SGLT-2 Inhibition: A Potential New Treatment for Diabetic Kidney Disease?

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Key Words

Diabetic nephropathy · Progression · Diabetes

Abstract

Diabetic nephropathy is the leading cause of kidney failure. Treatments with drugs that block the renin–angiotensin system have proven beneficial in slowing kidney disease progression among those with diabetes; their benefit is limited and they do not stop disease progression. Despite multiple clinical trials of various interventions including dual blockade of the renin–angiotensin system over the past 15 years, no new therapies have emerged to slow kidney disease progression in diabetes. SGLT-2 inhibitors are a new class of antihyperglycemic drugs that have been shown to lower blood glucose by inhibition of the sodium-glucose transporter 2 in the proximal tubule of the kidney. Several of these inhibitors have been marketed for treatment of hyperglycemia in patients with type 2 diabetes mellitus. In a recent double-blind randomized and placebo-controlled trial of cardiovascular outcomes, an SGLT-2 inhibitor-based intervention using empagliflozin was shown to be superior to placebo-based regimen for reducing the risk of major cardiovascular events among people with type 2 diabetes and established cardiovascular disease. In a pre-specified secondary analysis of renal outcomes from this trial, Wanner et al. [N Engl J Med 2016;375:323–334] recently reported that empagliflozin administration was also associated with significant reductions in the

progression of kidney disease including the rate of decline in estimated glomerular filtration rate (eGFR), progression of albuminuria and initiation of renal replacement therapy. While the results of this trial are striking and impressive, the majority of those enrolled in the trial did not have evidence of diabetic kidney disease as assessed by eGFR or albuminuria. Thus, whether or not they represent a breakthrough in the treatment of diabetic nephropathy remains to be determined. Several ongoing clinical trials are in the planning stages to evaluate SGLT-2 inhibition in a population of patients with overt kidney disease. These trials will help to substantiate, or not, the potential for this class of drugs to be added to the armamentarium of therapeutic strategies to prevent progression of kidney disease in diabetes. © 2017 S. Karger AG, Basel

The World Health Organization recently reported that the prevalence of diabetes worldwide in 2014 is 422 million, and this number is on the rise [1]. Diabetes is now recognized as the leading cause of kidney failure globally. It is insidious in onset; difficult to detect; is associated with increased cardiovascular morbidity and mortality; disproportionately afflicts African-Americans, Hispanics, Native Americans and Asian-Pacific islanders; and is incurable [2]. Treatment with anti-hyperglycemic drugs including insulin and oral hypoglycemic agents can control blood glucose and reduce the risk for kidney damage

Table 1. Risk comparison for renal outcomes

Renal outcome	Empagliflozin, n (%)	Placebo, n (%)	Hazards ratio (95% CI)	p value
Incident or worsening nephropathy or cardiovascular death	675/4,170 (16.2)	497/2,102 (23.6)	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4,124 (12.7)	388/2,061 (18.8)	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4,091 (11.2)	330/2,033 (16.2)	0.62 (0.54–0.72)	<0.001
Doubling Scr and eGFR <45 ml/min/1.73 m ²	70/4,645 (1.5)	60/2,323 (2.6)	0.56 (0.39–0.79)	<0.001
Initiation of renal replacement therapy	13/4,687 (0.3)	14/2,333 (0.6)	0.45 (0.21–0.97)	0.04
Doubling Scr and eGFR <45 ml/min/1.73 m ² and initiation of renal replacement therapy or death from renal disease	81/4,645 (1.7)	71/2,323 (3.1)	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1,430/2,779 (51.5)	703/1,374 (51.2)	0.95 (0.87–1.04)	0.25

Adapted from Wanner et al. [15].

[3]. There is a major unmet need in identifying new therapies that might slow down the progression of kidney disease in people with type 2 diabetes, beyond that afforded by angiotensin converting enzyme inhibitors and angiotensin receptor blockers [4–6]. Several studies utilizing various approaches including combinations of renin–angiotensin–aldosterone system blockade among other strategies have failed to demonstrate improvement in kidney disease outcomes among patients with diabetes and kidney disease [7–10]. Recently, drugs that inhibit the sodium–glucose transporter 2 in the proximal tubule of the kidney have been shown to safely and effectively lower blood glucose in hyperglycemic patients with type 2 diabetes mellitus, and have potential benefit for patients with kidney disease in this setting [11–13]. The purpose of this article is to review a recently published clinical trial focused on the potential beneficial renal effects of empagliflozin, an SGLT-2 inhibitor in patients with type 2 diabetes and established cardiovascular disease.

