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Review

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A Paradigm Shift in the Treatment of Type 2 Diabetes and Heart Failure

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Despite good control of all risk factors for myocardial infarction, including blood glucose, blood pressure, lipids, and smoking, the probability of heart failure is significantly higher in diabetic patients than in healthy individuals. This observational study shows that the current treatment guidelines, which focus on the prevention of myocardial infarction, are insufficient in preventing heart failure development. Now, understanding the mechanisms of heart failure in diabetic patients and developing treatment guidelines based on these mechanisms are urgently needed. Instead of narrowly viewing that heart failure is caused by poor cardiac function, we need to take a bird's-eye view that heart failure is caused by a shift in the hemodynamic set point (blood pressure, heart rate, circulating blood volume, and autonomic balance) toward overloading the heart due to the persistent drive of the pathological kidney-brain-heart coupling. Clinical evidence, which shows that sodium-glucose-coupled transporter [Na^+/glucose co-transporter (SGLT)-2] inhibitors slowed the progression of chronic kidney disease (CKD) and reduced heart failure hospitalizations and deaths, underscores the importance of the renocardiac syndrome in heart failure development in diabetic patients.

Key words: **SGLT2 inhibitor, Chronic kidney disease, Heart failure, Kidney-brain-heart coupling, Sympathetic nerve system, Renin-angiotensin aldosterone system**

Why is Heart Failure in Diabetic Patients Highlighted Now?

Ensuring quality of life and longevity, which is equivalent to a healthy person, is the goal of treating diabetes, and to achieve this, diabetes clinical practice guidelines declared that the onset and progress of both microvascular complications (retinopathy, nephropathy, neuropathy) and arteriosclerotic diseases (coronary artery disease, cerebrovascular disease, peripheral artery disease) must be prevented by correcting hyperglycemia, hypertension, and dyslipidemia[1].

Is the goal being met by the total care management recommended by the diabetes practice guidelines in real-world practice? To analyze this clinical question, the Swedish medical database, which is collected across the country, was used[2], and the results showed that diabetic patients with good control of all five risk factors (blood glucose, low-density lipoprotein cholesterol (LDL-C), blood pressure, albuminuria, smoking) were suppressed to the same or better probability of myocardial infarction and cerebral infarction as the general population. However, even in such situations, it was found that diabetic patients were still at higher risk of hospitalization for heart failure than the general population (hazard ratio, 1.45; 95% confidence interval (CI), 1.34–1.57), indicating that the current practice guidelines, which focus primarily on preventing myocardial infarction, are insufficient in preventing heart failure development and that developing treatment guidelines based on the pathogenesis of heart failure in diabetic patients is an urgent need. In this study, risk factors that are deeply involved in disease development were compared between acute myocardial infarction and heart failure. The major risk factors influencing the development of myocardial infarction are HbA1c, systemic blood pressure, and LDL-C, while risk factors affecting the onset of heart failure mostly include atrial fibrillation, body mass index, and estimated glomerular filtration rate (eGFR). Notably, myocardial infarction and heart failure differ greatly in the risk factors involved in their

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development.

After World War II, reduction in the number of myocardial infarction deaths was a key issue for the Western industrialized nations. Epidemiological studies have revealed that smoking, hypertension, hyperlipidemia, and hyperglycemia are the major risk factors of myocardial infarction. Drugs have been developed to lower blood pressure, blood sugar, and cholesterol levels, and thanks to these drugs, the incidence of acute myocardial infarction has decreased noticeably. However, conventional hypoglycemic drugs did prevent neither myocardial infarction nor heart failure, despite the association between higher HbA1c and higher incidence of myocardial infarction and heart failure.

