FAILURE OF BIOMARKERS TO PERSONALIZE CLINICAL PRACTISE IN DIABETIC KIDNEY DISEASE

ARE WE ASKING THE RIGHT QUESTIONS?

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Individuals with type 2 diabetes mellitus (T2DM) and impaired renal function are not homogeneous in their clinical presentation and pathophysiology. Other, non-diabetic kidney diseases (such as glomerulonephritides) may be present, especially if the clinical presentation is atypical (e.g. nephrotic syndrome, haematuria). Patients with a phenotype considered "typical" rarely undergo biopsy, and therefore the prevalence of well-defined non-diabetic pathologies in this population remains unknown. Clinically, progression can take place via the "classical" pattern of "diabetic nephropathy" (DN) going from hyperfiltration to microalbuminuria and macroalbuminuria before eGFR declines, while other cases experience a decrease of eGFR without ever developing proteinuria. To cover this diversity "diabetic kidney disease" (DKD) is the preferred term with DN only being one of many possible disease manifestations. Histological lesions in DKD are also highly variable. Even in cohorts with a relatively homogenous and typical phenotype (microalbuminuria with preserved eGFR), only one third of patients shows biopsy findings indicative of DN (mesangial expansion, thickening of the glomerular basement membrane), while the majority has nonspecific changes or even normal images on light microscope (Fioretto P; Diabetologia 1996; 39:1569). Consequently, the individual prognosis as well as the response to a specific therapy is variable. Inhibition of the renin–angiotensin system, GLP-1 agonist or SGLT2 inhibitor therapy significantly reduced hard endpoints in prospective randomized controlled interventional trials and the implementation of this "cohort-oriented medicine" has improved the prognosis of patients with DKD. However, the "number needed to treat" is high and, when prescribing drugs with side effects, we harm those, who do not adequately respond. In addition, with more effective agents available, the questions about optimum combination therapy is emerging.

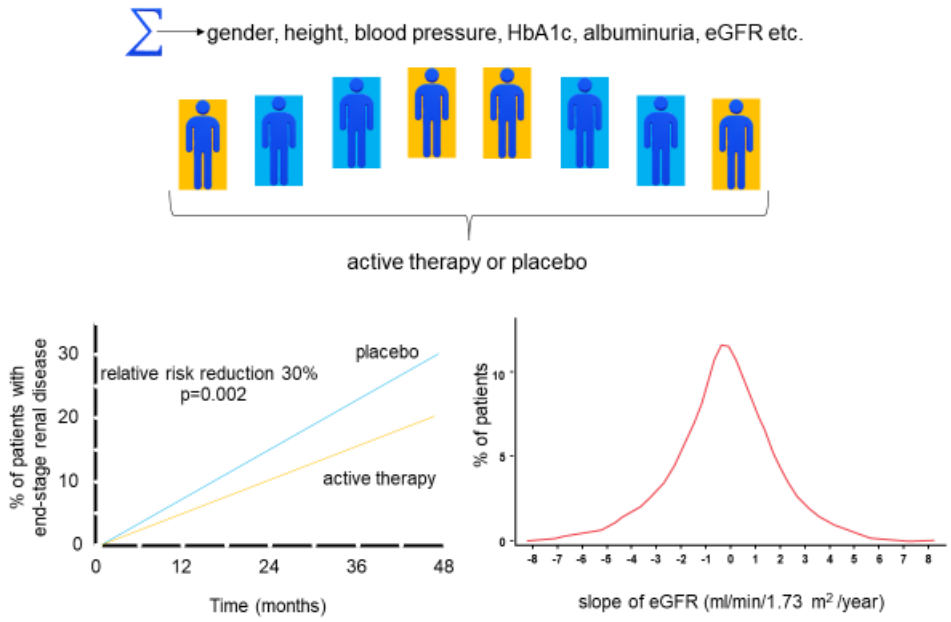
Over the last decades, great efforts to better characterize patients with DKD were undertaken to improve the prediction of individual prognosis and treatment response. While prognostic biomarkers aim to predict the trajectory of DKD based on the present ("as-is") state, predictive biomarkers estimate the consequence of a specific intervention on the prognosis. The European Union has supported several multinational research projects (e.g. SYSKID, SUMMIT, Beat-DKD) to implement stratified or even personalized therapy in complex diseases such as DKD, but unfortunately no novel biomarker candidates have yet found their way into clinical practice.

Critics argue that biomarkers in diseases such as DKD are obviously of little value while others propose that extended profiling and application of modern analysis strategies like machine learning will ultimately identify the "right" biomarkers or biomarker panels.

