Update of Treatment With SGLT2 Inhibitors

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MUI

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

SUPPLEMENT TO

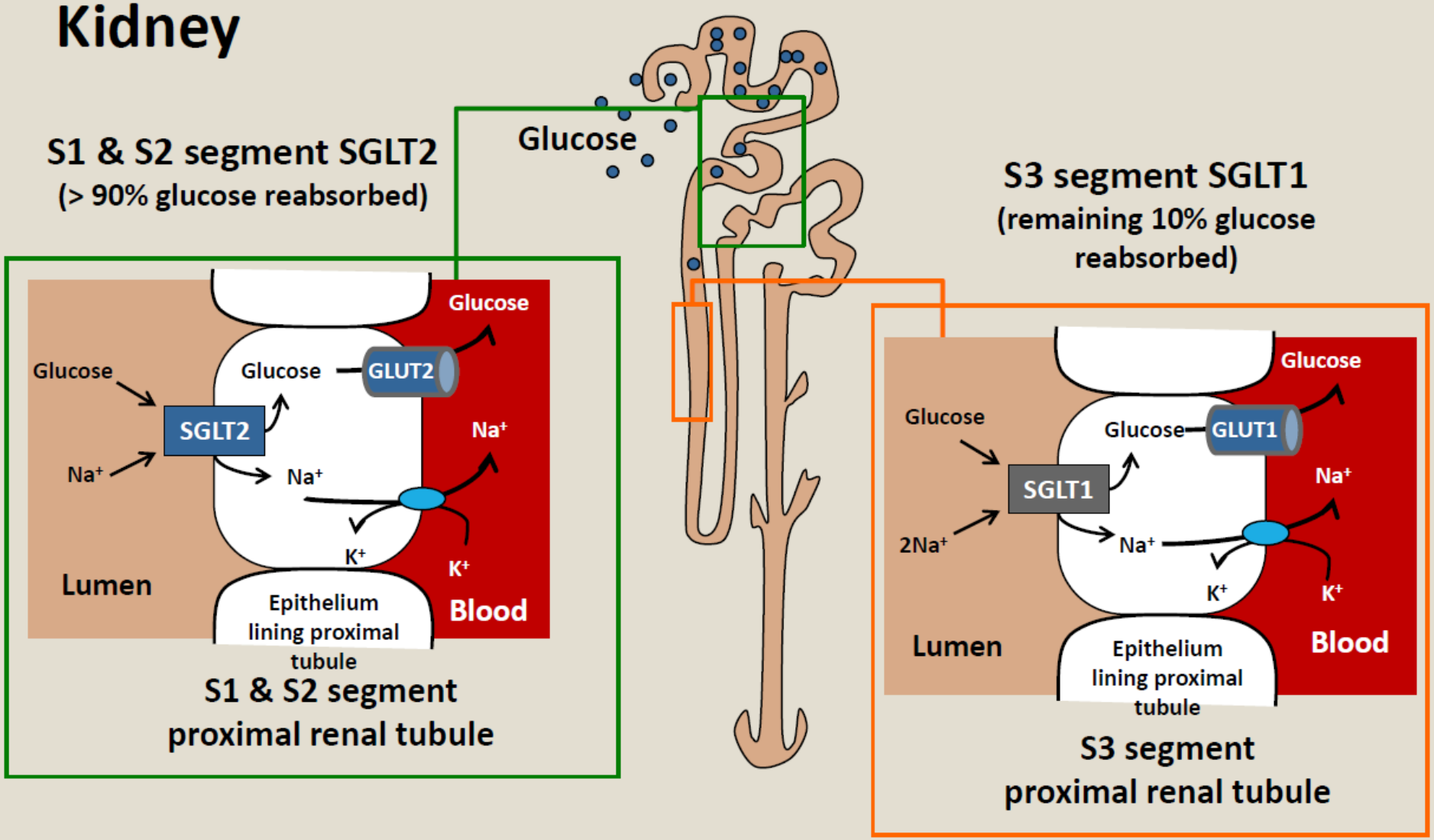
kidney INTERNATIONAL

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

VOLUME 98 | ISSUE 4S | OCTOBER 2020

www.kidney-international.org

Location of Sodium Glucose Transporters in the Kidney



Adapted from Bailey CJ, Day C. *Br J Diabetes Vasc Dis.* 2010;10:193-199.

4.2 Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practice Point 4.2.1: An SGLT2i can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met or who are meeting glycemic targets but can safely attain a lower target (Figure 24).

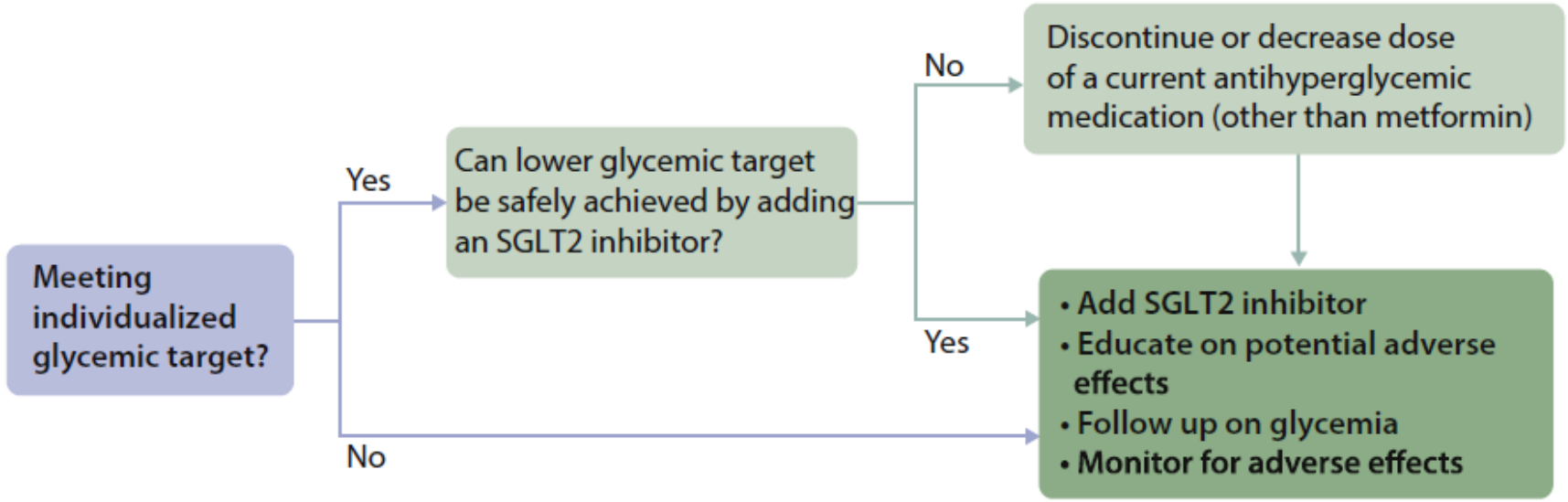
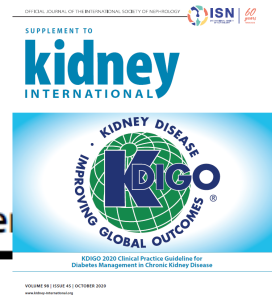


Figure 24 | Algorithm for initiation of SGLT2 inhibitor therapy for patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m^2, who are already being treated with antihyperglycemic medications. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

Practice Point 4.2.2: For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.



Practice Point 4.2.3: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 4.2.4: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 4.2.5: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 4.2.8: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 4.2.1).

Current evidence suggests that neither metformin nor an SGLT2i should be initiated in patients with T2D and an eGFR <30 ml/min per 1.73 m^2 (Figure 18; Sections 4.1 and 4.2).[245,246] Metformin should be discontinued below an eGFR of 30 ml/min per 1.73 m^2. For patients who initiate an SGLT2i at an eGFR ≧30 ml/min per 1.73 m^2 and subsequently decline to an eGFR <30 ml/min per 1.73 m^2, the SGLT2i can be continued until initiation of kidney replacement therapy, in accordance with the approach studied in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[242]

Metabolism Clinical and Experimental 111 (2020) 154334

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Empagliflozin improves diabetic renal tubular injury by alleviating mitochondrial fission via AMPK/SP1/PGAM5 pathway

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ARTICLE INFO

Article history:
Received 19 April 2020
Accepted 4 August 2020

Keywords:
1401-02-27
AMP-activated protein kinases

ABSTRACT

Background and purpose: Excessive mitochondrial fission was observed in diabetic kidney disease (DKD). Phosphoglycerate mutase family member 5 (PGAM5) plays an important role in mitochondrial fission by dephosphorylating the dynamin-related protein 1 at Ser637 (DRP1S637). Whether PGAM5 participates in the mitochondrial fission in diabetic renal tubular injury is unknown. Clinical trials have observed encouraging effect of Sodium-glucose cotransporter 2 (SGLT2) inhibitors on DKD though the underling mechanisms remain unclear.

Background and purpose: Excessive mitochondrial fission was observed in diabetic kidney disease (DKD). Phosphoglycerate mutase family member 5 (PGAM5) plays an important role in mitochondrial fission by dephosphorylating the dynamin-related protein 1 at Ser637 (DRP1S637). Whether PGAM5 participates in the mitochondrial fission in diabetic renal tubular injury is unknown. Clinical trials have observed encouraging effect of Sodium-glucose cotransporter 2 (SGLT2) inhibitors on DKD though the underling mechanisms remain unclear. *Experimental approach:* We used KK-Ay mice as diabetic model and Empagliflozin (Empa) were administrated by oral gavage. The mitochondrial fission and the expressions of phosphorylated AMP-activated protein kinase (p-AMPK), specificityprotein1 (SP1), PGAM5 and DRP1S637 were tested. We also examined these changes in HK2 cells that cultured in normal glucose (NG), high glucose (HG) and high glucose+Empa (HG + Empa) environment. Then we verified our deduction using AMPK activator (5-aminoimidazole-4-carboxamide Riboside, AICAR), inhibitor (Compound C), si-SP1 and si-PGAM5. Lastly, we testified the interaction between SP1 and the PGAM5promotor by CHIP assay.

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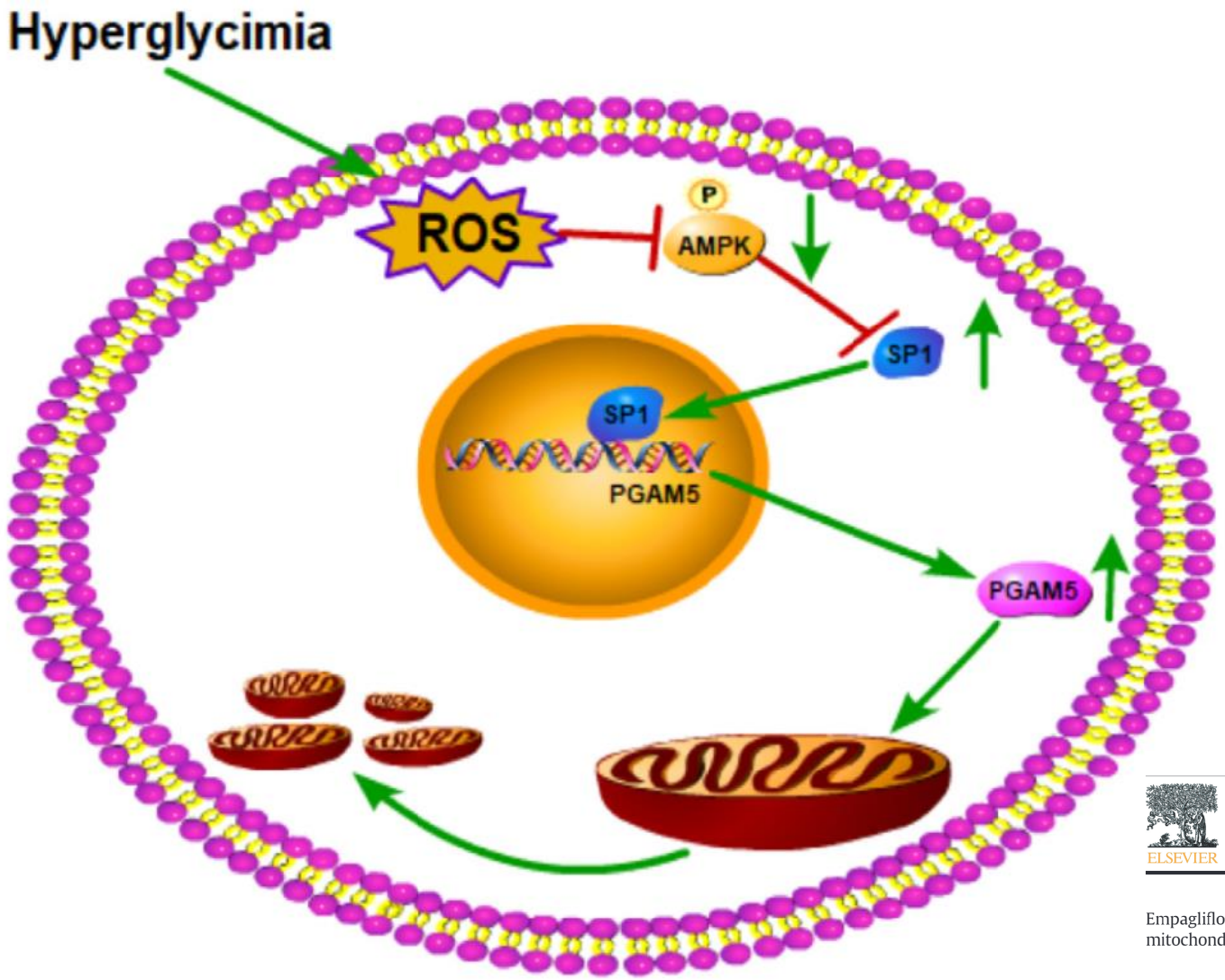

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Fig. 6. Proposed model for the signaling pathway by which PGAM5 participates in the diabetic tubular injury via an AMPK dependent pathway.

Key results: The mitochondrial fission and the expression of SP1, PGAM5 increased and the expression of p-AMPK, DRP1S637 decreased in diabetic or HG environment. These changes were all reversed in Empa or AICAR treated groups. These reversal effects of Empa could be diminished by Compound C. Either si-SP1 or si-PGAM5 could alleviate the mitochondrial fission without affection on AMPK phosphorylation. Finally, the CHIP assay confirmed the interaction between SP1 and the PGAM5 promotor.

Conclusions and implications: The PGAM5 aggravated the development of diabetic renal tubular injury and the Empa could improve the DKD by alleviating mitochondrial fission via AMPK/SP1/PGAM5 pathway.

