Is There Room for New Drugs in the Treatment of Advanced Heart Failure: SGLT2i?

Victor Sarli Issa[1]

Hospital Universitário de Antuerpia,[1] *Antuerpia – Belgium*

Over the last years, we have witnessed the inclusion of the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) for the treatment of patients with heart failure. Drugs in this group share the fact that they are able to inhibit glucose transport in the proximal tubule and thus promote glycosuria and blood glucose reduction in patients with diabetes. Other effects of these medications include increasing diuresis and natriuresis, lowering blood pressure, stimulating erythropoiesis, improving cardiac energy metabolism, reducing inflammation, inhibiting the sympathetic nervous system, preventing cardiac remodeling, preventing ischemia-reperfusion injury, inhibiting the Na+/H+ exchanger, reducing hyperuricemia, increasing autophagy and lysosomal degradation, decreasing epicardial fat, increasing erythropoietin levels, increasing circulating vascular progenitor cells, decreasing oxidative stress, and improving vascular function.[1]

SGLT2i were initially tested for glycemic control in patients with diabetes mellitus,[2-4] and it was quickly noted that, in addition to their antidiabetic effect, these drugs were able to significantly reduce cardiovascular events, especially episodes of decompensated heart failure. Based on these results, the natural sequence was to evaluate SGLT2i in patients with heart failure. The initial results obtained were among patients with heart failure with reduced ejection fraction, with the DAPA-HF (evaluating dapagliflozin) and EMPEROR-Reduced (evaluating empagliflozin) studies, which showed that inhibition of sodium-glucose cotransporter 2 (SGLT2) reduced the combined risk of cardiovascular death or hospitalization due to heart failure in patients with heart failure with reduced ejection fraction, with or without diabetes.[5] More recently, we have seen positive results in the context of heart failure with preserved ejection fraction, although the effects of medication have mainly focused on the group of patients with slightly reduced ejection fraction.[6]

Taken together, these results indicate that SGLT2i are safe and beneficial for a wide range of patients with heart failure. Nevertheless, it is noteworthy that certain patients are underrepresented in these clinical trials, such as patients with advanced heart failure. This group is known to be more severe, with higher presence of comorbidities and lower tolerance to medications, especially in the context of polypharmacy. Even though there have not been any clinical trials testing the use of SGLT2i in this specific population, some interesting data allow us to delve deeper into this topic.[7]

In relation to the presence of comorbidities, perhaps no other condition has the same prevalence and relevance in the context of heart failure as renal dysfunction, a recognized marker of worse prognosis in patients with advanced heart failure. In this regard, a meta-analysis of 7 clinical trials involving 14,113 patients with heart failure identified that the use of SGLT2i was associated with a lower risk of progression of renal dysfunction (risk ratio 0.673; 95% confidence interval 0.549 to 0.825; $p < 0.001$; $I^2 = 17.7\%$), notwithstanding a higher risk of volume depletion (risk ratio 1.177; 95% confidence interval 1.040 to 1.333; $p = 0.010$; $I^2 = 0.0\%$). This finding has significant prognostic and therapeutic implications.[8]

From a clinical and hemodynamic point of view, data from a single-center cohort of 17 patients with advanced heart failure who had received a CardioMEMS system, which allows continuous monitoring of pulmonary artery pressure, showed that pulmonary pressures fell after initiation of SGLT2i, without any change in the dosage of diuretics (Figure 1).[9] While it is recognized that this is an initial experience, these results indicate relevant clinical and hemodynamic effects in this patient population.

From a clinical and prognostic point of view, it is known that the occurrence of arrhythmias is a frequent event in patients with advanced heart failure and a relevant cause of death. Accordingly, a *post hoc* analysis of the DAPA-HF study[10] aimed to identify the effect of dapaglifozin specifically on the occurrence of ventricular arrhythmias and sudden death in patients with heart failure with reduced ejection fraction. The study found that, among the participants who received dapagliflozin, the composite outcome (ventricular arrhythmia, resuscitated cardiac arrest, or sudden death) occurred in 140/2373 patients (5.9%), compared to 175/2371 patients (7.4%) in the placebo group (hazard ratio 0.79; 95% confidence interval 0.63 to 0.99, $p = 0.037$), and this effect was consistent for each component of the composite outcome taken alone.

