Chapter 1

Introduction and aim of the thesis

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Introduction

Chronic kidney disease (CKD) is a worldwide health problem associated with significant morbidity and mortality. Globally, diabetic nephropathy (diabetic kidney disease) is the leading cause of CKD. Blood vessels in the kidneys of patients with diabetic nephropathy are damaged, which affects the organs’ ability to filter out exogenous and endogenous substances. Figure 1 shows a conceptual model for stages in the initiation, progression, and complications of CKD. In many patients progression of CKD occurs at a slow but relentless rate. Treatment of CKD aims to slow the progressive decline in renal function in order to ultimately delay the initiation of renal replacement therapies (RRT; chronic dialysis and renal transplantation). However, despite the increase in prevalence of CKD and the need for novel treatment strategies to mitigate the burden of the disease, few proven therapies are effective, and the residual risk remains very high. We clearly need to find new targets and drugs or improve the use of older ones. However, for each new drug the renal or cardiovascular efficacy needs to be established in generally long-lasting and expensive hard outcome trials. These end points should thus be accurate (to measure what it is purporting to measure), precise (to measure with minimal variability), and reliable (duplicate independent measurements should produce the same result).

The currently used established hard end point(s) in clinical trials of CKD progression is the composite of RRT and doubling of serum creatinine. Although this end point has been, and is still used in many landmark clinical trials in renal and cardiovascular disease, it is subject to debate for several reasons. First, the individual components may not have optimal accuracy, precision and reliability. Second, the end point occurs only when renal function has substantially deteriorated requiring clinical trials of long duration or large sample sizes. Thus, in order to accrue sufficient end points within a reasonable amount of time, patients at late stages of disease with severely reduced eGFR levels and high proteinuria need to be included, whereas patients at earlier stages of disease, who may particularly benefit from the therapy, are mostly excluded. Consequently, there has been interest in the last years to develop alternative end points which will take less long to occur with the hope to design more efficient trials in order to facilitate and accelerate the development of novel interventions for CKD.
Renal replacement therapy as hard end point

RRT is used as a clinical end point in large intervention trials because it represents a more or less exact moment in time when the kidney fails to function. In addition, it is associated with a high burden of disease including a decreased quality of life and significant mortality. Although it is beyond doubt that the initiation of RRT has a direct impact on an individual's wellbeing and therefore represents a clinically meaningful end point, there are limitations of using RRT as end point in trials. Although RRT has been considered an objective end point, the decision to start RRT are based on many subjective factors including dialysis availability, local guidelines, preferences of physicians and patient wellbeing. These subjective factors can make RRT a less ideal end point and may influence clinical trial results.

Glomerular filtration-based renal end points

Glomerular filtration has, rightly or wrongly, been used as the ultimate measure of the function of the kidneys. GFR-based parameters are therefore prominent components of a renal end point. Several have been used.

Fixed serum creatinine threshold as a renal end point

A defined serum creatinine threshold of 6 mg/dL (530 µmol/L) or estimated GFR (eGFR) threshold of 15 ml/min/1.73m² is used as the filtration component of a hard renal end point in several trials. Since the same serum creatinine value represents different eGFR values for different patients recent trials included a predefined eGFR threshold rather than a predefined serum creatinine threshold in the definition of the hard renal end point. A threshold of 15 ml/min/1.73m² has been chosen since it represents the threshold at which most practice guidelines recommend to start planning RRT. The advantage of using a fixed serum creatinine or eGFR threshold compared to RRT is that a similar end point definition is applied to all patients as opposed to RRT initiation.

Doubling of serum creatinine as a renal end point

Doubling of serum creatinine has been accepted as a valid component of a hard renal end point. Most patients show a linear loss of renal filtration over time and thus doubling of serum creatinine reflects a sustained loss in patients starting eGFR. The doubling of serum creatinine end point is thus directly related to eGFR decline. Although the same serum creatinine value
represents different eGFR values for different patients, the change in serum creatinine over time within a patient will reflect a deterioration of eGFR for that patient.

