

Extension of anticoagulation after venous thromboembolism

Risk factors influencing the decision

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Venous thromboembolism, risk factors, recurrence, bleeding

Summary

Whereas every clinician agrees on the need for anticoagulation initially after the diagnosis of venous thromboembolism (VTE), the opinions regarding optimal duration of secondary prophylaxis differ. The decision is complicated by the large number of identified risk factors associated with the risk of recurrence. In addition consideration has to be taken to the risk factors for bleeding and individual patient preferences. Data from long-term follow-up studies up to a decade indicate that some risk factors for recurrence decline and others seem to gain importance with time. In this review data has been extracted from the most illustrative trials to highlight controversies but also where there is consensus in order to give the clinician some support for the individual decisions on extension of anticoagulation after VTE.

Schlüsselwörter

Venöse Thromboembolie, Risikofaktoren, Rückfall, Blutung

Zusammenfassung

Während unter den Ärzten dahingehend Konsens herrscht, dass sofort eine Antikoagulationstherapie einzuleiten ist, wenn eine venöse Thromboembolie (VTE) diagnostiziert wird, gehen die Meinungen bezüglich der optimalen Dauer der sekundären Thromboseprophylaxe auseinander. Die Entscheidung wird durch die große Anzahl nachgewiesener Risikofaktoren erschwert, die das Rezidivrisiko bedingen. Darüber hinaus sind die Risikofaktoren für das Auftreten von Blutungen und die Präferenzen der Patienten zu berücksichtigen. Daten aus Langzeitstudien, deren Follow-up bis zu zehn Jahren betrug, weisen darauf hin, dass bestimmte Rezidivrisikofaktoren mit der Zeit an Bedeutung verlieren, während andere im Laufe der Zeit größeres Gewicht erlangen. Dieser Überblick enthält Daten aus den aussagekräftigsten Studien. Es soll gezeigt werden, wo gegensätzliche Ansichten vorliegen und wo Konsens besteht. Der Arzt erhält damit eine Entscheidungshilfe bei der Festlegung der Dauer der Antikoagulationstherapie nach VTE.

Verlängerung der antikoagulativen Behandlung nach venöser Thromboembolie

Entscheidungsrelevante Risikofaktoren

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The manifestations and complications of deep vein thrombosis (DVT) are summarized in Table 1. Some patients will never suffer from any of these complications, as it is typically the case with a distal deep vein thrombosis after a temporary and removable risk factor, e. g. surgery. The risk of pulmonary embolism is low and the long-term prognosis for the venous circulation in the affected leg compared to the contralateral leg does not differ much (1).

Conversely, patients with unprovoked, extensive, proximal DVT have a high risk of

developing the post-thrombotic syndrome (PTS), particularly if there is an ipsilateral recurrence with further valve destruction (2). The PTS starts with

- oedema, teleangiectasia and varicose veins,
- it develops further into irreversible skin changes with hyperpigmentation, lipodermatosclerosis and atrophie blanche and,
- in the most advanced form, venous ulcer.

The incidence of mild PTS is about 50% and of severe PTS with active or healed ulcer 6%

during 10 years after the first VTE (3). The incidence of pulmonary hypertension is 3.8% after two years (4).

Recurrent ipsilateral DVT is probably the strongest risk factor for development of PTS (hazard ratio (HR) 6.4, 95% confidence interval (CI) 3.1–13.3) (2). In addition, old age and signs of venous insufficiency within a week from the index event appear to be independent risk factors for future PTS (3).

In a somewhat similar pattern (4),

- recurrent pulmonary embolism is the strongest risk factor for pulmonary hypertension (odds ratio (OR) 19.0, 95% CI 4.5–79.8),
- followed by unprovoked nature of the embolic event (OR 5.7, 95% CI 1.4–23.0),
- large perfusion defect (OR 2.2, 95% CI 1.5–3.3) and
- young age (OR 1.8, 95% CI 1.2–2.6).

For the decision on extension of the anticoagulant treatment it is, however, usually not the risk of PTS or pulmonary hypertension but rather the risk of recurrent VTE that is taken into account.

