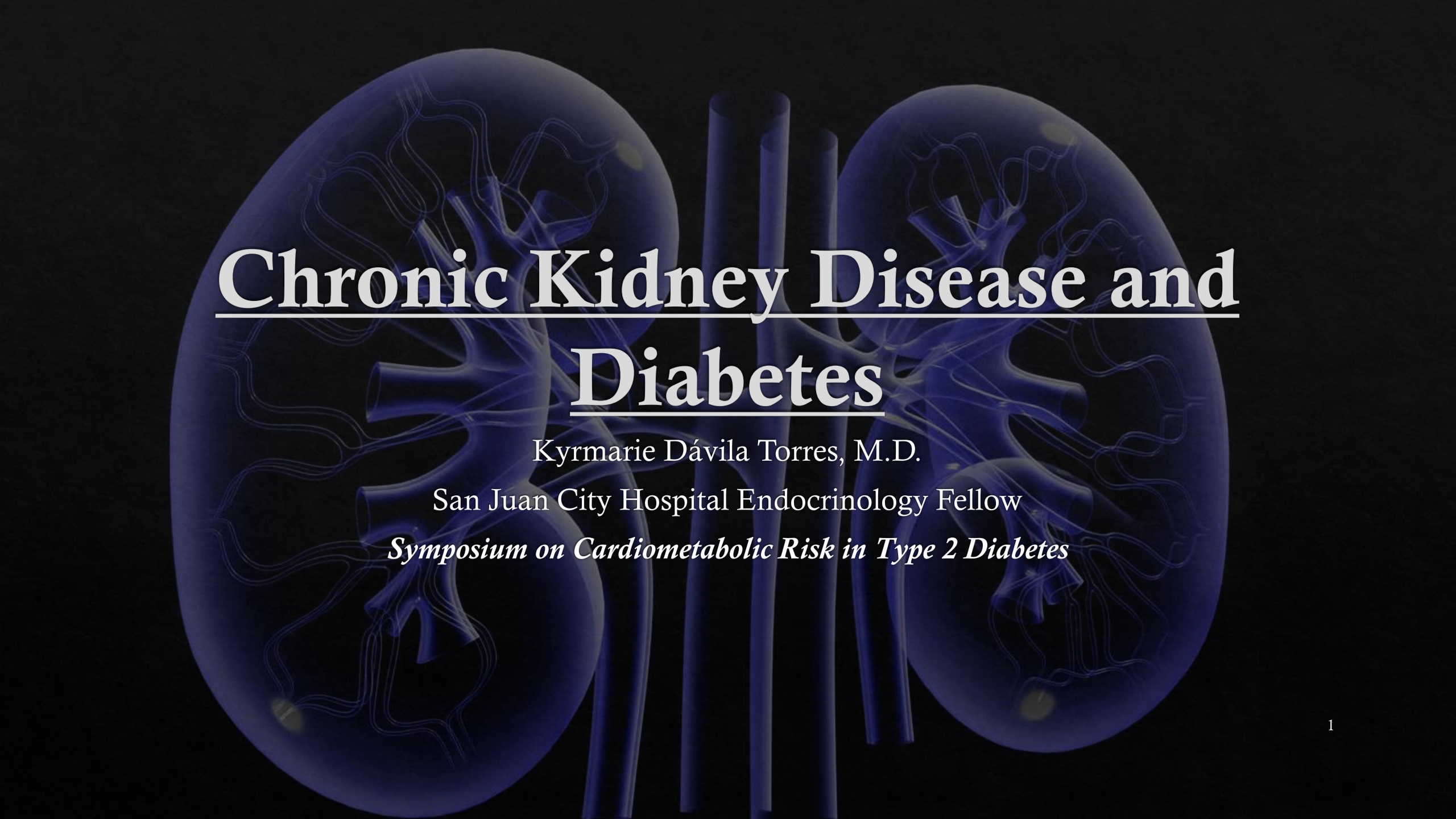


Chronic Kidney Disease and Diabetes

Kyrmarie Dávila Torres, M.D.

San Juan City Hospital Endocrinology Fellow

Symposium on Cardiometabolic Risk in Type 2 Diabetes

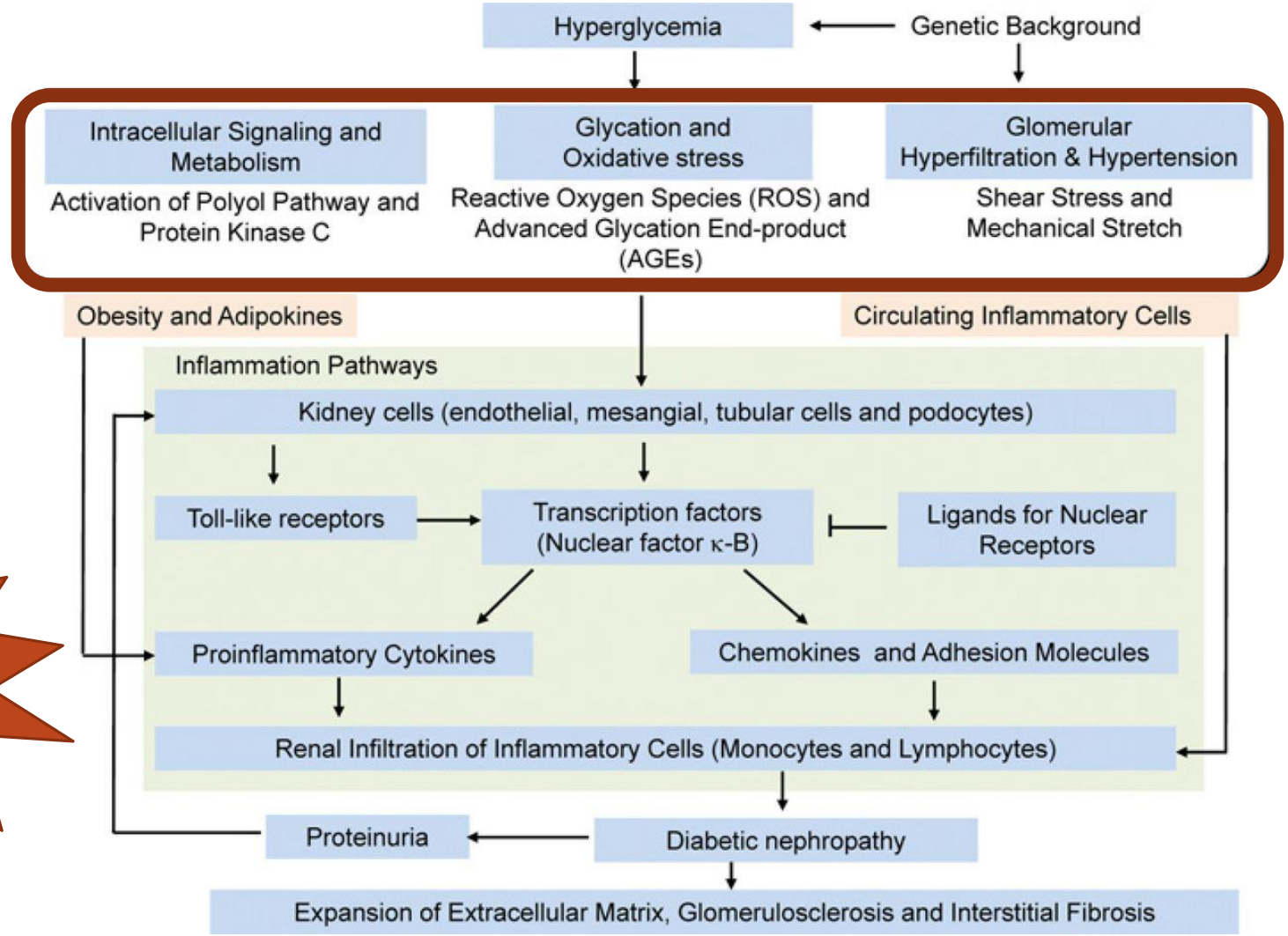
Learning Objectives

- Discuss the pathophysiology of Diabetic Kidney Disease
- Establish the relationship between CKD and CV disease
- Explain current approaches of T2D treatment that include renal preservation
- Discuss the evidence on renal outcomes in CVOTs of glucose lowering agents
- Discuss the possible mechanisms leading to renal protection of SGLT-2 inhibitors
- Review the study design of ongoing renal outcome trials

Definition of Diabetic Kidney Disease (DKD)

Structural	Functional
Glomerular basement membrane thickening	Altered renal hemodynamics
Mesangial expansion	Glomerular hyperfiltration
Microvascular changes	

Hyperglycemia Drives DKD

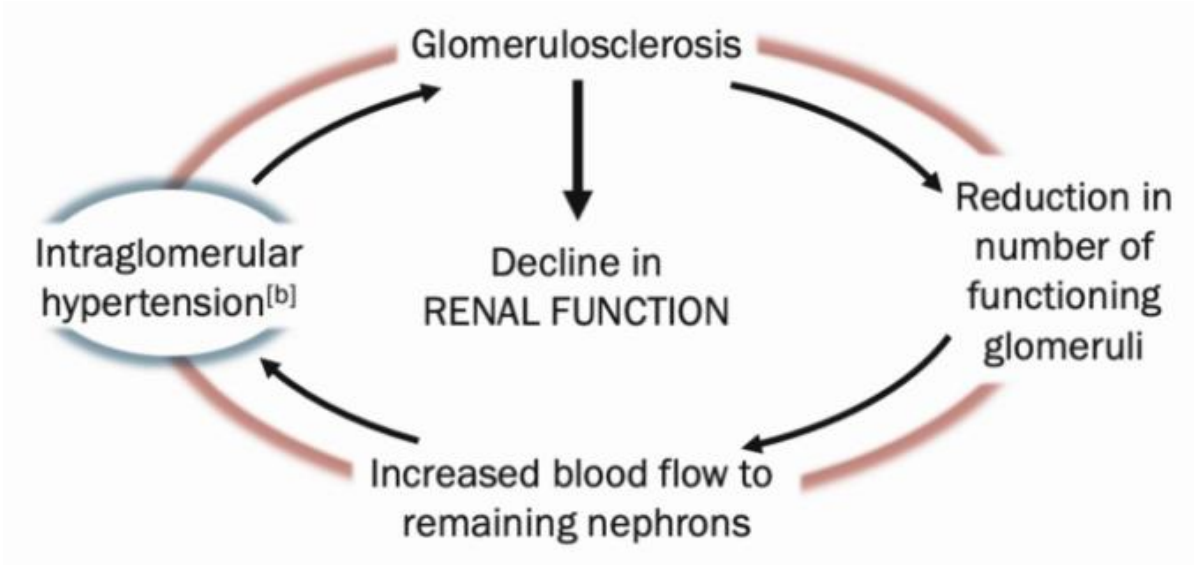


Oxidative Stress drives all three

Reference: Wada J et al; Clinical Science; 2013; 124; 3: 139-152

Hypertension Drives DKD

Uncontrolled hypertension is a risk factor for developing kidney disease and is associated with a more rapid progression of CKD.



Reference: a. Botdorf J, et at; Cardiorenal Med; 2011; 1: 183-192

b. El-Atat FA, et al; J Am Soc Nephrol; 2004; 15: 2816-2827

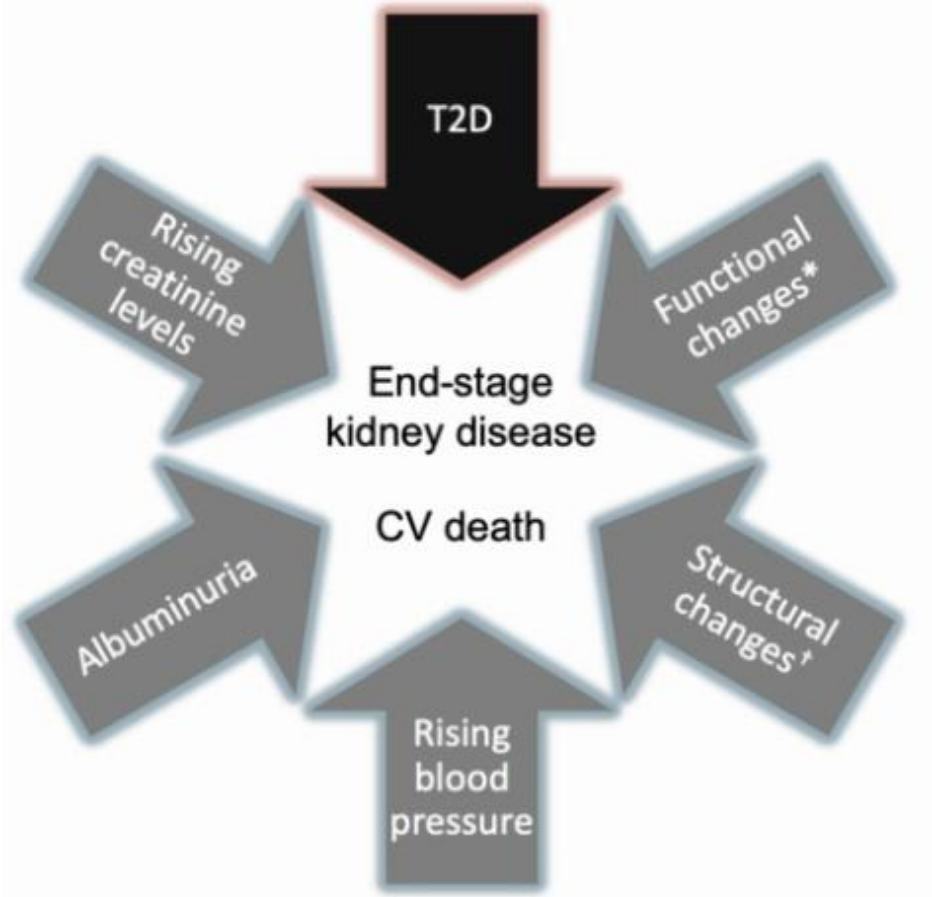
Renal Effects of Obesity

Hormonal	Physical	Structural	Functional
• RAAS • Sympathetic nervous system • Leptin	• Compression of renal parenchyma ("fatty kidney")	• Glomerulopathy (FSGS) • Glomerulomegaly • Albuminuria	• eGFR: Each 1 unit rise of BMI from 24 to 43 will increase eGFR by 2.5 mL

Afferent Vasodilation + Efferent Vasoconstriction = **HYPERFILTRATION**

Reference: KDIGO CKD Work Group; Kidney Int Supple.; 2013; 3: 1-150

The Natural History of T2D Increases the Risk of Microvascular and CV complications



Reference: NICE clinical guideline 28; December 2015

Puerto Rico

Total adult population:

2,596,000

Prevalence of diabetes in adults:

15.4%

Total cases of diabetes in adults:

400,600

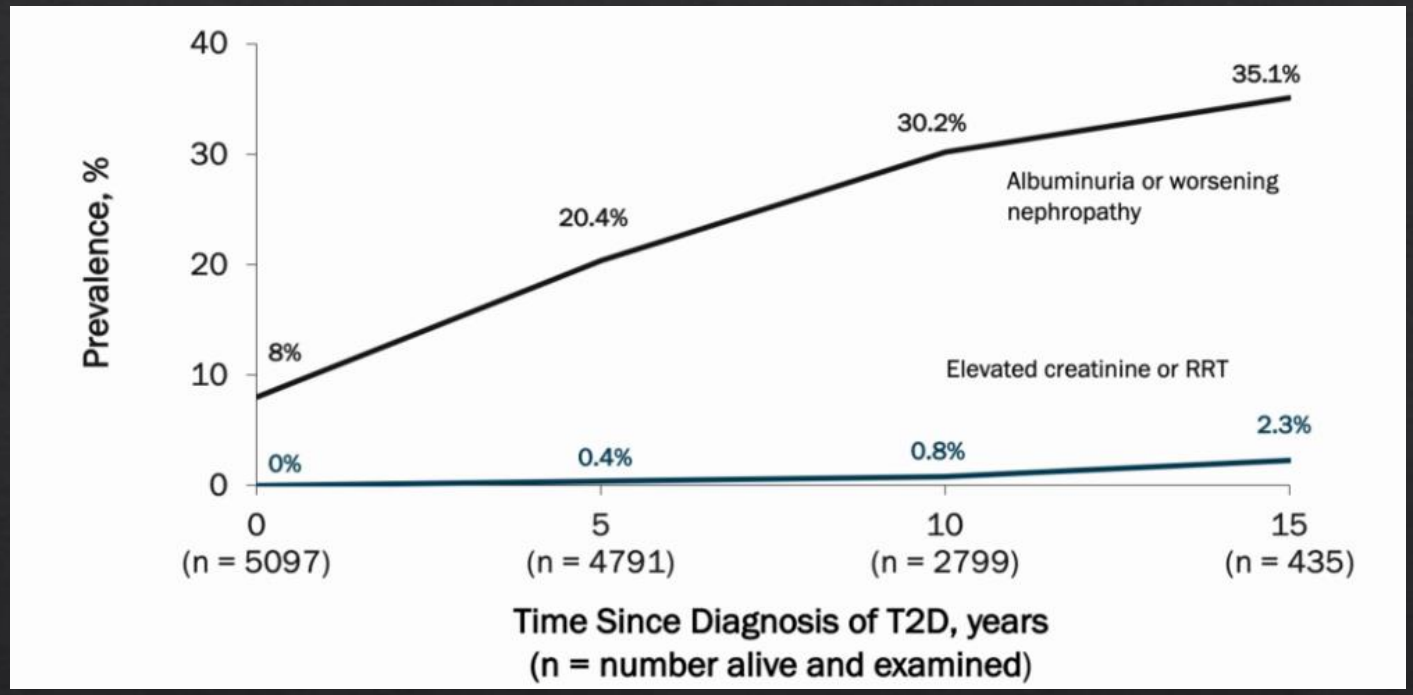
Reference: idf.org

Table 1: The Ten Leading Causes of Death and Age-Adjusted Death Rates in Puerto Rico and the United States, 2010

Rank	Puerto Rico^		United States	
	Cause of Death	Age-adjusted Death Rate*	Cause of Death	Age-adjusted Death Rate**
1	Diseases of Heart	125.7	Diseases of Heart	179.1
2	Malignant Neoplasms	123.8	Malignant Neoplasms	172.8
3	Diabetes	70.4	Chronic Lower Respiratory Diseases	42.2
4	Alzheimer's disease	46.1	Cerebrovascular diseases/Stroke	39.1
5	Cerebrovascular diseases/Stroke	36.7	Accidents (unintentional injuries)	38.0
6	Chronic Lower Respiratory Diseases	26.5	Alzheimer's disease	25.1
7	Homicides	26.3	Diabetes	20.8
8	Accidents (unintentional injuries)	26.2	Nephritis, nephrotic syndrome, and nephrosis	15.3
9	Nephritis, nephrotic syndrome, and nephrosis	23.8	Influenza and pneumonia	15.1
10	Influenza and pneumonia	20.0	Suicides	12.1

^ Preliminary Data
Rates are per 100,000 population; age-adjusted rates per 100,000 U.S. standard population based on the year 2000* and 2010** standards respectively.