The recently published EMPULSE trial[11] aimed to evaluate the effect of empagliflozin, initiated during hospital stay in patients admitted for decompensated heart failure, regardless of ejection fraction. The study included 530 patients who were followed for up to 90 days after discharge, and empaglifozin was found to be well tolerated. It also showed what the authors termed the greatest clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events, and time to first heart failure event, or a difference of 5 points or more in change from baseline Kansas City Cardiomyopathy Questionnaire, with total symptom score at 90 days (Figure 2).

Keywords

Heart Failure; Prognosis; Blood Vessels

Mailing Address: Victor Sarli Issa •
Antwerp University Hospital - Cardiology Department - Drie Eikenstraat 655, 2650 Edegem - Belgium
E-mail: victor.sarli.issa@gmail.com
Manuscript received April 06, 2022, revised manuscript April 12, 2022, accepted April 26, 2022

DOI: https://doi.org/10.36660/abchf.20220030

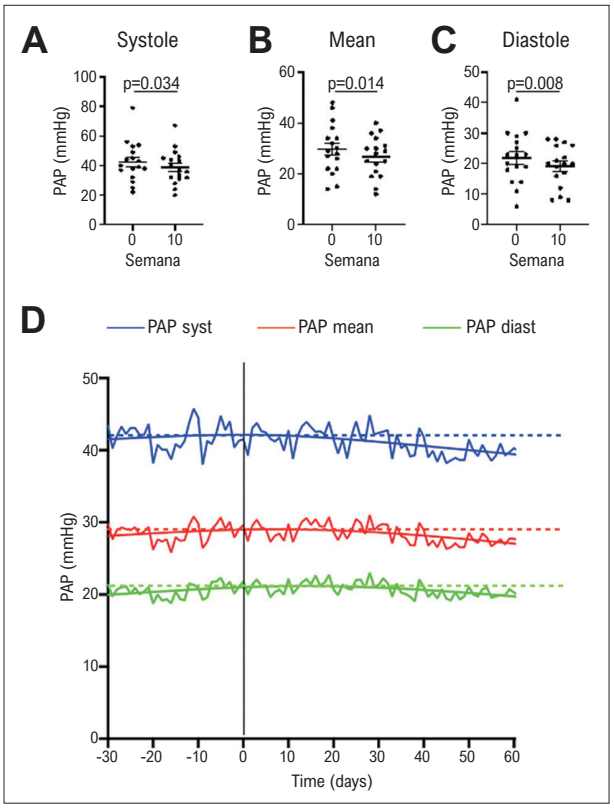

Figure 1 – *Systolic (A), mean (B), and diastolic (C) pulmonary artery pressures at baseline and 10 weeks after initiation of SGLT2i. (D) Pulmonary artery pressure evolution from 30 days prior to initiation of SGLT2i until 70 days after initiation of SGLT2i.[9] PAP: pulmonary artery pressure.*

Taken together, the current data indicate that SGLT2i are safe medications for use in patients with advanced heart failure, with a potential impact on prognosis. Will clinical trials in this specific population, however, be able not only to evaluate their effectiveness, but also to identify subgroups with greater risks or benefits?

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Issa VS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

