"8th SPED/ AACE Endocrine Clinical Update":

Slowing the Progression of Renal Disease in patients with Diabetes

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Disclosure

Angel L Comulada, MD, FACE

- ◆ Has received honorarium as Speaker &/or Consultant for the following Pharmaceutical Companies: Abbott, AstraZeneca, Daichi-Sankyo, GSK, Lilly, Medtronics, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Shering Plough
- ◆ Has received Grants &/or has contractual relationship as Principal Investigator for the following Pharmaceutical Companies: Abbott, Abbvie, AstraZeneca, BMS, Dalcor, VPI, Lilly, Merck, Novo Nordisk, Pfizer, Roche & Sanofi-Pasteur
- ◆ CMO & Medical Director of Pro-Health Clinical Services, Advanced Clinical Research and Advanced Pro-Health Management Solutions
- Medical Director of "Salud a Tu Alcance" Educational Program, Bayamon City
- ◆ Chief of Endocrinology Doctors' Center Hospital, Bayamon
- Past President of "Sociedad Puertorriqueña de Endocrinología y Diabetología"

Disclosure:

No Conflicts of Interest to Disclose

This presentation is intended for educational purposes only and does not replace independent professional judgment.

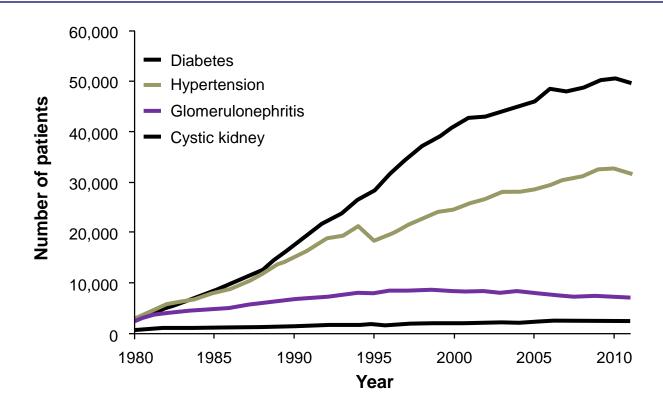
I am expressing my own views based on my reading, analysis and interpretation of the scientific information.

I am a member of SPED and other different organizations/companies, but I am <u>not</u> speaking in representation of, or presenting the views of the "Sociedad Puertorriqueña de Endocrinología y Diabetología", other Professional Societies, Public or Private Corporation, or Pharmaceutical Company.

Objectives:

- Summarize the epidemiology of Diabetes Kidney Disease, DKD
- Discuss the proposed pathophysiology of DKD
- Review and discuss proposed strategies and interventions to slow the progression of *DKD*

Diabetes Is the Leading Cause of Kidney Failure: US Data



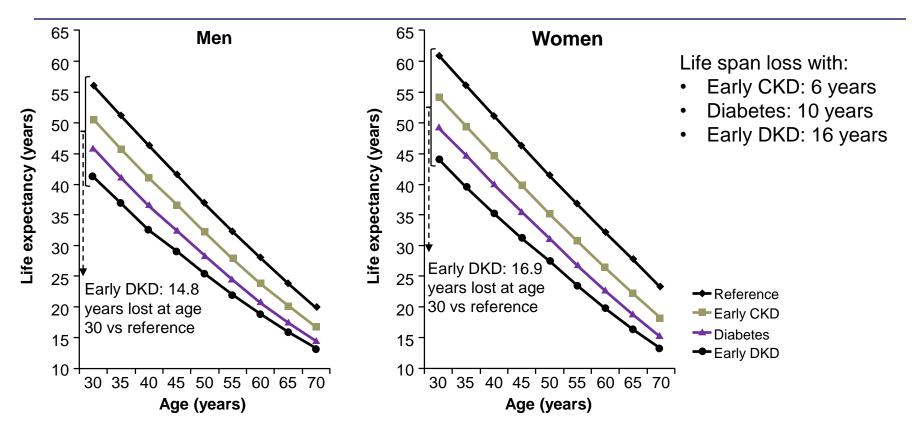
Epidemiology of DKD

 The average incidence of diabetic nephropathy is high (3% per year) during the first 10 to 20 years after diabetes onset.

• It is estimated that more than 20 and up to 40% of diabetic patients will develop chronic kidney disease (CKD).

 Diabetes with no clinical sign of kidney damage during the initial 20 to 25 years is significantly less likely (1% a year) to cause major renal complication later in life.

Diabetic Kidney Disease Shortens Life Span by 16 Years



Risk factors for diabetic nephropathy

- Ethnicity
- Family history
- Gestational diabetes
- Elevated blood pressure
- Dyslipidaemia
- Obesity
- Insulin resistance

- Elevated glycosylated haemoglobin level (HbA1c)
- Elevated systolic pressure
- Proteinuria
- Smoking

Non modifiable Risk Factors for Diabetic Nepropathy

- Evidences suggest that epigenetic mechanisms such as DNA methylation, noncoding RNAs and histone modifications can also play a pivotal role in the pathogenesis of diabetic nephropathy:
 - ◆ Cytokine TNF-alpha
 - ♦ IL-6 and
 - ◆ IL-1 beta gene promoter polymorphisms and modulation in expression have been linked to DN susceptibility in subjects.

 Diabetic nephropathy was defined by the evidence of proteinuria ≥ 300 mg/day, in a patient with diabetes.