Reference: Puerto Rico Chronic Disease Action Plan; 2014-2020



UKPDS: Prevalence of Kidney Disease Increases Over Time After Diagnosis of T2D

Reference: Adler AI et al; Kidney Int; 2003; 63: 225-232

Prognosis of CKD by GFR and Albuminuria Category

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				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 >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

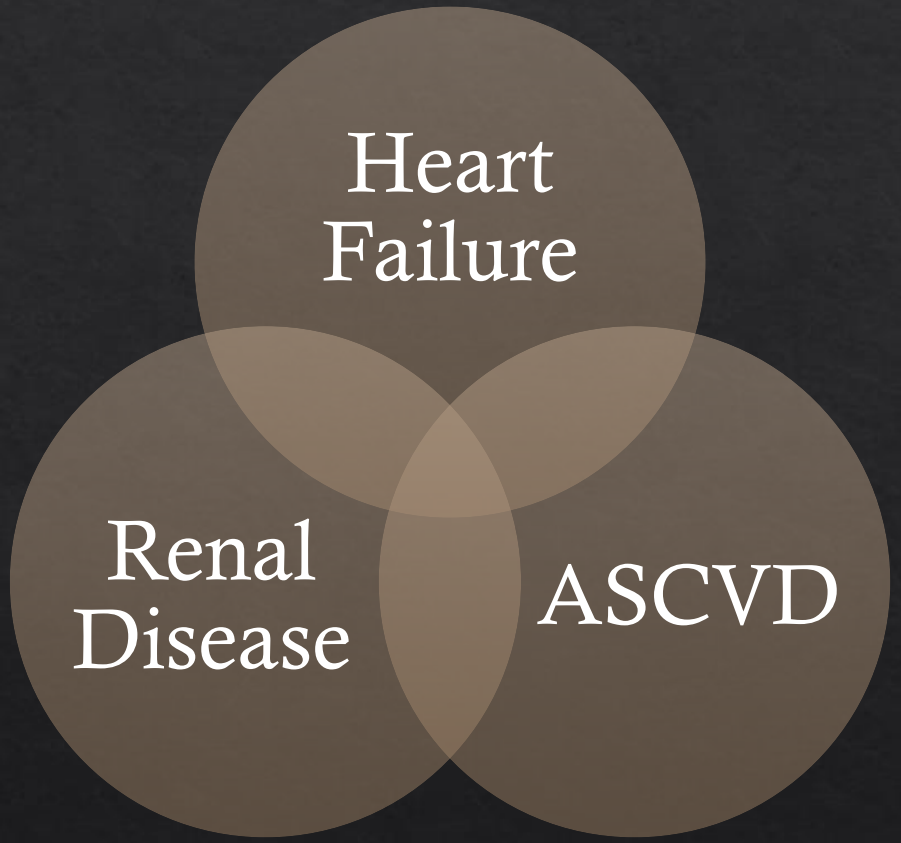
Reference: KDIGO CKD Work Group; Kidney Int Supple.; 2013; 3: 1-150

Myths About DKD

Myth	Fact
Progression of DKD is inevitable	DKD can sometimes be prevented and progression can be slowed through tight control of blood pressure and blood glucose
DKD is more common in T1D compared with T2D	Most guidelines do not differentiate between T2D and T1D; the risks of DKD are likely to be similar between types
DKD occurs exclusively in people with diabetic retinopathy	DKD is often, but not exclusively, associated with diabetic retinopathy
Albuminuria is always a feature of DKD	Albuminuria is a marker of kidney disease, but even when albuminuria is not observed in a patient with diabetes, it is not a guarantee that the patient is free of CKD
People with DKD need to see a nephrologist	Stable DKD can be managed outside of nephrology; referral depends on rate of progression

T2D: Central Role in CV and Renal Disease

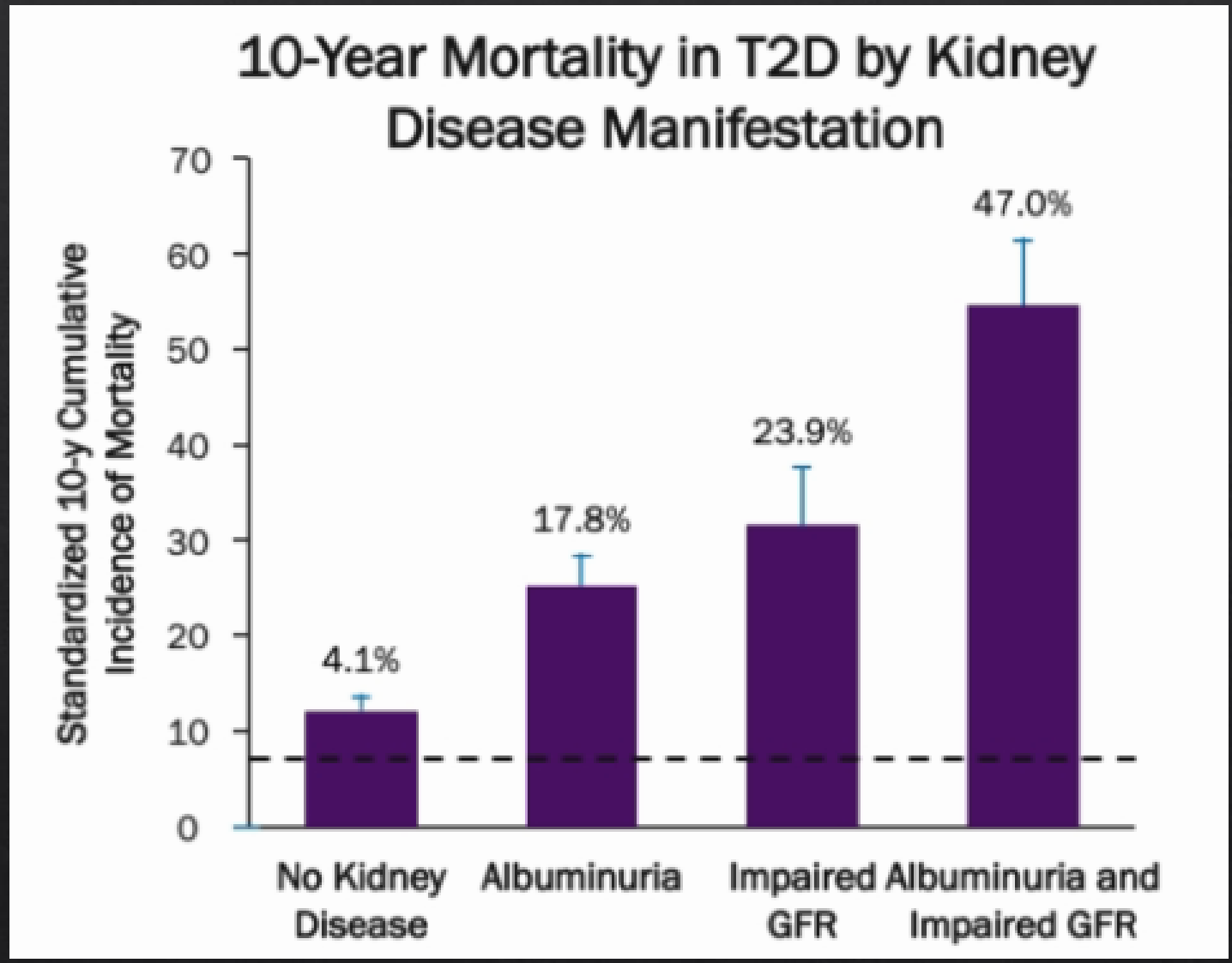
Combination of diabetes and CKD increases 4-fold risk of CVD and mortality



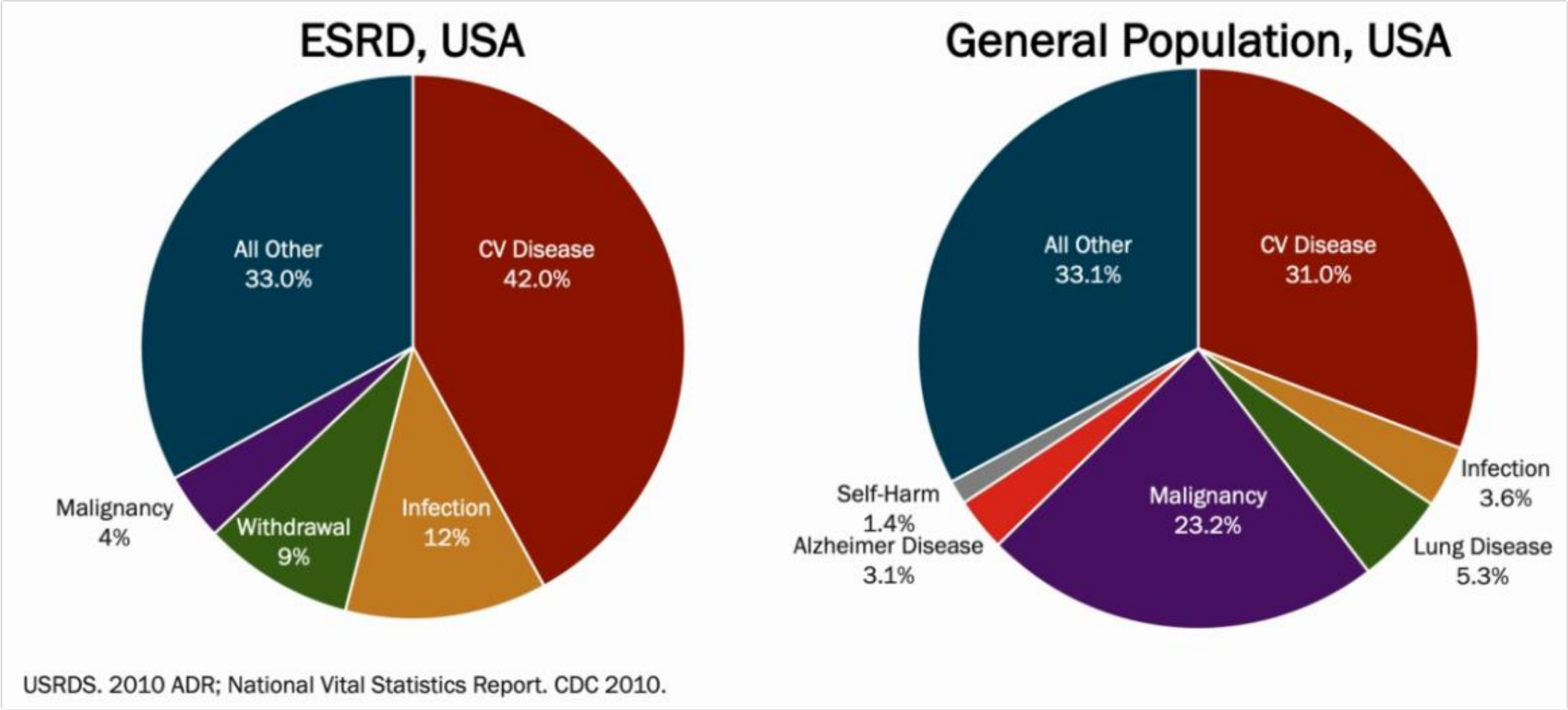
Reference: Verma S. et. al.; Lancet; 2018; 393: 3-5

Kidney Disease Powerfully Predicts Increased Mortality in People with Diabetes

The co-existence of kidney disease and diabetes is associated with greater mortality than the sum of excess risks associated with either diabetes or kidney disease alone.



Reference: Afkarian M, et al.; J Am Soc Nephrol; 2013; 24: 302-308



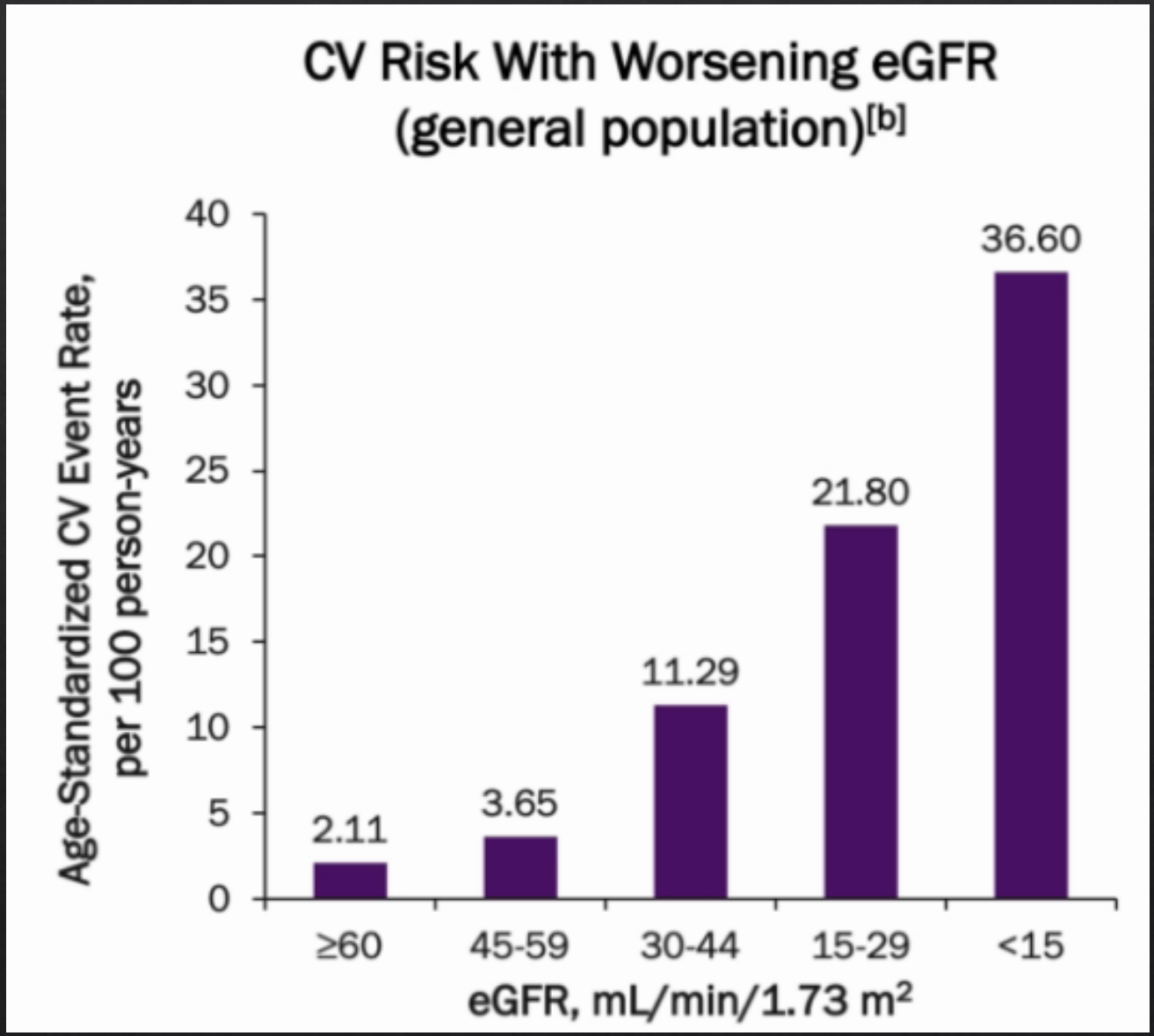
What Do People With CKD Die From? CV Disease Is a Major Cause!

Reference: USRDS; CDC 2010; ADR; National Vital Statistics Report; CDC

Effects of CKD and CVD

Increased risk of CV events

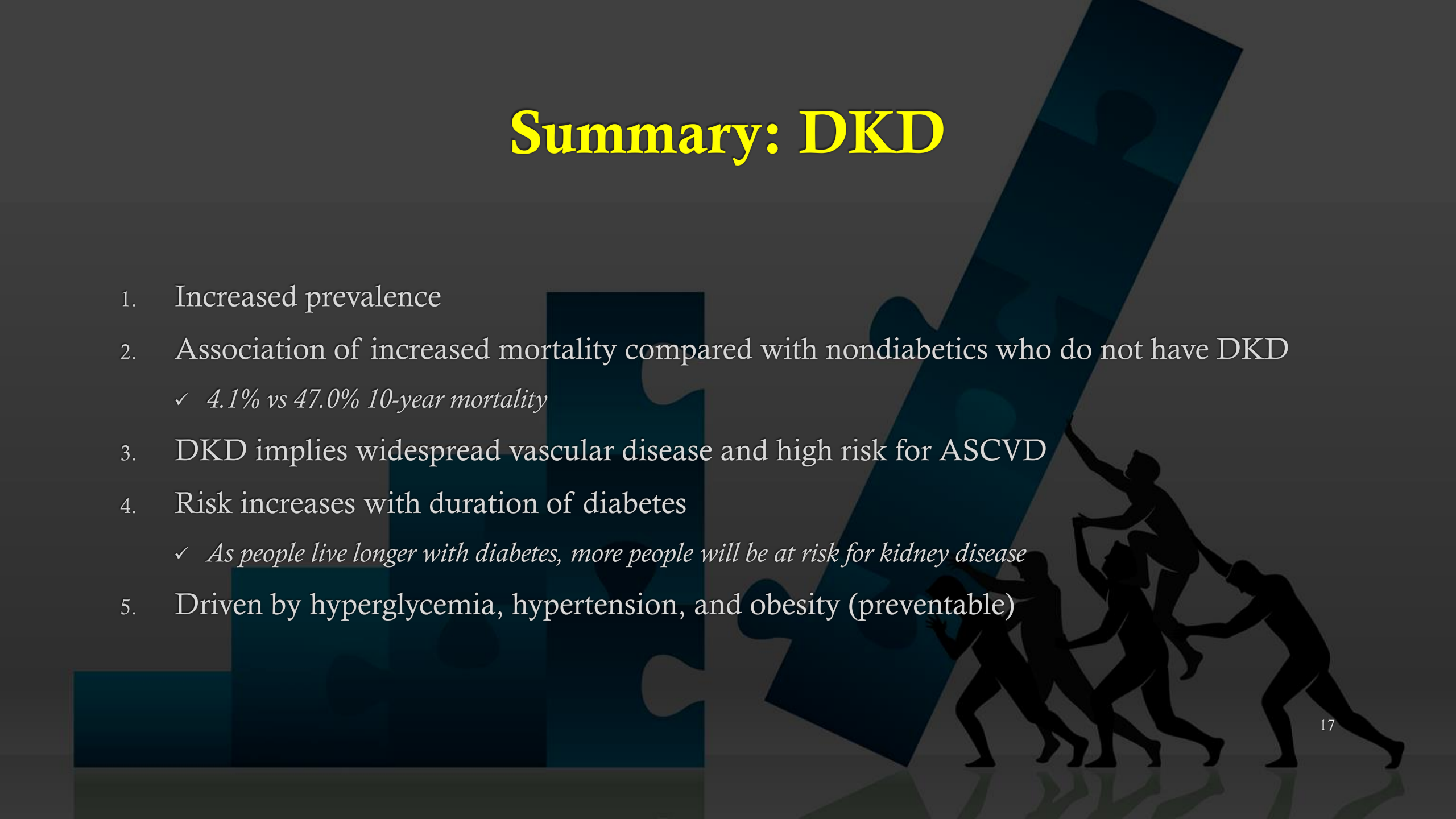
- ✓ *Heart failure*
- ✓ *Recurrent MI*
- ✓ *Sudden cardiac death*
- ✓ *Worse MI outcome*



