SGLT2 Inhibition and the Kidney

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Disclosures

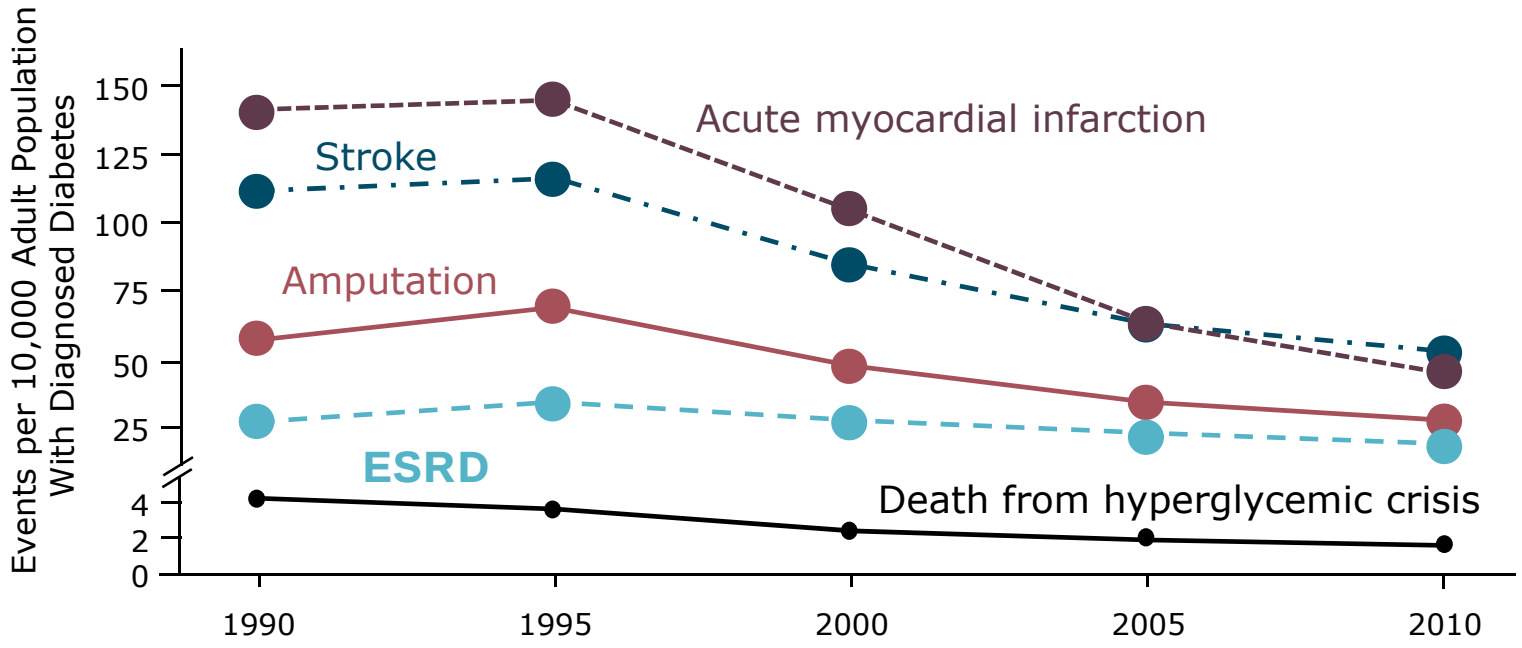
Relationships with commercial entities:

- Consulting, honoraria: Boehringer Ingelheim, Lilly, Janssen, Merck, AstraZeneca, Mitsubishi-Tanabe, Sanofi
- Clinical trials: CREDENCE, TRANSLATE, BETWEEN, DIAMOND, DAPA-CKD, EMPA-Kidney, ERADICATE-HF

Objectives

- Sodium glucose cotransport-2 inhibition:
  - Mechanisms for renal protection
  - Cardiovascular safety and renal outcome trials
- Ongoing studies

Rate of CV events in diabetes has declined, while ESRD has not



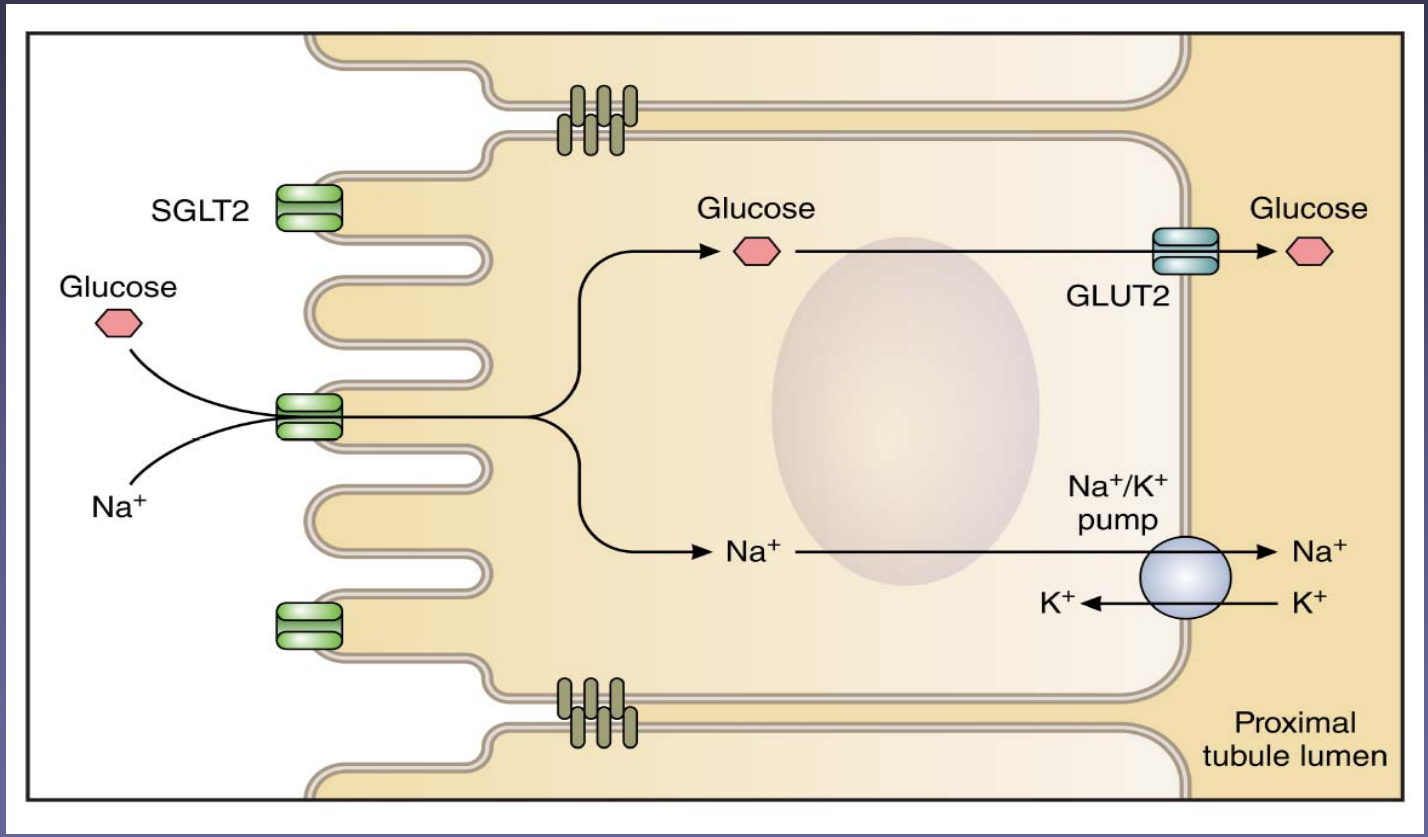
Gregg et al. N Engl J Med. 2014;370(16):1514-23
Gregg et al. JAMA 2019 (April 15th)

Risk Factors and Targets to Prevent Renal/CV Disease

Glucose	HbA_{1c} target individualized, but generally ~7%[1]
BP	Target of <130/80 mmHg[2]
RAAS inhibition	ACE inhibitor or ARBs, especially for urine albumin excretion ≥30 mg/g[1]
Lipids	Lipid-lowering recommended to reduce risk of atherosclerotic events; statins not recommended in patients on hemodialysis[1]

1. National Kidney Foundation. *Am J Kidney Dis* 2012;60:850; 2. ACC/AHA 2017 High Blood Pressure Clinical Practice Guideline. *J Am Coll Cardiol*. 2017. https://doi.org/10.1016/j.jacc.2017.11.006.

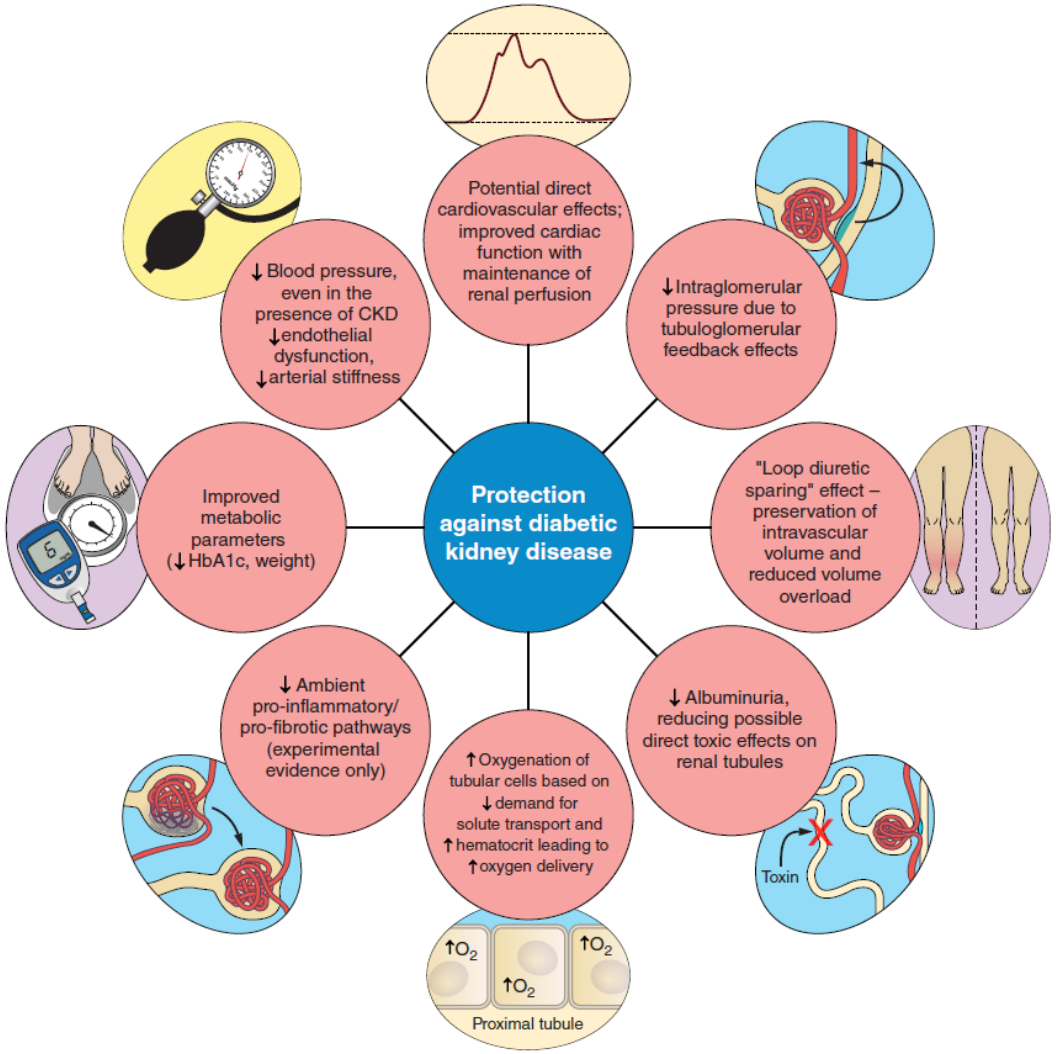
SGLT2 inhibition



SGLT2, sodium–glucose co-transporter 2

Heerspink//Cherney HJ, *et al. Circulation* 2016;134:752–772

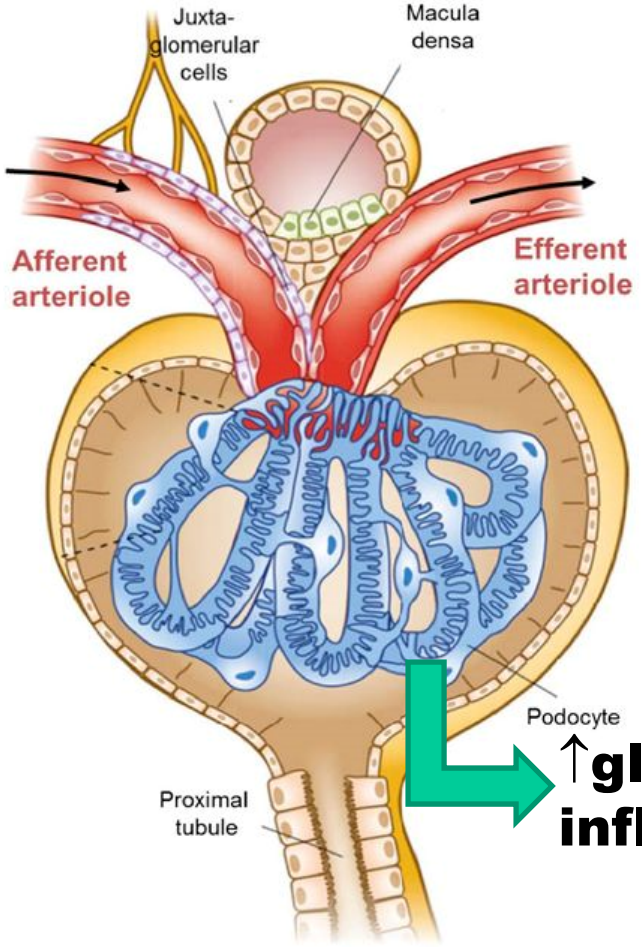
Proposed renal protective pathways with SGLT2 inhibitors



Heerpsink//Cherney. Kidney Int 2018

Factors implicated in the pathogenesis of hyperfiltration in diabetes

Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)

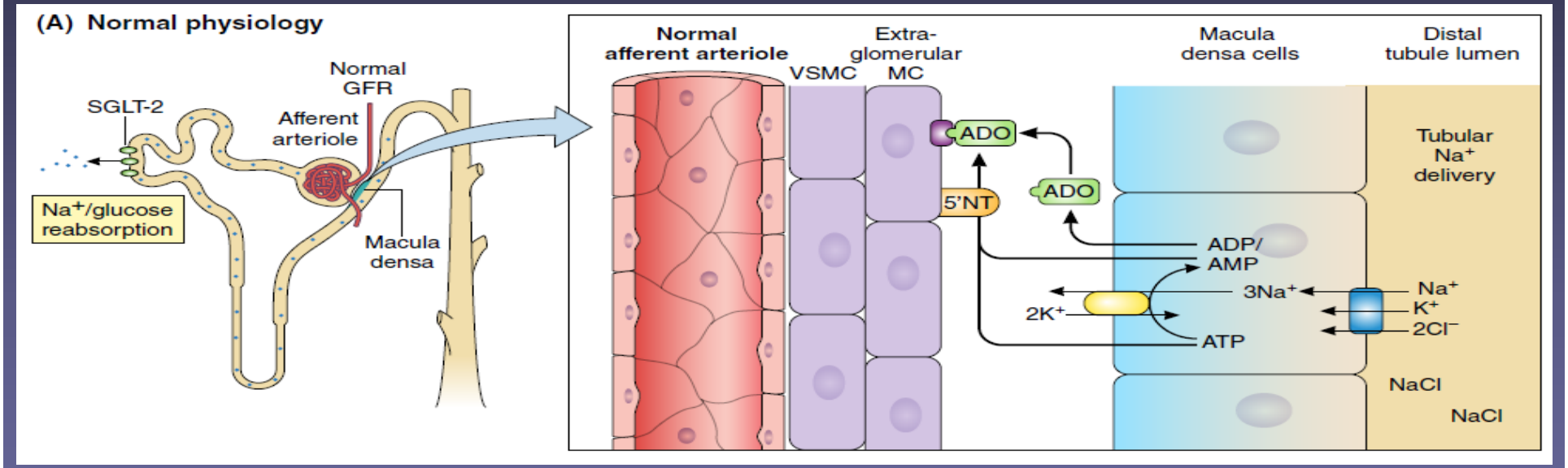


Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

↑glomerular pressure → inflammation, fibrosis

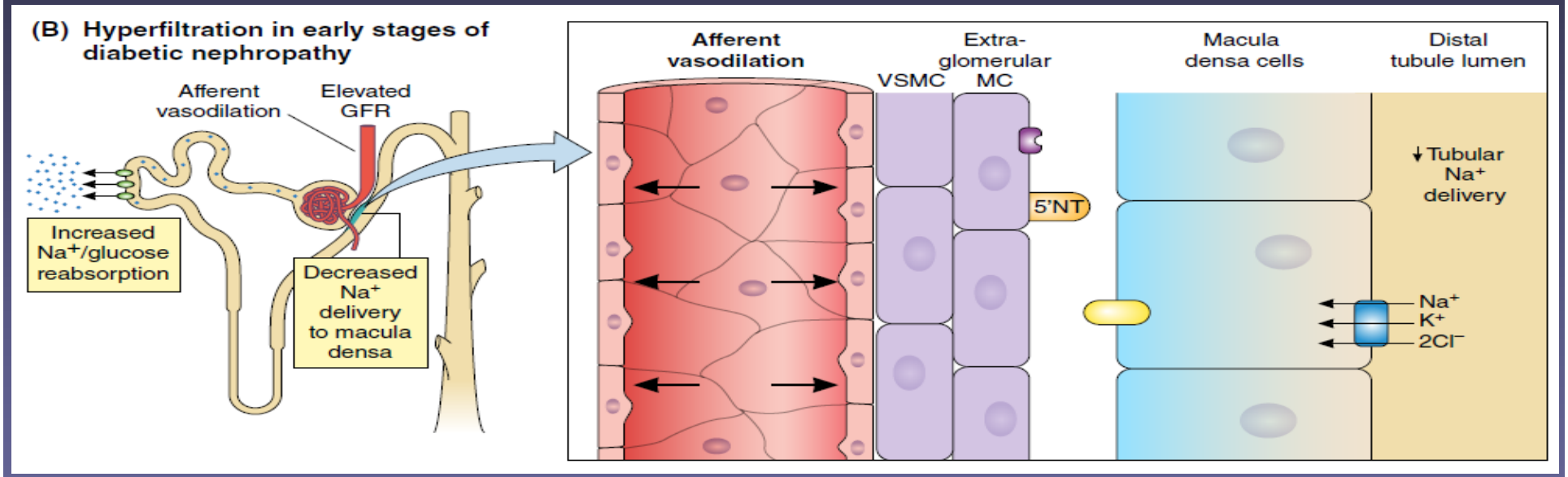
Tonneijck et al. JASN 2017

The "Tubular Hypothesis": Normal Physiology



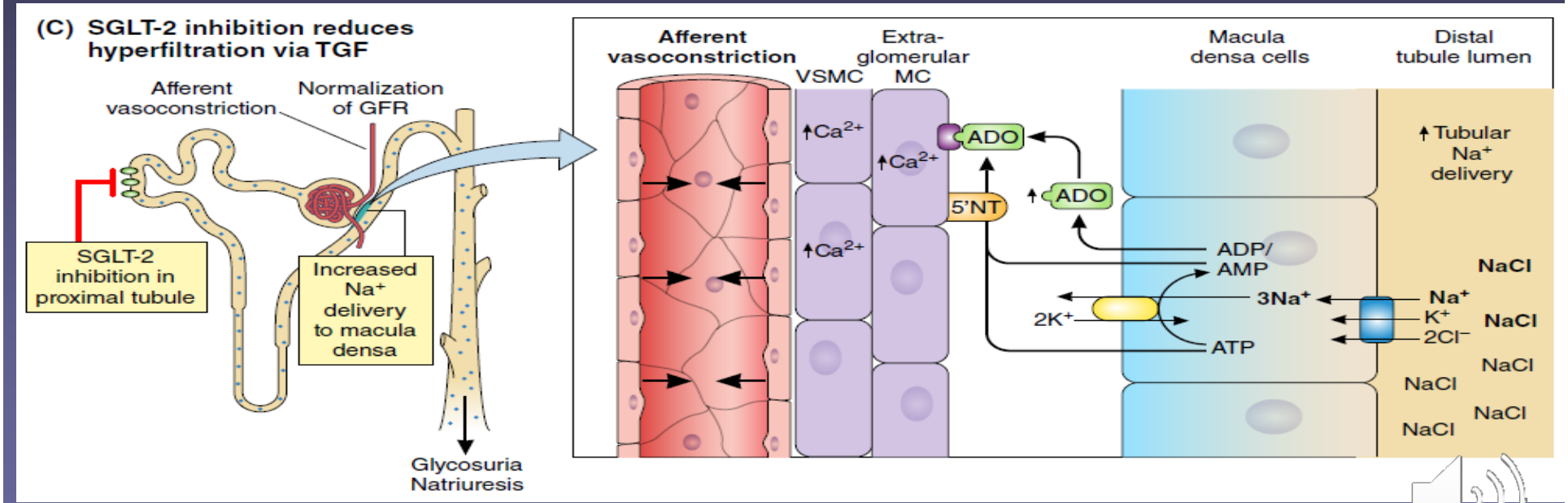
Heerspink//Cherney. Circulation 2016

The "Tubular Hypothesis": Diabetes and Hyperfiltration



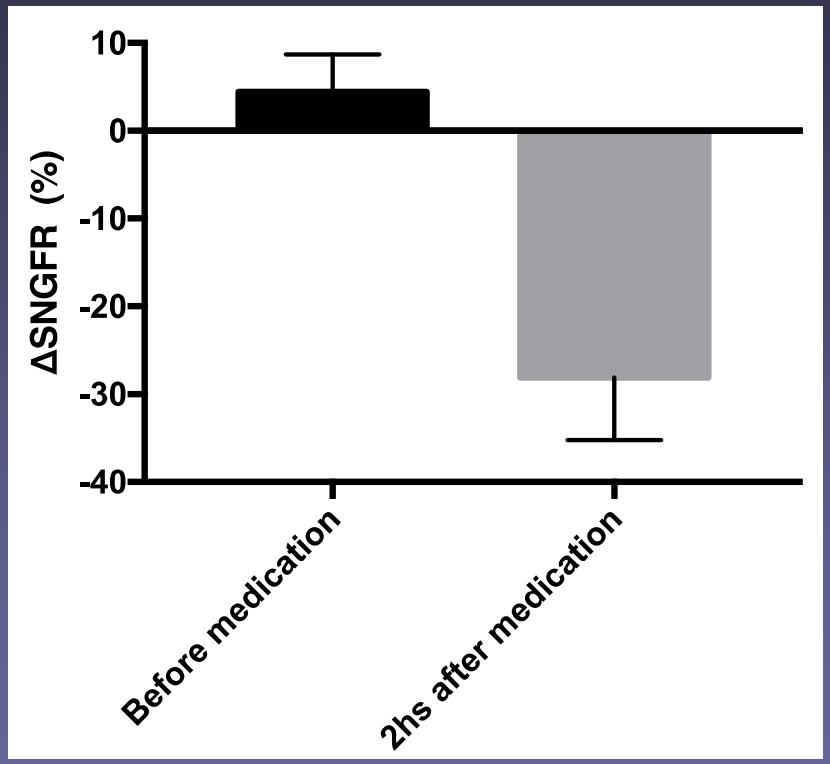
Heerspink//Cherney. Circulation 2016

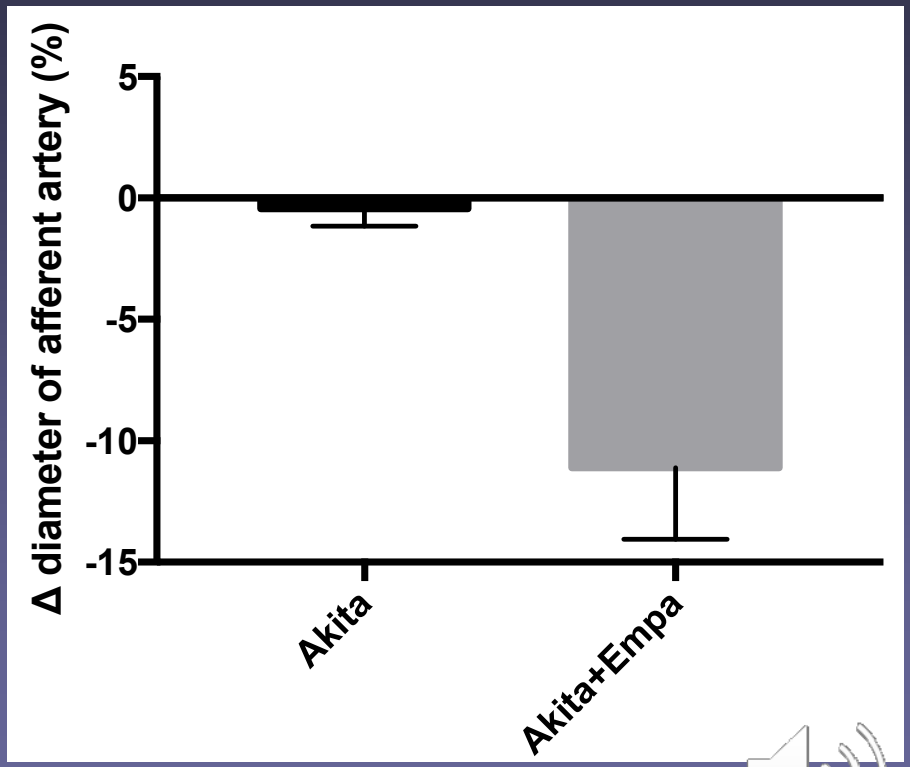
The "Tubular Hypothesis": Diabetes and SGLT2 Inhibition



Heerspink//Cherney. Circulation 2016

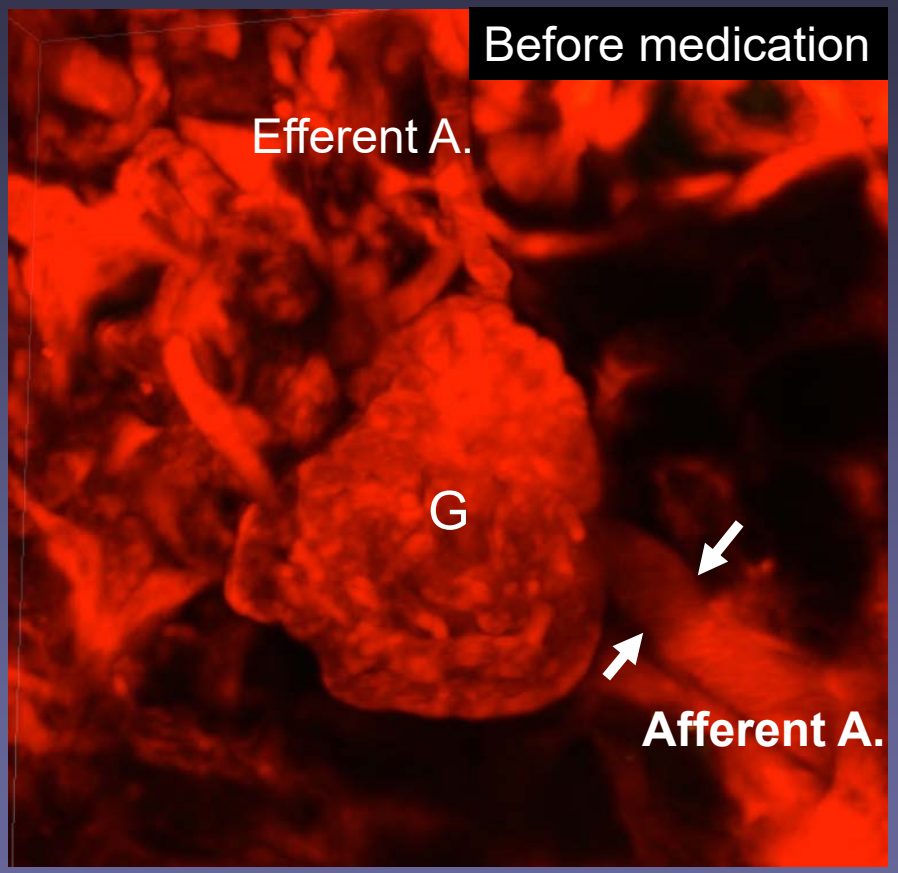
Animal models in T1D: SGLT2i, afferent constriction