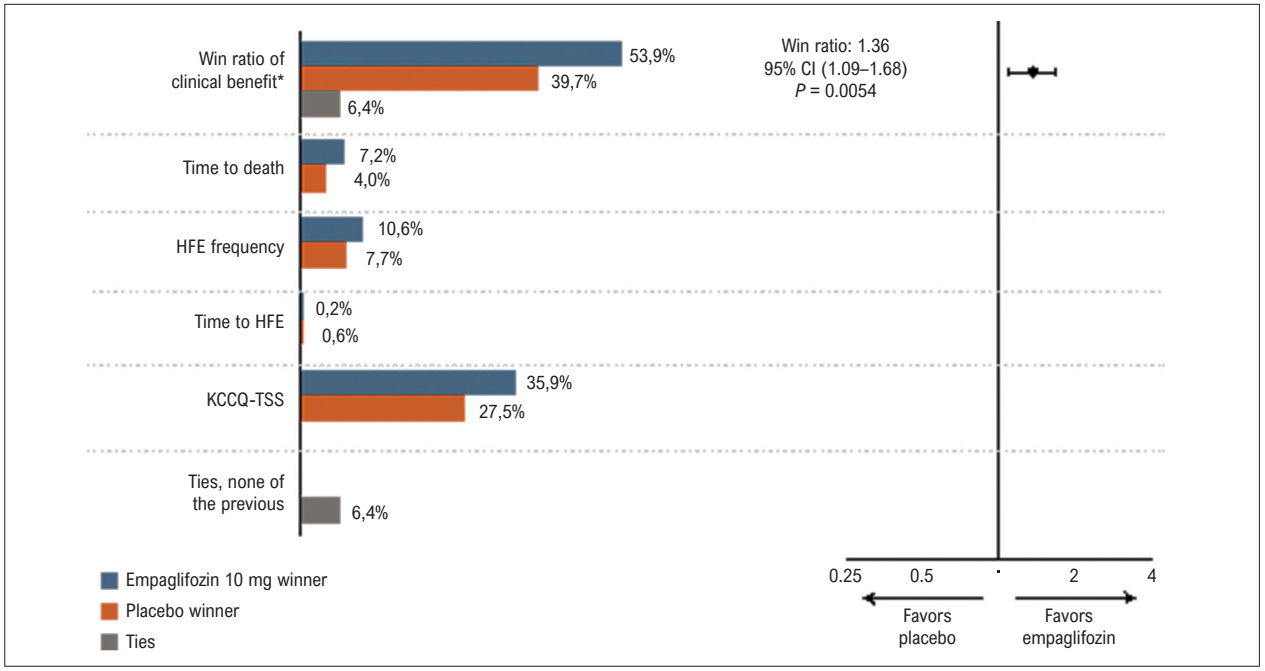

Figure 2 – *Stratified win ratio calculated using a non-parametric generalized pairwise comparison within heart failure status strata.[11] CI: confidence interval; HFE: heart failure event; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire, total symptom score.*

References

1. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci. 2020;5(6):632-44. doi: 10.1016/j.jacbts.2020.02.004.
2. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. doi: 10.1056/NEJMoa1504720.
3. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and Cardiovascular and Renal Events in type 2 Diabetes. N Engl J Med 2017;377:644-57. doi: 10.1056/NEJMc1712572.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57. doi: 10.1056/NEJMoa1812389.
5. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients with Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021;144(16):1284-94. doi: 10.1161/CIRCULATIONAHA.121.056824.
6. Al-Abdouh A, Mhanna M, Barbarawi M, Abusnina W, Gupta VA. A Meta-Analysis of the Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Heart Failure and Preserved Ejection Fraction. Am J Cardiol. 2022;164:138-41. doi: 10.1016/j.amjcard.2021.10.017.
7. Charansonney OL. SGLT-2 Inhibitors in Frail Patients with Heart Failure. Int J Cardiol. 2022;352:102-3. doi: 10.1016/j.ijcard.2022.01.067.
8. Li X, Zhang Q, Zhu L, Wang G, Ge P, Hu A, et al. Effects of SGLT2 Inhibitors on Cardiovascular, Renal, and Major Safety Outcomes in Heart Failure: A Meta-analysis of Randomized Controlled Trials. Int J Cardiol. 2021;332:119-26. doi: 10.1016/j.ijcard.2021.03.077.
9. Kirschbaum K, Vasa-Nicotera M, Zeiher AM, Cremer S. SGLT2 Inhibitor Therapy and Pulmonary Artery Pressure in Patients with Chronic Heart Failure-further Evidence for Improved Hemodynamics by Continuous Pressure Monitoring. Clin Res Cardiol. 2022;111(4):469-72. doi: 10.1007/s00392-021-01954-4.
10. Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, et al. Effect of Dapagliflozin on Ventricular Arrhythmias, Resuscitated Cardiac Arrest, or Sudden Death in DAPA-HF. Eur Heart J. 2021;42(36):3727-38. doi: 10.1093/eurheartj/ehab560.
11. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure: A Multinational Randomized Trial. Nat Med. 2022;28(3):568-74. doi: 10.1038/s41591-021-01659-1.