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Inflammopharmacology
https://doi.org/10.1007/s10787-020-00732-4

Inflammopharmacology

ORIGINAL ARTICLE

Empagliflozin suppresses inflammation and protects against acute septic renal injury

Zaid H. Maayah[1] · Mourad Ferdaoussi[1] · Shingo Takahara[1,2] · Shubham Soni[1] · Jason R. B. Dyck[1,3]

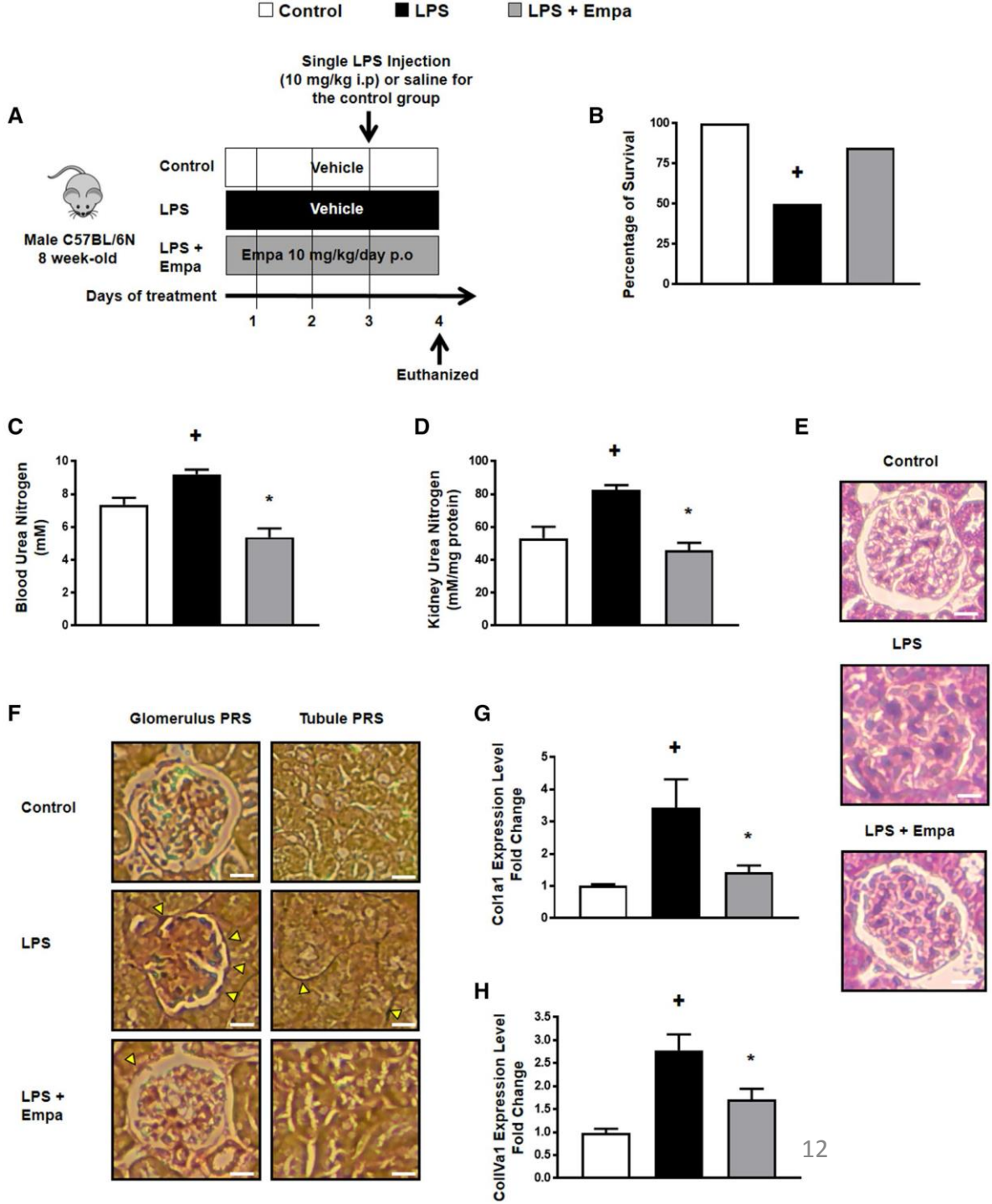
Received: 11 March 2020 / Accepted: 10 June 2020

Abstract

Background Sepsis-induced systemic inflammation response syndrome is the leading cause of morbidity and mortality among patients in intensive care units in North America. While sepsis is associated with multiple organ damage, acute renal injury represents a hallmark of sepsis. Since systemic and renal inflammation is known to play a vital role in morbidity and mortality associated with sepsis, identifying a potent anti-inflammatory agent may help minimize morbidity and mortality associated with acute septic kidney injury. Since recent work has suggested that empagliflozin, a renal sodium-glucose cotransporter 2 (SGLT2) inhibitor, may assist in the treatment of inflammatory diseases, our objective was to examine the effect of empagliflozin on acute sepsis-induced renal injury.

Method Mice were treated with three daily doses of empagliflozin or vehicle, with lipopolysaccharide (LPS) administered

Fig. 1 Empagliflozin prevents LPS-induced acute septic renal injury. **a** Scheme of study design for investigating the protective effects of empagliflozin on lipopolysaccharide (LPS)-induced acute septic renal injury. **b** Percentage of survival in control and vehicle or empagliflozin-treated LPS mice ($n = 6–13$). **c** blood urea nitrogen, **d** kidney urea nitrogen. **e** Representative images of haematoxylin–eosin and **f** Picrosirius red staining of the kidney with scale bars of 25 µm. **g, h** Quantification of mRNA expression levels; **g** Collagen1a1 (col1a1) and, **h** CollagenIVa1 (colIVa1) that were normalized to Rpl32 in control and vehicle or empagliflozin-treated LPS mice ($n = 10$). Results are shown as means ± SEM. Comparisons between three groups were made by one-way ANOVA with a Tukey Kramer's post hoc multiple comparison test. + $p < 0.05$ vs vehicle control group. * $p < 0.05$ vs LPS vehicle group



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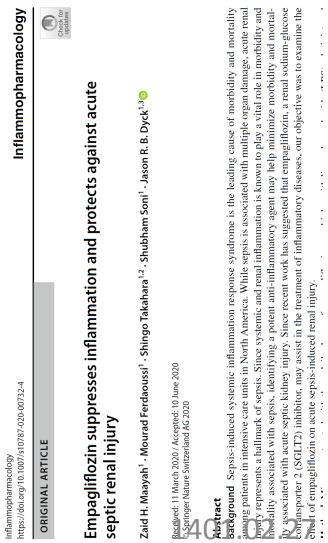

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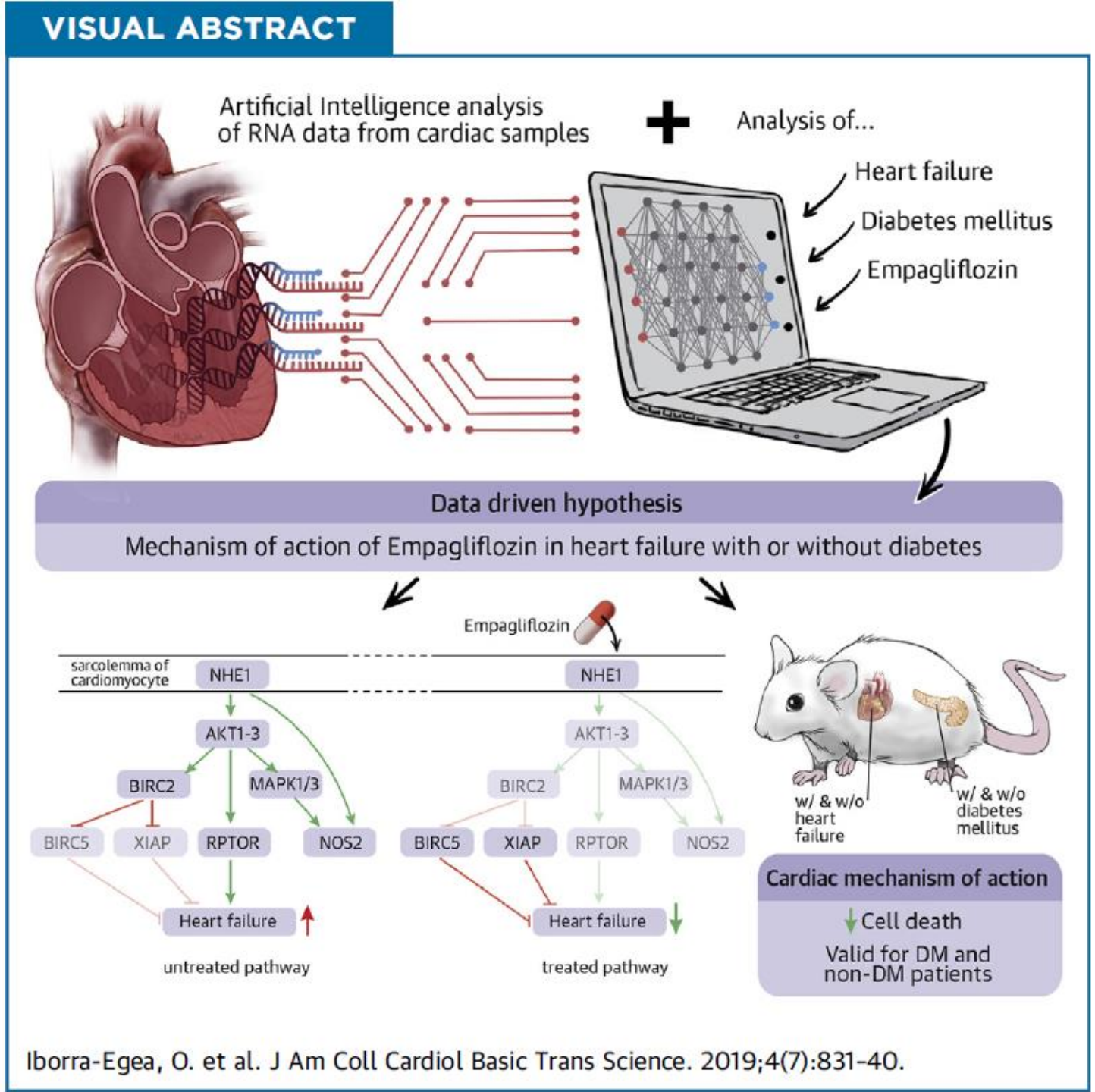
In summary, our results indicate that empagliflozin treatment improves survival in a mouse model of LPS-induced septic shock. We show for the first time that the beneficial effect of empagliflozin is mediated via reducing LPS-induced acute renal injury. Importantly, our data indicate that empagliflozin suppresses systemic and renal inflammation to contribute to the improvements observed in a model of LPS-induced acute renal injury (Fig. 5). Based on this, we suggest that empagliflozin could be attempted in clinical trials involving septic patients in intensive care units, given that empagliflozin is already being used clinically for other indications. Thus, empagliflozin may hold great promise as a repurposed therapy to reduce morbidity and mortality in patients with acute septic renal injury.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 7, 2019

PRECLINICAL RESEARCH

Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes

Oriol Iborra-Egea, MSc,[a,b,c] Evelyn Santiago-Vacas, MD,[a,b,c] Salva R. Yurista, MD,[d] Josep Lupón, MD, PhD,[a,b,c] Milton Packer, MD,[e] Stephane Heymans, MD,[f] Faiez Zannad, MD,[g] Javed Butler, MD,[h] Domingo Pascual-Figal, MD,[i]



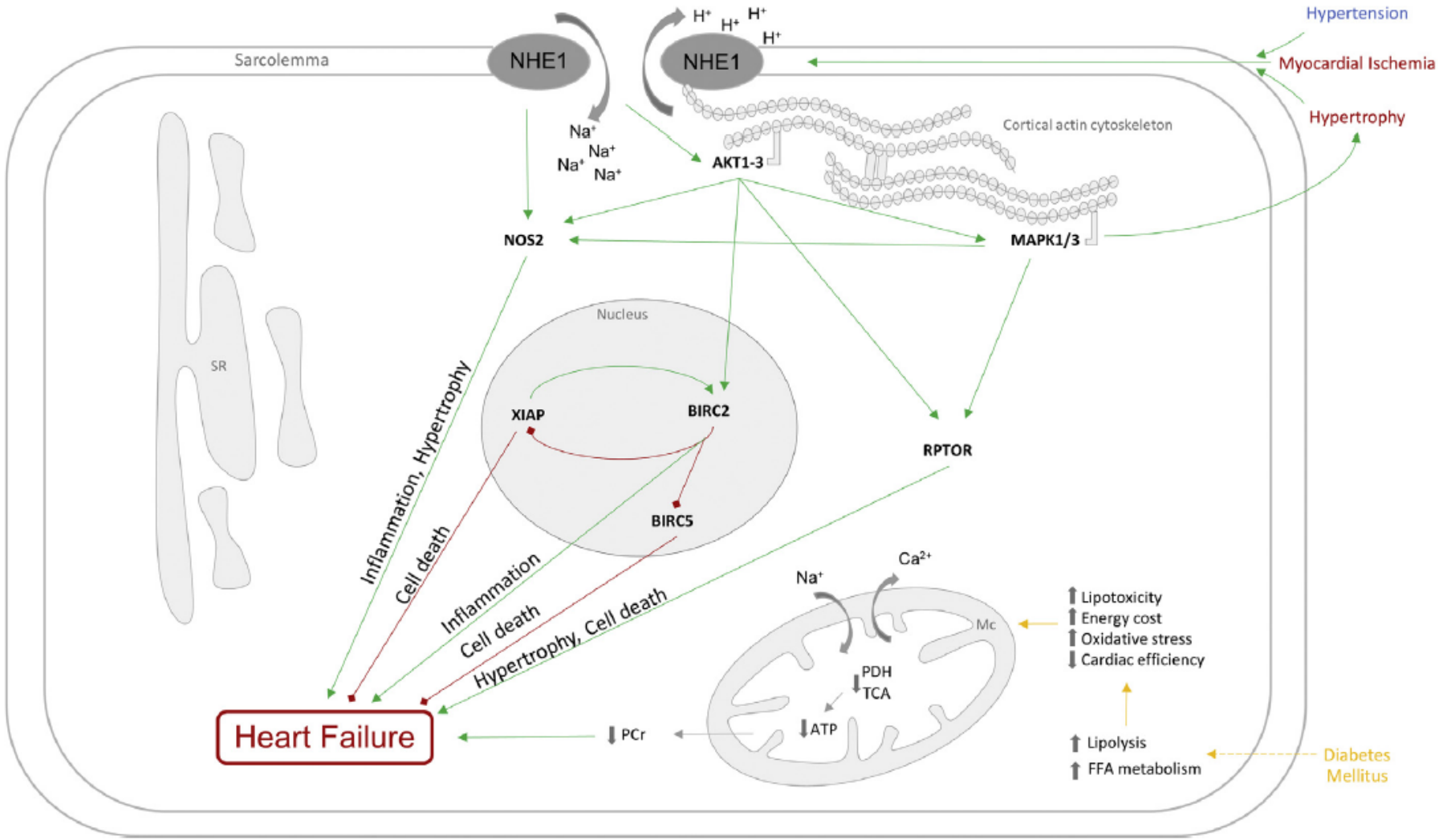
Iborra-Egea, O. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(7):831-40.

TABLE 2 Proteins Known to Be Modulated by Empagliflozin

Gene Name	Protein Name	Reference (PMID)
STAT3	Signal transducer and activator of transcription 3	29311992
NOS2	Nitric oxide synthase, inducible	29311992
IL6	Interleukin-6	29311992
BDH1	D-beta-hydroxybutyrate dehydrogenase, mitochondrial	27289126
IFNG	Interferon gamma	29311992
ALDH2	Aldehyde dehydrogenase, mitochondrial	29311992
GCG	Glucagon	26590679
INS	Insulin	27289126
ACE2	Angiotensin-converting enzyme 2	26880444
BDNF	Brain-derived neurotrophic factor	25344694
HDAC1	Histone deacetylase 1	27829948
HDAC2	Histone deacetylase 2	27829948
HDAC3	Histone deacetylase 3	27829948
HDAC8	Histone deacetylase 8	27829948

PMID = unique identifier number used in PubMed for each article.

