



Paving the way to precision medicine for diabetic kidney disease: the PRIORITY trial

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Introduction

Diabetic kidney disease (DKD) is a common complication of both type 1 (T1D) and type 2 diabetes (T2D) (1). It is the leading cause of chronic kidney disease (CKD) worldwide and may result in end stage kidney disease requiring renal replacement therapy, either dialysis or kidney transplant. DKD is also associated with adverse cardiovascular (CV) outcomes and increased risk for mortality (2). However, many patients with diabetes do not develop advanced DKD even after prolonged follow-up and their response to different treatments may vary (3).

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are the mainstay therapy of DKD, however their efficacy in preventing end-stage renal disease is far from complete (4). More recently other treatments have been shown to protect the diabetic kidney, such as sodium-glucose cotransporter-2 inhibitors (SGLT2i) (5,6), mineralocorticoid receptor antagonists (MRAs) (7-9), endothelin receptor antagonists (ERAs) (10) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (11). Ideally, drugs should only be prescribed to patients who will benefit from treatment, and avoid unnecessary prescription to low-risk populations. This requires sensitive biomarkers that can accurately predict the onset of DKD and the subsequent response to treatment.

Increased urinary albumin to creatinine ratio (UACR),

which results from hyperfiltration and glomerulopathy, is considered an early marker of DKD. Nonetheless, 40–70% of patients may develop renal dysfunction without preceding albuminuria (12), and not all microalbuminuric patients progress to renal failure, suggesting the presence of large heterogeneity in the pathophysiology and course of DKD (13). The lack of sensitive and specific diagnostic tools for risk stratification limits personal tailoring of treatment, i.e., precision medicine.

CKD273 classifier is a urine proteomic quantitative marker based on a combination of 273 different peptides measured by capillary electrophoresis-mass spectrometry (CE-MS). It was developed and validated using urinary samples obtained from a large multinational cohort of 3,600 individuals. Analysis of urinary protein excretion using this platform effectively differentiated subjects with CKD of various etiologies from healthy controls, with a reported area under the curve (AUC) of 0.955 (14). Follow-up studies examined the predictive strength of CKD273 in different cross-sectional and longitudinal cohorts investigating renal outcomes. Importantly, increased CKD273 preceded the appearance of microalbuminuria by approximately 3.5 years. Urinary proteomic signature was also proposed to serve as a “liquid biopsy”. Preliminary analyses showed that it can discriminate between various CKD etiologies and correlate with the severity of fibrosis detected in kidney biopsies.

A more in depth review on CKD273 has been recently published (15).

The PRIORITY (Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention Of Early Diabetic nephropathy In Type 2 Diabetic Patients With Normoalbuminuria; NCT02040441) trial investigated the efficacy of CKD273 in predicting the development of DKD in a prospective cohort. It also studied the effects of treatment with the MRA spironolactone on the development of microalbuminuria in high-risk patients according to CKD273.

PRIORITY trial: design and main findings

PRIORITY was a multinational prospective two part study: observational and interventional (16). Patients (N=1,775) with T2D, normoalbuminuria: UACR <30 mg/g and estimated Glomerular Filtration Rate (eGFR) >45 mL/min/1.73 m² were stratified to high- and low-renal risk according to a pre-specified single value of the CKD273 classifier. High-risk patients (CKD273 >0.154) were randomized to receive either low-dose spironolactone (25 mg; n=102) or placebo (n=107) in a double-blind manner. The primary endpoint was the development of confirmed microalbuminuria in the observational cohort (high vs. low risk). The main secondary objective of the trial was to assess spironolactone's effect on the rate of appearance of microalbuminuria (intervention cohort).

After a median follow-up of 2.5 (IQR, 2.0–3.0) years, patients classified as high-risk by CKD273 were more likely to achieve the primary outcome of confirmed microalbuminuria (HR =3.92), even after adjusting for baseline risk markers (age, sex, HbA1c, systolic blood pressure, retinopathy, UACR and eGFR; HR =2.48). They also showed higher risk for some of the other pre-specified secondary renal parameters: occurrence of a single measurement of microalbuminuria, eGFR reduction of >40%, new CKD stage 3 or new CKD stage 4. Interestingly, high risk classification by CKD273 seemed to be associated with worse CV outcomes, albeit without reaching statistical significance. The authors also calculated the additive predictive accuracy of the CKD273 classifier for microalbuminuria. Receiver operator characteristic curve (ROC) for known baseline risk markers detailed above yielded an AUC of 0.76, which was increased to 0.78 by adding the CKD273. The difference was statistically significant (P=0.004), however the magnitude of the effect was modest.

