

Does Metformin Assist New Anti-Diabetic Drugs to Succeed?

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To the Editor

Metformin is the most widely used oral anti-diabetic drug and is currently recommended as first line therapy for all newly diagnosed type 2 diabetes [1]. Metformin-induced activation of the energy-sensor adenosine monophosphate (AMP)-activated protein kinase (AMPK) is well documented [2]. Metformin inhibits the complex 1 of the mitochondrial electron chain, which induces a drop in cellular energy charge [3, 4]. Reduced cellular adenosine triphosphate (ATP) concentration and an increase in both adenosine diphosphate (ADP)/ATP and AMP/ATP ratios activates the AMPK, a critical energy sensor of cellular energy homeostasis that integrates multiple signaling networks to coordinate a wide array of compensatory, protective and energy-sparing responses [5].

Glucose-Lowering Effects of Metformin

Metformin exerts its glucose-lowering effect primarily by decreasing hepatic glucose production through suppression of gluconeogenesis and enhancing insulin suppression of endogenous glucose production and, to a lesser extent, by reducing intestinal glucose absorption and possibly improving glucose uptake and utilization by peripheral tissues, such as skeletal muscle and adipose tissue [6] (Fig. 1). Further, metformin may also improve glucose metabolism by interacting with the incretin axis through the action of glucagon-like peptide 1 (GLP-1) [7]. Although the mechanisms for metformin-mediated increments in GLP-1 levels remain unknown, it has been hypothesized that metformin stimulates GLP-1 secretion directly and/or indirectly and prolongs the half-life of GLP-1, and that metformin may potentiate the glucose-lowering effects of GLP-1 by increasing target tissue sensitivity to GLP-1 [8].

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A Significant Influence of Glycemic Variability (GV) on Microvascular and Macrovascular Complications in Patients With Diabetes

With the spread of continuous glucose monitoring (CGM), glycemic GV is attracting attention. Emerging evidence suggests that GV contributes to adverse clinical outcome in patients with diabetes [9]. A recent meta-analysis assessing GV has shown associations of GV with microvascular and macrovascular complications and mortality in type 1 and type 2 diabetes [10]. Proposed mechanisms for GV-induced adverse vascular outcomes include increased oxidative stress and enhanced expression of proteins involved in vascular pathology [11].

A Dose-Dependent Effect of Metformin on GV

Although various mechanisms have been suggested as metformin-mediated glucose-lowering, it remains unknown which of these mechanisms plays a crucial role at various daily doses of metformin. Our previous [12] and present study using CGM demonstrated that metformin improved GV in a dose-dependent manner (Fig. 2).

The Effect of Combination of Dipeptidyl Peptidase 4 (DPP4) Inhibitors With Metformin on GV

The present study using CGM showed that the combination of DPP4 inhibitor with metformin improved GV (Fig. 2). Effects of combination of metformin with incretin-related drugs (DPP4 inhibitors, GLP-1 analogs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors on GV were shown in Table 1 [13-19]. The combination of metformin with incretin-related drugs significantly improved GV as compared with the combination of metformin with other drugs. The combination of metformin with dapagliflozin (SGLT2 inhibitor) also significantly improved GV as compared with the combination of dapagliflozin with insulin.

Many Participants Had Been Taking Metformin in the Trials of New Anti-Diabetic Drugs That Showed Excellent Cardiovascular Outcomes

