Dapagliflozin Does Not Impact Renal Function in Patients with Type 2 Diabetes

Written by ***Maria Vinall***

Treatment with dapagliflozin (DAPA) is not associated with an increased risk of acute renal toxicity or long-term deterioration of renal function in patients with type 2 diabetes mellitus (T2DM) according to the results of a pooled analysis of 12 studies [NCT00263276; NCT00972244; NCT00528372; NCT00736879; NCT00528879; NCT00855166; NCT00357370; NCT00680745; NCT00683878; NCT00673231; NCT00643851; NCT00859898]. The results were reported by Agata Ptaszynska, MD, Bristol-Myers Squibb, Princeton, New Jersey, USA.

The renal safety of DAPA is of special interest for 2 reasons: diabetic patients are at risk of nephropathy and urinary tract infections, and DAPA, a sodium-glucose cotransporter 2 inhibitor, decreases hyperglycemia by inhibiting renal glucose reabsorption. The purpose of this analysis was to assess the impact of DAPA on various aspect of renal function.

Adverse events (AEs) and laboratory test results were pooled from 12 Phase 2b/3 double-blind, placebo-controlled, randomized studies of T2DM patients receiving DAPA. Data were analyzed up to Week 24 (n=4545) for all 12 studies and beyond Week 24 (n=2854) for 6 of these 12 studies. DAPA 2.5-, 5-, and 10-mg/day doses were included in the analysis, but Dr. Ptaszynska focused on the more clinically significant 5- and 10-mg data. T2DM patients aged 18 to 79 years, body mass index ≤45 kg/m^2, and HbA1C from >6.5% to ≤12% were eligible for participation in the original studies.

Mean age of patients in the analysis was 55 years (56 years in the longer studies) and ~50% were women. Patients were Caucasian (~84%), African American (~3% total; ~10% of the US study population), Asian (~10%), and other (~3%). At baseline, mean duration of diabetes ranged from 3 to 4 years for patients in the short-term studies and slightly less than 6 years for those in long-term studies. Most patients (52.8% to 54.4%) had mild renal impairment and normal albuminuria values. Mean HbA1C was approximately 8.2% in both the short- and long-term studies.

At Week 1, estimated glomerular filtration rate (eGFR) decreased from baseline by –2.92 mL/min/1.73 m^2 (DAPA 5 mg) and –4.15 mL/min/1.73 m^2 (DAPA 10 mg) but returned to or above baseline by Week 24. There was no long-term effect on eGFR over 2 years. Modest decreases occurred in blood pressure, which were sustained over 102 weeks. Mean serum creatinine changed minimally from baseline to Week 24 and Week 102 in all groups. DAPA had no adverse effect on albuminuria through Week 102.

Renal AEs were similar between DAPA- and placebo-treated patients. Most events were transient changes in renal function measures. There were no reports of acute nephrotoxicity through 102 weeks and no AEs through impairment of other tubular functions (eg, regulation of electrolytes). Volume depletion events were uncommon and mild (mostly reported as nonserious AEs of hypotension). Urinary stones were reported more frequently among placebo patients. There were no changes in sodium potassium or calcium levels. Small increases were noted for magnesium and phosphorous.

In addition to not affecting renal function, DAPA was associated with improved glycemic control, reduced blood pressure, and reduced body weight; therefore, its use may support preservation of kidney function in patients with T2DM.

Population-Based Screening for Type 2 Diabetes: The ADDITION-Cambridge Trial

Written by ***Maria Vinall***

After completing a randomized controlled trial to examine the impact of a population-based diabetes screening program on mortality in England, Rebecca K. Simmons, PhD, Medical Research Council Epidemiology Unit, Cambridge, United Kingdom, concluded that screening for diabetes was not associated with a reduction in mortality and that the benefits of screening may be limited to those with detectable disease.

