JAMA Cardiology | Special Communication

Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure
Proposal of a Novel Mechanism of Action

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IMPORTANCE Only 1 class of glucose-lowering agents—sodium-glucose cotransporter 2 (SGLT2) inhibitors—has been reported to decrease the risk of cardiovascular events primarily by reducing the risk of the development or progression of heart failure. In a landmark trial called Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [EMPA-REG Outcomes], long-term treatment with empagliflozin prevented fatal and nonfatal heart failure events but did not reduce the risk of myocardial infarction or stroke in diabetic patients.

OBSERVATIONS The beneficial effect of SGLT2 inhibitors on heart failure cannot be explained by their actions on glycemic control or as osmotic diuretics. Instead, in the kidneys, SGLT2 functionally interacts with the sodium-hydrogen exchanger, which is responsible for the majority of sodium tubular reuptake following filtration. The activity of sodium-hydrogen exchanger is markedly increased in patients with heart failure and may be responsible for both resistance to diuretics and to endogenous natriuretic peptides. In addition, in the heart, empagliflozin appears to inhibit sodium-hydrogen exchange, which may in turn lead to a reduction in cardiac injury, hypertrophy, fibrosis, remodeling, and systolic dysfunction. Furthermore, the major pathophysiological derangements of heart failure and a preserved ejection fraction may be mitigated by the actions of SGLT2 inhibitors to reduce blood pressure, body weight, and fluid retention as well as to improve renal function. The benefits of spironolactone in patients with heart failure with either a reduced or a preserved ejection fraction may also be attributable to the actions of the drug to inhibit the sodium-hydrogen exchange mechanism.

CONCLUSIONS AND RELEVANCE The benefits of SGLT2 inhibitors in heart failure may be mediated by the inhibition of sodium-hydrogen exchange rather than the effect on glucose reabsorption. This hypothesis has important implications for the design and analysis of large-scale outcomes trials involving diabetic or nondiabetic patients with chronic heart failure.

JAMA Cardiol. doi:10.1001/jamacardio.2017.2275
Published online August 2, 2017.

Viewpoint

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The advent of large-scale cardiovascular outcome trials in type 2 diabetes has opened the gateway to our understanding of both diabetes and cardiovascular disorders. Many long-term clinical studies in diabetic patients have demonstrated little change in the risk of major cardiovascular events despite meaningful improvements in glycemic control,[1-3] thus raising important questions about the role of abnormal glucose metabolism in the development and progression of macrovascular disorders. Although prolonged treatment with antidiabetic agents has been recently reported to be associated with a significant reduction in cardiovascular risk,[4-6] the patterns of benefit have differed significantly across therapeutic classes. Some glucose-lowering agents appear to exert a favorable effect primarily by reducing the occurrence of atherosclerotic thrombotic cardiovascular events (eg, myocardial infarction and stroke), with no benefit on heart failure[5,6]; certain antidiabetic agents have been associated with an increased risk of heart failure.[7,8] Only 1 class of glucose-lowering agents—sodium-glucose cotransporter 2 (SGLT2) inhibitors—has been reported to decrease the risk of cardiovascular events primarily through reducing the risk of the development or progression of heart failure.[4,9]

A Special Effect of SGLT2 Inhibition on Heart Failure

A landmark trial involving 7020 patients with type 2 diabetes at high risk of cardiovascular events (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [EMPA-REG Outcomes]) found that long-term treatment with empagliflozin did not reduce the risk of myocardial infarction or stroke, but the drug did meaningfully lower the occurrence of heart failure events (Table). Empagliflozin diminished the risk of developing heart failure in patients who largely had no prior history of heart failure. This finding was re-

Table. Cardiovascular Outcomes in the EMPA-REG Outcomes Trial

Outcome	No. (%)		Hazard Ratio (95% CI)	*P* Value
	Placebo (n = 2333)	Empagliflozin (n = 4687)		
Cardiovascular death	137 (5.9)	172 (3.7)	0.62 (0.49-0.77)	<.001
Fatal or nonfatal myocardial infarction	126 (5.4)	223 (4.8)	0.87 (0.70-1.09)	.23
Fatal or nonfatal stroke	69 (3.0)	164 (3.5)	1.18 (0.89-1.56)	.26
Cardiovascular death (excluding stroke) or heart failure hospitalization	198 (8.5)	265 (5.7)	0.66 (0.55-0.79)	<.001
Hospitalization for heart failure	95 (4.1)	126 (2.7)	0.65 (0.50-0.85)	.002
Investigator-reported heart failure	143 (6.1)	204 (4.4)	0.70 (0.56-0.87)	.001
Heart failure reported as a serious adverse event	136 (5.8)	192 (4.1)	0.69 (0.55-0.86)	.001