Reference: a. KDIGO CKD Work Group; Kidney Int Suppl; 2013; 3: 1-150
b. Go AS et al; NEJM; 2004; 351: 1296-1305

Summary: DKD

1. Increased prevalence
2. Association of increased mortality compared with nondiabetics who do not have DKD
   - ✓ *4.1% vs 47.0% 10-year mortality*
3. DKD implies widespread vascular disease and high risk for ASCVD
4. Risk increases with duration of diabetes
   - ✓ *As people live longer with diabetes, more people will be at risk for kidney disease*
5. Driven by hyperglycemia, hypertension, and obesity (preventable)



Non-modifiable

- Increasing age
- Long duration of diabetes
- Ethnicity
- Family history of CKD

Modifiable

- Poor glucose control
- Hypertension
- Hyperlipidemia
- Obesity
- Smoking

Risks Factors for DKD

Reference: Thomas MC; et at; Nat Rev Dis Primers; 2015; 1: 15018

Renal Outcomes in CVOTs and Sub-analyses with DPP-4 Inhibitors

TECOS (*Sitagliptin*): worsening of eGFR

SAVOR-TIMI 53 (*Saxagliptin*): lower ACR but no benefit to eGFR

EXAMINE (*Alogliptin*): no renal data

CARMELINA (*Linagliptin*): no significant change

MARLINA-T2D (*Linagliptin*): no significant change

TECOS
Long term CV effects with Sitagliptin vs Placebo

Study Design

- 14,671 T2D followed for 3 years

Renal composite

- Change in eGFR over time
- Baseline eGFR < 50 mL (**9.4%**)

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Reference: Green J et al; NEJM; 2015; 373: 232

Results: Greater eGFR decline with Sitagliptin (LSM ~1.34 mL/min in 48 months; 0.45 mL/year; P < 0.001) than in the placebo group

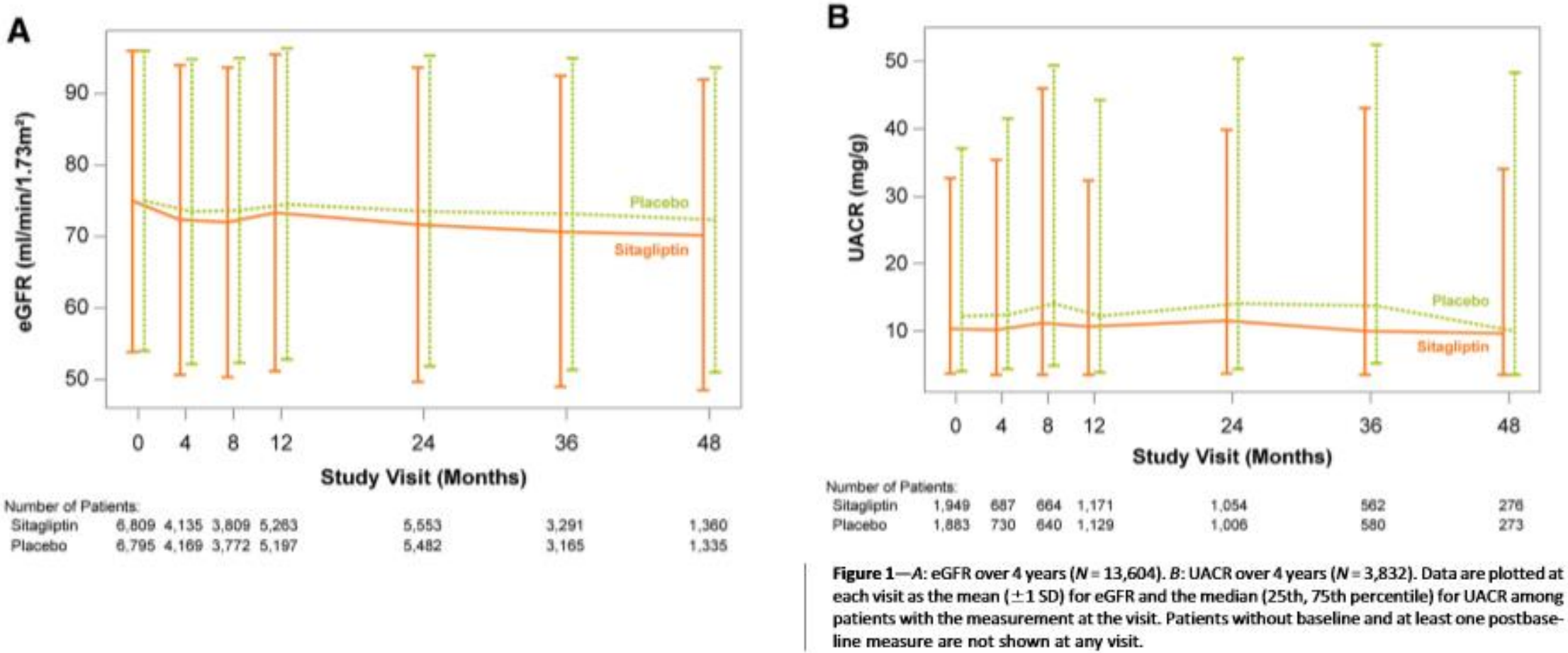


Figure 1—*A*: eGFR over 4 years (*N* = 13,604). *B*: UACR over 4 years (*N* = 3,832). Data are plotted at each visit as the mean (±1 SD) for eGFR and the median (25th, 75th percentile) for UACR among patients with the measurement at the visit. Patients without baseline and at least one postbaseline measure are not shown at any visit.

Reference: Cornel et at; care.diabetesjournals.org

SAVOR-TIMI 53
CV safety and efficacy of Saxagliptin vs Placebo

Study Design

9,696 T2D patients followed for 2.1 years

Renal composite

80% patients on ACE Inhibitors or ARB's

26.8% micro and **9.9%** macro albuminuria

eGFR > 50 mL (**84%**)

eGFR ≥ 30-50 mL (**14%**)

eGFR < 30 mL (**2%**)

Reference: Mosenzone O et at; Diabetes Care 2017; 40: 69

Results: 34.4% mean UACR decrease (mostly for macroalbuminuria); no change in eGFR; no cardiovascular benefits (despite lower UACR).

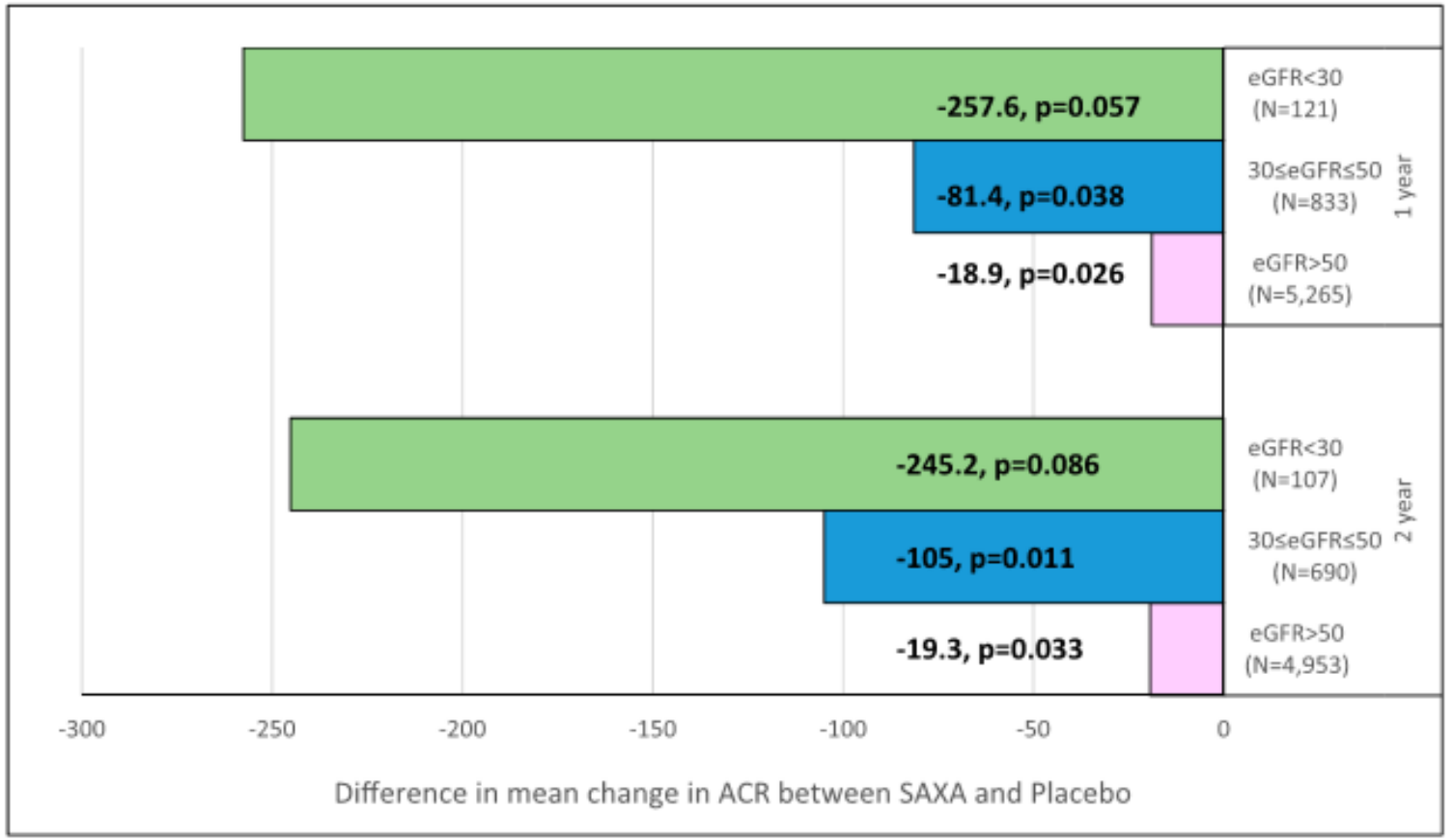
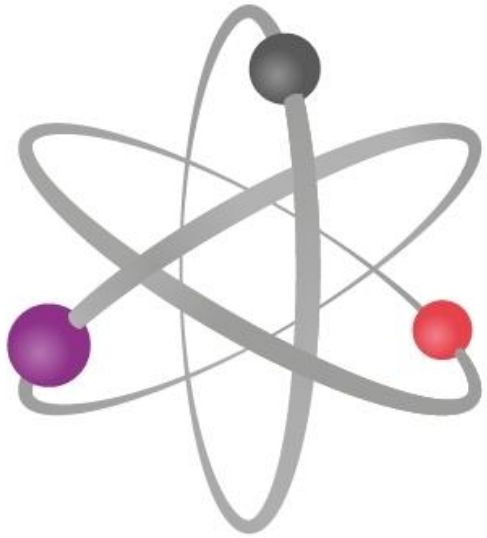


Figure 1—Difference in mean change in ACR (mg/g) as continuous variable among treatment arms by eGFR baseline categories. The change in ACR as a continuous variable by baseline eGFR categories was analyzed using repeated-measures ANOVA, with baseline CV risk group (previous CVD or MRF) and treatment arm as model terms. SAXA, saxagliptin.

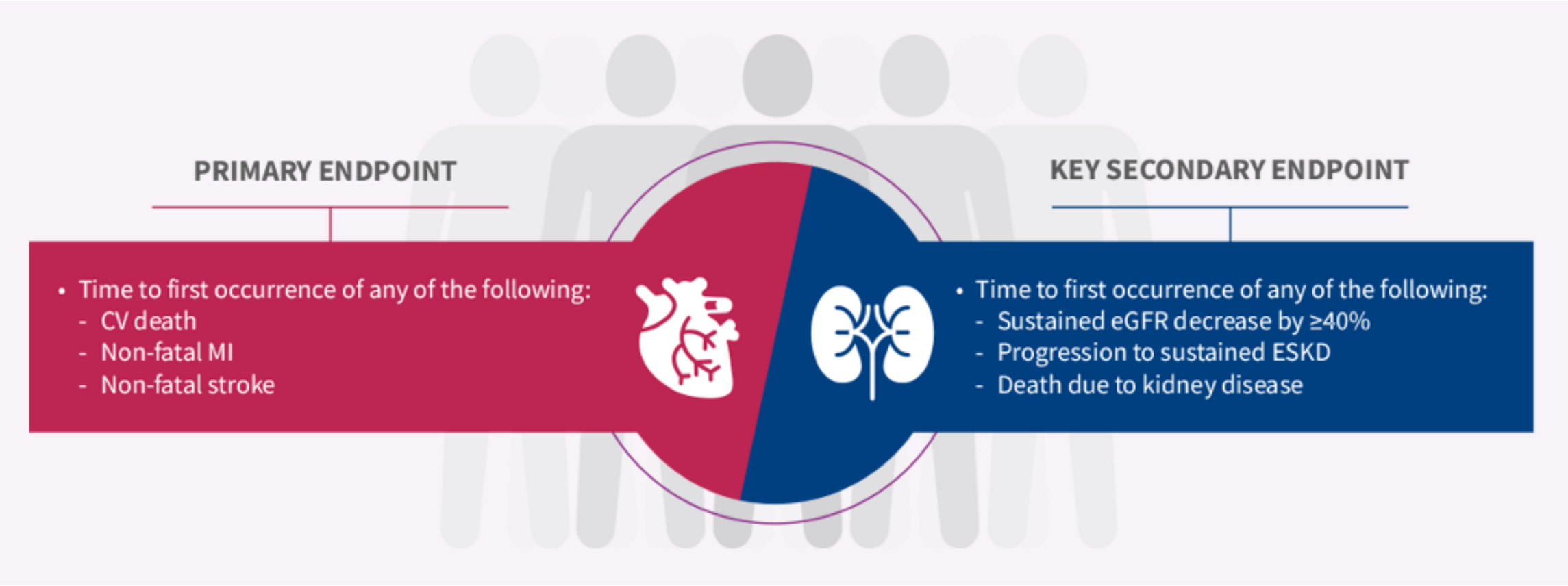
Reference: Mosenzone O et at; Diabetes Care 2017; 40: 69



CARMELINA

The CARMELINA® (CArdiovascular safety and Renal Microvascular outcomE with LINAgliptin in patients with type 2 diabetes at high vascular risk) CVOT investigated the long-term CV and kidney safety profile of linagliptin versus placebo, on top of standard of care

Reference: Carmelinatrial.com



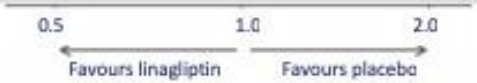
Reference: Carmelinatrial.com

- ✓ No significant kidney composite outcome
- ✓ Reduction in albuminuria progression, microvascular complications

Figure. Kidney and microvascular outcomes

The key secondary kidney outcome was pre-specified, adequately powered, and adjudicated in CARMELINA

	HR (95% CI)	HR (95% CI)	P value
Pre-specified outcomes			
CARMELINA: kidney composite outcome*	1.04 (0.89-1.22)		0.6164
ESKD or death due to KD	0.87 (0.69-1.10)		0.2371
Microvascular composite outcome^	0.86 (0.78-0.95)		0.0032
Albuminuria progression	0.86 (0.78-0.95)		0.0032



*Sustained end-stage kidney disease (ESKD), sustained decrease of ≥40% in estimate glomerular filtration rate (eGFR) from baseline or death due to KD. ^Sustained ESKD, sustained decrease of ≥50% in eGFR, death due to KD, albuminuria progression, retinal photocoagulation or intravitreal injection of and anti-vascular endothelial growth factor therapy for diabetic retinopathy, vitreous haemorrhage or diabetes-related blindness.

Reference: Rosenstock J et at; 2019; JAMA; 321; (1): 69

Baseline Renal Data

Albuminuria	126 mg/g	94%
CKD 3	eGFR 30-59 mL/min	13%
CKD 5	eGFR <15 mL/min	26%

MARLINA-T2D (Linagliptin)
Evaluation of glycemic and renal efficacy of once daily administration of Linagliptin 5 mg for 24 week

Reference: Groop PH et al; Diabetes, Obesity and Metabolism; 2017; 19: 1610

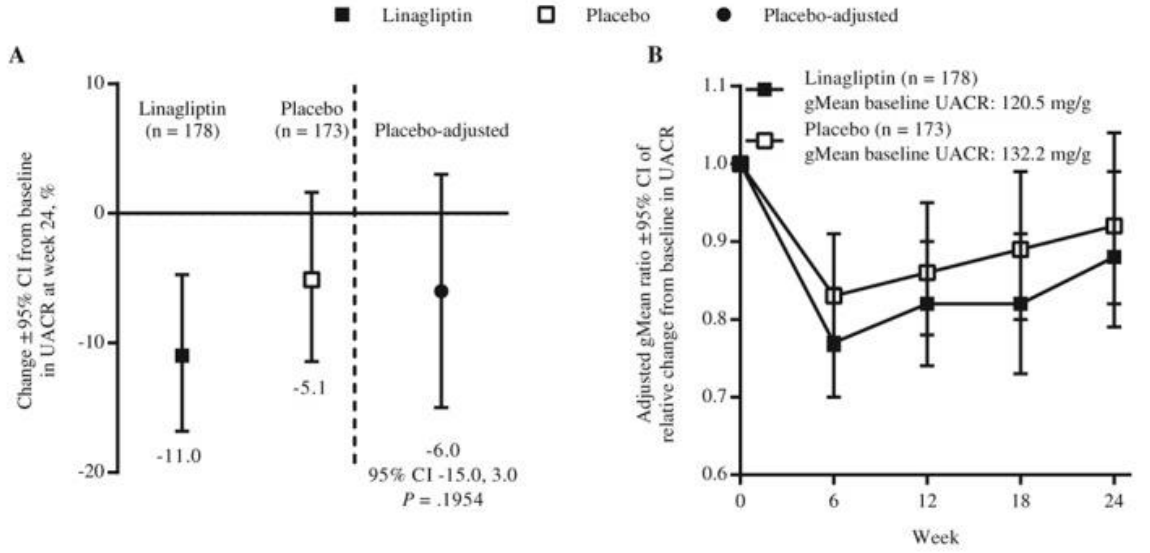
MARLINA-T2D (Linagliptin)

Secondary outcome measures

- The time weighted average of percentage change from baseline in UACR during the course of 24 weeks of treatment
- The change from baseline in estimated glomerular filtration rate (eGFR) after 24 weeks of treatment

Reference: Groop PH et al; Diabetes, Obesity and Metabolism; 2017; 19: 1610

RESULTS: NO SIGNIFICANT CHANGE IN UACR OF eGFR



C

	Number of participants					
	Linagliptin	Placebo	Adjusted gMean ratio	95% CI	*P* value	Interactio *P* value
All participants	178	173	0.94	0.85, 1.03	.1954	
Baseline HbA1c <8.5% (69 mmol/mol)	130	128	0.97	0.87, 1.08	.5868	.2504
Baseline HbA1c ≥8.5% (69 mmol/mol)	48	45	0.85	0.71, 1.03	.0957	
Baseline UACR <300 mg/g	140	134	0.90	0.81, 1.00	.0589	.1190
Baseline UACR ≥300 mg/g	38	39	1.08	0.88, 1.33	.4454	
Asia	112	114	0.95	0.84, 1.07	.3749	
Europe	32	30	0.87	0.70, 1.10	.2508	.7231
North America	34	29	1.00	0.79, 1.25	.9707	

