CDFI). The control leg was examined by CDFI. In the second control examination after a mean 20 months (range 17-22 months) CDFI was repeated in both legs. Thereafter the patients were sent the second questionnaire in which present symptoms (varices, pain, edema, ulcer, pigmentation) in the lower legs were asked. The use of compression stockings was recorded. The patients were asked to estimate the degree of their lower leg symptoms in the leg with DVT (no symptoms, moderate symptoms, severe symptoms).

Table 7. The study design.

Beginning	First control	Second control
Positive phlebogram	Bilateral CDFI	Bilateral CDFI
	→ →	
Questionnaire	Unilateral ascending phlebography	Questionnaire

The radiological studies were carried by experienced physicians. CDFI was performed by duplex scanner using a 5 MHz probe. The examination covered the venous segments in the femoral and popliteal levels bilaterally. The patients were studied in reverse Trendelenburg position at 20 degrees. Tourniquets were used in provocations of venous reflux. The diagnosis of reflux was based on a reverse flow duration more than 0.5 seconds during the provocation. The peak velocity was measured during the pathological reflux. A diagnosis of total obstruction was made if there was no detectable flow in the venous segment. If a postthrombotic change in a venous wall was noted, but a detectable flow was seen, the obstruction was determined as partial. Standard ascending phlebography was used to estimate the rate of recanalization.

5. Statistical methods

Statistical analyses were made by Chi-square test for cross-tabulated data. The statistical significance between comparisons was reached if the probability was less than 0.05 (I,II,IV). The software package Paradox 3.5 was used as database program and SPSS 5.0 for statistical analysis (II). In study I, data was analyzed by using software package excel 3.0. In study IV, excel version 7.0 was used.

Relative risks were estimated with 95 per cent confidence intervals (CI95%) in uni- and multivariate analysis (SPSS 7.5 and BMDP PC90) in logistic regression analysis. Dichotomous variables were used in the logistic regression analysis to increase the fit of the model (III).

RESULTS

1. Incidence and risk indicators of DVT in surgical patients and in the general population (II,III).

1.1 Incidence and prevalence

In the general population the number of DVT cases occurring during the 5-year follow-up was 23 (CI95% 11-35). The overall figure of DVT was 140 per 100000 person-years. The incidence was 143 per 100000 in women and 124 per 100000 in men. The age-specific incidences tended to increase among women, as demonstrated in Figure 2. The reported life-time prevalence in all cohorts and in both genders was 3.1%. The prevalence of DVT was higher in older cohorts and in women. The prevalences are illustrated in Figure 3.

Figure 2. The incidence of DVT in surgical and in the general population.