Risk factors for recurrence

A large number of studies have reported on risk factors for recurrence of VTE. These may be thrombosis-related or patient-related as shown in Table 2. The overall risk of recurrence is 30% over eight years (95% CI 23.6–37.0) (2). With a duration of secondary prophylaxis of only six weeks versus six months the risk of recurrence is 31.2% and 27.1%, respectively, which is not a statis-

tically significant difference (3). There is, however, a significant benefit in favour of six months for the first six years after the event. But we can do better than these overall estimates.

The randomized controlled trials (RCTs) and cohort studies have provided us with important data on most of the pertinent risk factors. We can now utilize this information to tailor the treatment for the individual patient, or if that is to onerous, published guidelines can be followed (5). The guidelines differ between

- unprovoked and provoked VTE and take into account
- the number of events and to some extent
- the presence of a thrombophilic defect.

In the following text it will become evident that the problem usually is more complex and therefore more sophisticated assessments are now possible.

Location of VTE

Distal DVT is intuitively less hazardous than more proximal location in view of narrower veins and smaller thrombus volume. The risk of recurrence for patients with distal DVT was in the French DOTAVK trial much lower, 2.6% with six or 12 weeks of secondary prophylaxis, than with proximal DVT, 17% with three or six months of therapy (6). In THRIVE III after six months of anticoagulation (placebo group) (7) and in DURAC I after six weeks or six months of anticoagulation (8) the risk of recurrence two years after distal DVT was 8.6%, which in both studies was lower than for proximal DVT (THRIVE III $p=0.096$, DURAC I $p=0.002$). During the 10-year follow-up in DURAC I there was an accumulation of recurrences reaching 22.8% by 10 years but this was more pronounced with proximal DVT reaching 32.5% (Fig. 1a).

Patients with pulmonary embolism had even faster accumulation of recurrences initially, but in the long-term follow-up the difference between proximal DVT and pulmonary embolism as index events almost disappeared. The same pattern was detected in a metaanalysis of individual patient data from 2474 patients in five RCTs (9). Within

the anatomical area of *proximal* DVT there may also be a progressively increasing risk with more proximity, since in a cohort study of 1149 patients the rate of recurrence over three months was 5.1% for popliteal DVT, 5.3% for femoral DVT and 11.8% for iliac DVT (10).

Is it therefore reasonable to consider short treatment in case of distal DVT and longer for proximal DVT or pulmonary embolism?

The associated question is whether recurrences differ in nature for patients with initial proximal DVT versus pulmonary embolism. The 10-year follow-up in the DURAC I trial showed that patients with initial DVT tend to recur four times as often as DVT than as pulmonary embolism. Conversely, those with initial pulmonary embolism will more often have the same clinical manifestation next time than DVT (3). Furthermore, recurrent pulmonary embolism does not only increase the risk of pulmonary hypertension, as discussed, but may be fatal.

Douketis et al. described the case-fatality rate of recurrences from the combined DURAC I trial (8) and the cohort study of Prandoni et al. (2) as 3.8% for initial DVT and 5.7% for initial pulmonary embolism, when only recurrences that were definite or probable pulmonary embolism were taken into account (11). The mortality from pulmonary embolism is higher when patients have a limited cardiopulmonary reserve. These patients should definitely be considered for indefinite duration of anticoagulation.

Thrombosis located in the splanchnic or intracranial veins deserve mentioning in this context, although not discussed else-

Tab. 1 The complications of deep vein thrombosis (DVT)

progression of DVT	<ul style="list-style-type: none"> ● Phlegmasia coerulea dolens ● Phlegmasia alba dolens → loss of limb
destruction of venous valves or failure of thrombus to resolve	<ul style="list-style-type: none"> ● venous insufficiency (post-thrombotic syndrome) → venous ulcers
pulmonary embolism	<ul style="list-style-type: none"> ● death ● pulmonary hypertension
recurrent venous thromboembolism	any of the above

where in this review. There are no RCTs or prospective cohort studies for these entities. A typical duration of treatment is six months, but if any thrombophilic defect has been identified (see below), a consensus paper recommended indefinite anticoagulation (12). The same applies for life-threatening pulmonary embolism.

Removable, unknown or permanent risk factor

It was proposed by Baglin et al. that the triggering risk factor is classified as surgical, idiopathic or other (after fracture, illness, immobilization, travel or oestrogen) (13). The cumulative two years' recurrence rate was

- 0% for the surgical patients,
- 19.4 % (95% CI 13–26) for those with unprovoked VTE and
- 8.8% (95% CI 5.1–12.5) for the last group.

