When to start dialysis?: Clinical and methodological issues involved

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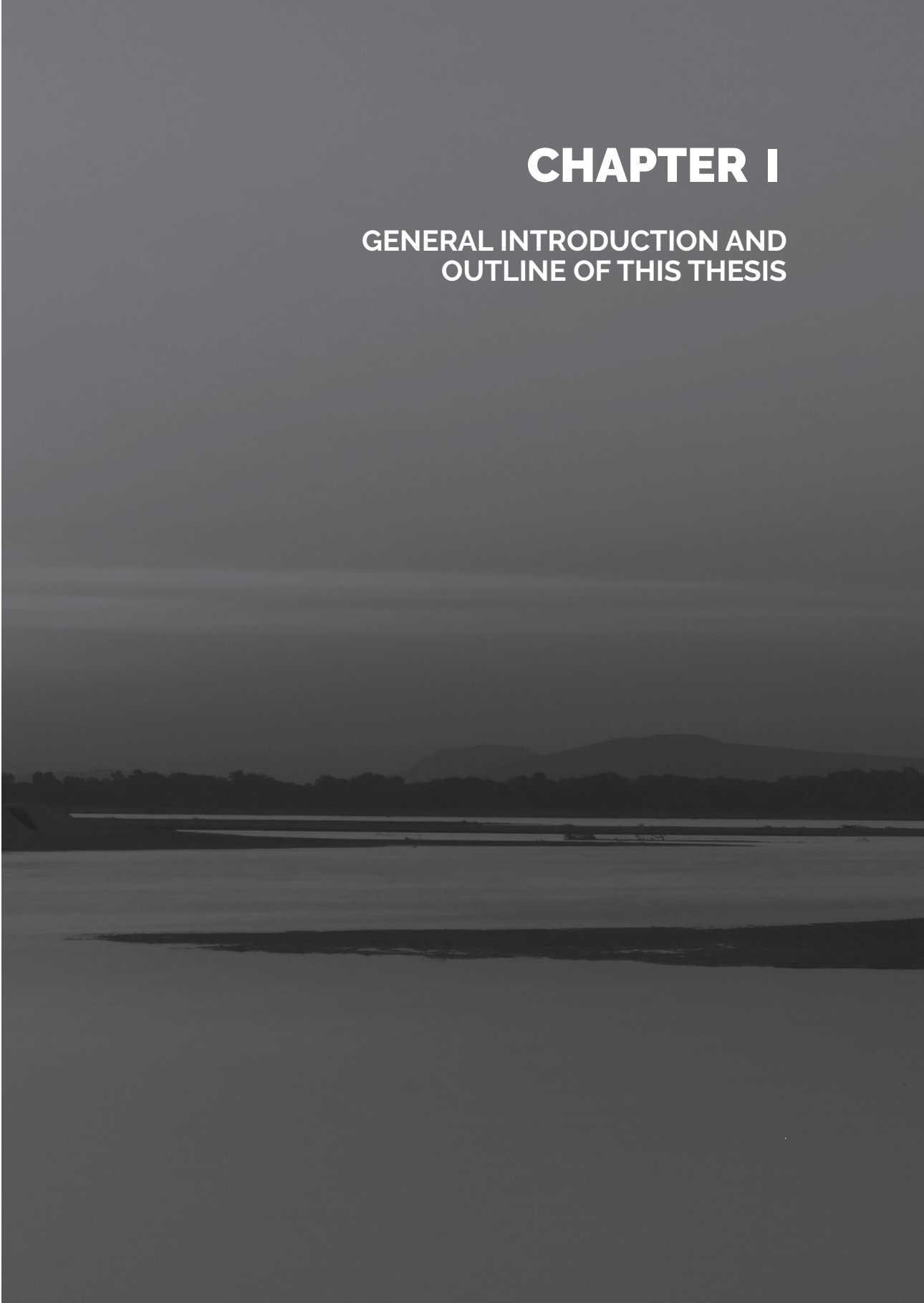
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS



