Pioglitazone and cardiovascular risk in T2DM patients: is it good for all?

Muhammad Abdul-Ghani[1], Amin Jayyous[1], Nidal Asaad[2], Sherif Helmy[2], Jassim Al-Suwaidi[2]

[1]Academic Health System, [2]Cardio-Metabolic Institute, Hamad General Hospital, Doha, Qatar

Correspondence to: Muhammad Abdul-Ghani. Academic Health System, PO Box 3050, Hamad General Hospital, Doha, Qatar.
Email: abdulghani@uthscsa.edu.

Provenance: This is an invited Editorial commissioned by Section Editor Kaiping Zhang (AME College, AME Group, Hangzhou, China).

Comment on: Vaccaro O, Masulli M, Nicolucci A, *et al.* Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol 2017;5:887-97.

Submitted Mar 01, 2018. Accepted for publication Mar 09, 2018.
doi: 10.21037/atm.2018.03.19
View this article at: http://dx.doi.org/10.21037/atm.2018.03.19

Both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (myocardial infarction, stroke, amputation) complications of type 2 diabetes mellitus (T2DM) are responsible for the increased morbidity, mortality and health care expenditure in T2DM patients (1,2). Thus, decreasing the risk of diabetic vascular complications will have great impact on both public health and health care expenditure.

Diabetes is the leading cause of blindness and end stage renal disease in western countries (2), and T2DM individuals have a 2.5–4-fold increase in the risk of cardiovascular disease (3). Cross sectional studies have demonstrated that one-third to one-half of all people with diabetes have evidence for organ damage (4). Although not everyone with diabetes is destined to develop complications, a recent epidemiological study (4) reported that two or more complications are apparent in almost one-fifth of people with diabetes.

The risk of microvascular complications is strongly associated with the severity of hyperglycemia (5,6). Further, it is very well established that lowering the plasma glucose concentration in T2DM patients markedly reduces their risk of retinopathy and nephropathy. Each 1% decrease in the HbA1c is associated with ~40% reduction in the risk of retinopathy and nephropathy (5-9). Thus, maintaining a durable glycemic control at <7.0% is recommended by all professional organizations (10-12).

Although subjects with T2DM have a markedly increased risk of cardiovascular disease (myocardial infarction and stroke) and a worse prognosis following any cardiovascular event (3,13), lowering the plasma glucose concentration had little benefit to reduce CVD risk in T2DM patients (6,14,15). Suggesting that hyperglycemia *per se* is a weak CVD risk factor and other factors contribute to the increased CVD risk in T2DM. Conversely, lowering blood pressure and LDL cholesterol markedly reduced CV risk in T2DM patients (16-20). Moreover, most T2DM individuals manifest moderate to severe insulin resistance which is associated with multiple metabolic abnormalities (obesity, dyslipidemia, hypertension, endothelial dysfunction, procoagulant state), all of which are important risk factors of CVD (21). Further, the molecular mechanism of insulin resistance has been suggested to accelerate the atherosclerotic process (22,23). These observations have led to the hypothesis that insulin resistance is the mechanism which links T2DM and high CVD risk (22,23). Based upon this hypothesis, it is anticipated that antidiabetic agents that improve insulin sensitivity will reduce CV risk in T2DM independent of their ability to lower plasma glucose concentration.

Pioglitazone is the only true insulin sensitizer available for treatment of T2DM (24-26). In addition to lowering plasma glucose concentration, pioglitazone decreases insulin resistance (by 35–40%) in skeletal muscle, liver and adipocytes (27), decreases plasma triglyceride concentration, increases HDL cholesterol converts small dense atherogenic LDL particles to larger more buoyant ones, and reduces blood pressure (28), pioglitazone also reduces plasma FFA,

