Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Editorial
J Hypertens Res (2023) 9(1–2):1–5

Hypertension and diabetic patients: how to treat in the era of SGLT2-inhibitors?

Claudio **Borghi** [1], Federica **Fogacci** [2]

[1] Department of Medical and Surgical Sciences, Hypertension and Cardiovascular Risk Research Center, Alma Mater Studiorum University of Bologna, Bologna, Italy
[2] Department of Chest and Vascular Heart, Cardiovascular Medicine Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Received: July 3, 2023, Accepted: July 15, 2023

Hypertension and diabetes are two of the most important risk factors for cardiovascular and renal disease. The prevalence of hypertension is very high in the diabetic population, while a remarkable percentage of hypertensive patients have some degree of abnormality in glucose control [1, 2]. The presence of diabetes in patients with hypertension is associated with an increase in the risk of major cardiovascular complications with a risk of cardiovascular death that is more than twice in patients with both risk factors when compared to hypertension alone [3]. The treatment of hypertension in the diabetic population has been reported to improve the clinical outcome with a significant reduction in the rate of major cardiovascular events (MACE) as well as a decrease in the separate risk of myocardial infarction, stroke, and heart failure [4]. The reduction in the absolute risk of cardiovascular complications has resulted to be greater in diabetic in comparison to the non-diabetic population and this emphasizes the importance of adequate blood pressure control in presence of glucose abnormalities. In terms of drug classes, the recent ESH Guidelines reconfirm the primary role of drug combinations [1] including RAAS-inhibitors, calcium-channel blockers, and diuretics. In particular, the results of the ADVANCE and ADVANCE-ON studies [5, 6] have clearly demonstrated a favorable effect of the combination of perindopril and indapamide in patients with hypertension and diabetes. Similar data have been observed in the diabetic population of the ACCOMPLISH trial where the treatment with an ACE-inhibitor and a calcium-channel blocker was more effective than the combined use of an ACE-inhibitor and diuretic [7]. Basically, the multi-risk dimension of the diabetic patients would suggest a more personalized choice of the different classes of drugs, with the combination of RAAS inhibitors and CCB in patients with additional metabolic risk factors (e.g. uric acid, triglyceride, etc), while the diuretic treatment would be more effective in patients with some signs of volume expansion and CCB's contraindications.

More recently, the role of sodium-glucose co-transport 2-inhibitors (SGLT2i) in the management of diabetic patients has been well-established after the publication of a series of seminal studies focusing on the cardiovascular protective effects of this class of drugs in patients with diabetes [8, 9] (Figure 1). In particular, the treatment with SGLT2i improves serum glucose, blood pressure, serum uric acid and renal function and this is leading to an improvement in the cardiovascular and renal outcomes that was largely confirmed in the diabetic and non-diabetic population [10].

So, the next question is: How should we integrate the use of SGLT-2 inhibitors with the use of more consolidated antihypertensive drugs? First, by considering that the beneficial effect of SGLT2i can be integrated with that of an effective antihypertensive treatment. The CVD-REAL 2 study, an extensive metanalysis carried out in patients with diabetes [11], has reported a decrease in the relative risk of MI, stroke, heart failure and all-cause of death in patients treated with various SGLT2 inhibitors. According to the results of randomized clinical trials (Table 1)