Towards a lesser change in estimated glomerular filtration rate as an end point

Although the inclusion of doubling of serum creatinine or a fixed serum creatinine threshold as a component of a hard renal end point increases the event rate and power of clinical trials it is still a late event in progression of kidney disease. Therefore, it is most appropriate in clinical trials for patients with later stages of kidney disease or those with rapid progression. To examine alternative earlier renal end points for randomized controlled trials the National Kidney Foundation (NKF) in collaboration with the Food and Drug Administration (FDA) studied alternative options as described in a series of studies and reports.\textsuperscript{10-14} The first meta-analyses evaluated in a heterogeneous database of 1.7 million participants from 35 cohorts the risk of end-stage renal disease (ESRD) as a function of the percentage change in eGFR over a 2-year baseline period.\textsuperscript{11} The study demonstrated a strong and consistent association between changes in eGFR and ESRD: A 30% decline in eGFR during a 2-year baseline period was associated with an approximately five-fold increased risk of ESRD compared to no change in eGFR whereas a 57% decline in eGFR (equivalent to a doubling of serum creatinine) was associated with a 30-fold increased risk of ESRD. These results were confirmed and extended in a second meta-analysis of 37 randomized controlled clinical trials involving 9488 participants.\textsuperscript{13} This meta-analysis tested the associations across different treatments frequently used in the CKD population and documented a strong association between small percentage changes in eGFR and development of ESRD regardless of the intervention used, baseline proteinuria, or eGFR. Although of interest, these observational studies are not sufficient to claim valid surrogacy. It is imperative to also assess whether the treatment effects on the surrogate (e.g. 30% or 40% eGFR decline) correlates with the treatment effect on the established end point.

One challenge when using lesser declines in eGFR as end point is that many interventions to slow the progression of CKD, including low protein diet, renin-angiotensin-aldosterone-system inhibitors, sodium glucose co-transport inhibitors, and endothelin receptor antagonists, differentially affect eGFR over time: initially the cause an acute fall in eGFR whereas during long-term follow-up the slow rate of eGFR decline. The initial acute effect is often a hemodynamic effect, reflecting a reduction in intra-glomerular pressure, and is associated with long-term renoprotection. When a lesser change in eGFR is used as end point,
the initial acute effect on GFR may lead to more end points in the active treatment arm which decreases statistical power and can bias clinical trial results.

Estimated glomerular filtration rate slope as a renal end point

An intuitively more representative end point to evaluate the effect of an intervention on renal function is to compare the slope of (c)GFR decline over time. This takes into account all the available data of a patient over time. This end point has been used in past clinical trials although it is not accepted by the regulatory agencies as hard end point to obtain drug marketing authorization. GFR slope as end point provides good statistical power under two key assumptions. First, the rate of GFR decline is constant during follow up; and second, the treatment effect does not depend on the underlying rate of GFR decline. These assumptions are frequently violated.

As discussed above, many renoprotective interventions have acute (reversible) effects on GFR in the opposite direction as the effect during long-term treatment. The acute effect can obscure the interpretation of trial results since the drug effect on the overall GFR slope may be neutral whereas the effect may be beneficial if the initial acute effect is excluded. Such ambiguity has indeed been observed in past clinical trials. For example, the effect of a low protein diet on overall GFR slope was neutral while low protein diet significantly slowed the chronic rate of GFR decline. On the other hand, the primary comparison of ramipril versus amlodipine in the AASK trial was inconclusive because the overall rate of GFR decline did not differ between the treatment arms due to the fact that amlodipine caused an initial rise in GFR. When the initial effect of amlodipine on GFR was excluded, the slope of chronic renal function decline was in fact slower in the ramipril arm. As a result of this ambiguity it is recommended that GFR or serum creatinine is measured after treatment discontinuation to verify whether a potential initial effect on GFR is reversible after treatment discontinuation. One can also calculate GFR decline from a pre-defined post-randomization visit to avoid the problems with potential acute effects on GFR. However, one should be careful since this approach violates the comparisons of randomized comparisons because the treatment groups can differ at the post-randomization time point.