FIGURE 2 NHE1-Identified Signaling Pathways in Cardiomyocytes in Heart Failure



Each relationship represents a mechanism that may directly or indirectly (via downstream effectors) impact on HF, either through the activation (green arrows) or inhibition (red arrows) of downstream proteins. AKT1 = RAC-alpha serine/threonine-protein kinase 1; AKT2 = RAC-beta serine/threonine-protein kinase 2; AKT3 = RAC-gamma serine/threonine-protein kinase 3; ATP = adenosine triphosphate; BIRC2 = baculoviral IAP repeat-containing protein 2; BIRC5 = baculoviral IAP repeat-containing protein 5; LEP = leptin; MAPK1 = mitogen-activated protein kinase 1; MAPK3 = mitogen-activated protein kinase 3; MC = mitochondria.;NHE1 = sodium/hydrogen exchanger 1; NOS2 = nitric oxide synthase = inducible; PCr = phosphocreatine. ; PDH = pyruvate dehydrogenase; RPTOR = regulatory-associated protein of mTOR; SR = sarcoplasmic reticulum; TCA = tricarboxylic acid; XIAP = E3 ubiquitin-protein ligase XIAP.

SUMMARY

The mechanism of action of empagliflozin in heart failure with reduced ejection fraction (HFrEF) was deciphered using deep learning in silico analyses together with in vivo validation. The most robust mechanism of action involved the sodium-hydrogen exchanger (NHE)-1 co-transporter with 94.7% accuracy, which was similar for diabetics and nondiabetics. Notably, direct NHE1 blockade by empagliflozin ameliorated cardiomyocyte cell death by restoring expression of X-linked inhibitor of apoptosis (XIAP) and baculoviral IAP repeat-containing protein 5 (BIRC5). These results were independent of diabetes mellitus comorbidity, suggesting that empagliflozin may emerge as a new treatment in HFrEF. (J Am Coll Cardiol Basic Trans Science 2019;4:831–40)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at vperkovic@georgeinstitute.org.au.

*A complete list of the CREDENCE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 14, 2019, at NEJM.org.

N Engl J Med 2019;380:2295-306.
DOI: 10.1056/NEJMoa1811744

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N=2202)	Placebo (N=2199)	All Patients (N=4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

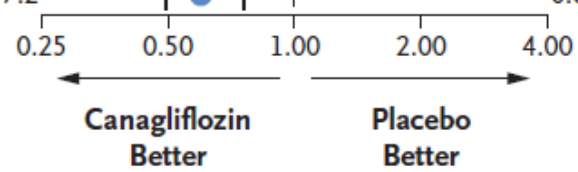


Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

Shown are the primary composite outcome and renal-specific composite outcome, according to the patients' estimated GFR at screening and urinary albumin-to-creatinine ratio (UACR) at baseline, in the canagliflozin group and the placebo group. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. CV denotes cardiovascular, and ESKD end-stage kidney disease.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

Clinical Kidney Journal, 2018, 749–761

doi: 10.1093/ckj/sfy090
Advance Access Publication Date: 25 October 2018
CKJ Review

CKJ REVIEW

The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study

William G. Herrington[1,2], David Preiss[1,2], Richard Haynes[1,2], Maximilian von Eynatten[3], Natalie Staplin[1,2,4], Sibylle J. Hauske[3], Jyothis T. George[3], Jennifer B. Green[5], Martin J. Landray[1,2,4,*], Colin Baigent[1,2,*] and Christoph Wanner[6,*]

Empagliflozin and Cardiovascular and Kidney Outcomes across KDIGO Risk Categories

Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Multinational Trial

*Adeera Levin,[1] Vlado Perkovic,[2] David C. Wheeler,[2,3] Stefan Hantel,[4] Jyothis T. George,[5] Maximilian von Eynatten,[5] Audrey Koitka-Weber,[5,6,7] and Christoph Wanner,[7] on behalf of the EMPA-REG OUTCOME Investigators**

Background and objectives In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome), empagliflozin, in addition to standard of care, significantly reduced risk of cardiovascular death by 38%, hospitalization for heart failure by 35%, and incident or worsening nephropathy by 39% compared with placebo in patients with type 2 diabetes and established cardiovascular disease. Using EMPA-REG Outcome data, we assessed whether the Kidney Disease Improving Global Outcomes (KDIGO) CKD classification had an influence on the treatment effect of empagliflozin.

Design, setting, participants, & measurements Patients with type 2 diabetes, established atherosclerotic cardiovascular disease, and eGFR≥30 ml/min per 1.73 m^2 at screening were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. *Post hoc*, we analyzed cardiovascular and kidney outcomes, and safety, using the two-dimensional KDIGO classification framework.

Table 1. Baseline characteristics and concomitant medications of participants were similar between treatment groups across Kidney Disease Improving Global Outcomes risk categories

Parameter	Kidney Disease Improving Global Outcomes Risk Category[a]							
	Low		Moderately Increased		High		Very High	
	Placebo, $n=1099$	Empagliflozin,[b] $n=2223$	Placebo, $n=675$	Empagliflozin,[b] $n=1343$	Placebo, $n=357$	Empagliflozin,[b] $n=710$	Placebo, $n=186$	Empagliflozin,[b] $n=359$
Men	787 (72)	1571 (71)	490 (73)	970 (72)	254 (71)	500 (70)	136 (73)	255 (71)
Age, yr	62±9	61±8	64±9	64±9	66±9	66±8	66±8	67±8
BMI, kg/m^2	30.5±5.2	30.5±5.2	31.0±5.2	30.7±5.3	30.7±5.4	30.6±5.3	30.2±5.3	30.6±5.7
HbA1c, %	8.0±0.8	8.0±0.8	8.1±0.9	8.1±0.9	8.2±0.9	8.2±0.9	8.2±0.9	8.1±0.8
Systolic BP, mm Hg	133±16	132±15	138±17	137±17	139±20	139±19	140±19	141±18
Diastolic BP, mm Hg	77±10	77±9	77±11	77±10	76±11	76±10	76±10	75±10
LDL cholesterol, mg/dl	83±34	85±35	85±34	85±36	89±39	88±37	89±39	90±40
eGFR (MDRD), ml/min per 1.73 m^2	83±16	84±17	74±20	74±20	60±19	61±20	44±8	43±9
≥60	1099 (100)	2223 (100)	470 (70)	926 (69)	145 (41)	286 (40)	0	0
<60	0	0	205 (30)	417 (31)	212 (59)	424 (60)	186 (100)	359 (100)
UACR, mg/g								
<30	1099 (100)	2223 (100)	205 (30)	417 (31)	76 (21)	139 (20)	2 (1)	10 (3)
30–300	0	0	470 (70)	926 (69)	136 (38)	285 (40)	69 (37)	126 (35)
>300	0	0	0	0	145 (41)	286 (40)	115 (62)	223 (62)
UACR, median (IQR), mg/g	7.1 (4.4−14.1)	8.0 (5.3−14.1)	43.3 (16.8−94.6)	43.3 (17.7−89.3)	141.4 (37.1−630.3)	134.4 (39.8−484.4)	406.2 (110.5−908.8)	422.6 (114.0−1067.0
Background medications								
ACE inhibitors/ARBs	846 (77)	1754 (79)	556 (82)	1119 (83)	305 (85)	585 (82)	147 (79)	299 (83)
Diuretics	405 (37)	841 (38)	295 (44)	605 (45)	172 (48)	360 (51)	110 (59)	216 (60)
History of heart failure	95 (9)	181 (8)	77 (11)	146 (11)	48 (13)	84 (12)	23 (12)	50 (14)
Smoking status								
Never smoked	464 (42)	902 (41)	260 (39)	556 (41)	144 (40)	288 (41)	80 (43)	164 (46)
Ex-smoker	489 (45)	967 (44)	326 (48)	623 (46)	169 (47)	353 (50)	85 (46)	164 (46)
Currently smokes	146 (13)	354 (16)	89 (13)	164 (12)	44 (12)	69 (10)	21 (11)	31 (9)
Duration of diabetes, yr								
≤1	35 (3)	78 (4)	11 (2)	31 (2)	2 (1)	14 (2)	4 (2)	5 (1)
>1–5	216 (20)	424 (19)	103 (15)	189 (14)	41 (12)	65 (9)	10 (5)	25 (7)
>5–10	301 (27)	597 (27)	159 (24)	344 (26)	69 (19)	156 (22)	35 (19)	64 (18)
>10	547 (50)	1124 (51)	402 (60)	779 (58)	245 (69)	475 (67)	137 (74)	265 (74)
Metformin use	885 (81)	1752 (79)	514 (76)	1022 (76)	219 (61)	476 (67)	104 (56)	172 (48)
Insulin use	447 (41)	933 (42)	338 (50)	648 (48)	211 (59)	412 (58)	130 (70)	232 (65)

www.cjasn.org Vol 15 October, 2020

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P*-value for interaction
	n with event/*N* analyzed (%)				
3-point MACE					
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)		
KDIGO risk categories*					0.52
Low risk	175/2223 (7.9)	97/1099 (8.8)	0.89 (0.69, 1.14)		
Moderately increased risk	146/1343 (10.9)	79/675 (11.7)	0.93 (0.71, 1.23)		
High risk	99/710 (13.9)	69/357 (19.3)	0.69 (0.51, 0.94)		
Very high risk	65/359 (18.1)	37/186 (19.9)	0.88 (0.59, 1.32)		
Fatal/nonfatal MI					
All patients	223/4687 (4.8)	126/2333 (5.4)	0.87 (0.70, 1.09)		
KDIGO risk categories*					0.54
Low risk	84/2223 (3.8)	46/1099 (4.2)	0.89 (0.62, 1.28)		
Moderately increased risk	62/1343 (4.6)	37/675 (5.5)	0.85 (0.56, 1.27)		
High risk	43/710 (6.1)	30/357 (8.4)	0.70 (0.44, 1.11)		
Very high risk	32/359 (8.9)	13/186 (7.0)	1.26 (0.66, 2.40)		
Fatal/nonfatal stroke					
All patients	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89, 1.56)		
KDIGO risk categories*					0.26
Low risk	61/2223 (2.7)	22/1099 (2.0)	1.37 (0.84, 2.24)		
Moderately increased risk	55/1343 (4.1)	18/675 (2.7)	1.51 (0.88, 2.57)		
High risk	30/710 (4.2)	18/357 (5.0)	0.84 (0.47, 1.51)		
Very high risk	16/359 (4.5)	11/186 (5.9)	0.72 (0.33, 1.56)		
Cardiovascular death					
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)		
KDIGO risk categories*					0.85
Low risk	53/2223 (2.4)	40/1099 (3.6)	0.65 (0.43, 0.98)		
Moderately increased risk	46/1343 (3.4)	39/675 (5.8)	0.59 (0.39, 0.91)		
High risk	39/710 (5.5)	35/357 (9.8)	0.54 (0.34, 0.85)		
Very high risk	33/359 (9.2)	23/186 (12.4)	0.73 (0.43, 1.24)		
Hospitalization for heart failure					
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)		
KDIGO risk categories*					0.46
Low risk	35/2223 (1.6)	20/1099 (1.8)	0.87 (0.50, 1.50)		
Moderately increased risk	34/1343 (2.5)	30/675 (4.4)	0.56 (0.34, 0.92)		
High risk	34/710 (4.8)	23/357 (6.4)	0.72 (0.42, 1.22)		
Very high risk	22/359 (6.1)	22/186 (11.8)	0.48 (0.26, 0.86)		
All-cause mortality					
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)		
KDIGO risk categories*					0.50
Low risk	84/2223 (3.8)	61/1099 (5.6)	0.68 (0.49, 0.94)		
Moderately increased risk	69/1343 (5.1)	57/675 (8.4)	0.61 (0.43, 0.86)		
High risk	61/710 (8.6)	47/357 (13.2)	0.63 (0.43, 0.92)		
Very high risk	54/359 (15.0)	29/186 (15.6)	0.93 (0.59, 1.46)		

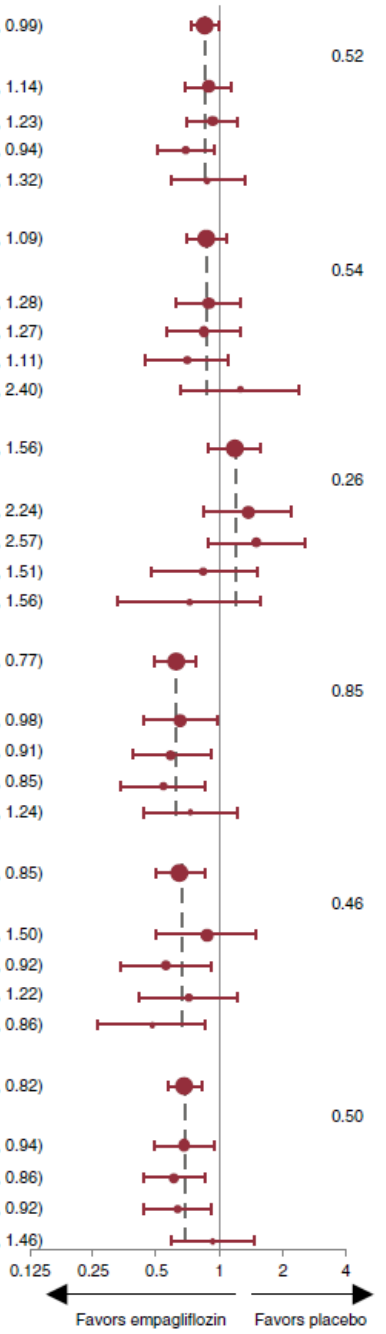
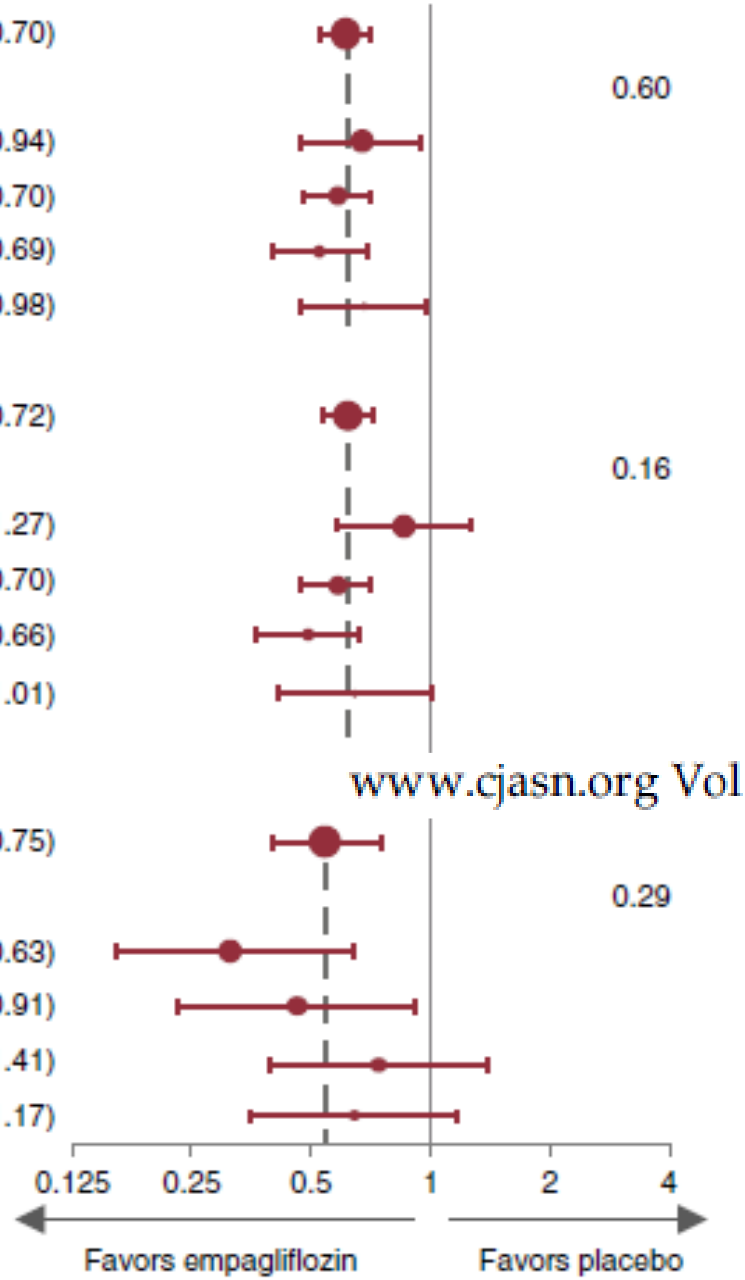


Figure 2. | **Forest plot showing that the risk reduction of cardiovascular outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.** *Sixty-eight patients were excluded as the subgroup variable was missing. 95% CI, 95% confidence interval; MACE, major adverse cardiovascular event; MI, myocardial infarction.

