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Chapter 9 |

Summary and general discussion

Introduction

Chronic kidney disease (CKD) is a progressive disease associated with an increased risk of morbidity and mortality. Currently, neither a screening test nor a screening strategy to detect patients in the earliest stages of CKD has been generally accepted. Consequently, patients are usually detected when they become symptomatic, typically when their kidney function has dropped below 30 mL/min/1.73m^2. When the kidney function decreases further, renal replacement therapy may be essential for survival. Different therapeutic interventions in the course of CKD are shown to be effective in slowing or preventing disease progression. This thesis focused on the progression of CKD from pre-dialysis to dialysis. The natural course of CKD (i.e. the pattern of decline of renal function), risk factors for CKD progression, and different disease outcomes were studied. This has been set forth in further detail in **Chapter 1**. Several chapters of this thesis presented analyses on the effect of one determinant, or risk factor, on a particular outcome. It is also interesting to study whether the association between a particular risk factor and the outcome under study differs between patients with specific characteristics. **Chapter 2** introduced the concept of interaction and how to transparently present the assessment of interaction effects. It is recommended to report both the separate and joint exposure effects compared to the unexposed group (the joint reference category). This permits evaluation of interaction on both an additive and multiplicative scale. The assessment of additive interaction seems most relevant from a public health perspective. **Chapter 3** introduced several surrogate measures, such as the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI), to evaluate the presence of additive interaction within multiplicative regression models.

Summary of the principal findings

Part 1: Pre-dialysis care

The association between a positive first-degree family medical history of diabetes mellitus, cardiovascular disease, or kidney disease and the rate of decline of renal function and the risk of mortality in pre-dialysis patients was studied in **Chapter 4**. The analysis has been performed in 439 incident pre-dialysis patients with available family medical history who were included in the retrospective PREdialysis PAtients REcords (PREPARE)-1 cohort. This analysis showed a comparable (age- and sex-standardized) prevalence of a positive first-degree family history of diabetes mellitus in incident pre-dialysis patients (CKD stages 3-5) and the general population (18% *versus* 16%). A positive first-degree family history of cardiovascular disease was more prevalent in pre-dialysis patients than in the general population (29% *versus* 16%). Similarly, first-degree family members of pre-dialysis patients more frequently had CKD as compared to the general population (26% *versus* 3%). Pre-dialysis patients with a positive family history of diabetes mellitus had an increased mortality risk in the first year of pre-dialysis care as compared to pre-dialysis patients without first-degree family with diabetes mellitus (adjusted hazard ratio, HR_{adj}: 2.9; 95% confidence interval, CI 1.3 to 6.7), also an association was found for a positive family history of cardiovascular disease and mortality (HR_{adj} 2.4; 95% CI 1.1 to 5.4).

The mortality risk in patients with a positive family history of kidney disease was HR_{adj} 0.2; 95% 0.1 to 1.0. In addition, no associations between a positive family history of diabetes mellitus, cardiovascular disease, and/or kidney disease and the rate of decline of kidney function have been found. These results suggest that obtaining first-degree family medical history may help to identify CKD patients at increased risk of mortality in the first year of pre-dialysis care.

Chapter 5 presented a study on the effect of serum phosphorus and serum calcium levels on the progression of CKD in pre-dialysis patients. The study population for this analysis consisted of 500 incident pre-dialysis patients who were included in the PREPARE-2 cohort. First, it was described whether pre-dialysis patients were actually treated according to the NKF-KDOQI (National Kidney Foundation Disease Outcomes Quality Initiative) and KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for phosphorus and calcium at the start of pre-dialysis care. Second, it was investigated whether achievement of these guidelines was associated with a prolonged dialysis-free survival. It was found that at least 56% of the patients complied with the guidelines for phosphorus and calcium. Phosphorus levels above the KDOQI and KDIGO target ranges were associated with shorter dialysis-free survival (HR 1.9 [95 %CI 1.4 to 2.6] and HR 2.6 [95% CI 1.9 to 3.5]). Each single 0.1 mmol/L increase in phosphorus level was associated with a shorter dialysis-free survival (HR 1.2 [95% CI 1.2 to 1.3]). Furthermore, each 0.1 mmol/L increase in phosphorus level changed the mean rate of decline of renal function with -0.94 mL/min/1.73m^2/year (95% CI -1.12 to -0.76). No associations between calcium levels and dialysis-free survival nor decline of kidney function have been found. These results may suggest that successful management of mineral metabolism in pre-dialysis patients is beneficial in postponing the start of dialysis therapy and in decreasing the rate of decline of kidney function.

