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1 The Lancet. Predicting the failure of 3 by S. Lancet 2005; 365: 1597.

Deep vein thrombosis

Some of Paul Kyrie and Sabine Eichinger’s recommendations about long-term prevention of recurrent venous thromboembolism (Mar 26, p 1163)1 do not seem to be consistent with the results of randomised trials.

First, they recommend stopping anticoagulant therapy for unprovoked (spontaneous) proximal deep vein thrombosis after 3 or 6 months, even though the two trials that compared this practice with continuing warfarin treatment were stopped early because of overall superiority of long-term therapy.2,3

Second, for those who are treated with long-term warfarin, they suggest that there may be a lower risk of bleeding with low-intensity warfarin (international normalised ratio [INR] 1.5–2.0) than with conventional-intensity warfarin (INR 2.0–3.0), which would be sufficient to offset the demonstrated lower efficacy of low-intensity therapy.4 However, in the only study that compared low-intensity and conventional-intensity warfarin for long-term treatment of venous thromboembolism, there was no evidence of a reduction in major bleeding with low-intensity therapy (0.9 per 100 patient-years with conventional-intensity and 1.1 per 100 patient-years with low-intensity; difference 0.2 per 100 patient-years, 95% CI 0.0 to 0.4).4

Kyrie and Eichinger suggest that less success in keeping patients’ INR values in the target range in clinical practice than in clinical trials is likely to favour the use of low-intensity therapy because of a lower likelihood of bleeding. However, a higher proportion of INR values outside the target range, half of which are expected to be below an INR of 1.5, is expected to further reduce the efficacy of low-intensity anticoagulant therapy.1 Since rates of the composite outcome of recurrent venous thromboembolism, episodes of major bleeding, and death were lower with conventional-intensity warfarin than with low-intensity warfarin in the randomised trial that compared these treatments (figure), it is unlikely that low-intensity is the preferred option for long-term warfarin therapy.

A first episode of unprovoked proximal deep vein thrombosis or pulmonary embolism identifies patients as having a substantial risk of recurrent venous thromboembolism after anticoagulant therapy is stopped.5 Although high individual risk of bleeding or a patient’s preference supports time-limited treatment for many such patients, current evidence from randomised trials favours long-term anticoagulant therapy in the majority of this group. Since these trials were done in Canada and the USA, and because the risks and benefits of long-term anticoagulant therapy could differ by location, there is greater confidence that the results of these trials are generalisable to clinical practice in North America than elsewhere. Clinical or laboratory factors that identify subgroups of patients with unprovoked proximal deep vein thrombosis or pulmonary embolism who have a low enough risk of recurrent venous thromboembolism to not warrant long-term anticoagulant therapy would be welcome.

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In their comprehensive Seminar on deep vein thrombosis,1 Paul Kyrie and Sabine Eichinger do not mention ABO blood group among the conditions associated with the risk of developing such a disease.

The association between ABO blood type and venous thromboembolism was first described in 1969 by Jick and colleagues. Since then, many studies have shown a particular and unbalanced distribution of blood groups in patients with venous thromboembolism. In 1998, Wautrecht and colleagues2 compared 367 patients with deep vein thrombosis with healthy controls and showed that the distribution of ABO blood groups was significantly different (p<0.001): patients were more frequently of blood group B (16.1% vs 8.3%) or AB (6.5% vs 3.4%) and less frequently of blood group O (29.4% vs 46.1%) than were controls.

Several studies have found a relation between phenotypic expression of
ABO blood group and concentrations of factor VIII and von Willebrand factor in plasma: blood group O individuals had significantly (about 25%) lower concentrations of both glycoproteins. More recently, an ABO genotyping study in 250 patients confirmed all these data and showed that individuals carrying the A1 allele had a significantly higher risk of developing venous thrombosis. Regarding pathogenesis, although the main hypothesis relies on a presumed direct functional genesis, the real mechanistic implication of non-O blood group in the genesis of deep vein thrombosis is not known yet. Further studies are warranted to clarify this strong association.

Nonetheless, all these results indicate that ABO phenotyping and genotyping analyses may be valuable components in assessing future diagnostic thrombophilic risk profile and might have implications in the policy of thrombosis prophylaxis and treatment.

A second point which, in my opinion, needs to be discussed concerns the Seminar’s section on high clotting factor concentrations. Kyrie and Eichinger state that “a raised concentration of factor VIII, IX, or factor X is an independent risk factor of first spontaneous deep vein thrombosis... Whether high clotting factor concentrations are related to a genetic background is unknown”. The latter statement has now been challenged by the findings of Berger and colleagues. They studied, by means of a genome-wide linkage analysis, 13 families of patients with venous thrombosis and reproducibly elevated factor VIII concentrations. Given the high genetic complexity of factor VIII trait, Berger and colleagues did a parametric exploratory linkage analysis of factor VIII, taking an imprinting effect into account. This technique, called MOD-score analysis (which represents an extension to linkage analysis for genetically complex traits), gave evidence for linkage under a paternal imprinting model at chromosomes 5 and 11. This finding strongly suggests that high factor VIII concentrations in venous thromboembolism represent a complex trait caused by several inherited genetic factors.

We declare that we have no conflict of interest.

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Authors’ reply

Clive Kearon and colleagues raise the issue of long-term vitamin K antagonist therapy for patients with first unprovoked deep vein thrombosis. They refer to two clinical studies that were prematurely terminated because of superiority of extended anticoagulation. The trial by Kearon and colleagues was stopped because of the very high risk of recurrence among patients allocated to 3 months of warfarin use. However, in two subsequent studies in France and Italy, the recurrence risk among patients treated with comparable 3-month protocols was substantially lower. In the study by Ridker and colleagues, all patients received 6 months of conventional-intensity warfarin and were then randomised to low-intensity (rather than conventional-intensity) warfarin or placebo. The findings by Kearon and colleagues and Ridker and colleagues are thus not convincing enough to support a recommendation for long-term conventional-intensity anticoagulation to all patients with a first spontaneous proximal deep vein thrombosis.

From experience, findings obtained under well defined clinical trial conditions cannot always be reproduced in routine clinical practice. The rate of bleeding associated with anticoagulation is one good example. In the second of Kearon and colleagues’ cited studies, in which they compared conventional-intensity with low-intensity warfarin, the annual major haemorrhage rate among patients randomised to conventional-intensity warfarin was substantially lower than that of comparable trials, but also of studies that investigated the risk of bleeding in usual medical care. One explanation for these differences might be the fact that Kearon and colleagues’ study excluded patients with a high bleeding risk.

We agree with Kearon and colleagues that a composite outcome of recurrence and bleeding is of importance to assess the value of an anticoagulant treatment strategy. However, the recommendation for conventional-intensity warfarin as the preferred option for long-term secondary thromboprophylaxis on the basis of a single study with a very low bleeding rate seems premature. We rather support the better definition of subgroups of patients in whom the risk of recurrent venous thromboembolism is high enough to outweigh the risk of anticoagulation-associated bleeding.

ABO blood group has indeed been repeatedly implicated as a risk factor for deep vein thrombosis. In a large case control study (Leiden Thrombophilia study) in which the role of ABO blood group, von Willebrand factor, and factor VIII was investigated, only high factor VIII conferred an increased risk of deep vein thrombosis in the multivariate analysis. The authors surmised that blood group and von Willebrand factor are