SUMMARY

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Diagnosis of a first episode of suspected DVT

The diagnosis of suspected DVT relies on noninvasive objective testing. Compression ultrasonography (CUS) represents the preferred method in symptomatic outpatients. Due to its low sensitivity for isolated-calf DVT, CUS must be repeated in all patients with normal findings at baseline. It was hypothesized that repeat CUS may be avoided in patients with either a normal D-dimer test or a low clinical pre-test probability (PCP) score at presentation. Chapter 1 provides the results of a prospective study in which consecutive outpatients with suspected DVT were managed on the basis of CUS and D-dimer results. Of 946 included patients, 686 (72.5%) had a normal baseline CUS and underwent D-dimer (Instant-IA) evaluation. Only 88 (12.8%) had an abnormal D-dimer test result, and were scheduled for repeat CUS. None of them developed pulmonary embolism before the repeat CUS test. The repeat CUS test was abnormal in 5 of them. Overall, 681 patients with a normal diagnostic workup were followed-up for 3 months (598 with both a normal CUS and D-dimer at presentation, and 83 with a normal serial CUS). None of these patients was lost to follow-up, and 3 (cumulative incidence, 0.4%; 95% CI, 0 to 0.9) had an objectively confirmed episode of symptomatic venous thromboembolism (1 DVT, and 2 PE). It was concluded that the CUS/D-dimer strategy is at least as safe and more efficient as the alternative noninvasive diagnostic approaches since, in the majority (87%) of patients serial CUS could be avoided. This reduced the mean number of repeat CUS and extra hospital visits from 0.7 to 0.1 per patient, as compared to serial CUS (or IPG) testing.

The study described in Chapter 2 is based on a similar approach as that used in Chapter 1. However, a different D-dimer assay (SimpliRED) was employed in
combination with CUS. Additionally, a PCP assessment was prospectively obtained in all patients, but patients were managed on the basis of CUS and D-dimer results only. Altogether, 1739 symptomatic outpatients were included, of whom 22% had an abnormal baseline CUS result. Of the 1348 subjects with normal CUS, 520 (39%) had abnormal D-dimer testing, and were scheduled for repeat CUS at 1 week. Two (0.4%) of these patients developed symptomatic pulmonary embolism before repeated testing, and 17 (3%) had abnormal CUS findings at 1 week. Overall, 1329 patients with a normal diagnostic workup (828 with both a normal CUS and D-dimer at presentation, and 501 with a normal serial CUS) were followed-up for 3 months: none of them was lost to follow up, and 17 (cumulative incidence, 1.3%; 95% CI, 0.7 to 2.0) had objectively confirmed episodes of symptomatic venous thromboembolism (11 DVT and 6 PE). Since PCP scores were obtained in all patients at presentation, the potential value of combining this clinical information with D-dimer results could be addressed in a scenario analysis. Of the 561 patients with both a low PCP and normal D-dimer test, 10 had confirmed symptomatic venous thromboembolism, for a cumulative incidence of 1.8% (95%CI: 0.9-3.3%). This suggests that based on a normal D-dimer and a low PCP, about one-third of the referred patients might be safely spared the initial ultrasound test.

**Diagnosis of suspected recurrent DVT**

The diagnosis of recurrent DVT is notoriously difficult. Serial IPG and serial CUS have high accuracy, but can only be used if the test was already normalised. Such a normalisation of CUS usually occurs in about 50% of patients during the first year after DVT. After the acute episode, venous thrombi usually disappear gradually as result of both anticoagulant treatment and spontaneous fibrinolysis. This can be accurately quantified by measurement of the vein diameter during compression with the ultrasound transducer. Chapter 3 addressed the accuracy of a combined CUS method, based on two criteria 1) vein noncompressibility (the usual qualitative CUS), and the thrombus thickness measurement (quantitative). The study consisted of 2 phases, a cross-sectional survey and a prospective investigation, involving 149 and 145 patients, respectively. CUS normalisation occurred in only 30% of patients within 1 year, but a significant reduction of the thrombus thickness was observed in the majority of patients. During the prospective phase of the study, 29 patients presented with suspected recurrent DVT which was confirmed by venography in 11 (38%). The vein incompressibility criterion alone had an accuracy of 100%, but was appli-
cable in only one-fifth of patients. The combined ultrasound method had a 100% sensitivity and specificity for recurrent proximal DVT (95% CI, 69% to 100%, and 81 to 100%, respectively), and could be used in all patients. Furthermore, the combined CUS method had a high reproducibility (interobserver variation kappa, 0.95; 95% CI, 0.88 to 1.00). The combined CUS method was then evaluated in a large prospective cohort study. This study, described in Chapter 4, was designed to assess the safety of withholding anticoagulation from patients with a normal serial combined CUS work-up, and included 205 consecutive patients with suspected recurrent ipsilateral DVT. Of them, 150 had a normal serial combined CUS and only 2 (1.3%; 95% CI, 0.02% to 4.7%) had a confirmed nonfatal venous thromboembolic complication during the scheduled 6-month follow-up. It was concluded that it is safe to withhold anticoagulant treatment from patients with suspected recurrent ipsilateral DVT based on a normal serial combined CUS. Adequate venograms were obtained in 42 (81%) of 52 patients with abnormal baseline CUS results, and confirmed recurrent proximal-vein thrombosis in 38 (positive predictive value, 90%; 95 CI, 77% to 97%). Venography was abnormal in all 10 patients with noncompressible previous normal or normalised veins, and in 28 of the 32 patients in whom thrombus thickness was increased.

