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Dear All,

**Re Pioglitazone and bladder cancer**

We understand that EMA is shortly to have its routine review concerning the safety of pioglitazone with regard to risk of bladder cancer.

ABCD is the national association of diabetes consultant specialists in the UK.

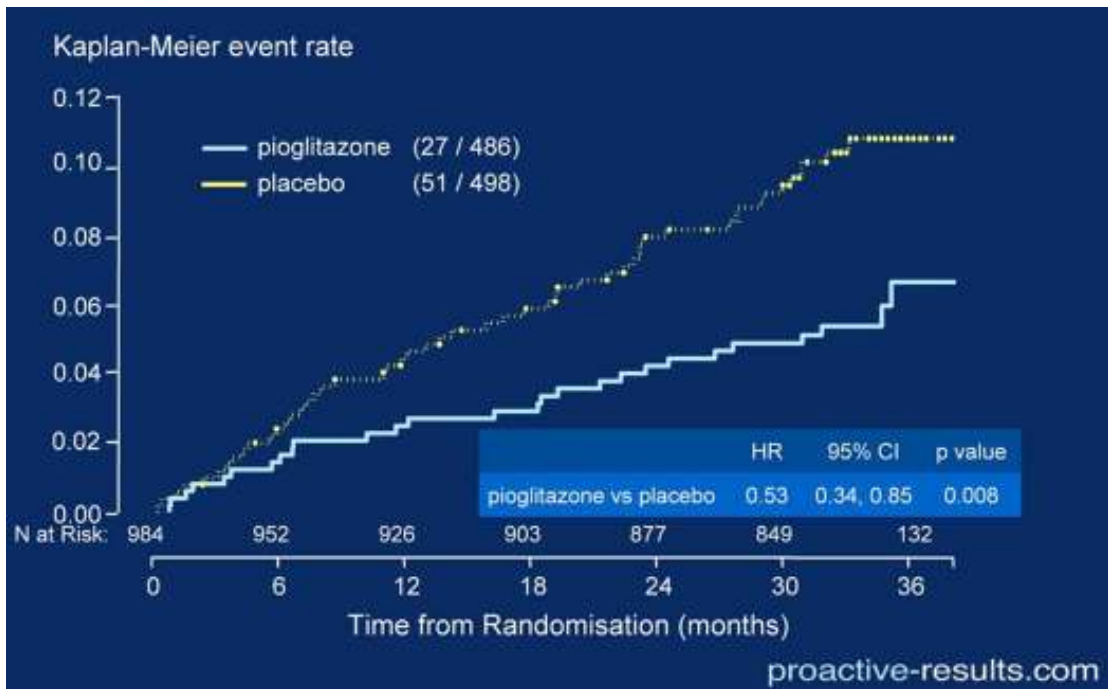
Diabetes UK is the largest organisation in the UK working for people with diabetes, funding research, campaigning and helping people live with the condition. We have over 160,000 members. We work for people with diabetes, their carers, family and friends.

ABCD and Diabetes UK deem patient safety to be of paramount importance and we applaud close scrutiny of all data by professionals equipped with the appropriate skills to interpret it.

Nevertheless ABCD and Diabetes UK are extremely concerned that France and Germany have suspended new prescriptions of pioglitazone in advance of the EMA meeting.