Reference: Groop PH et al; Diabetes, Obesity and Metabolism; 2017; 19: 1610

LEADER (*Liraglutide*): **22%** reduction of renal risk; **26%** lower albuminuria; no effect on eGFR

SUSTAIN-6/PIONEER 6 (*Semaglutide*): **36%** reduction of macroalbuminuria; no effect on eGFR

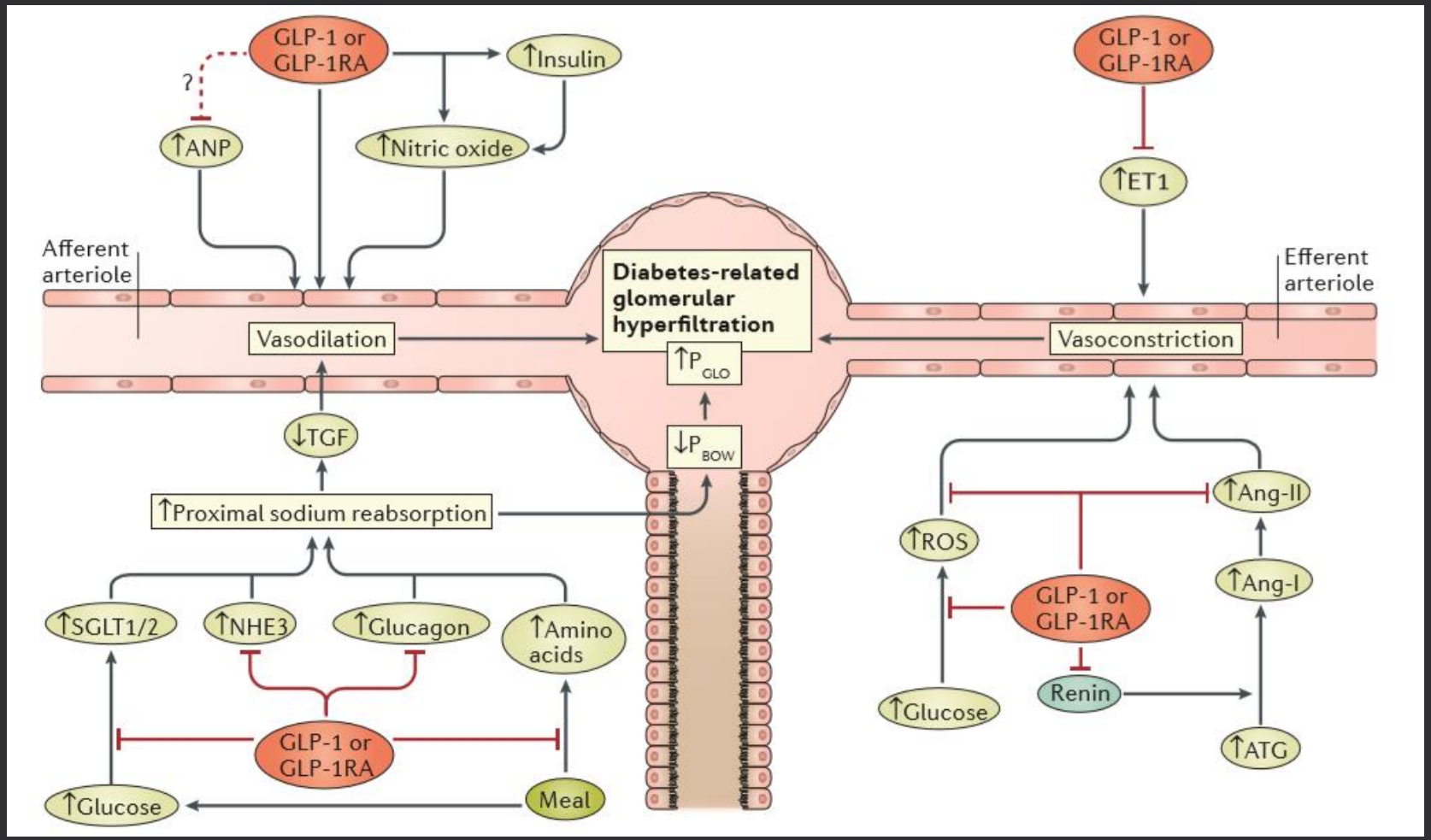
EXSCEL (*Exenatide*): no renal data

HARMONY (A*lbiglutide*): no renal data

ELIXA (*Lixisenatide*): no renal data

REWIND (*Dulaglutide*): ADA 2019

CVOTs and Sub-analyses with GLP-1 Receptor Agonists



***NHE3, sodium–hydrogen exchanger isoform 3**

Reference: Marcel HA; Nature Reviews Nephro; 2017

Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus

Increased **natriuresis** improves haemodynamics in the setting of diabetes-related glomerular hyperfiltration

Electrolyte and fluid homeostasis by influencing feeding and drinking behaviour as well as **electrolyte transport** in the kidneys and gastrointestinal tract

Reference: Marcel HA; Nature Reviews Nephro; 2017

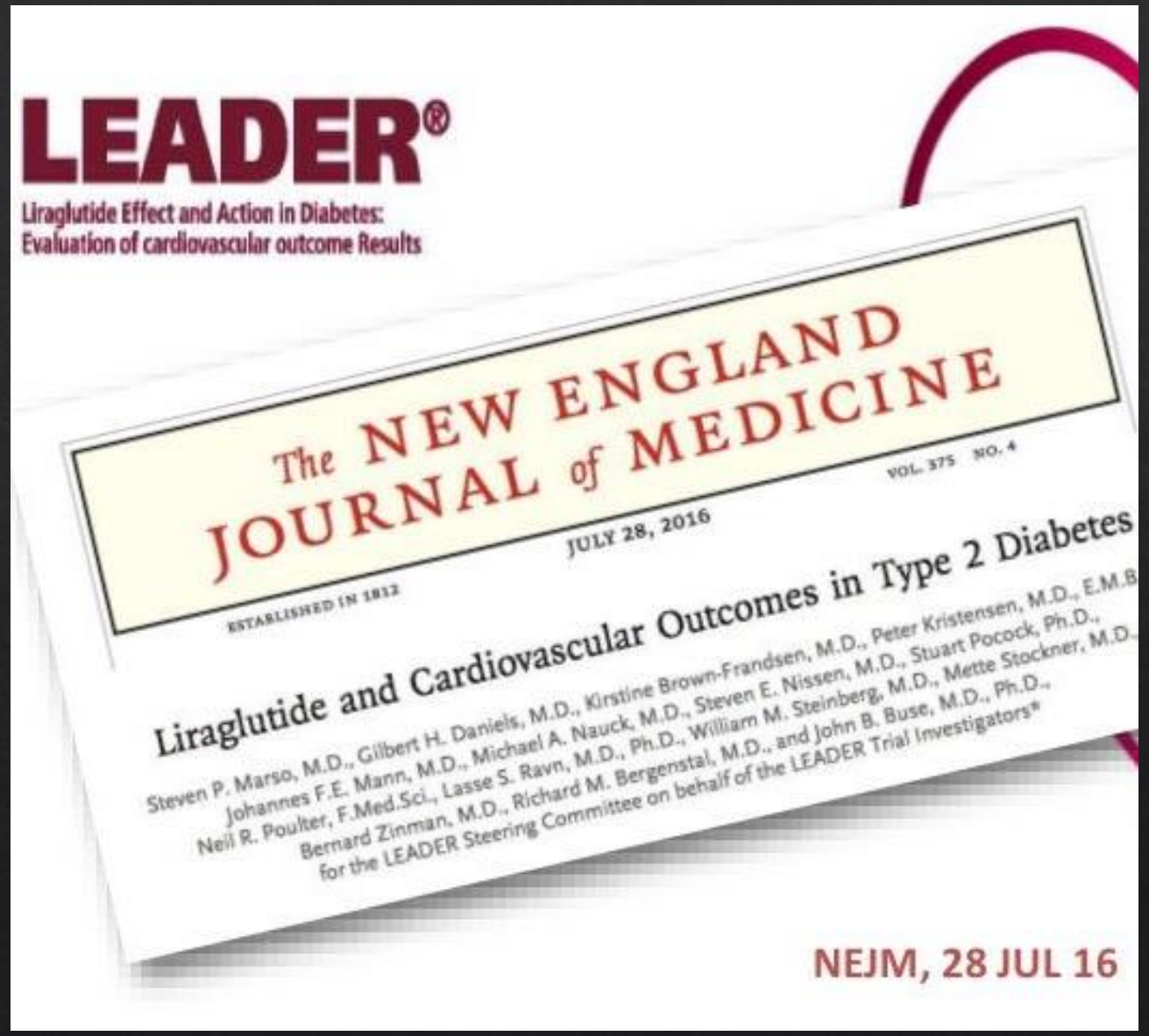
Leader TRIAL (Liraglutide)

Study Design

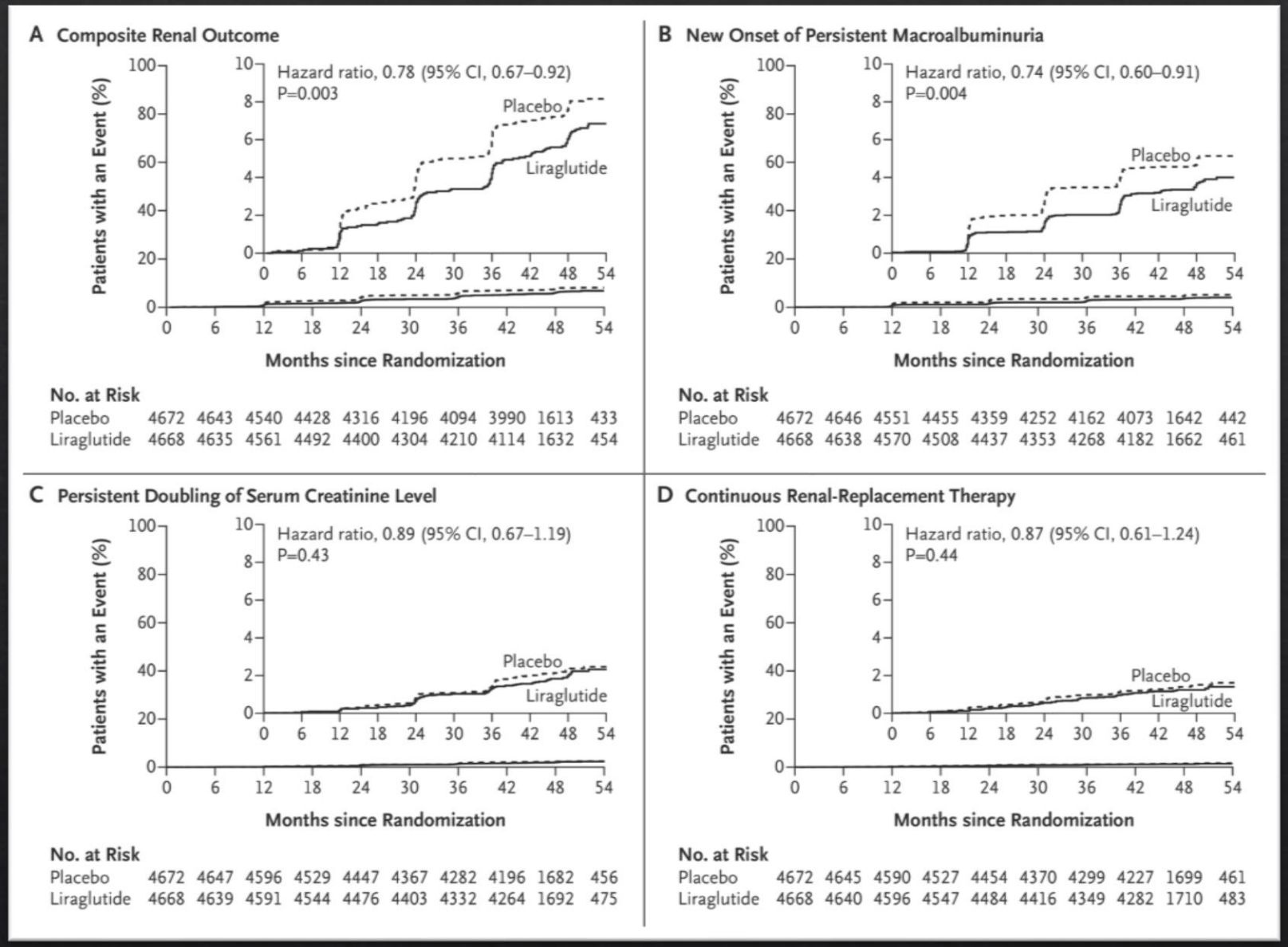
- 9,340 T2D patients, followed 3.8 years
- **24.7%** eGFR < 60 mL/min

Renal composite

- New onset macroalbuminuria
- DSCr
- eGFR < 45 mL/min

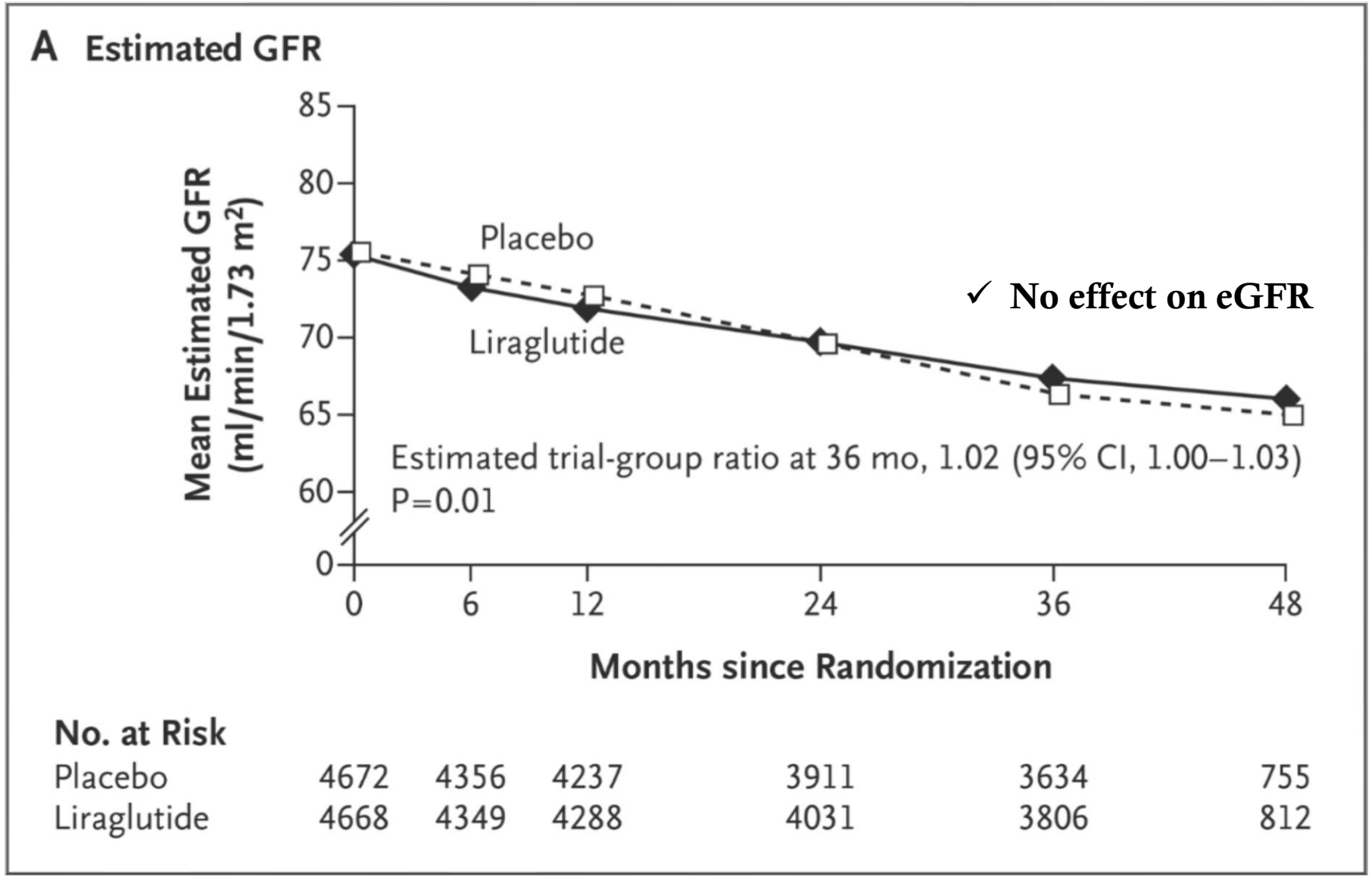


Reference: Marso SP et at; NEJM; 2016; 375: 311



- ✓ **26% Reduction of New Onset Albuminuria**

Reference: Marso SP et at; NEJM; 2016; 375: 311



✓ **No effect on eGFR**

Reference: Marso SP et at; NEJM; 2016; 375: 311

SUSTAIN-6
Cardiovascular effects of Semaglutide

Study Design

- 3,297 T2D patients, followed for 2.1 years
- Included CKD 3 (eGFR < 60 mL/min)

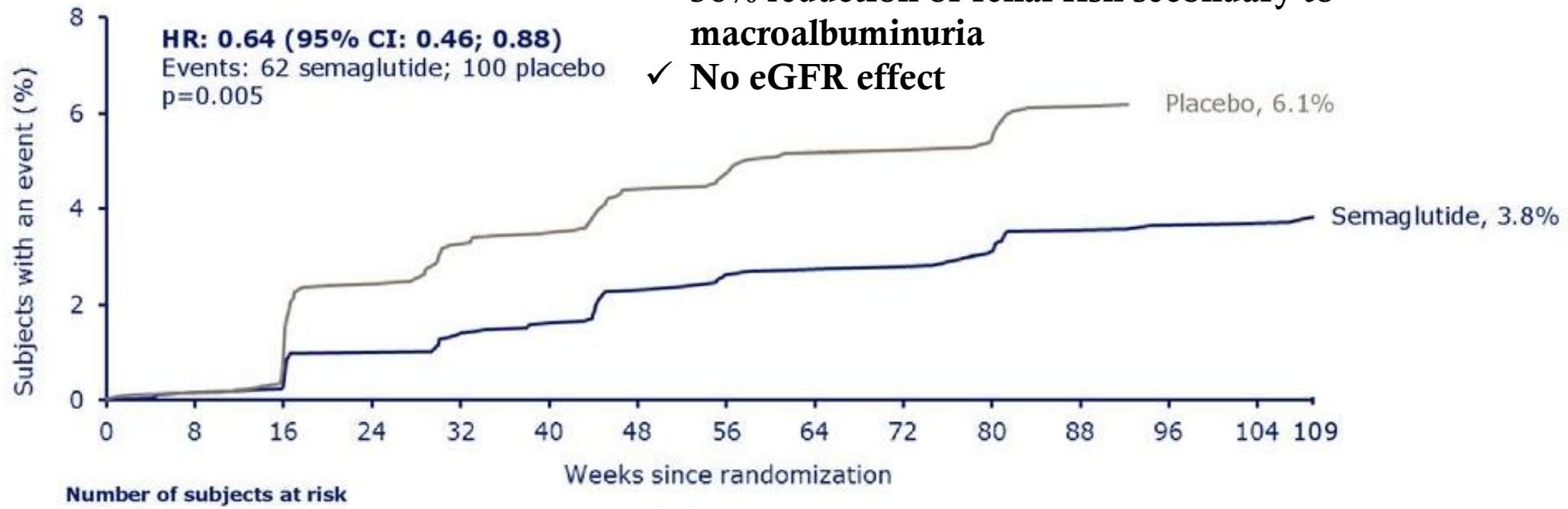
Renal Composite

- Persistent macroalbuminuria
- DSCr
- eGFR< 45 mL/min

Reference: Marso S, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016 Sept 16. doi: 10.1056/NEJMoa160714.

