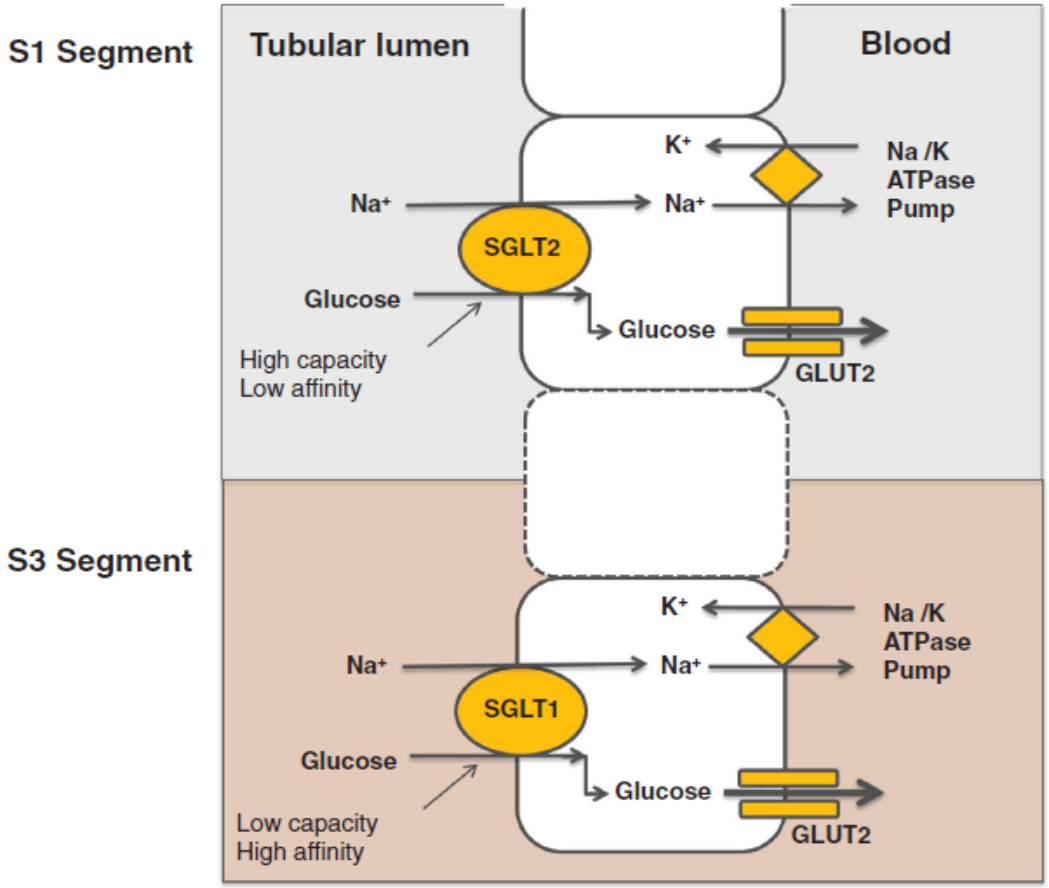
Updates 0n SGL2 Inhibitors In CKD

Farahnaz Dadras ,MD

Iran University Of Medical Sciences

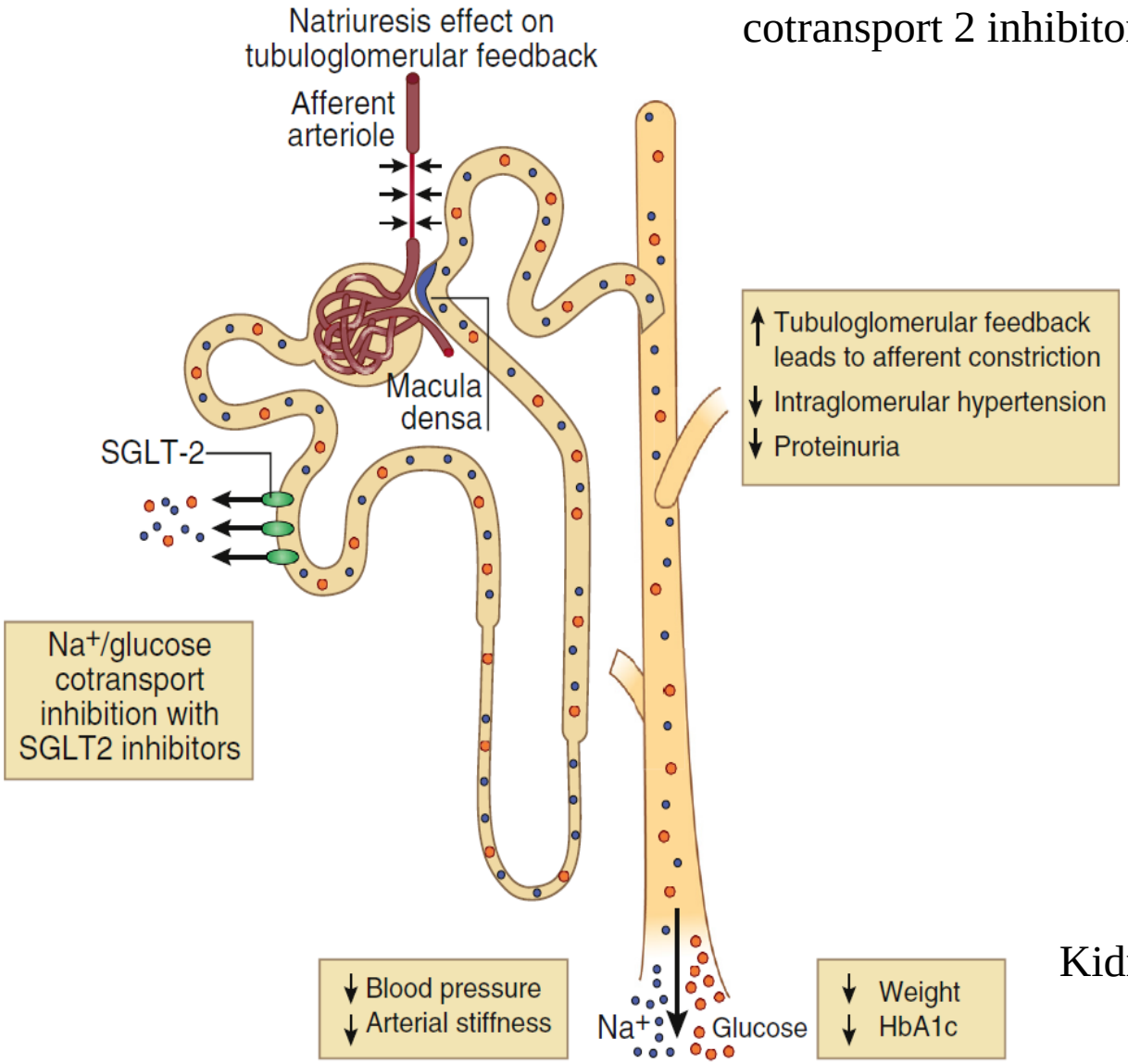
Mechanism of renal glucose transport in proximal tubule