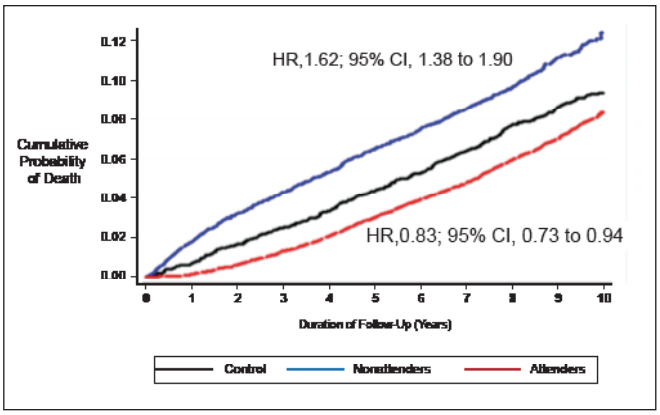
Although modeling studies suggest that screening might reduce diabetes-related mortality by 26% to 40% if conducted among middle-aged adults every 3 to 5 years, there was no evidence from randomized trials to confirm if these estimates are correct. The ADDITION-Cambridge cluster-randomized controlled trial was conducted to assess the impact of a population-based screening program on mortality among people at high risk of undiagnosed diabetes [Simmons RK et al. *Lancet* 2012].

The study population comprised 20,184 individuals aged 40 to 69 years, from 32 general practices in Eastern England, who were considered to be at high risk of diabetes based on a validated risk score that included age, sex, body mass index (BMI), and prescription of antihypertensive medication or steroids as criteria. Twenty-seven practices were cluster randomized to a screening group (comprised of 16,047 individuals) and 5 practices to a no-screening control group (4137 individuals). Both the patients and practitioners in the no-screening group were unaware of the patients' high-risk status. All participants were tagged for mortality at the Office for National Statistics and followed for 10 years. Screening included random capillary blood glucose and HbA1C tests, a fasting capillary test, and a confirmatory oral glucose tolerance test. The primary analysis was a comparison of all-cause mortality rates and cardiovascular, cancer, and diabetes-related mortality rates between the screening and control groups. Analysis was by intention to screen accounting for clustering.

Baseline practice characteristics (list size, mean diabetes prevalence, and mean index of multiple deprivation score) were similar between screening and no-screening groups. Mean age (58 years), percentage of male participants (64%), BMI (30.5 kg/m^2), and prescribed antihypertensives (45%) were also similar between groups.

Over a median of 9.6 years of follow-up, 15,089 (94%) of the 16,047 high-risk individuals in screening practices were invited for screening. In all, 11,737 (73.1%) attended and 466 (2.9%) were diagnosed with diabetes. A total of 4137 individuals were followed in the no-screening practices. There were no differences in mortality rates by study group (Table 1). The difference in the cumulative incidence of death between the groups over time was not significant (HR, 1.06; 95% CI, 0.90 to 1.25; p=0.46). Compared with the control group, screening attenders had lower mortality (HR, 0.83; 95% CI, 0.73 to 0.94) and non-attenders had a higher mortality (HR, 1.62; 95% CI, 1.38 to 1.90; Figure 1).

Figure 1. Cumulative Incidence of Death in Attenders, Nonattenders, and No-Screening Control Group.



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The investigators concluded that the benefits of screening for diabetes may have been overestimated and restricted to those found to have diabetes and treated early. The benefits of screening might be improved by the detection and management of related cardiovascular risk factors alongside assessment of diabetes risk, repeated rounds of screening, and the identification of non-attenders and strategies to maximize their utilization of screening.

Further reading: Simmons et al. *Lancet* 2012.

Table 1. Mortality Rate by Study Group.

Endpoint	Screening Group (Intervention)		No Screening Group (Control)		Hazard Ratio (95% CI)
	Number of Deaths	Rate per 1000 Person-years	Number of Deaths	Rate per 1000 Person-years	
All-cause mortality	1532	10.5	377	9.9	1.1 (0.9–1.3)
CVD mortality	482	3.3	124	3.3	1.0 (0.8–1.4)
Cancer mortality	697	4.8	169	4.4	1.1 (0.9–1.3)
Diabetes-related mortality	75	0.5	16	0.4	1.3 (0.8–2.1)