SGLT2 Inhibitors new treatment indications

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Associate Prof.

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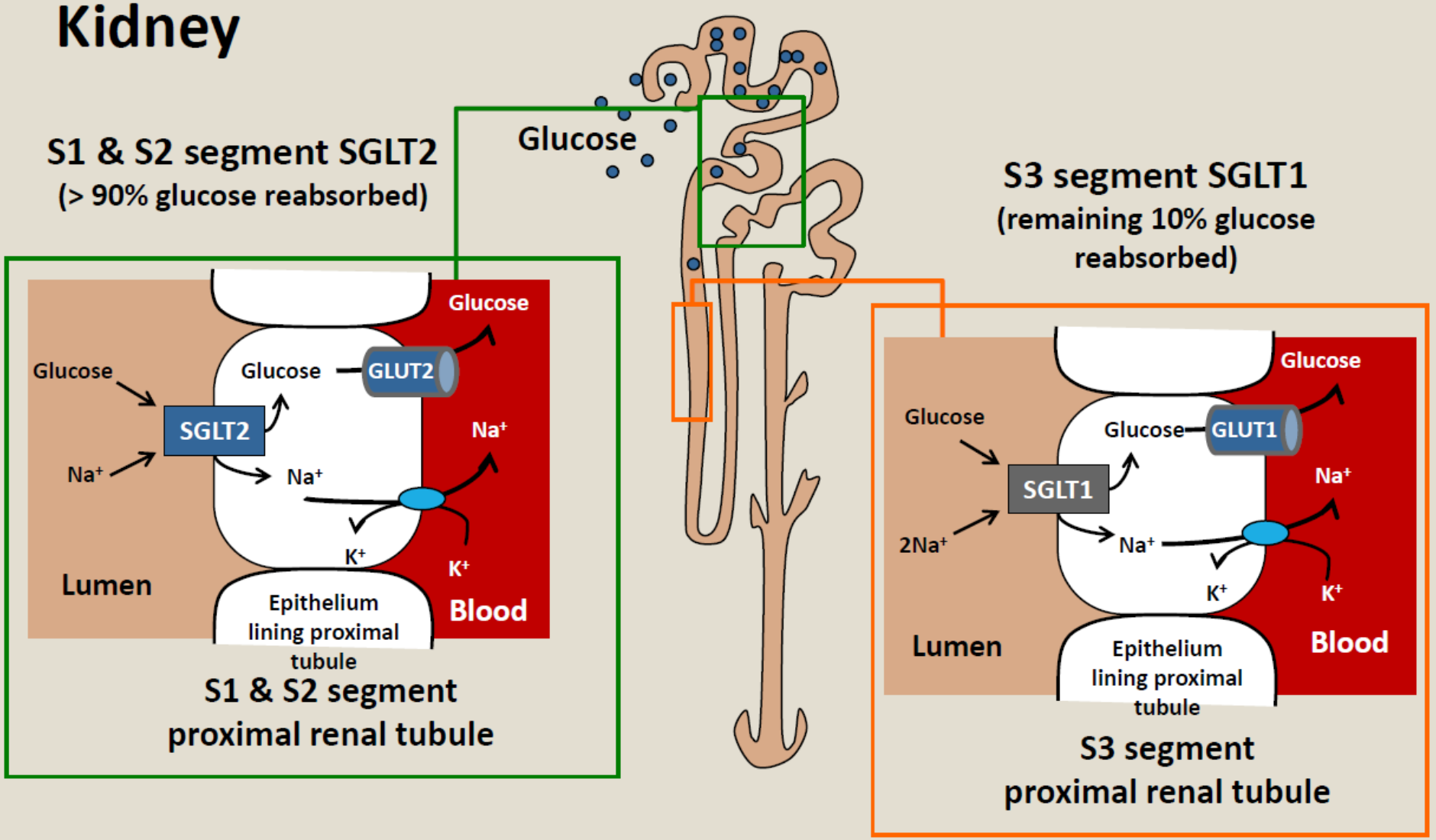
Location of Sodium Glucose Transporters in the Kidney



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

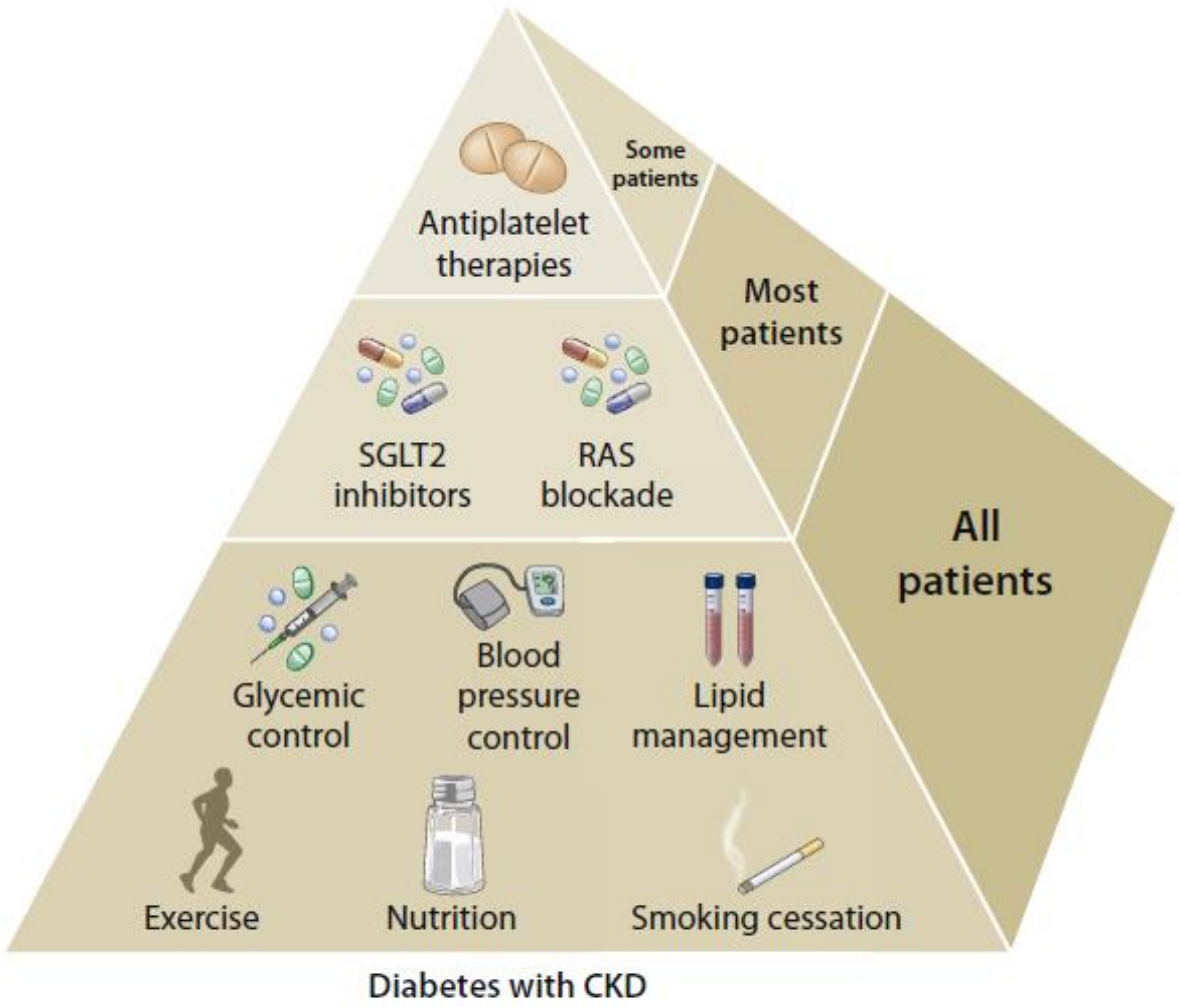
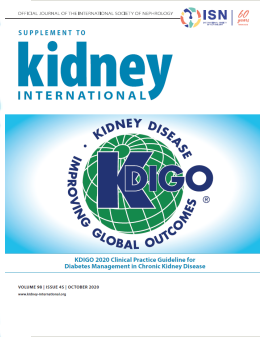


Figure 2 | Kidney–heart risk factor management. Glycemic control is based on insulin for type 1 diabetes and a combination of metformin and SGLT2 inhibitors (SGLT2i) for type 2 diabetes, when eGFR is ≥30 ml/min per 1.73 m^2. SGLT2i are recommended for patients with type 2 diabetes and chronic kidney disease (CKD). Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension. Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among high-risk individuals, with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention. RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter-2.

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control (Figure 18).

Lifestyle therapy is the cornerstone of management for patients with T2D and CKD. In addition, metformin and SGLT2i should be used in combination as first-line treatment for all or nearly all patients with an eGFR ≥30 ml/min per 1.73 m^2 (Figure 18 and Figure 19; see Sections 4.1 and 4.2). Additional antihyperglycemic drugs can be added to this base drug therapy as needed to achieve glycemic targets, with GLP-1 RA generally preferred. These recommendations are guided



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).

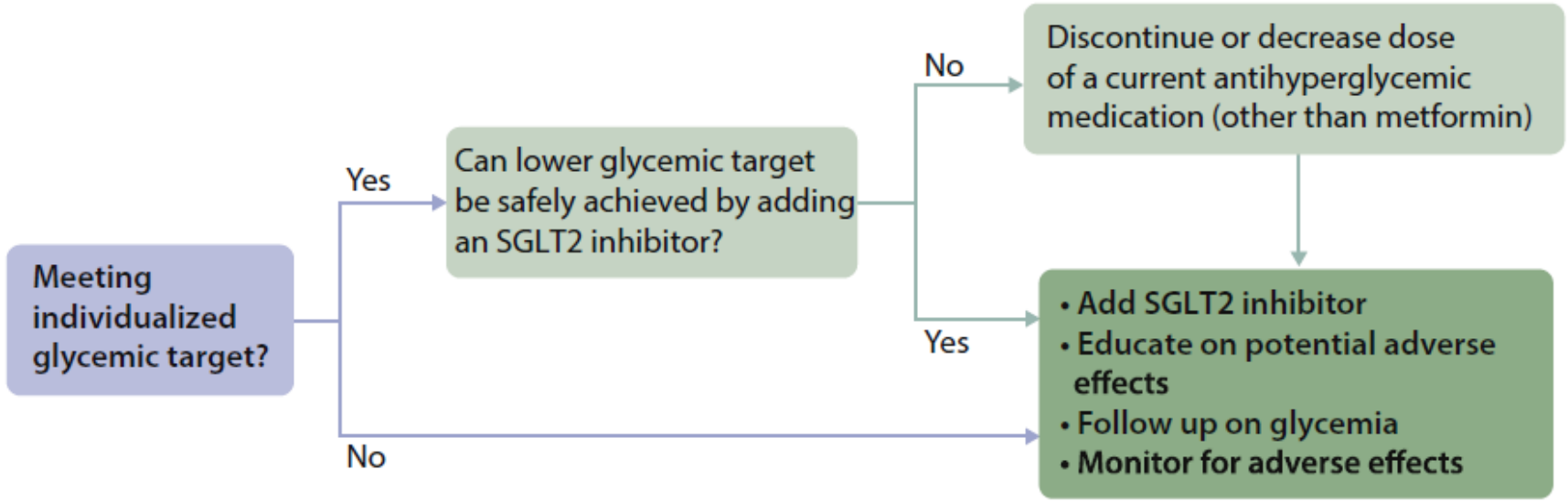
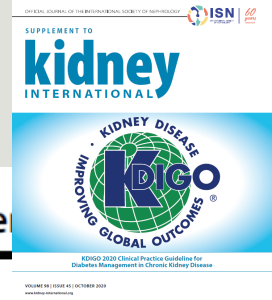


Figure 24 | Algorithm for initiation of SGLT2 inhibitor therapy for patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m^2, who are already being treated with antihyperglycemic medications. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose cotransporter-2;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

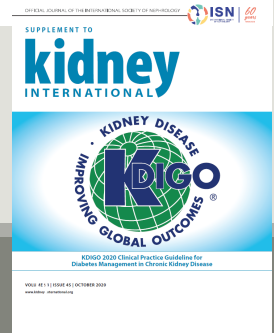
Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

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]

			Primary outcome		Kidney outcomes		
Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Effect on albuminuria or albuminuria-containing composite outcome	Effect on GFR loss[a]	Adverse effects
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m²	Progression of CKD[b]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death[c]	↔/↓	↓	↓↓	Genital mycotic infections, DKA

Figure 19 | Overview of select large, placebo-controlled clinical outcome trials assessing the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. ACR, albumin-creatinine ratio; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GI, gastrointestinal symptoms (e.g., nausea and vomiting); GLP-1, glucagon-like peptide-1; HF, hospitalization for heart failure; MACE, major adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death (3-point MACE), with or without the addition of hospitalization for unstable angina (4-point MACE); NA, data not published; SGLT2, sodium–glucose cotransporter-2. ↔, no significant difference. ↓, significant reduction in risk, with hazard ratio (HR) estimate >0.7 and 95% confidence interval (CI) not overlapping 1. ↓↓, significant reduction in risk, with HR estimate ≤0.7 and 95% CI not overlapping 1. [a]Variable composite outcomes that include loss of eGFR, ESKD, and related outcomes. [b]Progression of CKD defined in CREDENCE as doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes and in CARMELINA as 40% decline in eGFR, ESKD, or renal death. [c]DECLARE-TIMI 58 dual primary outcomes: (i) MACE and (ii) the composite of hospitalization for heart failure or CV death. [d]SUSTAIN-6: injectable semaglutide; PIONEER 6: oral semaglutide.