Healthy kidneys maintain the fluid and mineral balance in the body, remove waste products from the blood and produce hormones, such as erythropoietin and renin.[1] In case of chronic kidney disease (CKD) there is a gradual damage of kidney structure or deterioration of function for at least 3 months with implications for health.[2] CKD is a major public health problem worldwide as the population prevalence of CKD exceeds 10%.[1]

CKD is classified based on glomerular filtration rate (GFR) and albuminuria.[2] We can distinguish five stages of CKD; the higher the stage the worse the kidney function. CKD stage 5 is also referred to as end-stage renal disease (ESRD) and in this last stage there could be need for renal replacement therapy (RRT). RRT consists of either dialysis or kidney transplantation. Dialysis and transplantation became available in the 1960s. Since then nephrologists strived to optimize RRT. Kidney transplantation is often preferable to dialysis for most patients, it results in an improved survival and a better quality of life.[3] However, not all patients are eligible for a kidney transplantation, because of comorbid conditions, or they have to wait several years until a renal allograft is available, due to limited availability of donor organs.[4] These patients rely on dialysis as RRT. The most common treatment modalities of chronic dialysis are hemodialysis and peritoneal dialysis. In hemodialysis the blood from the body is purified by an artificial kidney machine that is connected to the patient using a vascular access conduit. In peritoneal dialysis the peritoneum is used as an endogenous semi-permeable membrane to remove waste products and water excess.[5] Wastes are removed by means of a dialysate, which is transported through a catheter implanted in the abdominal cavity of a patient. After the filtering process the fluid leaves the body through the catheter and is refreshed several times a day.

Following current research guidelines for CKD patients, timely referral to specialist kidney care is recommended, that is when a patient reaches a GFR below 30 ml/min/1.73 m^2, or CKD stage 4.[2] This is also called pre-dialysis care, which aims to slow down kidney disease progression and to prepare patients for their potential start of RRT. These guidelines also state that progressive CKD should be managed in a multidisciplinary care setting, including education and counseling on different RRT modalities, dietary advice, and psychological and social care.[2]

Detailed knowledge of the rate of change in kidney function in moderate to advanced CKD patients before the start of RRT, could guide clinical decision-making and anticipate treatment choices and priorities.[6,7,8] Substantial heterogeneity exists in reported kidney function decline in CKD patients. This could relate to variations in patient characteristics between cohorts or to variability in the methodology of these studies. By design, kidney function decline could be studied prospectively in cohorts including patients with certain CKD stages, or retrospectively

in studies selecting patients based on the fact they initiated dialysis. These populations differ with regard to patient selection. In cohorts including patients with certain CKD stages, patients are followed from a similar stage in CKD progression and these patients could end up on RRT or receive no form of RRT. When patients on dialysis are selected, CKD progression is determined in a specified period prior to this dialysis initiation. As a consequence, the observed decline rates in these patients could overestimate the true underlying kidney function decline in the overall CKD population. The identification and follow-up of CKD patients at a well-defined point in the course of kidney disease progression thus seems more appropriate. As patients are included irrespective of their outcome, patient identification is not only based on patients starting dialysis, but include patients with long-term stable CKD, progressive CKD or even patients with (partial) recovery of their kidney function. Failure to select such a population potentially severely biases results of studies regarding the natural course of CKD progression.[9]

A second methodological issue that influences outcome parameters such as kidney function decline or mortality in cohort studies is the selection of incident or prevalent patients. Incident patients are new patients that could be followed from the start of a condition of interest, for instance from dialysis initiation. Prevalent patients are existing patients already having the condition of interest that could be followed from one point in time, i.e. a specific calendar date onwards. In the example of dialysis, prevalent patients would show varying dialysis vintages at cohort entry. Consequently, they are in a different disease stage at cohort entry. One might imagine that some patients are more susceptible to harm of the condition of interest and might even die prior having the chance to be included in the prevalent cohort.[10, 11] These individuals will be missing in the prevalent cohort, while this is not the case for individuals followed from the start of the condition of interest, that is, incident patients. Such cohort sampling could influence the validity of a risk factor study. It is therefore important to gain insight into how results in the nephrology research field are influenced by the type of patients selected and consider these differences prior to study setup.

