

**Sitagliptin and risk of fractures in type 2 diabetes: results from the TECOS trial**

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**Background and aims:** Type 2 diabetes is associated with an increased risk of fractures, and some diabetes treatments, such as thiazolidinediones (TZDs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, may further elevate this risk. Data regarding the association of dipeptidyl peptidase-4 inhibitors and fractures are mixed. In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) we examined in a prespecified intent-to-treat analysis, the self-reported incidence of clinician- or radiograph-verified fractures.

**Materials and methods:** The TECOS prospective double blind study randomized 14,671 patients to the addition of sitagliptin (N=7,332) vs. placebo (N=7,339) to existing diabetes treatments. Open-label use of antihyperglycaemic therapy was encouraged with individually appropriate glycaemic targets, aiming to achieve between-group glycaemic equipoise.

**Results:** At baseline, mean (SD) age was 65.5 (8.0) years, diabetes duration 11.6 (8.1) years, and HbA1c 7.2% (0.5%). 29.3% were women and 32.1% were non-White. Over median 3.0 years, 3.9% of patients had a non-fatal myocardial infarction, 3.1% were hospitalized for heart failure, and 2.1% had a non-fatal stroke. Over 43,222 person years of follow-up, 375 patients (2.6%) had a fracture, including 146 major fractures (hip: n=34; upper extremity: n=81; spine: n=31). An increased fracture risk was associated independently, in adjusted analyses with older age (p<0.001), female sex (p<0.001), White race (p=0.001), lower diastolic blood pressure (p<0.001), diabetic neuropathy (p=0.003), and insulin therapy (p=0.021). A lower risk was associated with metformin therapy (p=0.038). In patients on sitagliptin, 189 fractures (8.7 per 1000 person-years) occurred vs. 186 (8.6 per 1000 person-years) with placebo (hazard ratio 1.01 [95% CI 0.82-1.23], p=0.94). Sitagliptin was also not associated with major fractures (p=0.78) or hip fracture specifically (p=0.75).

**Conclusion:** In TECOS, fractures were not uncommon, especially in older patients, and occurred at rates similar to heart failure hospitalization or stroke. There was no significant difference in fracture rates between sitagliptin and placebo. This finding can help clinicians when considering their choice of second-line diabetes treatments in patients at high risk for fractures.

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