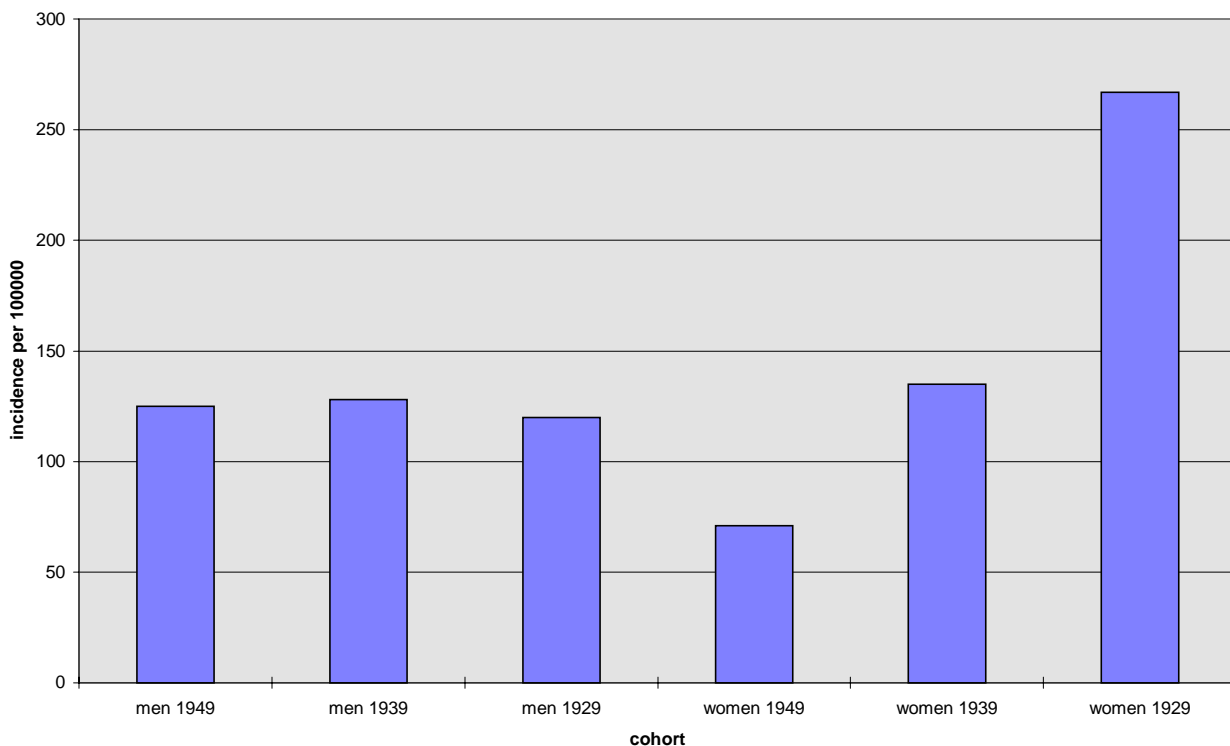
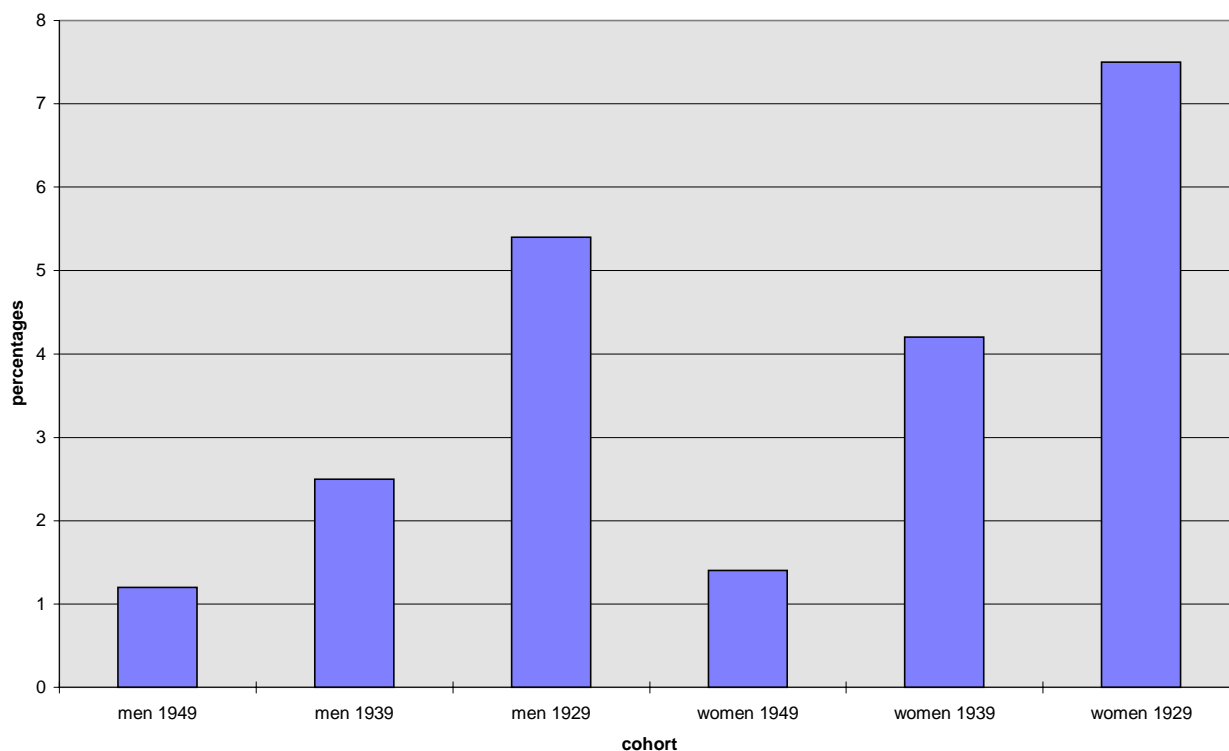


Figure 3. The prevalence of DVT by age and gender in the general population.



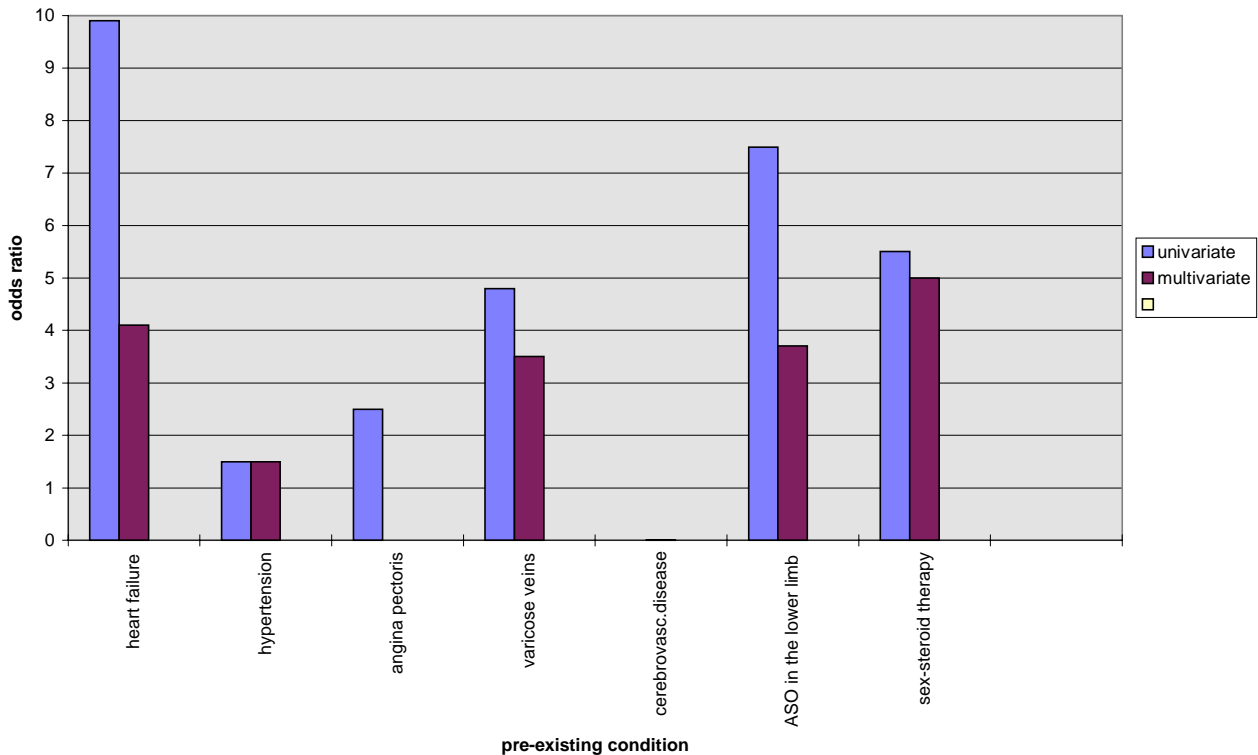
Among surgical patients the number of symptomatic postoperative DVTs recorded was 34 (0.45%). In 94% of cases the vascular procedure was directed to the infrarenal aorta or lower extremity. The incidence of postoperative DVT was 1.2% in infrarenal aortic surgery. The patients with postoperative DVT were slightly older, but the difference was not significant.

