Chapter 1

General introduction

1. BACKGROUND

Chronic kidney disease is an important public health problem worldwide. The prevalence of chronic kidney disease has been estimated around 13% in the United States and around 10% in the Netherlands.[1,2] A progressive loss in over a period of months or years leading to inadequate removal of fluid and waste products is characteristic for chronic kidney disease. The diagnosis of chronic kidney disease is often made in patients who are known to be at risk of kidney problems, such as those with hypertension or diabetes mellitus.[3]

Chronic kidney disease is defined as persistent renal damage (detected by a renal biopsy or albuminuria) or a glomerular filtration rate below the 60 ml/min for three months or longer.[4] The diagnosis of chronic kidney disease is irrespective of the underlying type of kidney disease and can be classified into five clinical stages according to the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) (Table 1).[4] Patients with stage 5 chronic kidney disease are often considered for renal replacement therapy in the form of dialysis (hemodialysis or peritoneal dialysis) or transplantation. For hemodialysis, vascular access, i.e., a catheter, fistula or graft, is needed for dialysis. For peritoneal dialysis, a catheter is implanted in the abdominal cavity of the patient.

Table 1. Classification of chronic kidney disease

Stage	Glomerular filtration rate (ml/min)	Kidney damage Albuminuria (>30 mg/24h)
1	>90	Yes
2	60-90	Yes
3	30-60	Not necessary for diagnosis
4	15-30	Not necessary for diagnosis
5	<15	Not necessary for diagnosis

1.1 Vascular complications in patients with kidney disease

Vascular complications such as arterial thrombosis (myocardial infarction or ischemic stroke), venous thrombosis (deep vein thrombosis or pulmonary embolism) and vascular access (fistula, graft or catheter) related complications in patients on hemodialysis are important threats for chronic kidney disease patients. Many hospitalizations and deaths in chronic kidney disease patients, especially in dialysis patients, are consequences of vascular related problems.[5-11]

1.1.1 Venous and arterial thrombosis

Venous thrombosis is a collective term for deep vein thrombosis and pulmonary embolism, and several more rare forms of obstructive clots in veins. Established risk factors for venous

thrombosis include immobilization, surgery, pregnancy, malignancy, hormone replacement therapy, oral contraceptive use and genetic risk factors (including factor V Leiden).[12] Arterial thrombosis, including coronary heart disease and ischemic stroke, is mostly secondary to atherosclerosis due to hypertension, hyperlipidemia, diabetes, smoking and obesity.[13] Chronic kidney disease is an established risk factor for arterial thrombosis.[14-16] Until recently, it has been unclear whether chronic kidney disease also increases the risk of venous thrombosis. The Longitudinal Investigation of Thromboembolism Etiology (LITE) study was the first study that showed an increased risk of venous thrombosis for patients with a chronic kidney disease in individuals older than 45 years of age.[17]

The LITE study focused on patients with stage 3 chronic kidney. However, studies that investigated the risk of venous thrombosis in the early stages of chronic kidney disease were lacking as well as studies that investigate the risk of venous and arterial thrombosis in dialysis patients. Furthermore, the association between kidney disease and venous thrombosis was not explained and no studies were available that investigated high-risk groups of patients with chronic kidney disease that may benefit from thromboprophylaxis.

1.1.2 Vascular accesses in patient on hemodialysis

Hemodialysis patients require vascular accesses for hemodialysis therapy. The options to gain vascular access are fistulas, grafts or catheters. While evidence from randomized-controlled trials is lacking, there is a broad consensus that fistulas and grafts are superior to central venous catheters. Catheter use for hemodialysis has been associated with increased risk of thrombotic complications,[18,19] short access survival,[19,20] and increased risk of infections.[21-24] Therefore, the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF K/DOQI) guidelines[25] recommend the use of fistulas or grafts instead of catheters for vascular access in hemodialysis patients.

Despite this preference and recommendation for graft or fistula use instead of catheters, only few studies have investigated the association between catheter use and mortality in hemodialysis patients.[27-29] Furthermore, a limited number of studies have investigated the association between fistula use versus graft use and mortality.[29,30]

1.2 Objective and outline of this thesis

The main objective of this thesis was to investigate vascular complications in patients with kidney disease. Specifically, our aims 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

These results may help to define new treatment strategies in the prevention of venous thrombosis and in the treatment of hemodialysis patients.