flected in a major decrease in the risk of heart failure requiring hospitalization, a lower incidence of heart failure identified by investigators as a serious adverse event, and a reduction in the use of newly prescribed loop diuretics.[4,9,10] Furthermore, empagliflozin decreased cardiovascular deaths that are specifically associated with the development and progression of heart failure: deaths from pump failure were reduced by 68%, and sudden or presumably sudden cardiovascular deaths were reduced by 32%. In contrast, cardiovascular deaths related to atherosclerotic ischemic events were not affected by long-term treatment with SGLT2 inhibitors (Table).[4]

The reliability of these findings is supported by the large number of events and the fact that similar benefits were seen in 2 separately randomized groups that received different doses of empagliflozin.[4] An important limitation of the data was the failure of the trial to characterize whether the reduced risk of heart failure was associated with the prevention of heart failure with a reduced ejection fraction, the prevention of heart failure with a preserved ejection fraction, or a favorable effect on both conditions. Similar effects may also be seen with other SGLT2 inhibitors (ie, canagliflozin and dapagliflozin), although data are insufficient to establish a class effect.[11,12] Finally, most of the existing data support the ability of these drugs to prevent heart failure, but there is little experience with SGLT2 inhibitors as a treatment for patients with established heart failure.

The beneficial effect on heart failure of drugs that inhibit SGLT2 cannot be explained by the actions of these agents on indices of glycemic control.[4,10] Although the pathogenesis of heart failure in diabetic patients is poorly understood, there is little evidence that glucotoxicity contributes in any meaningful way to cardiac systolic or diastolic dysfunction. In the EMPA-REG Outcomes trial, major differences in the risk of heart failure were seen across the treatment groups, even though (by design) the difference in glycemic control in patients treated with placebo or empagliflozin was marginal.[4,9] Furthermore, when the totality of data from large randomized trials with glucose-lowering agents is critically examined, there has been no association between changes in glycemic control and the risk of heart failure.[1-9] Accordingly, the primary measures of efficacy and safety for cardiovascular outcome trials for new diabetic agents have not included heart failure as an important component of composite end points.[2-6]

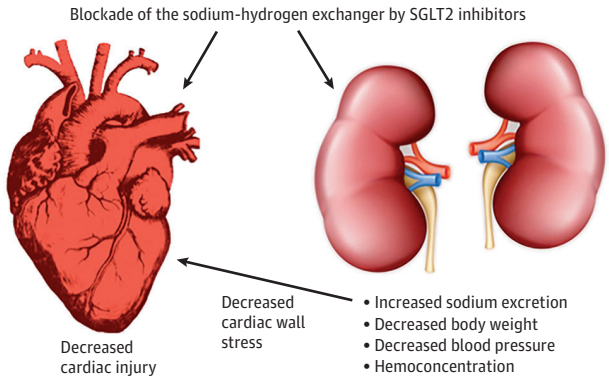
The most commonly cited explanation for the beneficial effects of SGLT2 inhibitors on heart failure has been that these drugs act primarily as a diuretic.[13] Certain diuretics reduce the incidence of heart failure in patients at increased cardiovascular risk,[14] and their use is associated with a short-term increase in urine volume, which is followed by a sustained decrease in systolic blood pressure, usually with little change in plasma volume and body weight.[15-17] Long-term use is frequently accompanied by potassium depletion and worsening of renal function.[18,19] Diabetic patients treated with SGLT2 inhibitors also exhibit a short-term diuresis and long-term decreases in systolic blood pressure,[4,9,17] but these effects are accompanied by sustained reduction in body weight and plasma volume (without electrolyte disturbances), meaningful degrees of hemoconcentration, and a long-term improvement in renal function.[17,20-24] These important differences indicate that SGLT2 inhibitors are not likely to prevent heart failure by acting simply as conventional diuretics.[25]

Effect of SGLT2 Inhibitors on the Kidneys

Whereas most conventional diuretics act on the loop of Henle and the distal tubules, SGLT2 inhibitors act principally in the proximal tubules of the kidneys.[26,27] In the diabetic kidney, SGLT2 inhibition not only promotes the excretion of glucose in the urine but also enhances the delivery of sodium to the macular densa.[20,27] Such an action (through tubuloglomerular feedback) leads to afferent arteriolar vasoconstriction and a decrease in glomerular hyperfiltration,[26,28] which in turn would be expected to slow the progression of diabetic renal disease. However, afferent arteriolar vasoconstriction is already present in patients with heart failure,[29,30] and enhancement of such vasoconstriction would not be expected to have favorable effects on the kidney in nondiabetic patients with heart failure.

