Better prediction of drug response in diabetic kidney disease

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Introduction and aims

Published in adapted form

Personalized medicine in diabetic kidney disease:
a novel approach to improve trial design and patient outcomes.

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Introduction

Current treatment for renal and cardiovascular (CV) complications in type 2 diabetes consists of targeting multiple modifiable risk factors including glucose, blood pressure, cholesterol, body weight, and albuminuria. In particular, adequate glycemic control and intervention in the renin-angiotensin-aldosterone-system (RAAS) with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) have been shown to afford microvascular protection.[1–3] However, despite the widespread use of these interventions, the residual risk for end-stage renal and CV disease remains high.[4] In the last decade, many attempts have been made to further lower the cardio-renal risk by more stringent RAAS blockade using combinations of either ACEi and ARB or direct renin inhibition as adjunct to ACEi or ARB.[5,6] Additionally, other strategies have been explored: lowering of albuminuria with the glycosaminoglycan sulodexide; increasing hemoglobin with the erythropoietin stimulation agent darbetpoieitin-alpha; lowering of endothelin with the endothelin receptor antagonist (ERA) avosentan; and targeting inflammation and oxidative stress with bardoxolone methyl, among other interventions.[7–11] Although these therapies appeared to be promising, they did, however, not result in additional renal or CV protection, and sometimes even led to an increase in risk. There are multiple potential explanations why these drugs did not lead to a further reduction in renal and CV risk, but it appears that the individual variation in drug responses played an important role.[12–14]

Drug response is highly variable between individuals

Analyses from past clinical trials in DKD suggest that a distinct group of patients benefit from the experimental drug but many others do not. Analyses from the RENAAL trial, which demonstrated the renoprotective effect of the ARB losartan in patients with type 2 diabetes and kidney disease, reported that individuals with the largest reduction in albuminuria during the first months of therapy showed the greatest risk reduction for progression of kidney disease during subsequent follow-up.[14] Conversely, the risks of progressive renal function loss did not decrease among patients who did not experience a reduction in albuminuria. Similar observations were made in the ALTITUDE trial. Although
the ALTITUDE trial did not show a beneficial effect of adding the renin inhibitor aliskiren to ACEi or ARB in the overall type 2 diabetic population, 37% of patients showed a reduction in albuminuria of more than 30% during aliskiren therapy, and these patients had a 55% lower risk of renal function loss compared to placebo treated individuals who did not experience a reduction in albuminuria.[15] In other trials, subgroups of patients have been identified who did not tolerate the drug of interest and experienced more CV events during the trial. In the BEACON trial for example, patients on bardoxolone methyl with a brain natriuretic peptide (BNP) > 200 pg/ml or previous heart failure were at highest risk of heart failure.[12] After excluding these patients in a post hoc analysis, the risk of heart failure was similar in the bardoxolone methyl and placebo arm. In the ASCEND trial, the edema and heart failure during avosentan therapy occurred more often in patients who had a rise in body weight more than 1.0 kg during the first weeks of therapy.[13] Thus, careful selection of patients (e.g. BNP criteria in BEACON) and monitoring of body weight during the first weeks of treatment may have helped identify patients who did not tolerate these drugs.

Recently, two large outcome trials demonstrated the beneficial renal effects of the ERA atrasentan and the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin, conveying a major breakthrough in the treatment of DKD. [16,17] However, pharmacological interventions that show a clear benefit in reducing renal outcomes on a population level do not uniformly reduce renal risk in each patient. This was already shown for the ARBs losartan and irbesartan in the early 2000s. Despite their high efficacy in reducing renal events in patients with DKD on a population level, they did not confer renoprotection in a substantial number of patients. There was a large individual variability in response to ARB treatment, both in terms of cardiorenal outcomes and in surrogate risk markers, such as blood pressure and albuminuria.[14,18,19] A similar phenomenon was observed with the albuminuria lowering response to SGLT2 inhibitors. This was illustrated in a prospective randomized controlled crossover trial with the SGLT2 inhibitor dapagliflozin, where treatment with dapagliflozin resulted in a substantial lowering of albuminuria. However, there was a large variation in albuminuria response between patients, with some of them showing only a small decrease or even an increase in albuminuria levels (Figure 1).[20] It is yet unknown
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how this response variability relates to long-term cardiorenal outcomes; post hoc analyses of the recently completed SGLT2 trials will help to answer these questions.

