Nutrition, Metabolism & Cardiovascular Diseases (2018) **28**, 722–726

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

Glucose lowering strategies and cardiovascular disease in type 2 diabetes – teachings from the TOSCA.IT study

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Received 6 March 2018; received in revised form 17 April 2018; accepted 19 April 2018
Handling Editor: A. Giaccari
Available online 27 April 2018

KEYWORDS
Type 2 diabetes;
Cardiovascular disease;
Hypoglycaemic drugs;
Pioglitazone;
Sulphonylureas

Abstract TOSCA.IT is an institutional, non-industry-supported, head-to-head study comparing long term cardiovascular effects, efficacy and safety of two antidiabetes drugs (pioglitazone vs sulphonylureas) used in combination with metformin in patients with type 2 diabetes mellitus. The study results show that in the absence of clinically evident cardiovascular disease both treatment strategies represent suitable alternatives; however, in consideration of the greater durability of the metabolic effects, the lower risk of hypoglycemia and the potential benefit on atherosclerotic cardiovascular disease, the combination of metformin and pioglitazone may be considered as the preferential therapeutic option. In this review the study is critically evaluated against the background of the evidence accumulated over the last decade on the impact of different glucose lowering drugs on cardiovascular events in people with type 2 diabetes.

Introduction

Cardiovascular diseases (CVD) remain the most common cause of death and morbidity in people with type 2 diabetes (T2DM), despite noticeable advances in the prevention and treatment of CVD in recent years. Whereas the correction of major cardiovascular risk factors has proven highly effective also in people with diabetes [1,2], the trials designed to evaluate the cardiovascular effects of intensive vs less intensive glucose control have provided heterogeneous results (reviewed in 3). Overall, more intensive glucose control has been associated with a significant, albeit limited, benefit on the occurrence of cardiovascular events; nonetheless, total and cardiovascular mortality have not significantly decreased with this approach [3]. Among other reasons, this might be partly due to untoward effects of hypoglycemic drugs on the cardiovascular system, in particular, to the potentially adverse effects of SUs that may have counterbalanced the benefits of improved glucose control.

Against this background, it is relevant to review the available evidence on the impact of different glucose lowering drugs on cardiovascular events, independently of their glucose lowering effect, to guide the choice of hypoglycemic treatment(s) for people with type 2 diabetes. Metformin is the recommended first line drug for type 2 diabetes [4], but the progressive nature of the disease requires a stepwise therapeutic approach combining different hypoglycemic agents when metformin alone is no longer sufficient [5]. The increasing number of available drugs with different mechanisms of action and the lack of randomized controlled trials directly comparing the

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https://doi.org/10.1016/j.numecd.2018.04.008

different combination regimens - not only in achieving a satisfactory blood glucose control, but also in terms of their impact on diabetes complications – makes the choice of the best second line treatment a challenge for clinicians.

Over the last decade, several cardiovascular outcome trials (CVOT) on glucose lowering drugs other than insulin have been completed [6–17]. These trials are driven by regulatory requirements of Food and Drug Administration industry guidance for the licensing of antidiabetes drugs issued following the rosiglitazone case and are primarily designed to assess the cardiovascular safety of the study drug(s). With few exceptions, they are based on a non-inferiority design versus placebo and have a relatively short duration. Therefore, although highly relevant, these studies, by design, cannot provide information on the comparative effectiveness and risk/benefit balance of different hypoglycemic drugs; furthermore, they leave unanswered the question of whether the study drug(s) impact on the natural history of the cardiovascular complications of diabetes. It is common knowledge, in fact, that the cardiovascular complications of diabetes are largely attributable to the heavy atherosclerotic burden, and prior studies have shown that any effect on atherosclerotic cardiovascular end points takes much longer to become evident [18,19]. Finally, the prevalent/exclusive enrolment of participants with prior CV events casts doubts on the generalizability of the results to lower risk populations, which represent most people with diabetes. There is clear need for trials where the crucial question of the comparative balance between risks and benefits of different treatment strategies for T2DM are evaluated in a head-to-head comparison, with a sufficiently long follow-up, in more representative samples of people with type 2 diabetes. TOSCA.IT is the only published trial designed as head-to-head comparison of two active glucose lowering strategies, thus partially filling this void. Nevertheless, the recent trials open new perspectives by showing that some of the newest hypoglycemic drugs have clear cardiovascular benefits in secondary prevention. In particular, the sodium-glucose transporter-2 (SGLT-2) inhibitor empagliflozin [12] was the first to show a reduction in cardiovascular mortality, subsequently confirmed – although with a smaller magnitude – by canagliflozin [15]. In addition, the glucagon-like peptide-1 (GLP-1) agonists liragutide (LEADER) and semaglutide (SUSTAIN -6) have shown significant benefits on cardiovascular outcomes in comparison with placebo [13,14]. Based on this evidence the standards of medical care in diabetes of the American Diabetes Association recommend the use of SGLT2 inhibitors and liraglutide as second line treatment in people with established CVD [20].

