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Review

Emerging roles of sodium–glucose cotransporter 2 inhibitors in cardiology

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ABSTRACT

The ultimate goal of treatment in people with diabetes mellitus is to prevent development of cardiovascular (CV) disease, resulting in prolongation of healthy life expectancy. Although impaired glycemic metabolism has a central role in its pathology, a number of studies have demonstrated that remedy for its imbalance cannot necessarily be accomplished as a therapeutic goal. A comprehensive medical approach against multi-factorial pathologies in diabetes, such as insulin resistance, obesity, hypertension, and dyslipidemia, in addition to diet and exercise therapy should be rather performed in the routine clinical setting. Along with such conceptual transition, what is required in anti-diabetes agents has also changed, and several anti-diabetes agents have been newly placed on the market in this decade. Such agents are required to undergo global pre- or post-marketing clinical trials assessing CV safety. A growing body of clinical evidence from those trials is now accumulating, and empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, has first demonstrated significant risk reduction, relative to placebo, in CV death, overall mortality, and hospitalization for worsened heart failure in high-risk patients with diabetes mellitus. An SGLT2 inhibitor is a unique glucose-lowering agent and at the same time has multifaceted effects on hemodynamic and metabolic parameters beyond glycemic control. A major mode of action of SGLT2 inhibitors appears to be 'glycosuria' and 'natriuresis,' leading to amelioration of systemic glycemic homeostasis and potential cardio-renal protection. However, the precise mechanisms by which SGLT2 inhibitors affect benefits on the CV systems are yet to be fully elucidated. Thus, although we are now facing several unanswered concerns lurking behind the successful trial, SGLT2 inhibitors surely play several important roles in high-quality management of not only diabetes, but also CV medicine. This review summarizes our current understandings and future perspectives of SGLT2 inhibitors in CV medicine.

Contents

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Introduction

Type 2 diabetes mellitus (T2DM) is closely associated with higher risk of development of cardiovascular (CV) disease, leading to resultant impaired quality of life and shortened life expectancy [1,2]. Because CV mortality in people with T2DM without previous myocardial infarction (MI) is comparative to patients with previous MI without T2DM [3], intensive clinical management complying with secondary prevention is needed. Previous randomized clinical trials have shown that intensive glucose-lowering treatment could reduce the development of microvascular complications, while risk reduction associated with reduction of HbA1c was less evident in macrovascular complications than that in microvascular [4–6]. In addition, some CV outcome trials failed to demonstrate that intensive glucose-lowering treatment relative to standard care could reduce the risk of macrovascular events [7–9]. On the other hand, 'metabolic memory' or 'legacy effect' induced by previous intensive intervention into glycemic control was observed in the post-trial monitoring, suggesting that it would take longer to see the benefits of glycemic improvement [10,11]. Thus, although impaired glycemic metabolism has a central role in diabetes pathology, there remains substantial controversy whether intensive glucose-lowering treatment can improve CV outcomes [12–14]. Importantly, there is apparently possible association between hypoglycemia and worsened CV outcome through activated inflammatory cytokines and neurohormonal disturbance [15]. T2DM is often characterized with metabolic syndrome, such as hypertension and dyslipidemia. These metabolic abnormalities are commonly based on the systemic insulin resistance (IR), which plays a central role in the pathophysiology. Accumulated adipose tissues can cause IR even in the pre-diabetes stage without hyperglycemia, leading to progression of diabetes and atherosclerosis [16] (Fig. 1). However, intensive lifestyle intervention aimed at body weight reduction also failed to reduce the development of composite CV events [17], enhancing difficulty in continuing longer-term weight control and improving CV outcome by lifestyle intervention only. Given these multi-factorial contributions to the nature of diabetes, early, safe, and comprehensive medical intervention to ameliorate the systemic IR is now emphasized in the clinical management of people with diabetes [18,19].

