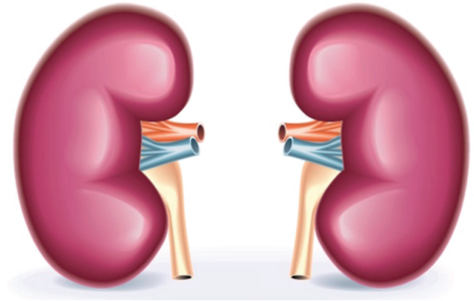
Progression of CKD from pre-dialysis to dialysis - Dinanda van Appeldoorn-de Jager

# Progression of CKD from pre-dialysis to dialysis:

natural course, risk factors, and outcomes



Dinanda van Appeldoorn-de Jager

Stellingen behorend bij het proefschrift

# “Progression of CKD from pre-dialysis to dialysis: natural course, risk factors, and outcomes”

1. Als niet nauwkeurig gedefinieerd wordt welke vorm van interactie bestudeerd wordt, is het zeer aannemelijk dat de aan- of afwezigheid van multiplicatieve interactie wordt bestudeerd.
   *Dit proefschrift*

2. Anamnese van familiegeschiedenis van diabetes en hart- en vaatziekten bij pre-dialyse patiënten kan bijdragen aan het identificeren van patiënten met een hoger sterfterisico tijdens pre-dialyse.
   *Dit proefschrift*

3. Het patroon van achteruitgang in nierfunctie is hetzelfde in hemodialyse en peritoneale dialysepatiënten.
   *Dit proefschrift*

4. Het onderzoek naar oorzaken van niet-cardiovasculaire sterfte in dialysepatiënten is minstens zo belangrijk als het onderzoek naar oorzaken van cardiovasculaire sterfte.
   *Dit proefschrift*

5. Vroege doorverwijzing voor multidisciplinaire pre-dialyse zorg is geassocieerd met betere overleving tijdens dialyse.
   *Dit proefschrift*

6. Dé progressie van een chronische nierziekte is niet te kwantificeren.

7. Een randomized controlled trial design is niet per definitie het beste studiedesign.
   *vrij naar J.P. Vandenbroucke in* PLoS Medicine*, 2008*

8. Zonder counterfactual wereld, is het niet mogelijk met 100% zekerheid een causale factor te identificeren.

9. Causal directed acyclic graphs (DAGs) are of no practical use, unless we make an assumption linking the causal structure represented by the DAG to the data obtained in a study.
   *Miguel A. Hernán and James M. Robins in* Causal Inference*, Chapter 6*

10. Waarom werd de mens pas op de laatste dag geschapen? Opdat men hem, wanneer hij te ijdel wordt, kan zeggen: de mug werd eerder geschapen dan jij.
    *joodse wijsheid*

17 oktober 2012
Dinanda van Appeldoorn-de Jager

# Progression of CKD from pre-dialysis to dialysis: natural course, risk factors, and outcomes

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**Proefschrift**

ter verkrijging van

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*Voor Ferdinand en Boaz*

**Contents**

# Chapter 1 |

## Introduction, aim, and outline of this thesis

## Introduction

Chronic kidney disease (CKD) is a severe condition, characterized by an abnormal urinary protein excretion and/or impaired kidney function due to kidney damage. The prevalence of CKD in the Netherlands is 11%.[1] Furthermore, worldwide the prevalence and incidence of CKD are increasing.[2-4] CKD develops as a result of an underlying primary kidney disease, such as diabetes mellitus, glomerulonephritis, or renal vascular disease.[5] The primary kidney disease causes fibrosis and sclerosis of the functional kidney units, the glomeruli, that leads to impaired kidney function.[6] Usually, kidney function is expressed by the glomerular filtration rate (GFR). The GFR is the flow rate of filtered fluid through the kidney corrected for the body surface area (mL/min/1.73m$^2$). In healthy persons, the GFR is typically larger than 90 mL/min/1.73m$^2$, while in patients with severely impaired kidney function the GFR may even be below 10 to 15 mL/min/1.73m$^2$.[7] Decreased GFR has been associated with complications in virtually all organ systems, such as the cardiovascular system, bone, skin, lungs, and the central nervous system. Important symptoms for these complications include hypertension, anemia, accelerated atherosclerosis, mineral bone disease, malnutrition, and neuropathy.[7] Furthermore, patients with impaired kidney function are at increased all-cause mortality risk[8;9] and especially cardiovascular mortality is shown to be increased in these patients.[10-12]

### *CKD progression*

After the initial damage of the kidney, a series of adaptive changes takes place in the kidney ('adaptive glomerular hyperfiltration'), which is first sufficient to adapt to the initial kidney damage, but finally causes destruction of the remaining functional kidney tissue.[5] This destructive process is often mediated by comorbidities like hypertension and proteinuria.[6] Hence, CKD frequently shows a progressive course. Obviously, in the ideal situation patients are identified at the earliest stages of CKD to allow early medical intervention or behavioral changes. Population wide screening or screening a subset of high risk patients for the presence of CKD therefore seems the solution to detect patients when they are in the pre-clinical phase. However, the quest for a suitable and valid screening test for CKD detection turns out to be hard and the ideal test has not been found yet.[13] Consequently, many patients are only identified when their GFR is severely impaired and symptoms start to develop, which is usually when the GFR has dropped below 30 mL/min/1.73m$^2$. CKD may progress until end-stage renal disease develops and renal replacement therapy, which is either kidney transplantation or dialysis treatment, is needed to survive. Fortunately, therapeutic interventions aimed at treating the primary kidney disease and at strictly controlling the comorbidities early in the course of CKD are shown to be effective in slowing or preventing the progression towards end-stage renal disease.[6;14-17]

### *Treatment guidelines*

Since adequate management of CKD patients is associated with the progression rate of their disease, guidelines have been developed to improve the delivery of care in these patients. For example, in 2003 the National Kidney Foundation Disease Outcomes Quality Initiative (NKF

KDOQI) guidelines have been introduced,[18] while in 2009 the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have been established.[19] Both guideline series are based on clinical evidence and expert opinion. The KDIGO guidelines however, build on more recent evidence and are therefore intended and recommended to replace the KDOQI guidelines. In the Netherlands, CKD patients are recommended to be treated according to the guidelines of the Dutch Federation of Nephrology (NfN),[20] which are based on both the KDOQI and KDIGO guidelines. The clinical practical guidelines include suggestions for the treatment of complications of kidney dysfunction, like hypertension, hyperphosphatemia, and anemia, and also provide suggestions for preparation for renal replacement therapy.

*Multidisciplinary pre-dialysis care*

Ideal preparation for renal replacement therapy comprises of referral to a multidisciplinary team, consisting of a nephrologist, a dietician, and a social worker. The nephrologist is responsible for management of the kidney disease for example by combating the presence of uremic symptoms, and medication prescription, while the dietician is involved in dietary counseling, for example with respect to protein and salt restriction. It is the social workers duty to provide the patient with practical support when requested. For example help with filling out forms. This multidisciplinary approach strives for adequate control of CKD progression, preparation of vascular access for dialysis treatment, and guidance with regard to diet, lifestyle, and smoking cessation.[21] An important aspect of the multidisciplinary approach is that patients are provided with extensive information about their disease and possible treatment strategies, which enables them to make deliberate decisions on their therapy. In order to get as optimal pre-dialysis care as possible, timely referral to a multidisciplinary team is essential. Sometimes a distinction is made between 'late referral', defined as referral at or less than three months prior to the start of renal replacement therapy, and 'early referral', defined as referral more than one year prior to the start of renal replacement therapy. Late referral has been associated with increased morbidity and mortality after initiation of renal replacement therapy.[22-24] Causes of late referral may be either physician related (e.g. due to poor communication between the treating physician and the nephrologist), patient related (e.g. lifestyle or social economic factors), or just unavoidable (e.g. a very slowly progressing disease that remains unnoticed for a long period).[22;25] Important consequences of late referral include insufficient patient information, higher hospitalization rates, increased loss of kidney function, uremia, and increased mortality.

**Aim and scope of this thesis**

Management of patients on pre-dialysis care appears an important factor in improving outcomes of CKD patients with severely impaired kidney function. For that reason, efforts should be made to optimize multidisciplinary pre-dialysis care. The effects of pre-dialysis care on the level of GFR at start of dialysis may have important consequences even after the start of dialysis. Furthermore, other factors may play an important role in the progression of CKD. The aim of this

thesis is to study the progression of CKD from the phase of pre-dialysis care to the dialysis phase. More specifically, the following objectives are formulated:

a) To study the association between pre-dialytic risk factors (family history and serum phosphate and calcium levels) and disease progression during pre-dialysis care;
b) To study the association between a pre-dialytic risk factor (the duration of pre-dialysis care) and disease progression after the start of dialysis;
c) To study differences in outcomes (decline of kidney function and mortality) during pre-dialysis care and dialysis after the start of dialysis.

To that end, the thesis is divided into three parts; each part is concentrating on a different patient category: the first part addresses patients new on pre-dialysis care; the second part addresses patients in the transition period between pre-dialysis care and dialysis; the third part addresses patients new on dialysis.

**Outline of this thesis**

*Methodological background*

Clinical (epidemiological) studies are particularly suitable to study the effect of a risk factor on a particular outcome. To study whether an association between a risk factor and the outcome under study differs between specific sub-groups of patients, specific analytical tools are required. These analytical tools deserve extra attention and are therefore introduced separately in **Chapters 2** and **3**. These chapters describe specific epidemiological methods to measure interaction and how to report interaction within clinical studies. The methods thus described will be used later in this thesis.

*Part 1: Pre-dialysis care*

**Chapter 4** presents a study that was performed in the PREPARE (PREdialysis PAtients REcords)-1 cohort, a retrospective Dutch cohort study in incident pre-dialysis patients. This study investigated whether a positive family history of diabetes, cardiovascular disease, and/or kidney disease is associated with disease progression, as measured by a faster decline of kidney function and increased mortality in the first year of pre-dialysis care.

It has been shown that pre-dialysis care is associated with prolonged survival, also after the start of dialysis; therefore it is important to focus on the treatment of patients during this pre-dialysis phase. As stated earlier, several guidelines for treatment of CKD patients exist. **Chapter 5** aims to describe whether patients are actually treated according to the recommended guidelines for mineral metabolism (serum phosphate and serum calcium) and whether achievement of these guidelines is associated with a prolonged dialysis-free survival during the first two years of pre-dialysis care. This analysis was performed in the prospective Dutch PREPARE-2 cohort, which includes incident pre-dialysis patients.

*Part 2: From pre-dialysis care to the start of dialysis*

Since mortality in dialysis patients is largely increased, we studied in a cohort of Dutch incident dialysis patients, the NECOSAD (NEtherlands COoperative Study on the Adequacy of Dialysis) study, whether patients who were treated by a nephrologist before the start of dialysis treatment (i.e. patients who were referred early) have a better survival during dialysis treatment as compared to patients who were referred late. We additionally studied whether high-risk populations such as diabetics and elderly (aged 70 years and above) have additional benefit of early referral. (**Chapter 6**) In addition to time of referral, other risk factors may play a role in the poor prognosis of dialysis patients, for example, the declining kidney function, which is an important characteristic of CKD. To study whether the pattern of decline of (residual) renal function attenuates after the initiation of dialysis treatment, we explored the decline of GFR in 1861 patients from the NECOSAD cohort in the year before until one year after the initiation of dialysis treatment (**Chapter 7**).

*Part 3: Dialysis therapy*

As outlined above, CKD is a severe 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** presents a comparison of the cardiovascular and non-cardiovascular mortality rates of dialysis patients with the mortality rates in the general population. This study was performed in a large database of European incident dialysis patients (ERA-EDTA Registry).

In **Chapter 9** the results presented in the previous chapters are summarized and discussed in a broader context, including the clinical implication of these results and suggestions for further research.

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# Chapter 2 |

## Interaction on an additive scale

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*Nephron Clin Pract 2011;119:c154–c157*

**Abstract**

Many clinical epidemiological studies investigate whether a certain exposure, or risk factor, is associated with the incidence of disease or mortality. It may be of interest to study whether this association is different in different types of patients, or to study joint effects. To investigate whether the effect of one risk factor differs across the strata of another risk factor, the presence of interaction among two risk factors can be examined. In statistics, interaction refers to the inclusion of a product term of two risk factors in a statistical model. Statistical interaction thereby evaluates whether the association deviates from either additivity or multiplicativity, depending on the scale of the model. From a public health perspective, the assessment of interaction on an additive scale may be most relevant. For a transparent presentation of interaction effects, it is recommended to report the separate effect of each exposure as well as the joint effect compared to the unexposed group as a joint reference category to permit evaluation of interaction on both an additive and multiplicative scale.

## Introduction

### Interaction between risk factors

Many clinical epidemiological studies investigate whether exposure, or a risk factor, is associated with the development or progression of disease or mortality. It may be of interest to study whether this association is different in different types of patients. For example, we might want to know whether the observed association between exposure to life style risk factors and the incidence of chronic kidney disease (CKD) differs between men and women.[4] Besides observational studies, randomized clinical trials commonly evaluate whether treatment effects differ across certain subgroups. For example, the Cathedia study randomized 750 critically ill patients requiring acute renal replacement therapy to receive jugular or femoral vein catheterization, and studied if rates of infectious complications differed in predefined subgroups of catheter insertion time, body mass index, sex, and type of renal replacement therapy.[2] In order to address such research questions, it can be examined whether the effect of one risk factor on a certain outcome differs across strata of another risk factor. In other words, the presence of interaction can be examined.

In the literature, interaction is studied and reported in several different ways.[6;7] A literature survey concluded that the reporting of interaction in the medical and epidemiological literature is inadequate.[6] One common mistake is the comparison of *p* values across subgroups and to conclude that interaction is present when there is a statistically significant association in one category (for example, men) but not in the other (women).[6;8] This paper illustrates to what extent different approaches of the concept interaction can result in different answers to a research question and shows how interaction can be examined on an additive scale using incidence rates.

### Statistical interaction

In statistics, interaction refers to the inclusion of a product term of two risk factors in a statistical model for a better fit of the model.[9] Statistical interaction thereby evaluates whether the association deviates from either additivity or multiplicativity, depending on the scale of the model. In this way, the presence of interaction and its interpretation depend on the underlying scale of the model. For example, in a linear regression model, statistical interaction indicates that the association between the two risk factors and the outcome under study is no longer additive (for example, the interaction between salt intake and age in the association with blood pressure as a continuous outcome variable). In contrast, logistic and Cox regression models are multiplicative models. Statistical interaction in such models (for example, the interaction between salt intake and age in association with hypertension as a dichotomous outcome variable) indicates a deviation from multiplicativity, rather than from additivity. This may not be a problem as long as the researcher is aware that the choice of the statistical model and underlying scale has an impact on the interpretation of the interaction effect. However, from a public health perspective, the assessment of interaction on an additive scale may be most relevant.[8-10]

**Interaction on an additive scale**

A departure from risk additivity implies that the number of cases attributable to the combined effect of two risk factors is more or less than the sum of the number of cases that would be caused by each risk factor separately. In the absence of bias, departures from risk additivity imply that some subgroups would obtain a greater absolute risk reduction from the intervention than others would.[9-11] Therefore, the additive scale, which uses absolute risks, may be most relevant for public health and clinical decision making.[8]

**Example 1**

Because CKD is a risk factor for cardiovascular disease (CVD) but CVD may also promote CKD, it can be hypothesized that CKD and CVD have a synergistic effect on future cardiovascular and mortality outcomes. With data from a cohort study in 26,147 individuals from 4 community-based studies[3] the presence of additive interaction between CKD and CVD in the association with a composite outcome of cardiac events, stroke and death can be examined. The figure shows the incidence rates of the composite outcome in 10 years of follow-up.[3] In persons without CKD and CVD at baseline, the rate of the composite outcome was 16.9/1,000 person-years (PY). This can be considered as the background rate: from all persons without CVD and CKD at baseline, 16.9/1,000 PY had a cardiac event or died within 10 years. In persons with CKD at baseline, this was 44.9/1,000 PY, resulting in a risk difference of 44.9 – 16.9 = 28/1,000 PY. In the absence of bias, this additional 28/1,000 PY can be attributed to exposure to CKD. In persons with CVD at baseline, the incidence rate was 52.7/1,000 PY, 52.7 – 16.9 = 35.8/1,000 PY more as a result of exposure to CVD. If no interaction between CKD and CVD was present, we would expect an outcome rate in persons exposed to both CKD and CVD at baseline of 16.9 + 28 + 35.8 = 80.7/1,000 PY: 16.9/1,000 PY will have the outcome anyway, an extra 28/1,000 PY as a result of exposure to CKD and an additional 35.8/1,000 PY as a result of exposure to CVD. The observed rate, however, was 116.4/1,000 PY.[3] Thus, the composite outcome occurred in 116.4 – 80.7 = 35.7 persons/1,000 PY more than we would expect on the basis of the sum of the separate effects of CVD and CKD (Figure 1).

This more than additive effect means that, as a result of interaction between CKD and CVD, an excess risk of 35.7 cases/1,000 PY has been observed. Assuming causality, this implies that if the occurrence of CKD could be prevented in the general population, this would not only prevent the 28 cases/1,000 PY, but in addition the 35.7 cases/1,000 PY would be prevented that would have occurred because of an interaction between CKD and CVD. In contrast, when examined on a multiplicative scale the combination of CKD and CVD appeared protective in this study,[3;5] whereas more patients reached the outcome than was expected on the basis of the separated risks of CKD and CVD. This example shows that by using absolute risks, additive interaction may be considered most relevant because of its potential implications for public health.

**Example 2**

In the Cathedia study of 750 critically ill patients the presence of interaction between catheter site and subgroups of BMI has been examined by including a product term of catheter site (femoral or jugular) and BMI (in tertiles) in a Cox proportional hazards regression model.[2] A significant interaction ($p$<0.001) was found for the effect of BMI on the association between catheter site and catheter colonization.

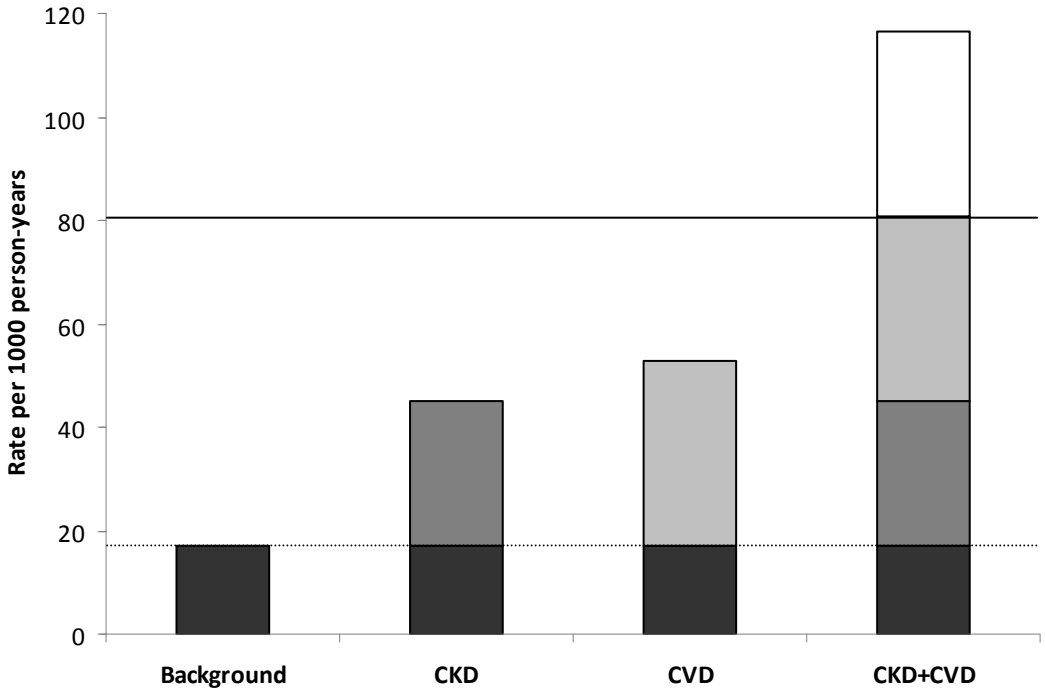


**Figure.** Incidence rates of composite outcome per 1,000 PY in 26,147 individuals during 10 years of follow-up without CKD or CVD, with CKD or CVD or with both CKD and CVD at baseline.[3] The dotted line indicates the background rate (16.9/1,000 PY); the straight line indicates exact additivity of effects.

**Example 2 (continued)**

Inherent to the Cox regression model, this means a deviation from multiplicativity of effects. When the regression coefficient of the product term is not given, the magnitude and the direction of the interaction effect cannot be interpreted from the *p* value only, nor whether there is interaction on an additive scale. However, the authors also reported absolute incidence rates of catheter colonization in strata of BMI and catheter site (Table 1, showing the upper and lower tertiles of BMI). These incidence rates provide the reader with sufficient information to evaluate the presence of interaction on both an additive and multiplicative scale. Patients with a low BMI (<24.2) had a higher incidence of colonization in the jugular versus femoral group (45.4 vs. 23.7/1,000 catheter-days, respectively). In the femoral group, patients with a high BMI (>28.4) also had a higher incidence of colonization compared with patients with a low BMI (50.9 vs. 23.7 per 1,000 catheter-days, respectively). Finally, patients with a high BMI in the jugular group did not have the expected rate of 72.6/1,000 catheter-days (the background rate 23.7 + risk difference jugular 21.7 + risk difference BMI 27.2 = 72.6/1,000 catheter-days) but 24.5/1,000 catheter-days, implying a less than additive effect. A less than additive effect is also referred to as interaction on an additive scale. In this example, the interaction effect was both less than additive and less than multiplicative. However, the interpretation of results can differ depending on the scale on which the presence of interaction is examined. The first example showed that it is possible to find a less than multiplicative effect, but a more than additive effect within the same data.[3;5] Or, as the next example illustrates, it is also possible to find different effects in subgroups on a multiplicative scale, whereas the effects are similar on an additive scale.

**Table 1.** Incidence rates of catheter colonization per 1000 catheter-days by femoral or jugular vein catheterization and body mass index (BMI) in 750 critically ill patients requiring acute renal replacement therapy.[2]

| Catheter site | BMI | Incidence rate |
|---|---|---|
| Femoral vein | <24.2 kg/m$^2$ | 23.7 |
| Jugular vein | <24.2 kg/m$^2$ | 45.4 |
| Femoral vein | >28.4 kg/m$^2$ | 50.9 |
| Jugular vein | >28.4 kg/m$^2$ | 24.5 |

**Example 3**

A cohort study of incident dialysis patients (Netherlands COoperative Study on the Adequacy of Dialysis, NECOSAD) studied the association between self-rated health and mortality and examined the presence of interaction of self-rated health with age.[1] The crude mortality rates and adjusted hazard ratios are shown in Table 2. If we consider the crude effects per age stratum, in patients younger than 65 years of age, mortality rate associated with a poor self-rated health would be almost 20 times higher (24.5/1.4 per 100 PY) than in patients with a good self-rated health. In patients of 65 years or older, the mortality rate associated with poor self-rated health would be almost 4 times higher (35.3/9 per 100 PY) than in patients with a good self-rated health. On the basis of these stratum-specific relative risks, self-rated health seems more strongly associated with mortality in younger than in older dialysis patients. However, the absolute mortality rate among older patients with an excellent self-rated health is much higher than among younger patients (9.0 and 1.4/100 PY, respectively). On an additive scale, the effects of having a poor self-rated health appear similar for the younger (23.2 extra cases/100 PY) and older patients (26.3 extra cases/100 PY).

**Table 2.** Crude mortality rates per 100 person-year and adjusted hazard ratios in 1,443 dialysis patients in seven years of follow-up.[1]

| Age | SRH | Mortality rate/100py | Hazard ratio (95% CI) |
|---|---|---|---|
| ≥ 65 years | Poor | 35.3 | 10.6 (2.5,45.7) |
| ≥ 65 years | Good | 9.0 | 4.5 (0.9,21.8) |
| < 65 years | Poor | 24.5 | 8.0 (1.9,34.5) |
| <65 years | Good | 1.4 | 1 (reference) |

SRH: Self-rated health, py: person-year, 95% CI: 95% Confidence interval

**Conclusion**

The interpretation of statistical interaction is not consistent. From a public health perspective, the assessment of interaction on an additive scale may be most relevant. When using product terms in statistical models, one should consider whether the underlying scale of the model is additive or multiplicative. Since logistic regression is the most commonly used model in clinical research, the majority of analyses of epidemiologic data are performed on a multiplicative scale. An accompanying paper in this series presents surrogate measures of additive interaction that can be used to evaluate interaction on an additive scale, using effect measures derived from

multiplicative models.[12] For a transparent presentation of interaction effects it is recommended to report the separate effect of each exposure as well as the joint effect, each relative to the unexposed group as joint reference category (as shown in Tables 1 and 2).[8;13] This will provide the reader with sufficient information to evaluate the presence of interaction on both an additive and multiplicative scale.[8]

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# Chapter 3 |

## Reporting of interaction

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**Abstract**

Interaction is the situation whereby the association of one risk factor with a certain outcome variable differs across strata of another risk factor. From a public health perspective, the assessment of interaction on an additive scale may be most relevant. Although additive models exist, logistic and Cox regression models are the most commonly used models in epidemiology. The resulting relative risks can be translated to an additive scale. The present paper presents surrogate measures to evaluate the presence of additive interaction when dealing with data on a multiplicative scale (relative risks). For a transparent presentation of interaction effects it is recommended to report the separate effect of each exposure as well as their joint effect compared to the unexposed group as joint reference category to permit evaluation of interaction on both an additive and multiplicative scale.

## Introduction

### Interaction between risk factors

Interaction is the situation whereby the association of one risk factor with a certain outcome variable differs across strata of another risk factor.[1;2] From a public health perspective, the assessment of interaction on an additive scale may be most relevant.[1;2] An accompanying paper shows how interaction can be examined as departure from additivity using incidence rates.

Although additive models exist, logistic and Cox regression models are the most commonly used models in epidemiology. Furthermore, the case-control study design inherently leads to multiplicative modeling. Consequently, the majority of analyses of epidemiologic data are performed on a multiplicative scale. The resulting relative risks or rate ratios, however, can be translated to an additive scale.

The aim of this paper is to recommend a transparent presentation of interaction effects and to present surrogate measures that can be used to evaluate interaction on an additive scale, using effect measures derived from multiplicative models.

