Diabetic Kidney Disease

What We Knew, What We Know, and What We Still Do Not Know

By Lidia Anguiano and Hans-Joachim Anders

What we knew

The epidemic increase in the prevalence of diabetes mellitus (DM) has led to an increase in the incidence and prevalence of DM-associated complications, including diabetic kidney disease (DKD). Two major concerns in DKD are progression to ESKD and the high risk for cardiovascular morbidity and mortality. Treatments based on inhibition of the renin angiotensin system (RAS) alone have significant effects on microalbuminuria, an early marker of vascular dysfunction, but not necessarily of progressive DKD (1). Indeed, RAS inhibitors can reduce the rates of cardiovascular morbidity and mortality (2).

Regarding chronic kidney disease (CKD) progression, bardoxolone methyl showed promising results but increased the incidence of heart failure in the phase 3 trial, so the sponsor stopped the DKD program (3). Over the years, preclinical studies in animal models of DKD have predicted numerous targets for therapy outside the renin-angiotensin-aldosterone axis, but most have failed in subsequent randomized clinical trials in humans or have shown only mild effects on urinary albumin excretion (4). Retarding the progression of DKD to ESKD had remained an unsolved, unmet medical need until recently.

What we know

Recently, inhibition of sodium-glucose co-transporter 2 (SGLT-2) showed combined effects on cardiovascular and renal outcomes in DKD patients. The EMPA-REG OUTCOME trial showed unexpected and significant renoprotective effects of a combination of RAS inhibitors with empagliflozin, although the trial was not specifically designed to test kidney endpoints (5). This renoprotective effect was associated with strongly reduced fatal cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke (6). These results were recently replicated in the CREDENCE study for canagliflozin, a trial whose primary composite endpoint was ESKD, doubling of serum creatinine level, or death of renal or cardiovascular causes (7).

Other upcoming compounds include dipeptidyl peptidase 4 inhibitors and glucagon-like peptide-1 agonists, which were shown to improve glycemic control and lower the rates of macroalbuminuria, and also to lower the risk of cardiovascular outcomes (8, 9) but at a lower effect size than SGLT-2 inhibitors. Other agents, such as protein kinase Cβ inhibitors, Janus kinase 1 and 2 inhibitors, and endothelin A receptor antagonists are still under study in patients with diabetes, either because there is no available phase 3 clinical trial or because adverse effects were observed.

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Recently, the “omics” techniques have become powerful tools for the identification of new potential biomarkers of DKD progression. Genome-wide association studies allow for the identification of genetic variants influencing DKD predisposition, which could help with the characterization of the biology basis of DKD. Two recent studies using proteome analysis (proteomics) (10) and metabolites analysis (metabolomics) (11) have taken a systematic approach to the identification and quantification of urinary proteins and metabolites.

**What we do not know**

The profound renoprotective effects of dual RAS inhibition with SGLT-2 inhibition in DKD raise the question whether these effects can be replicated also in non-DKD, a question currently under study. The prospects of a potentially wider use of SGLT-2 inhibitors raise the question about their safety profile. Genital infections, urinary tract infection, ketacon- dosis, pyelonephritis, bone fractures, and lower-limb amputation for gangrene have inconstantly been reported across trials of SGLT-2 inhibitors, but the related concerns affect their implementation into clinical practice (5, 7).

The renoprotective effects of SGLT-2 inhibitors come as a breakthrough not only from a clinical perspective but also because they warrant a new paradigm in the understanding of DKD pathophysiology. The previous “glomerulocentric” view of DKD was largely driven by the idea that RAS inhibitors reduce proteinuria by decreasing glomerular afterload, which was obviously insufficient to significantly affect DKD progression. With SGLT-2 inhibitors, the focus now moves to the proximal tubule as the primary driver of DKD. The SGLT-2-driven resupply of filtered glucose and sodium in the proximal tubule is massively increased by glucose filtration in DM, which, as a consequence, permanently inhibits the tubuloglomerular feedback and by diluting the afferent arteriole drives persistent glomerular hyperfiltration. Only dual RAS inhibition with SGLT-2 inhibition seems to correct glomerular hemodynamics; hence, GFR initially drops when SGLT-2 inhibitors are started (5). However, other mechanisms of action may apply, such as reducing tubular reabsorption load and hence tubular “stress,” a diuretic effect that improves cardiac preload. Furthermore, it has been pos-

tulated that the natriuresis that occurs in SGLT-2 inhibition is promoted by the downregulation of Na+/H+ exchanger 3 (NHE3), which may serve as an additional mechanism to restore whole-body sodium homeostasis and reduce cardiac failure (12). SGLT-2 inhibitors are also known to increase the production of ketone levels, which seems to arise from an effort to raise glucagon levels and through a reduction in ketone body excretion through the kidneys. It has been suggested that ketone bodies are oxidized by the heart in preference to glucose and that this leads to an improvement of cardiac function in the failing heart. Another proposed mechanism of action is that increased ketone levels are associated with inhibition of histone deacetylase, which may prevent prohypertrophic transcription pathways (12).

Another unsolved issue is the potential clinical use of the upcoming “omics” data. Which of these markers could outweigh the current albuminuria/eGFR-driven approach at affordable costs remains to be worked out in the future. Finally, the gap between the design of preclinical studies versus clinical trials has remained a major hurdle for translational research and drug development programs. Overcoming this hurdle with animal models that more closely mimic the characteristics of the target population, concomitant, and mirroring the design and endpoints of randomized clinical trials in preclinical animal studies should be possible, but these issues have not yet been rigorously addressed. Lluka Anguiano, PhD, and Hans-Joachim Anders, MD, are in the renal division of the Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Germany.

**References**


**Clinical Trials on Diabetic Kidney Disease:**

**What Have We Learned from Landmark Trials?**

By Vecchi Batuman

In the era of evidence-based medicine, high-quality clinical trials are the key to the development of sound practice guidelines. Many landmark trials have enabled us to make significant progress in our approach to diabetic nephropathy, the leading cause of ESRD worldwide, although we are still short of a cure. The two enduring lessons learned from these trials are that glucose control and BP control by renin-angiotensin-aldosterone system (RAAS) antagonists help reduce the risk of diabetic kidney disease but do not entirely prevent it. The main trials that constitute the basis of this dual approach are briefly discussed here, along with a table summarizing the key findings extracted from them (Table 1).

Although the pathophysiology of diabetes is complex, the main factor responsible for kidney and eye damage is glucose toxicity. So, intuitively one would expect that glucose control should make a difference.

Both the Diabetes Control and Complications Trial (DCCT), conducted from 1983 to 1993, and the follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), showed that “intensive control” of hyperglycemia (achieving hemoglobin A1c (HbA1c) <7%) is effective in reducing the microvascular complications of dia-

**References**