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

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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-carboximide Riboside, AICAR), inhibitor (Compound C), si-SP1 and si-PGAM5. Lastly, we testified the interaction between SP1 and the PGAM5promotor by CHIP assay.

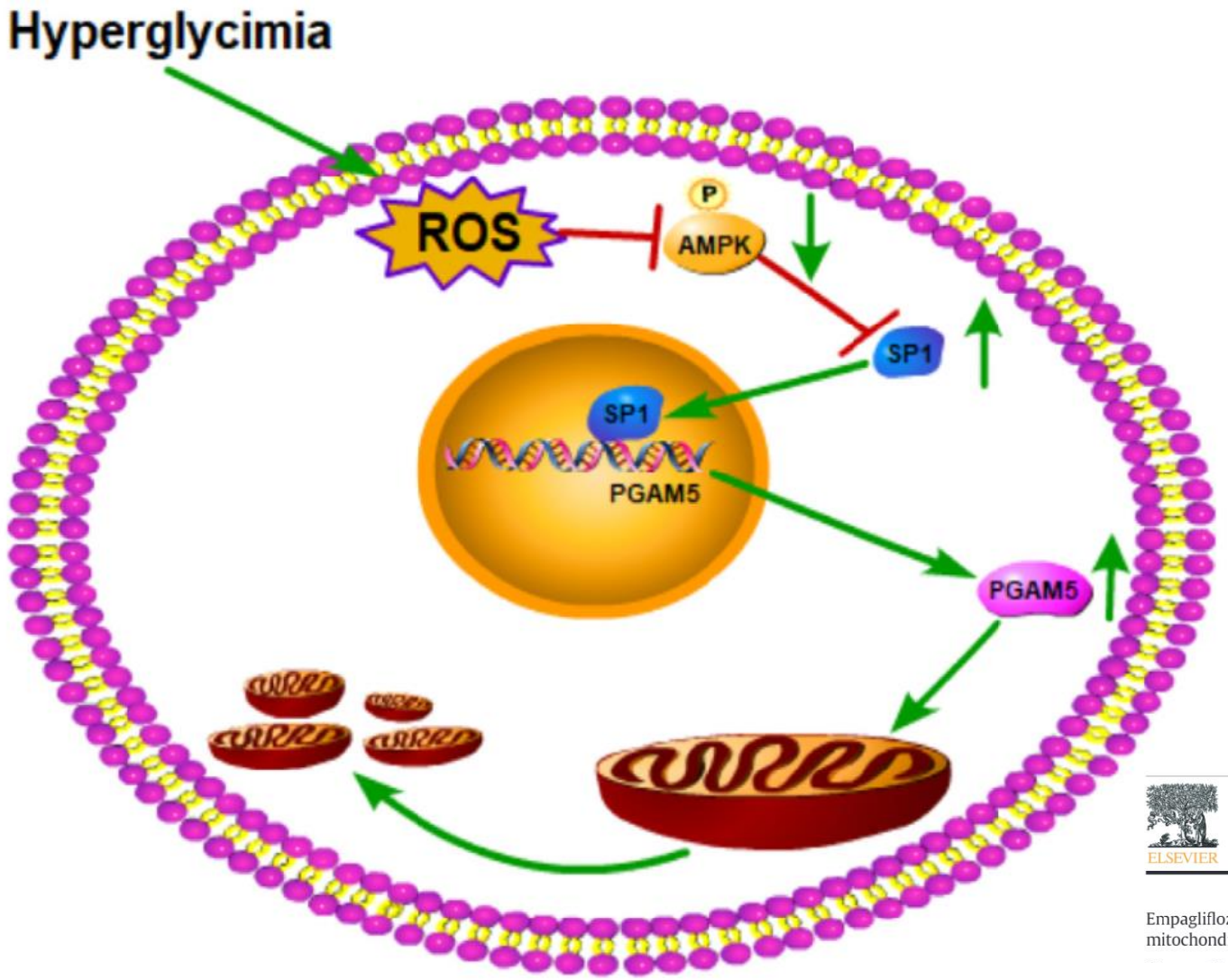

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Fig. 6. Proposed model for the signaling pathway by which PGAM5 participates in the diabetic tubular injury via an AMPK dependent pathway.

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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ELSEVIER

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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]

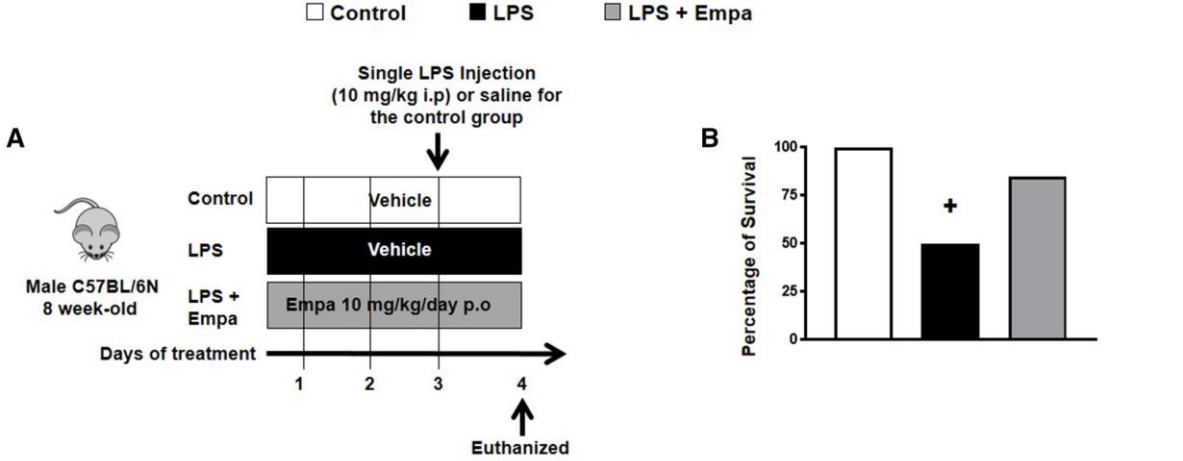
Received: 11 March 2020 / Accepted: 10 June 2020

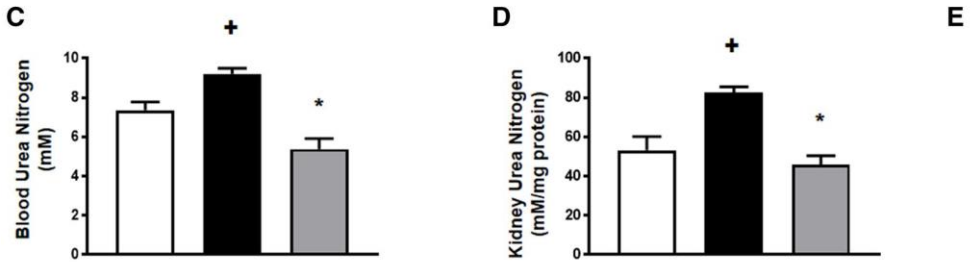
Abstract

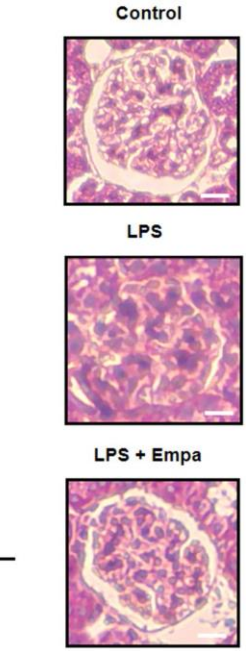
Background Sepsis-induced systemic inflammation response syndrome is the leading cause of morbidity and mortality among patients in intensive care units in North America. While sepsis is associated with multiple organ damage, acute renal injury represents a hallmark of sepsis. Since systemic and renal 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.

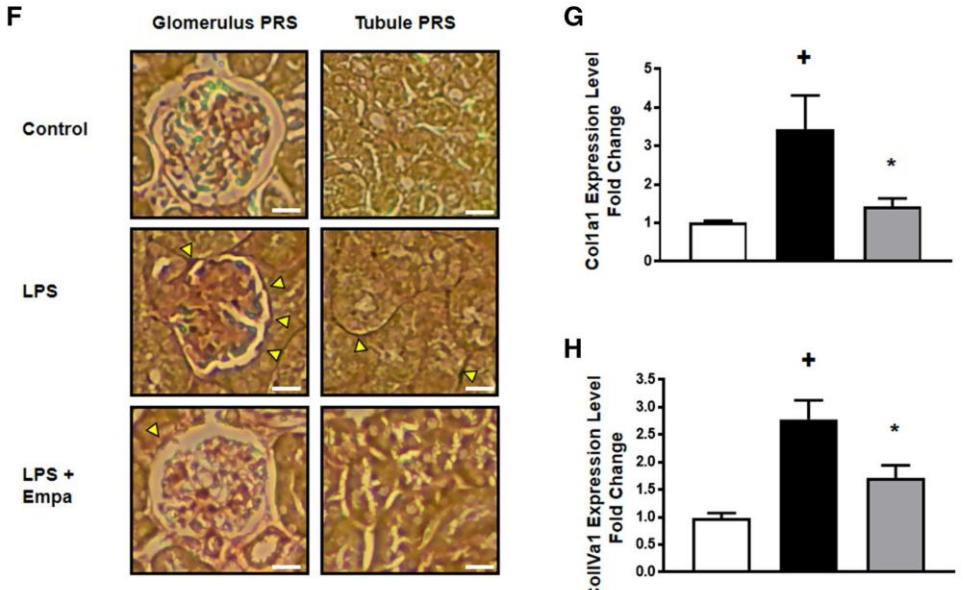
Method Mice were treated with three daily doses of empagliflozin or vehicle, with lipopolysaccharide (LPS) administered

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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Empagliflozin treatment suppresses systemic inflammation in mice following LPS injection

Using systemic cytokines and chemokine multiplex assay, we found that cytokines, IL-5, IL-6, IL-16, IL-17, TNF-α, Leukemia inhibitory factor (LIF) and interferon gamma (INF-γ), and chemokine, monokine induced by gamma interferon (MIG), Interferon gamma-induced protein 10 (IP-10), CCL5, CCL17, CCL19 and CCL20, were all upregulated in LPS mice with vehicle (Fig. 4). Interestingly, IL-1β, and all other cytokines and chemokines were significantly decreased in LPS-injected mice treated with empagliflozin (Fig. 4). Overall, these data provide evidence that empagliflozin may reduce mortality and renal injury in mice with established septic shock through the suppression of systemic inflammation.