Part 2: From pre-dialysis to dialysis

Besides pre-dialytic risk factors that influence CKD progression during pre-dialysis care, other pre-dialytic risk factors may exist which influence CKD progression even after the start of dialysis therapy. **Chapter 6** studied one of these possible risk factors. It was investigated whether patients who were referred very early for pre-dialysis care had improved survival during dialysis therapy as compared to patients who were referred late. The 1438 patients included in this research were derived from the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD) cohort. NECOSAD is a cohort study of incident dialysis patients. From the patients included, 32% were late referred (i.e. less than three months before the start of dialysis), 12% early (between three and twelve months before the start of dialysis therapy) and 56% very early (more than one year before the start of dialysis therapy). Early (HR 1.5 [95% CI 1.0 to 2.4]) and late (HR 1.8 [95% CI 1.3 to 2.5]) referrals were associated with increased mortality compared with very early referral. It was additionally investigated whether high-risk sub-populations of diabetics and elderly (aged 70 years and above) had additional benefit of very early referral. Although we found a similar pattern within those high-risk populations as compared to the total study population, we did not find additional benefit of very early referral

for diabetics and elderly. So, very early referral to pre-dialysis care is beneficial for all CKD patients, irrespective of their diabetic status or age.

In addition to time of referral, decline of kidney function in the period preceding the start of dialysis may play a role in the progression of CKD after the start of dialysis. **Chapter 7** presented the results of an analysis on the decline of (residual) renal function around the start of dialysis therapy. It was investigated whether the decline of the estimated glomerular filtration rate (eGFR) attenuates in the year before until one year after the start of dialysis therapy. This study, including 1861 incident dialysis patients from the NECOSAD cohort, showed that the apparent decline of the eGFR slowed down from -0.53 mL/min/1.73m^2/month (95% CI -0.58 to -0.48) to -0.12 mL/min/1.73m^2/month (95% CI -0.20 to -0.04) after two to four months of dialysis. The decline in hemodialysis patients attenuated from -0.51 mL/min/1.73m^2/month (95% CI -0.57 to -0.44) to -0.14 mL/min/1.73m^2/month (95% CI -0.26 to -0.02), while the decline in peritoneal dialysis patients attenuated from -0.55 mL/min/1.73m^2/month (95% CI -0.62 to -0.48) to -0.11 mL/min/1.73m^2/month (95% CI -0.23 to 0.01). In both hemodialysis and peritoneal dialysis a similar pattern in decline of eGFR was observed, i.e. the rate of decline slowed down after two to four months after the start of dialysis, though at a different level of eGFR.

Part 3: Dialysis therapy

The preceding chapters made clear that CKD is a severe, progressive condition that even with adequate treatment is associated with increased morbidity and mortality. The prevailing theory is that the increased mortality risk can be largely explained by an increased cardiovascular mortality risk. **Chapter 8** presented an analysis of mortality in incident dialysis patients and the general population. The cardiovascular and noncardiovascular mortality rates of 123,407 incident dialysis patients derived from the European renal Registry (ERA-EDTA) were compared with those in the European general population. The crude cardiovascular and noncardiovascular mortality rates in patients were respectively 38.1/1000 person-years (95% CI 37.2 to 39.0) and 50.1/1000 person-years (95% CI 48.9 to 51.2) higher than in the general population. The age-standardized cardiovascular and noncardiovascular mortality rates were respectively 8.8 (95% CI 8.6 to 9.0) and 8.1 (95% CI 7.9 to 8.3) times higher than in the general population. Accordingly, incident dialysis patients have a generally increased risk of death, which is not specifically caused by excess cardiovascular mortality.