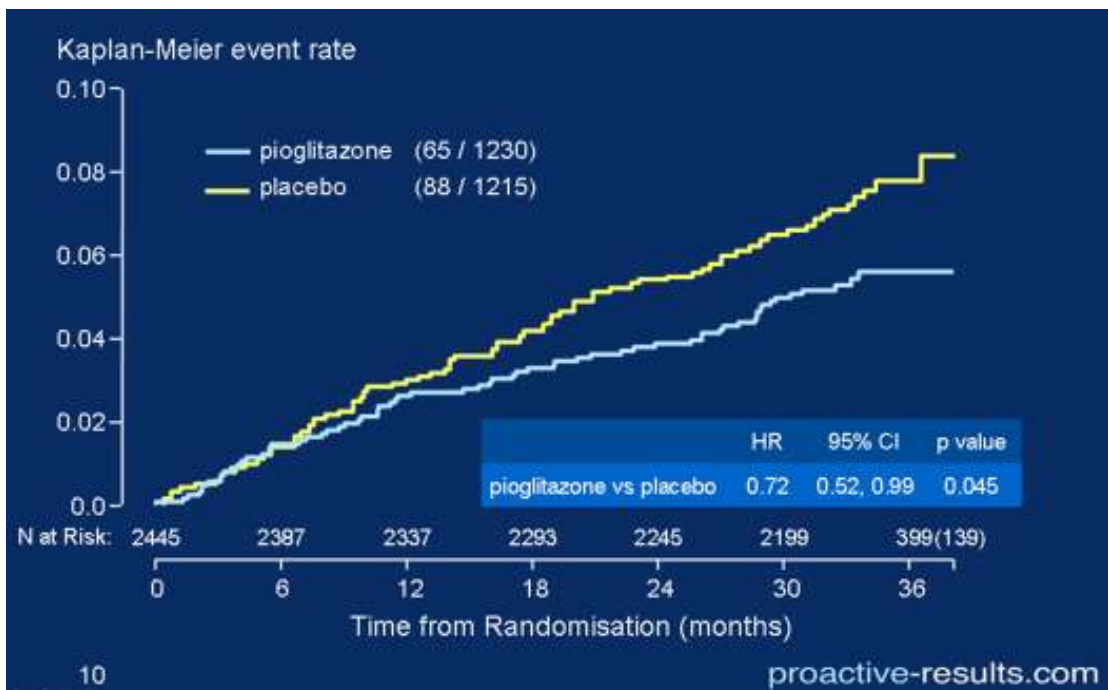
Type 2 diabetes is more than anything a disease of people dying prematurely of cardiovascular disease. Pioglitazone is the only glycaemic medication other than metformin with randomised controlled trial evidence that it reduces death, myocardial infarction and stroke (1). If it is suspended prematurely we may be losing an agent with such benefit for the sake of as yet uncertain, unproven risk.

Pioglitazone is particularly beneficial in reducing the chances of a patient who has had a stroke from having further stroke (Figure 1) (2).



**Figure 1:** Kaplan-Meier curve of the time to fatal/nonfatal stroke in the patients in PROactive who had had a previous stroke. The solid line represents the pioglitazone group; the dashed line represents the placebo group. CI = confidence interval; HR = hazard ratio. Also published in Wilcox R, et al, Stroke 2007; 38: 865–873.

Similarly pioglitazone reduces the chances of a patient who has had a myocardial infarction or acute coronary syndrome from having a repeat event (Figure 2) (3).



**Figure 2:** Kaplan-Meier curve of the time to fatal/nonfatal myocardial infarction (MI) (excluding silent MI) in patients in PROactive who had had a previous myocardial infarction. The solid line represents the pioglitazone group; the dashed line represents the placebo group. CI = confidence interval; HR = hazard ratio. Also published in Erdmann E, et al, J Am Coll Cardiol 2007; 49: 1772–1780

Whilst a meta-analysis of rosiglitazone trials raised the possibility of cardiovascular harm associated rosiglitazone (4), a similar meta-analysis of pioglitazone trials showed that among a diverse population of patients with type 2 diabetes, pioglitazone treatment was associated with a significantly lower risk of death, myocardial infarction or stroke (5).

A retrospective cohort study using the UK general practice research database (91521 patients with diabetes) suggested that pioglitazone was associated the lowest all cause mortality amongst the oral hypoglycaemic agents (6).

Randomised controlled trials of markers of carotid and coronary atherosclerosis (carotid intima-media thickness and intravascular ultrasound) have shown benefit for pioglitazone compared to sulphonylureas (7,8).

