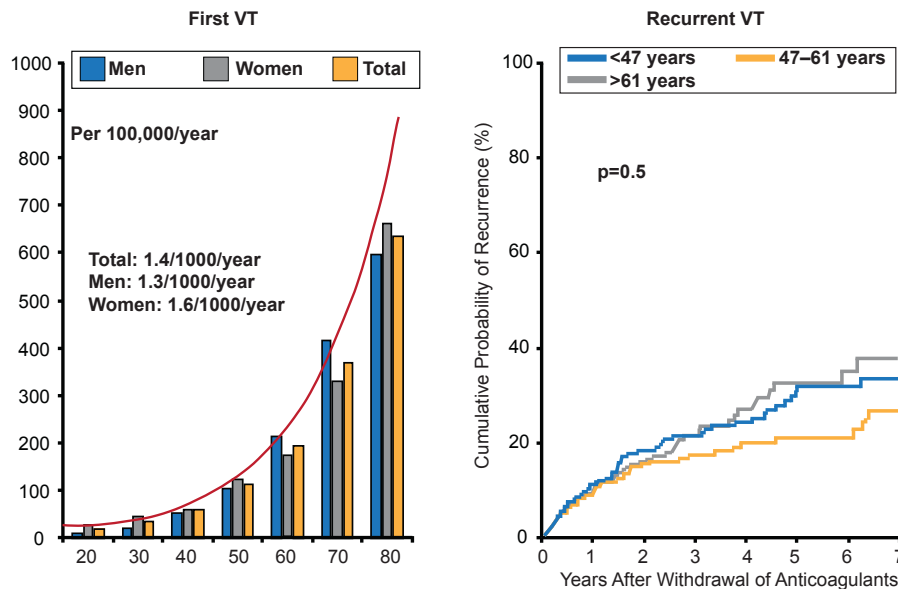# Recurrent Venous Thrombosis

Written by **Maria Vinall**

The risk of recurrent venous thrombosis (VT) is higher than for a first event, thus prevention is even more relevant. Suzanne Cannegieter, MD, Leiden University Medical Center, Leiden, The Netherlands, discussed paradoxes and the risk factors for recurrent VT including thrombophilia, clinical presentation with primary deep vein thrombosis (DVT), shorter duration of anticoagulation, and increasing age [Prandoni P et al. *Haematologica* 2007].

Important concepts in the prevention of recurrent VT include the recognition that the causes of VT differ between individuals, there are different types of risk factors, and the risk profile for recurrence is different from that of a first event. The thrombosis potential model developed by Rosendaal [*Lancet* 1999] can be used to indentify high-risk groups, different types of risk factors, and why certain individuals develop thrombosis at specific points in time.

Paradoxically, although thrombophilia is a significant predictor of a first thrombotic event, it is not a predictor of recurrent events. Thus testing for heritable thrombophilia or prothrombotic defects does not add any strategic information for prevention of a recurrent venous thromboembolism (VTE). Patients whose initial thrombotic event is idiopathic have a higher risk of a second thrombotic event than patients whose initial event is provoked (HR, 1.9; 95% CI, 1.2 to 2.9) [Christiansen SC et al. *JAMA* 2005]. Clinical risk factors, on the other hand, do predict the risk of recurrence in that patients with postoperative VTE have a very low rate of recurrence [Baglin T et al. *Lancet* 2003].

Although the incidence rates of first VT increase exponentially with age, and are slightly higher in women than in men, [Naess IA et al. *J Thromb Haemost* 2007] age does not play a role in recurrent VT (Figure 1) [Eischer L et al. *Medicine (Baltimore)* 2009; Flinterman LE et al. In preparation].

Figure 1. Effect of Age on Recurrent VT

Unlike first events, in which the differences between men and women are small, the incidence of recurrence is significantly (p<0.001) higher in men [Kyrle PA et al. *N Engl J Med* 2004] who seem to have a 50% higher risk of recurrent VTE after stopping anticoagulant treatment versus women [McRae S et al. *Lancet* 2006].
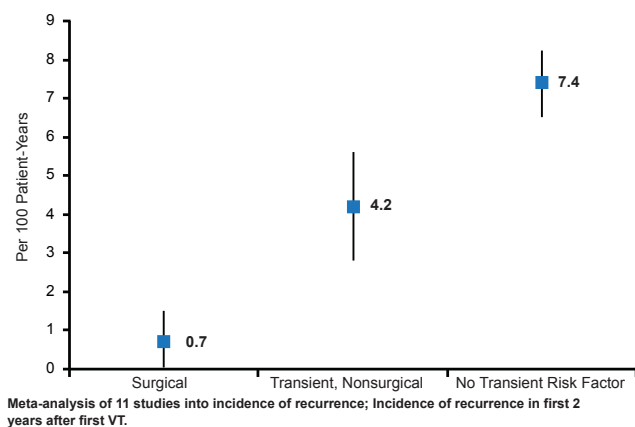
TYPES OF RISK FACTORS

Different transient risk factors can identify which patients should undergo short-term versus indefinite treatment. In general, recurrent risk is low when a transient risk factor was present at the first event. The risk reduction is related to the strength of the transient risk factor. For example, surgery is a strong risk factor for VT, but the risk of recurrence is low if VTE was provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked (Figure 2) [Iorio A et al. *Arch Intern Med* 2010].

