Editorial

Incretin-related drugs and cardiovascular events: A comparison of GLP-1 analogue and DPP-4 inhibitor

It has been established that cardiovascular disease (CVD) is associated with diabetes mellitus. The prevalence of diabetes mellitus is increasing worldwide. In addition, CVD, including coronary artery disease, stroke, and heart failure, is a cause of morbidity and mortality in patients with diabetes mellitus. Therefore, prevention of the onset and progression of CVD is essential for management of patients with diabetes mellitus.

It has been shown that intensive glucose lowering over a period of 20 years, but not over 10 years, is effective for prevention of myocardial infarction and cardiac death in patients with diabetes mellitus [1]. Unfortunately, some large clinical trials failed to confirm a reduction in CV events under the condition of glucose lowering [2,3]. On the contrary, the ACCORD trial demonstrated that intensive glucose lowering increased the rate of death from any cause and that the numbers of CV events in the intensive glucose lowering group and the conventional control group were similar [3]. Although it is not clear why intensive glucose lowering therapy does not decrease CV events and increases the rate of death from any cause in type 2 diabetic patients with a high risk of CVD, it is thought that intensive glucose lowering-induced hypoglycemia causes activation of the sympathetic nervous system, leading to onset of arrhythmia, myocardial infarction, and sudden death. When considering treatment of diabetes mellitus, attention should be given to intensive control of glucose lowering without causing hypoglycemia or spiking of glucose fluctuation. Recently, incretin-related drugs, including dipeptidyl peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 analogues, have become available as oral agents for treatment of patients with type 2 diabetes and are widely used for such patients. It is well known that incretin-related drugs decrease glucose levels with flattening of glucose fluctuation and without hypoglycemia.

The vascular endothelium is involved in the release of various vaso dilators, including nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors [4]. NO plays important roles in the regulation of vascular tone, inhibition of platelet aggregation, and suppression of smooth muscle cell proliferation [4]. Endothelial dysfunction is the initial step in the pathogenesis, maintenance, and development of atherosclerosis, leading to CV events [4]. Diabetes mellitus is associated with endothelial dysfunction [5]. Endothelial function is a therapeutic target for atherosclerosis. In patients with diabetes mellitus, it is clinically important for endothelial function to be restored by appropriate interventions, including pharmacological therapy, supplementation, therapy and lifestyle modifications, for preventing the development of atherosclerosis and thus reducing CV events.

Therapy for glucose lowering is effective for improvement or restoration of endothelial function in patients with diabetes mellitus [5]. Incretin-related drugs also improve endothelial function in patients with diabetes mellitus [6]. It is thought that decreased NO bioavailability due to a decrease in NO production and/or increase in NO inactivation induces endothelial dysfunction by an increase in reactive oxygen species, so-called as oxidative stress. Abnormality of vasoconstriction consisting of an increase in the endogenous eNOS inhibitor asymmetric N\(^\circ\)N\(^=\)-dimethyl-L-arginine, increases in vasoconstrictors such as angiotensin II, endothelin-1, and norepinephrine, and pro-inflammation also contribute to endothelial dysfunction.

Possible mechanisms by which incretin-related drugs improve endothelial function are shown in Fig. 1. GLP-1 is secreted from endocrine L-type cells in the intestine by sensing an increase in glucose levels in the intestinal tract. GLP-1 is degraded by DPP-4. A GLP-1 analogue and a DPP-4 inhibitor increase circulating levels of GLP-1. Several experimental studies have shown that GLP-1 per se directly enhances phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and Akt in endothelial cells, and improves endothelium-dependent vasodilation through activation of the AMPK/endothelial NO synthase (eNOS)/NO pathway \textit{in vivo} [7,8]. The DPP-4 inhibitor sitagliptin improves endothelial function through the activation of protein kinase A (PKA)-induced eNOS phosphorylation, resulting in a decrease in atherosclerosis in apolipoprotein E (apoE) knockout mice [9]. These findings suggest that GLP-1 activates the eNOS/NO pathway through the enhancement of phosphorylation of AMPK, Akt, and PKA in endothelial cells. DPP-4 inhibitors cause a reduction in glucose levels by inhibition of GLP-1 degradation, inactivation of Rho-associated kinase probably due to a decrease in oxidative stress, and an increase in the number of endothelial

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progenitor cells by inhibition of stromal cell-derived factor 1 alpha degradation, leading to an improvement in endothelial function by activation of the eNOS/NO pathway. GLP-1 analogues cause a reduction in glucose levels by an increase in GLP-1 levels and reduction in body weight, leading to an improvement in endothelial function by activation of the eNOS/NO pathway. It is expected that incretin-related drugs will prevent CV events through an improvement in endothelial function.