### Reporting of interaction

Because the presence of interaction and its interpretation depend on the underlying scale of the statistical model that is used,[3;4] the presentation of the methods and results must clarify which statistical model and scale the authors have used to evaluate the presence of interaction in their research. For a transparent presentation of interaction effects it is recommended to report the separate effect of each exposure as well as the joint effect, each relative to the unexposed group as joint reference category (as shown in Tables 1 and 2).[5;6] Such a two-by-four table will provide the reader with sufficient information to evaluate the presence of interaction on both an additive and multiplicative scale.[6] Botto and Khoury[5] summarized the advantages of such a table for data presentation. If possible, it is recommended to report absolute risks or rates as well.

**Table 1.** Mortality rates (MR, per 1000 person-year) for all-cause mortality in incident dialysis patients with inflammation (hsCRP>10), a deletion in the pro-inflammatory CC-chemokine receptor 5 gene (CCR5Δ32) or a combination of both.*

| Inflammation | CCR5Δ32 | MR | Expected MR, assuming additivity | Expected MR, assuming multiplicativity |
|---|---|---|---|---|
| Yes | Yes | 133 | 227[a] | 225[b] |
| Yes | No | 228 | | |
| No | Yes | 90 | | |
| No | No | 91 | | |

*Modified from Muntinghe et al[7]; [a]calculated as: background rate + effect of inflammation + effect of CCR5Δ32 = 91 + (228-91) + (90-91) = 227; [b]calculated as: relative effect of presence of inflammation * relative effect of CCR5Δ32 * background rate = (228/91) * (90/91) * 91 = 225.

**Measures of additive interaction derived from multiplicative models**

Three measures have been devised by Rothman[2] to evaluate additive interaction using effect measures derived from multiplicative models, such as logistic or Cox regression models.[8] These are the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S).[2;8] To calculate these measures, a simple logistic or Cox regression model should be built. This model should include a new composite variable, containing four expo-sure categories. The four categories indicate (1) the reference category (background risk; no exposure, or --), (2) a category for exposure to one of the risk factors under study (-+), (3) a category for exposure to the other risk factor to be examined (+-), and (4) a category for joint exposure to both risk factors under study (++).[3;8;9] Subsequently, the measures to evaluate additive interaction in relative risk data[3;8-11] can be calculated as follows ('RR', relative risk, refers to either odds ratio in a logistic regression model or hazard ratio in a Cox regression model):

(a) RERI = $RR_{++} - RR_{+-} - RR_{-+} + 1$. RERI can be interpreted as the extra risk due to interaction calculated as the difference between the (expected) effect based on the summation of the separate effects of the two risk factors under study and the (observed) effect in the joint exposure category.
(b) AP = $RERI/RR_{++}$ . AP can be interpreted as the proportion of the events under study (e.g. disease or mortality) that is due to interaction among persons with both exposures. AP is often expressed as a percentage.
(c) S = $(RR_{++} - 1)/([RR_{+-} - 1] + [RR_{-+} - 1])$. S can be interpreted as the excess risk from exposure to both risk factors when interaction is present, relative to the risk from exposure when interaction is absent.

When additive interaction is absent, both RERI and AP are equal to 0 and S is equal to 1. In practice, the indices will hardly ever be exactly 0 or 1. The associated 95% confidence interval (CI) may help in deciding whether additive interaction is absent (if 0 is clearly within the 95% CI of RERI and AP or 1 is clearly within the 95% CI of S). Several methods to calculate CIs around RERI, AP, and S have been proposed. Details, including Excel sheets for calculation, can be found elsewhere.[9;10;12-14]

The reference category should be the category with the lowest risk, since RERI, AP, and S are difficult to interpret when effects are protective.[2] It is possible to include additional terms to control for confounding in the statistical model. However, in contrast to S, RERI and AP may vary across strata defined by covariates.[11] Therefore, although some advocate RERI as the best choice of measures of additivity,[15] S seems the measure of choice in assessing the presence of additive interaction in multivariate models.[11]

**Example with hazard ratios**

In a study on the effects of soluble TNF-like weak inducer of apoptosis (sTWEAK) plasma levels on mortality, the interaction effect between sTWEAK levels and the presence of inflammation in hemodialysis patients were investigated.[16] The authors conclude, based on RERI 2.0 (95% CI –0.3 to 4.3), AP (43%), and S 2.2 (95% CI 0.8 to 5.9), that high sTWEAK levels have more than additive effects on all-cause mortality in hemodialysis patients with inflammation. Table 2 provides the underlying hazard ratios and the calculation of the measures.

**Table 2.** Hazard ratios for all-cause mortality with 95% confidence interval (CI) in 218 hemodialysis patients with inflammation (high IL-6 levels), high soluble TNF-like weak inducer of apoptosis (sTWEAK) levels, or a combination of both.*

| Inflammation | High sTWEAK levels† | Hazard ratio (95% CI) |
|---|---|---|
| Yes | Yes | 4.72 (2.24 to 9.94) |
| Yes | No | 2.70 (1.36 to 5.38) |
| No | Yes | 0.99 (0.37 to 2.61) |
| No | No | 1 (reference) |

*Modified from Carrero et al[16], †high sTWEAK was defined as above the 66th percentile. The three measures of additive interaction can be calculated as follows:

$RERI = RR_{+\,+} - RR_{+\,-} - RR_{-\,+} + 1 = 4.72 - 2.70 - 0.99 + 1 = 2.0$;

$AP = RERI/RR_{+\,+} = 2.0/4.72 = 0.43 = 43\%$;

$S = (RR_{+\,+} - 1)/([RR_{+\,-} - 1] + [RR_{-\,+} - 1]) = (4.72 - 1)/([2.70 - 1] + [0.99 - 1]) = 2.2$.

**Implication of additive interaction**

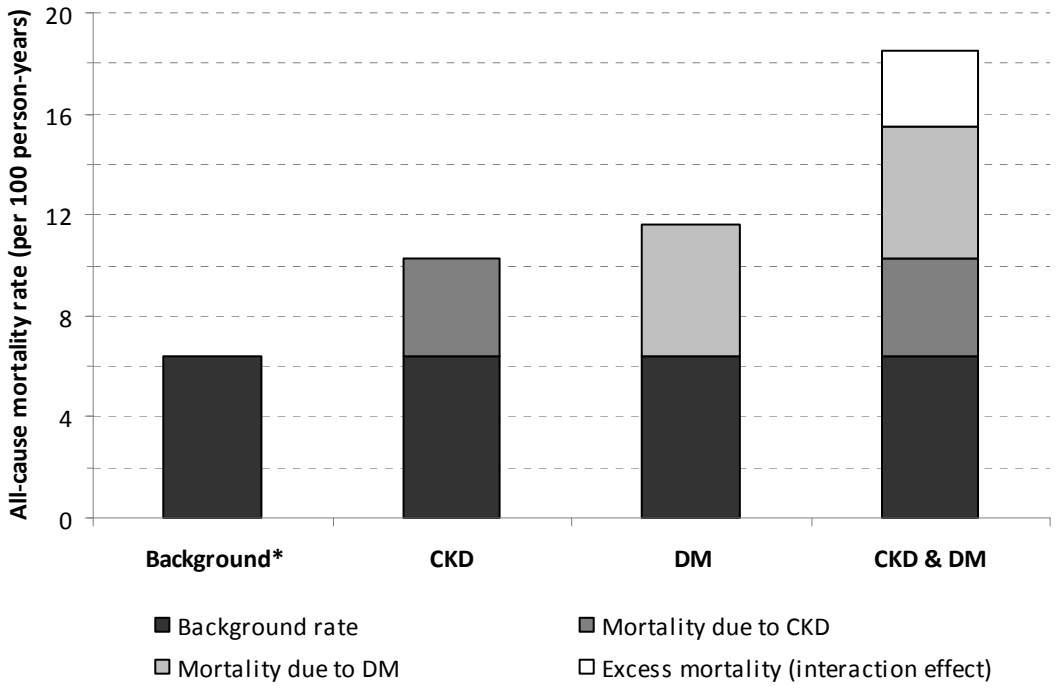
The joint effect of chronic kidney disease (CKD) and diabetes mellitus (DM) in the association with all-cause mortality was assessed in a cohort study of 19,737 individuals being at high risk for (first) myocardial infarction or who had previous acute coronary syndromes together with average cholesterol levels.[17] The all-cause mortality rate was lowest in subjects without both CKD and DM (background rate of 6.4/100 person-years, py) (Figure 1). The mortality rate in subjects with CKD (background rate + additional effect of CKD of 3.9/100py) was slightly increased. Likewise, the mortality rate in subjects with DM (background rate + additional effect of DM of 5.2/100py) was increased. On top of the combined effect of background, CKD, and DM an additional effect was present. This excess effect of 3/100py is called the interaction effect. Assuming causality, this implies that if the occurrence of CKD could be prevented in this population, this would not only prevent the 3.9 cases per 100py, but in addition the 3 cases per 100py (i.e. in total 7 deaths in 100 persons that are followed for 1 year) would be prevented that would have occurred because of interaction between CKD and DM.

**Conclusion**

Measures of additive interaction (RERI, AP, S) can be derived from multiplicative models to examine the presence of interaction on an additive scale using relative risks. For a transparent presentation of interaction effects it is recommended to report the separate effect of each

exposure as well as their joint effect, each relative to the joint reference category to permit evaluation of the presence of interaction on both an additive and multiplicative scale.

**Figure 1.** All-cause mortality rates per 100 person-years in 19,737 patients with chronic kidney disease (CKD), diabetes mellitus (DM), or a combination of both. The median follow-up period for all patients was 64 months.*




*Modified from Tonelli et al[17], †Background means all-cause mortality rate in patients without CKD, DM, or both

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# Chapter 4 |

# Associations between a family history of diabetes mellitus, cardiovascular disease, or kidney disease and disease progression in pre-dialysis patients

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*Submitted*

## Abstract

### Background

This study compared the prevalence of a first-degree family history (FH) of diabetes mellitus (DM), cardiovascular disease (CVD), and kidney disease (KD) in pre-dialysis patients and a random sample of the general population. Furthermore, the associations between FH and the decline of kidney function and mortality in the first year of pre-dialysis care were assessed.

### Methods

This study included 439 incident pre-dialysis patients (60±15 years; 55% male; $eGFR_{MDRD}$, 13.2±6.3 mL/min/1.73m$^2$). A random sample of the general population (PREVEND study, N=3,236; 49±12 years; 45% male) was used as reference. Mortality risks were estimated using Cox regression analysis (adjusted for sex and race, $HR_{adj}$). Differences in the slope of decline of kidney function ($eGFR_{MDRD}$) were estimated using linear mixed effect models, adjusted for sex and race.

### Results

The prevalences of $FH_{DM}$, $FH_{CVD}$, and $FH_{KD}$ were 18% *vs.* 16%, 29% *vs*. 16%, and 26% *vs*. 3% in first-degree relatives of pre-dialysis patients and the general population, respectively. The sex and race adjusted mortality risk for patients with $FH_{DM}$ (n=103) was HR 2.9 (95% CI 1.3 to 6.7) relative to patients without $FH_{DM}$. For $FH_{CVD}$ (n=134) HR was 2.4 (95% CI 1.1 to 5.4) relative to patients without $FH_{CVD}$ and in patients with $FH_{KD}$ (n=108) HR was 0.2 (95% CI 0.1 to 1.0) relative to patients without $FH_{KD}$. The difference in decline of kidney function between patients with and without $FH_{DM}$ was -1.17 mL/min/1.73m$^2$/year (95% CI -2.59 to 0.25), -0.54 (95% CI -1.91 to 0.83) for $FH_{KD}$, and 0.77 (95% CI -0.55 to 2.09) for $FH_{CVD}$.

### Conclusion

Patients with $FH_{DM}$ and $FH_{CVD}$ are at increased mortality risk in the first year of pre-dialysis care. Therefore, obtaining information about FH may help to identify pre-dialysis patients at increased risk of adverse outcome.

## Introduction

People with a high risk of diabetes mellitus and hypertension have more frequently proteinuria and a lower kidney function.[1] Screening specific high-risk groups of people with diabetes mellitus, hypertension or age 55 years and above is found to be the most effective strategy to detect chronic kidney disease (CKD).[2] Therefore, it can be hypothesized that the presence of specific comorbidities influences the prevalence and possibly the progression of CKD.

An important risk factor for CKD is familial clustering of this disease.[3-6] The prevalence of CKD, a history of hypertension, and diabetes mellitus is higher in first-degree relatives of CKD patients as compared to first-degree relatives of the general population.[7] Surprisingly, first-degree relatives of CKD patients who were under treatment by a nephrologist showed a very low awareness of kidney disease compared to the awareness of other illnesses such as hypertension or diabetes mellitus.[8]

Based on the observation that individuals with familial focal and segmental sclerosis have a poorer prognosis as compared to sporadic cases, it has been hypothesized that the clinical course of patients with sporadic end-stage renal disease (ESRD) in general is better as compared to the clinical course in patients with familial clustering of ESRD. To study this, survival of dialysis patients with familial clustering of ESRD was compared with survival of dialysis patients with sporadic ESRD.[9] It was found that, after adjustment for comorbid conditions, a family history of ESRD in either first- or second-degree relatives did not affect survival in 3,442 incident dialysis patients.

Although no effect of a positive family history on survival during dialysis was found, it might be postulated that a positive family history affects progression of patients not yet on dialysis. Therefore, this study assessed whether the prevalence of diabetes mellitus, cardiovascular disease, and kidney disease was different between first-degree relatives of pre-dialysis patients and first-degree relatives in a random sample of the Dutch general population. In addition, it was studied whether familial clustering of these illnesses in first- and/or second-degree relatives influenced the progression of kidney disease as measured by a faster decline of kidney function and an increased mortality risk in pre-dialysis patients.

## Methods

### *Study Design*

PREPARE-1 is a retrospective follow-up study of incident pre-dialysis patients. These patients were treated in eight pre-dialysis outpatient clinics of community and university hospitals in the Netherlands between January 1, 1999 and December 31, 2001. The clinical course during standard treatment of all consecutive patients was followed through medical records until censoring, i.e. the start of dialysis, death, transplantation or end of study (January 1, 2008), whichever occurred first. Predefined data on demography, biometry, clinical symptoms, and comorbidities were collected from written medical records at the start of pre-dialysis care (study inclusion). Data on laboratory measurements were extracted from the Hospital

Information System. The study was approved by the institutions' Medical Ethics Committee's and conducted in accordance with the Good Clinical Practice Guidelines.

*Patients*

Inclusion criteria for the PREPARE-1 Study were: the patient was at least eighteen years of age and he or she was referred to a pre-dialysis outpatient clinic for specialized pre-dialysis care. In practice, this refers to patients with a creatinine clearance of less than 20 mL/min in whom the need for renal replacement therapy is expected being within one year. Patients with prior renal replacement therapy or a total pre-dialysis follow-up of less than one month were not included in the study.

*Data Collection*

Primary kidney disease was classified according to the ERA-EDTA coding system.[10] Uncalibrated serum creatinine values were used to estimate the glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease equation.[11]

*Reference population*

A random sample of the Dutch general population was used as a reference population. This sample is part of the PREvention of Renal Vascular End-stage Diseases (PREVEND) study, a prospective cohort study in inhabitants of the city of Groningen, the Netherlands. The PREVEND study was established in 1997 to investigate the natural course of microalbuminuria and its relation with renal and cardiovascular disease in the general population. The specific random sample (n=3,432) that was used for this analysis was a subsample of the PREVEND study without the enrichment for albuminuria and therefore entirely reflects the general population. Subjects were aged 25-75 years at study inclusion. Study participants were requested to send in a morning urine sample and to fill out a questionnaire on demographic, renal, and cardiovascular history. All patients gave written informed consent prior to study participation. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. Further details of the study can be found elsewhere.[12]

*Determinants*

For pre-dialysis patients family history of specific illnesses, i.e. (a) diabetes mellitus, (b) cardiovascular disease, and (c) kidney disease, was collected from patient-reported information derived from medical records. If positive, it was recorded which of the following first-degree relatives was/were affected: father, mother, brother, sister and/or child. In addition it was assessed which of the following second-degree relatives was/were affected: grandfather, grandmother, grandchild and/or nephew/niece. If family history for a specific disease was not mentioned in the status, it was assumed to be negative. For the reference population family history was recorded by means of questionnaires. Subjects were asked whether father, mother,

brother or sister (a) got medication or a special diet as treatment for diabetes mellitus; (b) had experienced a cerebrovascular accident (except for transient ischemic attack), myocardial infarction or got heart surgery (including angioplasty); and (c) suffered from a kidney disease for which more than six weeks of dialysis was required. In case information for a specific disease was missing, family history for that disease was assumed to be negative.

*Endpoints*

For the present analyses, two different endpoints were studied. First, the risk (hazard) of death in the first year of pre-dialysis care and during complete pre-dialysis follow-up was estimated. Death during pre-dialysis care was assessed from the medical records and hospital databases. Second, the rate of decline of kidney function in the first year of pre-dialysis care was estimated as the slope (steepness) of the decline of eGFR.

*Statistical analyses*

Characteristics of all patients at the start of pre-dialysis care as well as characteristics of the reference population were expressed as mean and standard deviation or percentage, as appropriate. The prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives of pre-dialysis patients was compared to the prevalence of these illnesses in first-degree relatives of the general population. To adjust for age and sex differences between the study population and the reference population, we applied direct standardization using the age- and sex-distribution from the general population (PREVEND subsample) as the reference. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between a first- and/or second-degree family history and mortality in the first year of pre-dialysis care and during total pre-dialysis follow-up. Additional adjustments were made for sex and race. The rate of decline of kidney function was estimated using linear mixed effects models. The models were used to estimate the difference in decline of eGFR (mL/min/1.73m$^2$/year) between patients with a family history of one or a combination of the abovementioned illnesses and patients with a negative family history. These analyses were also adjusted for sex and race. Under the assumption that the decline of kidney function in a relatively short period is almost linear[13], we restricted follow-up time for this analysis to the first year of pre-dialysis care. Statistical analyses were performed with SPSS statistical software (version 17.0; SPSS, Chicago, IL).

**Results**

*Study population*

The retrospective PREdialysis PAtients REcords (PREPARE-1) Study included 547 patients. Of these, 439 (80.3%) patients had data available on family history. Two hundred fifty-four (57.9%) out of these 439 patients had at least one first- or second-degree relative with diabetes mellitus (n=103), cardiovascular disease (n=134) or kidney disease (n=108). Characteristics of these patients are shown in Table 1.

**Table 1.** Baseline characteristics of PREPARE-1 patients (N=439) grouped by whether their first- and/or second-degree family history of diabetes mellitus, cardiovascular disease, and kidney disease is either positive or negative.

| | Family history | |
|---|---|---|
| | Positive (n=254) | Negative (n=185) |
| Age *years* | 58.5 (14.8) | 59.7 (16.0) |
| Sex *% male* | 52.4 | 59.5 |
| Race *%* | | |
| Caucasian | 91.7 | 89.7 |
| Blacks | 2.8 | 3.8 |
| Asian | 2.0 | 2.2 |
| Other | 3.5 | 4.3 |
| Primary renal disease *%* | | |
| Diabetes mellitus | 18.1 | 15.7 |
| Glomerulonephritis/sclerosis | 8.7 | 12.4 |
| Hypertension | 7.5 | 11.4 |
| Pyelonephritis | 8.7 | 11.4 |
| Polycystic kidneys, adult type | 13.8 | 1.6 |
| Renal vascular disease | 6.3 | 8.6 |
| Miscellaneous | 26.4 | 24.9 |
| Unknown | 10.6 | 14.1 |
| Body mass index $kg/m^2$ [n=403] | 25.9 (4.8) | 25.7 (4.6) |
| Current smoker % [n=434] | 25.1 | 22.4 |
| Khan comorbidity score *%* | | |
| Low | 35.8 | 31.9 |
| Medium | 24.4 | 31.4 |
| High | 39.8 | 36.8 |
| Systolic BP *mmHg* [n=425] | 150.7 (26.6) | 153.7 (29.2) |
| Diastolic BP *mmHg* [n=425] | 83.2 (12.8) | 83.7 (13.4) |
| eGFR $mL/min/1.73m^2$ [n=396] | 13.4 (6.1) | 12.9 (6.5) |

Values indicate mean (standard deviation) or percentage, as appropriate; values between square brackets indicate the number of patients for whom information was available on that particular parameter; DM: diabetes mellitus; CVD: cardiovascular disease; KD: kidney disease; BP: blood pressure; eGFR: estimated glomerular filtration rate.

*Prevalence*

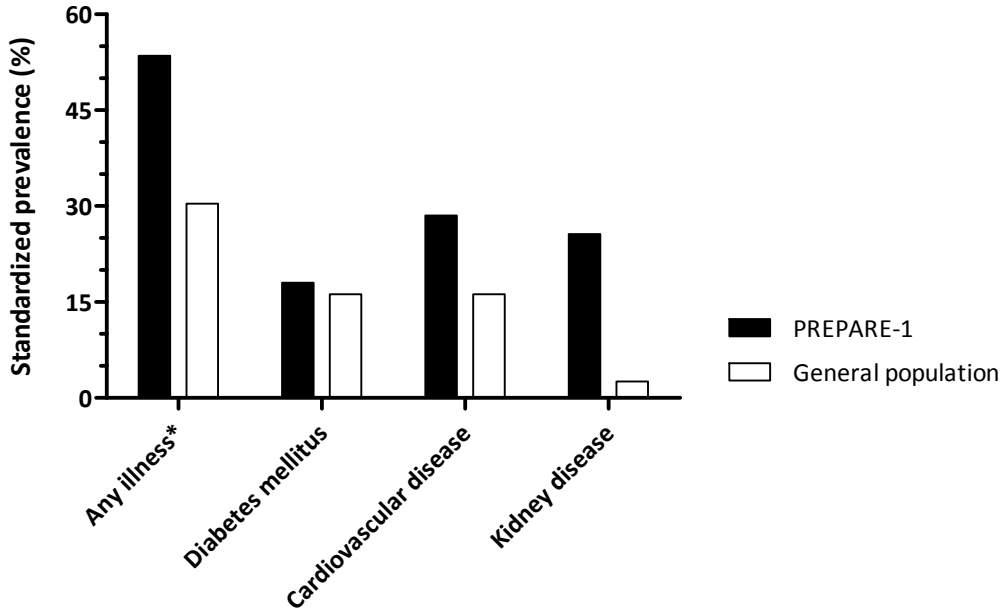
The age- and sex-adjusted prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives was compared between pre-dialysis patients and a random sample of the Dutch general population. Baseline characteristics of the 3,236 (94.3%) members of a sample of the general population (N=3,432) with available family history are shown in Table 2. The age- and sex-standardized prevalences of diabetes mellitus (18% *versus* 16%), cardiovascular disease (29% *versus* 16%), and kidney disease (26% *versus* 3%) were higher in first-degree relatives of pre-dialysis patients as compared to the general population. (Figure 1)

**Table 2.** Baseline characteristics of a random sample of the Dutch general population (N=3,236), grouped by whether their first-degree family history of diabetes mellitus, cardiovascular disease, and kidney disease is either positive or negative.

| | Family history | |
|---|---|---|
| | Positive (n=1,023) | Negative (n=2,213) |
| Age *years* | 52.3 (12.0) | 48.0 (12.4) |
| Sex *% male* | 44.2 | 45.4 |

Values indicate mean (standard deviation) or percentage, as appropriate; DM: diabetes mellitus; CVD: cardiovascular disease; KD: kidney disease.

**Figure 1.** Age- and sex-standardized prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives of pre-dialysis patients (N=439) and in a random sample of the Dutch general population (N=3,236). [a]First-degree relatives with at least one of the following illnesses: diabetes mellitus, cardiovascular disease, and kidney disease.




*Mortality*

During follow-up 51 pre-dialysis patients died (mortality rate 8.6/100 person-years, py; [95% confidence interval, CI 6.2 to 11.0]) of whom 34 patients (5.7/100py [95% CI 3.8 to 7.7]) had first- and/or second-degree relatives with diabetes mellitus, cardiovascular disease, and/or kidney disease, and 17 patients (2.9/100py [95% CI 1.8 to 4.6]) had a negative family history of these illnesses. Mortality rates for patients with a family history of diabetes mellitus, cardiovascular disease, and/or kidney disease were 2.9/100py (95% CI 1.8 to 4.6), 3.7/100py (95% CI 2.4 to 5.6), and 0.8/100py (95% CI 0.4 to 2.0), respectively. In the first year of pre-dialysis care, the mortality risks in patients with a family history of diabetes mellitus (HR 2.9 [95% CI 1.3 to 6.7]) or cardiovascular disease (HR 2.4 [95% CI 1.1 to 5.4]) were increased as

compared to patients without such family histories. The strength of these associations diminished when referring to complete follow-up during pre-dialysis care. (Table 3)

**Table 3.** Univariate and multivariate relative mortality risks for mortality associated with a positive family history in 439 pre-dialysis patients during the first year of pre-dialysis care and during the total pre-dialysis follow-up.

| | Any illness[a] | Diabetes mellitus | Cardiovascular disease | Kidney disease |
|---|---|---|---|---|
| First year | | | | |
| FH+ (events/N) | 18/254 | 11/103 | 12/134 | 2/108 |
| FH- (events/N) | 5/185 | 12/336 | 11/305 | 21/331 |
| Crude HR (95% CI) | 2.45 (0.91; 6.60) | 2.96 (1.31; 6.71) | 2.44 (1.08; 5.54) | 0.25 (0.06; 1.07) |
| Adjusted HR (95% CI)[b] | 2.35 (0.87; 6.34) | 2.92 (1.28; 6.66) | 2.39 (1.05; 5.42) | 0.24 (0.06; 1.04) |
| Total follow-up | | | | |
| FH+ (events/N) | 34/254 | 17/103 | 22/134 | 5/108 |
| FH- (events/N) | 17/185 | 34/336 | 29/305 | 46/331 |
| Crude HR (95% CI) | 1.31 (0.73; 2.34) | 1.55 (0.87; 2.79) | 1.53 (0.88; 2.67) | 0.27 (0.11; 0.68) |
| Adjusted HR (95% CI)[b] | 1.29 (0.72; 2.32) | 1.63 (0.90; 2.93) | 1.46 (0.84; 2.55) | 0.28 (0.11; 0.72) |

FH+: positive family history; FH-: negative family history; HR: hazard ratio; CI: confidence interval; [a]At least one of the following family histories: diabetes mellitus, cardiovascular disease, kidney disease or a combination of these; [b]Adjusted for sex and race.