The cardiovascular effect of semaglutide, a GLP-1 analog with

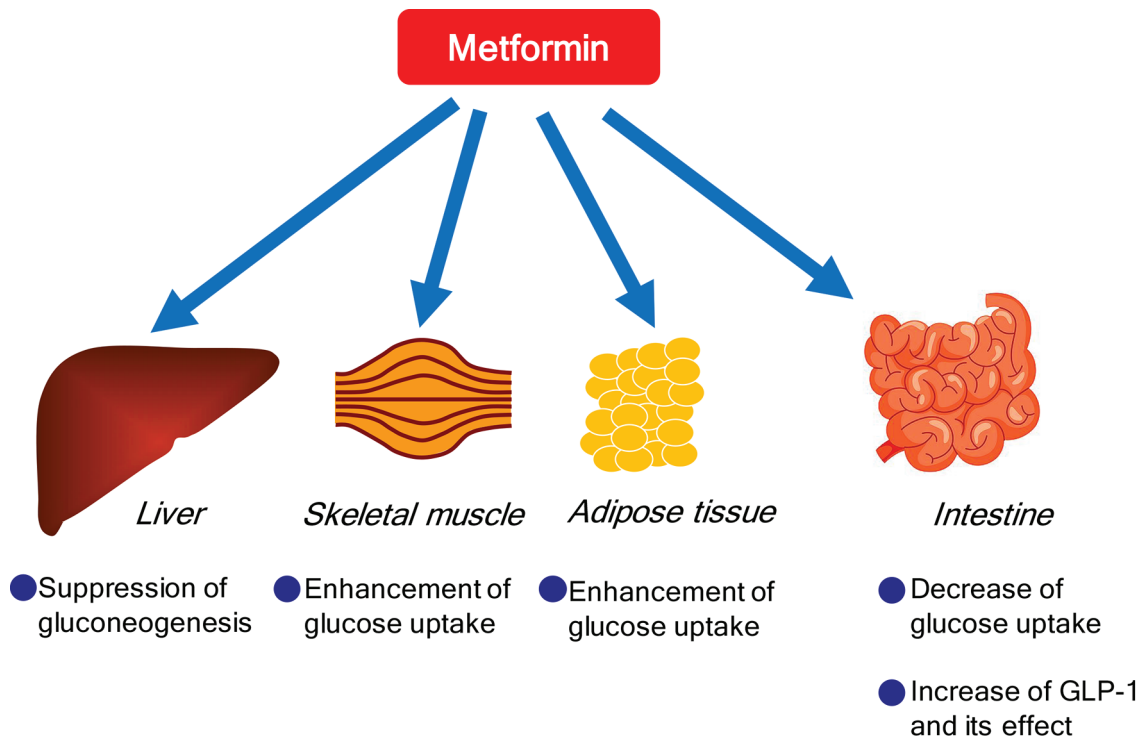


Figure 1. Glucose-lowering effects of metformin.

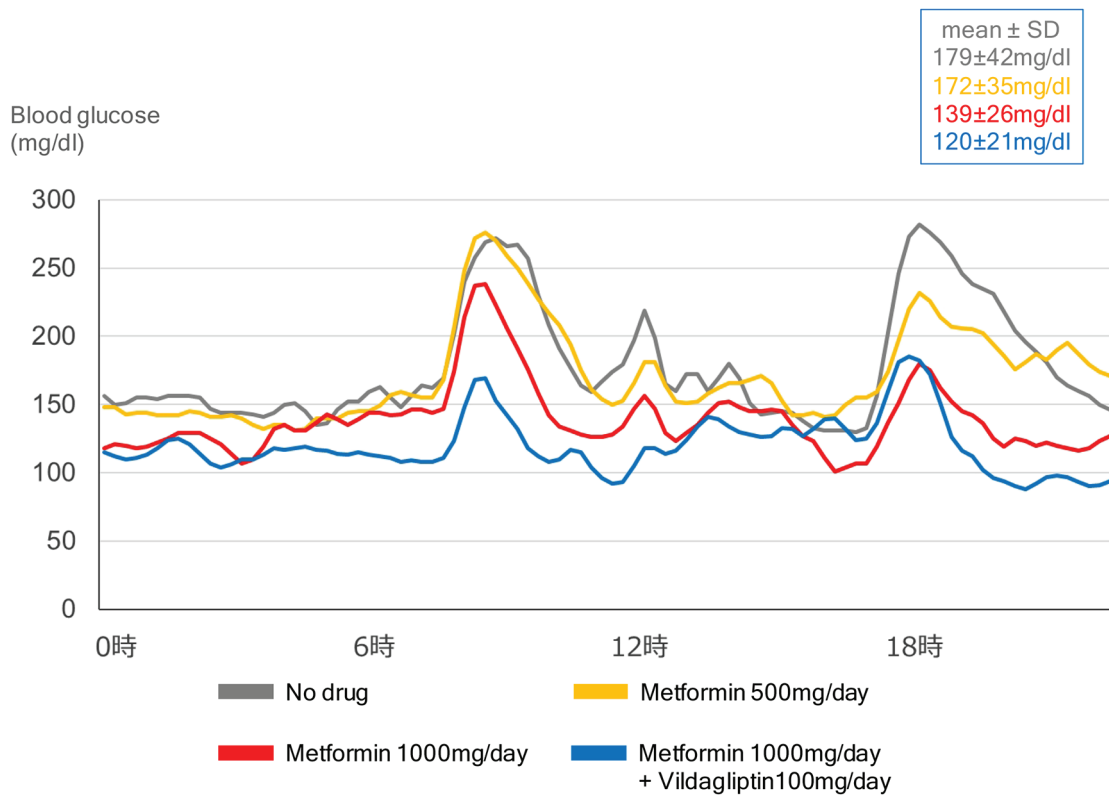


Figure 2. Effects of dose of metformin and combination of metformin with vildagliptin (DPP4 inhibitor) on glycemic variability, in a 55-year-old type 2 diabetic woman with body mass index of 29.2 kg/m².