Table 1 Staging of diabetic nephropathy

Stages	DN staging Tervaert et al. [11]	DN staging Gheith et al. [13]		
Stage 1	Glomerular basement membrane thickening	From onset to 5 years. Borderline GFR, no albuminuria, hypertension. But kidney size increased by 20% along with an increase in renal plasma flow		
Stage 2	Mild or severe mesangial expansion	From 2 years after onset with basement membrane thickening and mesangial prolieration, normal GFR and no clinical symptoms		
Stage 3	Nodular sclerosis	5–10 years after onset with or without hypertension, with glomerular damage and microal- buminuria (30–300 mg/day)		
Stage 4	Advanced diabetic glomerulosclerosis that includes tubulointerstitial lesions and vascular lesions	Irreversible proteinuria, sustained hypertension and GFR below 60 ml/min/1.73 m ²		
Stage 5	-	End-stage kidney disease with GFR < 15 ml/min/1.73 m ²		

DN diabetic nephropathy, GFR glomerular filtration rate

Prognosis of CKD by GFR and Albuminuria Categories

Prognosis of CKD by GFR and Albuminuria Categories: **KDIGO 2012**

Normal or high

Mildly decreased

decreased

Moderately to

Kidney failure

Mildly to moderately

severely decreased

Severely decreased

G1

G2

G3a

G3b

G4

G5

GFR categories (ml/min/ 1.73m²) Description and range

	P		
	A 1	A 2	А3
	Normal to mildly increased	Moderately increased	Severely increased
	<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
≥90			
60-89			
45-59			
30-44			
15-29			
<15			

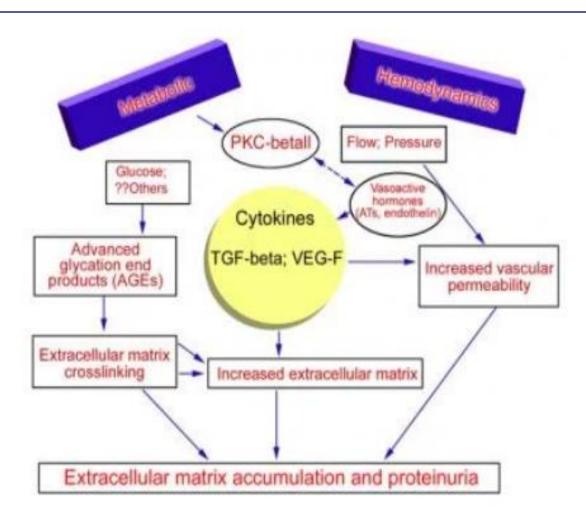
Persistent albuminuria categories Description and range



- Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy. These different histologic patterns appear to have similar prognostic significance:
 - ◆ Thickening of the glomerular basement membrane (GBM) occurs.
 - Mesangial expansion is directly induced by hyperglycemia, perhaps via increased matrix production or glycation of matrix proteins.
 - ◆ Glomerular sclerosis is caused by intraglomerular hypertension (induced by dilatation of the afferent renal artery or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli).

- The key change in diabetic glomerulopathy is augmentation of extracellular matrix.
- The earliest morphologic abnormality in diabetic nephropathy is the thickening of the GBM and expansion of the mesangium due to accumulation of extracellular matrix.

- The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are:
 - Hyperglycemia (causing hyperfiltration and renal injury)
 - Advanced glycation products
 - Activation of cytokines
- Many investigators now agree that diabetes is an autoimmune disorder, with overlapping pathophysiologies contributing to both type 1 and type 2 diabetes; and recent research highlights the pivotal role of innate immunity (toll-like receptors) and regulatory T-cells (Treg).



Potential serum biomarkers of diabetic nephropathy:

- Neutrophil gelatinase-associated lipocalin (NGAL)¹
- Beta-trace protein (beta TP)¹
- MicroRNA-130b (miR-130b) in type 2 DM.

1: Motawi et al. found that serum NGAL and BetaTP were significantly elevated in T2DM patients and can serve as early biomarkers of tubular and glomerular markers respectively.

Western and Pima Indian populations suggest that the prevalence of overt nephropathy is about 21% in patients with type 1 DM, and 20–25% in patients with Type 2 DM, depending solely on the duration since onset of disease.

- The progression of kidney disease in type 1 diabetes mellitus is unpredictable and seems to be connected to the intensity of blood sugar and pressure control.
 - ◆ Initial studies reported that ~ 80% microalbuminuric patients progress to proteinuria over 6–14 years.
 - ◆ Patients with microalbuminuria in Joslin type 1 cohort and DCCT/EDIC study :
 - **→**58% patients with RAAS
 - → 50% patients w/o RAAS

Regressed to normoalbuminuria over 6 years and within 10 years, solely with better control of diabetes, hypertension and lipids.

→ Improvement in microalbuminuria also resulted in 89% lower risk of developing a decreased GFR in type 1 DM patients.

- Progression and regression of kidney disease in type 2 DM is highly variable:
 - ◆ The UKPDS study reported at 15 years follow up
 - → Microalbuminuria in 38% patients
 - ★ Microalbuminuria-macroalbuminuria-ESKD at 2.8% patients per year
 - **→** Reduced GFR in 29% patients
 - ★ Microalbuminuria-macroalbuminuria-ESKD at 2.3% per year

- Progression and regression of kidney disease in type 2 DM is highly variable:
 - ◆ Pima Indians study reported that macroalbuminuria was 50% during a median follow- up of 20 years.
 - → Gradual loss of kidney damage with time:
 - ★ 7.3% patients were diagnosed with microalbuminuria at the onset
 - ★ 17.3% at 5 years
 - ★24.9% at 10
 - **★**28% at 15 years.

Strategies and interventions to slow the progression of *DKD*

- The primary goal of DKD treatment is to prevent microalbuminuria from progressing to macroalbuminuria and an eventual decrease in renal function and associated heart disorders:
 - Avoid smoking
 - ♦ Keep Healthy weight
 - Nutritional plan
 - Intensive glycaemic control
 - ◆ Antihypertensive treatment by blocking RAAS system
 - Lipid-modifying statin therapy

- Smoking
 - ◆ Education, CBT, smoking cessation aids and medications
- Healthy Weight and Nutritional Plan:
 - Nutritional plan of a CKD or DKD patient is challenging and designed to delay progression of kidney damage and the associated secondary conditions such as hypertension, hyperlipidemia, uremia, etc.
 - ◆ It also needs continuous monitoring and must be personalized to the patients' treatment regimen.

