SGLT2 INHIBITORS AND FRACTURE RISK IN PATIENTS WITH TYPE 2 DIABETES: A DRUG-SPECIFIC SIGNAL RATHER THAN A CLASS EFFECT

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Background. Type 2 diabetes (T2D) is associated with an increased risk of fragility fractures despite normal or even elevated bone mineral density. Concerns about the skeletal safety of sodium-glucose cotransporter 2 (SGLT2) inhibitors arose after an imbalance in fractures was reported with canagliflozin.

Keywords: SGLT2 inhibitors, type 2 diabetes, fracture risk, canagliflozin, falls, bone health.

Aim. To evaluate whether the use of SGLT2 inhibitors is associated with an increased risk of fractures and to identify possible contributing factors.

Methods. Cardiovascular and renal outcome trials, pooled safety analyses, large observational cohort studies and meta-analyses indexed in PubMed were reviewed, with fracture incidence as the primary outcome of interest.

Results. In the CANVAS Program, canagliflozin was associated with a higher incidence of fractures compared with placebo (15.4 vs 11.9 per 1000 patient-years; HR 1.26). However, this signal was not reproduced in the CREDENCE trial, nor in pooled analyses of empagliflozin and dapagliflozin. In a large real-world cohort study, initiation of canagliflozin did not increase fracture risk compared with GLP-1 receptor agonists. Meta-analyses of randomized trials have not demonstrated a significant class-wide increase in fracture risk. The early fracture imbalance in CANVAS may be partly explained by an increased propensity to fall due to osmotic diuresis, volume depletion and orthostatic hypotension rather than by a direct skeletal effect.

Conclusions. Current evidence does not support an increased fracture risk as a class effect of SGLT2 inhibitors. Nevertheless, in patients with established osteoporosis, a history of falls, frailty or advanced chronic kidney disease, bone status and fall risk should be assessed when selecting therapy, and differences between individual agents should be taken into account.

References

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