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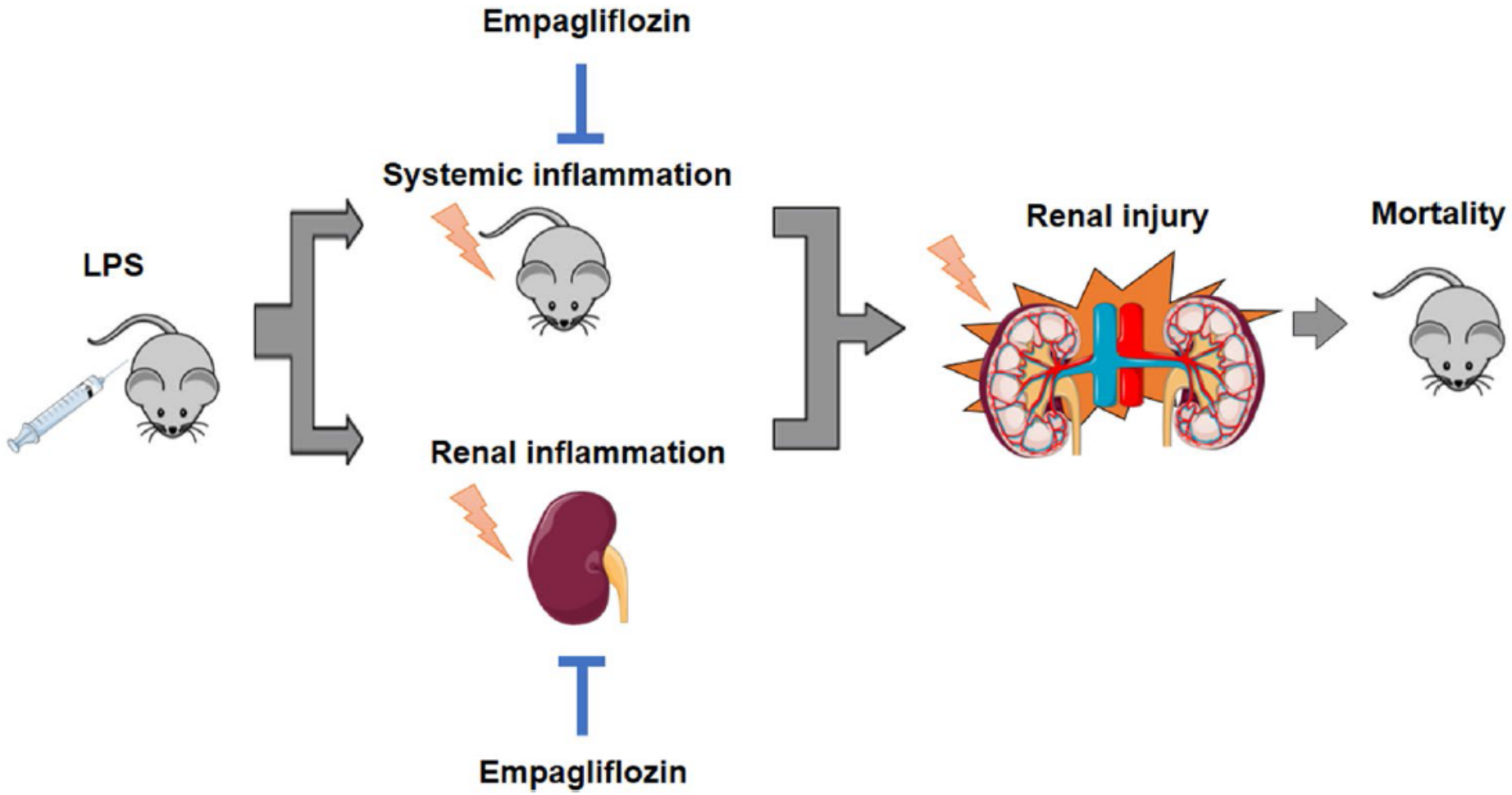
Fig. 5 Schematic of the anti-inflammatory effects of empagliflozin and the protection against acute septic renal injury in a mouse model of lipopoly-saccharide (LPS)-induced sepsis



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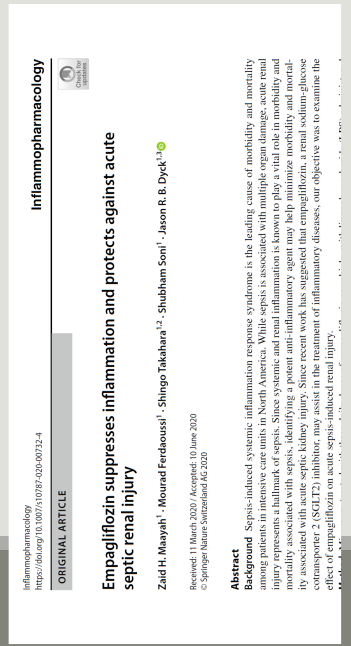

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In summary, our results indicate that empagliflozin treatment improves survival in a mouse model of LPS-induced septic shock. We show for the first time that the beneficial effect of empagliflozin is mediated via reducing LPS-induced acute renal injury. 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]

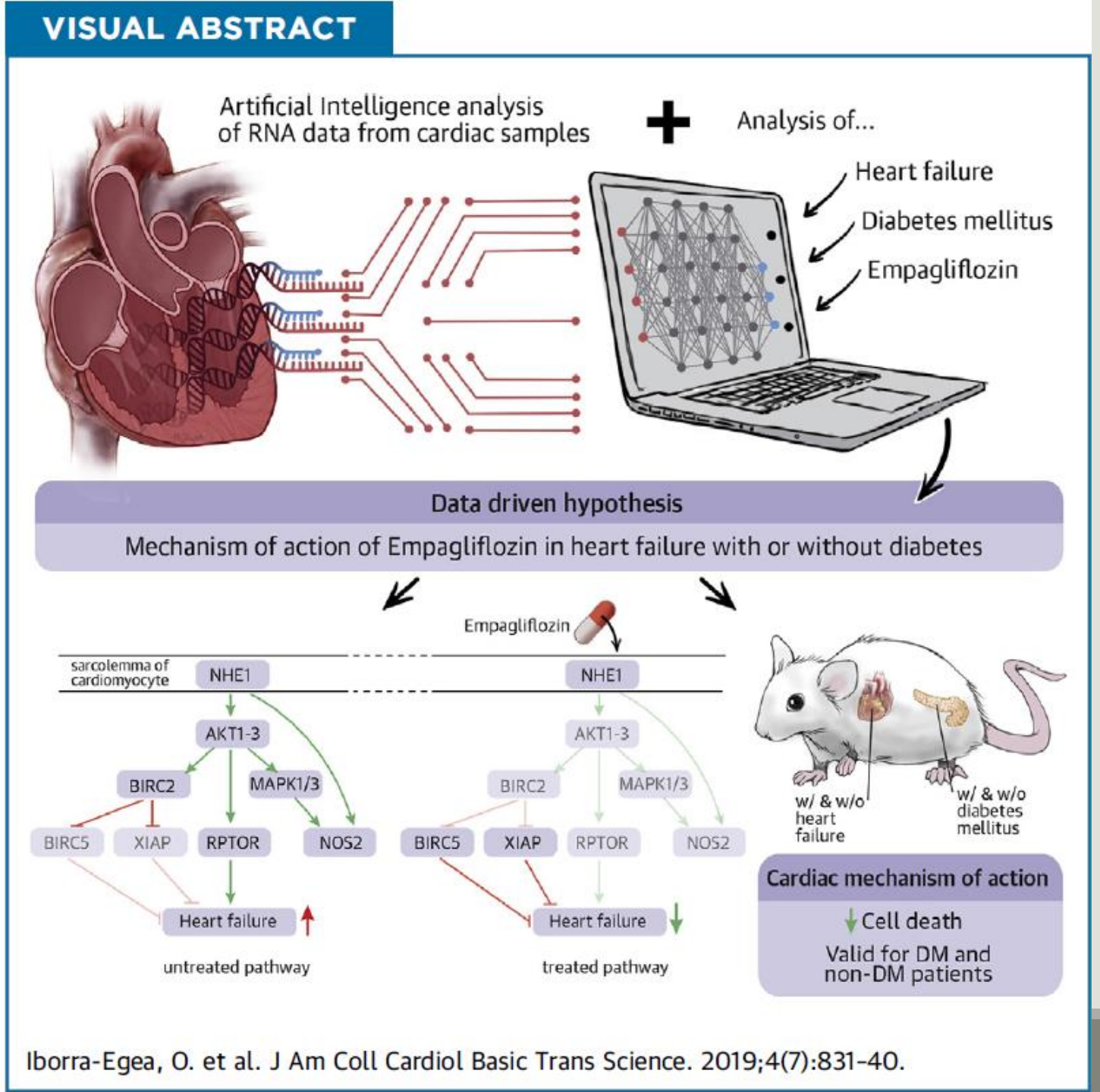
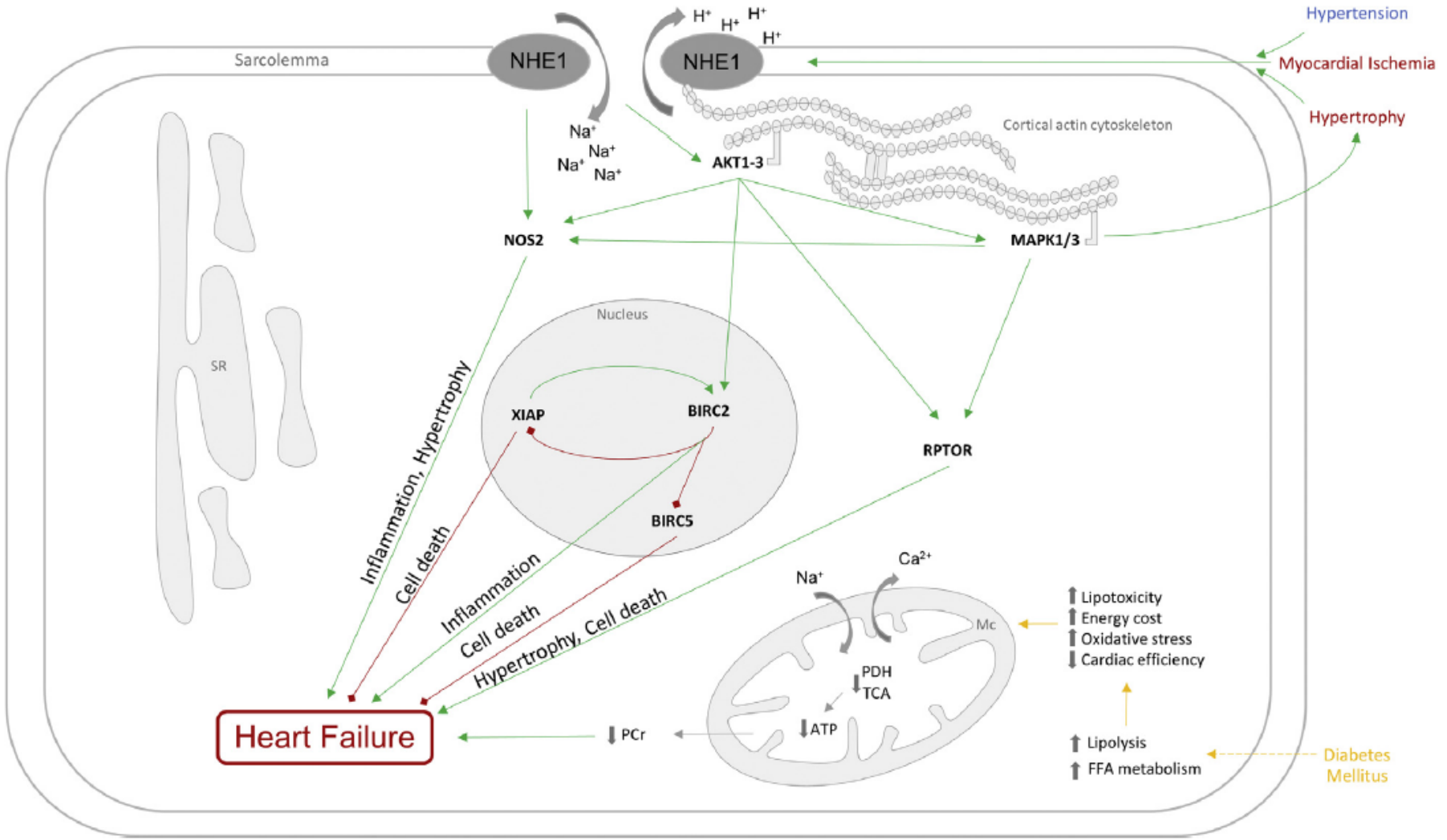

VISUAL ABSTRACT
Artificial Intelligence analysis of RNA data from cardiac samples
+
Analysis of...
Heart failure
Diabetes mellitus
Empagliflozin
Data driven hypothesis
Mechanism of action of Empagliflozin in heart failure with or without diabetes
Empagliflozin
sarcolemma of cardiomyocyte
NHE1
NHE1
AKT1-3
AKT1-3
BIRC2
MAPK1/3
BIRC2
MAPK1/3
BIRC5
XIAP
RPTOR
NOS2
BIRC5
XIAP
RPTOR
NOS2
Heart failure
Heart failure
untreated pathway
treated pathway
w/ & w/o heart failure
w/ & w/o diabetes mellitus
Cardiac mechanism of action
Cell death
Valid for DM and non-DM patients
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

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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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.