*Decline of eGFR*

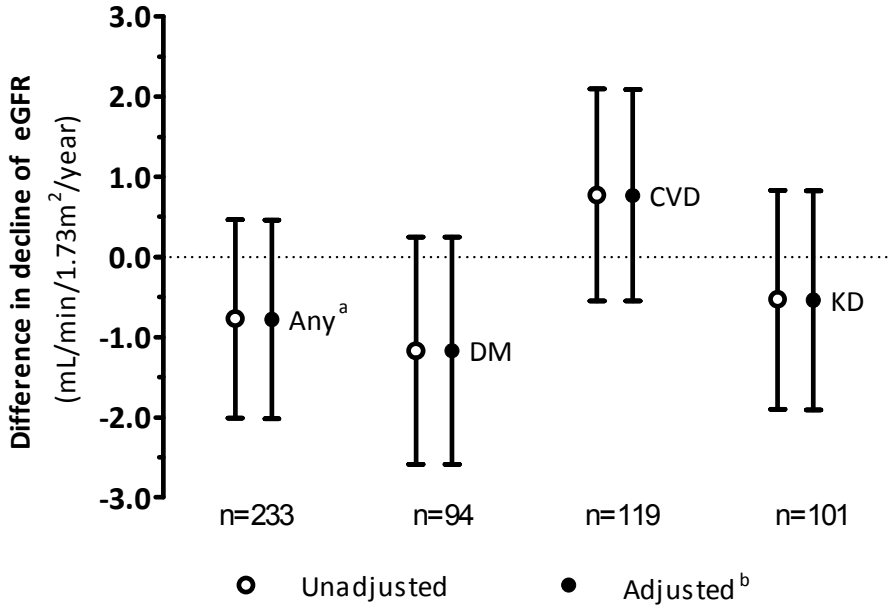
Decline of eGFR in the first year of pre-dialysis care was estimated as the slope of decline of eGFR using linear mixed effect models. In patients with a complete negative family history of diabetes mellitus, cardiovascular disease and kidney disease the mean sex and race adjusted rate of decline of eGFR in this period was -3.65 mL/min/1.73m$^2$/year (95% CI -4.26 to -3.04). The crude and adjusted differences in the decline of kidney function between patients with and without a family history of diabetes mellitus, cardiovascular disease, and kidney disease in the first year of pre-dialysis care as well as during total follow-up are shown in Figure 2.

*Post-hoc analyses*

To test the robustness of the results, it was investigated whether the increased mortality risk and the trend for a faster decline of kidney function in patients with a family history of diabetes mellitus could be explained by the presence of diabetes mellitus in the pre-dialysis patients themselves. To that end additional analyses were performed with further adjustment for having diabetes mellitus as comorbidity at baseline. These analyses showed a mortality risk of 2.66 (95% CI 1.13 to 6.29) and a difference in the rate decline of kidney function of -1.15 mL/min/1.73m$^2$ (95% CI -2.58 to 0.27) in the first year of pre-dialysis care. These results indicate that there is an association between a positive family history of diabetes mellitus and mortality, which is independent of whether the patient has diabetes mellitus. Similarly, it was

tested whether the increased mortality risk in patients with a family history of cardiovascular disease could be explained by the presence of cardiovascular comorbidity in the patients. After additional adjustment for the presence of cardiovascular comorbidities at baseline, the hazard ratio for mortality was 2.32 (95% CI 1.02 to 5.28). Furthermore, it was tested whether patients with multiple affected relatives with diabetes mellitus and/or cardiovascular disease have an even poorer prognosis as compared to patients with only one affected relative. This analysis showed that for every extra relative with a positive family history of diabetes or cardiovascular disease the mortality risk was 1.34 (95% CI 1.09 to 1.66) as compared to patients without a positive family history.

**Figure 2.** Decline of kidney function in the first year of pre-dialysis care in 396 incident pre-dialysis patients with a family history of diabetes mellitus (DM), cardiovascular disease (CVD), or kidney disease (KD). [a]First-degree relatives with at least one of the following illnesses: diabetes mellitus, cardiovascular disease, and kidney disease; [b]Adjusted for sex and race.




**Discussion**

This study shows that cardiovascular disease and kidney disease are both more prevalent in first-degree relatives of pre-dialysis patients as compared to the general population. Diabetes mellitus is slightly more prevalent in relatives of pre-dialysis patients as compared to the general population. In addition, a family history of diabetes mellitus (HR 2.9; 95% CI 1.3 to 6.7) and cardiovascular disease (HR 2.4; 95% CI 1.1 to 5.4) is associated with an increased mortality risk in the first year of pre-dialysis care. These results underline the importance of obtaining

family history data from patients with CKD (pre-dialysis) as this may help to identify patients at risk of accelerated disease progression.

To our knowledge, this is the first study focusing on the impact of family history on the progression of CKD as measured by decline of kidney function and mortality during pre-dialysis. It has been shown previously that in dialysis patients a family history of ESRD is not associated with the duration of dialytic survival.[9] The present results add that in pre-dialysis patients a positive family history of diabetes mellitus is associated with a three times increased mortality risk in the first year of pre-dialysis care. Previous studies showed indications for familial clustering of diabetic-associated ESRD.[3-6] In the joint presence of diabetes mellitus and ESRD, mortality risks are shown to be further increased,[1] because diabetes mellitus is characterized by vascular damage that leads eventually to mortality. In the present analysis we also show that a family history of diabetes mellitus is associated with a trend for a faster decline of kidney function in the first year after the start of pre-dialysis care, likely through the same mechanism. The difference in the yearly decline of kidney function in patients with a family history of diabetes mellitus compared to patients without relatives having diabetes mellitus was -1.17 mL/min/1.73m$^2$ (95% CI -2.59 to 0.25). Although this may seem a minor difference, this decline adds to the 'usual' decline of kidney function of about 4.5 mL/min/1.73m$^2$/year in these patients.[14] Especially in view of the low mean kidney function at start of pre-dialysis care (mean eGFR approximately 13 mL/min/1.73m$^2$), this difference is clinically relevant.

The present study also shows that patients with a family history of cardiovascular disease have a two times increased mortality risk in the first year of pre-dialysis care. Our findings extend earlier studies, which showed that the presence of cardiovascular comorbidity in pre-dialysis patients is associated with an increased mortality risk.[15] Furthermore, it has been described that pre-dialysis patients with cardiovascular comorbidities have a faster decline of kidney function as compared to patients without these comorbidities.[16;17] The present results add that such an association is not attributable to a family history of cardiovascular disease. We also show that a family history of kidney disease is associated with a trend for lower mortality risk in pre-dialysis patients, without an association with the rate of decline of kidney function in the first year of pre-dialysis care. To our knowledge, no previous study has focused on this topic before.

Finally, we found that the association between a family history of diabetes mellitus or cardiovascular disease is independent of whether the patient has diabetes mellitus or cardiovascular disease. In addition, we showed that patients with multiple affected relatives with diabetes mellitus and/or cardiovascular disease have an even poorer prognosis as compared to patients with only one affected relative. Taken together, these results give strong indications for a hereditary component which might play a role in faster disease progression in pre-dialysis patients.

When interpreting the present results several points need to be considered. First, family history in pre-dialysis patients (PREPARE-1) was assessed based on available data in patients' medical records, while in healthy subjects (PREVEND) family history was assessed by

questionnaires. Both sources of information might be influenced by underreporting, possibly resulting in biased results due to misclassification. However, in view of the large prevalence differences observed, we expect comparable results even if misclassification might have occurred. Second, in the present study we found that patients with a family history of diabetes or kidney disease have a significantly increased mortality risk in the first year of pre-dialysis care. However, when referring to complete follow-up the association disappeared. This may be explained as follows: patients with a positive family history may be inclined to attend a nephrologist when they get complaints, which clearly might be earlier as compared to patients with a negative family history. Therefore, patients with a negative family history might have died even before their first visit to a nephrologist. Alternatively, patients with a positive family history of diabetes or cardiovascular disease have a largely increased mortality risk and die early in the course of pre-dialysis care or even before the start of pre-dialysis care. The patients who still survive a few years after the start of pre-dialysis are the relatively strong patients. Consequently, the association between a positive family history and mortality on the long-term decreases. Third, the decline of eGFR in the first year of pre-dialysis care was estimated using the MDRD equation[11]. When we would have used the CKD-EPI equation[18] instead, similar results would have been found (results not shown). We also chose to analyze the combined effect of first- and/or second-degree relatives affected with disease. When we restricted our analysis to patients with affected first-degree relatives only, we found similar or even stronger associations with the mortality risk and decline of kidney function, but with slightly wider confidence intervals due to less power (results not shown). Finally, based on the assumption that possible effects of family history are mainly due to genetic differences, the present analyses were adjusted for sex and race only. Other parameters, such as the presence of proteinuria and serum albumin levels, were assumed to be within the causal pathway between family history and the outcomes under study.

Our data have clinical implications. A family history of diabetes mellitus or cardiovascular diseases is associated with a two to three times increased mortality risk. The present study thus provides a strong indication for a hereditary component which might play a role in the faster progression of kidney disease in pre-dialysis patients. In the light of the frequently observed familial clustering of illnesses such as diabetes mellitus, the results of the present study underline the importance of proper identification of high-risk populations. Identification of high-risk populations is not only important for people who might be unaware of their severe disease state, but the present results also highlight the influence of family history on prognosis in patients who were already identified. Furthermore, our results implicate that awareness of family medical history may be helpful in the identification of CKD patients at risk for disease progression in an early stage. It remains to be studied whether timely and more aggressive treatment of pre-dialysis patients with a positive family history is beneficial in decreasing their mortality risk.

In conclusion, a family history of diabetes mellitus and cardiovascular disease is associated with an increased mortality risk in the first year of pre-dialysis care. Therefore, obtaining information about FH may help to identify pre-dialysis patients at increased mortality risk.

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**Disclosure**

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# Chapter 5 |

# Compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium in relation to disease progression in pre-dialysis patients

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*Submitted*

**Abstract**

**Background**

Mineral metabolism disorders are associated with poor outcome in (pre-)dialysis patients. This study assessed whether non-compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care is associated with shorter dialysis-free survival and accelerated decline of kidney function. It was also studied whether these associations differed between patients aged < or ≥65 years.

**Methods**

Incident pre-dialysis patients (N=500, 68% male, age 65±14 years, phosphorus 1.42±0.32 mmol/L, calcium 2.32±0.15 mmol/L) from the PREPARE-2 cohort were included. Associations with the start of dialysis were studied using Cox regression models, while decline of kidney function was studied using linear mixed models. The analyses were adjusted for age, sex, and primary kidney disease. Furthermore, analyses were stratified for age < or ≥65 years.

**Results**

Phosphorus levels above the KDOQI (HR 1.9 [95 %CI 1.4;2.6]) and KDIGO (2.6 [95% CI 1.9;3.5]) target ranges were associated with shorter dialysis-free survival. For calcium levels, these risks were 1.3 (95% CI 0.8;2.3) and 1.4 (95% CI 0.9;2.1), respectively. Furthermore, each 0.1 mmol/L increase in phosphorus (HR 1.2 [95% CI 1.2;1.3]), but not calcium (1.0 [95% CI 0.9;1.1]), was associated with shorter dialysis-free survival. No association between guideline compliance and decline of kidney function was found. However, each 0.1 mmol/L increase in phosphorus (-0.9 mL/min/1.73m$^2$ [95% CI -1.1;-0.8]), but not calcium (-0.2 [95% CI 0.7;0.2]), was associated with a faster decline of kidney function. All results were similar in patients aged <65 *versus* ≥65 years.

**Conclusions**

High phosphorus levels are associated with a shorter dialysis-free survival and a faster decline of kidney function. No associations between calcium levels and dialysis-free survival and decline of kidney function were found. Results were similar for patients aged <65 *versus* ≥65 years.

## Introduction

Disturbances of the mineral metabolism including hyperphosphatemia and hypocalcemia are highly prevalent in patients with chronic kidney disease (CKD).[1;2] In dialysis patients it has been shown that these disturbances are associated with a higher prevalence of muscle and skin problems[3] and an increased all-cause mortality risk.[4-7] Furthermore, in pre-dialysis patients hyperphosphatemia is associated with both a faster decline in kidney function and an increased all-cause mortality risk.[7]

The observed associations between mineral metabolism disorders and poor outcome in CKD patients led to the introduction of two treatment guidelines. First, the American National Kidney Foundation-Kidney Disease Outcome Quality Initiative (KDOQI) guideline was introduced in 2003.[1] More recently, in 2009, the Kidney Disease: Improving Global Outcomes: Chronic Kidney Disease-Mineral and Bone Disorder (KDIGO CKD-MBD) guideline has been established.[2] Differences between both guidelines include the definition of renal osteodystrophy, which has been changed to describe the bone pathology associated with CKD, and the target ranges for serum phosphorus and serum calcium concentrations.

The KDOQI target ranges for phosphorus are specific for different stages of CKD. In CKD stages 3-4 phosphorus concentrations should be maintained between 0.87 and 1.49 mmol/L, while in CKD stage 5 the concentrations should be maintained between 1.13 and 1.78 mmol/L. For calcium the KDOQI guideline established a target range between 2.10 and 2.54 mmol/L in CKD stages 3-4, while the concentrations should be within the normal range, but preferably toward the lower end (between 2.10 and 2.37 mmol/L) in CKD stage 5.[1] According to the KDIGO guideline, patients with CKD stages 3-5 should have phosphorus and calcium concentrations within the normal range, which is between 0.81 and 1.45 mmol/L and between 2.1 and 2.5 or 2.6 mmol/L, respectively.[2]

Several studies have shown that only 50-89% of the patients with CKD stage 4 and 29- 72% of the patients with CKD stage 5 have phosphorus concentrations within the target ranges as recommended by the KDOQI guideline.[6-9] To our knowledge there are not yet studies which focus on compliance with the KDIGO guideline. The aim of the present study was to examine the compliance with the KDOQI and KDIGO guidelines for phosphorus and calcium at the start of pre-dialysis care. Furthermore, it was studied whether compliance is associated with the risk of dialysis within two years after the start of pre-dialysis care and decline of kidney function during pre-dialysis care. Finally, in light of the growing ageing population, it was investigated whether the associations were different for patients aged <65 *versus* ≥65 years.

## Methods

### *Study design*

The PREdialysis PAtients REcords (PREPARE-2) Study is an ongoing, prospective study of incident pre-dialysis patients treated in one of 25 nephrology outpatient clinics in the Netherlands. Patients were included between July 2004 and June 2011, at the start of pre-dialysis care. They were treated by their nephrologists in their regular scheme according to the

treatment guideline of the Dutch Federation of Nephrology[10], a Dutch guideline analogous to the KDOQI and KDIGO guidelines.[1;2] At study inclusion and in subsequent six month intervals clinical data were collected. Patients were followed-up till the start of dialysis, death, or censoring. Censoring was defined as: receiving a kidney transplant, move to an outpatient clinic not participating in the PREPARE-2 Study, recovery of kidney function, refusal of further study participation, or September 1, 2011, whichever came first. For the present analysis follow-up was restricted to the first two years of pre-dialysis care. The study was approved by the medical ethics committees or institutional review board of all participating centers.

*Patients*

To be eligible for inclusion in the PREPARE-2 Study, patients had to be at least eighteen years of age and they should have been referred to a specialized pre-dialysis outpatient clinic for pre-dialysis care. In practice, this refers to patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m$^2$, in whom the need for renal replacement therapy was expected within one year. Patients with a failing kidney transplant were also included in the study if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

*Data collection*

Data on demography, biometry, primary kidney disease, comorbidities, and medication use were collected at study inclusion and/or during follow-up. Laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association into four categories (diabetes mellitus, glomerulonephritis, renal vascular disease, and other).[11]

*Determinants*

The glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease formula.[12] Phosphorus, calcium, albumin, and creatinine (uncalibrated) concentrations were measured using routine laboratory techniques at each outpatient clinic. Calcium concentrations were corrected for albumin concentrations to better reflect the free calcium.[13] For the present analyses, patients were classified based on the achievement of the target ranges for phosphorus and calcium as recommended by the KDOQI and KDIGO guidelines (below, within, and above the KDOQI or KDIGO target ranges).[1;2] The KDOQI target ranges for phosphorus were specific for different stages of CKD: 0.87 to 1.49 mmol/L for CKD stages 3-4 (i.e. eGFR between 15 and 60 mL/min/1.73m$^2$) or 1.13 to 1.78 mmol/L for CKD stage 5 (i.e. eGFR below 15 mL/min/1.73m$^2$). For calcium the KDOQI target ranges were 2.10 to 2.54 mmol/L for CKD stages 3-4 or within the normal range, but preferably toward the lower end; 2.10 to 2.37 mmol/L for CKD stage 5.[1] According to the KDIGO guideline the target range for phosphorus is between 0.81 and 1.45 mmol/L and for calcium between 2.1 and 2.5 or 2.6

mmol/L, irrespective of CKD stage.[2] For the current analysis we used 2.5 mmol/L as the upper limit of the calcium target range. To convert phosphorus in mmol/L to mg/dL, multiply by 0.3229. To convert calcium in mmol/L to mg/dL, multiply by 0.2495.

*Statistical analyses*

Continuous variables were expressed as mean±standard deviation and categorical variables as percentages. The following baseline parameters were available for a subset of patients: albumin in 370 patients, calcium in 368 patients, phosphorus in 389 patients, parathyroid hormone in 271 patients, eGFR in 403 patients, systolic bloodpressure in 496 patients, diastolic bloodpressure in 496 patients, body mass index in 489 patients. To enhance power, missing values were imputed using multiple imputation techniques. Multiple imputation is a recommended technique whereby missing data for each subject are imputed using a predicted value that is based on the subject's other known characteristics.[14;15] For the current analyses we used age, sex, primary kidney disease, albumin, creatinine, calcium, phosphorus, parathyroid hormone, bloodpressure (both systolic and diastolic), body mass index (all at baseline), eGFR at every study visit, follow-up time, and reason for end of study to impute the missing data. Multiple imputation was performed ten times using standard multiple imputation methods in SPSS. Incidence rates for the association between compliance with KDOQI and KDIGO guidelines for phosphorus and calcium and the start of dialysis within two years of pre-dialysis care were calculated. In addition, we used Cox proportional hazards models to estimate hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) for the risk of starting dialysis within this period. These analyses were additionally adjusted for the possible confounding effects of age, sex, and primary kidney disease. Furthermore, linear mixed effects models were used to analyze whether the yearly rate of decline of kidney function was different for patients with phosphorus and calcium concentrations below, within, and above the target ranges. These analyses were also adjusted for age, sex, and primary kidney disease. Under the assumption that the decline of kidney function in a relatively short period is almost linear,[16] we restricted follow-up time for this analysis to the first year of pre-dialysis care. Finally, it was examined whether the associations studied differed between elderly patients and younger patients. To that end, analyses were stratified for patient age at inclusion (<65 *versus* ≥65 years). All analyses were performed with SPSS (version 17.0; SPSS, Chicago, IL).

**Results**

*Study population*

Between July 2004 and June 2011, 500 patients were included in the PREPARE-2 Study, of whom 216 (43.2%) were aged <65 years and 284 (56.8%) ≥65 years. Baseline patient characteristics are listed in Table 1. At baseline 234 (46.8%) patients were using one or more phosphate-binding drugs, including calcium carbonate (n=184), sevelamer (n=101), calcium acetate (n=8), and aluminium hydroxide (n=1).

*Achievement of guidelines*

The majority of the patients (>56%) complied with the KDOQI and KDIGO guidelines for phosphorus and calcium at the start of pre-dialysis care. Up to 43% of the patients had phosphorus and/or calcium concentrations above the target ranges and at most 8% below the target ranges (Figure 1). Results were similar for patients aged <65 *versus* ≥65 years (Figure 2).

**Table 1.** Patient characteristics (N=500) at start of pre-dialysis care.

| | All patients (N=500) |
|---|---|
| Age *year* | 64.9 (14.3) |
| Sex *% male* | 68.0 |
| Primary kidney disease *%* | |
| Renal vascular disease | 30.4 |
| Diabetes mellitus | 14.4 |
| Glomerulonephritis | 13.2 |
| Other | 42.0 |
| Comorbidities *%* | |
| Diabetes mellitus, type I | 3.4 |
| Diabetes mellitus, type II | 22.3 |
| Cardiovascular disease* | 41.2 |
| Systolic bloodpressure *mmHg* | 142.5 (22.2) |
| Diastolic bloodpressure *mmHg* | 77.9 (11.6) |
| Body mass index $kg/m^2$ | 26.8 (5.2) |
| eGFR $mL/min/1.73m^2$ | 16.8 (6.1) |
| Chronic kidney disease *%* | |
| Stage 3 (30-59 mL/min/1.73m$^2$) | 2.4 |
| Stage 4 (15-29 mL/min/1.73m$^2$) | 53.8 |
| Stage 5 (<15 mL/min/1.73m$^2$) | 43.8 |
| Serum albumin *g/L* | 40.6 (4.5) |
| Corrected serum calcium *mmol/L* | 2.32 (0.15) |
| Serum phosphorus *mmol/L* | 1.42 (0.32) |
| Parathyroid hormone *pmol/L* | 25.2 (20.9) |

Values are mean (standard deviation) or percentage as appropriate; eGFR, estimated glomerular filtration rate; *cerebrovascular accident, peripheral vascular disease, angina pectoris, myocardial infarction, congestive heart failure.

*Follow-up*

Median (inter-quartile range) follow-up from the start of pre-dialysis care until censoring was 1.16 (0.56; 2.00) years. During follow-up, 215 (43%) patients started with dialysis, while 110 (22%) patients were censored for different reasons, i.e. refusal of further study participation (n=33), transplantation (n=31), mortality (n=29), recovery of kidney function (n=8), treatment was continued in another outpatient clinic not participating in PREPARE-2 (n=8), and other reasons (n=1). The remaining 175 (35.0%) patients were censored because of reaching the end of the observation period (two years of follow-up or September 1, 2011).

**Figure 1.** Compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care (N=500).

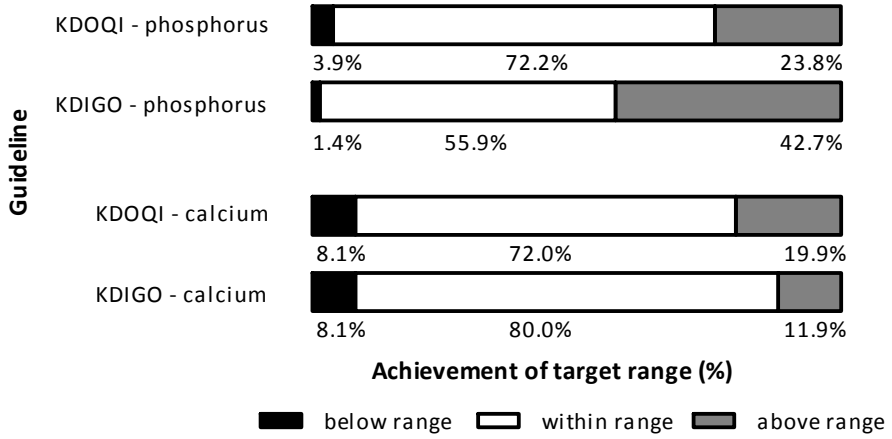



**Figure 2.** Compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care in patients aged <65 (n=216) and patients aged ≥65 years (n=284).

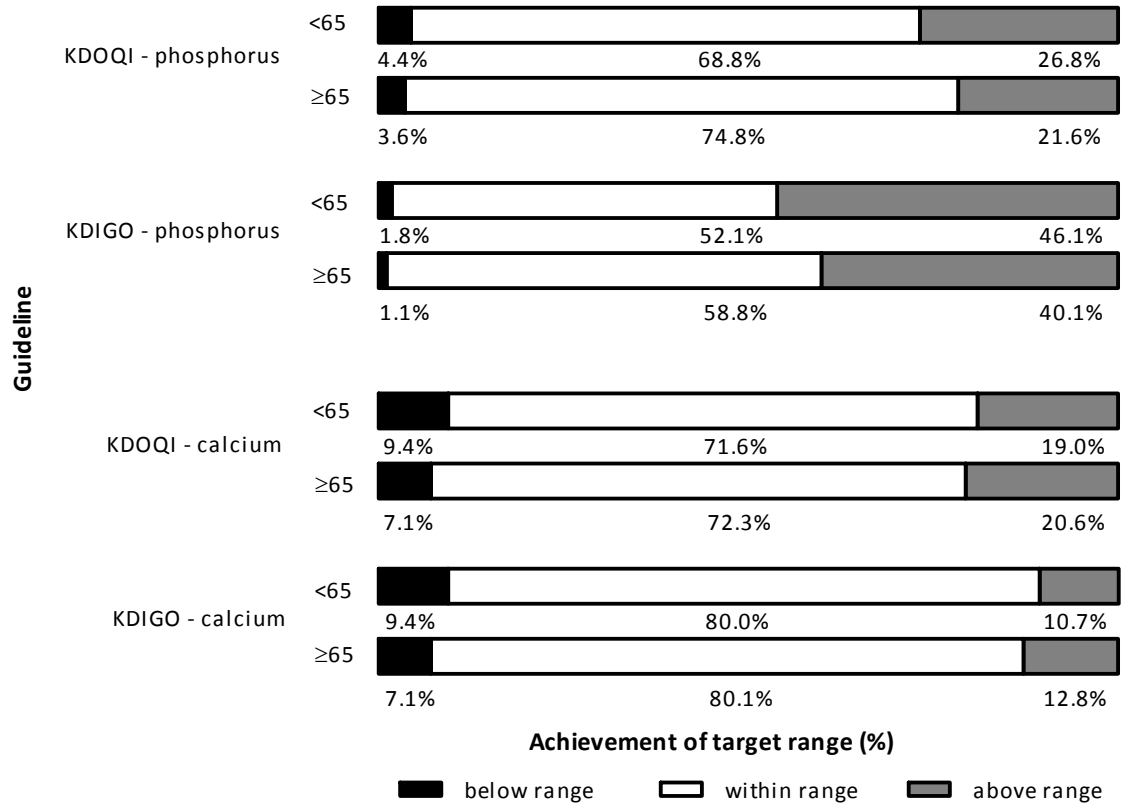
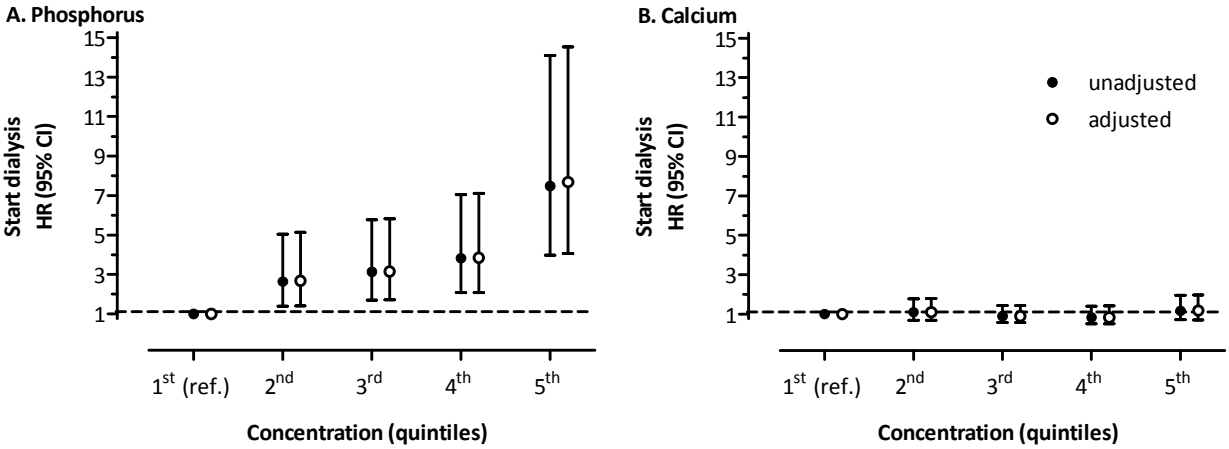


**Figure 3.** Association between serum phosphorus and serum calcium levels (quintiles) and the risk for the start of dialysis within the first two years of pre-dialysis care (n=500). In this figure, the quintile limits for phosphorus are: 1.15, 1.30, 1.47, and 1.63 mmol/L and the quintile limits for calcium are: 2.19, 2.27, 2.35, and 2.45 mmol/L.




