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Relook at DPP-4 inhibitors in the era of SGLT-2 inhibitors

Singh AK *et al*. DPP-4Is in SGLT-2Is era

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Abstract
SGLT-2 inhibitors (SGLT-2Is) have shown a significant improvement in cardio-renal outcomes and are preferred agents in people with cardiovascular diseases, heart failure, and diabetic kidney disease. However, the glucose-lowering potential of SGL-2Is gets compromised with a progressive decline in renal functions, unlike DPP-4 inhibitors (DPP-4Is). Notably, the glucose-lowering potential of DPP-4Is is nearly similar to SGLT-2Is and perhaps larger with a modest baseline HbA1c. Thus, the role of DPP-4Is in the management of type 2 diabetes mellitus cannot be ignored even in the era of SGLT-2Is.

Key Words: DPP-4 inhibitors; SGLT-2 inhibitors; GLP-1 receptor agonists; Cardiovascular outcomes; Renal outcomes

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Core Tip: Despite the newer anti-diabetic agents such as SGLT-2 inhibitors (SGLT-2Is) and GLP-1 receptor agonists (GLP-1RAs) having taken center-stage in the management of type 2 diabetes mellitus (T2DM) due to an additional cardiac and renal benefits as shown in several cardiac- and renal-outcome trials, the role of DPP-4 inhibitors (DPP-4Is)

cannot be undermined. While long-acting GLP-1RAs have shown a favorable HbA1c lowering compared to DPP-4Is, there is no clinically meaningful HbA1c lowering difference between SGLT-2Is *vs* DPP-4Is. Moreover, the HbA1c lowering potential of DPP-4Is is favorable in people with T2DM having a modest baseline HbA1c (8.0%-8.5%) compared with SGLT-2I that lowers HbA1c larger in a background of higher baseline HbA1c (> 8.5%-9.0%). Furthermore, the HbA1c lowering potential of SGLT-2Is is compromised with the declining renal function while DPP-4Is reduce HbA1c favorably in people with chronic kidney disease (CKD). These findings suggest that despite the positive renal outcomes with SGLT-2Is, the role of DPP-4Is cannot be overlooked even in the presence of CKD.

TO THE EDITOR

We read with interest a minireview by Florentin *et al*[1] putting their arguments in favor of DPP-4 inhibitors (DPP-4Is) as a second-line drug after metformin in people with type 2 diabetes mellitus (T2DM) in particular who are elderly and have chronic kidney disease (CKD) stage 3A or lower. This wonderfully written minireview discusses the role of DPP-4Is in the era of two other novel anti-diabetic agents such as SGLT-2 inhibitors (SGLT-2Is) and GLP-1 receptor agonists (GLP-1RAs) that have shown a remarkably beneficial effect on cardiovascular (CV) and renal endpoints making them an ideal second or arguably even first-line drug in people with T2DM having established CV disease (CVD), heart failure (HF) and CKD. While authors have discussed the pharmacological differences amongst different DPP-4Is and put a perspective on the CV outcome trials in the era of SGLT-2Is and GLP-1RAs, few vital details seem to be missing and some of the statements appear rather ambiguous that need clarification. The most important area that is surprisingly missing in this review is the efficacy comparison between DPP-4Is *vs* SGLT-2Is or GLP-1RAs. Expectedly, the HbA1c lowering effect of DPP-4Is would be inferior to GLP-1RAs owing to their mechanism of action that causes a physiological *vs* pharmacological rise of GLP-1 respectively and indeed, several head-to-head studies of long-acting GLP-1RAs have shown a superior HbA1c lowering beside a significant

