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Full Length Article

Theme 2: Epidemiology, Biomarkers, and Imaging of Venous Thromboembolism (and postthrombotic syndrome)

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1. Background

Venous thromboembolism (VTE), the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major contributor to the global burden of disease. VTE is the third most common cardiovascular disease after myocardial infarction and stroke, which all together contribute to one in every four deaths worldwide. The estimated mean incidence of VTE is 1–2 per 1000 persons per year [1], which increases with age. 35% of the patients develop a PE and 6% of the VTEs are fatal in the acute phase and 20% after one year. Patients with PE have an almost two-fold higher 30-day case-fatality rate (~10%) compared to those with a DVT (~5%). This fatality rate increases even further for patients with underlying cancer (~20%). VTE is treated and prevented with anticoagulant therapy. However, surviving patients may suffer from post-thrombotic syndrome within the first year (25%), develop a recurrent VTE (3-5% per year), or have major bleeding due to anticoagulant therapy (1-3% per year).

Prevention of a first or second event, and of post-thrombotic syndrome, is key to reduce the morbidity and mortality associated with VTE. Results from epidemiologic, genetic, and other studies need to be used to develop (clinical) prediction models, which are essential for adequate medical management.

2. Past Achievements and Current Shortcomings

In the past decades, numerous studies have identified dozens of genetic and acquired risk factors for a first event. Among the strongest environmental risk factors are major surgery, pregnancy and puerperium, cast immobilization and cancer. From genetic studies several mutations and polymorphisms have been identified, such as factor V Leiden, deficiencies in the anticoagulant proteins C and S and antithrombin, and SNPs, such as in the fibrinogen gene. When a triggering event was present shortly before the VTE occurred, such as surgery, long-haul travel or pregnancy, we call the VTE event provoked. In still about a third of all first VTE cases, no such trigger was present and hence these events are called unprovoked or idiopathic. The risk of recurrence is strongly dependent on the type of the first event: in the 12 months after stopping anticoagulants therapy the recurrence risk was very low (less than 1%) in patients who had their first event after surgery while it was 7.4% in patients with a first unprovoked event [2].

Remarkably, the risk profile for recurrent VTE is different from that for a first event: for a first VTE, age is the strongest risk factor. Sex is not clearly related to the risk of a first event, while thrombophilia clearly is. In contrast, recurrence risk is hardly influenced by age and men have a 2-3-fold higher risk than women. Thrombophilia has little or no effect on recurrence risk. Therefore, risk factors for a first event cannot be used to predict the risk of a second event. Other types of factors, such as biomarkers or results from imaging modalities (that are not causally related to the development of a recurrent thrombosis) may be more useful to determine recurrence risk.

VTE can be effectively prevented with anticoagulants, but as a side effect (fatal) bleedings often occur which severely limits their potential, in particular in the prevention of a recurrent event. The annual risk of major bleeding during treatment with vitamin K antagonists is 2-4%, with an intracranial bleeding rate of 0.6% per year and a case fatality rate associated with major bleeding of 13% [3]. It is therefore essential that patients at high risk of recurrent VTE are distinguished from those at low risk, so that the latter do not necessarily have to be exposed to the risks of this therapy, which they may need to take for the rest of

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these patients' lives. Currently, three prediction models for recurrence exist that all consist of only a few factors, some of which are not good predictors (such as age).

3. Proposal

In order to improve risk estimation for first and recurrent VTE, we propose to focus future research on the five topics listed below in the next five years. The central approach is to integrate epidemiological studies with results of laboratory studies into biomarkers, genetics, and imaging studies to develop novel, comprehensive, and better risk assessment models for identifying patients at risk of VTE.

3.1. Epidemiology

How can epidemiology contribute to better care in patients with or at risk for VTE and reduce their burden of disease? Epidemiology– according to the WHO definition – is the study of the distribution and determinants of health-related states or events and the application of this study to control or prevent these. In an ideal world, the resulting knowledge would enable us not only to accurately predict who will develop VTE, but also to select the best management for every patient in terms of reduction of complications and long-term morbidity and mortality. Obviously, this aim has not been met. Despite a large number of risk factors identified [4], there is still a large uncertainty with regard to prediction of VTE.

Because only 1–2 persons per 1000 per year [5] will develop a *first* VTE, prediction plays a major role in management and prophylactic anticoagulant treatment must be limited to particular subgroups. With the identification of risk factors for a first VTE, high-risk groups can be identified for primary prevention. Examples are orthopedic surgery [4] or hospitalized patients with cancer [6]. A second focus of research is identification of predictors for a *recurrent* VTE. As stated above, these are not necessarily the same factors as for a first event, as illustrated by the example of the higher recurrence risk in men [7]. About 20 to 25 percent of patients with a first VTE will develop a recurrent event within five years [8]. Identification of predictors of recurrence might select subgroups of patients that benefit from more intense treatments. A good example is an unprovoked VTE [9].

