Thromboembolic disease of the venous and the arterial system
Mahmoodi, Bakhtawar Khan

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Thromboembolic diseases of venous and arterial systems have historically been viewed as two different diseases with distinct risk factors. This notion was challenged in the last decade since an increased incidence of atherosclerosis and arterial thromboembolism (ATE) had been observed in subjects with venous thromboembolism (VTE). Moreover, an increasing amount of data indicated that classic atherosclerosis risk factors (i.e., hypertension, hyperlipidemia, diabetes, obesity, and smoking) may also predispose individuals to VTE, though results were sometimes inconsistent. Moreover, not all data in literature support the hypothesis that VTE and ATE may be two different phenotypes of the same disease. For instance, hereditary thrombophilic deficiencies of the natural anticoagulant proteins (i.e., antithrombin, protein C and protein S) are considered strong risk factors for VTE; while their association with ATE has been controversial. Similarly, overt proteinuria in patients with nephrotic syndrome is considered an established risk factor for VTE, while its association with ATE in non-diabetics has been less well recognized. Microalbuminuria on the other hand has been considered an established risk factor for ATE, whereas its association with VTE was for the first time studied in the current thesis. Finally, decreased estimated glomerular filtration rate (eGFR) is also a long and well recognized risk factor for ATE, whereas its possible link to increased risk of VTE has been studied only recently. Thus whether VTE and ATE are two different entities or two different phenotypes of the same disease is a matter of intensive research in the field of cardiovascular research and has been the main topic of current thesis.

**Classic atherosclerosis risk factors and risk of venous thromboembolism**

The association of classic atherosclerosis risk factors (i.e., hypertension, dyslipidemia, smoking, obesity and diabetes) and incident VTE has been reported in various epidemiological studies. Although the exact pathophysiological mechanisms accounting for this potential association have yet to be unraveled, endothelial dysfunction, which is strongly associated with atherosclerosis risk factors, is considered the main culprit. This also fits the Virchow triad, as endothelial dysfunction or damage is one of the three components of the Virchow triad that historically classified the pathophysiological mechanisms of factors that may lead to VTE. In chapter 3 we assessed the association of various atherosclerosis risk factors and VTE. Whereas in univariate analysis various atherosclerosis risk factors were related to VTE, after age and sex adjustment only body mass index and albuminuria remained significant predictors of VTE. This
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demonstrates that crude association of atherosclerosis risk factors and VTE that is observed may be due to aging alone, and that in epidemiological studies appropriate adjustment or matching should take place. The results of studies investigating the association of atherosclerosis risk factors and incident VTE are consistently positive for overweight or obesity, whereas for hypertension, dyslipidemia, and diabetes these are equivocal.\(^{13-15,17-21,23-26}\) The differences between studies with respect to the predictive yield of these latter risk factors could be ascribed to differences in study populations with respect to presence of concomitant established and/or unknown VTE risk factors. For instance, subjects with diabetes may have a higher risk of VTE, but concomitant use of statins and/or antiplatelet agents in subjects with diabetes may neutralize this increased risk for VTE. Many of the studies that have been conducted thus far did not adjust for such potential confounders. In conclusion, at the moment there is insufficient data to consider hypertension, dyslipidemia, diabetes and smoking as established VTE risk factors. To assess whether there is an association of these variables with VTE, and whether these associations are causal, ideally clinical intervention studies should be conducted randomizing subjects to treatment or to no/less intensive treatment of these risk factors, with incident VTE serving as end-point. Of note, this may be less appropriate for dyslipidemia, because of the pleiotropic effects of statins.\(^{42}\) For dyslipidemia and smoking, prospective observational cohort studies that adjust for potential confounders might be a better choice to study their relevance as VTE risk factors.