- Healthy Weight and Nutritional Plan:
 - An ideal meals plan recommended for DKD patients with compromised kidney function includes:
 - ★A proper amount of fat to prevent malnutrition
 - ★ Limiting saturated fatty acid consumption
 - ★ Taking vegetable oils and omega-rich fatty acid containing oils in moderation.

- Healthy Weight and Nutritional Plan:
 - An ideal meals plan recommended for DKD patients with compromised kidney function includes:
 - → Many clinical studies have highlighted the renoprotective effects of a low protein diet on DKD:
 - ★ A protein-deficient diet (0.6 to 0.7 g/ kg/day) needs to be integrated into the overall care of renal insufficiency with customized dietary interventions to avoid malnutrition.
 - ★In animal type 2 DM models a very low protein diet (VLPD) improved tubulo-interstitial damage, inflammation and fibrosis, through restoration of autophagy via reduction of a mammalian target of rapamycin complex 1 (mTORC1) activity.

- Healthy Weight and Nutritional Plan:
 - An ideal meals plan recommended for DKD patients with compromised kidney function includes:
 - ★A low-salt diet is highly recommended for DKD patients.
 - ★ Restricted sodium intake allows better blood pressure control.
 - ➤ High salt intake and urinary protein excretion were associated with annual creatinine clearance decline in type 2 DKD patients as reported by Kanauchi et al.

- Healthy Weight and Nutritional Plan:
 - An ideal meals plan recommended for DKD patients with compromised kidney function includes
 - → Potassium intake specifically from foods such as grains, potatoes, corn, soybean, nuts, tomatoes, banana, melons, kiwi etc. must be restricted.
 - → Phosphorus excretion is also reduced during chronic kidney damage leading to increased blood phosphorus levels. Since phosphate is in homeostatic equilibrium with the skeletal muscle calcium levels, an imbalance leads to a significant calcium loss and debilitating bone disease.

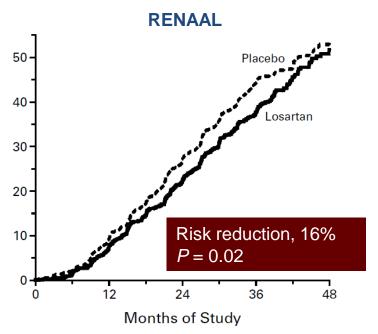
- Healthy Weight and Nutritional Plan:
 - ◆ An ideal meals plan recommended for DKD patients with compromised kidney function includes:
 - →A target of 1600 kcal of energy per day in which 60 percent comes from carbohydrate and 40 percent from proteins.
 - ★In a recent study, such a regimen achieved a commendable control in blood lipid and glucose values in a patient with stage 4 chronic kidney disease.
 - ★ However, patient adherence to the recommended diet seems to be gender-specific.

Strategies and interventions to slow the progression of *DKD*

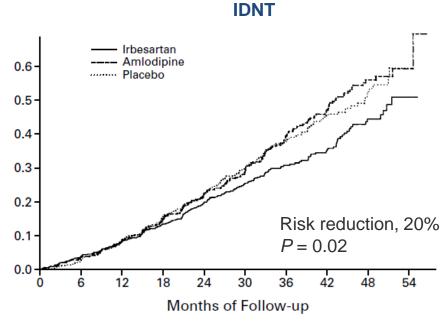
Medications

The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

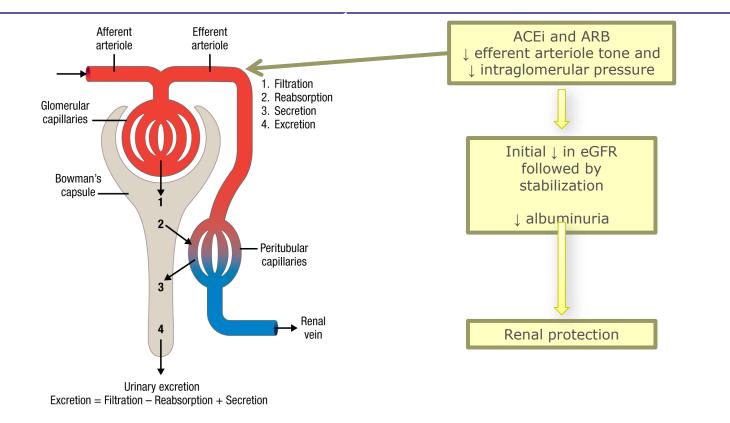


Brenner B, et al. N Engl J Med. 2001;345(12):861-869.

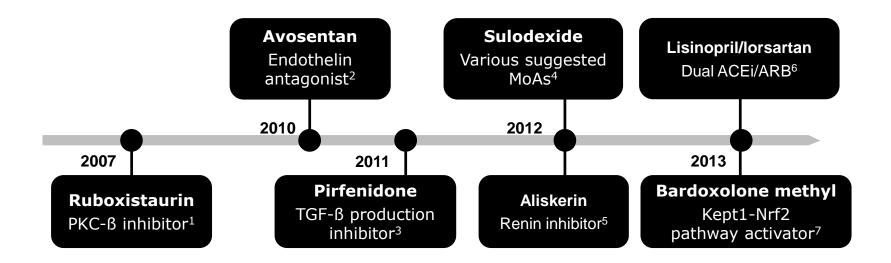


Lewis EJ, et al. N Eng J Med. 2001;345(12):851-860.

ACEi/ARB Reduce Intraglomerular Pressure: Mechanism for Renal Protection



Since RENAAL and IDNT, New Therapeutic Strategies for Patients With T2DM and CKD Have Failed



[.] Tuttle KR, et al. Clin J Am Soc Nephrol. 2007;2(4):631-636.

^{2.} Mann JFE, et al. *J Am Soc Nephrol.* 2010;21(3):527-535.

^{3.} Sharma K, et al. J Am Soc Nephrol. 2011;22(6):1144-1151.

