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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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)

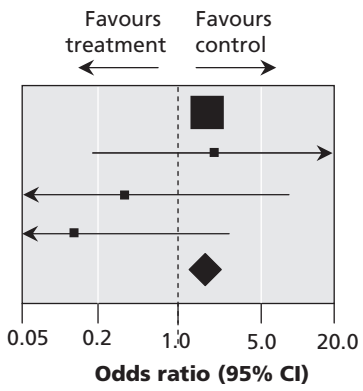
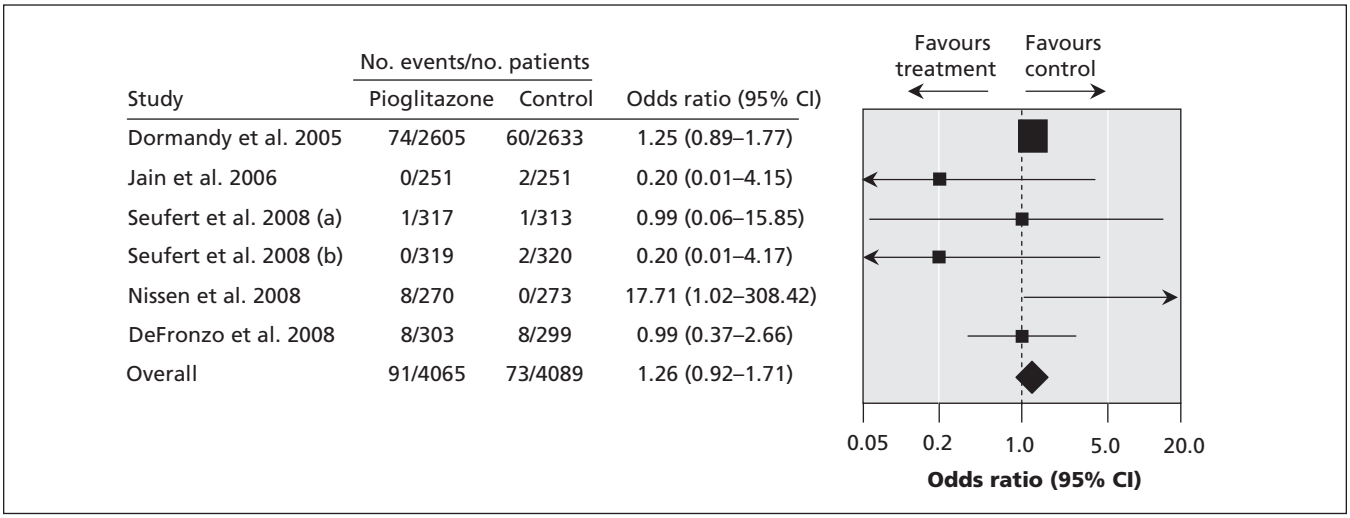
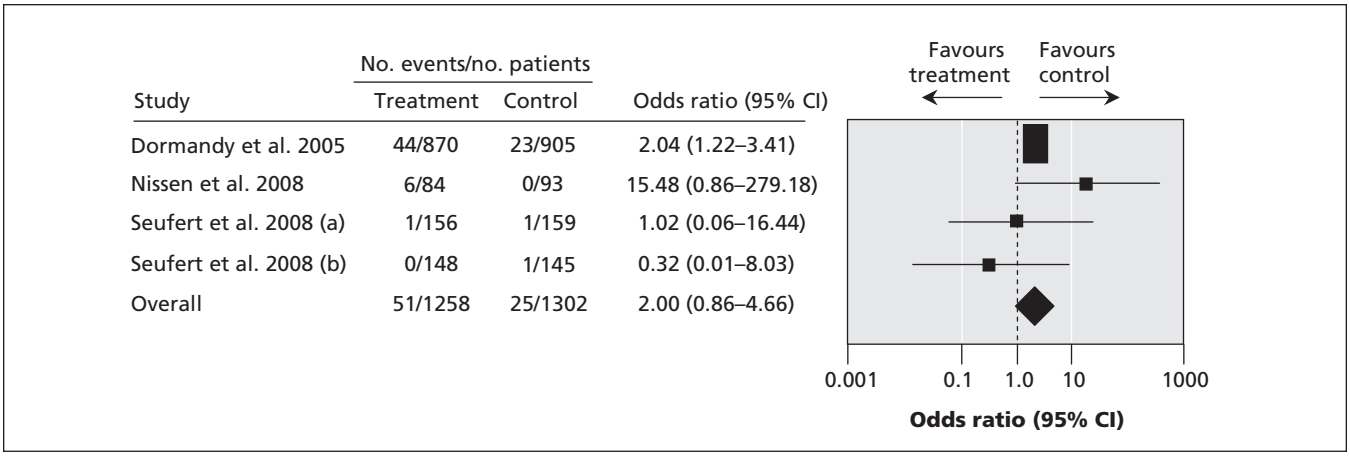