Strengths and limitations

The ultimate goal of performing epidemiological studies is to obtain an estimate of (one or more risk factors for) disease occurrence which is both valid and precise.[1] The precision of estimation is reflected by the width of the confidence interval around the point estimate. Two types of validity can be distinguished: internal and external validity. Internal validity (or: comparability) refers to the validity of the inferences concerning the members of the source population, while external validity (or: representativeness) refers to the validity of the inferences concerning the people outside the study population.[1] Important threats for internal validity are bias and

confounding. The research presented in this thesis has been corrected for possible confounders where possible. Here strengths and limitations of the cohorts presented in this thesis will be discussed, especially focusing on potential biases that might have threatened validity.

Pre-dialysis: PREPARE-1 'versus' or 'and' PREPARE-2?

The first cohort that has been introduced in this thesis was the retrospective PREPARE-1 cohort (**Chapter 4**). This cohort has been identified and assembled from medical records in eight different community and university hospitals between 1999 and 2001. It includes adult incident pre-dialysis patients who were referred to a pre-dialysis outpatient clinic, usually with a creatinine clearance less than 20 mL/min. Furthermore, in these patients the need for the start of renal replacement therapy was expected to be within one year. Patients with prior renal replacement therapy, or those who had pre-dialysis care for less than one month, were excluded from the study. The second cohort of pre-dialysis patients that has been presented is the prospective PREPARE-2 cohort (**Chapter 5**). This multicenter cohort has been identified and assembled between 2004 and 2011. Adult patients from 25 different community and university hospitals throughout the Netherlands, included in this study were referred to a pre-dialysis outpatient clinic. In practice, this refers to patients with a creatinine clearance between 20 and 30 mL/min. The need for renal replacement therapy in these patients was expected to be within one year. Patients with a failing kidney transplant were included in the study when the transplantation was at least one year before. When comparing the characteristics of the PREPARE-1 and PREPARE-2 cohorts, several similarities will be noticed. Both cohorts are multicenter cohort studies, including incident pre-dialysis patients with an expected need for the start of renal replacement therapy within one year. Important differences between both studies include the time period of data collection and the criterion for the level of creatinine clearance that should be present in PREPARE-1 patients, which criterion was not present in PREPARE-2. Do those differences between the two cohorts significantly impact the interpretation of the results of the inferences based on them?

First, what might have been the influence of the different data collection periods between the two cohorts? Between 1999 and 2011 important changes in the treatment of pre-dialysis patients may have taken place as a consequence of the introduction of several treatment guidelines for CKD.[2-8] Furthermore, in the Netherlands in those years, the multidisciplinary guideline for pre-dialysis patients has been introduced.[9] Consequently, patients included in the PREPARE-1 study may have been treated differently as compared to the majority of the patients included in the PREPARE-2 study. It is not expected that this has had major influence on the results of the different analyses though, since analyses in both cohorts were aimed at studying etiology. This means that if it were studied whether for example increased levels of a certain blood parameter, such as serum phosphorus, are associated with the decline of kidney function, similar results would be have found within the PREPARE-1 cohort as in the PREPARE-2 cohort. Treatment differences (e.g. with phosphate binders) as such are not expected to influence the strength of the association - if any association exists - between phosphorus levels and decline of

kidney function, simply because effects of phosphorus levels are studied, not how those levels are achieved.

Table 1. Baseline characteristics of the PREPARE-1 (1999-2001) and PREPARE-2 (2004-2011) cohorts.