Second, statistical power of (c)GFR slope analyses is compromised if the treatment effect is greater in those with a faster progression. In this situation the larger treatment effect in those with a fast progression is diluted by the smaller treatment effects in those with a moderate or slow progression. As a result, the difference between the GFR slopes attenuates
and statistical power decreases. In such instances, a time-to-event analysis (e.g. time to doubling of serum creatinine) may be more powerful since these analyses reflect the treatment effect in the patients who reach the event which usually are the patients with the fastest rate of GFR decline.

**Aim of the thesis**

Clinical trial end points assess the efficacy and safety of drugs being tested. The current established trial end points in CKD are a mixture of a filtration based end point (doubling of serum creatinine or eGFR slope) and overall function of kidney (renal replacement component). The question is whether we have to focus only on the filtration component, the overall function, or its combination. The aim of this thesis is therefore to analyze the existing clinical trial data to critically examine the advantages and disadvantages of the components of the current hard clinical end point in order to ultimately define the most optimal renal end point in clinical trials of CKD.

The decline in eGFR over time (eGFR slope) has been used as an end point to establish drug efficacy.\(^{15, 16, 18}\) For analysis and interpretation of drug efficacy, it is assumed that renal function declines linearly over time. In recent years, a few studies have suggested that eGFR does not decline linearly over time.\(^{19, 20}\) This means modeling eGFR decline as a trial end point using linear models may not always be appropriate. However, these studies investigated the linearity of renal function trajectories in single cohorts with specific characteristics using different analytical methods. To overcome these limitations, we undertook in **chapter two** a systematic analysis to determine whether eGFR trajectories are linear or nonlinear in six clinical trials of patients with and without diabetes, at different stages of CKD using a uniform analytical approach.

The slope of eGFR decline provides great statistical power than a dichotomous outcome, such as a fixed percentage eGFR decline, but only if the treatment effect does not depend on the underlying rate of renal function decline, so called uniform treatment effect. However, some interventions to slow the progression of CKD such as a low protein diet, are proportional to the underlying rate of renal function decline. Whether the effects of Angiotensin Receptor Blockers (ARBs) on eGFR slope are uniform or proportional has not been investigated. Therefore, in **chapter three** we tested whether the effects of ARBs on the slope...
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of eGFR are uniform or proportional in patients with type 2 diabetes and nephropathy and whether eGFR slope would improve statistical power in clinical trials with ARBs.

In addition to the eGFR slope, a sustained doubling of serum creatinine from baseline, corresponding to a 57% decline in estimated eGFR, is also frequently used as a component of a composite kidney end point in clinical trials. However, the doubling of serum creatinine was somewhat arbitrarily chosen and empirical evidence whether a doubling in serum creatinine is the most optimal increase to establish drug efficacy is lacking. In chapter four we investigated if alternative end points defined by lesser declines in eGFR (increases in serum creatinine) would improve statistical power of clinical trials.

Renal Replacement Therapy (RRT) and doubling of serum creatinine are considered the objective hard end points in nephrology intervention trials. Since both are assumed to reflect changes in renal filtration capacity, drug effects, if present, are attributed to renal function protection. However, the decisions to start RRT are not only based on renal filtration capacity but also on other factors. However, the decision to start RRT may not only based on renal filtration capacity but may also be driven by subjective parameters such as availability of renal replacement therapies, local guidelines, health insurance of the patient, differences among doctors in interpretation of the guideline, and patient suitability for RRT.21,22 Since drugs are developed on the expectation that they will slow loss of the filtration capacity the multiple parameters which drive RRT decision may impact results of clinical trials using a combined end point of RRT and a fixed percentage decrease in eGFR. To this end we compared in chapter five the time to RRT with the time to a fixed eGFR threshold, and assessed the effect of the renoprotective drug irbesartan on both components.

This thesis ends by summarizing the main findings and by discussing future perspectives in regards to the use of renal end points in clinical trials of CKD progression.
Figure 1: Conceptual model for CKD. Continuum of development, progression, and complications of CKD and therapeutic interventions to improve outcomes. Thick horizontal arrows between circles represent the progressive nature of CKD. Complications refer to all complications of CKD, including complications of decreased GFR, cardiovascular disease, and adverse effects of drugs to prevent or treat the disease.²
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References

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Chapter 2

Progressive renal function loss, a straight line? Longitudinal eGFR trajectories in patients with and without type 2 diabetes and nephropathy

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