The authors of this article support the idea that only biomarkers can lead to "personalized" or "targeted therapy" – and we do see advances in DKD as well. Nonetheless, we critically question, whether it is enough to increase the scale of high throughput screening as all analysis strategies rely on a specific model of the disease. We believe that it is urgently necessary to re-evaluate our basic concept of progression of DKD to avoid failures that are not based on the quality of the biomarkers chosen.

Biomarkers in interventional studies

Figure 1:



A typical interventional DKD study design and analysis setting. A subpopulation of a cohort of individuals with the target disease (e.g. T2DM) is selected based on biomarkers. They are assigned to a placebo or an intervention group and analysed according to the incidence of a categorical endpoint (renal replacement therapy, bottom left) or the slope of eGFR under active therapy (bottom right, figure adapted from Wanner C et al. J Am Soc Nephrol 2018; 29:2755)

Interventional studies usually apply strict inclusion and exclusion criteria for patient selection. The exact definition of the target population not only serves to define the indication for a new agent but also aims at recruitment of a "homogeneous" cohort to reduce variance in treatment response. To achieve the goals, we use biomarkers being aware that complete homogeneity cannot be achieved (in Figure 1, for instance, patients have different body weight). Hence, we focus on specific aspects that we consider particularly important in the context of the study. Interestingly the biomarkers used (especially in studies on DKD) often are mainly associated with prognosis (i.e. disease progression in the absence of an intervention). From a clinical point of view, this paradox nonetheless seems reasonable: The patients with the worst prognosis under a state-of-the-art therapy are in largest need for a new treatment. However, this may very well not be the population, which will have the best response to a certain drug. A cohort with a relatively homogeneous prognosis can see heterogeneity in treatment response. Thus, predictive biomarkers that estimate efficacy of therapy and the impact of the treatment on the prognosis would be preferable. Certainly, some prognostic biomarker may also be predictive.

Let us assume we test a novel antihypertensive agent and we know that the progression of kidney disease is linearly, positively and causally related to blood pressure. We also know that the higher the initial blood pressure the more effective antihypertensive agents are at lowering it. In this situation, severe hypertension would be a prognostic as well as predictive biomarker.

This example rests on the assumption, that the correlation between the disease progression and biomarker expression is linear, that both are causally linked to a common pathophysiological mechanism and that the latter is the target of the drug's mechanism of action. Once a biomarker does not meet all these criteria, its power for selection of a homogenous group for prognosis may still hold true, while the predictive value will decrease. Unfortunately, for most interventions we do not have predictive characteristics available and consequently we choose our target population exclusively by prognostic similarity.

Why is our armamentarium of predictive biomarkers so limited? First, we often have a very limited understanding of the actual molecular mechanism of interaction between a disease and a drug beyond the binding of the agent to its target structure. The unexpected finding that SGLT2 inhibitors positively influence the course of DKD regardless of their primary mechanism of action (reduction of HbA1c) serves as an example. On the other hand, the quality and clinical utility of biomarkers is often judged exclusively by their prognostic potential. We quickly discard novel biomarkers, which are not superior to established parameters such as eGFR and albuminuria in predicting the course of the disease. We should accept that excellent predictive markers may have little prognostic value just as we have realized that excellent prognostic markers do not necessarily tell us about the response to a drug.

In a next step the „homogeneous" patient population of a study is randomized to an active treatment or control group and followed over a period of time and we may choose a categorical variable (e.g. initiation of renal replacement therapy) as the primary endpoint. Figure 1 shows that the intervention significantly reduces the relative risk by 30% as compared to placebo. However, it is also obvious that it is not successful in all, as 20% of participants still reach the primary endpoint. Based on the data we cannot answer the crucial question for an individual: Do I belong to the 20% or 80%? We only have a probabilistic assessment. The definition of the endpoint also implies that we do not know how individual patients do under active therapy. It is possible that treatment completely stabilizes kidney function in some participants, whereas others reach end-stage kidney disease (ESKD). Alternatively, active therapy might slow progression in all participants in the treatment arm as compared to placebo. The need for renal replacement therapy is a decisive event but even when a drug slows the progression of DKD this is important (the lower the eGFR, the higher the cardiovascular risk or the prevalence of anaemia or renal osteodystrophy etc.). Alternatively, we can use a decline of eGFR as our endpoint, which is a continuous variable. Figure 1 (bottom right) is taken from the EMPAREG Outcome trial. The SGLT2 inhibitor Empagliflozin reduced the incidence of hard renal endpoints and this finding was paralleled by a significantly smaller mean eGFR decline over time (-1.8 in the placebo

group but vs. -0.3 ml/min/1.73m^2/year in the active treatment group) (Wanner C et al. J Am Soc Nephrol 2018; 29:2755). However, concurrently a marked inter-individual variability of the treat effect is obvious.