Dashed line indicates hazard ratio, hazard ratio (HR)=1, i.e. no association; *adjusted for age, sex, and primary kidney disease.

*Start of dialysis*

Of the 215 patients who started with dialysis therapy, 131 (60.9%) patients started with hemodialysis and 84 (39.1%) patients with peritoneal dialysis. Based on the results of quintile-analyses (Figure 3), linear relationships between phosphorus and calcium concentrations and the risk for the start of dialysis therapy within two years of pre-dialysis care were assumed. A linear analysis showed that for each 0.1 mmol/L increase in phosphorus concentration, the unadjusted HR for the start of dialysis was 1.22 (95% CI 1.16 to 1.27), which was 1.22 (95% CI 1.17 to 1.28) after adjustment for age, sex, and primary kidney disease. Each 0.1 mmol/L increase in calcium concentration was associated with an unadjusted HR of 1.02 (95% CI 0.91 to 1.14) for the start of dialysis, which was 1.02 (95% CI 0.90 to 1.15) after adjustment. The incidence rates for the start of dialysis associated with phosphorus and calcium concentrations below the KDOQI and KDIGO target ranges were slightly lower, and these for above the target ranges were slightly higher as compared to the incidence rates for concentrations within the target ranges (Table 2). The corresponding crude and adjusted hazard ratios showed a similar pattern. In patients aged <65 *versus* patients aged ≥65 years, the associations between phosphorus and calcium levels and the start of dialysis were similar (Table 3).

*Decline of kidney function*

The mean rate of decline of kidney function in the first year of pre-dialysis care was -2.16 mL/min/1.73m$^2$/year (95% CI -3.20 to -1.12). Furthermore, within this period, for each 0.1 mmol/L increase in phosphorus concentration the mean decline of renal function changed with -0.95 mL/min/1.73m$^2$/year (95% CI -1.13 to -0.77), which was -0.94 (95%CI -1.12 to -0.76) after adjustment for age, sex, and primary kidney disease.

**Table 2.** Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the start of dialysis (incidence rates per 100 person-years [py] and hazard ratios together with 95% confidence interval [CI]) within the first two years of pre-dialysis care.

| | | KDOQI | | | KDIGO | | |
|---|---|---|---|---|---|---|---|
| | | Rate/100py (95% CI) | Hazard ratio (95% CI) | | Rate/100py (95% CI) | Hazard ratio (95% CI) | |
| | | | Crude | Adjusted | | Crude | Adjusted |
| Phosphorus | Below | 16 (6; 41) | 0.49 (0.15; 1.59) | 0.47 (0.14; 1.56) | 6 (1; 72) | n.a. | n.a. |
| | Within | 32 (26; 37) | 1.00 (ref.) | 1.00 (ref.) | 24 (19; 29) | 1.00 (ref.) | 1.00 (ref.) |
| | Above | 58 (44; 72) | 1.86 (1.37; 2.54) | 1.85 (1.36; 2.54) | 60 (49; 70) | 2.59 (1.91; 3.51) | 2.59 (1.91; 3.50) |
| Calcium | Below | 33 (20; 53) | 1.02 (0.57; 1.83) | 0.99 (0.54; 1.81) | 33 (20; 54) | 0.93 (0.51; 1.67) | 0.91 (0.50; 1.67) |
| | Within | 32 (27; 38) | 1.00 (ref.) | 1.00 (ref.) | 35 (30; 41) | 1.00 (ref.) | 1.00 (ref.) |
| | Above | 54 (39; 68) | 1.67 (1.13; 2.45) | 1.69 (1.14; 2.51) | 42 (29; 61) | 1.20 (0.77; 1.86) | 1.21 (0.77; 1.91) |

*Adjusted for: age, sex, and primary kidney disease; ref.: reference category; n.a.: not applicable (too few events).

Each 0.1 mmol/L increase in calcium concentration was associated with a change of the mean decline of renal function of -0.27 mL/min/1.73m$^2$/year (-0.71 to 0.18), which was -0.24 (-0.69 to 0.21) after adjustment. No association between compliance with the guidelines and the rate of decline of kidney function was found (Table 4). Similarly, in patients <65 and in patients ≥65 years no associations between phosphorus and calcium levels and decline of kidney function were found.

**Table 3.** Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the start of dialysis hazard ratios adjusted for age, sex, and primary kidney disease, together with 95% confidence interval [CI]) within the first two years of pre-dialysis care.

| Phosphate | | KDOQI | | KDIGO | |
|---|---|---|---|---|---|
| | | <65 years | ≥65 years | <65 years | ≥65 years |
| | Below | 0.70 (0.19; 2.62) | n.a. | n.a. | n.a. |
| | Within | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| | Above | 2.03 (1.26; 3.27) | 1.70 (1.07; 2.70) | 2.85 (1.82; 4.48) | 2.39 (1.59; 3.59) |
| Calcium | | KDOQI | | KDIGO | |
| | | <65 years | >65 years | <65 years | >65 years |
| | Below | 0.72 (0.29; 1.78) | 1.47 (0.68; 3.17) | 0.66 (0.27; 1.66) | 1.34 (0.62; 2.90) |
| | Within | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| | Above | 1.76 (1.04; 2.97) | 1.57 (0.90; 2.68) | 1.31 (0.65; 2.64) | 1.07 (0.54; 2.14) |

**Table 4.** Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the rate of decline of kidney function (eGFR, mL/min/1.73m$^2$/year) with 95% confidence interval (CI) within the first year of pre-dialysis care.

| Guideline | Parameter | Model | Difference in rate of decline of eGFR (95% CI) | | |
|---|---|---|---|---|---|
| | | | Below | Within | Above |
| KDOQI | Phosphorus | Crude | 0.2 (-6.9 to 7.2) | 0.0 (ref.) | -0.7 (-3.5 to 2.1) |
| | | Adjusted* | 0.1 (-6.9 to 7.2) | 0.0 (ref.) | -2.5 (-8.8 to 3.8) |
| | Calcium | Crude | 1.1 (-2.7 to 4.8) | 0.0 (ref.) | 2.0 (-1.3 to 5.2) |
| | | Adjusted* | 1.1 (-2.6 to 4.8) | 0.0 (ref.) | 2.0 (-1.2 to 5.2) |
| KDIGO | Phosphorus | Crude | -5.2 (-26.1 to 15.8) | 0.0 (ref.) | 0.4 (-2.0 to 2.8) |
| | | Adjusted* | -5.4 (-26.4 to 15.7) | 0.0 (ref.) | 0.4 (-1.9 to 2.8) |
| | Calcium | Crude | 0.8 (-2.8 to 4.5) | 0.0 (ref.) | 1.8 (-2.6 to 6.2) |
| | | Adjusted* | 0.9 (-2.8 to 4.5) | 0.0 (ref.) | 1.8 (-2.5 to 6.2) |

Positive values indicate a slower, whereas negative values indicate a faster rate of decline of kidney function as compared to the reference category; *adjusted for: age, sex, and primary kidney disease; ref.: reference category.

**Discussion**

The current study, including 500 incident Dutch pre-dialysis patients, showed that at start of pre-dialysis care at least 56% of the patients comply with the KDOQI and KDIGO guidelines for phosphorus and calcium. More than 43% of the patients have concentrations above the target

ranges, while at most 8% of the patients have concentrations below the target ranges. In addition, it was shown that patients with phosphorus concentrations above the target ranges at start of pre-dialysis care have a shorter dialysis-free survival. A similar association was found with respect to guidelines for calcium, although less pronounced. Non-compliance with the guidelines for phosphorus and calcium was not associated with a faster rate of decline of kidney function. Nevertheless, each 0.1 mmol/L increase in phosphorus concentration was associated with both a faster rate of decline of kidney function and a shorter dialysis-free survival. Together, these results underline the importance of adequate management of phosphorus and calcium concentrations right from the start of pre-dialysis care.

This study shows that higher phosphate concentrations are associated with a higher risk for the start of dialysis within two years after the start of pre-dialysis care. Associations between disturbances of the mineral metabolism and poor outcome have been shown frequently. For example, in healthy young adults, elevation of serum phosphorus concentrations is associated with coronary atherosclerosis.[17] Besides, in patients with CKD or end-stage renal disease, associations between phosphorus levels and cardiovascular morbidity and mortality have been observed.[18-22] Disorders of the mineral metabolism are shown to develop early in the course of CKD and worsen with progressive loss of kidney function.[20] Moreover, in pre-dialysis patients elevated phosphorus concentrations are associated with a faster rate of decline of kidney function[7], which was confirmed by the analysis in which we estimated the risk associated with each 0.1 mmol/L increase in phosphate level. To adequately manage phosphorus and calcium concentrations in patients with CKD, guidelines have been introduced, which include specified target ranges for phosphorus and calcium. Achievement of the KDOQI guidelines for mineral metabolism has been studied occasionally in patients with CKD stage 3-5 (not on dialysis),[7-9] though studies on the achievement of KDIGO guidelines in these patients are, to our knowledge, lacking. The present study investigated the compliance with the KDOQI and KDIGO guidelines in patients at start of pre-dialysis care.

From an epidemiologic point of view, we have to discuss different factors that might have influenced our observations. First, due to the strong interplay between different parameters of the mineral metabolism, it is difficult to unravel separate effects of phosphorus or concentrations on disease progression in CKD. Multivariate adjustment might help to overcome this problem, but should be used with caution to avoid adjustment for intermediate factors. For example, adjustment for the presence of proteinuria might (partly) remove the observed association between baseline phosphorus level and decline of kidney function, since proteinuria might have developed as a(n indirect) consequence of the baseline phosphorus level. For that reason, we only adjusted our analyses for the effects of age, sex, and primary kidney diseases. Second, associations might have been obscured by (changes in) the multiple (pharmacological) interventions that are given to restore the disordered mineral metabolism. To limit the possible effects of changes in lifestyle and medication use, we only studied short-term effects within the first year or the first two years of pre-dialysis care. In addition, even when the decline of kidney function was analyzed only within the first six months of pre-dialysis care, results were

comparable with the results of the original analyses (not shown). Third, patients were classified in three categories based on whether the KDOQI or KDIGO target ranges were achieved. The majority of the patients had phosphorus and calcium concentrations within the target ranges, while a minority had concentrations below and the remainder above the target ranges. Consequently, the power for the different analyses using the classification in three categories was relatively low. This can also be seen by the wide 95% confidence intervals in several analyses. Despite the wide confidence intervals, trends were visible especially for the categories above the target ranges, which was confirmed in the analyses with phosphorus expressed in mmol/L. Fourth, in the analyses using the classification of phosphorus in three categories only slightly increased risks for the start of dialysis therapy within two years of pre-dialysis care were observed, while the analyses using phosphorus levels as a continuous parameter, showed much larger associations. How can this be explained? In the analysis using the categorization of patients into three categories, patients with extremely low and these with levels just below the target range were all categorized into one category. Similarly, patients with extremely high levels were categorized in the same category as patients with only slightly increased levels. Therefore, there is less contrast between the groups and associations are weaker. Fifth, calcium levels above the target ranges as proposed by the KDOQI guideline, but not the KDIGO guideline, were associated with an increased risk for the start of dialysis within the first two years of pre-dialysis care. This can be explained as follows: the KDOQI guideline has different target ranges for patients with CKD stages 3-4 *versus* these with stage 5, with a smaller target range for the latter patient group. The target range proposed by the KDIGO guideline however, applies to all patients, irrespective of their CKD stage. Consequently, a subset of the patients with CKD stage 5 has calcium levels that are above the KDOQI target range, but within the KDIGO target range. Therefore, there is more contrast between the 'within' and 'above' categories of the KDOQI guideline as compared to the KDIGO guideline. Furthermore, no association was found between each unit increase in calcium level and the risk to start with dialysis, despite that there was an association between calcium levels above the KDOQI target range and the start of dialysis. This indicates that in general there is no association between calcium levels and the start of dialysis, only for (extremely) high levels of calcium. Finally, recently it has been observed that compliance with guidelines for mineral metabolism in dialysis patients was influenced by several unmodifiable patient factors, including dialysis vintage and age.[23] In light of this observation and the worldwide growing elderly population, we did additional analyses to examine whether the association between compliance with guidelines, the start of dialysis, and the decline of kidney function is different for elderly pre-dialysis patients (≥65 years) and pre-dialysis patients aged <65 years. These analyses showed that there were no differences in effect between the two age groups.

The present analysis showed that the majority of the patients complied with the guidelines for phosphorus and calcium at the start of pre-dialysis care. This may be explained by a good balance of the mineral metabolism in these patients, but also may merely reflect the (compliance to) therapy which has been initiated previously. Irrespective of the cause of achievement,

though, we were able to assess whether compliance with the guidelines was associated with the risk to start dialysis therapy within two years after the start of pre-dialysis care. Within this analysis a small trend was observed that patients with phosphorus or calcium concentrations below the target ranges had a longer dialysis-free survival as compared to patients with concentrations within the target ranges. This might be explained by a better general health condition of these patients, or by a better compliance to previously started treatment. It was also shown that patients with phosphorus (and to a lesser extent calcium, i.e. only when referring to the KDOQI guideline) concentrations above the target ranges had a shorter dialysis-free survival time as compared to patients with concentrations within the recommended ranges. This might be explained as follows: CKD patients have a tendency towards hyperphosphatemia due to the reduced phosphorus filtering capacity of the kidney.[20] Hyperphosphatemia is one of the main factors in causing secondary hyperparathyroidism, which is an important factor in causing uremic complications. The presence of uremic complications may be one of the reasons to start dialysis therapy.[24]

Our data have clinical implications. The present analysis showed that phosphorus concentrations - and to a lesser extent calcium concentrations - above the target ranges as recommended by the KDOQI and KDIGO guidelines are associated with a shorter dialysis-free survival. Furthermore, each unit increase in phosphorus concentration is associated with a faster decline of kidney function within the first year of pre-dialysis care. A better preserved kidney function not only postpones the time to the start of dialysis, but once started with dialysis a better preserved kidney function is also associated with improved quality of life and a better survival.[25] Thus, compliance to the KDOQI or KDIGO guidelines for phosphorus and calcium, might have consequences even after the start of dialysis.

**Disclosure**

The authors have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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# Chapter 6 |

# Association between time of referral and survival in the first year of dialysis in diabetics and elderly

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**Abstract**

**Objective**

The objective of the study was to estimate the association between time of referral and survival during dialysis in diabetics and patients aged ≥70 years.

**Design, setting, and subjects**

This study was a prospective follow-up study in 1438 incident dialysis patients (1996-2004, 62% male, 60±15 years) in the Netherlands.

**Main outcome measures**

Referral (time between first pre-dialysis visit to a nephrologist and dialysis initiation) was classified as: late (<3 months), early (3–12 months) or very early (≥12 months). All-cause mortality risk within the first year of dialysis was calculated [HR (95% confidence interval, CI), adjusted for age, sex and primary kidney disease (PKD)]. Additive interaction between time of referral and diabetes mellitus (adjusted for age and sex) or age (adjusted for sex and PKD) was assessed by synergy index [S (95% CI)].

**Results**

Thirty-two percent were late referred, 12% early and 56% very early; 21% had diabetes; and 30% were ≥70 years. Early and late referrals were associated with increased mortality compared with very early referral [$HR_{adj,early}$: 1.5 (1.0, 2.4), late: 1.8 (1.3, 2.5)]. A similar trend was observed in diabetics and non-diabetics. However, no interaction between time of referral and diabetes was present [$S_{late}$ 0.8 (0.4, 1.9), $S_{early}$ 1.2 (0.4, 3.6)]. Likewise, in patients aged <70 and ≥70 years, time of referral was associated with increased mortality, without interaction [$S_{late}$ 0.9 (0.4, 1.8), $S_{early}$ 0.8 (0.3, 2.0)].

**Conclusion**

Late referral is associated with increased mortality in the first year of dialysis. Diabetes or high age does not have an additional worsening effect, implying that timely referral is important in future dialysis patients irrespective of diabetes or high age.

## Introduction

The incidence and prevalence of chronic kidney disease and the number of patients needing renal replacement therapy increases worldwide.[1;2] This is a consequence of technical developments, improved access to renal replacement therapy, an ageing population and an increase in the incidence of diabetic nephropathy.[2-4] In addition, due to the high prevalence of risk factors like hypertension and diabetes, morbidity and mortality in patients on dialysis is considerably higher compared to the general population.[5]

Late referral to a nephrologist, resulting in short pre-dialysis care, is considered as another risk factor for increased morbidity and mortality after initiation of dialysis treatment.[6;7] More precisely, late referral is associated with a high mortality, a high hospitalization rate, impairment of the patient's quality of life, more comorbidities and less favorable levels of biochemical parameters such as hemoglobin and serum albumin at initiation of dialysis.[8] In addition, late referral impairs the choice of the initial dialysis modality.[9] In the case of late referral, there is no time for elaborate multidisciplinary pre-dialysis care. In contrast, early referral provides the opportunity for preparation of a good access and the initiation of high-quality cooperative treatment, which is, amongst other treatments, aimed at maintaining a desired nutritional status.[10]

A few studies showed that late referral in specific high-risk subgroups of dialysis patients, such as diabetics and the elderly, was associated with a high mortality.[11-13] It remains unclear, however, whether late referral in these specific high-risk patients is more dangerous than in dialysis patients without these additional risk factors. Therefore, the aims of the present prospective cohort study were to determine (i) the association between time of referral and mortality in the first year of dialysis in specific subgroups of (a) patients with diabetes mellitus and (b) patients 70 years and older and (ii) whether late referral in these high-risk patients has an additional negative effect on top of the presence of diabetes mellitus or advanced age. To that end, it was examined whether additive interaction between time of referral and diabetes mellitus or age is present.

## Materials and methods

### *Design*

End-stage renal disease patients were selected from The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study. This is a multi-centre prospective cohort study in 38 dialysis centers in The Netherlands. At 3 months after the start of dialysis, blood and 24-hour urine samples were taken for further determinations (see below). Patients were followed up till the time of death or censoring. Censoring was defined as leaving the study because of kidney transplantation, withdrawal from the study or a transfer to a dialysis centre that did not participate in the study. For the present analysis, follow-up was maximized at 1 year.

*Patients*

Adult patients (≥18 years) starting dialysis for the first time were eligible for inclusion in the study. For the present analysis, patients were included when they started dialysis between August 1996 and March 2004. Medical ethics committees of all participating hospitals gave their approval for the study. All participants gave their written informed consent prior to inclusion in the study.

*Data collection*

Data regarding time of referral were collected from patient records. The following data were collected at baseline (i.e. the period between 4 weeks prior to and 2 weeks after start of dialysis): age, gender, body mass index (BMI), dialysis modality (hemodialysis or peritoneal dialysis), ethnicity and blood pressure (both systolic and diastolic). Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[14]. The severity of comorbidities was reflected by the Khan comorbidity score, which is a combination of the effects of comorbidity and age giving rise to three risk groups: low, medium and high.[15] Comorbidities were recorded as doctors' diagnosis of diabetes mellitus, cardiovascular disease or malignancies. The standardized and validated seven-point subjective global assessment (SGA) scale was used by trained research nurses to assess nutritional status.[16;17] An SGA score equal to or above 6 was regarded as 'good nutritional status', whereas scores below 6 were regarded as 'poor nutritional status'. Creatinine and urea levels were determined in plasma and 24-h urine samples. Residual renal function (residual glomerular filtration rate, rGFR) was calculated as the mean of creatinine and urea clearance and corrected for body surface area (mL/min/1.73m$^2$) and as weekly kt/$V_{urea}$, in which V was estimated according to the formula of Watson et al.[18] The protein equivalent of nitrogen appearance (PNA) was calculated according to Bergström et al.[19] and normalized to standard body weight ($V_{Watson}$/0.58).

*Time of referral*

Time of referral was determined by calculating the time in months between the first pre-dialysis visit to a nephrologist and the initiation of dialysis. This difference was categorized into three categories: 'late referral' (defined as first contact with nephrologist 0–3 months before start of dialysis), 'early referral' (first contact with nephrologist between 3 and 12 months before start of dialysis) or 'very early referral' (first contact with nephrologist at least 12 months before start of dialysis).

*Statistical analyses*

Baseline characteristics were expressed as mean and standard deviation (SD) or percentage and compared using analysis of variance for continuous variables and chi-square tests for categorical variables. To determine the association between time of referral and mortality during the first year of dialysis, absolute mortality rates were calculated [expressed as mortality rates per 100

person years (py)] in the total study population and within the three categories of time of referral. One-year cumulative survival was estimated by Kaplan–Meier analysis. Log-rank tests were used to compare survival probabilities. Cox regression analysis was used to calculate hazard ratios (HR) for mortality together with 95% confidence intervals, adjusted for age, sex and primary kidney disease. Within specific subgroups, that is diabetics *versus* non-diabetics, and patients aged <70 *versus* ≥70 years of age, the presence of interaction between the risk factor of interest (i.e. either diabetic status or age) and time of referral in relation to mortality was examined. The presence of diabetes mellitus was defined as having diabetes mellitus either as primary kidney disease or as comorbidity. Interaction is the phenomenon whereby the joint effect of two risk factors is larger than the sum of their independent effects. In the present study, interaction was defined as departure from additivity and was estimated by calculating the synergy index (S) together with 95% confidence interval.[20;21] For the evaluation of presence of additive interaction in multiplicative regression models, such as Cox regression models, no interaction terms have to be included in the regression model. However, a Cox regression model should be constructed including a new composite variable containing four exposure categories. The four categories indicate (i) the reference category (background risk, no exposure, or − −), (ii) a category for exposure to one of the risk factors under study (− +), (iii) a category for exposure to the other risk factor to be examined (+ −) and (iv) a category for joint exposure to both risk factors under study (+ +). Subsequently, based on the hazard ratios derived from the Cox regression model, the synergy index can be calculated as follows: Synergy index (S) = ($HR_{++}$ − 1)/[($HR_{+-}$ − 1) + ($HR_{-+}$ − 1)]. The synergy index is a measure for additive interaction in multiplicative regression models and can be interpreted as the extra risk due to exposure to the combination of both risk factors of interest relative to the risk due to exposure of both risk factors separately when the two risk factors were independent of each other (i.e. without interaction). When there is no interaction, the synergy index equals 1.[22] These analyses were adjusted for age, sex and chronic comorbidities (malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy and psychiatric diseases) in the subgroup of diabetics *versus* non-diabetics and for sex, primary renal disease and chronic comorbidities (diabetes mellitus, malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy and psychiatric diseases) in the subgroup of patients aged <70 *versus* ≥70 years of age. All statistical analyses were performed with SPSS statistical software (v.16.0.2; SPSS, Chicago, IL, USA).

## Results

### *Patients*

In the period between August 1996 and March 2004, 1835 patients were included in the NECOSAD study. Of these, 1438 patients with a mean (SD) age of 60.0 (15.1) had data on time of referral available and were therefore included in the present analysis. Patients not included were not different from the patients included with respect to age and sex but had slightly lower Khan comorbidity scores. Of the patients included, 56% were referred very early, whereas 12%

**Table 1.** Baseline characteristics and clinical parameters (at start of dialysis) in dialysis patients (N=1438) grouped by time of referral (late: <3 months; early: 3-12 months or very early: ≥12 months before start of dialysis).

| | Time of referral | | | *p* |
|---|---|---|---|---|
| | Late (N=456) | Early (N=172) | Very early (N=810) | |
| Age *years* | 60.3 (16.3) | 60.1 (14.5) | 59.8 (14.5) | 0.89 |
| ≥70 year *%* | 32.7 | 27.9 | 29.1 | 0.34 |
| Sex *% male* | 58.3 | 62.2 | 64.2 | 0.12 |
| BMI *kg/m$^2$* | 24.3 (4.2) | 25.1 (4.6) | 25.2 (4.4) | <0.01 |
| Systolic BP *mmHg* | 149.4 (24.3) | 146.1 (22.4) | 149.1 (23.5) | 0.28 |
| Diastolic BP *mmHg* | 82.7 (14.5) | 82.4 (13.5) | 82.5 (13.0) | 0.95 |
| Chronic therapy *% HD* | 70.0 | 65.1 | 61.9 | 0.02 |
| Primary renal disease *%* | | | | 0.02 |
| Diabetes Mellitus | 14.5 | 19.8 | 16.3 | |
| Glomerulonephritis | 9.6 | 15.1 | 15.8 | |
| Renal vascular disease | 22.1 | 19.8 | 17.9 | |
| Khan comorbidity score *%* | | | | 0.01 |
| Low | 33.6 | 35.5 | 38.3 | |
| Medium | 32.7 | 28.5 | 35.8 | |
| High | 33.8 | 36.0 | 25.9 | |
| Comorbidities | | | | |
| Diabetes Mellitus *%** | 20.9 | 29.3 | 23.3 | 0.09 |
| Cardiovascular disease *%* | 39.6 | 39.2 | 39.1 | 0.98 |
| Malignancies *%* | 13.8 | 12.7 | 6.7 | <0.01 |
| Nutritional status | | | | |
| Serum albumin *g/L* | 34.3 (6.4) | 35.5 (5.5) | 36.0 (5.8) | <0.01 |
| nPNA *g/kg/day* | 1.0 (0.2) | 1.1 (0.2) | 1.2 (0.3) | 0.20 |
| rGFR *mL/min/1.73m$^2$* | 4.4 (4.3) | 5.1 (3.0) | 5.5 (2.8) | <0.01 |
| Kt/$V_{urea}$ *week* | 2.0 (0.5) | 2.2 (0.3) | 2.3 (0.6) | 0.14 |

Unless otherwise stated: mean (SD) or percentage; N: number of patients; BMI: body mass index; BP: blood pressure; HD: hemodialysis; nPNA: normalized protein equivalent of nitrogen appearance; rGFR: residual glomerular filtration rate; Kt/V: dialysis adequacy; *Diabetes Mellitus as primary renal disease + comorbidity.

and 32% were referred early and late, respectively. The majority of the patients were male (62%), 23% had diabetes mellitus, and 30% were aged ≥70 years. Most patients started with hemodialysis (65%). The majority of the patients (72%) had a good nutritional status. Patients who were referred late started more frequently with hemodialysis and had relatively higher comorbidity scores at the start of dialysis. This was possibly due to a higher prevalence of

malignancies. They also had a lower residual renal function at the start of dialysis compared to those who were referred very early (Table 1).