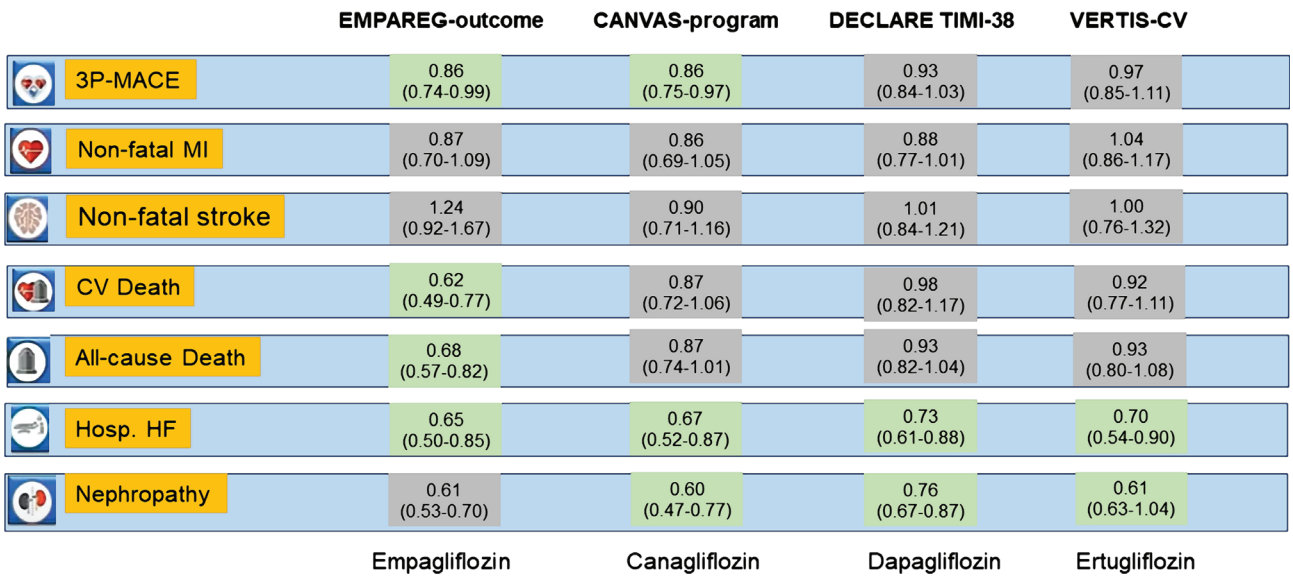

Figure 1. Clinical outcome of major cardiovascular and renal events in patients treated with SGLT2-inhibitors. Results of Randomized Clinical Trials.

the percentage of hypertensive patients among those involved in such analysis is expected to range from 82 to 90%, we can easily imagine that the benefit of SGLT2i can be additive to that of antihypertensive drugs.

The second and most important point is the treatment with SGLT2i can improve blood pressure control in the diabetic population. This has been confirmed in two large metanalysis involving different molecules [12, 13] carried out in the hypertensive and diabetic population and showing a reduction of both systolic (-3.5 mmHg) and diastolic blood pressure (-1,7 mmHg) regardless of the method of measurement (office, 24-hour ABPM) and the intensity of antihypertensive treatment.

An improved blood pressure control has been reported in the EMPA-REG study in the subpopulation of patients with presumed resistant hypertension [14] where the effects on blood pressure control have been associated with a significant improvement in clinical outcome regardless of the previous history of hypertension.

A typical population with a high prevalence of hypertension are the patients with heart failure with preserved ejection fraction (HFpEF), as confirmed by the results of the EMPEROR-Preserved and DELIVER studies [15, 16] where a previous history of hypertension was present in about 90% of the subjects at baseline. In this patient population, the treatment with SGLT2 was highly successful in terms of cardiovascular outcome, supporting a positive interaction between the mechanisms of action of such drugs and the pathophysiology of blood pressure control. The reduction of the primary outcome in the DELIVER trial was more significant (-29 vs. -7%) in the subpopulation with blood pressure levels above the median value (128 mmHg) that included most of the patients with hypertension with a large proportion of diabetic subjects [16].

Moreover, the blood pressure-lowering effect of empagliflozin has been proven to be increased by the concomitant administration of ACE-inhibitors and diuretics [17] with a dose-dependent effect that suggests a potential for blood pressure control for doses of SGLT2i greater than those currently used for the treatment of diabetic patients. This evidence supports the possibility of future development of fixed-dose single-pill combinations of antihypertensive

Table 1. The percentage of hypertensive patients from extensive studies that included patients with type 2 diabetes mellitus and cardiovascular disease.