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

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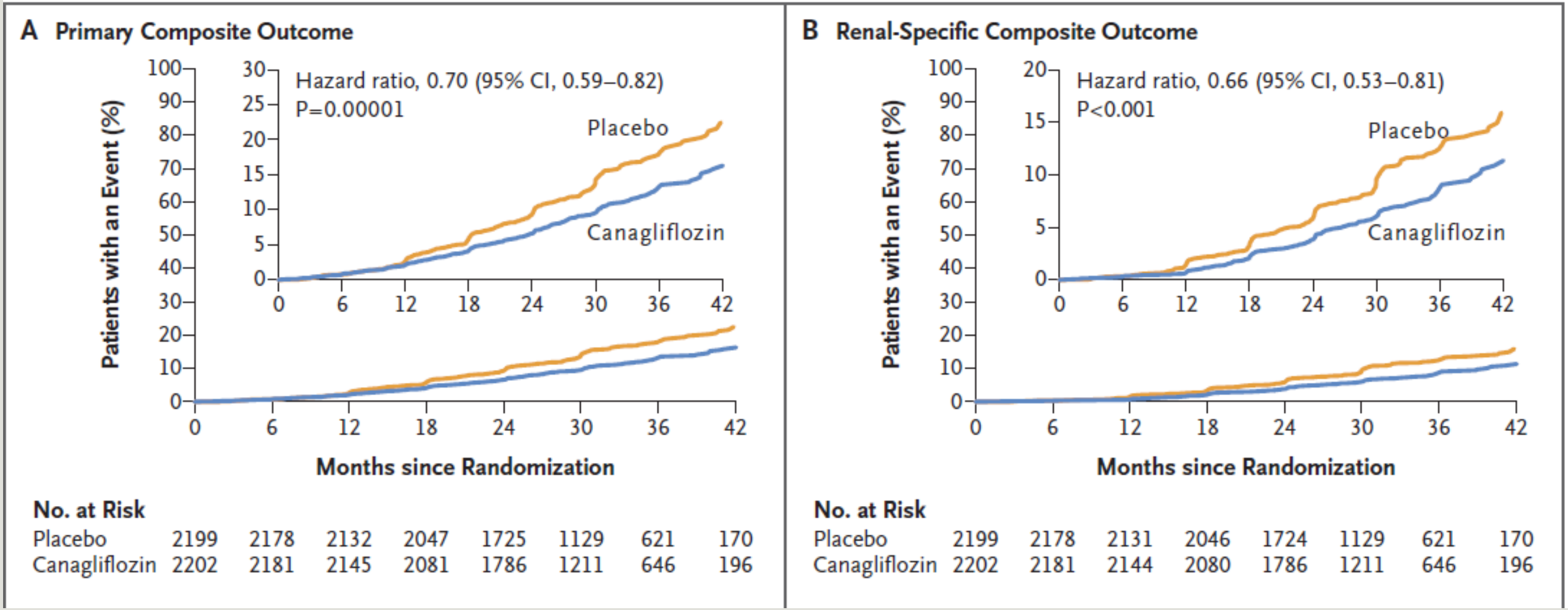
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

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)



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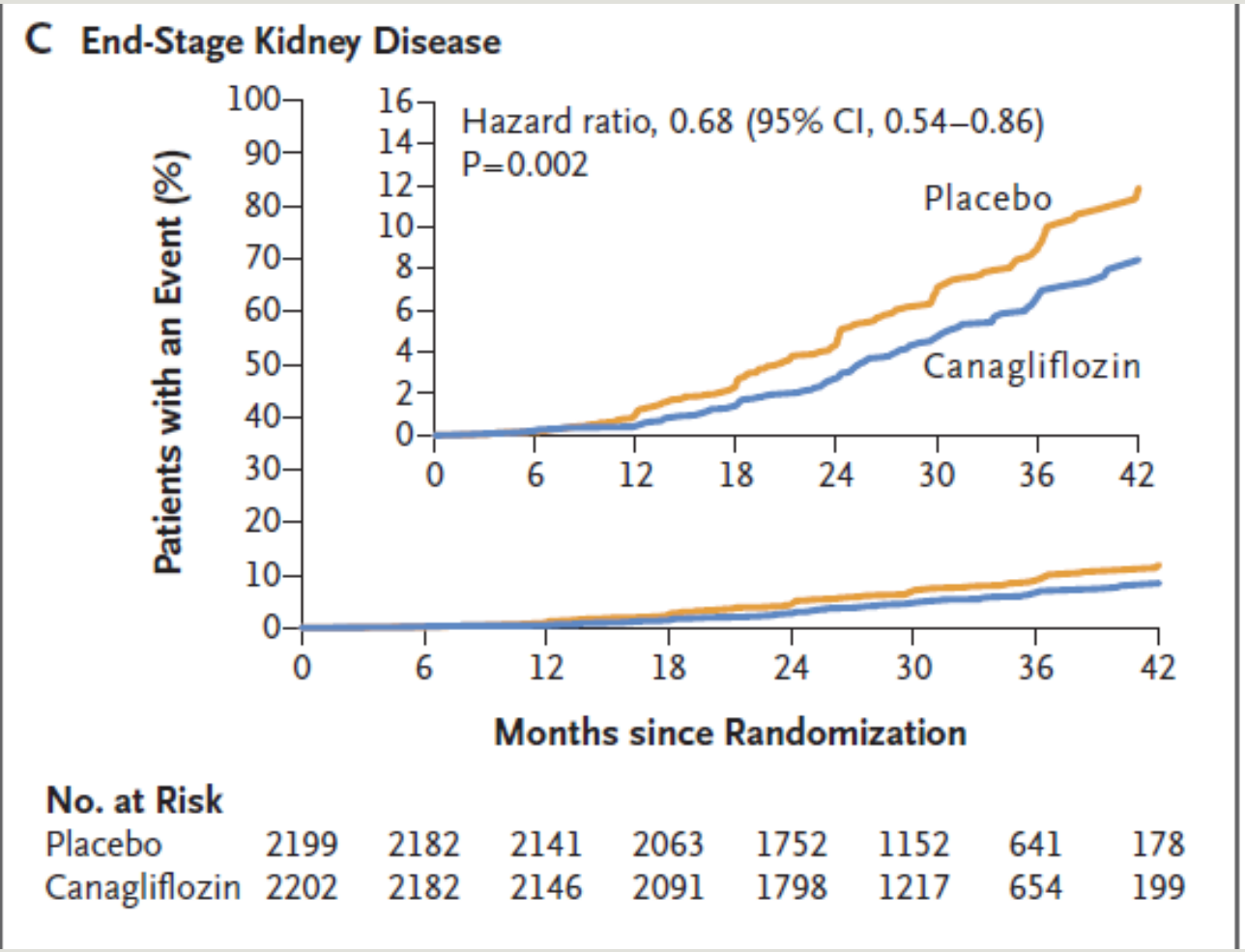

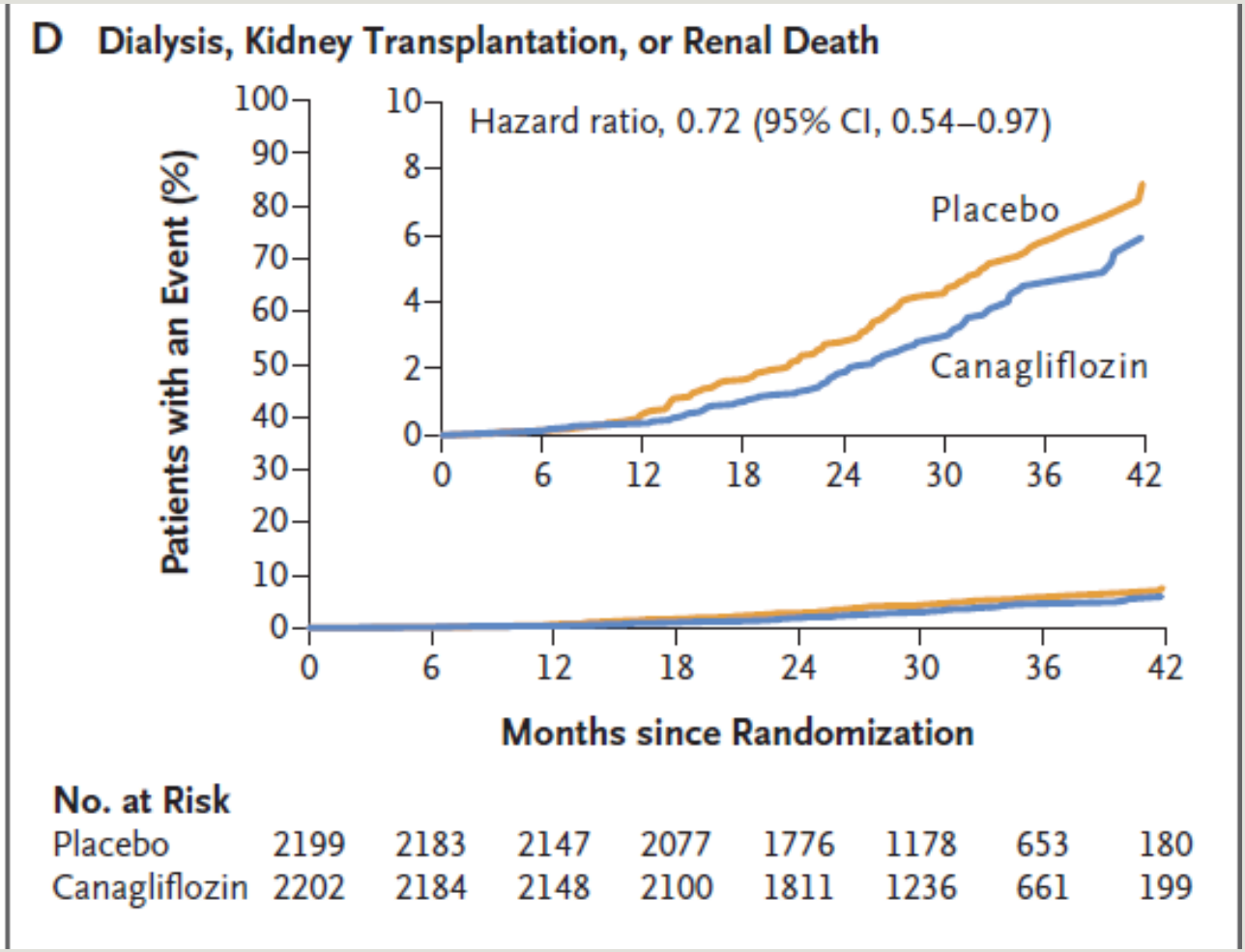

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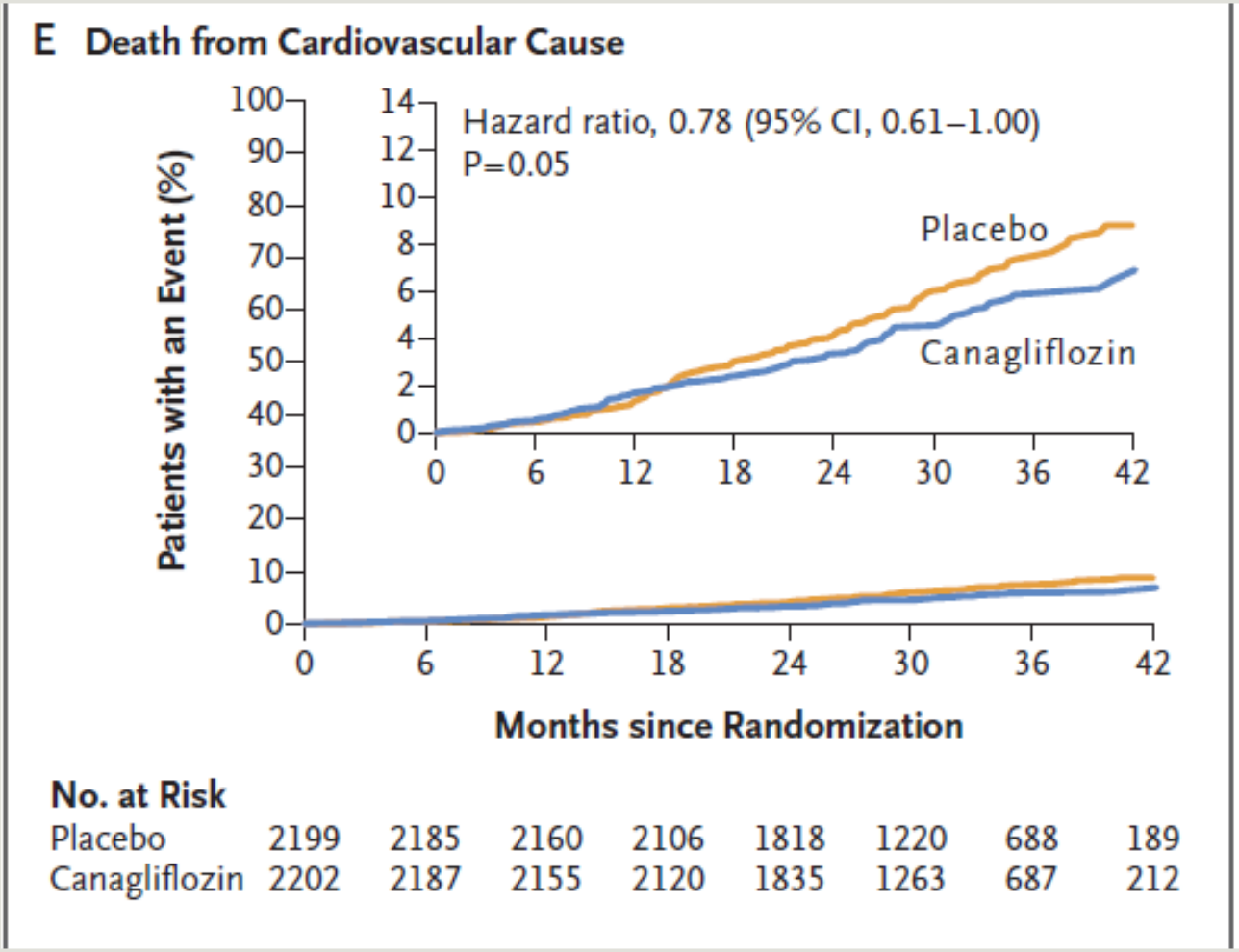