Heart failure is a condition caused by an overresponse of organ linkages that regulate hemodynamics. In particular, heart and kidney linkage has attracted much attention as an event that is often experienced in daily clinical practice, which has come to be called cardiorenal syndrome or renocardiac syndrome, depending on which is the cause and the result[3]. The 42% of Japanese patients with type 2 diabetes have kidney disease greater than or equal to microalbuminuria[4]. Kidney disease complications increase the risk of developing heart failure. It is not an exaggeration to say that heart failure in patients with type 2 diabetes mellitus develops in the context of concomitant kidney disease. Therefore, therapeutic strategies that protect the kidney from damage and weaken the pathological communication between the heart and kidney are effective[5-7].

There is a Limit to Preventing the Onset and Progression of Diabetic Kidney Disease with Only Stringent Glucose-Lowering Treatment

Strict glycemic control is effective in preventing chronic kidney disease (CKD) development and progression when initiated in the early stage of diabetes[8, 9]. A legacy effect, namely, early intervention effects that last longer, is also observed on renal outcomes. However, in cases where the disease duration is as long as about 10 years, even if strict glycemic control is started in the middle, the development and progression of CKD are largely not averted.

In ACCORD trials that employed type 2 diabetic patients with a history of cardiovascular diseases or with cardiovascular risk factors, intensive glycemic control with a target of HbA1c $<6.0\%$ has no any inhibitory effect on cardiovascular diseases but rather led to an increase in mortality, leading to early termination of the study[10]. A post hoc analysis of the ACCORD trial has examined whether there was a difference in mortality from intensive glycemic control depending on the presence or absence of CKD complications[11]. In ACCORD trials, most CKD had only microalbuminuria (69%), and only 22% had eGFRs less than 60 ml/min/1.73 m^2. In patients with CKD, compared with standard therapy, intensive glucose lowering was significantly associated with both 31% higher all-cause mortality (hazard ratio, 1.306; 95% CI, 1.065–1.600) and 41% higher cardiovascular mortality (hazard ratio, 1.412; 95% CI, 1.052–1.892). By contrast, in patients without CKD, no significant effects were found. Taken together, these evidences suggest that intensive glycemic control is a proven strategy for CKD prevention in early diabetes; however, once CKD develops, benefits are less and risks are higher.

Renin-Angiotensin System Inhibitors Have been Recommended as First-Line Drugs to Suppress the Progression of Diabetic Kidney Disease

Relying on stringent glucose-lowering treatment alone to control diabetic kidney disease progression has limit. Based on evidence from clinical trials published in 2001, drugs inhibiting the renin-angiotensin system (RAS), namely, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists (ARB), have long been the only drug proven to be effective for diabetic kidney disease. ARB reduced the hard endpoint of kidney disease, namely, composite endpoints of elevated serum creatinine (doubled), end-stage renal failure (needs or needs imminent dialysis or transplantation), and death, by about 20%[12, 13]. Indeed, the effects of ARB on proteinuria were enormous. The number of patients with nephrotic syndrome due to diabetic kidney disease has decreased dramatically, but its effect on inhibiting transition to end-stage renal failure (dialysis therapy and renal transplantation) was not satisfactory enough. Indeed, when comparing changes in the frequency of complications type 2 diabetic patients over the past 20 years, the frequency of transition to end-stage renal failure has not improved much compared to the steadily declining myocardial infarction, cerebral infarction, and peripheral artery disease[14].

The Savior, the SGLT2 Inhibitor, is Here!

For residual risk in diabetic patients on RAS inhibitor therapy, a number of clinical trials have been conducted to test the efficacy and safety of drugs proven to improve diabetic kidney disease in animal studies, although none of which has been proven

effective.

