Vascular complications in kidney disease

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Chapter 11

Summary and general discussion

11. INTRODUCTION

The main objectives of this thesis were to:

- investigate the association between kidney disease and venous and arterial thrombosis
- provide insight in the mechanism of the association between kidney disease and thrombosis
- investigate the mortality risks for hemodialysis patients with catheter, fistula or graft vascular accesses
- investigate the association between genetic risk factors for arterial and venous thrombosis and mortality in dialysis patients

In this chapter, the main findings are summarized and strengths and limitations of our studies are discussed. In addition, clinical implications, recommendations for future research and main conclusions are provided.

11.1 Main findings

In **chapter 2**, we investigated the association between self-reported liver disease, kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke and arterial thrombosis in a large case-control study (MEGA study). We showed that self-reported kidney disease was associated with an almost 4-fold increased risk of venous thrombosis. Liver disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke and arterial thrombosis were also associated with an increased risk of venous thrombosis. Furthermore, we showed that combinations of these major illnesses with immobilization, increased factor VIII levels, increased factor IX levels, increased von Willebrand factor levels, factor V Leiden, and blood group non-O further increased the risks of venous thrombosis.

In **chapter 3**, we investigated the association between the early stages of kidney disease and venous thrombosis in a large cohort including 8495 subjects (PREVEND study). Most individuals with early stages of kidney disease are asymptomatic and unaware of their decreased kidney function or the presence of albuminuria. The incidence rate of venous thrombosis for patients with chronic kidney disease stages 1–3 was 3.7 per 1000 person-years. Patients with chronic kidney disease stages 1–3 had an almost 2-fold increased risk of venous thrombosis as compared with subjects without chronic kidney disease.

As kidney disease appeared to be associated with venous thrombosis in **chapters 2 and 3**, we investigated in the MEGA study (**chapter 4)** whether the association between kidney disease and venous thrombosis could be explained by body mass index, immobilization, surgery, corticosteroid use, diabetes mellitus, malignancy, arterial disorders, factor V Leiden,

prothrombin G20210A, and coagulation factors levels. We showed that a moderately to severely decreased kidney function (estimated glomerular filtration rate <60 ml/min) was associated with an almost 3-fold increased risk of venous thrombosis as compared with normal kidney function. Furthermore, we found that factor VIII levels and von Willebrand factor levels were increased in patients with a moderately to severely decreased kidney function. Adjustment for factor VIII or von Willebrand factor in the association between decreased kidney function and venous thrombosis attenuated the risk of venous thrombosis indicating an effect of kidney function on thrombosis through these factors. In contrast, adjustments for body mass index, factor V Leiden, prothrombin G20210A, diabetes mellitus, malignancy, arterial disorders, immobilization, surgery or corticosteroid use did not affect the risks of venous thrombosis.

In chapter 2 and 3, kidney disease was associated with venous thrombosis. In **chapter 5,** we wanted to identify high-risk groups with kidney disease that may benefit from thromboprophylaxis. Therefore, we investigated joint effects of reduced kidney function and common risk factors for venous thrombosis in the MEGA study. Moderately and severely reduced kidney function in combination with arterial thrombosis resulted in a 5-fold increased risk of venous thrombosis, with malignancy in a 6-fold increased risk, with surgery in a 14-fold increased risk, with immobilization in a 17-fold increased risk, with the factor V Leiden mutation in a 4-fold increased risk and with the prothrombin G20210A mutation in a 10-fold increased risk of venous thrombosis. The risks of venous thrombosis increased further in the presence of more than one risk factor of venous thrombosis in combination with moderately and severely decreased kidney function.

Chapter 2 to 4 specifically focused on non-dialysis patients. In **chapter 6**, we assessed the absolute risk of venous thrombosis, myocardial infarction and ischemic stroke in a cohort of end-stage renal disease patients receiving dialysis treatment (NECOSAD). The incidence rate of venous thrombosis was 12 per 1000 person-years. The incidence rate of myocardial infarction was 62 per 1000 person-years. For ischemic stroke, we found an incidence rate of 28 per 1000 person-years. The incidence rates in dialysis patients as compared with the general population were 6-fold increased for venous thrombosis, 12-fold increased for myocardial infarction, and 8-fold increased for ischemic stroke after adjustment for age and sex.

