Evaluation of renal end points in nephrology trials

Weldegiorgis, Misghina Tekeste

Chapter 6

Summary and future perspectives

Summary

Chronic Kidney Disease (CKD) places an increasing burden on health care systems, due to its increasing prevalence, poor outcomes, and high cost of renal replacement therapy (RRT).[1] Globally, diabetic nephropathy is the leading cause of CKD.[2] To date, very few interventions have been proven to be effective for slowing the progression of kidney function decline.[3] The currently used interventions, ACE-inhibitors and Angiotensin Receptor Blockers, are effective in slowing the progression of disease, but not all patients respond to these drugs leaving them at high residual risk. Novel interventions are thus desired to address the high unmet medical need of CKD.

Clinical outcome trials are required to ultimately establish a drug's efficacy and safety. Currently, the composite of renal replacement therapy (RRT) and doubling of serum creatinine is the established hard end point(s) in clinical trials of CKD progression. The decision to start RRT is in part based on the filtering capacity of the kidney, and thus based on the serum creatinine level which can be measured objectively, but it is also based on a subjective decision of the physician and patient depending on patient wellbeing, health insurance, or local guidelines. The RRT component is thus a mixture of loss of filtration power as well as other factors including the health of the patient. The doubling of serum creatinine component on the other hand is purely driven by the filtration capacity of the kidney. These two components of the currently used hard renal end point thus reflect different measures but have in common that they are late events in the progression of CKD thereby requiring large trials of long duration. This may hinder the initiation of new clinical trials in CKD. Alternative end point that has been used in clinical trials of CKD progression is the rate of change in glomerular filtration rate (eGFR slope). However, eGFR slope is not a clinically meaningful end point as it does not directly reflect how a patient feels, functions or how long the patient survives. Thus, each of the components of the currently used renal end points have their advantages and disadvantages.

This thesis aimed to examine the components of the current hard clinical end point for clinical trials of CKD progression in order to define the most optimal renal end point for clinical trials of CKD.

The decline in eGFR has been used as an end point to establish drug efficacy. For analysis and interpretation of drug efficacy, it is assumed that renal function declines linearly over time. However, the paradigm that renal function declines linearly over time has been questioned by recent studies. **Chapter two** compared the eGFR trajectories in a large cohort of patients with and without diabetes, at different stages of CKD using a uniform analytical

approach. The results showed that the vast majority of non-diabetic patients had a linear renal function decline. In patients with type 2 diabetes the renal function trajectories tended to fluctuate more but the results suggested it is reasonable to assume that the majority of patients had a more or less linear renal function decline. Collectively, these data suggested that for clinical trial purposes creatinine based end points can be used both in diabetic and non-diabetic populations, although in trials of patients with diabetes the nonlinearity proportion should be taken into consideration when calculating the power of a clinical trial.

The slope of eGFR decline appears to be a useful end point and provides more statistical power than a dichotomous outcome if the treatment effects on eGFR are uniform (i.e. do not depend on the underlying rate of renal function decline). In **chapter three** we tested whether the effects of ARBs on the slope of eGFR are uniform or proportional in patients with type 2 diabetes and nephropathy. We observed attenuation of both the mean and variability of the slope suggesting larger treatment effects in those with faster rate eGFR decline. These results indicate that the absence of a treatment effect in the subgroup of patients with a slow progressive renal function loss dilutes the greater treatment effect in fast progressors, thereby compromising statistical power. Similar observations have been made in the Modification of Diet in Renal Disease (MDRD) trial in which it was shown that the intervention, dietary protein restriction, exerted proportional treatment effects as well.[5] Thus, when designing new trials and using eGFR slope as end point, information about the drug's effect on eGFR slope (i.e. uniform or proportional) should ideally be present in order to make a well informed decision whether eGFR slope is an appropriate end point to select.