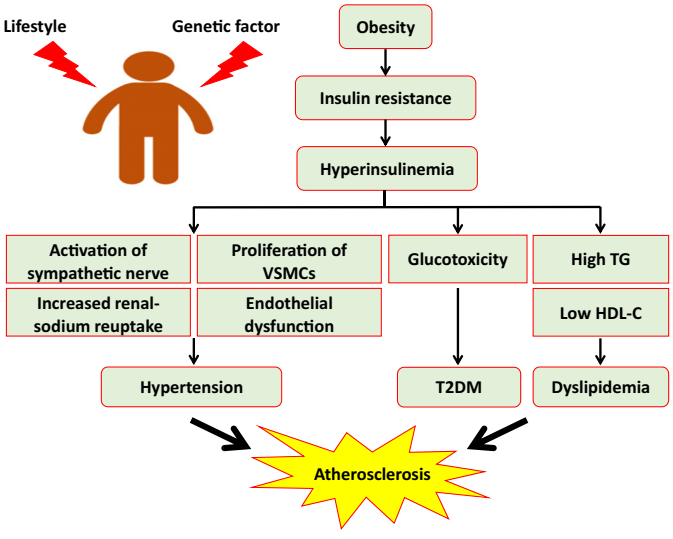

Fig. 1. Insulin resistance as a basis of metabolic abnormalities. Insulin resistance mainly induced by obesity serves as a basis of metabolic abnormalities, such as hypertension, type 2 diabetes mellitus, and dyslipidemia, leading to development and progression of atherosclerosis in collaboration with increased inflammation and oxidative stress. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; VSMCs, vascular smooth muscle cells.

Which is the *ideal* glucose-lowering agent to improve CV outcome? In Japan, a wide range of glucose-lowering agents are now available according to the clinical manifestation in people with T2DM [20]. Metformin, which suppresses gluconeogenesis from liver and improves systemic IR, is the first-line agent globally. The effectiveness of metformin has been evidenced by a number of previous studies, such as UKPDS34 [21]. Pioglitazone also has strong evidence to attenuate atherosclerosis [22,23] and to improve CV outcome [24,25]. The circumstances surrounding anti-diabetes agents are now changing at a rapid pace, due in part to the appearance of newer agents and requirement of pre- or post-marketing CV safety trials. In this review, a comparison of each agent is out of scope, but we would like to summarize our current understanding and future perspectives of sodium–glucose cotransporter 2 (SGLT2) inhibitors in CV medicine.

Need for CV safety trial in novel anti-diabetes agents

Needless to say, the most important aim of diabetes treatment is to prevent the development of CV disease and to improve CV outcome. However, in 2007 Nissen and Wolski [26] reported a shocking result of a meta-analysis from 42 randomized trials with rosiglitazone, showing possible increased risk of MI [odds ratio: 1.43 (95% CI, 1.03–1.98, $p = 0.03$)] and CV death [odds ratio: 1.64 (95% CI, 0.98–2.74, $p = 0.06$)], compared to control group. This unexpected result evoked long-standing debate over its interpretation and study design in clinicians and authorities, although no excess CV risk was observed in the subsequent study [27]. As a consequence, the US Food and Drug Administration released a guidance requiring the demonstration of CV safety of novel anti-diabetes agents for the pharmaceutical industry to approve the agent. This shifted the clinical landscape of T2DM markedly, and many large-scale CV trials have been launched, with an estimated great increase in the number of participants globally [28,29]. At the same time, three newer anti-diabetes agents, such as dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and SGLT2 inhibitors, were developed and became the eligible target for evaluation of CV safety.

DPP-4 inhibitors increase the concentrations of incretin hormones and subsequent insulin secretion dependent on plasma glucose level. In Japan, the prescription rate of this class appears to be above 70% in people with T2DM, presumably due to its sufficient glucose-lowering effect and safety. Data from three CV safety trials using this class are currently available [30–32]. Although there were some differences in medical background of participants and follow-up duration, non-inferiority of DPP-4 inhibitors relative to standard care was observed in the composite primary CV outcome. However, in the SAVOR-TIMI 53 trial (saxagliptin) increased risk of hospitalization for heart failure (HF) as a secondary endpoint was unexpectedly found in patients who received saxagliptin treatment [30,33], although whether DPP-4 inhibitors contribute to the increased risk of worsened HF and the mechanisms are yet to be determined [34,35].

GLP-1 is an incretin hormone that promotes insulin secretion from islet beta cells in response to elevated level of plasma glucose. Since the GLP-1 receptors are distributed in a wide range of systemic organs or tissues, enhanced GLP-1 signaling may exert direct or indirect CV protection via metabolic amelioration and anti-inflammatory effects [36]. At present, there appear to be clashing views in CV outcome trials using GLP-1RAs. As in the case with DPP-4 inhibitors, the ELIXA trial (lixisenatide) also demonstrated a neutral effect on major CV events in patients with T2DM and a recent acute coronary syndrome [37]. Next, the LEADER trial (liraglutide) successfully showed significant reduction in the rates

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