Vascular complications in kidney disease

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Chapter 6

Venous and arterial thrombosis in dialysis patients

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ABSTRACT

Background: Whether the risk of both venous and arterial thrombosis is increased in dialysis patients as compared to the general population is unknown. In addition, it is unknown which subgroups are at highest risk. Furthermore, it is unknown whether having a history of venous thrombosis or arterial thrombosis prior to dialysis treatment increases mortality risk.

Methods: A total of 455 dialysis patients were followed for objectively verified symptomatic thrombotic events between January 1997 and June 2009.

Results: The incidence rates in dialysis patients as compared to the general population was 5.6-fold (95% CI 3.1-8.9) increased for venous thrombosis, 11.9-fold (95% CI 9.3-14.9) increased for myocardial infarction, and 8.4-fold (95% CI 5.7-11.5) increased for ischemic stroke. The combination of hemodialysis, lowest tertile of albumin, history of venous thrombosis, and malignancy was associated with subsequent venous thrombosis. Increased age, renal vascular disease, diabetes, high cholesterol levels, history of venous thrombosis, and history of arterial thrombosis were associated with subsequent arterial thrombosis. The all-cause mortality risk was 1.9-fold (95% CI 1.1-3.3) increased for patients with a history of venous thrombosis and 1.9-fold (95% CI 1.4-2.6) increased for patients with a history of arterial thrombosis. A potential limitation of this study was that in some risk categories associations with venous thrombosis did not reach statistical significance due to small numbers.

Conclusion: Dialysis patients have clearly elevated risks of venous thrombosis and arterial thrombosis and occurrence of venous thrombosis or arterial thrombosis prior to the start of dialysis is associated with an increased mortality risk.

INTRODUCTION

In the past, venous and arterial thrombosis have been regarded as separate diseases with different causes.[1] In the last decade, however, several investigators suggested that venous and arterial thrombosis might not be fully separate entities as several studies have shown that patients with venous thrombosis have an increased risk of arterial thrombosis and vice versa.[2-6] Additional studies have shown that arterial and venous thrombosis share some risk factors, although this has only consistently been shown for obesity.[7-11]

Early stages of chronic kidney disease have been associated with both venous and arterial thrombosis.[12,13] However, end-stage renal disease has only been associated with arterial thrombosis,[14-20] and not with venous thrombosis including deep vein thrombosis and pulmonary embolism. One study in the US Renal Data System (USRDS) showed that dialysis patients had an age-adjusted 2.3-fold increased risk of for a primary discharge diagnosis of pulmonary embolism occurring within the first year of dialysis treatment as compared to the general population.[21] However, deep vein thrombosis was not assessed in this study.

Therefore, the primary aim of this study was to assess the absolute risk of deep vein thrombosis and pulmonary embolism (venous thrombosis) and myocardial infarction and ischemic stroke (arterial thrombosis) in a cohort of end-stage renal disease patients receiving dialysis treatment. We also assessed whether venous thrombosis and arterial thrombosis shared risk factors in dialysis patients. Finally, we determined whether having a history of venous and arterial thrombosis prior to start of dialysis treatment increased the mortality risk.

METHODS

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective multicenter cohort study in which incident adult end-stage renal disease patients in the Netherlands were included. Eligibility included age older than 18 years, and no previous renal replacement therapy. All patients gave informed consent and the study was approved by all local medical ethics committees. We followed 455 patients, from January 1997 in three dialysis centers that participated in NECOSAD, until a thrombotic event (venous thrombosis, myocardial infarction, and ischemic stroke), death, or censoring, i.e. transfer to a nonparticipating dialysis center, withdrawal from the study, transplantation, or end of the follow-up period (June 2009). These three centers were chosen for logistic reasons, i.e. they provided a large number of patients.

Demographic and clinical data

Data on age, sex, primary kidney disease, smoking status, diabetes, medication, and history of thromboembolic events (venous thrombosis, myocardial infarction, or ischemic stroke) were collected at the start of dialysis treatment. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA).[22] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases. Other kidney diseases consisted of patients with interstitial nephritis, polycystic kidney diseases, other multisystem diseases and unknown diseases.

