Diabetic Kidney Disease

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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 biologic basis of DKD. Traditional techniques such as protein 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, ketoadiposis, pyelonephritis, bone fractures, and lower-limb amputation for gangrene have incorrectly 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 “glomerulosentric” 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 respite of filtered glucose and sodium in the proximal tube is massively increased by glucose filtration in DM, which, as a consequence, permanently inhibits the tubuloglomerular feedback and by diluting theafferent arteriole drives persistent glomerular hyperfiltration. Only dual RAS inhibition with SGLT2 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 posulated that the natriuresis that occurs in SGLT-2 inhibition is promoted by the downregulation of Na+/H+ exchanger β isoforms, 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, concomitantly, 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.

Lida Anguiano, PhD, and Hans-Joachim Andre, MD, are in the renal division of the Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Germany.

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 ESKD 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 diabetes (1). The UK Prospective Diabetes Study (UKPDS), the largest prospective study of patients with newly diagnosed type 2 diabetes, showed similar beneficial effects. A summary review of the major glycemic control trials clearly shows that intensive control achieving an HbA1c level around 6.5% to 7% helps reduce the risk of albuminuria and kidney disease (2). For example, the ADVANCE trial, which enrolled over 11,000 patients with type 2 diabetes, showed that achieving an HbA1c level of 6.5% led to a reduction of approximately 20% in kidney disease (2, 3). By contrast, ACCORD, a similarly large trial, showed that more aggressive glucose control targeting an HbA1c level of 6% is not beneficial.

The landmark captopril trial published in 1993 (4) was the landmark captopril trial published in 1993 (4) was a breakthrough not only from a clinical perspective but also because it was shown that the use of SGLT2 inhibitors raises the question of their safety profile. Genital infections, urinary tract infection, ketoadiposis, pyelonephritis, bone fractures, and lower-limb amputation for gangrene have incorrectly 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 “glomerulosentric” 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 respite of filtered glucose and sodium in the proximal tube is massively increased by glucose filtration in DM, which, as a consequence, permanently inhibits the tubuloglomerular feedback and by diluting theafferent arteriole drives persistent glomerular hyperfiltration. Only dual RAS inhibition with SGLT2 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 posulated that the natriuresis that occurs in SGLT-2 inhibition is promoted by the downregulation of Na+/H+ exchanger β isoforms, 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).

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The landmark captopril trial published in 1993 (4) was
followed by many others that confirmed the beneficial effects of both the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the course of diabetic nephropathy (Table 1). Thus, based on the lesson learned from these landmark trials the antiangiotensin strategy became the standard of care in patients with both type 1 and type 2 diabetes with kidney disease. It seemed intuitive that by combining angiotensin-converting enzyme inhibitors with angiotensin receptor blockers we might achieve more effective renoprotection, but we learned from the ONTAR-GET and NEPHRON-D studies that this approach was not viable because of the increased risk of adverse events, including worse renal outcomes (5).

Thus, the combined strategy of intensive glycemic control and blood pressure control by the use of RAAS antagonists offered hope to patients with diabetes and seemed successful—most trials showed a marked decrease in proteinuria and a slower progression of kidney disease. Still, diabetic nephropathy remains the most common cause of ESKD, both in the United States and worldwide. Why? Did we hit a wall with this strategy? Searching for alternative or complementary approaches, other trials using a direct renin antagonist, an antioxidant (bardoxolone), and an endothelin type A receptor antagonist were disappointing and, in fact, yielded adverse outcomes (Table 1).

Medical care has improved much and is organized better since the publication of these landmark trials, and these strategies are now available to larger populations of individuals with diabetes and kidney disease. We are far better at achieving simultaneously better glycemic control and BP

