Journal of Diabetes and Its Complications 37 (2023) 108630

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Understanding the mechanisms mediating cardio-renal benefit of empagliflozin in type 2 diabetes mellitus

Dimitrios Patoulias [a,*], Ali H. Eid [b], Manfredi Rizzo [c,d]

[a] Outpatient Department of Cardiometabolic Medicine, Second Department of Cardiology, Aristotle University of Thessaloniki, General Hospital "Hippokration", Thessaloniki, Greece
[b] Department of Basic Medical Sciences, College of Medicine, QU Health, Qatar University, Doha, Qatar
[c] School of Medicine, Promise Department, University of Palermo, Italy
[d] School of Medicine, Mohammed Bin Rashid University, Dubai, United Arab Emirates

ARTICLE INFO

Keywords
Empagliflozin
SGLT-2 inhibitor
Type 2 diabetes
Cardiovscular
Renal
Outcome

In a recently published, post-hoc analysis of the hallmark EMPA-REG OUTCOME trial, Krämer et al.[1] assessed whether changes in cardiac and haemodynamic markers achieved with empagliflozin in subjects with type 2 diabetes mellitus (T2DM) may mediate its significant benefits across a number of surrogate cardiovascular and kidney outcomes. They have demonstrated[1] that empagliflozin treatment resulted in a significant decrease in pulse pressure (PP), mean arterial pressure (MAP) and cardiac workload, compared with placebo; at week 12, placebo-adjusted mean changes from baseline were − 2.5 mmHg for PP, −2.2 mmHg for MAP and − 315 mmHg x beats per minute (bpm) for cardiac workload ($p < 0.0001$ for all). They have also found that such benefits were present for both empagliflozin groups (10 mg and 25 mg) combined, while treatment differences were maintained throughout to week 164.[1]

However, despite the significant improvement in the above mentioned cardiac and haemodynamic parameters, none of those effects was shown to largely, or even moderately, mediate the beneficial effects of empagliflozin on cardiovascular and kidney outcomes, including cardiovascular (CV) death, heart failure (HF) or hospitalization for HF (HHF), incident or worsening diabetic nephropathy, new-onset macroalbuminuria, and the composite of sustained estimated glomerular filtration rate (eGFR) decline ≥40 % compared to baseline, renal replacement therapy or renal death.[1] These findings highlight the importance of understanding the mechanisms by which sodium-glucose co-transporter-2 (SGLT-2) inhibitors, and innovative anti-diabetic therapies in general, mediate cardio-renal benefit in T2DM.

Previously published, post-hoc analyses of the EMPA-REG OUTCOME trial documented that changes in haematocrit and haemoglobin levels with empagliflozin, reflecting plasma volume status, were the most important mediators of the significant reduction in CV death, HF death and HHF, observed with empagliflozin treatment.[2,3] Indeed, the same hypothesis of haemoconcentration seems to apply with other SGLT-2 inhibitors, regarding their favorable effects on cardiovascular and kidney outcomes.[4,5] On the other hand, it has been doubted over the last years whether SGLT-2 inhibitors exert a major, significant effect on vascular, haemodynamic markers in subjects with T2DM, and whether those effects can, at least partially, explain the cardio-renal benefits seen with this class of drugs.[6,7]

Therefore, despite the established, significant prognostic value of vascular stiffness indices in T2DM patients,[8,9] along with the importance of blood pressure lowering,[10] it seems that there is still a long way towards the understanding of the mechanisms mediating their cardio-renal benefits.[11,12] This is somewhat in contrast with what has been documented with the other class of antidiabetic drugs that confer important cardio-renal benefits in T2DM, namely the glucagon-like

* Corresponding author at: Outpatient Department of Cardiometabolic Medicine, Second Department of Cardiology, Aristotle University of Thessaloniki, Hippokration General Hospital of Thessaloniki, Konstantinoupoleos 49, 54642 Thessaloniki, Greece.
E-mail address: dipatoulias@gmail.com (D. Patoulias).

https://doi.org/10.1016/j.jdiacomp.2023.108630
Received 28 August 2023; Accepted 15 October 2023
Available online 23 October 2023

peptide-1 receptor agonists (GLP-1RAs), for which the significant improvement in glycemic control[13–15] and the anti-atherosclerotic effects[16–18] seem to play a crucial role in reducing the risk for surrogate cardiovascular and kidney outcomes.

Thus, to date, it appears that we have more questions than answers regarding the mechanisms underlying the cardio-renal benefits provided by SGLT-2 inhibitors in T2DM, while this class of drugs has proven to be very efficacious even in subjects without T2DM, namely in those patients with HF and reduced or preserved left ventricular ejection fraction, chronic kidney disease, or even with both diseases.[19] Despite the fact that there is a large amount of evidence retrieved from experimental studies concerning the potential mechanisms implicated into the cardio-renal protection conferred by SGLT-2 inhibitors, along with the very interesting post-hoc analyses of the hallmark cardiovascular and renal outcome trials, such as that published by Krämer et al.,[1] we should also wait for future, well-designed, robust clinical studies to answer the reasonable questions regarding the mechanistic aspects of action of SGLT-2 inhibitors.

Yet, even if the underlying mechanisms leading to a reduction of cardiovascular and renl risk are not fully elucidated, we shouldn't delay the use of innovative anti-diabetic treatments with proven cardio-renal benefit; this will help us to tackle the progression of T2DM pandemic, along with prevention or delay in progression of T2DM-related cardiovascular and renal complications. As clinicians, it is our responsibility to translate the results from the cardio-renal outcomes trials into clinical practice[20], following the scientific evidence and the international guidelines, in order to give to our T2DM patients a longer and healthier life!