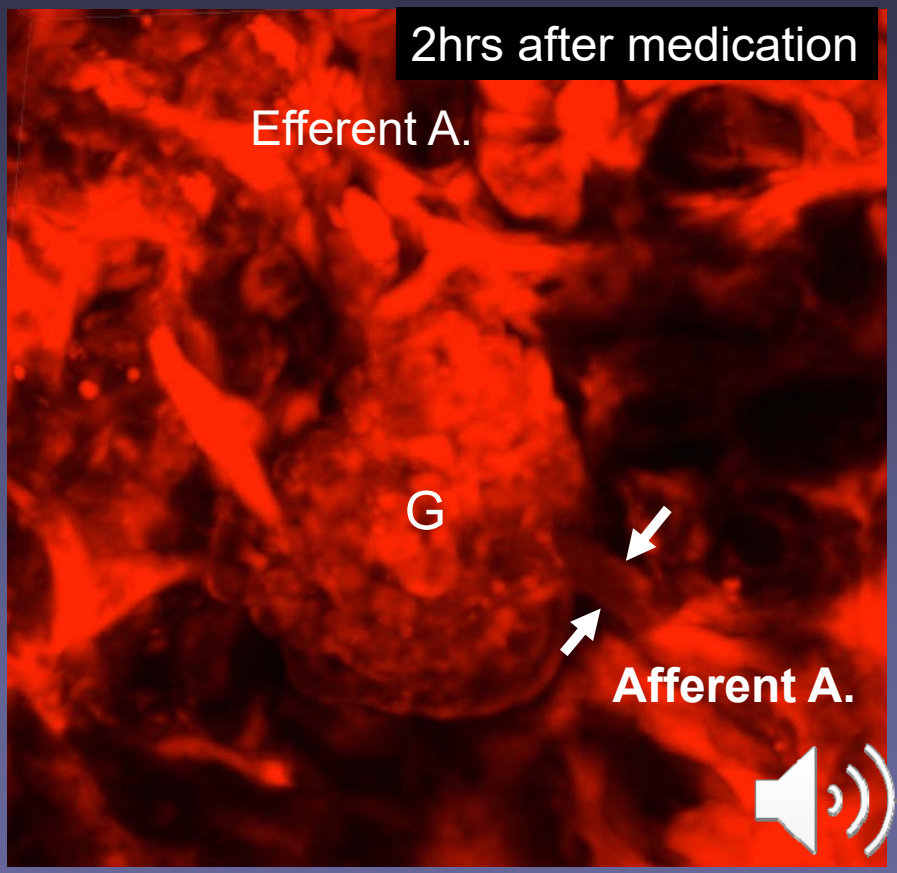




Kidokoro et al. Circulation 2019

In vivo imaging of A.A. change before and after empagliflozin

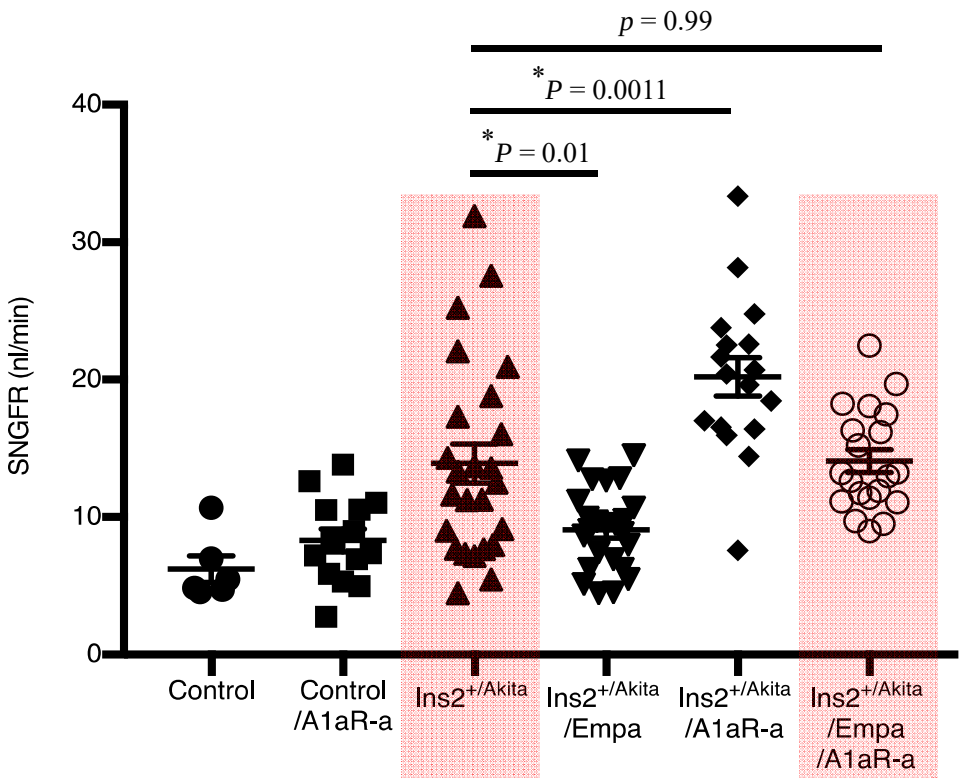




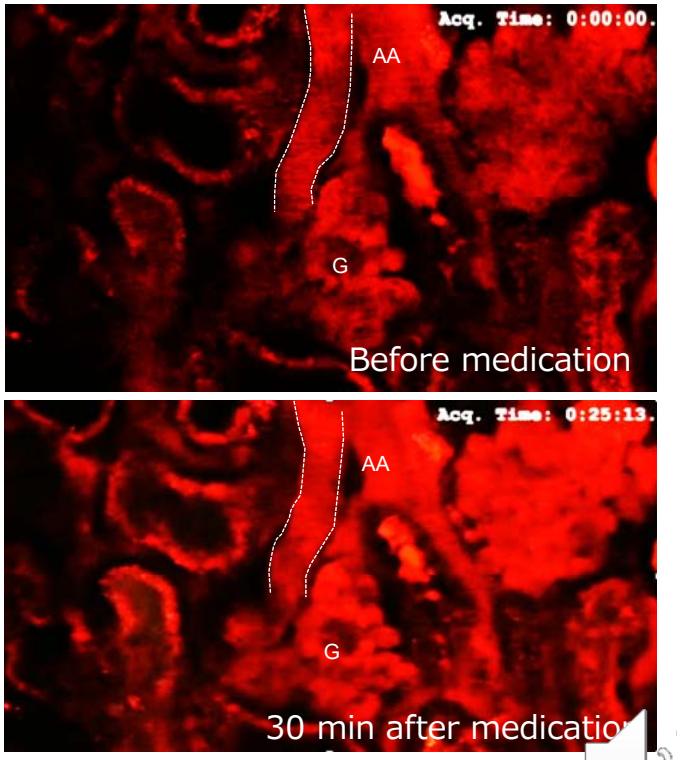
Kidokoro et al. Circulation 2019

Red: BSA-Alexa594

The alteration of SNGFR by empagliflozin under A1aR antagonist



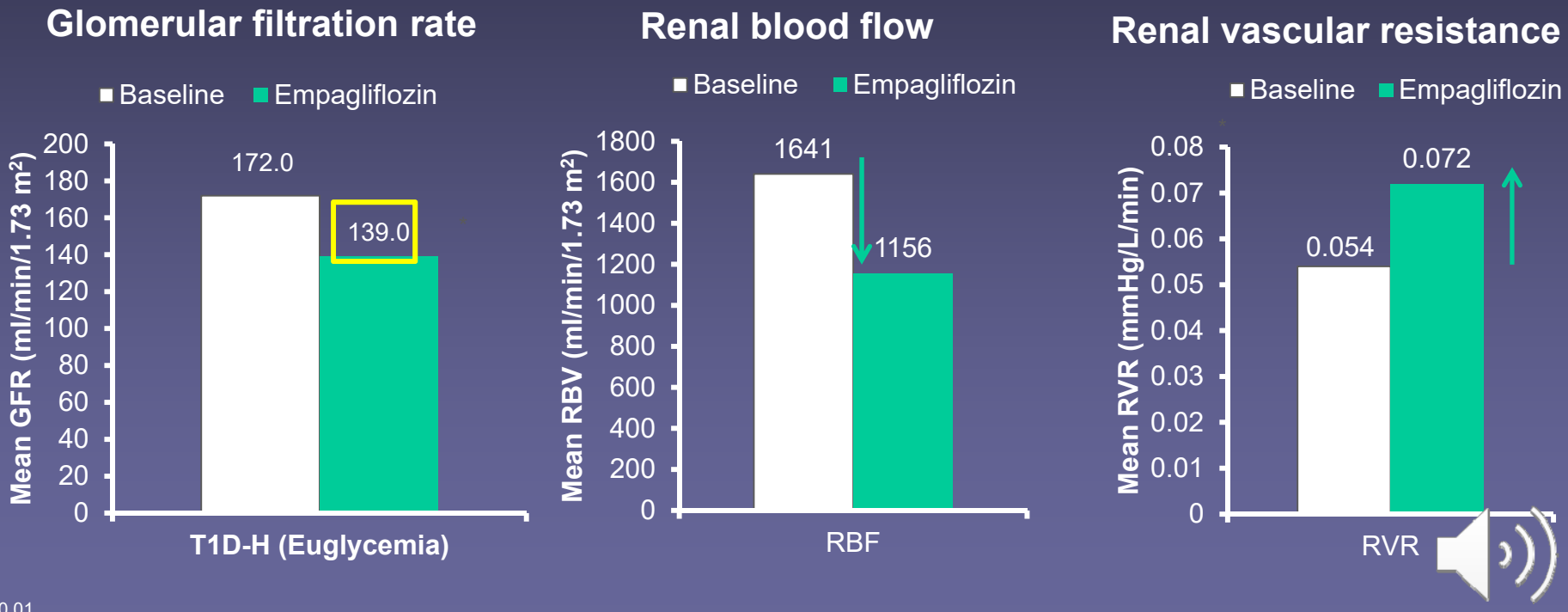
Kidokoro et al. Circulation 2019



Red: BSA-Alexa5

Type 1 diabetes – Reduced hyperfiltration was mediated by effects on renal blood flow and vascular resistance

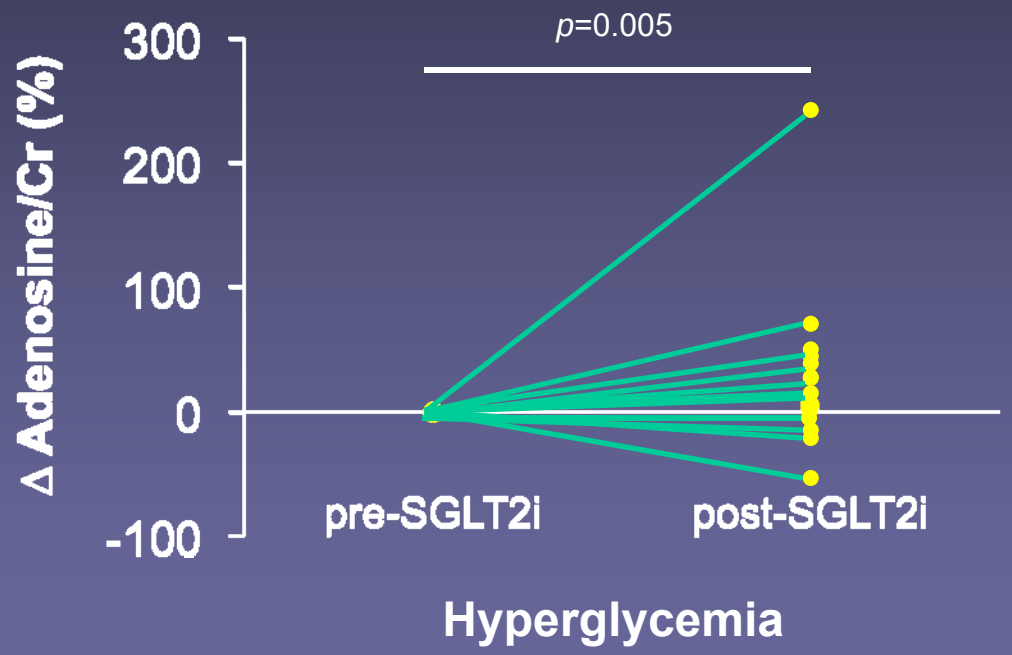
- Reduced **renal blood flow** (RBF) & increased **renal vascular resistance** (RVR) after empagliflozin treatment are consistent with **afferent arteriole vasoconstriction**



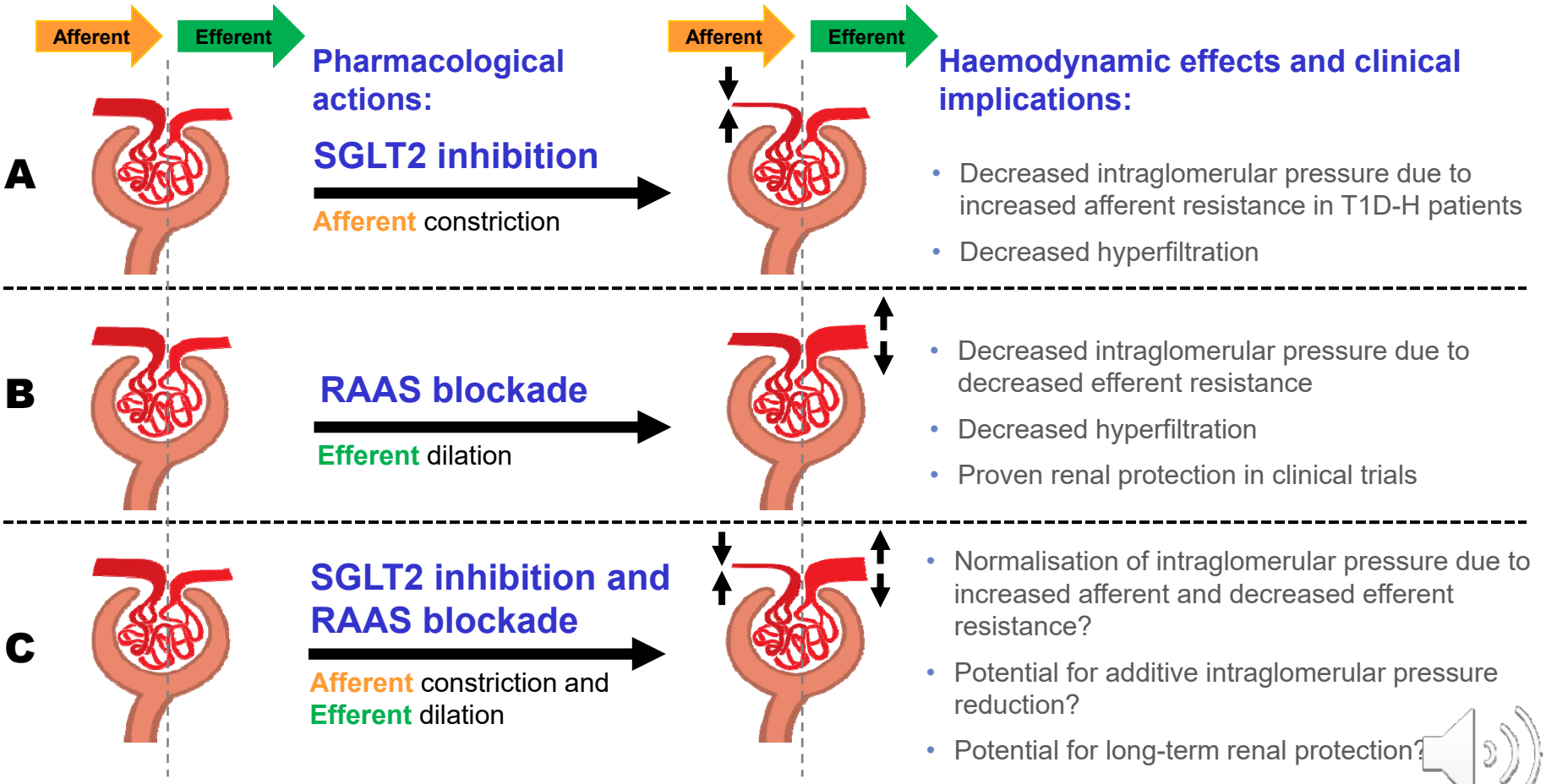
* $p<0.01$

Cherney et al. *Circulation* 2014;129:587–597

What is the mediator responsible for afferent vasoconstriction?

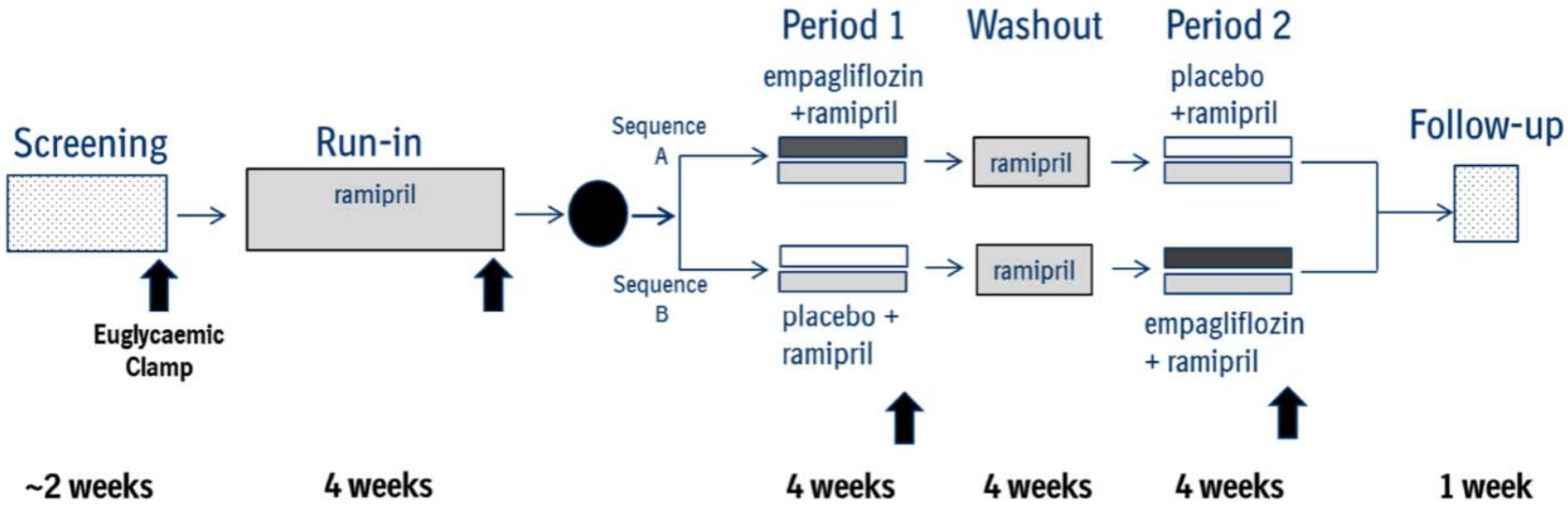


Rajasekaran//Cherney. Am J Physiol - Renal 2017



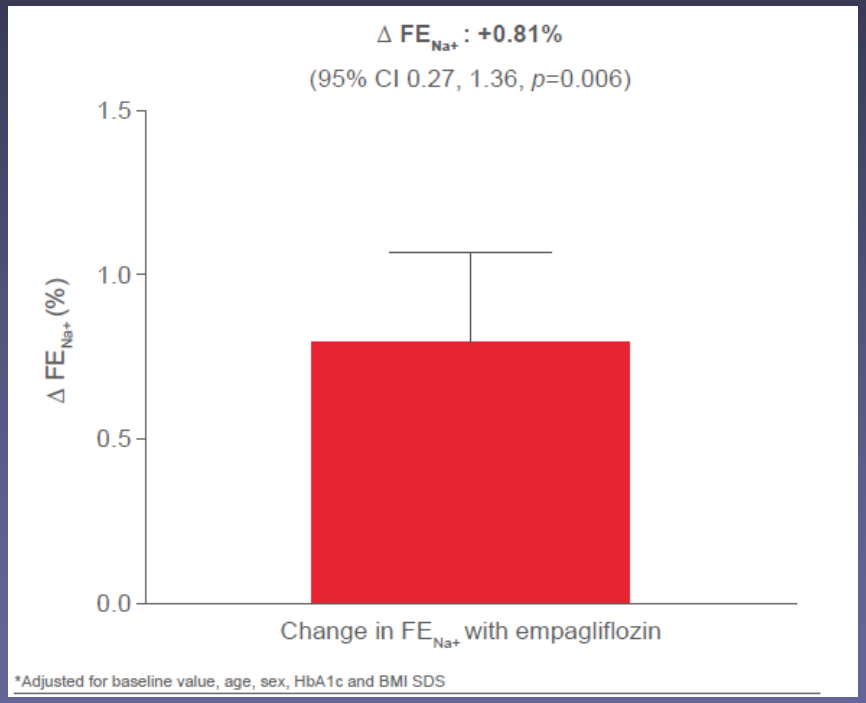
Skrtić//Cherney. *Diabetologia* 2014;57:2599–2602

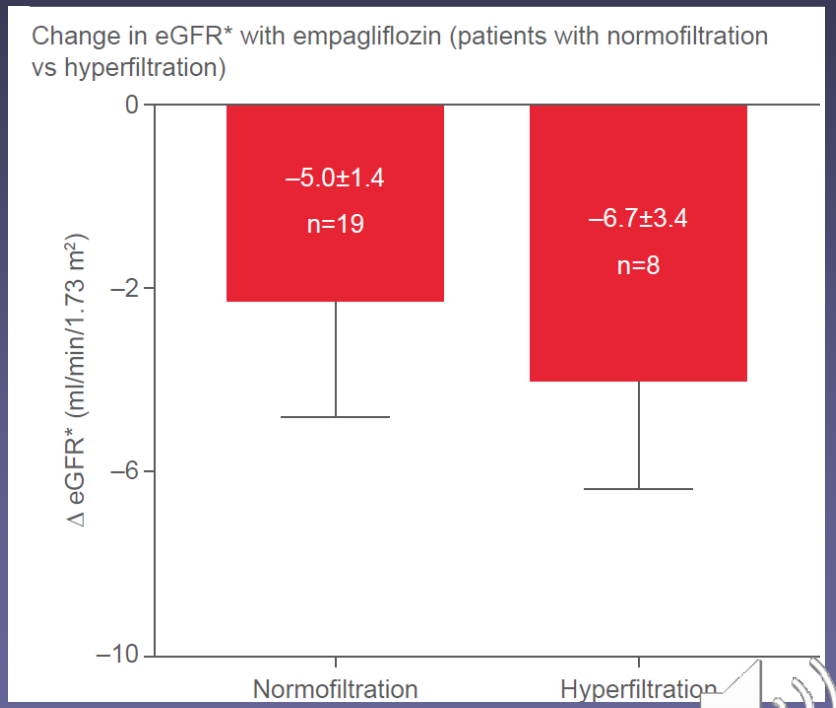
BETWEEN Trial: Effect of ACEi + SGLT2i on Hyperfiltration



Hypothesis: dual therapy will abolish hyperfiltration

Single dose of empagliflozin on FENa+, eGFR – T2D children

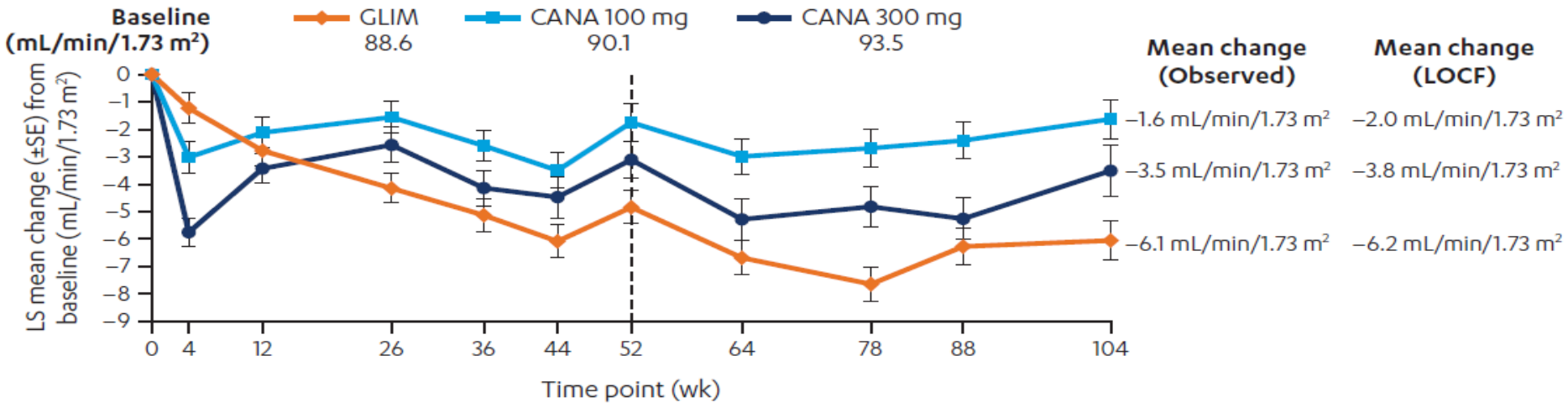




Bjornstad//Cherney. Diabetes Care 2018

Canagliflozin vs. SU (104 weeks) – Normal renal function

Change in eGFR over time



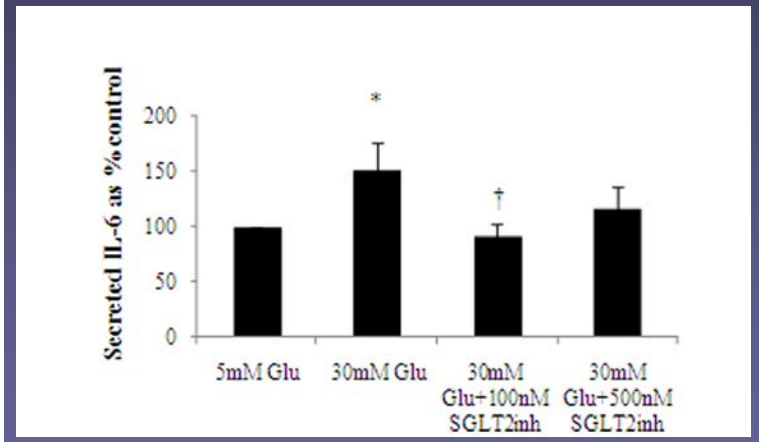
*N = 1,449 (Baseline); N = 1,380 (Week 4); N = 1,332 (Week 12); N = 1,262 (Week 26); N = 1,225 (Week 36); N = 1,175 (Week 44); N = 1,157 (Week 52); N = 1,120 (Week 64); N = 1,059 (Week 78); N = 1,022 (Week 88); N = 970 (Week 104).

- Changes in eGFR in CKD stages 1 - 4, even though less HbA1c lowering
- SGLT2 inhibition: 30-50% decrease in albuminuria

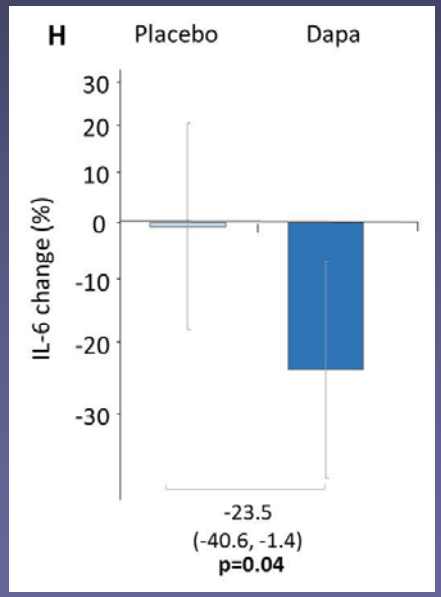
Cefalu WT, et al. Presented at the 73rd Scientific Sessions of the America Diabetes Association, June, 2013, Chicago, IL, USA. Poster 65-LB

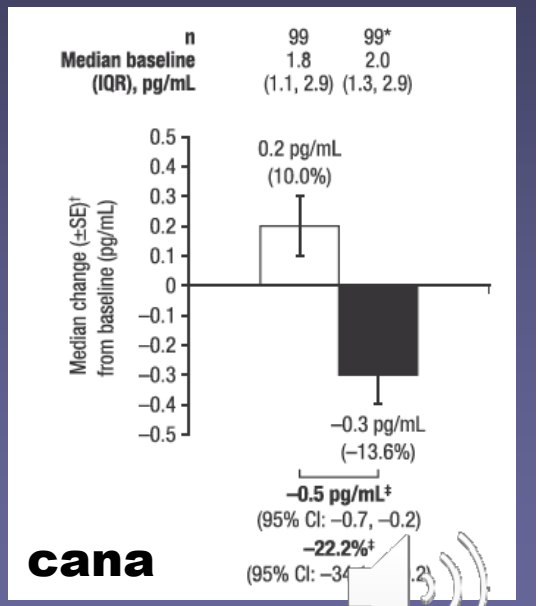
Inflammatory biomarkers *in vitro* and in humans

In vitro



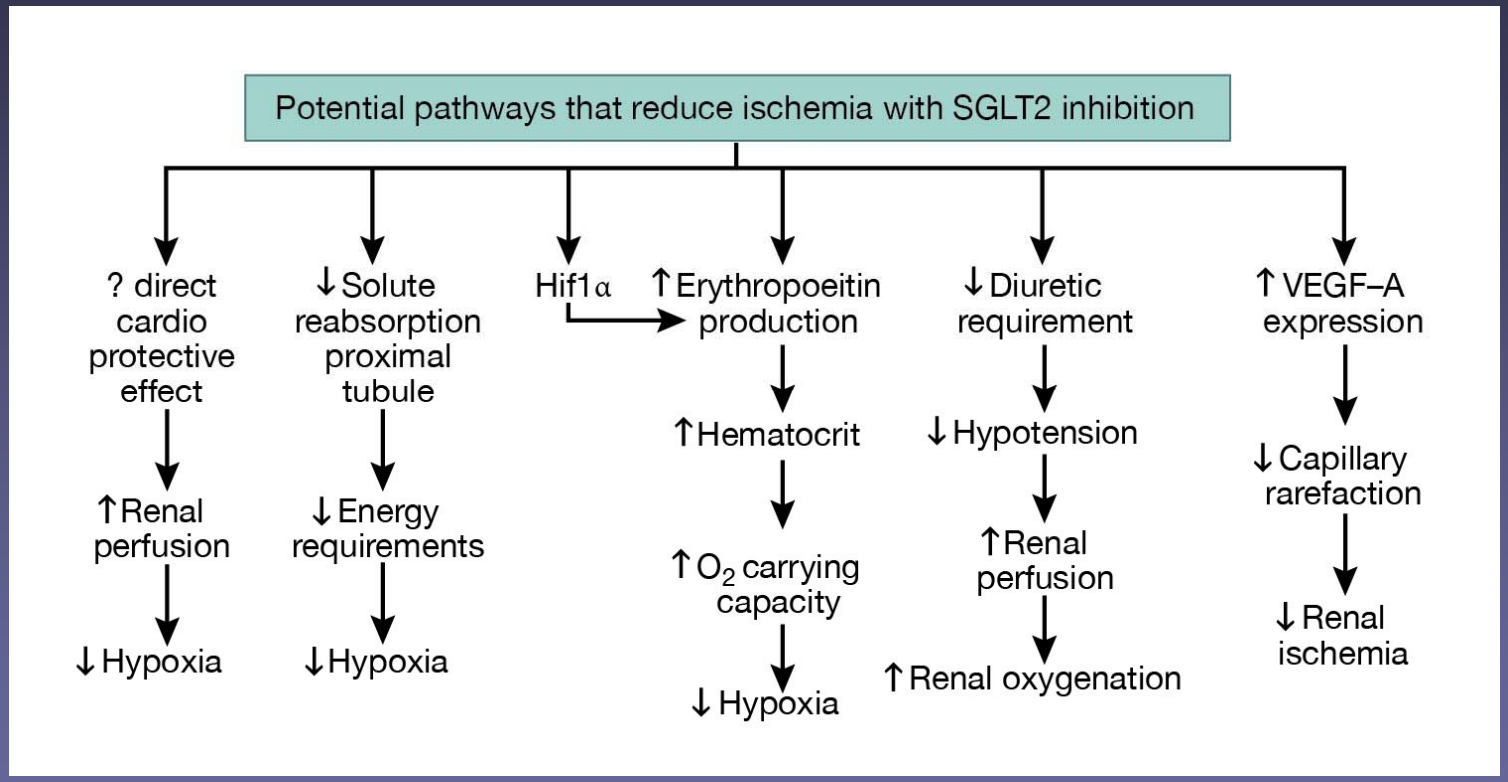
Humans





Dekkers et al. Diab Obes Metab 2018
Panchapakesan et al. PLoS One 2013;8:e54442
Garvey et al. Metabolism 2018

