Pioglitazone and risk of bladder cancer: clarification of the design of the French study

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To the Editor: In the July 2012 issue of this journal, Neumann et al [1] presented results from a cohort study using data from the French national health insurance information system. In this paper, the authors report that pioglitazone exposure in patients aged 40–79 years was significantly associated with an increased risk of bladder cancer (adjusted HR 1.22 [95% CI 1.05, 1.43]).

The authors' rationale for excluding patients over 79 years of age from the study population is not clear, and this exclusion conflicts with other published papers, which include all patients over 40 years of age [2, 3]. In a report submitted to the European Medicines Agency (EMA) in June 2011 [4], the authors' analysis of the entire population aged ≥ 40 years resulted in a statistically non-significant finding, with an adjusted HR of 1.15 (95% CI 0.99, 1.33). Thus, only after the exclusion of patients older than 79 years do their findings become statistically significant. The authors have not reported a pre-specified statistical analysis plan, either in the *Diabetologia* article [1] or in the report submitted to the EMA [4], and this indicates that the analysis based on this exclusion was made post hoc. An appropriate rationale for excluding patients older than 79 years is also not provided.

Pioglitazone is usually a second- or third-line glucose-lowering agent, and patients are typically characterised by older age, longer diabetes duration and higher rates of complications and comorbidities, all of which are also associated

with an increased risk of bladder cancer, thereby leading to an inherent selection bias (channelling bias). In addition, given that a number of covariates (duration of diabetes, smoking, chronic kidney disease, etc.) in the current report were unaccounted for, causal inferences from such observational studies are difficult and may lead to biased estimates. Unfortunately, the authors do not seem to have adequately addressed these limitations in their discussion.

Providing readers with relevant data points so that conclusions between studies can be made is important, especially in the context of low incident events and numerous covariates.

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Duality of interest The author is an employee of Takeda Global Research & Development Center, Inc., Deerfield, IL, USA.

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