	PREPARE-1	PREPARE-2
N	547	500
Age *years*	60.2 (15.2)	64.9 (14.3)
Sex *% male*	57.2	68.0
Primary kidney disease *%*		
Diabetes	19.4	13.8
Glomerulonephritis/-sclerosis	9.3	13.5
Hypertension	8.8	15.7
Polycystic kidney disease	7.5	8.8
Pyelonephritis	10.4	5.4
Renal vascular disease	6.8	15.7
Miscellaneous	26.3	13.5
Unknown	11.5	13.5
Cardiovascular comorbidity *%*	50.3	41.2
Estimated GFR *mL/min/1.73m^2*	13.0 (6.1)	16.8 (6.1)
Body mass index *kg/m^2*	25.8 (4.7)	26.8 (5.2)
Serum calcium *mmol/L*	2.29 (0.21)	2.32 (0.16)
Serum phosphate *mmol/L*	1.54 (0.39)	1.42 (0.32)

Values indicate mean (standard deviation) or percentage, as appropriate. GFR: glomerular filtration rate.

In addition, the level of creatinine clearance that was present at study inclusion was probably slightly lower in PREPARE-1 as compared to PREPARE-2 (<20 mL/min *versus* 20-30 mL/min). The impact of this difference may be reflected by the mean eGFR at baseline. The mean (standard deviation) eGFR at baseline was 13.0 (6.1) mL/min/1.73m^2 in the PREPARE-1 population and was slightly higher in PREPARE-2: 16.8 (6.1) mL/min/1.73m^2 (Table 1). This may reflect differences in the referral pattern between the PREPARE-1 and PREPARE-2 study population, namely that nowadays patients are referred earlier than before. Indeed, previous studies show that changes in referral pattern may be present.[10;11] Table 1 also shows a difference in the distribution of underlying primary kidney diseases in PREPARE-1 *versus* PREPARE-2. Especially lifestyle-related causes of kidney disease (i.e. hypertension and renal vascular disease) are more prevalent in PREPARE-2 than in PREPARE-1. This trend has also been described in literature.[12] Furthermore, despite the increased prevalence of cardiovascular disease in the general population in the last decades, this trend was not visible when comparing PREPARE-1 and PREPARE-2 (i.e. patients included between 1999 and 2001 and patients included between 2004 and 2011). Probably because these inclusion periods were relatively close in time. The mean body mass index however, was slightly larger in PREPARE-2 than in PREPARE-1.

Finally, the most obvious difference between PREPARE-1 and PREPARE-2 is the study design itself (retrospective *versus* prospective). Both studies were designed to include consecutive patients. Datacollection in the PREPARE-1 study took place by extracting data from patient records. In principal, all patients who matched with the inclusion criteria were included in the study. Datacollection in the PREPARE-2 study took place by taking direct measurements. Furthermore, patients were asked to fill out quality of life questionnaires. This was not possible in the PREPARE-1 cohort, since data were collected from patient records only. In PREPARE-2 data could only be collected if a patient was asked and provided consent for study participation. It is likely that, for example, the very sick people did not agree with study participation or, more likely, were not asked to participate in the study at all. On the other hand, patients without or with only a few medical complaints may have refused to participate because they did not want to be confronted with their disease. Consequently, the study might be based on a biased study sample and the associations found in the patients included may be different for patients not selected in the study (selection bias).[1;13] In this case, it is difficult to reason the direction of the bias. The consequence of this selection bias however, may be limited when findings are generalized with caution.

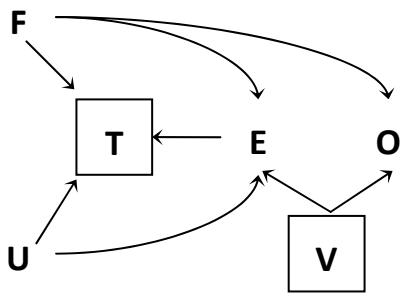
Dialysis: NECOSAD and the ERA-EDTA Registry

The NECOSAD study presented in **Chapters 6 and 7** is a prospective multicenter cohort study in the Netherlands. Incident end-stage renal disease patients who started with dialysis therapy were enrolled between 1997 and 2008. After inclusion patients were followed until death or censoring. The database includes information on many different parameters, which enables the possibility of extensive adjustment for possible confounders within the analyses. In a random sample of patients, data were collected from patients' records, including information on the type and duration of pre-dialysis care the patient received. These retrospectively collected data were used in **Chapter 6** to determine the duration of pre-dialysis care and in **Chapter 7** to estimate the level of eGFR during pre-dialysis. A major advantage of these retrospectively collected data is that it enabled us to study CKD progression in the transition period between pre-dialysis and dialysis.

