When to start dialysis?: Clinical and methodological issues involved

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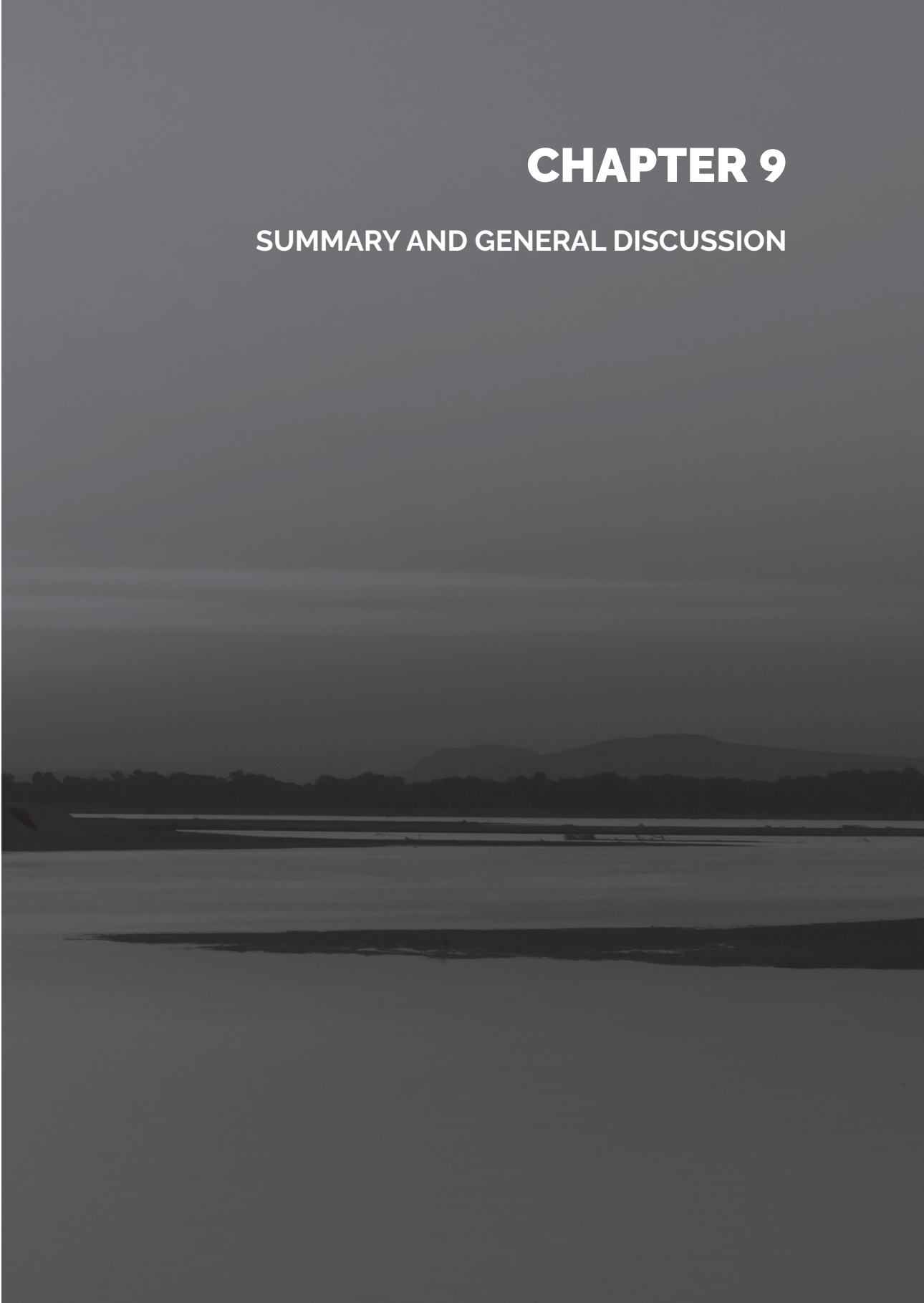
CHAPTER 9

SUMMARY AND GENERAL DISCUSSION



In this thesis, we provided insight into clinical and methodological issues involved in studying when to start dialysis in terms of survival in patients with moderate to advanced CKD. For this purpose we focused on methodological issues, such as in which type of cohort and patients CKD progression should be studied and what the best method is for analyzing kidney function trajectories. Subsequently, we studied clinical issues like kidney function trajectories and risk factors for CKD progression important for guiding clinical decision-making and anticipating treatment choices. For finding an optimal moment for dialysis initiation, we highlighted the importance of taking account of lead-time bias and immortal time bias and we showed options how to deal with these issues. In this chapter a summary is presented of our main observations, strengths and limitations of our research are discussed and implications are provided, including recommendations for future research.