Doubling of serum creatinine (equivalent to a 57% eGFR decline) is a late event in CKD, thus, there is an ongoing discussion in considering lesser declines in eGFR as alternative end points for clinical trials to reduce sample sizes, follow-up time, and cost of conducting the trial. In **chapter four** we determined whether adopting lesser decreases in eGFR (20%, 30%, or 40%) as an end point would have yielded more end points while maintaining a similar magnitude of treatment effects, and whether acute effects on GFR decline would have influenced these results in 2 large trials of ARBs. Compared to a doubling of serum creatinine, we observed a larger number of alternative end points when adopting lesser eGFR declines as end point, leading to greater precision of the estimate of treatment effects. However, we also observed attenuation of the magnitude of the treatment effect, which prevented a gain in statistical significance. However, when eGFR decline was computed from month 3 of follow-up rather than from the randomization value, attenuation of the treatment effect was

diminished. This result suggest that the attenuation of the treatment effect appears to be due in part to acute effects of ARBs on eGFR. The results of this chapter indicate that despite increases in precision, use of end points defined by eGFR declines lesser than a doubling of serum creatinine may not improve statistical power, particularly in settings in which a drug exerts an acute effect on GFR opposite in direction to its chronic effect on eGFR. These results were confirmed in a meta-analysis of 43 studies involving 12,821 individuals. The study showed a trend towards an attenuation of the treatment effect, in particular with drugs that exert acute effects on GFR, which in turn prevented a gain in statistical power.[4] It was eventually concluded that in the absence of acute eGFR effects a 40% and possibly 30% eGFR decline may be a valid end point. The end point of 30% or 40% eGFR decline is now used in new clinical trials of CKD progression such as the FIDELIO DKD trial, a clinical trial involving 4800 patients with diabetic kidney disease and the TESTING trial, a clinical trial determining the efficacy of methylprednisolone in 750 patients with IgA Nephropathy.

In **chapter five** we first investigated if the initiation of RRT, a composite of different measures as described above, is based on reaching a predefined eGFR level in patients with type 2 diabetes and nephropathy. We observed a large discrepancy between the time to reach a fixed eGFR threshold of 11 ml/min/1.73m^2 and the time to RRT. In addition, we showed with joint model analyses that the time-varying eGFR holds a stronger association with reaching a filtration based end point (eGFR of 11 ml/min/1.73m^2) compared to RRT. We then continued to show that these effects may have clinical impact as the effect of the ARB irbesartan is smaller on the RRT end point compared to an end point purely based on the filtration capacity of the kidney (i.e. serum creatinine ≥6.0 mg/dL or fixed eGFR threshold). These data imply that the current practice of evaluating renoprotective drugs with a combined RRT and doubling of serum creatinine end point does not only characterize the drug effect on the filtration capacity of the kidney but on a combination of parameters involving a patient's wellbeing and possibly their combination. Unfortunately, in past clinical trials the reasons for initiation of RRT were not documented. Future renal protection trials should systematically register this information in order to dissect which factors drove the decision of RRT and through which factors the drug/intervention exerted its effect.

Conclusion

How should we combine and interpret all the results from the studies described in this thesis? In a clinical trial we would like the renal end point to be representative of renal function.

However, renal function is a composite of different functions of the kidney: excretion of waste products, maintaining extracellular volume control, acid-base control, production and conversion of various hormones. The question is whether (1) we should focus on all these properties of the kidney, (2) focus only on filtration loss and use a 30%, 40%, or 57% eGFR decline as end point being aware of the potential acute eGFR effects, or (3) combine these two. We have to realize, however, that each of these options may lead to a different interpretation of the drug effect. For example, a drug that improves the tolerance of the patient to withstand the consequences of severely compromised renal function may delay the decision of RRT (patient does not complain), whereas eGFR continues to decline. One could question whether this is "true" renoprotection from a pharmacological point of view. On the other hand, a drug may worsen the symptoms of reduced renal function but does slow the progression of eGFR decline. In this example the choice of RRT would have led to a potential neutral or harmful trial result despite a beneficial effect on the rate of eGFR decline.