Hypoxia-related pathways and SGLT2 inhibition

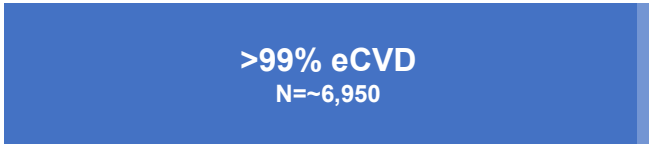


Raalte//Cherney. Kidney International 2018

Cardiovascular safety trials in patients with T2D

In the T2D patient population, most patients do not have established CV disease[1]

EMPA-REG OUTCOME[2]



(N=7,020)

Placebo MACE rate
43.9/1000 pt-yrs

CANVAS[3]

(N=10,142)

Placebo MACE rate
31.5/1000 pt-yrs

DECLARE[4,5]

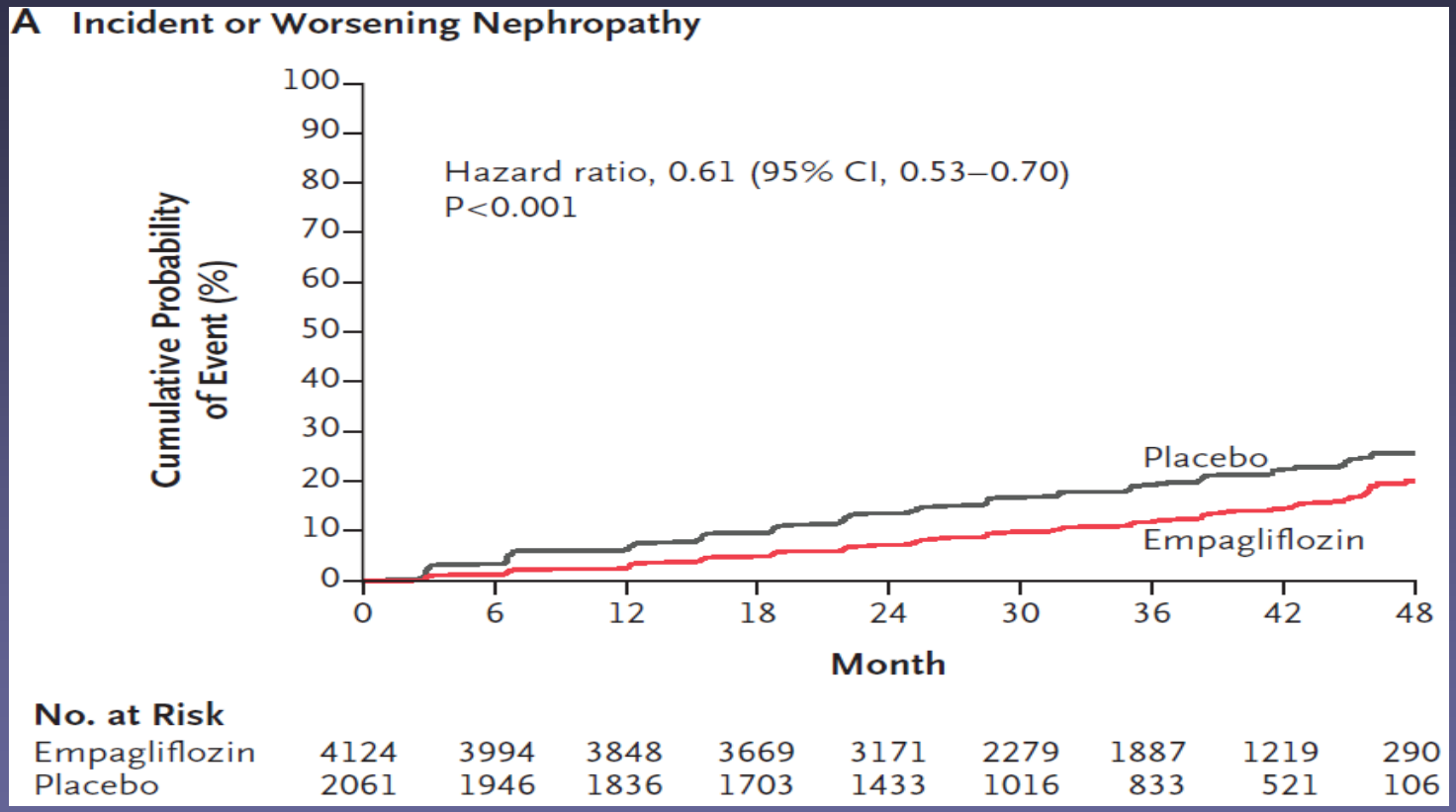
(N=17,160)

Placebo MACE rate
24.2/1000 pt-yrs

CV, cardiovascular; eCVD, established CV disease; MACE, major CV events; SGLT-2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; **2**. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; **3**. Neal B, et al. *N Engl J Med* 2017;377:644–657; **4**. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; **5** Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

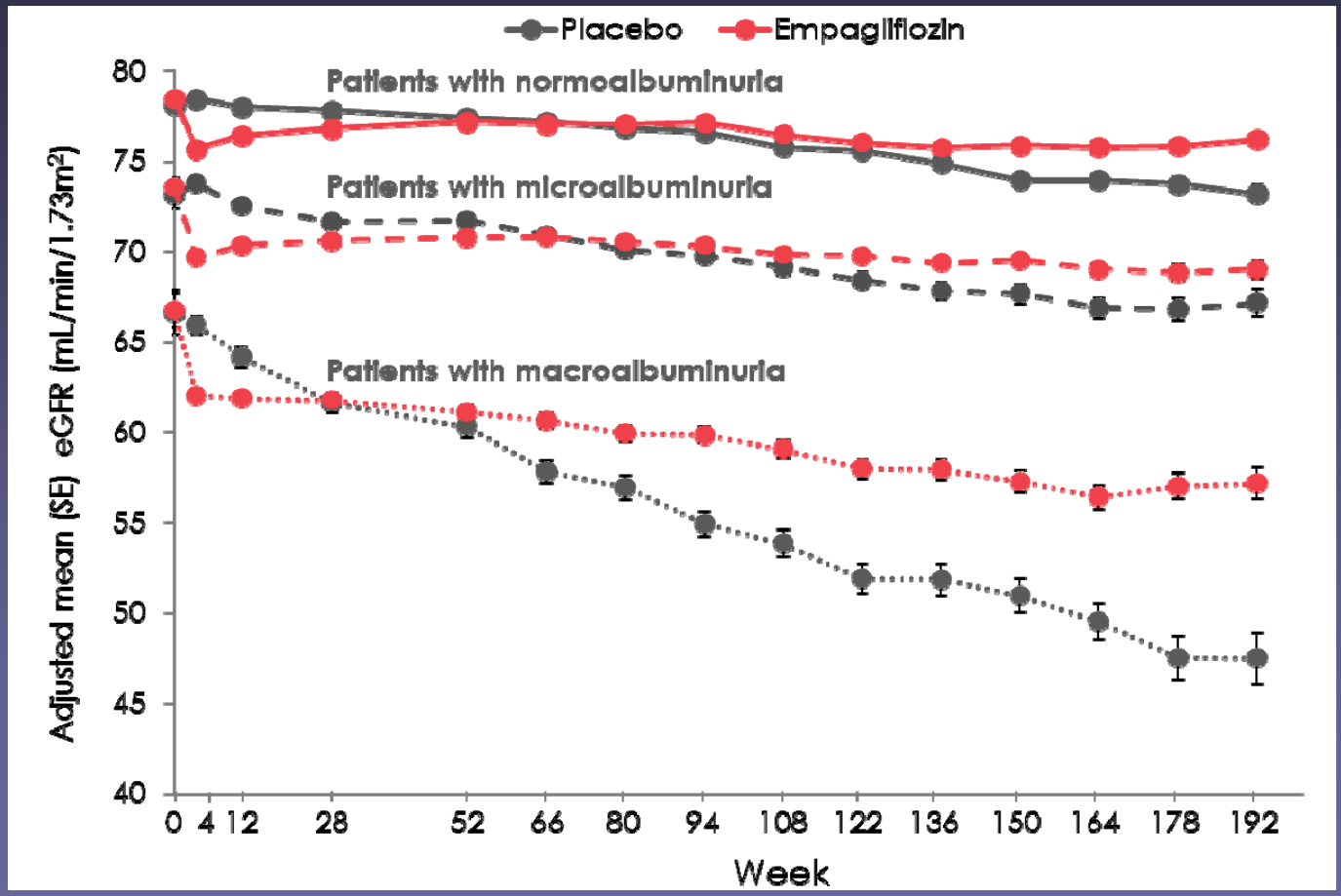
EMPA-REG OUTCOME: ↓risk MACE, death, heart failure (n=7020)



<0.4% in HbA1c, preserved effects in patients with CKD

Wanner et al. *N Engl J Med* 2016;375:323–334

eGFR change according to baseline UACR status



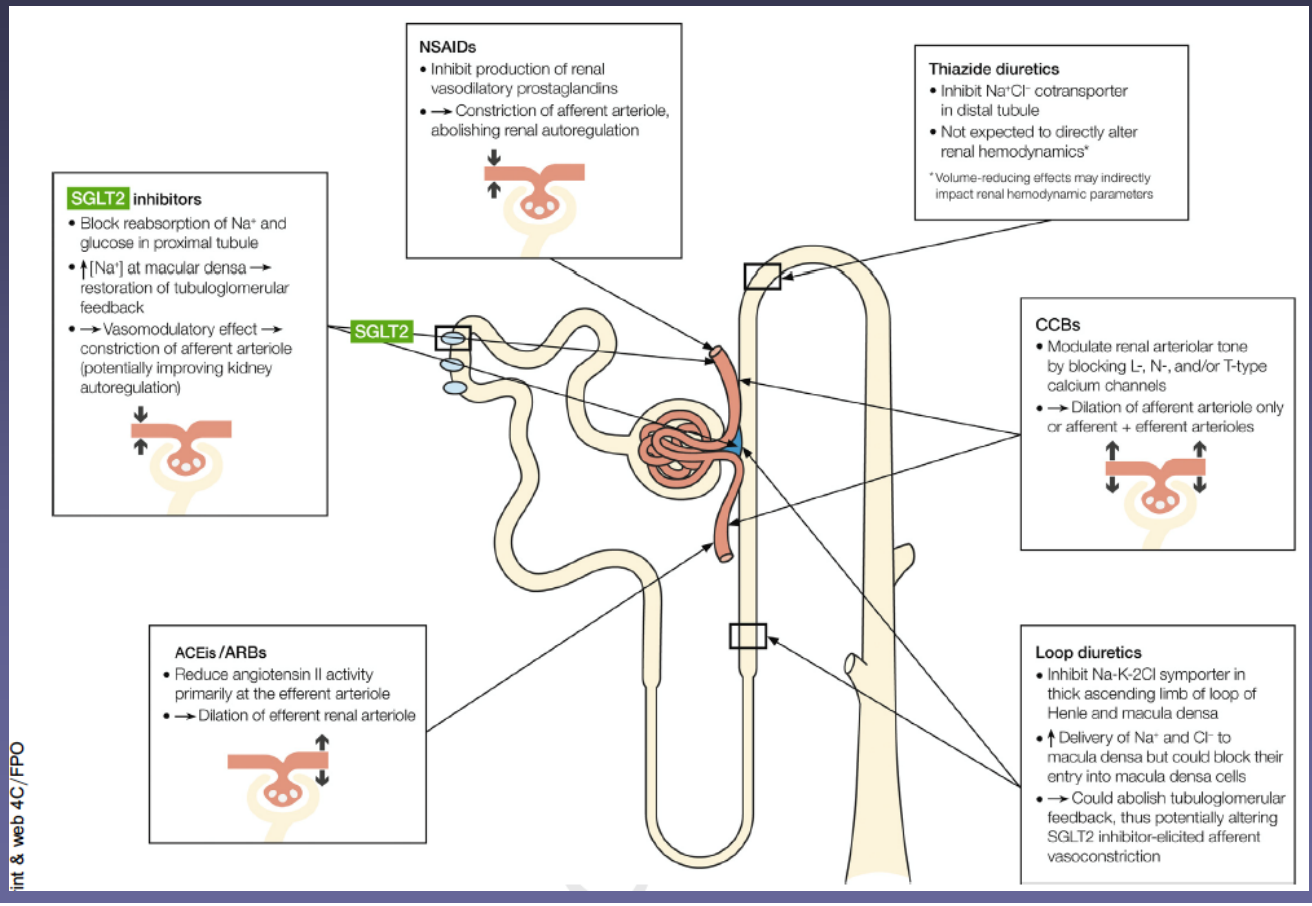
UACR -12%

UACR -42%

UACR -49%

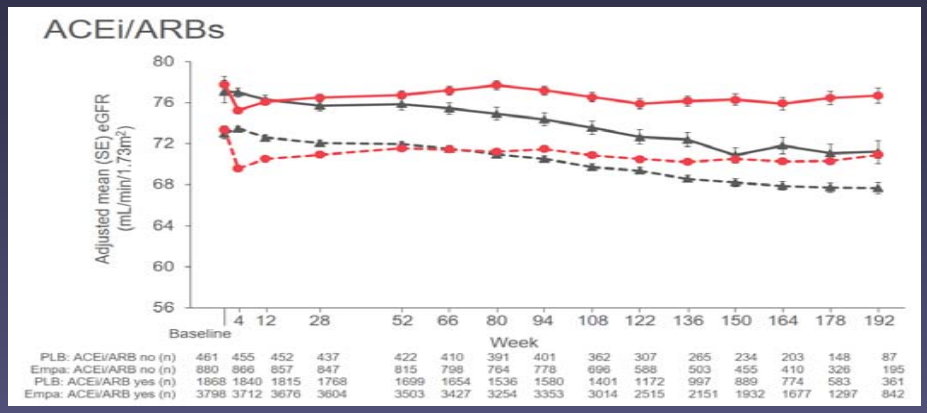
Cherney et al. Lancet Diab Endo 2017

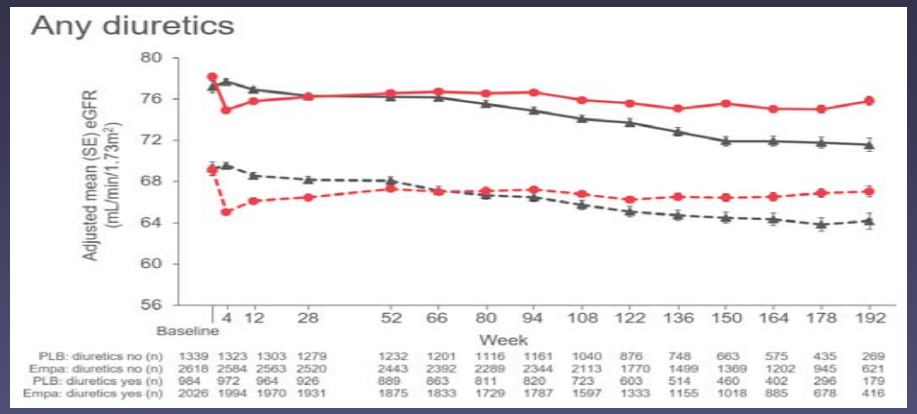
Does use of other “vasoactive agents” alter renal effects?

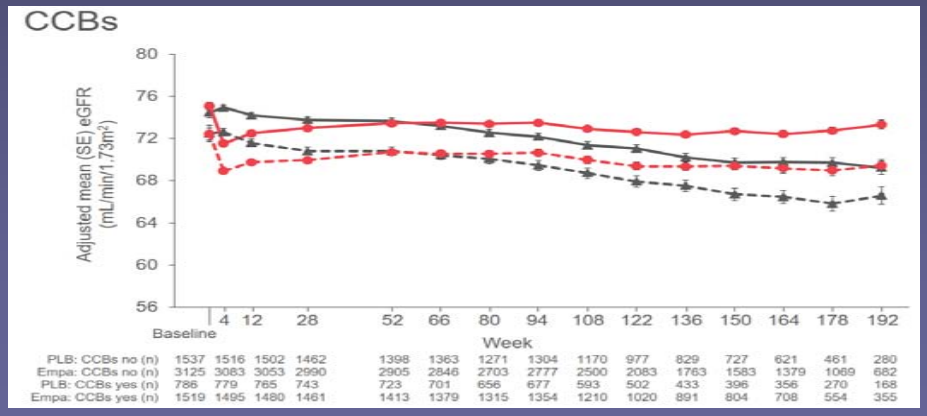


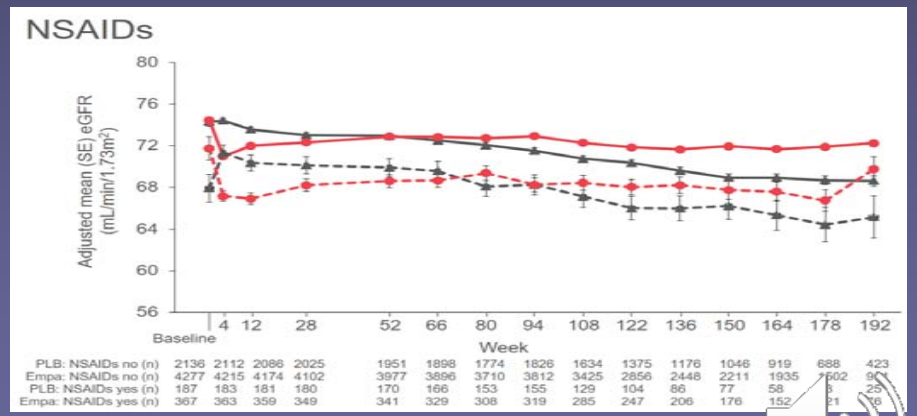
Cherney et al. KI 2019

eGFR over time by baseline medication use







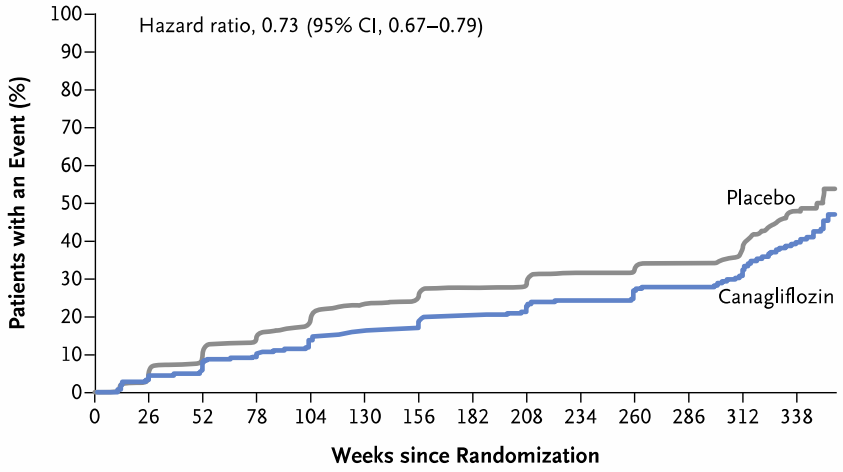


PLB: Background med no — Empa: Background med no — PLB: Background med yes — Empa: Background med yes

Cherney et al. KI 2019

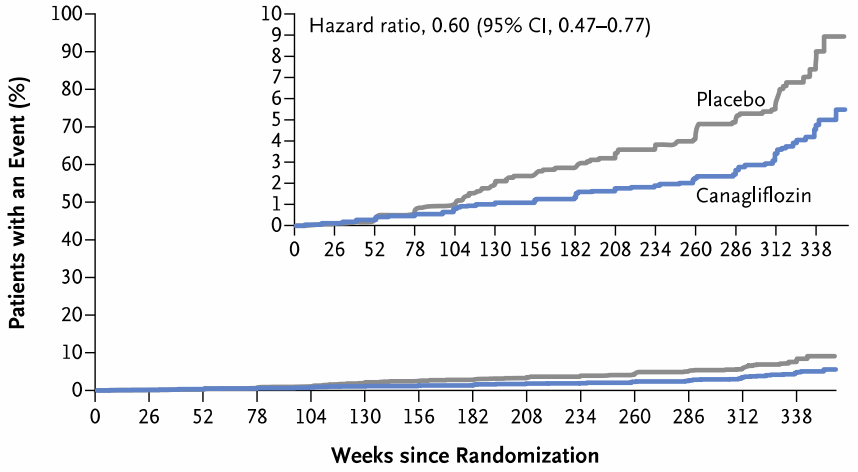
CANVAS Program: 14% ↓risk of 3-point MACE, renal benefits

C Progression of Albuminuria



No. at Risk														
Placebo	3819	3473	3096	2700	1690	877	724	652	626	565	548	485	303	67
Canagliflozin	5196	4791	4475	4027	2968	1951	1730	1593	1528	1408	1354	1213	775	185

D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



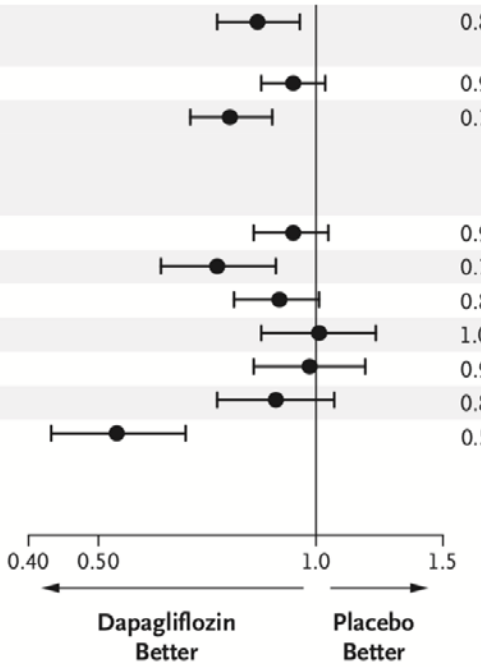
No. at Risk														
Placebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
Canagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

*increase in risk of fracture and amputation

Neil et al. NEJM June 12, 2017

DECLARE TIMI 58: Lowest Risk Cohort

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)	

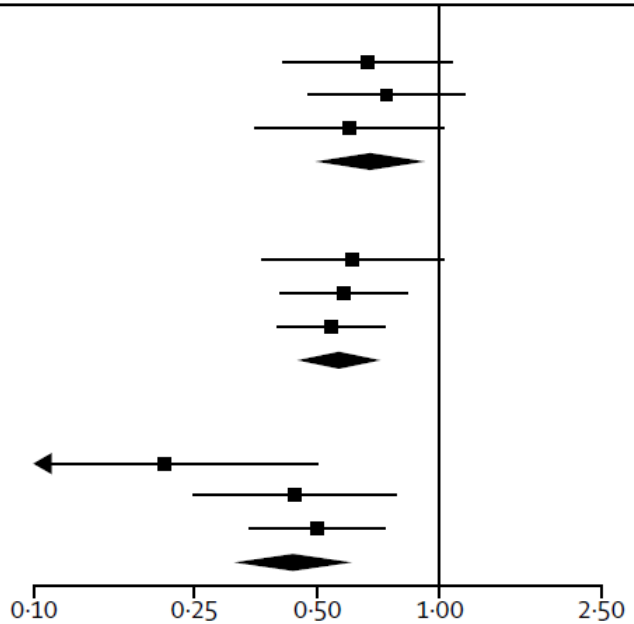


Wiviott et al. NEJM 2018

Meta-analysis: SGLT2i trials on composite of worsening of renal function, ESKD, or renal death by eGFR level

A

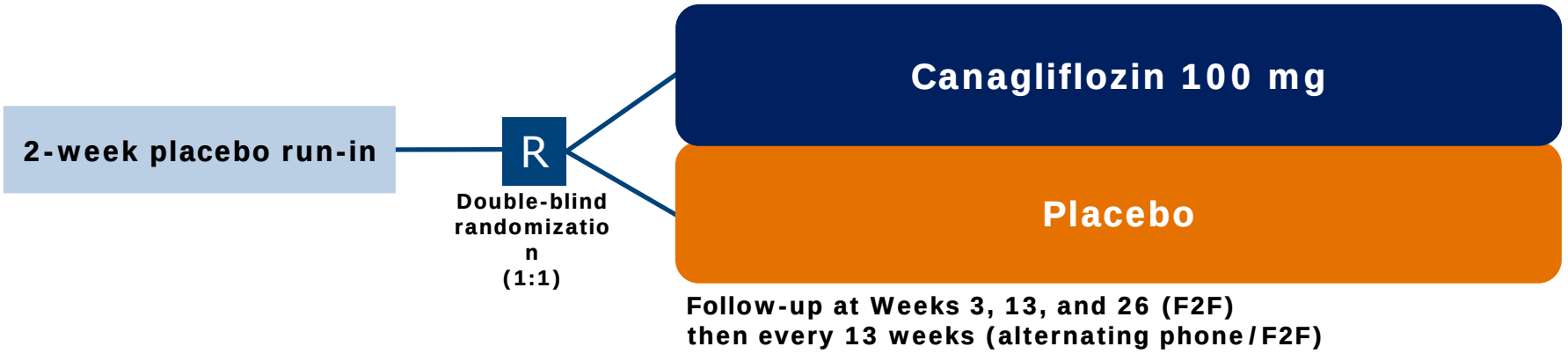
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406	1232	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043	486	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**



Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m^2
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

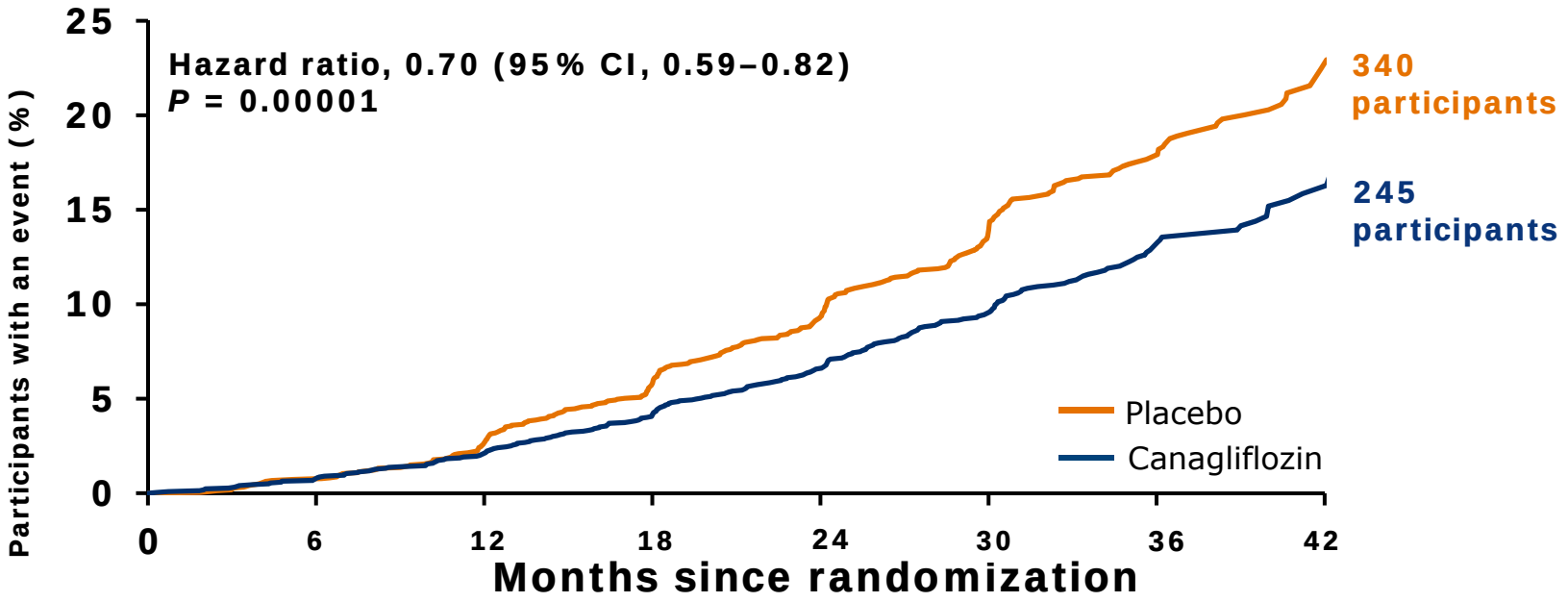


Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

Perkovic et al. *NEJM* 2019 (slides from George Clinical website)