1.3 Clinical data used in this thesis

In this thesis, data from the **MEGA** (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) study, the **PREVEND** (Prevention of Renal and Vascular Disease) study, the **NECOSAD** (Netherlands Cooperative Study on the Adequacy of Dialysis) study, the **ERA-EDTA** (European Renal Association-European Dialysis and Transplant Association) Registry, and the **4D** (German Diabetes Dialysis) study were used.

1.3.1 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. Between March 1999 and September 2004, consecutive patients aged 18 to 70 years with a first objectively confirmed episode of deep venous thrombosis or pulmonary embolism were included from six participating anticoagulation clinics in the Netherlands. As control persons, initially partners of patients aged <70 years without venous thrombosis were included. Later on persons without venous thrombosis were approached via a random-digit-dialing method.

In **chapter 2**, we investigated the risk of venous thrombosis for several self-reported major illnesses, including kidney disease, liver disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke, and arterial thrombosis. In **chapter 4**, we investigated 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 factor levels. Based on our studies in chapter 2 and 3 in which we found an increased risk of venous thrombosis in kidney disease patients, we set out to identify kidney disease patients who were at high risk of venous thrombosis. Therefore, in **chapter 5**, we investigated joint effects of decreased kidney function with one or more other risk factors for thrombosis to identify high-risk groups that may benefit from thromboprophylaxis.

1.3.2 PREVEND study

For the study described in **chapter 3**, we collaborated with the Prevention of Renal and Vascular Disease (PREVEND) study group from the University Medical Center Groningen. The PREVEND study is a prospective cohort study in which all inhabitants of the city of Groningen, The Netherlands, aged 28–75 years (n = 85 421) were invited to send a morning urine sample to be screened for albuminuria. Of the responders, the PREVEND cohort was selected and tested for renal function and proteinuria in 24-hours urine samples. The study participants (n = 8 495) were followed for the occurrence of several outcomes, including venous thrombosis. In the PREVEND cohort, we determined the absolute and relative risks of venous thrombosis for patients with chronic kidney disease stages 1, 2, and 3.

1.3.3 NECOSAD study

For the studies described in **chapters 6, 8, 9 and 10**, we used data from the **NECOSAD** study. The NECOSAD is a prospective multicenter cohort study in which incident adult end-stage renal disease patients in the Netherlands were included from 38 dialysis centers. Outcome measures used in our study were patency loss, venous and arterial thrombosis, and death.

Chapters 2, 3 and 5 focused on the risk of venous thrombosis in kidney disease patients in earlier stages. In **chapter 6**, we explored the risk of venous and arterial thrombosis associated with dialysis. To that end, we assessed the absolute risk of deep vein thrombosis, pulmonary embolism, myocardial infarction and ischemic stroke in a cohort of end-stage renal disease patients receiving dialysis treatment.

In **chapter 8**, we investigated death risks in hemodialysis patients comparing catheter use with arteriovenous access use. In **chapter 9**, we compared patency loss and mortality between graft users and fistula users.

In the previous studies, we showed that dialysis patients were at increased risk of vascular access complications, and of venous and arterial thrombosis. Therefore, in **chapter 10**, we investigated whether polymorphisms in genes within the protein C pathway, which plays an important role in endothelial barrier function, anticoagulant processes and thrombosis, were associated with mortality in dialysis patients.

1.3.4 4D-study

For independent replication of the results of the NECOSAD study in **chapter 10**, we collaborated with the 4D-study group. The 4D-study was a double-blind, randomized trial on the effect of atorvastatin in hemodialysis patients with type 2 diabetes mellitus who had received less than two years of previous hemodialysis treatment. The primary endpoint was

a composite of cardiac death, non-fatal myocardial infarction and stroke, whichever occurred first. Patients were randomly assigned to either 20 mg of atorvastatin or placebo once daily until the date of death, censoring, or the end of study in March 2004.

1.3.5 ERA-EDTA Registry

For the study described in **chapter 7**, we collaborated with the ERA-EDTA Registry. The ERA-EDTA Registry collects 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. We used a cohort of dialysis patients from 11 European countries: Austria, Belgium, Denmark, Finland, Greece, Iceland, Calabria (Italy), the Netherlands, Norway, Sweden and the autonomous communities of Andalusia, Asturias, Basque country, Catalonia, Castile-La Mancha, Castile and Leon, Extremadura, and Valencian region in Spain.

In **chapter 7**, we assessed the rates of death from myocardial infarction, stroke, and pulmonary embolism in an ERA EDTA cohort of incident dialysis patients and compared them with those in the general population.

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