Chapter 1

Introduction and scope of the thesis

Adapted from: Current Opinion in Nephrology and Hypertension, 2015.
Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide, and forecasts for 2030 indicate that the number of patients requiring renal replacement therapies will more than double (1). The increase in requirement of renal replacement therapies and the availability of only few proven effective therapies highlight the need to develop new drugs and intervention strategies. To develop new drug interventions, regulatory authorities (i.e. Food and Drug Administration, European Medicine Agency) require that the demonstrated benefits outweigh risks. To this end, new drugs have to show a beneficial effect in well-designed clinical trials on accepted clinically meaningful endpoints, and these benefits must offset any adverse effects the patient may experience during the use of the drug. In trials of CKD progression, end-stage renal disease (ESRD) is an accepted, clinically meaningful endpoint because it is accompanied by a large disease burden and shortened survival. However, since progression to ESRD may take decades, large and complex clinical trials are needed to demonstrate drug efficacy (2-4). This results in large financial and human investments to test new drugs for patients with CKD. The increasing size of clinical trials and related investments in combination with high drug attrition rates in late phase clinical trials has fostered exploration of alternative approaches to test the efficacy and safety of new drugs (5-7).

One intuitive alternative is replacing clinically meaningful endpoints by surrogate endpoints. A surrogate endpoint is an intermediate outcome, usually a laboratory measurement of a relevant risk marker, which substitutes the clinically meaningful endpoint (8). An example of an accepted surrogate endpoint in trials of CKD progression is doubling of serum creatinine, equivalent to a halving of kidney function. However, doubling of serum creatinine is still a late event in progression of kidney disease and therefore trials still require large sample sizes and long duration of follow-up to determine drug efficacy. Therefore, there is interest in exploring alternative surrogate endpoints that can be ascertained earlier in the course of renal disease, leading to shorter durations of follow-up in clinical trials.

Examples of such surrogates are lesser declines than a halving in estimated glomerular filtration rate (eGFR), transition in eGFR classes, or changes in albuminuria. eGFR represents the filtration power of the kidney and is accepted as
the best index of overall kidney function. eGFR decline is a necessary intermediate on the pathway of ESRD and it is therefore not surprising that various studies showed a strong and graded association between small reductions in eGFR and risk of developing ESRD. Based on the strong mathematical and biological association between eGFR and ESRD, lesser declines than a halving of GFR have received ample attention as potential surrogate endpoint in a series of meta-analyses of observational studies and clinical trials (9-14). As an alternative to GFR, albuminuria is proposed as a surrogate endpoint (15). The difference with eGFR, which is a direct marker of kidney function, is that albuminuria, just like blood pressure, is not only a marker of kidney damage but also causally implicated in renal disease progression (15,16). Treatment with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) decreases albuminuria and confers renoprotection. Post-hoc analyses from clinical trials repeatedly showed that the initial reduction in albuminuria with ACEi or ARB is the driving parameter for renoprotection (17-19). Emerging clinical trial data show that ACEi or ARBs are not the only drugs that decrease albuminuria and slow the progression of CKD. First, a randomized clinical trial showed that pentoxifylline, a xanthine derivative registered for treatment of peripheral vascular disease, decreases albuminuria in patients with diabetes and nephropathy and slows the progression of renal function decline relative to placebo (20). In addition, the recent PLANET trials reported that atorvastatin, but not rosuvastatin, decreased proteinuria after 14 weeks treatment (21).

However, developing novel surrogate endpoints based on a single renal risk marker such as eGFR decline or albuminuria may not be optimal. In the current drug development and registration process a single renal risk marker is selected and a drug is targeted towards that risk marker. However, there are multiple causes of renal disease that may not all be captured by a single risk marker alone, and drugs have multiple effects beyond the target risk marker (so-called off-target effects). These additional drug effects may also influence the ultimate renal endpoint; they either contribute to or counteract the on-target risk marker effect. For example, in addition to blood pressure lowering, RAS intervention also lowers albuminuria which contributes to the renal protective effect. However, these drugs also increase serum potassium, which is associated with increased renal risk. Hence, the rise in serum potassium may blunt the beneficial effect of blood pressure lowering (and
Introduction and scope of the thesis

Albuminuria reduction (22,23). Several recent clinical trials showed no benefit on clinically meaningful outcomes despite the drug exerting beneficial effects on the on-target parameter (4,24-28). In these cases off-target drug effects may confound the relationship between a single risk marker or surrogate and renal outcome. This suggests that a score that integrates all known drug-induced effects is potentially more accurate in predicting the ultimate drug effect than using a single risk marker alone (29).