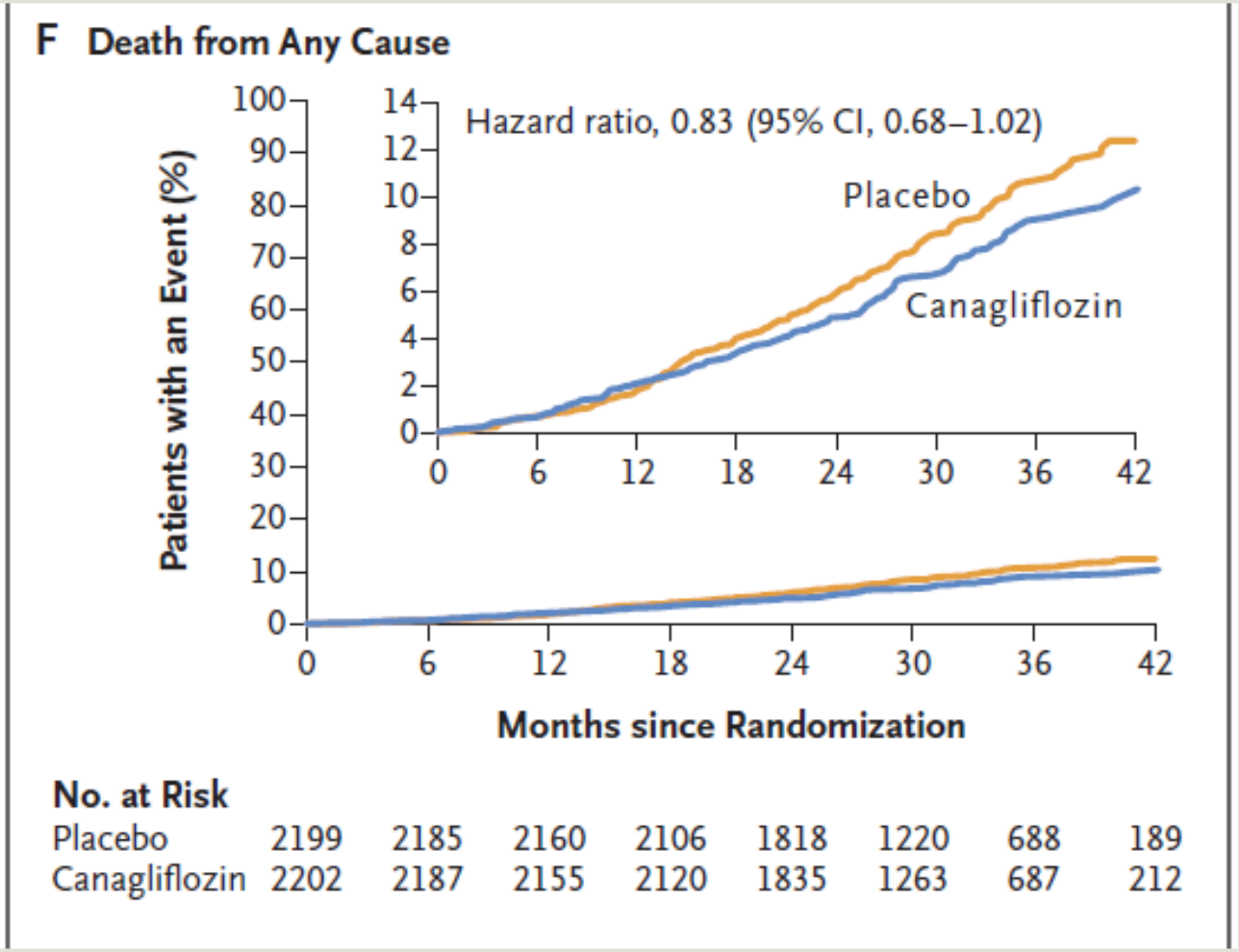

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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)	

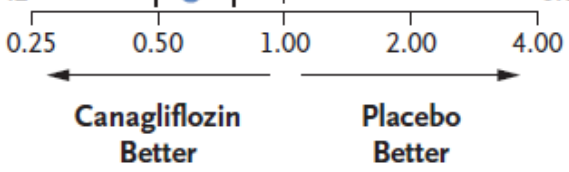
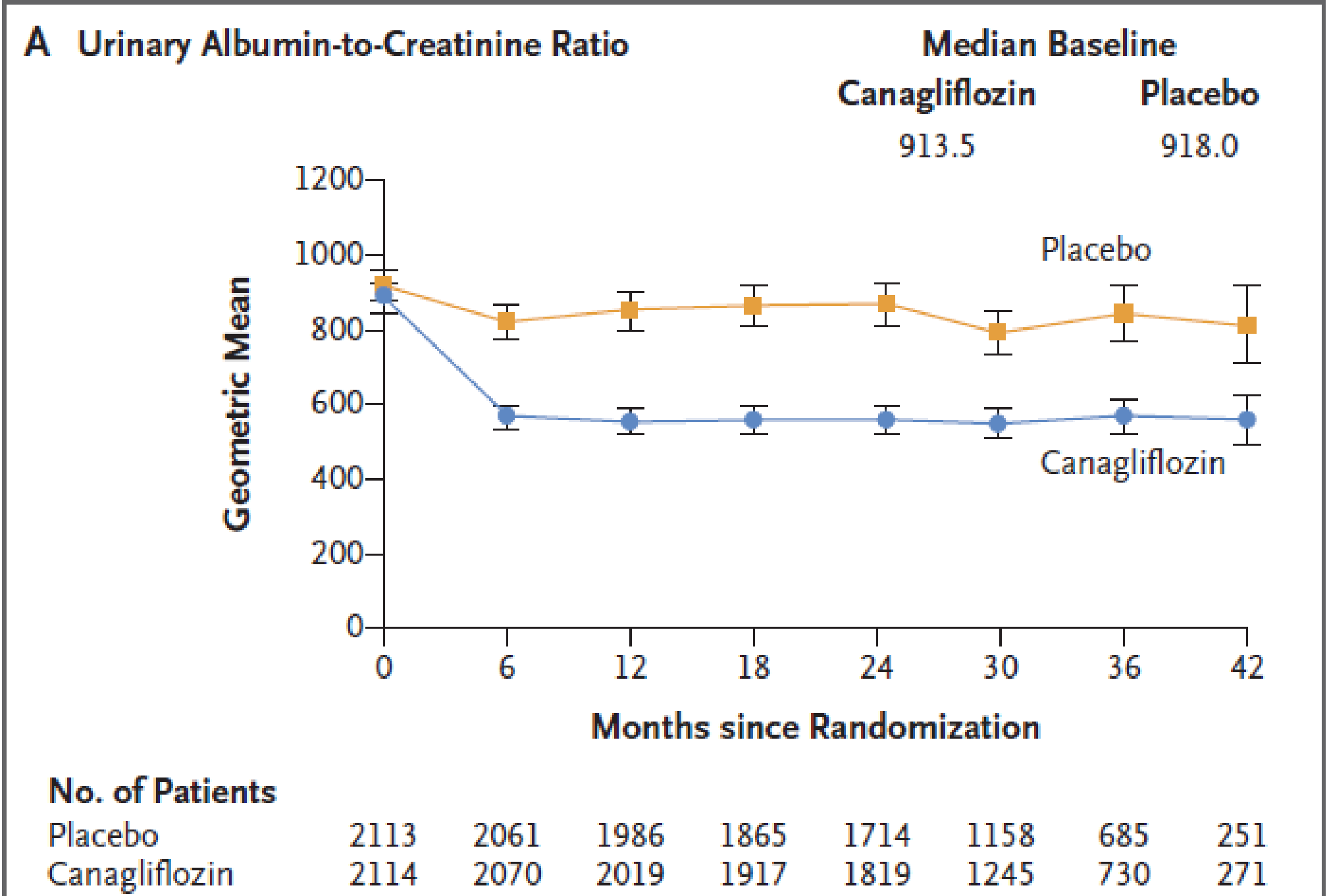


Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

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.



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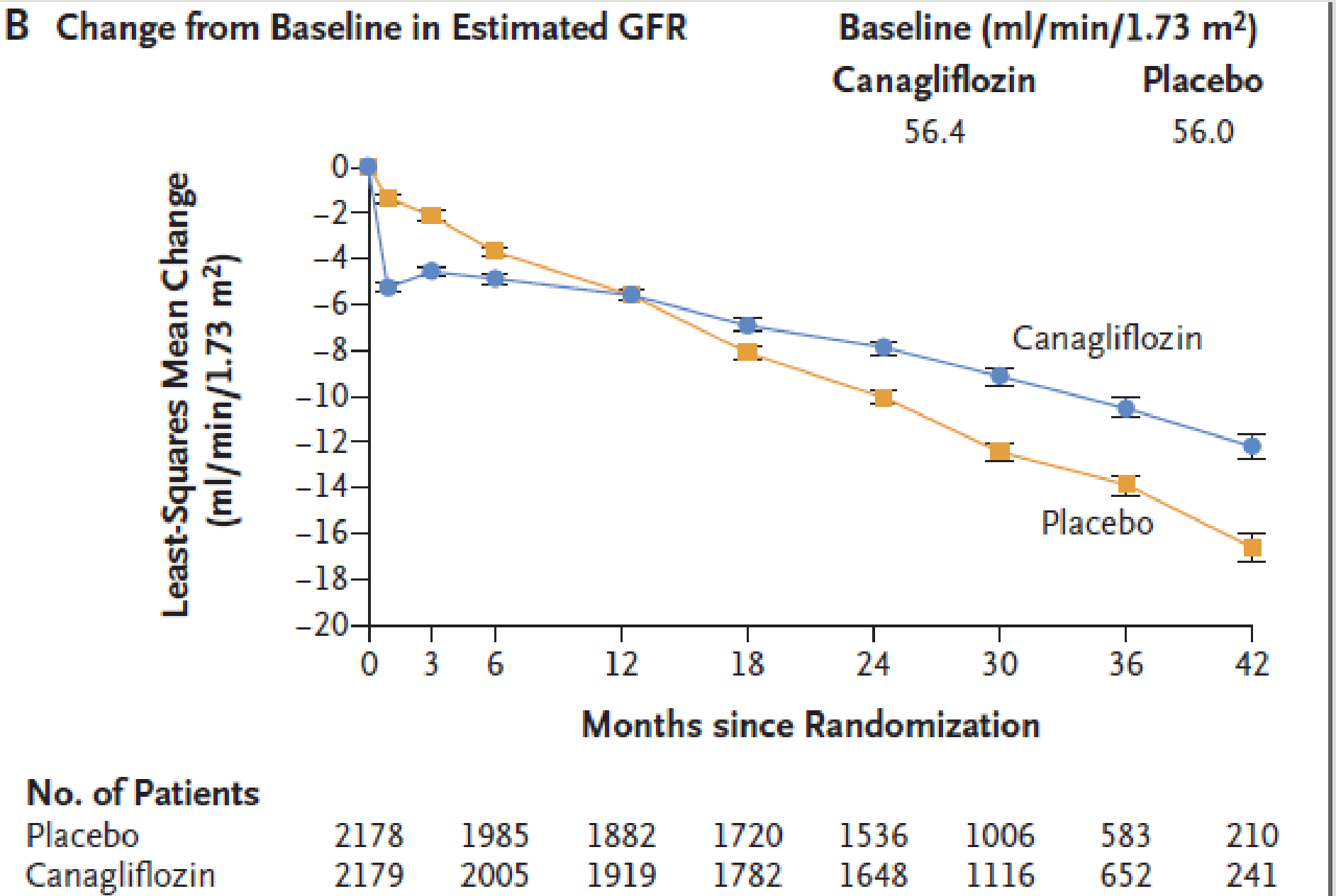

Figure 3. Effects on Albuminuria and Estimated GFR.