The use of retrospectively collected data however, also inherently involves selection bias: we only have data available from (a subset of) patients who survived at least until the start of dialysis therapy. Causal directed acyclic graph (DAGs) may be used to identify biases, such as selection bias and confounding. Very briefly, a DAG consists of nodes (variables) and arrows, indicating a direct (causal) effect of a particular variable on another variable. The term 'acyclic' refers to the fact that there are no cycles included in a DAG: a variable can not cause itself (directly or through another variable).[14;15] The DAG presented in Figure 1 illustrates the problem of selection bias we encountered in **Chapter 7**. In this chapter we aimed to study the effect of the duration of pre-dialysis care (exposure, E in Figure 1) on survival (outcome, O) after the start of dialysis. This association may be confounded by age, sex, and primary kidney disease (summarized in Figure 1 as vector 'V'). The analysis presented was adjusted for these possible

confounders, indicated by the square around V. Since we were using data of the NECOSAD cohort, we only had data of patients who were included in the cohort, i.e. those who started with dialysis therapy (T). The square around T indicates that we conditioned on a particular value of T, namely T=1, i.e. patients who started with dialysis therapy. The duration of pre-dialysis care as well as the decision to start with dialysis therapy may be influenced by several physician-related factors (motivation). These physician-related factors however, were not measured in the NECOSAD study and therefore are designated 'U' (unknown) in Figure 1. There might be another factor (F), the presence of uremic symptoms, which is directly associated with the outcome under study and the start of dialysis therapy. Furthermore, as a consequence of conditioning on the start of dialysis (the square around T), the path between the presence of uremic symptoms and the duration of pre-dialysis care is open via the physician-related factors. Now we can see the problem of selection bias: we conditioned (selected) on T and since T is a consequence of F and U, this means that we may know the value of F if we would know the value of U and vice versa. For example, if we know that a patient started with dialysis therapy because he/she developed uremic symptoms, it is less likely that he/she started dialysis therapy because the physician insisted to do so. Since the presence of uremic symptoms is directly associated with survival after the start of dialysis, and the physician-related factors are associated with the duration of pre-dialysis care, it might be obvious that selection bias has been introduced: a path has been opened between the exposure and the outcome under study (E←U→[T]←F→O). As might be seen in Figure 1, there is also an association between the duration of pre-dialysis care (E) and the start of dialysis (T) as well as between the presence of uremic symptoms (U) and the duration of pre-dialysis care (E). Consequently, there is also selection bias through E→[T]←F→O. This bias may even be stronger than the first one, since for the first bias it might be hypothesized that the associations between the physician-related factors (F) and the duration of pre-dialysis care (E) and between the presence of uremic symptoms (U) and the duration of pre-dialysis care (E) counterbalance the selection bias through E←U→[T]←F→O.

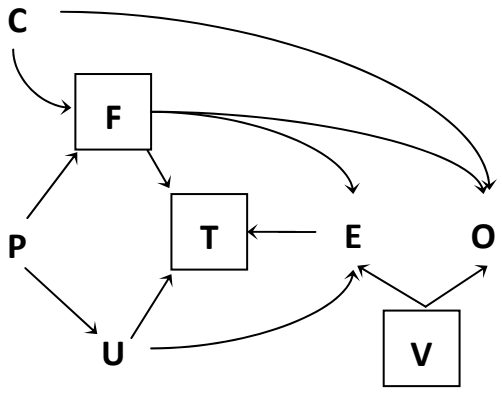
Figure 1. Causal DAG for investigating the association between the duration of pre-dialysis care and survival during dialysis in NECOSAD patients (see **Chapter 7** for details).