^{4.} Packham DK, et al. J Am Soc Nephrol. 2012;23(1);123-130.

^{6.} Fried LF, et al. N Engl J Med. 2013;369(20):1892-1903.

^{7.} de Zeeuw D, et al. N Engl J Med. 2013;369(26):2492-2503.

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Research Article

Carvedilol as nephroprotective agent: a meta-analysis of randomized controlled trials

Sharanabasayyaswamy B. Hiremath^{1*}, Srinivas D. Lokikere²

- Results: Carvedilol failed to show significant effect on UACR when compared with all active treatments (standardised mean difference, SMD = 0.80 mg/g, 95% CI = 2.37, 0.76, n=5, N=1036) and placebo (mean difference, MD = -0.88 mg/g, 95% CI=-5.26, 3.51, n=2, N=75). It was superior to beta-1 blockers (SMD = -0.26 mg/g, 95% CI=-0.39, -0.13, n=2, N=963) and inferior to ACEIs/ARBs (MD = 7.45, 95% CI=0.29, 14.61, n=2, N=73).
- Conclusions: There are low quality evidences to suggesting nephroprotective efficacy of carvedilol to be superior to beta-1 blockers in patients especially with diabetes as co-morbidity. Considering the drawbacks of our study, results need to be cautiously interpreted.

Many Renal Effects of SGLT2 Inhibition Have Been Proposed







Volume











And many others...

Renoprotective effects of SGLT2 inhibitors

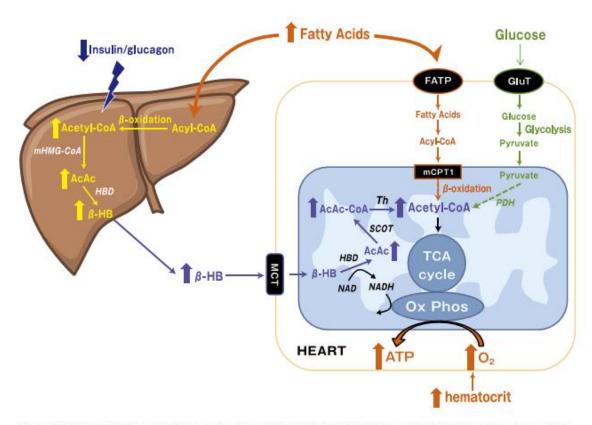
- Effects mediating decreased glucose reabsorption:
 - ◆ SGLT2 inhibitors exerted cardiovascular and kidney protective effects, which appeared to be partly independent of the original glucoselowering effect.
 - ◆ SGLT2 inhibitors have both direct and indirect renoprotective effects:
 - → Direct effects involve the suppression of hyperplasia/hypertrophy, inflammation, and fibrosis in the proximal tubular cells, utilization of ketone bodies, restored tubuloglomerular feedback, decreased oxygen consumption, improvement in anemia, and preconditioning against ischemia/reperfusion.
 - → Indirect effects involve a reduction in insulin levels and resistance, uric acid concentration, body weight, and blood pressure.

Renoprotective effects of SGLT2 inhibitors

- Suppression of proximal tubular hyperplasia and hypertrophy:
 - In animal models empagliflozin and phlorizin (non-selective SGLT inhibitors) were shown to ameliorate renal swelling.
 - One of the major changes in the earliest stage of diabetic kidney disease is proximal tubular hyperplasia and sequential hypertrophy. Renal swelling mainly occurs due to this tubular hypertrophy and is particularly apparent in the cortex and the outer stripe of the outer medulla. Glucose reabsorption by the renal tubules in hyperglycemia induces the expression of growth factors such as TGFβ, VEGF, and IGF, and is considered to be the main cause of tubular hypertrophy.

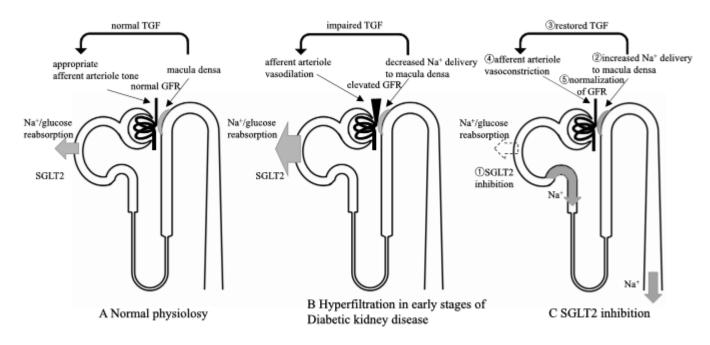
- Suppression of inflammation and fibrosis by a reduction in the intracellular glucose concentration:
 - ◆ Proximal tubular cells reabsorb glucose via SGLT2 and are exposed to high intracellular glucose concentrations, which induces the expression of inflammatory cytokines, growth factors, and fibrotic mediators and increases the production of advanced glycation products and reactive oxygen species.
 - ♦ SGLT2 inhibitors are assumed to help suppress these events related to the onset and progression of kidney disease. Indeed, the exposure of HK2 cells, a human proximal tubular cell line, to empagliflozin was shown to reduce inflammatory and fibrotic signals, including toll-like receptor 4 (TLR4), NF-κB, IL-6, AP-1, and collagen IV (9). Hypoxia caused by interstitial fibrosis is regarded as a "final common pathway" leading to end-stage kidney disease irrespective of the original cause (10). Thus, the amelioration of hypoxia by SGLT2 inhibitors may have significant treatment implications.

- Ketone bodies as an alternative fuel source
 - ◆ SGLT2 inhibitors cannot help but affect the dynamics of energy metabolism and consumption through changes in glucose storage in the body.
 - ♦ Consequently, it was hypothesized that cardiomyocytes and renal tubular cells exposed to SGLT2 inhibitors undergo a fuel shift from free fatty acids (FFAs) to β-hydroxybutyrate (β-HB), which produces more energy per oxygen consumption and improves work efficiency.