**Thrombophilia and risk of venous and arterial thromboembolism**

Thrombophilia is the clinical term for a hypercoagulable state that was originally used to define young patients with VTE mainly due to hereditary defects. The five best established hereditary thrombophilic defects include the two prevalent gain-of-function mutations (i.e., the factor V Leiden and the prothrombin G20210A mutation) and the relatively rare hereditary deficiencies of the natural anticoagulant proteins (i.e., protein S, protein C and antithrombin). Since these thrombophilic defects alone, or in combination with acquired risk factors, are responsible for only about 50-75% of VTE cases,\(^{43}\) it is likely that other unknown acquired and genetic risk factors eventually will be identified. Considering the fact that literature indicates that the later the identification of a thrombophilic defect, the weaker the associated risk of VTE, potential new hereditary risk factors are expected to be even weaker risk factors for VTE than the presently known factors. An exception to this assumption would be if thrombophilic families that have tested negative for
the known hereditary defects are analyzed. However, any discovered new thrombophilic defects in such families will probably be family specific, be very rare and responsible for only a very low number of VTE on a population level. In contrast, if a risk factor is only weakly associated with VTE incidence, but highly prevalent in the general population, this may account for a considerable proportion of the overall VTE incidence at population level. At the same time the value of such a weak but prevalent risk factor for risk assessment at an individual patient level will be limited. Therefore, experts presently question the clinical relevance of screening for VTE prevention even for strong thrombophilic defects, such as the antithrombin, protein C and protein S deficiencies. Their uncertainty is primarily based on two reasons: first, in the setting of continuous thromboprophylaxis, the risk of major bleeding outweighs the risk of VTE in the general population; second, in the setting of temporary external risk factors for VTE, thromboprophylaxis is momentarily recommended even in non-deficient subjects. Hence, screening asymptomatic relatives of patients with protein S, protein C or antithrombin deficiencies may be unnecessary. Of note, the risk of bleeding associated with long-term oral anticoagulants in subjects with protein S, protein C or antithrombin deficiency might be lower than is reported in the general population.

In chapter 6 we therefore assessed the absolute risks of VTE and the effect of screening on the VTE risk, in asymptomatic relatives of patients with protein S, protein C or antithrombin deficiency, in a prospective analysis. The overall VTE risks were comparable to the risks of VTE in our previous retrospective analysis, which was performed in these same thrombophilic families. Hence, screening and subsequent prophylactic recommendations may not affect the overall risk of VTE in relatives of protein S, protein C or antithrombin deficient patients. However, thromboprophylaxis was utilized in only half of all high-risk situations and still a trend for risk reduction of provoked VTE was observed. Moreover, all provoked VTE occurred when thromboprophylaxis was not used, underlining the effectiveness of thromboprophylaxis in these deficient subjects. On the other hand current guidelines strongly recommend thromboprophylaxis at time of high-risk situations such as surgery, immobilizations and trauma, even in non-deficient subjects. Consequently, augmentation of thromboprophylaxis in these settings, in accordance with the prevailing guidelines, may make screening unnecessary as provoked VTE in deficient subjects would then also be reduced. Exceptions to this rule may be asymptomatic female relatives of patients with these deficiencies, as they are also exposed to higher VTE risk during pregnancy and oral contraceptive use. The
possible relevance of discouraging oral contraceptive was demonstrated by the observation that 2 out of 6 deficient women using oral contraceptives developed VTE during oral contraceptives use (chapter 6). Therefore, screening of asymptomatic female relatives of patients with protein S, protein C or antithrombin deficiencies may be considered beneficial, because, if proven positive for the index deficiency, use of oral contraceptives should be discouraged in these women.

Though the association of the known hereditary thrombophilic defects with VTE is well acknowledged, the risk of arterial thromboembolism (ATE) has been shown to be only slightly increased in subjects with Factor V Leiden or prothrombin G20210A mutation.49 Data on the association of protein S, protein C or antithrombin deficiencies with ATE is based on case-series and case-control studies that reported inconsistent results.30,31 As assessed in chapter 7, only protein S and protein C deficiencies, but not antithrombin deficiency, were risk factors for ATE before 55 years of age. That protein S and C deficiencies were found to be risk factors at young age could be ascribed to the fact that at higher age other ATE risk factors (i.e. classic atherosclerosis risk factors) overrule the risk of ATE conferred by these relatively weak risk factors (i.e., protein S and protein C deficiencies). Why only protein S and protein C deficiencies, but not antithrombin deficiency, were found to be associated with an increased risk of ATE might be due to non-anticoagulant effects of protein C and protein S.50-52 It could be speculated that the higher risk for ATE in subjects with protein C deficiency could be ascribed to the potent cytoprotective effects of the protein C pathway.51 The higher risk for ATE in subjects with protein S deficiency may be explained by the fact that protein S is synthesized by endothelial cells,52 whereas antithrombin is synthesized by hepatocytes. Endothelial injury as a trigger of thrombosis may therefore be enhanced by a preexisting defect in protein S synthesis at the site of injury. Furthermore, some cytoprotective effects also have been attributed to protein S.50,52