Spironolactone failed to significantly improve the rate of

new microalbuminuria in the intervention group. On the contrary, treatment was associated with increased risk for development of CKD stage 3, and significant hyperkalemia and gynecomastia.

CKD273 classifier for risk stratification of DKD: advances and limitations

PRIORITY is the first prospective multicenter trial verifying the predictive value of CKD273 for microalbuminuria in a cohort of patients with T2D and normoalbuminuria. Previous studies testing the accuracy of the assay and its use for prediction of DKD were all performed on retrospective cohorts, which might lead to biases in the interpretation of the data. The demonstration that CKD273 can reliably predict the development of DKD in a large prospective trial is a major achievement and an important step towards better stratification of DKD risk that will eventually enable making more precise clinical decisions as to treatment. There are several issues, however, that should be addressed before such an assay can be implemented in clinical practice.

The accuracy of a given biomarker depends greatly on the population tested, the selected cut-off, and the reliability of the test. All these factors should be integrated into a framework of pre- and post-test probability. In PRIORITY, patients classified as high risk by CKD273 had almost four times increased risk to develop new microalbuminuria. Yet, the sensitivity of the test was still low, with the majority (~70%) of patients in the high-risk group not progressing to albuminuria within the time frame of the study. Of note, 9% and 8% of the low-risk patients developed microalbuminuria and impaired renal function (eGFR <60 mL/min/1.73 m²), indicating that at this stage, the negative predictive value of the assay is still not sufficiently high to exclude future development of DKD. It is possible, nonetheless, that longer, register-based follow-up of PRIORITY population, as planned by the investigators, may result in better separation between the groups.

Adding CKD273 to baseline clinical characteristics enabled better prediction of future development of microalbuminuria, however the difference in the AUC of the ROC analysis was small, and the clinical significance of this small increment is questionable. The apparent small increase in DKD prediction with CKD273 compared to clinical assessment alone may be due to the unique design of the trial, which combined observational and interventional investigations within the same period.

Consequently, patients and caregivers were not blinded to results of the CKD273 test; this may have led to more rigorous treatment of the patients that were classified as high-risk. Furthermore, compared to the low-risk group, more patients in the high-risk group were given ACEi/ARBs (87% *vs.* 61%) at baseline by their treating physicians. Of note, it has been previously suggested that treatment with ACEi may increase CKD273 values (17). Previous studies provided some information on the validity and reproducibility of CKD273 (17), this however was not assessed in the clinical setup of PRIORITY. Further studies are required to address these issues.

At this stage, the availability of CKD273 is limited as it is performed in only three laboratories worldwide. Furthermore, the analysis is expensive (each test costs ~850€). Nevertheless, one can envision that further improvements of the accuracy of the assay, along with price reduction, will render the assay cost-effective, as early targeted treatment to high-risk patients may reduce future expenditures.

Spirolactone for primary prevention of DKD

In its second intervention part, PRIORITY investigated the effect of early spironolactone treatment to patients classified as high-risk by CKD273. The lack of statistically significant effect of spironolactone on the occurrence of new confirmed microalbuminuria can be attributed to the study being underpowered—identifying a smaller number of “high-risk”, randomized patients (12.1%) than initially expected (15%) or following them for a too short duration.

Another explanation is the high dropout rate in the spironolactone group (25%) compared with placebo (9%) due to side-effects, such as hyperkalemia and gynecomastia. In addition, treatment with spironolactone was associated with occurrence of new CKD stage 3 (eGFR <60 mL/min/1.73 m²; 32% *vs.* 14%). This may result from the hemodynamic effects of Renin Angiotensin Aldosterone System (RAAS) pathway inhibition; nevertheless, this finding is worrisome, considering the fact that reduced renal function is associated with increased risk for mortality (2).

MRAs improve UACR in patients with T2D and albuminuria on top of ACEi/ARBs, but an effect on eGFR is lacking (8). Similar findings were observed with finerenone, a third generation non-steroidal and more selective MRA that is associated with lower risk of hyperkalemia and sex-hormone associated side effects (7). Finerenone’s CV and renal efficacy is currently being investigated in large populations of

patients with DKD (FIGARO-DKD and FIDELIO-DKD trials, respectively) (9). Further studies are required to assess whether early treatment with spironolactone and newer MRAs may prevent the development of microalbuminuria and/or advanced renal failure.

Precision medicine in DKD: future perspective

In recent years, several biomarkers have emerged as possible candidates to assist in the management of patients with T2D at risk for DKD. Such markers are based on differential expression of proteins, mRNAs and metabolites in blood or urine samples [reviewed in (18)]. In *Table 1* we suggest a scheme that can be useful for systemic assessment of such biomarkers, and apply it to CKD273 in the context of PRIORITY.