Summary of main observations

Knowledge about the rate of CKD progression prior to the start of RRT is important for clinical decision-making and anticipating treatment choices and priorities. In **chapter 2** we showed in a systematic review and meta-analysis that substantial heterogeneity exists in reported kidney function decline in patients with advanced CKD not on dialysis. To our knowledge, we have been the first to make a clear distinction between studying kidney function decline in CKD cohorts and in dialysis-based studies. In the latter, patients are selected based on the fact they started dialysis, possibly leading to an overestimation of the true underlying kidney function decline prior to dialysis initiation. We included 60 studies (43 CKD cohorts, 17 dialysis-based studies) and found a substantial difference in weighted annual mean [95%-confidence interval (95%-CI)] kidney function decline for these two study designs: 2.4 (2.2, 2.6) mL/min/1.73m^2 in CKD cohorts versus 8.5 (6.8, 10.1) mL/min/1.73m^2 in dialysis-based studies [difference 6.0 (4.8, 7.2)]. Importantly, due to biased estimates in studies that included solely patients that progressed towards dialysis, data on CKD progression from studies that prospectively followed CKD patients should be used to guide clinical decision-making in non-dialysis patients.

Besides the type of study design, the selection of prevalent or incident patients also impacts the validity of a risk factor study. In **chapter 3** we discussed the potential differences in effect estimates for a range of clinical risk factors in association to all-cause mortality when comparing a prevalent to an incident dialysis population. We found that effect estimates may differ substantially, most often resulting in weaker effects in prevalent than incident patients, but varying to stronger effects and even opposite effects. In line, we showed differences in the risk factor prevalence in prevalent and incident patients that could be considerable. These differences between incident and prevalent cohorts may be explained by selection bias. In a

prevalent dialysis cohort, patients must have survived a certain amount of time in order to be included in the cohort. Patients dying early in the dialysis course will have more mortality-related risk factors than patients who survived until sampling in the prevalent cohort, and the patients included in the prevalent cohort are not a random sample of all patients in the incident cohort. Now, when studying a risk factor-outcome association, patients with the risk factor under study included in a prevalent cohort have survived until sampling, and are thus less likely to have other risk factors for mortality. As prevalent patients with the studied risk factor are by design less likely to have other risk factors for mortality than prevalent patients without the studied risk factor, there is a problem of incomparability and the risk estimation from such a comparison is likely biased. This is the problem of selection bias. Importantly, the fact that the selection of patients is associated with the risk factor under study in itself does not necessarily bias the estimates of the risk factor-outcome association. Selection bias will arise when other factors are involved that determine patient selection and are also a risk factor for the outcome (irrespective of their relation to the studied risk factor). When all such factors are measured appropriately and adjusted for, selection bias could be solved. However, in general this is unlikely; therefore we would argue for the use of incident cohorts when studying these risk factor-outcome associations.

In addition to choosing the appropriate study design and participants to be included, CKD progression has to be studied properly. In **chapter 4** we aimed to create awareness about the distinction between using linear mixed-effects models (LMMs) and linear regression analysis on individual slopes. With the clinical example of the effect of baseline diastolic blood pressure on kidney function decline we showed that these two approaches yielded different results. Effect estimates differed approximately twenty percent. We showed that LMMs are the preferred and recommended model for research questions regarding kidney function trajectories over time at population level. Typically, the kidney function of included patients is estimated at several time points. During follow-up, some patients may drop out earlier than others and for different reasons. This heterogeneity with respect to dropout and number of kidney function estimates between individuals are accurately handled by LMMs. Missing values of kidney function are handled properly in LMMs when they are related to previously observed eGFR values, because the LMM estimates the individual slope also based on complete observed data of other similar individuals in the dataset. Missing values in other covariates are not handled by the LMM. Finally, individual differences in both baseline kidney function and slopes of kidney function decline are taken into account by the fixed and random effects in LMMs.

After gaining more insight into the way we should obtain and analyze data on CKD progression appropriately, we focused on the association between kidney function decline and the symptom development in non-dialysis dependent patients with advanced CKD of ≥65 years and a kidney function that dropped below 20 mL/min/1.73m^2 (**chapter 5)**. These patients were followed in the EQUAL study for one year. LMMs were used to assess the association between kidney function decline and symptom development. Previous studies were limited by their cross-sectional design and showed no association between kidney function and symptoms. To our knowledge, we are the first that have shown in more than a thousand patients that a faster kidney function decline was associated with a steeper increase in both symptom number and severity. Our results seem to suggest the need for repeated thorough assessment of symptom development during outpatient clinic visits, in addition to the monitoring of kidney function decline, for anticipating the need for dialysis initiation.

