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Editorial

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# Can SGLT2 Inhibitor be Used for Diabetes Mellitus or Vascular Diseases?

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Recently, antidiabetic agents have been evaluated as vascular protective agents. Newly identified antidiabetic agents such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors have been studied for their efficacy and safety for cardiovascular events (CVE)[1], and our previous basic experiments revealed some of their mechanisms[2, 3]. Among antidiabetic agents, sodium-glucose cotransporter 2 (SGLT2) inhibitor is the most attractive drug and the focus of attention because of its CVE-reducing effects in large-scale clinical trials. In fact, the SGLT2 inhibitor canagliflozin has demonstrated CVE-reducing effects in the CANVAS program[4].

In the present study[5], Rahadian *et al.* investigated a mechanism by which canagliflozin attenuates atherosclerosis and CVE mainly using diabetic and atherogenic mouse model. Atheroma formation in the aortic arch was significantly decreased by orally administered canagliflozin. Canagliflozin inhibited gene expressions of contributing factors for vascular inflammation and advanced glycation end products (AGE)-receptor for AGE system, decreased serum AGE and oxidative stress marker levels, and subsequently improved vascular relaxation. Blood glucose and total cholesterol but not body weight and blood pressure were significantly decreased by canagliflozin. Further *in vitro* experiments using endothelial cells demonstrated that methylglyoxal (MGO), an AGE, decreased vascular relaxation signals and increased vascular inflammation signals. The summarized mechanism is provided in **Fig. 1**.

Such a study, which elucidates the detailed mechanism of clinical investigation using basic science, is very important in the "bench-to-bedside" aspect. The present study confirmed one aspect of vascular protective mechanism by canagliflozin. Regarding the present data, I had two discussion points. First, this vascular protective effect might be a class effect of SGLT2 inhibitor or specific drug effect of canagliflozin. In fact, the same group performed similar experiments and observed similar effects using another type of SGLT2 inhibitor, empagliflozin[6]. In addition, other groups have also reported vascular protective effects of other SGLT2 inhibitors, luseogliflozin[7] and dapagliflozin[8]. These experimental data and clinical trials[1] suggested that SGLT2 inhibitor may show vascular protective effects as a class effect. Second, this vascular protective effect is dependent or independent of the glucose lowering effect. In the present study[5], the authors discussed that this effect might be dependent on glucose lowering and clearance of glucose toxicity. However, canagliflozin decreased inflammatory gene expressions induced by MGO as shown in Fig. 5A, but this was not statistically significant. This suggested the possibility of direct vascular protective effect of canagliflozin in endothelial cells. In addition, we previously reported that SGLT2 inhibitor directly attenuated vascular smooth muscle cell proliferation in *in vitro* experiments[9]. The direct vascular protective effects of SGLT2 inhibitor beyond blood glucose control should be investigated further in future studies. Furthermore, the serum insulin level was increased by canagliflozin in the present study (Table 2, 3)[5]. According to the glucose lowering mechanism of SGLT2 inhibitor, insulin secretion could be decreased, as reported in a clinical study[10]. SGLT2 inhibitor may be able to improve insulin secretion in an STZ (streptozotocin)-induced diabetic model, and this point should be investigated in detail.

New antidiabetic agents make diabetes care more exciting. In the 21st century breakthroughs in diabetology, we should focus on not only the glucose lowering effect but also pleiotropic effects to improve the

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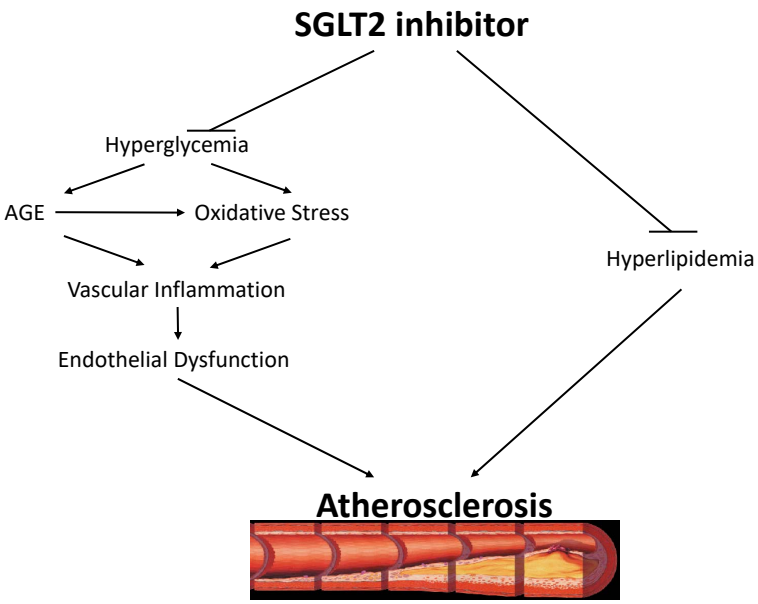


**Fig.1.** The mechanism by which SGLT2 inhibitor demonstrates vascular protective effect

quality of life and lifespan of patients with diabetes mellitus. Antidiabetic agents should be able to evolve from being just glucose lowering agents to being the best partner of patients to improve the quality of life.

## Conflict of Interest

Takashi Nomiyama has received lecture fees from Ono Pharmaceutical Co. Ltd, Sumitomo Dainippon Pharma Co.Ltd and MSD K. K.

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