Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome

A systematic review and meta-analysis

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Summary
Perioperative antithrombotic clinical regimens have reduced the incidence of postoperative deep venous thrombosis (DVT). Long-term effects of asymptomatic postoperative DVT have been studied in a number of clinical trials and the present review describes the clinical significance of asymptomatic postoperative DVT regarding the possible development of postthrombotic syndrome (PTS). We performed a systematic review of reference databases focusing upon studies including patients suspected of having postoperative DVT and reporting subsequent cases of PTS at the end of a well-defined follow-up period. The included studies were stratified according to type of screening method and applied statistics. Over-all evaluation included meta-analyses based upon the Cochrane software package. The overall relative risk of developing PTS was 1.58 (95% confidence intervals: 1.24 – 2.02) in patients suffering from asymptomatic DVT as compared to patients without DVT (p < 0.0005). In conclusion, asymptomatic postoperative DVT is associated with an increased risk of late development of PTS. The finding emphasizes that postoperative DVT, diagnosed by means of well-defined objective measures, remains the correct scientific endpoint in trials evaluating the efficacy of preoperative antithrombotic treatment regimens.

Keywords
Postthrombotic syndrome, deep vein thrombosis, surgery

Introduction

The postthrombotic syndrome (PTS) is a poorly defined clinical condition consisting of a variety of chronic presentations including oedema, telangiectasia, varicose veins and venous ulcers of the lower limbs. It has never been established which of the mentioned symptoms are associated with previous deep vein thrombosis (DVT) although the degree of proximal extension of a DVT correlates positively to the severity of late venous symptoms (1–3). The lack of strict definitions complicates comparisons between studies though many classification systems of PTS have been proposed (4).

The incidences of postoperative DVT and pulmonary embolism (PE) vary according to type of surgical procedure, age and preoperative thromboprophylactic measures. The reported incidence of postoperative DVT depends on the sensitivity of diagnostic procedures. Low values are found in register-based publications (5), whereas high numbers are reported following intensive screening with sensitive methods (6).

The clinical significance of asymptomatic DVT is relatively unknown but it is a well-established experience that patients who suffer a fatal PE have rarely experienced previous symptoms from the thrombotic lesion that precedes PE. Symptomatic DVT is considered a pathophysiological precursor of the postthrombotic syndrome (PTS) as up to 80% of patients develop this late complication (1, 7).

The aim of the present systematic review is to establish whether there is an epidemiological association between asymptomatic postoperative DVT and the development of PTS.

Methods

A comprehensive electronic literature search was performed in the Medline, Embase and Lilacs databases. The search terms are listed in table 1. Furthermore, conference proceedings of the International Society on Thrombosis and Haemostasis published later than 1989 and reference lists of previously retrieved papers were scrutinized. No language restrictions were applied.

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The individual authors were contacted if the retrieved data was insufficient for the planned analyses.

**Inclusion criteria for papers addressing the association between postoperative DVT and postthrombotic syndrome**

Patients had undergone major surgery and were screened for asymptomatic DVT postoperatively. Identical standardized screening methods were used in all patients in each trial, regardless of randomisation during a well-defined postoperative period of time. DVT was considered asymptomatic if it was diagnosed primarily by means of a sensitive screening test in patients without symptoms suggesting venous thromboembolism. Registration of treatment of postoperative thromboembolism was not mandatory for inclusion in the analyses.

Uniform criteria were applied for all patients in each individual study when the diagnosis of PTS was established, and the definition of PTS was based upon elements reported by the individual authors of the included studies.

**Data extraction and handling**

Data from the individual papers were extracted independently by two of the authors (PW-J & LN). In order to include patients in the analyses we required documentation of either asymptomatic primary DVT or no DVT, thus excluding patients with symptomatic DVT.

In order to evaluate the correlation between early postoperative DVT and late development of PTS, a number of meta-analyses were performed. Calculations included tests of statistical heterogeneity based upon fixed sample sizes and random effect models (8). Results were expressed as relative risks (RR) with 95% confidence limits. A funnel-plot was applied to uncover potential publication bias providing visualisation of any asymmetry around a vertical line represented by the common odds ratio (OR), as the standard error of OR is plotted against the OR for each trial (9).