1.2 Risk indicators

In the general population the associations between DVT and pre-existing medical conditions were studied in a univariate analysis. The results showed the relative risk of DVT to be significant in subjects with angina pectoris (OR 2.5, CI95% 0.6-11.2), arterial disorder in the leg (OR 7.5, CI95% 2.3-24.4), heart failure (OR 9.9, CI95% 2.3-37.1), varicose veins (OR 4.8, CI95% 1.9-12.0) and sex-steroid therapy (OR 5.5, CI95% 2.0-15.0). To determine confounding effects the variables associated with significantly increased risk were fitted to a logistic regression model; varicose veins (OR 3.5, CI95% 1.2-9.9), sex-steroid therapy (OR 5.0, CI95% 1.5-16.5), arterial disorder in the leg (OR 3.7, CI95% 1.0-13.6) and heart failure (OR 4.1, CI95% 0.5-34.2) remained significantly associated with DVT. The association seemed to be strongest in patients with varicose veins or sex-steroid therapy. In addition, the subgroup of individuals who had received treatment (surgical or sclerotherapy) for varicose veins evinced a significant association with DVT in the univariate analysis (OR 6.5, CI95%

2.3-18.6). The effect of confounding factors can be seen in the uni- and multivariate analyses as shown in figure 4.

Figure 4. Risk associations in the general population.



In the surgical patients no statistically significant association was found between concomitant diseases and postoperative DVT ($p>0.05$). The rate of concomitant diseases was quite high in both groups. The most common conditions in both groups were hypertension (50% in DVT patients, 36% in others), coronary disease (35% in DVT patients, 39% in others) and diabetes (18% in DVT patients, 25% in others). Smoking was not associated with postoperative DVT. Cases of postoperative DVTs accumulated in procedures involving the infrarenal aorta or lower extremity. There were no cases of postoperative DVT in patients who had undergone carotid or suprarenal aortic surgery. A statistically significant difference was found between carotid surgery (0 cases of postoperative DVT) and infrarenal aortic surgery (5 cases of postoperative DVT, $p=0.02$), as well as between carotid surgery and surgery of the lower extremity (14 cases of postoperative DVT, $p=0.03$).

2. Outcome of DVT (studies I,IV)

2.1 Incidence of postthrombotic symptoms after DVT

In the retrospective study the initial DVT was located in the calf in 27 (39%). The number of more proximal DVTs was 43 (61%). In the prospective follow-up the acute DVT was restricted to the calf in 13 (46%) patients and extended more proximally in 15 (54%). The severity of subjective symptoms in different follow-up groups is presented in table 8. The number of asymptomatic patients was low (13%) in the retrospective study. The severity of symptoms seemed to increase in patients with DVT 10 years previously compared with the 5-year follow-up group ($p<0.05$). In the prospective study with a 2-year follow-up the number of asymptomatic patients was also fairly low (27%). In the retrospective study 61% of the patients had consulted a doctor at least once because of the leg symptoms.

Table 8. The severity of subjective symptoms in 2-, 5- and 10-year follow-up groups.

Group	Subjective symptoms			
	patients (n)	asymptomatic	moderate	severe
prospective 2-year follow-up	26	27%	50%	23%
retrospective 5-year follow-up	46	13%	65%	22%
retrospective 10-year follow-up	24	12.5%	37.5%	50%

The most common symptoms in the leg were pain and edema. In the prospective follow-up pain was mentioned by 62% of the patients, and edema (46%) and pigmentation (35%) were likewise common complaints. In the control legs the rates of pain, edema and pigmentation were 35%, 27% and 8% at the end of the 2-year follow-up. In the 5-year and 10-year follow-up groups pain (45-38%), edema (52-54%) and pigmentation (50-67%) were commonly noted. The rate of pigmentation tended to increase with a longer follow-up period. In addition, the rate of pigmentation was low in the control legs. The reported rate of ulceration was low in all follow-up groups, only sporadic cases being revealed. The rates of the most common symptoms are presented in Table 9.

Table 9. The specific symptoms in 2-, 5- and 10-year follow-up groups (*=prospective study, **=retrospective study, n=number of patients).