Ferrannini E, Mark M, Mayoux E. CV protection in the EMPAREG OUTCOME trial: a "Thrifty Substrate" hypothesis. Diabetes Care 39: 1108-1114, 2016.

- Effects mediating decreased sodium reabsorption
 - Restoration of tubuloglomerular feedback
 - ◆ In diabetic patients, activated SGLT2 enhances the reabsorption of Na and reduces the distal tubular concentration of Na, which is sensed as a decrease in the effective circulating plasma volume by the macula densa, resulting in afferent arteriolar dilation. It has been proposed that the increase in the urinary concentration of Na that occurs with SGLT2 inhibitor use attenuates TGF, causing afferent arteriolar constriction and a resultant decrease in intraglomerular pressure, with an eventual decrease in the GFR.
 - In a trial investigating the effects of the 8-week administration of empagliflozin on the GFR of T1DM patients, the mean GFR in patients with hyperfiltration (GFR ≥135 mL/min/1.73 m²) at the baseline (n=27) decreased by 33 mL/min/1.73 m²; this was accompanied by a decrease in the plasma NO level and effective renal plasma flow, and an increase in renal vascular resistance (15). The patients with a GFR of 90-134 mL/min/1.73 m² at the baseline (n=13) did not show these alterations. In addition, RAAS mediators led to significant increases in the patients with hyperfiltration. These findings may be explained by a decrease in effective renal plasma flow due to the natriuretic effect of the SGLT2 inhibitor; in addition, the coadministration with RAAS inhibitors might have induced additive renoprotective effects. SGLT2 inhibitors can correct hyperfiltration in normoalbuminuric T1DM patients with a normal renal function, and they are expected to have a role in the primary prevention of diabetic kidney disease; however, this role remains to be proven.



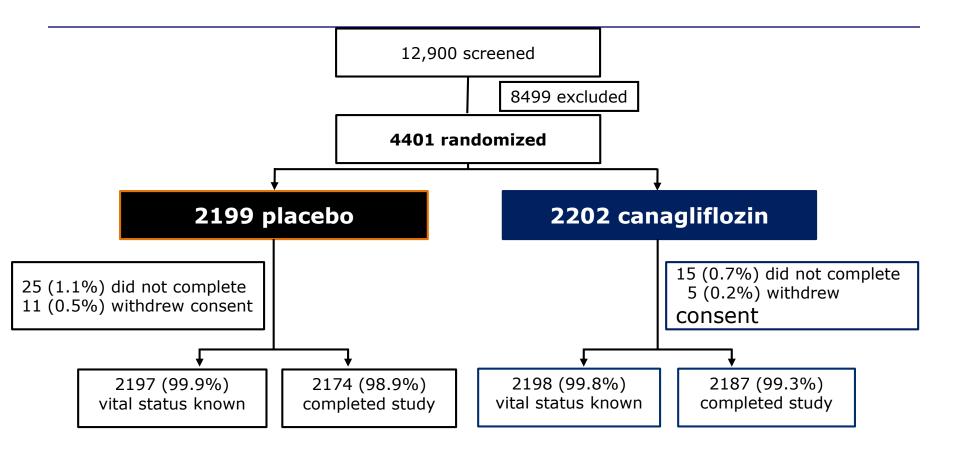
Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129: 587-597, 2014.

- The Systemic Effects of SGLT2 Inhibitors Probably Lead to Renoprotection
 - ◆ accumulated evidence indicates the efficacy of improved blood glucose control in the suppression of new-onset microalbuminuria and progression to macroalbuminuria.
 - The reduction in insulin levels and the improvement of insulin sensitivity
- Serum uric acid reduction
 - ♦ In some clinical trials, SGLT2 inhibitor use led to a modest but significant reduction in the serum uric acid concentration (8). The mechanism of the increased uricosuria may be attributed to the action of SLCA9 (GLUT9) isoform b, which absorbs the luminal glucose - which is increased by SGLT2 inhibition and which secretes uric acid back into the lumen in exchange
- Body weight reduction
- Blood pressure reduction

CREDENCE Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

Primary and Renal Outcomes

Enrollment and Follow-up



4395 (99.9%) vital status known; 4361 (99.1%) completed study*

Primary Endpoint Definitions

ESKD

- Chronic dialysis for ≥30 days
- Kidney transplantation
- eGFR <15 mL/min/1.73 m² sustained for ≥30 days by central laboratory assessment

Doubling of serum creatinine

• Doubling from the baseline average sustained for ≥30 days by central laboratory assessment

