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The Glycemic, Cardiovascular and Hepatic Outcomes of Pioglitazone Treatment: Evidence for Its Increased Use

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Introduction

The Federal Drug Administration (FDA) has begun to require large, prospective post-marketing cardiovascular outcome studies because of possible concerns regarding the negative effects of newly approved drugs used to treat type 2 diabetes on cardiovascular disease (CVD)[1]. Unexpectedly, two classes of drugs, glucagon-like peptide (GLP)-1 agonists and sodium glucose transporter (SGLT)-2 inhibitors, have shown beneficial effects on CVD in these studies[2]. However, these drugs are expensive. It is not well appreciated that pioglitazone is also beneficial for CVD outcomes[3] and, of course, much cheaper. Furthermore, pioglitazone is currently the most effective treatment for non-alcoholic steatohepatitis (NASH) which commonly accompanies type 2 diabetes and can develop into cirrhosis[4]. This Commentary will present the glycemic, CVD and hepatic evidence for resurrecting the use of pioglitazone in the treatment of type 2 diabetes.

The Glycemic Treatment Outcomes

Type 2 diabetes is characterized by both decreased insulin secretion and decreased insulin sensitivity[5], the latter also known as insulin resistance. When type 2 diabetes is diagnosed, patients have lost on average 50% of their insulin secretion, and unfortunately, it continues to progressively decrease regardless of treatment[6]. Pioglitazone, a thiazolidinedione (TZD), reduces insulin resistance[7] which allows the remaining insulin secretion to be more effective. This accounts for the results of the ADOPT Study in which newly or recently diagnosed (but only treated with lifestyle management) type 2 diabetic patients were given metformin, a sulfonylurea (glyburide) or another TZD (rosiglitazone)[8]. Treatment failure was defined as a confirmed fasting plasma glucose concentration of more than 180 mg/dl. The cumulative incidence of monotherapy treatment failure at 5 years was 15% with rosiglitazone, 21% with metformin and 34% with glyburide. Thus, the remaining insulin secretion in these patients was more effective for a longer period with the drug that lowered insulin resistance. Since metformin decreases hepatic insulin resistance, whereas TZDs lower both peripheral and hepatic insulin resistance[7], the response to the biguanide between that of the TZD and the sulfonylurea is also consistent with this explanation.

The effectiveness of TZDs in lowering HbA1c levels has been clinically established[9]. HbA1c levels decreased 2% or more in both in poorly controlled, treatment naïve patients[10] and in those who are taking maximal (tolerated) doses of both metformin and

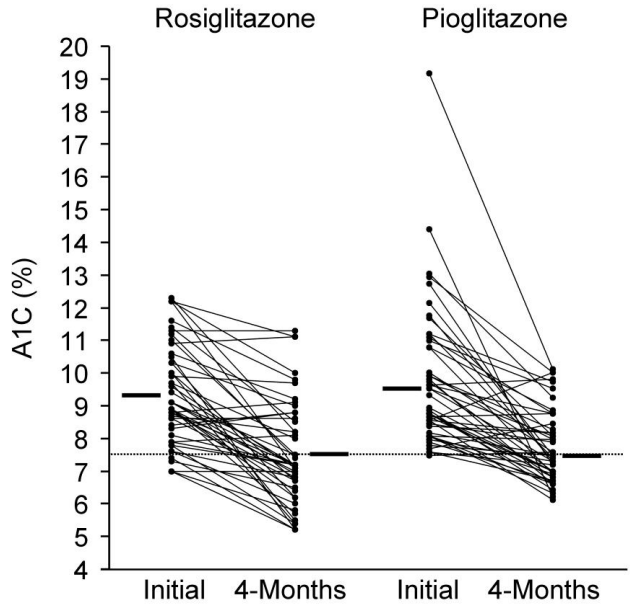

Figure 1: A1C levels before and after adding maximal doses of a thiazolidinedione (8 mg of rosiglitazone or 45 mg of pioglitazone) to type 2 diabetic patients who had failed maximally (tolerated) doses of metformin plus a sulfonylurea. Mean A1C values are depicted as bars. (Figure originally published by the author in reference 11.)

a sulfonylurea (Figure 1)[11]. Therefore, robust glycemic evidence exists for using pioglitazone, even for patients failing 2 or more other non-insulin drugs later in the course of the disease.