Serum albumin, hemoglobin, creatinine, urea, total cholesterol, and triglycerides were routinely measured in the dialysis centers at 3 months after start of dialysis. Total protein, urea, and creatinine levels were also routinely measured in 24-hour urine samples. Renal function, expressed as glomerular filtration rate (GFR), was calculated as the mean of creatinine and urea clearance corrected for body surface area (ml/min per 1.73 m^2).

Venous thrombosis and arterial thrombosis

Symptomatic venous thrombosis (deep vein thrombosis of the leg and pulmonary embolism) and symptomatic arterial thrombosis (myocardial infarction and ischemic stroke) during follow-up were identified from hospital diagnosis registration systems and from chart review of all 455 patients. Moreover, we used medical records to validate the thrombotic events. Peripheral vascular atherosclerotic diseases were not considered as arterial events due to lack of detailed information of these disease entities in our patients charts.

Venous thrombosis was considered confirmed when diagnosed by compression ultrasound for deep vein thrombosis of the leg and/or when diagnosed by spiral computed tomography or ventilation-perfusion lung scanning for pulmonary embolism. Venous thrombosis was considered unprovoked in the absence of surgery, trauma, presence of a catheter, immobilization for >7 days or hospitalization, oral contraceptives, hormone therapy, pregnancy, malignant disease, or long-distance travel for >4 hours at or within one month before the development of venous thrombosis. Medical records were reviewed with a standardized check-list to categorize venous thrombosis into provoked or unprovoked.

Myocardial infarction had to be confirmed by typical symptoms, electrocardiogram features, elevated levels of cardiac enzymes, radionuclide imaging techniques, or coronary angiography. Ischemic stroke had to be diagnosed by computed tomography or magnetic resonance imaging.

Mortality

We classified causes of death according to the codes of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) which is a standardized classification of death causes in dialysis patients.[22] We grouped death causes into cardiovascular and non-cardiovascular. Cardiovascular mortality was defined as death due to myocardial ischemia and infarction (code 11); cardiac arrest/ sudden death (code 15); cardiac failure/ fluid overload/ pulmonary edema (codes 14,16,18); hyperkalemia /hypokalemia (code 12,17); pulmonary embolism (code 21); cerebrovascular accident (code 22); hemorrhage from ruptured vascular aneurysm (code 26); mesenteric infarction (code 29); cause of death uncertain/unknown (code 0). Non-cardiovascular mortality was defined as death caused by pulmonary infection (code 31-33); infections elsewhere (code 34); septicemia (code 35); tuberculosis (code 36-37); generalized viral infection (code 38); peritonitis (code 39); suicide (code 52); treatment cessation (code 51, 53-54) ; cachexia (code 64) ; malignancies (codes 66-68); miscellaneous (codes 13, 23-28, 41-46, 61-63, 69-73, 81-82, 99-102).

Statistical analysis

Continuous variables are presented as mean with standard deviation (SD) or as median and interquartile rage (IQR) depending on the normality of the data. Categorical variables are presented as counts with corresponding percentages. The observation time for venous thrombosis in each participant was calculated as the time elapsed between the start of dialysis and a censoring event (withdrawal from the study, transplantation, death, or June 2009), or the first episode of venous thrombosis during dialysis. The observation time for arterial thrombosis in each participant was calculated as the time elapsed between the start of dialysis and a censoring event (withdrawal from the study, transplantation, death, or June 2009), or the first episode of arterial thrombosis during dialysis. Incidence rates for arterial and venous thrombosis were calculated by dividing the number of patients with a venous thrombosis or arterial thrombosis by the total observation time at risk. When calculating the incidence rates for venous thrombosis, we ignored the occurrence of arterial thrombosis and vice versa. Incidence rates and 95% confidence intervals (95% CIs) were calculated with Poisson regression models for venous thrombosis, myocardial infarction, and ischemic stroke in dialysis patients. We used indirect standardization to compare these incidence rates to the age- and sex-weighted incidence rates in the general population obtained from the HUNT2 study for venous thrombosis[23] and the Framingham study for myocardial infarction[24] and ischemic stroke.[25] The presented incidence rates in the general population are based on the age- and sex-distribution of the dialysis patients in our study. Cumulative incidences for venous thrombosis and arterial thrombosis were analyzed by using time-to-event analyses accounting for competing risk of transplantation and death.[26] Furthermore, we calculated adjusted hazard ratios (HRs) with 95% CIs to evaluate the effect of clinical and laboratory

characteristics on the development of venous thrombosis and arterial thrombosis. Finally, we determined whether having a history of venous and arterial thrombosis prior to start of dialysis treatment increased the (cardiovascular and non-cardiovascular) mortality. SPSS statistical software (version 17.0; SPSS, Chicago, Illinois) was used for the analyses.