Biomarker approaches to personalize treatment

The large clinical outcome trials highlight the need for a more careful consideration of the individual variability in drug response. This would entail a personalized medicine approach in which pharmacological treatment is tailored to an individual’s predicted therapy response or risk of disease. The use of biomarkers (such as albuminuria and NT-proBNP) to predict long-term drug efficacy can aid personalized drug therapy.

In a clinical trial setting, biomarkers can be used to enrich trials with patients who are likely to show a favorable drug response: patients with ‘bad’ responses in these biomarkers would be excluded from trials and patients with ‘good’ responses would be included.

Predictive biomarkers

Biomarkers can be used to identify a population more likely to respond before exposing the population to the drug of interest. These so-called predictive biomarkers – which can be genes, proteins, metabolites, or others – have been used in clinical trials in oncology and cystic fibrosis.

Figure 1. Correlation between albuminuria changes during the first and the second 6-week period of exposure to dapagliflozin. This figure is derived from reference [21].
In cancer, genetic information is often derived from tumor biopsies, and the genetic polymorphisms help to predict the response to anticancer drugs. For example, epidermal growth factor inhibitors are more beneficial in lung cancers with a mutant epidermal growth factor receptor. Unfortunately, only few predictive biomarkers have been discovered to guide therapy in patients with DKD. One study reported that polymorphisms in the ACE gene predict the response to ARBs, a finding which is also observed in non-DKD. Overall, there is a paucity of predictive biomarkers in endocrinology or nephrology compared to oncology. This is likely explained by the fact that the underlying molecular mechanisms driving DKD progression are less well described compared to oncology where the information obtained from tumor biopsies has driven science and knowledge of which molecular pathways initiate and sustain tumor growth. This has in turn led to clinical trials enriched for populations and interventions specifically targeting these molecular processes. The nephrology community should learn from these lessons and start implementing these trials in patients with DKD.

**Dynamic biomarkers**

Another approach to enrich clinical trials is to select patients after they have been exposed for a short time (up to a few weeks) to the new intervention (Figure 2). Only patients with a positive biomarker response and who tolerate the drug are selected and randomly assigned...
to long-term treatment with the new intervention or placebo. The SONAR trial is an example of this type of enrichment. The trial enrolled patients with more than 30% albuminuria reduction after six weeks exposure to the tested endothelin antagonist atrasentan, whereas patients with increased sodium retention to atrasentan exposure were excluded from the trial. In this way the trial aimed to find the optimal balance of efficacy (albuminuria reduction) and safety (sodium retention) in order to select patients more likely to benefit from the drug. Additionally, a subgroup of patients without an albuminuria reduction more than 30% was enrolled to assess the long-term efficacy of atrasentan in the biomarker nonresponsive subgroup. In patients who had a reduction in albuminuria of more than 30% and showed no clinical signs of sodium retention during short-term treatment with atrasentan, subsequent long-term treatment with atrasentan significantly reduced the risk of the primary composite renal outcome of doubling of serum creatinine or end-stage kidney disease compared with placebo. The occurrence of hospital admission for heart failure was somewhat higher with atrasentan than with placebo in these patients. However, the incidence rate of heart failure was substantially lower than that observed during treatment with the ERA antagonist avosentan, suggesting that the enrichment approach used in SONAR may have prevented a higher incidence of heart failure. Of note, favorable renal effects of atrasentan were also observed in patients without an initial albuminuria reduction of more than 30%. This may be due to the trial design (no wash-out after the enrichment period) or difficulties to distinguish responders from non-responders due to random variations in albuminuria. It is also possible that atrasentan exerts other beneficial effects beyond albuminuria reduction that lead to long-term renoprotection. Further study is warranted to investigate this in more detail.