### Table 1. Selected landmark clinical trials on diabetic nephropathy

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Number, diagnosis</th>
<th>Follow-up</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT, 1993 (2)</td>
<td>1441, T1DM</td>
<td>6.5 years</td>
<td>Intensive vs. standard glycemic control</td>
<td>Intensive glycemic control (HbA1c 7.3% vs. 9.1%) reduced incidence of micro- and macroalbuminuria by 39% and 54%.</td>
</tr>
<tr>
<td>EDIC/DCCT, 2014 (3)</td>
<td>1441, T1DM</td>
<td>18 years</td>
<td>Intensive vs. standard glycemic control</td>
<td>Renoprotective effect of intensive control persisted and resulted in 45% reduction in risk of microalbuminuria at 18 years.</td>
</tr>
<tr>
<td>UKPDS, 1998 (4)</td>
<td>3867, T2DM</td>
<td>10 years</td>
<td>Intensive vs. standard glycemic control</td>
<td>Intensive glycemic control vs. standard control (HbA1c 7.0% vs. 7.3%) reduced risk of microalbuminuria by 33%.</td>
</tr>
<tr>
<td>ADVANCE, 2013 (5)</td>
<td>11,140, T2DM</td>
<td>5 years</td>
<td>Intensive vs. standard glycemic control</td>
<td>Intensive glycemic control (HbA1c 6.5% vs. 7.3%) reduced risk of micro-, macroalbuminuria, and ESKD by 9%, 30%, and 65%; for those with macroalbuminuria, number needed to treat to prevent one ESKD was 41.</td>
</tr>
<tr>
<td>ACCORD, 2008 (6)</td>
<td>10,251, T2DM</td>
<td>Terminated at 3.5 years</td>
<td>Intensive vs. standard glycemic control</td>
<td>Targeting HbA1c 6.0 vs. 7.0%–7.9% resulted in excess mortality (HR 1.22; 95% CI 1.01–1.46; p = 0.04).</td>
</tr>
<tr>
<td>“Captopril” trial, 1993 (7)</td>
<td>409, IDDM</td>
<td>4 years</td>
<td>Captopril vs. placebo</td>
<td>Captopril slowed down progression of kidney disease in IDDM patients; captopril was more effective than BP control alone.</td>
</tr>
<tr>
<td>RENAAL, 2001 (8)</td>
<td>1513, T2DM</td>
<td>3.4 years</td>
<td>Losartan vs. placebo</td>
<td>Every 10 mm Hg systolic BP rise increased risk of ESKD or death by 6.7%; losartan decreased proteinuria by 35% (p &lt; 0.001); serum creatinine doubling risk was reduced by 25% (p = 0.006, and ESKD by 28% (p = 0.002).</td>
</tr>
<tr>
<td>IDNT, 2001 (9)</td>
<td>1715, T2DM</td>
<td>2.6 years</td>
<td>Irbesartan vs. amldipine vs. placebo</td>
<td>Irbesartan was renoprotective with lower risk of serum creatinine doubling (33%; p = 0.003) and ESKD (23%; p = 0.07) compared with amlodipine and placebo.</td>
</tr>
<tr>
<td>ROADMAP 2001 (10)</td>
<td>4447, T2DM</td>
<td>3.2 years</td>
<td>Olmesartan vs. placebo</td>
<td>Olmesartan reduced time to microalbuminuria onset, and BP control was similar in both arms.</td>
</tr>
<tr>
<td>ONTARGET, 2008 (11)</td>
<td>25,620, T1DM</td>
<td>55 months</td>
<td>Telmisartan/ramipril combo vs. telmisartan vs. ramipril</td>
<td>Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling, and death (HR 1.09; 95% CI 1.01–1.18; p = 0.037).</td>
</tr>
<tr>
<td>VA NEPHRON D, 2013 (12)</td>
<td>1448, T2DM</td>
<td>Terminated at 2.2 years</td>
<td>Losartan/irbesartan combination vs. losartan alone</td>
<td>Combination therapy offered no renal benefit but resulted in excessive risk of hyperkalemia and acute renal failure.</td>
</tr>
<tr>
<td>ALTITUDE, 2012 (13)</td>
<td>8561, T2DM</td>
<td>Terminated at 2.7 years</td>
<td>RAS blockade plus aliskiren vs. placebo</td>
<td>Addition of aliskiren to maximal ARB offered no additional benefit; hyperkalemia and hypotension were significantly increased in the aliskiren arm.</td>
</tr>
<tr>
<td>BEACON, 2011 (14)</td>
<td>2185, T2DM</td>
<td>Terminated at 9 months</td>
<td>Bardoxolone methyl vs. placebo</td>
<td>Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83, p = &lt; 0.001).</td>
</tr>
<tr>
<td>ASCEND, 2010 (15)</td>
<td>1392, T2DM</td>
<td>Terminated at 4 months</td>
<td>Avosentan vs. placebo</td>
<td>Avosentan reduced proteinuria compared with placebo, but had excess adverse cardiovascular events.</td>
</tr>
<tr>
<td>CREDENCE, 2019 (16)</td>
<td>4401, T2DM</td>
<td>Terminated at 2.6 years</td>
<td>Canagliflozin vs. placebo</td>
<td>Relative risk for renal events (doubling of creatinine or ESKD) was significantly lower in canagliflozin group.</td>
</tr>
</tbody>
</table>

*Table adapted from Chan GC and Tang SC. Diabetic nephropathy: Landmark clinical trials and tribulations. Nephrol Dial Transplant 2016; 31:359–368.*