Just when many nephrologists were on the verge of giving up on developing new diabetic kidney disease drugs, in 2014, SGLT2 inhibitors were launched as novel blood glucose-lowering agents, which were badly discredited before they were used. Without any scientific evidence, patients were encouraged to drink water to prevent stroke due to dehydration. The EMPA-REG OUTCOME study, published in 2015, entirely changed the reputation of SGLT2 inhibitors for the better[15]. In 2008, the United States Food and Drug Administration issued a guideline requiring pharmaceutical companies to conduct safety assessment studies in patients at high risk for cardiovascular disease to eliminate or reduce adverse cardiovascular effect risk for a new diabetes drug being developed, and the results were unexpected in a good way. Empagliflozin was not only proved safe but also reduced major adverse cardiac events (a composite endpoint of death, nonfatal myocardial infarction, or nonfatal stroke), reducing overall mortality and hospitalization for heart failure by more than 30%. Canagliflozin in the CANVAS Program[16] and dapagliflozin in DECLARE-TIMI 58 [17] showed similar efficacy as empagliflozin in EMPA-REG OUTCOME in preventing hospitalization for heart failure and death. With these three clinical studies as evidence, it is unquestionable that SGLT2 inhibitors prevent heart failure development in diabetic patients.

SGLT2 Inhibitor Exerts Therapeutic Effect on Diabetic Kidney Disease

A post hoc analysis of the EMPA-REG OUTCOME trial was performed to determine whether the speed of eGFR decline over time in patients without albuminuria, patients with microalbuminuria, and patients with overt albuminuria was affected by empagliflozin[18]. The results suggested that, irrespective of patients' albuminuria status at baseline, empagliflozin may slow down eGFR decline over time in T2DM patients, suggesting that SGLT2 inhibitors may improve renal outcomes type 2 diabetic patients.

CREDENCE was the first study to examine the therapeutic effects of SGLT2 inhibitors on diabetic kidney disease[19]. All the patients had an eGFR of 30 to <90 ml/minute/1.73 m^2 and albuminuria (ratio of albumin [mg] to creatinine [g], >300: 5000) and were treated with maximum tolerated dose of RAS inhibitors. Study participants' mean eGFR was 56 mL/min/1.73 m^2, and the median urinary albumin value was 927 mg/g. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/minute/1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. However, the study was terminated early because the interim analysis met the predetermined criteria for efficacy. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI 0.59–0.82; $P=0.00001$). During the study period, the difference in HbA1c between the placebo group and the SGLT2 inhibitor canagliflozin group was small, averaging 0.25%, indicating that therapeutic effect of canagliflozin on diabetic kidney disease is independent of its glucose-lowering effect. If all diabetic kidney disease patients in the CREDENCE study were 63 years old and had an eGFR of 56 mL/min/1.73 m^2 at the time of study entry, it would statistically simulate the extent to which therapeutic interventions with canagliflozin would make a difference in prognosis. In the placebo group patients, eGFR was calculated to decrease by 4.59 mL/min/1.73 m^2 each year; therefore, after 10 years, eGFR will decrease to less than 10 mL/min/1.73 m^2, which is one of the benchmarks for introducing dialysis. Elseways, in the canagliflozin group patients, eGFR was expected to decline to less than 10 mL/min/ 1.73 m^2 after 25 years as the rate of decline in eGFR slows to 1.85 mL/min/1.73 m^2 per year, meaning that, if canagliflozin is additionally administered to a type 2 diabetic patient with CKD with overt albuminuria who has already been treated with ACE inhibitor or ARB, renal replacement therapy can be postponed for 15 years. In other words, placebo group patients will be on dialysis at age 73, whereas canagliflozin group patients will not be on dialysis until age 88. This is the consequence of the paradigm shift in DKD treatment caused by SGLT2 inhibitors.

Why Diabetic Patients are at Higher Risk for Heart Failure?

