

Time to rethink the role of sodium-glucose co-transporter 2 inhibitors in the elderly

To the Editor We have read with great interest the results of a recent cross-sectional study by Gómez-Huelgas et al,¹ published in *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*). A closer look at the baseline characteristics of patients reveals that this study included elderly obese patients with type 2 diabetes and significant comorbidities, mainly arterial hypertension (up to 89.0%), macrovascular disease (up to 32.4%), and advanced chronic kidney disease (up to 31.1%). Patients were stratified according to glycemic control, depending on glycated hemoglobin A_{1c} levels (tight, moderate, and poor control). Minimal differences between the 3 study groups were detected.¹

It is certain that, at the time of this study, sodium-glucose co-transporter 2 (SGLT2) inhibitors were still considered as novel drugs, with limited preliminary data concerning their efficacy and safety. However, it is now established (based on data obtained from the 3 hallmark cardiovascular outcome trials, namely, the EMPA-REG OUTCOME [Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose], CANVAS [Canagliflozin Cardiovascular Assessment Study], and DECLARE-TIMI 58 [Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58]) that SGLT2 inhibitors represent a reasonable treatment option in patients with established atherosclerotic cardiovascular disease, decreasing the risk of major adverse cardiovascular events by 14% (hazard ratio [HR], 0.86; 95% CI, 0.80–0.93), of cardiovascular death or hospitalization for heart failure by 23% (HR, 0.77; 95% CI, 0.71–0.84), and of chronic kidney disease progression by 44% (HR, 0.56; 95% CI, 0.47–0.67).² Recent evidence also highlights their superiority compared with dipeptidyl peptidase-4 inhibitors, in terms of cardiovascular morbidity or mortality and all-cause mortality.³ In addition, they exert only a modest effect on glycemic control of patients with type 2 diabetes and concomitant chronic kidney disease, with a mean reduction in glycated hemoglobin levels up to 0.29%; thus, they do not correlate with “intensification” of glycemic control.⁴

Regarding safety outcomes, SGLT2 inhibitors do not seem to increase the risk of hypoglycemia, while a previous meta-analysis demonstrated that, when added to metformin, SGLT-2 inhibitors are associated with the lowest odds for hypoglycemia, compared with the remaining second-line oral antidiabetic agents.⁵ Of course, extra caution is needed as far as the risk of diabetic ketoacidosis and lower extremity amputation is concerned.² An appropriate adjustment of the remaining antidiabetic regimen may be needed.

Overall, the insulin-independent mechanism of action and the multilevel pleiotropic effects of SGLT2 inhibitors make them an attractive treatment option in the elderly population. Oral once-daily administration and availability of fixed combinations with metformin might also be considered as an advantage. However, this hypothesis needs to be tested in large prospective clinical trials with SGLT2 inhibitors, enrolling exclusively the geriatric population.

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Authors' reply We greatly appreciate the comments of Dimitrios et al¹ regarding our recent publication² and the role of sodium-glucose co-transporter 2 (SGLT2) inhibitors in the elderly.

Patients with type 2 diabetes are at higher risk of hospitalizations because of heart failure and renal disease and have significantly worse cardiovascular outcome than patients without type 2 diabetes. The association between heart failure or renal disease and type 2 diabetes is even stronger among elderly adults.³

Drawing from the extensive evidence obtained in recent years on the cardiovascular benefits of SGLT2 inhibitors, we know that their greatest effects are on reducing the risk of hospitalization for heart failure and renal disease progression in patients with type 2 diabetes. These benefits seem to be consistent regardless of age.⁴

However, regarding safety, SGLT2 inhibitors significantly increase the risk of serious adverse events such as diabetic ketoacidosis, amputations, bone fractures, or volume depletion.⁴ Although the rates of these events are very low and can be reduced with an appropriate SGLT2 inhibitor selection strategy and close patient monitoring, their magnitude has not been fully described in older patients. Indeed, SGLT2 could pose a greater risk to the elderly.^{4,5}

Therefore, due to the lack of evidence and the limited experience in the use of SGLT2 in the elderly, we suggest that SGLT2 should be carefully prescribed on an individual basis to older patients with type 2 diabetes, in accordance with the recommendations from a Spanish multidisciplinary consensus statement on the management of hyperglycemia in the elderly.⁵ In older patients with robust health status, SGLT2 inhibitors may be an effective and safe option. However, the harm could outweigh the benefits in vulnerable or frail patients. For these patients, antidiabetic alternatives such as dipeptidyl peptidase-4 inhibitors or basal insulin should be considered.^{4,5}

We agree with Dimitrios et al¹ on the need for randomized clinical trials on SGLT2 that specifically focus on elderly patients with type 2 diabetes and believe that these trials should include

a comprehensive frailty evaluation and a subsequent subgroup analysis.

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