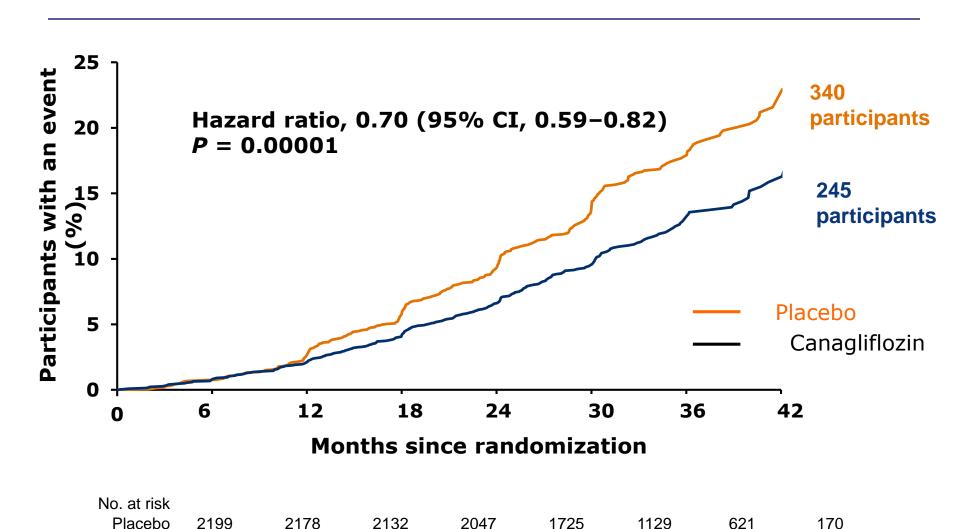
Renal death

• Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated

CV death

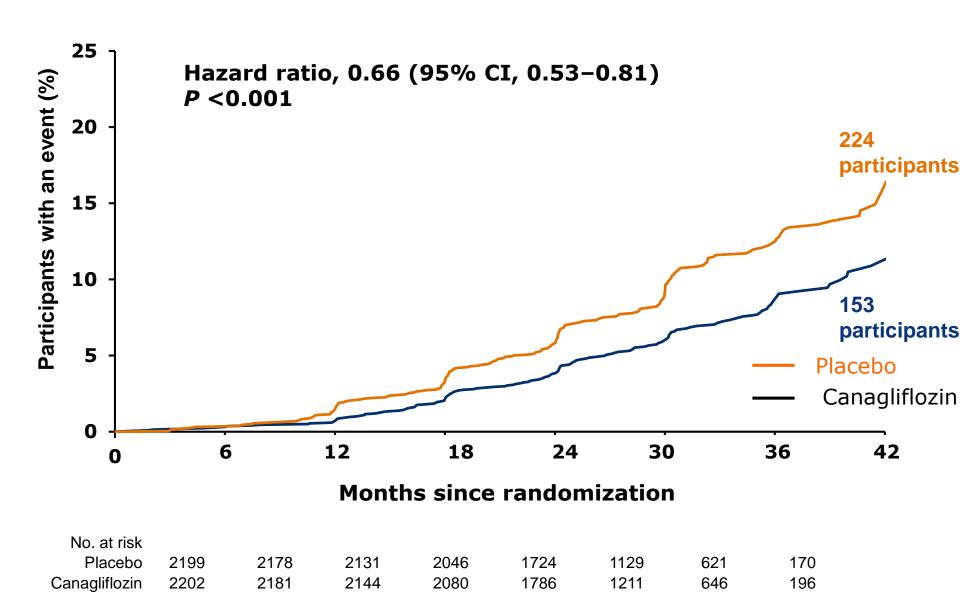
 Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