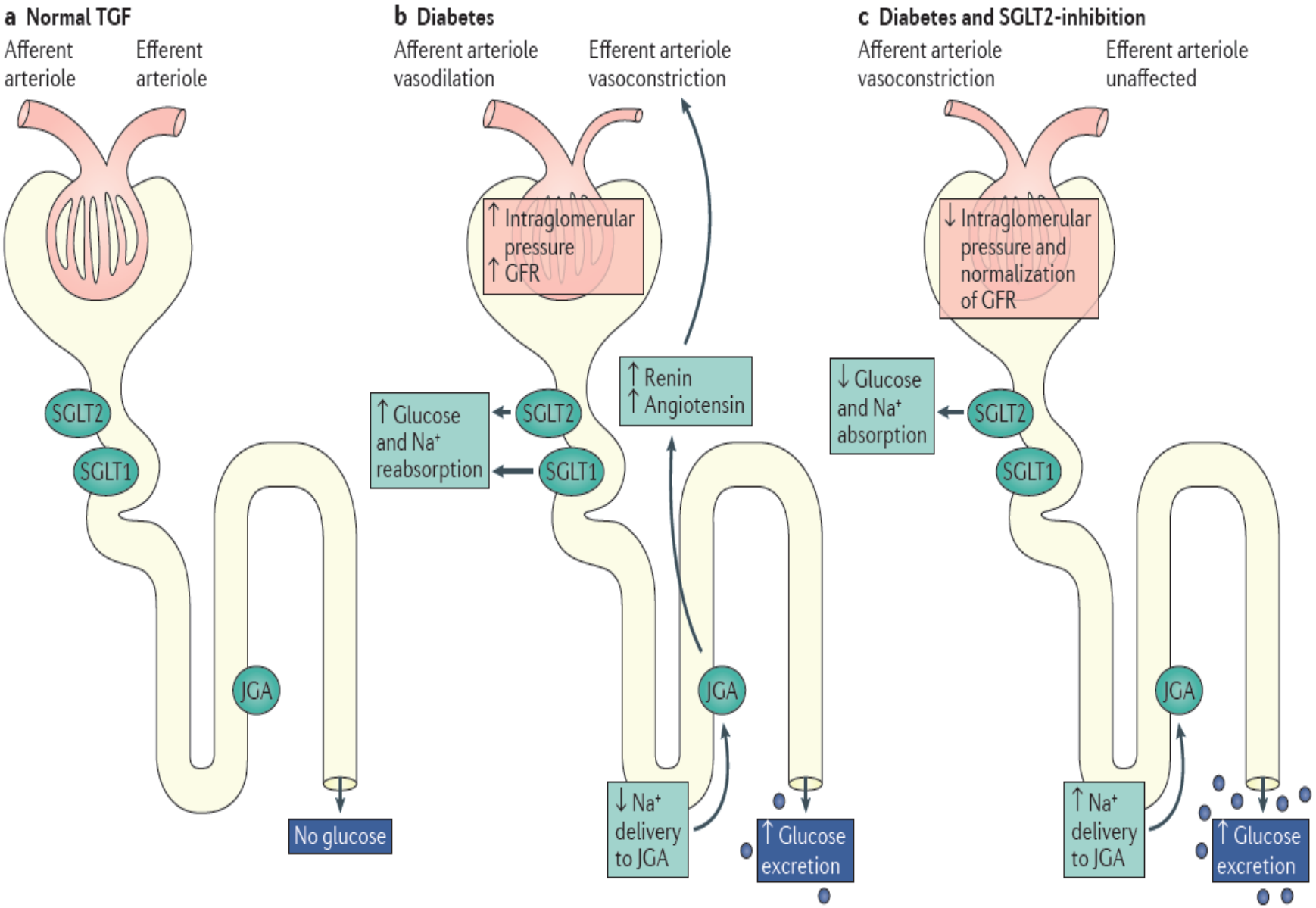
Mechanisms of renal glucose transport in the proximal tubule

- John F

Mechanism of action of sodium glucose cotransport 2 inhibitors



Kidney International (2018)



De Fronzo et al. Nat Rev Nephrol 2017;1:11

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SUPPLEMENTARY ARTICLE

A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors

Emily Brown | Surya P. Rajeev | Daniel J. Cuthbertson | John P. H. Wilding

- Diabetes Obes Metab. 2019;21(Suppl. 2):9–18.

SGL2i AND THEIR CLINICAL EFFECTS

- SGL2 inhibition results in 70 to90 g of UGE
- Energy loss of about 300 kcal/d.
- SGL2i reduce blood glucose & HbA1c between 0.6% to 1%
- Weight loss of around 2 to 3 kg is expected
- Modest reduction in blood pressure(2-3mmHg of systolic BP).

Emily Brown, et al . Diabetes Obes Metab. 2019;21(Suppl. 2):9–18.

Effects on energy balance

The glucosuria and osmotic diuresis reduce glycaemia and body weight.

The reduction in steatosis, visceral and subcutaneous adipose tissue accounts for the late effects on bodyweight.

Emily Brown, et al . Diabetes Obes Metab. 2019;21(Suppl. 2):9–18

The reduction in insulin levels secondary to SGLT2 inhibition also results in lipolysis and an increase in circulating free fatty acids (FFA).

- This influx of FFA is directed into ketogenesis
- in the liver resulting in production of ketone
- bodies which is taken up by most tissues including heart.
- This has been postulated one of the reasons for the cardio protective effect of SGLT2i.

- Marc Evans. Diabetes Ther (2019) 10:1719–1731

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

SGLT2 Inhibition by Empagliflozin Promotes Fat Utilization and Browning and Attenuates Inflammation and Insulin Resistance by Polarizing M2 Macrophages in Diet-induced Obese Mice

Liang Xu [a], Naoto Nagata [a], Mayumi Nagashimada [a], Fen Zhuge [a], Yinhua Ni [a], Guanliang Chen [a], Eric Mayoux [b], Shuichi Kaneko [c], Tsuguhito Ota [a,c,*]

[a] Department of Cell Metabolism and Nutrition, Brain/Liver Interface Medicine Research Center, Kanazawa University, Kanazawa, Ishikawa 920-8640, Japan
[b] Boehringer-Ingelheim, Cardio-metabolic Diseases Research, Biberach, Germany
[c] Department of System Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa 920-8640, Japan

- More recently, skin sodium content has been closely associated with left ventricular mass and systolic blood pressure.

- With 23Na-magnetic resonance imagingstudies suggest
- that the skin may act as a buffer for excessive sodium intake.

- Treatment with dapagliflozin was shown to decrease
- the sodium content of the skin by 5.8% in one study.

- Schneider MP, et al. Skin sodium concentration correlates
- with left ventricular hypertrophy in CKD. J Am Soc Nephrol.
- 2017;28:1867-1876

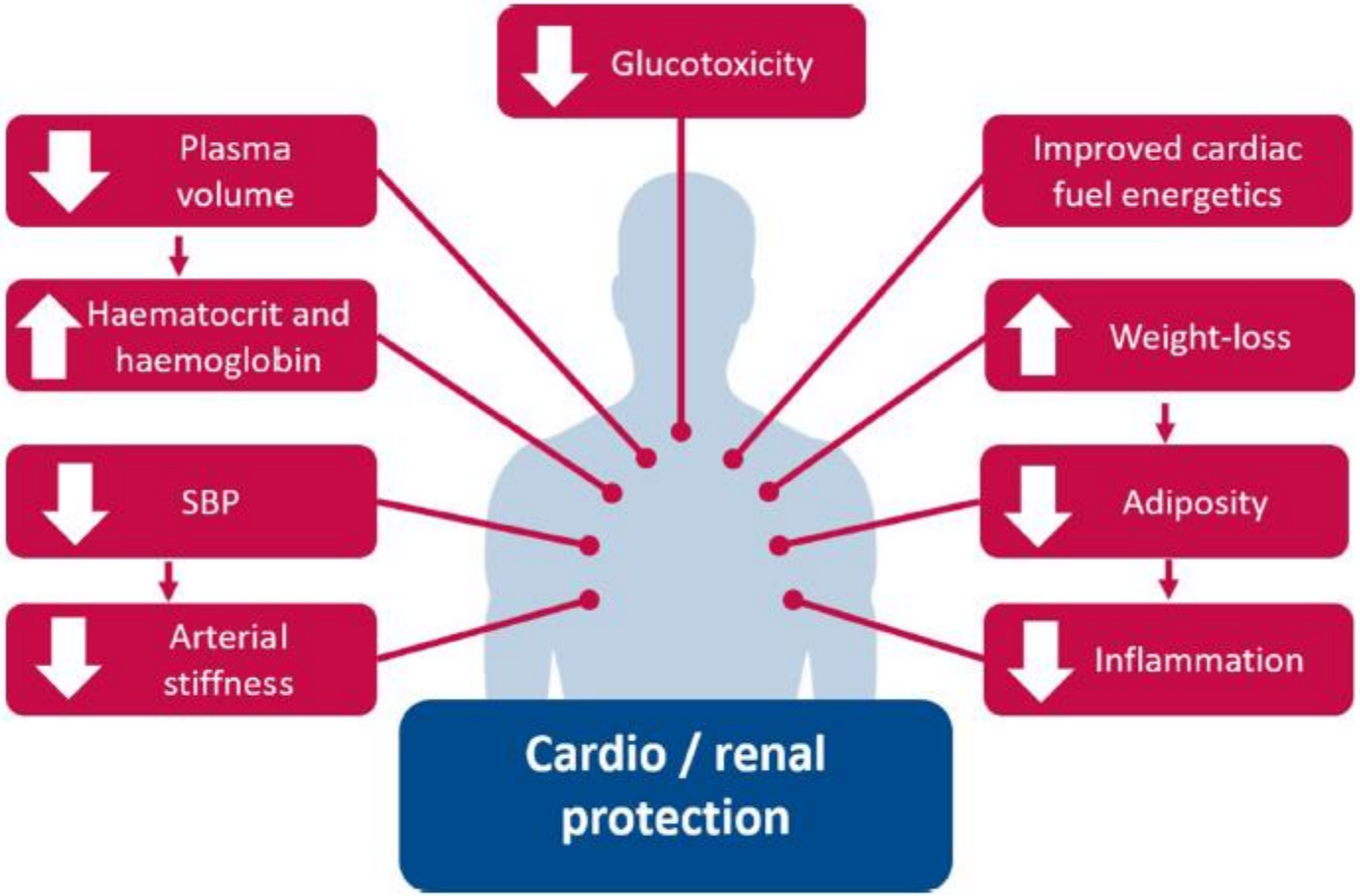


Fig. 3 SGLT2 inhibitor cardiorenal protection mechanistic overview. SBP systolic blood pressure

- Marc Evans. Diabetes Ther (2019) 10:1719–1731

Renoprotective pathways

- SGLT2 inhibition is consistently associated with an

acute, dose-dependent reduction in eGFR by~5 mL/min/1.73 m2 and ~30% to 40% reduction in albuminuria and hyperfiltration..