Other authors have usually analyzed the subsets as provoked and unprovoked VTE and in most trials patients with cancer were

Tab. 2 Risk factors for recurrence of venous thromboembolism

thrombus-related	<ul style="list-style-type: none"> ● location: distal versus proximal leg versus pulmonary embolism ● triggering event: removable versus unknown versus permanent risk factor ● number of thromboembolic events ● failure to resolve
patient-related	<ul style="list-style-type: none"> ● demographic characteristics: age, race, sex, body weight ● thrombophilic defects ● general activation of the haemostatic system ● concomitant disease: cancer, paroxysmal nocturnal haematuria, nephrotic syndrome etc.

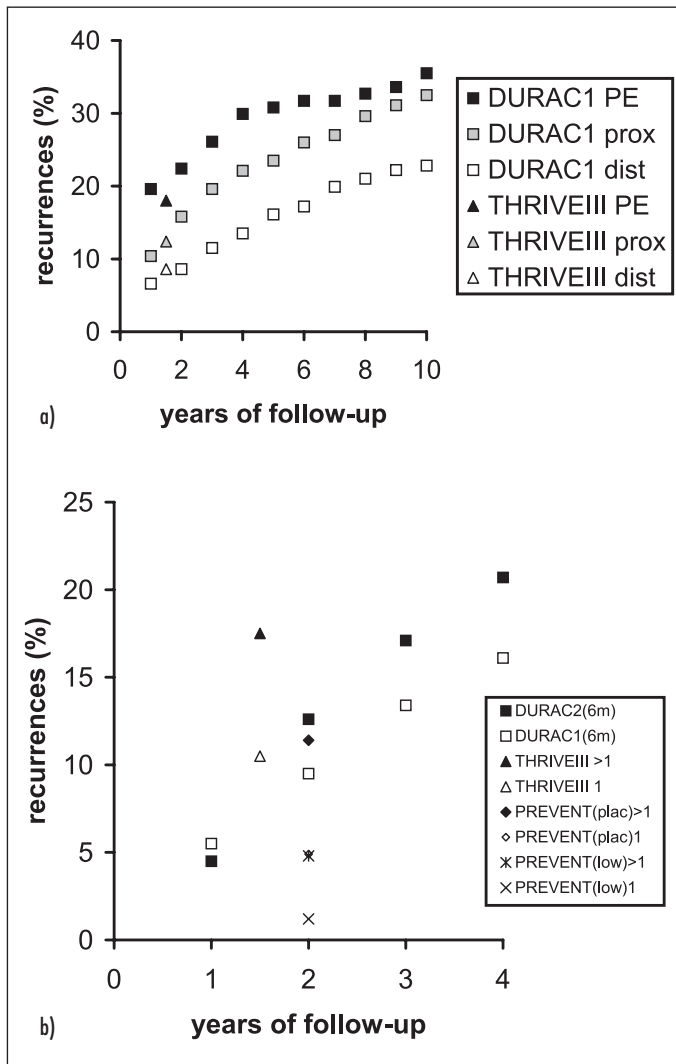


Fig. 1 Venous thromboembolism and the risk of recurrence **a)** effect of the location (3, 8) **b)** effect of multiple versus one previous event (8, 9, 15, 16): The results of the placebo arm and the low-intensity arm in the PREVENT study are shown separately-

excluded. Without exception these trials showed a higher risk of recurrence among those with unprovoked VTE, which in absolute terms amounts to 10% higher during the first two years.

Long-term follow-up demonstrates that this difference becomes more pronounced with time and in DURAC I after 10 years the cumulative rate of recurrence was 20.6% for provoked and 34.2% for unprovoked VTE (unpublished data). Multivariable analysis showed that unprovoked VTE is a strong and independent risk factor for recurrence (3). Several studies have consequently only recruited patients with unprovoked VTE and this subset poses the difficult question of limited or indefinite duration of secondary prophylaxis, as discussed below (see paragraph on D-dimers).