SUSTAIN 6: New or worsening nephropathy

- ✓ **36% reduction of renal risk secondary to macroalbuminuria**
- ✓ **No eGFR effect**



Number of subjects at risk

Semaglutide	1648	1630	1605	1580	1563	1541	1525	1518
Placebo	1649	1629	1570	1545	1518	1498	1471	1465

Kaplan-Meier plot for time from randomization to first (external) event adjudication committee–confirmed new or worsening nephropathy using "in-trial" data from subjects in the full analysis set. HR is from a proportional hazard model.
Marso SP *et al. N Engl J Med.* 2016;375(19):1834–1844.
HR, hazard ratio; CI, confidence interval.

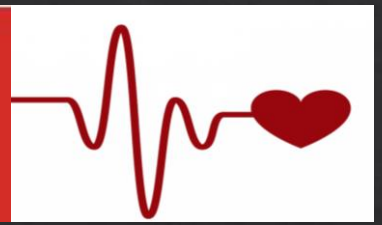
Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

*Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators**

Reference: REWIND; Hertzel C G et al; www.thelancet.com; published June 10, 2019

Trulicity REWIND Trial

Potential for reduction in cardiovascular events



Study design

- 9,901 T2D patients
- Duration of T2D ~ 10 years
- Follow up 5.4 years
- **31%** established CVD

Outcomes

- **Primary**: 3-MACE
- **Secondary**: Microvascular Disease (renal, retinal disease)

Baseline Renal Data

Micro-Macro Albuminuria	**35%**
eGFR < 60 mL/min/1·73 m²	**22.2%**

Reference: REWIND; Hertzel C G et al; www.thelancet.com; published June 10, 2019

The incidence of the composite microvascular renal outcome was lower with dulaglutide than placebo

Renal:
- ✓ Macroalbuminuria
- ✓ Sustained decline in GFR 30%
- ✓ RRT

Eyes:
- ✓ Photocoagulation
- ✓ Anti-VEGF therapy
- ✓ Vitrectomy

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome	594 (12·0%)	2·35	663 (13·4%)	2·66	0·88 (0·79–0·99)*	0·026
Myocardial infarction	223 (4·5%)	0·87	231 (4·7%)	0·91	0·96 (0·79–1·15)	0·63
Non-fatal myocardial infarction	205 (4·1%)	0·80	212 (4·3%)	0·84	0·96 (0·79–1·16)	0·65
Fatal myocardial infarction	26 (0·5%)	0·10	20 (0·4%)	0·08	1·29 (0·72–2·30)	0·40
Stroke	158 (3·2%)	0·61	205 (4·1%)	0·81	0·76 (0·62–0·94)	0·010
Non-fatal stroke	135 (2·7%)	0·52	175 (3·5%)	0·69	0·76 (0·61–0·95)	0·017
Fatal stroke	26 (0·5%)	0·10	33 (0·7%)	0·13	0·78 (0·47–1·30)	0·34
Cardiovascular death†	317 (6·4%)	1·22	346 (7·0%)	1·34	0·91 (0·78–1·06)	0·21
Non-cardiovascular death	219 (4·4%)	0·84	246 (5·0%)	0·95	0·88 (0·73–1·06)	0·18
All-cause death	536 (10·8%)	2·06	592 (12·0%)	2·29	0·90 (0·80–1·01)	0·067
Hospital admission for heart failure or urgent visit	213 (4·3%)	0·83	226 (4·6%)	0·89	0·93 (0·77–1·12)	0·46
Hospital admission for unstable angina	88 (1·8%)	0·34	77 (1·6%)	0·30	1·14 (0·84–1·54)	0·41
Composite microvascular outcome (eye or renal outcome)	910 (18·4%)	3·76	1019 (20·6%)	4·31	0·87 (0·79–0·95)	0·0020
Eye outcome‡	95 (1·9%)	0·37	76 (1·5%)	0·30	1·24 (0·92–1·68)	0·16
Renal outcome§	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004

All hazard ratios (HRs) were estimated with Cox proportional hazards models and p values are two-sided. *After accounting for α=0·009 spent on the primary outcome for the interim analysis, the α for the final analysis is 0·0467, and the HR is 0·88 (95·33% CI 0·79–0·99). †Includes deaths of unknown cause. ‡Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy. §New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy.

Table 2: Primary and secondary outcomes

Reference: REWIND; Hertzel C G et al; www.thelancet.com; published June 10, 2019

AWARD-7: Dulaglutide vs Insulin Glargine in T2D with mod-severe CKD

Study design

- Multicenter, open-label, randomized trial
- T2D with CKD (stages 3–4); on max tolerated ACE/ARB
- HbA1c of 7·5–10·5%
- Duration: 52 weeks

Primary outcome

- HbA1c at 26 weeks, with a 0·4% non-inferiority margin

Secondary outcome

- Estimated glomerular filtration rate (eGFR)
- Estimated UACR

Reference: Katherine R Tuttle KR et at; AWARD-7; www.thelancet.com/diabetes-endocrinology; published online June 14, 2018

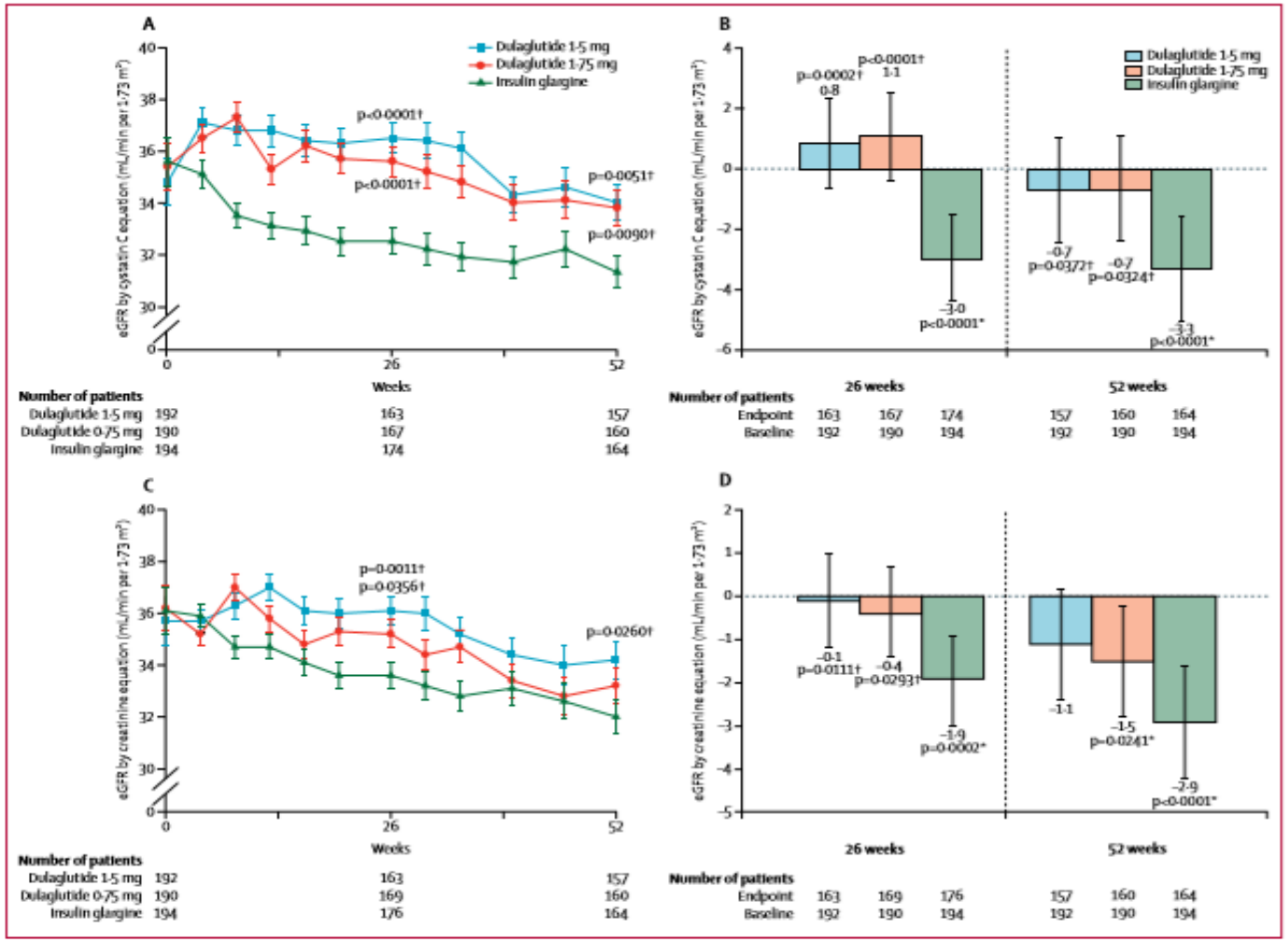


Figure 3: Change in estimated glomerular filtration rate

Values estimated by Chronic Kidney Disease Epidemiology Collaboration equation by cystatin C or creatinine. (A and C) Data presented as estimated glomerular filtration rate (eGFR) values by geometric least squares mean (LSM, SE) from log-transformed analysis; statistical significance was only tested for between-group differences versus insulin glargine. (B and D) Data presented as actual untransformed change from baseline in eGFR values (LSM, 95% CI); p values are reported for statistical significance versus baseline (within group) and versus insulin glargine. Values shown above or below the bars are LSM. Numbers of patients analysed at baseline and endpoints are shown under the x axis. Data are for safety population by use of a mixed-effects repeated measures model analysis. p values are reported for statistical significance at the 26 and 52 week prespecified analyses points. *Versus baseline. †Versus insulin glargine.

- ✓ **At 52 weeks, eGFR was higher with dulaglutide 1·5 mg**

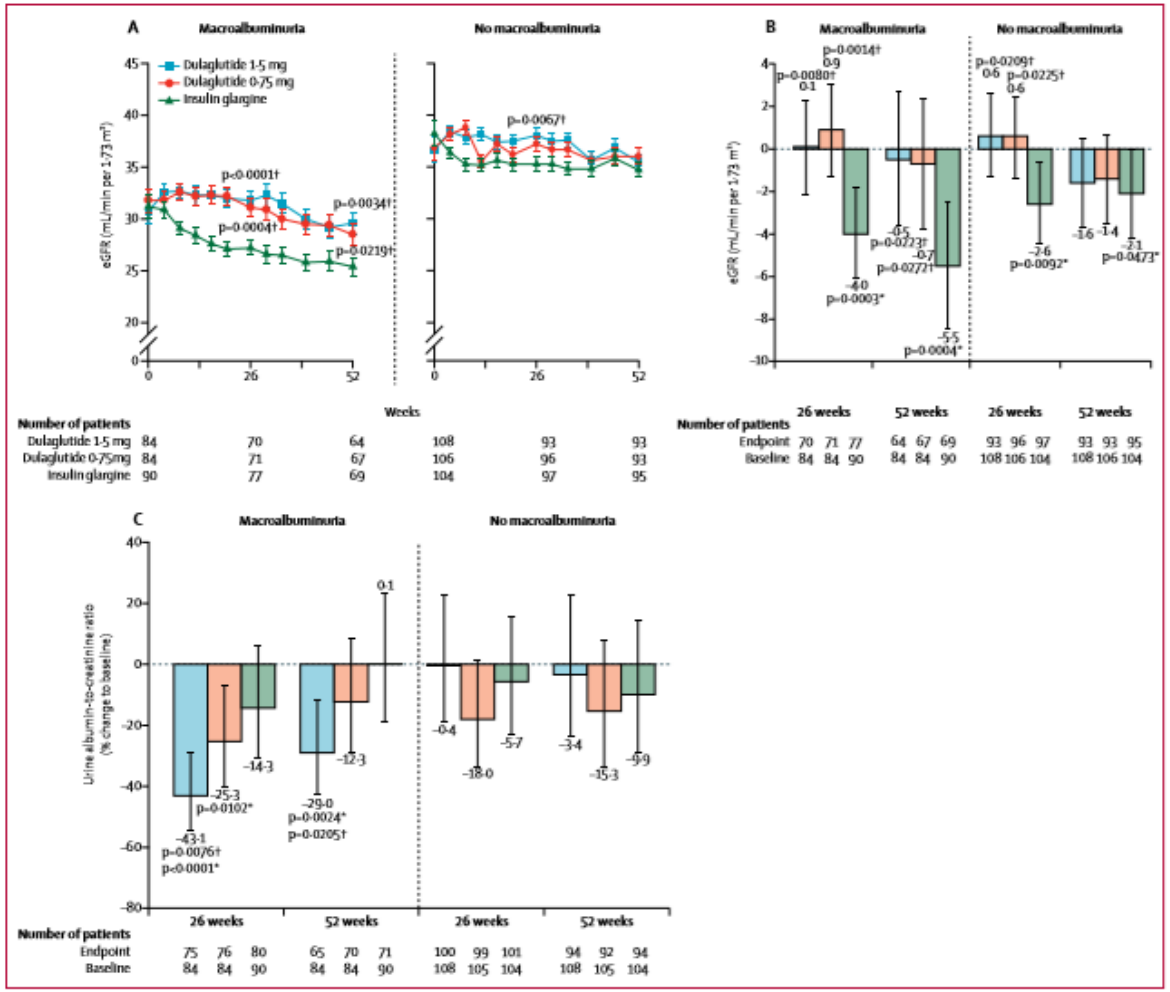


Figure 4: Changes in estimated glomerular filtration rate and albuminuria by macroalbuminuria status at baseline
(A) Estimated glomerular filtration rate (eGFR; calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation by cystatin C) by macroalbuminuria status at baseline, presented as geometric least squares mean (LSM, SE) from log-transformed analysis; statistical significance was only tested for between-group differences versus insulin glargine. (B) Actual untransformed change from baseline in eGFR (calculated by CDK-EPI equation by cystatin C) by macroalbuminuria status at baseline, with values presented as LSM (95% CI), with p values reported for statistical significance versus baseline (within group) and versus insulin glargine; values shown above or below the bars are LSM. (C) Urine albumin-to-creatinine ratio (UACR) by macroalbuminuria status at baseline, presented as LSM (95% CI) for percentage change from baseline, with p values reported for statistical significance versus baseline (within group) and versus insulin glargine. Data presented for safety population, by use of a mixed-effects repeated measures model analysis. p values are reported for statistical significance at the 26 and 52 week prespecified analyses points. Numbers of patients analysed at baseline and endpoints are shown under the x axis. *Versus baseline. †Versus insulin glargine.

- ✓ **At 52 weeks, the effects of dulaglutide 1·5 mg and 0·75 mg on UACR reduction were not significantly different from that of insulin glargine**

  - **22·5%** with dulaglutide 1·5 mg
  - **20·1%** with dulaglutide 0·75 mg
  - **13·0%** with insulin glargine

Reference: Katherine R Tuttle KR et at; AWARD-7; www.thelancet.com/diabetes-endocrinology; published online June 14, 2018

SGLT2 Inhibitors: Take Home Message

Blood Pressure and Body Weight Benefit

Improve CV outcomes in high-risk T2D

- Empagliflozin (EMPA REG)
- Dapagliflozin (DECLARE-TIMI 58)
- Canagliflozin (CANVAS-R)

Improve renal outcomes in high-risk T2D

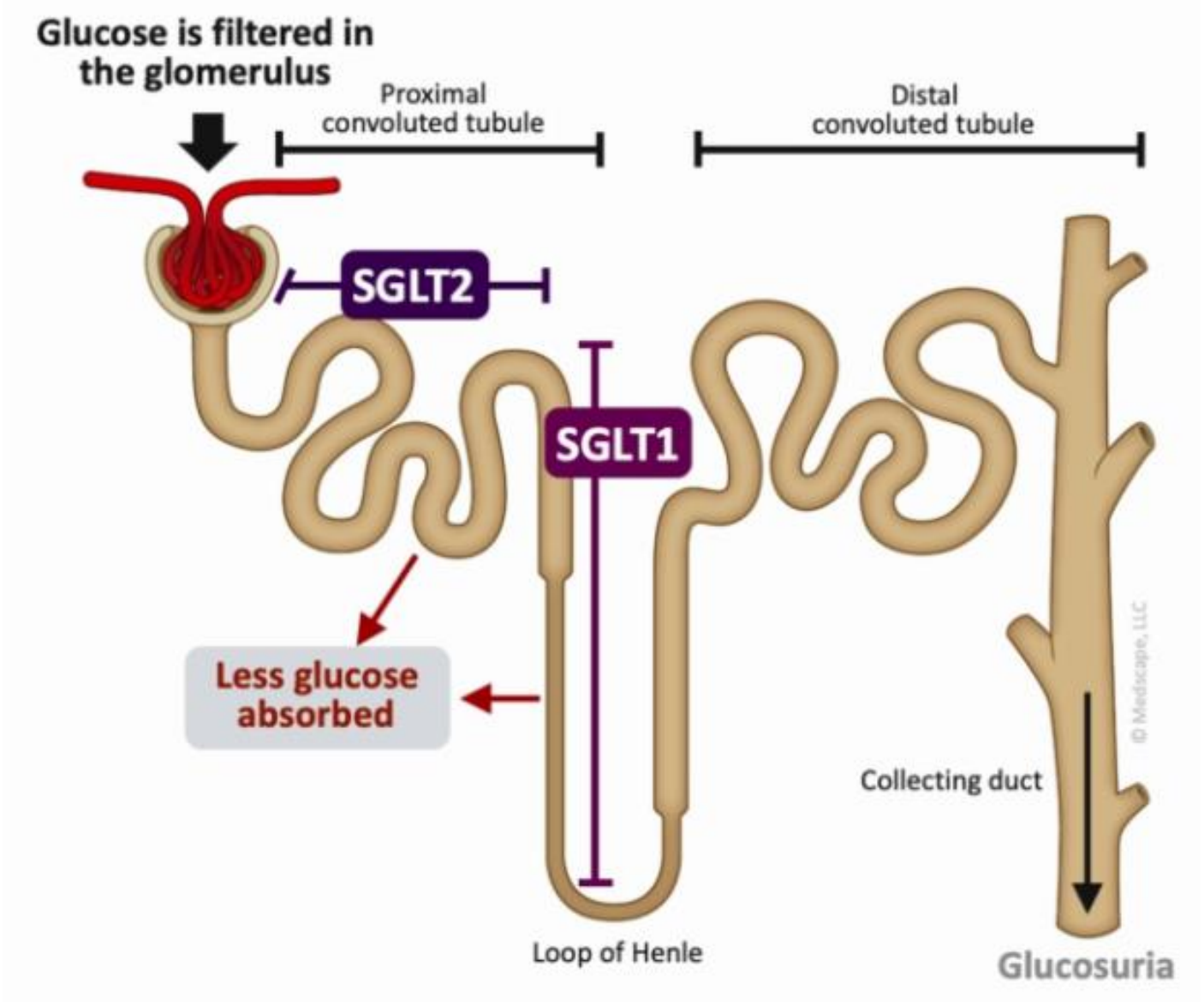
- Canagliflozin primary renal trial (CREDENCE)