In the previous chapter, we mainly investigated non-fatal cases of venous thrombosis, myocardial infarction and stroke. In **chapter 7**, we evaluated mortality rate ratios for pulmonary embolism, myocardial infarction and stroke in dialysis patients from the ERA-EDTA registry as compared with the general population. The age- and sex-standardized mortality rate from pulmonary embolism was 12 times higher in dialysis patients than in the general population.

For myocardial infarction and stroke, we showed that dialysis patients had, respectively, an 11-fold and 8-fold increased mortality risk as compared with the general population after adjustment for age and sex.

In **chapters 8 and 9**, we focused on vascular access related complications in hemodialysis patients. We found that the mortality rate was 1.5-fold higher in patients with a catheter for hemodialysis than in those with an arteriovenous access for hemodialysis. Especially elderly patients with a catheter as vascular access had high mortality rates on dialysis. Furthermore, we showed that graft use as compared with fistula use in hemodialysis patients with a vascular access was associated with a 1.4-fold increased risk of primary patency loss and with a 1.5-fold increased mortality risk.

In chapters 6 to 9, we showed that dialysis patients were at increased risk of vascular access related complications and venous and arterial thrombosis. In **chapter 10**, we investigated whether polymorphisms in the protein C pathway (factor V Leiden, *THBD* rs1042580, *PROC* rs1799808 and 1799809 and *PROCR* rs867186, rs2069951, and rs2069952) were associated with mortality in dialysis patients in the NECOSAD cohort and the German 4D cohort. The protein C pathway plays an important role in endothelial barrier function and anticoagulant processes and abnormalities in this pathway are associated with venous or arterial thrombosis or vascular access related complications. Factor V Leiden was associated with a 1.5-fold increased 5-year all-cause mortality risk and carriers of the AG/GG genotypes of the PROC rs1799809 had a 1.2-fold increased 5-year all-cause mortality risk in the pooled cohorts. The other genotyped single nucleotide variants in the thrombomodulin gene (*THBD* rs1042580), the protein C gene (*PROC* rs1799808 and 1799809), and the endothelial protein C receptor gene (*PROCR* rs867186, rs2069951, and rs2069952) were not associated with 5-year all-cause mortality.

11.2 Strengths and limitations

In this section, the strengths and limitations of our studies in the MEGA study, PREVEND study, NECOSAD study, 4D study and the ERA-EDTA registry are discussed.

11.2.1 MEGA study

The studies described in **chapter 2, 4 and 5** are based on data collected from the MEGA study. The MEGA study is a large, population-based case-control study on risk factors for venous thrombosis. The major strengths of the MEGA study include the large patient sample, the detailed information about established risk factors in both patients and controls, and the presence of blood samples for creatinine measurements.

A limitation of the MEGA study is that blood samples were collected after the thrombotic event. Therefore, we cannot exclude the possibility that differences in creatinine levels between cases and controls resulted from the thrombotic event itself. However, it is not likely that thrombotic events influence creatinine levels. Furthermore, we showed that there were no major differences in estimated glomerular filtration rates when patients were tested within 3-6 months, 6-12 months or after 12 months suggesting that creatinine levels were not influenced by a temporally raised effect.

Another limitation was that those who died soon after a first venous thrombotic event (4% of the patient population) could not participate as a case in the MEGA study. This has probably led to an underestimation of our risk estimates, as patients with chronic kidney disease are more likely to die from venous thrombosis than patients without a major illness.[1,2]

In addition, we had no information about proteinuria. It would be useful to explore whether proteinuria is associated with an increased risk of venous thrombosis and whether the association between decreased kidney function and venous thrombosis can be explained by the presence of proteinuria. Proteinuria, especially in the nephrotic range (defined as proteinuria of more than 3 grams per 24 hours), has been associated with venous thrombosis, which may be caused by changes in the plasma levels of some proteins involved in coagulation.[3-6]

Moreover, we cannot provide risk estimates by the primary kidney disease. This is because most of the subjects with impaired kidney function in our study had no symptoms and were never, or not yet diagnosed with impaired kidney function. It would certainly be useful to study the risks of thrombosis for the various types of primary kidney disease, since the thrombosis risk could be elevated for only specific primary kidney diseases.