What are the reasons for these gaps in knowledge with respect to identification of high risk groups? First, even though dozens of risk factors are currently known, we can still not find a cause in about a third of all patients with VTE, indicating that several other causal factors must exist that we are not aware of. Second, even though a large number of risk factors are identified, only few of them are strong enough to be of value in clinical practice [8]. Thus, the predictive accuracy of current prediction models is at most, only moderate [10]. If used in clinical practice, these models expose a high number of patients at risk for recurrent VTE or bleeding complications respectively, so a finer discriminative power is needed. Third, VTE in different settings probably represents completely different pathophysiologies rather than variations within one entity (e.g. VTE in cancer patients most likely has a different underlying mechanism than VTE in healthy long-haul travelers or in pregnant women) [11,12]. This is not only suggested by epidemiological data but also by many laboratory studies. Fourth, all VTE manifestations are generally taken together in studies (e.g. PE vs. DVT, distal vs. proximal DVT) while evidence suggests that these are not random variations of the same disease. Fifth, not all prediction models are feasible for use in clinical practice. Not all single polynucleotide polymorphisms identified are available for testing in routine laboratories. Complicated risk models incorporating many variables have higher predictive value [13], but may be difficult to use in routine clinical practice. In addition, even these complicated models explain only about one third of VTE recurrence.

How can we overcome these problems and properly identify patients at high risk of first or recurrent VTE? First of all, we need to identify more risk factors for VTE. Not only will this help to better understand its etiology, it will also be of clinical use, as in that case, more otherwise 'idiopathic events' can be changed into 'provoked events', which will reduce the duration of anticoagulant treatment. Furthermore, more knowledge is needed on the differences in pathophysiology of VTE in different situations such as VTE that occurs after prolonged exposure to hypoxia (long-haul air travel), after surgery (tissue damage), hormonal changes (oral contraceptive use and pregnancy), or during cancer. Lastly, researchers should investigate risk factors for first or recurrent VTE in particular settings and develop prediction models for these specific settings. An example of this method is the Khorana score for cancer patients [14]. Another approach to better prediction of VTE is to combine comprehensive prediction models with many factors with easy-to-use online calculators [10,13], which may facilitate more comprehensive models with a higher predictive accuracy.

To date, prediction of (recurrent) VTE in individual patients is difficult. Efforts on a broad scale are necessary to improve results of epidemiological studies, promoting better care in this important group of patients.

3.2. Genetics

VT is a multifactorial disease with both established environmental and genetic risk factors. The genetic burden underlying VT is characterized by a strong heritability whose estimates varied from 35% to 60% according to various studies [15,16]. The recent availability of high-throughput genotyping technologies and their application in the framework of genome-wide association studies (GWAS) have enabled the identification of several new loci associated with the risk of first VT [17]. However, the genetic factors identified so far explain only about 5% of VT heritability and the question is how to investigate this missing heritability. One research strategy to achieve this goal might be to increase sample sizes and ensure thorough meta-analyses of comparable data. Importantly, the number of discovered variants is strongly correlated with experimental sample size, which predicts than an ever-increasing discovery sample size will increase the number of discovered variants [18]. A meta-GWAS in VT is underway including more than 7500 VT patients and 52,630 controls. Furthermore, risk factors for first and recurrent VT are not identical. Genetic factors that clearly affect the risk of first events do not or hardly increase the rate of recurrence. Identifying genetic risk factor specific for recurrence is of importance as it could influence treatment decision, in particular duration of anticoagulant treatment after a first VT event [19]. To date, no GWAS has been published on recurrent VT with comparison at the genomic level of individuals with recurrent VT [cases] to those with only 1 event [controls]. Overall, there is a need for consortia collaboration to reach a sufficient sample size to achieve this goal.

Incidence of VT differs according to ethnicity. Asian and Native American individuals have been reported to have a significantly lower rate of VTE than whites and blacks; the latter present with the highest rate [20]. Moreover, the prevalence of known genetic risk factors of VT are different according to ethnicity as Factor V Leiden and prothrombin G20210A mutation are very rare or absent among nonwhites. Until now all GWAS have been performed in individuals of European ancestry (whites). Genetic variation is greatest in populations of recent African ancestry. Studies of populations of recent African ancestry in particular is likely to increase the yield of rare variants and narrow the large chromosomal regions of association identified in the 'younger' population due to extended linkage disequilibrium of the tendency for adjacent genetic loci to be inherited together. Carefully designed epidemiological research (including GWAS) should be expanded to nonwhite populations to identify genetic risk factors for VT.

Much of the speculation about missing heritability form GWAS has focused on the possible contribution of rare variants (MAF < 0.5%). Such variants are not sufficiently frequent to be captured by current GWAS genotyping arrays. The primary technology for the detection of rare variants is sequencing, which may target regions of interest or