RESULTS

Baseline characteristics of the 455 patients are shown in Table 1. Overall, the mean age was 60.4 years, 65.7% were male, 64.6% had hemodialysis treatment at initiation of dialysis including 85 patients with a catheter (18.7%) and 209 patients with an arteriovenous access (45.9%), and 18.2% of patients had diabetes as primary kidney disease. Of the 455 patients, 23 (5.1%) had a history of venous thrombosis and 116 (25.5%) had a history of arterial thrombosis prior to the start of dialysis therapy. Patients were followed for a median observation period of 2.4 years (range 0.1 to 11.7 years).

During the observation period, 15 patients developed venous thrombosis, of whom seven had pulmonary embolism, seven deep vein thrombosis, and one presented with both. Four patients (26.7%) with pulmonary embolism died. Of the 15 venous thrombotic events, 5 were unprovoked and 10 were provoked (hospitalization, n=4; catheter-related, n=4; surgery, n=2, presence of malignancy, n=2). Of the 4 patients who developed venous thrombosis during hospitalization, one had an exacerbation of ulcerative colitis, one patient had sepsis, one had a pancreatitis, and one had an exacerbation of Wegener's disease. Of the 4 patients who developed catheter associated venous thrombosis, three had a deep vein thrombosis and one had a pulmonary embolism. One patient developed venous thrombosis during hospitalization after coronary artery bypass grafting and another patient developed venous thrombosis shortly after thrombectomy of a thrombosed dialysis shunt. Of note, none of the patients had an arteriovenous access in the lower limb. Furthermore, 96 patients developed an arterial thrombosis (72 patients developed myocardial infarction of which 15 were fatal (20.8%) and 33 patients developed ischemic stroke of which 6 were fatal (18.2%).

Table 1. Baseline characteristics

	N=455	
Age, years	60.4	± 15.1
Sex		
Male	299	(65.7%)
Female	156	(34.3%)
Dialysis modality (%)		
Hemodialysis	294	(64.6%)
Peritoneal dialysis	161	(35.4%)
Primary kidney disease (%)		
Diabetes mellitus	83	(18.2%)
Glomerulonephritis	48	(10.5%)
Renal vascular disease	75	(16.5%)
Other	249	(54.7%)
Body mass index, kg/m^2	25.0	± 5.2
Diabetes mellitus as comorbidity	122	(26.8%)
Malignancy	24	(5.3%)
History of venous thrombosis	23	(5.1%)
History of arterial thrombosis	116	(25.5%)
Smoking		
Never	174	(40.7%)
Ever	254	(59.3%)
Hemoglobin, mmol/L	6.9	± 1.0
GFR, ml/min	3.3	(1.9-5.6)
Proteinuria, gram per day	1.1	(0.5-2.4)
Anticoagulation use	21	(6.7%)
Erythropoietin use	276	(60.7%)
Erythropoietin dose, IU/week	6000	(4000-8000)
Albumin, g/L	33.0	(29.0-37.0)
Cholesterol, mmol/L	4.4	(3.6-5.4)
Triglycerides, mmol/L	1.9	(1.3-2.6)