The Cardiovascular Treatment Outcomes

Atherosclerosis is characterized by both insulin resistance[12] and inflammation[13]. The reduction of insulin resistance by pioglitazone[7] is well established. The TZD rosiglitazone reduces inflammation[14] and we have recently found a similar effect with pioglitazone[15]. In addition, pioglitazone improves the atherogenic lipoprotein profile by converting the small, dense LDL cholesterol particles to larger, "fluffy" (less atherogenic) ones, increasing HDL cholesterol levels and reducing triglyceride levels[16]. Thus, pioglitazone might be expected to have a beneficial effect on CVD, and indeed, this has been demonstrated. In randomized control trials (RCTs), pioglitazone significantly reduced carotid intima-media thickness in type 2 diabetic patients compared with patients treated with other anti-hyperglycemic drugs in whom there was an increase[17,18]. Pioglitazone also significantly reduced re-stenosis after coronary artery stenting in type 2 diabetic patients[19,20]. In the PROactive study in patients with type 2 diabetes who had clinical evidence of macrovascular disease, pioglitazone significantly reduced the pre-specified secondary outcome of all-cause mortality, nonfatal myocardial infarction (excluding silent episodes) and stroke[21] with a predominant effect on incident myocardial infarction and stroke[22]. The hazard ratio (HR) on the pre-specified secondary outcome was 0.84 showing a significant 16% beneficial effect. The HRs for the significant beneficial effects of the GLP-1 agonists ranged from 0.74 to 0.88 and for the two SGLT-2 inhibitor studies were both 0.86. Pioglitazone had a greater effect on recurrent CVD events in the PROactive Study with HRs of 0.72 for recurrent myocardial infarctions and 0.53 for recurrent strokes[22]. In the IRIS Study in patients with insulin resistance and a previous stroke or transient ischemic attack but without diabetes, pioglitazone significantly reduced recurrent strokes or myocardial infarctions with an HR of 0.76[23]. There are at least 8 retrospective or prospective observational cohort studies showing that pioglitazone significantly reduced CVD outcomes and/or all-cause mortality in type 2 diabetic patients[3,24,25]. Therefore, robust cardiovascular evidence exists for using pioglitazone with benefits that are similar to the HR levels of the more costly GLP-1 agonists and SGLT-2 inhibitors and even lower HR levels for recurrent myocardial infarctions and strokes.

The Hepatic Treatment Outcomes

Non-alcoholic fatty liver disease (NAFLD), characterized by the accumulation of >5% of hepatic fat, occurs in approximately 25% of the general population[26]. Obesity and type 2 diabetes are major risk factors with approximately 70% of these individuals developing NAFLD (Figure 2)[27]. Up to 40% of these patients will progress to NASH which can reverse back to NAFLD[27]. However, up to 20% of

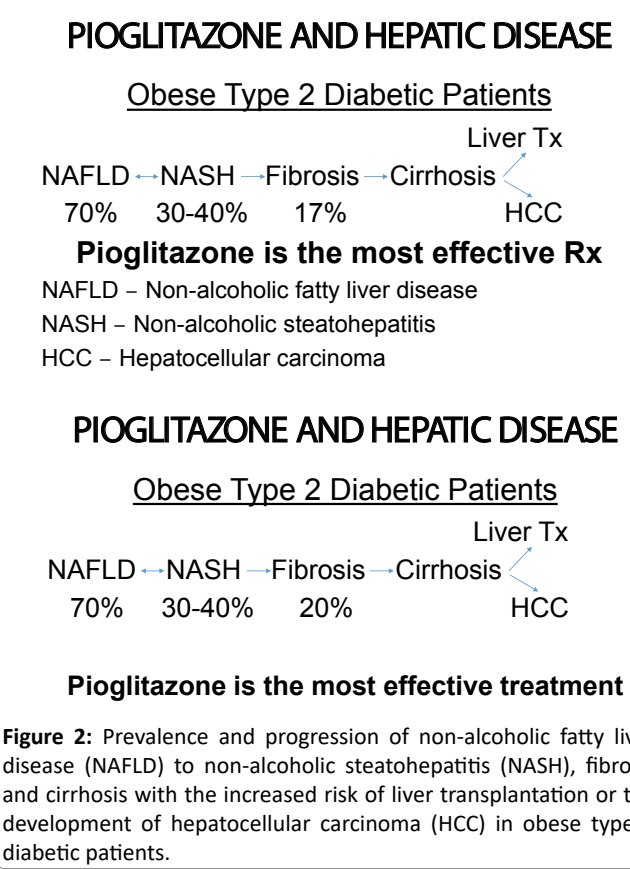

Figure 2: Prevalence and progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis with the increased risk of liver transplantation or the development of hepatocellular carcinoma (HCC) in obese type 2 diabetic patients.

