Summary and general discussion
This thesis aimed to address three aspects of the management of venous thromboembolism. The first concerned the etiology of the disease. Novel risk factors for pulmonary embolism were investigated and, in addition, the old premise that long distance travel is associated with the development of venous thromboembolism was challenged. Secondly, new methods for the diagnostic management of patients presenting with clinically suspected venous thromboembolism were studied. An integrated non-invasive diagnostic approach was evaluated and the question whether the D-dimer test is useful in cancer patients was addressed. Finally, the third aspect of treatment and prognosis was investigated. The role of thrombolysis in the treatment of venous thromboembolism was systematically reviewed and new prognostic indicators for the natural history of pulmonary embolism were studied.

**Etiology**

Thrombophilic factors have been investigated to a much lesser extent in patients with pulmonary embolism as compared to those with deep venous thrombosis. It has been hypothesised that a thrombophilic abnormality contributes more strongly to the development of thrombi in the deep venous system of the leg than to the development of pulmonary embolism. In chapters 2 and 3 we investigated the risk of pulmonary embolism in patients with elevated levels of the procoagulant proteins IX or XI, or polymorphisms of the factor XIII or TAFI gene, respectively. We found that high levels of factors IX or XI are associated with a two to three fold increased risk of pulmonary embolism, a risk similar to that reported for deep venous thrombosis. Carriers of the TAFI-438A or FXIIIA-43Leu/Leu genotype are protected against pulmonary embolism, with odds ratios of 0.1 and 0.5, respectively. Also, these odds ratios seem in line with those found in patients with deep venous thrombosis. These findings support the view that the etiology of both deep venous thrombosis and pulmonary embolism is the same and that the risk of embolization is not determined by the thrombophilic abnormality. It remains unclear why some patients primarily present with deep venous thrombosis while others have chest symptoms as evidence of their venous thromboembolic disease. In addition, the observation suggesting that the factor V Leiden mutation is associated with a lower risk of pulmonary embolism as compared with deep venous thrombosis, is not fully understood. Studies in patients with 'isolated' pulmonary embolism (which was defined as no evidence of deep venous thrombosis on ultrasonography of the legs) showed lower frequencies of the factor V mutation. However, it is known from venography studies (a more accurate method to detect deep venous thrombosis) that in the great majority of patients with pulmonary embolism, (asymptomatic) deep venous thrombosis is present. Still the possibility exists that the chance of developing symptomatic pulmonary embolism is smaller than the chance to develop deep venous thrombosis when having the factor V mutation.
In chapter 4 we evaluated to which extent the factor VIII value at presentation is due to an acute phase reaction. Our study showed that high factor VIII levels at presentation were as high in patients as in controls. After three months, factor VIII plasma concentrations clearly decreased, but both in patients and controls. Therefore, screening for high factor VIII levels should be delayed to at least 3 months after the acute event.

The last study of this part of the thesis addressed the controversy regarding the relationship between travel and venous thromboembolism (chapter 5). An analysis of 3 studies, totalling 1947 patients, showed that no increased risk is present among long distance travellers who travel less than 10 hours. The pooled odds ratio for venous thromboembolism in these travellers was 0.9 (95% confidence interval [CI]: 0.6-1.4).

**Diagnosis**

Clinicians often deviate from the recommended algorithm for the diagnosis of pulmonary embolism consisting of ventilation-perfusion scintigraphy and pulmonary angiography. In almost half the Dutch hospitals, angiography and nuclear medicine facilities are partly available. In addition, even if both facilities are available at a daily basis, surveys revealed that angiography is only performed in ten percent of the patients who had a non-diagnostic ventilation-perfusion scintigram result. We therefore developed a diagnostic strategy reducing the need for lung scintigraphy and avoiding the need for angiography and evaluated the safety of this new strategy (chapter 6). The strategy started with a clinical probability estimate as assessed by the attending physician and a D-dimer test. When the clinical probability of pulmonary embolism was low and the D-dimer test result normal, pulmonary embolism was ruled out, no anticoagulant therapy was given and the patient was followed for a three-month period. In all other cases, (ventilation)-perfusion scintigraphy was performed and, if non-diagnostic, compression ultrasonography of the legs was done three times over a one-week period. If perfusion scintigraphy was normal or ventilation-perfusion scintigraphy non-diagnostic and serial compression ultrasonography normal, pulmonary embolism was again ruled out. In patients with an abnormal ultrasonogram of the legs or a high probability ventilation-perfusion scintigram, pulmonary embolism was diagnosed and treatment was instituted. The outcome measure of the study was the venous thromboembolic complication rate during three months follow-up in all patients in whom pulmonary embolism was excluded. Of the 631 included patients, the diagnosis was refuted on the basis of a low clinical probability estimate and a normal D-dimer test result in 95 patients, normal perfusion scintigraphy in 161 patients and non-high probability lung scintigraphy followed by normal serial ultrasonography in 210 patients. Of these 466 patients, venous thromboembolic complications during follow-up occurred in 6 (complication rate 1.3%. 95% CI: 0.8-2.4).
0.5-2.8%). This rate compares favourably with the complication rates after normal scintigraphy or angiography. Hence, the non-invasive algorithm evaluated appeared a safe alternative to the current diagnostic standard for pulmonary embolism.

