Venous thrombosis is a fairly common disorder that manifests mainly as deep vein thrombosis of the leg or pulmonary embolism. It affects 1 in 1000 individuals annually and has a substantial mortality rate. Its causes are both genetic (prothrombotic abnormalities sometimes referred to as a group as thrombophilia) and acquired. Among the latter are cancer, female hormone use, and all forms of prolonged immobility (surgery, trauma, plaster casts, medical diseases). Venous thrombosis has a high recurrence rate of several percent per year; hence, efforts to reduce this risk are in order. A targeted approach is to use antithrombotic prophylaxis liberally during transient circumstances of increased risk. However, because a substantial number of recurrent events occur without a clear provoking factor, this approach will prevent only a fraction of all recurrent events. There is little doubt that indefinite treatment with anticoagulants will reduce the risk of recurrence, but it will be at the price of an increased number of major, debilitating, and in some cases fatal hemorrhages. Given that current treatment with anticoagulants still carries an annual risk of major hemorrhage of 1% to 2%, indiscriminate indefinite treatment of every patient with a first thrombosis is clearly not in order. The challenge therefore is to identify those patients who are at an elevated risk of recurrence and investigate the potential benefit of prolonged or indeterminate anticoagulant prophylaxis in these patients. One group that is a candidate for such an approach is made up of patients with nontransient risk factors for thrombosis (ie, thrombophilia).

One would think that in this era of evidence-based medicine such a risky strategy would be recommended only in light of clear evidence pointing to the benefits outweighing the evidence. Quite surprisingly, indeterminately prolonged anticoagulant treatment is often prescribed not only in the absence of any evidence but in the presence of evidence pointing in the opposite direction. What would studies look like that would convince us that in a particular circumstance anticoagulation would be beneficial? They would ideally be randomized trials of patients with a certain condition, contrasting those with and without anticoagulation. Outcomes would be thrombosis and hemorrhage, and the prevention of thrombosis would need to outweigh the excess of hemorrhage with treatment; hence, these studies would need to be large to be powerful enough to allow meaningful comparisons. This is the typical method by which the benefit of anticoagulation has been studied in patients at high risk of a first event, although it is arguably often underpowered to study hemorrhagic risk.

There are no such studies on the benefit of long-term anticoagulation after a first event in patients with genetic prothrombotic abnormalities. Such trials would be logistically difficult because, to include sufficient numbers of patients with a particular defect, thousands if not tens of thousands of patients would need to be tested for prothrombotic abnormalities before randomization between normal care and prolonged anticoagulation. Moreover, to study the balance between benefit and risk over the long term, the study would need to run for 5 to 10 years. Although this seems the only way to demonstrate convincingly that long-term treatment is beneficial, there is a simpler approach possible to demonstrate its futility. Only if patients with thrombophilia have a higher recurrence rate than patients without thrombophilia could a strategy targeted at these patients be of potential interest. If their recurrence rate is not elevated, there is no sense in treating these patients differently or, for that matter, in establishing the presence of thrombophilia.

Several studies have suggested that deficiencies of antithrombin, protein C, and protein S, which are the rarest prothrombotic abnormalities but also the strongest with respect to the risk of a first thrombosis, lead to a mildly elevated risk of recurrent thrombosis compared with patients with a first event without these defects. In a large collaborative study, the European Prospective Cohort on Thrombophilia (EPCOT), an annual recurrence rate of 5% was observed. This number is based on individuals from families that were thrombosis prone and therefore does not necessarily apply to patients with thrombosis who do not have a positive family history. In fact, there is evidence that the thrombosis risks in thrombophilic families are higher than in patients who are not part of such families, regardless of the prothrombotic defect. This is likely so because thrombophilic families harbor several known and unknown genetic defects. Follow-up studies of unselected patients with venous thrombosis showed at most a mildly increased risk of venous thrombosis for those with deficiencies of natural anticoagulants, with relative risk estimates between 1.5 and 1.8, compared with patients without these defects. For factor V Leiden and prothrombin 20210A carriers, the literature is fairly consistent in reporting an absence of an excess risk of recurrence for heterozygous carriers. This implies that testing for these common variants after a first event has no clinical utility. One hypothetical exception to this conclusion would be if ho-
mozygous or double heterozygous carriers of factor V Leiden and prothrombin 20210A mutation had an elevated risk of recurrence, particularly because it is known that these combined defects yield a high risk of a first thrombotic event.\textsuperscript{16}

