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Pioglitazone: inexpensive; very effective at reducing HbA_{1c}; no evidence of bladder cancer risk; plenty of evidence of cardiovascular benefit

We were disappointed to see in the recent article by Ripamonti *et al*., published in *Diabetic Medicine* [1], that there still are people pursuing a connection between pioglitazone and bladder cancer, despite all of the accumulated evidence that this association is a red herring [2]. The possibility of a connection first came about during pre-clinical studies because of an association between pioglitazone and bladder cancer in male, but not female, rats; no such association was observed in other animals [2]. Subsequently, a possible connection was raised in the PROActive Study [3]. However, follow-up of PROActive clearly demonstrated that the excess cases of bladder cancer in this study could not possibly have been related to pioglitazone as they occurred far too early in the trial to be related to the study medication (Table 1) [4]. To clarify the situation, the Food and Drug Administration mandated a 10-year prospective study to establish whether there was any connection between pioglitazone and bladder cancer [5]. The outcome of this study showed no connection between pioglitazone and bladder cancer [5].

In the era of uncertainty [4] before the publication of the Food and Drug Administration study [5], many retrospective studies with mixed results were published, leading to continuing controversy about the association between pioglitazone and bladder cancer. Unfortunately, in most of these retrospective analyses, the pioglitazone-treated group was fundamentally different from the comparison group and many established risk factors for bladder cancer (such as obesity, history of smoking and uncontrolled diabetes) were probably higher in the pioglitazone-treated patients, leading to statistical anomalies [2]. Including such studies in a meta-analysis and then concluding that there might be a link between pioglitazone and bladder cancer, as Ripamonti *et al*. have done [1], is a fundamentally flawed process. Of note, in the recently published prospective, randomized, placebo-controlled Insulin Resistance Intervention after Stroke study, no increased risk for bladder cancer was observed in the pioglitazone-treated group [6]. When viewed collectively, we do not believe that the published data support an association between pioglitazone and bladder cancer [7].

Meanwhile, pioglitazone is now off patent and, therefore, inexpensive. It is highly effective at reducing and maintaining the reduction in HbA_{1c}. Further, there is considerable evidence to suggest that pioglitazone reduces cardiovascular events in high-risk patients [3,6,8,9], most likely by slowing down or reversing the atherosclerotic process [2,7,10]. In this regard it may complement sodium-glucose co-transporter-2 inhibitors and long-acting glucagon-like peptide-1 receptor agonists, which reduce cardiovascular outcomes in high-risk patients, seemingly by entirely different mechanisms [10]. It may well be that pioglitazone, sodium-glucose co-transporter-2 inhibitors and long-acting glucagon-like peptide-1 receptor agonists would complement each other to further reduce cardiovascular events in high-risk patients [10]. There is also evidence that sodium-glucose co-transporter-2 inhibitors reduce the oedema associated with pioglitazone [10]. We do not feel that it is appropriate, as suggested by Ripamonti *et al*. [1], to devote further resources to yet more research into a connection between pioglitazone and bladder cancer. Rather, randomized controlled trials should be undertaken to establish whether combining pioglitazone with sodium-glucose co-transporter-2 inhibitors or with glucagon-like peptide-1 receptor agonists, or combining sodium-glucose co-transporter-2 inhibitors with glucagon-like peptide-1 receptor agonists, leads to increased reduction in cardiovascular events, and whether triple therapy with these agents would reduce such outcomes even more [10].

Table 1 Bladder cancer appearing during the first year of the PROactive study [4]. The number of months into the trial when each bladder cancer was diagnosed. Cases are presented in the order that each cancer was diagnosed. Results are rounded to the nearest 0.5 of a month

Case number	PROactive study group	Diagnosis of bladder cancer (months into trial)
1	Pioglitazone	0.5 (13 days)
2	Pioglitazone	0.5 (14 days)
3	Pioglitazone	1.0
4	Pioglitazone	3.0
5	Pioglitazone	4.0
6	Placebo	5.5
7	Pioglitazone	6.0
8	Placebo	7.0
9	Pioglitazone	7.5
10	Placebo	8.0
11	Pioglitazone	12.0

PROactive study = PROspective pioglitAzone Clinical Trial in macroVascular events [3]

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Competing interests

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