Figure 1 shows the incidence rates per 1000 person-years for venous thrombosis (combination of deep vein thrombosis and pulmonary embolism), deep vein thrombosis (alone), pulmonary embolism (with or without deep vein thrombosis), myocardial infarction, and ischemic stroke in dialysis patients as compared to the estimated age- and sex-weighted incidence rates in the general population (HUNT2 study[23] for venous thrombosis and Framingham study[24,25] for myocardial infarction and ischemic stroke). The incidence rate of venous thrombosis (12.3 (95% CI 7.2-19.9) per 1000 person-years) in dialysis patients was 5.6 (95% CI 3.1-8.9) times higher than the estimated age- and sex-weighted annual incidence rate in the general population (HUNT2 study,[23] 2.2 per 1000 person-years). The incidence of both provoked venous thrombosis (8.2 per 1000 person-years; 95% CI 4.2-14.6) and unprovoked venous thrombosis (4.0 per 1000 person-years; 95% CI 1.4-8.9) were higher than the age-

and sex-weighted annual incidence rates of provoked and unprovoked venous thrombosis in the general population (HUNT2 study,[23] 1.1 per 1000 person-years for provoked venous thrombosis and 1.1 per 1000 person-years for unprovoked venous thrombosis). The absolute risk of myocardial infarction (62.1 (95% CI 49.0-77.8) per 1000 person-years) was 11.9 (95% CI 9.3-14.9) times higher in dialysis patients than the estimated age- and sex-weighted incidence rate in the general population (the Framingham study,[24] 5.2 per 1000 person-years). Moreover, the absolute risk of ischemic stroke (27.6 (95% CI 19.3-38.4) per 1000 person-years) was 8.4 (95% CI 5.7-11.5) times higher in dialysis patients than the estimated age- and sex-weighted annual incidence rate in the general population (the Framingham study,[25] 3.3 per 1000 person-years). The cumulative incidence at eight years of follow-up was 4.1% for venous thrombosis and 24.8% for arterial thrombosis.

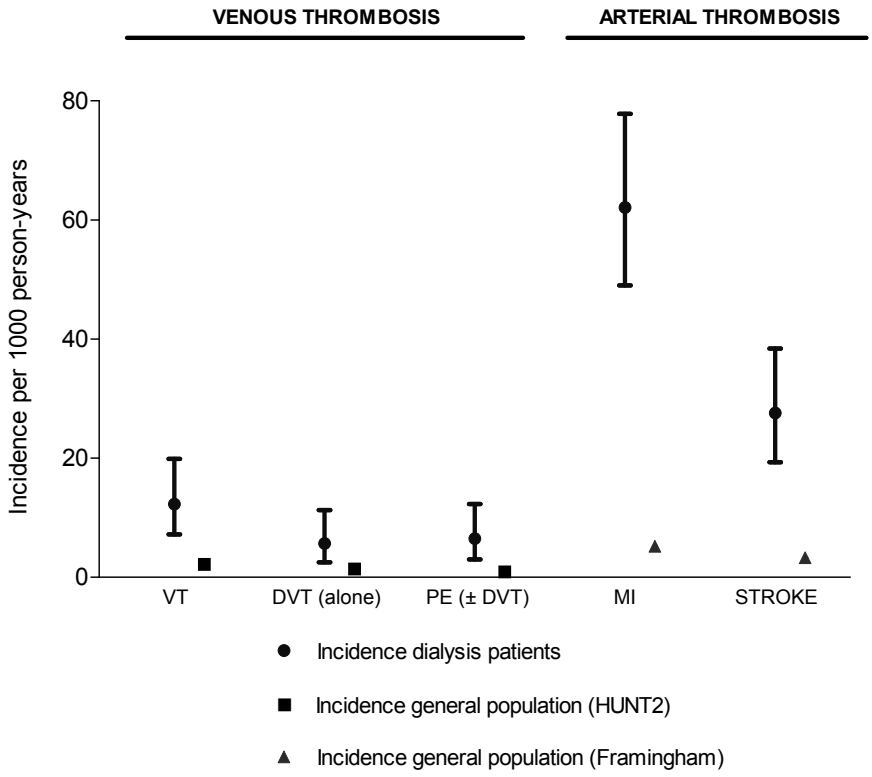

Figure 1. Incidence rates per 1000 person-years for venous and arterial thrombosis in dialysis patients as compared to the age- and sex- weighted incidence rates in the general population
MI indicates myocardial infarction; STROKE, ischemic stroke; VT, venous thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism

Table 2 shows the risk of venous or arterial thrombosis for different baseline variables after adjustment for age and sex. Venous and arterial thrombosis did not share risk factors in these dialysis patients, except for history of venous thrombosis which was associated with both venous and arterial thrombosis. Hemodialysis therapy, highest tertile of albumin, malignancy, and history of venous thrombosis were associated with venous thrombosis after adjustment for age and sex, although not significant. The combination of hemodialysis, highest tertile of albumin, history of venous thrombosis, and malignancy were associated with a 12.0-fold (95% CI 1.7-84.9) increased risk of venous thrombosis as compared with the absence of these risk factors. History of arterial thrombosis was not associated with subsequent venous thrombosis (hazard ratio 1.0; 95 CI 0.3-3.9). However, after exclusion of vitamin K antagonist users (anticoagulation use), the hazard ratio increased to 1.6 (95% CI 0.3-8.0). Increased age, diabetic nephropathy, renal vascular disease, history of arterial and venous thrombosis, diabetes as comorbidity, and the highest tertile of cholesterol were associated with arterial thrombosis. The combination of increased age (≥65 years), renal vascular disease, history of arterial and venous thrombosis, diabetes, and the highest tertile of cholesterol was associated with an 11.3-fold (95% CI 1.8-72.3) increased risk of arterial thrombosis as compared with the absence of these risk factors.

During the observation period, 197 patients died (99 cardiovascular mortality and 98 non-cardiovascular deaths). Patients with a history of venous or arterial thrombosis before starting dialysis had an increased mortality risk while on dialysis after adjustment for age, sex, diabetes, and primary kidney disease (Table 3): the all-cause mortality risk was 1.9-fold (95% CI 1.1-3.3) increased for patients with a history of venous thrombosis and 1.9-fold (95% CI 1.4-2.6) increased for patients with a history of arterial thrombosis as compared to patients without a history of venous or arterial thrombosis. Patients with a history of venous thrombosis had a non-significantly 2.0-fold (95% CI 0.9-4.4) increased risk of cardiovascular mortality and a non-significantly 1.8-fold (95% CI 0.8-4.0) increased risk for non-cardiovascular mortality. Patients with a history of arterial thrombosis had a 2.4-fold (95% CI 1.6-3.7) increased risk for cardiovascular mortality and a 1.5-fold (95% CI 1.0-2.4) increased risk for non-cardiovascular mortality.

Table 2. Association of baseline characteristics with subsequent venous and arterial thrombosis after adjustment for age and sex

		Venous thrombosis Hazard ratios* (95% CI)		Arterial thrombosis Hazard ratios* (95% CI)	
Age, years	< 65	1.0	(reference)	1.0	(reference)
	65-75	0.3	(0.1-1.6)	1.1	(0.7-1.7)
	>75	1.2	(0.3-4.5)	1.6	(1.0-2.8)
Sex	Male	0.8	(0.3-2.1)	1.3	(0.9-2.1)
	Female	1.0	(reference)	1.0	(reference)
Dialysis modality	Hemodialysis	2.6	(0.7-9.7)	0.7	(0.4-1.1)
	Peritoneal dialysis	1.0	(reference)	1.0	(reference)
Primary kidney disease	Diabetes mellitus	0.5	(0.1-2.2)	2.0	(1.2-3.4)
	Glomerulonephritis	0.4	(0.1-2.2)	1.2	(0.5-2.5)
	Renal vascular disease	NE		2.5	(1.5-4.2)
	Other	1.0	(reference)	1.0	(reference)
Body mass index, kg/m^2	<30.0	1.0	(reference)	1.0	(reference)
	≥30.0	1.6	(0.4-5.8)	0.8	(0.4-1.6)
Diabetes mellitus as comorbidity		1.5	(0.5-4.3)	1.5	(1.0-2.3)
Malignancy		3.0	(0.6-13.8)	0.6	(0.2-1.7)
History of venous thrombosis		3.4	(0.7-15.5)	2.3	(1.1-4.9)
History of arterial thrombosis		1.0	(0.3-3.9)	2.9	(1.9-4.5)
Smoking		1.2	(0.4-3.6)	1.5	(0.9-2.3)
Erythropoietin use		0.8	(0.3-2.3)	1.2	(0.8-1.8)
Hemoglobin, mmol/L	<6.5	1.0	(reference)	1.0	(reference)
	≥6.5 to 7.2	0.7	(0.2-2.3)	1.0	(0.6-1.7)
	>7.2	0.6	(0.2-2.0)	1.3	(0.8-2.1)
GFR, ml/min	0 to 5	1.0	(reference)	1.0	(reference)
	>5 to 10	0.9	(0.3-3.3)	1.0	(0.6-1.6)
	>10	1.6	(0.2-12.4)	0.9	(0.3-2.3)
Proteinuria, gram per day	0 to 0.3	1.0	(reference)	1.0	(reference)
	>0.3 to 3.5	0.3	(0.1-1.1)	1.3	(0.7-2.3)
	≥3.5	0.8	(0.2-3.2)	1.2	(0.6-2.6)
Albumin, g/L	<30.1	1.0	(reference)	1.0	(reference)
	≥30.1 to 35.5	0.8	(0.2-2.5)	0.7	(0.5-1.2)
	>35.5	0.4	(0.1-1.6)	0.8	(0.5-1.2)
Cholesterol, mmol/L	<3.9	1.0	(reference)	1.0	(reference)
	≥3.9 to 5.0	0.9	(0.2-3.6)	1.1	(0.6-1.9)
	>5.0	1.6	(0.5-5.7)	1.6	(1.0-2.8)
Triglycerides, mmol/L	<1.4	1.0	(reference)	1.0	(0.6-1.7)
	≥1.4 to 2.3	1.1	(0.2-5.0)	0.8	(0.5-1.4)
	>2.3	1.3	(0.3-5.7)	1.1	(0.7-1.9)