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P*-value for interaction
	n with event/*N* analyzed (%)				
Incident or worsening nephropathy					
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)		
KDIGO risk categories*					0.60
Low risk	78/2180 (3.6)	56/1086 (5.2)	0.67 (0.47, 0.94)		
Moderately increased risk	254/1323 (19.2)	187/655 (28.5)	0.58 (0.48, 0.70)		
High risk	117/430 (27.2)	89/219 (40.6)	0.52 (0.40, 0.69)		
Very high risk	66/148 (44.6)	52/88 (59.1)	0.68 (0.47, 0.98)		
Progression to macroalbuminuria					
All patients	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72)		
KDIGO risk categories*					0.16
Low risk	69/2180 (3.2)	39/1086 (3.6)	0.86 (0.58, 1.27)		
Moderately increased risk	244/1323 (18.4)	179/655 (27.3)	0.58 (0.47, 0.70)		
High risk	94/415 (22.7)	75/209 (35.9)	0.49 (0.36, 0.66)		
Very high risk	45/130 (34.6)	33/70 (47.1)	0.64 (0.41, 1.01)		
Doubling of serum creatinine,† initiation of kidney replacement therapy, or death from kidney					
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)		
KDIGO risk categories*					0.29
Low risk	13/2205 (0.6)	20/1094 (1.8)	0.31 (0.16, 0.63)		
Moderately increased risk	16/1334 (1.2)	17/671 (2.5)	0.46 (0.23, 0.91)		
High risk	25/704 (3.6)	15/356 (4.2)	0.74 (0.39, 1.41)		
Very high risk	24/352 (6.8)	19/186 (10.2)	0.64 (0.35, 1.17)		



www.cjasn.org Vol 15 October, 2020

Figure 3. | **Forest plot showing that the risk reduction of kidney outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.** Cox regression analysis in patients treated with one or more doses of study drug. *Sixty-eight patients were excluded as the subgroup variable was missing. †Accompanied by eGFR≤45 ml/min per 1.73 m^2. Macroalbuminuria: urine albumin-creatinine ratio >300 mg/g.

Results Of 6952 patients with baseline eGFR and urinary albumin-creatinine ratio values, 47%, 29%, 15%, and 8% were classified into low, moderately increased, high, and very high KDIGO risk categories, respectively. Empagliflozin showed consistent risk reductions across KDIGO categories for cardiovascular outcomes (*P* values for treatment by subgroup interactions ranged from 0.26 to 0.85) and kidney outcomes (*P* values for treatment by subgroup interactions ranged from 0.16 to 0.60). In all KDIGO risk categories, placebo and empagliflozin had similar adverse event rates, the notable exception being genital infection events, which were more common with empagliflozin for each category.

Conclusions The observed effects of empagliflozin versus placebo on cardiovascular and kidney outcomes were consistent across the KDIGO risk categories, indicating that the effect of treatment benefit of empagliflozin was unaffected by baseline CKD status.

www.cjasn.org Vol 15 October, 2020

CardioRenal Medicine

Cardiorenal Med 2020;10:1–10
DOI: 10.1159/000503919
Received: August 2, 2019
Accepted: October 2, 2019
Published online: November 19, 2019

Systematic Review

The Effects of SGLT2 Inhibitors on Cardiovascular and Renal Outcomes in Diabetic Patients: A Systematic Review and Meta-Analysis

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CardioRenal Medicine

Cardiorenal Med 2020;10:1–10

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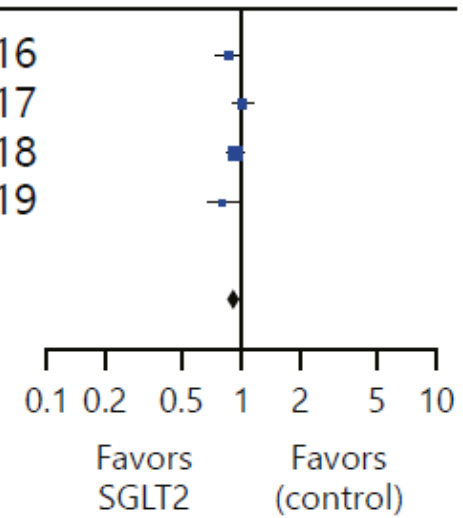
Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	490	4,687	282	2,333	19.5	0.86 (0.75, 0.99)	2016
CANVAS	585	5,795	426	4,347	25.1	1.03 (0.92, 1.16)	2017
DECLARE-TIMI 58	756	8,582	803	8,578	41.5	0.94 (0.86, 1.03)	2018
CREDENCE	217	2,202	269	2,199	13.9	0.81 (0.68, 0.95)	2019
Total (95% CI)		21,266		17,457	100.0	0.93 (0.87, 0.99)	
Total events	2,048		1,780				

Heterogeneity: $\chi^2 = 6.76$, df = 3, $p = 0.08$; $I^2 = 56\%$

Test for overall effect: $Z = 2.35$, $p = 0.02$



Color version available online

Fig. 1. Forest plot for composite cardiovascular outcome in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

Conclusion

Among patients with type 2 diabetes and established CV disease or at risk for CV disease, SGLT2i are associated with significantly lower MACE, HHF, and all-cause mortality. The evidence is strongest with regard to reducing HHF. The evidence is weaker when it comes to the population subset with eGFR <60 mL/min/1.73 m^2, though it exhibited trends towards significance. SGLT2i are also associated with significantly lower adverse renal events, with the effects apparent even in the population with eGFR <60 mL/min/1.73 m^2.

CardioRenal Medicine

Cardiorenal Med 2020;10:1–10

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Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

David Z I Cherney, Claire C J Dekkers*, Sean J Barbour, Daniel Cattran, Abdul Halim Abdul Gafor, Peter J Greasley, Gozewijn D Laverman, Soo Kun Lim, Gian Luca Di Tanna, Heather N Reich, Marc G Vervloet, Muh Geot Wong, Ron T Gansevoort, Hiddo J L Heerspink, for the DIAMOND investigators*

Lancet Diabetes Endocrinol 2020; 8: 582–93

This online publication has been corrected. The corrected version first appeared at thelancet.com/

Summary

Background SGLT2 inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These benefits are unlikely to be mediated by improvements in glycaemic control alone. Therefore, we aimed to examine the kidney effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes.

Methods DIAMOND was a randomised, double-blind, placebo-controlled crossover trial done at six hospitals in Canada, Malaysia, and the Netherlands. Eligible participants were adult patients (aged 18–75 years) with chronic kidney disease, without a diagnosis of diabetes, with a 24-h urinary protein excretion greater than 500 mg and less than or equal to 3500 mg and an estimated glomerular filtration rate (eGFR) of at least 25 mL/min per 1·73 m², and who were on stable renin–angiotensin system blockade. Participants were randomly assigned (1:1) to receive placebo and then dapagliflozin 10 mg per day or vice versa. Each treatment period lasted 6 weeks with a 6-week washout period in between. Participants, investigators, and study personnel were masked to assignment throughout the trial and analysis. The primary outcome was percentage change from baseline in 24-h proteinuria during dapagliflozin treatment relative to placebo. Secondary outcomes were changes in measured GFR (mGFR; via iohexol clearance), bodyweight, blood pressure, and concentrations of neurohormonal biomarkers. Analyses were done in accordance with the intention-to-treat principle. This study is registered with ClinicalTrials.gov, NCT03190694.

Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

David Z I Cherney, Claire C J Dekkers*, Sean J Barbour, Daniel Cattran, Abdul Halim Abdul Gafor, Peter J Greasley, Gozewijn D Laverman, Soo Kun Lim, Gian Luca Di Tanna, Heather N Reich, Marc G Vervloet, Muh Geot Wong, Ron T Gansevoort, Hiddo J L Heerspink, for the DIAMOND investigators*

	n	Change in proteinuria during dapagliflozin treatment, % (95% CI)	Change in proteinuria during placebo treatment, % (95% CI)	Difference in proteinuria, % (95% CI)	$P_{interaction}$
Age (years)					0·49
≥60	15	−16·3% (−37·1 to 11·4)	−26·9% (−46·4 to −0·3)	14·5% (−24·9 to 74·6)	
<60	38	−13·2% (−26·0 to 1·8)	−10·7% (−23·9 to 4·8)	−2·9% (−22·5 to 21·7)	
Sex					0·75
Male	36	−17·6% (−28·6 to −4·9)	−20·8% (−31·5 to -8·4)	4·0% (−15·2 to 27·5)	
Female	17	−8·5% (−31·9 to 23·0)	−5·2% (−29·4 to 27·5)	−3·5% (−36·5 to 46·5)	
Region					0·94
Europe	20	−24·3% (−41·2 to −2·5)	−22·9% (−40·1 to −0·6)	−1·9% (−31·4 to 40·4)	
North America	22	−3·4% (−20·5 to 17·4)	−8·9% (−25·3 to 11·2)	6·1% (−19·7 to 40·1)	
Asia	11	−18·3% (−36·0 to 4·3)	−20·1% (−37·4 to 2·0)	2·2% (−27·6 to 44·3)	
Kidney diagnosis					0·22
IgA	25	−14·5% (−28·6 to 2·3)	−29·5% (−41·1 to −15·7)	21·3% (−5·9 to 56.3)	
FSGS	11	−18·4% (−39·1 to 9·3)	−10·1% (−32·9 to 20·4)	−9·2% (−40·0 to 37·3)	
Hypertensive nephropathy	7	−13·3% (−40·6 to 26·6)	−22·3% (−48·5 to 17·2)	11·6% (−36·1 to 95·1)	
Other	10	−16·0% (−44·5 to 27·3)	26·5% (−16·5 to 91·5)	−33·6% (−63·1 to 19·5)	
Proteinuria (mg per 24 h)					0·87
≥1000	31	−14·8% (−26·3 to −1·4)	−13·6% (−25·4 to 0·1)	−1·3% (−19·8 to 21·3)	
<1000	21	−15·1% (−35·3 to 11·3)	−17·0% (−36·7 to 8·8)	2·2% (−30·3 to 50·0)	
mGFR (mL/min per 1·73 m^2)					0·0040
>60	20	−26·6% (−39·5 to −10·9)	0·8% (−17·0 to 22·4)	−27·2% (−44·6 to −4·2)	
≤60	33	−7·7% (−22·7 to 10·4)	−25·7% (−38·0 to −11·0)	24·3% (−3·6 to 60·3)	
Systolic blood pressure (mm Hg)					0·32
≥130	24	−16·5%(−30·8 to 0·6)	−26·1% (−38·7 to −10·9)	13·0% (−13·3 to 47·2)	
<130	29	−13·2% (−28·8 to 5·9)	−6·6% (−23·7 to 14·4)	−7·1% (−30·0 to 23·4)	
BMI (kg/m^2)					0·63
≥25	39	−9·5% (−23·8 to 7·5)	−14·2% (−27·8 to 2·1)	5·5% (−17·4 to 34·6)	
<25	14	−25·7% (−39·3 to −8·9)	−22·7% (−37·0 to −5·3)	−3·8% (−27·8 to 28·3)	
Diuretic use					0·28
Yes	14	−13·0% (−34·6 to 15·6)	−28·4% (−46·2 to −4·9)	21·6% (−18·7 to 81·8)	
No	39	−15·5% (−27·5 to −1·4)	−11·3% (−24·1 to 3·6)	−4·7% (−23·4 to 18·6)	
Overall treatment effect	53	**−15·0% (−25·7 to −2·8)**	**−15·8% (−26·5 to −3·5)**	**0·9% (−16·6 to 22·1)**	

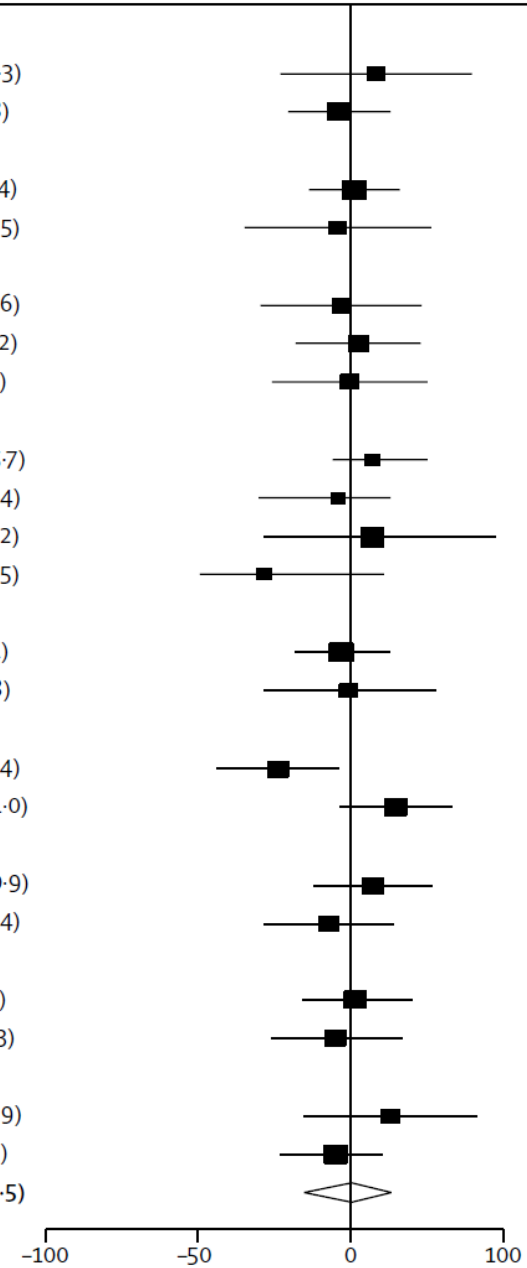

Figure 4: Effects of dapagliflozin on 24-h proteinuria in patient subgroups defined by baseline characteristics

Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

David Z I Cherney, Claire C J Dekkers*, Sean J Barbour, Daniel Cattran, Abdul Halim Abdul Gafor, Peter J Greasley, Gozewijn D Laverman, Soo Kun Lim, Gian Luca Di Tanna, Heather N Reich, Marc G Vervloet, Muh Geot Wong, Ron T Gansevoort, Hiddo J L Heerspink, for the DIAMOND investigators*

Interpretation 6-week treatment with dapagliflozin did not affect proteinuria in patients with chronic kidney disease without diabetes, but did induce an acute and reversible decline in mGFR and a reduction in bodyweight. Long-term clinical trials are underway to determine whether SGLT2 inhibitors can safely reduce the rate of major clinical kidney outcomes in patients with chronic kidney disease with and without diabetes.

Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

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Canadian Journal of Cardiology 36 (2020) 1691.e3 www.onlinecjc.ca

Letters to the Editor

The Multiple Effects of SGLT2 Inhibitors Suggest Potential Benefit in COVID-19 Patients

To the Editor:

Recent evidence has shown that inflammation is a potential contributor to the progression and exacerbation of COVID-19.[1] Indeed, SARS-CoV-2 often induces a robust immune response and releases cytokines, which might contribute to multiorgan dysfunction and mortality.[1] Growing evidence suggests that COVID-19 is not solely a respiratory illness, and that the infection can directly or indirectly infect organs or vascular endothelial cells causing endotheliitis. Because of the urgent need for additional therapies and because COVID-19 disproportionately affects individuals with cardiovascular/cardiometabolic comorbidities, herein we discuss the rationale for using the antidiabetic sodium-glucose cotransporter 2 the **Da**pagliflozin in **Re**spiratory Failure in Patients With COVID-19 (DARE-19) trial (ClinicalTrials.gov: NCT04350593), in which dapagliflozin for respiratory failure in COVID-19 patients with cardiometabolic comorbidities is currently being tested. However, because excessive inflammation is common in severely affected COVID-19 patients, SGLT2 inhibitors might also be effective in COVID-19 patients without underlying comorbidities.

Overall, because SGLT2 inhibitors are not merely antidiabetic drugs, have minimal side effects, excellent safety and tolerance, and multifaceted benefits, they are worthy of consideration as a potentially effective treatment for COVID-19 patients with or without cardiometabolic comorbidities.

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ELSEVIER

Canadian Journal of Cardiology 36 (2020) 1691.e3 www.onlinecjc.ca

The Multiple Effects of SGLT2 Inhibitors Suggest Potential Benefit in COVID-19 Patients

the **Da**pagliflozin in **Re**spiratory Failure in Patients With COVID-19 (DARE-19) trial (ClinicalTrials.gov: NCT04350593), in which dapagliflozin for respiratory failure

UK Kidney Association

UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease

Final version: 18 October 2021
Review date: 18 October 2026

RECOMMENDATIONS FOR USE IN PEOPLE WITH AN eGFR ≥25mL/min/1.73m^2		
Section 2	**PEOPLE WITH TYPE 2 DM**	**Grade**
1.	We recommend initiating SGLT-2inhibition* in those with: (a) uACR of ≥25 mg/mmol attributed to diabetic nephropathy (b) Established coronary disease or stable symptomatic heart failure (irrespective of ejection fraction).	**1A**
2.	We recommend initiating SGLT-2 inhibition in those with a uACR of ≥25 mg/mmol attributable to a non-diabetic cause‡	**1B**
3.	We suggest initiating SGLT-2 inhibition to modify cardiovascular risk in those with an eGFR 25-60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited.	**2B**
Section 3	**PEOPLE WITHOUT DM**	
1.	We recommend initiating SGLT-2 inhibition* in those with stable symptomatic heart failure (irrespective of ejection fraction).	**1A**
2.	We recommend initiating SGLT-2 inhibition* in those with a uACR of ≥25 mg/mmol, excluding people with polycystic kidney disease or on immunological therapy for renal disease.‡	**1B**

RECOMMENDATIONS FOR IMPLEMENTATION		
Sections 2 & 3	**PEOPLE WITH OR WITHOUT DM (excluding TYPE 1)**	**Grade**
1.	We recommend using SGLT-2 inhibitors with demonstrated efficacy for their given indications.*	**1A**
2.	We recommend using clinically appropriate single agent RAS blockade in combination with SGLT-2 inhibition, wherever RAS blockade is indicated and tolerated.	**1A**
3.	We suggest following NICE guidelines on screening for albuminuria (NICE NG203): a single uACR of ≥70 mg/mmol or a confirmed measurement between 25-69 mg/mmol fulfil recommendations for use of SGLT-2 inhibition based on albuminuria.	**2C**
4.	We suggest using uACR to assess for sufficient proteinuria to guide SGLT-2 inhibitor use: reagent strips and protein:creatinine ratio should generally not be used (NICE NG203). We recognise that more pragmatic approaches to identifying risk of kidney disease progression may be necessary whilst local access to uACR measurement is improved.	**2C**
5.	We suggest that when used to slow kidney disease progression or heart failure risk, SGLT-2 inhibition can be continued until the need for dialysis or kidney transplantation arises.	**2B**
6.	We suggest that co-prescription of SGLT-2 inhibition with MRA can be considered, where each are individually indicated.	**2B**
7.	We suggest the beneficial effects of SGLT-2 inhibition on renal outcomes in people with type 2 DM are likely to be a class effect, but there is insufficient data in people without DM to be conclusive.	**2B**
8.	We suggest the beneficial effects of SGLT-2 inhibition on heart failure are likely to be a class effect, irrespective of the presence or absence of DM.	**2B**

Section 5a	DIABETIC KETOACIDOSIS	Grade
1.	We recommend that people with type 1 DM should only have SGLT-2 inhibitors initiated under the strict direction of the diabetes team.	1C
2.	We recommend that people with type 2 DM at greater risk of DKA (defined in Table 5a.1) should have SGLT-2 inhibitors initiated with caution after discussion with the diabetes team.	1C
3.	We recommend SGLT-2 inhibitors are discontinued when a patient develops DKA.	1A
4.	We suggest that after an episode of DKA and where a clear contributing factor has been identified, there should be discussion with the person and clinical team to establish whether the benefits of re-introducing an SGLT-2 inhibitor outweigh the risks.	2D
5.	When initiating SGLT-2 inhibitors, we suggest that individuals should be advised on the signs and symptoms of DKA and be instructed to temporarily withhold SGLT-2 inhibitors and to seek immediate medical advice if symptoms develop.	1C
6.	We recommend always offering advice on sick day guidance when initiating SGLT-2 inhibitors and reminding them of this at every medication review.	1C
7.	We suggest that individuals taking SGLT-2 inhibitors should be advised against following a ketogenic diet.	2C
8.	We suggest that for people who choose to intermittently fast (e.g. for Ramadan), and particularly for those who are elderly, on diuretics or have CKD, consider withholding SGLT-2 inhibitors for the duration of the fasting period and for those people with diabetes ketone testing should be undertaken if unwell.	2D

Section 5b	HYPOGLYCAEMIA	
1.	We recommend considering reducing the dose of insulin/SUs/meglitinides when initiating SGLT-2 inhibitors to reduce the risk of hypoglycaemia.	**1C**
2.	We recommend that when initiating SGLT-2 inhibitors in people taking SUs (e.g. gliclazide) or meglitinides (e.g. repaglinide) when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing dose of SU or meglitinide by 50% to reduce risk of hypoglycaemia.	**1C**
3.	We recommend that when starting SGLT-2 inhibitors in people taking insulin when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing the insulin dose by 20% to avoid hypoglycaemia.	**1C**
4.	We recommend that when starting SGLT-2 inhibitors in people taking only metformin ± pioglitazone ± DPP-4i/gliptins or GLP-1RA therapy, no dosage adjustment is necessary.	**1C**

Section 5c	ACUTE KIDNEY INJURY, HYPOVOLAEMIA AND POTASSIUM	
1.	We recommend that individuals initiated on an SGLT-2 inhibitor do not routinely require an early assessment of renal function or potassium following initiation of treatment.	**1C**
2.	We suggest that if an individual has a renal function assessment within the first few weeks post initiation of an SGLT-2 inhibitor, a decline in eGFR needs to be interpreted with caution and in the context of an expected drug effect to avoid unwarranted discontinuation of treatment.	**2B**
3.	We suggest that individuals on diuretics are counselled on the symptoms of hypovolaemia and advised to seek medical attention if they develop any such symptoms after starting SGLT-2 inhibition.	**2B**
4.	We suggest that clinicians consider an early clinical review and if appropriate a diuretic or antihypertensive dose reduction in individuals they consider at high risk of hypovolaemia.	**2C**
5.	We recommend that SGLT-2 inhibitors are temporarily withheld during acute illness (see sick-day guidance in section 5a.1.2).	**1C**

Section 5d	**PERIPHERAL VASCULAR DISEASE AND AMPUTATION RISK**	
1.	We suggest avoiding initiation of SGLT-2 inhibitors in the presence of active foot disease (infection, ulceration and ischaemia) and withholding treatment in those who develop foot complications whilst taking an SGLT-2 inhibitor.	**2B**
2.	We suggest a shared decision-making approach, with appropriate counselling on risks and benefits of treatment and the importance of routine preventative foot care measures for: • Individuals at high risk of amputation (previous amputations, existing PVD, peripheral neuropathy) • Re-initiation of SGLT-2 inhibitors after treatment and full resolution of a foot complication that occurred whist taking SGLT-2 inhibitors.	**2B**
Section 5e	**FRACTURE RISK**	
1.	In people with CKD treated with SGLT-2 inhibitors, we suggest monitoring of bone parameters including calcium, phosphate and PTH should be performed as appropriate for CKD stage (see NICE NG203).	**2D**

Section 5f	MULTIMORBIDITY AND FRAILTY	
1.	We suggest an approach to care that takes account of frailty and multimorbidity where these apply. This can include: • Establishing the person's goals, values and priorities • Consideration of the balance of disease and treatment burden (for example, prognostic benefits in people with limited life expectancy or frailty) • Agreeing an individualised management plan.	**2D**

Section 5g	MYCOTIC GENITAL INFECTIONS AND FOURNIER'S GANGRENE	
1.	We recommend that all people are counselled on the risks of mycotic genital infections prior to initiation of SGLT-2 inhibitors.	1D
2.	We recommend that all people are counselled on self-care to maintain good genital hygiene.	1C
3.	We recommend that all people are counselled on the symptoms of mycotic genital infections and how to seek help including self-management.	1D
4.	We suggest that for those individuals with a history of recurrent mycotic genital infections on SGLT-2 inhibition, consideration is given to offering prophylactic anti-fungal treatment, which should be reviewed after 6 months of therapy or earlier if clinically indicated.	2D
5.	We suggest that SGLT-2 inhibitor therapy can be continued during the treatment of mycotic genital infections.	2D
6.	We highlight the specific MHRA warning and suggest that all people are counselled on the symptoms of Fournier's gangrene and advised to stop SGLT-2 inhibitors and to seek urgent help if they develop such symptoms.	2D

Section 5h	**URINARY TRACT INFECTION**	
1.	We recommend temporary discontinuation of SGLT-2 inhibitors when treating pyelonephritis or urosepsis (see sick-day guidance in section 5a.1.2).	**1C**
Section 5i	**CHILDREN, PREGNANCY AND BREASTFEEDING**	
1.	We suggest SGLT-2 inhibitors are not used in children under 18 years of age.	**2D**
2.	We suggest that all women of child-bearing potential are counselled, prior to conception, on the risks of SGLT-2 inhibitors during pregnancy.	**2D**
3.	We suggest SGLT-2 inhibitor therapy is discontinued upon planning, suspicion or confirmation of pregnancy.	**2D**
4.	We suggest SGLT-2 inhibitors are not used in women who are breastfeeding.	**2D**

Section 7a	PEOPLE WITH TYPE 1 DM	
1.	We recommend that SGLT-2 inhibitors be initiated in people with type 1 DM, only under the strict direction of the diabetes team.	1C
2.	We suggest considering referring people with type 1 DM to the specialist diabetes team, for consideration of an SGLT-2 inhibitor, if they have an eGFR ≥25 mL/min/1.73m^2 and an uACR ≥25 mg/mmol attributable to diabetic nephropathy despite being on maximum tolerated ACEi/ARB.	2D
3.	We recommend all people with type 1 DM started on SGLT-2 inhibitors be provided with ketone monitoring, be advised on the signs and symptoms of DKA and to seek immediate medical advice if any of these symptoms develop or ketone levels are >0.6 mmol/L.	1B

SUMMARY STATEMENTS		
Section 7b	**KIDNEY TRANSPLANT RECIPIENTS**	**Grade**
1.	There is currently insufficient evidence on safety and efficacy to provide recommendations for use of SGLT-2 inhibition in people with a functioning kidney transplant.	-
2.	Any use of SGLT-2 inhibition to treat diabetes mellitus in a kidney transplant recipient should be evaluated by multi-disciplinary discussion.	**2D**
Section 7c	**HEART FAILURE WITH PRESERVE EJECTION FRACTION and ACUTELY DECOMPENSATED HEART FAILURE**	
1.	There is currently insufficient evidence to provide further recommendations for use of SGLT-2 inhibition in people with acutely decompensated heart failure.	-

- NICE CKD guidance is available at www.nice.org.uk/guidance/ng203

Perspective

Kidney360

Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics

David Lam[1] *and Aisha Shaikh*[1,2]

KIDNEY360 2: 742–746, 2021. doi: https://doi.org/10.34067/KID.0000412021

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have emerged as an effective therapy for improving outcomes in diabetic and nondiabetic kidney disease (1,2). Clinical trials have demonstrated the benefits of SGLT2is for secondary prevention of adverse cardiovascular (CV) effects in patients with established atherosclerotic disease and/or heart failure with reduced ejection fraction (3–7). It is imperative for clinicians to

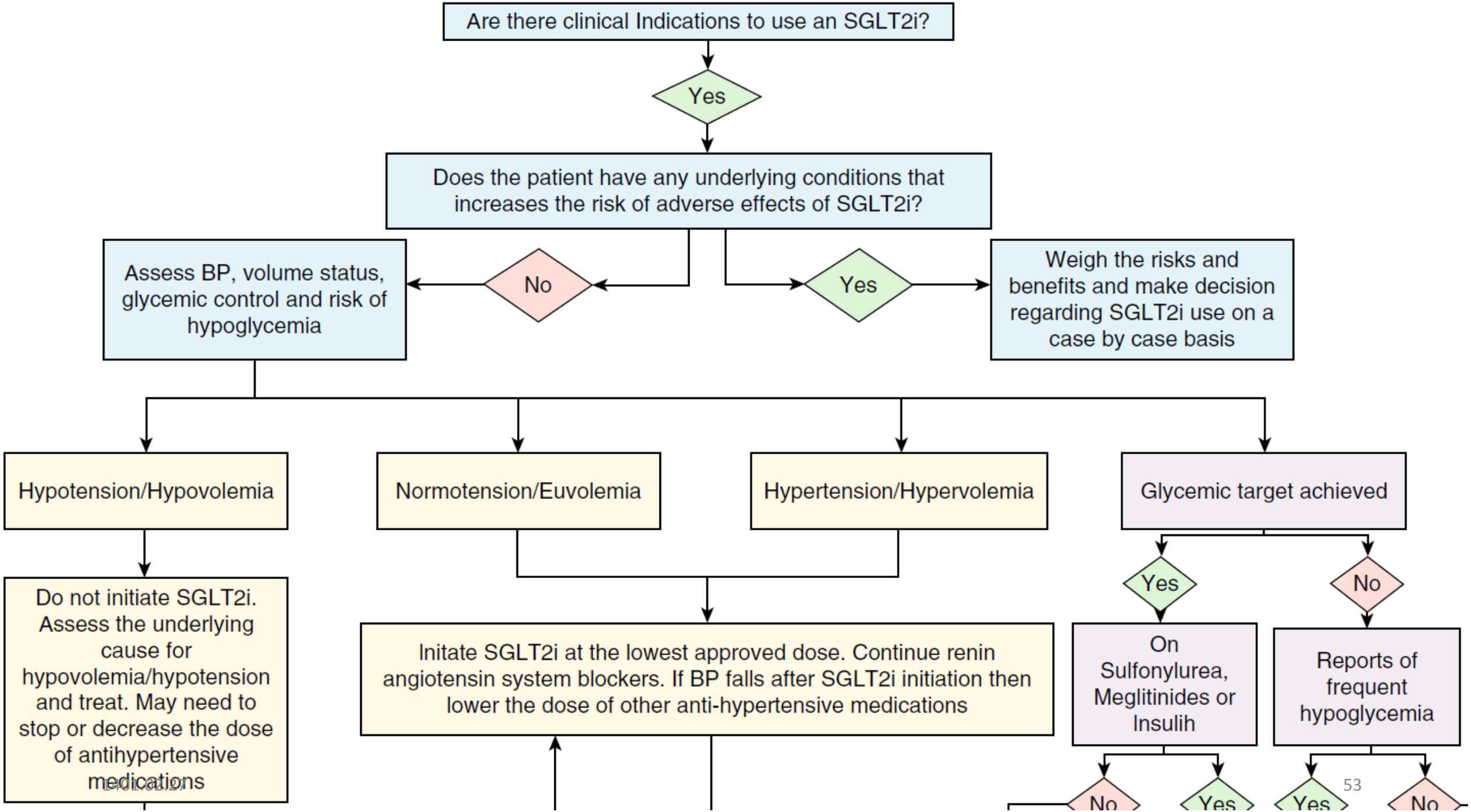
demonstrated a 14% reduction in the primary end point of major adverse cardiac events in patients with a history of CV disease (3,4). In DECLARE-TIMI, dapagliflozin reduced the risk of CV death and hospitalization for heart failure by 17% in patients who had, or were at risk for, atherosclerotic heart disease (5).