Ongoing primary renal trials

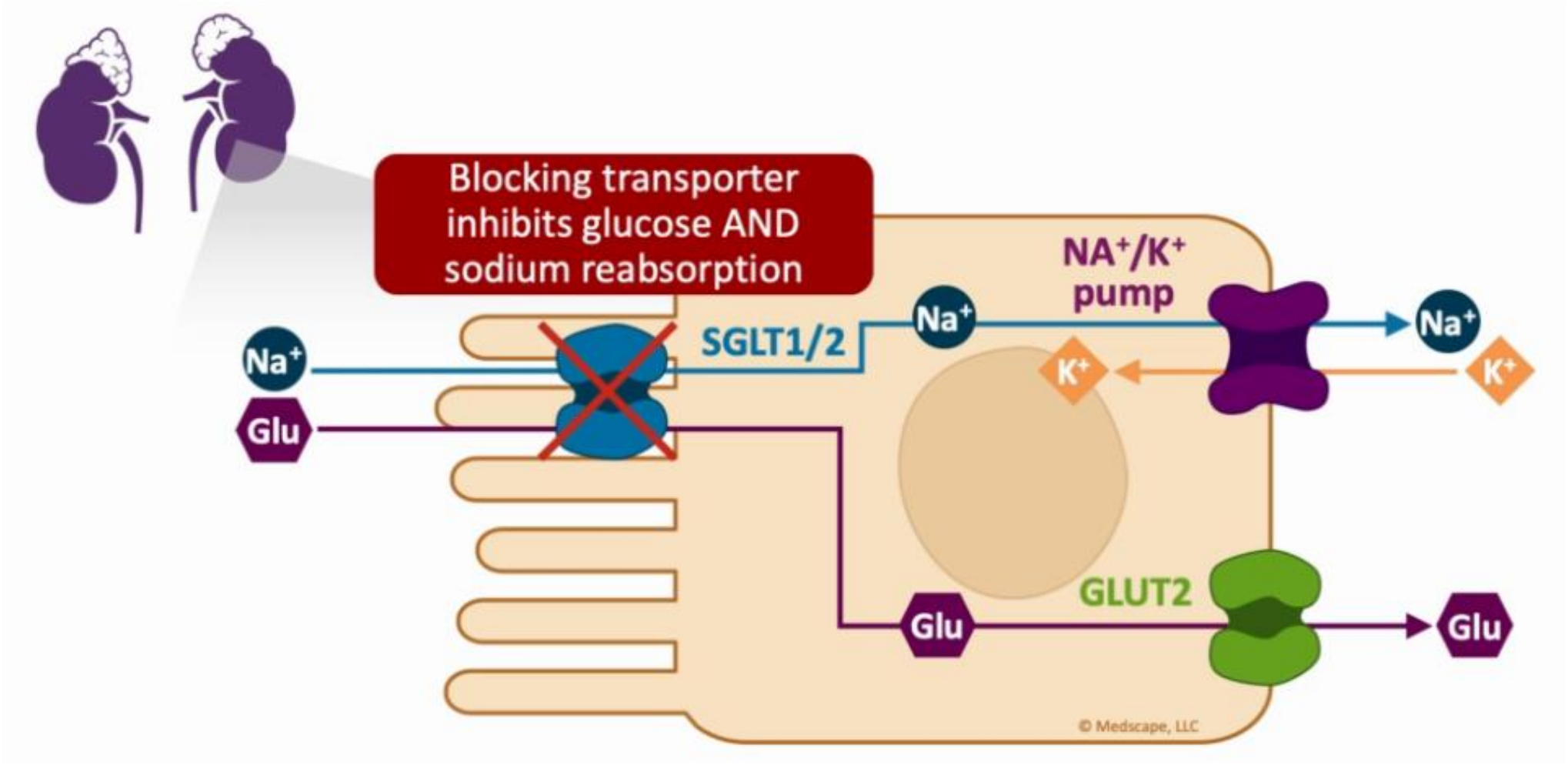
- Empagliflozin (EMPA-KIDNEY)
- Dapagliflozin (DAPA-CKD)

SGLT-2 Inhibitions Improves Glycemic Control In T2D

- ✓ Selective inhibition of SGLT2
- ✓ Reduction in body weight: ~ 400 kcal/d loss from UGE
- ✓ Glycemic control declines with impaired eGFR and renal function: diuretic with "brakes"

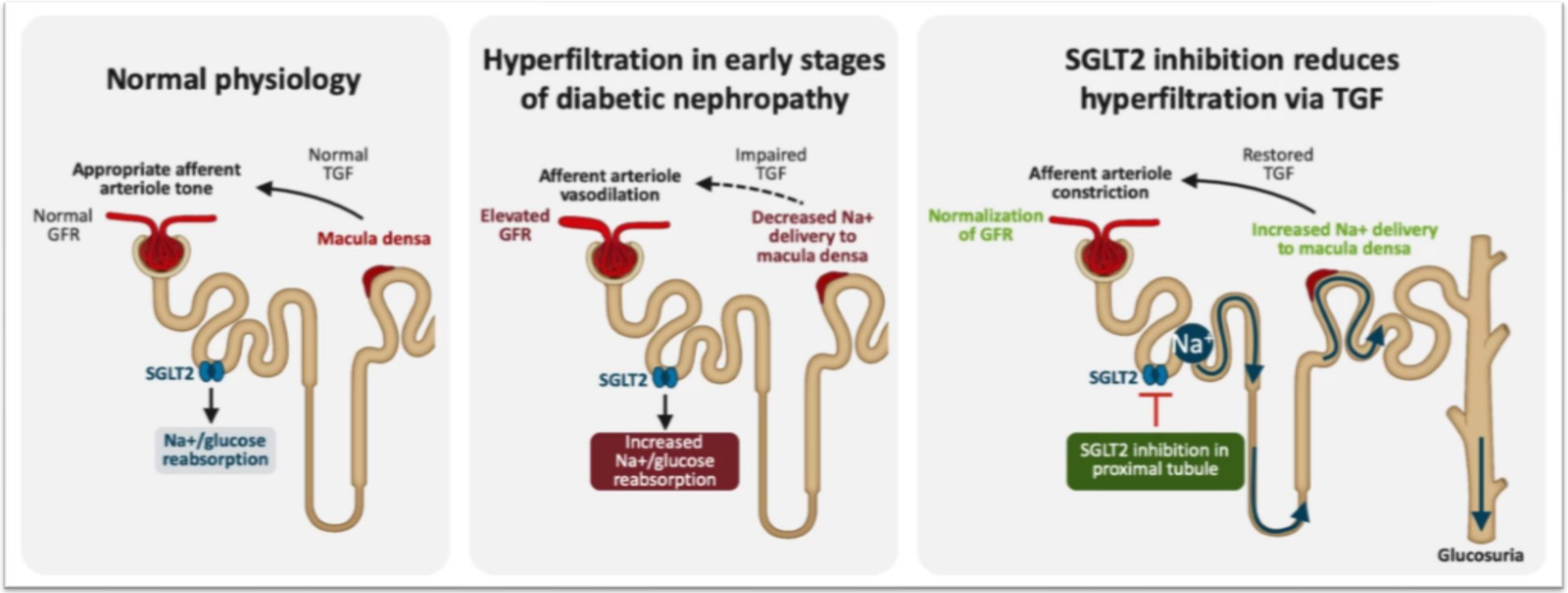


Reference: Wright EM, et al; Physio Rev; 2011; 91: 733-794



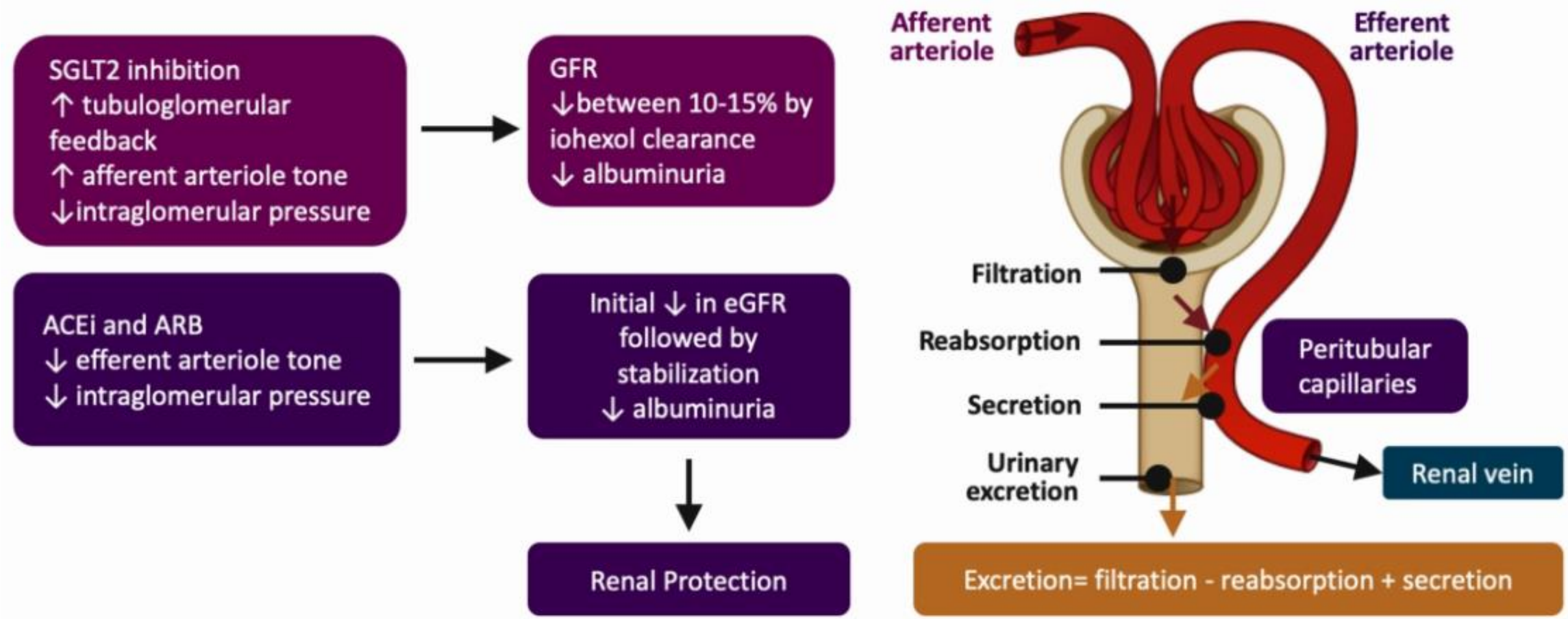
Glucose Transport in the Proximal Tubule

Reference: Bakris GL et al; Kidney Int; 2009; 75: 1272-1277



SGLT2 Inhibitors Lower GFR

Reference: Cherney DZ, et al; Circulation; 2014; 129: 587-597



SGLT2 Inhibitors and ACEi/ARB Reduce Intraglomerular Pressure Possible Mechanism for Renal Protection

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

:Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334

Empagliflozin and Progression of Kidney Disease in T2D-Secondary Outcomes From EMPA-REG

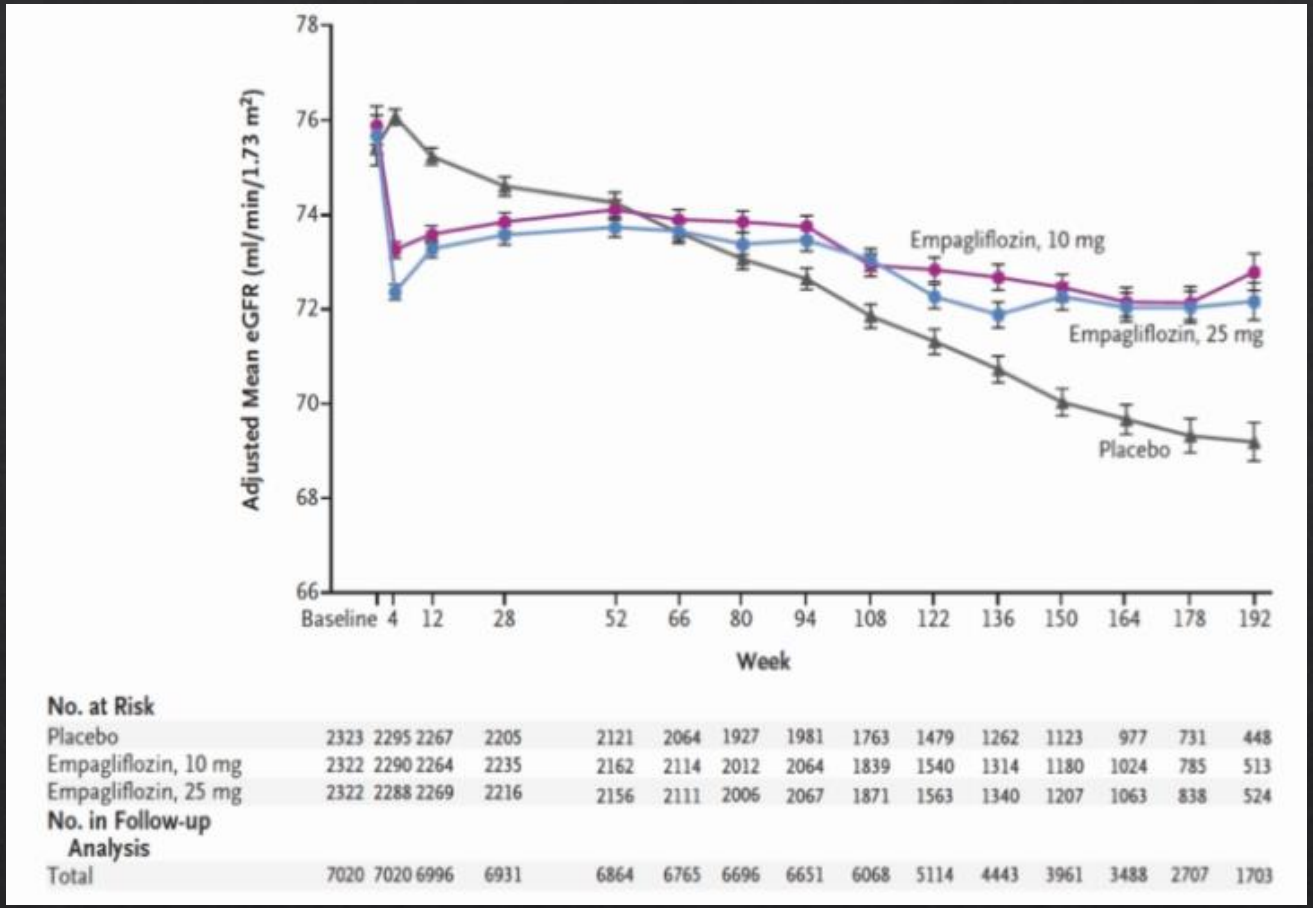
Hypothesis: Rates of progression of kidney disease and clinically relevant renal events will be lower among patients receiving Empagliflozin than among those receiving placebo.

Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334

Intervention and Renal Composite

Population	Intervention	Renal composite	Follow-up
• 7020 patients with T2D at high CV risk and with an eGFR > 30 mL/min/1.73m^2 • **26%** CKD eGFR < 60 mL/min	• Empagliflozin 10mg or 25mg once daily	• Progression to macroalbuminuria • DSCr (post hoc) • Initiation of RRT • Death from renal disease • Incident microalbuminuria	• Up to 48 months

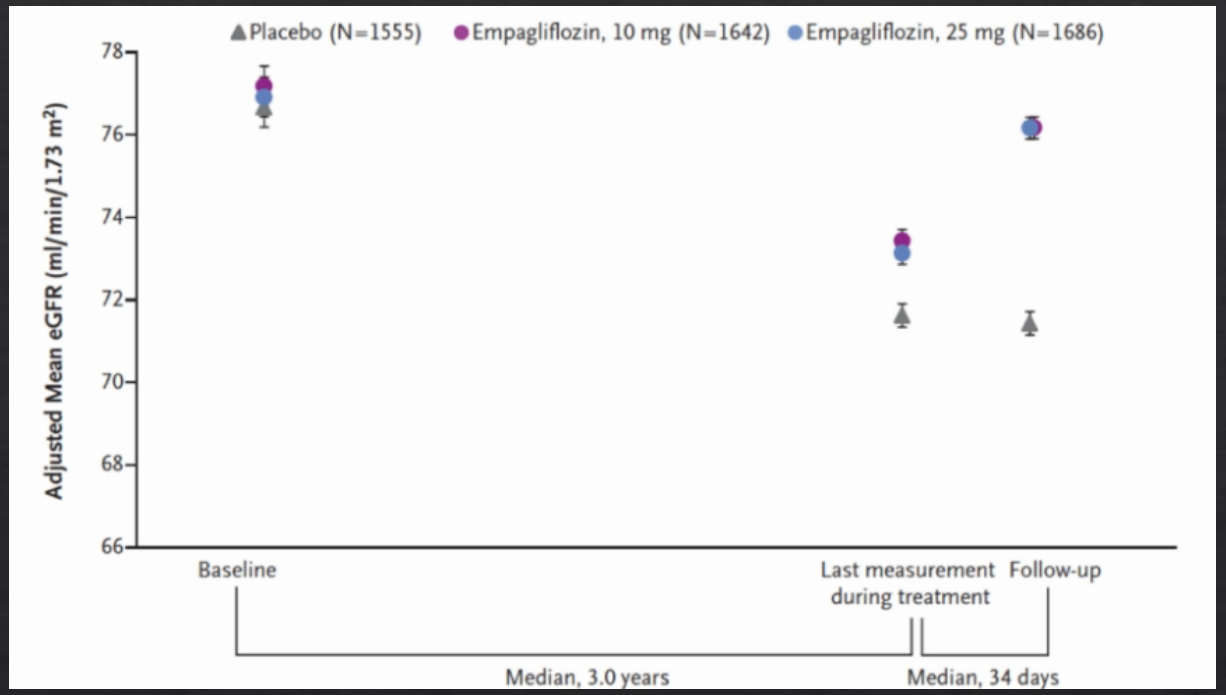
Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Change in eGFR over 192 weeks