Besides the type of patients selected in which for instance CKD progression is studied, it is also important how CKD progression is subsequently analyzed. To provide insight into this kidney function trajectory or CKD progression, patients are typically followed over time and their kidney function is estimated at several time points. Some patients may drop out earlier during follow-up than others and for different reasons. Furthermore, patients could show a different level of kidney function at study entry or differ in the rate of kidney function decline. In addition, the number of available kidney function estimates may vary widely between patients. This heterogeneity with respect to kidney function and dropout is important to take

into account when estimating kidney function trajectories. In general two methods are used in literature to estimate kidney function trajectories over time: linear regression to estimate individual slopes and linear mixed-effects models (LMMs), i.e. repeated measures analysis. Notably, abovementioned heterogeneity is not properly taken into account using linear regression. In contrast, in LMMs all information and variability in the data is retained. However, the underlying concepts, use and interpretation of LMMs are not always straightforward.

Besides the above-mentioned methodological issues related to scientific studies on CKD progression prior to RRT, there are also numerous clinical issues unresolved. For instance, the possible relationship between CKD progression and symptoms remains unknown in patients with advanced CKD. Patients with CKD suffer from a wide range of symptoms.[12, 13] In previous literature, it has been shown that CKD symptom burden is negatively correlated with health-related quality of life, and positively correlated with increased morbidity and mortality rates.[14, 15] Although symptom burden increases with morbidity, no specific time point demarcates the onset of symptoms in patients with progressive loss of kidney function.[16] The interplay between kidney function and symptoms is still unclear, and especially the coherence between change in kidney function and symptoms is unknown. The few studies published on kidney function and symptoms are mostly limited by their cross-sectional design.[17-19] Therefore, research into the association between kidney function decline and symptom development in a longitudinal setting remains an undiscovered area.

In addition to the possible relationship between kidney function deterioration and symptom development, the identification of modifiable risk factors for CKD progression is important for preventive or treatment strategies.[20, 21] Well-known risk factors include hypertension and diabetes mellitus.[1] Also, high phosphate levels have been consistently associated with CKD progression, as well as FGF-23 excess and the calcium-phosphorus product.[22-26] Less evidence exists on the association between disturbances in serum levels of calcium and kidney function decline. Conflicting results are reported, where some found no association between serum calcium and CKD progression, and others reported that low serum calcium was associated with a faster kidney function decline.[25, 27] These studies did not differentiate between CKD stages. Instead of pooling all patients with CKD stage 3 to 5, it is important to study the effect of such risk factors in separate CKD stages to gain insight into possible different effects among stages.

Knowledge of CKD progression in a broader sense, including methodological and clinical issues, is important to anticipate when or not to initiate dialysis. However, the optimal moment of

dialysis initiation in patients with advanced CKD is still unclear. Dialysis should not be started too early because of the burden of the dialysis therapy itself. On the other hand, we should not withheld therapy for too long in order to prevent serious complications related to ESRD itself. Clinical guidelines describe that dialysis is usually started at a kidney function of 5-10 ml/min/1.73m^2.[28] Thus far, the only randomized trial on this topic that has been performed in CKD patients is the IDEAL study.[29] No clear difference was obtained in survival rates between early and late dialysis initiation. In addition, previous observational studies showed conflicting results, either favoring later or earlier start of dialysis, and were also subjected to lead-time bias and immortal time bias, two issues arising from counting survival from dialysis initiation. First, a direct comparison between early and late starters will introduce lead-time bias. A potential survival benefit observed in early starters compared to a later-starting comparative group, could be only due to the fact that survival time is counted from an earlier moment in time in the former patients.[30]