In **chapter 6** we focused on studying the effect of serum calcium on CKD progression for separate CKD stages. More specifically, we studied the association between baseline serum calcium and the subsequent rate of kidney function decline in separate CKD stages 3a, 3b, 4 and 5. Therefore, we used LMMs in a CKD 3-5 cohort of 15755 adult citizens of Stockholm, for whom creatinine tests taken during 2006-2011 and concurrent calcium testing was available at cohort entry. Our results showed that in the advanced CKD stages 3b to 5, higher baseline serum calcium was associated with less rapid kidney function decline. Thereby, lower serum corrected calcium seemed to be indicative for vitamin D deficiency. However, in CKD stage 3a no association was observed between baseline serum calcium and the subsequent rate of kidney function decline. This paper illustrated that studying CKD progression in separate CKD stages could be very informative, because effect estimates differ among stages of disease.

Knowledge of CKD progression in a broader sense is important to anticipate when or not to initiate dialysis. However, there are more issues to keep in mind for finding the optimal moment to initiate dialysis when relying on observational study data. In **chapter 7** our results confirmed that lead-time bias is not only a methodological problem, but has also clinical impact when investigating the optimal kidney function for dialysis initiation in terms of survival. 1143 patients with eGFR data at dialysis initiation, including 852 patients with mGFR data, were included from the NECOSAD cohort. The effect of lead-time bias was assessed using Cox proportional hazards models, and survival was either counted from the time of dialysis initiation or from a common starting point (GFR=20 mL/min/1.73m^2). We estimated the common starting point to correct for lead-time bias in two ways, using an average annual kidney function decline and using individual decline rates prior to dialysis initiation, therefore two HRs were obtained for

lead-time corrected results. Without lead-time correction, no difference between early and late starters was present based on the estimated glomerular filtration rate (GFR) (HR 1.03 [95% confidence interval: 0.81-1.30]). However, after correction for lead-time bias, early initiation showed a survival disadvantage (HR between 1.10 [0.82-1.48] and 1.33 [1.05-1.68]). Based on measured GFR, the potential survival benefit for early starters without lead-time correction (HR 0.80 [0.62-1.03]) completely disappeared after lead-time correction (HR between 0.94 [0.65-1.34] and 1.21 [0.95-1.56]). Our results indicated that early dialysis initiation, based on the definition of kidney function alone, was not associated with an improvement in survival. Of note, lead-time bias was solved here, although immortal time bias and confounding by indication were still an issue.

Therefore, 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.** Data of 341 patients with advanced CKD were used from the observational PREPARE-2 study in an attempt to estimate the optimal kidney function for dialysis initiation. We emulated a randomized trial in which patients would have been randomized to one of 16 treatment arms at baseline, each treatment arm representing a kidney function value between 5-20 ml/min/1.73 m^2 at which dialysis could be initiated. We mimicked a randomized trial in which an intention to treat analysis was applied. Marginal structural survival models with a cumulative incidence competing risk approach were fitted through inverse probability weights. By using inverse probability weights we aimed to correct for the non-random assignment of the treatment rules. During follow-up 154 patients started dialysis, 34 were transplanted and 83 patients died of whom 48 patients died after dialysis initiation. No optimal treatment rule was observed to be associated with the lowest cumulative mortality, due to large uncertainty around effect estimates (reflected by wide confidence intervals). This pilot study appeared to be too small to show any differences between different kidney function estimates at which dialysis was initiated and therefore no clinically relevant conclusions could be drawn. Our results indicate that analyses should be performed in larger observational studies in which also detailed information on the morbid condition of patients, and time-varying kidney function and confounders are recorded.

Bigger picture from CKD progression to dialysis initiation

Following current research guidelines for patients with CKD, 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.[1] This pre-dialysis care 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.[1] Detailed knowledge on the rate of kidney function decline in patients with moderate to advanced CKD prior to the start of RRT could guide clinical decision-making and anticipate treatment choices and priorities.[2-4] With our meta-analysis, we showed that patients with moderate to advanced CKD have a weighted mean annual kidney function of 2.4 (2.2, 2.6) mL/min/1.73m^2. In addition, we underlined the importance of studying CKD progression in an incident cohort in which patients are identified at a well-defined point in the course of kidney disease progression. Also, we showed the importance of analyzing CKD progression using LMMs that accurately handle dropouts, heterogeneity in number of kidney function estimates between individuals and individual differences in both baseline kidney function and slopes of kidney function decline. We stressed that these methodological issues lead to different results and are extremely important to take into account before applying results in a clinical setting.