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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.)

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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

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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**

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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)

	Empagliflozin	Placebo	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)	

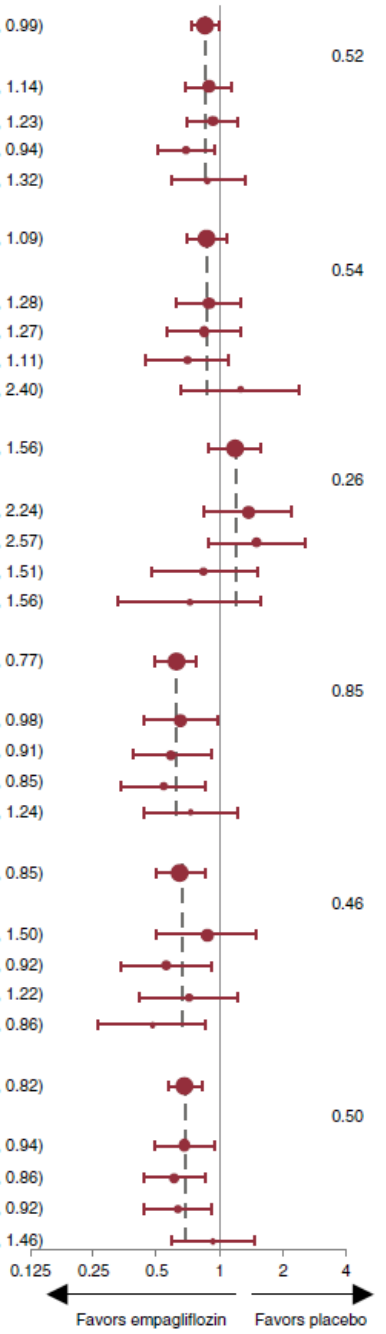

Figure 2. | **Forest plot showing that the risk reduction of cardiovascular outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.** *Sixty-eight patients were excluded as the subgroup variable was missing. 95% CI, 95% confidence interval; MACE, major adverse cardiovascular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

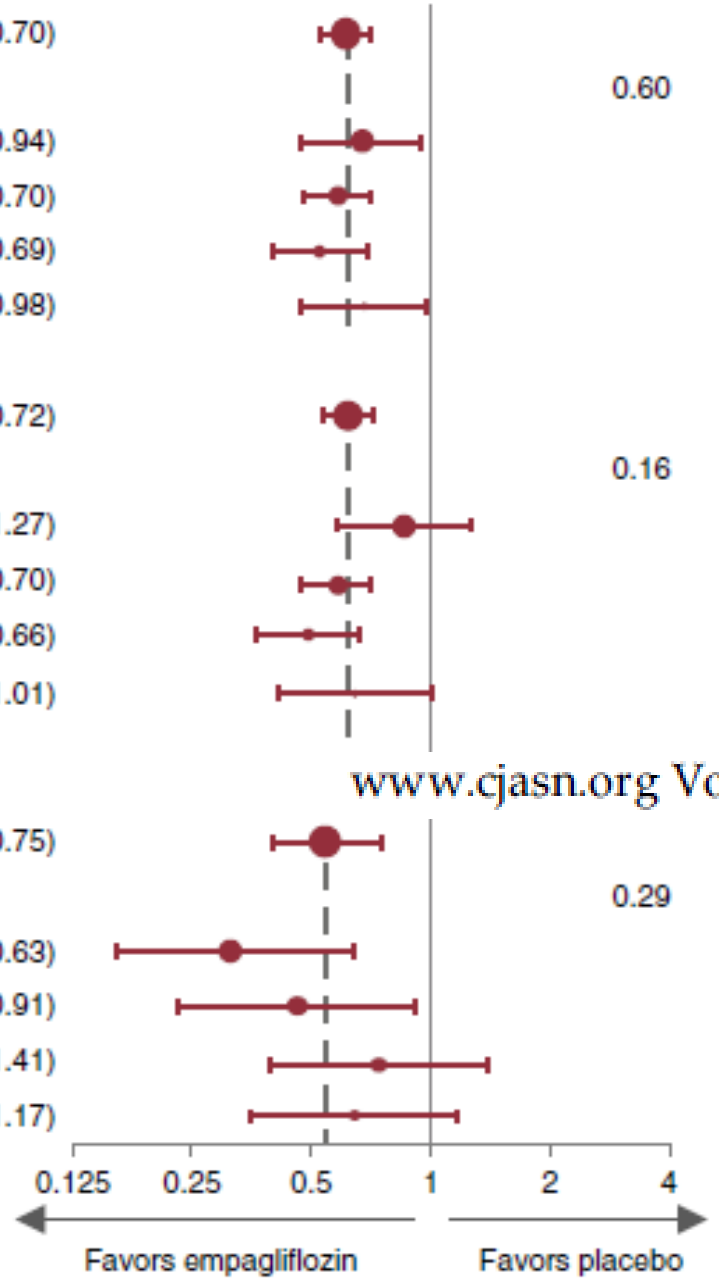

Figure 3. | **Forest plot showing that the risk reduction of kidney outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.** Cox regression analysis in patients treated with one or more doses of study drug. *Sixty-eight patients were excluded as the subgroup variable was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

www.cjasn.org Vol 15 October, 2020

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.

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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

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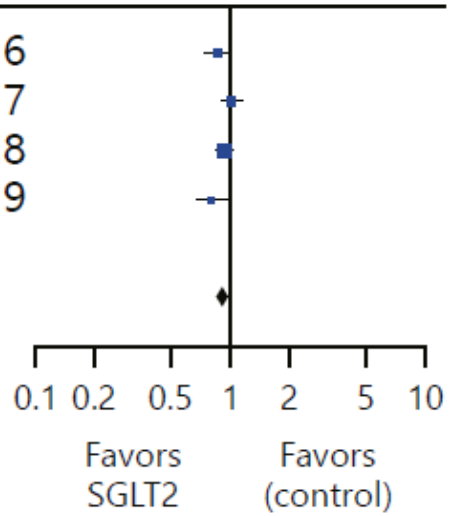
Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	490	4,687	282	2,333	19.5	0.86 (0.75, 0.99)	2016
CANVAS	585	5,795	426	4,347	25.1	1.03 (0.92, 1.16)	2017
DECLARE-TIMI 58	756	8,582	803	8,578	41.5	0.94 (0.86, 1.03)	2018
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.

Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	176	1,212	99	607	35.7	0.89 (0.71, 1.12)	2016
CANVAS	134	1,110	127	929	37.4	0.88 (0.70, 1.11)	2017
DECLARE-TIMI 58	85	606	104	659	26.9	0.89 (0.68, 1.16)	2018
CREDENCE	0	0	0	0		Not estimable	2019
Total (95% CI)		2,928		2,195	100.0	0.89 (0.77, 1.02)	
Total events	395		330				

Heterogeneity: $\chi^2 = 0.00$, df = 2, $p = 1.00$; $I^2 = 0\%$
Test for overall effect: $Z = 1.71$, $p = 0.09$

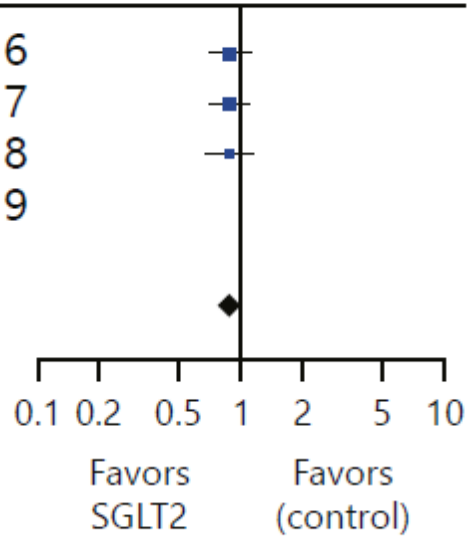


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Fig. 2. Forest plot for the composite cardiovascular outcome in patients with eGFR <60 mL/min/1.73 m^2 with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

CardioRenal Medicine
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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	81	4,645	71	2,323	13.5	0.57 (0.42, 0.78)	2016
CANVAS	124	5,795	125	4,347	20.4	0.74 (0.58, 0.95)	2017
DECLARE-TIMI 58	127	8,582	238	8,578	34.0	0.53 (0.43, 0.66)	2018
CREDENCE	153	2,202	224	2,199	32.0	0.68 (0.56, 0.83)	2019
Total (95% CI)		21,224		17,447	100.0	0.63 (0.56, 0.71)	
Total events	485		658				

Heterogeneity: $\chi^2 = 5.12$, df = 3, $p = 0.16$; $I^2 = 41\%$

Test for overall effect: $Z = 7.85$, $p < 0.00001$

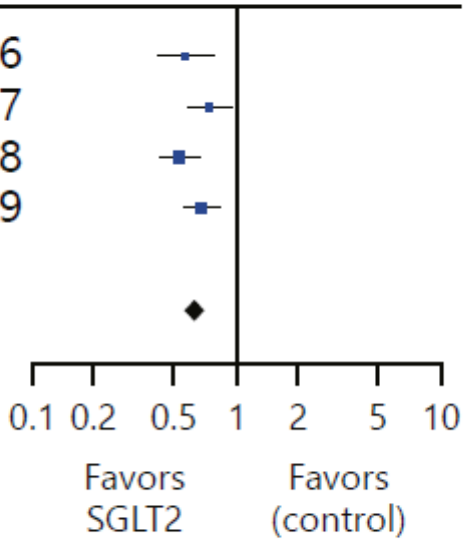

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Fig. 3. Forest plot for the composite renal outcome in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

CardioRenal Medicine

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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	207	998	161	507	45.0	0.65 (0.55, 0.78)	2016
CANVAS	43	1,110	40	929	9.2	0.90 (0.59, 1.37)	2017
DECLARE-TIMI 58	21	606	38	659	7.7	0.60 (0.36, 1.01)	2018
CREDENCE	118	1,297	181	1,295	38.2	0.65 (0.52, 0.81)	2019
Total (95% CI)		4,011		3,390	100.0	0.67 (0.59, 0.76)	
Total events	389		420				

Heterogeneity: $\chi^2 = 2.19$, df = 3, $p = 0.53$; $I^2 = 0\%$

Test for overall effect: $Z = 6.13$, $p < 0.00001$

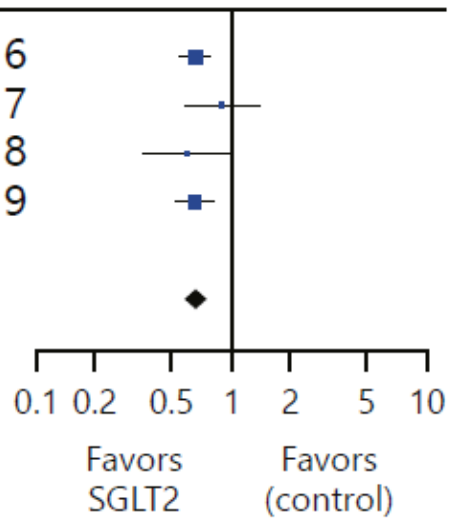

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Fig. 4. Forest plot for the composite renal outcome in patients with eGFR <60 mL/min/1.73 m^2 with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

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.