Rationale and main results of TOSCA.IT

Within the panorama of the completed and ongoing trials, TOSCA.IT represents one of the few examples of institutional, non-industry-supported, head-to-head study exploring the comparative long-term CV effects, as well as efficacy and safety of two second-line antidiabetic drugs in a population of patients with early T2DM and low prevalence of prior CVD, largely neglected in prior cardiovascular outcomes trials. The sulphonylureas (SUs) are still the most commonly used drugs upon metformin failure worldwide, most likely because of their perceived efficacy, the long-lasting experience accumulated by clinicians, and their economic affordability. However, the cardiovascular safety of SUs has been questioned. The controversy started with the University Group Diabetes Project showing an increased mortality in patients treated with tolbutamide as compared to insulin or diet alone, and the debate is still ongoing after 50 years of their use [20,21]. Recent meta-analyses of randomized controlled trials do not show an increase in CV risk associated with second generation SUs (Glibenclamide, Glipizide, Glimepiride, Gliclazide); the largest body of evidence supporting the adverse CV effects of SUs comes from observational studies which, by design, are not suited to evaluate cause effect-relationship due to the lack of appropriately matched controls [21]. The picture becomes even more complex when these drugs are evaluated in association with metformin. In a subgroup of patients enrolled in the UKPDS, those given metformin plus SUs showed significantly higher mortality compared to patients treated with SU alone [22]. Since SUs are often used in combination with metformin, these data emphasize the need to evaluate the CV effects and other relevant health outcomes of this treatment strategy as compared to a therapeutic approach based on metformin plus a hypoglycemic drug from another class, with a different mechanism of action.

Thiazolidinediones are glucose lowering drugs that, at variance with SUs, exert their hypoglycemic effect by improving insulin action without any direct stimulatory influence on pancreatic beta cells, thus entailing a minimal risk of hypoglycemia; moreover, they ameliorate the cardiovascular risk factor profile. These represent quite good reasons to hypothesize that this class of drugs may have great potential for cardiovascular protection. Whereas rosiglitazone has been dismissed because of a purported increased CV risk, pioglitazone has been shown to reduce the incidence of CV events as compared to placebo in people with diabetes and prior CVD in the PROactive study [6]. Furthermore in the IRIS study, involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was significantly lower among patients who received pioglitazone than among those who received placebo [23]. Moreover two studies – PERISCOPE and CHICAGO - have shown with intravascular ultrasound technique that pioglitazone significantly reduces the progression of atherosclerosis of the carotid or coronary arteries [24,25]. The use of pioglitazone in clinical practice, however, has been restricted by concerns over purported increased rates of heart failure, fractures and bladder cancer [26–28]. It is therefore relevant to evaluate this compound in relation to its long-term impact on cardiovascular events and general safety, also considering that pioglitazone is the only insulin sensitizer currently available in clinical practice.

Against this background TOSCA.IT was designed as a pragmatic trial – i.e. following the indications and contraindication for the study drugs, no run in and no prespecified goals for treatment – comparing, in a usual care setting the long-term effects on the incidence of cardiovascular events, glucose control and safety, of adding a sulphonylurea or pioglitazone to metformin in the treatment of patients with type 2 diabetes inadequately controlled with metformin monotherapy [29].

The main results of the study have been published recently [17]. The trial was performed at 57 sites in Italy and enrolled 3028 patients with type 2 diabetes aged 50–75 years insufficiently controlled with metformin alone, who were randomly assigned to pioglitazone or SUs, determined by local practice (mostly glimepiride or gliclazide). Average diabetes duration was 8 years, glycated hemoglobin 7.7% and prevalence of prior CVD 11%. The occurrence of end point events was much lower than estimated and the trial was stopped after a median follow-up of 57.3 months, on the basis of a futility analysis, with no difference in the primary cardiovascular outcome - a composite of first occurrence of all cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization (HR 0.96,95% CI 0.74–1.26). Premature permanent discontinuation of the study medications was significantly more frequent in the pioglitazone than in the SU arm (28.1% vs 15.9%, $p < 0.001$), this was largely due to the alert issued by EMA and AIFA in July 2011 regarding a suspected increased risk of bladder cancer with Pioglitazone. The "on treatment" analysis was performed to partially account for the unbalanced rate of premature treatment(s) discontinuation which may have diluted possible differences between the study arms. In this analysis the occurrence of the key secondary outcome – a composite of atherosclerotic cardiovascular events – was significantly reduced by almost 30% in the pioglitazone plus metformin group.

