Heart Metab. (2015) 68:39-40

Antidiabetic treatment and cardiovascular events: all a matter of perspective!

Alda Huqi, MD
Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy
E-mail: al.huqi@gmail.com

Diabetic patients are known to be at increased risk for developing macrovascular (ie, cardiovascular disease) and microvascular complications, such as eye, nerve, and kidney disease.[1] The pathophysiology of type 2 diabetes mellitus (T2DM) is complex, mainly characterized by insulin resistance (IR) in fat, muscle, and liver tissues, and is associated with pancreatic α- and β-cell dysfunction.[2] Accordingly, there are numerous treatment strategies offering effective glycemic control.[3]

However, while lowering glycated hemoglobin A_{1c} (HbA_{1c})—a biomarker reflecting blood glucose concentration—is associated with beneficial effects on the microvasculature, its effects on cardiovascular outcome are a matter of continuous scientific controversy. For instance, the trials UKPDS (United Kingdom Prospective Diabetes Study) and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Modified Release Controlled Evaluation) tested different glycemic control strategies across a wide spectrum of patients with diabetes and did not find a clear benefit in terms of myocardial infarction, cardiac mortality, and hospitalization for heart failure, among other outcomes, during active therapy.[4-6] On the contrary, in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), near-normal glycemic control was associated with significantly increased risks of death from any cause and death from cardiovascular causes.[7]

In 2008, the US Food and Drug Administration (FDA) released a guidance statement asserting the need to assess the cardiovascular safety of some of the drugs used in T2DM.[8] When additional data became available, the FDA issued an explicit safety communication, recommending restrictions for their use.[9] This announcement was reversed in 2013 when further evaluation of data showed that it was uncertain whether the changes in cardiovascular risk were due to the drug or due to chance alone.[10] Regardless of the ultimate recommendations, the safety issues highlighted by the FDA translated into a change in focus and led to the construction of noninferiority trials that aimed to assess the safety profiles of the new treatments.

Indeed, while superiority trials are performed with the aim of demonstrating that a treatment strategy is more efficacious than an established one, the purpose of a noninferiority trial is to show that a new therapy is at least as good as the existing treatment. Superiority trials can identify both harmful and beneficial effects of the new therapy. However, the lack of a significant difference in results does not necessarily imply that the new treatment is equally effective.

Recently, the results of the trials ELIXA (Evaluation of LIXisenatide in Acute coronary syndrome) and TECOS (Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin)—for whom inception dates back to the period when the FDA issued the safety

Heart Metab. (2015) 68:39-40

Abbreviations

ACCORD: Action to Control Cardiovascular Risk in Diabetes; **ADVANCE:** Action in Diabetes and Vascular disease: PreterAx and DiamicroN Modified Release Controlled Evaluation; **ELIXA:** Evaluation of LIXisenatide in Acute coronary syndrome; **FDA:** US Food and Drug Administration; **IR:** insulin resistance; **T2DM:** type 2 diabetes mellitus; **TECOS:** Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin; **UKPDS:** United Kingdom Prospective Diabetes Study; **VADT:** Veterans Affairs Diabetes Trial

announcements mentioned above—were presented at the American Diabetes Association's 2015 Scientific Sessions (accessible at http://adascisessions.civi-go.com/). Each trial tested a different incretin drug versus placebo and proved neutral, with no increase in the incidence of major cardiac events in high-risk patients.

Currently, there are a number of other ongoing safety trials. As these data become available, some doubts are cropping up regarding whether such trials are the best overall strategy for improving the outcomes in diabetic patients. Determining whether a specific type of glucose-lowering drug has any additional benefit over standard of care is very difficult. The drug development industry relies on the effects that a molecule exerts on the surrogate biomarker (ie, HbA_{1c} levels). Whether or not this translates into a clinical benefit is not necessarily predictable and should be tested with a clinically meaningful perspective.

To further complicate the subject, it should be recognized that antidiabetic drugs are in the unusual position that biologically plausible, yet contradictory, arguments could be made that (i) they might cause cardiovascular harm and (ii) they might come with cardiovascular benefit. The recently published, long-term follow-up results from the VADT (Veterans Affairs Diabetes Trial) provide data supporting the hypothesis that more intense glycemic control can improve "macrovascular" cardiac events. However, the observed benefit was modest (17% lower risk of cardiovascular events with no mortality benefit) and the time horizon quite long (10 years of follow-up).[11]

The results of the ELIXA and TECOS trials, although neutral, were presented with enthusiasm: the drugs did not cause harm! However, it should be stressed that these (and other trials like them to come) were mainly designed to satisfy FDA requirements and demonstrate safety, as for any new glucose-lowering drug. In this scenario, the capture of a clinically meaningful benefit becomes particularly challenging. Keeping in mind that diabetic patients are vulnerable both to cardiovascular disease and cardiovascular side effects, pharmaceutical and marketing stategies that target both effects should be prioritized. ■

REFERENCES

1. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570-2581.
2. Godoy-Matos AF. The role of glucagon on type 2 diabetes at a glance. *Diabetol Metab Syndr*. 2014;6:91.
3. Deacon CF, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes—a review and meta analysis. *Diabetes Obes Metab*. 2012;14:762-767.
4. ADVANCE Colloborative Group; Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.
5. 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;359:1577-1589.
6. ACCORD Study Group; Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818-828.
7. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.
8. US Food and Drug Administration, US Department of Health and Human Services. Endocrinology and Metabolic Drugs Advisory Committee docket: The role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4368b1-01-FDA.pdf. Updated June 20, 2008.
9. US Food and Drug Administration, US Department of Health and Human Services. FDA Drug safety communication: Updated Risk Evaluation and Mitigation Strategy (REMS) to restrict access to rosiglitazone-containing medicines including Avandia, Avandamet, and Avandaryl. http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm. Updated November 27, 2013.
10. US Food and Drug Administration, US Department of Health and Human Services. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm. Updated January 9, 2014.
11. Hayward RA, Reaven PD, Wiitala WL, et al; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372:2197-2206.