patients with NASH can progress to fibrosis and many of them will develop cirrhosis with its increased mortality, need for liver transplantation and its increased risk for hepatocellular carcinoma. Although many surrogate markers are under investigation to diagnose NAFLD, NASH and hepatic fibrosis[28], NASH requires a liver biopsy for diagnosis[29]. The criteria for the diagnosis of NASH require the joint presence of steatosis, ballooned hepatocytes and lobular inflammation[26,29]. Peri-sinusoidal fibrosis is often present but is not necessary for the diagnosis of NASH[29].

Insulin resistance characterizes NAFLD[30] and pioglitazone reduces insulin resistance[7]. Additionally, pioglitazone also reduces inflammation[31]. Therefore, it might be expected that pioglitazone would have a beneficial effect on NASH, and that is indeed the case. Seven studies have consistently demonstrated a significant improvement in the histological features of NASH[32-38]. Unsurprisingly, rosiglitazone, the other TZD, was also beneficial in improving the histological features of NASH with resolution of NASH in a number of patients treated with both TZDs[39]. Other treatments of NASH have been inconsistent or negative[40]. Therefore, robust hepatic evidence exists for using pioglitazone.

Adverse Effects

All medications have some adverse effects and those of pioglitazone are well known. These include weight gain, fluid retention, heart failure, decreased bone mineral density with an increased risk of fractures, especially in women, dilutional anemia (which is not clinically significant) and possibly increased risks for macular edema and bladder cancer[41]. In spite of the weight gain, pioglitazone decreases insulin resistance. This is because the increased fat is deposited peripherally while intra-abdominal fat, the accumulation of which is associated with insulin resistance, is reduced[42]. Regarding fluid retention and heart failure, we do not use pioglitazone in patients with a history of heart failure or in those who have peripheral edema before the drug would be started[41].

The use of pioglitazone plummeted when its possible association with bladder cancer was raised. Since then there have been 20 studies evaluating the association, 13 of which have shown no association and 7 finding a statistically significant HR for the association[3,43]. A recent meta-analysis of 19 of these studies did not show a significant association between ever vs never use of pioglitazone or with cumulative doses of the drug but did show a significant association with use greater than one year[3]. However, a subsequent meta-analysis (which included the author of the first case control study that found a significant difference) concluded that since most of the observational studies were very heterogeneous and were affected by bias and poor controlling for confounding, it was not appropriate to pool the outcomes of these highly heterogeneous studies, i.e., not suitable for meta-analyses[44]. Be that as it may, statistically significant positive associations must be clinically significant as well[45]. Since HRs reflect relative differences, absolute differences must be examined to determine if findings really make a clinical difference. In the case of associations between pioglitazone and bladder cancer, this means evaluating event rates and the number needed to treat to harm (NNTH). The incidence of bladder cancer was <0.3% in patients who were either exposed or not exposed to pioglitazone[3]. In a Medicare population of nearly 250,000 patients, "the absolute differences were incredibly small, requiring over 1000 person-years of treatment to observe one excess bladder cancer event for pioglitazone compared to DPP-4s or sulfonylureas"[46]. Since hematuria is the initial sign of bladder cancer, we order urinalyses before starting the drug and at every routine diabetes visit. Working in a large county clinic, we frequently use pioglitazone as the third agent after metformin and a sulfonylurea and have not encountered bladder cancer in the many hundreds of patients taking the drug since 2003.

