Atrial fibrillation is the most common cardiac arrhythmia (1, 2) and is associated with an increased risk of death (3). In addition to the hemodynamic consequences such as loss of atrial contraction and loss of the chronotropic response to increased circulatory demands, atrial fibrillation causes important morbidity and mortality due to thromboembolic events, mainly stroke and myocardial infarction (4). Although atrial fibrillation can be terminated in the vast majority of patients (5), its recurrence can often not effectively be prevented (6-8). In these patients, heart rate control and anticoagulation are primary therapeutic goals.

Oral anticoagulation with warfarin or phenprocoumon prevents approximately two thirds of thromboembolic events in patients with atrial fibrillation (9, 4, 10). Apart from typical risk factors for atherosclerosis (10), it is so far difficult to identify patients at high risk for thromboembolic events. In this issue, Vene et al. report that high baseline D-dimer levels are associated with future cardiovascular events in a series of 113 patients with chronic atrial fibrillation (11). Oral anticoagulation with warfarin reduced D-dimer levels, but D-dimer levels remained elevated in patients with cardiovascular events when compared to patients without events. The study is based on the previous concept of a “pro-coagulatory state” in patients with atrial fibrillation (12, 13) that may be initiated by reduced blood flow in the paralyzed, fibrillating atrium. Elevated D-dimer levels indicate increased fibrin formation and/or degradation and, hence, provide a biological marker for such a “pro-coagulatory state”. In addition, D-dimers may also be increased as part of an acute inflammatory response, and potentially also in extensive atherosclerotic disease. In view of this consideration, it is unfortunate that other markers of inflammation (CRP, white blood cell count) were not reported in the publication by Vene et al. (11).

High D-dimer levels have been found in survivors of a stroke (14, 15), patients with atherosclerosis (16), and in patients with dementia (17). The present results confirm the suspicion that high fibrin turnover may be a contributing (risk) factor rather than a consequence of cardiovascular events in patients with atrial fibrillation. Whether this is due to the suspected pro-coagulatory effect of atrial fibrillation, due to accompanying inflammation, or due to extensive atherosclerosis, may be determined in future studies. The study by Vene et al. (11) also illustrates the advantages and disadvantages of a single centre study: Patient allocation and treatment was relatively uniform, but the small patient number required a combined end point without any effect on mortality reported. These limitations notwithstanding the data by Vene et al. (11) are a valid starting point for larger, prospective studies to determine the value of D-dimer levels for the prediction of cardiovascular events in patients with atrial fibrillation. Such studies will answer the open question whether D-dimer levels are a modifiable risk factor for thromboembolic events, as has been suggested by others (18), or an epiphenomenon of atherosclerosis and inflammation in patients with atrial fibrillation.

In another article of the current issue, Poli and co-authors (19) published a study on the contribution of a specific genetic alteration to thromboembolic events in patients with atrial fibrillation. Due to the clinical observation that, despite a high risk for cerebral stroke, the majority of patients with atrial fibril-
lation will not experience this complication, the authors hypothesized that genetic factors may account for this difference. Thus, the frequencies of polymorphisms of the coagulation factors V gene (R506Q; APC resistance) and prothrombin gene (G20210A), the most frequent abnormalities associated with venous thromboembolism, were investigated in a large sample of age- and gender-matched individuals with and without atrial fibrillation (each n = 336). The factor V Leiden allele (1691A, causing 506Q) can be identified in 2-7% individuals of diverse ethnic groups and, thereby, it is a polymorphic variant rather than a mutation by definition. In the Physicians’ Health Study, Ridker et al. (20) found that this allele is more frequently associated with primary or recurrent venous thrombosis in men, but not with myocardial infarction or stroke. Subsets of patients appeared to have more than one risk factor and, thereby, a marked risk for thrombotic complications. De Stefano et al. (21) found that heterozygosity for both, the factor V Leiden and the mentioned prothrombin polymorphism has a 2.6-fold higher risk of recurrent thrombosis when compared with heterozygosity of factor V Leiden alone. The overall prevalence estimate of the prothrombin polymorphism was 2-3% in European populations, comparable to that reported by Poli et al. (19). Despite the demonstration that the prothrombin 20210A variant causes a gain of function by mRNA accumulation and protein synthesis (22), reported cases with idiopathic thrombophilia may challenge the complexity underlying thrombotic disease, since some homozygous carriers for the 20210A allele failed to show clinical manifestations (23).

Poli et al. (19) addressed the issue whether arterial hypercoagulability and thromboembolic events (together with atrial fibrillation) can be related to one of these two variants. Only few related data is available so far (24) and the role of genetic factors causing venous thrombosis in arterial hypercoagulability has been questioned (25). Along this line, Poli et al. (19) reported no significant difference in the frequency of the factor V Leiden and the prothrombin 20210A variant among atrial fibrillation patients with or without thromboembolic events. In contrast, 24 (7.14%) patients with atrial fibrillation and only 11 (3.3%) controls were heterozygote carriers of the 20210A allele. This difference led the authors to conclude that the variant is associated with atrial fibrillation itself. However, no explanation was given to substantiate the plausibility of this proposition or to provide supportive data.

For many association studies, conflicting data have been reported on whether an investigated genetic variant is of importance or not for a certain (polygenic) condition. Often, genetic association studies (case-control design) lack the statistical power necessary to declare statistical significance (26). Since the allele frequencies in the present study differed not too much between patients and controls (20210A allele: 3.6% in atrial fibrillation, and 1.6% in controls, respectively), a larger sample size (i.e., several thousands individuals per group) is clearly required to define a potential association. The influence of different allele frequencies in cases and controls on the minimal sample size that was needed to reach on odds ratio of 2.0 (power 0.80) for a reasonable association of a genetic marker with a condition has been nicely demonstrated (26). Thus, a prevalence of a marker allele of 10% in controls and 18% in cases may be sufficient when investigated in a setting of 307 individuals per group at minimum. A lower disease allele frequency in each group and/or a smaller difference of allele frequencies (in the study by Poli et al. (19): about 2%), would require larger sample sizes before a conclusion can be drawn.

Given the current excitement over polymorphisms (SNPs), high-throughput genotyping association studies are currently en vogue in academia and industry. Therefore, a lot of efforts must be placed on well designed and appropriate studies. Association studies, ideally, should have large sample sizes, small P values, report on genetic variants with a potentially physiological relevance and, in addition, the initial study should be independently replicated. So far, in the growing body of citable association studies (>6,000 Medline entries) only a few studies strictly meet these criteria. These and probably other standards still will evolve as knowledge improves on polygenic disease and will further influence the way for conducting association studies in complex genetic traits that are certainly most challenging for geneticists.

A comprehensive understanding of the physiological sequence causing blood coagulation in patients with atrial fibrillation, especially the specific alterations leading to thrombus formation in the left atrium, and the identification of novel risk factors for thromboembolic events in patients with atrial fibrillation – either pathophysiologic or genetic in nature – could be helpful to characterize patients at risk for thromboembolic events and subsequently to optimize management of patients at risk.
References