**Treatment of DVT**

Adequate treatment with unfractionated heparin (UFH) is usually based on continuous intravenous infusion combined with frequent assessment of the activated partial thromboplastin time (aPTT) to maintain this value within the therapeutic range. Timely achievement of therapeutic aPTTs is crucial for the optimal treatment of DVT. In Chapter 5 the use and validation of UFH nomograms for treatment of DVT is reviewed. A higher proportion of patients treated on the basis of a nomogram had therapeutic aPTT levels within 24 hours, as compared to patients treated without use of such nomograms (OR, 3.6; 95% CI, 2.6 to 4.9; p<0.0001). Furthermore, the incidence of recurrent VTE was significantly lower among patients treated according to a nomogram (OR, 0.3; 95% CI, 0.1 to 0.8; p=0.001), while major and minor bleeding events occurred with comparable frequencies in nomogram-treated patients and controls. Chapter 6 outlines the findings of a prospective cohort trial that evaluated the usefulness of a weight-based algorithm for the administration of UFH in patients with a first episode of DVT. After an intravenous loading dose, UFH was only administered subcutaneously. Of the included 70 patients, 61 (87%) had adequate aPTT
levels within 24 hours, and 69 (99%) within 48 hours. Only 7 patients (10%) had an aPTT above the therapeutic range for more than 12 hours. None of the patients had major bleeding, and recurrent VTE occurred in 3 patients (4.3%).

Clinical course of DVT

Long-term prospective follow-up studies of patients with DVT clearly demonstrated that VTE is a chronic disease. Prolonged treatment durations with oral anticoagulants result in a significant reduction of recurrent VTE, but also in a higher risk of (major) bleeding events. DVT patients who also have cancer are more prone to develop both recurrent VTE and bleeding while on anticoagulants. In Chapter 7 we analyzed a cohort of 842 patients, including 181 subjects with cancer at referral or detected during admission. The 1-year cumulative incidence of recurrent VTE in cancer patients during the period of anticoagulation was 20%, which was more than 3-fold higher than that observed in patients without cancer. The 1-year cumulative incidence of bleeding during anticoagulation was 12% and was more than 2-fold higher in cancer patients. The increased risk for recurrent VTE and bleeding in cancer patients was not due to more frequent anticoagulant intensities outside the therapeutic range. The extent of cancer at baseline (TNM stages) was associated with the risk of recurrent VTE and bleeding. Overall, the incidence of recurrent VTE was 2 to 3-fold higher in patients with TNM stages I-II, and 5-fold higher in patients with TNM III-IV. Similarly, the incidence of major bleeding was 2 to 3 times higher among patients with TNM III, and up to 5 times higher in patients with TNM IV, as compared with patients without cancer.

About 20-30% of the patients with DVT will develop, within 5 years from the initial episode, a post-thrombotic syndrome (PTS) characterised by mild (swelling, pain, skin changes, and dilated superficial veins), to severe (chronic pain, pitting oedema, and leg ulcer) leg symptoms. In Chapter 8 various aspects of PTS, including incidence, pathophysiology, diagnosis, treatment and prognosis are reviewed. A cluster of heterogeneous conditions appear to play a role in the onset of PTS including venous hypertension and ipsilateral recurrent DVT. PTS can be prevented by adequate anticoagulation for sufficient durations in combination with elastic stockings. Surgical procedures do not appear to yield significantly better results than conservative management.

Treatment of peripheral arterial disease

Peripheral arterial disease (PAD) is a widespread disease in Western countries.
Intermittent claudication, its commonest form, has a prevalence of 5% in males over 50 years and is associated with generalized atherosclerosis and a 2-fold increased death rate, largely from myocardial infarction and stroke, as compared to individuals without intermittent claudication. Many treatments for intermittent claudication are available, including conservative strategies (physical, pharmacological), and surgical procedures (revascularisation), but their clinical benefit is controversial. In Chapter 9 and 10 a review of the evidence supporting several of these conservative approaches for intermittent claudication is provided.

In Chapter 9 the efficacy of physical training, smoking cessation, pentoxifylline, and nafronyl is evaluated. Both (supervised) physical training and smoking cessation improved the patients' walking ability (a statistically significant increase of about 140 meters with physical training, and a nonsignificant increase of about 50 meters with smoking cessation) as compared with control. However, the strength of this conclusions is weak. Similarly, pentoxifylline and nafronyl significantly improved the patients' walking ability (on the average, of about 20 meters more with pentoxifylline, and of about 45 meters more with nafronyl), as compared with placebo.

In Chapter 10 the potential usefulness of antiplatelet and anticoagulant drugs in the conservative management of intermittent claudication is reviewed. Several drugs (including picotamide, indobufen, defibrotide, sulodexide, triflusal, and low molecular weight heparins) significantly improved the walking ability of the treated patients as compared with controls. However, only ticlopidine was associated with a statistically significant reduction in the number of revascularisation procedures (OR, 0.62; 95% CI, 0.41 to 0.93), and of mortality (OR 0.68; 95% CI, 0.49 to 0.95). The evidence for aspirin (generally regarded as the first-line choice) was weak.

Up to 25% of patients with PAD undergo surgical revascularisation procedures within 10 years from the onset of symptoms. Without additive treatment, reocclusion will occur in 20-60% of cases within 5 years. Anticoagulant or antiplatelet compounds are commonly advocated to improve the long-term patency of surgically re-opened vessels, and to reduce the number of amputations. However, their effectiveness is controversial. In Chapter 11 the evidence supporting the prescription of these agents after revascularisation procedures in patients with PAD is reviewed. Patency was significantly increased by aspirin plus dipyridamole (OR 0.69; 95% CI, 0.53 to 0.90, p=0.005), and by ticlopidine (OR 0.53; 95% CI, 0.33 to 0.85, p=0.009); while the amputation rate was non-significantly reduced by ticlopidine and by vitamin K antagonists. A non-significant 20% reduction in mortality was observed with aspirin (plus dipyridamole).