Increased incidence of fractures in women who received rosiglitazone in ADOPT (A Diabetes Outcome Progression Trial)

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Background and Aims: Fractures (Fx) occur more frequently in people with type 2 diabetes (T2DM) than in non-diabetics. More Fx adverse events (AE) were reported by subjects randomized to rosiglitazone (RSG) than either metformin (MET) or glyburide (GLY) in A Diabetes Outcome Progression Trial (ADOPT), a clinical trial of initial monotherapy in subjects with newly diagnosed T2DM (median follow-up=4 years). This increase in Fx AE occurred in women but not men.
Materials and Methods: AE in ADOPT were collected prospectively, but analysis of Fx was not pre-specified. To explore the time-course of Fx AE in ADOPT and potential risk factors, we examined data from the 1840 women randomized.
Results: In ADOPT, at least one Fx was reported by 111 women (RSG n=60, 9.3%, 2.74/100 patient-years [PY]; GLY n=21, 3.5%, 1.29/100 PY; MET n=30, 5.1%, 1.54/100 PY). The hazard ratio (95% CI) for RSG vs GLY was 2.13 (1.30, 3.51) and for RSG vs MET was 1.81 (1.17, 2.80). The cumulative incidence for RSG, GLY and MET appeared similar for approximately 1 year post-randomisation with divergence of RSG in women but not men after that time. The majority of fractures observed in women who received RSG during ADOPT were in the upper arm (humerus, n=5), hand (n=8) or foot (n=22). Overall, 76.6% of women were post-menopausal at baseline (BL). Among all women in ADOPT, those with Fx were older (58.8±9.6 years [mean±SD], range 37-76 years vs 56.2±10.3 years, 26-76 years; p=0.01) and more were post-menopausal (84.7% vs 76.1%, p=0.04) than those without Fx. BL characteristics were compared within treatment groups (RSG: n=645, 2187 PY; GLY: n=605, 1631 PY; MET: n=590, 1948 PY). Fx rates were higher in older women (<65 years vs ≥65 years) taking RSG (2.5/100 PY vs 3.6/100 PY) or GLY (1.1/100 PY vs 1.9/100 PY), but not MET (1.5/100 PY vs 1.6/100 PY). No other differences were apparent in BL characteristics (ethnicity, HbA1c, FPG, BP, weight, BMI, smoking and others) between women with Fx compared to those without Fx. No prior medical history or prior/concomitant medication use could be identified as a potential risk factor for Fx. The pattern of prior/concurrent AE of potential relevance to Fx was comparable among the treatment groups.
Conclusion: Further investigation into the risk factors for increased Fx in women is required to better understand the clinical implications of these findings.