First or recurrent VTE

The DURAC II trial is so far the only one specifically recruiting patients with a second episode of VTE for comparison of two durations of anticoagulation: six months or indefinitely (14). After four years of follow-up 111 patients treated for six months had 23 recurrences compared to three recurrences among 116 patients still on therapy (RR 8.0, 95% CI 2.5–25.9) but at the cost of a trend to more major haemorrhages with extended duration (3 versus 10). In two trials the risk of recurrence was compared between subsets with one or more than one episodes of VTE. There was an increased risk of recurrence after multiple episodes both in the THRIVE III trial (7) and the PREVENT trial (15) (Fig. 1b).

In the DURAC studies patients with the first event with randomization to six months of anticoagulation (8) and patients with the second event with randomization to six months (14) were treated and followed according to identical protocols. A comparison over four years is therefore also presented in Figure 1b. There was a small but progressive difference in the recurrence rate to the disadvantage of patients with two previous events.

Additional support can be derived from a prospective cohort study of 1719 patients, where the hazard ratio for recurrence after multiple versus one event was 2.11 (95% CI 1.62–2.74) (16). Unfortunately, it is impossible to extract data from these trials to determine whether two events in the same leg is worse than one in each leg regarding the risk of recurrence. As mentioned, we do know that ipsilateral recurrence is detrimental for the development of PTS. From that perspective two events, one in each leg and one of them distal, may warrant shorter duration of anticoagulation than two in the same leg, and even more ominous is recurrent pulmonary embolism.

Failure of thrombus to resolve

Whereas the mentioned risk factors are apparent already at the time of diagnosis, residual thrombosis can only be identified during follow-up. The criteria for residual thrombosis are poorly defined and there are differences between studies regarding

- proportion of the vein area (20% or 40%, 2 or 3 mm),
- the number of compression points and
- the timing of the ultrasound examinations.

A few studies have demonstrated an association between residual DVT and recurrence with a hazard ratio of 2.1 ($p = 0.02$) (17) and 2.4 (95% CI 1.3–4.4) (18) and an OR of 5.6 ($p = 0.03$) for recurrence after three to six months (19). On the contrary, in a study with assessment of both residual DVT and D-dimer levels in 400 patients the hazard ratio for recurrence in case of residual DVT was 1.2 (95% CI: 0.72–2.07; $p > 0.05$) in multivariate analysis (20). Currently, the

simpler and less expensive use of fibrin D-dimers dominates over ultrasonography for assessment of the overall risk of recurrence.

Age and race

Both the rate of pulmonary embolism and of DVT increases with age (22). In a Swedish autopsy study the risk of pulmonary embol-

ism increased 22% with every decade of life (23). The risk of recurrence is also influenced by age, as demonstrated in population studies (17, 24), corresponding to 17% increase per decade (17).

In a meta-analysis of individual data from five RCTs the risk of recurrence increase up to age 70, but there was no significant change beyond that (10). However, in the PREVENT and THRIVE III trials no influence of age on recurrence was detected

(8, 16). This should be taken into account when the risk of bleeding is weighed in, as discussed later.

A higher annual incidence of VTE (25) has been described among

- Caucasians (23 per 100 000) and
- African-Americans (29 per 100 000) than among
- Hispanics (14 per 100 000) and
- Asian-Pacific Islanders (6 per 100 000).

