JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Sodium–glucose cotransporter 2 inhibitors: A drug with antidiabetic and cardioprotective properties

Recently, two large double-blind randomized controlled trials testing the effect of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with heart failure with and without diabetes have led to a paradigm shift for the indication of this class of drugs. Key clinical features and main results in these two studies are summarized in Tables 1 and 2. The Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial included 4,744 patients with heart failure and a reduced ejection fraction (HFrEF)[1]. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. Patients who received dapagliflozin showed a 26% lower risk of developing primary outcomes, compared with patients who received a placebo. Importantly, this trial included patients without diabetes, in addition to patients with diabetes. In a prespecified exploratory analysis, the cardioprotective effect was observed in patients with diabetes, prediabetes and normoglycemia[2]. In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), 3,730 patients with HFrEF were recruited[3]. The primary outcome was a composite of adjudicated cardiovascular death or hospitalization for heart failure. Patients in the empagliflozin group had a 25% reduction in developing primary outcome, compared with patients in the placebo group. Similarly, the beneficial effect was observed in both patients with and without diabetes.

In the DAPA-HF study, prespecified extensive analyses in patients with and without diabetes were carried out[2]. The results for each individual component of primary outcome and each secondary outcome were consistent in patients with and without diabetes. In addition, analysis of patients without type 2 diabetes at baseline and with hemoglobin A1c <5.7% or 5.7–6.4% showed that dapagliflozin was equally effective in reducing primary outcomes in these two subgroups (Table 2). In addition, the change of hemoglobin A1c from baseline was only modest (patients with diabetes, –0.261% in the 4th month; patients without diabetes, +0.003% at the 4th month; *P* for interaction <0.001). All these results provide strong evidence to support that SGLT2 inhibitors reduce the risk of heart failure through glucose-independent mechanisms.

Several mechanisms by which SGLT2 inhibitors reduce the risk of heart failure have been proposed and are still under debate[4]. Natriuresis and change in tissue sodium handling, reduction in plasma volume and cardiac preload, reduced blood pressure, and improved vascular function are likely to contribute the cardioprotective effects of SGLT2 inhibitors. In addition, some other mechanisms might be beneficial, including reduced inflammation and oxidative stress, a shift toward ketone body metabolism, decreased plasma uric acid level, suppressed damage mediated by advanced glycation end-products and so on.

The results of the DAPA-HF and EMPEROR-Reduced trials are likely to extend the current application of SGLT2 inhibitors, especially to patients without diabetes and with HFrEF. A key question for patients with heart failure is whether the cardioprotective effect can also be observed in patients with heart failure and a preserved ejection fraction (HFpEF). As the pathophysiology of HFpEF is heterogeneous[5], and it is different but with some overlap from the pathophysiology of HFrEF, the answers to the question await the results of two ongoing trials (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure [DELIVER], NCT 03619213, and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [EMPEROR-Preserved], NCT 03057951). Another important question is whether the cardioprotective effect in patients with and without diabetes is a class effect. The ongoing CHIEF-HF study (a Study on the Impact of Canagliflozin on Health Status, Quality of Life and Functional Status in Heart Failure, NCT 04252287) evaluates the effect of canagliflozin in patients with HFrEF or HFpEF, with or without diabetes. However, the primary outcome is the change of a symptom score, instead of hard outcomes, such as hospitalization for heart failure or cardiovascular death. In addition, there are some ongoing studies being carried out to explore the mechanisms of how ertugliflozin lowers the risk of heart failure. These results will provide more information for the cardioprotective effect of SGLT2 inhibitors in the future.

The renal protection effects of SGLT2 inhibitors in patients with and without diabetes are tested in two large randomized controlled trials (a Study to Evaluate the Effect of Dapagliflozin on Renal

*Corresponding author. Hung-Yuan Li
Tel.: +886-2-23123456 ext. 63540
Fax: +886-2-23123456 ext. 63486
E-mail address: larsli@ntuh.gov.tw
Received 12 September 2020; revised 14 September 2020; accepted 15 September 2020

Table 1 | Comparison of baseline clinical characteristics in the dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF) and the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced).

	DAPA-HF		EMPEROR-Reduced	
	Dapagliflozin	Placebo	Empagliflozin	Placebo
n	2,373	2,371	1,863	1,867
Age (years)	66.2 ± 11.0	66.5 ± 10.8	67.2 ± 10.8	66.5 ± 11.2
Female sex, *n* (%)	564 (23.8)	545 (23.0)	437 (23.5)	456 (24.4)
NYHA functional classification, *n* (%)				
II	1,606 (67.7)	1,597 (67.4)	1,399 (75.1)	1,401 (75.0)
III	747 (31.5)	751 (31.7)	455 (24.4)	455 (24.4)
IV	20 (0.8)	23 (1.0)	9 (0.5)	11 (0.6)
LVEF (%)	31.2 ± 6.7	30.9 ± 6.9	27.7 ± 6.0	27.2 ± 6.1
Median NT-pro BNP, pg/mL (IQR)	1,428 (857–2,655)	1,446 (857–2,641)	1,887 (1,077–3,429)	1,926 (1,153–3,525)
Ischemic cause of heart failure, *n* (%)	1,316 (55.5)	13,158 (57.3)	983 (52.8)	946 (50.7)
History of HHF, *n* (%)	1,124 (47.4)	1,127 (47.5)	577 (31.0)	574 (30.7)
Device therapy, *n* (%)				
ICD	622 (26.2)	620 (26.1)	578 (31.0)	593 (31.85)
CRT	190 (8.0)	164 (6.9)	220 (11.8)	222 (11.9)
Diabetes, *n* (%)	993 (41.8)	990 (41.8)	927 (49.8)	929 (49.8)
CKD, *n* (%)	962 (40.6)	964 (40.7)	893 (48.0)	906 (48.6)
eGFR (mL/min/1.73 m^2)	66.0 ± 19.6	65.5 ± 19.3	61.8 ± 21.7	62.2 ± 21.5
Heart failure medications				
ACE inhibitor	1,332 (56.1)	1,329 (56.1)	1,314 (70.5)†	1,286 (68.9)†
ARB	675 (28.4)	632 (26.7)		
ARNI	250 (10.5)	258 (10.9)	340 (18.3)	387 (20.7)
MRA	1,696 (71.5)	1,674 (70.6)	1,306 (70.1)	1,355 (72.6)

Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. †Total number (%) for the use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) were shown. ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; DAPA-HF, the dapagliflozin and prevention of adverse outcomes in heart failure trial; EMPEROR-Reduced, the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction; HHF, hospitalization for heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease [DAPA-CKD], NCT 03036150, and the Study of Heart and Kidney Protection with Empagliflozin [EMPA-KIDNEY], NCT 03594110). In DAPA-CKD, patients with estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73 m^2 and albuminuria were recruited, with or without diabetes. This trial investigates the effect of dapagliflozin on the first occurrence of composite renal outcomes, including a sustained decline in eGFR ≥50%, end-stage renal disease, cardiovascular death or renal death, compared with a placebo. The results released recently are promising, and the full report will be published soon. In EMPA-KIDNEY, patients with eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 with albuminuria were recruited, whereas patients with type 2 diabetes and prior atherosclerotic diseases with eGFR >60 mL/min/1.73 m^2 were excluded. The trial tests the effect of empagliflozin on the first occurrence of a sustained decline in eGFR ≥40%, end-stage kidney disease, cardiovascular death or renal death. The study is estimated to be completed in 2022. Taken together, the results from DAPA-CKD and EMPA-KIDNEY trials will broaden our understanding of the renal protective effects of SGLT2 inhibitors in patients with chronic kidney diseases and without diabetes. In addition, data on patients with eGFR lower than current label will provide more information on the effectiveness and safety in patients with advanced chronic kidney diseases.

In conclusion, data from DAPA-HF and EMPEROR-Reduced trials suggest that SGLT2 inhibitor is a drug with both antidiabetic and cardioprotective properties. In the near future, its renal protection effect in patients with chronic kidney diseases will be revealed. With these results, the application of SGLT2 inhibitors is expected to be widespread, which will improve the clinical outcomes of patients with diabetes, heart failure or chronic kidney diseases.

DISCLOSURE

The author declares no conflict of interest.

Hung-Yuan Li*
Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Table 2 | Comparison of outcomes in the dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF) and empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced).

	DAPA-HF			EMPEROR-Reduced		
	Dapagliflozin	Placebo	HR (95% CI)	Empagliflozin	Placebo	HR (95% CI)
Primary composite outcome, *n* (%)	386 (16.3)	502 (21.2)	0.74 (0.65–0.85)	361 (19.4)	462 (24.7)	0.75 (0.65–0.86)
Type 2 diabetes at baseline, *n* (%)						
Yes	215 (20.0)	271 (25.5)	0.75 (0.63–0.90)†	200 (21.6)	265 (28.5)	0.72 (0.60–0.87)
No	171 (13.2)	231 (17.7)	0.73 (0.60–0.88)†	161 (17.2)	197 (21.0)	0.78 (0.64–0.97)
Patients without type 2 diabetes at baseline, *n* (%)						
Hemoglobin A1c <5.7%	53 (12.1)	71 (16.9)	0.67 (0.47–0.96)†	NA	NA	NA
Hemoglobin A1c 5.7–6.4%	118 (13.7)	160 (18.0)	0.74 (0.59–0.94)†	NA	NA	NA
Change of laboratory and other measures from baseline‡						
A1c (%)	−0.21 ± 1.14*	0.04 ± 1.29		−0.28 ± 0.03*	−0.12 ± 0.03	
Weight (kg)	−0.88 ± 3.86*	0.10 ± 4.09		−0.73 ± 0.13*	0.08 ± 0.13	
Systolic blood pressure (mmHg)	−1.92 ± 14.92*	−0.38 ± 15.27		−2.4 ± 0.4	−1.7 ± 0.4	

The primary composite outcome in dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF) trial included hospitalization for heart failure, an urgent visit for heart failure and cardiovascular death. The primary composite outcome in empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) included cardiovascular death and hospitalization for worsening heart failure. *$P < 0.05$ versus placebo. †*P*-values for interaction in DAPA-HF trial were 0.80 for patients with and without type 2 diabetes at baseline and 0.72 for patients with A1c <5.7% and hemoglobin A1c (A1c) 5.7–6.4%. *P*-value for interaction in patients with and without diabetes was not reported in EMPEROR-Reduced. ‡In DAPA-HF, changes from baseline to 8 months were shown. In EMPEROR-Reduced, changes from baseline to 52 weeks are shown. NA, not available.

REFERENCES

1. McMurray JJV, Solomon SD, Inzucchi SE, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381: 1995–2008.
2. Petrie MC, Verma S, Docherty KF, *et al*. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020; 323: 1353–1368.
3. Packer M, Anker SD, Butler J, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383: 1413–1424.
4. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020. https://doi.org/10.1038/s41569-020-0406-8
5. Del Buono MG, Iannaccone G, Scacciavillani R, *et al*. Heart failure with preserved ejection fraction diagnosis and treatment: an updated review of the evidence. *Prog Cardiovasc Dis* 2020. https://doi.org/10.1016/j.pcad.2020.04.011

Doi: 10.1111/jdi.13413