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RECENT ADVANCES IN THE TREATMENT OF VENOUS THROMBOEMBOLISM: IMPLICATIONS FOR THE NEXT CENTURY.*

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Venous thromboembolism (VTE) is a serious disorder and frequently heralds a fatal outcome. The prevalence of VTE is approximately 2-3 per 1,000 inhabitants of the Western world per year. The various treatment modalities for deep vein thrombosis (DVT) and pulmonary embolism (PE) have changed considerably over the last 10-20 years and will continue to do so within the next century. The clinical implications of DVT and PE will be discussed with a focus on complications, prevention of these complications by rapid (initial) anticoagulant treatment with unfractionated (UFH) or low-molecular-weight heparin (LMWH), and by long-term treatment with coumarins.

CLINICAL IMPLICATIONS OF A FIRST VTE EVENT

The long-term clinical course of a first acute DVT has been revealed by carefully conducted, prospective, cohort studies in consecutive outpatients; measurements included recurrent VTE, and death.[1,2] Potential risk factors for these outcomes were evaluated, in particular the late discovery of malignancy.

The average cumulative incidence for recurrent VTE after the qualifying event was approximately 15% at the first year and gradually increased to approximately 25% at eight years of follow-up. Of the initial cohort of patients, approximately 15% died within the first year and about 70% survived the total of the eight years follow-up. Death was frequently due to cancer which became clinically overt mainly within the first year of follow-up, this being an association particularly found in patients having either idiopathic or recurrent DVT at follow-up.[2] This association of malignancy with specific subtypes of DVT has not been confirmed in a recent study from Canada.[3] The elucidation of this association may have an impact on the design of cancer screening and the detection of occult malignancy at an early stage. Such prospective studies are required irrespective of the eventual clinical usefulness of screening for malignancy.

The types of cancer which became clinically manifest were, in order of frequency: prostate, lung, colon, anus, breast, pancreas and others.[3] The frequency of cancer observed in the first year was approximately 7.6-8%.[2,3] Similarly, incidence of fatal outcomes - also due to malignancy in most cases - was observed in a six-month prospective follow-up study in patients with confirmed PE.[4]

INITIAL TREATMENT UFH VERSUS LMWH

Rapid initiation of optimal anticoagulant treatment is an absolute requirement in patients with confirmed DVT to prevent recurrent VTE at follow-up. A double-blind placebo-controlled study in the Netherlands[5] firmly revealed the necessity for initial dose-adjusted heparin treatment.

Patients who presented with proximal DVT and received a placebo infusion, in addition to coumarin treatment being commenced concurrently, had a 20% recurrent

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VTE at three months' follow-up, versus 6.7% in those who received initial UFH treatment concurrent with coumarins.

Once heparin treatment is started, careful laboratory control of coagulation, using an activated partial thromboplastin test (APTT) to assess adequate heparinization early in the course of therapy, is a matter of some importance. The APTT is used to adjust the dose of heparin at regular intervals, to maintain the clotting time prolonged within the prescribed therapeutic range, i.e. an APTT that is increased at least 1.5 times the normal range. Subtherapeutic heparinization within the first 24 hours is associated with a high rate of recurrent VTE at follow-up (23.3%) versus 4.6% in patients receiving therapeutic doses of heparin.[6]

These and other studies[7] support the clinical significance of immediate and optimal heparinization in patients with DVT. However, even in the best centres some patients treated with intravenous heparin will receive sub-optimal therapy, reflecting a practical limitation of the use of UFH rather than a poor standard of care. Initial treatment with LMWH is the likely practical solution to this dilemma. The advantages of LMWH over UFH are a longer plasma half-life, an almost complete bio-availability following subcutaneous injection, as well as a reduced inter- and intra-individual variability following subcutaneous injection. These pharmacological characteristics allow for fixed dose treatment which only need adjusted for specific bodyweight categories without a need for laboratory monitoring.

Initial in-hospital studies comparing the efficacy and safety of fixed bodyweight-adjusted dose LMWH given subcutanously in contrast to a UFH-adjusted dose given intravenously in a randomised fashion revealed promising results, i.e. at least a comparable efficacy, improved safety and, interestingly, a reduced mortality at follow-up.