Important clinical parameters such as hemoglobin and serum albumin, which were only available 3 months after initiation of dialysis treatment, were not correlated to time of referral. SGA score and rGFR at 3 months after the start of dialysis, however, were slightly lower in patients who were referred early or late compared with patients referred very early (Table 2). After 3 months of dialysis treatment, 89% of the patients used phosphorus binders, 86% were using erythropoietin (EPO), and 35% were treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Medication use was not different between categories of referral. During the 1-year follow-up, 13% of all patients died, 5% of the patients were censored because of receiving a kidney transplant, 4% were censored because of refusal of further treatment, and 2% were censored because of recovery of renal function.

**Table 2.** Clinical parameters (at 3 months after start of dialysis) in dialysis patients (N=1374) grouped by time of referral (late: <3 months; early: 3-12 months or very early: ≥12 months before start of dialysis).

| | Time of referral | | | *p* |
|---|---|---|---|---|
| | Late (N=433) | Early (N=164) | Very early (N=777) | |
| Nutritional status | | | | |
| Serum albumin *g/L* | 35.5 (5.5) | 35.7 (5.5) | 36.0 (5.0) | 0.29 |
| nPNA *g/kg/day* | 1.1 (0.3) | 1.1 (0.2) | 1.2 (0.4) | 0.71 |
| SGA *% good* | 63.2 | 71.0 | 76.9 | <0.01 |
| Hb *g/dL* | 10.9 (1.7) | 11.2 (1.6) | 11.2 (1.6) | 0.04 |
| $Ca^{2+}$ *mmol/L* | 2.3 (0.2) | 2.3 (0.3) | 2.4 (0.3) | <0.01 |
| $PO_4^-$ *mmol/L* | 1.8 (0.6) | 1.9 (0.6) | 1.8 (0.5) | 0.07 |
| PTH *pmol/L* | 20.4 (24.8) | 21.6 (21.8) | 23.2 (32.5) | 0.32 |
| $HCO_3^-$ *mmol/L* | 23.5 (3.9) | 23.0 (3.9) | 23.2 (3.6) | 0.23 |
| rGFR *mL/min/1.73m²* | 3.4 (3.2) | 3.4 (2.4) | 4.0 (3.1) | <0.01 |
| Total $Kt/V_{urea}$ *week* | 3.0 (1.0) | 2.9 (0.9) | 3.0 (1.0) | 0.35 |

Unless otherwise stated: mean (SD) or percentage; N: number of patients; nPNA: normalized protein equivalent of nitrogen appearance; SGA: subjective global assessment; Hb: hemoglobin; $Ca^{2+}$: plasma calcium; $PO_4^-$: plasma phosphorus; PTH: parathyroid hormone; $HCO_3^-$: plasma bicarbonate; rGFR: residual glomerular filtration rate; $Kt/V_{urea}$: combination of renal and dialysis adequacy.

**All-cause mortality in the first year of dialysis: all patients**

The cumulative incidence of mortality during the first year of dialysis in patients referred late, early and very early was 18%, 15% and 9%, respectively (p<0.001). Absolute all-cause mortality rates within the first year of dialysis were higher for late referred patients (18.7/100 py) compared to early referred patients (15.5/100 py) or very early referred patients (10.0/100 py).

Both unadjusted and adjusted hazard ratios for death during the first year of dialysis were higher in late and early referred patients compared to very early referred patients (Table 3).

**Table 3.** Time of referral in 1438 dialysis patients associated with the all-cause mortality risk (hazard ratio, HR and 95% confidence interval) in the first year after start of dialysis treatment.

| Time of referral | N | HR (95% CI) | $HR_{adj}$ (95% CI) |
|---|---|---|---|
| Very early (≥12 months) | 810 | 1.0 (ref) | 1.0 (ref) |
| Early (3-12 months) | 172 | 1.6 (1.0, 2.6) | 1.5 (1.0, 2.4) |
| Late (<3 months) | 456 | 2.1 (1.6, 2.9) | 1.8 (1.3, 2.5) |

N: number of patients; $HR_{adj}$: adjusted for age, sex, and primary kidney disease

**All-cause mortality in the first year of dialysis: diabetics *versus* non-diabetics**

The all-cause mortality rate was higher in patients with diabetes compared to patients without diabetes [HR (95% CI) 1.9 (1.4, 2.6)]. In addition, the all-cause mortality risk was higher when patients were referred late or early (compared to very early referred patients) in both diabetics and non-diabetics (Figure 1A) even after adjustment for possible confounders (Table 4).

**Table 4.** Time of referral in subgroups of dialysis patients with and without diabetes mellitus and patients aged <70 *versus* ≥70y was associated with all-cause mortality risk (hazard ratio, HR and 95% confidence interval) in the first year after start of dialysis treatment.

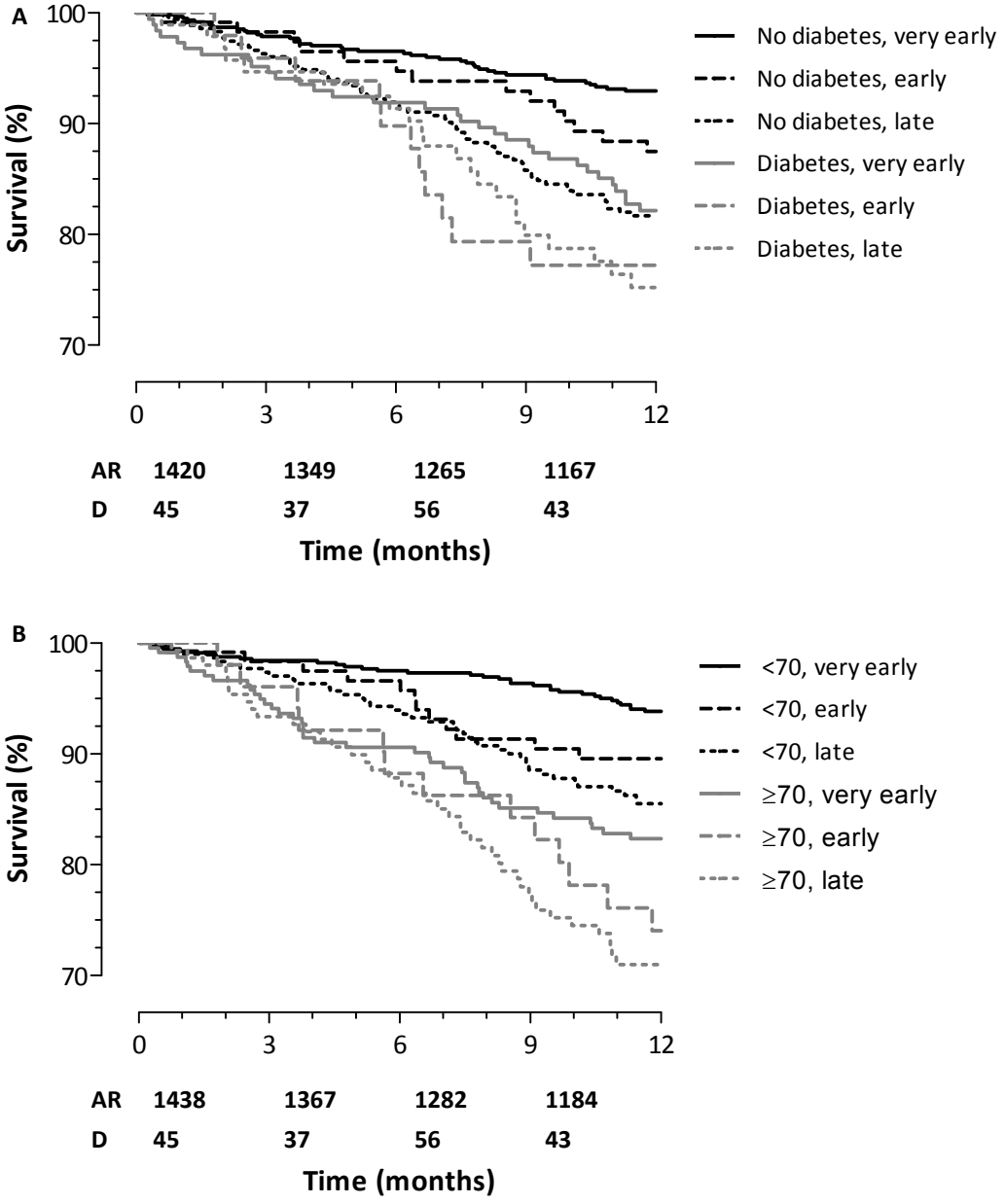
| Diabetes | Time of referral* | N | MR/100py | HR (95% CI) | $HR_{adj}$ (95% CI)[1] | $HR_{adj}$ (95% CI)[2] |
|---|---|---|---|---|---|---|
| No | Very early | 616 | 7.3 | 1.0 (ref.) | 1.0 (ref) | 1.0 (ref) |
| No | Early | 118 | 11.6 | 1.8 (1.0, 3.3) | 1.7 (0.9, 3.0) | 1.5 (0.8, 2.8) |
| No | Late | 356 | 18.7 | 2.7 (1.8, 4.1) | 2.6 (1.7, 3.9) | 2.3 (1.6, 3.4) |
| Yes | Very early | 187 | 19.5 | 2.6 (1.7, 4.2) | 2.4 (1.5, 3.8) | 2.0 (1.2, 3.2) |
| Yes | Early | 49 | 30.2 | 3.6 (1.9, 7.0) | 3.5 (1.8, 6.9) | 2.9 (1.4, 5.7) |
| Yes | Late | 94 | 19.6 | 3.8 (2.3, 6.3) | 3.3 (2.0, 5.5) | 2.9 (1.7, 4.9) |
| ≥70 yrs | Time of referral* | N | MR/100py | HR (95% CI) | $HR_{adj}$ (95% CI)[3] | $HR_{adj}$ (95% CI)[4] |
| No | Very early | 571 | 6.4 | 1.0 (ref.) | 1.0 (ref) | 1.0 (ref) |
| No | Early | 121 | 9.8 | 1.8 (0.9, 3.4) | 1.6 (0.8, 3.2) | 1.8 (0.9, 3.5) |
| No | Late | 305 | 11.0 | 2.5 (1.6, 3.9) | 2.1 (1.3, 3.4) | 2.2 (1.4, 3.6) |
| Yes | Very early | 239 | 19.6 | 3.2 (2.0, 5.0) | 2.6 (1.6, 4.1) | 2.1 (1.3, 3.3) |
| Yes | Early | 51 | 29.8 | 4.6 (2.4, 8.8) | 3.7 (1.9, 7.1) | 2.4 (1.2, 4.7) |
| Yes | Late | 151 | 35.4 | 5.4 (3.4, 8.5) | 4.0 (2.5, 6.4) | 3.0 (1.9, 4.9) |

N: number of patients; MR: mortality rate per 100 person years (py); $HR_{adj}$ (95% CI): [1]adjusted for sex and age; [2]adjusted for age, sex, and chronic comorbidities (malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy, psychiatric diseases); [3]adjusted for sex and primary kidney disease; [4]adjusted for sex, primary kidney disease and chronic comorbidities (diabetes mellitus, malignancies, liver cirrhosis, cardiovascular diseases, left ventricular hypertrophy, psychiatric diseases); *Time of referral, defined as very early: ≥12 months, early: 3-12 months, or late: <3 months before start of dialysis.

**All-cause mortality in the first year of dialysis: <70 years *versus* ≥70 years**

Patients aged ≥70 years had higher mortality rates compared to patients aged <70 years [HR (95% CI) 2.6 (2.0, 3.5)]. In both age groups, delayed referral was associated with an increased mortality risk in the first year of dialysis (Figure 1B, Table 4).

**Figure 1.** Effect of time of referral on one-year survival in high-risk subgroups of diabetics and non-diabetics (p<0.001, panel A), and patients aged <70 and ≥70 years of age (p<0.001, panel B). Time of referral is categorized as very early (≥12 months), early (3-12 months), or late (<3 months). The tables below the graphs indicate the number of patients at risk (AR) and number of events (D) per 3 months interval.



**Additive interaction**

Within subgroups of diabetics *versus* non-diabetics and patients aged <70 years *versus* ≥70 years, the presence of additive interaction between the risk factor of interest (diabetes and age) and time of referral could be assessed by calculating the synergy index (S) derived from the fully adjusted models (Table 4). In late referred diabetics, no interaction between diabetic status and time of referral was found [$S_{late}$ (95% CI) 0.8 (0.4, 1.9)]. The synergy index (95% CI) in early referred diabetics was 1.2 (0.4, 3.6), indicating the absence of additive interaction. In late referred patients aged ≥70 years and in early referred patients aged ≥70 years, S (95% CI) was 0.9 (0.4, 1.8) and 0.8 (0.3, 2.0), respectively.

**Discussion**

In our cohort consisting of 1438 incident dialysis patients, 32% were referred late, 12% early and 56% very early. The time of referral was positively associated with survival in the first year of dialysis treatment. Late referral resulted in a nearly doubled all-cause mortality risk in the first year of dialysis; early referral resulted in a 1.5-fold risk compared to very early referral. After adjustment for possible confounders, no additive interaction effect was observed between time of referral and diabetic status or between time of referral and age. The present results indicate that delayed referral (i.e. late or early, compared to very early referral) is associated with an increased mortality risk in the first year after initiation of dialysis, regardless of diabetic status or age.

To our knowledge, this study is the first assessing the association between time of referral and mortality during dialysis in specific subgroups of high-risk patients within the setting of a prospective cohort study. Our results are in line with previous studies, which showed that late referral increases the risk of morbidity and mortality once on dialysis.[23;24] Risk factors identified for late referral were, among others, the number and severity of comorbidities, ethnicity and not having a health insurance.[25;26] It has been shown that late referral is associated with poorer prognosis related to undesired levels of clinically important parameters such as serum albumin and hemoglobin at the start of dialysis.[27;28] Two studies investigated whether the risk was different in type II diabetics either on hemodialysis[11] or peritoneal dialysis.[13] To our knowledge, only one study investigated the association between late referral and poor outcome in very elderly (≥75 years) dialysis patients.[12] However, these three studies included a relatively small number of patients. The first two studies, on the relationship between pre-dialysis care and mortality within diabetics, showed that early referral, defined as first contact with a nephrologist >6 months before start of dialysis, was associated with improved long-term survival in patients with diabetes. The latter study showed that the relative risk of death for late referral in patients aged 75 years and over was similar to the risk in patients aged <75 years of age. The present study is in line with these previous findings and adds that after adjustment for possible confounders, there is no extra detrimental effect of age or diabetic status on the effect of time of referral, as shown by absence of additive interaction (synergy index ~ 1).

Several methodological issues in this study require careful consideration. First, since this is an observational study looking at the effect of a treatment, the risk of confounding by indication is considerable. Patients may, for example, be referred late because of their worse clinical condition, resulting in a poor prognosis, which might lead to biased results. Since in our study patients who were referred late or early had a slightly increased comorbidity burden (i.e. higher comorbidity score and higher prevalence of malignancies) at initiation of dialysis compared to very early referred patients, it seems that the presence of confounding by indication cannot be excluded. However, the prevalence of mortality due to different causes (e.g. malignancies) was not different between the groups. Therefore, we can assume that the present results are valid. With respect to precision of the results, the precision of our results is reflected by the width of the confidence intervals. Concerning adjustment, it should be noted that adjustment of our analysis for possible confounders was performed with caution. Since many confounding risk factors for mortality in our dialysis patients could have been influenced by treatment during pre-dialysis follow-up, the risk of correction within the causal pathway is present. Therefore, the present analyses were adjusted only for age, sex, primary kidney diseases and chronic comorbidities which are associated with prognosis but not influenced by the pre-dialysis treatment regimen.

In a sensitivity analysis, we checked whether our definition of time of referral influenced the results. When using a more strict definition for late referral (i.e. only those who never received pre-dialysis care were categorized as being late referred instead of all patients having had up to 3 months pre-dialysis care) the results were similar to those of the present analysis. Finally, since the present analysis included mainly Dutch Caucasians, with a relatively low prevalence of diabetes mellitus, it should be investigated whether these findings are applicable to other populations.

How can the present results be explained? It might be that patients had to start dialysis treatment unplanned because of a sudden worsening of their clinical situation. Unplanned dialysis start decreases the likelihood that patients have a mature arteriovenous fistula or peritoneal dialysis catheter, which is associated with poor outcome on dialysis.[29] Another explanation might be that, in our study, 3 months after the initiation of dialysis treatment, nutritional status, reflected by the SGA score, was lower in late referred patients compared to early or very early referred patients. It has been shown that a low SGA score is strongly associated with both an increased short-term and long-term mortality risk.[30] Furthermore, late referred patients started more frequently on hemodialysis. Hemodialysis is associated with a faster decline of residual renal function compared to peritoneal dialysis.[31] Not surprisingly, after 3 months of dialysis treatment, rGFR in early or late referred patients was slightly lower compared to very early referred patients. Although at start of dialysis rGFR was slightly lower in these patients as well, it can be argued that the decline in the lowest range of renal function might have more impact than the decline at relatively better renal functions. Therefore, we suggest that in our cohort the rate of decline of residual renal function might explain the higher

mortality risk in dialysis patients who were referred early or late compared to patients who were referred very early.

Our data have clinical implications. The present analysis showed that very early referral (>12 months before the start of dialysis treatment) has beneficial effects in all patients preparing for dialysis. Moreover, in patients having diabetes mellitus and patients aged 70 years and over, the protective effect of early referral is still present. Since early referral is beneficial irrespective of diabetic status or age, all dialysis patients should be prepared for dialysis as early as possible. There is no reason to refrain high-risk patients like diabetics and the elderly from timely referral.

To summarize, time of referral is associated with increased mortality in the first year after the initiation of dialysis. This association is not influenced by older age or the presence of diabetes mellitus. These data implicate that timely referral is important in all future dialysis patients.

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# Chapter 7 |

# The course of decline of renal function before and after the start of dialysis

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*Submitted*

**Abstract**

Preservation of renal function is associated with improved quality of life and survival in dialysis patients. We explored the course of the glomerular filtration rate GFR (calculated as the mean of urea and creatinine clearance, corrected for body surface area) in 1861 patients in the year before until one year after the start of hemodialysis (HD) and peritoneal dialysis (PD). Decline of GFR was estimated using linear mixed models and adjusted for age, sex, primary kidney disease, cardiovascular disease, and diabetes. The decline attenuated from -0.53 mL/min/1.73m$^2$/month (95% CI -0.58;-0.48) to -0.12 (95%CI -0.20;-0.04) at 2-4 months of dialysis. The decline in HD attenuated from -0.51 (95%CI -0.57;-0.44) to -0.14 (95%CI -0.26;-0.02); in PD from -0.55 (95%CI -0.62;-0.48) to -0.11 (95%CI -0.23;0.01). In patients with GFR equal or above the median GFR at the start of dialysis the decline attenuated at 3 months from -0.70 (95%CI -0.78;-0.62) to -0.21 (95%CI -0.36;-0.05). In patients with GFR lower than the median GFR at start the decline attenuated at 1 month from -0.73 (95%CI -0.88;-0.58) to -0.04 (95%CI -0.27;0.19). In conclusion, the apparent decline of GFR in the year before until one year after the start of dialysis slows down after 2-4 months of dialysis. This is similar in HD and PD patients, although at a different level of GFR. Dialytic removal of urea and creatinine may be an explanation for this. Further studies are needed to examine alternative explanations.

## Introduction

Preservation of renal function has important clinical consequences. For example, in dialysis patients the presence of residual renal function is associated with better quality of life and prolonged survival.[1-3] Residual renal function reflects not only remaining glomerular filtration rate (GFR) and urine production, but also contributes to the removal of uremic toxins by tubular secretion. Furthermore, it is associated with lower concentrations of serum markers of inflammation, and with prevention of the development of left ventricular hypertrophy.[4-7]

Several studies showed that the decline of residual renal function in hemodialysis (HD) patients is faster than in peritoneal dialysis (PD) patients.[8-11] In addition, it has been suggested that urea clearance declines with a constant rate in the months preceding the start of dialysis, but acutely decreases with ~2 mL/min at the time of the start of dialysis.[12] It is unclear whether this abrupt deterioration was real or just artificially introduced by the method used to model the decline of renal function. Furthermore, it might be questioned whether this change in the rate of decline of renal function, if present, takes place immediately at the start of dialysis or whether this takes some time to develop.

The aim of this study was to explore the course of GFR before and after the start of dialysis using data from the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD) cohort. More specifically, we examined whether the decline of GFR is constant from the year before until one year after the start of dialysis, or attenuates at some point during this follow-up period. To that end, linear mixed effects models were used to estimate the rate of decline of GFR for the total time window and these were compared with linear mixed effects models allowing attenuation in the decline of renal function at different time points during follow-up. In addition, it was investigated whether the course of decline of renal function was influenced by dialysis modality or by the level of GFR at start of dialysis.

## Methods

*Study design*

NECOSAD is a multicenter prospective cohort study of incident dialysis patients from 38 dialysis centers in The Netherlands. At start as well as at three months, six months, and subsequently every six months after the start of dialysis, blood and timed urine collections were taken. The collection period was 24 hours for pre-dialysis and PD patients, and comprised the whole interdialytic interval in HD patients. Patients were followed till time of death or censoring because of kidney transplantation, recovery of renal function, withdrawal from the study or a transfer to a non-participating dialysis center. In a sample of NECOSAD patients, included before April 2003, trained research nurses followed the clinical course during pre-dialysis through medical charts for a maximum of one year before the start of dialysis. In these medical charts, the start of pre-dialysis care was defined as the first time a patient was informed about the need to prepare for dialysis therapy. From the pre-dialysis period up to a maximum of ten assessments of creatinine and urea in plasma and 24-hour urine were recorded. These data have been added to the NECOSAD database 'post-hoc'. For all patients included in the study, start of

dialysis was regarded as the baseline measurement even if pre-dialysis data were available. Medical ethics committees of all participating hospitals gave their approval for the NECOSAD study.

*Patients*

To be eligible for inclusion in NECOSAD adult patients (at least 18 years of age) had to start with dialysis as their first renal replacement therapy and should have provided their written informed consent prior to study inclusion. For the present analysis, patients with at least one GFR measurement in the year before until one year after the start of dialysis were included and follow-up was restricted to one year after start dialysis.

*Data collection*

For all patients the following baseline data were collected between four weeks prior to and two weeks after the start of dialysis: age, sex, body mass index, dialysis modality, and blood pressure. Primary kidney disease was classified using the codes of the European Renal Association-European Dialysis and Transplantation Association.[13] Comorbidities were recorded as doctors' diagnosis of diabetes mellitus or cardiovascular disease. The severity of comorbidities was reflected by the Davies comorbidity score, which is based on the presence or absence of seven comorbid conditions (malignancy, ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, and other significant pathology e.g. chronic obstructive airways disease), giving rise to three risk groups: low risk (without any comorbid condition), medium risk (one or two comorbid conditions), and high risk (three or more comorbid conditions).[14]

*Outcome: decline of renal function*

Creatinine and urea levels were determined in plasma and 24-hour urine samples. GFR was calculated as the mean of creatinine and urea clearance, and corrected for body surface area (mL/min/1.73m$^2$). If urine production was less than 200 mL/24-hr GFR was set at 0 mL/min/1.73m$^2$. Furthermore, patients were considered anuric at the first of two subsequent time points with GFR=0 mL/min/1.73m$^2$.

*Statistical analyses*

Baseline characteristics were expressed as mean and standard deviation or percentage. The rate of decline of renal function was estimated using linear mixed effects models. Here the GFR is modeled as a linear function of follow-up times; with per subject a random intercept and a random time effect. The fixed regression coefficient for time (β1) estimates the rate of decline of GFR per month. To allow for a change in the slope before and after a certain change point an additional covariate was added, being equal to 0 for measurements taken before the change point and being equal to (time-change point) for measurements taken after the change point. The regression coefficient for this covariate (β2) measures the difference in slope before and

after the change point. Different change points (-11 months, -10 months up to 11 months after the start of dialysis) were considered, resulting in 23 different models. Akaike's Information Criterion (AIC), which is based on the value of the maximum likelihood and on the number of parameters in the model, was used to select the model with the best fit: a lower AIC indicates a better model fit. The change point model with the best fit was then fitted by restricted maximum likelihood to estimate the monthly decline of GFR. In this model, β1 reflects the monthly decline of renal function *before* the change point, while β2 indicates whether the rate of decline changes after the change point and (β1+β2) reflects the decline *after* the change point. Models were adjusted for age, sex, primary kidney disease, cardiovascular disease, and diabetes at start of dialysis. In addition, to study whether the course of decline of renal function differs between HD and PD patients, modality at start of dialysis was added as a covariate. The analyses were based on the intention-to-treat principle meaning that modality switches during follow-up were ignored. To study possible differences in decline between HD and PD patients, interaction terms were added to the model (time1*modality and time2*modality). The first interaction term reflected whether the rate of decline in HD patients differed from decline in PD patients before the change point, while the second interaction term reflected whether the change in the rate of decline of GFR after the change point was different between HD and PD patients. Finally, it was investigated whether the course of renal function was dependent on the level of GFR at start of dialysis. To that end, an extra covariate indicating whether a patient had a GFR level equal/above or below the median GFR level at start of dialysis was added and interaction terms were compared. All statistical analyses were performed with SPSS version 17.0.

## Results

### *Study population*

The NECOSAD study included 2051 incident patients with end-stage renal disease, who started dialysis between August 1996 and February 2007. At the start of dialysis, as well as at three months, six months, and subsequently every six months thereafter, blood and 24-hour urine samples were taken. In addition, in a subset of the patients included (n=1130), pre-dialysis data were collected retrospectively from medical records. For the present analysis, 1861 patients with at least one GFR measurement available in the year before until one year after the start of dialysis were included. Characteristics at the start of dialysis of these 1143 HD and 718 PD patients are shown in Table 1.