- As CKD progresses, increases in intraglomerular pressure
- are associated with glomerular fibrosis and inflammation.

- SGL2 inhibition reduce oxygen-consuming workload of reabsorption, with possible improvements tubulointerstitial cell structure and even function.

- Increased EPO may be a sign of tubulointerstitial recovery after treatment with SGLT2i.
- .

Kluger *et al. Cardiovasc Diabetol* (2019) 18:99
https://doi.org/10.1186/s12933-019-0903-4

Cardiovascular Diabetology

REVIEW Open Access

Class effects of SGLT2 inhibitors on cardiorenal outcomes

Aaron Y. Kluger[1,2*], Kristen M. Tecson[1,2,3], Andy Y. Lee[4,5], Edgar V. Lerma[6], Janani Rangaswami[7,8], Norman E. Lepor[9,10], Michael E. Cobble[11] and Peter A. McCullough[1,3,4,5]

- Three SGL2 inhibitors have been studied in cardiovascular outcome trials(CVOTs).
- EMPA-REG OUTCOME
- CANVAS and CANVAS_R
- DECLARE-TIMI 58
- CREDENCE

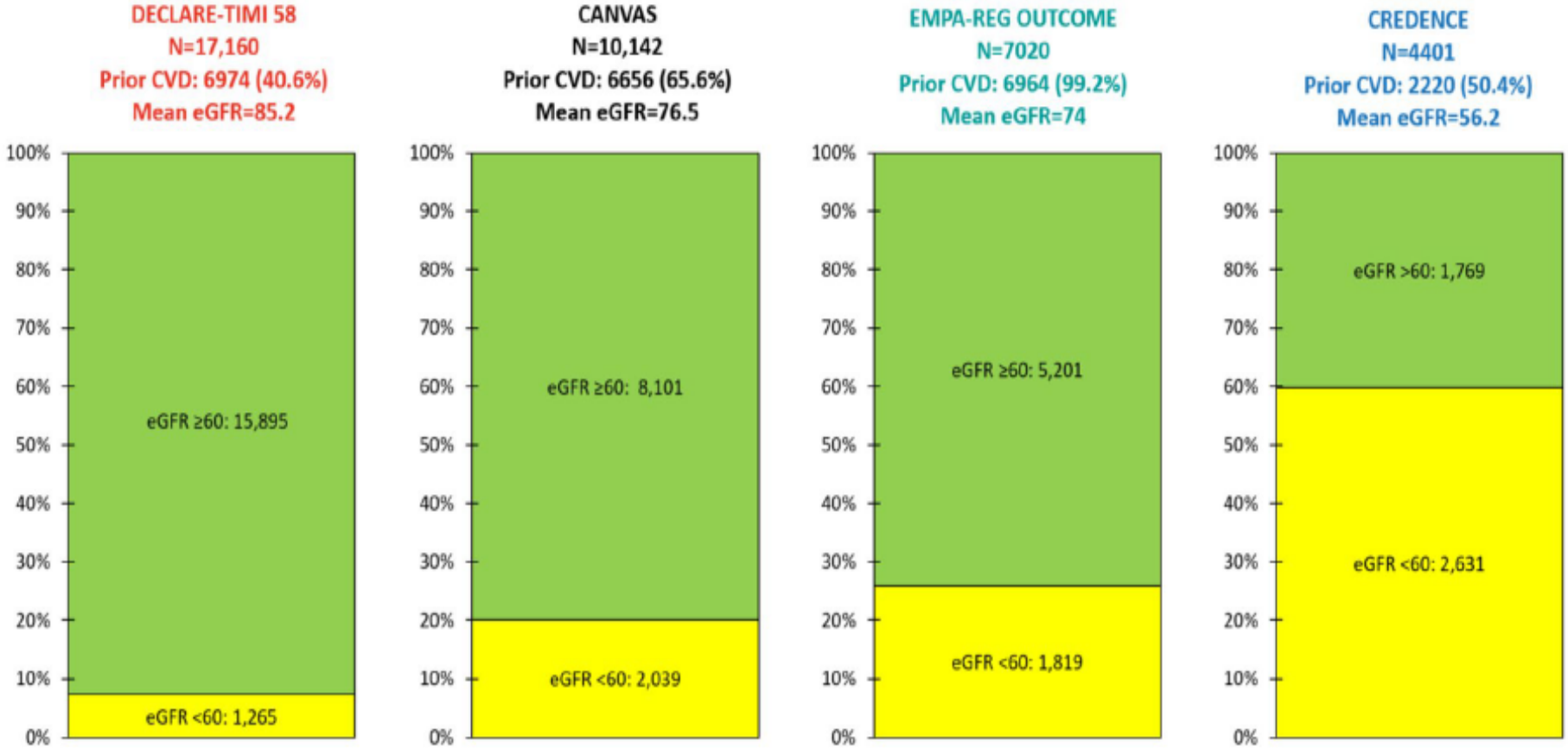


Fig. 1 Baseline estimated glomerular filtration rates (eGFRs) and prior cardiovascular disease (CVD) rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Prior CVD displayed as incidence (percentage)