4. Heart failure with reduced ejection fraction. In the DAPA-HF trial, dapagliflozin reduced worsening of

Clinical Indications for SGLT2i Use

The use of SGLT2is is clinically indicated in the following circumstances.

1. Type 2 diabetes mellitus (T2DM) and albuminuric kidney disease (albuminuria of ≥200 mg/g of creatinine plus eGFR of 25–90 ml/min per 1.73 m^2). In the CREDENCE Trial, canagliflozin decreased the primary cardiorenal end point by 30%, compared with placebo, in patients with diabetic kidney disease (1). In the DAPA-CKD trial, dapagliflozin reduced the primary cardiorenal end point by 39%, compared with placebo, in patients with diabetic and nondiabetic kidney disease (2).
2. Nondiabetic albuminuric kidney disease (albuminuria ≥200 mg/d plus eGFR of 25–75 ml/min per 1.73 m^2). In the DAPA-CKD trial, a third of the patients did not have T2DM, and the cardiorenal benefits of dapagliflozin were similar among patients with nondiabetic and diabetic kidney disease (2).
3. T2DM with CV disease. In the EMPA-REG and CANVAS trials, empagliflozin and canagliflozin demonstrated a 14% reduction in the primary end point of major adverse cardiac events in patients with a history of CV disease (3,4). In DECLARE-TIMI, dapagliflozin reduced the risk of CV death and hospitalization for heart failure by 17% in patients who had, or were at risk for, atherosclerotic heart disease (5).
4. Heart failure with reduced ejection fraction. In the DAPA-HF trial, dapagliflozin reduced worsening of heart failure and CV death by 26% in patients with an ejection fraction of ≤40% (6). In the EMPEROR-Reduced trial, empagliflozin reduced the primary outcome of CV death and hospitalization for heart failure by 25% in patients with an ejection fraction of ≤40% (7).
5. T2DM and hyperglycemia. Several professional society guidelines recommend using SGLT2is as either first-line therapy or as an add-on therapy to metformin for the management of hyperglycemia in patients with T2DM (9–11).


Are there clinical Indications to use an SGLT2i?
Yes
Does the patient have any underlying conditions that increases the risk of adverse effects of SGLT2i?
No
Assess BP, volume status, glycemic control and risk of hypoglycemia
Yes
Weigh the risks and benefits and make decision regarding SGLT2i use on a case by case basis
Hypotension/Hypovolemia
Normotension/Euvolemia
Hypertension/Hypervolemia
Glycemic target achieved
Yes
No
Do not initiate SGLT2i. Assess the underlying cause for hypovolemia/hypotension and treat. May need to stop or decrease the dose of antihypertensive medications
Initate SGLT2i at the lowest approved dose. Continue renin angiotensin system blockers. If BP falls after SGLT2i initiation then lower the dose of other anti-hypertensive medications
On Sulfonylurea, Meglitinides or Insulih
Reports of frequent hypoglycemia
No
Yes
Yes
No

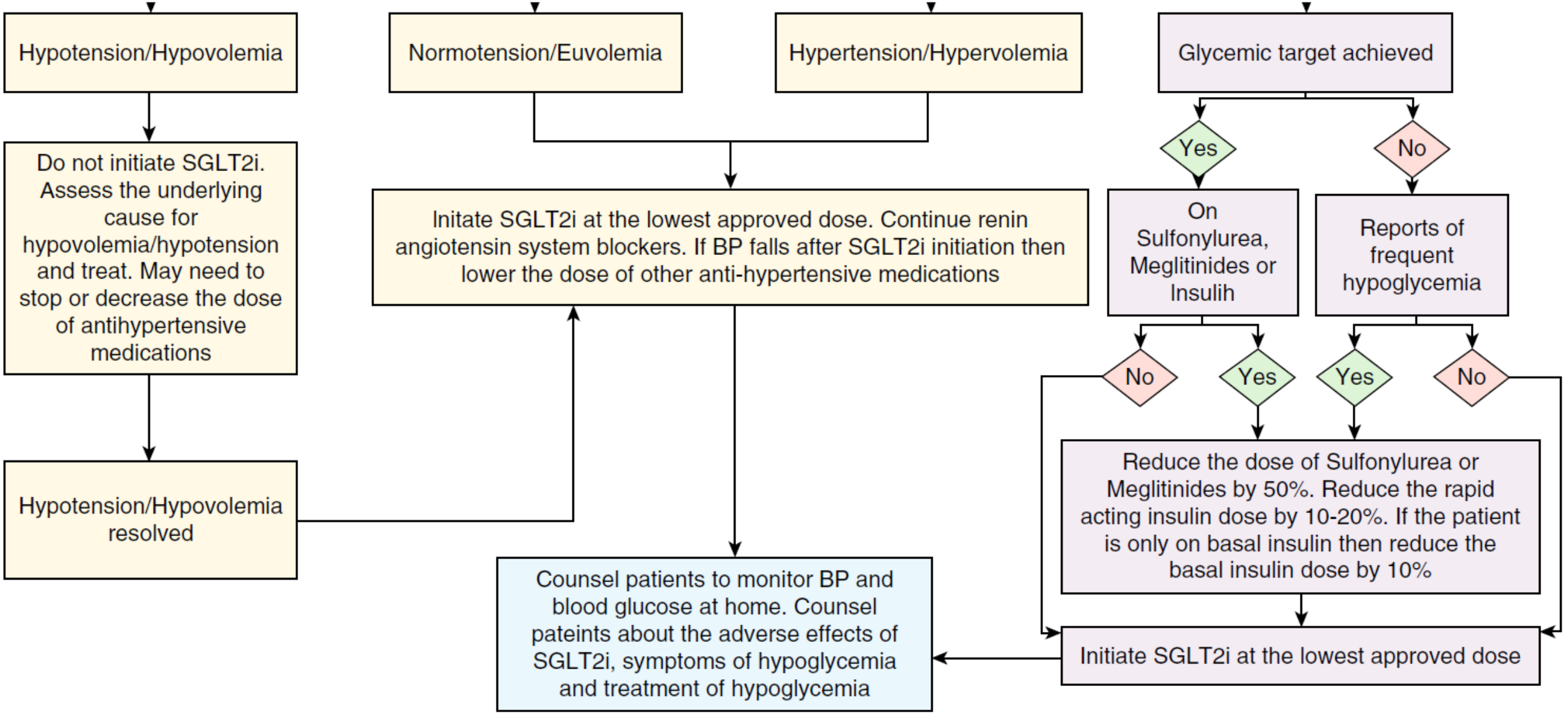


Figure 1. | Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.

Table 1. Handout for patients when initiating sodium-glucose cotransporter-2 inhibitor therapy

It is recommended that the patients follow the recommendations stated below and must contact their provider if they have any questions or concerns

Increase in urine output
- You may notice an increase in your urine output after starting this medication
- Monitor your weight at home

BP
- Monitor your BP at home because this medicine may lower BP
- Inform your doctor if your BP is too low, or if you experience light headedness or dizziness

Blood glucose
- Monitor your blood glucose level at home because this medicine may lower blood glucose
- Inform your doctor if your blood glucose is low

Follow the "sick-day rule"
- Do not take this medicine on days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting, or diarrhea
- You can resume the medicine once you are able to eat and drink
- If you continue to feel sick, then call your doctor because you may need to have blood tests to rule out diabetic ketoacidosis

Stop the medication 3–4 d before a scheduled surgery that requires you to be "nothing by mouth" (meaning you are instructed to not eat or drink anything for several h before your surgery)

Avoid very low carbohydrate and keto diets because they may increase the risk of diabetic ketoacidosis

Wound on your feet or legs
- If you notice a wound, ulcer, or skin breakdown on your feet or legs, then hold this medicine and inform your doctor

Burning or pain during urination
- If you experience pain or burning on urination, then inform your doctor because you may need further evaluation

Redness or itching in the genital area, or foul-smelling vaginal or penile discharge
- Keep the genital area clean
- If you notice redness or itching in the genital area, or foul-smelling vaginal or penile discharge, then inform your doctor; you may need a cream or oral medication to treat an underlying infection

Conclusions

SGLT2is offer cardiorenal protection for patients with and without T2DM. Using a simple strategy for assessing the risks and modifying antihypertensive, diuretic, and antiglycemic agents can mitigate the potential adverse effects of SGLT2is. With the growing evidence for safe use and renal-protective effects of SGLT2is, nephrologists now have a therapeutic agent to combat the pandemic of diabetic kidney disease.

frontiers in Medicine

SYSTEMATIC REVIEW
published: 01 November 2021
doi: 10.3389/fmed.2021.728089

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Effects of SGLT2 Inhibitors on Renal Outcomes in Patients With Chronic Kidney Disease: A Meta-Analysis

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Introduction: The effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on renal outcomes in patients with chronic kidney disease (CKD) were initially demonstrated in recent trials. However, the magnitude of renal benefits for CKD patients with different baseline features and underlying diseases remains unclear.

Method: We systematically searched the Embase, PubMed, Web of Science, and Cochrane library databases from inception to April 15, 2021 to identify eligible trials. The primary outcome was a composite of worsening kidney function, end-stage kidney

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Edited by:
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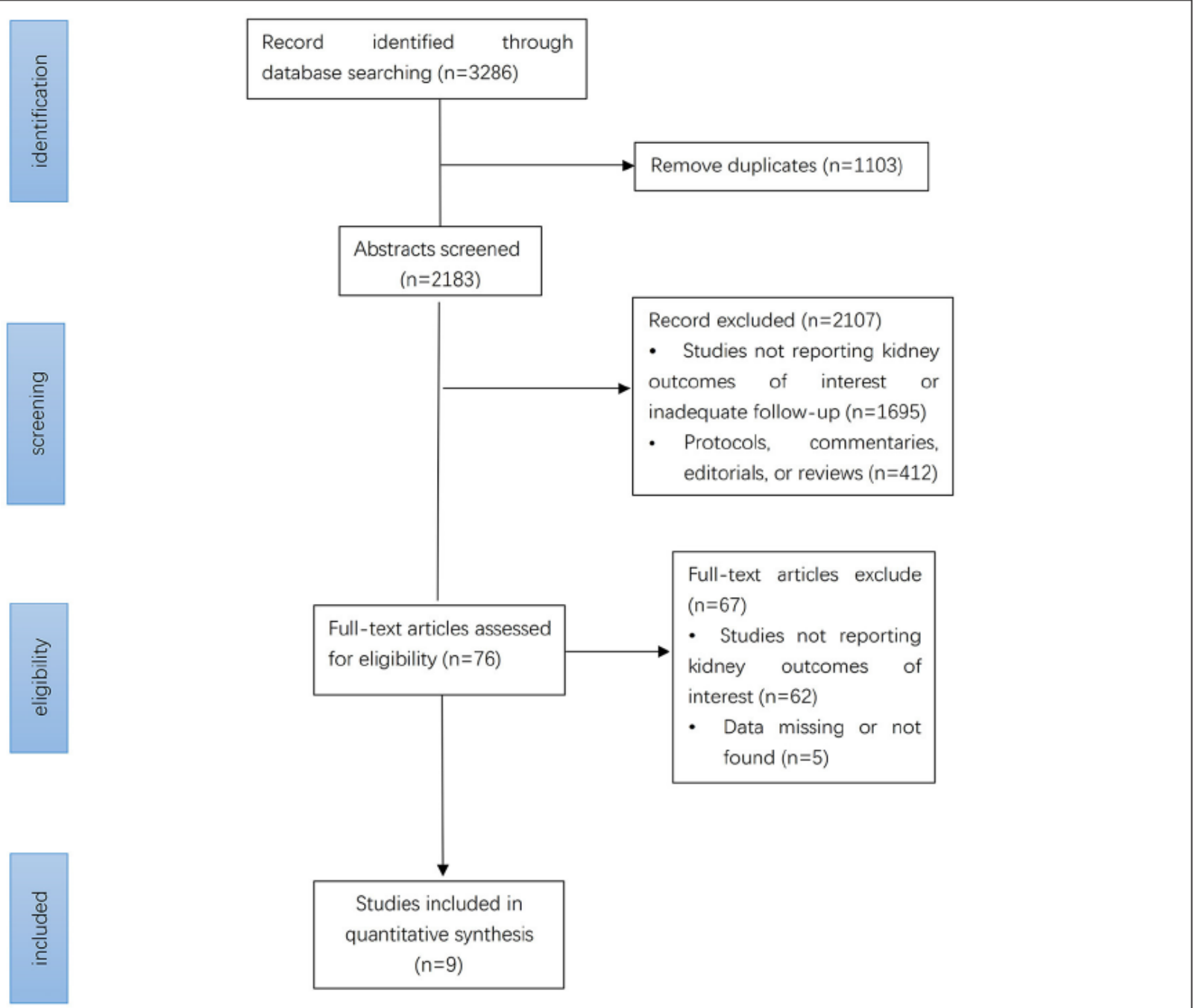

FIGURE 1 | Identification of eligible studies: flow diagram.

TABLE 1 | Baseline characteristics of patients included in different studies.