The included studies were stratified according to screening technique and type of statistical unit (the individual patient or leg) chosen for the analyses. We used the Cochrane software package (Review Manager version 4.2, http://www.cochrane-net.org/revman) for the statistical analyses.

**Results**

**Included studies**

The literature search identified 10 original papers addressing the association between asymptomatic DVT and PTS (10–19). Two papers obviously referred to the same patient population (12, 13), for which reason the larger of the studies was chosen (13). Two papers did not report on the incidence of PTS in non-thrombotic patients and were excluded (10, 11).

In two studies (13, 19), the incidence of PTS was expressed as the number of observations per leg and, in four studies, per patient (15, 17, 18). In one study (14), both ratios were presented. A description of the seven trials included is provided in table 2.

In two studies, there was a clear distinction between primary asymptomatic and symptomatic DVT (15, 16) and in these cases symptomatic patients were excluded from further analysis. In four studies, no patients presented symptoms suggesting DVT (14, 17–19). The largest study (13) reported four symptomatic cases among 137 primary DVT diagnoses, however, follow-up examination did not distinguish between symptomatic and asymptomatic patients. Diagnoses were based upon the $^{125}$I-fibrinogen uptake test and all individuals were included in the analyses.

In two studies, all patients with thrombi were primarily treated with anticoagulation therapy (14, 18). In two studies, some patients received treatment (13, 19). No information was given regarding primary anticoagulation therapy in the three remaining studies (15–17).

Patients were followed up according to a scheduled timetable in one study only (16). The other study designs were cross-sectional.

**Description of included studies and definitions of PTS**

The definitions of PTS in the individual studies and the definitions used in the meta-analyses are summarized in table 2.

Lindhagen and co-workers (13) published the largest study including questionnaires, clinical examination, venous-occlusion plethysmography, venous pressure measurement and Doppler-examination. They defined ‘clinical’ and ‘objective’ venous insufficiency criteria leading to almost similar results. We chose data according to the ‘clinical’ interpretation of their results for the present meta-analysis.

The study by Andersen & Wille-Jørgensen (14) reported both subjective symptoms (questions on presence of oedema, restless legs, cramps, and pains) and objective findings (presence of oedema, new varicose veins, pigmentation and the use of compression stockings). Furthermore, the patients routinely underwent strain gauge plethysmography, but as the results of these investigations were given as continuous data, they were unsuitable for inclusion in the meta-analyses. The self-reported use of compression stockings was accepted as the definition of PTS in the individual patient analysis, whereas occurrence of new varicose veins was adopted as PTS criterion in the individual leg analysis.

Francis et al. (19) defined PTS on the basis of subjective symptoms of leg pain, swelling, varicosities and ulcers as reported by the patient. They also chose a definition based upon a physical examination of oedema, ulceration, pigmentation, and venous varicosities as well as air-, photo- and impedance ple-
thysmography. We used their data obtained from the physical examination as the criterion for PTS in the meta-analyses.

In each of the remaining four studies we adopted the definitions of PTS as reported:
1. Caprini and coworkers (15) used a questionnaire reporting the presence of oedema, discomfort, pigmentation or ulcers as reported by the patient.
2. A systematic follow-up with an interview followed by objective investigations at defined periods was performed in the study by Mudge et al. (16). Their definition of PTS required the presence of at least one of the following criteria: varicose veins, eczema, oedema, skin pigmentation, or liposclerosis.
3. In the Italian study by Siragusa et al. (17), a score was computed based on a questionnaire reporting the occurrence of pain, cramps, itching, and paresthesias combined with an objective investigation for presence of oedema, induration, discoloration, pains at compression, and ulcers.
4. Ginsberg et al. (18) used a definition that incorporated clinical relevance combined with objective evidence on venous valve incompetence as assessed by photoplethysmography, venous Doppler or venous air plethysmography.

### Incidences of PTS

The RR value for the development of PTS between groups with and without postoperative DVT is illustrated in figure 1. Three different stratification levels were applied in the analyses, all disclosing higher incidences of PTS in patients with primary asymptomatic DVT as compared to patients with no DVT.