Symptom or sign	2-year follow-up(*) n=26	5-year follow-up(**) n=46	10-year follow-up(**) n=24
pain	62%	45%	38%
edema	46%	52%	54%
pigmentation	35%	50%	67%

2.2 Recanalization, valvular incompetence and obstruction

Ascending phlebography was carried out on average 7.5 months after the acute DVT. A high rate of recanalization was detected. Findings in 75% of the phlebographies were considered normal. A total obstruction was found in 7% of the legs with DVT and the obstruction was estimated to be partial in 18%.

The results of CDFI in the popliteal segment at the time of the first control examination (7 months) showed deep venous pathology in 25% of legs with DVT. The distribution of the pathological findings showed 57% reflux, 14% partial obstruction and 29% total obstruction. The results of CDFI at the second control examination (20 months) reflected deep venous pathology in 50% of legs with DVT, the distribution being 54% reflux, 38% partial obstruction and 8% total obstruction. In the femoral segment findings of deep pathology were rare; only one sporadic case with deep reflux was noted at the first check-up. Also in the control legs findings of deep venous pathology were rare; one sporadic reflux was diagnosed during the first control. The findings in the venous studies at the popliteal segment are set out in Table 10.

Table 10. The number of deep and superficial findings in the popliteal segment during the 20-month follow-up.

	Patients (n)	deep reflux (partial/total)	obstruction	superficial reflux
Popliteal segment				
7 months after DVT	28	4	3	3
20 months after DVT	26	7	6	5

2.3 The relationship between extent of initial DVT and outcome

In the popliteal segment there was no association between the site of the acute DVT and the CDFI finding at the end of the follow-up. If the acute DVT was restricted to the calf area, there were 6 cases (46%) in which deep venous pathology was found in the popliteal segment. This segment was affected in 7 cases (53%) in patients with more proximal DVT in the acute phase. The site of the initial DVT was not associated with the severity of subjective symptoms in the retrospective study ($p > 0.05$), nor was any difference in the prospective material ($p > 0.05$).

DISCUSSION

1. Incidence and prevalence of DVT

1.1 General population

In the present study the incidence of DVT in both genders falls between the figures from previous studies, 124 per 100000 in men and 143 per 100000 in women. In a population-based study conducted in Malmö, an annual rate of DVT rose from 69 to 327 per 100000 in men and from 97 to 217 per 100000 in women in aged 40-69 (Nordström et al. 1992). In a cohort study of 855 men the incidence of DVT was 182 per 100000 observation-years from age 50 to 80 years (Hansson et al. 1997). The Worcester DVT study was an extensive study based on hospital discharges. In this study an annual rate of DVT in middle-aged patients (ages 40-69) rose from 24 to 144 per 100000 in men and 10 to 99 per 100000 in women (Andersson et al. 1991). The present data shows an age-associated increase in women, whereas no such phenomenon was seen and the incidences remained constant.

The life-time prevalence of DVT is 3.1% in this study. The prevalence tends to raise towards older age groups. The life-time prevalence is higher in women (3.5%) compared with men (2.4%). The prevalence of thromboembolic events at age 69 years was 2.0% in the cohort study of 855 men and the prevalence was higher among older persons (Hansson et al. 1997). Franks and associates (1992) observed a high (6%) life-time prevalence of venous thromboembolism in London area. In the Tecumseh health study the life-time prevalence of DVT was only 1% in men but 3.6% in women whereas Gjörës (1956) showed a similar prevalence (2.2%) in both genders.

When the results of the present data are compared with previous studies there are several issues that should be noted. Previous studies have given fairly variable estimates of DVT in the general population. As discussed in previous sections, differences in study designs may be the main source of variability. The present study is a questionnaire study with a 5-year follow up time. These results are based on self-reported figures. The use of questionnaires, participation rate, the relatively small sample of new DVT cases and events during the follow-up period are factors which may affect the results. On the other hand, the diagnosis of an acute DVT in the Tampere area has been based almost exclusively on a phlebography. Therefore, the present data reflects the frequencies of clinically significant and symptomatic DVTs.

Judging from the findings of this present material the incidence of DVT among middle-aged people (40-60 years) is approximately 140 per 100000 annually. It can be estimated that the mean annual number of new DVT cases in the age-groups 36-64 in Finland is about 2600. This estimate is in line with levels previously estimated among Caucasians (Nordström et al. 1992, Hansson et al. 1997). Symptomatic DVT is not a rare disease in Finland.

1.2 Surgical patients

The incidence of postoperative DVT in patients undergoing vascular procedures is low (0.45%) judging from the present material. Figures have varied widely in previous studies; the range has been 8-43% (Hamer 1972, Myhre et al. 1974, Angelides et al. 1977, Olin et al. 1993). These studies have been very different and they cannot be compared. Olin and coworkers (1993) showed an important problem when they revealed a high rate of asymptomatic postoperative DVTs (18%) after aortic aneurysm repair. Fletcher et al. (1997) diagnosed postoperative DVT in 10% of patients after surgery of the aortic or lower extremity regions, this despite adequate prophylaxis with heparin. There are no large-scale surveys of the incidence of DVT in vascular surgery.