CKD progression could, besides conservative management, ultimately lead to the need for RRT or dialysis initiation. The KDIGO guideline for decision-making on timing of dialysis initiation states that dialysis should be initiated based on uremic signs and symptoms, often in the eGFR range between 5 and 10 mL/min/1.73m^2.[5] However, there is a wide variety in starting moments in patients with advanced CKD. The only randomized trial performed on when to start dialysis is the Initiating Dialysis Early And Late (IDEAL) study.[6] Patients were randomized to an early versus late start dialysis based upon estimated GFR (eGFR). In this study physical symptoms played an important role in deciding if and when to initiate dialysis. A large proportion of patients randomized in the late starting group initiated earlier due to the presence of uremic symptoms. However, the relationship between kidney function and symptoms has so far only been studied in a cross-sectional setting or between categories of symptoms and kidney function decline (stable, improved or worsening).[7-9] To date, no association was found between kidney function and symptoms. In this thesis, we confirmed the absence of a cross-sectional association between kidney function level and symptoms. However, we elaborated the evidence by showing that a faster kidney function decline associates with a more progressive increase in both the number and the severity of symptoms in incident patients who dropped below 20 ml/min/1.73m^2 for the first time. This suggests the need for repeated thorough assessment of symptom development during outpatient clinic visits, for instance with patient reported outcome measures (PROMs), in addition to the monitoring of kidney function decline, for clinical decision-making in preparation for the possible start of RRT. Current research such as the SWIFT (symptom monitoring with feedback trial) in Australia/New Zealand and

OPT-ePRO (OPTimising routine collection of electronic Patient-Reported Outcomes into disease registries) in the UK are investigating the effectiveness of routinely capturing PROMs in renal care. Ultimately, a clinical decision rule, including kidney function decline and symptom development, may be useful to decide when to start dialysis. Of course, we have to keep in mind that nonspecific symptoms could be related to other comorbid conditions or illnesses precipitating early dialysis initiation among some providers.

Returning to the question on when to start dialysis, in the only trial performed so far, the IDEAL study, no difference was observed in the survival between the early and late starting groups. Our expectation is that starting too early would be harmful whereas on the other hand, waiting too long would also be harmful. To determine the optimal moment of dialysis initiation, a randomized trial with many different arms would be required to include all possible starting moments. Preferably the starting moment would be defined based on a combination of kidney function and symptom burden. The number of patients needed to sufficiently power all comparisons renders this randomized trial unfeasible. It is unlikely that long-term trials will ever be conducted to compare each of the possible starting moments. Hence, appropriate analysis of observational data is our best chance to estimate the timing of dialysis initiation.

Several observational studies have investigated when to start dialysis in terms of kidney function and showed contradictory results. Some studies suggested better survival for patients who started dialysis early (i.e. high kidney function), whereas most studies suggested better survival for those who started late (i.e. low kidney function).[10-26] However, when studying the starting moment of dialysis in an observational cohort setting, several issues have to be kept in mind. This concerns lead-time bias and immortal time bias. Step by step we tried to solve these issues in an observational study setting. Of these aforementioned studies, only four have taken account of lead-time bias, but none were based on both estimated GFR and measured GFR and all had small study populations.[12, 13, 17, 25] We showed that lead-time bias is not only a methodological problem, but also has clinical impact when studying the timing of dialysis initiation. Observations in this thesis showed that the survival benefit for early starters completely disappeared when early starting was defined based on measured GFR. In that analysis immortal time bias was still an issue, although the influence of this bias was considered minimal because a low percentage dropped out due to death in the study. Immortal time bias and lead-time bias could be solved by emulating a randomized trial using observational data as we showed in our pilot study. Previously, Sjölander *et al* used a similar statistical approach based on expanded risk sets and inverse probability weighting to address both lead-time bias and immortal time bias in comparing different strategies for dialysis initiation.[27] The results

obtained, using this method, suggested roughly equal survival curves for early and intermediate starters and better survival for late starters, although not significant. However, this approach did not deal with the competing events of kidney transplantation and only three treatment arms were considered.