Based on the considerations and studies described in this thesis, we conclude that the optimal end point in clinical trials of CKD progression should be a composite end point which properly represents the multiple aspects of renal function. We propose that a hard end point in clinical trials of CKD progression should consist of an objectively measured component reflecting change in filtering capacity as well as the clinically relevant end point of renal replacement therapy. The change in filtering capacity could be the traditionally used doubling of serum creatinine but alternatives such as a 40% or in some instances 30% eGFR decline can be considered. In any case a good balance between the filtering component and RRT component is required and should not be driven by either of them.

Future perspectives

The results described in this thesis, supported by meta-analyses and simulations,[4, 6] suggest that a 30 or 40% decline in GFR would be an acceptable alternative end point in clinical trials in some circumstances. However, simulation studies have illustrated that the use of a 30% or 40% eGFR decline end point is limited at higher baseline GFR,[6] and we have shown that for agents that cause an "acute effect" on GFR, a 30% or 40% eGFR decline end point may not increase statistical power. As such, these alternative end points are less applicable in drug development for drugs targeted at earlier stages of kidney disease and for many drugs with potential hemodynamic effects. Alternative strategies to overcome these limitations should be

investigated. One of these strategies include assessing changes in albuminuria as a potential surrogate end point or assess alternative approaches of using eGFR decline or a combination of these. Albuminuria has been proposed as surrogate outcome[7] but the debate as to whether it is a valid surrogate end point continues.[8] At higher GFR, a trial design to compare mean slopes of GFR decline versus time between randomized groups may have greater statistical power than comparison of time to a GFR decline. However, acute effects are generally proportional to baseline GFR, so they pose a more serious problem at higher GFR. In addition, we have shown that ARBs exert proportional treatment effects which limit statistical power of clinical trials using eGFR slope as end point. Solutions for these limitations include evaluation of "on treatment" slope rather than "total slope from randomization" and evaluation of reversal of acute effects following discontinuation of treatment, or both. However, as is the case with albuminuria there is no generally accepted method, and controversies remain. Further studies addressing these aspects are very important in particular since it has been shown that slowing progression of kidney disease at early stages of disease is more beneficial than interventions at later stages of disease when overt nephropathy is present.[9]

The results described in this thesis were mainly obtained from analyses of clinical trials investigating the effect of ARBs in patients with type 2 diabetes and nephropathy. It is not clear how these findings will generalize to drugs of other classes. For example, it is unknown whether other new interventions, such as endothelin antagonists or sodium-glucose-co-transport inhibitors exert uniform or proportional treatment effects. Thus additional research on the applicability of the findings described in this thesis to other drugs and interventions is warranted.

References

1. Levey AS, Coresh J: Chronic kidney disease. Lancet 379(9811):165-180, 2012
2. Jha V, Garcia-Garcia G, Iseki K, et al: Chronic kidney disease: Global dimension and perspectives. Lancet 382(9888):260-272, 2013
3. Miyata T, Kikuchi K, Kiyomoto H, van Ypersele de Strihou C: New era for drug discovery and development in renal disease. Nat Rev Nephrol 7(8):469-477, 2011
4. Greene T: A model for a proportional treatment effect on disease progression. Biometrics 57(2):354-360, 2001
5. Inker LA, Lambers Heerspink HJ, Mondal H, et al: GFR decline as an alternative end point to kidney failure in clinical trials: A meta-analysis of treatment effects from 37 randomized trials. Am J Kidney Dis 64(6):848-859, 2014
6. Greene T: GFR decline as an alternative end point for kidney failure - A simulation study of the validity and utility of eGFR-based surrogate time-to-event end points in chronic kidney disease. Am J Kidney Dis 64(6):867-79, 2014
7. Lambers Heerspink HJ, Gansevoort RT: Albuminuria is an appropriate therapeutic target in patients with CKD: The pro view. Clin J Am Soc Nephrol 10(6):1079-1088, 2015
8. Fried LF, Lewis J: Albuminuria is not an appropriate therapeutic target in patients with CKD: The con view. Clin J Am Soc Nephrol 10(6):1089-1093, 2015
9. Schievink B, Kropelin T, Mulder S, et al: Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. Diabetes Obes Metab 18(1):64-71, 2016