### *Follow-up*

Median (interquartile range) follow-up in the period of one year before and one year after the start of dialysis was 1.00 (1.00; 1.13) years. During the one year after the start of dialysis, 228 (12.3%) patients became anuric, i.e. GFR was 0 mL/min/1.73m$^2$ at two subsequent time points. Furthermore, 194 (10.4%) patients were censored for death, 83 (4.5%) patients for transplantation, 56 (3.0%) patients for refusal of further treatment, 20 (1.1%) patients for

recovery of renal function, and 22 (1.2%) patients for other reasons. Hence, one year after the start 1486 (79.8%) patients were still on dialysis.

**Table 1.** Characteristics of NECOSAD patients with at least one glomerular filtration rate (GFR) measurement in the period of one year before and one year after start of dialysis (N=1861) at start of dialysis.

| | HD (N=1143) | PD (N=718) |
|---|---|---|
| Age *year* | 63.5 (13.9) | 53.5 (14.9) |
| Sex *% male* | 59.8 | 66.2 |
| Primary kidney disease *%* | | |
| Renal vascular disease | 20.6 | 12.8 |
| Diabetes mellitus | 14.5 | 14.2 |
| Glomerulonephritis | 8.6 | 19.1 |
| Other | 56.3 | 53.9 |
| Davies comorbidity score *%* | | |
| Low | 43.0 | 60.3 |
| Medium | 45.9 | 33.4 |
| High | 11.1 | 6.3 |
| Comorbidities *%* | | |
| Cardiovascular disease [n=1704] | 42.4 | 26.3 |
| Diabetes mellitus* [n=1703] | 23.0 | 19.5 |
| Body mass index $kg/m^2$ [n=1852] | 25.0 (4.4) | 24.9 (4.8) |
| Systolic blood pressure *mmHg* [n=1850] | 149.8 (24.2) | 148.1 (23.2) |
| Diastolic blood pressure *mmHg* [n=1850] | 80.7 (12.6) | 86.3 (13.5) |
| GFR $mL/min/1.73m^2$ [n=1147] | 4.9 (3.8) | 5.7 (3.3) |
| Medication use *%* | | |
| ACE Inhibitors | 15.0 | 21.0 |
| ARBs | 4.3 | 7.2 |
| B-blockers | 20.1 | 21.3 |
| Diuretics | 20.4 | 20.9 |

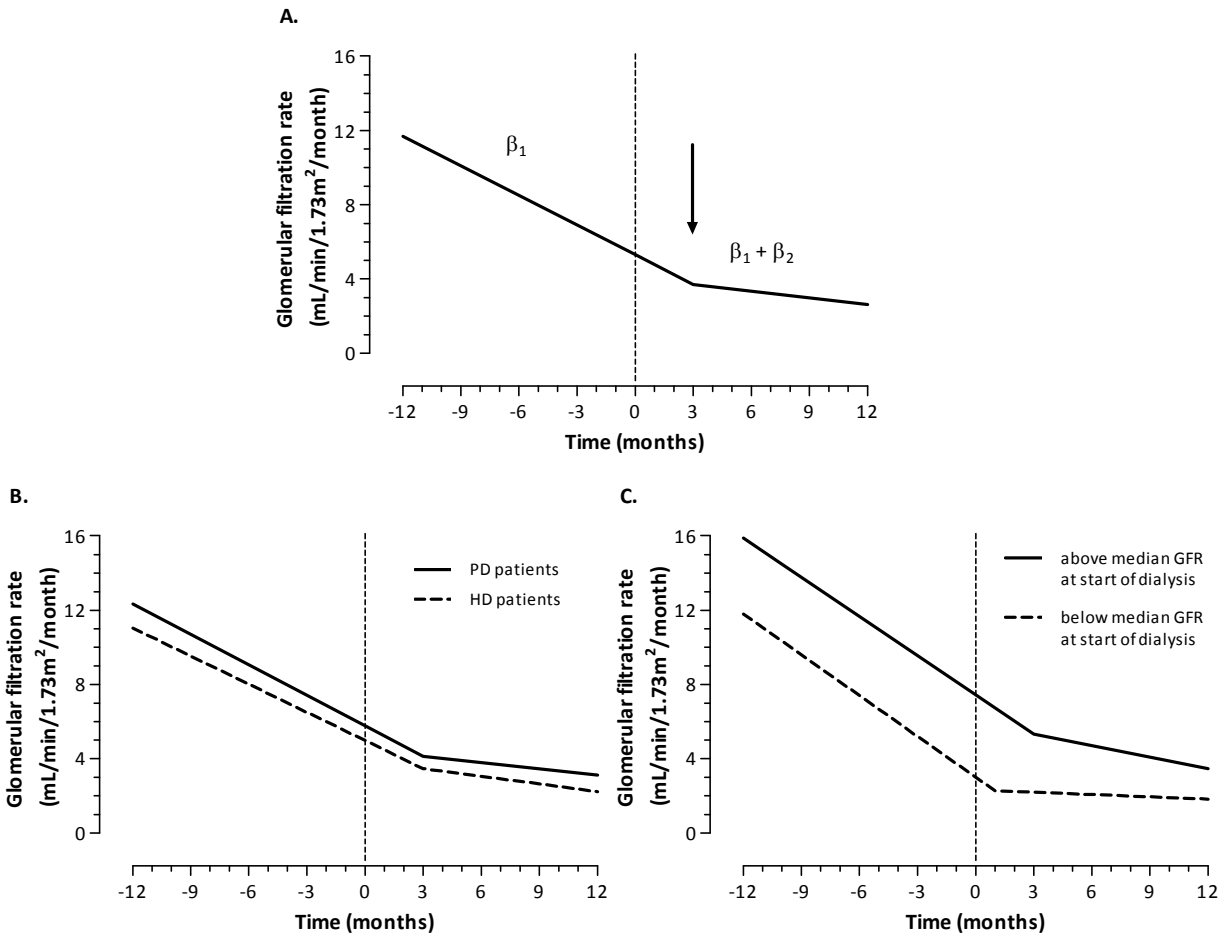
Values are given as mean (standard deviation) or percentage, as appropriate; values between square brackets indicate the number of patients for whom data were available on that particular parameter; HD, hemodialysis; PD, peritoneal dialysis; ACE: angiotensin I converting enzyme; ARB: angiotensin II receptor blocker; *including diabetes mellitus as primary kidney disease.

*The best fitting models for the course of renal function*

Decline of GFR was estimated using linear mixed effects models. The best fitting model to describe the course of renal function with a possible change in decline was selected based on the Akaike's Information Criterion (AIC),[15] whereby a lower AIC indicated a better model fit. The model which fitted best in all patients was the model which allowed for a change in the rate of decline three months after the start of dialysis (Figure 1A). This model was significantly better as compared to the model that fitted a constant linear decline (i.e. a model without change point). In HD and PD patients the best fitting models were the models with a change in the rate

of decline at three months after the start of dialysis (Figure 1B). In patients who started dialysis when their GFR was equal or above the median GFR level at start of dialysis, the rate of decline of renal function changed after three months of dialysis. In patients who started dialysis when their GFR level was below the median GFR level at start of dialysis, the rate of decline changed after one month of dialysis (Figure 1C).

**Figure 1.** Schematic representation of the course of decline of GFR before and after the start of dialysis in 1861 dialysis patients (panel A), in 1143 HD and 718 PD patients separately (panel B), and in 573 patients with GFR at start of dialysis below and 574 patients with GFR at start of dialysis equal/above the median GFR at start of dialysis (panel C). The courses of decline were estimated by linear mixed effects models adjusted for possible confounders (age, sex, primary kidney disease, cardiovascular disease, and diabetes mellitus) whereby decline attenuates a few months after the start of dialysis (change point, indicated by arrow in panel A). In these figures, population averages of the covariates were used. $\beta_1$ represents decline before the change point, $\beta_1 + \beta_2$ decline after the change point. The dashed line at 0 months indicates the start of dialysis.




*Rates of decline of renal function*

Estimates for the rates of decline of GFR derived from the best fitting models are shown in Table 2. It shows that the rate of decline attenuated to a slower rate after a few months of dialysis. To

investigate whether the course of decline of renal function was dependent on the level of GFR at start of dialysis, patients with an available GFR measurement at the start of dialysis (n=1147) were stratified on whether their GFR level was equal/above or below the median GFR level at start of dialysis. Both categories show attenuation to a slower rate of decline after a few months of dialysis. (Table 3)

**Table 2.** Course of decline of glomerular filtration rate (GFR) in 1143 hemodialysis (HD) and 718 peritoneal dialysis (PD) patients in the period of one year before until one year after the start of dialysis.

| | Time[1] | Crude | | Adjusted[2] | |
|---|---|---|---|---|---|
| | | Decline per month (95% CI)[3] | | Decline per month (95% CI)[3] | |
| | | Before | After | Before | After |
| All | 2 months | -0.61 (-0.67;-0.54) | -0.15 (-0.26;-0.04) | -0.62 (-0.69;-0.56) | -0.15 (-0.26;-0.05) |
| | 3 months | -0.52 (-0.57;-0.47) | -0.12 (-0.21;-0.03) | **-0.53 (-0.58;-0.48)** | **-0.12 (-0.20;-0.04)** |
| | 4 months | **-0.48 (-0.53;-0.43)** | **-0.05 (-0.14;0.04)** | -0.48 (-0.53;-0.44) | -0.07 (-0.16;0.01) |
| HD | 2 months | -0.57 (-0.67;-0.47) | -0.15 (-0.32;0.02) | -0.60 (-0.69;-0.50) | -0.16 (-0.32;-0.01) |
| | 3 months | **-0.49 (-0.57;-0.41)** | **-0.12 (-0.25;0.01)** | **-0.51 (-0.57;-0.44)** | **-0.14 (-0.26;-0.02)** |
| | 4 months | -0.46 (-0.53;-0.39) | -0.06 (-0.20;0.08) | -0.47 (-0.53;-0.40) | -0.08 (-0.21;0.04) |
| PD | 2 months | -0.63 (-0.71;-0.55) | -0.15 (-0.28;-0.01) | -0.64 (-0.73;-0.56) | -0.14 (-0.28;0.00) |
| | 3 months | -0.54 (-0.61;-0.48) | -0.12 (-0.23;0.00) | **-0.55 (-0.62;-0.48)** | **-0.11 (-0.23;0.01)** |
| | 4 months | **-0.50 (-0.56;-0.44)** | **-0.06 (-0.17;0.05)** | -0.50 (-0.56;-0.44) | -0.06 (-0.17;0.06) |

Results of the best fitting models are shown in bold; [1]Timepoint (months after the start of dialysis) at which the decline per month was allowed to change; [2]Adjusted for age, sex, primary kidney disease, and comorbidities (diabetes mellitus and cardiovascular disease); [3]Decline of GFR in mL/min/1.73m$^2$/month in the period before and after the change point.

**Table 3.** Course of decline of glomerular filtration rate (GFR) in 574 patients who started dialysis when their GFR level was equal/above and in 573 patients who started dialysis when their GFR level was below the median GFR level at start of dialysis.

| | Time[1] | Crude | | Adjusted[2] | |
|---|---|---|---|---|---|
| | | Decline (95% CI)[3] | | Decline (95% CI)[3] | |
| | | Before | After | Before | After |
| Above median GFR | 3 months | -0.73 (-0.82;-0.64) | -0.21 (-0.37;-0.05) | -0.70 (-0.78;-0.62) | -0.21 (-0.36;-0.05) |
| Below median GFR | 1 month | -0.75 (-0.90;-0.60) | -0.02 (-0.25;0.20) | -0.73 (-0.88;-0.58) | -0.04 (-0.27;0.19) |

[1]Timepoint (months after the start of dialysis) at which the decline per month was allowed to change; [2]Adjusted for age, sex, primary kidney disease, and comorbidities (diabetes mellitus and cardiovascular disease); [3]Decline of GFR in mL/min/1.73m$^2$/month in the period before and after the change point.

*Differences in the decline of GFR between HD and PD patients*

Differences in the rate of decline of GFR between HD and PD patients were estimated using a model that allowed a change in the rate of decline after three months of dialysis. The decline of GFR before the change point was similar for PD and HD patients (mean difference: 0.004 mL/min/1.73m$^2$/month [95% CI -0.10; 0.11]), also after adjustment for possible confounders (mean difference 0.02 mL/min/1.73m$^2$/month [95% CI -0.08; 0.12]). After the change point no

difference in the unadjusted rate of decline of GFR was found between HD and PD patients (mean difference 0.03 mL/min/1.73m$^2$/month [95% CI -0.11; 0.18]). After adjustment for possible confounders the mean difference in decline in GFR between HD and PD patients was -0.02 mL/min/1.73m$^2$/month (95% CI -0.16; 0.12).

*Post-hoc analyses*

To investigate the robustness of the results, analyses were repeated restricted to patients with specific reasons for censoring. These analyses showed that the decline of renal function was not different in patients who died within the first year of dialysis or who were transplanted during follow-up. Furthermore, it was investigated whether the mean rate of decline of GFR was influenced by the decline in patients who became anuric during follow-up. This analysis showed that the decline of renal function in all patients was similar to the decline in patients who maintained some level of GFR and did not become anuric during follow-up.

**Discussion**

This large study showed that in both HD and PD patients the rate of decline of GFR is not constant, but attenuates at two to four months after the start of dialysis. Before this 'change point' the rate of decline of GFR was faster as compared to thereafter. The time of attenuation of the decline of GFR may depend on the level of GFR at the start of dialysis. No evidence was found for a faster decline of GFR in patients on HD as compared to PD; neither before, nor after the change point.

More than twenty-five years ago, a faster decline of renal function in patients on HD as compared to PD has been observed.[8] This finding has been confirmed by others[9;16;17] even with improved statistical procedures accounting for dependency among observations and informative censoring.[10;11] In contrast to the present analysis, these studies did not include the course of decline of GFR during pre-dialysis. Furthermore, many of the previous studies calculated the decline of GFR relative to the GFR at start of dialysis, without accounting for differences in GFR between HD and PD patients at start. Since GFR at start of dialysis in PD patients in general is higher as compared to HD patients, an equal amount of (absolute) decline of GFR in HD and PD patients will lead automatically to a larger relative decline of GFR in HD as compared to PD. The results of the present study show that the rate of decline of renal function in HD and PD patients is similar, although at a different level of GFR.

One study found that the decline of urea clearance in patients treated with high-flux biocompatible HD was similar to the decline in patients treated with continuous ambulatory PD.[12] It was also found that the rate of decline of urea clearance was similar before and after the start of dialysis, although a step-decline of about 2 mL/min was observed at start of dialysis. In the present analysis we did not observe a step-decline of GFR at the start of dialysis. This can be explained as follows: In the previous analysis, decline of urea clearance was estimated by fitting two separate linear regression models: one model for decline in the period preceding the start of dialysis, the other model for decline in the period after the start of dialysis. As a result, if a

difference (step-decline) in the rates of decline would have been present, it should have been observed at start of dialysis by definition. An advantage of the present analysis is that both the period before and after the start of dialysis was taken into account in the same regression model to estimate the decline of GFR.

Several methodological issues should be considered. First, there were missing GFR measurements. Restricting the analyses to complete cases might result in biased estimates. It is likely that GFR values were missing for observed reasons, i.e. missing at random. The present analyses were performed with linear mixed effects models, which are able to deal with data missing at random, without restricting the analyses to complete cases. Second, data on decline of renal function before the start of dialysis were collected retrospectively. The present results can thus (only) be generalized to patients who start dialysis. Finally, for the present analysis it was assumed that decline of renal function progresses linearly. Alternatively the decline of renal function could follow a different pattern like for example an exponential pattern. Therefore, we examined the residuals of our best fitted linear mixed effects model (i.e. the model with a change point at three months). The residuals of that model showed an approximately normal distribution. Furthermore, previous studies also observed a linear decline of estimated GFR.[18] Therefore, the assumption of linear decline seems reasonable.

A possible explanation for attenuation in the rate of decline of GFR after the start of dialysis is that the reduced decline rate of GFR might be due to the dialysis procedure itself, during which urea and creatinine are removed from the extracellular compartment. When the generation rates of both solutes would remain unaltered, their removal would result in lower plasma concentrations. As the plasma concentration is in the denominator of the clearance formula, this would result in a relatively higher value of GFR, calculated from urea and creatinine clearances. It would also imply that residual GFR calculations in dialysis patients are to some extent influenced by dialytic removal of low molecular weight solutes. When this is the case, the observed decline rate may be an artifact and the real glomerular filtration rate is not necessarily affected. Another possibility is that the start of dialysis may be accompanied with specific treatment and lifestyle changes such as changes in medication and diet. These changes may have a beneficial effect on preservation of the GFR that might get apparent only a few months after the start of dialysis.

The results of the present study show that the rate of decline of GFR decreases after a few months of PD or HD treatment. Preservation of renal function is associated with a more adequate dialysis therapy, improved quality of life, and consequently reduced morbidity and mortality, as has been shown by previous observational studies.[1-3] These studies also demonstrated that dialysis is started at a wide variety of kidney functions, indicating that other (additional) criteria are used for the decision on when to start dialysis.[19] Therefore, the debate on the advantages of an earlier start of dialysis is still going on. Recently, the results of the Initiation Dialysis Early and Late (IDEAL) Study, the first randomized controlled trial in which patients were randomly assigned to either early or late start of dialysis, have been published. The results of this trial did not show differences in the risk of mortality or adverse events

(cardiovascular events, infections or complications of dialysis) between patients with early *versus* late start of dialysis.[20] In the IDEAL study the estimated glomerular filtration levels (by the Cockroft and Gault equation) at the start of dialysis were 12.0 mL/min for the early-start group and 9.8 mL/min for the late-start group, while it was as low as 5.2 mL/min/1.73m$^2$ in the present study. Whether the subsequent course in decline in GFR after start of dialysis at the levels of GFR as observed in IDEAL is comparable to the present study needs to be awaited since data on decline of renal function in the IDEAL Study have not yet been published.

In conclusion, the present study shows that the rate of decline of renal function is not constant from pre-dialysis until one year after the start of dialysis, but changes after two to four months of dialysis. This pattern was observed in both dialysis modalities. The observation that the apparent decline of renal function attenuates somewhat earlier when the GFR level at start of dialysis is lower, might suggest that the attenuation in the rate of decline of renal urea and creatinine clearance depends at least partly on the level of remaining renal function. In addition, it was shown that the attenuation in the rate of decline of these parameters was not different for patients who were finally censored because of death, kidney transplantation or who did not become anuric during follow-up. Further studies are needed to examine possible explanations for the attenuation in the rate of decline of GFR after the start of dialysis.

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**Disclosure**

The authors have had no involvements that might raise the question of bias in the work reported, in the conclusions, implications, or opinions stated. The results presented in this paper have not been published previously in whole or in part, except in abstract format.

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# Chapter 8 |

## Cardiovascular and noncardiovascular mortality among patients starting dialysis

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**Abstract**

*Context*

Cardiovascular mortality is considered the main cause of death in patients receiving dialysis and is 10 to 20 times higher in such patients than in the general population.

*Objective*

To evaluate if high overall mortality in patients starting dialysis is a consequence of increased cardiovascular mortality risk only or whether noncardiovascular mortality is equally increased.

*Design, setting, and patients*

Using data from between January 1, 1994, and January 1, 2007, age-stratified mortality in a European cohort of adults starting dialysis and receiving follow-up for a mean of 1.8 (standard deviation, 1.1) years (European Renal Association-European Dialysis and Transplant Association [ERA-EDTA] Registry [N=123,407]) was compared with the European general population (Eurostat).

*Main outcome measures*

Cause of death was recorded by ERA-EDTA codes in patients and matching International Statiscal Classification of Diseases, 10$^{th}$ Revision codes in the general population. Standardized cardiovascular and noncardiovascular mortality rates, their ratio, difference, and relative excess of cardiovascular over noncardiovascular mortality were calculated.

*Results*

Overall all-cause mortality rates in patients and the general population were 192 per 1000 person-years (95% confidence interval [CI], 190-193) and 12.055 per 1000 person-years (95% CI, 12.05-12.06), respectively. Cause of death was known for 90% of the patients and 99% of the general population. In patients, 16,654 deaths (39%) were cardiovascular and 21,654 (51%) were noncardiovascular. In the general population, 7,041,747 deaths (40%) were cardiovascular and 10 183 322 (58%) were noncardiovascular. Cardiovascular and noncardiovascular mortality rates in patients were respectively 38.1 per 1000 person-years (95% CI, 37.2-39.0) and 50.1 per 1000 person-years (95% CI, 48.9-51.2) higher than in the general population. On a relative scale, standardized cardiovascular and noncardiovascular mortality were respectively 8.8 (95% CI, 8.6-9.0) and 8.1 (95% CI, 7.9-8.3) times higher than in the general population. The ratio of these rates, i.e., relative excess of cardiovascular over noncardiovascular mortality in patients starting dialysis compared with the general population, was 1.09 (95% CI, 1.06-1.12). Relative excess in a sensitivity analysis in which unknown/missing causes of death were regarded either as noncardiovascular or cardiovascular varied between 0.90 (95% CI, 0.88-0.93) and 1.39 (95% CI, 1.35-1.43).

*Conclusion*

Patients starting dialysis have a generally increased risk of death that is not specifically caused by excess cardiovascular mortality.

## Introduction

Patients with chronic kidney disease are at higher mortality risk compared with the general population.[1;2] Cardiovascular disease is the most common cause of death in these patients, as noted more than 30 years ago.[3] Several studies have shown that cardiovascular disease accounts for 40% to 50% of deaths in patients with end-stage renal disease.[4-6] Cardiovascular mortality risk in patients receiving hemodialysis or peritoneal dialysis is observed to be 10 to 20 times that in the general population.[4;6]

In addition to mortality, cardiovascular morbidity is highly prevalent in patients receiving dialysis.[7] Approximately 75% of such patients have left ventricular hypertrophy as determined by ultrasound.[8] The prevalence of coronary artery disease or congestive heart failure in patients receiving dialysis is approximately 40%.[9] The high risk of cardiovascular morbidity and mortality in patients receiving dialysis is associated with a high prevalence of known risk factors for cardiovascular disease in the general population (hypertension, diabetes, dyslipidemia). In addition, specific characteristics of the dialysis population play a role, including increased presence of multiple comorbid conditions, volume overload, and disturbed calcium phosphate metabolism.[4;10-13] Moreover, chronic kidney disease has been regarded as a risk factor for cardiovascular disease.[14-17] Therefore, current clinical guidelines recommend that clinicians consider and treat individuals with chronic kidney disease as being at high risk for cardiovascular disease.[18]

The current concept is that the overall high mortality in patients receiving dialysis is largely explained by increased cardiovascular mortality.[18 (pp S8, S9)] In many reports on classic or novel cardiovascular risk factors, specific reference is made to high cardiovascular mortality. It is believed that the life span of patients receiving dialysis is reduced mainly as a consequence of premature cardiovascular death.[19] To evaluate whether this is indeed the case, we estimated cardiovascular and noncardiovascular mortality in a large cohort of European patients receiving dialysis and compared these estimates with mortality data from the general European population.

## Methods

### *Study population*

The study cohort consisted of incident patients from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry who were starting hemodialysis and peritoneal dialysis.[20] The ERA-EDTA Registry collects data on renal replacement therapy through national and regional registries in Europe, including date of birth, sex, primary renal disease, date of start of therapy, subsequent changes in treatment modality, and date and cause of death.

Patients were included if they originated from registries reporting less than 25% missing or unknown causes of death. Cause of death was classified by means of the ERA-EDTA coding system for causes of death.[21;22] The inclusion period for the present study was between January 1, 1994, and January 1, 2007. For the present analysis, patients underwent follow-up for a

maximum of 3 years (cumulative survival≈50%) from start of dialysis until death or censoring, which occurred at time of recovery of renal function, transplantation, or January 1, 2007 (end of study), whichever occurred first.

*Reference Population*

Mortality data from the general populations of the 9 countries from which patients were included were used for reference. Data were obtained from Eurostat, the statistical office of the European Union.[23;24] Eurostat provides cause-specific mortality data, classified by International Statistical Classification of Diseases, 10th Revision (ICD-10) codes, stratified by 5-year age categories and sex.[25]

*Definition of Study Outcomes*

Cardiovascular mortality in patients was defined as death attributable to myocardial ischemia and infarction, heart failure, cardiac arrest due to other or unknown cause, or cerebrovascular accident (ERA-EDTA codes 11, 14-16, 18, and 22). Unknown (ERA-EDTA code 0) or missing causes of death were defined as unknown/missing. Noncardiovascular mortality was defined as all other causes of death, i.e. infection, suicide or refusal of treatment, withdrawal, cachexia, malignancies, and miscellaneous (ERA-EDTA codes 12, 13, 17, 21, 23-29, 31-33, 35-39, 41-46, 51-54, 62-64, 66-73, 81, 82, and 99-102).

Cardiovascular mortality in the general population was defined as diseases of the circulatory system, i.e. acute rheumatic fever; chronic rheumatic heart disease; hypertensive diseases; ischemic heart diseases; pulmonary heart diseases and diseases of pulmonary circulation; other forms of heart disease; cerebrovascular diseases; diseases of arteries, arterioles, and capillaries; diseases of veins, lymphatic vessels, and lymph nodes, not elsewhere classified; and other and unspecified disorders of the circulatory system (Eurostat codes ICD-10 I00-I99). ICD-10 codes R96-R99 (ill-defined and unknown causes of mortality) were regarded as unknown/missing cause of death in the general population, while all other codes (thus all causes except ICD-10 I00-I99 and R96-R99) were regarded as noncardiovascular causes of death.

Data were collected in accordance with national and regional laws, which are usually based on European legislation but which may differ slightly between the different countries or regions from which participants were included. For patients starting dialysis, this generally includes requesting informed consent for data collection within the framework of the registries and permission to send these data to the ERA-EDTA registry in an anonymous form.

*Statistical analyses*

Data were stratified by 10-year age categories and sex. The lowest age category consisted of patients aged 20 to 24 years, whereas all patients 85 years and older were combined in the highest age category. For each individual patient, person-time at risk was calculated as the time between start of dialysis and censoring or death. Total person-time at risk within the patient populations was calculated as the sum of the individual person-times. Person-time at risk within

the general population was calculated using the demographic large-scale method, a method for calculating person-time within dynamic populations. Using this method, person-time at risk in the 9 general populations of the countries from which patients starting dialysis were included was calculated as the sum of the mean sizes of the general populations in the subsequent calendar years. In addition, the total number of all-cause, cardiovascular, and noncardiovascular deaths during the study period within both populations were determined.

