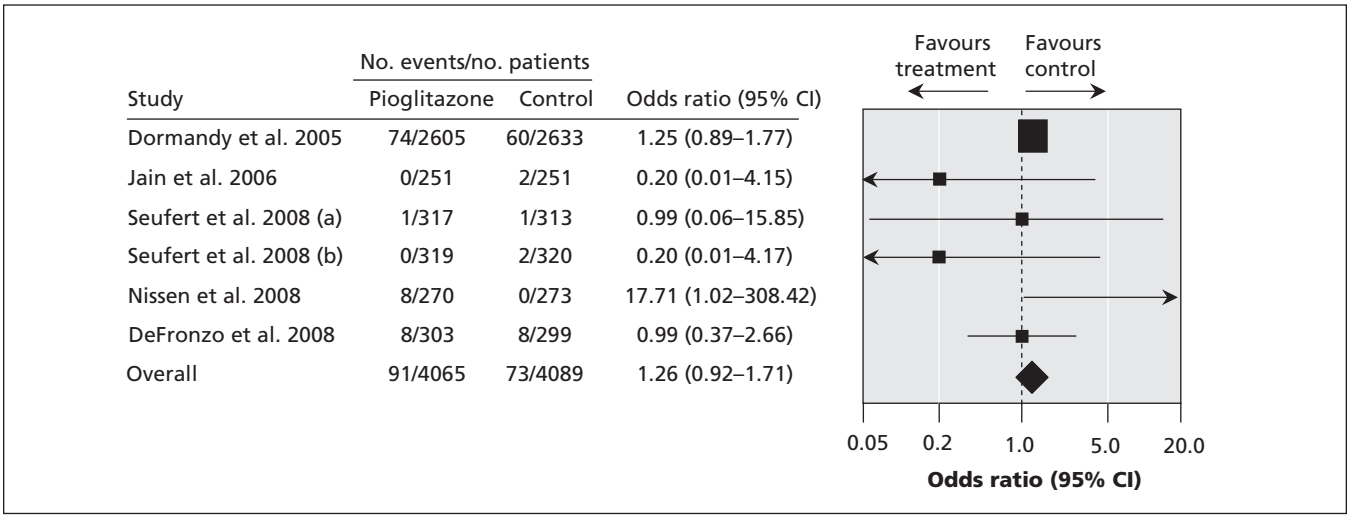
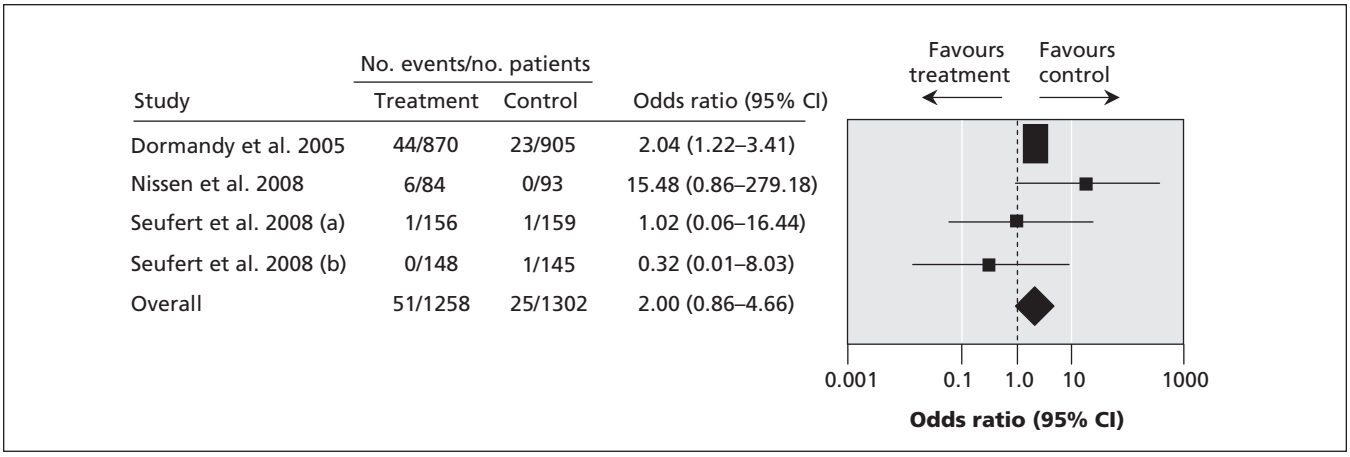


Study	No. events/no. patients: Pioglitazone	Control	Odds ratio (95% CI)
Dormandy et al. 2005	74/2605	60/2633	1.25 (0.89–1.77)
Jain et al. 2006	0/251	2/251	0.20 (0.01–4.15)
Seufert et al. 2008 (a)	1/317	1/313	0.99 (0.06–15.85)
Seufert et al. 2008 (b)	0/319	2/320	0.20 (0.01–4.17)
Nissen et al. 2008	8/270	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.