E: duration of pre-dialysis care; F: uremic symptoms; O: mortality; T: inclusion in NECOSAD/start of dialysis; U: physician-related factors.

In literature, it has been described how it is sometimes possible to adjust for selection bias: by using inverse probability weighting (IPW). In short, IPW is a technique whereby each patient that has been selected for the study not only accounts for his/herself, but also for the patients that have not been selected for the study, but who had similar characteristics.[16] In the present example: patients who had similar values for F and U who started with dialysis (those who were included in the NECOSAD cohort) *versus* patients who did not start with dialysis. IPW assigns a weight that is inverse to the probability that a patient started with dialysis. For example, if three patients had similar characteristics with respect to F and U and one of them started with dialysis, then the two patients who did not start with dialysis receive a weight of zero, i.e. they are not included in the analysis. The patient who started with dialysis receives a weight which is the inverse of the probability to start with dialysis: 1 / (1/3) = 3. Subsequently, a pseudo-population will be created in which the three patients in the original study population are replaced by three copies of the patient who started with dialysis. Now valid estimates can be made, if it can be assumed that the outcome in the selected patients (the patients who started with dialysis) truly represents the unobserved outcomes of the patients who were not selected (did not start with dialysis). This assumption however, is not testable in the NECOSAD study, since we do not have information of the patients who did not start with dialysis. In theory, we can use data from the PREPARE-1 or PREPARE-2 study to check the assumption. In practice however, this requires additional untestable assumptions, such as that PREPARE-1 or PREPARE-2 patients are comparable to potential NECOSAD patients.

Figure 2. Adjustment for selection bias may introduce selection bias.



C: clinical factors (e.g. residual renal function); E: duration of pre-dialysis care; F: uremic symptoms; P: patient-related factors (e.g. psychological factors); O: mortality; T: inclusion in NECOSAD/start of dialysis; U: physician-related factors; V: vector (age, sex, primary kidney disease).

Besides IPW another method is available to adjust for the selection bias depicted in Figure 1. If it would be possible to block the path E←U→[T]←F→O, the selection bias would have been adjusted for. From Figure 1 it might be clear that there are two possibilities to block this path:

either conditioning on U or conditioning on F. Since U is unmeasured (unknown) in our study, we can only adjust for F. Adjustment for F will also lead to a block of the path E→[T]←F→O, which was a more important bias than the bias just mentioned. When adjusting for F, other factors related to F should also be taken into account. (Figure 2) For example, patient related factors ('P'), such as psychological factors, may be related to the development as well as the reporting of uremic symptoms. These psychological factors may also influence the physician's decisions, since patients will tell their doctors how they feel. In addition, other clinical parameters ('C'), such as the level of residual renal function may be associated with both the development of uremic symptoms and mortality. In this case, adjustment for F again introduces (another) selection bias, since the path between E and O is open (E←U←P→[F]←C→O). To summarize, the analyses presented in **Chapter 7** may be biased by selection bias. Despite different methods available to adjust for selection bias, adjustment for this bias was not feasible or would have introduced selection bias. Still, the conclusions of the analyses presented are valid, assuming that these are only generalized to patients who started with dialysis therapy and the mechanisms for the decisions to start with dialysis are exactly similar.

The ERA-EDTA Registry cohort presented in **Chapter 8** included by far the most patients of all cohorts presented in this thesis. This registry annually collects data of incident renal replacement therapy patients from European national and regional renal registries. In fact, the cohort consisted of multiple cohorts of incident dialysis patients from different countries throughout Europe. The database included patients' age, sex, primary renal disease, modalities and changes in renal replacement therapy, and dates and causes of mortality. A major strength of this database is the large number of patients included. Analyses can be performed with great precision. The number of parameters available however, is only limited. This large database including data of different registries also has an additional important limitation. Missing information may be hard to retrieve, if possible. In **Chapter 8** more than 10% of the mortality causes were unknown/missing. The sensitivity analysis presented in this chapter however, showed that the final conclusion of the study was not influenced by the amount of missing mortality causes.