Table 1. Effects of Combination of Metformin With Incretin-Related Drugs (DPP4 Inhibitors, GLP-1 Analogs) and SGLT2 Inhibitors on Glycemic Variability

	Effective combination therapy	Improvement of glycemic variability	Comparative combination therapy
Takahashi et al. [13]	Metformin (750 mg) + linagliptin (5 mg)	>	Metformin (1,500 mg) monotherapy
Kim et al. [14]	Metformin + vildagliptin	>	Metformin + glimepiride
Kim et al. [15]	Metformin (≥ 1,000 mg) + vildagliptin (100 mg)	>	Metformin (≥ 1,000 mg) + pioglitazone (15 mg)
Kim et al. [16]	Metformin + sitagliptin (100 mg)	>	Metformin + glimepiride (2 mg)
Frias et al. [17]	Metformin (≥ 1,500 mg) + once-weekly exenatide (2 mg)	>	Metformin (≥ 1,500 mg) + placebo
Ma et al. [18]	Metformin + liraglutide	>	Metformin + NPH insulin
Henry et al. [19]	Metformin (≥ 1,500 mg) + dapagliflozin (10 mg)	>	Insulin (≥ 30 units) + dapagliflozin (10 mg)

an extended half-life of approximately 1 week, in type 2 diabetes was examined in SUSTAIN-6 [20]. In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo. The cardiovascular effect of liraglutide, a GLP-1 analog, when added to standard care in patients with type 2 diabetes, was evaluated in LEADER Trial [21]. In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

The cardiovascular safety profile of dapagliflozin, a

SGLT2 inhibitor in patients with type 2 diabetes, was studied in DECLARE-TIMI 58 [22]. In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, dapagliflozin did not result in a higher or lower rate of major adverse cardiovascular events (MACEs) than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure. The effects of empagliflozin, a SGLT2 inhibitor, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk, were examined in EMPA-REG OUTCOME [23]. Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause. Patients

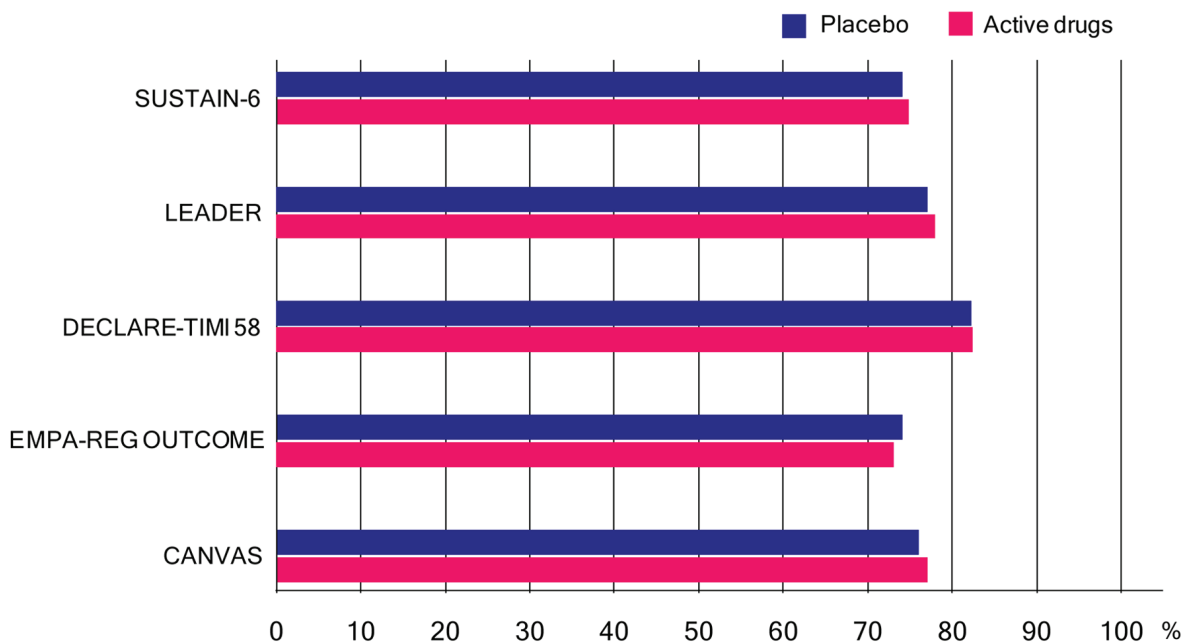


Figure 3. Percentage of patients who had been taking metformin (or biguanides) in SUSTAIN-6, LEADER Trial, DECLARE-TIMI 58, EMPA-REG OUTCOME and CANVAS program. In only SUSTAIN-6, not metformin but biguanides was written in the table which showed baseline characteristics of the patients.

treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo in CANVAS program [24].

Many patients had been taking metformin in these trials (Fig. 3). As previously mentioned, metformin improves GV which is beneficial for cardiovascular outcome in patients with diabetes. Besides effect on GV, cardio-protective effects of metformin such as improvements in hypertension, endothelial function, myocardial injury, cardiac hypertrophy, diabetic cardiomyopathy and cardiac hypertrophy were reported [2]. The United Kingdom Prospective Diabetic Study (UKPDS) demonstrated that metformin had the advantage of counteracting the cardiovascular complications associated with diabetes [25].

In conclusion, a new class of anti-diabetic drugs may have obtained good results on cardiovascular events thanks to the synergistic effect with metformin or the cardioprotective effect of metformin.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

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