Konstantinos A. Toulis MD MSc
Dimitrios G. Goulis MD PhD
Athanasios D. Anastasilakis MD PhD
Aristotle University of Thessaloniki, Thessaloniki, Greece

Competing interests: None declared.

REFERENCES

1. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180:32-9.
2. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326:472.

DOI:10.1503/cmaj.1090003

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-

positive and false-negative findings rapidly increases as multiple subgroups are evaluated.[2] Subgroups should only be evaluated for the direction of effect: in our study there was an increased risk of fractures in women with diabetes who received either pioglitazone or rosiglitazone.

In addition, in implementing a random-effects model, Toulis and colleagues not only reduced the power of the meta-analysis[3] but also shifted the weight of the analysis toward smaller, short-term studies that recorded relatively few events. When one is dealing with a rare adverse event that occurs only with prolonged therapy, it is only with adequately powered trials of longer duration that one will be able to discern these effects, as seen with the thiazolidinediones and fracture risk. Indeed, use of the random-effects model has been shown to lead to biased results in the analysis of rare events.[3]

Finally, the manufacturers of pioglitazone have released results confirming the increase in fracture risk seen with pioglitazone (1.9 fractures per 100 patient-years in the pioglitazone group and 1.1 fractures per 100 patient-years in the comparator group in 19 company-conducted trials).[4] Hence, the available biologic, clinical and epidemiologic evidence confirms that fractures are a class effect of both of the thiazolidinediones: rosiglitazone and pioglitazone.

Yoon K. Loke MBBS MD
School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, United Kingdom
Sonal Singh MD MPH
Section on General Internal Medicine, Department of Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Competing interests: None declared.

REFERENCES

1. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180:32-9.
2. Deeks JJ, Higgins JPT, Altman DG, et al. What are subgroup analyses? In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions. Version 5.0.1*. Oxford (UK): The Cochrane Collaboration; 2008 Sept. Available: www.cochrane-handbook.org (accessed 2009 Mar. 12).
3. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77.
4. Grossman LD. *Increased incidence of fractures in female patients who received long-term treatment with ACTOS (pioglitazone hydrochloride) tablets for type 2 diabetes mellitus*. Toronto (ON): Eli Lilly Canada Inc.; 2007. Available: www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2007/actos_hpc-cps_2-eng.php (accessed 2009 Mar. 12).

DOI:10.1503/cmaj.1090004

Correction

A recent News article[1] mistakenly identified Derek Jones as an ex-officio member of the Inter-Agency Advisory Panel on Research Ethics. In fact, Jones is the former executive director of the panel, who was interviewed for the article but was not present at the launch of the Tri-Council Guidelines. *CMAJ* apologizes for any inconvenience this information may have caused.

REFERENCES

1. Eggertson L. Ethics guidelines strengthened but reach remains limited. *CMAJ* 2009;180:379-80.

DOI:10.1503/cmaj.090515

How to submit a letter

To send a letter to the editor concerning a published article, visit www.cmaj.ca and click "Submit a response" at the top right-hand side of the article. All letters submitted through www.cmaj.ca will be considered for publication in the print journal. To submit a letter that does not pertain to an article in the journal, email your letter to pubs@cma.ca with a note indicating whether or not you would like it to be considered for publication.

Letters written in response to an article published in *CMAJ* are more likely to be accepted for print publication if they are submitted within 2 months of the article's publication date. Letters accepted for print publication are edited for length (usually 250 words) and house style.

Mécanisme de présentation des lettres

Pour écrire à la rédaction au sujet d'un article publié dans le *JAMC*, rendez-vous sur le site www.jamc.ca, ouvrez l'article en question et cliquez sur "Submit a response" parmi les choix énumérés en bleu à droite de l'article. On étudiera toutes les lettres reçues sur le site web pour éventuelle publication dans la version imprimée du Journal. Si votre lettre traite d'un autre sujet qu'un article publié dans le Journal, écrivez à pubs@cma.ca et précisez si vous souhaitez ou non que votre lettre soit étudiée en vue de sa publication.

Les lettres répondant à un article publié dans le *JAMC* sont plus susceptibles d'être acceptées pour publication imprimée si elles sont présentées dans les deux mois de la date de publication de l'article. Les lettres acceptées pour publication imprimée sont révisées en fonction du style du *JAMC* et raccourcies au besoin (elles doivent habituellement compter au maximum 250 mots).