The results of published studies were assessed by the Cochrane review group on peripheral vascular diseases:[8] this report comprises all randomised controlled clinical trials which were identified by electronic (Medline and Embase) or hand (relevant journals) searches, and by communication with colleagues and relevant pharmaceutical companies. All studies were independently reviewed by three investigators; discordant results were solved by majority voting. Only those studies which directly compared fixed-dose LMWH with an adjusted dose UFH for treatment of DVT and PE were included, and only if they were truly randomised, precluding prior knowledge of next treatment allocation. Further inclusion criteria were: an unconfounded comparison; an objective confirmation of VTE before randomisation by either contrast venography or compression ultrasonography for the diagnosis of DVT, and ventilation-perfusion lung scanning and pulmonary angiography for the diagnoses of PE; a prospective long-term follow-up for objectively confirmed VTE recurrence and for mortality and an independent adjudication of pre-defined clinical end-points.

Studies that were excluded from the analysis were preliminary reports later presented in full, duplicate reports; dose-ranging studies which made use of doses of LMWH other than those currently in use; studies using intravenous or adjusted dose LMWH; studies using fixed dose UFH; and studies with heparinoids. The following relevant clinical outcomes were considered:

- symptomatic recurrent VTE at long-term follow-up ($\geq$ 3 months)
- major haemorrhage during the initial treatment
- death due to any cause and in particular death associated with clinically overt malignancy.

Of the 26 potentially eligible clinical trials, 13 satisfied the inclusion criteria; these studies were published over the years 1988-1997. Pooled analysis for all these clinical trials revealed a reduction of recurrent VTE, at three to six months' follow-up in favour of LMWH (OR 0.75; 95% CI 0.55-1.01; p=0.06). The pooled efficacy analysis in patients with PE revealed no such statistically significant difference (OR 0.91;95%; CI 0.42-1.97; p=0.81). As compared to UFH, patients who were treated with LMWH suffered fewer major haemorrhagic complications, for a pooled OR of 0.55 (95% CI 0.34-0.89; p=0.02).

Important and significant reduction in mortality was observed with LMWH treatment (OR 0.74; 95% CI 0.57-0.98; p=0.03). Mortality reduction was mainly confined to patients with malignancies.

This systemic review thus revealed that LMWH in a fixed dose given subcutanously and only adjusted for bodyweight, compared to APTT-adjusted therapeutic doses of UFH, was at least as effective and likely to be safer. These, and previous data, lead to clinical studies investigating the feasibility and clinical efficacy and safety of home treatment with LMWHs.

HOME TREATMENT WITH LMWH VERSUS IN-HOSPITAL TREATMENT WITH UFH

Two major clinical studies have been reported, e.g. the Dutch Tasman Study[9] and another study from Canada.[10] Both studies - though utilising different brands of LMWH - revealed similar clinical outcomes for efficacy, safety and mortality (Table 1). Moreover, both studies showed that out-of-hospital treatment with LMWH was, as

TABLE 1
Efficacy and safety outcomes in patients with proximal DVT treated with LMWH versus UFH in hospital.

TASMAN STUDY[9]		
	UFH	LMWH
	(n=198)	(n=202)
Recurrent VTE	17 (8.6%)	14 (6.9%)
Major bleeding	4 (2.0%)	1 (0.5%)
Mortality	16 (8.1%)	14 (6.9%)
CANADIAN STUDY[10]		
	UFH	LMWH
	(n=253)	(n=247)
Recurrent VTE	17 (6.7%)	13 (5.3%)
Major bleeding*	3 (1.2%)	5 (2.0%)
Mortality	17 (6.7%)	11 (4.5%)

* During the initial treatment phase or within 48 hours thereafter.

expected, associated with a considerable reduction in days spent in the hospital and hence an important reduction in financial outlays, without a detrimental effect on the quality of life.[9]

These data imply that out-of-hospital treatment of patients with proximal DVT is a feasible option, but with the following precautions:

- Symptomatic patients should primarily be referred to expert 'thrombosis centres' for proper diagnosis of DVT with objective techniques.
- Patients should be submitted to a careful medical history (inclusive of family history), and physical and laboratory examination to elucidate possible causes of thrombosis, including a further search for malignancy, if initial investigations raise suspicion.[11]
- The community facilities, which will be tasked to care for initiation and maintenance of proper anticoagulant treatment, must be prepared for their task and be capable of coping.