There are several reasons for the low incidence of DVT found in the present data. The results are based on FINNVASC-registry which covers most of the vascular procedures in Finland. The use of the information collected from the register includes problems related to validity of data. Furthermore, screening methods were not used to detect asymptomatic DVTs. The results reflect the cases of symptomatic DVTs. It can be estimated that postoperative DVT is underestimated in the present material. A clinical diagnosis of DVT is demonstrated to be unreliable (Sandler et al. 1984). Postoperative edema is a common phenomenon. This applies especially to patients undergoing vascular surgery for lower limb ischemia. In addition, the present data include fewer invasive vascular procedures such as interventional radiology.

2. Risk associations of DVT

2.1 General population

The present findings evidence an association between varicose veins and DVT in the general population. The significant effect of pre-existing varicose veins on subsequent DVT remains in multivariate regression analysis. To exclude the misclassification of varicose veins, patients reporting treatment for varicose veins were also studied. In the univariate analysis varicose veins are also significantly associated with DVT in persons surgically treated for varicose veins. A connection between varicose veins and DVT in the general population has not previously been demonstrated. In the Tecumseh health study varicose veins were common (68%) in the patients with DVT (Coon et al. 1973). One extensive retrospective review with 748 patients in the U.S. revealed varicose veins in only 5% of patients with DVT (Byrne 1955).

The present data show that heart failure and arterial insufficiency in the lower limbs may be associated with DVT. The effects were weaker in multivariate analysis as judged by the lower OR in logistic regression when all variables are included. Arterial hypertension and angina pectoris are not associated with DVT. Population-based evidence of this association between these diseases and DVT is lacking. Goldhaber and colleagues (1997) have observed an association between arterial hypertension and pulmonary embolism in women. Byrne (1955) have noted association between cardiac disease and DVT. Heart failure may produce stasis in the leg. Stasis is one of the etiologic factors in the pathogenesis of DVT, although it cannot cause DVT without presence of other factors (Wessler 1962).

The association between hormone replacement therapy and DVT can be seen in the present data. Although the number of cases was small, this association remained significant in multivariate analysis. In previous large-scale studies the prominent role of hormone replacement therapy as a risk factor for DVT is well documented (Daly et al. 1996, Grodstein et al. 1996, Jick et al. 1996). Obesity is not a risk factor for DVT in the present material. Goldhaber et al. (1997) have demonstrated the connection between obesity and pulmonary embolism in women. Lowe and coworkers (1999) noted a significant association between obesity and DVT in the patients who have undergone elective hip replacement.

2.2 Surgical patients

The present data show that 94% of patients with postoperative DVT have undergone surgical procedures involving the lower limb or the aortoiliac region. There is a significant difference in DVT rates between carotid surgery and surgery of the aortic and infrainguinal region. A limb trauma and endothelial damage to the venous wall are important etiologic factors in the pathogenesis of DVT (Hjelmstedt et al. 1968, Stamatakis et al. 1978, Geerts et al. 1994). This phenomenon has been widely studied in orthopedic patients undergoing hip or knee surgery (Stamatakis et al. 1978, Davidson et al. 1996). In the present study the similar finding can be seen in vascular surgery in the aortic or lower limb region. Previous studies have also shown that major surgery (long duration of operation, massive bleeding etc.) is associated with increased risk of DVT (Andersson et al. 1991a, Flordal et al. 1995).

The mean age of patients undergoing vascular surgery is relatively high (65 years) in the present data. Age is slightly higher in patients with DVT but this difference is not significant. In previous studies observing surgical population increased age has been associated with postoperative DVT (Kakkar et al. 1970, Sikorski et al. 1981, Davidson et al. 1996).

There is no association between DVT and other diseases and medical conditions in this material. Arterial hypertension, coronary heart disease and diabetes are commonly seen in patients with DVT and in patients without DVT. The rate of DVT has been 27% after myocardial infarction (Simmons et al. 1973). Bergqvist et al. (1985) studied the frequency of postoperative DVT after renal transplantation. Diabetes was a significant risk factor for DVT in that study. In the present study there are medical conditions and diseases which are not evaluated. FINNVASC-registry does not include certain diseases, such as cancer, which are closely linked with DVT.

3. Outcome of DVT

3.1 Postthrombotic symptoms after DVT

The long-term outcome of DVT has varied markedly in previous studies. Pain and edema are usually reported in 30-60% of patients followed up (Halstuk et al. 1984, Kakkar and Lawrence 1985, Lindhagen et al. 1985, Francis et al. 1986, Heldal et al. 1993, Lagerstedt et al. 1993). The rate of late symptoms after calf DVT has also been controversial in previous studies. Eichlisberger et al. (1994)

have noticed postthrombotic symptoms in 4% of the patients after calf DVT whereas the frequency of late symptoms has been clearly higher in other studies (Halstuk et al. 1984, Kakkar and Lawrence 1985, Francis et al. 1986, Schulman et al. 1986, Andersen et al. 1991, Haldal et al. 1993).

The present data show a high rate of subjective symptoms (pain and edema) after an acute DVT. In the retrospective study (5-10-year follow up) leg pain is present in 41% of the patients. In the prospective study (2-year follow-up) leg pain is reported in 62% of the patients. Edema is also common in these follow-up groups (46% in a 2-year follow up and 53% in a 5-10-year follow up). Pigmentation is also frequently reported in these follow-up groups (35-56%). Ulceration is reported only in sporadic cases. Bauer (1942) noted high rates of ulceration after DVT. However, the present data is in harmony with previous studies, in which the frequency of leg symptoms is quite high but the rate of ulceration is low (Killewich et al. 1985, Widmer et al. 1985, Bergqvist et al. 1990, Andersen et al. 1991, Beyth et al. 1995). In the present material the 2-year follow-up reveals a quite high rate of symptoms in the control legs (pain 35%, oedema 27%). This phenomenon has been observed in previous studies (Mudge and Hughes 1978, Browse et al. 1980, Francis et al. 1986). An objectively diagnosed CVI can be found in patients with no history of DVT (Lindhagen et al. 1985).