CREDENCE

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

***No heterogeneity across subgroups**

CREDENCE

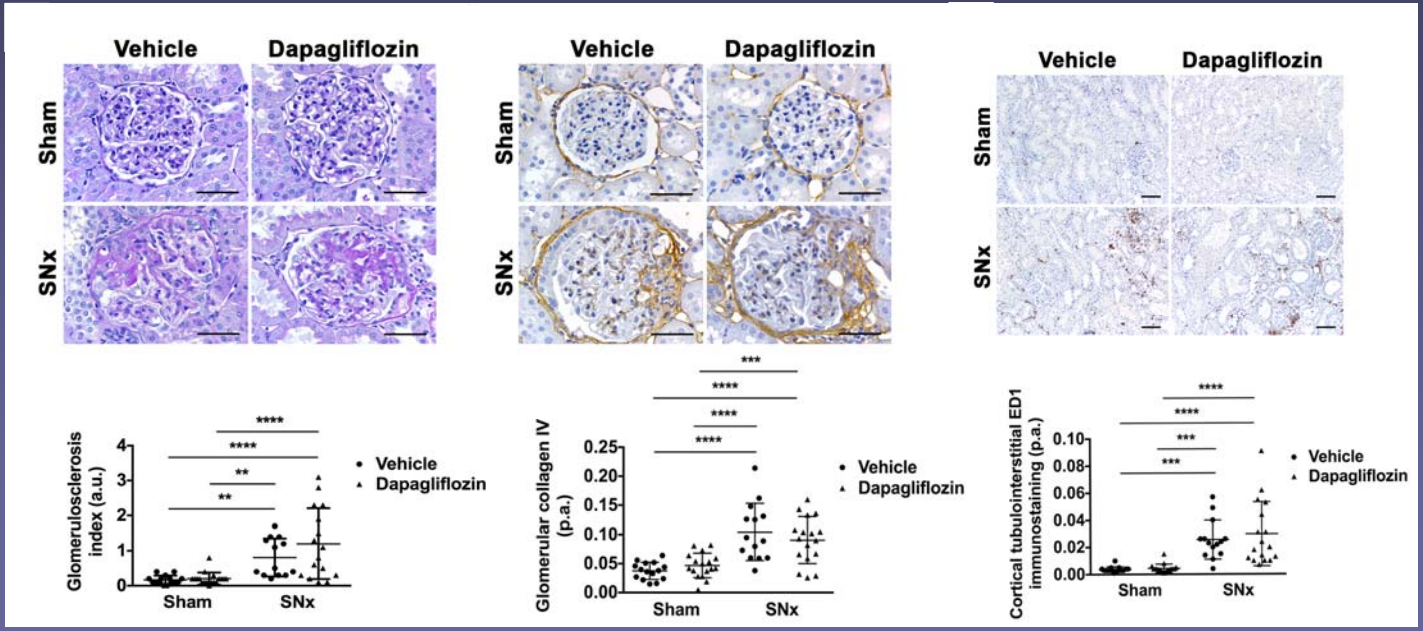
Renal protection in *non-diabetic* kidney disease? Pilot data in patients with FSGS

	Baseline	Post-Treatment	p-value
Age, years	37.2±9.2	-	
Female Sex - n (%)	4 (40)	-	
Baseline BMI (kg/m^2)	30.0±8.2	-	
FSGS duration, years	5.6±5.3	-	
GFR	93.9 ±18.2	85.9±16.9	NS
Renal plasma flow	513.5 ±161.2	496.6±152.0	NS
Filtration fraction	0.19±0.035	0.18±0.039	NS
Renal blood flow	881.7±287.1	853.0±245.6	NS
Renal vascular resistance	0.11±0.03	0.11±0.03	NS
24 hour urine protein	2.6±1.9	2.4±2.2	NS
Systolic blood pressure	112.7±8.5	112.8±11.2	NS
Diastolic blood pressure	71.8±6.5	69.6±8.4	NS
Body weight	88.2±25.1	87.0±25.4	NS
24h urine glucose (g/day)	0.2±0.2	37.5±23.4	<0.001
HbA_{1c} (%)	5.5±0.5	5.5±0.6	NS
Hematocrit	0.40±0.054	0.42±0.049	0.023

Rajasekeran//Cherney. AJP Renal 2018

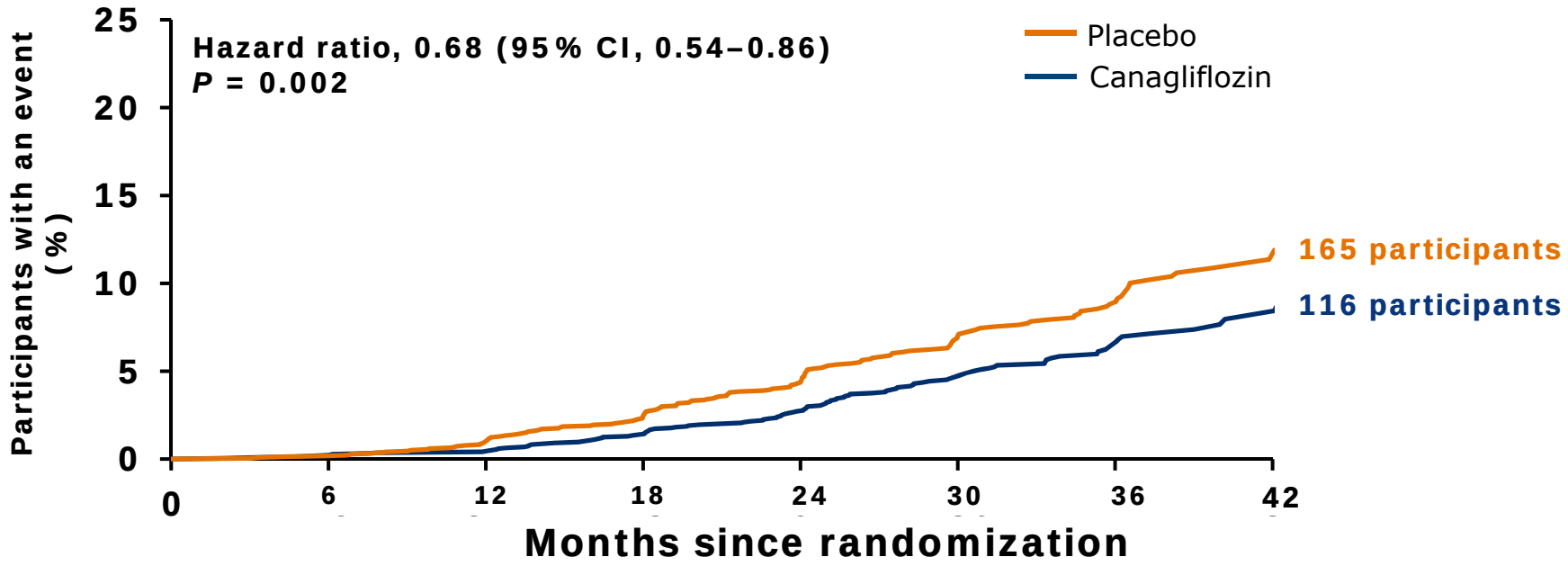
Renal function, structure: subtotally nephrectomized (SNx) Sprague-Dawley rats

- No effect: GFR_{INULIN}, $ERPF_{PAH}$, proteinuria
- Decrease in systolic BP (animals hypertensive)



Rajasekeran//Cherney. AJP Renal 2018

End-stage Kidney Disease



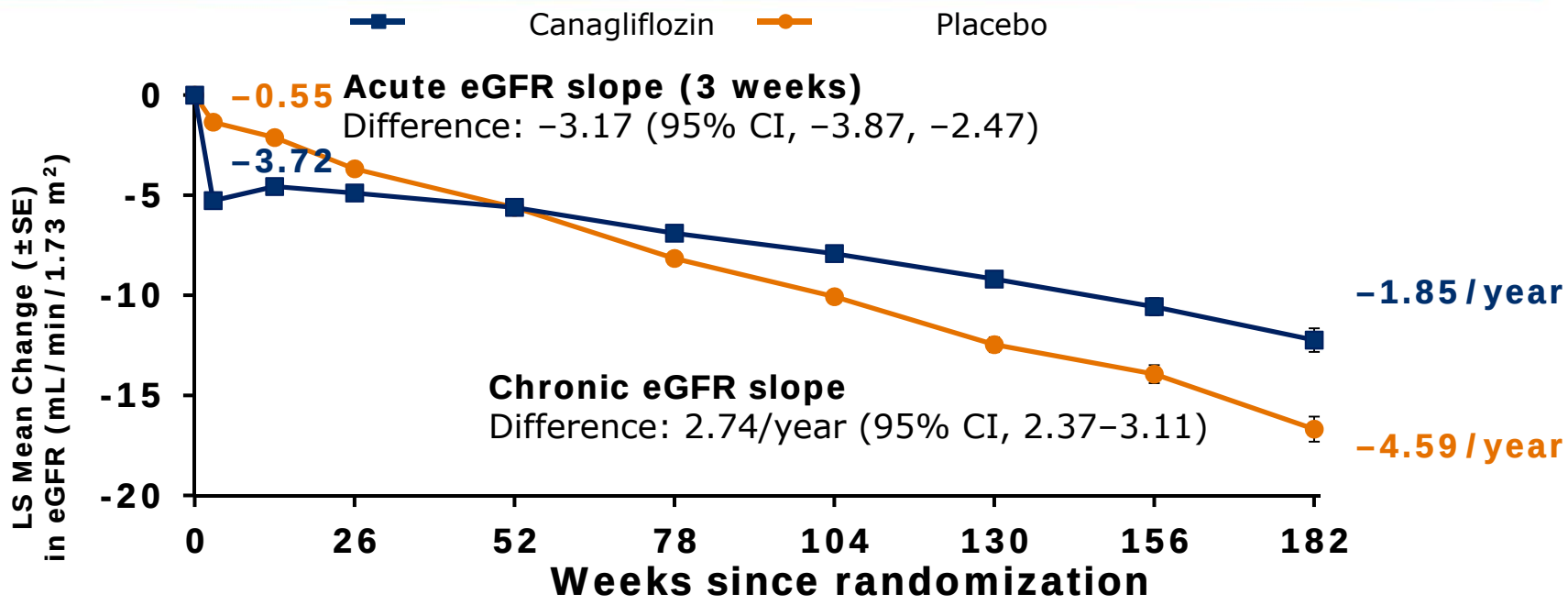
No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

CREDENCE

Summary

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 teste

Effects on eGFR



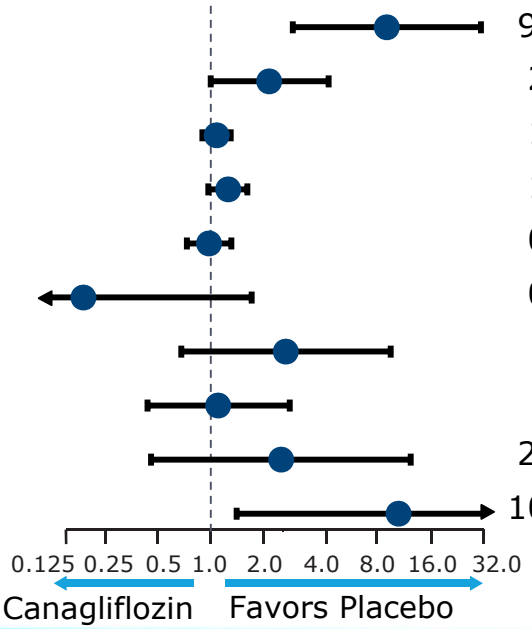
No. of Participants

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

CREDENCE

Other AEs of Interest

	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
Male genital mycotic infections*	28	3	9.30 (2.83–30.60)
Female genital mycotic infections†	22	10	2.10 (1.00–4.45)
Urinary tract infections	245	221	1.08 (0.90–1.29)
Volume depletion–related AEs	144	115	1.25 (0.97–1.59)
Malignancies‡	98	99	0.98 (0.74–1.30)
Renal cell carcinoma	1	5	0.20 (0.02–1.68)
Breast†	8	3	2.59 (0.69–9.76)
Bladder	10	9	1.10 (0.45–2.72)
Acute pancreatitis	5	2	2.44 (0.47–12.59)
Diabetic ketoacidosis	11	1	10.80 (1.39–83.65)



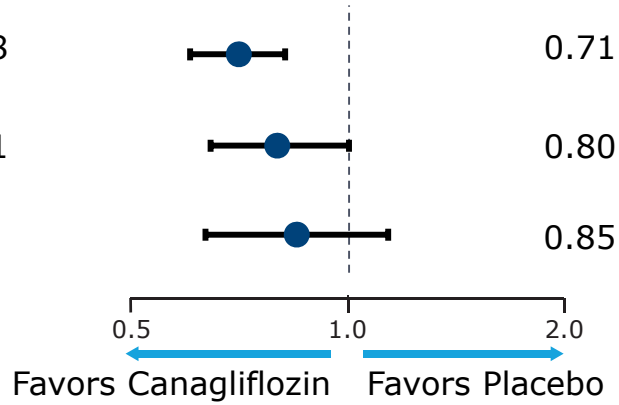
Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.

CREDENCE

Renal Safety

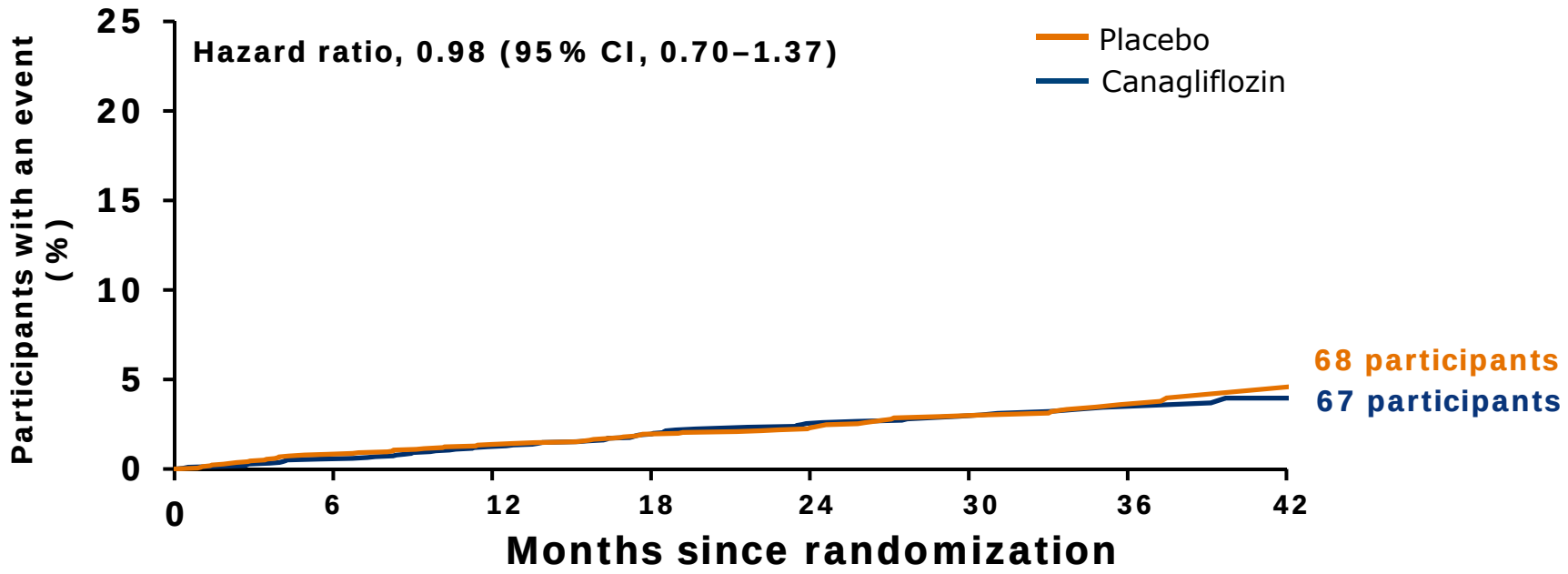
	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All renal-related AEs	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)



Includes all treated participants through 30 days after last dose.

CREDENCE

Fracture

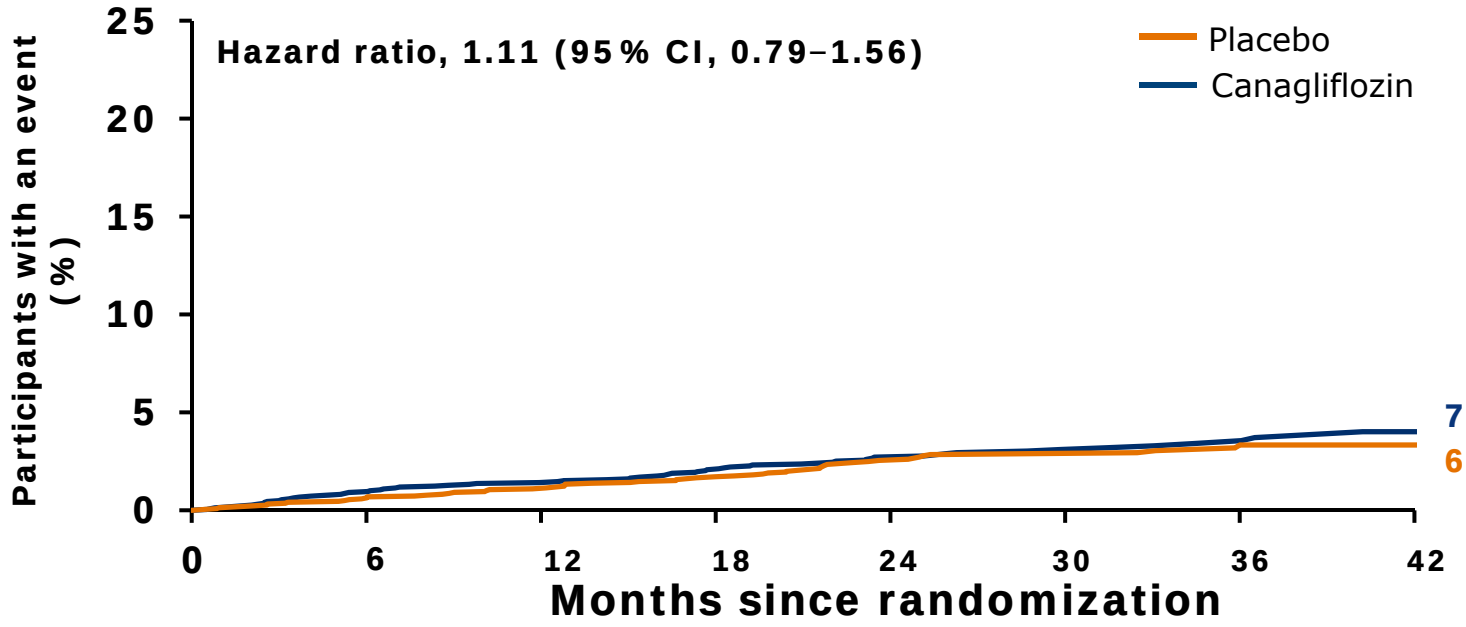


No. at risk								
Placebo	2197	2166	2128	2061	1769	1178	656	176
Canagliflozin	2200	2171	2121	2074	1785	1225	668	200

Includes all treated patients through the end of the trial.

CREDENCE

Lower Extremity Amputation



No. at risk								
Placebo	2197	2169	2131	2065	1766	1177	658	182
Canagliflozin	2200	2163	2118	2071	1788	1228	667	202

Includes all treated patients through the end of the trial.

CREDENCE

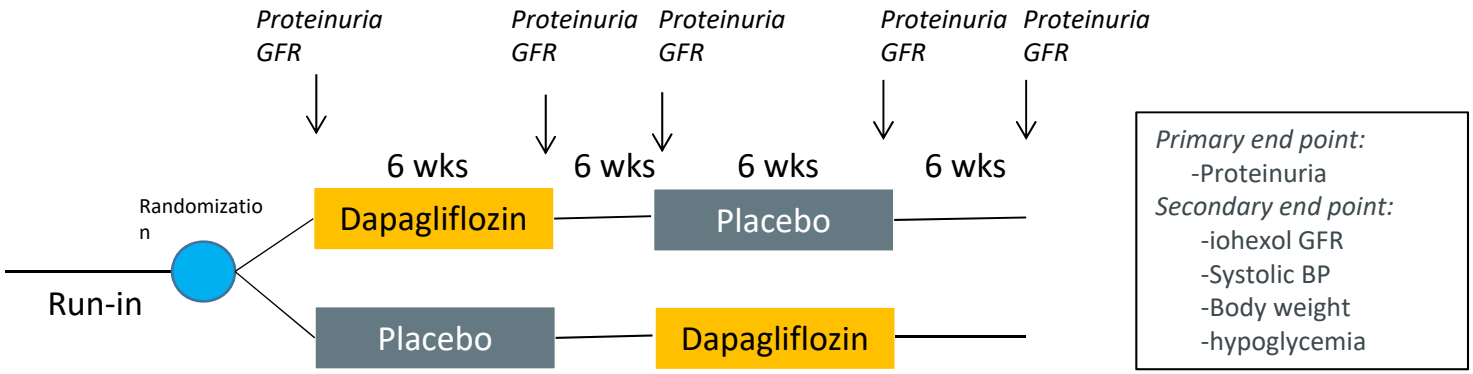
Human physiological evidence in T1D: cardiorenal protection

- ✓↓Hyperglycemia, low risk hypoglycemia
- ✓↓Body weight
- ✓↓Insulin requirements
- ✓↓Blood pressure
- ✓↑Hemoconcentration
- ✓↓Renal hyperfiltration
- ✓↓Plasma uric acid

What are the barriers for CREDENCE-like T1D Trial?

- Safety concerns around DKA
- Funding – public investment likely required
- Which outcomes to choose?
  - Cardiovascular: MACE, heart failure?
    - Enrich – e.g. longer T1D duration, HTN, DKD
  - Hard renal endpoints vs. GFR slope, albuminuria (“PERL”)
    - Enrich for DKD?
- Feasibility of required sample size based on endpoints

DIAMOND: A randomized cross-over trial to assess the proteinuria lowering effects of dapagliflozin in non-diabetic kidney disease

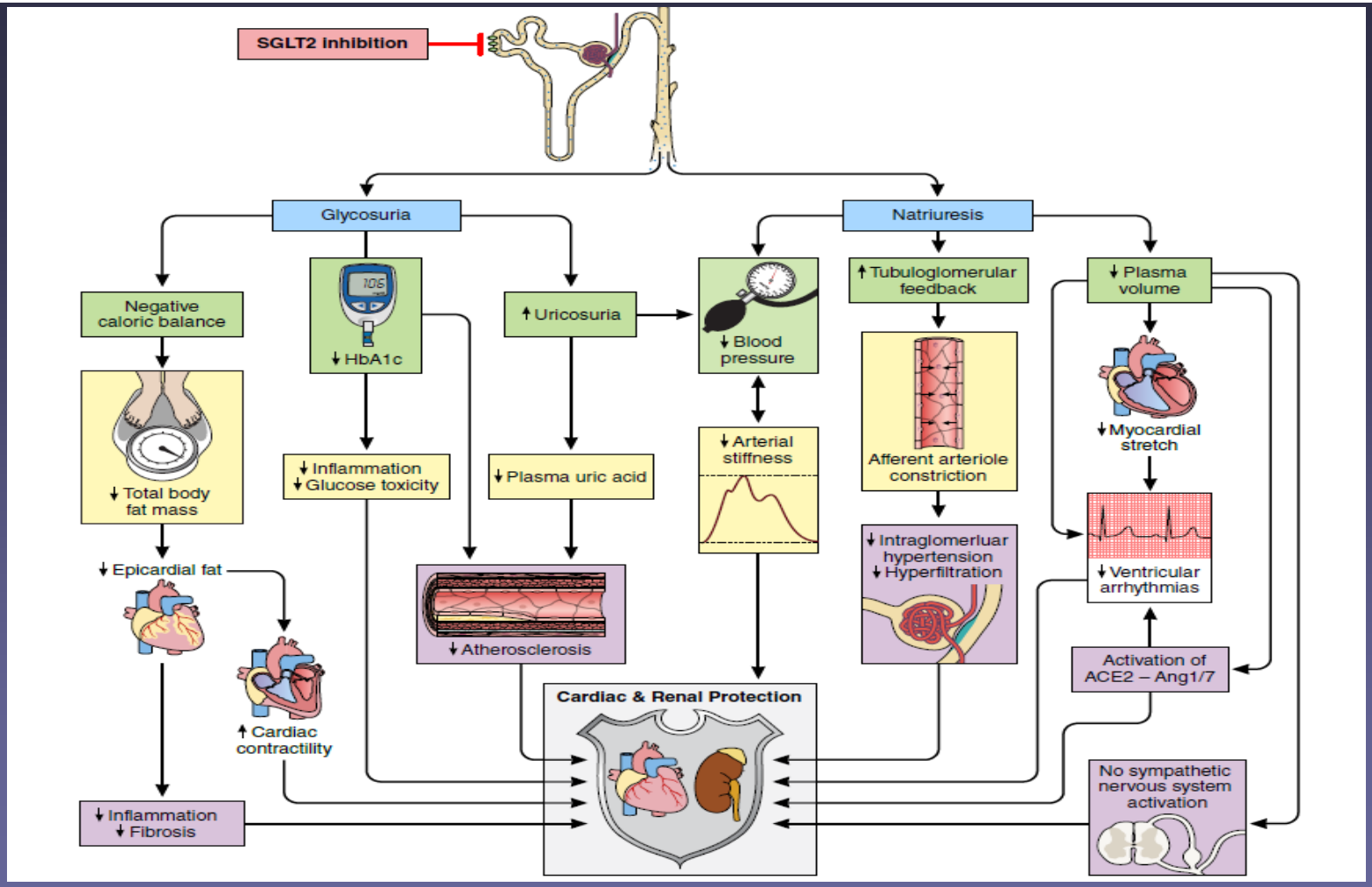


Primary end point:
-Proteinuria
Secondary end point:
-iohexol GFR
-Systolic BP
-Body weight
-hypoglycemia

Inclusion criteria
-Age > 18 and <75 yrs
-Uprot 500 -3500 mg /24hr
-eGFR>25 ml/min/1.73m^2
Exclusion criteria
-Type 1 / Type 2 diabetes
-Indication immunosuppressants

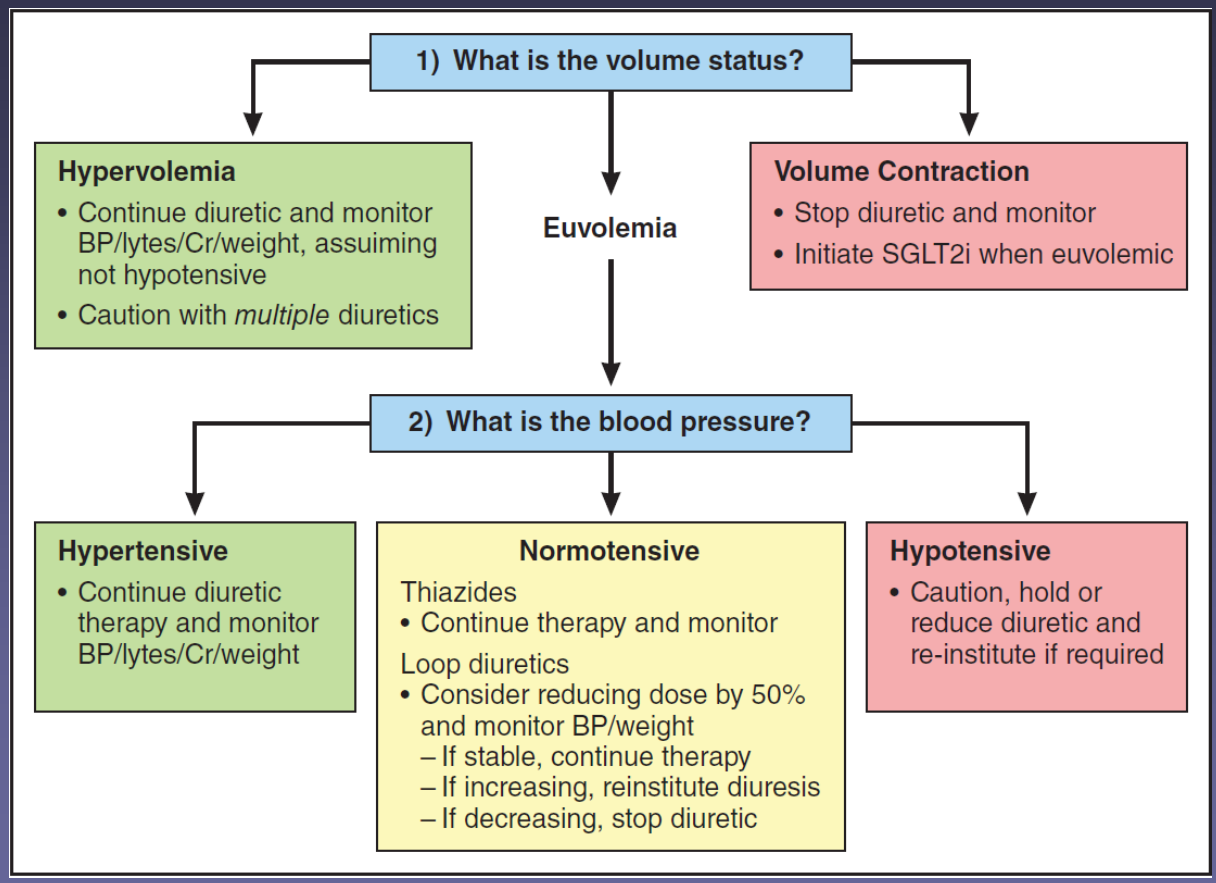
Sample size:
50 patients provide 80% power to detect 25% proteinuria lowering effect (alpha 0.05)

Dekkers et al. Submitted to ASN Washington 2019



Heerspink//Cherney. Circulation 2016;134:752–772
Inzucchi et al. Diabetes Care 2018 (in press – “mediation analysis”)

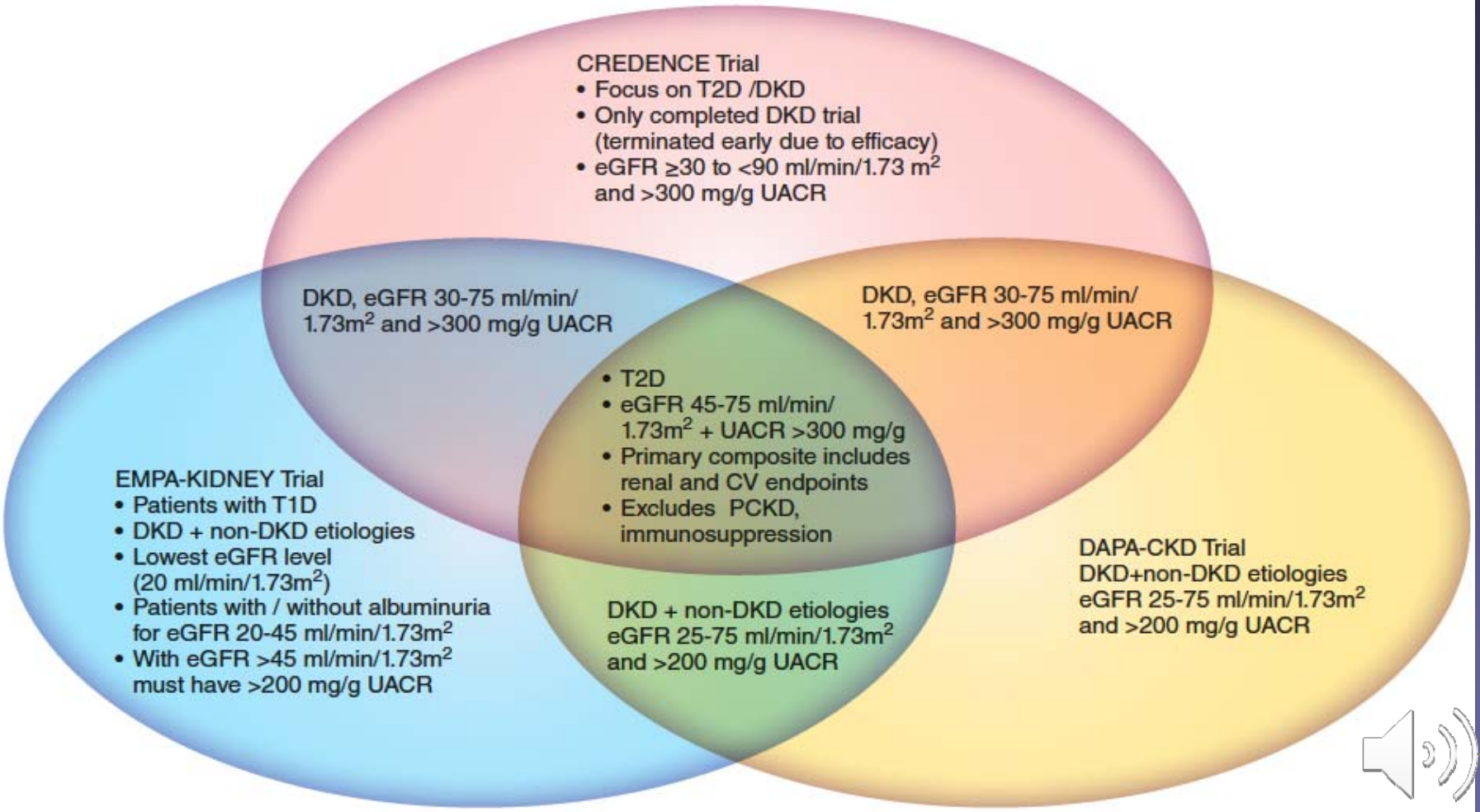
How to manage background diuretics?