In conclusion, even in thrombophilic families the risk of ATE is particularly driven by (classic) atherosclerosis risk factors. However, in young subjects without classic atherosclerosis risk factors, protein S or protein C deficiency increase the risk of ATE. In future studies, it will be interesting to assess any synergetic effects between thrombophilic defects and atherosclerosis risk factors for both venous and arterial thromboembolic events. Such studies, however, will be difficult to perform given the low prevalence of protein S, protein C and antithrombin deficiencies in
the general population as (very) large numbers of participants will be necessary for this question. For the more prevalent factor V Leiden and the prothrombin G20210A mutation, however, such studies could be very well feasible.

**Risk of arterial thromboembolism in patients with prior venous thromboembolism**

Several studies have consistently shown that the risk of ATE in subjects with prior VTE is higher than in matched controls.\(^2,3,5,10,11\) In contrast, studies in subjects with VTE reported contradictory results with respect to the presence of asymptomatic atherosclerotic lesions.\(^4,6,8,9,12\) If atherosclerosis is not or less associated with VTE, it may be postulated that the higher risk of ATE after VTE is probably due to medical conditions that predispose to both VTE and ATE. Examples of such predisposing conditions are cancer, antiphospholipid antibodies, infectious diseases, use of hormonal therapy and renal disease. On the other hand, thrombus formation in each the arterial and venous system is due to platelet aggregation and coagulation activation, which may also explain the stronger and more consistent association of VTE with subsequent ATE, as compared to the association of VTE with asymptomatic atherosclerosis. Moreover, the high risk of ATE especially after idiopathic VTE indicates that the association of VTE with subsequent ATE is not only due to aforementioned predisposing conditions. Another remarkable fact is that the risk of ATE after VTE is particularly high in the first year after diagnosis of VTE,\(^11\) as we also observed in chapter 8. This is surprising because the standard treatment for VTE, which consists of 3 to 6 months of oral anticoagulant drugs, should have lowered the risk of ATE. A possible explanation includes inaccuracy in the exact dates of the two diagnoses, because data were based on hospital registries that may be prone to inaccurate date entry. Other possibilities include: 1) Failure to restart aspirin after cessation of anticoagulant therapy in patients who were on aspirin before VTE diagnosis. 2) In addition to the anticoagulant effects of vitamin K antagonists by blocking γ – carboxylation of various vitamin K dependent coagulation factors in the liver, these drugs may also promote arterial calcification by blocking γ – carboxylation of peripheral vitamin K dependent proteins.\(^53-55\) In a recent small cross-sectional study long-term (>10 years) use of vitamin K antagonists was indeed associated with increased extracoronary arterial calcification.\(^53\) Two potentially important peripheral vitamin K dependent proteins are Matrix Gla protein (MGP) and Growth Arrest Specific gene 6 protein (Gas-6).\(^54\) These proteins have many diverse biologic functions. Produced by vascular smooth muscle cells, MGP functions primarily as a vascular calcification inhibitor and
Gas-6 affects vascular smooth muscle cell movement and apoptosis.\textsuperscript{54} On the other hand, it should be mentioned that the vitamin K antagonists appeared effective in various trials in ATE prevention that could be ascribed to the anticoagulant effects of these drugs.\textsuperscript{56,57} Finally, patients with VTE might be diagnosed earlier with subsequent ATE in the first year due to enrollment in the medical circuit.

For clinical implications, an important issue that warrants attention is the effectiveness of statins in the prevention of VTE. It is assumed that the VTE risk reduction by these drugs is not due to their cholesterol-lowering effects, but rather to the pleiotropic effects of statins.\textsuperscript{42} These include particularly endothelial stabilization that is accompanied by reduction of among others the tissue factor levels and reduction of thrombin generation.\textsuperscript{42} The JUPITER trial indeed reported primary VTE risk reduction in the intervention arm with rosuvastatin as compared to the placebo-controlled arm.\textsuperscript{58} Use of statin therapy in secondary preventions of VTE probably may have more clinical implications. Since patients with VTE have a high risk of recurrent VTE (about 5% in the first year)\textsuperscript{59} and – as we know now – also an increased risk of ATE, prospective randomized trials are needed to address the effect of statin therapy on VTE recurrence and ATE incidence after a prior VTE. The Du Lac randomized trial will address this issue. In this trial, subjects with a VTE, after cessation of standard oral anticoagulants treatment of 6 months, will be randomized to a maintenance intervention-arm with rosuvastatin versus a control-arm with placebo. All patients will be followed for 2 years with recurrent VTE serving as the primary endpoint, and the development of ATE as one of the secondary endpoints.