In the present study patients have been treated with a combination of heparin and warfarin. Despite this treatment the frequency of late symptoms appears to be high. Treatment of an acute DVT with anticoagulants is not capable to prevent late sequelae (Halstuk et al. 1984, Kakkar and Lawrence 1985, Monreal et al. 1993, Eichlisberger et al. 1994). Caprini and coworkers (1999) have noticed that adequate level of anticoagulant therapy may influence on resolution of a thrombus during the first year after DVT. Effect of adequate warfarin therapy to leg symptoms remains obscure. The use of thrombolytic therapy has given varying results (Rogers and Lutcher 1990). There are studies in which no difference has been found between thrombolytic and non-thrombolytic therapy (Kakkar and Lawrence 1985, Schulman et al. 1986). Several studies have shown a reduction in late sequelae in patients treated with thrombolytic therapy, but their complete elimination is not recorded (Rogers and Lutcher 1990, Eichlisberger et al. 1994).

The present data shows that site of an acute DVT is not associated with the rate of late subjective symptoms in the leg. The prediction of late symptoms after an acute DVT has been estimated to be difficult (Meissner et al. 1998, Prandoni et al. 1998). Most of the follow-up studies have not been able to show any difference in the rate of late sequelae in patients with calf or more proximal DVT (Lindhagen et al. 1985, Haldal et al. 1993, Monreal et al. 1993). Monreal et al. (1993), in a prospective study, have noted that DVT located in the popliteal segment results in poorer outcome. In the present data the outcome of an isolated calf DVT is no better than that of more proximal disease.

The time interval in which PTS occurs after DVT has not been established. The present study reveals that pain is reported in 62% of the patients at the end of 2-year follow-up. The development of leg symptoms may begin in an early phase after an acute thrombotic event. Brandjes and colleagues (1997) have shown that a clinical PTS may occur in 60% of patients during the first two years after a proximal DVT. In the present study the severity of subjective symptoms in the leg tends to increase from 22% to 50% when the 5- and 10-year follow up groups are compared.

The use of compression stockings is very low in the present data. The regular use of stockings was recorded in 11-12% of patients. Brandjes et al. (1997) have shown a significant reduction in the incidence of PTS during a 2-year follow up in patients using compression stockings. It can be estimated that limited use of compression stockings may have influenced on the high rate of late symptoms.

3.2 Recanalization and obstruction after DVT

In the present study a high rate of recanalization after an acute DVT is observed. There is a total obstruction in a venous segment in 7% of legs in the phlebographic examination 7 months after DVT. An obstructive change in the venous wall in deep popliteal segment is detected in 23% of legs with DVT at the end of a 2-year follow up. The frequency of recanalization in venous segments affected by DVT has been high in follow up studies with serial ultrasonography (Killewich et al. 1989, Meissner et al. 1993, Masuda et al. 1998). Venous valvular incompetence may occur despite an early lysis of a thrombus (Meissner et al. 1993). Johnson and colleagues (1995) have observed an association between obstructive changes in venous wall and valvular incompetence. In the present data obstructive changes and valvular incompetence are detected in separate patients. This may be connected with the relatively small follow up group. Franzeck et al. (1997) have evaluated 39 patients after a 12-year follow up. A combination of reflux and obstructive changes in the deep veins have been the most frequent reason for the development of postthrombotic syndrome.

3.3 Valvular incompetence after DVT

In the present data venous valvular incompetence in the deep popliteal segment is found in 27% of legs with DVT two years after an acute episode. Almost half of legs with a history of an isolated calf DVT show valvular incompetence or obstructive change in the popliteal segment at the end of a 2-year follow up. Pathologic findings in the femoral segments and in the control legs are rarely

recorded. Valvular incompetence is the most important factor in the development of signs and symptoms of PTS (Strandness et al. 1983, Killewich et al. 1985, Moore et al. 1986, Gooley et al. 1988, Labropoulos et al. 1996). Especially the distal deep valves are important (Shull et al. 1979, Moore et al. 1986, Labropoulos et al. 1996). Shull and associates. (1979) have demonstrated an association between ulceration and popliteal valvular incompetence.

In the present material presence of incompetence in the popliteal segment tends to rise from 14% to 27% during the follow up. The follow up group is relatively small which restricts possibilities to make firm conclusions. However, Killewich and coworkers (1989) noted valvular incompetence in 60% of patients after DVT in a 9-month follow up. Meissner et al. (1997) observed that 24% of calf venous segments developed valvular incompetence in a 12-month follow up. The frequency of valvular incompetence may increase several years after an acute DVT (Van Haarst et al. 1996). It would appear that development of valvular incompetence after DVT may begin particularly early.