Cherney/Udell. Circulation 2016

S sulfonylureas
A ACE-inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N non-steroidal anti-inflammatory
S SGLT2 inhibitors


CREDENCE Trial
• Focus on T2D /DKD
• Only completed DKD trial (terminated early due to efficacy)
• eGFR ≥30 to <90 ml/min/1.73 m²
and >300 mg/g UACR
DKD, eGFR 30-75 ml/min/ 1.73m² and >300 mg/g UACR
DKD, eGFR 30-75 ml/min/ 1.73m² and >300 mg/g UACR
• T2D
• eGFR 45-75 ml/min/ 1.73m² + UACR >300 mg/g
• Primary composite includes renal and CV endpoints
• Excludes PCKD, immunosuppression
EMPA-KIDNEY Trial
• Patients with T1D
• DKD + non-DKD etiologies
• Lowest eGFR level (20 ml/min/1.73m²)
• Patients with / without albuminuria for eGFR 20-45 ml/min/1.73m²
• With eGFR >45 ml/min/1.73m² must have >200 mg/g UACR
DKD + non-DKD etiologies eGFR 25-75 ml/min/1.73m² and >200 mg/g UACR
DAPA-CKD Trial
DKD+non-DKD etiologies
eGFR 25-75 ml/min/1.73m²
and >200 mg/g UACR

EMPA-KIDNEY: Primary Aim

- Empagliflozin 10mg vs. placebo (n=5000 with CKD*) on top of standard of care on the composite primary:
  - (i) Kidney disease progression (ESKD, sustained eGFR to <10 mL/min/1.73m², renal death, or a sustained eGFR decline ≥40%) **OR**
  - (ii) Cardiovascular death

EMPA-KIDNEY

MRC Population Health Research Unit

UNIVERSITY OF OXFORD

Conclusions and key messages

- SGLT2i in diabetes:
  - Renal effects independent of HbA1c lowering
  - eGFR dip: occurs in CKD stages 3a, 3b, CKD
  - ↓eGFR slope, albuminuria in T2D in CV safety trials
  - CREDENCE: 30%↓ in renal composite endpoint

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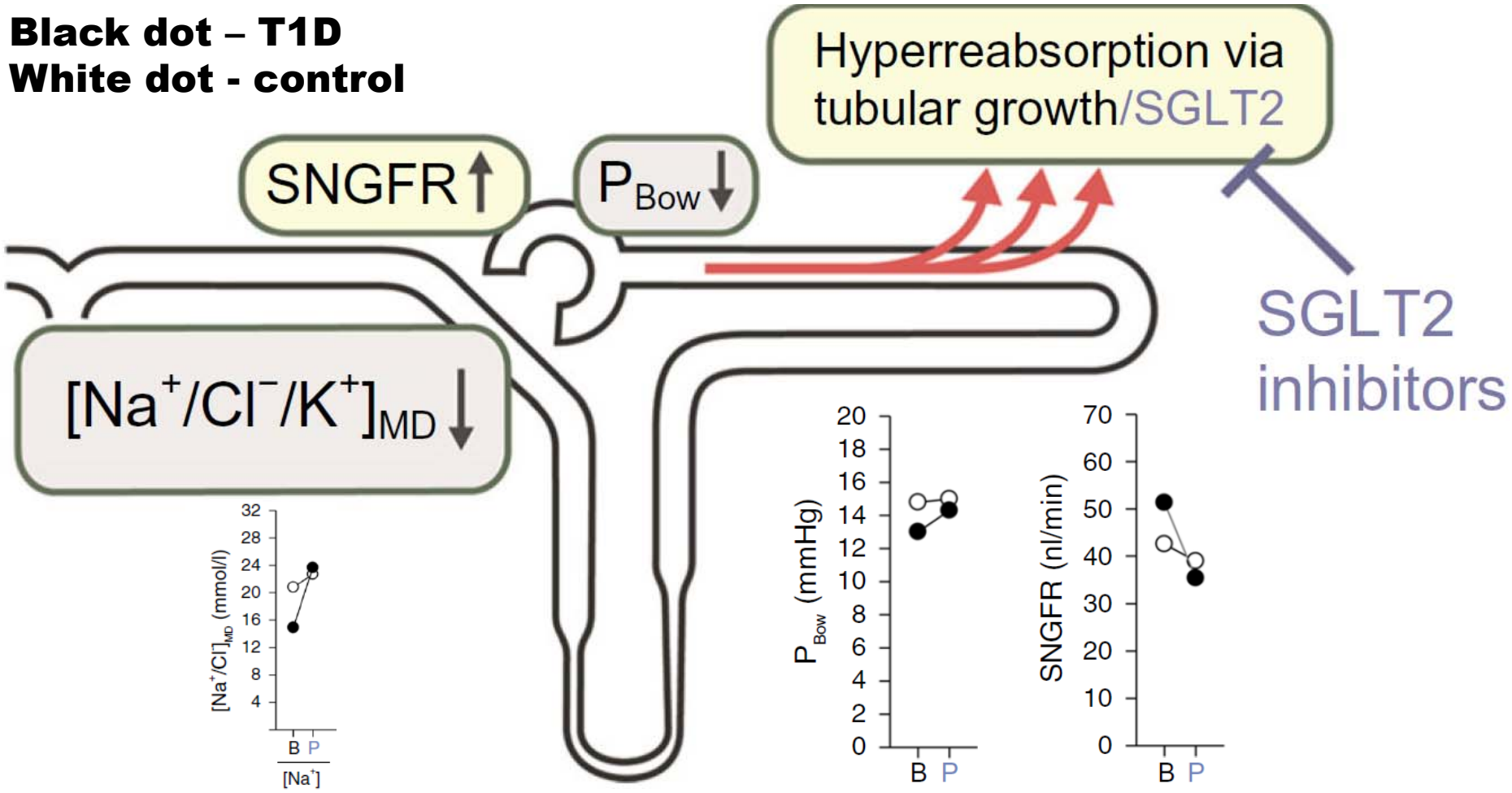
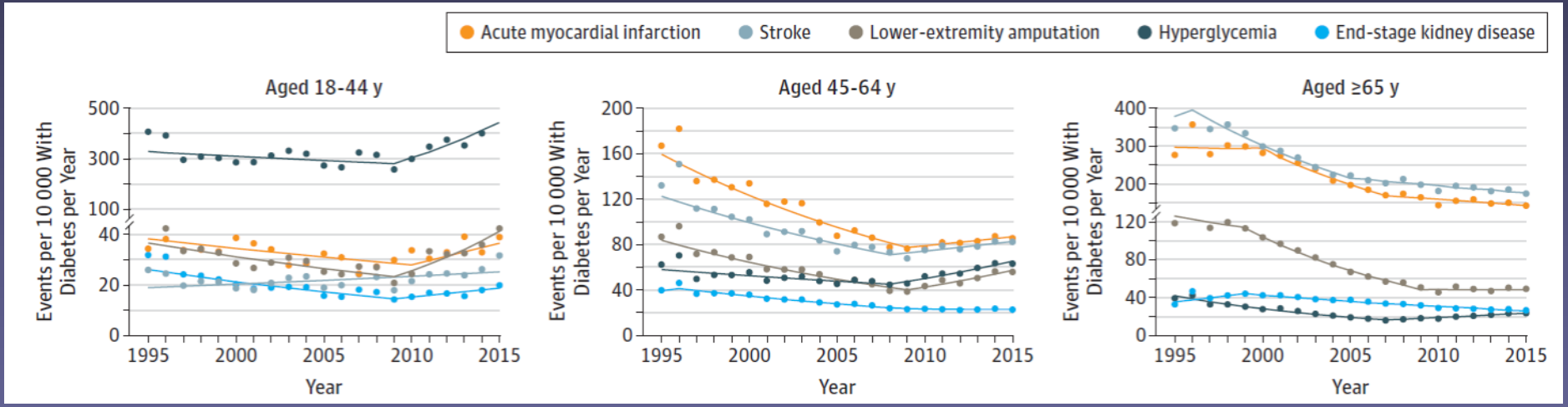
- Grant funding:
- Salary support:

Black dot – T1D
White dot - control



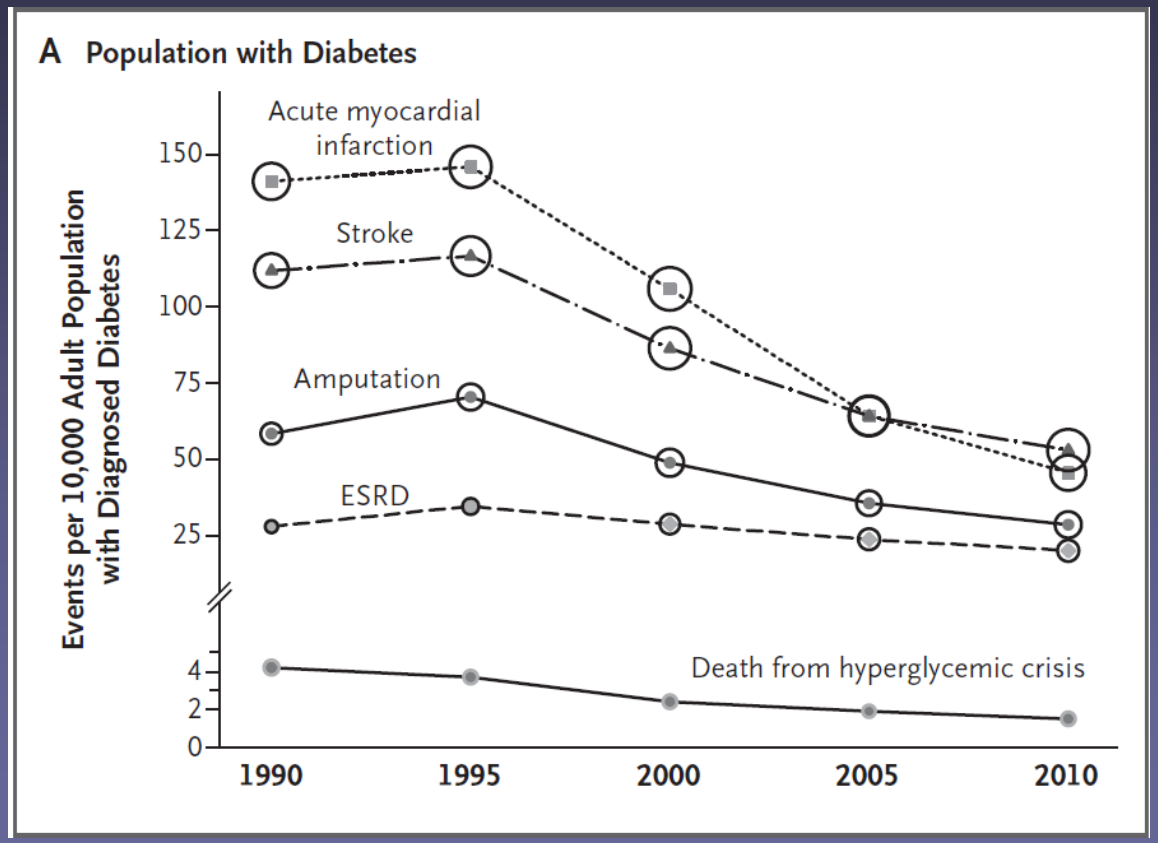
Vallon et al. Diabetologia 2017;60:215-225

Incidence of Hospitalization for Diabetes-Related Complications (US)



Gregg et al. JAMA 2019 (April 15th)

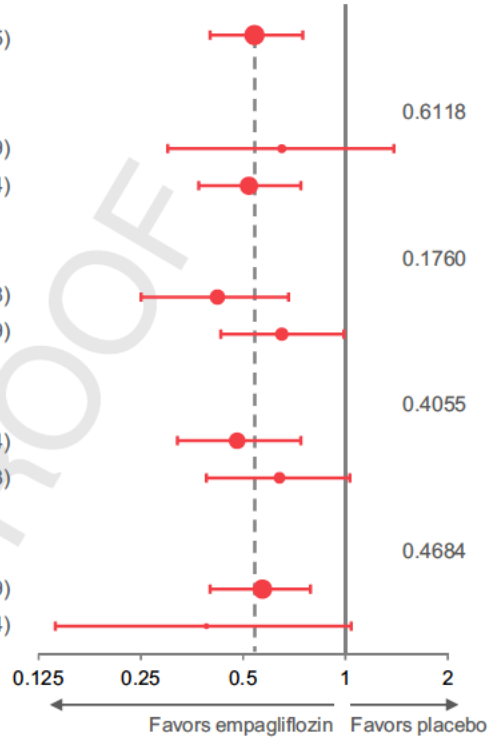
ESRD in patients with diabetes over time



Gregg EW *et al. N Engl J Med* 2014;370:1514

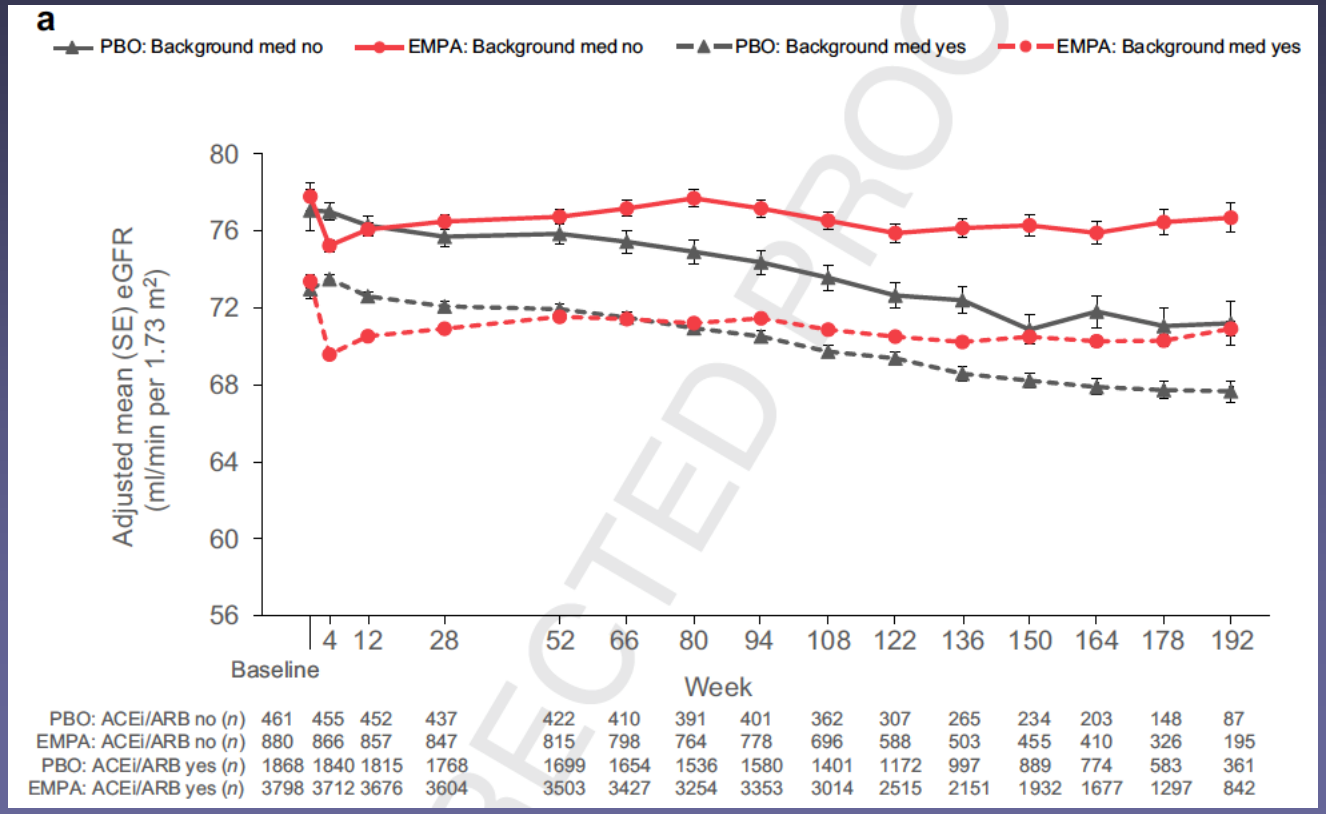
Doubling of serum creatinine, renal replacement therapy, renal death

	Empagliflozin *n* with event/*N* analyzed (%)	Placebo *n* with event/*N* analyzed (%)	Hazard ratio (95% CI)	Interaction *P* value
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)	
Use of ACEis/ARBs				0.6118
No	15/880 (1.7)	12/461 (2.6)	0.65 (0.30, 1.39)	
Yes	66/3765 (1.8)	59/1862 (3.2)	0.52 (0.37, 0.74)	
Use of any diuretic				0.1760
No	29/2618 (1.1)	34/1339 (2.5)	0.42 (0.25, 0.68)	
Yes	52/2027 (2.6)	37/984 (3.8)	0.65 (0.43, 0.99)	
Use of CCBs				0.4055
No	43/3126 (1.4)	42/1537 (2.7)	0.48 (0.32, 0.74)	
Yes	38/1519 (2.5)	29/786 (3.7)	0.64 (0.39, 1.03)	
Use of NSAIDs				0.4684
No	74/4278 (1.7)	62/2136 (2.9)	0.57 (0.40, 0.79)	
Yes	7/367 (1.9)	9/187 (4.8)	0.39 (0.14, 1.04)	



Cherney et al. KI 2019 (in press)

eGFR change according to baseline ACEi/ARB use



Cherney et al. KI 2019 (in press)

CANVAS Program: 14% ↓risk of 3-point MACE

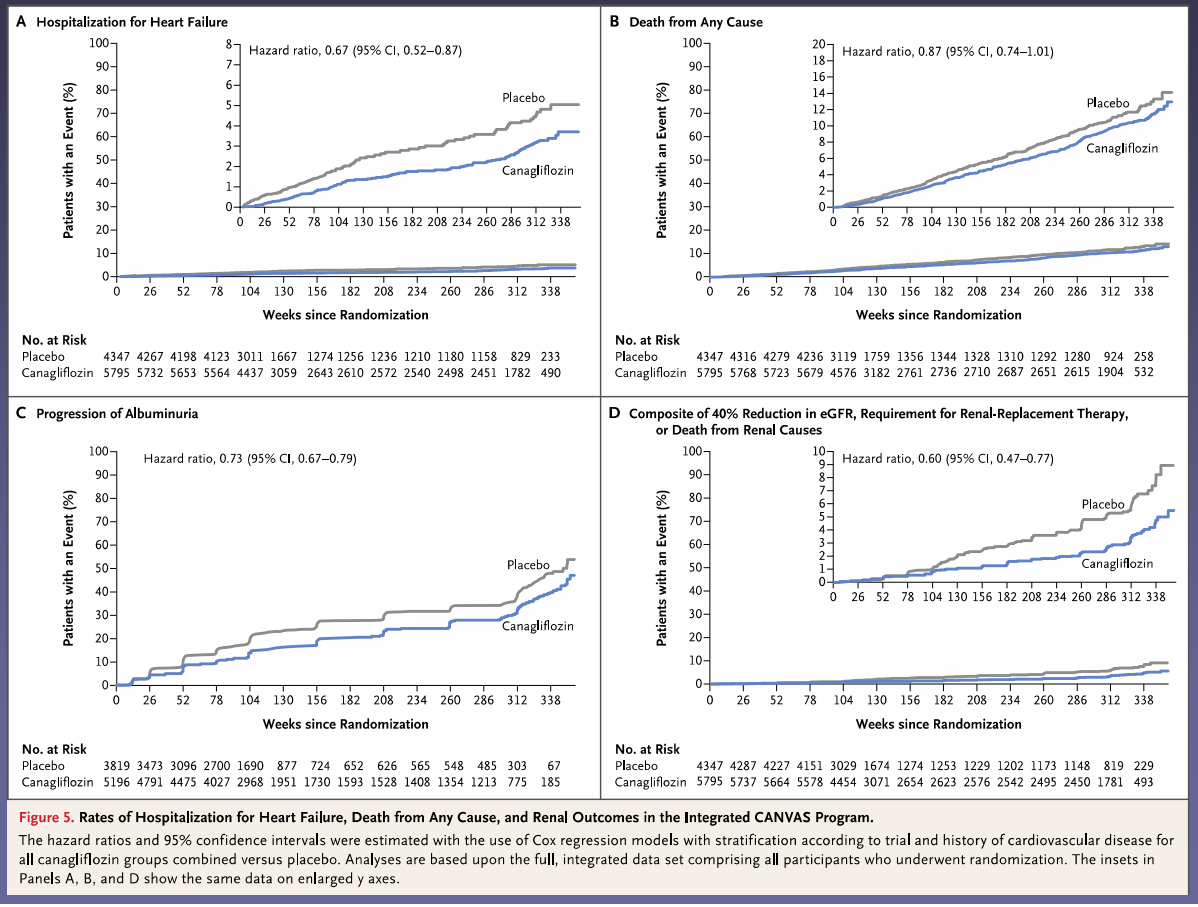
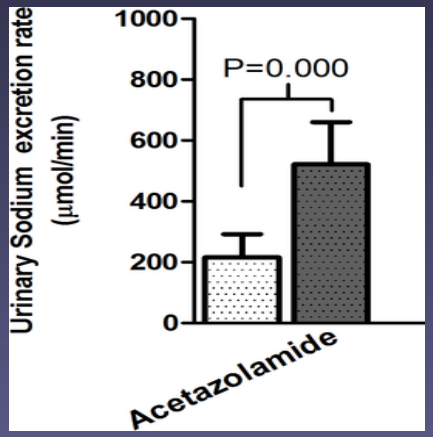


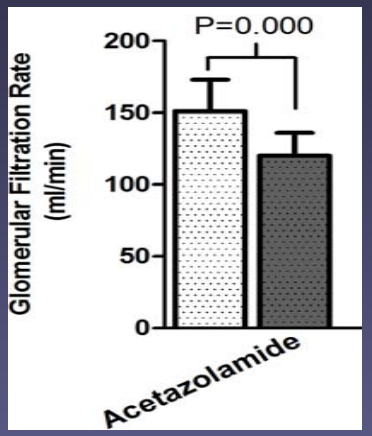
Figure 5. Rates of Hospitalization for Heart Failure, Death from Any Cause, and Renal Outcomes in the Integrated CANVAS Program.

The hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization. The insets in Panels A, B, and D show the same data on enlarged y axes.

Neil et al. NEJM June 12, 2017

How about in non-diabetic conditions? Acetazolamide, obesity-related hyperfiltration





- Acetazolamide:
  - ↓GFR/ERPF, ↑RVR in animals
  - ↓albuminuria in patients with diabetes
- Healthy controls: SGLT2i → 40-50 gm/d glucosuria
  - Canagliflozin – ↓5.9/2.6 mmHg, ↓eGFR 3%*
- ↓albuminuria, histologic renal injury obesity-glomerulopathy

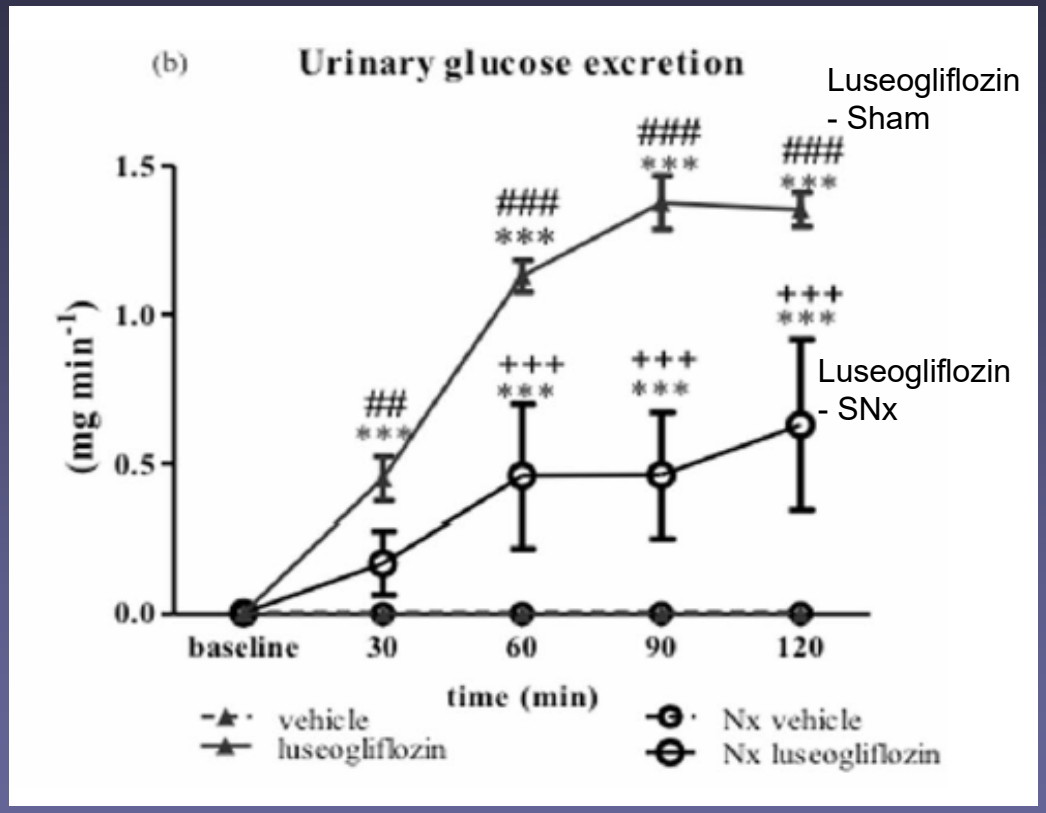
Zingerman et al. PLoS One 2015
Tucker/Blantz. KI 1984;26:112-21
*Sha et al. Diab Ob Met 2013;17:188
Wang et al. Int J Mol Sci 2018;19:137

How about in non-diabetic conditions?