**Drugs have multiple effects that are dissociated within individuals**

Apart from the between individual variation in response in the on-target risk marker, it appears that many drugs affect multiple risk markers of renal and CV disease progression beyond the one intended (i.e. an angiotensin receptor blocker may affect hemoglobin, serum potassium, or uric acid). Individual patients show a large variation in responses in
these off-target/unintended risk markers.[28] Intriguingly, the responses in these multiple cardio-renal risk markers also vary within each individual. In other words, blood pressure and albuminuria may decrease and potassium may increase following ARB initiation in one patient. Yet, in another patient, blood pressure increases while albuminuria and potassium decrease.[29,30] Similar variations in response have been observed for SGLT2 inhibitors and glucagon like peptide 1 receptor (GLP1) agonists. [31,32] As each of these individual changes in risk markers are associated with long-term renal and CV outcomes, the balance of these responses in multiple parameters within an individual determines the ultimate renal/CV outcome of the patient. This implies that the individual drug response in all renal and/or CV risk markers should be measured to monitor the individual drug response and the efficacy of a drug to prevent renal and/or CV events. It is important to note that all studies reviewed so far were post hoc analyses from randomized controlled trials, and did not depend on randomized group comparisons. They should therefore be carefully interpreted. However, despite this caveat, they highlight the large individual response variation in multiple short-term cardiorenal risk markers, which is hidden in the mean population responses reported in these trials. This variation in response offers an opportunity to reform the drug development process and the use of drugs in clinical practice focusing on a more individually targeted treatment approach, commonly referred to as personalized medicine.

**A composite of multiple biomarkers may improve prediction of long-term drug effects in diabetic kidney disease**

The concept of baseline risk scores based on multiple markers, such as the Framingham score, is widely accepted and used for the prediction of long term CV outcomes.[33,34] Similarly, as almost all drugs have effects on multiple markers, it seems logical to predict long-term drug effects based on short-term effects on multiple markers. The so-called PRE score integrates multiple short-term drug effects in order to predict the long-term drug effect on renal and cardiovascular outcomes and ultimately consists of clinical markers that are usually measured in routine clinical care, such as systolic blood pressure, cholesterol, albuminuria and hemoglobin. The PRE score was originally developed in patients with type 2 diabetes mellitus and kidney disease within the RENAAL
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For the ARBs losartan and irbesartan as well as for the calcium antagonist amlodipine, the PRE score predicted long-term renal and CV risk changes that were similar to the observed risk changes after treatment with these drugs.\[36\] The PRE score provided adequate estimations for the occurrence of heart failure events after treatment with the PPAR-\(\alpha/\gamma\) agonist aleglitazar.\[37\] Additionally, it predicted the long-term renal effects of the ERA atrasentan in a prospective setting.\[16,38\] Furthermore, it was shown that integrating multiple short-term responses of a drug at an individual patient level provides a better estimate as to who will benefit from an ARB compared to single risk markers.\[28\]

The results of past clinical trials in patients with DKD identify a large individual variation in drug response as potential culprit for the stagnation in improvement in reno- and cardioprotective therapies. Analyses from these trial support a personalized medicine approach to improve clinical trial design and pharmacotherapy in clinical practice. To implement personalized medicine in daily practice, novel methodologies for clinical trial design that take in account variations in individual drug response are required. Implementation of the PRE score in design of clinical trials is one such approach.