In addition, pioglitazone was associated with significantly better durability of the glucose lowering effect, higher HDL cholesterol and significantly fewer hypoglycemic events. No significant differences between treatment groups were observed with regard to weight gain, heart failure, cancer – including bladder cancer - fractures and macula edema.

Clinical messages from TOSCA.IT

1) An important message from this study comes from the low event rate recorded during the trial – less than half that expected on the basis of findings of the PROactive study conducted 10 years earlier. This observation is coherent with data from recent observational studies [30] and highlights the changing natural history of CVD in diabetes, largely attributable to the increasing implementation of effective preventive measures such as the use of statins, antihypertensive and antiplatelet agents.
2) The study results indicate that the incidence of cardiovascular events is similar with SUs (glimepiride and gliclazide) or pioglitazone. The apparent absence of cardiovascular benefits with pioglitazone, a drug with proven advantages in secondary prevention trials in people with or without diabetes [6,23] might be partly explained by the choice of the principal endpoint which includes all-cause death, but also by the features of the study population. TOSCA.IT has enrolled a population with low absolute cardiovascular risk (low prevalence of CVD (11%), relatively short diabetes duration (8 years) and well controlled cardiovascular risk factors). In such a population, neglected in prior trials, but more representative of the general population with type 2 diabetes [31], the beneficial effects of pioglitazone on total cardiovascular events (ischemic and non ischemic end points) may be too small to be detected.
3) The discrepancy between the results of TOSCA.IT and those of studies with pioglitazone in secondary prevention cohorts is coherent with the hypothesis that the cardiovascular effects of the hypoglycemic drugs may quantitatively differ in relation to the absolute CV risk of the study population(s). This hypothesis is also supported by a subgroup analysis of the CANVAS trial showing a differential effect of the SGLT2 inhibitor canagliflozin in patients with or without prior CVD, with a significant reduction in the outcomes only in patients with prior CVD [32]. Unfortunately available evidence shows that primary prevention trials are unfeasible and it is therefore unlikely for a definitive answer on this point to become available in the future. For the time being the SGLT2 inhibitors and liraglutide are the recommended second line treatment for patients with diabetes and clinically evident atherosclerotic cardiovascular disease while they represent one of several therapeutic options in type 2 diabetic patients with a lower cardiovascular risk [20].
4) The lower rate of ischemic cardiovascular events (the key secondary end-point) observed in patients treated with metformin plus pioglitazone in the "on treatment" analysis, cannot be taken as a conclusive evidence, it is however very much in line with the findings of the IRIS and the PROactive trials, and is also coherent with the anti-atherosclerotic effect of pioglitazone shown by the CHICAGO and PERISCOPE studies. Altogether, the available evidence, including also epidemiological observations on the relationship between impaired insulin action and increased risk of atherosclerotic cardiovascular diseases at the population level, supports the notion that insulin resistance is a risk factor for atherosclerosis, and interventions aimed at improving insulin sensitivity have a beneficial impact on the risk of ischemic cardiovascular events.
5) A further relevant information from TOSCA.IT is the long-term safety profile of the study drugs. Weight gain was modest (less than 2 Kg in 5 years, with no difference between study arms), although presumably higher than that observed with other anti-diabetes drugs. Severe hypoglycemia was infrequent

even in the SUs group (i.e 68% did not report any hypoglycemia during 5 years of follow-up and only 2% ever experienced severe hypoglycemia). The known side effects of pioglitazone (i.e heart failure, fractures, macular edema) were rare and no excess of bladder cancer was observed in patients treated with this drug. The appropriate selection of the study participants (i.e exclusion of patients with congestive heart failure NYHA 1 or higher, or with impaired renal function), the use of submaximal doses of the study drugs together with the selection of the compounds with the best safety profile within the class, are a likely explanation for the low rate of side-effects

Conclusions

In conclusion, notwithstanding some limitations, TOSCA.IT is an important pragmatic trial. Unlike other completed and ongoing trials, the study provides a head-to-head comparison of the effectiveness and safety of two largely available and economically affordable second-line hypoglycemic drugs. Altogether, this study indicates that, in T2DM patients with early diabetes and low prevalence of prior CVD inadequately controlled with metformin, both treatment strategies tested are suitable; however, considering the durability of the metabolic effects, the lower risk of hypoglycemia and the positive impact on plasma lipids and possibly on ischemic cardiovascular events, the combination of metformin and pioglitazone may be preferred to metformin plus a sulphonylurea. The study results are also relevant from the point of view of public health. We are facing a diabetes epidemic; the confirmed safety profile of older, widely available and economically affordable drugs such as pioglitazone and some SUs (gliclazide and glimepiride)- when used appropriately and selected for the right patients - offer effective treatment with a positive benefit−risk relationship, which is particularly relevant when availability and cost are major issues.