In Chapter 7 we studied whether the D-dimer test is safe and efficient in cancer patients, who constitute a substantial proportion of patients with suspected venous thromboembolism. The efficiency and safety of the D-dimer test in this patient category has been questioned previously because of the well known relation between cancer and fibrin formation. We studied 1739 consecutive patients with suspected deep venous thrombosis of whom 217 suffered from cancer. The negative predictive value of the D-dimer test was 97% in both cancer and non-cancer patients. In 63 of all 217 cancer patients (29%) the diagnosis of deep venous thrombosis could be ruled out on the basis of a normal D-dimer and ultrasonography test result and anticoagulant treatment was withheld. In these 63 patients one thromboembolic event occurred during follow-up (1.6%, 95% CI: 0.04%-8.53%). Thus, the negative predictive value of a whole blood D-dimer test in cancer patients seems as high as in non-cancer patients. Furthermore, it seems safe to withhold anticoagulant therapy in these patients. Therefore, it can be concluded that the D-dimer test can be safely used in cancer patients. The test seems also efficient since in approximately one third of cancer patients the diagnosis can be refuted at referral. In these patients, repeat ultrasonography (and therefore an extra hospital visit) can be avoided.

**Prognosis and treatment**

Since the introduction of heparin and vitamin K antagonists half a century ago, the mortality rate due to pulmonary embolism has reduced from approximately 25 to four percent. Since then, no further reduction in this rate has been achieved. A lower rate might be obtained when patients are treated more aggressively. In chapter 8 the efficacy and safety of fibrinolytic therapy ('thrombolysis') - which has been shown to be very effective in acute arterial thrombosis - for the treatment of venous thromboembolism is reviewed. A meta-analysis of eight randomised controlled trials in patients with pulmonary embolism, with a total of 453 patients, showed that the in-hospital all-cause mortality rate in patients receiving thrombolysis was 4.6 percent, whereas this figure was 6.0 percent in patients who received heparin alone (relative risk [RR], in favour of thrombolysis, 1.3; 95% CI: 0.6-2.5). The relative risks for outcomes as pulmonary embolism related mortality and venous thromboembolic recurrences were 1.7 (95% CI: 0.6-5.0) and 1.4 (95% CI: 0.6-3.3), respectively. However, on the other hand, the relative risks for major and minor bleedings were also (significantly) elevated (RR 1.8, 95% CI: 1.04-3.1 and 4.0, 95% CI: 1.8-9.0, respectively). It has to be noted that the studies included in the pooled analysis included small numbers of patients and used different agents and dose regimens, which limits the conclusions and warrants for careful
interpretations. Nevertheless, it seemed that the efficacy of thrombolysis did not outweigh the risk of major and minor bleedings. Therefore, at present, fibrinolytic therapy is not considered to be routinely indicated in patients with acute pulmonary embolism.

Since there is no role for thrombolysis in the standard treatment, attempts have been made to stratify the heterogeneous group of patients with pulmonary embolism. In patients with a high risk of pulmonary embolism related outcome events, the harm-benefit ratio could be in favour of thrombolysis. Echocardiographically assessed right ventricular dysfunction has been advocated as a tool to select high-risk patients for more aggressive therapy. Chapter 9 reviews the available literature concerning the prognostic value of echocardiographic right ventricular dysfunction. As appears from this review, the evidence for using echocardiography to predict adverse outcome in hemodynamically stable patients with right ventricular dysfunction is poor. The seven included studies showed several methodological shortcomings but suggested an at least two fold increased risk of pulmonary embolism related mortality. However, only two studies allowed for an estimation in hemodynamically stable patients. The positive predictive value for pulmonary embolism related mortality in these studies was only five percent. For hemodynamically stable patients a prognostic tool is of particular interest, since hemodynamically unstable patients already have an indication for thrombolysis. It is questionable whether echocardiography to assess right ventricular function is suitable for this purpose.

Another potential tool for selection of high risk patients is a novel marker for heart failure, the neurohormone Brain Natriuretic Peptide (BNP). This hormone, which releases in response to ventricular overload was investigated as a prognostic marker for adverse outcomes in 110 hemodynamically stable patients with acute pulmonary embolism (chapter 10). This study showed that the higher the BNP value, the higher the risk of pulmonary embolism related death. The positive predictive value for pulmonary embolism related death if the BNP value is above the 67th percentile (i.e. 21.7 pmol/L) was 16 percent (95 percent CI: 6-32%). Therefore, BNP seems a promising tool to guide more aggressive therapy in patients with acute pulmonary embolism.