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Risk of heart failure in diabetic patients receiving sulfonylureas

A recent viewpoint published in this Journal highlights the inadequate perception of clinicians of the relevance of heart failure (HF) in diabetes and of the impact that diabetes treatment enhancing the action of insulin can determine on patients' outcomes.¹ We largely share the author's concerns, but we think it is appropriate to offer further considerations on this issue in the light of the outcomes of the TOSCA.IT study.

Although the epidemiology and the mechanisms of the association of diabetes mellitus with HF are firmly established, strategies for early diagnosis and intervention are not clearly defined, partly because not all diabetic patients are at equal risk.² In a cohort study of 8231 patients with type 2 diabetes mellitus (T2DM) and 8845 non-diabetic people, followed up for 6 years, the cumulative incidence of HF was 14.2% with an annualized rate of 3.1% per year in people with diabetes and 5.9% with an annualized rate of 1.24% in those without diabetes.³ A recent review including 21 studies and 507 637 patients with T2DM reports a cumulative HF incidence of 10.7% over a mean follow-up of 4.8 years with an annualized incidence rate of 2.2% per year.⁴ In the same study, major predictors of HF were atherosclerotic cardiovascular disease, insulin use, degree of hyperglycaemia and age.³ Within this context, it is relevant to underline that the cumulative incidence of HF in TOSCA.IT over a mean follow-up of 4.7 years was 1.0% (0.8% in the sulfonylurea arm and 1.2% in the pioglitazone arm) with an annualized rate of 0.2% per year (HF was a secondary endpoint of the study and was adjudicated by an independent committee). This low incidence rate is largely explained by the features of the study population and confirms that the risk of HF is not equal in all people with diabetes. Specifically, the study population was largely free from prior cardiovascular events (only 12% reported prior events), mean glycated haemoglobin during the study was 7.3% with a low proportion (16%) of participants requiring rescue insulin therapy, average age and diabetes duration were relatively low (63 and 8 years, respectively). Furthermore, TOSCA.IT is a

pragmatic trial and the study drugs were used following the indications/contraindications that apply to real-life clinical practice. We, therefore, excluded patients with prevalent HF (New York Heart Association class \geq II) and impaired renal function. Due to our eligibility criteria, we excluded a group of people at high risk of HF.⁵ As for treatment when hospitalization for HF occurred, again the investigators followed clinical practice. For the time being, in patients with HF, pioglitazone is contraindicated, but sulfonylureas and insulin may be used as second or third-line treatment, although their safety in HF is under debate.⁵ We do agree that this may be reconsidered; however, their impact on HF is not clear since randomized controlled trials on this aspect are lacking. We also recognize that the lack of a placebo-controlled group in the TOSCA.IT study makes any inference on the safety of the study drugs with regard to HF methodologically inappropriate. However, the very low incidence of HF in both study arms—similar to that reported in non-diabetic populations—seems to justify the consideration that, in a low-risk population such as the one enrolled in this study, both pioglitazone and some sulfonylureas (glimepiride and gliclazide) represent a safe and effective anti-hyperglycaemic treatment, particularly if established contraindications to their use are taken into account and appropriate dosage and treatment strategy are utilized. This is further supported by the observation that other known side effects of the study drugs (i.e. weight gain and hypoglycaemic events) were also limited in this study as compared to other reports.

In our opinion, the results of TOSCA.IT give further support to the indications of the position statement from the Heart Failure Association of the European Society of Cardiology.²

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