OBSERVATIONS

The TOSCA.IT Trial: A Study Designed to Evaluate the Effect of Pioglitazone Versus Sulfonylureas on Cardiovascular Disease in Type 2 Diabetes

The recently published American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on the management of hyperglycemia in type 2 diabetes (T2D) (1) underlines the complexity of the therapeutic approach in T2D. This is due to both the increasing number of available drugs and to the paucity of solid data on the superiority of one compound over the others. By and large, antidiabetic drugs reduce blood glucose to a similar extent but have different impacts on cardiovascular (CV) risk factors, durability of efficacy, safety, and possible added values (2–4). A major challenge for clinicians is to select treatments that are capable of achieving and maintaining glucose control for as long as possible while minimizing the risk of chronic complications, including cardiovascular disease (CVD). This goal should be pursued with minimal side effects (mainly hypoglycemia). Although there is agreement on the use of metformin as initial treatment, the ADA/EASD statement underlines the lack of high-quality data to guide the choice of the best second-line treatment. To contribute to closing this gap, the Italian Society of Diabetology is conducting the Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT), a randomized, parallel-group, nonblinded trial designed to compare the impact on CVD of pioglitazone versus sulfonylureas as add-on drugs in patients inadequately controlled with metformin. The study is supported by the Italian Medicines Agency, a public institution funded and supervised by the Italian Ministry of Health, within the Independent Drug Research Program (contract FARM6T9CET), and by Diabete Ricerca, a nonprofit Research Foundation of the Italian Society of Diabetology. No financial support from drug companies has been planned or is expected. Patients with T2D, 50–75 years of age, on secondary failure with metformin monotherapy (≥2 g/day; HbA_{1c} 7.0–9.0%) are randomized to add on a sulfonylurea or pioglitazone. The primary efficacy outcome is a composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, and unplanned coronary revascularization. The principal secondary outcome is a composite of sudden death, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, major amputations, endovascular or surgical intervention on coronary, leg, or carotid arteries. Further secondary end points are heart failure, microangiopathy, costs, and quality of life. Recruitment is planned to end by June 2013, with 3,371 patients enrolled. To date, 2,400 patients have been randomized (70% of target). Follow-up will last 48 months.

TOSCA.IT is the only ongoing trial designed as a head-to-head comparison of pioglitazone versus sulfonylureas with CV end points and is also the only study, besides PROactive, evaluating the CV effects of thiazolidinediones. A previous trial (Thiazolidinedione Intervention With Vitamin D Evaluation) has been terminated prematurely because of concerns on the CV safety of rosiglitazone (5).

We are confident that TOSCA.IT will provide reliable information for an evidence-based choice between two of the most widely used and less expensive drugs for the management of T2D patients once metformin alone is no longer effective.

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