Study	% Hypertension
EMPAREG-OUTCOME	85.7
CANVAS	89.5
DECLARE-TIMI	82.0
VERTIS-CV	88.0

Table 2. Effects of SGLT2-I on serum uric acid levels and clinical outcome in patients with DM, HFrEF, HFpEF.

Drug	Study	Patients	Uric acid (all significant)	Clinical outcome
Empagliflozin	EMPAREG-OUTCOME	DM2	-1.04 mg/dL vs. Placebo	Reduced MACE
Empagliflozin	EMPEROR-RED	HFrEF	-1.11 mg/dL vs. Placebo	Reduced-MACE
Empagliflozin	EMPEROR-PRES	HFpEF	-0,8 mg/dL vs. Placebo	Reduced MACE
Dapagliflozin	DAPA-HF	HfrEF	-0.84 mg/dL vs. Placebo	Reduced MACE
Dapagliflozin	DELIVER	HFpEF	-0.93 mg/dL vs. Placebo	Reduced MACE

drugs and SGLT-2i for the current treatment of patients with hypertension and diabetes, and new results from the secondary analysis of available clinical studies are expected for the next future. A further area of favorable synergistic interaction between some classes of blood pressure-lowering drugs and SGLT2i is renal protection. Both SGLT2i and RAAS inhibitors have some positive effect on glomerular hemodynamics (involving both afferent and efferent arteriole) and intra-glomerular pressure resulting in a lesser decline in renal function and reduction in albumin excretion [18–21]. This renal protective effect may significantly prevent the progression toward chronic kidney disease (CKD) but can also contribute to cardiovascular prevention according to the primary role of CKD as a risk factor for myocardial infarction, stroke and heart failure [22]. The net benefit on renal function has been clearly demonstrated in patients with diabetes and heart failure, where the rate of decline in GFR [23] was cumulatively reduced in patients treated with SGLT2 inhibitors after an initial worsening due to tubule-glomerular balance during the first weeks of treatment.

Among the many "pleiotropic effects" of SGLT2i, one of the most important in terms of cardiometabolic prevention is the reduction of the circulating levels of uric acid. It is the final product of protein catabolism, and its production is closely related to the activity of the enzyme xanthine-oxidase (XO) which is responsible for the two final steps of purine catabolism. The activity of XO is associated with the release of oxygen radicals responsible for a remarkable amount of oxidative stress that is largely involved in the negative cardiovascular effects of hyperuricemia. A decrease in the circulating levels of uric acid has been demonstrated in patients treated with different SGLT2i without a dose-dependent effect [10] that clearly suggest a rate-limiting step in the mechanism of action urate-lowering effect of SGLT2 inhibitors that is largely based on the increase of renal urate excretion through the renal tubule. This uricosuric effect could be largely integrated with the action of xanthine-oxidase inhibitors with a synergistic effect on circulating serum urate levels.

The effect of SGLT2i on serum urate can contribute to their preventive cardiovascular effects in patients with diabetes and hypertension, where they have been reported to affect many of the components of cardiac and renal damage. A meta-analysis of data involving empagliflozin has reported a significant reduction in both systolic and diastolic blood pressure [24] associated with a decrease in serum urate levels. These results are largely in agreement with those of several randomized clinical trials investigating the cardiovascular protective role of SGLT2 inhibitors in patients with or without diabetes and/or heart failure (Table 2).

Inzucchi *et al.* [25] have provided a quantification of the clinical impact of serum uric acid reduction on the positive results of the EMPAREG-OUTCOME study reporting a cumulative contribution of over 25% after adjustment for all the possible confounding risk factors. In absolute term, this benefit largely corresponds to that reported in the LIFE study [26] where the urate-lowering effects of losartan were reported to statistically explain about 30% of the overall benefit reported in comparison to atenolol. This means that the future treatment of patients with hypertension and diabetes should primarily consider the use of drugs with a mechanism of action beyond blood pressure and glucose control that will remain the primary targets of treatment but whose control is not sufficient to prevent the overall risk of cardiovascular and renal disease. The use of SGLT2 inhibitors in combination with RAAS inhibitors and CCB's is expected to play this "all-around" role and new studies and clinical observations are expected to confirm this promising pharmacological approach to the management of the most dangerous combination of cardiovascular risk factors.