	Baseline	Acute	Chronic[#]	p^1	p^2
Fasting					
Plasma glucose (mmol·L^{-1})	5.8 ± 0.4 ^{x}	5.8 ± 0.4 ^{x}	5.5 ± 0.5 ^{x}	ns	0.02
Urine output (ml·min^{-1})	3.7 ± 2.4	4.1 ± 1.8	3.8 ± 2.1	ns	ns
Creatinine clearance (mL·min^{-1}·1.73m^{-2})	125 ± 37 ^{z}	109 ± 31^{x}	110 ± 31	ns	ns
Glucose filtration rate (µmol·min^{-1})	864 ± 306 ^{x}	746 ± 253 ^{x}	687 ± 218 ^{y}	0.03	ns
Glucose excretion rate (µmol·min^{-1})	0.8 ± 0.7	163 ± 74 ^{x}	172 ± 67 ^{y}	<0.0001	0.002
Renal glucose clearance (ml·min^{-1})	0.2 ± 0.1	30 ± 13	33 ± 12 ^{z}	<0.0001	0.002
Fractional glucose excretion (%)	0.08 ± 0.05	23 ± 8 ^{y}	26 ± 11 ^{z}	0.0002	0.003
Meal					
Plasma glucose (mmol·L^{-1})	7.2 ± 0.7 ^{a,x}	6.6 ± 0.6 ^{a,x}	7.0 ± 0.4 ^{b,x}	0.0001	0.04
Urine output (ml·min^{-1})	2.9 ± 1.7	3.1 ± 1.4 ^{c}	2.9 ± 1.3	ns	0.05
Creatinine clearance (mL·min^{-1}·1.73m^{-2})	135 ± 32 ^{z}	118 ± 29	119 ± 31	0.004	0.007
Glucose filtration rate (µmol·min^{-1})	1185 ± 286 ^{x}	954 ± 259 ^{x}	1027 ± 308 $^{c, y}$	ns	ns
Glucose excretion rate (µmol·min^{-1})	1.4 ± 1.9 ^{x}	388 ± 122 ^{a,x}	353 ± 113 ^{c,y}	<0.0001	0.002
Renal glucose clearance (ml·min^{-1})	0.2 ± 0.2 ^{y}	59 ± 20 ^{b}	50 ± 15 ^{c}	<0.0001	0.002
Fractional glucose excretion (%)	0.09 ± 0.05 $^{c, z}$	40 ± 7 ^{a,y}	35 ± 8 ^{c}	0.0001	0.005

Ferrannini et al. Diab Care 2017;40:771-776 (supplementary table)

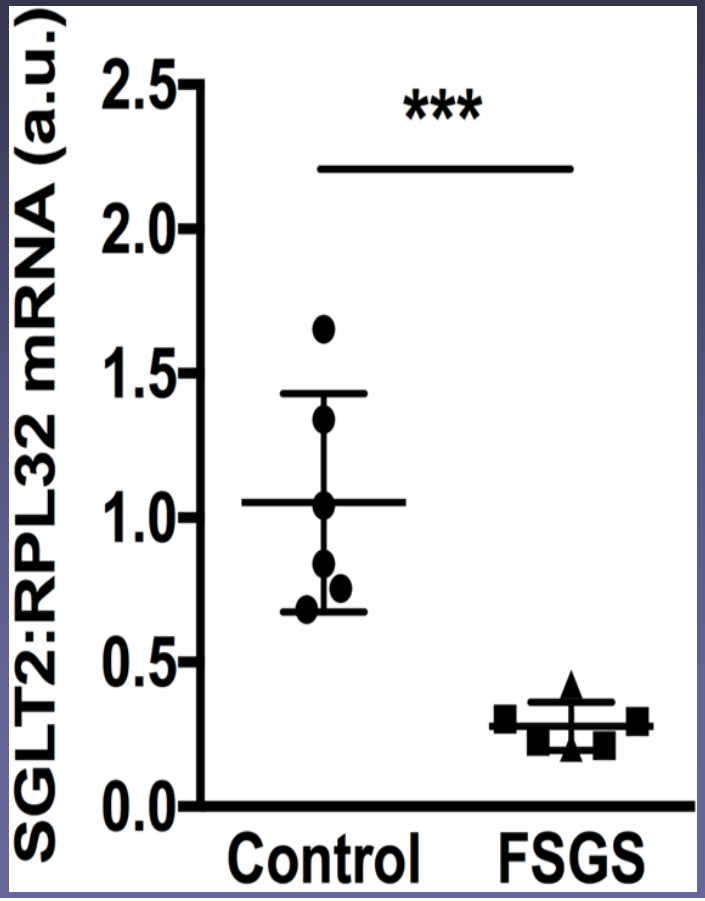
Acute effect of luseogliflozin in subtotally nephrectomized (SNx) SD rats



- No acute effect on MAP, CrCl, renal blood flow or urine sodium excretion

Ansary et al. Sci Rep 2017;7: *9555*

SGLT2 mRNA levels in kidney biopsy tissue from patients with obesity-related secondary FSGS



Rajasekeran//Cherney. AJP Renal 2018
Sridhar//Reich. ASN Poster 2018

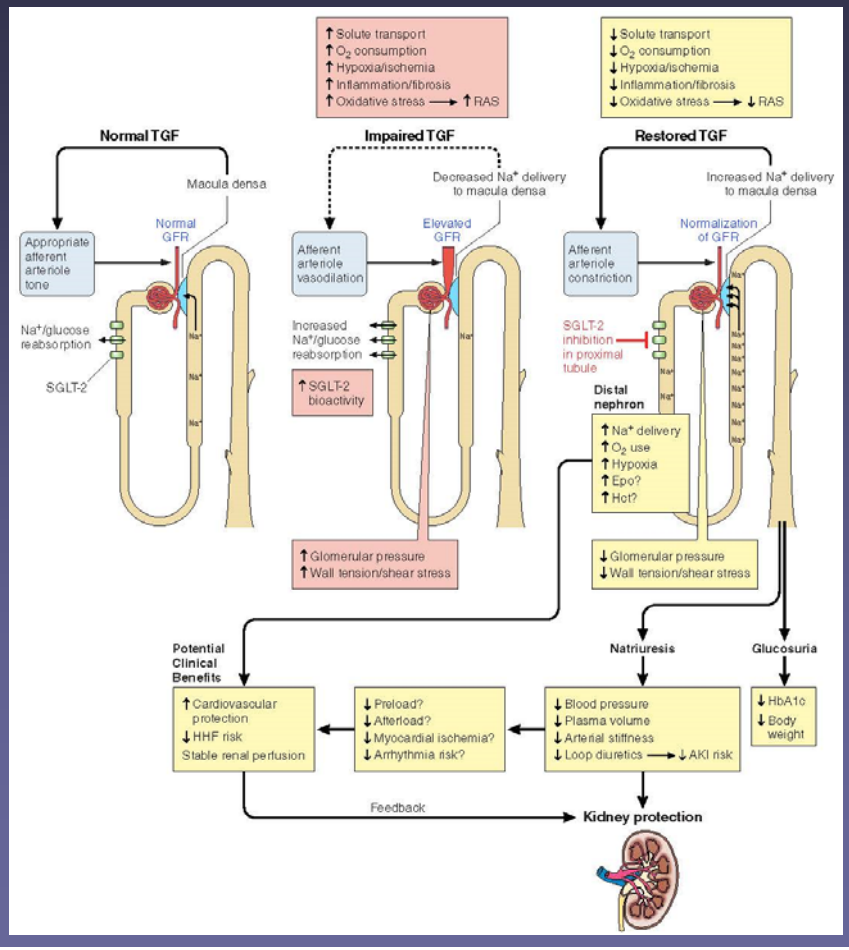
DIAMOND : DapagIIflozin and AlbuMinuria lOwering in Non-Diabetes

Randomized, double blind, placebo controlled cross-over trial to characterize the efficacy and safety of dapagliflozin 10 mg/day in patients with non-diabetic kidney disease

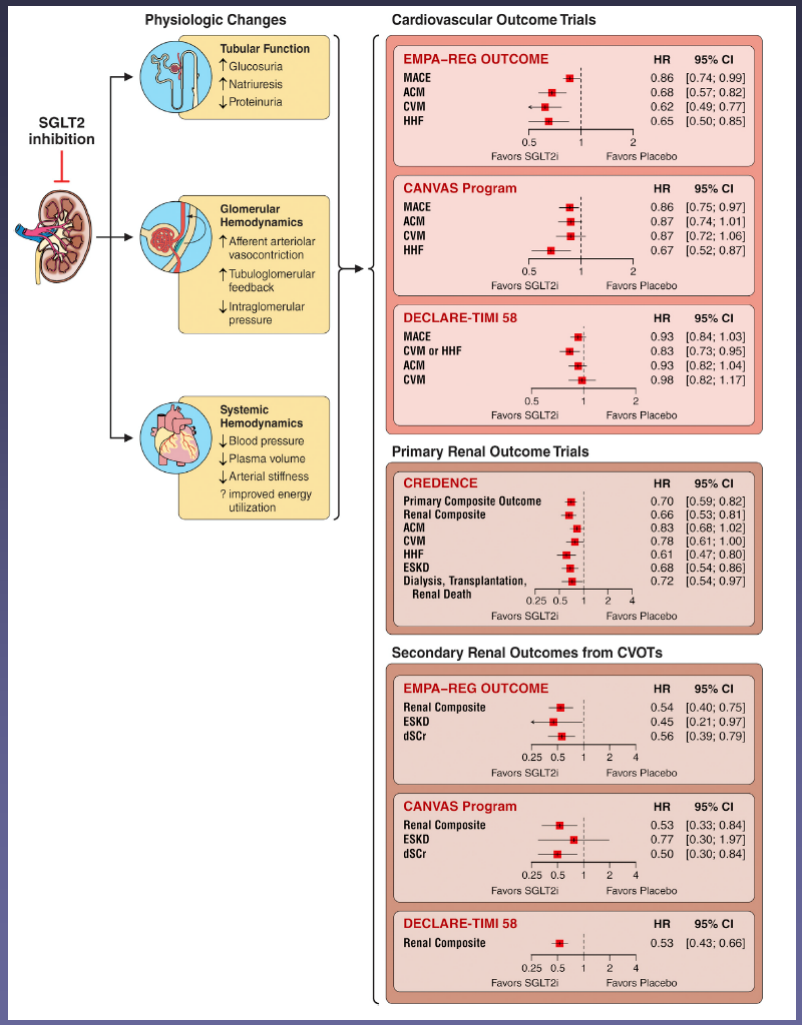
Participating sites:

- 3 sites in the Netherlands
- 2 sites in Canada
- 2 sites in Malaysia

A nephrocentric view of cardiorenal protection

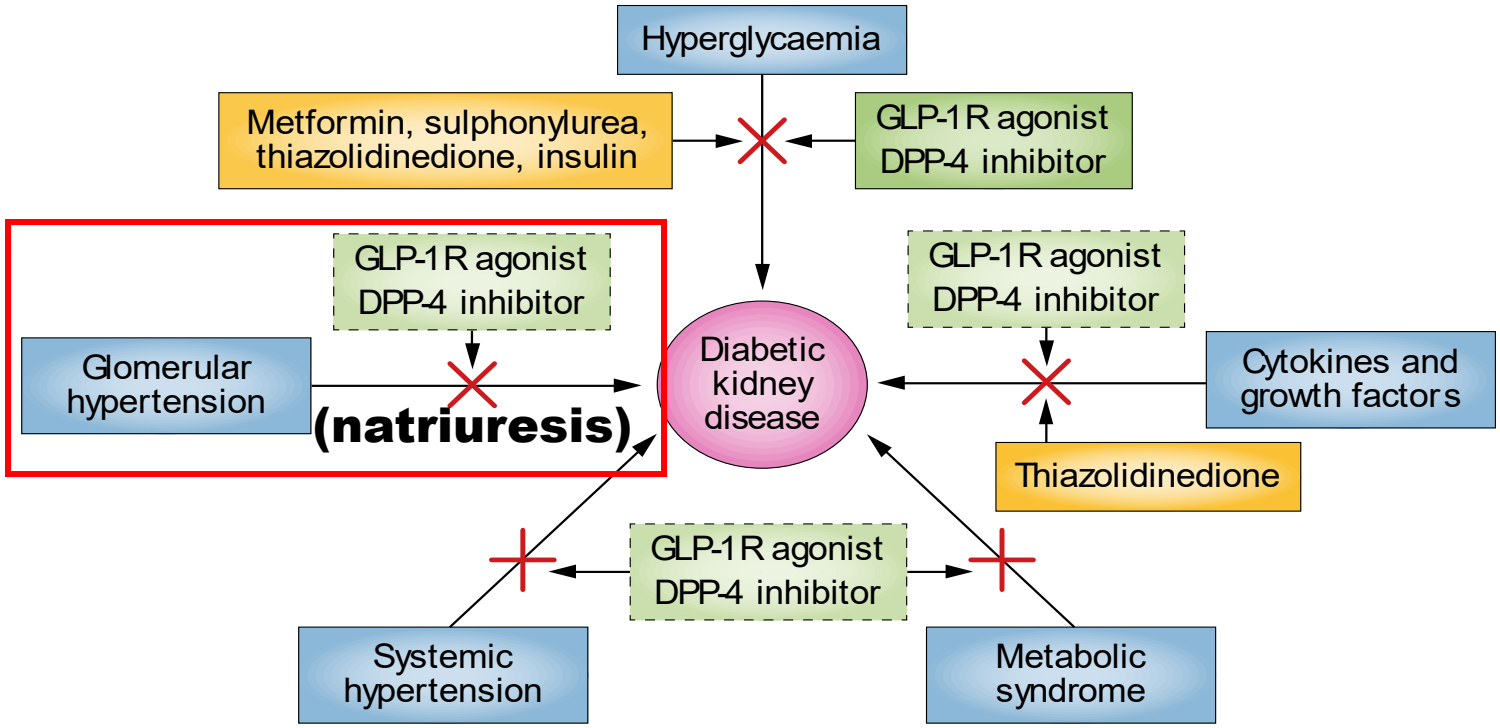


Cherney et al. Submitted 2019



Cherney et al. Cell Metabolism 2019

Incretins: a few words



Muskiet MH, et al. *Nat Rev Nephrol* 2014;10:88–103

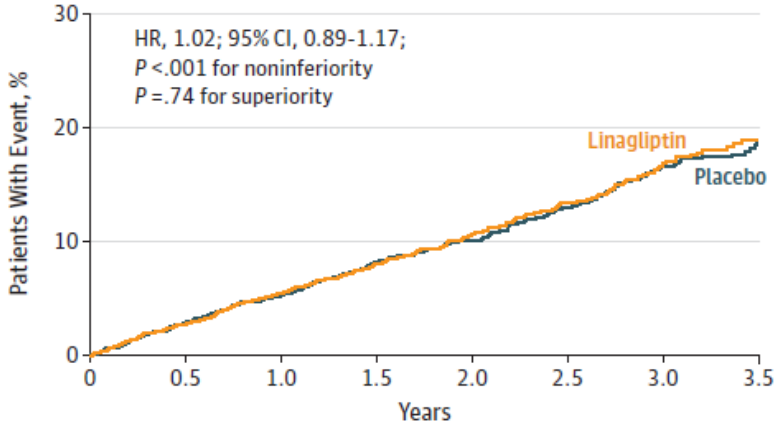
Trials with DPP4 inhibitors

- TECOS (sitagliptin), EXAMINE (alogliptin), SAVOR-TIMI 53 (saxagliptin)
- CV safety studies, neutral overall
- Neutral or minor ↓albuminuria
- No effect on GFR
- Not “diabetic kidney disease” cohorts

Green JB, et al. *N Engl J Med* 2015;373:232–242; White W, et al. *N Engl J Med* 2013;369:1327–1335; Scirica BM, et al. *N Engl J Med* 2013;369:1317–1326; Mosenzon O, et al. *Diabetes Care* 2017;40:69–76; Cornel et al. Diabetes Care 2016

CARMELINA: Time to Primary and Secondary Outcomes

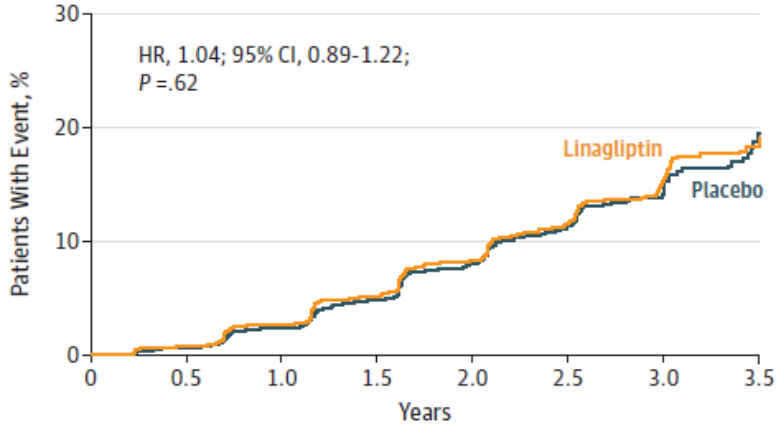
A Time to primary 3-point MACE outcome



No. of patients

Placebo	3485	3353	3243	2625	1931	1285	758	251
Linagliptin	3494	3373	3254	2634	1972	1306	778	269

B Time to secondary kidney outcome



No. of patients

Placebo	3485	3213	2995	2298	1608	1005	496	103
Linagliptin	3494	3227	3018	2345	1675	1040	518	109

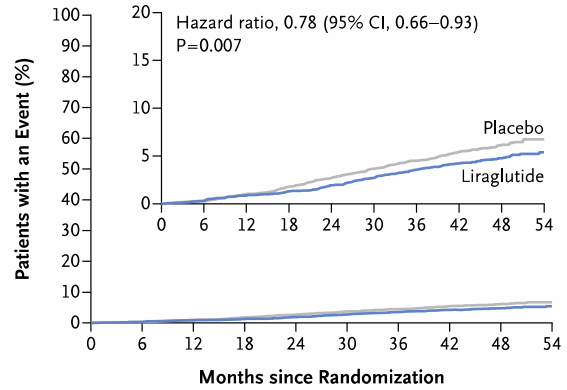
Hazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo.

B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

Rosenstock et al. JAMA 321;1:2019

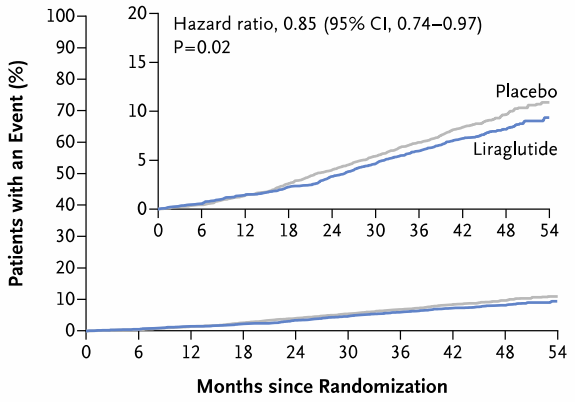
Cardiovascular Safety Studies and GLP1-RA

B Death from Cardiovascular Causes



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

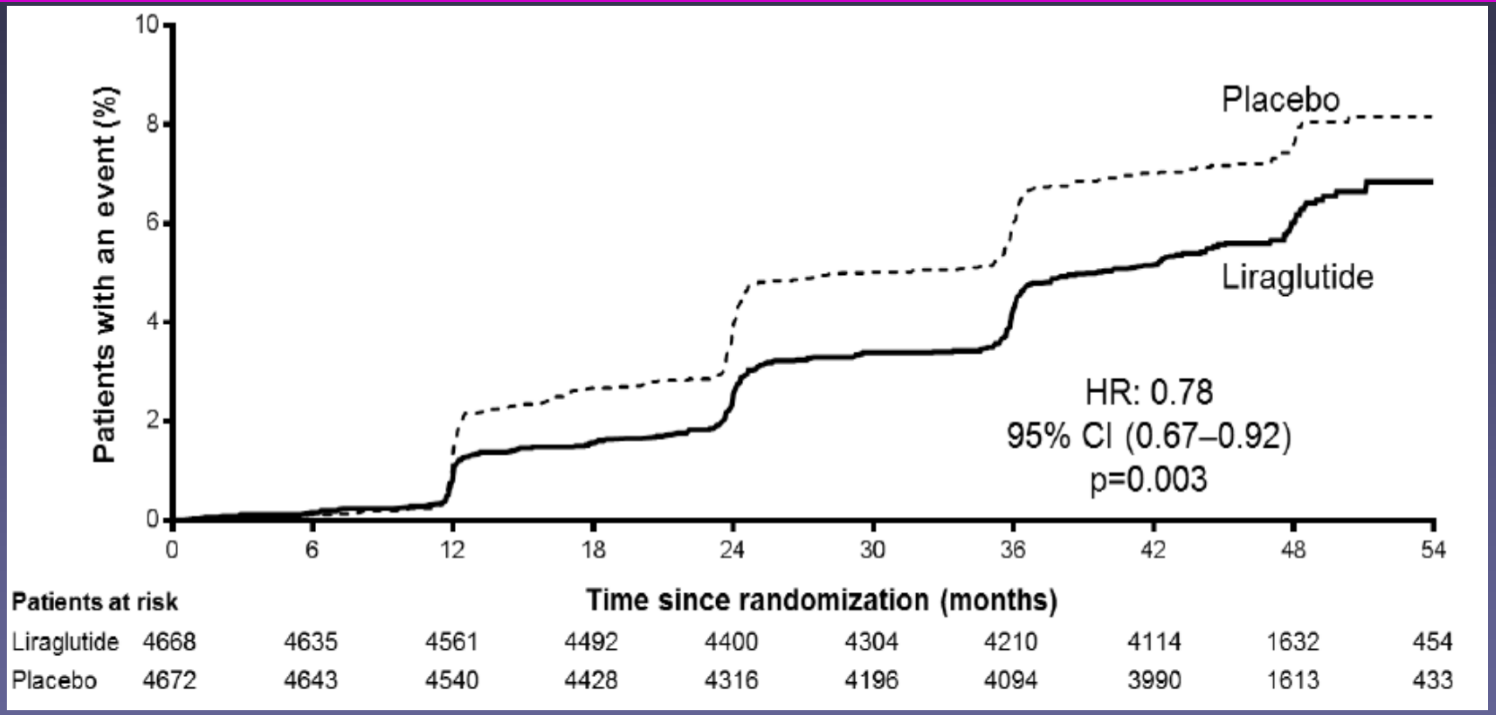
E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

Marso et al. NEJM 2016

Effects of GLP-1 RAs: Renal outcomes



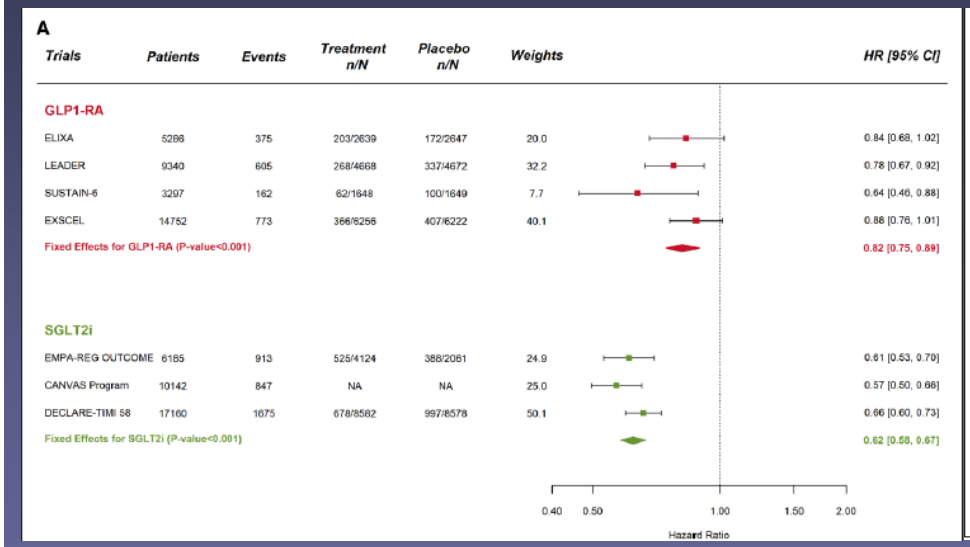
Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

Due to ↓risk of progression to albuminuria
Similar observations with semaglutide (SUSTAIN-6)

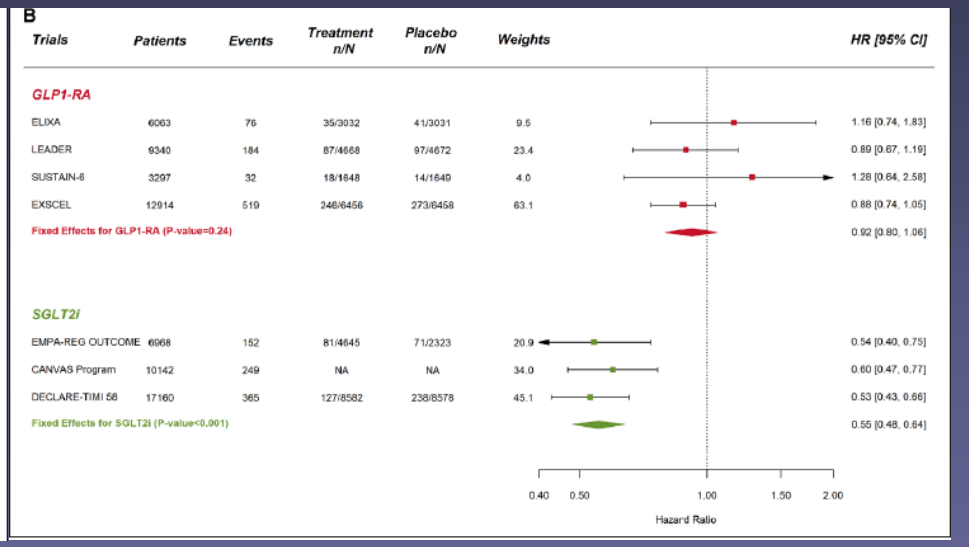
1. Mann J. Presented at the America Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. 13th June 2016, New Orleans, LA, USA; 2. Vilsbøll T. Presented at the 52nd EASD Annual Meeting 2016. Munich, Germany; 16th September 2016; OP S35.3

Meta-analysis of GLP1-RA and SGLT2i trials: renal end points

With albuminuria progression



Without albuminuria progression

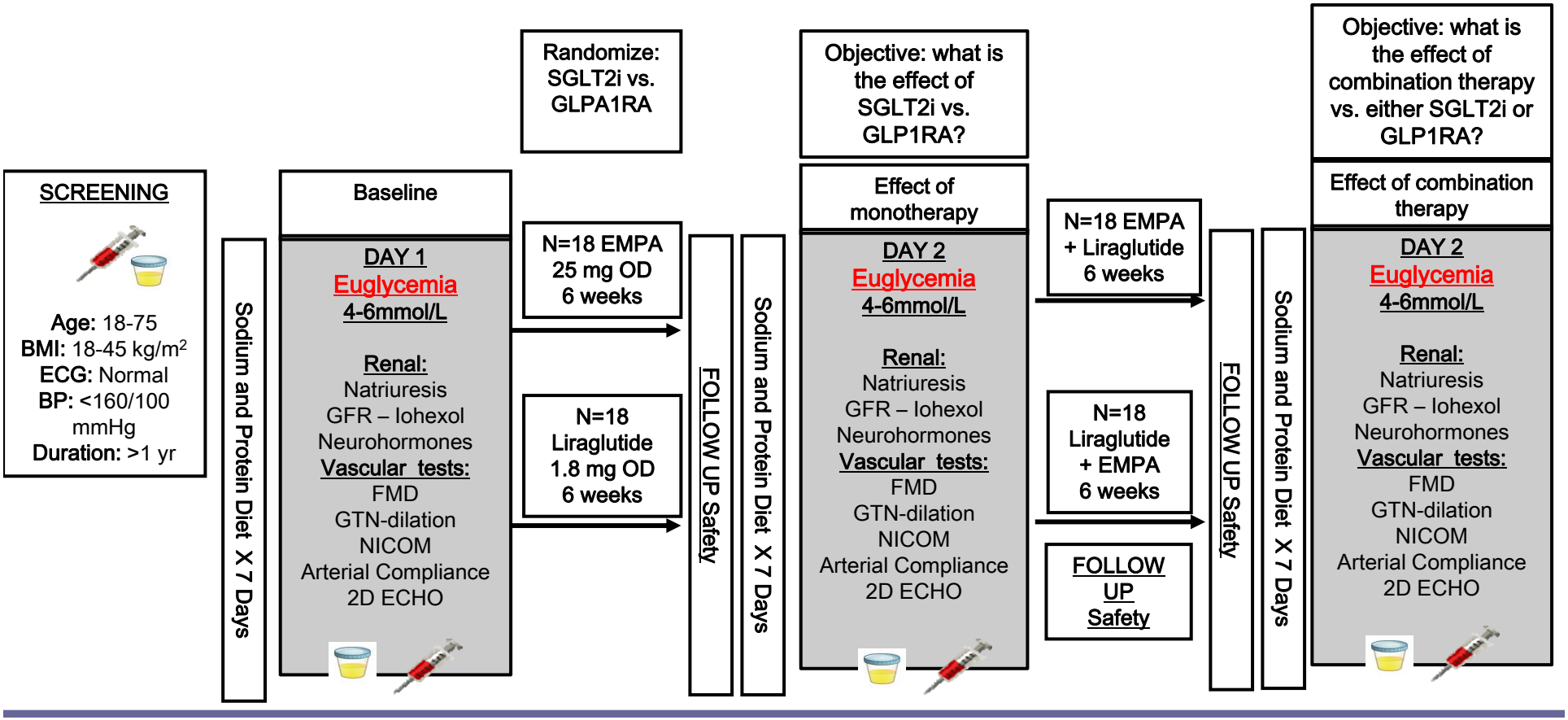


Zelniker et al *Circulation.* 2019;139:2022–2031.

