Letters

- Thiazolidinedione use and the risk of fractures

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The recent commentary by Lorraine Lipscombe[1] gave the impression that the 10-study meta-analysis by Loke and colleagues yields a new finding that there might be an association between thiazolidinediones and an increased risk of fractures in women.[2] In fact, this finding largely replicates an association reported 2 years ago in the publication of the results of ADOPT (A Diabetes Outcome and Progression Trial).[3]

GlaxoSmithKline reported the ADOPT findings to regulatory agencies worldwide; in Canada, the company also issued communications to both health care professionals[4] and the Canadian public[5] regarding this information. Working with Health Canada, GlaxoSmithKline has updated the product monograph for Avandia (rosiglitazone maleate) to include these data.

Lipscombe stated that clinical drug trials are often underpowered to detect unanticipated and rare adverse events and suggested that a standardized postmarketing surveillance process is needed.[1] Rosiglitazone is the most studied oral agent for the treatment of diabetes, with many years of clinical trial experience. As soon as the new safety information was available, it was promptly communicated to regulatory agencies, quickly published and directly communicated to physicians and patients. As such, we submit that the current system has worked well. Additionally, GlaxoSmithKline is making significant efforts to investigate the effects of rosiglitazone on bone, including adding bone-specific analyses to several clinical studies to better understand these observations about fracture risk. Avandia remains a valuable tool in the treatment of type 2 diabetes; its role has been recognized and clarified in the 2008 revision of the Canadian clinical practice guidelines for diabetes.[6]

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REFERENCES

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In their recent meta-analysis, Loke and colleagues provided evidence that long-term use of thiazolidinediones is associated with a higher risk of fractures among women but not men.[1] Potentially important clinical implications of this study may have been missed because of the broadness of the inclusion criteria (treatment groups included any thiazolidinedione and control groups included any active comparator or placebo) and the absence of subgroup analyses.

When we reanalyzed the data reported by Loke and colleagues on the basis of the actual treatment used (rosiglitazone or pioglitazone), we found that patients with type 2 diabetes who received rosiglitazone had a significantly higher risk of fracture than those in the control group (fixed-effects pooled odds ratio [OR] 1.64, 95% confidence interval [CI] 1.24–2.17, $p < 0.001$, $I^2 = 21\%$), whereas no significant difference in fracture risk was found between patients in the pioglitazone and control groups (fixed-effects pooled OR 1.26, 95% CI 0.92–1.71, $p = 0.15$, $I^2 = 22\%$)

Study	No. events/no. patients: Rosiglitazone	Control	Odds ratio (95% CI)
Kahn et al. 2008	92/1456	108/2895	1.74 (1.31–2.32)
AVM100264 trial	2/294	1/301	2.05 (0.19–22.78)
GSK049653 351 trial	0/30	1/30	0.32 (0.01–8.24)
GSK049653 334 trial	0/277	3/278	0.14 (0.01–2.76)
Overall	94/2057	113/3504	1.64 (1.24–2.17)

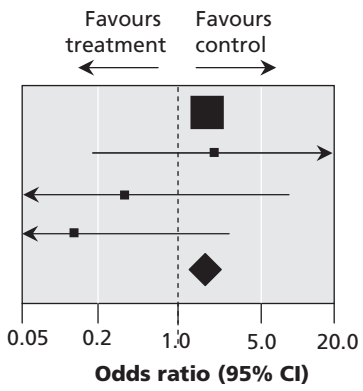

Figure 1: Fixed-effects odds ratios of fracture with use of rosiglitazone. Note: CI = confidence interval.