Subsequently, in both populations, age-specific cardiovascular and noncardiovascular mortality rates (per 1000 person-years) were calculated by dividing the total number of deaths by the total person-time lived in an age stratum. Differences between cardiovascular mortality rates in patients and the general population (ΔCV) were calculated by subtracting mortality rates in patients from the rates in the general population. Differences between noncardiovascular mortality rates (Δnon-CV) were calculated in the same manner. Absolute excess cardiovascular mortality over noncardiovascular mortality in patients compared with the general population was calculated as the difference between ΔCV and Δnon-CV. To correct for age differences between patients and the general population, standardization with weights derived from the age distribution of the general population was used. Standardized mortality rate ratios were calculated by dividing the sum of the stratum-specific standardized mortality rates in patients starting dialysis by the sum of these rates in the general population. Relative excess cardiovascular mortality was defined as the ratio of these 2 rate ratios for cardiovascular and noncardiovascular mortality being higher than 1, to indicate to what extent cardiovascular mortality exceeds noncardiovascular mortality in patients starting dialysis.

Several sensitivity analyses were performed to check the robustness of the results. First, unknown causes of death (either missing or ERA-EDTA code 0) were censored in the analyses. To evaluate the influence of these unknown causes of death, all unknown mortality causes were classified as either cardiovascular or noncardiovascular mortality. Second, to evaluate the effect of censoring at time of transplantation, an analysis was performed in which patients were not censored after transplantation. Third, since follow-up was arbitrarily prespecified at a cumulative survival of approximately 50%, follow-up was censored at 3 years. The effect of maximizing follow-up at 3 years was evaluated in an analysis in which total follow-up of all patients was used instead of only the first 3 years. Fourth, results were obtained using direct standardization, with weights derived from the age distribution of the general population. The influence of the choice of the weighting scheme was assessed in an analysis whereby weights were derived from the patients starting dialysis. If applicable, 2-sided $p<0.05$ was regarded as statistically significant. Statistical analyses were performed using SPSS version 14.0.2 (SPSS Inc, Chicago, Illinois).

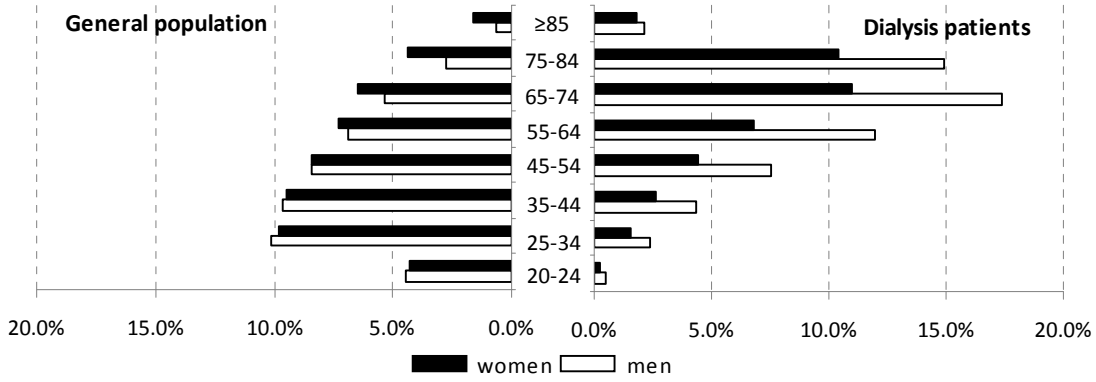
## Results

### *Study population*

Patients (N=123,407) were included from registries in 9 countries: Austria, Belgium (Dutch- and French-speaking), Denmark, Finland, Italy (Basilicata, Emilia-Romagna, Piemonte, Sardegna),

the Netherlands, Norway, Spain (Andalusia, Basque Country, Catalonia), and Sweden. All renal registries had 100% coverage of the general population in the corresponding region. Mean age of the patients at start of dialysis was 63.2 years, and the majority (61.2%) were men (Table 1).

**Figure 1.** Age and sex distribution in the general population (Eurostat, mean size during thirteen-year follow-up period: N=111,190,899: 53,633,232 men and 57,557,667 women, left panel) and dialysis patients (ERA-EDTA Registry, N=123,407 patients: 75,482 men and 47,925 women, right panel).




The general population included 1,445,495,838 person-years over the 13-year observation period. The mean age of patients starting dialysis was higher, and that group included more men than the general population (Figure 1). Follow-up During follow-up, 25,084 patients (20.3%) were censored (withdrawn alive) because of kidney transplantation, and 42,643 (34.6%) died. Cause of death remained missing or unknown for 4,335 patients (10.2%). Characteristics of patients with known and unknown causes of death were not different ($p>0.05$). Noncardiovascular death (21,654 patients [50.8%]) was the most prevalent cause of death, whereas 16,654 patients (39.1%) died of cardiovascular disease. The most common causes of noncardiovascular death were infections (6,220 patients [14.6%]) and malignancies (3,334 patients [7.6%]). The pattern of causes of noncardiovascular death was different across the age groups. Younger patients died relatively often as a consequence of infections, whereas the incidence of "social death" (e.g. refusal of treatment) and cachexia was highest in elderly patients (Table 2). In the general population, 10,183,322 persons (58.4%) died from noncardiovascular causes, 7,041,747 (40.4%) from cardiovascular causes, and 201,050 (1.2%) from unknown causes.

*Absolute differences in mortality rates and absolute excess mortality*

The overall all-cause mortality rate was higher in patients starting dialysis (191.7 per 1000 person-years [95% confidence interval, CI, 189.8-193.5]) than in the general population (12.055 per 1000 person-years [95% CI, 12.05-12.06).

**Table 1.** Baseline description of dialysis patients (N=123,407).

Unless otherwise stated: Mean (SD); CV: cardiovascular; *At start of follow-up; †During follow-up.

| | All patients N=123,407 | Age category* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 20-24 N=1,591 | 25-34 N=5,471 | 35-44 N=9,495 | 45-54 N=16,210 | 55-64 N=25,051 | 65-74 N=36,589 | 75-84 N=26,078 | ≥85 N=2,922 |
| Age *yr* | 63.2 (14.9) | 22.7 (1.4) | 30.6 (2.8) | 40.4 (2.9) | 50.4 (2.9) | 60.3 (2.9) | 70.2 (2.9) | 79.0 (2.7) | 87.6 (2.3) |
| Males *N (%)* | 75,482 (61.2) | 1,028 (64.6) | 3,311 (60.5) | 5,975 (62.9) | 10,239 (63.2) | 15,824 (63.2) | 22,267 (60.9) | 15,255 (58.5) | 1,583 (54.2) |
| Renal transplant† *N (%)* | 25,084 (20.3) | 1,131 (71.1) | 3,520 (64.3) | 5,236 (55.1) | 6,984 (43.1) | 6,040 (24.1) | 2,080 (5.7) | 90 (0.3) | 3 (0.1) |
| Follow-up *yr* | 1.8 (1.1) | 1.8 (1.0) | 1.8 (1.0) | 1.8 (1.0) | 1.9 (1.0) | 1.9 (1.0) | 1.8 (1.1) | 1.6 (1.1) | 1.3 (1.1) |

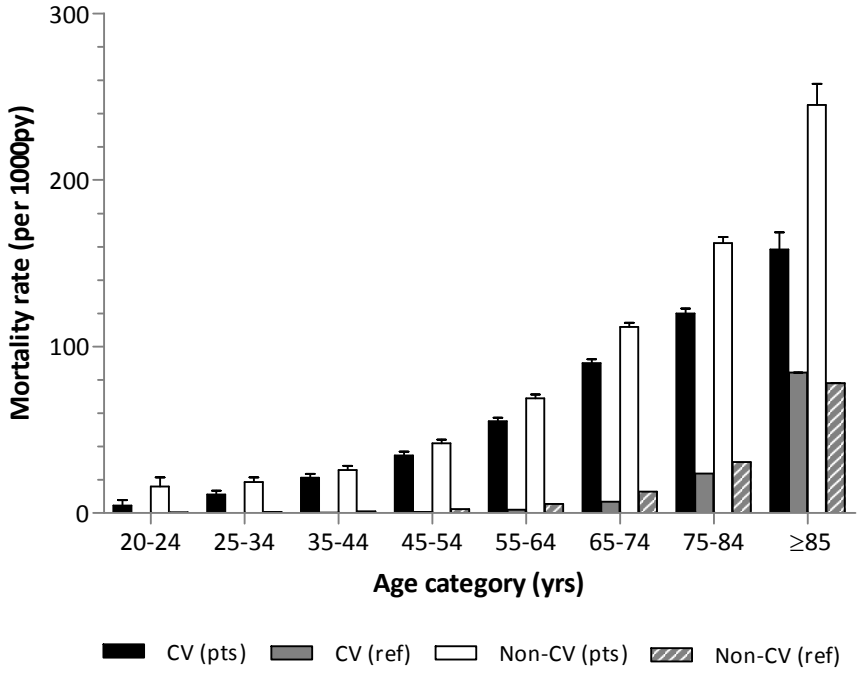
**Table 2.** Causes of death of dialysis patients in the first three years after start of dialysis.

All data are presented as N (%); *Age at death.

| | All patients N=123,407 | Age category* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 20-24 N=977 | 25-34 N=4,844 | 35-44 N=8,584 | 45-54 N=14,713 | 55-64 N=23,194 | 65-74 N=35,027 | 75-84 N=31,211 | ≥85 N=4,857 |
| Total deaths | 42,643 (34.6) | 46 (4.7) | 304 (6.3) | 880 (10.3) | 2,498 (17.0) | 6,343 (27.3) | 14,779 (42.2) | 15,207 (48.7) | 2,586 (53.2) |
| CV | 16,654 (39.1) | 8 (17.4) | 99 (32.6) | 346 (39.3) | 1,007 (40.3) | 5,973 (40.2) | 5,937 (40.2) | 5,819 (38.3) | 924 (35.7) |
| Non-CV | 21,654 (50.8) | 33 (71.7) | 168 (55.3) | 422 (48.0) | 1,214 (48.6) | 7,369 (49.9) | 7,369 (49.9) | 7,877 (51.8) | 1,432 (55.4) |
| Infections | 6,220 (14.6) | 9 (19.6) | 65 (21.4) | 135 (15.3) | 399 (16.0) | 979 (15.4) | 2,186 (14.8) | 2,105 (13.8) | 342 (13.2) |
| Malignancies | 3,334 (7.8) | 3 (6.5) | 12 (3.9) | 58 (6.6) | 223 (8.9) | 653 (10.3) | 1,276 (8.6) | 1,012 (6.7) | 97 (3.8) |
| Cachexia | 2,015 (4.7) | 0 | 6 (2.0) | 17 (1.9) | 70 (2.8) | 179 (2.8) | 570 (3.9) | 913 (6.0) | 260 (10.1) |
| Withdrawal | 2,212 (5.2) | 1 (0.1) | 5 (1.6) | 16 (1.8) | 57 (2.3) | 202 (3.2) | 674 (4.6) | 1,012 (6.7) | 245 (9.5) |
| Suicide/refusal treatment | 1,658 (3.9) | 1 (0.1) | 14 (4.6) | 33 (3.8) | 57 (2.3) | 172 (2.7) | 503 (3.4) | 722 (4.7) | 156 (6.0) |
| Miscellaneous | 6.215 (14.6) | 19 (41.3) | 66 (21.7) | 163 (18.5) | 408 (16.3) | 954 (15.0) | 2,160 (14.6) | 2,113 (13.9) | 332 (12.8) |
| Unknown | 4,335 (10.2) | 5 (10.9) | 37 (12.2) | 112 (12.7) | 277 (11.1) | 690 (10.9) | 1,473 (10.0) | 1,511 (9.9) | 230 (8.9) |

The cardiovascular and noncardiovascular mortality rates were lowest in young participants and increased with age in both populations. In particular, noncardiovascular mortality rates were higher than cardiovascular mortality rates in patients starting dialysis (Figures 2 and 3). For every age group ΔCV and Δnon-CV were positive, indicating excess cardiovascular as well as excess noncardiovascular mortality in patients starting dialysis compared with the general population. More important, for almost every age stratum, absolute excess was greater for noncardiovascular than for cardiovascular mortality (Table 3).

**Figure 2.** Absolute cardiovascular (CV) and non-cardiovascular (non-CV) mortality rates (per 1000py, mean with standard error) were higher in dialysis patients (pts) than in the general population (ref) at every age.



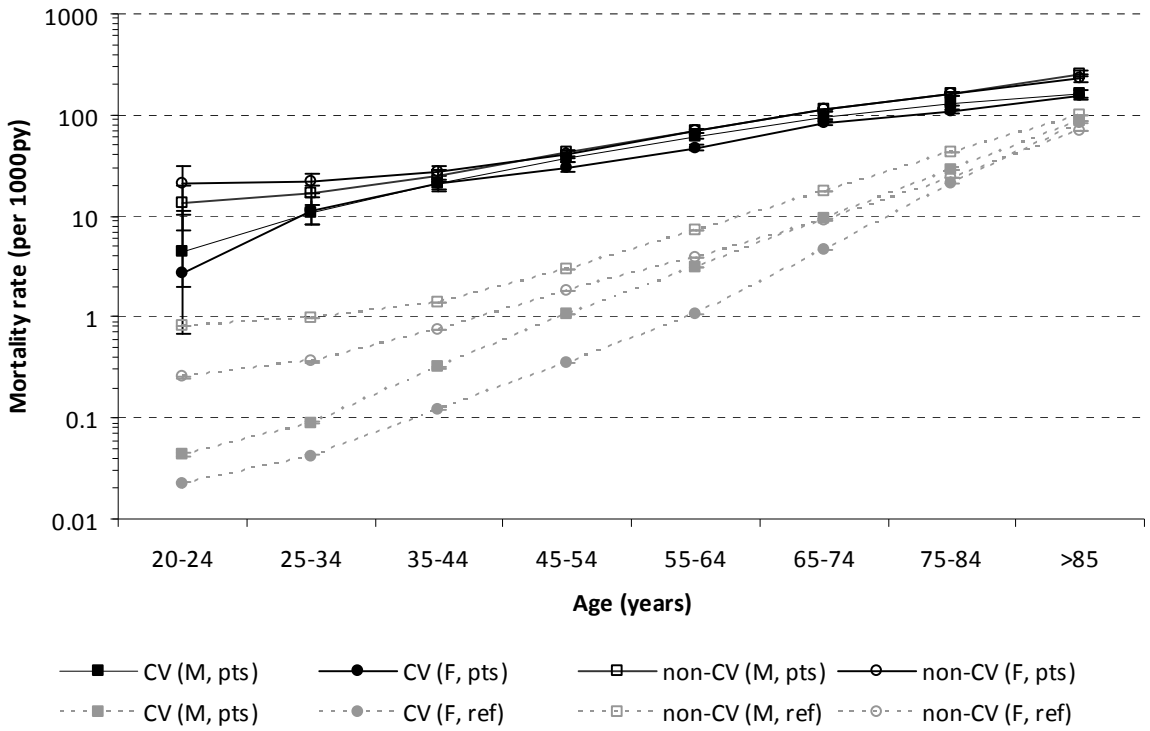

After age standardization, absolute excess noncardiovascular mortality in patients starting dialysis (50.1 per 1000 person-years [95% CI, 48.9-51.2]) was greater than absolute excess cardiovascular mortality (38.1 per 1000 person-years [95% CI, 37.2-39.0]) (Table 3). After age standardization, absolute excess cardiovascular mortality was comparable between men and women (37.3 per 1000 person-years [95% CI, 36.1-38.5] vs. 37.0 per 1000 person-years [95% CI, 35.6-38.5], respectively). However, absolute excess noncardiovascular mortality was greater in women than in men (55.8 per 1000 person-years [95% CI, 53.9-57.7] vs. 44.1 per 1000 person-years [95% CI, 42.7-45.5], respectively).

**Table 3.** Cardiovascular and non-cardiovascular mortality rates (per 1000py), their difference, and the excess risk of cardiovascular mortality over non-cardiovascular mortality in the dialysis population as compared to the general population.

| | Age | CV[1] | | Non-CV[1] | | Absolute Excess | | |
|---|---|---|---|---|---|---|---|---|
| | | Pts | Ref | Pts | Ref | ΔCV[2] | Δnon-CV[2] | Excess[3] |
| All | 20-24 | 3.9 | 0.0 | 16.0 | 0.5 | 3.8 (2.2, 5.5) | 15.5 (10.0, 20.9) | -11.6 (-17.3, -5.9) |
| | 25-34 | 11.0 | 0.1 | 18.7 | 0.7 | 10.9 (8.8, 13.1) | 18.0 (15.2, 20.8) | -7.1 (-10.6, -3.5) |
| | 35-44 | 21.2 | 0.2 | 25.8 | 1.1 | 20.9 (18.7, 23.2) | 24.7 (22.2, 27.2) | -3.8 (-7.1, -0.5) |
| | 45-54 | 34.6 | 0.7 | 41.7 | 2.4 | 33.9 (31.8, 36.1) | 39.4 (37.0, 41.7) | -5.4 (-8.6, -2.3) |
| | 55-64 | 55.1 | 2.0 | 68.8 | 5.5 | 53.1 (50.9, 55.2) | 63.3 (60.9, 65.7) | -10.2 (-13.5, -7.0) |
| | 65-74 | 90.0 | 6.8 | 111.7 | 12.9 | 83.3 (81.0, 85.6) | 98.8 (96.3, 101.4) | -15.6 (-19.0, -12.1) |
| | 75-84 | 119.8 | 23.8 | 162.1 | 30.6 | 96.0 (92.9, 99.1) | 131.5 (127.9, 135.1) | -35.5 (-40.2, -30.8) |
| | ≥85 | 158.1 | 84.3 | 245.1 | 78.0 | 73.8 (63.6, 84.0) | 167.0 (154.4, 179.7) | -93.2 (-109.5, -77.0) |
| | Unstand.[4] | 74.9 (73.7, 76.0) | 4.872 (4.87, 4.88) | 97.3 (96.0, 98.6) | 7.045 (7.04, 7.05) | 70.0 (68.8, 71.1) | 90.3 (89.0, 91.6) | -20.3 (-22.0, -18.6) |
| | Stand.[5] | 42.9 (42.0, 43.8) | 4.9* | 57.1 (56.0, 58.2) | 7.0* | 38.1 (37.2, 39.0) | 50.1 (48.9, 51.2) | -12.0 (-13.4, -10.5) |
| Men | 20-24 | 4.5 | 0.0 | 13.5 | 0.8 | 4.5 (2.4, 6.5) | 12.7 (10.6, 14.7) | -8.2 (-11.2, -5.3) |
| | 25-34 | 10.9 | 0.1 | 16.5 | 1.0 | 10.8 (8.0, 13.6) | 15.5 (12.1, 19.0) | -4.8 (-9.2, -0.3) |
| | 35-44 | 21.3 | 0.3 | 25.1 | 1.4 | 20.9 (18.1, 23.8) | 23.7 (20.6, 26.8) | -2.8 (-7.0, 1.4) |
| | 45-54 | 37.4 | 1.1 | 42.3 | 3.0 | 36.3 (33.5, 39.1) | 39.3 (36.3, 42.3) | -3.0 (-7.1, 1.1) |
| | 55-64 | 59.7 | 3.1 | 68.2 | 7.2 | 56.6 (53.8, 59.4) | 61.0 (58.0, 64.1) | -4.4 (-8.6, -0.3) |
| | 65-74 | 95.5 | 9.5 | 112.0 | 17.8 | 86.0 (83.0, 89.1) | 94.2 (90.9, 97.4) | -8.1 (-12.6, -3.7) |
| | 75-84 | 126.6 | 29.0 | 161.7 | 42.0 | 97.6 (93.5, 101.8) | 119.7 (115.1, 124.4) | -22.1 (-28.4, -15.9) |
| | ≥85 | 158.5 | 87.8 | 255.1 | 98.0 | 70.8 (56.9, 84.6) | 157.1 (139.5, 174.6) | -86.3 (-108.7, -64.0) |
| | Unstand.[4] | 78.3 (76.8, 79.8) | 4.611 (4.61, 4.62) | 95.9 (94.2, 97.5) | 7.807 (7.80, 7.81) | 73.7 (72.2, 75.2) | 88.1 (86.4, 89.7) | -14.4 (-16.6, -12.2) |
| | Stand.[5] | 41.9 (40.7, 43.1) | 4.6* | 51.9 (50.5, 53.3) | 7.8* | 37.3 (36.1, 38.5) | 44.1 (42.7, 45.5) | -6.8 (-8.6, -5.0) |
| Women | 20-24 | 2.8 | 0.0 | 20.6 | 0.3 | 2.7 (-0.5, 6.0) | 20.4 (17.1, 23.6) | -17.6 (-22.3, -13.0) |
| | 25-34 | 11.2 | 0.0 | 21.9 | 0.4 | 11.2 (7.7, 14.6) | 21.5 (16.7, 26.3) | -10.3 (-16.2, -4.4) |
| | 35-44 | 21.0 | 0.1 | 26.9 | 0.8 | 20.9 (17.3, 24.5) | 26.2 (22.1, 30.2) | -5.3 (-10.7, 0.1) |
| | 45-54 | 30.0 | 0.4 | 40.8 | 1.8 | 29.7 (26.4, 32.9) | 39.0 (35.2, 42.8) | -9.4 (-14.3, -4.4) |
| | 55-64 | 47.4 | 1.0 | 69.8 | 3.9 | 46.4 (43.1, 49.6) | 65.9 (61.9, 69.9) | -19.6 (-24.7, -14.4) |
| | 65-74 | 81.7 | 4.5 | 111.4 | 8.9 | 77.2 (73.7, 80.6) | 102.5 (98.5, 106.5) | -25.3 (-30.6, -20.0) |
| | 75-84 | 110.1 | 20.5 | 162.7 | 23.6 | 89.6 (85.1, 94.2) | 139.2 (133.6, 144.7) | -49.5 (-56.7, -42.3) |
| | ≥85 | 157.7 | 82.9 | 233.1 | 69.8 | 74.7 (59.7, 89.8) | 163.3 (145.0, 181.7) | -88.6 (-112.3, -64.8) |
| | Unstand.[4] | 69.6 (67.8, 71.3) | 5.115 (5.11, 5.12) | 99.6 (97.5, 101.7) | 6.335 (6.33, 6.34) | 64.5 (62.7, 66.2) | 93.3 (91.2, 95.3) | -28.8 (-31.5, -26.1) |
| | Stand.[5] | 42.2 (40.7, 43.6) | 5.1* | 62.1 (60.2, 64.0) | 6.3* | 37.0 (35.6, 38.5) | 55.8 (53.9, 57.7) | -18.8 (-21.1, -16.4) |

CV: cardiovascular; Δ: difference; [1]Stratum specific mortality rates in patients (Pts) and the general population (Ref); [2]Difference between stratum specific mortality rate in patients and the stratum specific mortality rate in the general population; [3]Excess cardiovascular over non-cardiovascular mortality, calculated as the difference between ΔCV and Δnon-CV: negative values indicate higher non-CV mortality, positive values higher CV mortality; [4]Unstandardized overall mortality rate, their difference and excess; [5]Directly standardized overall mortality rate (for calculation details, see text), their difference and excess; *confidence interval similar to unstandardized rate, since weights were based on age-distribution of the reference population.

**Figure 3.** Unstandardized cardiovascular (CV) and non-cardiovascular (Non-CV) mortality rates (per 1000 person-years, mean with 95% CI) of male (M) and female (F) dialysis patients (pts) and the general population (ref).




*Relative differences in mortality rates and relative excess mortality*

Overall unstandardized cardiovascular and noncardiovascular mortality rates were respectively 15.4 (95% CI, 14.2-16.5) and 13.8 (95% CI, 12.5-15.1) times higher in patients than in the general population. The directly standardized cardiovascular mortality rate was 8.8 (95% CI, 8.6-9.0) and the noncardiovascular mortality rate was 8.1 (95% CI, 7.9-8.3) times higher in patients starting dialysis than in the general population. The relative excess of cardiovascular over noncardiovascular mortality was 1.09 (95% CI, 1.06-1.12).

Although ΔCV, Δnon-CV, and relative excess mortality varied during the calendar period of the study (1994-2007), no change in mortality pattern toward either excess cardiovascular or excess noncardiovascular mortality was present. Minimum and maximum ΔCV in the study period were 8.0 (95% CI, 7.4-8.7) and 9.5 (95% CI, 8.1-11.0), respectively; minimum and maximum Δnon-CV were 7.6 (95% CI, 7.1-8.0) and 9.4 (95% CI, 8.4-10.5); and minimum and maximum excess were 1.01 (95% CI, 0.82-1.20) and 1.18 (95% CI, 1.08-1.27).

*Sensitivity analyses*

To test the robustness of the results, several sensitivity analyses were performed. First, cause of death was unknown in 10.2% of the patients and 1.2% of the general population. To evaluate the

influence of these unknown causes of death, an analysis was performed in which all unknown/missing mortality causes were classified either as noncardiovascular or cardiovascular. In the first extreme, the directly standardized noncardiovascular mortality rate increased to 9.8 (95% CI, 9.6-10.0), resulting in a relative excess cardiovascular mortality of 0.90 (95% CI, 0.88-0.93). For the other extreme, the directly standardized cardiovascular mortality rate increased to 11.2 (95% CI, 11.0-11.5), and the relative excess cardiovascular mortality would be 1.39 (95% CI, 1.35-1.43).

Second, patients were censored at time of transplantation. If not, the directly standardized mortality rate would be 8.1 (95% CI, 8.0-8.3) for cardiovascular mortality and 7.5 (95% CI, 7.4-7.6) for noncardiovascular mortality. This would result in a relative excess cardiovascular mortality of 1.08 (95% CI, 1.05-1.11).

Third, patients in the present analysis underwent follow-up during the first 3 years of dialysis. When patients underwent follow-up during their whole dialysis period, the directly standardized cardiovascular and noncardiovascular mortality rates were 8.6 (95% CI, 8.4-8.7) and 7.9 (95% CI, 7.7-8.0), respectively. This would result in a relative excess cardiovascular mortality of 1.09 (95% CI, 1.06-1.12).

Fourth, since the age distribution was different in patients starting dialysis and in the general population, mortality rates were standardized to the age distribution of the general population. When weights were derived from patients starting dialysis instead of the general population, the directly standardized cardiovascular and noncardiovascular mortality rates would be 7.5 (95% CI, 7.4-7.6) and 6.9 (95% CI, 6.8-7.0), respectively. This would result in a relative excess cardiovascular mortality of 1.09 (95% CI, 1.07-1.11).

