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COMMENTARY

Evidence-based comparison of glucagon-like peptide receptor agonists and sodium–glucose cotransporter 2 inhibitors

About 100 years ago, insulin was introduced as a clinical treatment for diabetes mellitus, and this dramatically reduced the mortality rate due to diabetic emergencies, such as diabetic ketoacidosis. Since then, preventing the onset and progression of vascular complications has become a major goal in the treatment of patients with diabetes. The most obvious laboratory abnormality in patients with diabetes is hyperglycemia, and many *in vitro* and animal studies have shown that hyperglycemia elicits harmful effects on the cells that comprise the vasculature or those that are involved in the progression of atherosclerosis through various mechanisms, such as increased oxidative stress, advanced glycation end-product signaling and protein kinase C activation. Thus, normalization of blood glucose levels has been thought to be a key therapeutic strategy for preventing vascular complications. Indeed, the Diabetes Control and Complications Trial (DCCT)[1] and the UK Prospective Diabetes Study (UKPDS)[2] clearly showed that glycemic control was effective in suppressing microangiopathy in patients with type 1 and type 2 diabetes mellitus. The Steno-2 study showed that glycemic control with interventions for multiple risk factors, such as dyslipidemia and hypertension, was effective for the prevention of cardiovascular diseases, such as myocardial infarction and stroke[3]. The Japan Diabetes Outcome Intervention Trial 3 (J-DOIT3) study, carried out in Japan, also supported this finding[4].

Over the past 30 years, there have been remarkable advances in treatments for blood pressure and dyslipidemia. In particular, renin–angiotensin system inhibitors and statins have become standard drugs for patients with hypertension and dyslipidemia, respectively. The widespread use of these drugs has contributed to decreasing the morbidity of cardiovascular diseases in patients with diabetes mellitus. In addition, novel antidiabetic agents have become available over the past 10 years; these improve hyperglycemia with low risks of hypoglycemia and weight gain, and include dipeptidyl peptidase-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors. These drugs improve not only the quantity, but also the quality of blood glucose control, and thus might contribute to reducing the morbidity caused by microangiopathy and macroangiopathy in patients with diabetes mellitus.

After the antidiabetic drug, rosiglitazone, was reported to raise the frequency of cardiovascular diseases[5], regulatory authorities mandated that large clinical trials of new antidiabetic agents be carried out to prove their safety regarding cardiovascular diseases for their approval. Although these novel antidiabetic agents were developed to lower blood glucose levels, these trials sought to evaluate the drugs in broader terms. Accordingly, the primary end-point of most of these trials is the non-inferiority of the drug in terms of the onset of cardiovascular diseases. Even if a trial does not find superiority regarding the onset of cardiovascular diseases, there is no doubt about the usefulness of the drug, because the effect of blood glucose lowering has already been proved in a prior trial. Intriguingly, however, several trials showed that some SGLT2 inhibitors and GLP-1 receptor agonists reduced the incidence of cardiovascular disease and hospitalization for heart failure, and slowed the progression of kidney disease. Based on this evidence, a recent consensus report by the American Diabetes Association and European Association for the Study of Diabetes recommends using SGLT2 inhibitors or GLP-1 receptor agonists in type 2 diabetes mellitus patients with atherosclerotic cardiovascular diseases, using SGLT2 inhibitors in patients with atherosclerotic cardiovascular diseases and heart failure, and using SGLT2 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease[6]. However, the relative benefits of these drugs for various outcomes remain unknown.