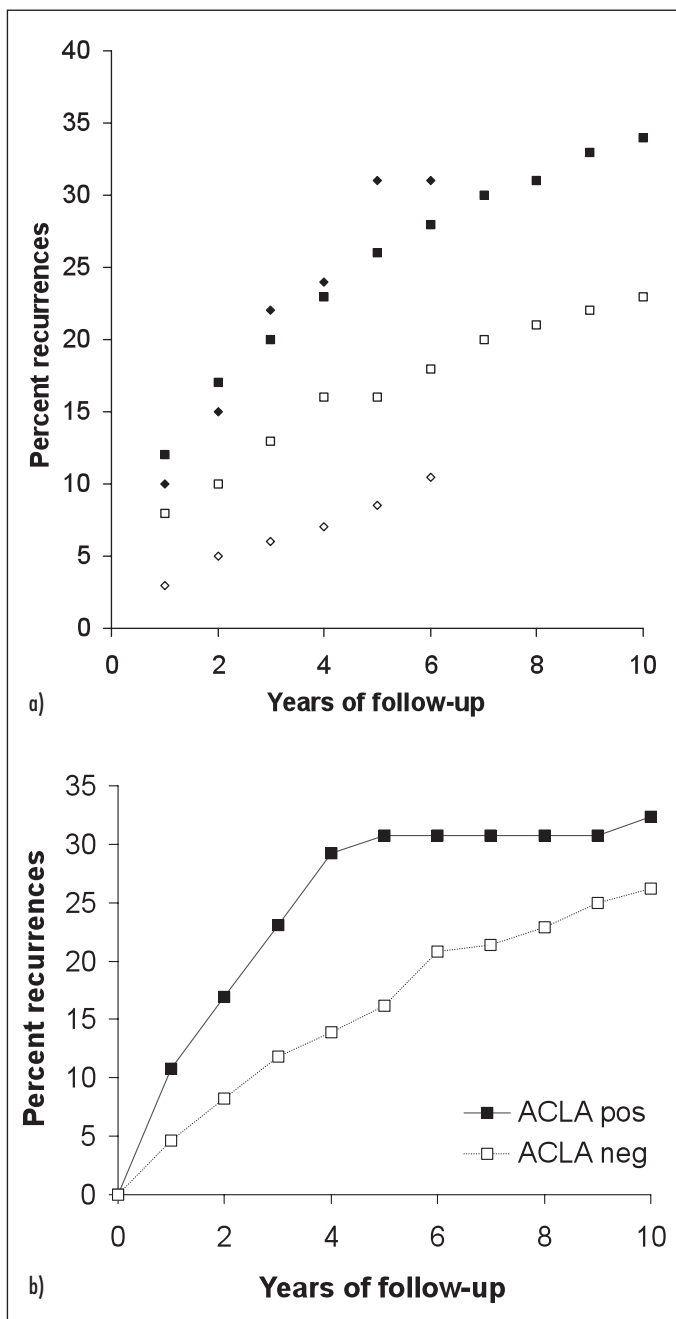
Pulmonary embolism seems to occur more often in African Americans than in Caucasians (22). In an autopsy study of 1200 cases pulmonary embolism was identified more often among Caucasians (15%) than in Japanese (7%) (26). On the other hand, when exposed to identical risk, i.e. major orthopedic surgery, the incidence of asymptomatic DVT appears to be similar in Asia and in North America (27–29).

Sex and body weight

The distribution of recurrences according to sex is almost invariably reported in studies, which allowed for a metaanalysis of 15 studies with 5416 patients (30). The relative risk of recurrence was higher for men than women both in RCTs (1.3, 95% CI 1.0–1.8) and in observational studies (2.1, 95% CI 1.5–2.9) with an overall RR of 1.6 (95% CI 1.2–2.0). This was independent of the VTE being unprovoked or provoked, location of thrombosis or number of events. The mechanism is unclear and requires further elucidation. The effect of male sex appears to be more pronounced with longer follow-up (Fig. 2a).

Obesity has been associated with an increased risk of pulmonary embolism in the Nurses' Health Study after adjustment for age (RR 3.2, 95% CI 1.7–6.0) (31) and also on autopsy investigation in women in the Framingham Heart Study (32) and in a Mayo Clinic cohort independent of hereditary thrombophilia (33). The effect of obesity seemed to be pronounced in surgical patients (34). Likewise, in patients with DVT obesity has been associated with an increased risk among medical outpatients (35, 36).

Obese individuals appear to have higher levels of factor VIII and factor IX but the



risk remained after adjustment for these factors, whereas obesity in combination with hormonal contraceptives generated a tenfold increase of risk among women with body mass index above 25 kg/m² (37).

The risk of recurrence was increased among obese patients in a population study (17) but not in the placebo group of the THRIVE III study (38).

Thrombophilic defects

The severe hereditary thrombophilic defects, **deficiency of antithrombin, protein C or protein S**, are rare and therefore difficult to study in a systematic way. Data is only available from retrospective family studies or case series. In a Dutch retrospective family study the rate of recurrence was 10% (95% CI 1–19) during the first year and by five years it had accumulated to 23% (95% CI 10–36) (39), which is not higher than in a general cohort of patients with VTE. This information is obviously not based on strong methodology and many cases of serious thromboembolic manifestations in such patients have been published. That, in turn, may be an effect of selection bias. It is, however, clear that VTE occurs at a comparatively young age in patients with these deficiencies (40).