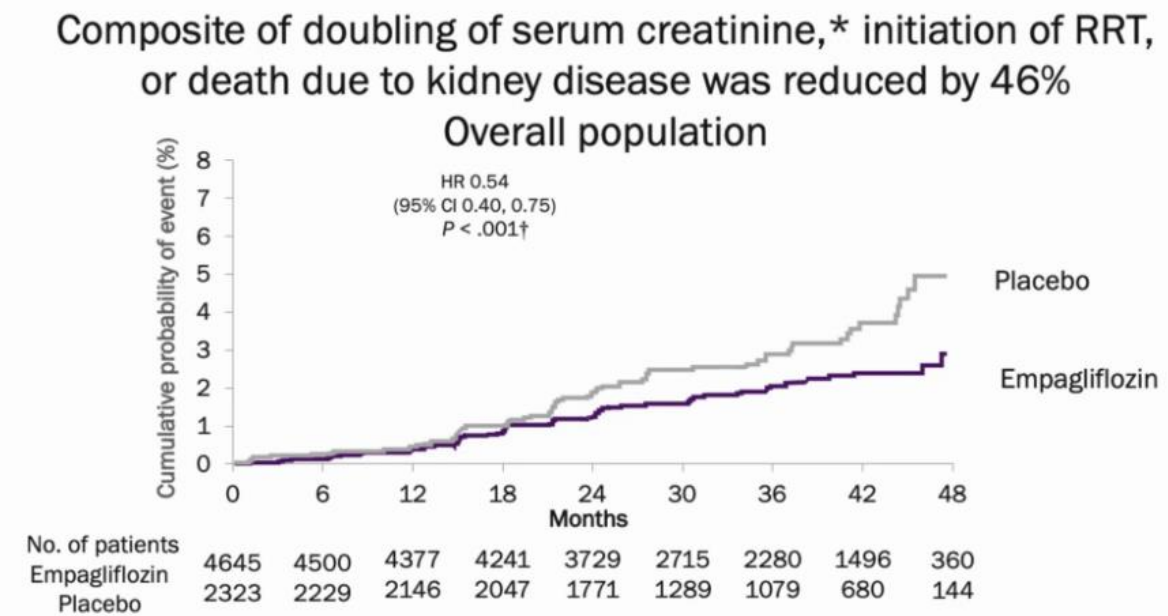
Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334



Change in eGFR from baseline to last measurement during treatment and follow-up

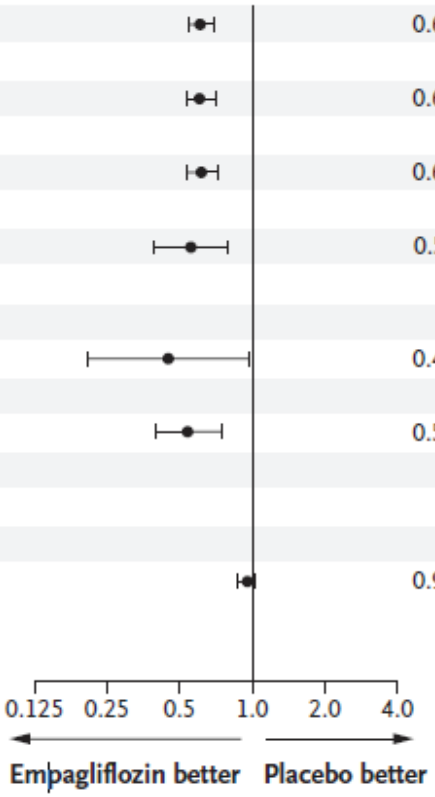
Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334

Hard Renal Outcomes



Reference: Wanner C. et al.; N Engl J Med; 2016; 375: 323-334

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Conclusions from EMPA-REG

"In patients with T2D at high CV risk, Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

DECLARE-TIMI 58: Dapagliflozin and cardiovascular outcomes in T2D

Hypothesis: Evaluate effects of Dapagliflozin on CV and renal outcomes

Design: Randomized, double blind, placebo-controlled trial

Population: 17,160 patients with T2D with or at high risk for CV disease

Outcome: CV death or hospitalization for HF

Duration: 4.2 years

Reference: Wiviott SD et at; NEJM; 2019; 380: 347

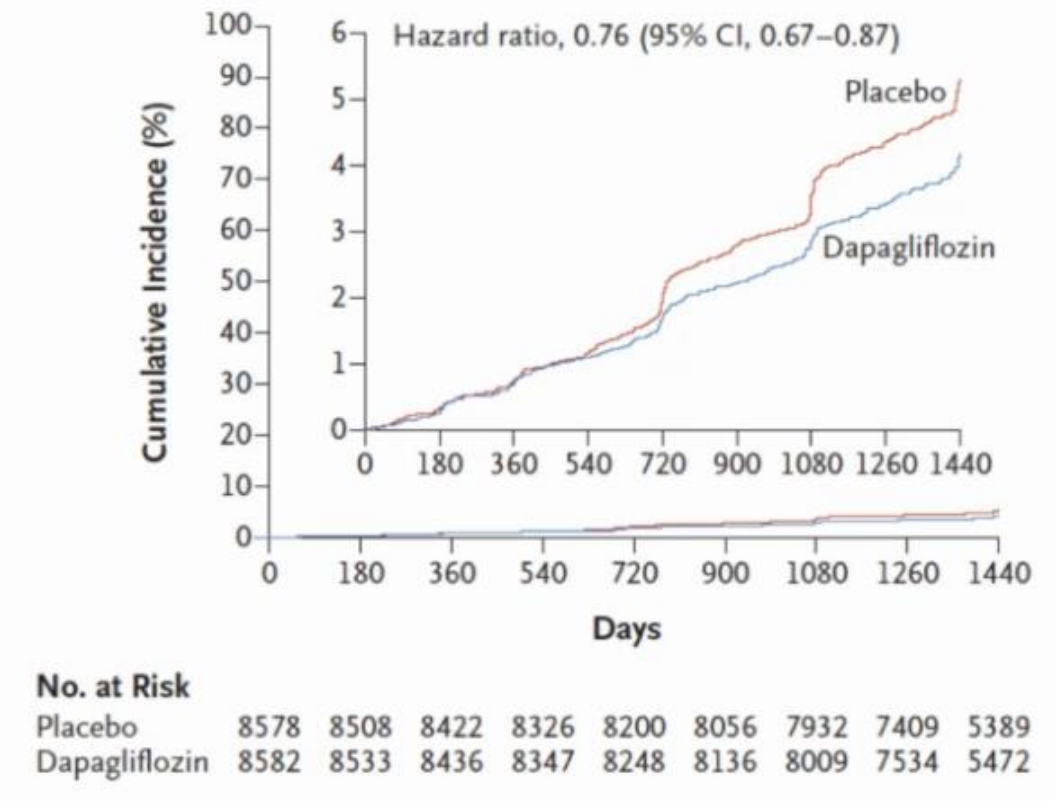
DECLARE-TIMI 58: Secondary Renal Outcome

Baseline eGFR ~85 mL/min (all patients had eGFR > 60 mL/min)

Renal Composite

- ≥ 40% decrease in eGFR to < 60 mL
- ESRD
- Death from renal or CV cause

Reference: Wiviott SD et at; NEJM; 2019; 380: 347



Renal Composite

24% in renal risk reduction

Reference: Wiviott SD et at; NEJM; 2019; 380: 347

Outcome	Dapagliflozin (N=8582)		Placebo (N=8578)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

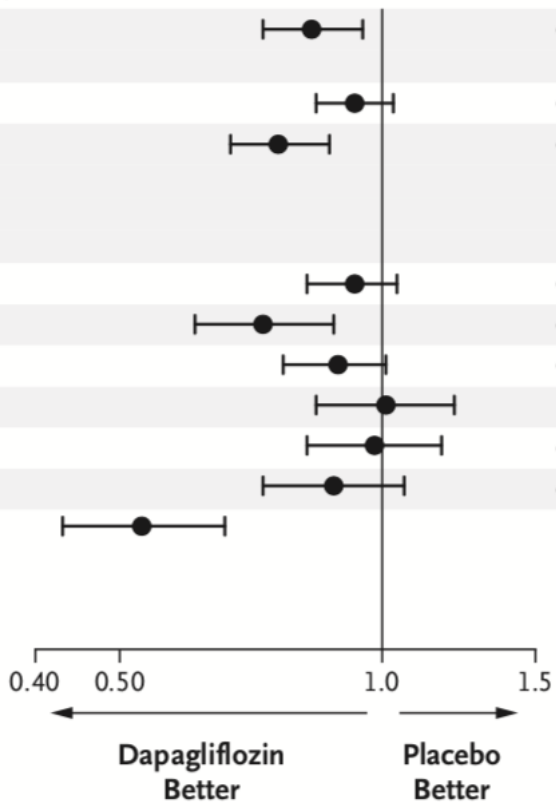


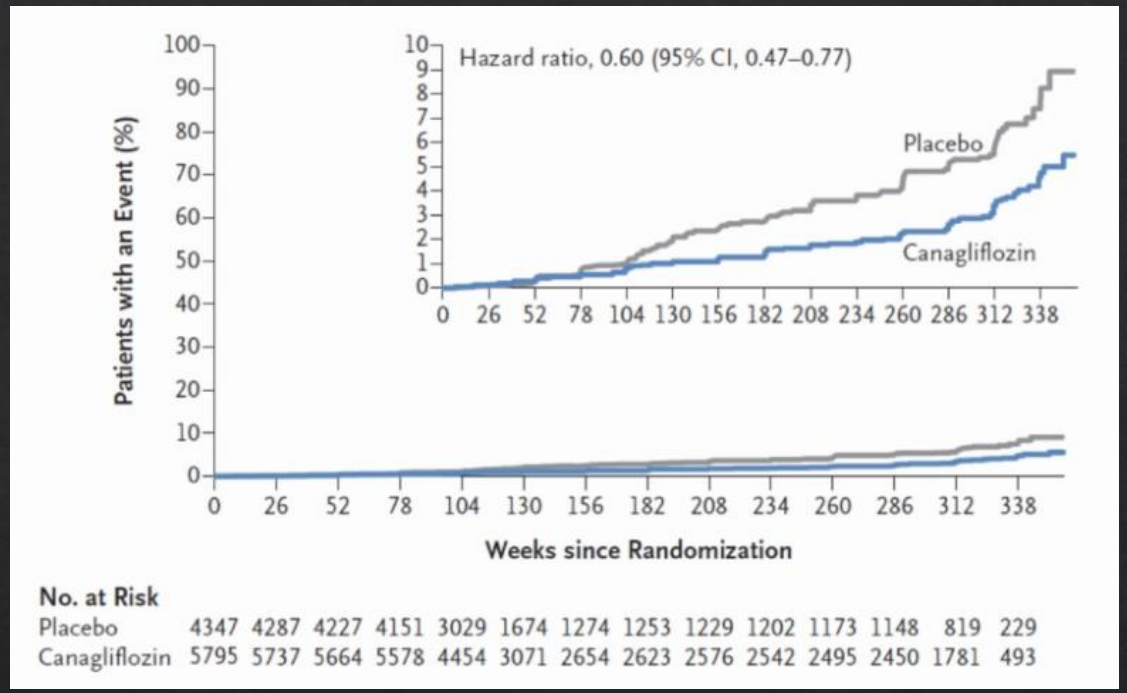
Figure 2. Key Efficacy Outcomes and Their Components.

Two-sided P values are shown for the two primary efficacy outcomes of cardiovascular death or hospitalization for heart failure and MACE. The abbreviation eGFR denotes estimated glomerular filtration rate, and ESRD end-stage renal disease.

Conclusion

"In patients with T2D who had or were at risk for atherosclerotic cardiovascular disease, treatment with Dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure."

Reference: Wiviott SD et at; NEJM; 2019; 380: 347



Canagliflozin: CANVAS/R – renal composite of 40% reduction in eGFR, requirement for RRT, or death from renal causes

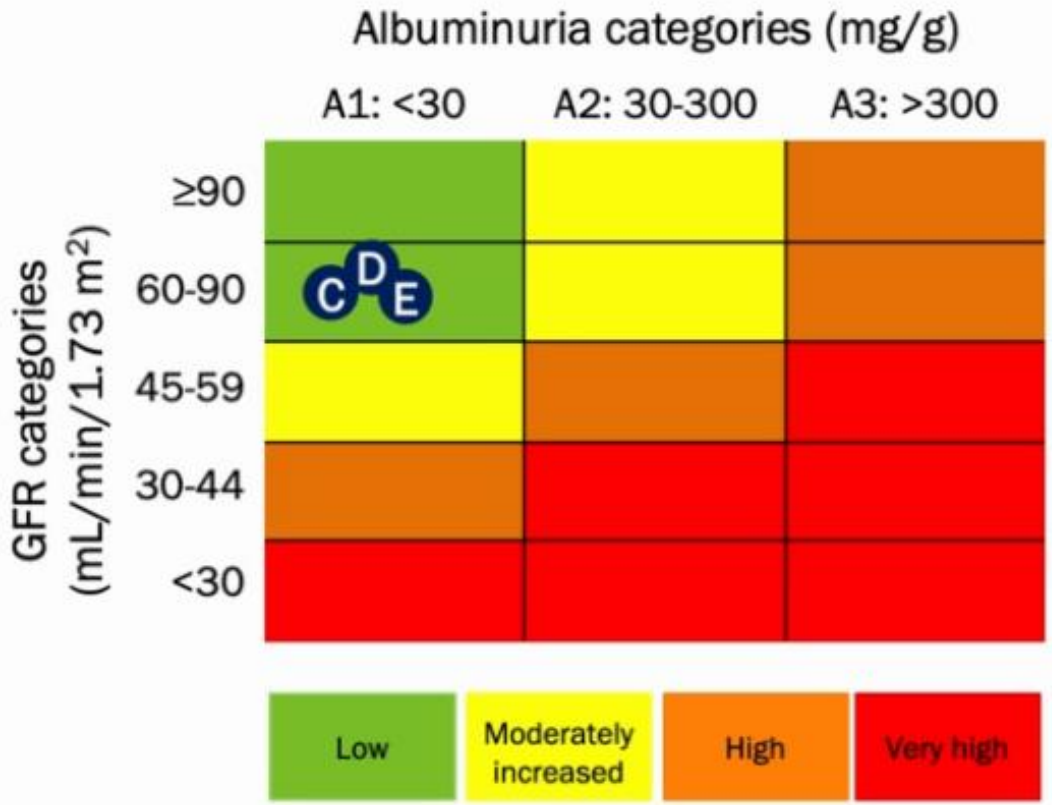
(20% CKD eGFR < 60 ml including 5.5% < 45 ml)

Reference: Neal B et al; NEJM; 2017; 377: 644-657

Conclusions from CANVAS/R

"In two trials involving patients with T2D and an elevated risk of cardiovascular disease, patients treated with Canagliflozin had a lower risk of cardiovascular events that those who received placebo but a greater risk of amputation, primarily at the level of the tow or metatarsal."

Reference: Neal B et al; NEJM; 2017; 377: 644-657



		Mean eGFR (mL/min/1.73m²)	Median UACR (mg/g)
D	DECLARE	85	13
C	CANVAS Program	76	12
E	EMPA-REG OUTCOME	74	18

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

Total of 29 sustained RRT events reported across trials

Low Renal Risk Populations in CV Outcomes Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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

Hypothesis

- Determine whether Canagliflozin reduces the progression of renal impairment relative to placebo

Study design

- 4401 patients with T2D
- eGFR ≥ 30 to < 90 mL/min/1.73m^2, and albuminuria (UACR > 300 to ≤ 5000 mg/g)
- **60%** eGFR < 60 mL/min
- Randomized, double-blind, placebo-controlled trial
- Duration: 2.62 years

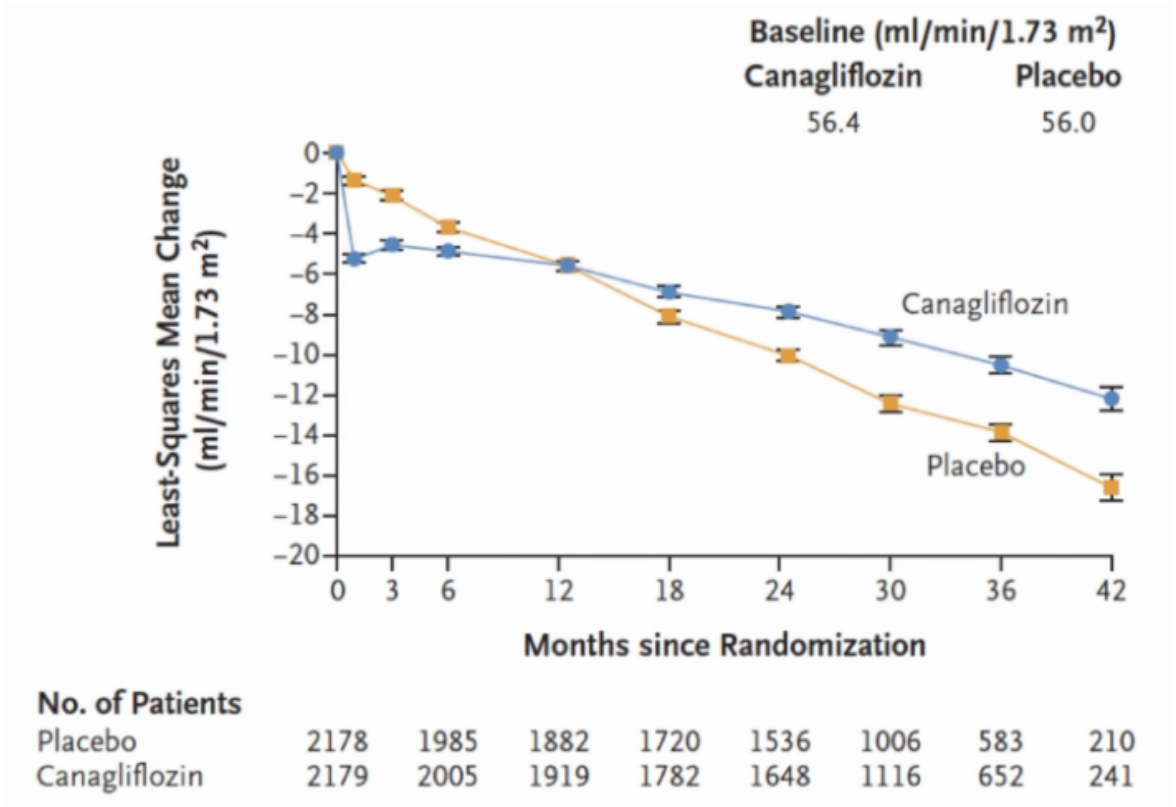
Primary Outcome

- Time to first of ESRD
- Doubling of serum creatinine
- Renal or CV death

Canagliflozin and Renal Events in Diabetes With established Nephropathy Clinical Evaluation (CREDENCE)