NE indicates not estimable. *hazard ratios adjusted for age and sex.

Table 3. History of venous and arterial thrombosis prior to start of dialysis treatment and mortality risk after adjustment for age and sex

	All-cause mortality Hazard ratios* (95% CI)		CV mortality Hazard ratios* (95% CI)		Non CV mortality Hazard ratios* (95% CI)	
No history venous or arterial thrombosis	1.0	(reference)	1.0	(reference)	1.0	(reference)
History of venous thrombosis	1.9	(1.1-3.3)	2.0	(0.9-4.4)	1.8	(0.8-4.0)
History of arterial thrombosis	1.9	(1.4-2.6)	2.4	(1.6-3.7)	1.5	(1.0-2.4)

*hazard ratios adjusted for age, sex, diabetes, and primary kidney disease.

DISCUSSION

In the present study, we observed that dialysis patients had absolute risks of more than one percent per year for venous thrombosis, myocardial infarction and ischemic stroke, with 6-fold increase of venous thrombosis, 8-fold increase of ischemic stroke, and 12-fold increase of myocardial infarction risk as compared to the age- and sex-weighted incidence rates in the general population. Finally, our data showed a strong association between a history of venous and arterial thrombosis prior to the start of dialysis and mortality during dialysis.

To our knowledge, this the first study that assessed the incidence of both deep vein thrombosis and pulmonary embolism in end-stage renal disease patients. One other study has examined the incidence of only pulmonary embolisms in end-stage renal disease patients. It showed that dialysis patients had a 2.3-fold increased risk for pulmonary embolism,[21] which is lower than in our study. However, as they only assessed pulmonary embolism in case of primary discharge diagnosis in the first year of dialysis, this could have resulted in an underestimation of the number of pulmonary embolisms. The observed risk of venous thrombosis in dialysis patients in our cohort is in contrast with previous autopsy studies.[27-30] These studies showed that pulmonary embolism was less common in dialysis patients than in non-dialysis patients.[27-30] However, the incidence of venous thrombosis may be underestimated in these autopsy studies, since only a small and selective proportion of dialysis patients undergo postmortem examination. Furthermore, postmortem diagnosis often provides little information about the clinical significance of thrombotic events. The increased risk for myocardial infarction and ischemic stroke in our Dutch cohort of dialysis patients is in line with previous studies.[14-20] Studies revealed that cardiovascular mortality rates were 8 to 20 times higher than in the general population.[15-17]