The factor V Leiden (FVL, G1691A) and prothrombin (G20210A) polymorphisms are common, occurring in 2–several percent of the normal Caucasian population and have accordingly been studied extensively. The results regarding risk of recurrent VTE show significant discrepancy between studies. A metaanalysis of all available studies clarified the picture somewhat (41):

- Patients with FVL in the heterozygous form have an OR for recurrence of 1.41 (95% CI 1.14–1.75) based on 3104 cases.
- Those with the prothrombin polymorphism have an OR of 1.72 (95% CI 1.27–2.31) based on 2903 cases.

Although many studies ended with the conclusion that these defects in the heterozygous form confer a minimal incremental risk compared to the contribution from already having had a VTE event, this was

usually after a relatively short follow-up. In the DURAC I trial with follow-up for ten years the FVL in either the heterozygous or homozygous form emerged as an independent predictor of recurrence in multivariate analysis ($p = 0.03$ for both) (3). This was not seen with the prothrombin polymorphism, which is relatively rare in the Nordic population.

Patients who are double heterozygous for these defects appear to have a very high risk of recurrence, amounting to 65–100% after 6–7 years of follow-up in two studies, but the total number of patients was small.

Whereas the effect of FVL or prothrombin polymorphism in heterozygous form is relatively weak with an increased risk of 40–70%, the impact of high factor VIII (FVIII) levels is more profound. The cut-off is usually set at the 90th percentile, and FVIII levels above this limit are associated with more than doubling of the risk of recurrence in most studies. In the Leiden Thrombophilia Study it was initially reported that patients under 70 years of age with FVIII levels above the 75th percentile had an adjusted odds ratio of 4.8 (95% CI 2.3–10) (42) but in the extended follow-up, published ten years later, it had decreased to only 1.3 (95% CI 0.8–2.1).

Kyrle et al. reported a RR of 6.7 (95% CI 3.0–15) after a mean of 2.5 years (43) similar to the results of Legnani et al. in patients with unprovoked VTE, who had a RR of 6.2 (95% CI 1.6–24) with FVIII clotting method. Patients with provoked VTE had an overall low risk of recurrence, not influenced by high FVIII (RR 1.74, 95% CI 0.25–12) (44). The mechanism for elevated FVIII is in over 80% of those patients not related to inflammatory reaction and over a period of eight months no appreciable decrease occurred in 94% of those followed (45).

The **antiphospholipid syndrome** is more complex, since it is not defined by a single test. The diagnosis is supported by either a positive test for the lupus anticoagulant – in turn a composite of 2–3 clotting tests – or antibodies against cardiolipin or β_2 -glycoprotein I. Each one of the methods can be performed in many different ways and antibodies can be directed against different domains of β_2 -glycoprotein I. The coefficient of variation is large and the dis-

cussions continue about the appropriate definition of the syndrome. In addition, some studies recruited a mixture of patients with arterial and venous thromboembolic disease. It is therefore almost impossible to compare the results across studies.

Still, a metaanalysis was performed of seven case-control studies of patients with primary antiphospholipid syndrome and VTE (46). The controls were patients with the VTE diagnosis excluded (5 studies) or healthy (one study) or nested case-control (one study). The diagnosis was based on the lupus anticoagulant (4 studies) and/or cardiolipin antibodies (6 studies), but for the latter a variety of detection levels had been applied. The OR for first episode of VTE was for high titers of cardiolipin antibodies (above 98th percentile or 10 standard deviations) 3.21 (95% CI 1.1–9.3) and for lupus anticoagulant 11.1 (95% CI 3.6–48.5).

Increased risk of recurrent VTE was observed in the placebo group of the LAFIT trial with a RR of 3.5 (47). The diagnosis was based on cardiolipin antibodies and/or lupus anticoagulant and the follow-up was ten months. Likewise, in the six-months treatment group in the DURAC I trial with testing for cardiolipin antibodies IgG at the end of treatment and a follow-up of four years there was a twofold increase of the recurrence rate (48). Importantly, there was also a 2.5-fold higher mortality among the patients with the antiphospholipid syndrome, almost exclusively due to fatal arterial or venous thromboembolic events. However, after ten years a positive test for cardiolipin antibodies obtained at six months was not an independent risk factor for recurrence. Further analysis of the data reveals that beyond four years there were hardly any additional recurrences among the patients with these antibodies and the seronegative patients slowly caught up with them (Fig. 2b).