**Renal disease and risk of venous and arterial thromboembolism**

As presented in chapter 1, renal disease with overt proteinuria predisposes to both VTE and ATE. Though this association was assumed for decades, the absolute risks were unknown, due to lack of data on large patient cohorts. In chapter 2 we assessed the absolute risk of VTE (1.02\% per year) and ATE (1.48\% per year), in a large cohort of patients with nephrotic-range proteinuria. These risks were each about 8-fold higher than the age- and sex-weighted absolute risks in the general population. Compared with the general population, the risk of both VTE (about 140 fold) and ATE (about 50 fold) were particularly high in the first 6 months after diagnosis of nephrotic-range proteinuria. Therefore, one might consider primary thrombo-prophylaxis during this period. However, given the bleeding risk associated with the use of anticoagulants,\textsuperscript{45} in the setting of proteinuria-related
hypercoagulability, safer therapies such as antiproteinuric medications and statins warrants evaluation first. Indeed, our unpublished retrospective observational data in this same cohort of patients indicated that statin therapy was associated with a 50% reduction of the VTE risk (data not shown). Furthermore, in chapter 5 we assessed the effect of antiproteinuric therapy (i.e. losartan alone or in combination with diuretics and/or low sodium diet) on the procoagulant state in proteinuric patients. Antiproteinuric therapy indeed reversed the prothrombotic state in these patients, re-emphasizing the importance of proteinuria reduction as a treatment target. The pathophysiological mechanisms responsible for the increased risk of thromboembolism in patients with nephrotic-range proteinuria are unclear. Alterations in plasma levels of proteins involved in coagulation and fibrinolysis, urinary antithrombin loss, enhanced platelet aggregation, hyperviscosity, and hyperlipidemia are all considered to be predisposing factors.\textsuperscript{34,60-62} Of these, changes in the levels of plasma coagulation proteins and loss of antithrombin in the urine have been historically considered the main predisposing factors, especially for VTE. In contrast with these historical assumptions, we observed in chapter 5 that the levels of plasma antithrombin levels in patients with proteinuria were similar as in healthy controls, whereas all procoagulant proteins were elevated in these patients. Interestingly, except antithrombin, all pro- and other anticoagulant proteins were positively associated with the extent of proteinuria and inversely associated with serum albumin. The higher levels of various coagulation proteins in patients with proteinuria are assumed to be secondary to the decrease in levels of serum albumin, as in response to this decrease in serum albumin the liver upregulates the production of all liver-synthesized proteins, including coagulation proteins and lipoproteins.\textsuperscript{63} We postulate that upregulation of antithrombin synthesis might be counterbalanced by urinary loss. Antithrombin has a relatively low molecular weight, comparable to the molecular weight of albumin, and will therefore easily leak via the glomeruli in (pre)urine. Indeed, in a small pilot study, including three patients with proteinuria ranging from 0.5 g/d to 1.5 g/d, we could confirm urinary loss of considerable amounts of antithrombin (6-21%).