The study results also stimulate the design of clinical trials to generate more comparative outcome data with newer antihyperglycemic drugs. There is clear need for trials like TOSCA.IT, where the crucial question of the comparative balance between risks and benefit of different treatment strategies for T2DM is evaluated in a head-to-head comparison with a sufficiently long follow-up. For the time being, the clinical implications of this study—interpreted in the context of the available evidence—are that, while in people with established CVD the recommended second line treatment after metformin treatment added to metformin should include drugs with a documented cardiovascular benefit (pioglitazone, liraglutide, SGLT-2 inhibitors), in people with early diabetes and no prior CVD we have many options but few certainties. In particular, since we have very few head-to-head comparisons of hypoglycemic drugs in relation to their impact on cardiovascular events, the evidence provided by TOSCA.IT, together with other relevant information available in the literature [33], indicates that the choice of the second line treatment in these patients should not primarily focus on the cardiovascular effects of the drug(s) but should also take into consideration other relevant clinical aspects like the long term durability of glucose control, tolerability, side effects and cost.

References

[1] Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J, Multiple risk factor intervention trial Research Group. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the multiple risk factor intervention trial. Arch Intern Med 2004 July 12;164(13):1438−43.

[2] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebocontrolled trial. Lancet 2004 Aug 21-27; 364(9435):685−96.

[3] Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009 Sep 15;151(6):394−403.

[4] Approaches to glycemic treatment: standards of medical care in diabetes 2018. Diabetes Care 2018;41(Suppl. 1):S73−85. https://doi.org/10.2337/dc18-S008.

[5] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005−12 [Pharmacologic].

[6] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al., On behalf of the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspectivepioglitAzone Clinical Trial in macroVascular Events): a randomized controlled trial. Lancet 2005;366:1279−89.

[7] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125−35.

[8] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013 Oct 3;369(14):1317−26.

[9] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013 Oct 3;369(14):1327−35.

[10] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. ELIXA investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015 Dec 3; 373(23):2247−57.

[11] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al., TECOS study group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015 Jul 16;373(3):232−42.

[12] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117−28.

[13] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. LEADER trial investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4):311−22.

[14] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. SUSTAIN-6 investigators sustain 6. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375(19):1834−44.

[15] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017 Aug 17;377(7):644−65.

[16] Holman RR, Bethel MA, Mentz RJ. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017; 377:1228−39.

[17] Vaccaro O, Masulli M, Nicolucci A, Bonora E, Del Prato S, Maggioni AP, 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 randomized multicentre trial. Lancet Diabetes Endocrinol 2017 Nov;5(11):887–97.
[18] Holman RR, Paul SK, Bethel MA, Matthews DR. Neil HA.10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008 Oct 9;359(15):1577–89.
[19] Nathan DM, McGee P, Steffes MW, Lachin JM, DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. Diabetes 2014 Jan;63(1):282–90.
[20] Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2018. Diabetes Care 2018;41(Suppl. 1): S73–85.
[21] Abdelmoneim AS, Eurich DT, Light PE, Senior PA, Seubert JM, Makowsky MJ, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes Obes Metabol 2015;17(6):523–32.
[22] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–65.
[23] Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–31.
[24] Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino Sr RB, et al. Effect of pioglitazome compared with glimepiride on carotid intima media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296:2572–81.
[25] Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. For the PERISCOPE invstigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patiensts with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–73.
[26] Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015; 314:265–77.
[27] Zhu NZ, Jang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014; 68:115–23.
[28] Lorenzo CV, Margulis A, Pladevall M, et al. The risk of heart failure associated with the use of non-insulin blood glucose-lowering drugs; systematic review and meta-analysis of published observational studies. BMC Cardiovasc Disord 2014;14:129.
[29] Vaccaro O, Masulli M, Bonora E, Del Prato S, Giorda CB, Maggioni AP, et al. Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: impact on cardiovascular events. A randomized controlled trial. Nutr Metabol Cardiovasc Dis 2012;22(11):997–1006.
[30] Tancredi M, Rosengren A, Svenson AM, et al. Excess mortality in persons with type 2 diabetes. N Engl J Med 2015;373:1720–32.
[31] rapporto anno CINECA - SID Osservatorio ARNO diabete. 2017.
[32] Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (canagliflozin cardiovascular assessment study). Circulation 2018;137(4):323–34.
[33] Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? Lancet Diabetes Endocrinol Feb 28, 2018.