Besides predicting outcome, such biomarkers may provide information as to disease course and pathophysiology. Many of the CKD273 peptides are associated with fibrosis, such as collagen fragments and extracellular matrix proteins. Interestingly, several studies indicated that renal protective therapies may normalize urinary proteomic signature, suggesting that fibrotic changes are reversible in early stages of DKD (15).

Sophisticated markers are sometimes used to predict the responses to various treatments. In DKD, however, such personal tailoring has been limited so far, due to both shortage in good treatment possibilities and suitable diagnostic tests. In recent years new therapies for DKD have emerged (5-10,13,19). Remarkably, SGLT2i have been recently recommended by the American Diabetes Association (ADA) as the drug of choice for most patients with diabetes and renal risk (20). SGLT2i have been shown to consistently exert robust renal protective effects in different stages of DKD, including patients with normal UACR and eGFR (5,6,19). It will be interesting to study whether CKD273 can predict the response to treatment in patients who are at risk to develop DKD, as well as in patients with established DKD.

PRIORITY is an important first step towards a new era of precision medicine in DKD, however further improvements in the predictive power of the assay are required before it can be clinically used to stratify the patient’s risk and direct clinicians as to the choice of treatment. Integrating clinical parameters, along with proteomic-based analyses, such as CKD273 and probably additional large-scale genetic and metabolomic assays will eventually pave the way for precision medicine for DKD

Table 1 A systemic assessment of diagnostic tools aid in achieving precise medical management: PRIORITY trial and CKD273 biomarker as prototypes

	Criterion	Examples from PRIORITY and other studies with CKD273
Precision	Populations and settings	PRIORITY studied patients with T2D, normoalbuminuria (UACR <30 mg/g) and eGFR >45 mL/min/1.73 m ² and explored whether CKD273 marker can predict risk for new persistent albuminuria. Others investigated the diagnostic utility of CKD273 in different DKD stages and in patients with non-diabetic CKD, including its ability to serve as a non-invasive substitute for kidney biopsy (15)
	Reliability	Baseline CKD273 was tested once in PRIORITY. Previous analysis of a small cohort showed relatively low inter- and intra-assay standard deviation (below 10%), as well as low inter-laboratory variability (rank correlation coefficients between three labs of 0.881–0.904). Acute nephrolithiasis and to some extent ACEi treatment were associated with positive CKD273 results (37% and 9% respectively) (15,17)
	Improved specificity and sensitivity	In PRIORITY, CKD273 statistically improved prediction of new onset albuminuria, on top of a predictive model composed of other baseline markers (AUC =0.78 vs. 0.76), resulting in sensitivity of 30.5%, specificity of 90.2% and positive predictive value of 28.2%
Availability	Widely distributed technology and know-how	CKD273 requires sophisticated infrastructure, currently employed in three laboratories worldwide (16)
	Cost effective	CKD273 test is costly (~850€) (16). Cost-effectiveness analysis on hypothetical cohorts showed that although CKD273 is costlier than UACR, its use may result in more quality-adjusted life years when applied to high-risk populations (15). PRIORITY's data can be utilized to further address this issue on real life cohorts
Outcome	Predicts patient's outcome	PRIORITY has proven that CKD273 predicts occurrence of new onset albuminuria in its settings. Increased CKD273 was also associated with a decline in kidney function, and with non-significant trends towards worse CV outcomes
	Follow-up and re-evaluation by sequential testing	Small studies indicated that urinary proteome in patient with diabetes is affected by renal protective therapies (irbesartan or empagliflozin), indicating reversibility of fibrotic changes in DKD. Similar findings were observed in some patients with non-diabetic CKD (15). In PRIORITY, CKD273 was reported only at baseline
	Provides pathophysiological insights	Urinary proteomic signatures implicated several proteins and processes in DKD pathology, e.g., collagen fragments, tubuli-originated uromodulin, α 1-antitrypsin, clusterin and more (14,15). Further analysis of PRIORITY data that combines proteomic analysis with high quality follow-up is expected to expand our understanding of DKD's pathophysiology
	Predicts response to specific drug	In a small trial CKD273 was found to predict the reduction in albuminuria as a response to spironolactone (15). Exploratory analysis of PRIORITY data, and possibly future studies, can test other renal protective drugs
	Affects clinical management and outcome	This is the main secondary objective of PRIORITY. Spironolactone treatment for patients with high baseline CKD273 did not reduce the occurrence of microalbuminuria, but was associated with high adverse-events related dropouts. Nonetheless, further investigation is warranted with new renal protective possibilities

and probably also for non-DKDs.

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