These large clinical trials of DPP-4 inhibitors, EXAMINE [10], SAVOR-TIMI53 [11], and TECOS [12] were not able to certify the superior effects on CV events compared with a placebo in type 2 diabetic patients with recent myocardial infarction, type 2 diabetic patients with a history and at risk of CVD, and type 2 diabetic patients with CVD, while these trials certified the non-inferiority of effects of DPP-4 inhibitors on CV events compared with a placebo (Table 1). On the other hand, the LEADER trial using a GLP-1 analogue, liraglutide, showed for the first time prevention of cardiovascular events in patients with a high risk of CVD (Table 1) [13]. From the aspect of vascular function, the difference in the mechanisms of beneficial effects of a DPP-4 inhibitor and a GLP-1 analogue on endothelial function is body weight reduction. Recently, the EMPA-REG OUTCOME trial using an SGLT2 inhibitor, empagliflozin, showed prevention of CV events through a miraculous trio consisting of a slight decrease in glucose levels, a slight decrease in blood pressure, and a slight decrease in body weight [14]. These findings suggest that

![Diagram](https://via.placeholder.com/150)

**Fig. 1.** Putative mechanisms by which incretin-related drugs reduce cardiovascular events through the improvement of endothelial function. GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase-4; ROCK, rho-associated kinase; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; SDF-1α, stromal cell-derived factor 1 alpha.

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>Name of drug</th>
<th>Subjects (number)</th>
<th>Duration of diabetes (years)</th>
<th>Range of HbA1c (% mean)</th>
<th>Follow-up period (years)</th>
<th>Endpoints</th>
<th>Endpoints HR (95% CI)</th>
<th>P value</th>
<th>HHF HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor</td>
<td>EXAMINE</td>
<td>Alogliptin vs. placebo</td>
<td>Type 2 DM with recent ACS (n=5380)</td>
<td>7.2</td>
<td>6.5–11.0 (8.0)</td>
<td>1.5</td>
<td>Composite CV events: CV death, Non-fatal MI, Non-fatal stroke</td>
<td>0.98 (0.86, 1.12)</td>
<td>P=0.32</td>
<td>1.07 (0.79, 1.46)</td>
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<tr>
<td></td>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin vs. placebo</td>
<td>Type 2 DM with history of CVD/high risk of CVD (n=16,492)</td>
<td>10.3</td>
<td>6.5–12.0 (8.0)</td>
<td>2.1</td>
<td>Composite CV events: CV death, MI, Stroke</td>
<td>1.00 (0.89, 1.12)</td>
<td>P=0.99</td>
<td>1.27 (1.07, 1.51)</td>
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<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptin vs. placebo</td>
<td>Type 2 DM with CVD (n=14,671)</td>
<td>11.6</td>
<td>6.5–8.0 (7.2)</td>
<td>3.0</td>
<td>Composite CV events: CV death, Non-fatal MI, Non-fatal stroke, Hospitalization for UAP</td>
<td>0.98 (0.89, 1.08)</td>
<td>P=0.65</td>
<td>1.02 (0.90, 1.15)</td>
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<tr>
<td>GLP-1 analogue</td>
<td>LEADER</td>
<td>Liraglutide vs. placebo</td>
<td>Type 2 DM with high risk of CVD (n=9340)</td>
<td>12.8</td>
<td>≥7.0 (8.7)</td>
<td>3.8</td>
<td>Composite CV events: CV death, Non-fatal MI, Non-fatal stroke, Hospitalization for UAP</td>
<td>0.87 (0.78, 0.97)</td>
<td>P=0.01</td>
<td>0.87 (0.73, 1.05)</td>
</tr>
</tbody>
</table>

**Table 1**

Clinical trials using incretin-related drugs and CV events.

CV, cardiovascular; HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; DPP-4, dipeptidyl peptidase 4; DM, diabetes mellitus; MI, myocardial infarction; ACS, acute coronary syndrome; UAP, unstable angina pectoris; GLP-1, glucagon-like peptide 1.
incretin-related drug-induced body weight reduction may be one of the key players for prevention of CV events in type 2 diabetic patients.

Although the READ trial included only a small number of subjects and was a non-randomized trial to evaluate the safety and feasibility of liraglutide treatment in type 2 diabetic patients with recent acute coronary syndrome (ACS), the trial showed that liraglutide treatment was tolerated well by those patients [15]. It is expected that the GLP-1 analogue liraglutide will prevent CV events even in type 2 diabetic patients with recent ACS or myocardial infarction. Future large clinical studies are needed to confirm the efficacy of GLP-1 analogues for prevention of CV events in diabetic patients with all stages of atherosclerosis, including ACS.

Disclosures

None.

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References