SGLT2 inhibitors in older adults: overcoming the age barrier

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Sodium glucose co-transporter 2 (SGLT2) inhibitors were initially licensed as potent glucose lowering agents for the treatment of type 2 diabetes. Subsequent studies, aimed primarily at showing cardiovascular and renal safety, reported other benefits, including reductions in hospitalisation for heart failure and improved renal outcomes.[1] Because of these unique characteristics, SGLT2 inhibitors are now recommended as preferred treatment options in patients with type 2 diabetes with a high risk of or established cardiovascular disease, chronic kidney disease, or both.[2] However, despite their expanding indications, SGLT2 inhibitor uptake has not been consistent across all age groups. Concerns relating to potential adverse effects and insufficient safety data due to poor representation of older adults in clinical trials are probably major contributors to the relatively low prescription rates in older adults compared with younger adults.[3]

In *The Lancet Healthy Longevity*, Richard E Pratley and colleagues[4] report on the prespecified further analysis of data from the VERTIS-CV study. The authors assessed cardiorenal outcomes, kidney function, and other safety measures with the SGLT2 inhibitor ertugliflozin versus placebo in adults aged 65 years and older compared with those younger than 65 years. A separate post-hoc analysis of 903 patients aged 75 years and older was also included. Pratley and colleagues report that overall cardiovascular and renal outcomes in patients treated with ertugliflozin, including reduction in hospitalisation for heart failure and exploratory composite kidney outcomes, were similar across all age groups. The study provides much needed safety data on the use of SGLT2 inhibitors in older adults. Older people are highly susceptible to hypoglycaemia and this risk might be amplified when SGLT2 inhibitors are used in combination with sulfonylureas or insulin.[5] Additional concerns with SGLT2 inhibitors relate to the potential risk of volume depletion and an increased risk of genital mycotic infections and limb fractures,[5] which are all particularly pertinent in older people. In this regard, the findings by Pratley and colleagues are reassuring. Treatment with ertugliflozin was not associated with an increased risk of any of the aforementioned side-effects compared with younger adults and, specifically, there was no increased risk of fractures or volume depletion even with concomitant use of diuretics.[4] However, one caveat to these findings relates to the omission of the recording of frailty status of the older adults, which limits generalisability, as frailty is an important prognostic marker and must be given due consideration when setting treatment goals and making therapeutic choices.

Despite this caveat, the results of Pratley and colleagues' study[4] build on the small evidence base derived from post-hoc analyses of large outcome trials involving SGLT2 inhibitors. A large cohort of older adults (more than 4000 participants) and prespecified analyses that focus on safety outcomes relevant to older adults add credibility to this study.

How relevant are these results to clinical practice? Older adults with type 2 diabetes are at an increased risk of cardiovascular (and indeed chronic renal) complications and are consequently the group who are likely to benefit most from therapies that reduce this risk. Paradoxically, older adults are also the group that is least likely to be prescribed these drugs. Given the overwhelming evidence that newer agents like SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have substantial cardio-renal benefits and the endorsement by several guidelines as preferred agents in those with high cardio-renal risk, it is surprising that they are not being used more widely in the population with type 2 diabetes. In older adults in particular, the use of SGLT2 inhibitors and GLP-1 receptor agonists is still much outweighed by sulfonylurea and insulin prescriptions (in the present study, almost half of all older adults were on insulin and more than 40% were on sulfonylureas at baseline) despite the obvious risk of hypoglycaemia.[3,6] High sulfonylurea use presumably relates to cost in low-income countries, but this is less of an argument in high income countries. Tackling existing gaps in knowledge and addressing clinical inertia is paramount to resolve this discrepancy.

With the proportion of older adults likely to increase because of population ageing, there is a compelling need for more evidence on type 2 diabetes treatment in this age group.[7] Although it is encouraging that more studies are addressing this issue, the representation of older adults in clinical trials remains poor. Trials need to be more representative of the heterogeneity of older adults and should include relevant outcomes, such as functional status and quality of life, alongside the usual outcome measures relating to efficacy and safety. Until such

evidence is available, regrettably there will continue to be barriers to the use of effective therapies in this age group.

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