Study	Study design	Setting	Drug dose (mg/day)	Median follow up (months)	eGFR (ml/min/1.73m^2)	UACR (mg/g)	Age (yr)	Definition of renal outcomes
SGLT2i vs. placebo								
CANVAS	RCT	Multinational	Canagliflozin 300/100	29	30–59	>300	63.2 ± 8.3/63.4 ± 8.2	≥40% GFR decline, ESKD, renal death
CREDENCE	RCT	Multinational	Canagliflozin 100	31.4	30–59	>300	62.9 ± 9.2/63.2 ± 9.2	Doubling creatinine, ESKD, renal or CV death
DAPA-CKD	RCT	Multinational	Dapagliflozin 10	28.8	25–45	>1000	61.8 ± 12.1/61.9 ± 12.1	≥50% GFR decline, ESKD, renal or CV death
DAPA-HF	RCT	Multinational	Danagliflozin 10	18.2	30–59	–	66.2 ± 11.0/66.5 ± 10.8	≥50% GFR decline, ESKD, renal death
DECLARE–TIMI 58	RCT	Multinational	Danagliflozin 10	50.4	<60	>300	63.9 ± 6.8/64.0 ± 6.8	≥40% GFR decline, ESKD, renal death
EMPA-REG	RCT	Multinational	Empagliflozin 25/10	37.2	30–59	>300	63.1 ± 8.6/63.2 ± 8.8	Macroalbuminuria, doubling creatinine, ESKD, renal death
EMPEROR	RCT	Multinational	Empagliflozin 10	16	20–59	>300	67.2 ± 10.8/66.5 ± 11.2	≥40% GFR decline, ESKD
SCORED	RCT	Multinational	Sotagliflozin 200 OR 400	16.0/15.9	25–59	>300	69	≥50% GFR decline, ESKD, renal death
VERTIS CV	RCT	Multinational	ertugliflozin 15/5	42	30–59	>300	64.4 ± 8.1/64.4 ± 8.0	Doubling creatinine, ESKD, renal death

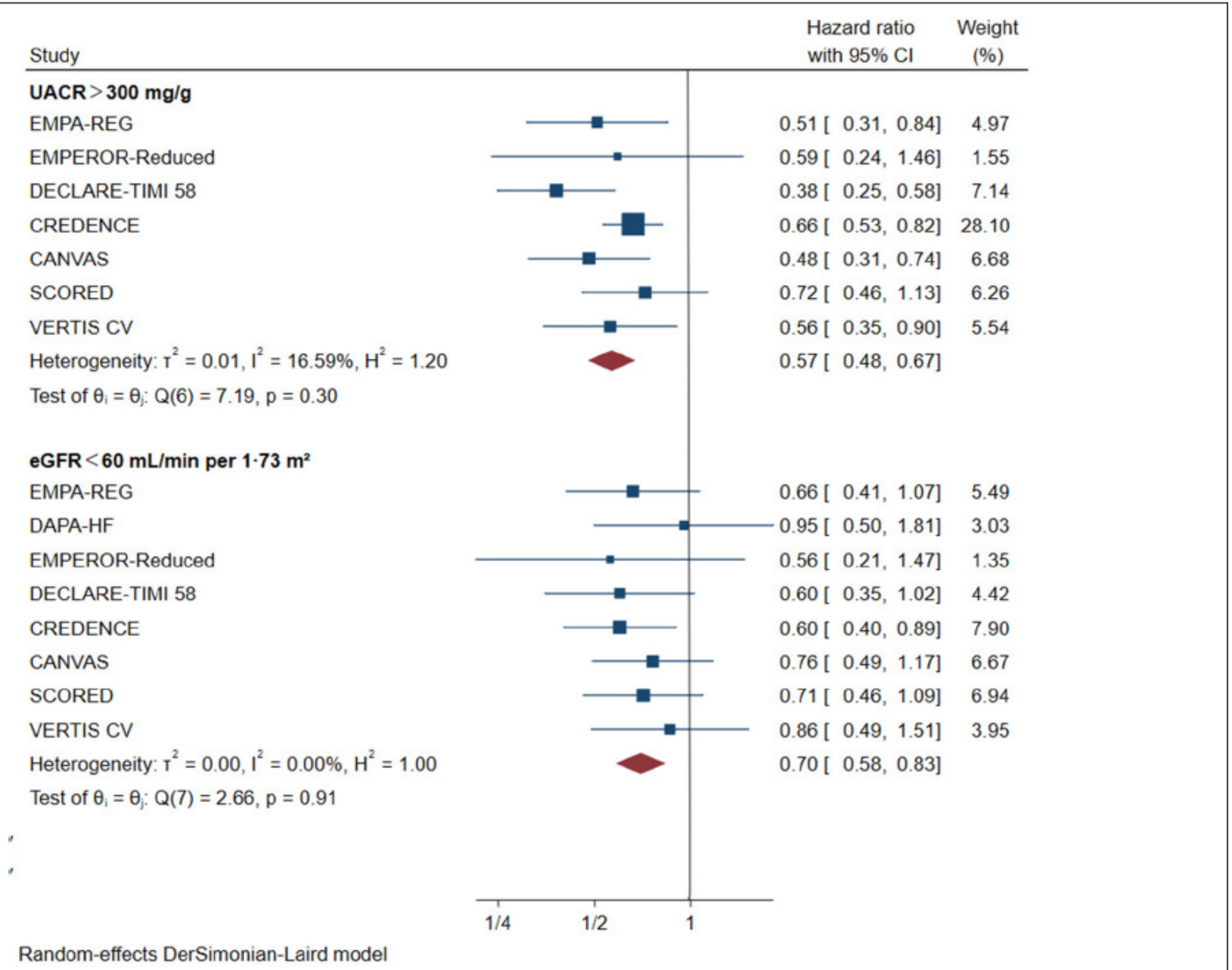

FIGURE 2 | Effect of SGLT2 inhibitors on ESKD, worsening kidney function, or death because of kidney disease. CI, confidence interval; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate. Worsening kidney function: defined as doubling of serum creatinine or sustained 40% decline in eGFR; ESKD, defined as requirement for chronic dialysis or kidney transplantation, or sustained eGFR <15 mL/min/1.73 m².

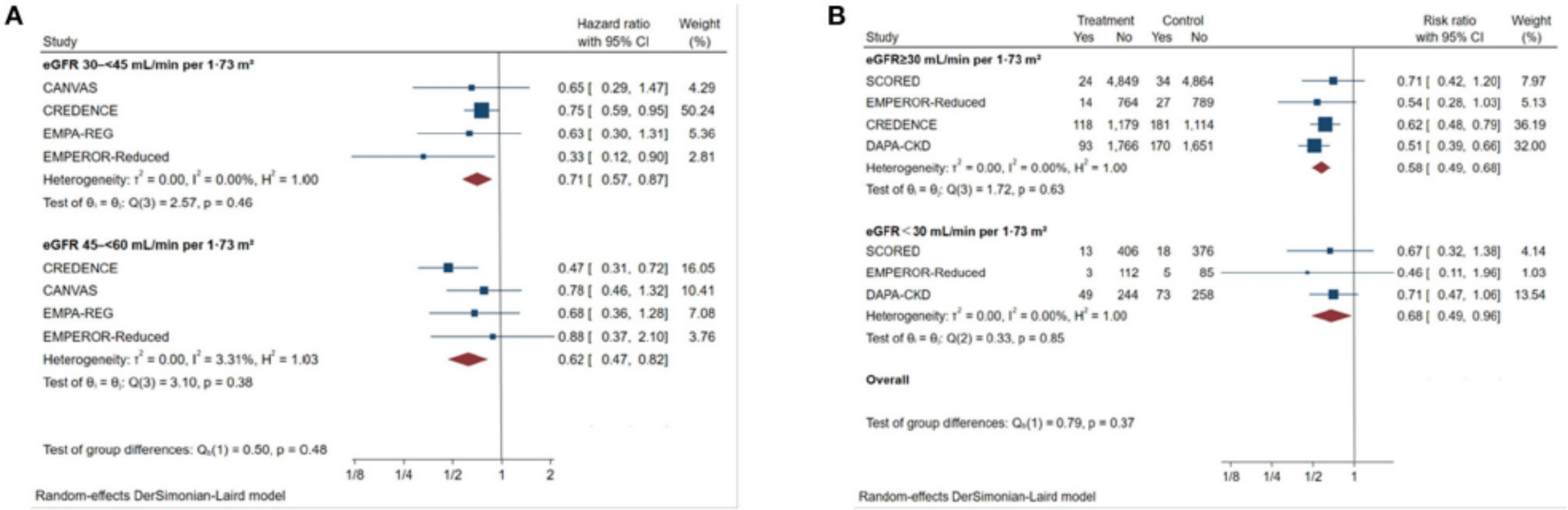

FIGURE 3 | Effect of SGLT2 inhibitors on ESKD, worsening kidney function, or death because of kidney disease across the spectrum of different levels of eGFR. **(A)** Patients with eGFR 45–60 mL/min/1.73 m^2; **(B)** patients with eGFR <30 mL/min/1.73 m^2. CI, confidence interval; eGFR, estimated glomerular filtration rate; worsening kidney function: defined as doubling of serum creatinine or sustained 40% decline in eGFR; ESKD, defined as requirement for chronic dialysis or kidney transplantation, or sustained eGFR <15 mL/min/1.73 m^2.

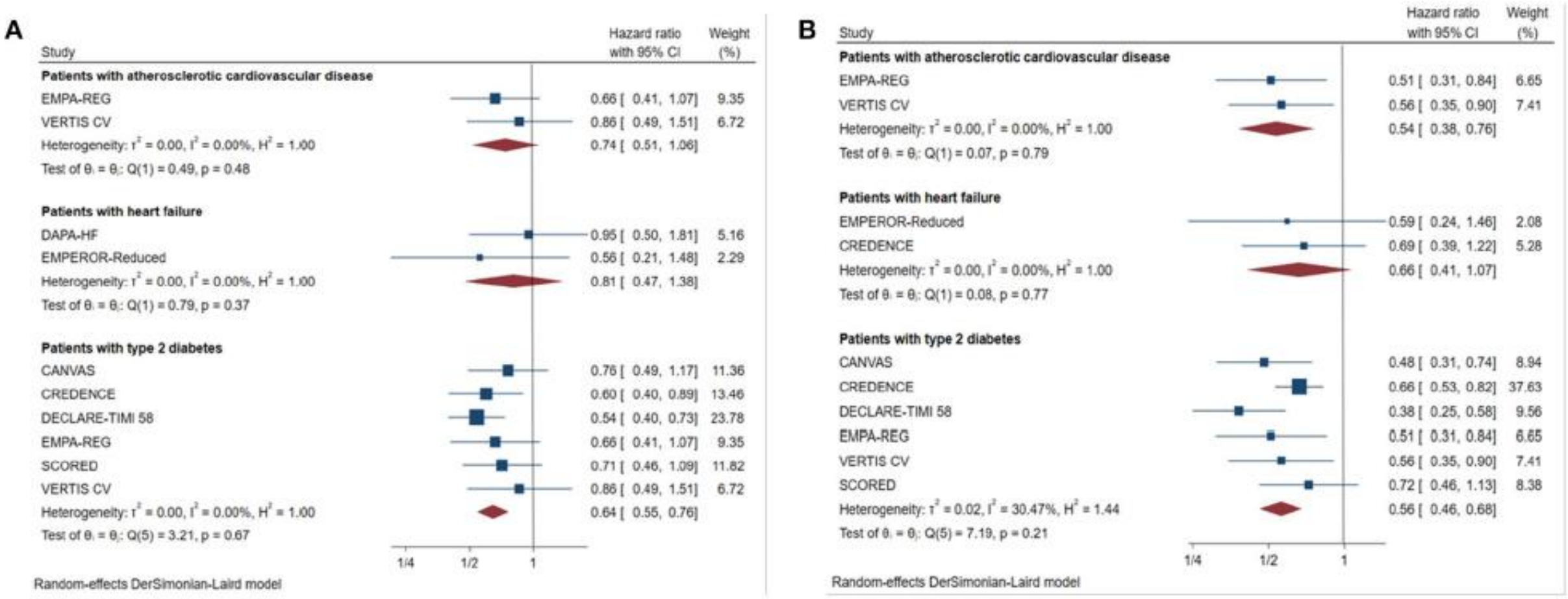

FIGURE 4 | Effect of SGLT2 inhibitors on ESKD, worsening kidney function, or death because of kidney disease in patients with different complications. **(A)** eGFR <60 mL/min/1.73 m²; **(B)** UACR > 300 mg/g; CI, confidence interval; worsening kidney function: defined as doubling of serum creatinine or sustained 40% decline in eGFR; ESKD, defined as requirement for chronic dialysis or kidney transplantation, or sustained eGFR <15 mL/min/1.73 m².

CONCLUSION

In conclusion, SGLT2 inhibitors significantly reduced the risk of primary renal outcomes in patients with CKD, and this benefit was consistent across the spectrum of different levels of eGFR. Additionally, consistent benefits were observed in patients with type 2 diabetes. However, no significant renal benefit was observed in patients with CKD associated with heart failure. In the population with ASCVD, renal benefits were only observed in CKD patients with macroalbuminuria, whereas no significant benefits were observed in those with eGFR <60 mL/min/1.73 m^2. In view of the limitations of our study, in the future, additional high-quality studies are needed to confirm the renal benefits of SGLT2 inhibitors in CKD patients with different baseline features and underlying diseases.

Therapeutics

SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications

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Lancet 2021; 398: 262–76

Published Online June 30, 2021 https://doi.org/10.1016/S0140-6736(21)00536-5

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SGLT2 inhibitors and GLP-1 receptor agonists are used in patients with type 2 diabetes as glucose lowering therapies, with additional benefits of weight loss and blood pressure reduction. Data from cardiovascular outcome trials have highlighted that these drugs confer protection against major cardiovascular disease in those with established atherosclerotic cardiovascular disease, reduce the risk of admission to hospital for heart failure, and reduce cardiovascular and all-cause mortality. Ongoing research using hard renal endpoints such as end stage kidney disease rather than surrogate markers might clarify the renoprotective benefits of both agents. When used for glucose lowering, SGLT2 inhibitors are most effective if the estimated glomerular filtration rate is more than 60 ml per min per 1·73m² at initiation and should be avoided where there is a risk of diabetic ketoacidosis. GLP-1 receptor agonists are contraindicated in those with a history of medullary thyroid cancer and used with caution in

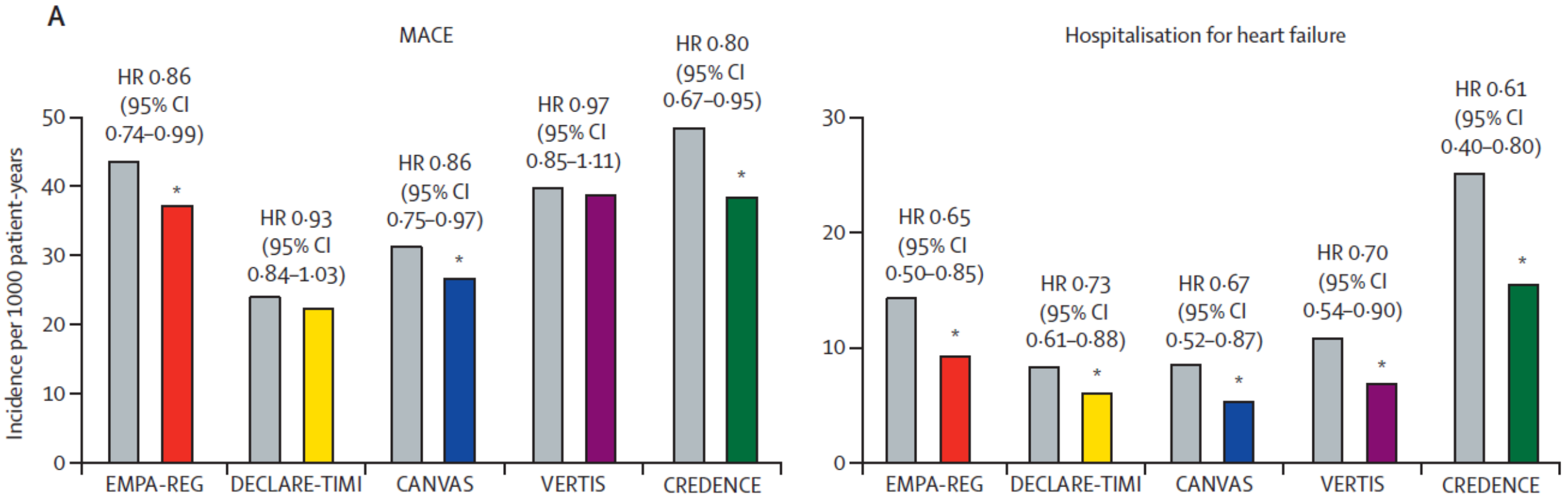

Figure: Cardiovascular outcomes from the key cardiovascular outcome trials with (A) SGLT2 inhibitors versus placebo (grey bars)

Clinical use of SGLT2 inhibitors in patients without diabetes

Cardiovascular and renal benefits in patients without diabetes

There have been no completed dedicated CVOTs or renal endpoint trials that have exclusively included patients without type 2 diabetes. Following on from the CREDENCE study, the effect of SGLT2 inhibitors in non-diabetic kidney disease is of interest given the common pathophysiological pathways in CKD.[8] DAPA-CKD examined the effects of dapagliflozin on CKD in patients with and without type 2 diabetes.[12] One other large clinical trial with renal specific endpoints, EMPA-KIDNEY (NCT03594110), has been initiated in people with and without type 2 diabetes, with non-proteinuric kidney disease, in other words those with an eGFR of less than 45 mL per min per 1·73 m^2, with or without albuminuria.