What action of SGLT2 inhibitors on the kidney might be beneficial to patients with heart failure? In the proximal renal tubule, SGLT2 colocalizes and functionally interacts with sodium-hydrogen exchanger (NHE) 3,[31,32] which is primarily responsible for the majority of sodium tubular reuptake following filtration.[33] The activity of NHE3 is markedly increased in heart failure and is believed to be responsible for both resistance to diuretics and resistance to endogenous natriuretic peptides.[34,35] Therefore, it is noteworthy that inhibitors of SGLT2 have been shown to interfere with the actions of NHE3; increases in bicarbonate excretion and an increased risk of acidosis following SGLT2 inhibition are consistent with such an action.[31,32,36] The natriuresis following NHE3 inhibition might be limited if there were a compensatory increase in the absorptive capacity for sodium in other parts of the nephron.[33] However, a natriuresis following NHE3 inhibition could be potentiated if it were accompanied by treatments that block sodium reabsorption in the loop of Henle and distal collecting systems (eg, loop diuretics and mineralocorticoid receptor antagonists)[37,38]; such drugs are used

Figure. Cardioprotective Effect of Sodium-Glucose Cotransporter 2 (SGLT2) on Sodium-Hydrogen Exchange in the Heart and Kidneys



Inhibition of sodium-hydrogen exchange in the kidneys leads to natriuresis, hemoconcentration, and decreases in both body weight and blood pressure, all of which act in concert to reduce cardiac wall stress. Cardiac dysfunction is additionally prevented by inhibition of sodium-hydrogen exchange in the heart failure, thus reducing intracellular calcium and cardiomyocyte injury.

routinely in patients with heart failure. The resulting decrease in intravascular volume might be expected to lead to important short-term and long-term decreases in cardiac wall stress, with a resultant favorable effect on the development and progression of heart failure (Figure).

Effect of SGLT2 Inhibitors on the Heart and Large Vessels

In experimental models, inhibition of SGLT2 slows the development and progression of cardiac hypertrophy and cardiomyopathy.[39-41] Some have postulated that such a benefit may be explained by changes in sodium reabsorption in the gastrointestinal tract or by improvement in the utilization of metabolic fuels in the heart[42,43]; yet the relevance of these findings in the laboratory to nondiabetic patients with heart failure remains unclear. It might be intriguing to speculate that the actions of SGLT2 and NHE3 are intertwined in the heart as they are in the kidneys, but SGLT2 is not expressed in the human heart[44]; nevertheless, empagliflozin inhibits sodium-hydrogen exchange.[45] The activity of the cardiac NHE is increased in experimental models of heart failure.[46,47] Such an increase is sufficient to enhance the intracellular concentration of sodium in cardiomyocytes, which (through the actions of the NHE) would result in an increase in intracellular calcium, leading to an increase in cardiomyocyte injury and the development of cardiomyopathy.[48-50] Baartscheer et al[45] have shown that the action of empagliflozin to inhibit the NHE leads to a reduction in intracellular calcium. This effect was no longer apparent if the activity of the NHE were already blocked by pretreatment with cariporide, an established inhibitor of the NHE in the heart.

Inhibition of NHE has been shown to minimize cardiomyocyte injury and to attenuate the development of cardiac hypertrophy, fibrosis, remodeling, systolic dysfunction, and heart failure; these benefits have been demonstrated in a broad range of experimental models, including those induced by pressure and/or volume overload, coronary artery occlusion, rapid cardiac pacing, α-adrenergic and β-adrenergic stimulation, and diabetes.[51-58] These benefits were incremental to those achieved by angiotensin-converting enzyme inhibition.[59] Pretreatment with cariporide was reported to reduce myocardial injury and the short-term risk of cardiovascular death or injury in patients undergoing coronary artery bypass surgery.[60,61] Concerns that short-term intravenous NHE inhibition might interfere with platelet function and increase the risk of stroke in the postsurgical setting may not be applicable to long-term use of oral agents in ambulatory patients.[61] It has also been postulated that the benefits of certain potassium-sparing diuretics (ie, amiloride in experimental cardiomyopathy and of spironolactone in laboratory models of cardiac injury and in clinical heart failure) are mediated by NHE inhibition.[62-64] A decade ago, long-term trials with orally active selective NHE inhibitors in patients with chronic heart failure and a reduced ejection fraction were contemplated but were never carried out.