References

1. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE

2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020 Jun; 75(6):1334-1357

2. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank K, Cunha PG, Danser AHJ, de Pinho RM, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelakovic B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Van de Borne P, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE; Authors/Task Force Members. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. 2023 Jun 21. doi: 10.1097/HJH.0000000000003480.
3. Bloomgarden Z.J A diabetes update. Diabetes. 2023 Jul;15(7):542-544.
4. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens. 2017 May; 35(5): 922-944
5. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370:829-840.
6. Zoungas S, Chalmers J, Neal B, et al; ADVANCE-ON Collaborative Group. Follow- up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med. 2014; 371:1392-1406.
7. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J,Gatlin M, Velazquez EJ for the Accomplish trial investigators. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. N Engl J Med 2008; 359:2417-28.
8. Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393: 31–39
9. Eugene Braunwald SGLT2 inhibitors: the statins of the 21st century. Eur Heart J (2022) 43, 1029–1030
10. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, Chen L. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018; 20:458–462.
11. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh SY, Thuresson M, Chen H, Surmont F, Hammar N, Fenici P, CVD-REAL Investigators and Study Group. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study. J Am Coll Cardiol. 2018 Jun 12;71(23):2628-2639.
12. Ren B, Chen M.Effect of sodium-glucose cotransporter-2 inhibitors on patients with essential hypertension and pre-hypertension: a meta-analysis. Ther Adv Endocrinol Metab. 2022 Dec 10; 13: 20420188221142450.
13. Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, Carbone S, Abbate A, Dixon DL.Effects of Sodium Glucose Cotransporter 2 Inhibitors on 24-Hour Ambulatory Blood Pressure: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017 May 18;6(5):e005686.
14. Ferreira JP, Fitchett D, Ofstad AP, Kraus BJ, Wanner C, Zwiener I, Zinman B, Lauer S, George JT, Rossignol P, Zannad F.Empagliflozin for Patients With Presumed Resistant Hypertension: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial. Am J Hypertens. 2020 Dec 31;33(12):1092-1101
15. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators.Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461.
16. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098
17. Mancia G, Cannon CP, Tikkanen I, Zeller C, Ley L, Woerle HJ, Broedl UC, Johansen OE. Impact of Empagliflozin on Blood Pressure in Patients with Type 2 Diabetes Mellitus and Hypertension by Background Antihypertensive Medication. Hypertension. 2016 Dec;68(6):1355-1364
18. van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to

Clinical Outcome. Clin J Am Soc Nephrol. 2017 Apr 3;12(4):700-710

19. Seidu S , Kunutsor SK, Cos X , Gillani S , Khunti K for and on behalf of Primary Care Diabetes Europe SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: A systematic review and meta-analysis. Prim Care Diabetes. 2018;12(3):265-283.
20. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC,von EynattenM- Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus. Circulation. 2014; 129:587–597
21. Heerspink HJ, Holtkamp FA, de Zeeuw D, Ravid M. Monitoring kidney function and albuminuria in patients with diabetes. Diabetes Care. 2011;34 Suppl 2: S325-S329.
22. Filippatos G , Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, Green JB, Rosenstock J, Schnaidt S, Brueckmann M, Pocock SJ, Packer MJ. Empagliflozin for Heart Failure with Preserved Left Ventricular Ejection Fraction with and Without Diabetes. Circulation. 2022; 146:00–00. DOI: 10.1161
23. GBD 2019 Risk Factors Collaborators Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020: 396, 1204-1222. doi: 10.1016/S0140-6736(20)30925-9.
24. Zhao D, Liu H, Dong P.J Empagliflozin reduces blood pressure and uric acid in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Hum Hypertens. 2019 Apr;33(4):327-339
25. Inzucchi, S. E. et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 41, 356-363, doi: 10.2337/dc17-1096 (2018).
26. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, Chen C, DahlöfB , LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study Kidney Int 2004 Mar;65(3):1041-9.