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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

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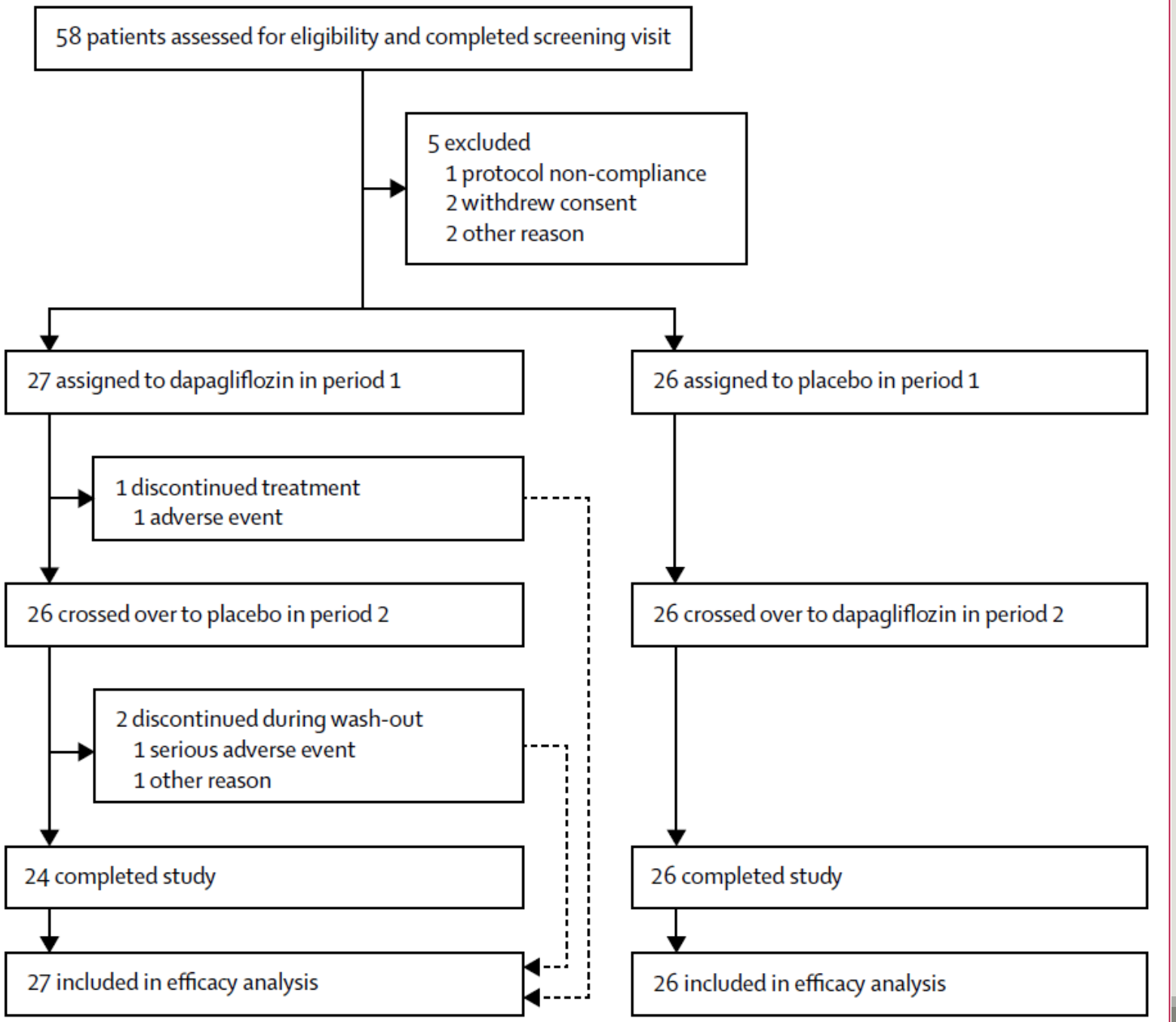

Figure 1: Trial profile

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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	Overall (n=53)	Placebo then dapagliflozin (n=26)	Dapagliflozin then placebo (n=27)
Age, years	51 (13)	51 (16)	52 (10)
Sex			
Female	17 (32%)	8 (31%)	9 (33%)
Male	36 (68%)	18 (69%)	18 (67%)
Ethnic origin			
Asian	17 (32%)	6 (23%)	11 (41%)
Hispanic	2 (4%)	0	2 (7%)
White	29 (55%)	17 (65%)	12 (44%)
Other	5 (9%)	3 (12%)	2 (7%)
Chronic kidney disease diagnosis			
IgA nephropathy	25 (47%)	14 (54%)	11 (41%)
FSGS	11 (21%)	3 (12%)	8 (30%)
Hypertensive nephropathy	7 (13%)	4 (15%)	3 (11%)
Other*	10 (19%)	5 (19%)	5 (19%)
Bodyweight, kg	83·0 (20·3)	79·6 (15·5)	86·2 (24·0)
BMI, kg/m²	28·0 (5·1)	27·2 (4·1)	28·8 (5·8)
Heart rate, beats per min	68·5 (13·7)	69·0 (15·6)	68·0 (12·0)
Systolic blood pressure, mm Hg	126·0 (14·8)	124·6 (13·1)	127·4 (16·4)
Diastolic blood pressure, mm Hg	76·2 (8·2)	75·2 (7·8)	77·2 (8·7)
HbA_{1c}, %	5·6 (0·4)	5·6 (0·4)	5·6 (0·5)
HbA_{1c}, mmol/mol	37·6 (4·7)	37·7 (4·3)	37·4 (5·1)
HDL cholesterol, mmol/L	1·3 (0·5)	1·2 (0·3)	1·4 (0·7)
LDL cholesterol, mmol/L	2·8 (0·9)	2·7 (1·0)	2·8 (0·8)
Haemoglobin, g/L	134·6 (20·4)	134·4 (20·8)	134·8 (20·4)
mGFR, mL/min per 1·73 m²†	58·3 (23·0)	57·8 (25·5)	58·9 (20·7)
≤60	33 (62%)	17 (65%)	16 (59%)
>60	20 (38%)	9 (35%)	11 (41%)
Proteinuria, mg per 24 h†	1110·0 (730·0–1560·0)	1105·0 (720·0–1530·0)	1170·0 (730·0–1690·0)
<1000	20 (38%)	11 (42%)	9 (33%)
≥1000	33 (62%)	15 (58%)	18 (67%)
Albuminuria, mg per 24 h	856·5 (559·5–1225·0)	844·0 (538·0–1142·0)	891·0 (599·0–1338·0)
Medication use			
ACE inhibitor	31 (58%)	16 (62%)	15 (56%)
Angiotensin receptor blocker	22 (42%)	10 (38%)	12 (44%)
Diuretic	14 (26%)	8 (31%)	6 (22%)
NSAID	2 (4%)	1 (4%)	1 (4%)
Vitamin D analogue	12 (23%)	9 (35%)	3 (11%)
Corticosteroids	4 (8%)	2 (8%)	2 (7%)

Data are n (%), mean (SD), or median (IQR). FSGS=focal segmental glomerulosclerosis. mGFR=measured glomerular filtration rate. ACE=angiotensin-converting enzyme. NSAID=non-steroidal anti-inflammatory drug. *Other diagnoses were Alport syndrome (n=2), VATER syndrome (n=1), membranous nephropathy (n=1), collagen 4 mutation (n=1), and unknown (n=6). †Further categories of mGFR and proteinuria are presented in the appendix (p 58).

Table 1: **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

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	Placebo	Dapagliflozin
NT-proBNP		
n	50	52
Baseline mean (SD), ng/L	125·0 (161·1)	118·8 (151·2)
Week 6 mean (SD), ng/L	152·6 (277·7)	108·7 (148·7)
Adjusted mean change from baseline (95% CI), %*	1·1% (–13·3 to 17·9)	–14·9% (–26·9 to –1·0)
Difference in mean change vs placebo (95% CI; p value), %*	..	–15·8% (–32·2 to 4·5; p=0·18)
Urine adenosine†		
n	50	51
Baseline mean (SD), µmol/mmol	0·19 (0·15)	0·20 (0·16)
Week 6 mean (SD), µmol/mmol	0·24 (0·25)	0·22 (0·17)
Adjusted mean change from baseline (95% CI), µmol/mmol	0·04 (–0·02 to 0·10)	0·02 (–0·04 to 0·08)
Difference in adjusted mean change vs placebo (95% CI; p value), µmol/mmol	..	–0·02 (–0·11 to 0·06; p=0·57)
Urine thromboxane B2†		
n	50	51
Baseline mean (SD), pg/mmol	0·096 (0·047)	0·092 (0·057)
Week 6 mean (SD), pg/mmol	0·093 (0·050)	0·106 (0·101)
Adjusted mean change from baseline (95% CI), pg/mmol	–0·003 (–0·023 to 0·018)	0·015 (–0·006 to 0·035)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0·017 (–0·012 to 0·047; p=0·24)
Urine 6-keto prostaglandin F1α†		
n	50	51
Baseline mean (SD), pg/mmol	0·117 (0·040)	0·117 (0·042)
Week 6 mean (SD), pg/mmol	0·120 (0·055)	0·128 (0·045)
Adjusted mean change from baseline (95% CI), pg/mmol	0·005 (–0·007 to 0·017)	0·011 (–0·001 to 0·023)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0·006 (–0·011 to 0·023; p=0·50)
Urine prostaglandin E2†		
n	50	51
Baseline mean (SD), pg/mmol	0·098 (0·103)	0·113 (0·150)
Week 6 mean (SD), pg/mmol	0·095 (0·143)	0·170 (0·266)
Adjusted mean change from baseline (95% CI), pg/mmol	–0·002 (–0·051 to 0·047)	0·057 (0·008 to 0·105)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0·059 (–0·010 to 0·128; p=0·092)
Urine PGEM†		
n	50	51
Baseline mean (SD), pg/mmol	0·095 (0·055)	0·100 (0·056)
Week 6 mean (SD), pg/mmol	0·096 (0·057)	0·097 (0·054)
Adjusted mean change from baseline (95% CI), pg/mmol	0·002 (–0·006 to 0·011)	–0·002 (–0·010 to 0·007)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	–0·004 (–0·016 to 0·008; p=0·50)

n is the number with data available. NT-proBNP=N-terminal pro B-type natriuretic peptide. PGEM=prostaglandin E2 metabolite. *Log-transformed data were back-transformed using the formula: 1– exponent(log value)×–100. †Biomarkers were corrected for urine creatinine.

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	Placebo (n=52)*	Dapagliflozin (n=53)
Any adverse event	13 (25%)	17 (32%)
Adverse event leading to study drug discontinuation†	0	1 (2%)
Any serious adverse event‡	1 (2%)	1 (2%)
Serious adverse event leading to study drug discontinuation	1 (2%)	0
Death	0	0
Adverse event of special interest		
Kidney-related adverse event§	0	1 (2%)
Urinary tract infection	0	1 (2%)
Genital infection	0	1 (2%)
Volume depletion		
Hypotension	1 (2%)	0
Dizziness	1 (2%)	0
Amputations	0	0
Fractures	0	1 (2%)
Diabetic ketoacidosis	0	0
Hypoglycaemia	0	0

Data are number of patients (%) with one or more adverse event of the specified type. *One patient discontinued the study during the first treatment period with dapagliflozin; this patient did not start the placebo treatment period and was therefore not included in the safety assessments for the placebo group. †The adverse event leading to discontinuation was swelling of the left foot. ‡The two serious adverse events were cellulitis (during placebo treatment) and colon cancer (during dapagliflozin treatment). §The kidney-related adverse event was investigator-reported acute kidney injury.