The primary composite endpoint in the PROactive study did not achieve statistical significance. Nevertheless, as shown by table 1 below, taken from that study, the first six factors in the primary composite endpoint: death, non fatal myocardial infarction, silent myocardial infarction, stroke, major leg amputation and acute coronary syndrome do show significant benefit for pioglitazone. Statistical significance is lost only when coronary and leg revascularisation are added. It has been suggested that this outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome and leg amputation to be available for coronary or leg revascularisation (9,10). This interpretation suggests a real benefit of pioglitazone in the treatment of Type 2 diabetes.

	Primary composite endpoint		Main secondary endpoint	
	Pioglitazone (n=2605)	Placebo (n=2633)	Pioglitazone (n=2605)	Placebo (n=2633)
Any endpoint	514	572	301	358
Death	110	122	129	142
Non-fatal MI (excluding silent MI)	85	95	90	116
Silent MI	20	23	NA	NA
Stroke	76	96	82	100
Major leg amputation	9	15	NA	NA
Acute coronary syndrome	42	63	NA	NA
Coronary revascularisation	101	101	NA	NA
Leg revascularisation	71	57	NA	NA

MI=myocardial infarction. NA=not applicable. This table describes the events that make up the primary composite endpoint, so if death is not the first event, it does not appear.

**Table 1:** Numbers of first events contributing to the primary composite and main secondary endpoints in the PROactive study. From Dormandy JA, et al, Lancet 2005; 366: 1279–1289.

Pioglitazone is widely prescribed in the UK and there are many patients who are stable with good glycaemic control on this agent. We believe that pioglitazone is making a major contribution to the improvement in glycaemic control amongst our patients – and it is accepted that improved glycaemic control is associated with improved microvascular outcomes (11,12).

It has been suggested that metformin, pioglitazone and GLP1 agonists may represent the optimum combination of agents for the modern management of type 2 diabetes based on the pathophysiology of the disease (13, 14).

If pioglitazone use is suspended many patients will experience worsening of glycaemic control and risk from acute hyperglycaemic syndromes as well as potentially increased microvascular and macrovascular damage.

Pioglitazone will shortly emerge from patent and with the exception of sulphonylureas there are no other popular alternative low cost pharmaceutical options.

A substantial number of people with diabetes are on triple oral hypoglycaemic therapy including pioglitazone so in the event of total withdrawal many will need to change to expensive options including injectables (a major stress on specialist resources nationally) or gliptins. A number of occupational drivers may lose their licence as a result of a total withdrawal of pioglitazone –these include occupational drivers on pioglitazone alongside GLP1-based treatment most of whom will migrate to insulin or be inadequately controlled.

Gliptins have an increasing market share and are a pressure on pharmaceutical budgets. Although heavily marketed across the UK, there are no long term safety data available and there are concerns that the ubiquity of the enzyme system which they inhibit might predispose to long term safety issues. Many people with diabetes will therefore be moving from one drug with a possible safety problem to another with an unknown long term safety record.

In financially stringent times the extra cost to the health care system of alternative agents may result in rationing of other evidence-based and NICE approved treatments for the management of diabetes.

The most powerful evidence with regard to side effects of pioglitazone come from the PROactive study as it is the only randomised controlled trial. We note that there were more bladder cancers in the pioglitazone group, although this did not achieve significance. There were significantly fewer breast cancers in the pioglitazone group (1).

We note that a publication in the current issue of Diabetes Care concerns spontaneous reports of bladder cancer the FDA Adverse Event Reporting System (15). It is of course possible that as it is well known that the link between bladder cancer and pioglitazone is being actively pursued, it is quite likely that bladder cancers are more likely to be reported in pioglitazone treated patients than in non-pioglitazone treated patients. .