This meta-analysis illustrates an increased incidence of PTS in patients with asymptomatic postoperative DVT as compared to patients without postoperative DVT (RR = 1.58, 1.24 - 2.02, p < 0.0005). A trend towards a higher incidence of PTS was found in patients with postoperative DVT as detected by the 125I-fibrinogen uptake test (RR = 1.23, 0.88 –1.71, p = 0.23), whereas statistical significant differences were found in patients with DVT diagnosed by means of venography (RR = 1.92, 95% confidence interval: 1.23 – 3.01, p < 0.005) or ultrasonography (RR = 4.65, 2.51 – 8.61, p < 0.00001).

Figure 2 demonstrates the RR values following stratification according to type of statistical unit (patient/leg) reported in each publication. The paper by Andersen and Wille-Jørgensen (14) was listed in both groups as both methods of analyses were reported and consequently, overall analysis was not performed.

Including papers basing statistics upon single leg examination, we calculated a borderline significant difference towards a higher rate of PTS in patients with verification of postoperative

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Primary screening method</th>
<th>N with DVT/N without DVT</th>
<th>Follow-up period (years)</th>
<th>Investigations for PTS</th>
<th>Definition of PTS in meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindhagen et al. 1984 (13)</td>
<td>Abdominal &amp; hip arthroplasty</td>
<td>125I-fibrinogen uptake test</td>
<td>Legs: 137/625</td>
<td>3 – 5</td>
<td>Clinical examination &amp; venous function tests</td>
<td>Clinical venous insufficiency</td>
</tr>
<tr>
<td>Mudge et al. 1988 (16)</td>
<td>Abdominal</td>
<td>125I-fibrinogen uptake test</td>
<td>Patients: 26/108</td>
<td>10</td>
<td>Clinical examination</td>
<td>At least three of these criteria: varicose veins, eczema, oedema, skin pigmentation or liposclerosis</td>
</tr>
<tr>
<td>Francis et al. 1988 (19)</td>
<td>Hip or knee arthroplasty</td>
<td>Venography</td>
<td>Legs: 19/78</td>
<td>2 – 5</td>
<td>Clinical examination &amp; plethysmography</td>
<td>Abnormal physical examination</td>
</tr>
<tr>
<td>Siragusa et al. 1997 (17)</td>
<td>Hip or knee arthroplasty</td>
<td>Venography</td>
<td>Patients: 46 / 52</td>
<td>2 – 4</td>
<td>Questionnaire and physical examination</td>
<td>Score system based on subjective and objective findings</td>
</tr>
<tr>
<td>Ginsberg et al. 2000 (18)</td>
<td>Hip or knee arthroplasty</td>
<td>Venography</td>
<td>Patients: 91 / 164</td>
<td>2 – 7</td>
<td>Clinical examination &amp; Plethysmography and Doppler investigations for valve insufficiency</td>
<td>“Clinical relevance” combined with objective evidence of venous valve incompetence</td>
</tr>
<tr>
<td>Caprini et al. 2001 (15)</td>
<td>Hip arthroplasty</td>
<td>Venous duplex ultrasound scan</td>
<td>Patients: 20 / 248</td>
<td>5 – 6</td>
<td>Questionnaire</td>
<td>Swelling, discomfort or discoloration</td>
</tr>
</tbody>
</table>
DVT (RR = 1.27, 0.96 – 1.68, p = 0.09). A significant difference (RR = 3.91, 2.28 – 6.68, p < 0.0001) was achieved summarising papers basing statistics upon the individual patient.

Other sensitivity analyses were performed. If the single study that reported PTS definition relying on subjective informations only (15) was excluded from the analysis, there was still a significant elevation of the overall risk (RR 1.43, 1.09 – 1.86, p < 0.01).

Stratification for abdominal (14, 16) and orthopedic surgery only (15, 17–19) demonstrated a significantly higher rate of PTS in the group of asymptomatic DVT compared to the group of no
DVT (RR 10.02, 1.39–72.22, p = 0.02 and RR 2.36, 1.64–3.41, p < 0.00001, respectively).

A funnel-plot (Fig. 3) of the data obtained from the combined analysis of the total patient material shows considerable asymmetry in relation to the vertical common OR line, suggesting the presence of publication bias, which occurs when small studies report no significant differences, or when an opposite effect remains unpublished.

Discussion

PTS is associated with considerable healthcare costs (20–22). Prevention of postoperative DVT, of which most cases are asymptomatic, leads to a reduction of fatal pulmonary embolism (23). Although symptomatic DVT is considered an important pathogenic factor in the development of PTS, the clinical significance of asymptomatic DVT still remains to be settled (24).