In general, analyses in the presence of missing data may be seriously biased, when data are missing not at random.[17] Missing not at random means that even if other non-missing data are taken into account, systematic differences exist between the patients with observed and with missing data.[18] In addition to missing not at random, two other types of missing data exist: missing completely at random and missing at random.[19] The first type of missing data refers to the situation whereby subjects with missing data are a random subset of the total study population, whereas the latter type refers to the situation whereby the probability that an observation is missing depends on other, observed, information. A variety of techniques has been proposed to deal with missing values, among others last observation carried forward, use a missing data category, use the mean of the observed values instead of missing data, and multiple imputation.[19] Multiple imputation is the only generally accepted technique in which other available patient characteristics are used to predict the value for missing data. In this thesis,

multiple imputation has been used to impute missing phosphorus and calcium levels in **Chapter 5**.

Clinical implications

In the context of these strengths and limitations the main findings of this thesis (Table 2) are translated into clinical implications. Within this thesis different risk factors for progression from pre-dialysis to dialysis were studied, of which some factors were modifiable and others unmodifiable. An example of an unmodifiable risk factor is family history. In **Chapter 4** we showed that a positive family history of diabetes mellitus or cardiovascular disease is associated with an increased mortality risk in the first year of pre-dialysis care. Associations between family history and disease severity have been found in different diseases, such as venous thrombosis,[20] thyroid cancer,[21] Alzheimer's disease,[22] and peripheral vascular disease.[23] The added value of family medical history may diminish in light of the increasing availability of genome wide screening tools.[24] However, it is an easy method to apply that may be regarded as a cheap "genetic biopsy".[25] In the present analysis we found a near significant effect of a positive family history on mortality during pre-dialysis. In light of the size of the effect estimate, we conclude that obtaining family medical history at the start of pre-dialysis care may be valuable in identifying patients at increased mortality risk during pre-dialysis care.

Table 2. Overview of the determinants and outcomes studied in this thesis.

Chapter	Patients	Determinant	Outcome	Association found?
4	Pre-dialysis	Family medical history	Decline kidney function	No
			Mortality	Yes (+)
5	Pre-dialysis	Serum calcium levels	Decline kidney function	No
			Start dialysis	No
		Serum phosphorus levels	Decline kidney function	Yes (+)
			Start dialysis	Yes (+)
6	(Pre-)dialysis	Duration of pre-dialysis care	Mortality	Yes (-)
7	(Pre-)dialysis	Decline kidney function	Course of decline	*
8	Dialysis	Mortality cause	Cause specific mortality	*

*Descriptive analyses, not intended to study associations; + increased risk; - lower risk

In **Chapter 5** an example of a study on a modifiable risk factor is presented. The main conclusion of this study is that increased serum phosphorus levels are associated with an increased risk for the start of dialysis therapy within two years of pre-dialysis care and a faster rate of decline of kidney function. These data may suggest that phosphorus levels should be kept as low as possible, for example by dietary phosphorus restriction or medication. In practice, the latter may be easier to apply, since dietary phosphorus restriction is known to be very difficult.[26] But first, additional studies, for example randomized controlled trials (RCTs), are needed to investigate whether the association found is causal or not, i.e. to sort out whether lowering phosphorus levels has a positive effect indeed.

Very early referral of CKD patients to a nephrologist is beneficial, irrespective whether a patient has diabetes mellitus or is aged 70 years or above; this is the conclusion of the study presented in **Chapter 6**. The latter finding is especially interesting, considering the ageing population and its associated problems. A recent systematic review confirms that early referral is associated with beneficial outcomes, such as reduced mortality and hospitalization, and better preparation for dialysis therapy.[27] Further studies are needed to sort out whether very early referral is also associated with other aspects such as quality of life. Furthermore, it might be investigated by whom the patients who were late referred were referred and whether patients who were late referred by a nephrologist have better outcomes as compared to patient who were late referred by, for example, a general practitioner.