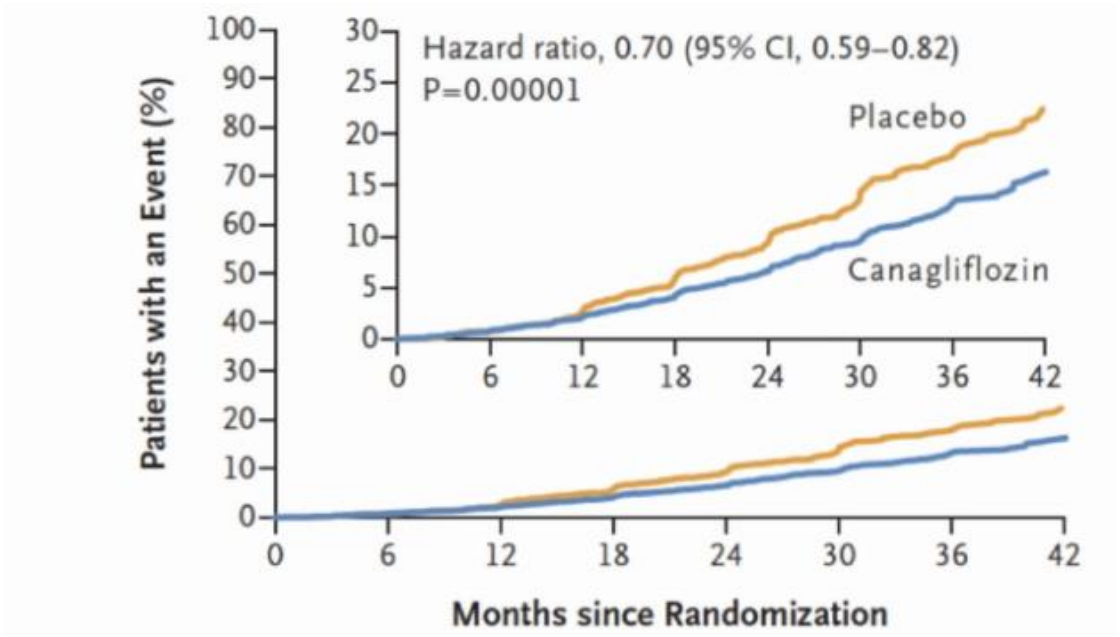
Reference: Perkovic V, et al; N Engl J Med; 2019

Change From Baseline in GFR



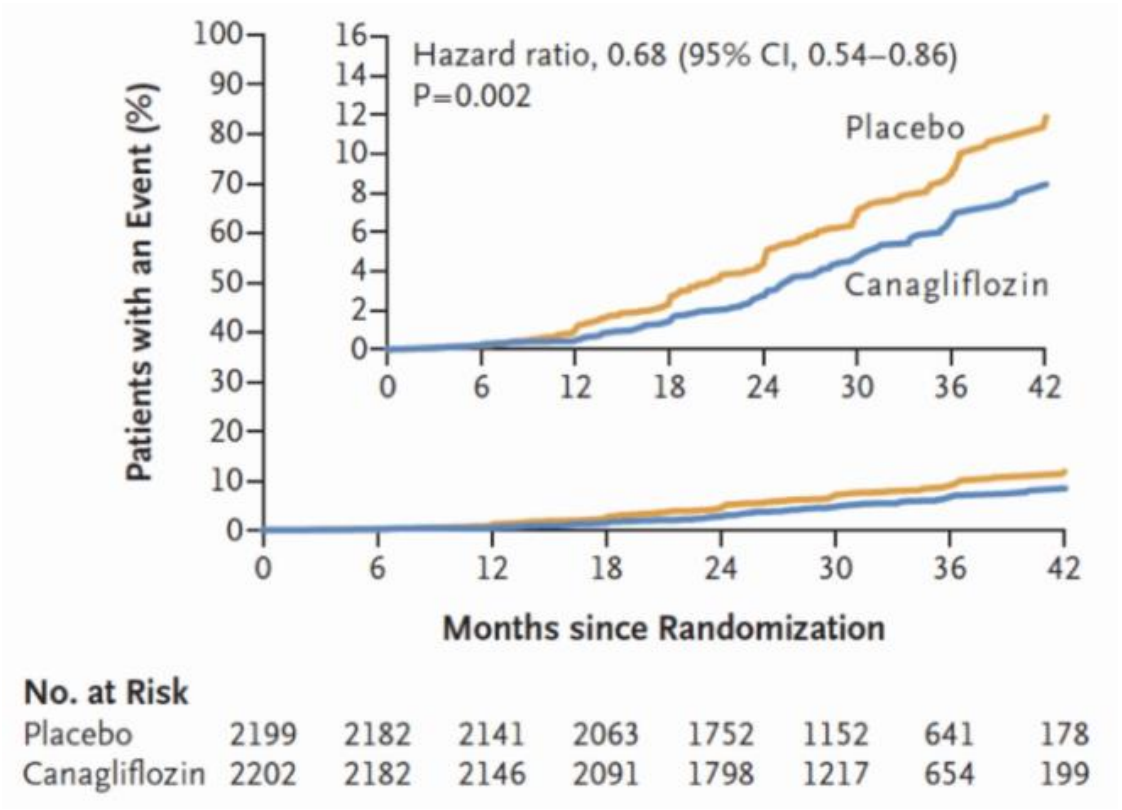
Reference: Perkovic V, et al; N Engl J Med; 2019

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



Reference: Perkovic V, et al; N Engl J Med; 2019

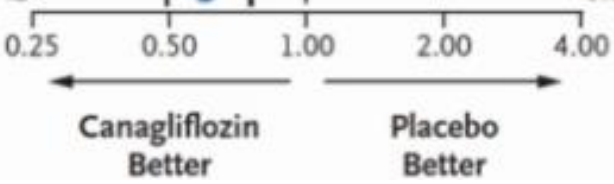
End-Stage Kidney Disease



Reference: Perkovic V, et al; N Engl J Med; 2019

Sub-group Analysis

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)	



Canagliflozin vs Placebo: Blood Pressure, Body Weight, and UACR

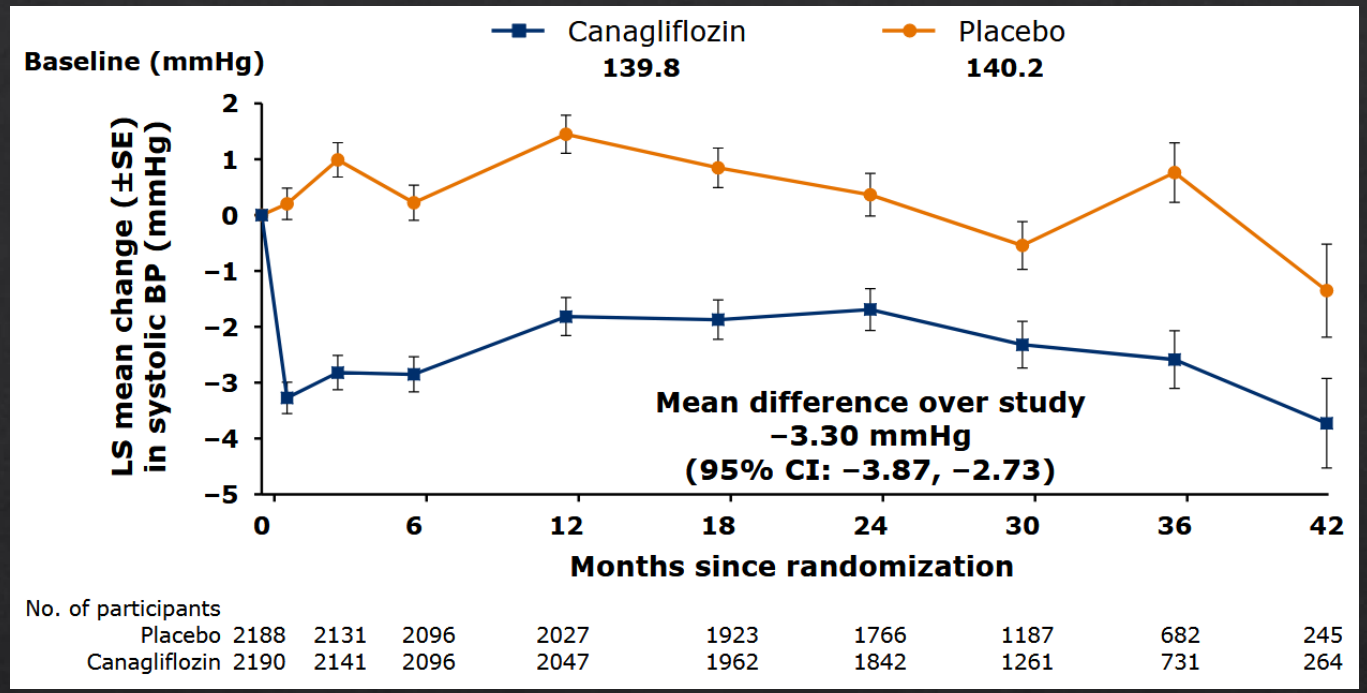
SBP
3.3 MMHG

DBP
0.95 MMHG

BODY WEIGHT
0.80 KG

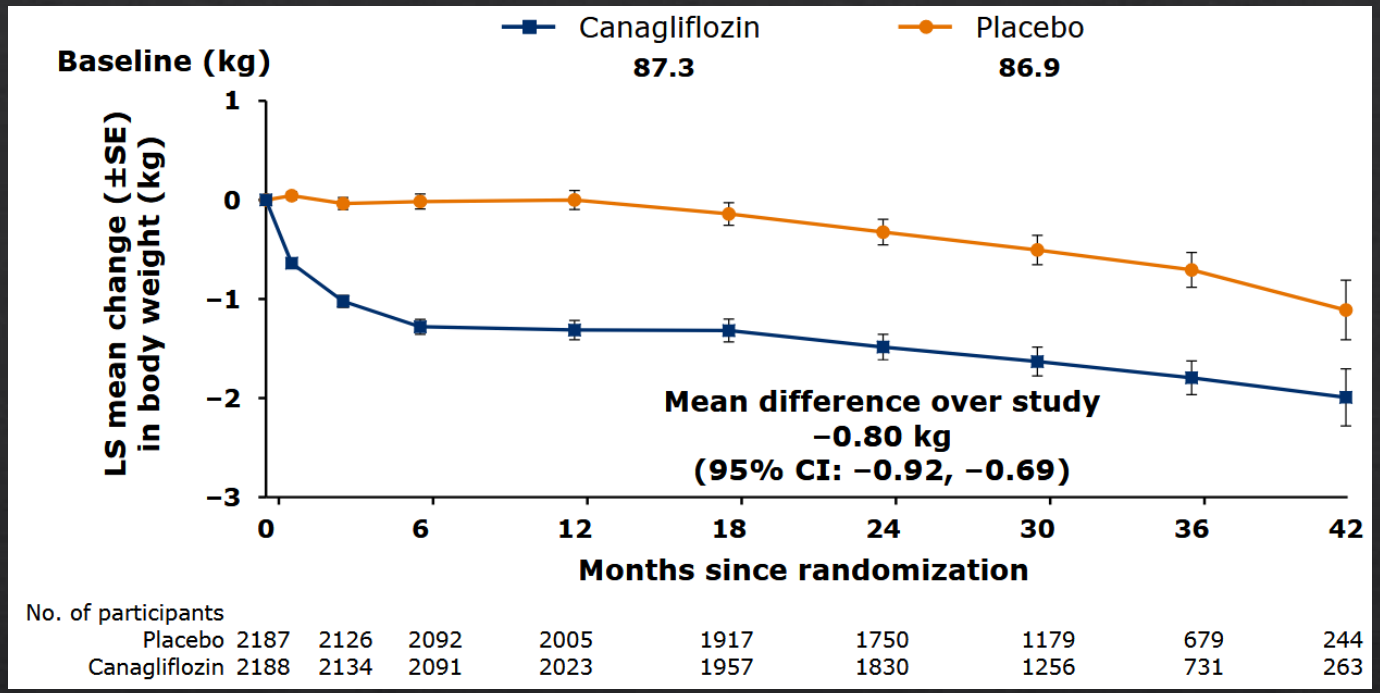
UACR
32%

Reference: Perkovic V, et al; N Engl J Med; 2019



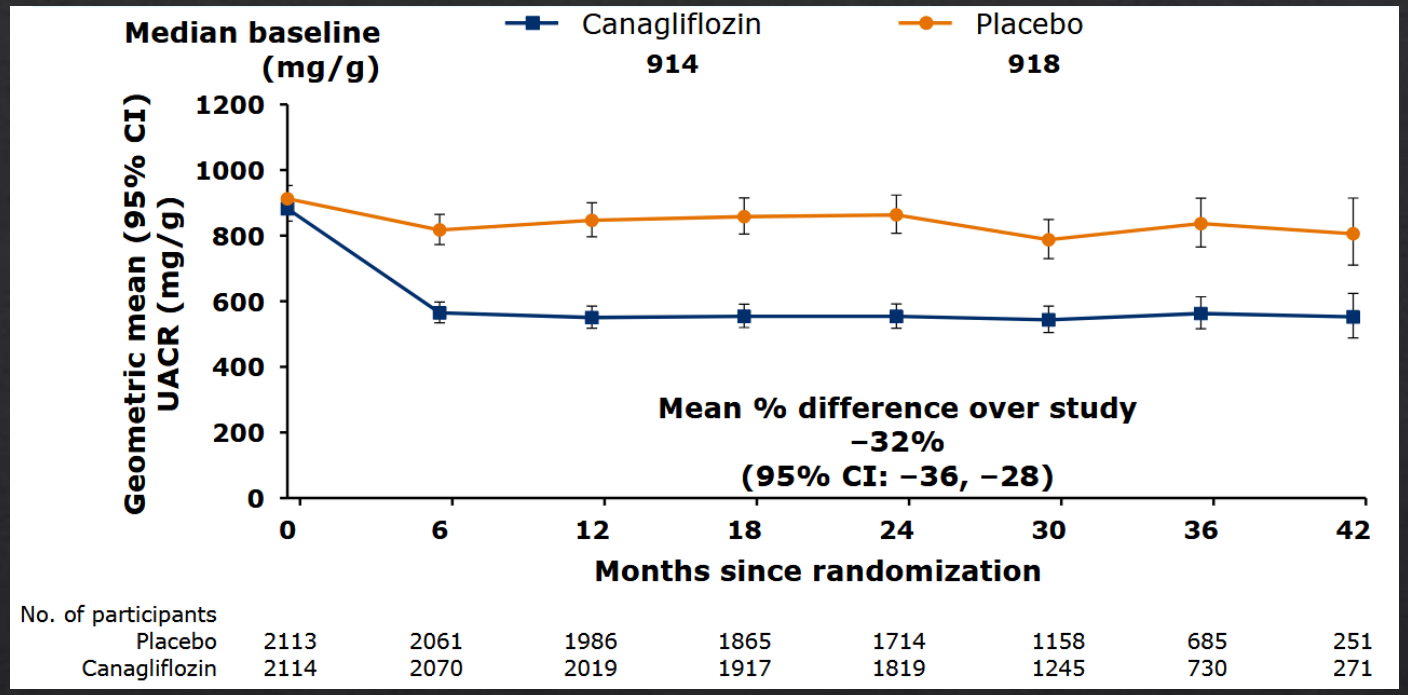
Effects on Systolic BP

Reference: Perkovic V, et al; N Engl J Med; 2019



Effects on Body Weight

Reference: Perkovic V, et al; N Engl J Med; 2019



Effects on Albuminuria (UACR)

Reference: Perkovic V, et al; N Engl J Med; 2019

Primary	**Hazard ratio (95% CI)**	***P* value**	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✔
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✔
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✔
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✔
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✔
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

Reference: Perkovic V, et al; N Engl J Med; 2019

Canagliflozin: Number Needed to Benefit Among 1000 Patients Treated for 2.5 years

Canagliflozin safely reduced the risk of kidney failure and prevented CV events in people with T2DM and CKD

ESRD, DSCr, Renal or CV Death	Hospitalization for HF	CV Death, MI, CVA
N = 22	N = 46	N = 40

Reference: Perkovic V, et al; N Engl J Med; 2019

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WILEY

CLINICAL TRIAL DESIGN

Rationale and protocol of the Study Of diabetic Nephropathy with AtRasentan (SONAR) trial: A clinical trial design novel to diabetic nephropathy

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Atrasentan: Non-Selective Endothelin Receptor Antagonist

Reference: Heerspink HJL, et al; Lancet; 2019

Study of Diabetic Nephropathy with Atrasentan (SONAR)

Hypothesis: treatment with Atrasentan would improve renal outcomes in carefully selected high-risk patients with diabetes and CKD

Design: randomized, double-blind, placebo-controlled trial

- Run-in period: Atrasentan responders – 30% decrease in UACR

Population: adult T2D eGFR 25-75 mL/min per and of 300 to 5000 mg/g, BNP < 200 pg/mL

Intervention: 0.75mg Atrasentan daily

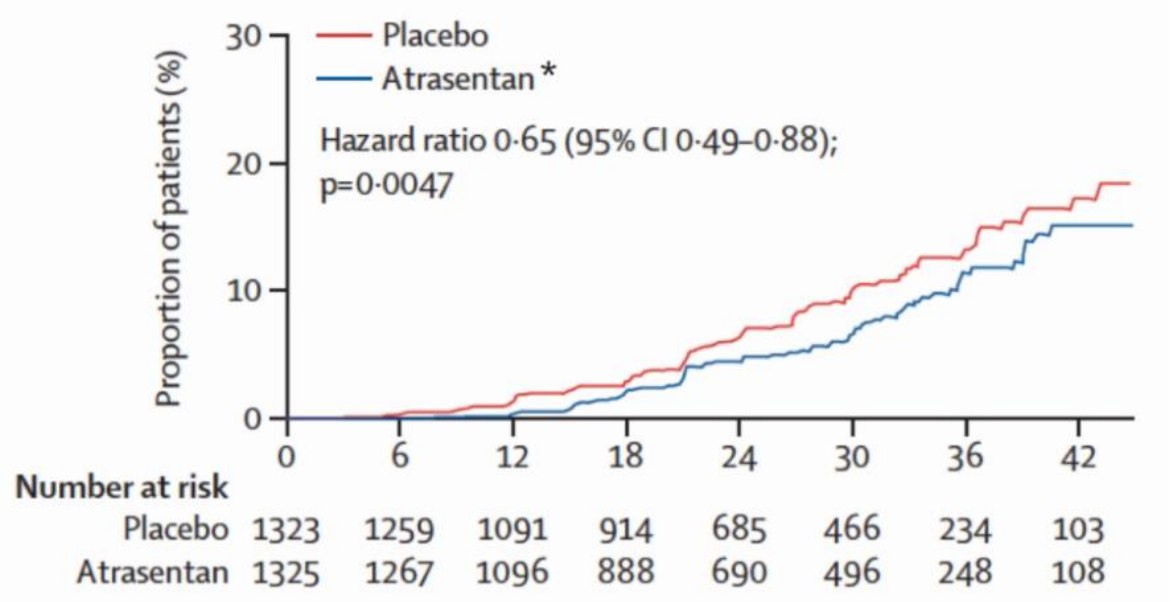
Outcome: time to DSCr, ESRD, or death from kidney failure

Follow-up: median 2.2 years (event-driven)

Reference: Heerspink HJL, et al; Lancet; 2019

SONAR

Primary Outcome



Reference: Heerspink HJL, et al; Lancet; 2019

THANK YOU FOR YOUR ATTENTION

ANY QUESTIONS?