Declaration of competing interest

None.

References

1 Krämer BK, Hauske SJ, Chilton R, et al. Changes in cardiac and vascular haemodynamics as potential mediators of improvements in cardiovascular and kidney outcomes with empagliflozin in type 2 diabetes. *J Diabetes Complications*. 2023;37:108588. https://doi.org/10.1016/j.jdiacomp.2023.108588.

2 Fitchett D, Inzucchi SE, Zinman B, et al. Mediators of the improvement in heart failure outcomes with empagliflozin in the EMPA-REG OUTCOME trial. *ESC Heart Fail*. 2021;8:4517–4527. https://doi.org/10.1002/ehf2.13615.

3 Inzucchi SE, Zinman B, Fitchett D, et al. How does Empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41:356–363. https://doi.org/10.2337/dc17-1096.

4 Li J, Neal B, Perkovic V, et al. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney Int*. 2020;98:769–777. https://doi.org/10.1016/j.kint.2020.04.051.

5 Segar MW, Kolkailah AA, Frederich R, et al. Mediators of ertugliflozin effects on heart failure and kidney outcomes among patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2022;24:1829–1839. https://doi.org/10.1111/dom.14769.

6 Bechlioulis A, Markozannes G, Chionidi I, et al. The effect of SGLT2 inhibitors, GLP1 agonists, and their sequential combination on cardiometabolic parameters: a randomized, prospective, intervention study. *J Diabetes Complications*. 2023;37, 108436. https://doi.org/10.1016/j.jdiacomp.2023.108436.

7 Patoulias D, Papadopoulos C, Kassimis G, et al. Effect of sodium-glucose co-transporter-2 inhibitors on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. *Vasc Med*. 2022;27:433–439. https://doi.org/10.1177/1358863X221101653.

8 Cardoso CR, Ferreira MT, Leite NC, Salles GF. Prognostic impact of aortic stiffness in high-risk type 2 diabetic patients: the Rio deJaneiro type 2 diabetes cohort study. *Diabetes Care*. 2013;36:3772–3778. https://doi.org/10.2337/dc13-0506.

9 Wijkman M, Länne T, Östgren CJ, Nystrom FH. Aortic pulse wave velocity predicts incident cardiovascular events in patients with type 2 diabetes treated in primary care. *J Diabetes Complications*. 2016;30:1223–1228.

10 Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967. https://doi.org/10.1016/S0140-6736(15)01225-8.

11 Vallon V, Verma S. Effects of SGLT2 inhibitors on kidney and cardiovascular function. *Annu Rev Physiol*. 2021;83:503–528. https://doi.org/10.1146/annurev-physiol-031620-095920.

12 Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol*. 2020;17:761–772. https://doi.org/10.1038/s41569-020-0406-8.

13 Buse JB, Bain SC, Mann JFE, et al. Cardiovascular risk reduction with Liraglutide: an exploratory mediation analysis of the LEADER trial. *Diabetes Care*. 2020;43:1546–1552. https://doi.org/10.2337/dc19-2251.

14 Konig M, Riddle MC, Colhoun HM, et al. Exploring potential mediators of the cardiovascular benefit of dulaglutide in type 2 diabetes patients in REWIND. *Cardiovasc Diabetol*. 2021;20:194. https://doi.org/10.1186/s12933-021-01386-4.

15 Mann JFE, Buse JB, Idorn T, et al. Potential kidney protection with liraglutide and semaglutide: exploratory mediation analysis. *Diabetes Obes Metab*. 2021;23:2058–2066. https://doi.org/10.1111/dom.14443.

16 Nikolic D, Giglio RV, Rizvi AA, et al. Liraglutide reduces carotid intima-media thickness by reducing small dense low-density lipoproteins in a real-world setting of patients with type 2 diabetes: a novel anti-Atherogenic effect. *Diabetes Ther*. 2021;12:261–274. https://doi.org/10.1007/s13300-020-00962-3.

17 Janić M, Rizzo M, Cosentino F, Pantea Stoian A, Lunder M, Šabović M, et al. Effect of Oral Semaglutide on cardiovascular parameters and their mechanisms in patients with type 2 diabetes: rationale and Design of the Semaglutide Anti-Atherosclerotic Mechanisms of action study (SAMAS). *Diabetes Ther*. 2022;13:795–810. https://doi.org/10.1007/s13300-022-01226-y.

18 Banerjee Y, Patti AM, Giglio RV, Ciaccio M, Vichithran S, Faisal S, et al. The role of atherogenic lipoproteins in diabetes: molecular aspects and clinical significance. *J Diabetes Complications*. 2023;37, 108517. https://doi.org/10.1016/j.jdiacomp.2023.108517.

19 Patoulias D, Fragakis N, Rizzo M. The therapeutic role of SGLT-2 inhibitors in acute heart failure: from pathophysiologic mechanisms to clinical evidence with pooled analysis of relevant studies across safety and efficacy endpoints of interest. *Life (Basel)*. 2022;12:2062.

20 Janez A, Muzurovic E, Stoian AP, Haluzik M, Guja C, Czupryniak L, et al. Translating results from the cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists into clinical practice: recommendations from a eastern and southern Europe diabetes expert group. *Int J Cardiol*. 2022;365:8–18. https://doi.org/10.1016/j.ijcard.2022.07.017.