Figure 1: Fixed-effects odds ratios of fracture with use of rosiglitazone. Note: CI = confidence interval.



Study	No. events/no. patients: Pioglitazone	Control	Odds ratio (95% CI)
Dormandy et al. 2005	74/2605	60/2633	1.25 (0.89–1.77)
Jain et al. 2006	0/251	2/251	0.20 (0.01–4.15)
Seufert et al. 2008 (a)	1/317	1/313	0.99 (0.06–15.85)
Seufert et al. 2008 (b)	0/319	2/320	0.20 (0.01–4.17)
Nissen et al. 2008	8/270	0/273	17.71 (1.02–308.42)
DeFronzo et al. 2008	8/303	8/299	0.99 (0.37–2.66)
Overall	91/4065	73/4089	1.26 (0.92–1.71)

Figure 2: Fixed-effects odds ratios of fracture with use of pioglitazone. Note: CI = confidence interval.



Study	No. events/no. patients: Treatment	Control	Odds ratio (95% CI)
Dormandy et al. 2005	44/870	23/905	2.04 (1.22–3.41)
Nissen et al. 2008	6/84	0/93	15.48 (0.86–279.18)
Seufert et al. 2008 (a)	1/156	1/159	1.02 (0.06–16.44)
Seufert et al. 2008 (b)	0/148	1/145	0.32 (0.01–8.03)
Overall	51/1258	25/1302	2.00 (0.86–4.66)

Figure 3: Random-effects odds ratios of fracture with use of pioglitazone among women. Note: CI = confidence interval.

(Figure 1, Figure 2). Indirect comparison between the 2 thiazolidinedione treatment groups was not feasible because no common comparator existed.[2]

After within-study data stratification on sex, it was possible to estimate a pooled OR only for patients who received pioglitazone (relevant data for rosiglitazone were available from only 1 study). Women receiving pioglitazone demonstrated evidence of significant fracture risk (fixed-effects pooled OR 2.14, 95% CI 1.33–3.44, $p = 0.02$, $I^2 = 13\%$); however, this finding did not persist in a sensitivity analysis with a random-effects model (pooled OR 2.00, 95% CI 0.86–4.66, $p = 0.11$) (Figure 3). As expected, men who received pioglitazone did not demonstrate evidence of a significantly higher fracture risk than those in the control group (fixed-effects pooled OR 0.84, 95% CI 0.53–1.34, $p = 0.46$, $I^2 = 0\%$).

In summary, pioglitazone use might not be associated with increased fracture risk in either women or men with type 2 diabetes. This finding has both clinical and research implications.

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Two of the authors respond:

Konstantinos Toulis and colleagues reanalyzed some of the data we presented in our meta-analysis[1] and concluded that pioglitazone use does not carry a fracture risk (in contrast to the finding for rosiglitazone). Their conclusion illustrates the pitfalls of relying on post-hoc subgroup analyses to ascertain the effects of drugs.

According to the Cochrane Handbook for Systematic Reviews of Interventions, the probability of false-