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

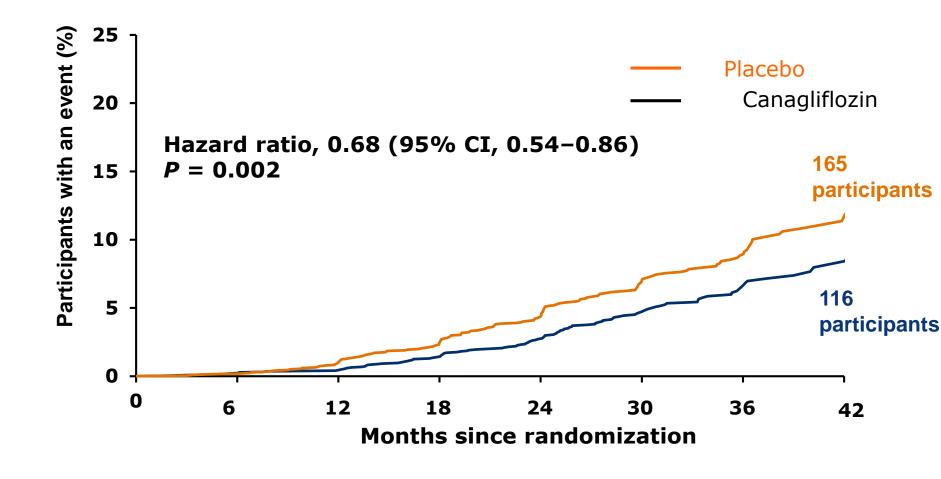


Canagliflozin

ESKD, Doubling of Serum Creatinine, or Renal Death

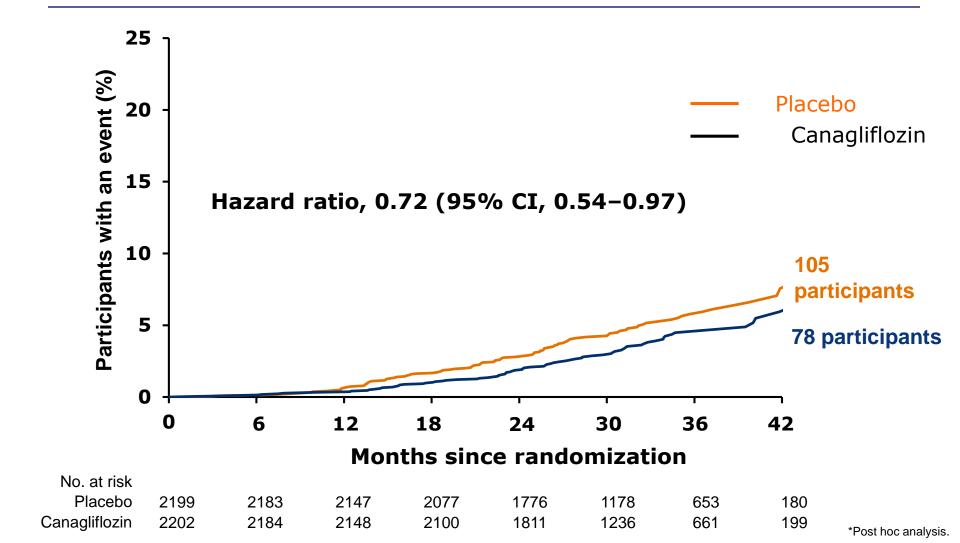


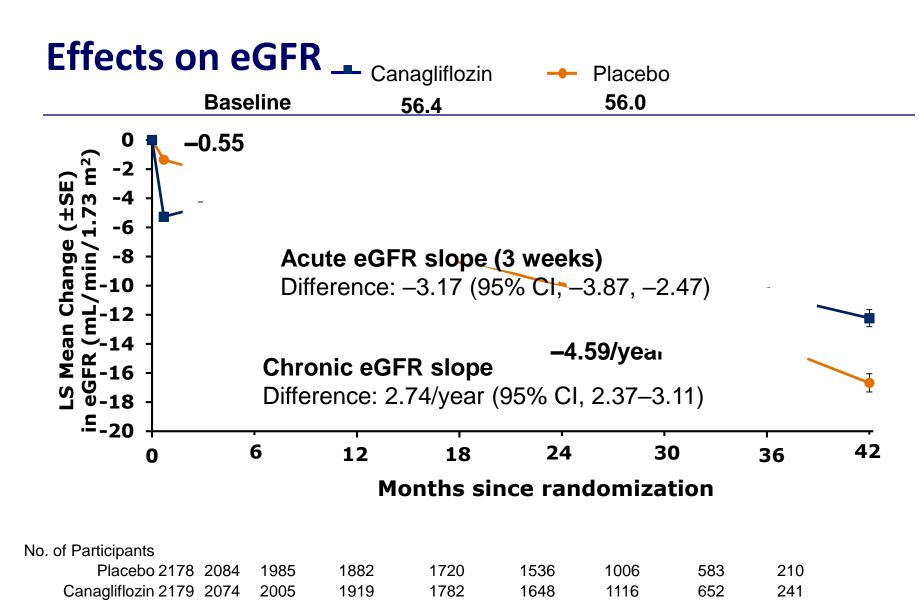
End-stage Kidney Disease



No. at risk Placebo Canagliflozin

Dialysis, Kidney Transplantation, or Renal Death*





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 m²/year (1.9 vs 4.6)

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

Findings From 2085 records identified, four studies met our inclusion criteria, assessing three SGIT2 inhibitors: empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program and CREDENCE), and dapagliflozin (DECLARE-TIMI 58). From a total of 38 723 participants, 252 required dialysis or transplantation or died of kidney disease, 335 developed end-stage kidney disease, and 943 had acute kidney injury. SGIT2 inhibitors substantially reduced the risk of dialysis, transplantation, or death due to kidney disease (RR 0.67, 95% CI 0.52-0.86, p=0.0019), an effect consistent across studies ($I^2=0\%$, $p_{\text{heterogeneity}}=0.53$). SGIT2 inhibitors also reduced end-stage kidney disease (0.65, 0.53-0.81, p<0.0001), and acute kidney injury (0.75, 0.66-0.85, p<0.0001), with consistent benefits across studies. Although we identified some evidence that the proportional effect of SGIT2 inhibitors might attenuate with declining kidney function ($p_{\text{trend}}=0.073$), there was clear, separate evidence of benefit for all eGFR subgroups, including for participants with a baseline eGFR 30–45 mL/min per 1.73 m² (RR 0.70, 95% CI 0.54-0.91, p=0.0080). Renoprotection was also consistent across studies irrespective of baseline albuminuria ($p_{\text{trend}}=0.66$) and use of RAS blockade ($p_{\text{heterogeneity}}=0.31$).

Interpretation SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease in individuals with type 2 diabetes and provided protection against acute kidney injury. These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent major kidney outcomes in people with type 2 diabetes.

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE			
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin			
Dose (mg)	10 and 25	100 and 300	10	100			
Number of participants	7020	10142	17160	4401			
Mean age (years)	63-1	63.3	63-9	63-0			
Sex							
Men	5016 (71.5%)	6509 (64-2%)	10738 (62-6%)	2907 (66-1%)			
Women	2004 (28-5%)	3633 (35-8%)	6422 (37-4%)	1494 (33-9%)			
Median follow-up (years)	3.1	2-4	4-2	2-6*			
eGFR inclusion criteria	≥30 (MDRD)	≥30 (MDRD)	CrCl ≥60 mL/min (Cockcroft-Gault)	30 to <90 (CKD-EPI)			
Baseline eGFR subgroup (mL/min per 1-73 m²)†‡							
≥90	1538 (21.9%)	2476 (24-4%)	8162 (47-6%)	0			
60 to <90	3661 (52-2%)	5625 (55.5%)	7732 (45·1%)	1809 (41-1%)			
45 to <60	1249 (17-8%)	1485 (14.6%)	1265 (7.4%)§	1279 (29-1%)			
<45	570 (8-1%)	554 (5-5%)	NA	1313 (29.8%)			
Missing baseline eGFR	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)	0			
UACR criteria (mg/g)	None	None	None	>300 to 5000			
Baseline UACR subgroup (mg/g)‡							
<30	4171 (59.4%)	7007 (69-1%)	11644 (67.9%)	0			
30-300	2013 (28.7%)	2266 (22-3%)	4030 (23-5%)	0			
>300	769 (11-0%)	760 (7.5%)	1169 (6.8%)	4401 (100-0%)			
Missing baseline UACR	67 (1.0%)	109 (1.1%)	317 (1.8%)	0			
Baseline use of RAS blockade	5666 (80-7%)	8116 (80-0%)	13 950 (81-3%)	4395 (99-9%)			

Data are n (%), unless otherwise specified. eGFR=estimate glomerular filtration rate. MDRD=Modification of Diet in Renal Disease equation. CrCl=creatinine clearance. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation. UACR=urine albumin-to-creatinine ratio. RAS=renin-angiotensin system. NA=not available. *Stopped early after a planned interim analysis on the recommendation of the independent data monitoring committee. †Based on the MDRD equation in EMPA-REG OUTCOME and the CANVAS Program and on the CKD-EPI equation in DECLARE-TIMI 58 and CREDENCE. ‡Based on screening (rather than baseline) eGFR and UACR measurements in the CREDENCE trial. §Includes all DECLARE-TIMI 58 participants with eGFR lower than 60 mL/min per 1-73m².