Treatment of HFrEF

The results of the DAPA-HF and EMPEROR-reduced trials strongly support the use of an SGLT2 inhibitor in the treatment of patients with established HFrEF with reductions in worsening HFrEF or cardiovascular deaths with or without type 2 diabetes.[17,18] Notably, 45–55% of patients did not have a history of type 2 diabetes at baseline.

The benefits were similar in patients with and without diabetes, suggesting that the benefits were independent of glycaemia. Post-hoc analysis of two CVOTs suggested that the same benefits are not seen in patients with heart failure with preserved ejection fraction,[27,28] and the results of dedicated studies in this patient group are still awaited (NCT03057951 and NCT03619213). Notably, dapagliflozin also reduced the risk of new onset of type 2 diabetes by 32% (hazard ratio [HR] 0·68; 95% CI 0·50–0·94) compared with those receiving placebo among at risk patients with prediabetes; a similar effect size to that seen with metformin in diabetes prevention studies (approximately 31%). In the SOLOIST-WHF study, in which all patients had type 2 diabetes, the benefits were consistent in those with HFrEF and heart failure with preserved ejection fraction.[19] After the results from DAPA-HF, the Federal Drug Administration and European regulators have approved the use of dapagliflozin to reduce the risk of cardiovascular death or worsening heart failure in patients with HFrEF, with and without type 2 diabetes.

Journal Pre-proof

Prescribing SGLT2 Inhibitors in Patients with Chronic Kidney Disease: Expanding Indications and Practical Considerations

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PII: S2468-0249(22)01372-9

DOI: https://doi.org/10.1016/j.ekir.2022.04.094

Reference: EKIR 1920

To appear in: *Kidney International Reports*

Received Date: 11 March 2022

Revised Date: 8 April 2022

Accepted Date: 25 April 2022

Abstract

Sodium glucose cotransporter-2 (SGLT2) inhibitors have emerged as a key disease modifying therapy to prevent the progression of chronic kidney disease. These agents prevent decline in kidney function through reduction in glomerular hypertension mediated via tubuloglomerular feedback independent of their effect on glycemic control. The proliferation of clinical trials on SGLT2 inhibitors has rapidly expanded the approved clinical indications for these agents beyond patients with diabetes. We review the current indications for SGLT2 inhibitors in patients with and without diabetic kidney disease including new evidence for use in patients with heart failure with or without reduced ejection fraction, stage 4 chronic kidney disease, and chronic glomerulonephritis. The EMPA-KIDNEY trial was recently stopped early for efficacy suggesting that SGLT2 inhibitors may soon be indicated for chronic kidney disease patients without albuminuria. We review practical considerations for prescription of SGLT2 inhibitors including the anticipated acute decline in eGFR upon initiation, initiating the lowest dosage used in clinical trials, volume status considerations, and adverse event mitigation. Combination therapy in patients with diabetes mellitus may be considered with agents including glucagon like peptide-1 receptor agonists, novel mineralocorticoid receptor antagonists, and selective endothelin receptor antagonists to reduce residual albuminuria and cardiovascular risk.

Introduction

In 2008, the U.S. Food and Drug Administration (FDA) mandated that new glucose lowering therapies undergo cardiovascular outcome trials (CVOTs).[1] This led to the approval of sodium-glucose cotransporter-2 (SGLT2) inhibitors of which four: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are available in North America, while sotagliflozin, a dual SGLT1 and SGLT2 inhibitor is approved in Europe, and other specific agents are available in Japan.

SGLT2 inhibitors have shown to reduce HbA1c by 0.6−1% in patients with T2DM and preserved renal function.[10, 11] This effect is primarily mediated by glucosuria resulting from blockade of the SGLT2 channel predominantly localized to the S1 segment of the proximal convoluted tubule which is responsible for >90% absorption of filtered glucose.[12] The resulting glucosuria can exceed 100g per day in individuals with T2DM and 50−60g per day in non-diabetics. The glucose lowering effect of SGLT2 inhibitors is attenuated in patients with eGFR <60ml/min/1.73m^2 and minimal when eGFR is <30 ml/min/1.73m^2.[13] Caloric loss from glucosuria typically results in 1−3 kg weight loss, [14] the majority of which is fat,[15, 16] and greater weight loss is observed in patients with higher baseline HbA1c.[17]

SGLT2 Inhibitors and Potassium

Hyperkalemia is a frequent clinical challenge in the care of CKD patients and may prohibit uptitration of renin-angiotensin-aldosterone system inhibitors (RAAS) blockade. SGLT2 inhibitors may enhance kaliuresis by increasing distal delivery of sodium and stimulating aldosterone.[25] In CREDENCE, which included patients with T2DM and CKD on RAAS blockade, canagliflozin reduced the incidence of hyperkalemia (K $\geq$6.0) by 23% without causing hypokalemia (<3.5mmol/L), and the need for new potassium binder usage in those treated with canagliflozin by 22%.[32]

Sotagliflozin is the first dual SGLT1 and SGLT2 inhibitor and is approved in Europe for both T1DM and T2DM. It has been postulated that SGLT1 inhibition delays intestinal glucose absorption and reduces postprandial glucose levels.[33-35] Furthermore, SGLT1 contributes to distal proximal tubular glucose reabsorption following SGLT2 inhibition when tubular glucose concentrations are increased which may result in additional glucosuric effects in patients with more advanced CKD.[36] In the SCORED trial, 10,584 patients with T2DM, eGFR 25-60ml/min/1.73m^2 with or without albuminuria were enrolled. However, this trial ended early at 16 months due to loss of funding. The primary endpoint (cardiovascular death, heart failure hospitalizations, and urgent heart failure visits) was reduced by 26% with sotagliflozin despite the relatively short trial duration (HR 0.74, 95% CI 0.63, 0.88).[37] In the SOLOIST-WHF trial initiation of sotagliflozin prior to or shortly following discharge reduced cardiovascular hospitalization or death, as well as urgent heart failure visits.[35] SGLT1 inhibition may result in increased rates of diarrhea, and the additional benefit of SGLT1 blockade to SGLT2 inhibition is not yet fully understood, although sotagliflozin does reduce hyperglycemia even in patients with CKD Stage 4.[38]

Current Indications for SGLT2 Inhibitors

Indications for SGLT2 inhibitors have expanded based upon growing evidence from randomized controlled trials and fall broadly into five categories: glycemic control/metabolic risk, reduction in ASCVD, heart failure, diabetic kidney disease with albuminuria, non-diabetic chronic kidney disease with albuminuria, and ejection fraction (**Table 1**).

Stage 4 Chronic Kidney Disease

The most robust evidence for use of SGLT2 inhibitors in stage 4 CKD is a prespecified analysis of DAPA-CKD in 624 of 4304 (14%) of patients with baseline eGFR 25-30 ml/min/1.73m^2. Consistent with results from the overall trial, a 27% reduction in the primary composite endpoint (50% sustained decline in eGFR, ESKD, or kidney/cardiovascular death) was observed. Dapagliflozin resulted in a 28% reduction in the risk for ESKD, with an eGFR slope decline in 2.15 ml/min/1.73m^2 in the dapagliflozin group in comparison to 3.38 ml/min/1.73m^2 in the placebo group with separation of the eGFR curves evident by 16 months.

No difference in adverse events including renal-related or volume depletion were noted. Furthermore, no significant heterogeneity by diabetes status or albuminuria was observed. While evidence for kidney-related endpoints remains limited for patients with eGFR below 25ml/min/1.73m^2, it should be emphasized that SGLT2 inhibitors may be continued until patients are on dialysis.

CKD Patients without Albuminuria

Meta-analysis of CVOTs has demonstrated that benefits of SGLT2 inhibitors on delaying CKD progression are consistent regardless of baseline albuminuria.[3, 4, 39, 49, 60] To definitively determine benefits in patients with low eGFR and low UACR, the EMPA-KIDEY trial included adults with or without diabetes with eGFR 20-45 regardless of albuminuria or eGFR 45-90ml/min/1.73m^2 with urine ACR ≥200mg/g on maximally tolerated RAAS blockade.[61] This study enrolled 6609 patients with a mean eGFR of 37.5m/min/1.73m^2. Notably this cohort includes patients with glomerular disease (n=1669) and hypertensive/renovascular disease (n=1444).[62] The primary outcome of this trial was a sustained ≥40% decline in eGFR, ESKD or death from renal or cardiovascular causes. The EMPA-KIDNEY trial was stopped early in March 2022 for efficacy suggesting that CKD patients without albuminuria also benefit from SGLT2 inhibitors and will soon markedly expand the population eligible for therapy.[63]

SGLT2 Inhibitors in Glomerulonephritis

While patients with glomerulonephritis commonly require immunosuppressive therapy, those who develop CKD secondary to chronic damage or scarring may share a common final pathway mediated by hyperfiltration that may be amenable to SGLT2 inhibition. In the TRANSLATE study short-term treatment with dapagliflozin did not significantly alter renal hemodynamics or reduce proteinuria in 10 patients with focal segmental glomerulosclerosis (FSGS).[64] Similarly, the DIAMOND trial first evaluated this hypothesis in non-diabetic CKD patients with eGFR >25ml/min/1.73m^2 and 500-3500mg/day proteinuria including patients with IgA nephropathy (n=25) and FSGS (n=11).[65] Dapagliflozin was associated with an acute dip in eGFR upon initiation suggestive of a beneficial hemodynamic effect, but did not result in a significant reduction in proteinuria compared to placebo over a 6-week treatment period, and the 17% reduction in UACR also did not reach significance.[65]

DAPA-CKD was the largest trial studying use of SGLT2 inhibitors in patients with chronic glomerulonephritis (n=695) to date, although patients with a history of immunosuppression in the prior 6 months were excluded.[8, 66] DAPA-CKD included 270 participants with IgA nephropathy of whom 254 (94%) had pathologic confirmation by kidney biopsy. The mean eGFR of participants was 43.8 ml/min/1.73m^2 with a median ACR 900 mg/g who were followed for a median of 2.1 years. In a pre-specified analysis of IgA nephropathy participants, the primary composite kidney outcome was lower for patients with dapagliflozin (HR 0.29, 95% CI 0.12, 0.73) with a mean annual rate of eGFR decline of 3.5 ml/min/1.73m^2 with dapagliflozin and 4.7 mL/ min/1.73m^2 with placebo. Furthermore, dapagliflozin resulted in

with dapagliflozin and 4.7 mL/ min/1.73m^2 with placebo. Furthermore, dapagliflozin resulted in a 26% reduction in albuminuria in comparison to placebo. Interestingly, the primary outcome event rate was more than double in the placebo group (24% at 32 months), compared to what would have been predicted for the average DAPA-CKD patient using the International IgA nephropathy risk prediction tool, suggesting a high-risk group of participants. Nevertheless, the overall findings were supportive of SGLT2 inhibitor use in IgA nephropathy.[65]

For FSGS, a pre-specified analysis of DAPA-CKD included 115 individuals with FSGS of which 105 (90%) were biopsy proven.[67] The primary composite kidney outcome did not reach statistical significance (HR 0.62, 95% CI 0.17, 2.17). However, participants treated with dapagliflozin demonstrated 26.1% reduction in albuminuria compared to 9.9% in placebo which persisted after a year. Furthermore, the annual mean rate of eGFR decline was lower in those receiving dapagliflozin (-1.9 ml/min/1.73m^2, 95% CI -3.0, -0.9) in comparison to placebo (-4.0 ml/min/1.73m^2, 95% CI -4.9, -3.0).

DAPA-CKD may have had secondary etiologies. In both IgA nephropathy and FSGS patients SGLT2 inhibitors were well tolerated with no cases of major hypoglycemia or diabetic ketoacidosis (DKA) in those receiving dapagliflozin.

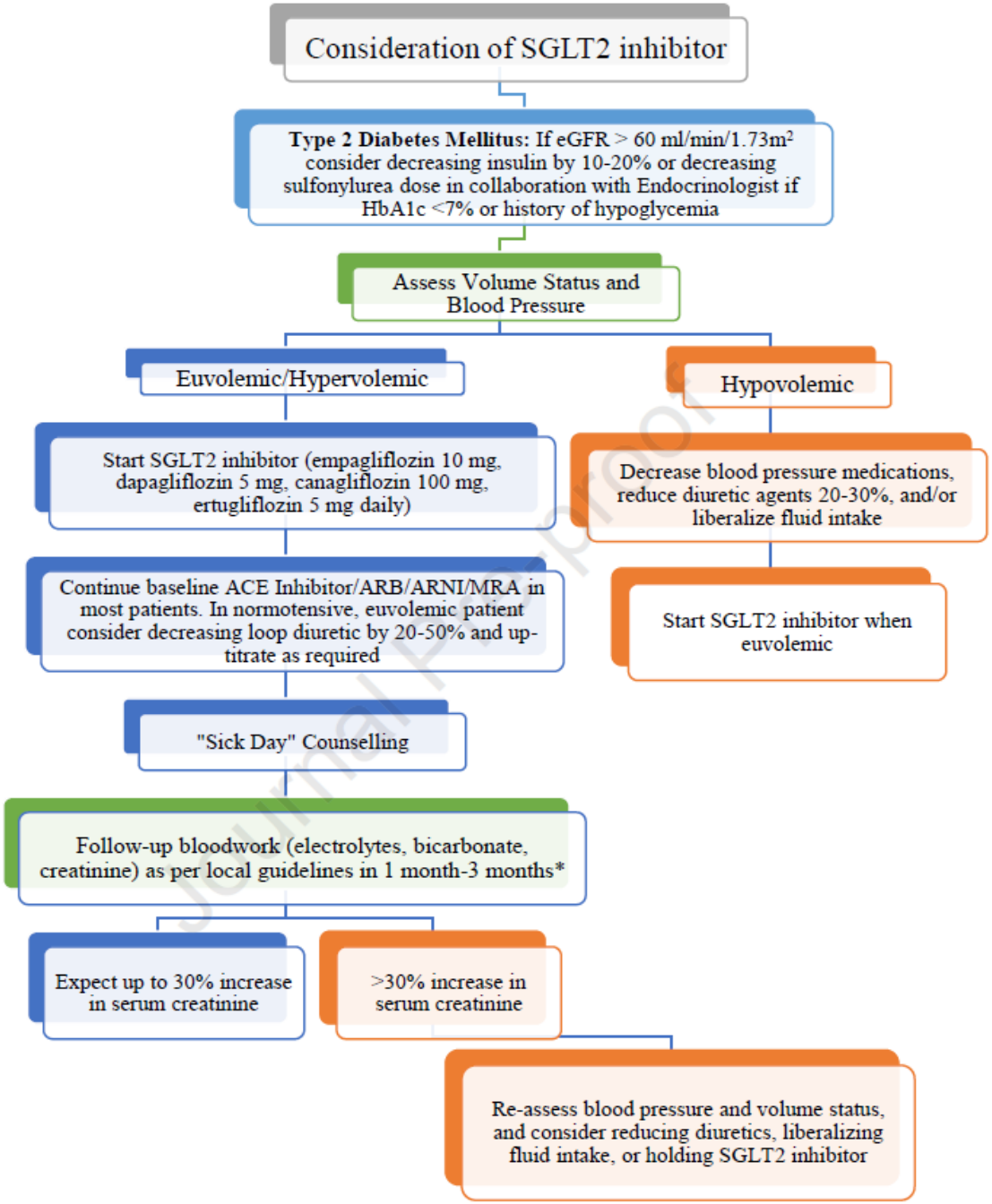

Figure 1: Proposed algorithm for SGLT2 inhibitor initiation.