Wanner et al. [15] also reported the results of pre-specified secondary end point of microvascular outcomes from the international EMPA-REG outcome trial [14]. In this study patients with type 2 diabetes mellitus with established cardiovascular disease and an estimated glomerular filtration rate (eGFR) of ≥ 30 ml/min/1.73 m² were randomly assigned to empagliflozin 10 or 20 mg or placebo once daily. The composite secondary outcome in this analysis was defined as composite microvascular outcome that included the first occurrence of any of the following: the initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness or incident or worsening nephropathy. Incident or worsening nephropathy was defined as progression to macroalbumin-

uria (>300 mg albumin/g creatinine), doubling of serum creatinine (Scr) from baseline level (accompanied by an eGFR of ≤ 45 ml/min/1.73 m²), initiation of renal replacement therapy or death from renal disease. In addition, incident albuminuria defined as urine albumin creatinine ratio of ≥ 30 mg albumin/g creatinine in patients with baseline urine albumin/creatinine ratio <30 mg albumin/g creatinine was evaluated. Among 7,020 participants in the trial, about 18% had a baseline eGFR between 45 and 59 (chronic kidney disease (CKD) stage 3a) and about 8% had an eGFR between 30 and 44 (CKD stage 3b) and about one-thirds had microalbuminuria and 11% had macroalbuminuria (table 1). Importantly, at baseline, the vast majority of participants were taking drugs that block the renin–angiotensin system. They found that incident or worsening nephropathy occurred in about 13% of those assigned to empagliflozin and about 19% of those assigned to placebo. There was a 38% risk reduction for progression to macroalbuminuria and a 44% relative risk reduction in doubling of Scr in the empagliflozin group as compared to placebo. While the incidence of renal replacement initiation was <1% in both empagliflozin and placebo, there was a significant 55% relative risk reduction among those assigned to empagliflozin. However, they did not find a significant reduction in the incidence of albuminuria in those assigned to empagliflozin as compared to placebo. In addition, evaluation of eGFR over time demonstrated an initial significant decline in eGFR among those assigned to empagliflozin during the first 6 months, followed by stabilization. The initial decline in eGFR among those assigned to empagliflozin was completely reversed after cessation of the drug during the end of the trial. In contrast, eGFR de-

clined steadily in the placebo group so that mean eGFR was approximately 5 ml/min/1.73 m² higher among the empagliflozin as compared to the placebo group. The authors concluded that, in this patient population, empagliflozin in doses of 10 or 25 mg was associated with lower risk for progression of kidney disease as well as lower risk for progression to macroalbuminuria. The overall renal benefit included those with an eGFR ≥ 60 ml/min/1.73 m² as well as those with eGFR 30–59 ml/min/1.73 m² enrolled in the study. Furthermore, the composite outcome of incident nephropathy or death was lower in those assigned to empagliflozin. It should be noted that empagliflozin was associated with better glycemic control as well as both lower blood pressure and body weight as compared to placebo. Whether these factors are responsible for the better renal outcomes with empagliflozin cannot be determined from a clinical trial. However, it is intriguing to speculate that renal protection could have contributed to renal protection by the known effects of empagliflozin to reduce hyperfiltration and presumably glomerular pressure factors known to be associated with kidney disease progression [16, 17]. The finding that the initial reduction in mean eGFR among those assigned to empagliflozin is consistent with the known effect of blockade of the SGLT-2 to increase sodium delivery to the macula densa activating the tubuloglomerular feedback mechanism to increase afferent arteriolar tone and thereby reduce glomerular filtration rate [18, 19]. Regarding safety, they found a similar rate of adverse events with empagliflozin in those with or without reduced eGFR including genital infections.

It is important to point out that while these findings are impressive and suggest a potential role for empagliflozin in the treatment/prevention of progression of kidney disease in this population of type 2 diabetics, there are several reasons to be cautious. First, it is important to note that they represent secondary pre-specified end point from a cardiovascular outcomes trial. Whether

these findings would hold up in a study designed to evaluate renal outcomes as the primary event remains to be determined. Second, the event rates for doubling of Scr and initiation of renal replacement therapy were very low reflecting the fact that most patients had mild or no kidney disease at all. This is substantiated by the fact that less than one-third of the study cohort had an eGFR below 60 ml/min/1.73 m², and only slightly more than half of those had albuminuria at baseline, which is a known risk factor for kidney disease progression [20]. Among those with an eGFR of ≥ 60 ml/min/1.73 m², the incidence of albuminuria event was lower, namely, around 27%. In this regard, several ongoing clinical trials with primary renal outcomes may provide supportive data. Third, as noted by the authors, their findings may not be generalizable to those diabetes and low cardiovascular risk or to blacks, given the low enrollment (5.1% of total study population). Finally, it is unclear why empagliflozin did not reduce incident albuminuria among those with normoalbuminuria at baseline. As one mechanism for albuminuria in diabetes is believed to be glomerular hypertension, one would have expected that the decrease in eGFR early on and maintained over time would have translated to a decrease in glomerular leak of albuminuria if glomerular hypertension were indeed the mechanism.

Overall, the results of the ‘Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes’ study are impressive and should give hope to physicians and their patients. However, it is too soon to conclude that empagliflozin should be routinely prescribed to slow down the progression of kidney disease among patients with diabetes at high cardiovascular risk. Additional studies including clinical trials specifically designed to evaluate kidney outcomes in those with established CKD are needed. A large-scale outcomes study involving another SGLT-2 inhibitor, dapagliflozin, in people with CKD is in the developmental phase and the results of such a study will help to substantiate, or not, the findings from empagliflozin.

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