**Abbreviations:** ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; ASCEND = A Study of Cardiovascular Events in Diabetes; BEACON = Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes; CI = confidence interval; CREDENCE = Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; HbA1C = hemoglobin A1c; HR = hazard ratio; IDDM = insulin-dependent diabetes mellitus; IDNT = Irbesartan Diabetic Nephropathy Trial; ONTARGET = ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint trial; RAS = renin-angiotensin system; RENAAL = Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan; ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention Study; TIDDM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; UKPDS = UK Prospective Diabetes Study; VA NEPHRON D = Veterans Affairs Nephropathy in Diabetes
control with the novel classes of antidiabetic drugs, including dipeptidyl peptidase-4 inhibitors, metformin, and most recently sodium glucose co-transporter 2 (SGLT-2) inhibitors, combined with anti-RAAS drugs. Although these agents are helpful in achieving better glycemic control, we do not yet have robust data on the benefits of the newer antidiabetic drugs on diabetic kidney disease, except for the SGLT-2 inhibitor canagliflozin. The CREDO trial, which included 4401 patients with type 2 diabetes, was terminated prematurely because the early data showed a clear benefit of canagliflozin on renal outcomes, including the doubling of serum creatinine or ESKD (6). The response from the medical community to the recently published results of this trial suggests that the use of SGLT-2 inhibitors may well rise to the level of standard of care in the treatment of patients at risk for diabetic nephropathy.

It could be argued that the landmark trials completed since the early 1990s have shown that the efforts to achieve optimal glucose control (i.e., HbA1c level of 6.5% to 7%; and optimal BP control, usually suggested as <130/80 mm Hg) with the use of RAAS antagonists are rewarded by favorable outcomes. Yet, both of these therapy targets remain controversial. The HbA1c levels may not always be accurate in different populations and may not be the best biomarker of glycemic control. More aggressive BP lowering (i.e., systolic pressure <120 mm Hg) may be better. But, to date, we do not have robust clinical trials to resolve these lingering questions.

Nevertheless, after a long and bumpy road, we have accumulated substantial evidence on which to base our current approach: to contain if not to fend off the diabetic nephropathy epidemic completely. Ongoing work suggests that among the newer antidiabetic agents, the SGLT-2 inhibitors may confer additional benefit for patients with diabetes who are at risk for microvascular complications. Clearly, much additional work is needed to curb the diabetic nephropathy epidemic.

Vecihi Batuman is with the department of internal medicine and chief, division of nephrology, at Tulane University.

References
6. Action to Control Cardiovascular Risk in Diabetes

Table References
2. Zoungas S, et al. Follow-up of blood-pressure lowe...
AURYXIA® (ferric citrate) is contraindicated in patients with iron overload syndromes. Overdosing of iron in pregnant women may carry a risk for adverse effects on the neonate. Overdosing of iron in pregnant women may carry a risk for adverse effects on the neonate. There is possible infant exposure when AURYXIA is taken by a nursing woman.

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- Monitor ferritin and transferrin saturation (TSAT). Patients may require a reduction in serum ferritin levels.

PREGNANCY AND LACTATION:
- Overdosing of iron in pregnant women may carry a risk for adverse effects on the neonate. Overdosing of iron in pregnant women may carry a risk for adverse effects on the neonate. There is possible infant exposure when AURYXIA is taken by a nursing woman.

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Rapid Growth in DKD Studies: Research Trends and Hotspots

If it seems like you’ve been seeing more published papers on diabetic kidney disease in recent years, you’re not mistaken. The number of DKD studies has risen rapidly and steadily over the past two decades, according to a review and meta-analysis published in the journal Medicine. And this study included a time period prior to the more recent spate of clinical trials.

More than 27,500 DKD papers were published from 2000 to 2017, reports the bibliometric analysis by Lu-Xi Zou, PhD, of Zhejiang University and Ling Sun, MD, of Xuzhou Central Hospital, China. Their open access study provides insights into “structure, hotspot, and evolution trends” in DKD research.

The systematic review identified a total of 27,577 DKD studies published between 2000 and 2017. The number of papers increased over time, with growth accelerating after 2007. Research papers accounted for nearly three-fourths of the total.

The top five journals publishing DKD papers were, in order, Nephrology Dialysis Transplantation, Kidney International, Diabetes, JASN, and Diabetologia. On analysis of co-citation networks, papers published in journals with higher impact factors had more citations and “greater influence in DKD research,” the authors write. Among the nephrology journals identified, JASN had the highest 5-year impact factor, followed closely by Kidney International.

“Diabetic kidney disease is a very important topic for JASN, and we are proud of the quality of research we are publishing on this critical public health issue,” said JASN Editor-in-Chief Josephine P. Briggs, MD.

The United States was the most productive country for DKD research, with 7100 publications. China was next, followed by Japan, Germany, and Italy. Analysis of country co-authorship showed very active networks of international collaboration in DKD research.

Harvard University was the top institutional producer of DKD research, followed by Steno Diabetes Center and University of Melbourne. Co-citation network analysis highlighted the contributions of H.H. Parving and colleagues during the study period—reflecting their studies establishing the renal and cardiovascular protective effects of renin angiotensin-aldosterone system blockade in patients with diabetes.

Drs. Zou and Sun discuss reasons for the burgeoning growth in DKD research, starting with the rising worldwide prevalence of diabetes. They also cite discoveries in histopathologic diagnosis, new therapeutic agents, and biomarkers, as well as the increasing ability to access and share massive volumes of medical data.