This systematic review of seven well-performed clinical studies demonstrates a significant 59% relative risk increment of developing late PTS following asymptomatic postoperative DVT as compared to patients without objectively verified postoperative DVT. Results are expressed as the relative risk reduction of developing PTS and all point in the same direction despite statistical heterogeneity (25).

Definition of PTS comprised one of the important methodological differences between the included papers. Due to lack of consensus regarding this definition, we adopted the categorization provided in each publication. In many of the studies there were several definitions on PTS. We chose the one considered the most clinically relevant from the available data in each publication.

Clinical heterogeneity between the studies was assessed by means of sensitivity analyses applied under various stratification conditions. A uniform trend of the results was observed, regardless of stratification, supporting the feasibility of performing the meta-analysis.

It remains to be clarified whether the treatment of asymptomatic thrombi has any impact on the incidence and severity of late development of PTS. This issue was not addressed in any of the included papers. The information in each trial on primary treatment of DVT was heterogenous. Primary treatment may lower the incidence of late PTS reducing the overall RR. This "towards-the-null-hypothesis bias" further supports the conclusion of this paper.

The duration from primary DVT to observation varied both within and between studies with the exception of one trial in which patients were followed up after a fixed observation schedule (16). The potential bias induced by this fact cannot be corrected for, but it is our assumption that it is equally distributed between the DVT and none-DVT group.

The sensitivity analyses revealed a difference in RR when the results were based on individual legs or individual patients. This was due to the fact that the largest study included in the meta-analysis on the individual legs evaluation reported a RR value of only 1.05 (13). Exclusion of the study that reported a definition of PTS based on subjective information only (15) did not change the overall conclusion. Potentially, other sensitivity analyses could have been carried out. It would have appeared relevant with a distinction between studies as to whether they were assessor-blinded or not, reported complete or incomplete follow-up, or had a prospective or retrospective design. However, the data in the included papers was incomplete in the context of performing further analyses on these topics.

Another question is whether thrombi defined as asymptomatic really were asymptomatic. A distinction between asymptomatic and symptomatic DVT was possible in only two of the papers (15, 16). Compared to daily surgical practice, randomised clinical trials apparently are associated with increased diagnostic effort. In the largest study in which thrombi were demonstrated following screening with the $^{125}$I-fibrinogen uptake test (13), only 3% presented clinical symptoms or signs suggesting DVT. This proportion is small and if it is similar in the other studies it seems justified to base calculations on the number of thrombi found by means of intense screening without stratification of the material into symptomatic and asymptomatic cases.

A funnel-plot reports the statistical strength as given by the standard error of the log OR against the OR values of the results from each included study (9). This measure of strength is in-
versey related to study size. An asymmetric distribution of the plot around the common OR value suggests heterogeneity. This phenomenon was observed in our analyses and may involve publication bias. The funnel-plot must be evaluated with caution as the study\(^1\) at the top of the plot reported results based upon evaluated legs rather than individual patients. If this study had described patients and not legs, the funnel-plot would have become more flat and symmetric thus suggesting less heterogeneity and lower probability of publication bias.

It is generally accepted that symptomatic DVT is an important pathogenic factor in the development of late PTS (1, 7). A recent review adopting the meta-analysis technique demonstrated that the reduction of asymptomatic DVT following major joint surgery, assessed by venography, was accompanied by a reduction of the incidence of symptomatic DVT (26). Consequently, it is not surprising that a reduction of the rate of asymptomatic postoperative DVT lowers the risk of developing PTS.

The overall risk reduction in the present analysis was 8%. Prevention of 13 asymptomatic postoperative DVT cases would save one patient from the development of late venous problems encompassed within the many definitions of PTS.

The overall association between non-symptomatic DVT and development of late PTS found in this study is supported by the sensitivity analyses and is not substantially weakened by methodological limitations and the observed bias as suggested by the asymmetry of the funnel-plot.

It is concluded that there is a significant association between postoperative asymptomatic DVT, diagnosed with sensitive screening methods, and occurrence of late PTS. These data, together with reports of correlation between asymptomatic and symptomatic postoperative DVT, justify that perioperative regimens of thromboprophylaxis are founded on controlled randomised studies that are based upon asymptomatic thrombi as a scientific endpoint.

References