Editorial

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Cardiovascular (CV) Risk and Non-Insulin Therapeutic Approach for Type 2 Diabetes Mellitus

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Description

Type 2 diabetes (DM) is a lifelong metabolic disorder characterized by hyperglycemia that gradually causes the onset and progression of vascular complications. It is considered as a global stress disorder that has a significant impact on human health (death) and medical costs. This editorial focuses on the development of drug therapies that go beyond insulin. The complex interaction between insulin secretion and insulin resistance evolved from the previously known "Ominous Triumvirate" to "Ominous Octet", with several organs involved in glucose metabolism. The pharmacological approach has shifted from biguanides to a wide range of drugs that appear to have beneficial effects on the cardiovascular system. Nevertheless, we have not yet achieved our desired therapeutic goals. Therefore, in the future, there should be a new class of anti-diabetes drugs that can act at multiple levels at the same time. In conclusion, given the increasing burden of type 2 diabetes, the current best strategies that may most contribute to lower morbidity and mortality should be directed to primary prevention.

Due to the complex pathophysiological background of type 2 diabetes with a wide range of cardiovascular (CV) risk factors present in addition to hyperglycemia itself. It should be emphasized here that the promising effects associated with reducing cardiovascular risk were observed in the "STOPNIDDM study" (an international study on the efficacy of alpha-glucosidase inhibitors in the prevention of type 2 diabetes) in the late 1990s). The key results of this study, which clearly demonstrated that acarbose can prevent or delay the progression of impaired glucose tolerance to DM type 2, which were recently confirmed in the Acarbose Cardiovascular Assessment (ACE) study. No effect on cardiovascular depletion risk was shown. Therefore, the "Empagliflozin Cardiovascular Outcome Event Study in Patients with Type 2 Diabetes to Eliminate Excess Glucose" (EMPAREG OUTCOME) shows the superiority of hypoglycemic agents in cardiovascular disease, heart failure, kidney and mortality. It was the first clinical study to be demonstrated. Endpoint compared to placebo. Suppose that glycated hemoglobin (HbA1c) is reduced by 0.45%, blood pressure is reduced by about 5/2 mmHg, and body weight is reduced by about 2%.

Immediately after the presentation of the EMPAREG OUTCOME study, Ferrannini et al. have developed the so-called "slifty substrate" hypothesis. It assumes that β-hydroxybutyric acid is absorbed by the heart and oxidized to fatty acids in mild but persistent hyperketonemia. The choice of this substrate improves the process of converting oxygen consumption into cardiomyocyte work efficiency. In addition, the increased oxygen release to the myocardium due to blood enrichment caused by diuresis may produce a strong synergistic effect with substrate substitution. The rationale for this hypothesis comes from experimental studies in diet-induced obese rats treated with dapagliflozin, ipragliflozin, or tofogliflozin, especially when fasting or feeding animals in pairs. It showed acceleration and increased circulating ketone body levels. In addition, this was confirmed in patients with type 2 diabetes after 4 weeks of treatment with 25 mg empagliflozin. At the same time, fasting and postprandial plasma concentrations of β-hydroxybutyric acid increased 2-3-fold, and these changes were similar over time, albeit diminished in size, in the group of drug-treated non-diabetic volunteers. This simple substrate hypothesis can also explain similar results from the combined results of the Canagliflozin Cardiovascular Assessment Study (CANVAS). However, the post-marketing period was too short to support the general conclusions at this time.

Finally, some of the GLP1 agonists, i.e. H. Liraglutide and semaglutide, a significant reduction in relative risk compared to placebo for the major endpoints of 3-point major cardiovascular events, and little or moderate cardiovascular and all causes of statistical heterogeneity between studies relative risk of death. However, their potential in pancreatic cell proliferation observed in experimental studies has not been addressed due to the relatively short post-marketing time.