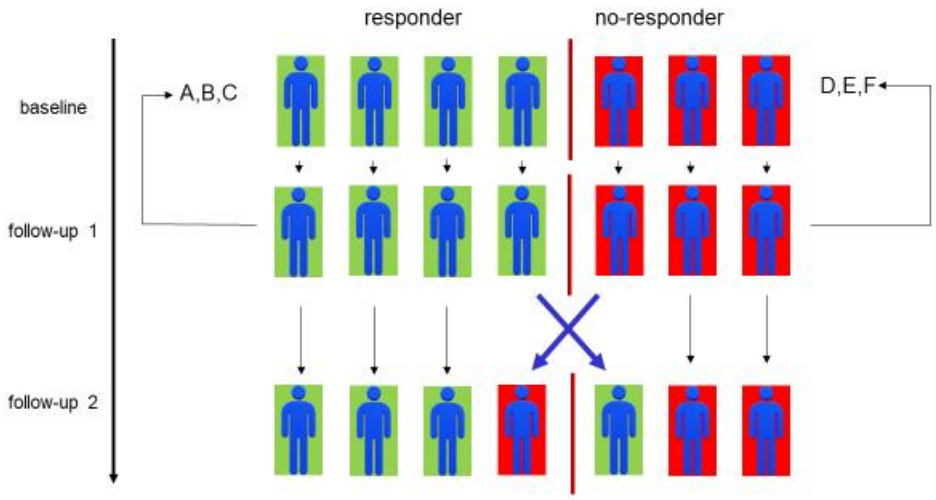
Predictive biomarkers to cover inter-individual heterogeneity in treatment response

Inter-individual heterogeneity in treatment response is a common phenomenon in clinical trials and practise that is not limited to Nephrology. The typical way to develop predictive biomarkers to tackle this problem is to define a „responder" and a „no-responder" group after completion of a trial. The allocation of participants to one group is obvious with discrete but more difficult with continuous endpoints (like decline in eGFR) as the latter mandates an often rather arbitrary cut-off definition. Next, we differentiate both groups via characteristics (i.e. biomarkers) present at baseline (post-hoc analysis). Unfortunately, a perfect separation is often not possible due to overlap resulting again in probabilistic statements. To improve accuracy the number of biomarkers analysed can be increased ("omics" screening) and advanced statistical or machine-learning techniques aim for novel discrimination-models. Within the EU project SYSKID we made some interesting observations in this respect (although in the field of prognosis). In early stages of DKD (eGFR >60 ml/min/1.73m2) prediction of the individual progression of the disease using clinical biomarkers showed limited accuracy with only marginal improvement when carefully selected molecular biomarkers associated with pathophysiology were added (Mayer G; Diabetes Care 2017; 40:391). In another study performed within Innovative Medicine Initiative Project Beat-DKD, the biomarker panel was extended massively, but the gain obtained in discrimination again was marginal (Kammer M; Kidney Int 2019; 96:138). Interestingly, within the SYSKID project the results were significantly better in patients with an eGFR <60 ml/min/1.73m^2. One possible interpretation is that progression is more homogenous in advanced kidney disease. An interesting question in this context is whether these findings imply that the pathophysiology of the disease becomes more homogeneous as the diseases progresses as this should also reduce heterogeneity in treatment response.

Intra-individual variability in progression of DKD: Implication for analysis strategies to define prognostic and predictive biomarkers

All approaches discussed aim at providing a better resolution of inter-individual heterogeneity of progression/response to therapy in DKD but rely on the concept of intra-individual stability of the disease trajectory. Once defined adequately the individuals allocated to the "responder" and "no-responder" group remain within their stratum over time. Figure 2 details a different scenario.

Figure 2:

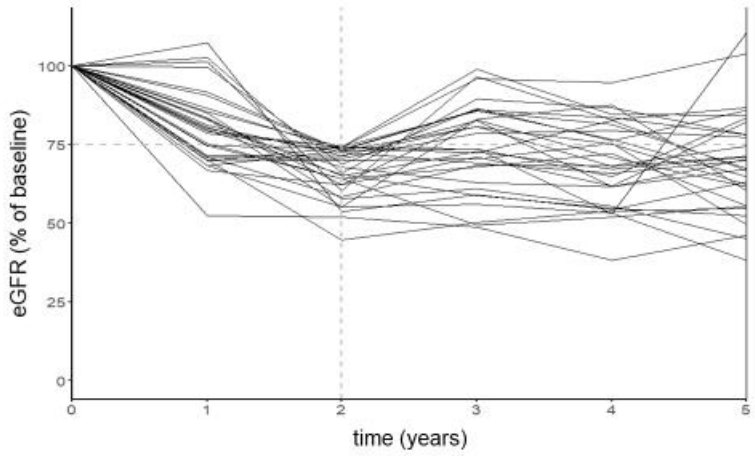


„Responder“ and „no-responder“ groups are identified based on data obtained at follow-up 1; subsequently a classifier is derived from baseline data that allows a perfect separation of both groups (“responders” have biomarkers A, B and C, “no-responders” D, E and F). Now we assume that the individual disease trajectories change at follow-up 2, “responders” become “no-responder” and vice versa. Clearly, a classifier that works at follow up 1 loses discriminatory power at follow up 2.