adipocytokines/other inflammatory markers/procoagulant factors, and increases plasma adiponectin (24-28), all of which would be expected to provide cardiovascular benefit. Thus, pioglitazone would be expected to provide additional cardiovascular benefits, independent of the reduction in plasma glucose concentration (29,30). Consistent with this, pioglitazone has been shown to slow the progression in carotid intima medial thickness in T2DM patients (31) and in subjects with impaired glucose tolerance (32). Further, pioglitazone reduced coronary atheroma volume (33) and decreased the risk of coronary restenosis in type 2 diabetes patients receiving coronary stent (34). Lastly, in large clinical outcome studies, pioglitazone significantly lowered the incidence of 3-point MACE (non-fatal myocardial infarction, non-fatal stroke, CV death) in T2DM patients with established CVD. In PROactive (35), 5,238 T2DM patients with existing CVD were treated for 2.9 years with pioglitazone or placebo plus standard of care for glycemic control and CV risk factors. Three-point MACE, the main secondary endpoint, was significantly reduced by 16% (HR =0.84, P=0.027). In IRIS (36), 3,876 insulin resistant (HOMA-IR >3.0), nondiabetic individuals with recent (within 6 months) ischemic stroke or TIA were randomized to pioglitazone or placebo for 4.8 years. Pioglitazone caused a 24% reduction in fatal/nonfatal stroke plus myocardial infarction (HR =0.76, P=0.007). Because glycemic control in subjects in both arms in the PROactive study were treated to target and participants in IRIS study did not have T2DM, the results of these studies demonstrate that pioglitazone reduced CVD risk independent of its glucose lowering action.

Both PROActive (35) and IRIS (36) studies demonstrated CV benefit of pioglitazone in T2DM patients with established CVD. Although T2DM patients with established CVD have the highest CV risk (3), T2DM patients without established CVD also manifest increased CV risk than non-diabetic individuals. The 7-year risk of myocardial infarction or CV death in T2DM patients without established CVD is similar to that of non-diabetic individuals with established CVD (3). Because at any given time, the majority of T2DM patients do not have established CVD, it is important to determine whether pioglitazone exerts CV benefit in T2DM patients without established CVD. The TOSCA-IT study was designed to answer this question.

TOSCA-IT study

TOSCA-IT study (37) is a randomized, prospective, open label study in which 3,028 poorly controlled T2DM patients (HbA1c =7.0–9.0%) on maximal dose of metformin therapy were randomized to receive pioglitazone (n=1,535) or sulfonylurea (SU) (n=1,493) therapy added to metformin. Participants were 50–75 years of age (mean =62 years), predominantly men (~60%), had diabetes for >2 years (mean =8.4 years), baseline HbA1c of 7.0–9.0% (mean =7.7%), and BMI of 20–45 kg/m^2 (mean =30.3). The vast majority of participants (89%) were free of CVD at baseline and had good control of CV risk factors. Mean systolic blood pressure was 134 mmHg, LDL cholesterol was 2.66 mM (~100 mg/dL); HDL cholesterol was 1.2 mM, 70% of participants received antihypertensive therapy, 60% received statin and 30% received antiplatelet therapy.

To avoid hypoglycemia, both pioglitazone and SU were started at low dose and the dose was escalated based upon blood glucose levels. However, neither medication reached a maximal dose in all patients at the end of the study. The mean pioglitazone dose was 23.0 mg/day, and the mean SU dose was 42.0 and 2.5 mg/day for gliclazide and glimepiride, respectively. Further, more patients discontinued the study in pioglitazone arm than SU arm (28% *vs.* 16%, P<0.0001).

Because the study was designed as a pragmatic study, the primary outcome was defined as composite of: total mortality (rather than CV death), non-fatal MI, non-fatal stroke and urgent coronary revascularization. A wider main secondary outcome included, in addition to the primary outcome, leg amputation, and all revascularizations (coronary, leg, and carotid).

The study was powered to detect 20% difference in the incidence of the primary outcome between the two treatment arms. Because the study was event driven, assuming an event rate of 3.5% per year, the investigators estimated that 498 events are required to test the working hypothesis. However, slow recruitment rate, low incidence of the primary outcome, and greater drop out rate in the pioglitazone arm (23%) resulted in a much smaller number of events than anticipated (213 *vs.* 498), and have led the investigators after 8 years of the study start to conclude that the chance that the study reaches its target was low (5%) and decided to terminate the study before reaching the target number of planned events.

Because of the obstacles faced in this study, it is not surprising that the intention to treat analysis, demonstrated that both the primary and main secondary outcomes failed to demonstrate significant difference between the two treatment arms. Because of high discontinuation rate in pioglitazone arm, the investigators performed on treatment analysis, and in this analysis, the primary outcome in

subjects receiving pioglitazone was not different than in subjects receiving SU (HR =0.95; 95% CI, 0.74–1.26, P=0.79). However, the key secondary outcome of 3-point MACE plus leg amputation and coronary and carotid revascularization was significantly reduced by 21% (HR =0.79; 95% CI, 0.47–0.96, P=0.03).