Table: Characteristics of included studies

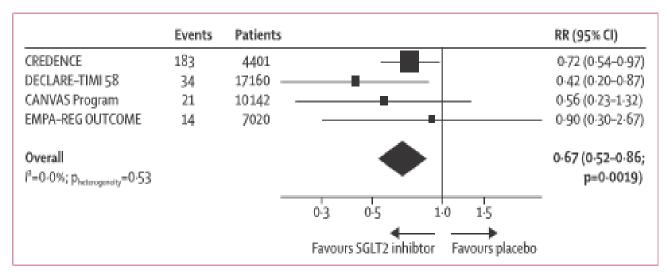


Figure 1: Effect of SGLT2 inhibitors on dialysis, transplantation, or death due to kidney disease
Weights were from random-effects meta-analysis. Data from DECLARE-TIMI 58 have not been previously
reported. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

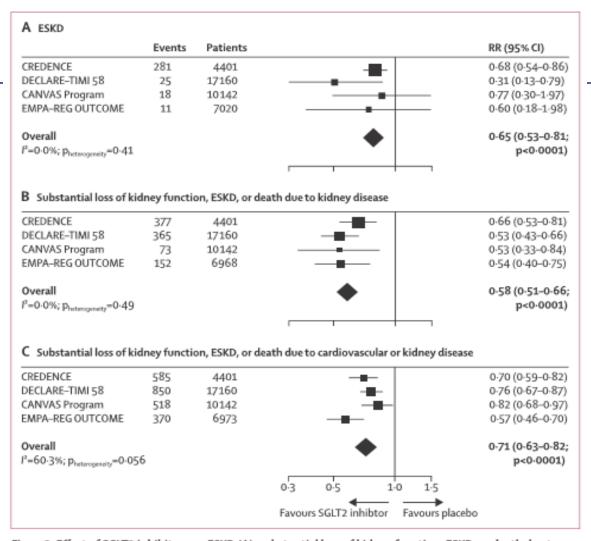


Figure 2: Effect of SGLT2 inhibitors on ESKD (A), substantial loss of kidney function, ESKD, or death due to kidney disease (B), and substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease (C)

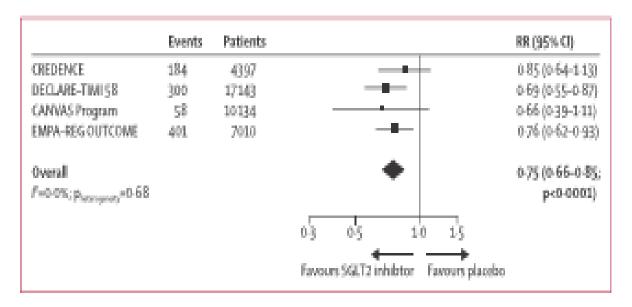
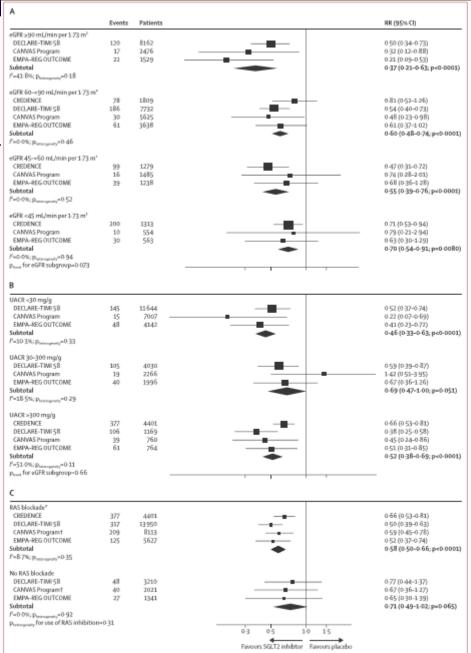


Figure 3: Effect of SGLT2 inhibitors on acute kidney injury

Weights were from random-effects meta-analysis. SGLT2-sodium-glucose co-transporter-2. RR-relative risk.

	Events	Patients		RR (95% CI)
Dialysis, transplantation, or death due to kidney disease	252	38723		0.67 (0.52-0.86)
ESKD	335	38723		0-65 (0-53-0-81)
Substantial loss of kidney function, ESKO, or death due to kidney disease	967	38671	-	0.58 (0.51-0.66)
Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease	2323	38676	-	0.71 (0.63-0.82)
Acute kidney injury	943	38684	-	0-75 (0-66-0-85)
			05 10	1-5
		Favor	ours SGLT2 inhibtor Favo	urs placebo

Figure 4: Summary of the effects of SGLT2 inhibition on major kidney outcomes ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.



of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR (A), UACR (B), and use of RAS blockade (C) Weights were from random-effects meta-analysis. p_{unal} values across eGFR and UACR subgroups were calculated against a t-distribution in random-effects meta-regression with use of restricted maximum likelihood with Hartung Knapp modification. p_{interpret} for between subgroup differences based on use of RAS inhibition was obtained from a random-effects model. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE-TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. Results from the CREDENCE trial are based on screening eGFR and UACR measurements. eGFR and UACR subgroup data from the CANVAS Program have not been previously published. ESKD=end-stage kidney disease.eGFR=estimated glomerular filtration rate. UACR-urine albumin-tocreatinine ratio. RAS=renin-angiotensin system. SGLT2=sodium-glucose co-transporter-2. RR=relative risk. "Use of RAS blockade was mandated as part of entry into the CREDENCE trial. †For analysis by baseline use of RAS blockade in the CANVAS Program, substantial loss of kidney function was defined as 40% decline in eGFR because no doubling of serum creatinine events occurred in participants not receiving RAS blockade.

Figure 5: Effect of SGLT2

inhibitors on substantial loss

Summary

- DKD is the main leading cause of ESKD worldwide.
- DKD involves metabolic and hemodynamic changes as pathophysiologic cause.
- Control of hyperglycemia, BP, lipids, weight and to quit smoking still as cornerstone therapy.
- Therapies to block RAAS and SGLT2 inhibitors have shown to decrease progression of DKD.