reduction in weight and systolic blood pressure (SBP) when compared with DPP-4Is. However, the HbA1c lowering effect of DPP-4Is is not clinically meaningful different from SGLT-2Is. To this end, several studies have evaluated the HbA1c lowering effect of SGLT-2Is *vs* DPP4Is in the past decade[2-8]. Although in most of these SGLT-2Is head-to-head studies with DPP-4Is, HbA1c reduction was similar between the two drug classes; DPP-4Is were used as an open-label active comparator arm only for exploratory analysis. One study that compared empagliflozin 10 and 25 mg with 100 mg sitagliptin as an active comparator in a double-blind randomized fashion found no difference in HbA1c lowering[3]. However, two studies that compared canagliflozin 100 and 300 mg with sitagliptin 100 mg as an active comparator in a double-blind randomized fashion, found 300 mg canagliflozin to be superior to 100 mg sitagliptin in HbA1c lowering, though no difference was noted with 100 mg canagliflozin (Table 1)[6,7]. Meta-analyses that compared HbA1c lowering with DPP-4Is *vs* SGLT-2Is yielded discordant results[9-12]. While some found no difference in HbA1c lowering, others showed a small but significant HbA1c lowering with SGLT-2Is compared to DPP-4Is (Table 1). Notably, weight and SBP reduction were consistently superior with SGLT-2I *vs* DPP-4I in all these head-to-head studies including meta-analyses. Another interesting piece of information that is missing and needs discussion is the differential HbA1c lowering effect of DPP-4Is vs. SGLT-2Is stratified on baseline HbA1c. While the SGLT-2Is appear to lower the HbA1c more favorably compared with DPP-4Is in the background of higher baseline value (HbA1c 8.5%-9.0%), DPP-4Is lowered HbA1c more favorably compared with SGLT-2I in people having modest baseline HbA1c value (< 8%-8.5%) (Table 1)[13-15]. This finding suggests DPP-4Is may have a favorable effect on HbA1c lowering compared to SGLT-2Is in people with T2DM having a modest baseline HbA1c, in absence of high CV risk. Although a reduction in HbA1c is always larger when baseline HbA1c is high, we do not know exactly why DPP-4Is reduce HbA1c larger compared to the SGLT-2Is when the baseline value is modest. Since SGLT-2Is HbA1c lowering ability is dependent on the renal threshold of glucose excretion (RT_G), modest baseline HbA1c may not produce further lowering of RT_G.

Nevertheless, we humbly disagree with the author's conclusion about "the lack of evidence with SGLT-2Is and GLP-1RAs in elderly patients with diabetes as well as the contraindication of SGLT-2Is in patients with CKD, grade 3A and lower, make DPP-4Is a safe choice in such populations." Let us recall that—(1) About one-fourth patients population (24.2%) in HF trial of SGLT-2I dapagliflozin were elderly [≥ 75 years, median age 79 years (76-82 years)] and they benefitted equally [Hazard ratio (HR), 0.68; 95% Confidence interval (CI), 0.53-0.88] when compared to the overall population (HR, 0.74; 95%CI, 0.65-0.85) in terms of reduction of the primary composite endpoint of CV death or HF hospitalization (HHF) or urgent HF visits ($P_{interaction}$ = 0.76)[16]; (2) Mean age of the population in CV-, HF- and renal-outcome trials of SGLT-2Is varied from as low as 62 years in renal outcome trial of dapagliflozin to as high as 72 years in HF trial of empagliflozin (EMPEROR-Preserved) that found a significantly beneficial renal and CV effect respectively[17]; (3) Current guidelines recommend using SGLT-2Is in patients with CKD if eGFR is ≥ 30 mL/min/1.73 m^2 and in addition, empagliflozin has been granted an additional label of use up to eGFR ≥ 20 mL/min/m^2 in patients with HF with reduced ejection fraction and CKD[18]; (4) The latest Kidney Disease: Improving Global Outcomes 2022 guideline which is currently under public review recommend using SGLT-2Is in patients with CKD if eGFR ≥ 20 mL/min/1.73 m^2 regardless of background HF. Moreover, once SGLT-2Is is initiated it is reasonable to continue even if the eGFR falls below 20 mL/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is initiated[19]; (5) Although there are no head-to-head randomized controlled trials that compared CV outcomes between DPP-4Is *vs* DPP-4Is, several large real-world, propensity-matched studies showed a significant reduction in HHF with SGLT-2Is compared with DPP-4Is in patients with T2DM, regardless of baseline high CV risk[20]; and (6) finally, the 2011 European Diabetes Working Party for Older People clinical guideline that recommended DPP-4I as a second-line drug of choice in elderly were made before the US Federal Drug Administration approval of first SGLT-2I canagliflozin in 2013 and first positive CV outcome with empagliflozin in 2015. These findings suggest author's conclusion is discordant with the available evidence[21].

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1	Ian H. de Boer, M. Luiza Caramori, Juliana C.N. Chan, Hiddo J.L. Heerspink et al. "KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease", Kidney International, 2020 Crossref	30 words — 2%
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