Table 3: Adverse events

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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	Placebo	Dapagliflozin
Fasting plasma glucose		
n	52	52
Baseline mean (SD), mmol/L	5·5 (0·7)	5·6 (1·2)
Week 6 mean (SD), mmol/L	5·4 (0·7)	5·3 (0·7)
Adjusted mean change from baseline (95% CI), mmol/L	−0·1 (−0·3 to 0·1)	−0·3 (−0·5 to −0·1)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	−0·2 (−0·5 to 0·1; p=0·16)
Haemoglobin		
n	51	53
Baseline mean (SD), g/L	134·5 (20·2)	133·3 (19·4)
Week 6 mean (SD), g/L	131·8 (21·0)	136·7 (18·2)
Adjusted mean change from baseline (95% CI), g/L	−2·3 (−4·1 to −0·4)	3·0 (1·2 to 4·8)
Difference in adjusted mean change *vs* placebo (95% CI; p value), g/L	..	5·3 (2·7 to 7·9; p<0·0001)
Haematocrit		
n	52	53
Baseline mean (SD), L/L	0·40 (0·05)	0·40 (0·06)
Week 6 mean (SD), L/L	0·39 (0·06)	0·41 (0·05)
Adjusted mean change from baseline (95% CI), L/L	−0·01 (−0·01 to −0·002)	0·01 (0·01 to 0·02)
Difference in adjusted mean change *vs* placebo (95% CI; p value), L/L	..	0·02 (0·01 to 0·03; p<0·0001)
Estimated glomerular filtration rate		
n	52	52
Baseline mean (SD), mL/min per 1·73 m²	59·9 (28·0)	57·4 (26·7)
Week 6 mean (SD), mL/min per 1·73 m²	59·2 (28·8)	57·2 (27·9)
Adjusted mean change from baseline (95% CI), mL/min per 1·73 m²	−0·8 (−2·5 to 0·9)	−1·8 (−3·5 to −0·1)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mL/min per 1·73 m²	..	−1·0 (−3·4 to 1·4; p=0·42)
Potassium		
n	52	53
Baseline mean (SD), mmol/L	4·2 (0·4)	4·1 (0·4)
Week 6 mean (SD), mmol/L	4·2 (0·4)	4·1 (0·4)
Adjusted mean change from baseline (95% CI), mmol/L	0·02 (−0·06 to 0·10)	0·00 (−0·08 to 0·08)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	−0·02 (−0·13 to 0·10; p=0·78)
Calcium		
n	52	52
Baseline mean (SD), mmol/L	2·3 (0·1)	2·3 (0·1)
Week 6 mean (SD), mmol/L	2·3 (0·1)	2·3 (0·1)
Adjusted mean change from baseline (95% CI), mmol/L	−0·01 (−0·03 to 0·02)	0·01 (−0·02 to 0·03)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	0·01 (−0·02 to 0·04; p=0·55)
Phosphate		
n	51	51
Baseline mean (SD), mmol/L	1·0 (0·2)	1·0 (0·2)
Week 6 mean (SD), mmol/L	1·1 (0·2)	1·1 (0·2)
Adjusted mean change from baseline (95% CI), mmol/L	0·01 (−0·04 to 0·06)	0·05 (−0·002 to 0·09)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	0·03 (−0·03 to 0·01; p=0·30)
Total protein		
n	49	51
Baseline mean (SD), g/L	68·7 (5·7)	68·8 (5·5)
Week 6 mean (SD), g/L	68·9 (6·0)	70·3 (6·2)
Adjusted mean change from baseline (95% CI), g/L	0·05 (−0·98 to 1·09)	1·13 (0·12 to 2·14)
Difference in adjusted mean change *vs* placebo (95% CI; p value), g/L	..	1·08 (−0·37 to 2·53; p=0·14)
HDL cholesterol		
n	52	53
Baseline mean (SD), mmol/L	1·3 (0·3)	1·3 (0·5)
Week 6 mean (SD), mmol/L	1·2 (0·3)	1·2 (0·3)
Adjusted mean change from baseline (95% CI), mmol/L	−0·03 (−0·13 to 0·08)	−0·10 (−0·20 to 0·00)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	−0·07 (−0·22 to 0·07; p=0·31)
LDL cholesterol		
n	52	53
Baseline mean (SD), mmol/L	2·7 (0·9)	2·6 (0·8)
Week 6 mean (SD), mmol/L	2·7 (0·9)	2·6 (0·8)
Adjusted mean change from baseline (95% CI), mmol/L	−0·07 (−0·21 to 0·07)	−0·06 (−0·20 to 0·08)
Difference in adjusted mean change *vs* placebo (95% CI; p value), mmol/L	..	0·02 (−0·18 to 0·21; p=0·88)

n is the number of patients with available measurements.

Table 4: **Changes in exploratory biochemical parameters during placebo and dapagliflozin treatment at 6 weeks**

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)**	

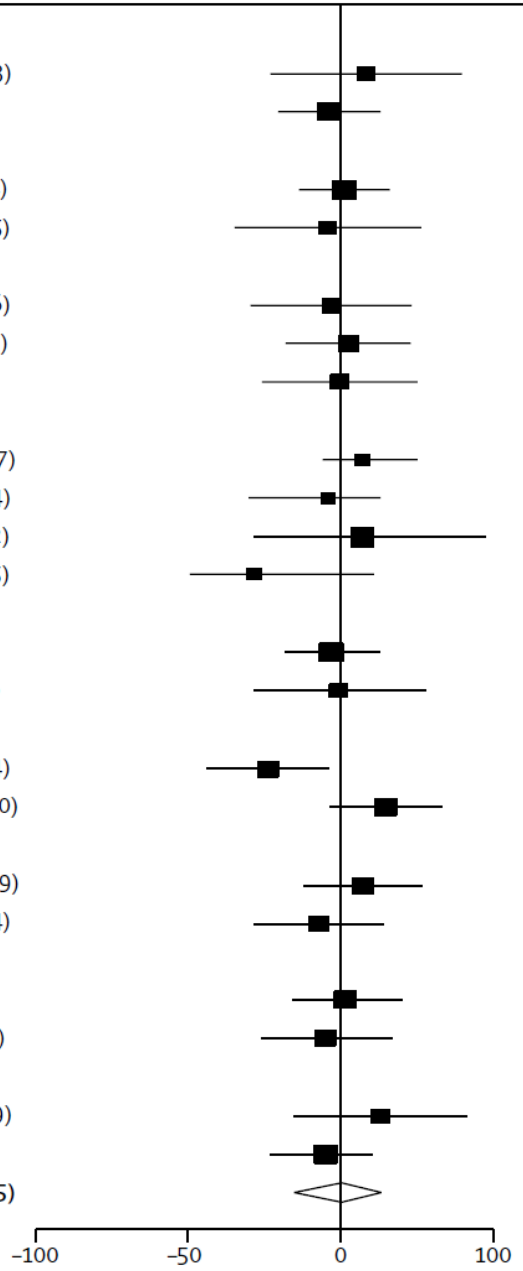

Figure 4: Effects of dapagliflozin on 24-h proteinuria in patient subgroups defined by baseline characteristics

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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Although originally intended to treat diabetes, cardiovascular outcome trials of SGLT2 inhibitors showed a profound reduction in cardiovascular mortality and heart failure hospitalization in diabetic patients, and more recently, also in nondiabetic heart failure patients. Interestingly, some of the cardiovascular benefits of SGLT2 inhibitors might be because of off-target, non-antihyperglycemic effects.[2] Although these mechanisms remain elusive, evidence suggests that SGLT2 inhibitors can directly or indirectly act on cardiac, renal, endothelial, and immune cells, or systemically, to reduce inflammation.[2] In fact, we recently reported that use of empagliflozin reduced cardiac inflammation in a model of heart failure,[3] and lessened renal damage, systemic inflammation, and mortality in a model of sepsis.[4] Heart failure and

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Similarly, it has been reported that macrophage interleukin-1β and tumour necrosis factor α secretion is also reduced in patients treated with SGLT2 inhibitors. This is relevant for COVID-19 when considering that endothelial/organ damage caused by SARS-CoV-2 results in immune cell activation and cytokine secretion, which can be reduced with the anti-inflammatory properties of SGLT2 inhibitors. Thus, SGLT2 inhibitors might potentially improve outcomes in COVID-19 patients by reducing the organ and/or systemic inflammatory response. This rationale led to the initiation of


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COMMENTARY

SGLT2 inhibition and COVID-19: The road not taken

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Keywords: ACE2, COVID-19, cytokine storm, SGLT2 inhibitors, sodium hydrogen exchanger

1 | INTRODUCTION

'Two roads diverged in a wood and I…

I took the one less travelled by,

And that has made all the difference'.

SGLT2 inhibitors (SGLT2i) are oral antidiabetic drugs that cause glycosuria, natriuresis and diuresis by inhibiting the sodium-glucose co-transporters in renal tubules. Substantial evidence supports their cardiovascular and renal benefits conferred by reduction in plasma glucose, blood pressure and weight, which in turn, outweigh their modest effect on glycaemia. Cumulative cardiorenal outcomes from large, randomised, placebo-controlled trials (>30 000 participants) have shown reduction in major adverse cardiovascular

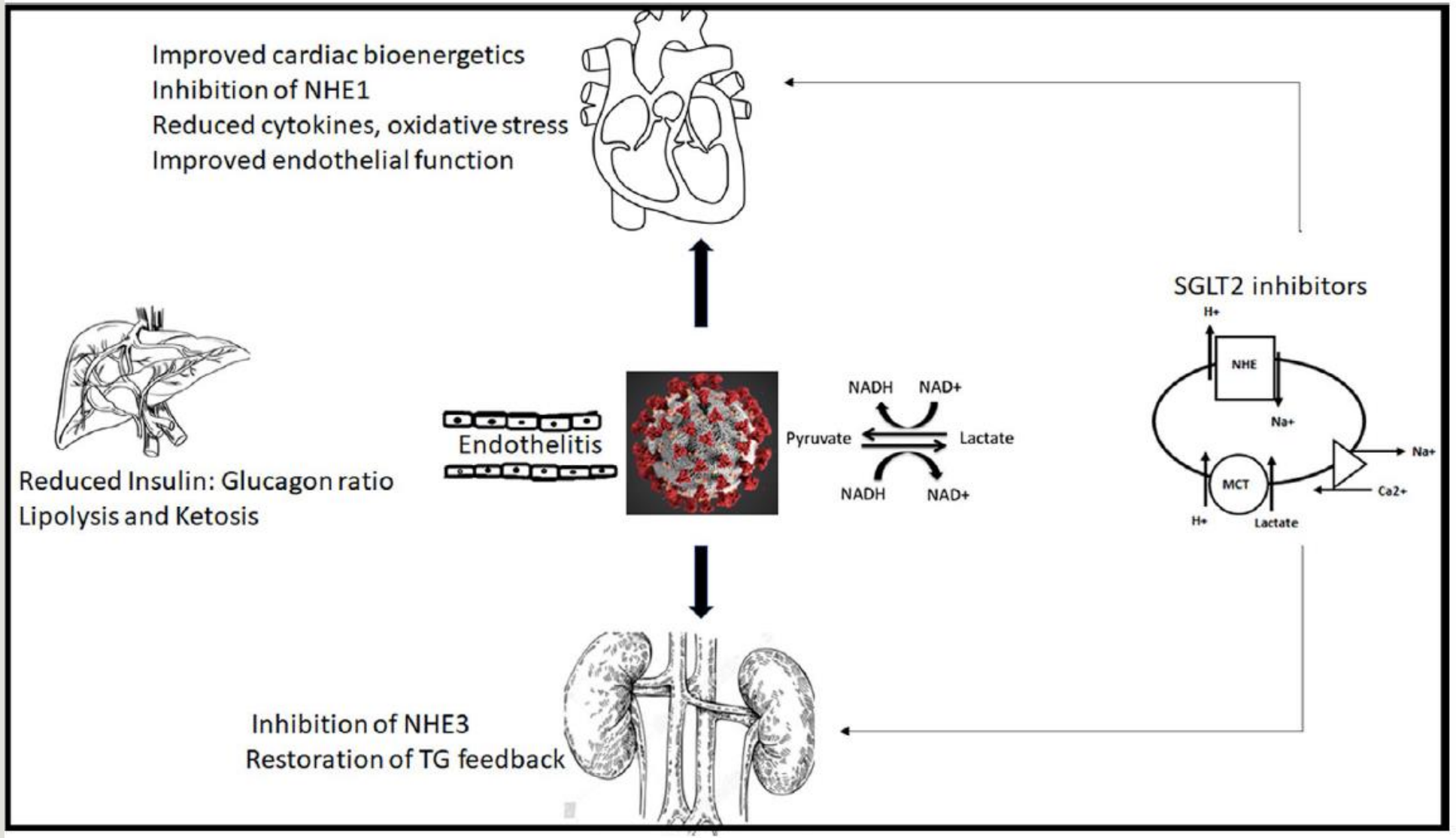

FIGURE 1 Schematic representation of the proposed pathophysiology of COVID-19 induced cardiac and renal dysfunction induced by endothelitis and increased lactate production under conditions of impaired tissue oxygenation induced anaerobic glycolysis which leads to increased cellular entry of H + along with lactate, leading to activation of the sodium hydrogen exchanger (NHE), sodium accumulation and cell oedema and destruction. SGLT2 inhibitors, apart from having beneficial effects on multiple cardiovascular risk factors (diabetes, hypertension and obesity) which predispose to adverse outcomes in COVID-19, may possibly have benefits in acute decompensated states by inhibiting the NHE, decreasing lactate and improving endothelial function. MCT, Monocarboxylate transporter (H + lactate symporter); NHE, sodium hydrogen exchanger;

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Review

COVID-19 in diabetic patients: Related risks and specifics of management

COVID-19 chez les patients diabétiques : risques associés et spécificités de prise en charge

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Diabetes is among the most frequently reported comorbidities in patients infected with COVID-19. According to current data, diabetic patients do not appear to be at increased risk of contracting SARS-CoV-2 compared to the general population. On the other hand, diabetes is a risk factor for developing severe and critical forms of COVID-19, the latter requiring admission to an intensive care unit and/or use of invasive mechanical ventilation, with high mortality rates. The characteristics of diabetic patients at risk for developing severe and critical forms of COVID-19, as well as the prognostic impact of diabetes on the course of COVID-19, are under current investigation. Obesity, the main risk factor for incident type 2 diabetes, is more common in patients with critical forms of COVID-19 requiring invasive mechanical ventilation. On the other hand, COVID-19 is usually associated with poor glycemic control and a higher risk of ketoacidosis in diabetic patients. There are currently no recommendations in favour of discontinuing antihypertensive medications that interact with the renin-angiotensin-aldosterone system. Metformin and SGLT2 inhibitors should be discontinued in patients with severe forms of COVID-19 owing to the risks of lactic acidosis and ketoacidosis. Finally, we advise for systematic screening for (pre)diabetes in patients with proven COVID-19 infection.