Hyperhomocysteinemia has become somewhat of a problem recently. Although levels above the 95th percentile are associated with an increased risk of VTE with OR 2.5–2.9 (49, 50) and also with increased risk of recurrence (19.% vs. 6.3% among those with lower levels) in one study (51) – but not in another (OR 0.9, 95% CI 0.5–1.6) (52), lowering of the level does not confer any clinical benefit.

It is not easy to summarize the data presented here on the different thrombophilic defects into a short recommendation. Extended – but not life-long anticoagulation may be appropriate for antiphospholipid syndrome and elevated FVIII, whereas for the hereditary thrombophilic defects the alternatives would be either as without the defect or for more severe or combined defects indefinite anticoagulation.

Tests for activation of coagulation

With an increasing number of identified polymorphisms that may affect the risk of VTE and recurrence, routine laboratory investigation becomes costly and calculation of risk turns complex. A global test of the activation of the coagulation system should include the

- effect of each individual defect and also
- adjust for protective polymorphic changes.

The fibrin D-dimer split product has been used successfully as a component in diagnostic strategies for suspected VTE. D-dimer becomes negative in approximately 85% of patients during anticoagulant treatment (53). After discontinuation of the vitamin K antagonist it reverts to positive in 40–46% of the patients during the following 1–3 months (53). This phenomenon is predictive of recurrence of VTE, particularly in case of initial unprovoked VTE (21, 54, 55). In patients with a positive D-dimer one month after discontinuation of anticoagulation the hazard ratio for recurrence with resumed anticoagulation versus no treatment is 0.18 (95% CI 0.05–0.63) (56). Patients with a negative D-dimer have an annual risk of recurrence of 4.4% and a few patients recur during the month anticoagulation is held. Furthermore, of the patients with a positive D-dimer (37% in this study) and randomized to no resumption of treatment, 13% had a recurrence during the following 11 months (56).

It is known that the risk of recurrence decreases after the first year and possibly these patients would have a cumulative risk of re-

currence of 40% over ten years. Thus, if a positive D-dimer would lead to a decision of indefinite anticoagulation, 60% of those or 22% of all patients would “in vain” remain on anticoagulation. This will of course be less of a burden when selective coagulation inhibitors without the need for monitoring will be approved.

There are other tests that also demonstrate activation of coagulation, such as thrombin generation and thromboelastography, but these are more laborious than D-dimer. Another simple test is the activated partial thromboplastin time (aPTT), which is slightly shortened in this situation (57). Yet another possibility is a test for the global function of the protein C pathway (58). D-dimer appears to have a higher negative predictive value (93.5%, 95% CI 92.4–94.5; pooled analysis of published studies) than the latter two tests (91.8%, 95% CI 89.8–93.6 and 90.1%, 95% CI 88.8–92.0, respectively).

Concomitant diseases

The most common disease identified in patients with VTE and with a strong association to thrombosis is **cancer**, to which about 18% of all VTE can be attributed (59). The effect is probably underestimated, since among patients with unprovoked VTE several will during the following years manifest a malignant disease, which may in its subclinical stage also have contributed to the thrombosis (60, 61). Presence of cancer is associated with approximately a threefold increase of the risk of recurrent VTE (62–64), and the relative risk increases with

- the stage of the cancer (64) and
- concomitant chemotherapy (17).

The recurrences often occur in spite of continued anticoagulation.

Systemic lupus erythematosus is associated with an increased risk of thrombosis in the context of secondary antiphospholipid syndrome. The nephrotic syndrome was associated with an incidence of thromboembolism of 33% during two years in a prospective study (65). The mechanism is renal loss of smaller proteins, including

the natural inhibitors antithrombin and protein C, whereas the larger FVIII and fibrinogen are retained and elevated by the inflammatory reaction. Although renal vein thrombosis is the most prominent thrombotic manifestation, pulmonary embolism is also common (66).