At the population level, the association of microalbuminuria or a mildly decreased eGFR (i.e. stage 1-3 chronic kidney disease, CKD) with thromboembolism is more relevant than that of nephrotic-range proteinuria, due to the higher prevalence of stage 1-3 CKD when compared to the prevalence of overt proteinuria (10-12% versus <0.1% of the general population, respectively).\textsuperscript{64,65} Whereas the association of microalbuminuria and decreased eGFR with ATE is well-recognized,\textsuperscript{35-40} we
described for the first time the association of microalbuminuria (i.e. mainly stage 1-2 CKD) with VTE in the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study (chapter 3). The association of decreased eGFR (i.e. CKD stage 3-4) with VTE was for the first time described by the investigators of the Longitudinal Investigation of Thromboembolism Etiology (LITE) project, which comprises the pooled data of the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS). As described in chapter 4 the association of decreased eGFR and VTE in the PREVEND study was particularly driven by the presence of albuminuria of ≥30 mg/24h, while the ARIC study suggested that microalbuminuria had no significant association with VTE risk, and that only eGFR showed an inverse association with VTE incidence. These discrepancies between the ARIC and the PREVEND studies could possibly be ascribed to differences in characteristics of the enrolled study participants. In the PREVEND study increased hazard ratios of VTE by eGFR level have been described that were comparable to those found in ARIC, but these did not reach statistical significance, which is likely due to limited power. In the PREVEND study a relatively limited number of subjects with more severely decreased eGFR participated. The PREVEND study is better powered to investigate the predictive value of albuminuria due to the enrichment of this study cohort with albuminuric subjects. The ARIC study on the other hand, is probably better powered for subjects with lower eGFR given the larger sample size and higher number of VTE events, but under-powered for albuminuria. The weaker hazard ratio conferred by albuminuria in ARIC as compared to PREVEND, may be due to several reasons. In PREVEND albuminuria is assessed in 24hr urine samples, the gold standard, that were not frozen before assessment. Frozen storage is known to induce a systematic decrease and more variability in albuminuria concentration. Furthermore, subjects with microalbuminuria in ARIC are mainly diabetics, while in PREVEND these are mainly non-diabetics, as per protocol insulin-using diabetics were excluded in PREVEND. This may have influenced the risk estimates, as diabetic subjects are usually on statin therapy and these subjects are more frequently treated for their cardiovascular morbidity with anti-platelet medication. To assess more definitively whether either eGFR or microalbuminuria or both are independent risk factors for VTE we are currently preparing a pooled individual patient level analysis of several databases, among others PREVEND and ARIC to increase the statistical power to address this issue.
The exact pathophysiological mechanisms linking decreased eGFR and increased albuminuria to VTE have yet to be identified. However, endothelial dysfunction might be the main culprit of this link that, in turn, is associated with mild coagulation disturbances, such as increased levels of factor VIII and plasminogen activator inhibitor-1.\(^{68-70}\) This is in contrast to the situation with nephrotic-range proteinuria, in which coagulation disturbances probably play a more prominent role. However, these assumptions are merely based on literature, as we did not assess endothelial dysfunction in either microalbuminuric subjects or in patients with nephrotic-range proteinuria. In the near future we are planning to assess the exact coagulation disturbances in patients with microalbuminuria. Depending on the results, it will subsequently be interesting to assess the impact of antiproteinuric therapy with for example losartan and the effect of statins on the coagulation disturbances in subjects with microalbuminuria.

As compared to the risk of VTE, the risk of ATE in patients with CKD is relatively better established. In a recent meta-analysis by the CKD Prognosis Consortium the independent association of both eGFR and albuminuria with ATE was confirmed, using pooled data of 21 general population-based cohorts with over one million study participants.\(^{40}\) Separate meta-analyses of the same consortium addressing the same issues in other populations, such as those at high risk of CKD and those with known CKD, are currently submitted. Notably, the classification of CKD according to the 2002 KDOQI classification has been increasingly criticized in the field of nephrology.\(^{71}\) These criticisms ranged from terminology, methodology, definition, classification to prognosis. Based on the four meta-analyses by the CKD Prognosis Consortium a proposal for a new guideline to reclassify CKD is being developed. Of note, this consortium is led by the department of Nephrology of the University Medical Center Groningen and the department of Epidemiology and Clinical Research of the Johns Hopkins University in Baltimore, USA.
Conclusions
In conclusion, VTE and ATE share some, such as obesity and renal disease, but not all risk factors as summarized in the above Figure. Even for those risk factors that seem to be associated with both VTE and ATE the associations with each of both endpoints are in general not of similar strength. There may be at least one exception. Urinary protein loss, ranging from microalbuminuria to nephrotic-range proteinuria, turned out to be associated with similar relative risks for VTE and ATE. Based on the current available data, it seems therefore that VTE and ATE are probably not different phenotypes of the same disease, but rather different multifactorial diseases that share some risks factors. Nevertheless, a shared preventative intervention might be beneficial that needs to be addressed in future studies. Especially, the role of albuminuria lowering by intervention in the renin-angiotensin-aldosterone system and the use of statins are interesting and could be highly relevant for prevention of recurrent VTE and prevention of ATE in patients with a prior VTE.
REFERENCES


Discussion and future perspectives


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