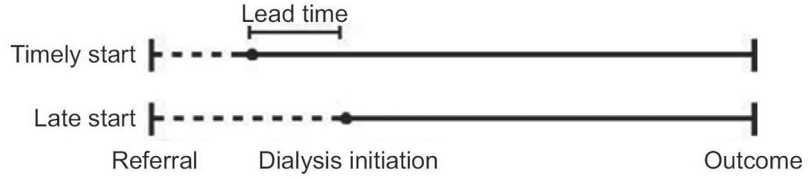


Figure 1 Lead time based on moment of referral and time of dialysis initiation.
Lead-time bias tends to favor earlier dialysis initiation, because patients starting dialysis with more residual kidney function enter dialysis earlier in the course of the disease than those starting dialysis with less residual function, and accordingly gain a spurious residual lifetime advantage. Analyzing survival from the moment of referral solves the problem of lead-time bias, as would analyzing from the moment a certain glomerular filtration rate is reached (e.g. 20 mL/min/1.73 m^2).[30]

The second issue involves that only people will be included who survive until they actually start dialysis, causing immortal time bias. Both issues can be solved by conducting a randomized trial.[29] Because survival time is then counted from a common starting point (e.g. a certain GFR) and people are classified based on the treatment strategy they are assigned to prior to dialysis initiation. Importantly, to determine the optimal starting moment of dialysis a randomized trial including many different treatment arms would be required to include all possible starting moments. Conducting an RCT may thus be unfeasible because of the patient number needed to sufficiently power all comparisons. Therefore we have to rely on observational study data. Considering these methodological and clinical issues, it is important to account for them in our question to find the optimal timing of dialysis initiation. For this purpose, more insight is needed into the impact of lead-time bias and how we can get rid of lead-time bias and immortal time bias by emulating a randomized trial using observational data.

OBJECTIVE AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide more insight into clinical and methodological issues to keep in mind when aiming to find the optimal moment for dialysis initiation in patients with moderate to advanced CKD. For this purpose we focused on methodological issues like in which type of cohort and patients CKD progression should be studied and what the best method is for analyzing kidney function trajectories. Subsequently, clinical issues like kidney function trajectories and risk factors for CKD progression are important to study for guiding clinical decision-making and anticipating treatment choices. In addition, it is important to know the impact of methodological issues involved to be able to find an optimal moment to initiate dialysis, including lead-time bias and immortal time bias.

In **chapter 2** we determined the decline of kidney function in patients with CKD stages 3-5 by performing a systematic review and meta-analysis. We highlighted the importance of the identification and follow-up of CKD patients at a well-defined point in the course of kidney disease progression. When having such a cohort, in general patients could be assembled in two ways, so called prevalent and incident cohort. In **chapter 3** we discussed the impact and considerations of using prevalent versus incident dialysis patients when investigating different risk factors in association to mortality. Besides the type of patients selected in which for instance CKD progression is studied, it is also important how the CKD progression is subsequently analyzed. For estimating the kidney function trajectories over time two approaches are generally applied: linear regression to estimate individual slopes and LMMs. In **chapter 4** we highlight important differences between these approaches. We illustrated this using a clinical example and offer a framework how to model and interpret the LMM. This methodology is subsequently used in chapters 5 and 6.

Symptom burden increases with higher morbidity and could logically increase with deterioration of kidney function, although to our knowledge this association has never been investigated in a longitudinal setting. In **chapter 5**, the association between kidney function decline and the symptom development in non-dialysis patients was investigated. Also, insight into modifiable risk factors is essential to anticipate treatment choices. In **chapter 6** we focused on the association between baseline serum calcium and subsequent rate of kidney function decline in separate CKD stages 3 to 5.

After having addressed the methodological and clinical issues during pre-dialysis, which are important to anticipate treatment choices and the fact that we rely on observational studies for finding the optimal moment to initiate dialysis, we focused on investigating the role of lead-time bias in this matter in **chapter 7**. Second, we performed a pilot study to investigate the suitability of emulating a randomized trial using observational study data to deal with both lead-time bias and immortal time bias in **chapter 8**. Finally, in **chapter 9** the results of this thesis, their implications and future research directions are discussed in the context of finding the optimal moment to initiate dialysis.

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