Recently, Zelniker *et al.*[7] carried out a trial-level meta-analysis, and compared the benefits of these agents for the major adverse cardiovascular events (MACE), hospitalization for heart failure and progression of kidney disease. The cardiovascular trials included in this trial were Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)-6, Exenatide Study of Cardiovascular Event Lowering (EXSCEL), and Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (HARMONY-Outcomes) for GLP-1 receptor agonists, and Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME), the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 for SGLT2 inhibitors. Both SGLT2 inhibitors and GLP-1 receptor agonists were found to reduce

*Corresponding author. Hirotaka Watada
Tel.: +81-3-5802-1579
Fax: +81-3-3813-5996
E-mail address: hwatada@juntendo.ac.jp
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MACE to a similar degree in patients with established cardiovascular diseases. Regarding the treatment effect on the individual components of MACE, both GLP-1 receptor agonists and SGLT2 inhibitors reduced the relative risk of myocardial infarction and cardiovascular death to a similar degree. In contrast, GLP-1 receptor agonists significantly reduced the relative risk of stroke, whereas SGLT2 inhibitors did not. The above findings were confirmed by the recent Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial[8]. This trial investigated the effects of a GLP-1 receptor agonist, dulaglutide, on three-point MACE, and found that the occurrence of MACE in the dulaglutide group was significantly lower than in the control group. Regarding the treatment effect on the individual components of MACE, only the occurrence of stroke was significantly lower in the dulaglutide group compared with the control group. If the meta-analysis of Zelniker *et al.*[7] had included the REWIND trial, the difference between the drugs in terms of the effect on stroke would have been more pronounced. Also of note, in the Peptide Innovation for Early Diabetes Treatment 6 trial that investigated the cardiovascular risk profile of oral semaglutide, a non-significant numerical decrease of stroke incidence was observed in the patients treated with semaglutide[9]. In contrast, SGLT2 inhibitors have a unique effect on preventing hospitalization for heart failure and an even more marked effect on preventing the progression of kidney diseases.

For the proper use of these drugs, it is important not only to establish their clinical effects, but also to clarify the mechanisms involved. Many processes might underlie the stroke prevention effects of GLP-1 receptor agonists. Indeed, GLP-1 reduces blood pressure in the clinical setting. In addition, many groups reported that GLP-1 receptor agonists directly suppressed the progression of atherosclerosis in animal studies. Regarding the ability of SGLT2 inhibitors to reduce the incidence of kidney diseases, these drugs are estimated to reduce the oxygen consumption of proximal tubular cells; this protects these cells and enhances tubuloglomerular feedback, thus protecting glomerular cells. Regarding their effects on heart failure, SGLT2 inhibitors exert diuretic effects, enhance the expression of anti-oxidative enzymes by increasing the concentration of ketone bodies and suppress Ca^{2+} influx by inhibiting the Na^{+}-H^{+} exchanger. However, further studies are essential for elucidating these mechanisms and identifying others.

Although the American Diabetes Association and European Association for the Study of Diabetes published consensus reports mentioning the order in which antidiabetic drugs should be prescribed[10], the specific manner in which they are used varies among countries, because the features of diabetes differ worldwide. Regarding pharmacotherapy for type 2 diabetes mellitus, the Japanese Clinical Practice Guideline for Diabetes 2016 stated the following: "The choice of glucose-lowering agents should be individualized for each patient according to the disease condition, with attention also given to their pharmacological and safety profiles. With informed consent obtained from the patient, the drug(s) should be initiated at a low dose and gradually titrated upwards as required depending on the glycemic control of the patient at that time."[11,12]. Unlike most guidelines or consensus reports, however, this guideline did not describe the order in which these drugs should be used in practice; instead, it emphasized the importance of individualized choice and paying special attention to safety profiles. Certainly, research comparing GLP-1 receptor agonists and SGLT2 inhibitors helps clinicians choose suitable drugs based on scientific evidence. However, in the clinical setting, it is more important to consider the balance between drug benefits and risks.

DISCLOSURE

HW has acted as an advisory board member for Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Eli Lilly, Kissei Pharma, Kowa, Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho and Takeda; as a speaker for Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Eli Lilly, Kowa, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho and Takeda; and has received research support from Astellas Pharma, Boehringer Ingelheim, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kissei Pharma, Kowa, Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, Ono Pharmaceutical, Pfizer, Sanofi, Sanwa Kagaku Kenkyusho, Taisho Toyama Pharmaceutical, Takeda, Teijin Pharma and Terumo Corp.

Hirotaka Watada*
Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan

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