The studies described in this thesis were conducted as part of the Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt DKD)
consortium, a public private partnership supported by the Innovative Medicines Initiative (IMI). BEAt-DKD aims to identify targetable mechanisms and pathways underlying initiation and progression of DKD and focuses on the identification and validation of biomarkers that reflect disease progression and/or treatment response. Additionally, BEAt-DKD aims to optimize clinical trial design and works towards integration of personalized approaches in the regulatory process of drug registration. Ultimately, these approaches can be used to improve the estimation of individual drug response on renal and/or CV outcomes, representing first steps towards personalized medicine in the management of DKD.

**Aims of this thesis**

This thesis investigates the utility of biomarker-based strategies to predict long-term cardio-renal response to different pharmacological therapies in patients with type 2 diabetes. In Chapter 2 and 3, we explore the ability of routinely measured single biomarkers to identify patients likely to show a favorable long-term drug response on cardiorenal outcomes. Chapter 4, 5 and 6 focus on the prediction of long-term drug effects by the PRE score, which integrates short-term changes in multiple biomarkers.

In **Chapter 2** we evaluate the use of a baseline predictive biomarker to predict drug effects on long-term outcomes. Previous studies indicate that the efficacy of renin-angiotensin-aldosterone system (RAAS) inhibition is impaired by sodium retention and volume overload in patients with diabetes. Chapter 2 evaluates the utility of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of vascular wall stress and fluid overload, to predict the response to additional therapy with the dual renin inhibitor aliskiren on cardio-renal endpoints in patients with type 2 diabetes mellitus.

In **Chapter 3** we investigate the use of risk markers as dynamic biomarkers to predict the long(er) term effects of statin therapy. Statin therapy is usually initiated to reduce cholesterol levels and lower cardiovascular risk. In patients with proteinuria, statins are shown to reduce both cholesterol and proteinuria levels, suggesting statin therapy
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may be renoprotective in some patients. In this chapter, we investigate whether we can use short-term changes in proteinuria and cholesterol as dynamic biomarkers to predict longer term renal effects of statins. We first evaluate the between-patient variability in cholesterol and proteinuria response to statin therapy, and whether treatment effects on cholesterol and proteinuria run in parallel within individuals. Then, we investigate the association of cholesterol and proteinuria response with estimated glomerular filtration rate (eGFR) decline.

As described previously, the PRE score translates multiple short-term drug effects into an estimated long-term drug effect on renal and/or cardiovascular outcomes. There are several existing risk scores that have been demonstrated to adequately predict the risk for renal disease progression. It is unknown whether these scores can also be utilized to predict response to drug therapy. In Chapter 4, we compare two existing risk scores with the PRE score in their ability to predict long-term renal effects of ARB therapy in patients with type 2 diabetes and kidney disease.

The PRE score has been shown to predict long-term drug response in different drug classes, including RAAS inhibitors, calcium antagonists and PPAR-\(\alpha/\gamma\) agonists.\[28,36,37\] In the last part of this thesis, we test whether the utility of the PRE score in predicting long-term drug response on cardio-renal outcomes extends to the novel drug classes of GLP1 analogues and SGLT2 inhibitors. In Chapter 5, we investigate the effects of the GLP1 analogue exenatide on long-term renal outcomes. We then integrate multiple short-term effects of exenatide using the PRE score to predict long-term effects of exenatide on the progression of renal disease and compare the predicted treatment effect with the actual observed effect in the trial. In Chapter 6, the PRE score is applied to phase 3 clinical trials with the SGLT2 inhibitor dapagliflozin in order to predict the potential benefit of dapagliflozin on kidney and heart failure outcomes in patients with type 2 diabetes and chronic kidney disease. These analyses are performed in a prospective setting; the actual renal effects of dapagliflozin in this population are currently being tested in a large dapagliflozin outcome trial.

This thesis ends by discussing future perspectives for using biomarker-based approaches to support personalized medicine within the field of diabetic kidney disease.


37. Schievink B, Grobbee, D. Michael Lincoff, A. Heart failure induced by aleglitazar treatment can be predicted based on short-term response in multiple risk markers. Submitted for publication.