**Comment**

We studied a cohort of 123,407 incident patients starting dialysis, of whom 35% died during 3 years of follow-up. Overall standardized death rates in patients starting dialysis were substantially higher than in the general population. The standardized cardiovascular mortality rate was 38.1 per 1000 person-years (95% CI, 37.2-39.0) higher in patients compared with the general population, and the noncardiovascular mortality rate was 50.1 per 1000 person-years (95% CI, 48.9-51.2). These results suggest that excess mortality in patients receiving dialysis is not specifically the result of increased cardiovascular deaths.

The present study showed that the proportion of cardiovascular and noncardiovascular mortality in patients starting dialysis was approximately 44% (16,654 of 38,308 known causes of death) and 56% (21,654 of 38,308 known causes of death), respectively. This is in accordance with findings from the United States (45% cardiovascular and 55% noncardiovascular, respectively).[26] In addition, the present study showed that the unstandardized cardiovascular mortality risk in patients starting dialysis was 15-fold higher than in the general population. This is in accordance with other studies demonstrating a 10- to 20-fold increased cardiovascular mortality risk for patients receiving dialysis.[4;6] The present analysis added that noncardiovascular mortality was 14-fold higher in such patients than in the general population.

Age-standardized cardiovascular and noncardiovascular mortality were respectively 8.8- and 8.1-fold higher than in the general population, resulting in a relative excess of 1.09 for cardiovascular mortality over noncardiovascular mortality. However, because cardiovascular mortality is lower than noncardiovascular mortality in the general population, these ratios are not easy to compare. Absolute mortality rates show that among patients receiving dialysis, the increased risk of dying from noncardiovascular disease is higher than that for dying from cardiovascular disease (after age standardization, 50.1 extra deaths per 1000 person-years and 38.1 extra deaths per 1000 person-years compared with the general population, respectively). These absolute rates are especially important, because they reflect the burden of disease from a societal perspective. Infections and malignancies were the most important causes of noncardiovascular mortality in patients starting dialysis, which is in line with earlier findings.[27;28] To summarize, the increased risk of cardiovascular mortality in patients starting dialysis goes together with an equally increased risk of noncardiovascular mortality.

Some methodological issues deserve attention. First, mortality data were collected from national and regional registries for patients starting dialysis and from whole countries for the general population. Because it is unlikely that there are national differences in cause-of-death classification, it is not likely that this collection method introduced bias. Furthermore, cause of death was unknown/missing in approximately 10% of the patients and 1% of the general population. This different percentage can be explained by the slightly different method for collecting cause-of-death data between the patients and the general population. Causes of death among patients starting dialysis were recorded by the treating nephrologist. When a patient died at home or elsewhere, the treating physician was dependent on information from others. When cause of death was inconclusive, the nephrologist may have classified the cause as unknown. Causes of death within the general population were, according to law, recorded by the physician who confirmed death and sent to the statistics office, resulting in relatively few missing causes of death. To evaluate the influence of unknown/missing causes of death within the present analysis, a sensitivity analysis was performed in which all unknown/missing mortality causes were classified either as noncardiovascular mortality or as cardiovascular mortality, resulting in a relative excess cardiovascular mortality of 0.90 and 1.39, respectively. This suggests that even in these extreme situations, cardiovascular and noncardiovascular mortality are both markedly increased but more or less to the same extent.

Second, renal failure, which is present in all patients receiving dialysis, is never counted as a cause of death within this group. In contrast, in the general population renal failure may be counted as a cause of death (ICD-10 code N17-N19). However, since renal failure is seldom reported as a cause of death in the general population (<1%), it is unlikely that this has biased the present results.

Third, it can be questioned whether cardiovascular mortality was systematically underestimated or overestimated in one population or the other. Causes of death were determined according to the most plausible cause of death in both populations. Therefore, it is unlikely that a bias was introduced by specific comorbid diagnoses that systematically trumped

other diagnoses in recording the cause of death. Moreover, although the ERA-EDTA coding system is less comprehensive than the ICD-10 coding system, the ERA-EDTA system provides the opportunity to assign a "general cardiovascular" code, such as "cardiac arrest/sudden death, other cause or unknown" or "other causes of cardiac failure" in cases lacking an appropriate code for a specific cause of death certainly related to cardiovascular problems.

Fourth, follow-up was censored at the time of transplantation, because patients are no longer at risk to die while receiving dialysis at that time. It can be argued that such censoring may have influenced the results. However, a sensitivity analysis showed that without censoring for transplantation, relative excess cardiovascular over noncardiovascular mortality was 1.08, indicating that the choice of censoring at time of transplantation did not influence our results. Similarly, maximum follow-up in all patients was restricted to the first 3 years of dialysis to exclude an effect of survivor bias. An additional analysis using total follow-up during dialysis showed that this restriction did not influence the results and conclusion of the study: relative excess cardiovascular over noncardiovascular mortality was 1.09.

Fifth, to correct for age differences, patients were standardized to the age distribution of the general population. The choice for the direct standardization method was based on technical considerations. When the age distribution of patients starting dialysis would have been used, relative excess would have been 1.09.

How can the results of this study be explained? First, the prevalence of risk factors such as hypertension or diabetes for cardiovascular disease is higher in patients starting dialysis than in the general population.[29] In addition, it has been suggested that the uremic milieu in patients receiving dialysis potentiates vascular calcification.[30-32] Although it is unknown whether vascular calcification is a simple risk marker or a causal factor, mortality in patients with cardiac disease who are receiving dialysis is increased compared with that in patients with cardiac disease who are not,[14] suggesting at least some role for vascular calcification in increased cardiovascular mortality in patients receiving dialysis compared with the general population.

Second, uremia in patients receiving dialysis is associated with a state of immune dysfunction characterized by immunoactivation, resulting in inflammation and immunosuppression, which contributes to the high prevalence of infections among such patients.[33] Alterations in the immune system can also be related to excess mortality risk attributable to cancer in patients receiving dialysis. Interestingly, the prevalence of virus-related cancers is higher in patients receiving dialysis than in the general population.[28] Moreover, asymmetric dimethylarginine is considered a full-scale uremic toxin in end-stage renal disease[34] and has been identified as a risk factor for noncardiovascular mortality,[35] further supporting the role of uremia in noncardiovascular mortality. Increased cardiovascular and noncardiovascular mortality risk in patients receiving dialysis can both be explained by the effects of uremia.

Third, end-stage renal disease is associated with conditions including presence of comorbid disease, weight loss, muscle weakness, fatigue, and low physical activity,[36] all of which contribute to a frail phenotype. Frailty itself is associated with a doubling in mortality risk and with 60% increased risk of the combined outcome of death and hospitalization in patients

receiving dialysis.[37] We speculate that frailty is associated with an increase in both cardiovascular and noncardiovascular mortality risk in patients receiving dialysis. Interestingly, certain so-called nontraditional cardiovascular risk factors, such as troponin,[38] fetuin-A,[39] and C-reactive protein[40] are associated with increased cardiovascular as well as noncardiovascular mortality in patients receiving dialysis, which supports this hypothesis.

In summary, the present study shows that cardiovascular and noncardiovascular mortality are equally increased during the first 3 years of dialysis, compared with the general population. This implies that the importance of noncardiovascular mortality in patients receiving dialysis has generally been underestimated. Therefore, research should focus more on methods to prevent noncardiovascular mortality.

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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.

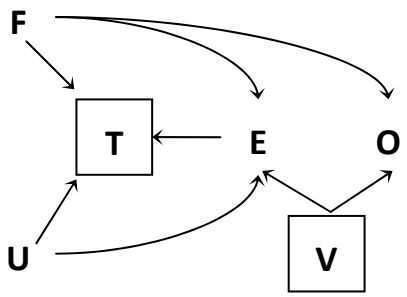
*Dialysis: NECOSAD and the ERA-EDTA Registry*

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.

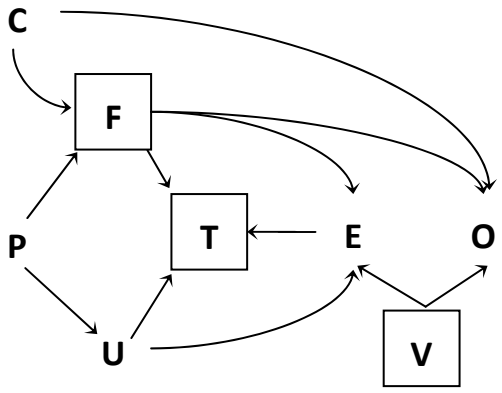
**Figure 1.** Causal DAG for investigating the association between the duration of pre-dialysis care and survival during dialysis in NECOSAD patients (see **Chapter 7** for details).




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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# Nederlandse samenvatting

**Introductie**

Chronische nierziekte (CNZ) is een progressieve ziekte, die geassocieerd is met een verhoogd risico op morbiditeit en mortaliteit. Momenteel is er geen algemeen aanvaarde test (screening) of strategie om patiënten op te sporen in de vroegste stadia van CNZ. Daarom worden patiënten meestal pas ontdekt wanneer zij symptomatisch worden, doorgaans is dat als hun nierfunctie al is gedaald onder de 30 mL/min/1,73m$^2$. Indien de nierfunctie verder afneemt, kan zich eindstadium nierfalen ontwikkelen en nierfunctievervangende therapie is dan van levensbelang. Er is aangetoond dat diverse therapeutische interventies in de loop van CNZ effectief zijn in het vertragen of voorkomen van progressie van de ziekte naar eindstadium nierfalen.

Dit proefschrift richtte zich op de progressie van CNZ van pre-dialyse tot dialyse. Het natuurlijk beloop van CNZ (d.w.z. het patroon van achteruitgang in nierfunctie), risicofactoren voor CNZ progressie en verschillende uitkomsten werden bestudeerd. Dit is gedetailleerd beschreven in **hoofdstuk 1**.

Een aantal hoofdstukken van dit proefschrift presenteerden analyses over het effect van een determinant, of risicofactor, op een bepaalde uitkomst. Het is ook erg interessant om te onderzoeken of de associatie tussen een bepaalde risicofactor en de te bestuderen uitkomst verschilt tussen patiënten met specifieke kenmerken. **Hoofdstuk 2** introduceerde het concept 'interactie' en hoe de beoordeling van interactie-effecten op een transparante manier gepresenteerd dient te worden. Het wordt aanbevolen om zowel de afzonderlijke als de gezamenlijke blootstellings effecten in vergelijking met de niet-blootgestelde groep (de gezamenlijke referentiecategorie) te presenteren. Dit maakt evaluatie van interactie op zowel additieve als multiplicatieve schaal mogelijk. De beoordeling van additieve interactie lijkt het meest relevant te zijn vanuit het oogpunt van de volksgezondheid. **Hoofdstuk 3** introduceerde een aantal alternatieve methoden, zoals 'relative excess risk due to interaction' (RERI), de 'attributable proportion due to interaction' (AP) en de 'synergie index' (SI) om de aanwezigheid van additieve interactie te evalueren wanneer gewerkt wordt met multiplicatieve regressie modellen.

**Samenvatting van de belangrijkste bevindingen**

*Deel 1: Pre-dialyse zorg*

Het verband tussen een positieve eerstegraads familie-anamnese van diabetes mellitus, cardiovasculaire ziekte, of nierziekte en de snelheid van achteruitgang van de nierfunctie en het risico op sterfte in pre-dialyse patiënten werd onderzocht in **hoofdstuk 4**. De analyse is uitgevoerd in 439 incidente pre-dialyse patiënten met beschikbare familieanamnese, die waren opgenomen in het retrospectieve (PREdialysis PAtients REcords) PREPARE-1 cohort. De studie toonde aan dat er een vergelijkbare prevalentie is van een positieve eerstegraads familie-anamnese van diabetes mellitus bij incidente pre-dialyse patiënten (CNZ stadia 3-5) en de algemene bevolking (18% *versus* 16%). Een positieve eerstegraads familie voorgeschiedenis van hart- en vaatziekten komt echter vaker voor in pre-dialyse patiënten dan in de (leeftijd en geslacht gestandaardiseerde) algemene bevolking (29% versus 16%). Ook eerstegraads

familieleden van pre-dialyse patiënten hebben vaker een chronische nierziekte ten opzichte van de algemene bevolking (29% versus 3%). Pre-dialyse patiënten met een positieve familiegeschiedenis van diabetes mellitus hadden een verhoogd sterfterisico in het eerste jaar van de pre-dialyse zorg in vergelijking met de pre-dialyse patiënten zonder eerstegraads familieleden met diabetes mellitus (gecorrigeerde hazard ratio, $HR_{adj}$ 2,9; 95% betrouwbaardheids interval, BI CI 1,3 tot 6,7), eveneens een verband werd gevonden voor een positieve familiegeschiedenis van hart- en vaatziekten en sterfte ($HR_{adj}$ 2,4; 95% BI 1,1 tot 5,4). Het sterfterisico in patiënten met een positieve familiegeschiedenis van nierziekte was $HR_{adj}$ 0,2 95% BI 0,1 tot 1,0. Daarnaast zijn er geen associaties tussen een positieve familiegeschiedenis van diabetes mellitus, hart- en vaatziekten, en / of nierziekte en de snelheid van achteruitgang van de nierfunctie gevonden. Deze resultaten suggereren dat het verwerven van familie-anamnese kan helpen om CKD patiënten te identificeren met een verhoogd risico op sterfte in het eerste jaar van de pre-dialyse zorg.

**Hoofdstuk 5** presenteerde een onderzoek naar het effect van het serum fosfaat en serum calcium niveaus op de progressie van CNZ in pre-dialyse patiënten. De onderzoekspopulatie voor deze analyse bestond uit 500 incidente pre-dialyse patiënten die deel uitmaakten van het PREPARE-2 cohort. Ten eerste werd beschreven of de pre-dialyse patiënten bij de start van pre-dialyse zorg daadwerkelijk voldeden aan de NKF-KDOQI (National Kidney Foundation - Disease Outcomes Quality Initiative) en KDIGO (Kidney Disease: Improving Global Outcomes) richtlijnen voor serum fosfaat en serum calcium. Ten tweede werd onderzocht of het bereiken van de richtlijnen voor fosfaat en calcium is geassocieerd met een langere dialysevrije overleving. Gebleken is dat ten minste 56% van de patiënten voldoet aan de richtlijnen fosfaat en calcium. Fosfaatniveaus boven de KDOQI en KDIGO doelen werden geassocieerd met een kortere dialysevrije overleving (HR 1,9 [95% BI 1,4 tot 2,6] en HR 2.6 [95% BI 1,9 tot 3,5]). Elke afzonderlijke 0,1 mmol/L stijging van het fosfaatniveau werd geassocieerd met een kortere dialysevrije overleving (HR 1,2 [95% BI 1,2 tot 1,3]). Verder veranderde met elke 0,1 mmol/L stijging van het fosfaatniveau het gemiddelde tempo van de daling van de nierfunctie met -0,94 mL/min/1,73m$^2$/jaar (95% BI -1,12 tot -0,76). Geen verband tussen calcium en de dialysevrije overleving, noch achteruitgang van de nierfunctie werd gevonden. Deze resultaten kunnen erop wijzen dat een goede handhaving van het mineraal metabolisme in pre-dialyse patiënten gunstig kan zijn voor het uitstellen van de start van dialysebehandeling en het verminderen van de snelheid van achteruitgang van de nierfunctie.

*Deel 2: Van pre-dialyse tot dialyse*

Naast de pre-dialyse risicofactoren die CNZ progressie beïnvloeden tijdens de pre-dialyse zorg zelf, zijn er mogelijk andere pre-dialyse risicofactoren die CNZ progressie beïnvloeden, zelfs na de start van de dialyse behandeling. **Hoofdstuk 6** bestudeerde een van deze mogelijke risicofactoren. We hebben onderzocht of de overleving tijdens dialyse van patiënten die al heel vroeg voor pre-dialyse zorg verwezen waren beter was dan de overleving van patiënten die laat verwezen waren. De 1438 patiënten die in dit onderzoek zijn opgenomen namen deel aan de

NECOSAD (NEderlandse COöperatieve Studie naar de Adequaatheid van Dialyse) studie. NEOCSAD is een cohort studie van incidente dialyse patiënten. Van de geïncludeerde patiënten, was 32% te laat verwezen (dat wil zeggen minder dan drie maanden voor het starten met dialyseren), 12% vroeg (tussen drie en twaalf maanden voor het starten met dialyseren) en 56% zeer vroeg (meer dan een jaar vóór het starten met dialyseren). Vroege (HR 1,5 [95% BI 1,0 tot 2,4]) en late (HR 1,8 [95% CI 1,3 tot 2,5]) verwijzingen werden in verband gebracht met een verhoogde mortaliteit vergeleken met zeer vroege verwijzing. Daarnaast werd onderzocht of hoogrisico populaties van diabetici en ouderen (70 jaar en ouder) extra voordeel van vroege verwijzing hadden. Hoewel we een vergelijkbaar patroon binnen die hoog risico populaties ten opzichte van de totale onderzoekspopulatie vonden, vonden we geen extra voordeel van zeer vroege verwijzing voor diabetici en ouderen. Dus, zeer vroege verwijzing is gunstig voor alle CNZ patiënten, ongeacht hun diabetische status of leeftijd.

Naast het moment van verwijzing, kan afname van de nierfunctie in de periode vóór het starten met dialyseren een rol spelen in de progressie van CNZ na de start van dialyse. In **hoofdstuk 7** werden de resultaten gepresenteerd van een analyse van de achteruitgang van de (rest) nierfunctie rond de start van de dialyse behandeling. Het werd onderzocht of de daling van de geschatte glomerulaire filtratiesnelheid (eGFR) veranderde in het jaar voor tot een jaar na de start van de dialyse behandeling. Deze studie, waarin 1861 incidente dialyse patiënten uit het NECOSAD cohort werden onderzocht, toonde aan dat de blijkbaar aanwezige daling van de GFR vertraagd van -0,53 mL/min/1,73m$^2$/maand (95% BI -0,58 tot 0,48) tot -0,12 ml/min/1,73m$^2$/maand; (95% BI -0,20 tot -0,04) na twee tot vier maanden dialyseren. De daling in hemodialyse patiënten neemt af van -0,51 mL/min/1,73m$^2$/maand (95% BI -0,57 tot -0,44) tot -0,14 mL/min/1,73m$^2$/maand (95% BI -0,26 tot -0,02), terwijl de daling in de peritoneale dialysepatiënten afnam van -0,55 mL/min/1,73m$^2$/maand (95% BI -0,62 tot -0,48) tot -0,11 mL/min/1,73m$^2$/maand (95% BI -0,23 tot 0,01). Voor hemodialyse en peritoneale dialyse werd een vergelijkbaar patroon in afname van de eGFR waargenomen, dat wil zeggen: het tempo van de daling vertraagde na twee tot vier maanden van dialyseren, maar dit was wel op een ander niveau van de eGFR.

*Deel 3: Dialyse behandeling*

De voorgaande hoofdstukken hebben duidelijk gemaakt dat CNZ een ernstige, progressieve aandoening is, die zelfs met een adequate behandeling in verband wordt gebracht met een verhoogde morbiditeit en mortaliteit. De heersende theorie is dat het verhoogde sterfte risico grotendeels kan worden verklaard vanuit een verhoogd cardiovasculair sterfte risico. **Hoofdstuk 8** presenteerde een analyse van de sterfte in incidente dialyse patiënten en de algemene bevolking. De cardiovasculaire en niet-cardiovasculaire sterfte van 123.407 incidente dialyse patiënten, afkomstig uit de Europese nierregistratie (ERA-EDTA) werden vergeleken met de sterfte in de Europese algemene bevolking. De ongecorrigeerde cardiovasculaire en niet-cardiovasculaire sterfte bij patiënten waren respectievelijk 38,1/1000 persoonsjaren (95% BI 37,2 tot 39,0) en 50,1/1000 persoonsjaren (95% BI 48,9 tot 51,2) hoger dan in de algemene

bevolking. De leeftijd gestandaardiseerde cardiovasculaire en niet-cardiovasculaire sterfte waren respectievelijk 8,8 (95% BI 8,6 tot 9,0) en 8,1 (95% BI 7,9 tot 8,3) keer hoger dan in de algemene bevolking. Dus, incidente dialyse patiënten hebben een algemeen verhoogd risico op overlijden, dat niet specifiek wordt veroorzaakt door een verhoogde cardiovasculaire mortaliteit.

**Conclusies**

De belangrijkste conclusies van dit proefschrift zijn:

- Een positieve eerstegraads familie-anamnese van diabetes mellitus en cardiovasculaire ziekte is geassocieerd met een verhoogde mortaliteit in het eerste jaar van de pre-dialyse zorg, maar niet met de achteruitgang van de nierfunctie.
- Verhoogde fosfaatniveaus, maar niet serum calcium niveaus, zijn geassocieerd met een verhoogd risico om binnen twee jaar van pre-dialyse zorg te moeten starten met dialyseren. Bovendien is een verhoging van het fosfaatniveau in verband gebracht met de snelheid van achteruitgang van nierfunctie.
- Late verwijzing naar pre-dialyse zorg is geassocieerd met een verhoogd sterfterisico in het eerste jaar van de dialyse behandeling. Dit effect is ook aanwezig in diabetici en ouderen (70 jaar en ouder).
- De daling van de nierfunctie is constant in de periode van een jaar vóór de start van de dialyse tot twee tot vier maanden van dialyse behandeling. Na die periode neemt het tempo van de achteruitgang van nierfunctie af. Dit patroon is vergelijkbaar in HD en PD patiënten.
- In dialysepatiënten zijn cardiovasculaire en niet-cardiovasculaire sterfte risico's even sterk toegenomen.

**Verder onderzoek**

Toekomstig onderzoek moet gericht zijn op het onderzoeken of de associaties die in dit proefschrift zijn onderzocht causaal zijn of niet. Daartoe kunnen gerandomiseerde studies worden uitgevoerd. Bijvoorbeeld, om het effect van fosfaatniveaus op de snelheid van achteruitgang van de nierfunctie te bestuderen, kunnen patiënten worden gerandomiseerd om fosfaat verlagende middelen te krijgen of bijvoorbeeld voedingsadviezen. Het effect van de duur van predialyse zorg op mortaliteit kan worden bestudeerd door patiënten te randomiseren voor een kortere of langere duur van predialyse zorg. Echter, in de praktijk zal de toegevoegde waarde van het uitvoeren van deze studie beperkt zijn, omdat dit onderzoek niet blind kan worden uitgevoerd. Bovendien kunnen veel blootstellingen niet worden gerandomiseerd (bijvoorbeeld medische familiegeschiedenis) en cohort onderzoeken kunnen worden gebruikt om dergelijke blootstellingen te onderzoeken. Bovendien kunnen ongewenste effecten (bijwerkingen) van blootstellingen op een valide manier worden bestudeerd als gebruik wordt gemaakt van observationele cohort studies.

Om de progressie van CNZ te onderzoeken, zou idealiter een (cohort) onderzoek worden uitgevoerd waarin patiënten zijn geïncludeerd vanaf het begin van hun ziekte en daarna. In de praktijk is een dergelijke studie niet uitvoerbaar, omdat CNZ een ziekte is met een lange preklinische fase. Tenzij een geschikte screeningsmethode beschikbaar komt, zullen CNZ patiënten over het algemeen alleen worden opgespoord als ze symptomatisch zijn geworden. Daarom zou een praktische oplossing zijn om patiënten te volgen vanaf de diagnose van hun nierziekten, bijvoorbeeld door het verzamelen van patiënten bij huisartsen. Maar nog steeds kan dan selectie bias aanwezig zijn, omdat CNZ onopgemerkt zal blijven in de subgroep van patiënten die nooit naar hun huisarts gaat. Bovendien zullen patiënten die worden geïdentificeerd met CNZ bij de huisarts waarschijnlijk allen in een verschillend stadium van de ziekte zijn. Een mooi uitgangspunt voor het starten van follow-up is dan ook de start van de pre-dialyse zorg. Alle patiënten bevinden zich dan in min of meer hetzelfde ziektestadium.

In dit proefschrift werden verschillende cohorten gebruikt om CNZ progressie te bestuderen na de start van de pre-dialyse zorg. Idealiter zouden alle analyses zijn uitgevoerd in een enkel cohort, waarin incidente pre-dialyse patiënten zouden zijn gevolgd tot aan hun overlijden (d.w.z. geen censurering op het moment van starten van nierfunctievervangende therapie). Binnen deze studie zal de gegevensverzameling zorgvuldig moeten worden gedaan om de kans op ontbrekende gegevens te beperken. Deze prospectieve cohort studie zal kunnen worden gebruikt om de determinanten en de uitkomsten die in dit proefschrift zijn gepresenteerd te onderzoeken, maar kan ook worden gebruikt om de invloed van pre-dialytische risicofactoren verder te onderzoeken op uitkomsten tijdens dialyse, zonder last te hebben van selectie bias. Daarnaast moeten, als deze studie gebruikt zou worden om sterfte tijdens de pre-dialyse behandeling te onderzoeken, ook verschillende oorzaken van sterfte afzonderlijk bestudeerd worden. In feite is een dergelijke studie inmiddels al ontworpen en zal deze binnenkort worden gestart, de ‘European Quality Study on when to start dialysis’ (EQUAL Study).

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**Dankwoord**
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# Publicatielijst

## Publicatielijst (List of publications)

**This thesis**

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# Curriculum vitae

**Curriculum vitae**

Dina Jezina (Dinanda) de Jager werd op 3 mei 1985 te Harderwijk geboren. In 2003 behaalde zij haar gymnasium diploma aan het Van Lodenstein College te Amersfoort. In datzelfde jaar startte zij haar studie Biomedische Wetenschappen aan de Universiteit van Leiden. Na het behalen van haar Bachelor diploma aldaar, zette ze haar studie voort aan de Universiteit van Utrecht. Daar behaalde ze in 2008 haar Master diploma Biomedical Sciences, met als specialisatie Clinical Epidemiology (*cum laude*). Tijdens zowel haar Bachelor als haar Master deed zij onderzoek aan de afdeling Klinische Epidemiologie van het Leids Universitair Medisch Centrum (LUMC) onder leiding van Prof. Dr. Friedo Dekker, Dr. Diana Grootendorst en Dr. Nynke Halbesma. Vanaf 2008 werd dit onderzoek voortgezet in een promotieonderzoek dat resulteerde in dit proefschrift. Met ingang van 1 september 2012 is Dinanda als post-doc werkzaam bij de afdeling Klinische Epidemiologie van het LUMC. Dinanda is getrouwd met Ferdinand van Appeldoorn en samen hebben zij een zoon (Boaz).