In addition, SGLT2 inhibitors may exert favorable effects in patients with chronic heart failure and a preserved ejection fraction. This disorder is common among diabetic patients and was likely to have been well represented among those who developed heart failure in large-scale diabetes trials.[4,9,65] Such patients characteristically exhibit severe cardiac and aortic stiffness related to aging, hypertension, obesity, glucose intolerance, and fluid retention often in association with varying degrees of renal insufficiency.[66-68] Each of these physiological derangements may be mitigated by the actions of SGLT2 inhibitors to reduce blood pressure, body weight, and fluid retention and to improve glucose tolerance and renal function.[20,21,69] Empagliflozin has been reported to have favorable effects on both arterial stiffness and diastolic cardiac filling in diabetes.[70,71] The reported benefits of spironolactone in patients with heart failure and a preserved ejection fraction[72] may also be explained by the actions of the drug to inhibit the sodium-hydrogen exchange mechanism in large vessels.[73]

Conclusions

The possibility that SGLT2 inhibitors may have beneficial effects on heart failure has been raised by the results of clinical trials in patients with diabetes. However, the favorable effects of these drugs may be primarily mediated by an inhibitory effect on the NHE mechanisms in both the kidney and the heart. These observations suggest that the reduction in the risk of heart failure with SGLT2 inhibitor treatment not only may be independent of its effects on glycemia but also can be distinguished from the actions of conventional diuretics.

The favorable actions of several distally acting diuretics (eg, spironolactone) on the renal and cardiac mechanisms underlying the progression of heart failure might also be mediated by their ability to inhibit both cardiac and renal NHE.[62-64,74,75] Of interest, in a post hoc subgroup analysis, the effects of empagliflozin to prevent heart failure in diabetic patients was reported to be attenuated in those receiving mineralocorticoid receptor antagonists.[9] Such an observation must be viewed very cautiously given the small number of events and the multiplicity of comparisons. Hypotheses based on subgroup analyses are frequently unconfirmed in subsequent trials; thus, the finding of an interaction is likely to be spurious. Nevertheless, we should remain mindful of the possibility of a clinically important interaction between SGLT2 inhibitors and spironolactone because their pharmacological actions overlap. Such an interaction would have been difficult to detect in the diabetes trials with em-

pagliflozin because only 6% of patients in the EMPA-REG Outcomes trial were being treated with mineralocorticoid antagonists.[4,9] Such an interaction will be much easier to detect in ongoing large-scale, long-term trials with SGLT2 inhibitors (empagliflozin and dapagliflozin) in diabetic and nondiabetic patients with chronic heart failure; in these trials, the background use of spironolactone and eplerenone is expected to exceed 60%.

The results of large-scale trials with SGLT2 inhibitors in patients with established heart failure are eagerly awaited. However, they are not likely to elucidate the mechanisms leading to heart failure in patients with glucose intolerance. These trials will not be testing the role of glycemia in the development of cardiac dysfunction. If successful, they will teach us more about the pathophysiology of heart failure than that of diabetes.

ARTICLE INFORMATION

Accepted for Publication: May 19, 2017.

Published Online: August 2, 2017. doi:10.1001/jamacardio.2017.2275

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Packer reported receiving personal fees from Amgen, Boehringer Ingelheim, Celyad, Cardiorentis, Novartis, Sanofi, Takeda, and ZS Pharma. Dr Anker reported serving as a paid consultant to Bayer; receiving personal fees from AstraZeneca, Boehringer Ingelheim, Servier, Stealth Biopeptides, and Vifor; and receiving grants from Abbott Vascular and Vifor. Dr Butler reported receiving consulting fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, CardioCell, Janssen, Merck, Novartis, Relypsa, and ZS Pharma. Dr Filippatos reported serving as a committe member for Bayer, Boehringer Ingelheim, Novartis, and Servier. Dr Zannad reported receiving personal fees as a steering committee member from Bayer, Boehringer Ingelheim, Boston Scientific, General Electric, Janssen, Novartis, Pfizer, Resmed, and Takeda; serving as a paid consultant for Amgen, AstraZeneca, CVRx, Quantum Genomics, Relypsa, Roche Diagnostics, and ZS Pharma; and being a founder of CardioRenal and CVCT. No other disclosures were reported.

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