In the present study there is no difference between calf and more proximal DVT in the presence of deep reflux or obstructive change in the popliteal segment 20 months after DVT. Valvular incompetence usually developed to previously affected segments by (Markel et al. 1992, Van Haarst et al. 1996, Janssen et al. 1998), but valvular incompetence in a venous segment may nevertheless occur without a previous DVT (Caps et al. 1995). Late involvement of the popliteal segment may influence on the outcome of calf DVT. Previous studies have shown the possibility of a new pathologic events after DVT. These events include recurrent DVTs and propagation of a thrombus into a new venous segment despite the use of anticoagulants (Krupski et al. 1991, Meissner et al. 1995, Prandoni et al. 1996). One might assume that these new events may explain why the outcome of calf and more proximal DVT has remained unpredictable.

SUMMARY

Deep venous thrombosis (DVT) is a disease which may lead to acute pulmonary embolism or chronic postthrombotic syndrome. This study aimed to estimate the incidence and prevalence of deep venous thrombosis in a Finnish population, the incidence of postoperative DVT in vascular procedures and the risk associations between DVT and other diseases. The subsequent development of late sequelae was also studied with different follow up periods after an acute DVT.

In a retrospective study late sequelae of DVT was studied 5 or 10 years after the acute phase in 70 patients. All had a previous DVT confirmed in a phlebographic examination. A questionnaire was used to get information on specific leg symptoms and their severity, visits to medical health care centres for this reason and the use of compression stockings. Subjective symptoms in the leg were common. Only 13% of the patients were asymptomatic. The most common symptoms were pain when standing (37%), evening pain (41%), edema (53%) and pigmentation (56%). There was no difference in severity of subjective symptoms between patients with calf of more proximal DVT. Regular use of compression stockings was rarely reported (11%) (**study I**).

The incidence and risk associations of postoperative DVT after vascular procedures were studied in the nationwide FINNVASC registry. A total of 7533 vascular procedures during a 23-month period were reviewed and analysed. There were 36 cases of postoperative DVT. The incidence of symptomatic postoperative DVT after vascular procedures was 0.45%. The majority of these DVTs (94%) were diagnosed after procedures involving infrarenal aorta or lower extremity. There were no significant differences between DVT patients and other patients in respect of the occurrence of other diseases. Age, gender and smoking were not associated with DVT (**study II**).

The incidence and risk associations of DVT in the general population were studied in a population-based questionnaire survey. A questionnaire was sent to all residents of Tampere born 1929, 1939 and 1949. Items included questions related to circulation in the lower extremities. Previous diseases were asked, including DVT in the lower limb. In the first questionnaire the number of respondents was 5568, in the second five years later 4903. The participation rates were 83-88%. The number of new DVT cases was 23. During the 5-year period the incidence of symptomatic DVT in the general population was approximately 140/100000. The life-time prevalence of DVT was 3.1%. The age-specific incidence of DVT increased with age in women and remained constant in men. Pre-existing varicose veins were significant and independent risk factors. Arterial insufficiency of the lower limb

and chronic heart failure were also associated with DVT, but this association was weaker. Sex-steroid therapy was also associated with DVT (**study III**).

The development of symptoms and objective findings after DVT was studied prospectively in a 2-year follow up with 26 patients. All had a phlebographically diagnosed DVT. Two control studies with color-flow duplex imaging (CFDI) were made (7 and 20 months after DVT) to follow up the situation in the femoral and popliteal deep venous segments. Ascending phlebography was repeated once (7 months after DVT) to estimate recanalization. Symptoms were common in legs with a previous DVT; pain (62%), edema (46%) and pigmentation (35%). The phlebographic examination showed recanalization in 93% of legs. After a 2-year follow up CFDI yielded pathologic findings in the popliteal segment in 50% of legs with DVT (27% deep reflux, 23% obstructive change in the venous wall). There was no difference in outcome between calf or more proximal DVT in the popliteal segment. (**study IV**).

CONCLUSIONS

1. The incidence of DVT is approximately 140 per 100000 annually among middle-aged people in the general Finnish population. It would appear that the incidence and the life-time prevalence (3.1%) are well within the range estimated in previous studies of Caucasian populations. The incidence of symptomatic postoperative DVT (36 cases in 7533 procedures) in patients undergoing vascular procedures is low. The majority (94%) of symptomatic DVTs are diagnosed in patients undergoing operations on the aorta or the lower limb.
2. In the general population DVT seems to be associated with varicose veins. Also chronic heart failure and arterial disease in the lower limb may be connected. In addition, sex-steroid therapy is associated with DVT.
3. The long-term subjective symptoms are frequently reported in legs with previous DVT. The reported rate of asymptomatic patients is low (13-27%). The severity of leg symptoms tends to increase with a longer follow-up period. On the other hand, approximately 70% of patients suffer from leg symptoms two years after DVT. The frequency of late findings (deep valvular incompetence or obstructive change in the venous wall) in the popliteal segment is high (50%) according to the 2-year follow up. Rapid recanalization is commonly observed. In the femoral segment venous reflux or obstructive change are rare. Late popliteal involvement can develop after an isolated calf DVT. There is no difference in the development of subjective symptoms after DVT between calf and more proximal DVT. The development of venous reflux or obstructive change in deep popliteal segment is not associated with the initial extent of an acute DVT.