Paroxysmal nocturnal haematuria is a haematopoietic disorder with intravascular haemolysis and activation of the coagulation. Approximately 40% of the patients develop VTE with a high risk of recurrence, often with fatal outcome (67). These patients are often given primary, long-term anticoagulant prophylaxis.

Myeloproliferative disorders are well known to confer an increased risk of thrombosis, often in the splanchnic venous system. This has recently been linked to the Janus kinase (JAK2) V617F mutation, which is found in a large proportion of the patients, particularly those with polycythaemia vera and also in essential thrombocytaemia (68).

Inflammatory bowel disease is associated with a moderate increase in the risk of thrombosis, probably related to elevated levels of fibrinogen and plasminogen activator inhibitor type 1 (PAI-1), reduced levels of antithrombin and sometimes also presence of cardiophilin antibodies (69).

In **Cushing's syndrome** the degree of hormonal disturbance is associated with an elevation of FVIII, which may explain the increased incidence of VTE, particularly observed after surgery for adrenalectomy (70).

Risk of bleeding

In the counterbalance of all the risk factors discussed so far, the risk of bleeding always has to be taken into account. In most of the RCTs patients with a high risk of bleeding were excluded. In the cohort studies the bleeding risk is rarely defined, which is due to the lack of reliable quantification systems. Whereas objectively verified clinical thromboembolism is a fairly uniform concept, the definition of major bleeding varies considerably between studies. This may improve in the future if a recommendation

from the International Society on Thrombosis and Haemostasis is followed (71).

Comorbid conditions known to increase the risk of bleeding are sometimes the same as those increasing the risk of thrombosis, such as cancer (62–64) and ischaemic stroke. In addition,

- hypertension,
- renal insufficiency,
- serious heart disease,
- diabetes mellitus,
- hepatic disease,
- anaemia and
- recent peptic ulcer have

been associated with an increased risk of bleeding (72–74). The same is true for myocardial infarction and this may be related to the ubiquitous medication with antiaggregant drugs, mainly aspirin. With increasing age the risk of bleeding slowly escalates and more sharply so after the age of 70 (10).

Although the presence of risk factors for bleeding should prompt a consideration of shortening the duration of anticoagulation, this is most important in the early phase of treatment. The risk of bleeding decreases quite dramatically with duration of anticoagulation during the first year and a half (10). Thus, if the patient has managed the first year well and has strong risk factors for recurrent VTE, the bleeding risk factors should not result in anything else than continued good supervision and annual re-assessment.

Reduction of the intensity of anticoagulation to International Normalized Ratio (INR) of 1.5–2.0 did disappointingly not lead to a reduction of haemorrhages compared to the conventional INR range of 2.0–3.0 (75). New anticoagulant drugs may have a better bleeding risk profile since the effect is more predictable than vitamin K antagonists, due to virtual elimination of interactions with other drugs and food.

Patient preferences

Last but not least, the discussion regarding appropriate duration of anticoagulation should always involve the patient or its caretaker. Poor compliance, highly variable INR

results or an adamant request from the patient to discontinue anticoagulation due to the burden of monitoring or fear of bleeding have to be considered. Conversely, some patients express a definite fear of recurrences, commonly after a previous large pulmonary embolism. Risks in both directions should be explained to the patient and, whenever possible, quantified in simple terms.

The decision to continue or to stop anticoagulation will in a certain proportion of patients turn out to be unfortunate, but if the patient understood and agreed to the strategy, which has to be documented, then the relation between the patient and physician is likely to remain good and continued care will be facilitated.

For some patients a definite decision on the duration of anticoagulation can be taken already at the start of treatment. This is the case particularly for those with a very low risk of recurrence (distal provoked DVT) or an extremely high risk (multiple events, life-threatening event with thrombophilic defect). For most of the patients it is necessary to review the risk factors after several months, and in case of continued anticoagulation then annually. At each of these visits the risk of recurrence and of bleeding are weighed against each other. Indefinite anticoagulation has not been shown to reduce mortality in any study. Discontinuation of treatment after six months is associated with a risk of recurrence, which for unprovoked VTE is about 10% during the first year. But that is the case also if the treatment is discontinued after 12 or 24 months. The support from a D-dimer test may be helpful, particularly when the balance of risk factors is fairly even. Published guidelines also offer some support but are often too general and individual assessment of risks and preferences is therefore the safest way to success.

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