SGLT2 inhibitors reduced the incidence of heart failure in diabetic patients regardless of existing atherosclerotic cardiovascular disease[20]. SGLT2 inhibitors are drugs that act on the kidneys, indicating that the kidney-centered interorgan communication plays a central role in the pathogenesis of heart failure. The lower the renal function, the higher the risk of developing cardiovascular events, such as myocardial infarction and cerebral infarction, heart failure, and atrial fibrillation. Accordingly, by suppressing renal function decline with SGLT2 inhibitors, the occurrence of these cardiovascular events can also be suppressed inevitably. The fact that SGLT2 inhibitors appear to have a strong prophylactic and therapeutic effect on

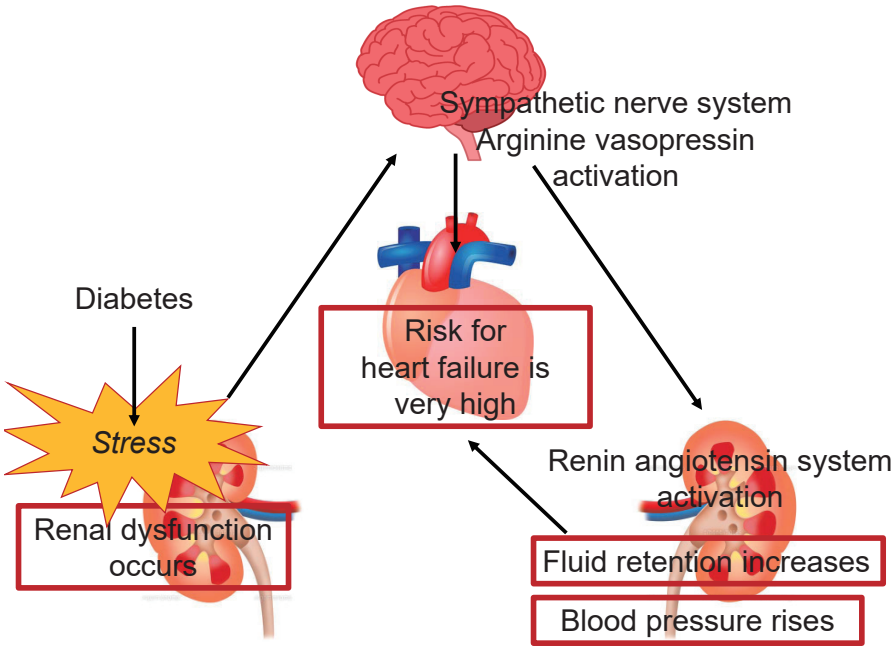

Fig. 1. Nonphysiological stress on the kidneys triggers pathological interorgan communication and heart failure

heart failure, among other cardiovascular events, is evidence that renocardiac communication plays a central role in the pathogenesis of heart failure.

Stress on the kidneys is transmitted to the brain, causing constitutive activation of neurohumoral factors, such as sympathetic nervous system, the RAS, and arginine vasopressin, shifting hemodynamic set points toward increasing blood pressure, increasing heart rate, increasing peripheral vascular resistance, and increasing fluid volume. Such a shift of the set point causes a functional and structural remodeling of the hemodynamically overloaded heart. Eventually, the compensating mechanisms broke down, and heart failure symptoms (shortness of breath, swelling, etc.) become apparent (**Fig. 1**). SGLT2 inhibitors reduce kidney stress and cut off the pathological interorgan connections leading to heart failure. Suppression of over-activated neurohumoral factors reduces the hemodynamic load on the heart. With this, SGLT2 inhibitors exert preventive and therapeutic effects on heart failure. The inhibitory effect on hospitalization for heart failure appears within 2–3 weeks at the latest after SGLT2 inhibitor prescription. Therefore, the effect is more conspicuous than the effect of suppressing cardiovascular events based on arteriosclerosis, which takes years.

Conclusions

SGLT2 inhibitors have caused a paradigm shift in the treatment strategies of T2DM patients. We have entered an era where diabetes treatment individualization and optimization are required. Glycemic control or organ protection—Which is more important? Determining these two balances according to the patient's background is necessary. The target value of HbA1c is also required to be changed according to the patient's background. SGLT2 inhibitors also prove effective in treating heart failure in nondiabetic patients[21]. By considering the mechanism of action of this drug, it is expected that the mechanism of the onset of diabetic kidney disease and heart failure will be elucidated and that it will lead to new drug discovery[5-7].

Declaration of Conflicting Interest

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