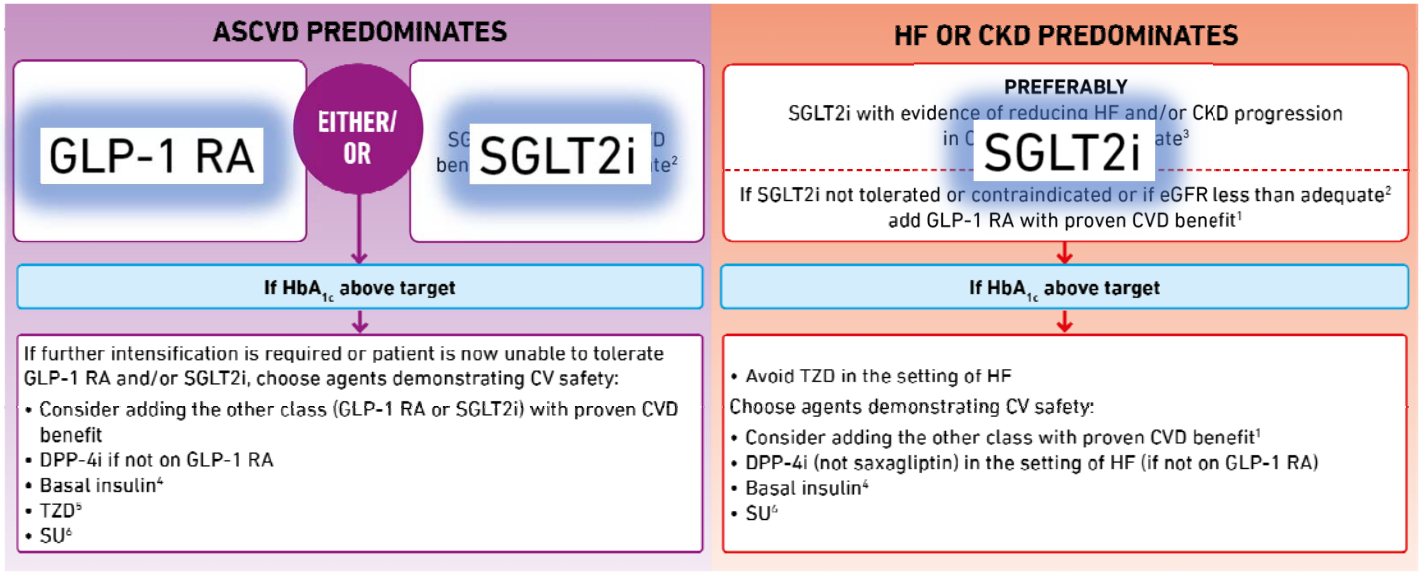
iNcretin And TReatment with Inhibition of sodiUm-glucose cotRansportEr-2 combinaTion Insights into Cardiorenal mechanisms ("NATRIURETIC")

- N=36 patients with T2D, eGFR≥30 ml/min/1.73m^2
- Primary hypothesis
  - SGLT2i-GLP-1RA combination: ↑natriuresis vs. either monotherapy
- Secondary hypotheses are that:
  - 1) SGLT2i: ↓GFR, stay stable with GLP1RA and with combined SGLT2i-GLP-1RA (safety)
  - 2) SGLT2i-GLP-1RA: ↓SBP, body weight, arterial stiffness, circulating volume, systemic vascular resistance
  - 3) exploratory neurohormonal analyses

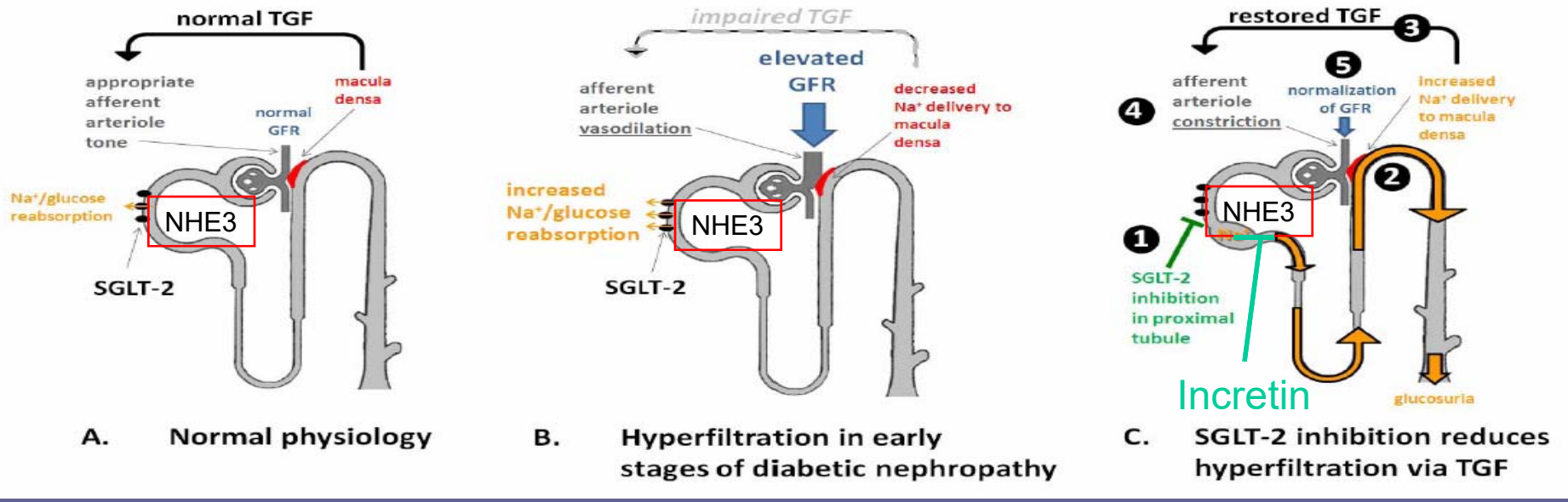
iNcretin And TReatment with Inhibition of sodiUm-glucose cotRansportEr-2 combinaTion Insights into mechanisms implicated in Cardiovascular disease ("NATRIURETIC")



Choosing Glucose-Lowering Medication in those with Established ASCVD or CKD



The "tubular hypothesis": Incretin agents and natriuresis



- *Expect* incretins: 'dip' in GFR, blood flow

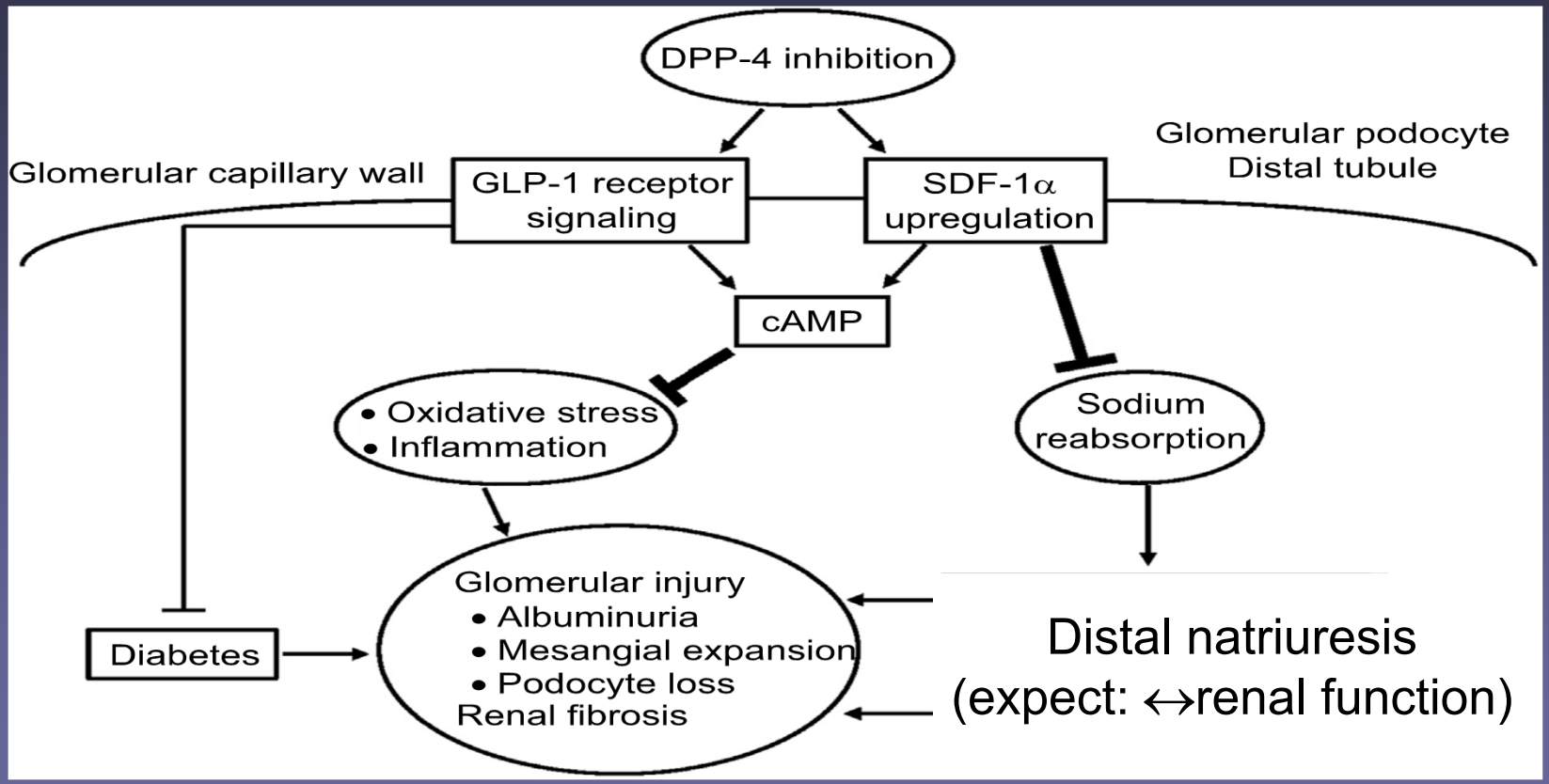
GFR, glomerular filtration rate; NHE3, sodium–hydrogen exchanger 3; SGLT2, sodium–glucose co-transporter 2; TGF, tubuloglomerular feedback

Cherney DZ, et al. *Circulation* 2014;129:587–597

Acute renal effects of GLP-1, GLP-1 RAs and DPP-4is

Study	Patient	Intervention	UrNa	GFR
Gutzwiller, 2004	Healthy men	3-Hr GLP-1 IV	↑60% FE_{NA}	↔
Skov, 2013	Healthy men	2-Hr GLP-1 IV	↑40% FE_{NA}	↔
Asmar, 2015	Healthy men	3-Hr GLP-1 IV	↔	↔
Muskiet, 2016	Healthy obese men	exenatide IV	↑86% FE_{NA}	↑20% acute
Gutzwiller, 2004	Insulin-resistant Obese	3-Hr GLP-1 IV	+ 37 mmol	–9 mL/min CrCl
Asmar, 2016	T2D	3-Hr GLP-1 IV	↔	↔
Lovshin, 2015	T2D+HTN	liraglutide sc 0.6mg acute 1.8 mg 21 days	+24 mmol	–5.76 mL/min eGFR
Tonneijck, 2016	T2D+Obese	exenatide IV	↑32% FE_{NA}	↔
Tonneijck, 2016	T2D	Lira vs sita vs placebo	↑FE_{NA} with sita, ↔lira (2 weeks)	↔

Renal protection with DPP-4 inhibition: Stromal cell-derived factor (SDF)-1α

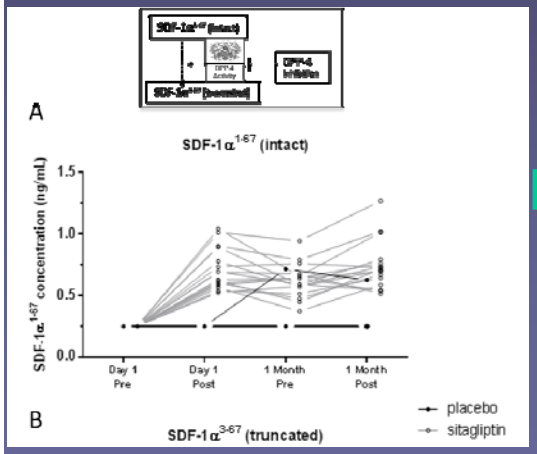


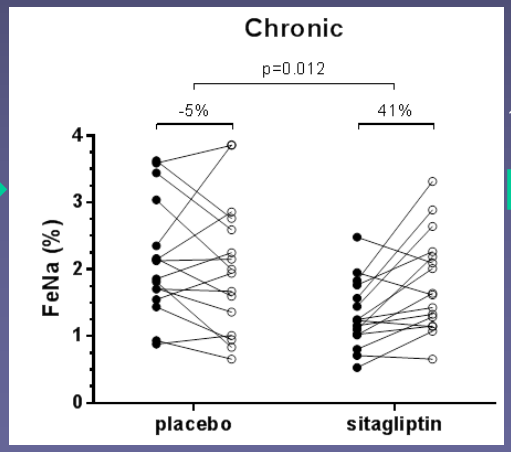
cAMP, cyclic adenosine monophosphate; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SDF, stromal cell-derived factor

Takashima S, et al. *Kidney Int* 2016;90:783–796

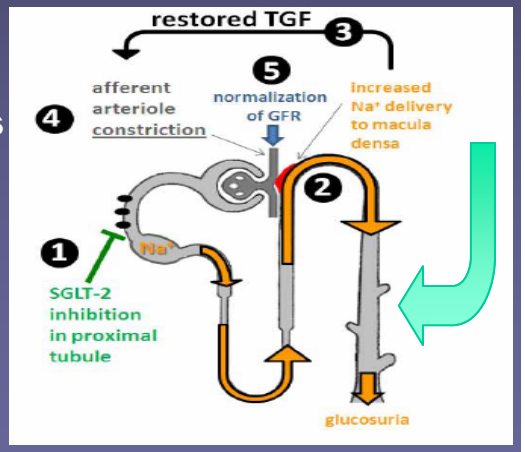
DPP4 inhibition and natriuresis

- DPP4 inhibition: ↑distal natriuresis, SDF-1α-dependent in animals
- DPP4 inhibition natriuresis: independent of GLP-1, NHE3
- Sitagliptin: ↑FE_{Na}, but no renal/systemic hemodynamic effect
- Natriuresis: too distal to affect GFR, too modest to ↓BP?



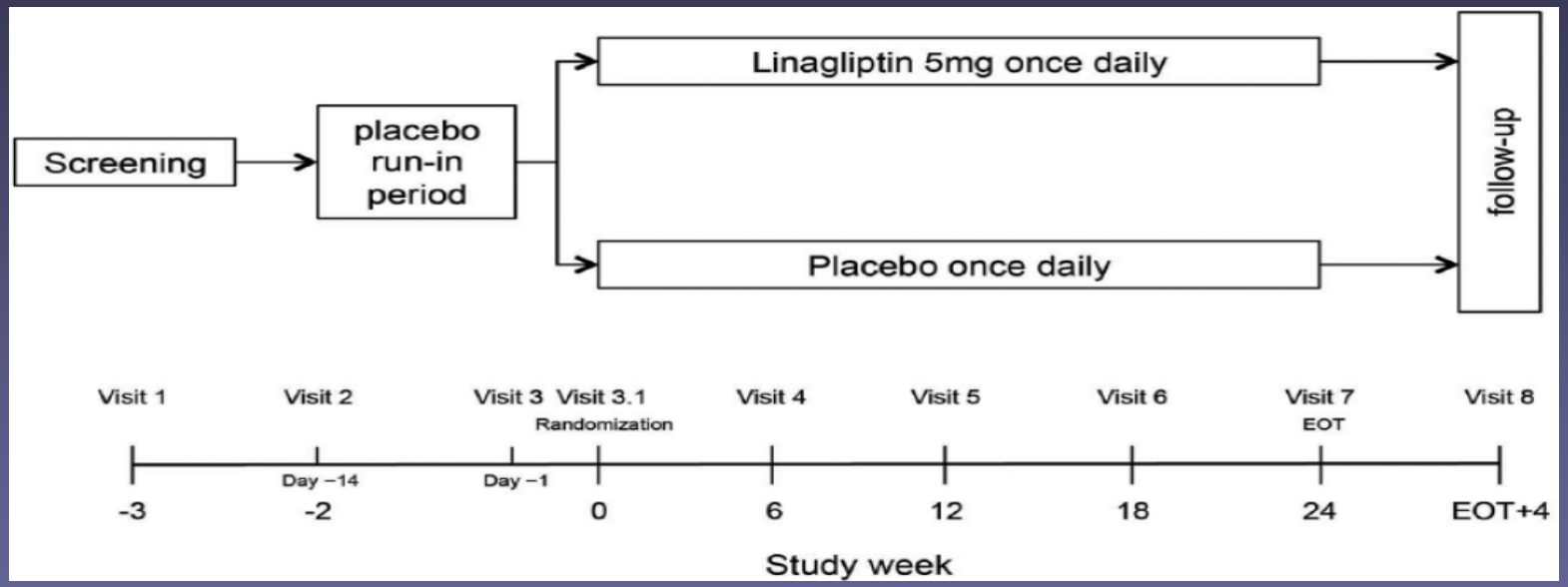


↑Natriuresis



Takashima et al. *Kidney Int* 2016;90:783–796
Lovshin//Cherney et al. Diabetes Care 2017

MARLINA-T2D: n=360, albuminuria, eGFR >30 mL/min/m^2, on RAASi

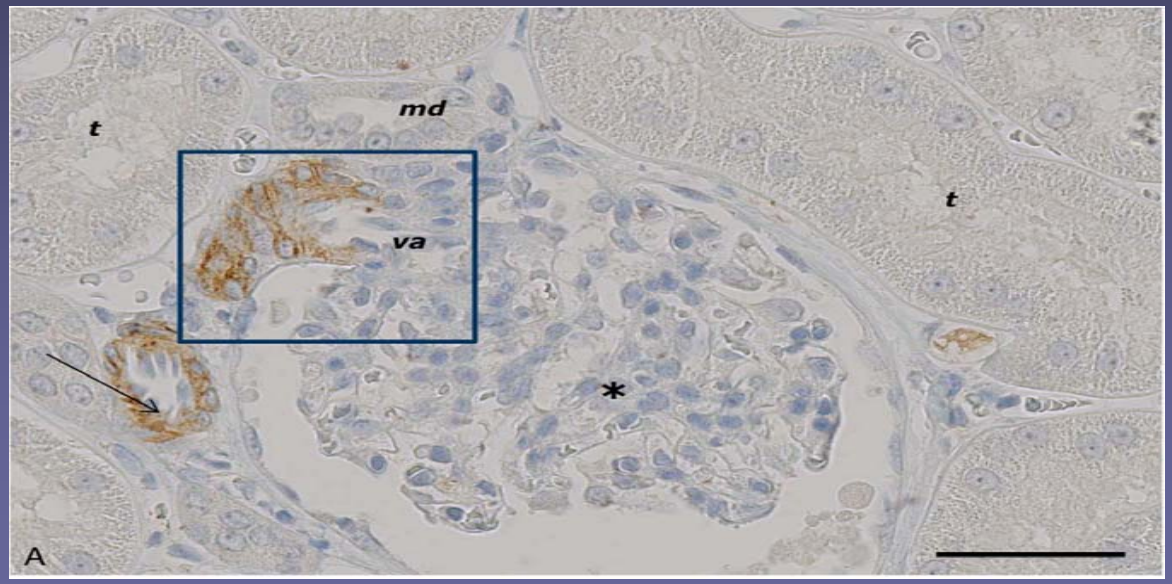


- ↓HbA_{1c}, *no* effect on albuminuria
- CARMELINA and CAROLINA trials – CVOTs (4 years)

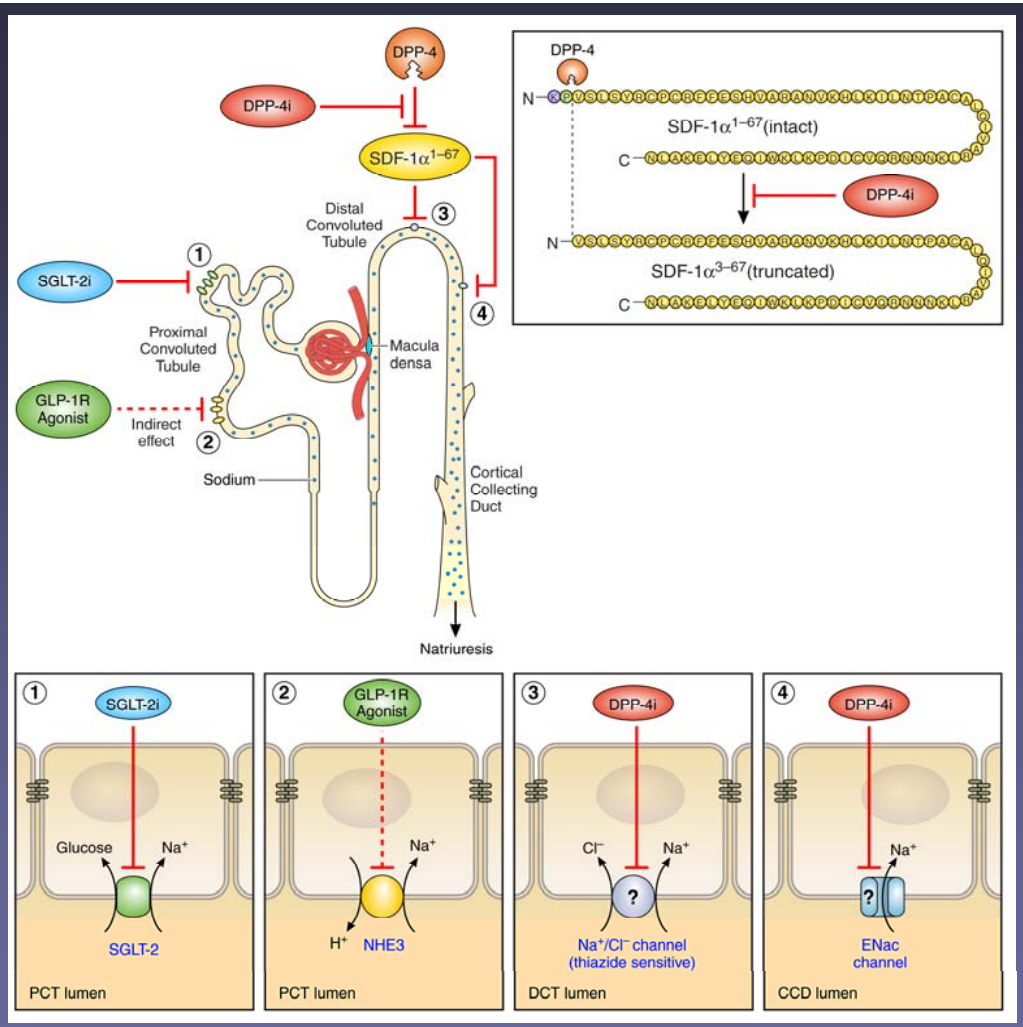
Groop PH, et al. *Diab Vasc Dis Res* 2015;12:455–462

Physiological basis for proximal natriuresis: GLP-1 receptor?

- GLP-1: ↑natriuresis in animals, via blockade of proximal NHE3
- ***HOWEVER***: GLP1 - Direct vasodilation - ↑GFR/blood flow
- Overall neutral impact on renal function

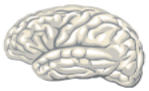
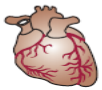
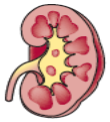


Pyke C, et al. *Endocrinology* 2014;155:1280–1290; Crajoinas RO, et al. *Am J Physiol Renal Physiol* 2011;301:F355–F363



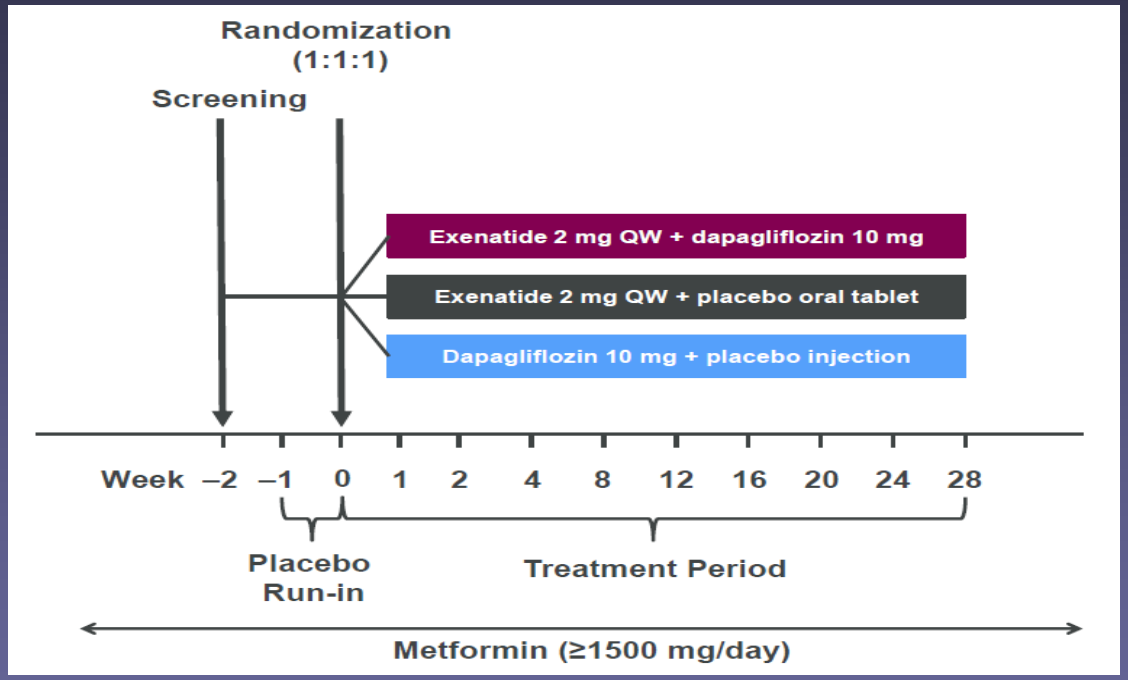
Lovshin//Cherney et al. Diabetes Care 2017

Theoretical effects of GLP-1RA and SGLT2i alone and in combination

	GLP-1 receptor agonist		SGLT2 inhibitor	Combination therapy
Appetite	↓		↑ (?)	↓
Bodyweight	↓		↓	↓↓
Ischaemic cardiovascular events	↓		↓	↓↓
Heart failure events	↔		↓	↓
Diuresis, natiruresis	↑ (acutely)		↑	↑
Urinary glucose excretion	↔		↑	↑
Renoprotection	↑		↑	↑↑

Nauck et al. Lancet Diab Endo 2016

Effects of GLP-1 RA and SGLT2i alone and in combination (DURATION-8)



- Greater ↓weight, HbA_{1c}, BP with combination vs. monotherapies

Frias JP, et al. *Lancet Diabetes Endocrinol* 2016;4:1004–1016

Other research-in-progress

- CREDENCE – 2019 (n=13 UHN)
- DAPA-CKD – recruitment stage (n=22 UHN)
- Empagliflozin CKD trial – Oxford group (UHN site)
- Ongoing cardiovascular / heart failure trials, with renal endpoints (DECLARE-TIMI58)

Inzucchi et al. Diab Vasc Disease Res 2015

Efficacy Objectives

Primary:

To assess the change from baseline in 24-hr proteinuria with dapagliflozin for six weeks relative to placebo treatment

Secondary:

- To assess the effect of dapa vs. placebo on $GFR_{iohexol}$
- To assess the effect of dapa vs. placebo on blood pressure
- To assess the effect of dapa vs. to placebo on body weight
- To assess the effect of dapa vs. placebo on neurohormones

GKC

- **Inclusion criteria**
- Age ≥18 and ≤75 years
- Urinary protein excretion >500 mg/24hr and ≤ 3500 mg/24hr
- eGFR ≥ 25 mL/min/1.73m^2
- Stable dose of ACEi or ARB for at least 4 weeks

- **Exclusion criteria**
- Diabetes, polycystic kidney disease
- Lupus nephritis, ANCA-associated vasculitis
- Indication for immunosuppressants
- Receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for primary or secondary renal disease within 6 months prior to enrolment.
- Active malignancy aside from treated squamous cell or basal cell carcinoma of the skin
- Pregnancy, breastfeeding or women not using contraception

GKC

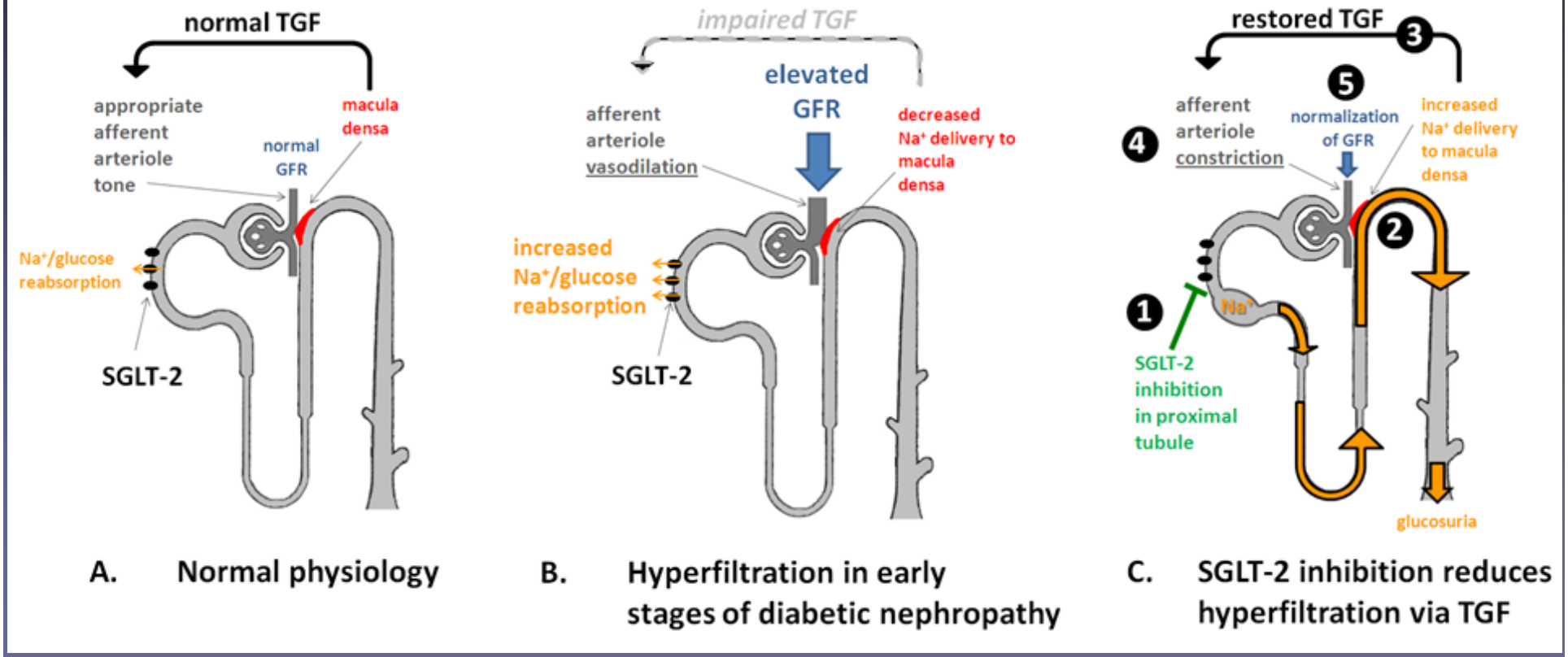
Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neil et al. NEJM June 12, 2017