- Kluger *et al. Cardiovasc Diabetol (2019) 18:99*

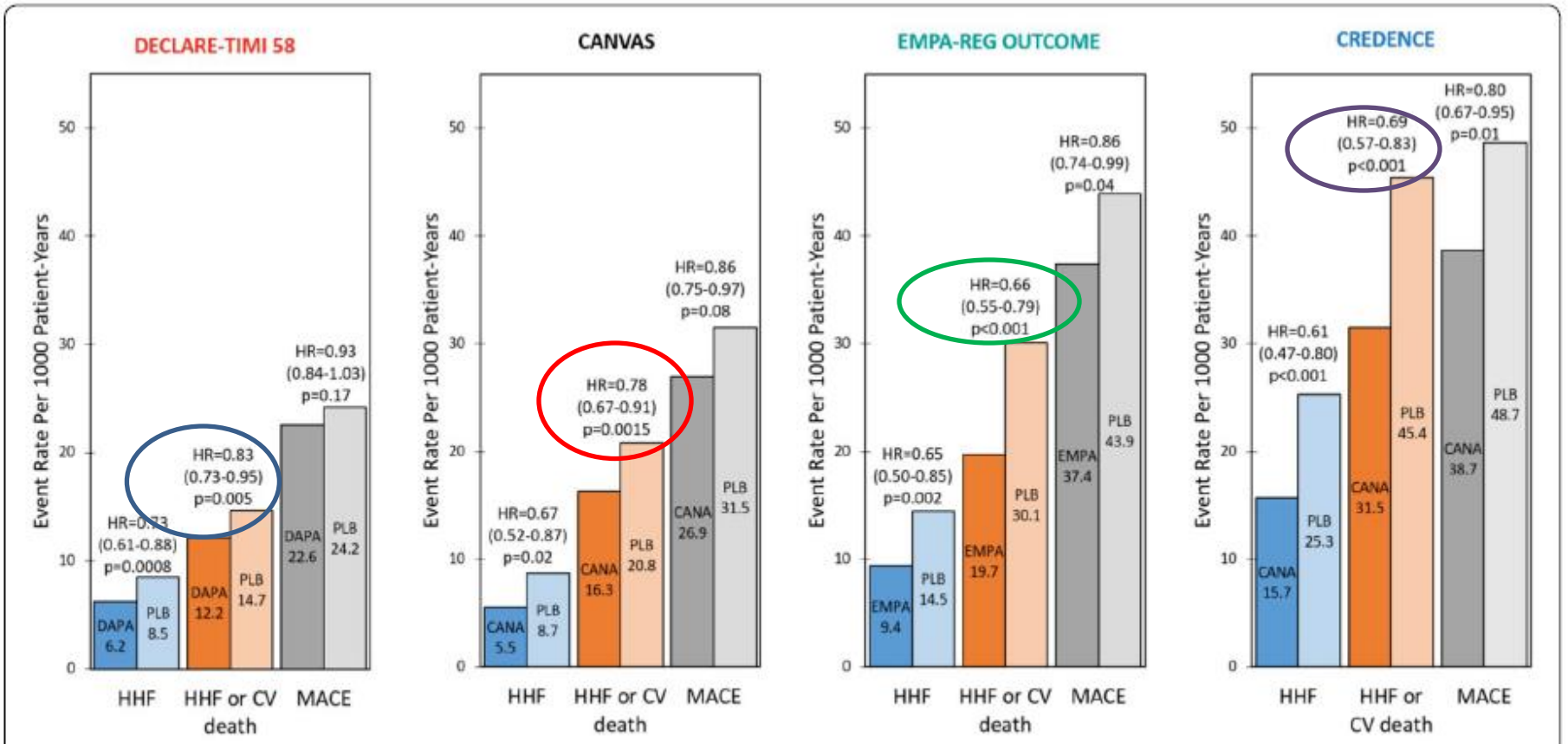
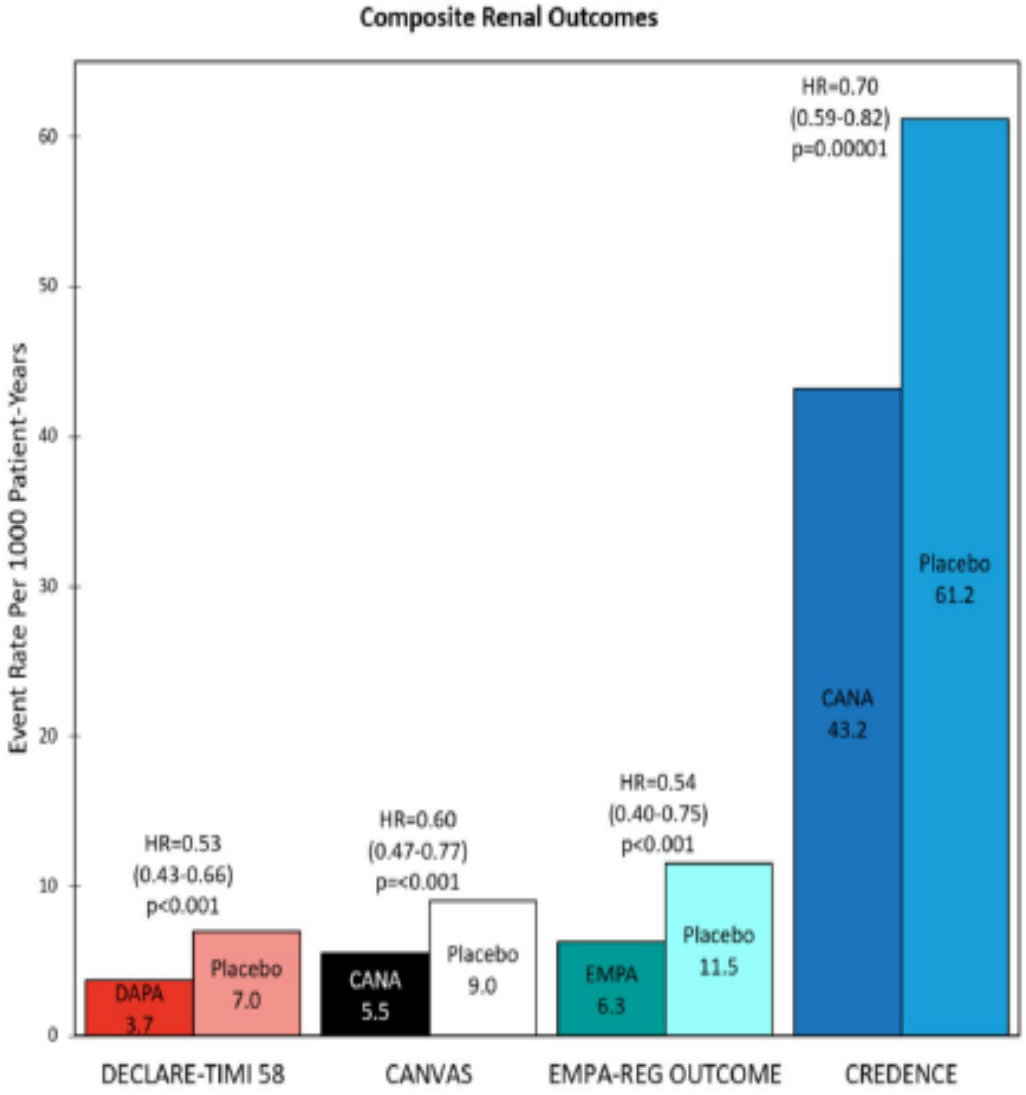
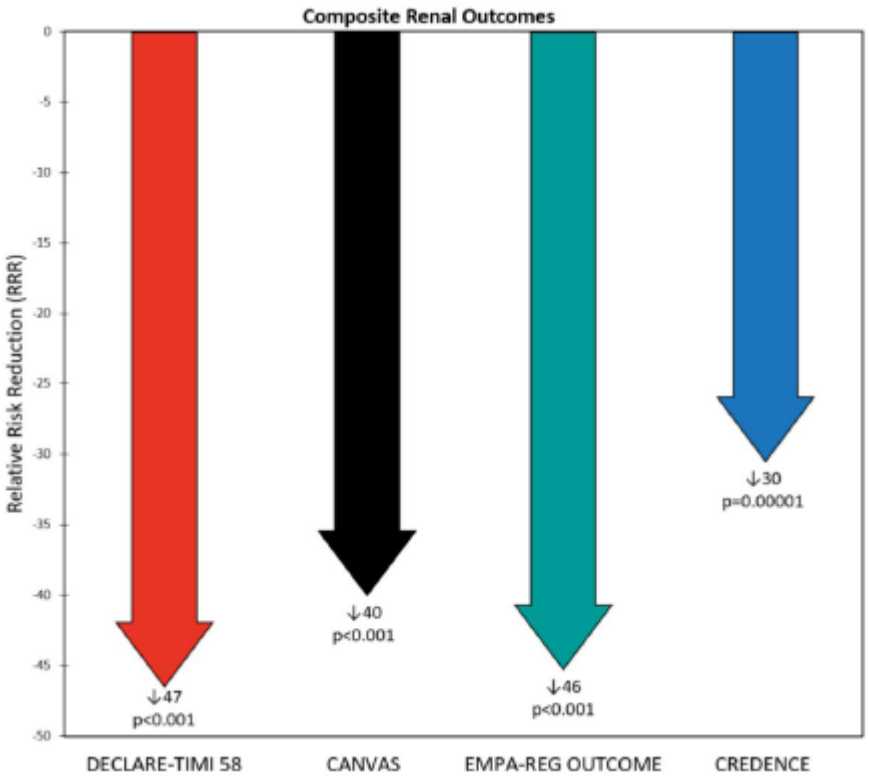


Fig. 2 Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) event rates per 1000 patients in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as hazard ratio, 95% confidence interval, p-value. *HR* hazard ratio, *DAPA* dapagliflozin, *CANA* canagliflozin, *EMPA* empagliflozin, *PLB* placebo

- Kluger *et al. Cardiovasc Diabetol (2019) 18:99*


Composite Renal Outcomes
Event Rate Per 1000 Patient-Years
0
10
20
30
40
50
60
HR=0.53
(0.43-0.66)
p<0.001
DAPA
3.7
Placebo
7.0
HR=0.60
(0.47-0.77)
p=<0.001
CANA
5.5
Placebo
9.0
HR=0.54
(0.40-0.75)
p<0.001
EMPA
6.3
Placebo
11.5
HR=0.70
(0.59-0.82)
p=0.00001
CANA
43.2
Placebo
61.2
DECLARE-TIMI 58
CANVAS
EMPA-REG OUTCOME
CREDENCE



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Baseline Renal Characteristics

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Mean eGFR, mL/min/1.73 m²	**56**	**56**	**56**
eGFR ≥90, %	5	5	5
eGFR ≥60 to <90, %	36	35	35
eGFR ≥45 to <60, %	29	29	29
eGFR ≥30 to <45, %	27	27	27
eGFR <30, %	4	4	4
Median UACR (IQR), mg/g	**923 (459-1794)**	**931 (473-1868)**	**927 (463-1833)**
UACR <30, %	<1	<1	<1
UACR 30-300, %	11	11	11
UACR >300-≤3000, %	77	76	77
UACR >3000, %	11	12	11