A final aspect of the MEGA study was the presence of two separate control groups (partner controls and random digital dialing). While both may serve a slightly different purpose, results pointed in the same direction and were roughly similar when both control groups were analyzed separately.

11.2.2 PREVEND study

Major strengths of the PREVEND study as compared with the MEGA study are the presence of data on albuminuria which was assessed in 24-h urine samples and the presence of follow-up data to calculate absolute risks. Therefore, in the PREVEND study, absolute risks of venous thrombosis could be calculated for chronic kidney disease stages 1 and 2, since both information on albuminuria and kidney function are needed for these stages.

An important limitation of this cohort study was that the kidney function and the presence of albuminuria were assessed long before the occurrence of the disease (mean 4.0 years), resulting in a possible dilution of the effect.

Another limitation was that venous thrombotic events were identified through anticoagulation clinic databases and registers for hospital discharge diagnoses and death certificates, which could lead to an underestimation of the incidence rates of venous thrombosis by missing patients who had venous thrombosis. However, the incidence rates for venous thrombosis in the PREVEND cohort (i.e. 1.4 per 1000 person-years) correspond well to those found in previous studies.[7]

Furthermore, there were only 52 subjects in the PREVEND study with an estimated glomerular filtration rate below 45 ml/min. Therefore, we had a limited power to investigate the association between venous thrombosis and an estimated glomerular filtration rate below 45 ml/min. Previous studies suggested that especially these patients had increased risks of adverse outcomes, such as cardiovascular diseases and mortality.[8,9]

11.2.3 NECOSAD study

The NECOSAD study is a large and well-defined Dutch cohort of incident hemodialysis patients with available data on many patient characteristics, laboratory measurements, and death.

Our studies in the NECOSAD cohort have some potential limitations that should be addressed. A limitation of our studies is that comparisons between types of vascular access (catheter, fistula or graft) in an observational design could be a problem due to confounding by indication. Differences in outcomes for different treatment modalities in dialysis patients may reflect the different prognosis at baseline. In our analyses, we took this into account by correcting for these confounders, but this cannot exclude possible residual confounding.

Another limitation of this study is that there were missing values for several laboratory values, such as the kidney function and serum albumin. Analyses excluding patients who had a missing values could lead to biased results in case missing is influenced by the treatment or outcome.[10] Therefore, imputation could lead to more reliable results than excluding the patients with missing data.[10,11]

Moreover, we had no detailed information about the type of vascular access. Data about the type of catheters (tunnelled or non-tunnelled), the insertion place of the catheters and the use of antimicrobial locks for catheters were not present. We also had no information on

several arteriovenous access characteristics (anatomic location, flow, vessel diameter, and intervention prior to cannulation) that are associated with vascular access dysfunction.

Furthermore, we had no information about failure of arteriovenous access before the first dialysis session. Failure of vascular access before successful cannulation for dialysis is higher for fistulas than for grafts.[12] Therefore, it could be that graft use as compared with fistula use could be beneficial in specific subgroups in terms of morbidity, including number of hospitalizations, and quality of life when we take into account the time period between creation of a vascular access and the first dialysis session.

11.2.4 4D-study

We investigated the association between seven single nucleotide variants and all-cause and cause-specific mortality in the NECOSAD cohort and replicated these findings in the German Diabetes Dialysis Study.

A potential limitation of this study is that we replicated our results in a dialysis population consisting of hemodialysis patients with diabetes mellitus. The NECOSAD cohort also includes non-diabetic patients and patients treated with peritoneal dialysis. Therefore, in the 4D-study, we could not investigate the association between mortality and singe nucleotide variants in peritoneal dialysis patients and in patients without diabetes mellitus.

11.2.5 ERA-EDTA Registry

The study cohort consisted of more than 100 000 incident dialysis patients derived from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry.[13] An important strength of this study, besides its large size, is the presence of data on renal replacement therapy, including date of birth, sex, primary kidney disease, date of start of renal replacement therapy, dialysis modality at baseline and during follow-up, and date and cause of death.