This was the subject of the study by Lijfering et al\textsuperscript{17} published in this issue of \textit{Circulation}. In a large family study of venous thrombosis, they performed a nested case-control study in which they contrasted those who had suffered recurrent thrombosis (cases) to those with only 1 thrombotic event (controls). As always in case-control studies, the reasoning is that if a factor, in this case the presence of double heterozygous or homozygous factor V Leiden or prothrombin 20210A mutation, has no effect on the outcome of interest, in this case recurrence, it would be equally prevalent among cases and controls. In contrast, a factor that increases the risk of recurrence will be found more often among those with than those without recurrent disease. Among 788 evaluable patients, 325 had recurrent thrombosis and 463 had only 1 thrombosis. Among the patients with recurrent thrombosis, 9.8\% (32 of 325) were homozygous or double heterozygous for factor V Leiden or prothrombin 20210A; this number was 9.5\% (44 of 463) among those with only 1 event. So, there was no excess risk of recurrence in those with 2 defects, which remained the case in analyses that took age, sex, anticoagulant treatment time, clustering in families, and duration of follow-up into account. Interestingly, a 2.8-fold increased risk of recurrent thrombosis was found for individuals with deficiencies of antithrombin, protein C, or protein S.

Although previous studies have looked into this same matter, they were small and yielded contradictory results. With 76 individuals with combined defects, the study by Lijfering et al yields a reliable risk estimate, and its size is its greatest strength. Most of the first events occurred several years to decades ago, which on the one hand may have introduced some bias toward the null because of misdiagnoses but on the other hand has the advantage of avoiding preferential inclusion of individuals with combined defects, because they were not known at the time. Still, it would have been interesting to see which patients had been tested and whether this had affected treatment. As in most case-control studies, the analysis was restricted to patients surviving their events. In theory, double heterozygous or homozygous factor V Leiden or prothrombin 20210A mutation could lead to an excess of fatal recurrent thrombosis, which could not have been detected by this study design.

The implications from this study follow from the observation that double heterozygous or homozygous carriers of factor V Leiden or prothrombin 20210A do not have a higher risk of recurrent venous thrombosis than patients who are heterozygous for these mutations or do not carry them. If there is no excess risk, there is no reason to treat these patients any differently with regard to the duration of anticoagulant treatment, and therefore there is no rationale for testing patients with a first thrombosis for factor V Leiden or prothrombin mutation. Is it possible that the observed null result was the effect of testing and subsequent increased care? First, as stated above, this is unlikely to have occurred in the Lijfering et al study by virtue of its being retrospective. Second, there is empirical evidence suggesting otherwise: If such an effect was present, tested patients would have a lower overall recurrence risk than nontested patients. This was investigated in another study that also used the case-control design of contrasting patients with recurrent disease with those with only 1 thrombotic event. If testing for thrombophilia reduced the risk of recurrence, patients with recurrence would have been tested less often than those with only 1 event. Among 197 patients with recurrent thrombosis, 35\% had been tested for thrombophilic defects compared with 30\% of 324 patients without recurrence who originated from the same prospective cohort (odds ratio, 1.2; 95\% confidence interval, 0.9 to 1.8).\textsuperscript{18}

It does seem counterintuitive that genetic factors that clearly affect the risk of first events do not or hardly increase the rate of recurrence; it may well be that for this reason (intuition) testing for thrombophilia will continue despite these findings. One explanation is that thrombosis always results from an interplay of several risk factors, both genetic and acquired, leading the “thrombosis potential” to cross a threshold.\textsuperscript{2} Those who develop thrombosis in the presence of a strong transient acquired risk factor have a low recurrence risk because this factor will not be present afterward (eg, surgery).\textsuperscript{12} Those who develop thrombosis in the absence of a transient risk factor apparently have a high thrombosis potential as a result of their genetic makeup, of which we can still measure only a small fraction. It is likely that those who do not have any of the known genetic risk factors carry as-yet unknown factors, so the recurrence risk is not different for those with or without known prothrombotic defects. Possibly, once we know more prothrombotic factors, particularly the ones that are common, this will change. For now, research should focus on acquired factors because they may be more amenable to removal or treatment than genetic factors.

\textbf{Acknowledgments}

This commentary is a tribute to Jan van der Meer, the senior author of the article on thrombophilia in this issue. Jan van der Meer, Professor of Hematology at the University Medical Center in Groningen, died at 58 years of age in 2009 after a short illness. After early work on coronary artery bypass grafting, he was very active in family studies on venous thrombosis and participated in many trials on venous thrombosis treatment. Jan was an empathic physician, an original thinker, and an inspiring supervisor for his students and fellows who is sorely missed.

\textbf{Disclosures}

None.

\textbf{References}


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