	DECLARE-TIMI 58	CANVAS	EMPA–REG OUTCOME	CREDENCE
Male genital infection[a]	+[b]	+[b]	+[b]	+[b]
Female genital infection[a]		+[b]	+[b]	+
Any AE	N/A	N/A	−[b]	−[b]
Serious AE	−[b]	−[b]	−[b]	−[b]
AE causing discontinuation	+[b]	+	−[b]	N/A
Hypoglycemia	−[b]	+	−	−
UTI	−	+	−	+
Fracture	+	+[b]	−	−
Hyperkalemia	N/A	+	N/A	−
Amputation	+	+[b]	N/A	+
AKI	−[b]	−	−[b]	−
Breast cancer	0	+	N/A	+
Bladder cancer	−[b]	−	N/A	+
DKA	+[b]	+	+	+[b]

AE adverse event, *N/A* not available, *UTI* urinary tract infection, *AKI* acute kidney injury, *DKA* diabetic ketoacidosis

[a] DECLARE-TIMI 58 did not differentiate genital infection by sex

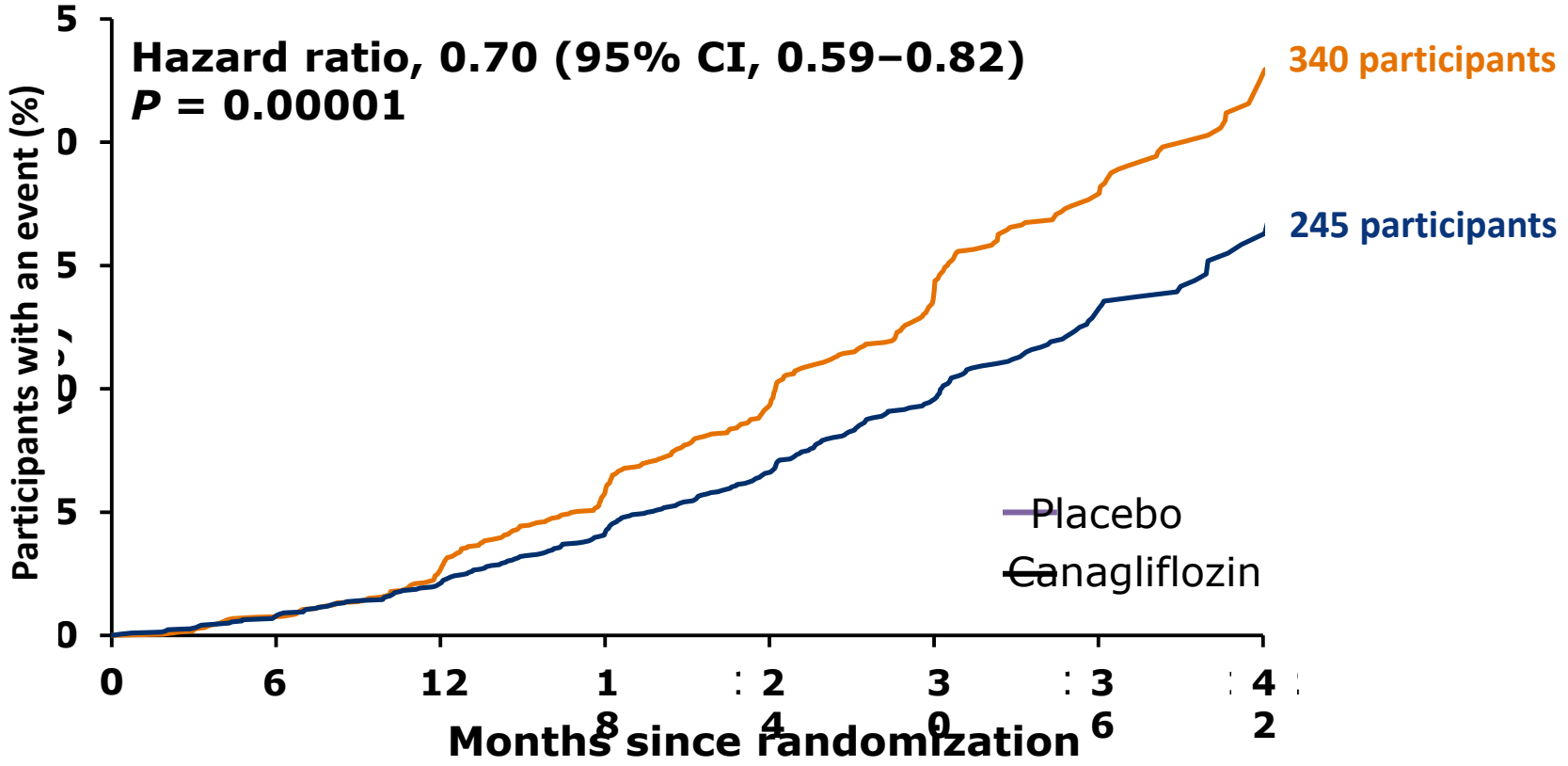
[b] indicates statistical significance at the α = 0.05 level. "+" = increased risk, "−" = decreased risk, "0" = no difference in risk

- Kluger *et al. Cardiovasc Diabetol (2019) 18:99*

Primary Aim of the CREDENCE Trial

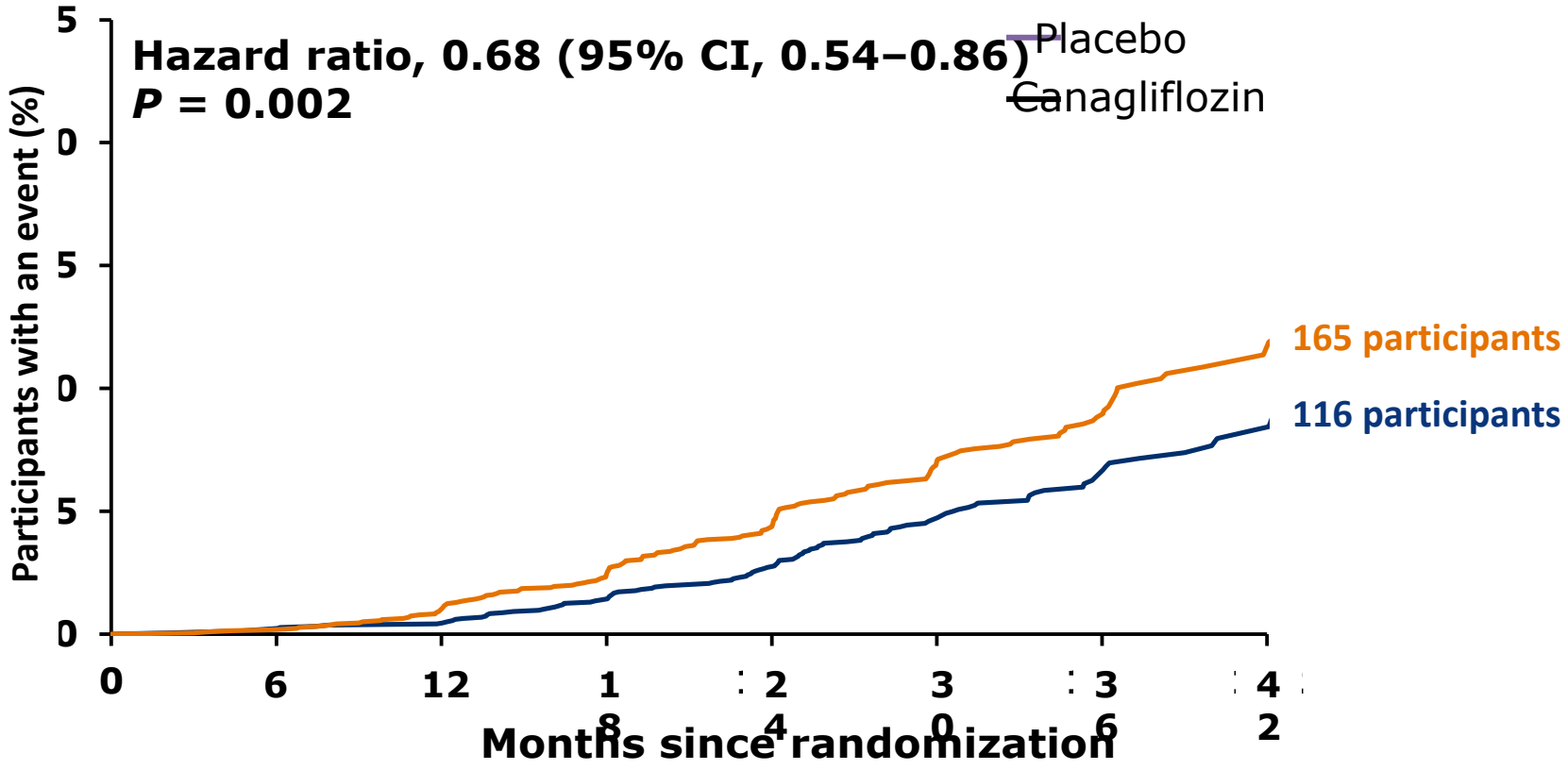
To assess the effects of the SGLT2 inhibitor, canagliflozin, on clinically important renal outcomes in people with T2DM and established CKD

Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



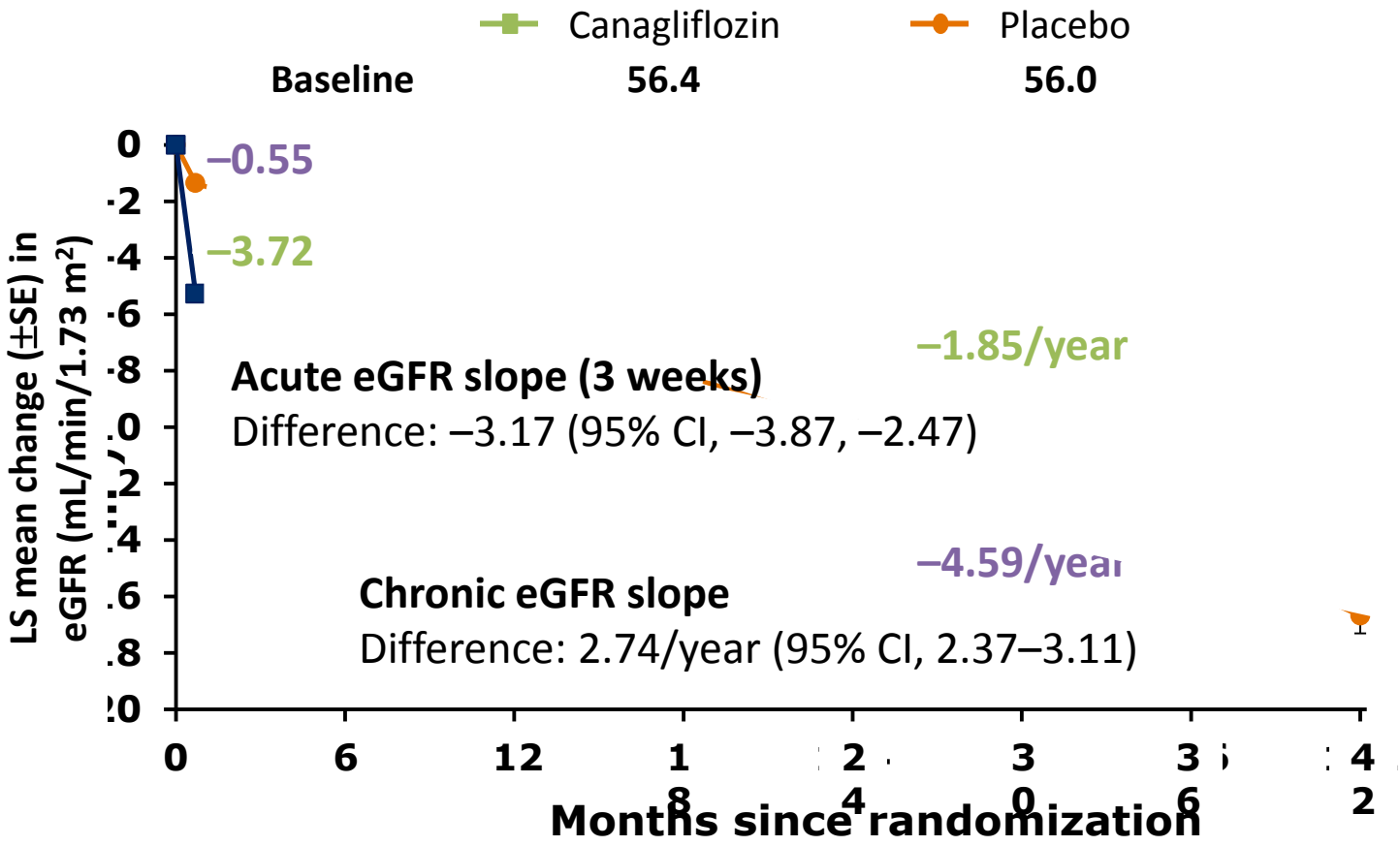
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