Methodological strengths and limitations for finding the optimal moment for dialysis initiation

The main strength of this thesis is the variety of methodological issues discussed that showed to have clinical impact on the reported CKD progression and when to start dialysis. Furthermore, for this purpose we used a broad range of study cohorts. These include NECOSAD, PREPARE-1, PREPARE-2, SCREAM and the EQUAL study.

Though this thesis has brought us closer to a methodologically sound approach for finding the optimal moment to initiate dialysis in terms of survival, two main issues remain to be solved. First, emulating a randomized trial requires a lot of detailed information to provide enough power to include all treatment strategies in the model. Therefore large observational databases are needed both in terms of assembled information and in number of patients, visits and events. Registries often not include the needed detailed information and cohort studies are often limited by their number of events. Second, to emulate a randomized trial there are several assumptions that need to be met. One of the assumptions is the absence of unmeasured confounding. In a real randomized trial patients are randomized across treatment arms and based on randomization it is assumed that patients in different treatment arms would have a similar prognosis. In observational studies clinical decision-making or the indication on when to start dialysis could be influenced by doctors' preference, patients' condition, general appearance of a patient, symptom burden etcetera. As in observational studies often not all this information is available, it is important to consider if enough information is available to assume that confounding by indication does not bias the results. Unfortunately, we did not have enough data at our disposal to correct for confounding by indication, which probably has influenced our results. The general, almost philosophical question remains if we could ever reliably assume the absence of confounding by indication or unmeasured confounding when studying the optimal moment of starting dialysis.

To emulate the random assignment, proper adjustment for all confounders is required to ensure exchangeability, for instance via inverse probability weighting. Inverse probability weighting is used in this thesis under the assumption of no unmeasured confounding. However, as we mentioned earlier this pilot study may have been limited by confounding by

indication hampering proper adjustment for non-random assignment. In general it is impossible to determine whether the emulation of a trial failed due to the presence of unmeasured confounding. However, Hernan and Robins propose indirect approaches that may alert a researcher about possible presence of unmeasured confounding, which could be considered in future research.[28] One approach is to consider negative controls for the outcome for which we do not expect a causal effect.[29] If the confounders for the study and control outcomes are sufficiently comparable, then the use of control outcomes might help to detect confounding. Another option is to consider control outcomes for which the effect size is known and is not equal to zero. Or treatment controls could be considered with treatment strategies with indications similar to the treatment strategies under study, but for which no effect is expected. A different approach is to consider extracting information from sources previously considered impractical for large-scale research. This could be, for instance, advanced image processing and novel technologies for natural language processing which might capture a patients' condition.[28]

Implications and recommendations for future research

In this thesis we showed the clinical impact of several methodological issues that should be taken into account when studying CKD progression and in order to find an answer to the question when to start dialysis.

From a methodological point of view, we have several recommendations for future research. We recommend studying associations of risk factors with CKD progression in an inception cohort, with incident patients using LMMs and stratification on disease stages to provide further insight into the presence or absence of the association of interest during disease progression.

Besides studying CKD progression, which could eventually lead to the need for RRT or dialysis initiation, we have to keep in mind two main issues when analysing data from observational studies to find the optimal moment for dialysis initiation are lead-time bias and immortal time bias. Since we rely on observational study data, we showed in a pilot study how observational data could be used to emulate a randomized trial to deal with both lead-time bias and immortal time bias. Our pilot study, using the PREPARE-2 data, appeared to be too small to show any differences between different kidney function estimates at which dialysis was initiated and no clinically relevant conclusions could be drawn. In our opinion, a true randomized trial is not feasible considering the sample size and detailed information needed, besides the associated long follow-up period to reach enough events. Furthermore, we should keep in mind the issue of confounding by indication as discussed previously. For future research on studying the optimal moment for dialysis initiation, we would recommend performing analyses in larger

observational studies with long follow-up and the data has to contain sufficient events to overcome the power issue, including at least 1500 patients with advanced chronic kidney disease and at least 300 deaths. We recommend that also detailed information on the morbid condition of patients is available, including evaluation of symptom number and severity to ensure that the assumption of no unmeasured confounding applies.[30] For future research it is important to realize that defining treatment rules according to both symptom burden and kidney function may require an even larger sample size. We recommend using a data structure that allows different time domains, so that all available kidney function values and time-varying confounders are included to perform time-varying instead of constant marginal structural survival analyses. The additional benefit is that the impact of possible measurement error or variability in kidney function values will be less extreme when all measurements are taken into account.

The question when to start dialysis is important and to a large extent still unsettled. We believe that the methodology and recommendations provided above will be highly useful to find a more definitive answer in future research.

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