Comparing the NNTH with the number to treat to benefit (NNTB) is revealing. Patients who received either a low dose of pioglitazone for any length of time or moderate or high dose of the drug for less than one year had HRs for bladder cancer that were not statistically significant compared with patients who had not received the drug[3]. If these patients were included in the comparison, they would markedly increase the NNTH. Restricting the comparison to patients receiving the moderate or high doses of the drug for more than one year in whom HRs were statistically significant, the median NNTH was 1941[3]. Using these NNTH data, nearly 2000 patients would have to be treated with pioglitazone to develop one additional case of bladder cancer (if indeed the drug were really causative). In contrast, the NNTB CVD events in nine studies was 50[3]. The NNTB the histology of NASH was less than 10[3]. Therefore, the 40-fold increase in the benefit of pioglitazone for CVD and the 200-fold increase for NASH should outweigh possible concerns about bladder cancer, especially since routine urinalyses would identify newly developed, easily treatable in situ tumors should one occur.

Conclusions

The 2020 American Diabetes Association's *Standards of Medical Care in Diabetes* retains its recommendation that first line therapy in type 2 diabetes should be metformin and comprehensive lifestyle (including weight management and physical therapy)[47]. In patients in whom atherosclerotic CVD predominates, i.e., those with established disease, either a GLP-1 agonist or an SGLT-2 inhibitor should be considered as second line therapy. However, not only are these new classes of drugs

expensive, they are contraindicated in patients with eGFRs <45 ml/min for SGLT-2 inhibitors or <30 ml/min for GLP-1 agonists. In contrast, there are no renal restrictions for pioglitazone. Given the data summarized above, the beneficial effects of pioglitazone on CVD seems comparable to (or even better for recurrent myocardial infractions and strokes) the effects of the two newer classes of anti-hyperglycemic drugs and the improvement or resolution of NASH is striking. Thus, the use of pioglitazone should be resurrected for its well-established benefits on glycemia, CVD and NAFLD, especially in patients with formulary and cost issues and certainly in those who are likely to have NASH.

References

1. Department of Health and Human Services food and Drug Administration. Guidelines for Industry. Diabetes Mellitus Evaluating Cardiovascular risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. www.fda.gov/download/drugs/
2. Bailey CJ, Day C. The future of new drugs for diabetes management. Diabetes Res Clin Pract 2019; 155: 107785.
3. Davidson MB, Pan D. An updated meta-analysis of pioglitazone exposure and bladder cancer and comparison to the drug's effect on cardiovascular disease and non-alcoholic steatohepatitis. Diabetes Res Clin Pract 2018; 135: 102-110. Corrigendum. Diabetes Res Clin Pract 2018; 142: 408-409.
4. Cusi K. Treatment of patients with type 2 diabetes and non-alcoholic fatty liver disease: current approached and future directions. Diabetologia 2016; 59: 1112-1120.
5. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006; 116: 1793-1801.
6. Holman RR. Assessing the potential for α-glucosidase inhibitors in prediabetic states. Diabetes Res Clin Pract 1998; 40(Suppl): S21-S25.
7. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care 2002; 25: 517-523.
8. Khan SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New Engl J Med 2006; 355: 2427-2443.
9. Yki-Jarvinen H. Thiazolidines. New Engl J Med 2004; 351: 1106-1118.
10. Aronoff S, Rosenblatt S, Egan JW, et al., the Pioglitazone 001 Study Group. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. Diabetes Care 2000; 23: 1605-1611.
11. 11. Tran MT, Navar MD, Davidson MB. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes mellitus. Diabetes Care 2006; 29: 1395-1396.
12. DeFronzo RA. Insulin Resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010; 53: 1270-1287.
13. Yuan T, Yang T, Chen H, et al. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol 2019; 20: 247-260.
14. Mohanty P, Aljada A, Chanim H, et al. Evidence for a potent anti-inflammatory effect of rosiglitazone. J Clin Endocrinol Metab 2004; 89: 2728-2735.
15. Hsia SH, Duran P, Lee ML, et al. Comparison of hydroxychloroquine with pioglitazone as third-line agents in type 2 diabetic patients failing metformin plus a sulfonylurea: a pilot study. J Diabetes 2019; doi: 10.1111/1753-0407.12989.
16. Hanefield M. The role of pioglitazone in modifying the atherogenic lipoprotein profile. Diabetes Obes Metab 2009; 11: 742-756.
17. Koshiyama H, Shimono D, Kuwamura N, et al. Inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. J Clin Endocrinol Metab 2001; 86: 3452-3455.
18. 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.
19. Nishio K, Sakurai M, Kusuyama T, et al. A randomized comparison of pioglitazone to inhibit restenosis after coronary stenting in patients with type 2 diabetes, Diabetes Care 2006; 29: 101-106.
20. Patel D, Walitt B, Lindsay J, et al. Role of pioglitazone in the prevention of restenosis and need for revascularization after bare-metal stent implantation: a meta-analysis. JACC Cardiovasc Interv 2011; 4: 353-60.
21. Dormandy JA, Charbonnel B, Eckland DJA, 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 randomized controlled trial. Lancet 2005; 365: 1279-1289.
22. Betteridge DJ, DeFronzo RA, Chilton RJ. PROactive: time for a critical appraisal. Eur Heart J. 2008 Apr;29(8):969-83. doi: 10.1093/eurheartj/ehn114.
23. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. New Engl J Med 2016; 374: 1321-1331.
24. Strongman H, Christopher S, Majak M, et al. Pioglitazone and cause-specific risk of mortality in patients with type 2 diabetes: extended analysis from a European multidatabase cohort study. BMJ Open Diab Res Care 2018;6:e000481. doi:10.1136/bmjdrc-2017-000481.
25. Miao S, Dong X, Zhang X, et al. Detecting pioglitazone use and risk of cardiovascular events using electronic health record data in a large cohort of Chinese patients with type 2 diabetes. J Diabetes 2019 Aug; 11(8): 684-689. doi: 10.1111/1753-0407.12894.
26. Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. New Engl J Med 2017; 377: 2063-2072.
27. Cusi K. Nonalcoholic fatty liver disease in type 2 diabetes mellitus. Curr Opin Endocrinol Diab Obes 2009; 16: 141-149.
28. Vilar-Gomez E, Athinarayanan SJ, Adams RN, et al. Post hoc analyses of surrogate markers of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in patients with type 2 diabetes in a digitally supported continuous care intervention: an open-label, non-randomised controlled study. BMJ Open 2019; 9: 023597.doi:10.11367/bmjopen-2018-023597.
29. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. Diabetologia 2016; 59: 1121-1140.
30. Utzschneider KM, Kahn SE. The role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2006; 91: 4753-4761.
31. Hsia SH, Duran P, Lee ML, et al. Comparison of hydroxychloroquine with pioglitazone as third-line agents in type 2 diabetic patients failing metformin plus a sulfonylurea: a pilot study. J Diabetes 2019. doi: 10.1111/1753-0407.12989.
32. Sanyal AJ, Mofrad PS, Sargeant C, et al. A pilot study of vitamin E

versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2004; 2: 1107-1115.

33. Promrat K, Lutchman G, Uwaifo GI, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 2004; 39: 188-196.

34. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic hepatitis. N Engl J Med 2006; 355: 2297-2307.

35. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008; 135: 1176-1184.

36. Sanyal AJ, Chalasani N, Kowdley KV et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. New Engl J Med 2010; 362: 1675-1685.

37. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus. Ann Intern Med 2016; 165: 305-315.

38. Bril F, Biernacki DM, Kalavapalli S, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 2019; 42: 1481-1488.

39. Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med 2017; 177: 633-640.

40. Musso G, Cassader M, Rosina F, et al. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systemic review and meta-analysis of randomised trials. Diabetologia 2012; 55: 885-904.

41. Davidson MB**,** Hsia S: Glycemia. In: Meeting the American Diabetes Association Standards of Care: An Algorithmic Approach to Clinical Care of the Diabetes Patient. American Diabetes Association, Alexandria, VA, 2017; 58-62.

42. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002; 87: 2784-2791.

43. Davidson MB. Pioglitazone (Actos) and bladder cancer; legal system triumphs over the evidence. J Diabetes Compl 2016; 30: 901-985.

44. Ripamonti ER, Azoulay L, Abrahamowicz M, et al. A systematic review of observational studies of the association between pioglitazone use and bladder cancer. Diabetic Med 2019; 36: 22-35.

45. Pocock SJ, Stone GW. The primary outcome is positive - is that good enough? N Engl J Med 2016; 375: 971-979.

46. Gary EM, Buse JB, Lund JL, et al. Comparative safety of pioglitazone versus clinically meaningful treatment alternatives concerning the risk of bladder cancer in older US adults with type 2 diabetes. Diabetes Obes Metab 2018; 20: 129.140.

47. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43: S98-S110.