A potential limitation of our study was that the cause of death was unknown in approximately 14% of the dialysis patients compared with 2.0% of the general population. This difference can be explained by the different method for assigning the cause of death in dialysis patients as compared with the general population. Causes of death among patients on dialysis were recorded by the primary nephrologist. When a patient died at home or elsewhere outside the hospital, the nephrologist will have been dependent on information from others, and may more likely report a cause of death as unknown. Conversely, causes of death within the general population are, according to law, recorded by the physician who confirmed the death and thereafter sent the data to the statistics office, resulting in few missing causes of death.

11.3 Clinical implications and future research

Vascular complications such as venous and arterial thrombosis and vascular access (fistula, graft or catheter) related complications are associated with many hospitalizations and deaths in chronic kidney disease patients, especially in dialysis patients.[14-20]

In **chapter 2**, we showed that self-reported kidney disease was associated with a 3.7-fold increased risk of venous thrombosis. Furthermore, we showed that self-reported rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke and arterial thrombosis in these patients were associated with an increased risk of venous thrombosis varying from a 1.5-fold increased risk for a history of arterial thrombosis and rheumatoid arthritis to a 4.9-fold increased risk for hemorrhagic stroke. Also other studies found an association between venous thrombosis and including liver disease,[21,22] kidney disease,[5,6,23] rheumatoid arthritis,[21,24] multiple sclerosis,[25] heart failure,[21,26,27] hemorrhagic stroke,[28] and arterial thrombosis.[21,29,30] Based on these estimates, thromboprophylaxis in patients with a major illness seems unjustified, since the number needed to treat would be excessively high, while introducing a considerable risk of major bleeding. However, risks increased in the presence of immobilization or trombophilia.

In **chapter 3**, we showed that patients with chronic kidney disease stage 1 and 2, and patients with chronic kidney disease stage 3 in the presence of albuminuria had increased risks of venous thrombosis. Patients with chronic kidney disease stage 3 without albuminuria had no increased risk of venous thrombosis. These findings are in line with several other studies suggesting a higher risk for chronic kidney disease stage 3 subjects with albuminuria than for CKD stage 3 subjects without albuminuria for different adverse outcomes, such as cardiovascular disease and the development of end-stage renal disease.[9,31-33] Based on the weak associations between early stages of chronic kidney disease and venous thrombotic risk (the incidence rate of subjects without chronic kidney disease was 1.3 per 1000 person-years and the incidence rate of subjects with chronic kidney disease stages 1-3 was 3.7 per 1000 person-years), the number needed to treat (approximately 400) will be too high to justify thromboprophylaxis for all patients with chronic kidney disease stages 1-3. Further studies are needed to show whether venous thrombosis prophylaxis in subgroups of patients with early stages of chronic kidney disease in the presence of albuminuria will be safe and cost-effective, especially as the high risk of anticoagulant treatment-related major bleeding episodes applies to chronic kidney disease stages 4 and 5, and not to the early stages of chronic kidney disease.[34]

In **chapter 4**, it was found that impaired kidney function affected venous thrombosis risk via concurrently raised factor VIII and von Willebrand factor levels. An increased body mass index,[35,36] factor V Leiden,[37,38] prothrombin G20210A,[37,38] diabetes mellitus,[35,39] malignancy,[38,40]

arterial thrombosis,[41,42] immobilization,[38] surgery,[38] and corticosteroid use[43] could not explain the association between an impaired kidney function and venous thrombosis. However, the exact mechanism through which chronic kidney disease leads to venous thrombosis via procoagulant changes (especially increases in factor VIII and von Willebrand factor levels) cannot be determined from these data with certainty. As von Willebrand factor and factor VIII are markers of endothelial damage,[44] it might be that endothelial damage, which is associated with chronic kidney disease, leads to increased factor VIII and von Willebrand factor levels and eventually to venous thrombosis. According to this view, chronic kidney disease would be an epiphenomenon to the risk of venous thrombosis, and the endothelial damage that leads to a procoagulant shift would be the underlying cause. Alternatively, the endothelial damage could be caused by the chronic kidney disease, which leads to a procoagulant state and finally to venous thrombosis. The exact mechanism could be of clinical importance, since targeting the actual risk factor could also influence the risk of venous thrombosis. Targeting epiphenomena would not influence the risk of venous thrombosis.

