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VIEWPOINT

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

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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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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.