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APPENDIX**The questionnaires used in the collection of self-reported information.****STUDY I.**

ikä

sukupuoli

Paino

Pituus

Tupakointi 1) tupakoin

2) olen lopettanut yli 5 vuotta sitten

3) en ole koskaan tupakoinut

Montako synnytystä teillä on ollut

Käyttättekö säännöllistä lääkitystä 1) en

2) kyllä

sydämen vajaatoiminta

sepelvaltimotauti

verenpainetauti

sokeritauti

veren hyytyminen

ehkäisy

särky

muu

leikkaukset

onko jalassa esiintynyt seuraavanlaisia oireita laskimotukoksen jälkeen

1) erityisesti seistessä alkava tai paheneva särky

2) iltaa kohden paheneva jomotus tai särky

3) jalan tuntuminen raskaalta iltaa kohti

4) kivun helpottaminen jalan ollessa kohoasennossa

5) kivun helpottaminen jalan roikkuessa alaspäin

6) turvotusta nilkan ja / tai säären alueella

7) turvotusta koko alaraajan alueella

8) "levottomat jalat" - oiretta

9) suonikohjuja jo ennen laskimotukosta

10) suonikohjujen ilmaantumista laskimotukoksen jälkeen

11) toisessa alaraajassa suonikohjuja

12) tummanruskea ja pysyvä värimuutos nilkassa ja / tai sääressä

13) pitkäaikainen haavauma jalassa

Oletteko käyttänyt puristussukkaa laskimotukoksesta lähtien 1) säännöllisesti

2) satunnaisesti

3) en lainkaan

Oletteko hakeutunut lääkärin hoitoon laskimotukoksesta johtuvien vaivojen vuoksi

1) en lainkaan

2) 1-2 kertaa

3) useammin

Mitä mieltä olette alaraajanne nykytilasta 1) alaraaja on oireeton ja terveen tuntuinen

2) alaraajassa esiintyy jonkin verran vaivoja

3) alaraajassa esiintyy paljon vaivoja ja ne haittaavat elämistä

STUDY III

(This study is a part of a larger questionnaire study. The questions related to the present study are demonstrated).

ikä

sukupuoli

paino

pituus

oletteko milloinkaan käyttänyt ehkäisypillereitä

oletteko tupakoinut säännöllisesti yli vuoden ajan elämässänne 1) en ole milloinkaan

2) olen nyt lopettanut

3) tupakoin

käytättekö alkoholipitoisia juomia 1) en lainkaan tai satunnaisesti

2) kyllä paljonko viikossa olutta ____ pulloa (1/3 l)

viiniä ____ pulloa (3/4 l)

viinaa ____ pulloa (1/2 l)

onko teillä esiintynyt pitempää lääkärinhoitoa vaatineita sairauksia

1) sokeritautia

milloin

alk.

2) kohonnutta verenpainetta

3) sydäninfarktia

4) sydämen sepelvaltimosairautta

5) sydämen vajaatoimintaa

6) hengityselinten sairautta

7) alaraajan pinnallista laskimotukosta

kumpi

jalka

8) alaraajan syvää laskimotukosta

kumpi

jalka

9) keuhkoveritulppaa

10) selkäsairautta tai iskiasta

11) munuaissairautta

12) alaraajojen murtumia

13) alaraajojen ruhjeitten aiheuttamia pitkäaikaisia vammoja

14) alaraajojen valtimoverenkiertohäiriöitä

15) aivoverenkiertohäiriöitä

16) säärihaavaa

17) muu

käytättekö säännöllistä lääkitystä 1) sokeritautiin

2) verenpaineeseen

3) sepelvaltimotautiin

4) rytmihäiriöihin

5) sydämen vajaatoimintaan

6) hengityselinten sairauteen

7) veren hyytymiseen

8) verenkierron parantamiseen

9) särkyihin

10) ummetukseen

11) muuhun sairauteen

12) kortisonia

13) nais- tai miessukuhormonia

onko teillä nyt tai onko ollut suonikohjuja

- 1) millä kohdalla (vasen reisi, vasen sääri, oikea reisi, oikea sääri)
 - 2) kuinka kauan kohjut ovat olleet (vuotta)
 - 3) missä yhteydessä kohjut tulivat
 - 4) onko teillä tällä hetkellä suonikohjuja
 - 5) onko kohjuista teille ulkonäöllistä haittaa
 - 6) onko teitä leikattu suonikohjujen takia (vuosina)
 - 7) onko suonikohjuja hoidettu lääkeainetta ruiskuttamalla
- onko teitä leikattu muun sairauden takia (vuosi/leikkaus)

STUDY IV

ikä

pituus

paino

tupakointitiedot 1) tupakoin edelleen

2) olen lopettanut alle 5 vuotta sitten

3) en ole koskaan tupakoinut tai olen lopettanut yli 5 v sitten

synnytykset (vuosina)

sairaudet 1) sydämen vajaatoiminta

2) sepelvaltimotauti

3) verenpainetauti

4) sokeritauti

5) syöpätauti (mikä)

6) muu

vakituinen lääkitys

alaraajojen oireilu: 1) onko teillä suonikohjuja

2) onko teillä alaraajasärkyjä

3) onko teillä päivittäistä turvotusta alaraajoissa

4) onko teillä esiintynyt ruskeaa värimuutosta säären / nilkan alueella

5) onko teillä säärihaavaa

oletteko käyttänyt puristussukkaa laskimotukoksen toteamisen jälkeen

1) päivittäin (yhteensä __ kuukautta)

2) satunnaisesti

3) en lainkaan

onko laskimotukoksen sairastaneessa alaraajassa oireita

1) paljon

2) kohtalaisesti

3) ei lainkaan