In **chapter 5**, kidney function showed an inverse association with venous thrombosis risk with a nearly 6-fold increased risk for those with severely decreased kidney function (estimated glomerular filtration rate <30 ml/min). Those with additional risk factors had an even higher risk of thrombosis, particularly patients who were immobilized or underwent surgery (around 15-fold increased risk). Furthermore, there was a cumulative effect when several risk factors were present simultaneously with renal function impairment, with over 50-fold increased risks. Furthermore, we showed that a high glomerular filtration rate of more than 125 ml/min was also associated with an increased risk of venous thrombosis (odds ratio 1.4; 95% CI 1.0-1.9). A high glomerular filtration rate has been shown to be an indicator for early kidney disease and a predictor of cardiovascular disease.[45-48] Based on the odds ratios of venous thrombosis for decreased kidney function ranging from 1.1 for mildly decreased kidney function (estimated glomerular filtration rate 60-90 ml/min) to 5.5 for severely decreased kidney function (estimated glomerular filtration rate <30 ml/min), thromboprophylaxis is probably not justified in all patients with decreased kidney function since it does not seem to outweigh the increased bleeding risk associated with decreased kidney function.[49,50] Randomized clinical trials are needed to investigate whether prophylaxis with anticoagulant medication is beneficial for specific subgroups of patients with chronic kidney disease.

In **chapter 6 and 7**, it was found that dialysis patients have an increased risk for non-fatal and fatal myocardial infarction, stroke and venous thrombosis.[51,52] This finding was in contrast to autopsy studies that showed that venous thrombosis was less common in dialysis patients than in non-dialysis patients.[53-56] However, autopsy studies are likely to be biased for this kind of comparisons. Clinicians should be aware of the increased risk of this disorder in dialysis patients, since it is the most common preventable cause of hospital death.[57]

In **chapter 8 and 9**, we showed that catheter use compared with arteriovenous access use was associated with increased mortality. Furthermore, we showed that graft use as compared with fistula use was associated with an increased risk of primary patency loss and with an increased mortality risk. Our findings are consistent with the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines[58] and the European Best Practice Guidelines[59] which recommend the use of a fistulas instead of grafts or catheters for vascular access. However, it could be that for subgroups grafts are good alternatives as first option for a vascular access, especially when we take into account that failure of vascular access before successful cannulation for dialysis is higher for fistulas than for grafts which we did not investigate in our studies.[12]

In chapter 10, our study showed that factor V Leiden was associated with an increased mortality risk in dialysis patients. Further studies are needed to explore the role of coagulation abnormalities in dialysis patients and to investigate the pathologic mechanisms of coagulation abnormalities in dialysis patients that leads to adverse outcomes. Recent studies also showed that single nucleotide variants in the factor V gene were associated with arteriovenous graft failure in dialysis patients.[60,61] However, the association between factor V Leiden and adverse outcomes in dialysis patients are weak and the prevalence of factor V Leiden is too low to decide on a strategy to screen all dialysis patients for factor V Leiden. Furthermore, it is unknown what the therapeutic consequence should be in case factor V Leiden is found in a dialysis patient.

11.4 Conclusions

The main conclusions of this thesis are:

- Kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke and arterial thrombosis are associated with an increased risk of venous thrombosis.
- Patients with chronic kidney disease stages 1–3 had an almost 2-fold increased risk of venous thrombosis as compared with subjects without chronic kidney disease.
- Impaired kidney function affects venous thrombosis risk via concurrently raised factor VIII and von Willebrand factor levels.
- Kidney function is inversely associated with venous thrombosis risk with a nearly 6-fold increased risk for those with severely decreased kidney function (estimated glomerular filtration rate <30 ml/min).
- Dialysis patients have an increased risk of fatal and non-fatal venous thrombosis, myocardial infarction and ischemic stroke
- Catheter use as compared with arteriovenous access use is associated with an increased mortality risk.

- Graft use as compared with fistula use is associated with an increased risk of primary patency loss and with an increased mortality risk.
- Factor V Leiden is associated with an increased mortality risk in dialysis patients.

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