End-stage Kidney Disease



No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Effects on eGFR

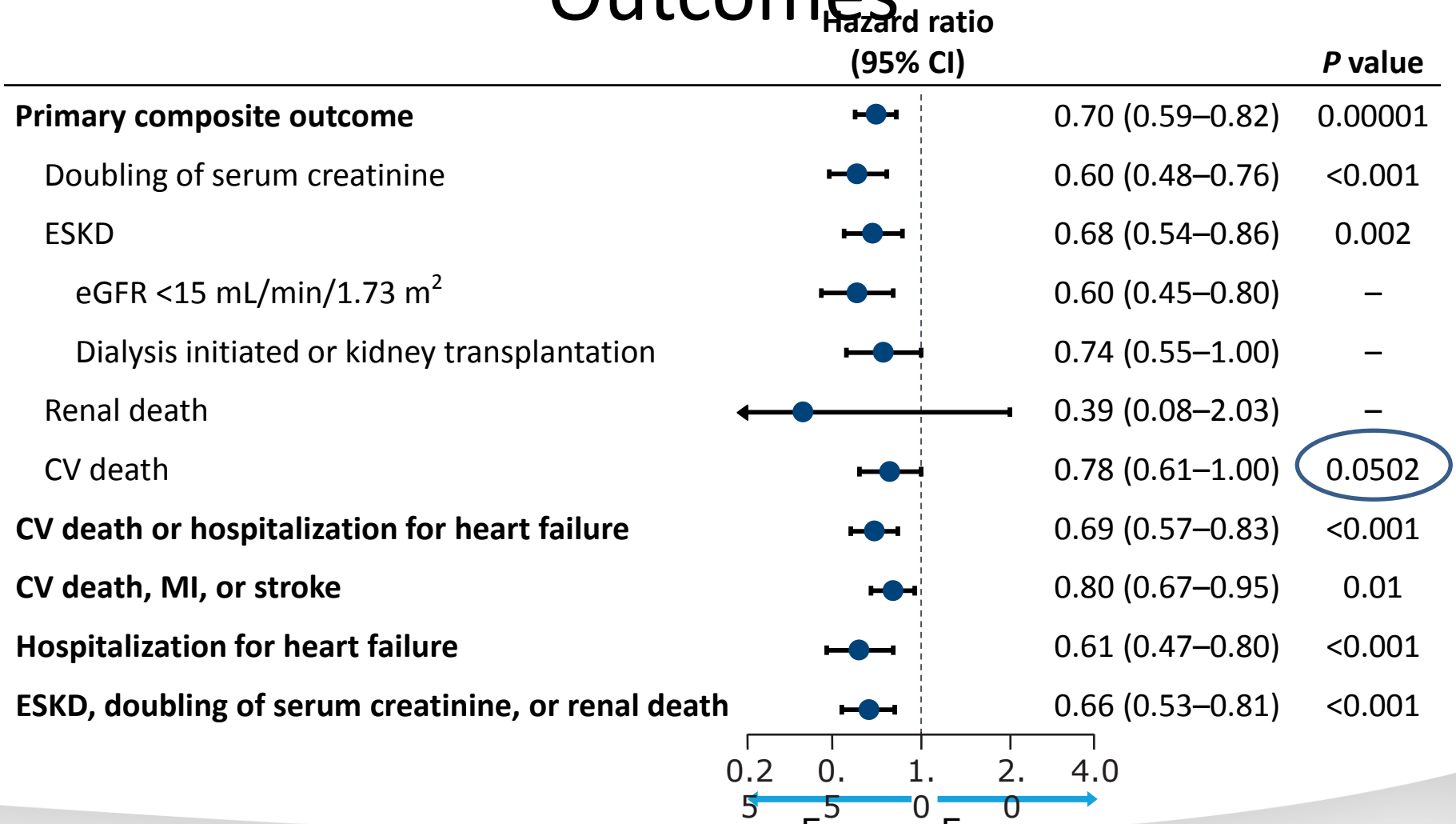


No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

Summary of Key Renal and CV Outcomes



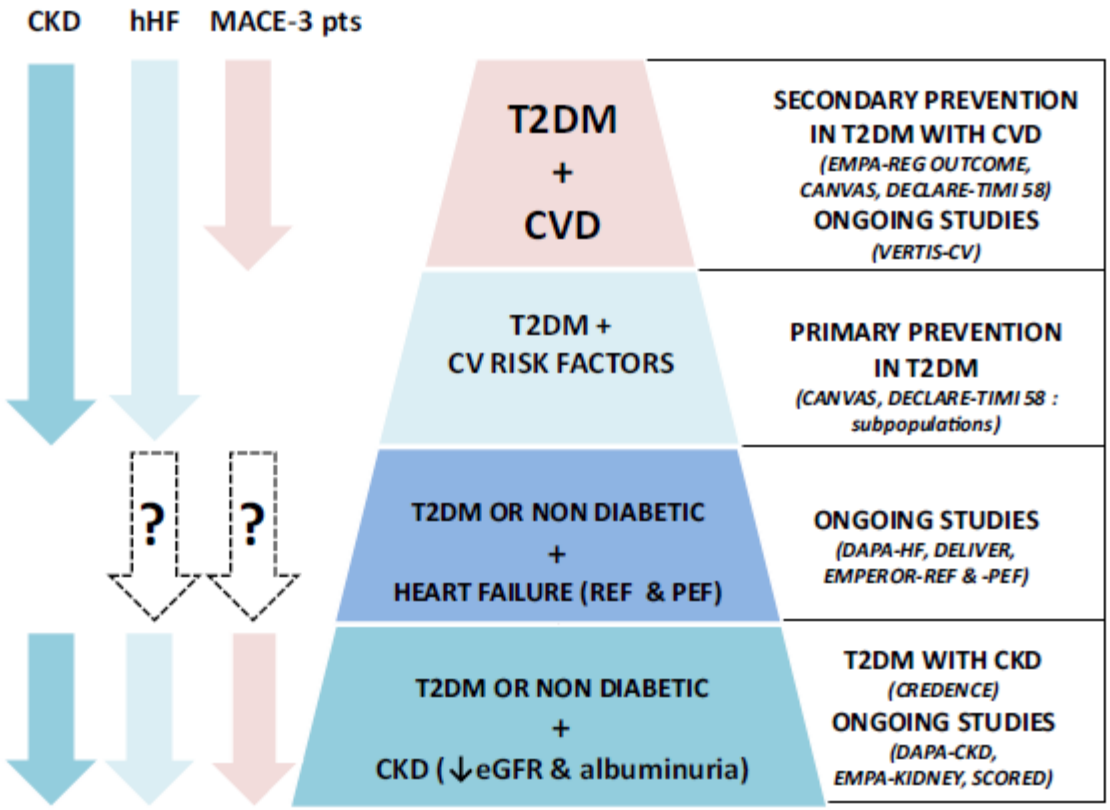


Fig. 2 – Schematic illustration of the already demonstrated and potential beneficial effects of SGLT2 inhibitors. CKD: chronic kidney disease. CV: cardiovascular. CVD: cardiovascular disease. eGFR: estimated glomerular filtration rate. hHF: hospitalisation for heart failure: MACE-3 points: major cardiovascular events (composite of cardiovascular mortality, myocardial infarction, stroke). T2DM: type 2 diabetes mellitus. REF: reduced ejection fraction: PEF: preserved ejection fraction.

Summary

- Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death **by 30%** (*P* = 0.00001)
  - The results were consistent across a broad range of prespecified subgroups
- Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling of serum creatinine, or renal death **by 34%** (*P* <0.001)
- Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome
  - **ESKD: 32% lower** (95% CI, 14–46)
  - **Dialysis, transplantation, or renal death: 28% lower** (95% CI, 3–46)
- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m^2/year (1.9 vs 4.6)

Clinical Kidney Journal, 2019, vol. 12, no. 3, 322–325

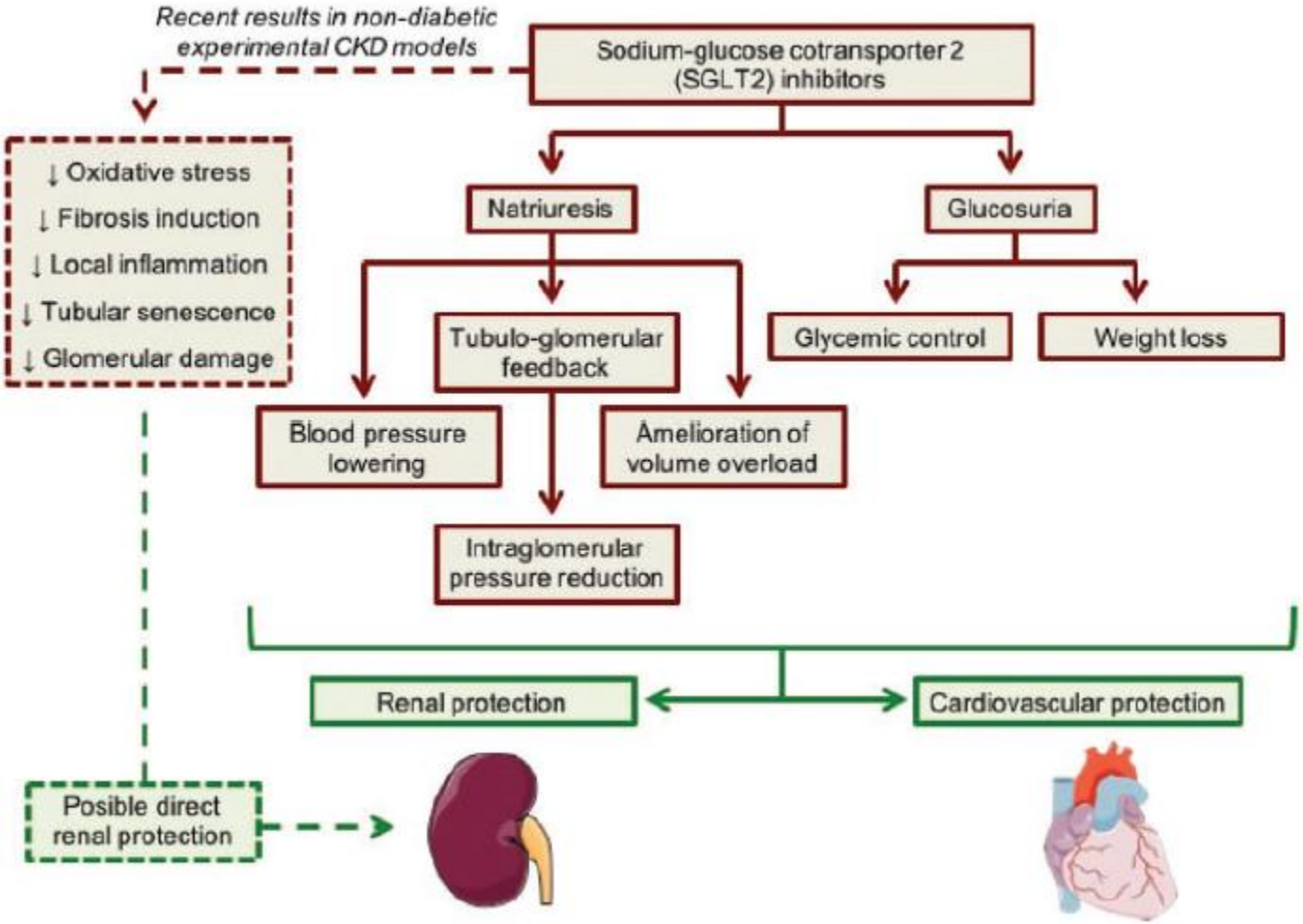
doi: 10.1093/ckj/sfz019
Advance Access Publication Date: 6 March 2019
Editorial Comment

EDITORIAL COMMENT

Sodium-glucose cotransporter inhibitors: beyond glycaemic control

Ander Vergara[1,2], Conxita Jacobs-Cachá[1,2,*] and María José Soler[1,2,*]

[1]Nephrology Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain and [2]Nephrology Research Group, Vall d'Hebron Research Institute (VHIR), Nephrology Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain


Recent results in non-diabetic experimental CKD models
Sodium-glucose cotransporter 2 (SGLT2) inhibitors
↓ Oxidative stress
↓ Fibrosis induction
↓ Local inflammation
↓ Tubular senescence
↓ Glomerular damage
Natriuresis
Glucosuria
Tubulo-glomerular feedback
Glycemic control
Weight loss
Blood pressure lowering
Amelioration of volume overload
Intraglomerular pressure reduction
Renal protection
Cardiovascular protection
Posible direct renal protection

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.