Is there evidence for significant intra-individual instability of eGFR trajectories in CKD/DKD? Let us assume Mr. M attends the outpatient clinic. He is 60 years old and has a 15-year history of T2DM and hypertension. His albuminuria is 400 mg/day and his eGFR has decreased from 80 to 56 ml/min/1.73m^2 within the past two years. The patient asks you whether he will soon need dialysis. The „KDIGO Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (CKD)” (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group Kidney Int Suppl 2013; 3: 1) contain a heatmap with stages of CKD and risk according to eGFR and albuminuria. Mr. M allocates to stage G3a/A3 and has a 147-fold risk increase of developing end stage renal disease when compared to the reference cohort (stage G1 and G2/A1, i.e. eGFR > 60 ml/min/173m^2 and albuminuria < 30 mg/day). To be more specific, it may be useful to gain additional information from former laboratory values of the patient. We notice that the eGFR decreased by 30% (or 24 ml/min/1.73m^2) within the last 24 months. In 1996 Nelson et al. published a figure showing that in PIMA Indians in albuminuria stage A3 eGFR decreases in a straight linear fashion (Nelson RG; N Engl J Med 1996; 335:1636). If we apply this observation to Mr. M he will require dialysis in approximately four years (projected eGFR 8

ml/min/1.73m^2). To double-check we also consult a paper by Coresh et al. (Coresh J; JAMA 2014; 311:2518) and are surprised. Given a 30% decrease of eGFR within two years and a baseline eGFR of 80 ml/min/173m2, the authors observed in a very large cohort an adjusted average 5-year absolute risk of end stage renal failure of only 1%. Even after adjustment for the competing risk of death, this number is much lower than initially predicted. Importantly this cannot be due to inter-individual variability only as Coresh et al. observed this risk in individuals first defined by a stable and homogenous progression of a 30% eGFR decline during a two-year period. Obviously, the course of the disease changed in many individuals thereafter to a non-linear pattern and all issues outlined in Figure 2 suddenly apply.
Based on the paper by Coresh we cannot rule out that intra-individual variability is caused by changes in therapy, as there is no information provided. So, do we have data on the eGFR trajectory in DKD on stable medication? Kröpelin et al. described changes in proteinuria over time in DKD cohorts receiving a stable angiotensin-receptor blocker (ARB) therapy within the RENAAL and IDNT trials (Kröpelin F; Nephrol Dial Transplant 2016; 31:1471). After treatment was initiated, proteinuria decreased by 30% in 36% of patients. In these individuals, proteinuria further decreased in 44%, remained stable in 32% and increased again in 24%. A similar longitudinal variability was noted in patients with an increase in albuminuria within the first six months. Figure 3 shows unpublished data derived from a longitudinal observational study in patients with T2DM (PROVALID).

Figure 3:



Selected patients had to be on stable therapy over five consecutive years and among them we identified those, who experienced an eGFR decline of at least 25% within the first two years (a certain drop in eGFR according to the KDIGO guidelines) to separate “responders” from “no-responders”. As can be seen the eGFR trajectories over the following years (take

note: therapy remained unchanged) in some of the “no-responder” patients eGFR continues to decline or remains at least 25% lower than the baseline value; in others, however, eGFR increases after year 2 and these patients would then be allocated to the responder group. Any model for the prediction of progression/treatment response, which was built on baseline data and 2 year follow up data thus would lose accuracy thereafter.

Conclusion and perspective

The progression trajectories of patients with chronic kidney disease such as DKD show marked inter-individual variability, even under stable therapy and the development of reliable biomarkers to identify subgroups with good or insufficient response is a strong clinical need. Extensive patient profiling by modern “omics” technologies, especially when combined with novel statistical tools has added precision to our predictions but there still is ample room for improvement. We believe that hitherto too little attention has been payed to the problem of intra-individual longitudinal variability of eGFR. To advance we need alternative analytical concepts to cover both aspects of heterogeneity. Systems theory allows to model dynamic systems and DC-REN, a recently initiated Horizon 2020 project, aims to introduce these methods to medicine and uses DKD as a prototypical disease.

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