Appendix 3 (as supplied by the authors): Observational studies of thiazolidinedione exposure and association with fractures

Study	Study type and data source	Study population	Ascertainment of drug exposure	Outcome ascertainment	Association of thiazolidinediones with fractures
Meier 08[1]	Case–control. UK General Practice Research Database with medical and prescription records of more than 5 million people	1020 diabetic men and women with low-impact fractures (301 wrist/forearm, 274 hip, 222 humerus, 148 rib, 56 vertebral, and 19 not stated). 3728 controls (matched on age, sex and general practice). Adjustments made for potential confounders such as use of other antidiabetic agents, smoking status, BMI and other co-morbidities.	Prescriptions were generated and directly transcribed into computer record; accuracy of the recorded data has been validated in previous studies. Information extracted on drug class and number of prescriptions prior to index date. Analysis was stratified by number of prescriptions, prespecified into 3 categories.	Trained general practitioners recorded medical diagnoses. Previous medical record reviews have shown good accuracy of the recorded diagnoses in the GPRD.	No significant association OR 0.90 (0.46–1.74) for patients with < 8 prescriptions (corresponding to 12–18 months' use). 3.2% of fracture patients had > 8 thiazolidinedione prescriptions, compared to 1.7% of controls. Adjusted OR for current use of > 8 prescriptions v. non-use was 2.43 (95% CI, 1.49–3.95). Adjusted OR by gender for > 8 prescriptions: Men: 2.50 (95% CI, 0.84–7.41), Women: 2.56 (95% CI, 1.43–4.58) For different fracture sites: Hip/femur: OR 4.54 (1.28–16.10) Wrist/forearm: OR 2.90 (1.19–7.10) Fracture risk was independent of age, body mass index and duration of diabetes.
WEUSRTP218108[2]	Retrospective cohort with about 9000 patients in each cohort and mean follow-up of just over 12 months. US Ingerix Research Database of patients with medical and prescription coverage in managed care.	Adults started on rosiglitazone, metformin or sulfonylurea. Follow-up continued until dispensing of second study drug or insulin, or if patient left the scheme. Cohorts were matched on baseline demographics and factors related to cardiac status, but not fracture outcomes. Possibility of residual imbalance remains.	Dispensing records indicating initiation of rosiglitazone, metformin or sulfonylurea, with no record of study drug or insulin use in preceding 6 months. Patients excluded if any other study drugs or insulin dispensed within 30 days of the initial study drug. No stratification by duration of drug exposure, thus missing out on potential differential effects related to cumulative dose or duration.	ICD-9 codes for insurance claims related to fractures. No chart review was carried out as part of this study, although insurers do regularly audit the accuracy of the claims.	**Men**: Rosiglitazone 90/4960 (1.81%) Metformin 90/4976 (1.81%) Sulfonylurea 98/4984 (1.97%) OR RSG v. Metformin: 1.00 (0.99–1.01); p=0.38 OR RSG v. Sulfonylurea: 0.92 (0.69–1.23); p=1.0 **Women**: Rosiglitazone 118/4017 (2.94%) Metformin 86/4001 (2.15%) Sulfonylurea 132/3993 (3.31%) OR RSG v. Sulfonylurea: 0.89 (0.69–1.14); p=0.38 OR RSG v. Metformin: 1.38 (1.03–1.82); p=0.03

References

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Appendix to: Loke YK, Singh S, Furberg C. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180(1):32-9.