Using such multiple risk parameter scores to establish drug efficacy in clinical trials is not much different from the risk prediction scores that are used to establish a patient's renal risk. When we aim to predict the risk of an individual we accept that multiple risk markers are of relevance to the clinical outcome, and thus risk prediction scores are developed consisting of multiple risk markers. In drug development a single risk marker is selected as target for therapy. However, nearly all drugs have effects on multiple risk markers. Therefore it seems logical to integrate these multiple drug effects to better predict the ultimate drug effect. Recently, a score was developed that integrates multiple short-term drug effects in order to predict the long-term drug effect on renal and cardiovascular outcomes. This so-called PRE score was used to establish the effect of the angiotensin receptor blockers losartan and irbesartan in patients with type 2 diabetes. Interestingly, the ARBs significantly changed 7 out of 11 measured renal risk markers. Integrating all risk markers in a PRE score showed that it provided a better prediction of the drug effect on hard renal outcomes than any change in single markers (30,31). External validation studies confirmed these results (32). Therefore, such scores may be better suited as surrogate endpoint in clinical trials than using a single marker alone.

Although using changes in multiple parameters to establish drug efficacy is intuitively appealing, the approach is still in its infancy and requires more prospective validation. In particular, the validity of the multiple parameter drug response score has been ascertained for drugs intervening in the RAS but it is unclear whether the score will be equally valid for other drugs. Especially whether the score can be used for novel drugs targeting for example inflammatory pathways requires further investigation. Moreover, the risk markers currently included in the score are limited to what is measured and recorded in the trials: physical measurements and standard biochemical measurements. Novel risk markers may be identified and integrated to improve its accuracy.
Another concern is that recent clinical drug trials in type 2 diabetes were terminated early for safety reasons, due to an increase in hospitalization due to heart failure in the active treatment arm. This was the case for the Nrf2 activator bardoxolone methyl, the endothelin antagonist avosentan and the peroxisome proliferator-activated receptor activator rosiglitazone (24,33,34). These drug failures illustrate that the validity of the score needs to be ascertained for other outcomes than ESRD, in order to provide a more complete profile of the benefit-risk profile of a given drug.

Scope of the thesis

Better prediction of drug effects on clinical outcomes may be achieved by risk scores that integrate the effect on multiple risk markers, instead of using single markers alone. Such an approach, with the so-called PRE score, was previously used for drugs intervening in the RAS, but before it can be implemented in practice more validation is required. In this thesis we determined whether this multiple parameter drug response score could also be used for other drug classes that are used to treat patients with type 2 diabetes. In addition, we aimed to address both safety and efficacy by predicting ESRD and heart failure outcomes. Another important aspect is that drug effects are frequently assessed on a group level, but whether the response in multiple risk markers in response to therapy can improve prediction of who is likely to benefit from treatment is not yet known. And lastly, a multiple parameter drug response score such as proposed in this thesis needs to be accepted by all stakeholders in drug development. This includes academics, the pharmaceutical industry and regulatory authorities, and their willingness to accept such a score needs to be ascertained.

In Chapter 2 we investigated whether early intervention with drugs that intervene in the RAS is more beneficial in delaying ESRD in patients with type 2 diabetes than intervention in later stages of the disease. Because ESRD can take decades to manifest, prospective clinical trial data is not available to answer this question. Therefore we built a model with patient data from completed clinical trials in nephrology from all stages of CKD. The model is based on disease stages defined by a combination of the risk markers albuminuria and eGFR.
Figure 1. Schematic representation of the PRE score. In step A the associations between multiple risk markers (e.g. blood pressure, albuminuria) and clinical outcomes (e.g. ESRD) are established. In step B these associations are applied to the baseline and follow-up risk marker measurements in each patient. The PRE score then predicts the individual risk change of clinical outcomes induced by treatment.

In Chapter 3 we performed a post-hoc analysis of the AleCardio trial in which patients with type 2 diabetes were treated with the dual PPAR agonist aleglitazar. The trial was stopped early due to futility and an increase in hospitalization due to heart failure in the treatment arm. Our aim was to predict whether the adverse heart failure outcomes could have been prevented by more stringent baseline inclusion criteria by using individual or multiple risk markers for heart failure. Secondly, we investigated whether the observed heart failure risk could have been predicted based on short-term response in individual risk markers, or a composite consisting of multiple risk markers. In Chapter 4 we applied the multiple parameter drug response score to a clinical trial of the endothelin antagonist atrasentan, to prospectively
predict the outcome of an ongoing phase III trial on the endpoints ESRD and hospitalization due to heart failure. In Chapter 5 we applied the multiple parameter drug response score on individual patients that were subjected to drugs that intervene in the RAS. We determined whether integrating the effect on multiple risk markers in response to RAS intervention would improve the prediction of who will benefit from treatment, compared to using single risk markers alone. In Chapter 6 we performed a questionnaire to investigate whether stakeholders in drug development would be willing to accept novel surrogate endpoints, and whether they deemed surrogate endpoints based on multiple risk markers more accurate than using single markers alone.
Introduction and scope of the thesis

References


Introduction and scope of the thesis