LONG-TERM TREATMENT WITH COUMARINS: SHIFT IN LENGTH OF TREATMENT?

Until recently, the duration of oral anticoagulation following a first or a recurrent episode of DVT has not been submitted to well-designed clinical investigation. Two studies from Sweden have now addressed this issue.[12,13]

In the first study,[12] direct comparison was made between six weeks' versus six months' treatment in patients with a first thromboembolic event; patients with an inherited risk factor predisposing to VTE (antithrombin, protein C or S deficiency) were excluded from the analysis. In the remaining patients a significant reduction of recurrent VTE was achieved in the six months' treatment group: OR for recurrence in the six weeks group was 2.1 (95% CI 1.4-3.1) without differences in mortality or major haemorrhage. By analysis of subgroups, the OR in patients with temporary risk factors for thrombosis was 1.9 (95% CI 0.8-4.5;$p=0.24$), while in patients with permanent risk factors, the OR was 2.3 (95% CI 1.5-3.6;$p<0.001$). Hence, the risk reduction for recurrent VTE was observed more prominently in patients with permanent risk factors receiving six months of treatment.

A similar VTE reduction was observed in patients with a second episode of DVT or PE, who were receiving continuing oral anticoagulant treatment (48 months' follow-up) as compared to six months of treatment.[12] As in the first study, patients with documented congenital risk factors were excluded.

After four years' follow-up, the rate of recurrence in the six months group was 20.7% versus 2.6% in the patients receiving continuing coumarin treatment, for a relative risk of 8.0 (95% CI 2.5-25.9). As expected, the risk for bleeding was lower in the six months' treatment group, i.e. 0.3 (95% CI 0.1-1.1).

From these and other data the following conclusions may be derived:

Key points:

- Patients with a first VTE event and having only a temporary risk factor are better off with 4-12 weeks of treatment (calf vein thrombosis: 4-6 weeks, proximal DVT or PE: 12 weeks).
- Patients with DVT or PE and without a temporary risk factor are better off with six months of treatment.
- Patients with a second episode of VTE deserve longer treatment. Duration should be carefully considered, taking into full account the risk for recurrent VTE and the risk of major bleeding especially with older patients.
- Continuing coumarin treatment for at least four years, e.g. the duration of follow-up in this study,[13] should be seriously considered at least on the basis of the data currently available.[14] The duration of anticoagulation in patients with inherited thrombophilia (excluded in the Swedish studies) is still uncertain and has been challenged recently.[15] Currently, 'indefinite' treatment is the prevailing option, though this is not based on solid evidence. This study[15] is critically analysed in an editorial[16] which is relevant in terms of hypothesis generation and for the design of future studies.

TREATMENT OF VENOUS THROMBOEMBOLISM BEYOND THE YEAR 2000

Treatment of patients suffering from thrombotic disorders will certainly continue to change; new anticoagulant drugs are under development with better efficacy-safety profiles. These developments will hopefully reduce the serious side-effects observed with the traditional anticoagulants, e.g. bleeding, heparin-induced thrombocytopenia, osteopoenia, spontaneous fractures following prolonged treatment with heparin and embryopathy following coumarin treatment in early pregnancy.

Newer heparin-like products will be clearly defined; these would be synthetic and hence independent of animal sources for their production. Pentasaccharide is such a preparation and clinical studies are now in progress to assess its clinical usefulness.

Domiciliary treatment will become more widespread worldwide, not only for patients with acute DVT but also for a substantial proportion of patients with PE. Further developments will follow further clinical trials, performed in well-organised settings worldwide.

Harmonisation of expert centres on an international basis will further substantially enhance the improved clinical management of patients with VTE.

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