The rate of decline of kidney function changes between two to four months of dialysis therapy (**Chapter 7**). This change in the rate of decline may reflect an effect of the start of dialysis therapy, the natural course of the decline or just an artifact introduced by the method used to model the decline. Furthermore, the pattern of decline of kidney function was similar in hemodialysis and peritoneal dialysis patients, although at a different level of GFR. Further studies are needed to find the real explanation for the change in the rate of decline of kidney function. The recent publication of the IDEAL (initiating dialysis early or late) trial[28] has encouraged the discussion on when to start dialysis therapy. Analyzing decline of kidney function in IDEAL or a similar trial would help interpreting the results of our analysis. However, other (observational) studies might be used as well.[29]

Dialysis patients are at increased mortality risk. It is generally believed that the increased mortality risk can be explained by the observed increased cardiovascular mortality risk in dialysis patients.[30;31] The study presented in **Chapter 8** shows that the increased mortality risk in dialysis patients is not solely attributable to cardiovascular causes, but also to noncardiovascular causes, such as infection and cancer. These results implicate that the focus in present research in dialysis should not only be on cardiovascular mortality but also on noncardiovascular mortality, especially infections and malignancies.

Conclusions

The main conclusions of this thesis are:

- A positive first-degree family medical history of diabetes mellitus and cardiovascular disease is associated with increased mortality in the first year of pre-dialysis care, but not with decline of kidney function.
- Increased levels of serum phosphorus, but not serum calcium, are associated with an increased risk to start with dialysis therapy within two years after the start of pre-dialysis care. In addition, an increase in the phosphorus level is associated with the rate of decline of kidney function.
- Late referral to pre-dialysis care is associated with an increased mortality risk in the first year of dialysis therapy. This effect is also present in diabetics and elderly (70 years of age and above).

- The decline of kidney function is constant in the period of one year before the start of dialysis until two to four months of dialysis therapy. After that period, the rate of decline of kidney function decreases. This pattern is similar in HD and PD patients.
- In dialysis patients, cardiovascular and noncardiovascular mortality are equally increased.

Future research

Future research should aim at investigating whether the associations described in this thesis were causal or not. To this end, randomized controlled trials may be performed. For example, to study the effect of phosphorus levels on the rate of decline of kidney function, patients may be randomized to phosphorus lowering agents or for example dietary advice. The effect of the duration of pre-dialysis care on mortality may be studied by randomizing patients to either short or very long pre-dialysis care. However, in practice the added value of performing this study is limited, since this study can not be blinded. Furthermore, many exposures can not be randomized (for example family medical history) and cohort studies may be used to study such exposures. Moreover, unintended effects of exposures can be validly studied using observational cohort studies.[32]

To investigate the progression of CKD, ideally a (cohort) study would be performed including patients from the start of their disease onwards. In practice, such a study is not feasible, for CKD is a disease with a long pre-clinical phase. Unless a suitable screening method becomes available, CKD patients will generally only be detected when they get symptomatic. Therefore, a practical solution would be to follow patients from their diagnosis of kidney disease onwards, for example by recruiting patients at general practitioners. But still selection bias may be present, since CKD will remain unnoticed by a subset of patients who never attend their general practitioner. Furthermore, patients who are identified as having CKD at the general practitioners will likely all be in different stages of the disease. A nice starting point for follow-up therefore, is the start of pre-dialysis care. All patients are more or less in the same disease stage.

In this thesis, different cohorts were used to study CKD progression after the start of pre-dialysis care. Ideally, all analyses would have been performed in a single cohort including incident pre-dialysis patients who are followed-up until death (i.e. no censoring for the initiation of renal replacement therapy). Within this study data collection should be performed carefully in order to limit the amount of missing data. This prospective cohort study might be used to investigate the determinants and outcomes presented in this thesis, but could also be used to further investigate the influence of pre-dialytic risk-factors on outcomes during dialysis without running into the problem of selection bias. Furthermore, when using this study to investigate mortality in pre-dialysis it should also study different causes of mortality separately. In fact, such a study has already been designed and will be started soon, the 'European Quality Study on when to start dialysis' (EQUAL Study).[33;34]

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