A possible explanation for the increased risk of venous thrombosis is the high rate of hospitalization, surgery, and immobilization resulting in stasis of the blood and in subsequent venous thrombosis. However, we also found an increased incidence of unprovoked venous

thrombosis suggesting that also other factors play a role in the development of venous thrombosis in dialysis patients. One of these other factors could be hypercoagulability. Several studies have shown that there is a hypercoagulable state in dialysis patients.[31,32] Another explanation for the increased risk of venous thrombosis in dialysis patients could be that the high usually rate of thrombus formation in grafts and fistulas in hemodialysis patients may cause pulmonary embolisms through dislodgement of thrombi.[33] An important finding that strengthens this hypothesis was that venous thrombosis was more frequent in hemodialysis patients than in peritoneal dialysis patients. Moreover, deep vein thrombosis and pulmonary embolism occurred in a similar frequency in this cohort of dialysis patients, whereas in the general population deep vein thrombosis is twice as frequent as pulmonary embolism.[23] In addition, one patient had a symptomatic pulmonary embolism shortly after a thrombectomy of a thrombosed dialysis shunt.

Recent studies have challenged the historical dichotomy of arterial and venous thrombosis as two different entities with distinct risk factors.[2-6] Indeed, arterial cardiovascular risk factors such as hypertension, smoking, and diabetes appeared to be risk factors for venous thrombosis as well.[7-11] In our study, venous and arterial thrombosis did not share risk factors in these dialysis patients, except for a history of venous thrombosis prior to the start of dialysis which was associated with both venous and arterial thrombosis. “Classic” cardiovascular risk factors in the general population, such as an increased age, diabetic nephropathy, renal vascular disease, history of arterial thrombosis, diabetes as comorbidity, and highest tertiles of cholesterol were associated with subsequent arterial thrombosis and not with venous thrombosis. Malignancy, a “classic” risk factor for venous thrombosis in the general population was associated with a non-significantly increased risk of subsequent venous thrombosis. Furthermore, we found a non-significant inverse association between serum albumin levels and venous thrombosis. Also in patients with nephrotic syndrome, serum albumin has been inversely associated with venous thrombosis.[34,35]

We showed that both a history of arterial thrombosis and venous thrombosis before the start of dialysis increased the mortality risk during dialysis. Prior studies also found that dialysis patients who had suffered cardiovascular disease had a poor long-term survival.[36,37] This finding is in agreement with previous studies that showed that venous thrombosis was associated with an increased risk for arterial thrombosis[3-5] and an increased long-term mortality risk in the general population.[38] Therefore, it is tempting to suggest that a history of venous thrombosis before the start of dialysis could be marker of underlying atherosclerosis which results in an increased risk of subsequent arterial thrombosis and an increased mortality risk. Atherosclerosis in patients with a history of venous or arterial thrombosis could also explain why the hazard ratios were higher for cardiovascular mortality than for non-cardiovascular mortality. We did not find an

association between a history of arterial thrombosis and subsequent venous thrombosis. This might be explained by the high prevalence of anticoagulation use in patients with a history of arterial thrombosis preventing also venous thrombosis. Indeed, after exclusion of vitamin K antagonist users, the risk of venous thrombosis for patients with a history of arterial thrombosis was 1.6-fold increased, but as numbers in this subgroup analysis became small, the results should be handled with caution.

A strength of this study is its prospective design in which objectively confirmed venous and arterial thrombotic events were considered as outcome measures. Nevertheless, our study has some potential limitations that should be addressed. A limitation of this study was that we could not measure levels or activity of coagulation factors or markers of hypercoagulability to investigate the role of these factors in the development of thrombotic events in dialysis patients. Another limitation of this study was that confidence intervals around the hazard ratios were wide for risk factors of venous and arterial thrombosis, indicating a limited power for detecting underlying risk factors for venous and arterial thrombosis in dialysis patients. Small numbers also restricted us to not perform further analyses of potential risk factors (such as hemodialysis or peritoneal dialysis) on mortality in patients with previous venous or arterial thrombosis. Nevertheless, this study is the largest to date that analyzed risk factors for both venous and arterial thrombosis and subsequent mortality in dialysis patients.

In conclusion, we showed that dialysis patients had high risks for venous and arterial thrombosis, while occurrence of these thrombotic diseases prior to the start of dialysis was associated with an increased mortality risk in this patient group. Furthermore, we showed that venous and arterial thrombosis did not share risk factors in these dialysis patients.

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