Figure 2. Transient Risk Factors

Meta-analysis of 11 studies into incidence of recurrence; Incidence of recurrence in first 2 years after first VT.

Adapted from Iorio A et al. *Arch Intern Med* 2010;170(19):1710.

Although they remain causes of recurrence, fixed risk factors (age, genetic thrombophilia) play no role in predicting subsequent recurrence once the thrombotic threshold is reached.

Progressive risk factors such as cancer malignancy [Prandoni P et al. *Blood* 2002], inflammatory bowel disease [Novacek G et al. *Gastroenterology* 2010], and increasing BMI [Eichinger S et al. *Arch Intern Med* 2008] do appear to be connected to recurrent VT and the amount of risk is associated with the strength of the risk.

New transient risk factors after a first event including hormone use, pregnancy, surgery, plaster cast, and air travel can increase the risk of VT recurrence 4- to 25-fold [Christiansen SC et al. *J Thromb Haemost* 2010]. If possible, exposure to these risk factors after a first event should be avoided, and if this is not possible, thromboprophylaxis is warranted.

Markers of the thrombogenic process (D-dimer, high levels of FVIII, thrombin generation levels, residual thrombois, and proximal or distal first event) may not be true causes but are good predictors of a low risk recurrence.

With respect to prevention, patients who have strong transient risk factors at the time of their first event are at low risk, while patients exposed to new transient risk factors are at higher risk of a second VT. Patients who are exposed at

the time of their first event to progressive risk factors are at high risk of a second VT, while in patients in whom none of the above risk factors were present at the time of their first event and who have only fixed risk factors, efforts must be made to distinquish higher from lower risk by means of a highly-detailed risk profile.

VTE is a common and chronic disease with a considerable risk of recurrence. Patients with acute unprovoked (idiopathic) deep vein thrombosis (DVT) or pulmonary embolism (PE) have a higher risk of VTE than patients with secondary thrombosis. Walter Ageno, MD, University of Insubria, Varese, Italy, discussed the optimal treatment duration to avoid VTE recurrence and risk stratification models to predict risk or recurrent VTE [Prandoni P et al. *Haematologica* 2007].

The risk of recurrent VTE is low (0.7% per patient year) if provoked by surgery, intermediate (4.2%) if provoked by a nonsurgical risk factor, and high (7.4%) if unprovoked. The risks for unprovoked VTE are common among middle-aged patients, in men in general, and in patients presenting with DVT [Prandoni P et al. *Haematologica* 2007; Ageno W et al. *Intern Emerg Med* 2011]. The risk effect can be used to determine whether patients should undergo short or indefinite treatment [Iorio A et al. *Arch intern Med.* 2010]. Patients are usually protected from recurrent VTE while on anticoagulation therapy, but the risk increases when therapy is stopped. For low-risk patients, 3 months of treatment is usually sufficient, while longer treatment durations do not appear to improve protection (1.5 months vs longer durations: HR, 1.52; 95% CI, 1.14 to 2.02; 3 months vs longer duration: HR, 1.19; 95% CI, 0.86 to 1.65) [Boutitie F et al. *BMJ* 2011].

Patients with unprovoked VTE, active cancer, or previous VTE have a risk of recurrence as high as 30% within 5 years after cessation of anticoagulation and a high case-fatality rate. Thus, 3 months of treatment may not be enough for these patients and indefinite anticoagulation treatment should be considered.

However, anticoagulation confers a considerable risk of bleeding and clinicians need to identify those patients who will not benefit from indefinite anticoagulation [Linkins LA et al. *Ann Intern Med* 2003]. Risk can vary depending on other factors such as age, presence of previous bleeding, cancer, renal failure, diabetes, and recent surgery.

Besides alternative treatment strategies (rivaroxaban, dabigatran, apixaban) to improve safety, clinicians are working to develop risk assessment tools. Tools that take into consideration concurrent clinical characteristics, location of first event, gender, obesity, positive D-dimer, residual vein obstruction, post-thrombotic syndrome, and thrombophilia have been shown to have predictive possibility. Risk stratification models to identify intermediate risk patients who can safely discontinue treatment at 3 months and bleeding risk assessment tools are also needed.