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EDITORIAL COMMENT

GLP-1 Receptor Agonists, the Holy Grail Preventing Atrial Fibrillation in Patients With T2D?*

Lisa Stoll, PhD, James C. Lo, MD, PhD

Type 2 diabetes (T2D), which accounts for 90% to 95% of all cases of diabetes, is on the rise and is expected to affect 700 million people globally by 2045.[1] People with T2D have double the likelihood of dying from stroke or heart disease compared with those without diabetes.[1] In fact, cardiovascular disease (CVD) is the leading cause of death in patients with T2D.[1] In addition, diabetes increases the risk of arrhythmias such as atrial fibrillation (AF), which is the most common sustained arrhythmia. AF development further increases the risk of stroke and mortality in patients with T2D.

Treatment of T2D mainly focuses on lowering blood glucose levels, which is achieved by medical treatment if lifestyle changes are unsuccessful. A variety of medications are available to treat hyperglycemia, including glucagon-like peptide 1 receptor agonists (GLP-1RAs). The hormone glucagon-like peptide-1 (GLP-1) is secreted by the gut in response to food intake and stimulates insulin secretion in the pancreatic beta cells. Recent studies by the Drucker lab have uncovered that the GLP-1 receptor is also present in atrial tissue in both humans and mice. Yet, the function of GLP-1RAs in the heart are just unraveling. Several clinical studies have observed a reduction in major adverse cardiovascular events in patients with T2D or history of CVD after treatment with GLP-1RAs such as liraglutide and semaglutide.[1] Nevertheless, only 1.6% of patients with both T2D and CVD receive GLP-1RAs.[1]

In this issue of *JACC: Basic to Translational Science*, Bohne et al[2] investigated the effect of GLP-1RA treatment in diabetic mice on AF risk. The idea that GLP-1RAs lower AF risk in animal models is not new. In fact, 2 previous studies demonstrated a reduced AF burden after GLP-1RA treatment. One study used a canine model of pacing-induced AF, which was treated with liraglutide for 3 weeks. They observed improved electrophysiological parameters and decreased AF inducibility in the treated group vs the control group.[3] In another study, rats underwent sham surgery or left anterior descending artery ligation to induce myocardial infarction (MI). MI increases the risk of arrhythmia and results in increased fibrosis. The rats received the GLP-1RA exendin-4, which reduced atrial arrhythmias and attenuated atrial action potential duration (APD) prolongation.[3]

Bohne et al[2] utilized *db/db* mice, which are known to have increased AF risk along with structural and electrical abnormalities. They treated these mice for 4 weeks with the GLP-1RA liraglutide by subcutaneous injection or GLP-1 using an implanted pump. Liraglutide treatment lowered AF susceptibility and duration. They further assessed if this lowered AF inducibility is due to improvement of electrical conduction in the atrial tissue. They observed that GLP-1RAs partially prevented the development of atrial fibrosis. In addition, the authors found that the APD prolongation observed in saline-treated *db/db* mice was partially reversed. Altered ion channel

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From the Weill Center for Metabolic Health, Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York, New York, USA.

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activity was also confirmed in isolated atrial tissue, indicating that these electrical changes are independent of glycometabolic improvements that are accompanied by liraglutide treatment.

This is the first study to show that GLP-1RAs reduce AF in a T2D mouse model. The T2D *db/db* mouse model used by the Rose lab is also known for development of diabetic cardiomyopathy. Some clinical studies with GLP-1RAs have demonstrated improvement in left ventricular ejection fraction, which is one parameter not affected in the study by Bohne et al.[2] In addition, some GLP-1RAs have been shown to increase heart rate in preclinical studies.[4] In the present study, the authors observed a trend of a mild increase in heart rate with GLP-1RA treatment vs saline treatment. The connection between glycemic control and AF risk in T2D is also still unclear, with clinical studies observing either a correlation or no relationship. In the present study, the authors confirmed the glucose-lowering effect of GLP-1RAs but could not rule out if this played a role in the decreased AF susceptibility.

This study further opens the door to future clinical studies that can test if treatment with GLP-1RAs could prevent AF development in patients with T2D and thereby lower the associated increase in morbidity and mortality. One downside of using GLP-1RAs is the risk of potential increases in heart rate. In general, the effects of GLP-1RAs on the heart are not fully understood, with the existing clinical studies not reaching a consensus on whether GLP-1RAs are antiarrhythmogenic. This raises the question of whether different types of GLP-1RAs might modify the risk, or if it depends on the patient cohort. In fact, most studies assessed CVD parameters in high-risk patients with T2D and a history of CVD. Most of the study cohort in the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial that used dulaglutide did not have previous cardiovascular disease.[5] Reduced composite cardiovascular outcomes were observed, but atrial arrhythmia risk was unaffected.[6]

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ADDRESS FOR CORRESPONDENCE: Dr James C. Lo, Weill Cornell Medicine, 413 East 69th Street, New York, New York 10021, USA. E-mail: jlo@med.cornell.edu.

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