We note that interim analysis of the Kaiser Permanente longitudinal cohort study found that overall ever use of pioglitazone was not associated with risk of bladder cancer but use for more than 2 years was weakly associated with increased risk. (16). This is obviously of concern for long term use. The authors of that paper do acknowledge that there were proportionately more in situ cancers among the pioglitazone users and that this might be observed if pioglitazone-treated patients underwent greater surveillance for bladder cancer.

The French regulatory body have looked at a national database of their own. We suggest the MHRA could consider inviting an interrogation of the UK general practice research database (6) looking side by side at cardiovascular outcomes, bladder and breast cancer and total mortality with regard to the different diabetes therapies.

ABCD and Diabetes UK wish to strongly encourage MHRA to resist EMA following the French and German lead with regard to pioglitazone, pending ongoing longterm investigations. While ABCD deems patient safety to be paramount, we are concerned that far more harm than good will be done if pioglitazone is suspended and that on current evidence the risk/benefit balance is strongly in favour of continuing the current licence for the use of pioglitazone to reduce the risks of diabetes-driven morbidity and mortality. In the making of decisions ABCD believes that all factors should be taken into account including macrovascular benefits of pioglitazone, the contribution of pioglitazone to good glycaemic control and associated microvascular benefits and the threat of glycaemic deterioration if pioglitazone is withdrawn. A position aligned with that of the FDA, which recommends withdrawal of pioglitazone only in those with active bladder cancer, and a risk benefit analysis in those with previous cancer, would seem a sensible interim position.

Yours sincerely

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## References

1. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366: 1279–1289.
2. Wilcox R, Bousser MG, Betteridge DJ, et al, on behalf of the PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007; 38: 865–873.
3. Erdmann E, Dormandy JA, Charbonnel B, et al, on behalf of the PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; 49: 1772–1780.
4. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med* 2007; 356: 2457–2471.
5. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298(10):1180-1188
6. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ*. 2009 Dec 3;339:b4731. doi: 10.1136/bmj.b4731.
7. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA*. 2006;296:2572-2581
8. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008;299(13):1561–1573
9. Ryder REJ. Rosiglitazone versus pioglitazone in relation to cardiovascular disease in type 2 diabetes – primum non nocere. *Practical Diabetes International* 2007; 24: 422-425
10. Ryder REJ. Pioglitazone: an agent which reduces stroke, myocardial infarction and death and is also a key component of the modern paradigm for the optimum management type 2 diabetes. In press: *Br J Diabetes Vasc Dis* 2011; 11: 10.1177/1474651411412658
11. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes UKPDS Group. *Lancet* 1998;352:837-853
12. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. UKPDS Group *Lancet* 1998;352:854-865

13. DeFronzo RA. Banting Lecture: From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes*. 2009; 58(4): 773–795.
14. DeFronzo RA. Holistic approach to glycaemic control. Online webcast lecture on website of the European Association for the Study of Diabetes (EASD). <http://easd.conference2web.com/play/2010/307990031> . [accessed 17 June 2011]
15. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care*. 2011 Jun;34(6):1369-71. Epub 2011 Apr 22.
16. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, Vaughn DJ, Nessel L, Selby J, Strom BL. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care*. 2011 Apr;34(4):916-22.

### **Declaration of interest**

#### ABCD

Current corporate sponsors of ABCD are NovoNordisk, MSD, Sanofi-Aventis, BMS/Astra Zeneca, Boehringer Ingelheim and Eli Lilly. Takeda UK are not current corporate sponsors.

#### DiabetesUK

Diabetes UK seeks to ensure that the commercial organisations with whom we work and the ways that we work with them are consistent with our organisational values. All relationships are based on the principles of integrity and openness, maintenance of independence, equality in partnership and mutual benefit for all concerned.

Diabetes UK will not accept more than five percent of total income per annum from one corporate partner with a vested interest in diabetes, nor more than 20 percent of total income per annum from commercial organisations with a vested interest in diabetes, so as not to compromise our integrity.

Takeda UK are not currently a commercial organisation with whom we work in partnership