Taking the TOSCA-IT study results collectively, one can conclude that, the study failed to demonstrate significant difference in CV outcome between pioglitazone-treated and SU-treated T2DM patients without established CVD. Despite the negative outcome of TOSCA-IT, it does not definitively rule out possible CV benefit of pioglitazone on CV risk in T2DM patients without established CVD. In addition to the technical limitations of TOSCA-IT study discussed above, several other factors could have contributed to the negative result of the study:

(I) In TOSCA-IT study, pioglitazone was compared to SU while in IRIS and PROactive studies, pioglitazone was compared to placebo. Although no conclusive evidence is available about the effect of SU on CV outcome in T2DM patents, it is possible that SU have exerted some degree of CV benefit which have contributed to the small difference between the two treatment arms in TOSCA-IT study. Results of the ADVANCE study (15) have demonstrated that subjects in the intensive arm (60% of whom had their glucose control intensified with gliclazide) have experienced a small (6%), though not significant, reduction in cardiovascular events. A small CV benefit, even if not significant, of SU in TOSCA-IT could narrow the difference between the two treatment arms;

(II) Both IRIS and PROactive studies utilized full dose of pioglitazone (45 mg/day) compared to a mean dose of 23 mg/day in TOSCA-IT. Thus, one can assume that approximately one half of patients received 30 mg of pioglitazone and the other half received 15 mg per day. Although the investigators did not stratify the outcome of the study based upon pioglitazone dose utilized, dose response studies (27) have demonstrated a weak effect of 15 mg dose on insulin sensitivity and other metabolic abnormalities of T2DM, e.g., FFA, adiponectin, etc. Thus, it is possible that the dose difference between TOSCA-IT study and IRIS and PROactive study could, at least in part, have contributed to the negative outcome of TOSCA-IT study;

(III) It is possible that, indeed pioglitazone is effective in lowering CV risk only in secondary prevention, not in primary prevention. Thus, only subjects with established CVD, like participants in IRIS and PROactive studies, would benefit from pioglitazone, while subjects without established CVD would not benefit from pioglitazone.

Because of these limitations of TOSCA-IT study, it is impossible to determine the CV benefit of pioglitazone in T2DM patients without established CVD. Nonetheless, the results of TOSCA-IT study emphasized two important aspects of pioglitazone actions in T2DM patients: (I) consistent with many previous studies [reviewed in (38)] pioglitazone produced more durable reduction in HbA1c than SU. Although the decrease in HbA1c at 6 months was greater in subjects receiving SU than pioglitazone, the HbA1c progressively increased after 6 months, and after 1 year, the mean HbA1c remained lower in subjects receiving pioglitazone compared to subjects receiving SU (P=0.01). Further, fewer patients had treatment failure in pioglitazone (11%) arm than in SU (16%) arm (P<0.0001). As expected, subjects receiving pioglitazone experienced lower rate of hypoglycemia than subjects receiving SU despite lower mean HbA1c. The incidence of minor hypoglycemic events was 3.2-fold greater in subjects receiving SU; (II) because of the long duration of the study (8 years), TOSCA-IT study provided important information about the long-term safety profile of pioglitazone and SU. In general, only small number of subjects experienced serious adverse events (~14%) and their rate was comparable in both groups. Interestingly, the incidence of bladder cancer, bone fractures and congestive heart failure was similar between both groups.

Implication for care

Metformin is the recommended first line therapy in T2DM patients (10-12). However, despite initial decrease in the HbA1c after initiating metformin therapy, the HbA1c progressively increases over time and after 5–6 years of starting metformin, the HbA1c increases back to the initial level (6). Thus, a second line therapy is recommended. The TOSCA-IT study can be viewed as a comparative effectiveness trail that compares pioglitazone versus SU as a second line therapy. Although the results of TOSCA-IT trial does not provide evidence in support of greater reduction in CV risk by pioglitazone, pioglitazone produced more durable reduction in the HbA1c with lower risk

of hypoglycemia. Weight gain was comparable between the two treatment groups, as was the incidence of series adverse events. Thus, with regards to metabolic control, the results of TOSCA-IT study provide evidence that favors pioglitazone over SU as a second line therapy in metformin failing patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Abdul-Ghani M, Asaad N, Helmy S, Al-Suwaidi J. Pioglitazone and cardiovascular risk in T2DM patients: is it good for all? Ann Transl Med 2018;6(10):192. doi: 10.21037/atm.2018.03.19