- Herrington WG, Preiss D, Haynes R et al.

- Clin Kidney J 2018; 11:749–761

Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers.

- Dekkers CCJ, Petrykiv S, Laverman GD et al.
- Dapagliflozin treatment decreases urinary kidney injury molecule 1(u KIM 1)levels.

- Diabetes Obes Metab 2018; 20: 1988–1993

Sodium-glucose linked cotransporter-2 inhibition does not attenuate disease progression in the rat remnant kidney model of chronic kidney disease.

- Zhang Y, Thai K, Kepecs DM et al.

- Dapagliflozin did not improve the GFR in the subtotal nephrectomy model of glomerulosclerosis in the rat.

- PLoS One 2016; 11: e0144640

- In a mouse model, luseogliflozin prevented fibrosis after kidney Injury induced by ischaemia–reperfusion.
- Increased expression (VEGF-A) in the kidneys of these animals was also observed.

- . Both the decrease of fibrosis and the VEGF-A overexpression
- were suppressed when luseogliflozin was associated
- with sunitinib—a VEGF receptor inhibitor.
- These results suggest that the protective effects of luseogliflozin
- were in part mediated by the VEGF-A pathway

Empagliflozin , SGL T2 inhibitor, attenuates renal fibrosis in rats exposed to unilateral ureteric obstruction: potential role of klotho expression.

- Abbas NAT, El Salem A, Awad MM.

- Naunyn Schmiedebergs Arch Pharmacol 2018; 39: 1347–1360

- SGLT2 inhibition decreased kidney fibrosis and inflammation biomarkers, such as (TGF-b1),

  alpha smooth muscle actin (a-SMA) or fibronectin.
- There is downregulation of the (NF-κB/TLR4) signalling pathway, as well as a partial recovery of tubular
- klotho levels .
- Empagliflozin may have a protective effect against
- inflammation and fibrosis.

- SGLT2 inhibitor dapagliflozinlimits podocyte damage in proteinuric nondiabetic nephropathy.

Cassis P, Locatelli M, Cerullo D et al. JCI Insight 2018; 3: pii: 98720

- In a murine protein-overload proteinuria model, dapagliflozin reduced proteinuria and glomerular damage.
- . In the in vivo model and in cultured cells, bovine serum albumin upregulated SGLT2 expression in podocytes in an NFκB-dependent manner.

- . This induced cytoskeleton changes that reverted with the administration of dapagliflozin.

. Interestingly, SGLT2 inhibition may directly target the podocytes and contribute to maintain the actin cytoskeleton architecture

.

REVIEW ARTICLE

WILEY

SGLT2 inhibition to address the unmet needs in diabetic nephropathy

Federica Barutta | Sara Bernardi | Giuseppe Gargiulo | Marilena Durazzo | Gabriella Gruden

Diabetes Metab Res Rev. 2019

TABLE 2 SGLT2 inhibitors in experimental diabetic nephropathy

Active Treatment	Animal Model	Study Design	Study Duration	Functional and structural effects	Mechanisms
Empagliflozin[84]	Type 1 DM (eNOS-KO STZ mice)	Empaglifozin 10 mg/kg/day vs. insulin	19 weeks	= Albuminuria = Glomerulosclerosis = Tubular atrophy	
Empagliflozin[85]	Type 2 DM (db/db mice)	Empaglifozin 10 mg/kg/day vs. metformin	10 weeks	= Albuminuria = Glomerulosclerosis = Kidney growth	↓ Fibrosis (fibronectin TGF-β)
Dapaglifozin[86]	Type 2 DM (OLEFT rats)	Dapaglifozin 1 mg/kg/day vs. voglibose	12 weeks	↓ Albuminuria ↓ Mesangial ↓ Interstitial fibrosis	↓ RAS activation ↓ Oxidative stress ↓ Inflammation
Dapaglifozin[87]	Type 1 DM (Akita mice)	Dapaglifozin 1 mg/kg/day vs. insulin	12 weeks	↓ Albuminuria ↓ Interstitial fibrosis	↓ Interstitial inflammation ↓ Fibrosis (TGF-β1) ↓ Oxidative stress
Dapaglifozin[88]	Type 2 DM (db/db mice)	Dapaglifozin 2 mg/kg/day vs. pioglitazone	9 weeks	= Albuminuria = Mesangial Expansion = Foot process width	
Luseoglifozin[89]	Type 1 DM and hypertension (STZ-Dahl Salt-sensitive rats)	Luseoglifozin 10 mg/kg/day vs. insulin	8 weeks	= Albuminuria = Hyperfiltration = Renal injury	
Luseoglifozin[90]	Type 2 DM (T2DN rats)	Luseoglifozin 10 mg/kg food vs. insulin	12 weeks	↓ eGFR decline ↓ Glomerulosclerosis, ↓ Renal fibrosis	↓ Nephrin excretion
Ipraglifozin[91]	Type 2 DM (BTBR ob/ob mice)	Ipraglifozin 4 mg/kg/day vs. 30% calorie restriction	18 weeks	↓ Albuminuria ↓ Hyperfiltration ↓ Mesangial expansion	↓ TCA cycle ↓ Oxidative stress

- As not all of the non diabetic CKD animal models responded to SGLT2 inhibitors , it is possible that the direct effects on the kidney are dependent on the specific CKD experimental model studied.

TABLE 3 Major ongoing SGLT2 inhibitor trials with renal outcomes

Study Name	EMPA- KIDNEY	CREDENCE	DAPA- CKD	VERTIS CV
Registration number	NCT03594110	NCT02065791	NCT03036150	NCT01986881
Intervention	Empaglifozin vs. placebo	Canaglifozin 100 mg vs. placebo	Dapaglifozin 5 and 10 mg vs. placebo	Ertuglifozin 5 and 15 mg vs. placebo
No. of patients	5000 (estimated)	4401	4000 (estimated)	8000 (estimated)
Study population	DM2 and non-DM2 with CKD	DM2 with CKD and high CV risk	DM2 and non-DM2 with CKD and high CV risk	DM2 with CVD
Renal inclusion criteria	eGFR 20-44 mL/min/1.73m^2 or eGFR < 90 mL/min/1.73m^2 with UACR ≥200 mg/g	eGFR 30-90 mL/min/1.73m^2 with UACR 300-5000 mg/g	eGFR 25-75 mL/min/1.73m^2 with UACR 200-5000 mg/g	eGFR ≥30 mL/min/1.73m^2
Estimated FU duration	3.1 y	5.5 y	4 y	6.1 y
Primary composite outcomes	CKD progression (↓ ≥ 40% eGFR, ESRD[a], eGFR <10 mL/min/1.73m^2, renal death) or CV death	ESRD[b], dSCr, or CV or renal death	ESRD[b], ↓ ≥ 50% eGFR or CV or renal death	MACE
Secondary renal outcomes	CKD progression, CV death or ESRD	Renal composite outcome (ESRD[b], dSCr, or renal death)	Individual components of the primary outcome	Renal composite outcome (dSCr, RRT, or renal death)
Estimated completion date	June 2022	June 2019[c]	November 2020	September 2019

[a]ESRD initiation of maintenance dialysis or receipt of a kidney transplant.

[b]ESRD initiation of maintenance dialysis or receipt of a kidney transplant or sustained <15 mL/min/1.73 m^2.

[c]The trial was stopped study early on July 2018 based on the achievement of pre-specified efficacy criteria for the primary composite.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM2, type 2 diabetes; dSCr, doubling of serum creatinine from baseline; eGFR, estimated glomerular filtration rate; ESRD; end-stage renal disease; FU, follow-up; MACE, major advanced cardiovascular events; UACR, urinary albumin excretion. EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DAPA-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

Thank you for your attention

Effects on uric acid, phosphate, PTH and vitamin D levels

- SGLT2i increase the renal clearance of uric acid .

- The uricosuric effect is due to the increased intraluminal concentration of glucose and is mediated by GLUT9 isoform 2 in the renal collecting ducts.

Original article

Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: A systematic review with an indirect comparison meta-analysis

Yakai Xin [a], Yu Guo [a,1], Yanle Li [d,1], Yujin Ma [a,b], Liping Li [a,b], Hongwei Jiang [a,b,c,*]