Other relevant references (amputation):
Fadini et al. Lancet Diab Endo 2017;5:680-681
Jabbour S, et al. WCIRDC 2016 Poster 119
Verma et al. Circulation 2017

The "Tubular Hypothesis": Diabetes and SGLT2 inhibition



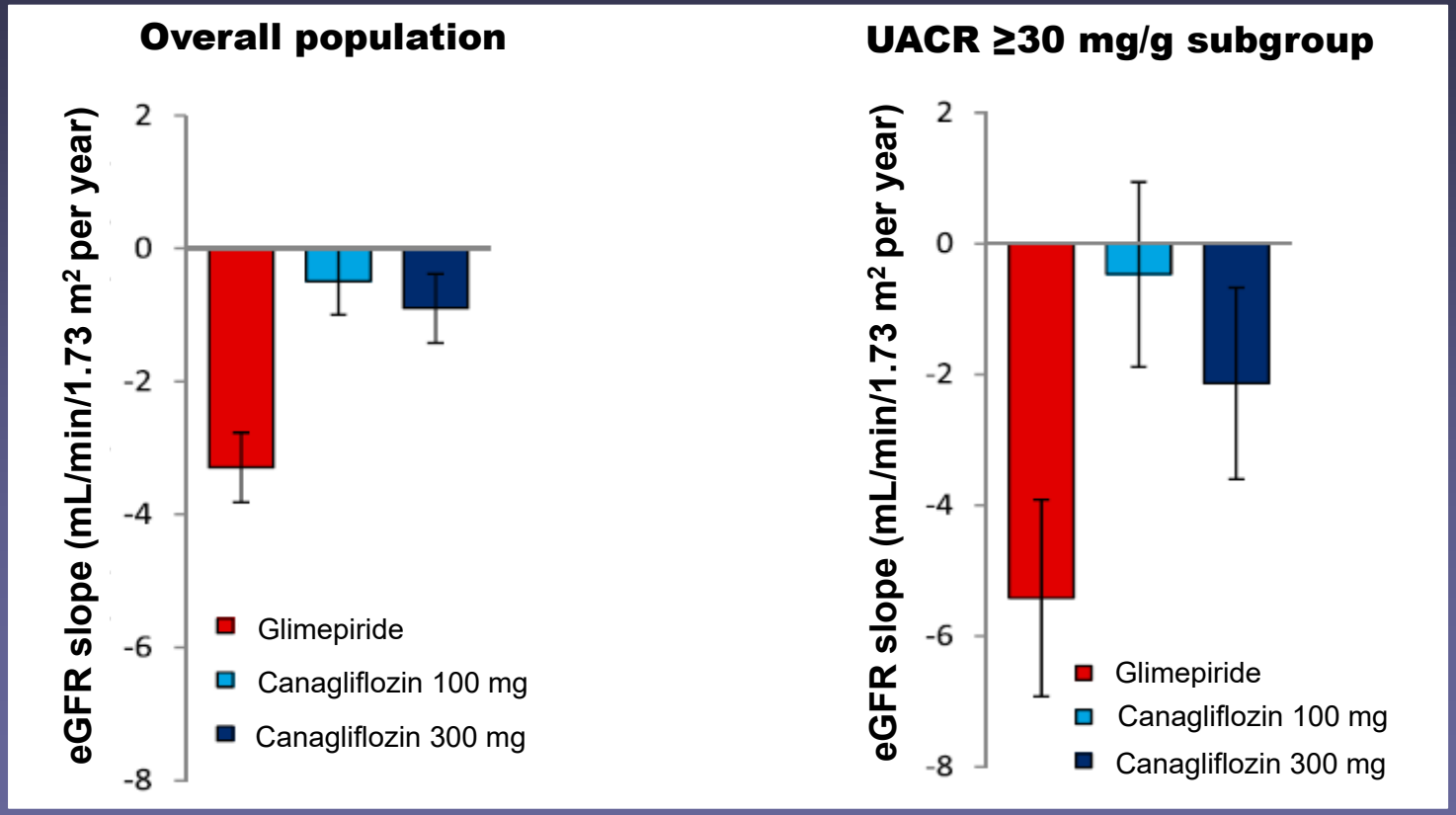
A. Normal physiology

B. Hyperfiltration in early stages of diabetic nephropathy

C. SGLT-2 inhibition reduces hyperfiltration via TGF

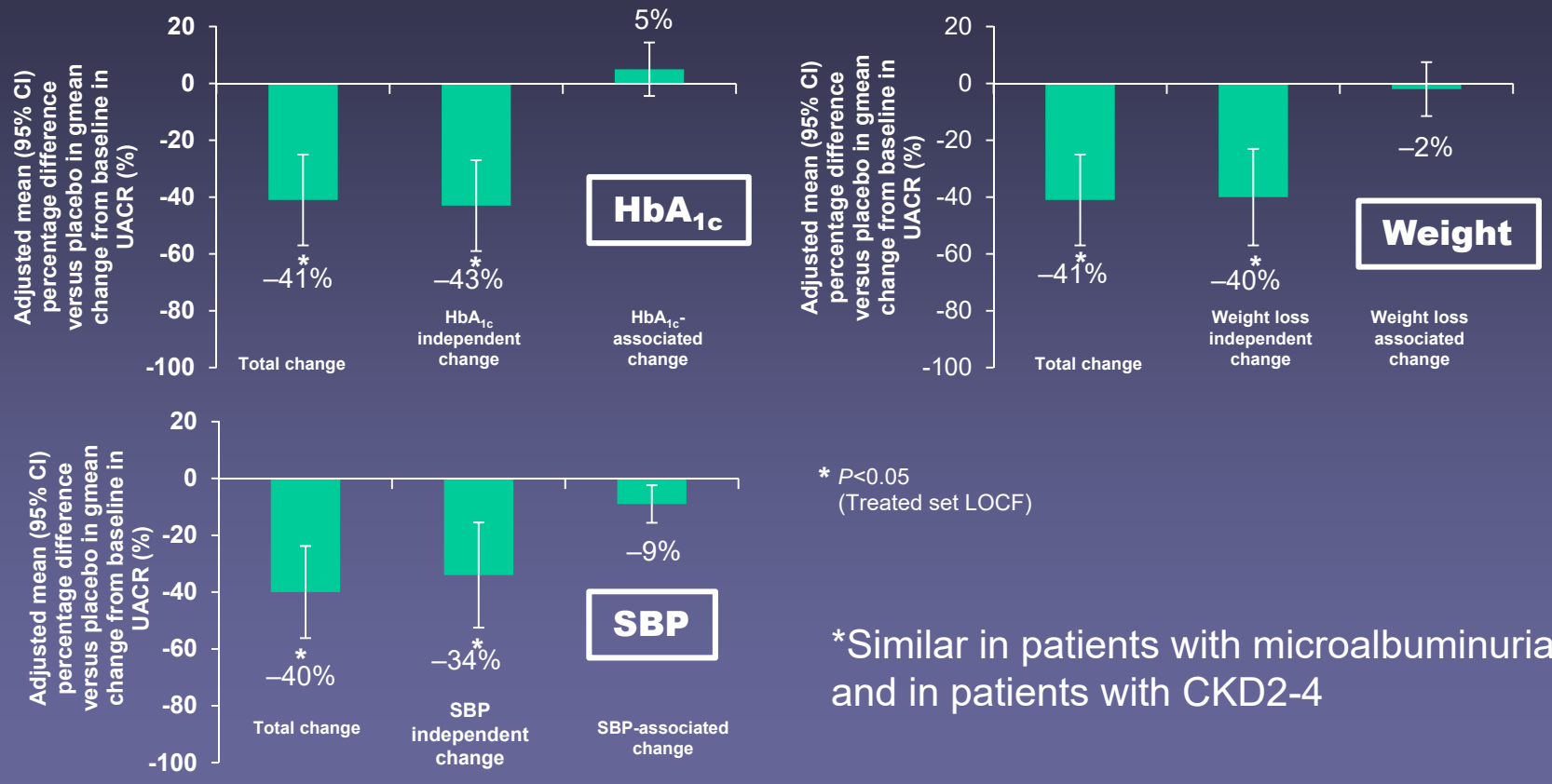
Cherney et al. Circulation 2014

eGFR slope and SGLT2 inhibition: independent of △BP, △weight, △HbA1c



Heerspink HJ *et al. J Am Soc Nephrol* 2016;28:1

Changes in UACR largely independent of HbA_{1c}, SBP, weight

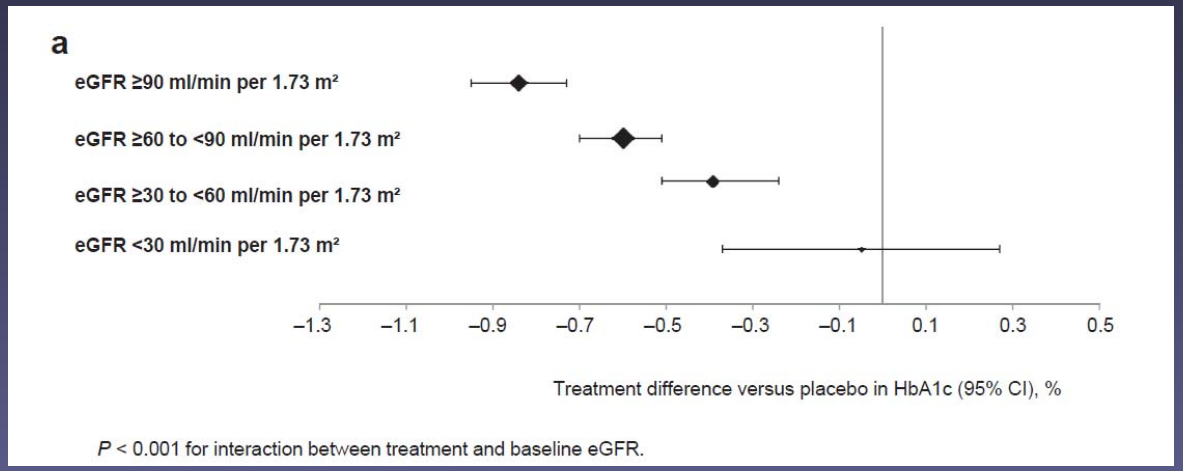


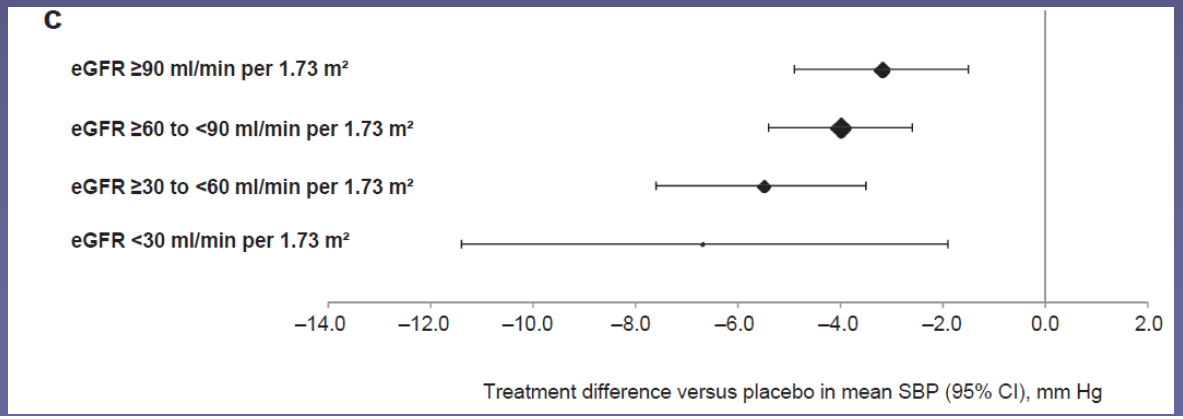
* *P*<0.05
(Treated set LOCF)

*Similar in patients with microalbuminuria, and in patients with CKD2-4

Cherney et al. *Diabetologia* 2016;59:1860–1870

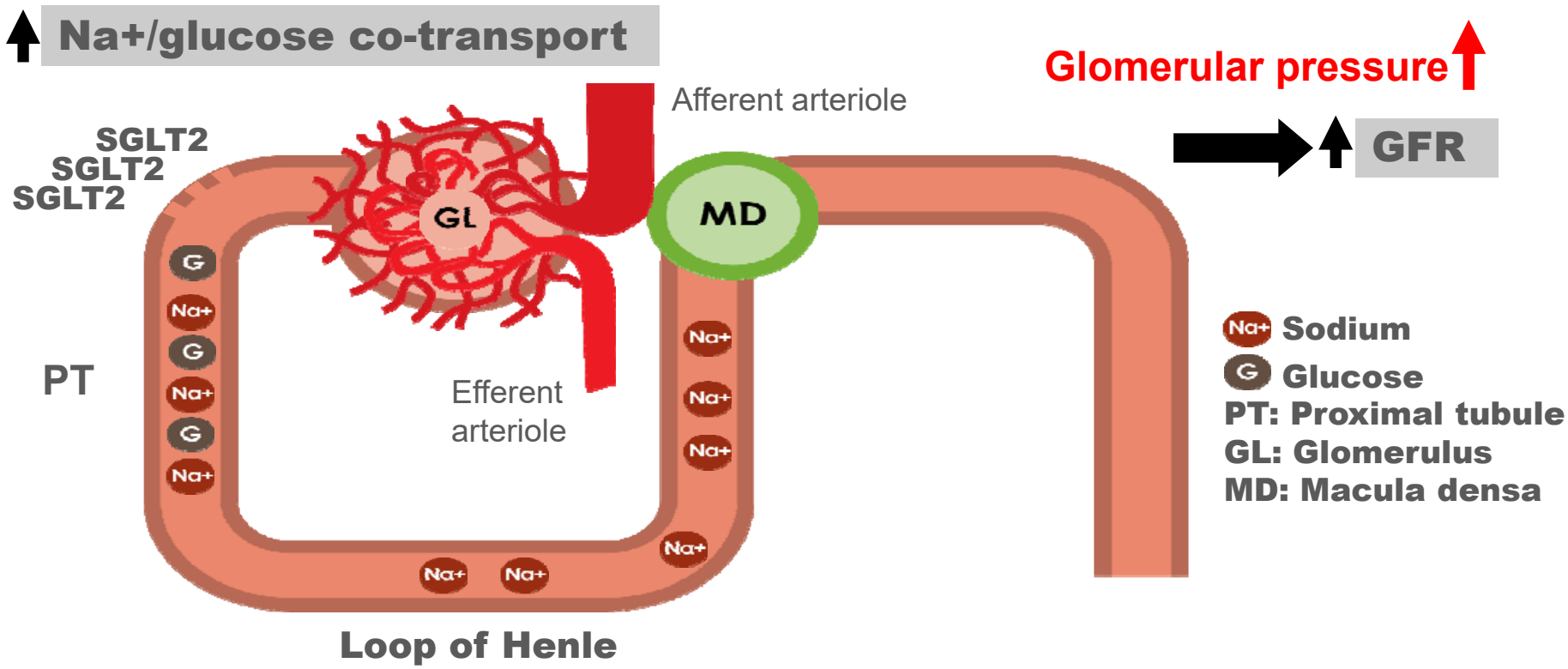
BP lowering vs. Hb A1c lowering in CKD with SGLT2 inhibition





Cherney et al. Kidney Int 2017

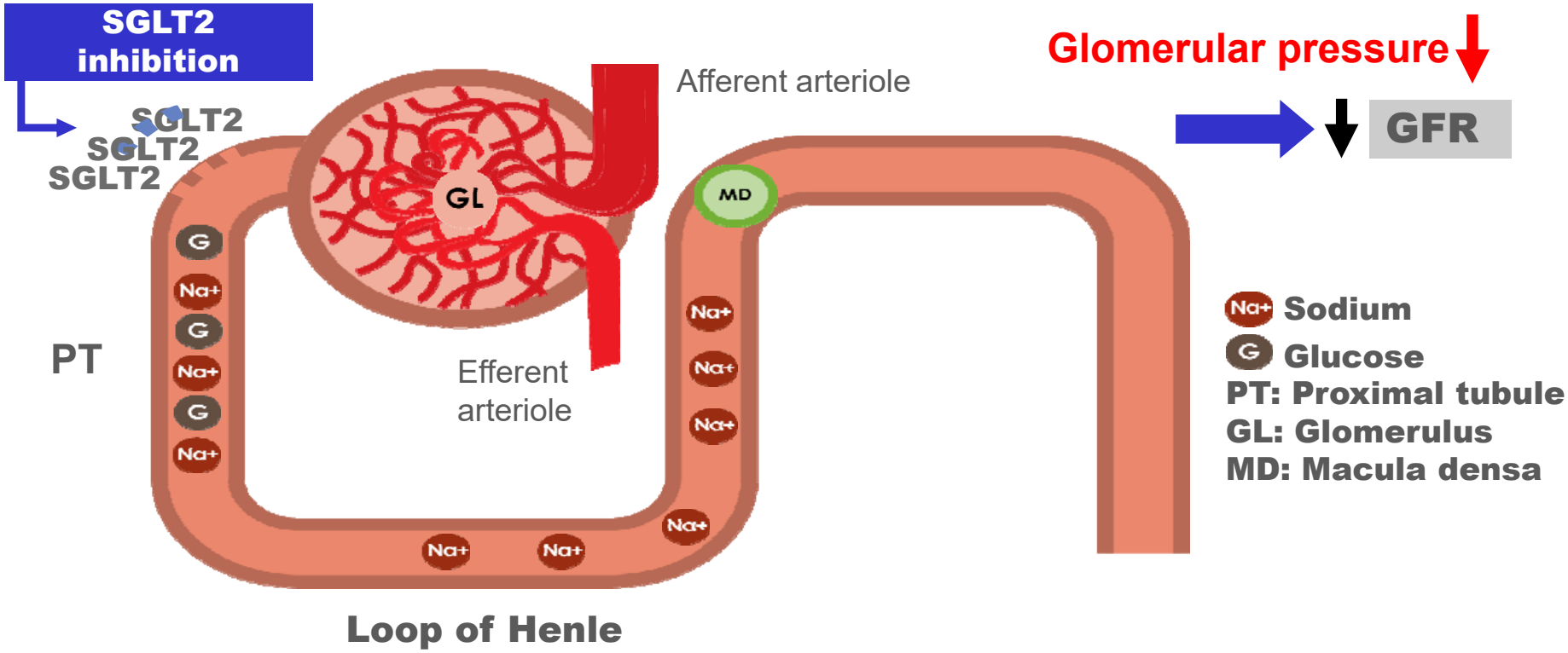
Diabetes causes glomerular hypertension



GFR, glomerular filtration rate; SGLT2, sodium-glucose co-transporter-2

Adapted from Cherney D *et al. Circulation* 2014;129:587

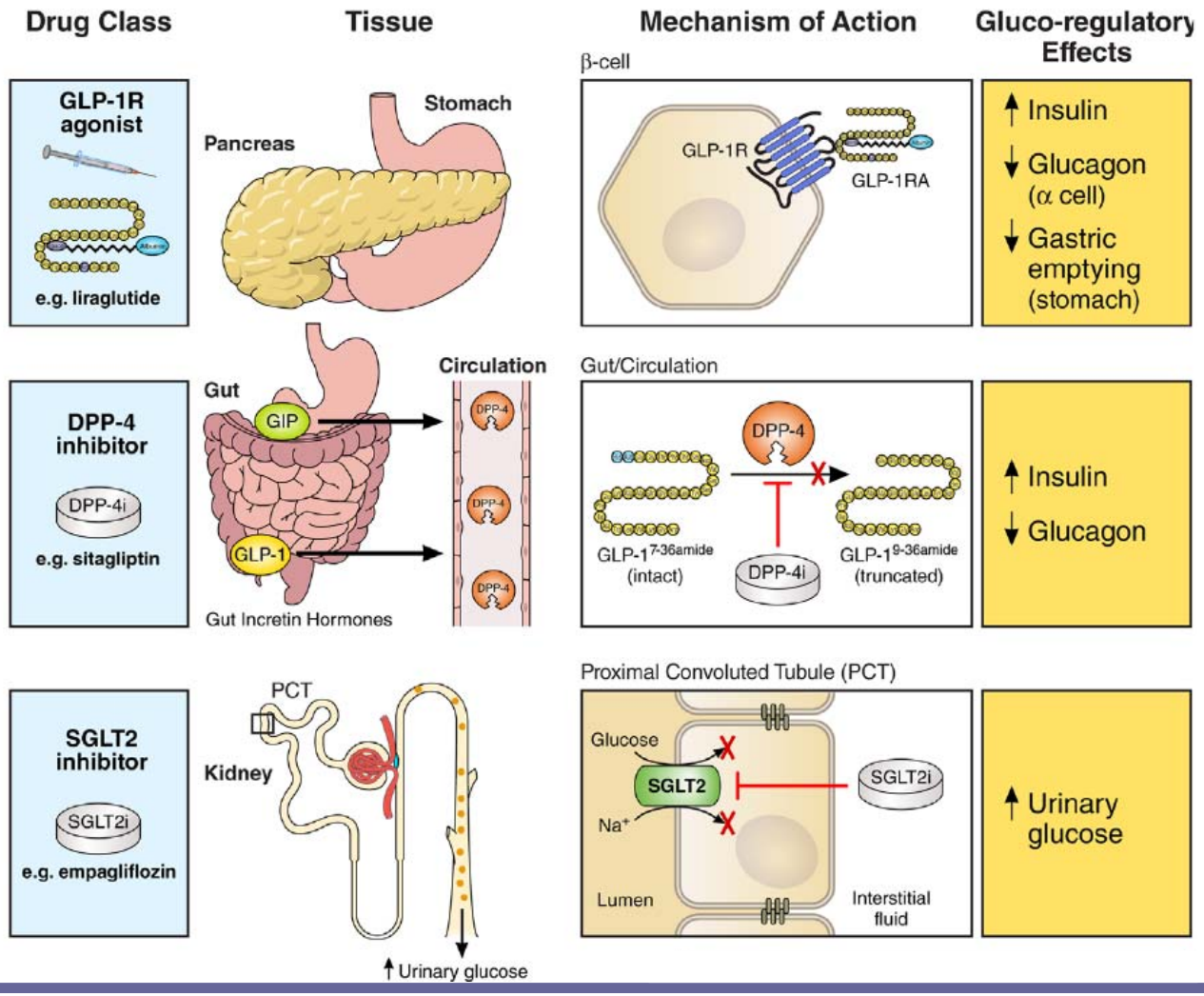
SGLT2i lowers intraglomerular pressure



GFR, glomerular filtration rate; SGLT2, sodium-glucose co-transporter-2

Adapted from Cherney D *et al. Circulation* 2014;129:587

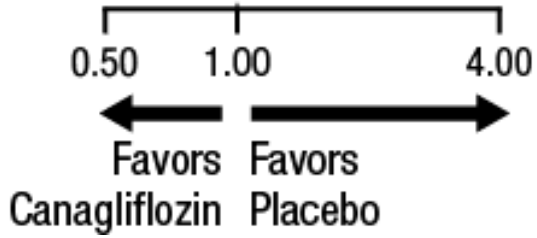
Newer anti-hyperglycemic agents



McReelis et al. Can J Ophthal 2017

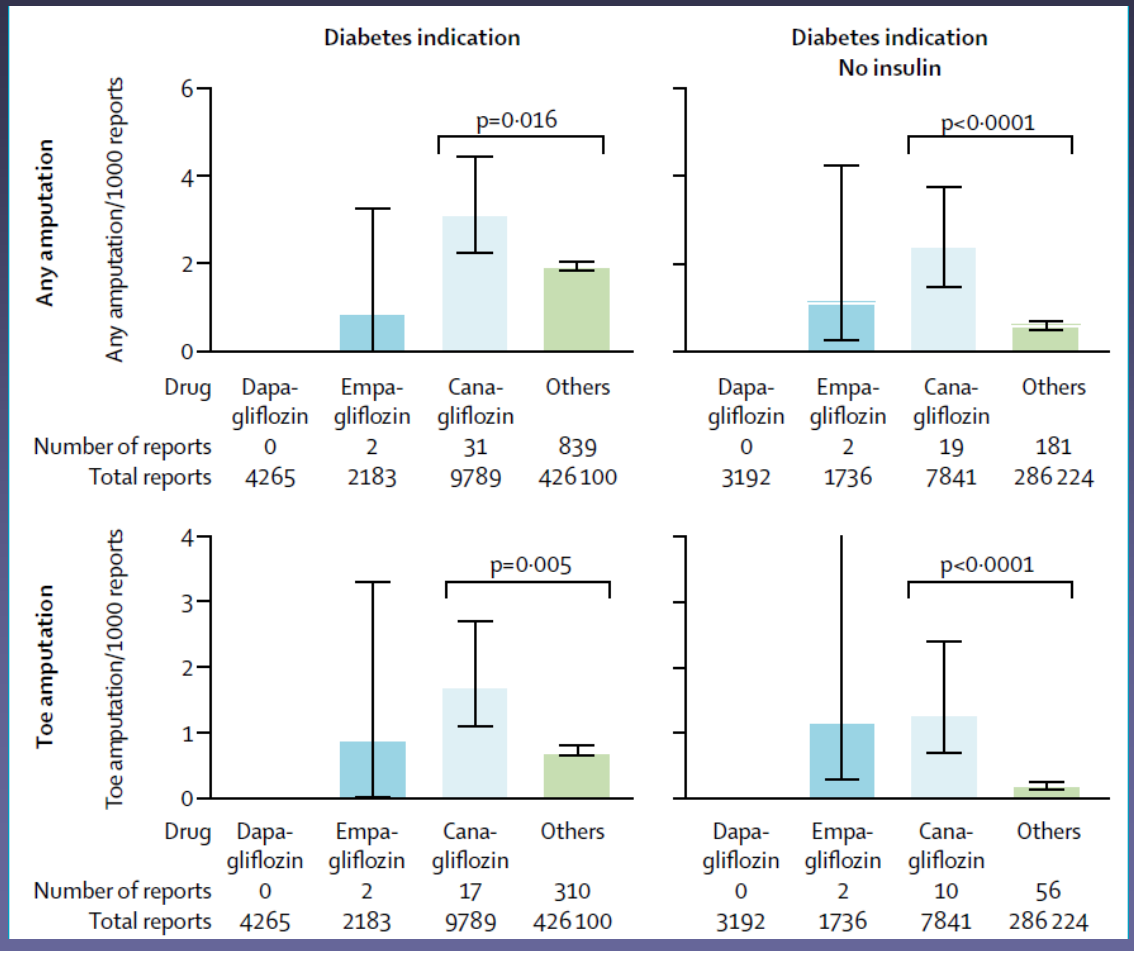
Amputation risk in CANVAS Program

	Canagliflozin Event rate per 1000 patient-years	Placebo Event rate per 1000 patient-years	Hazard ratio (95% CI)
All amputation	6.30	3.37	1.97 (1.41–2.75)
Minor amputation	4.48	2.44	1.94 (1.31–2.88)
Toe	3.44	2.16	
Transmetatarsal	1.03	0.29	
Major amputation	1.82	0.93	2.03 (1.08–3.82)
Ankle	0.04	0.07	
Below-knee	1.16	0.64	
Above-knee	0.62	0.21	



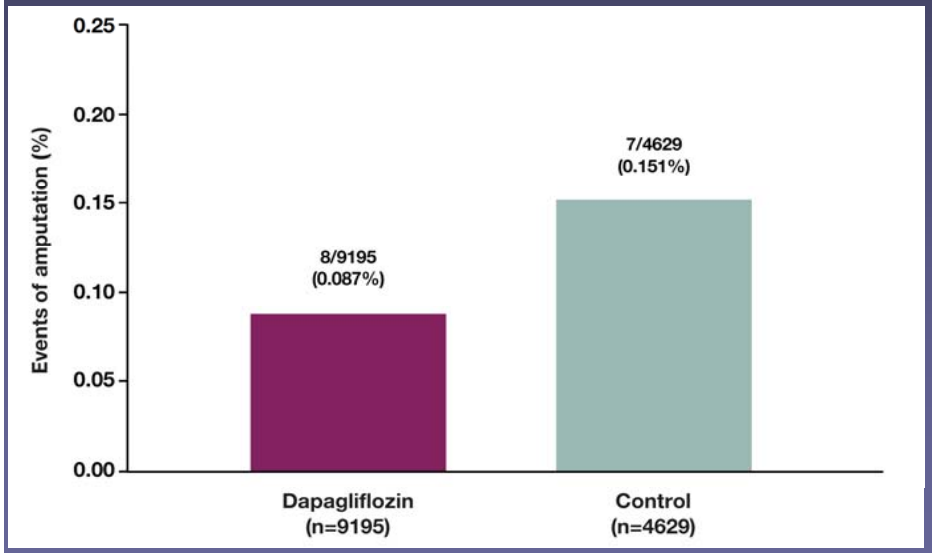
Neil et al. NEJM June 12, 2017

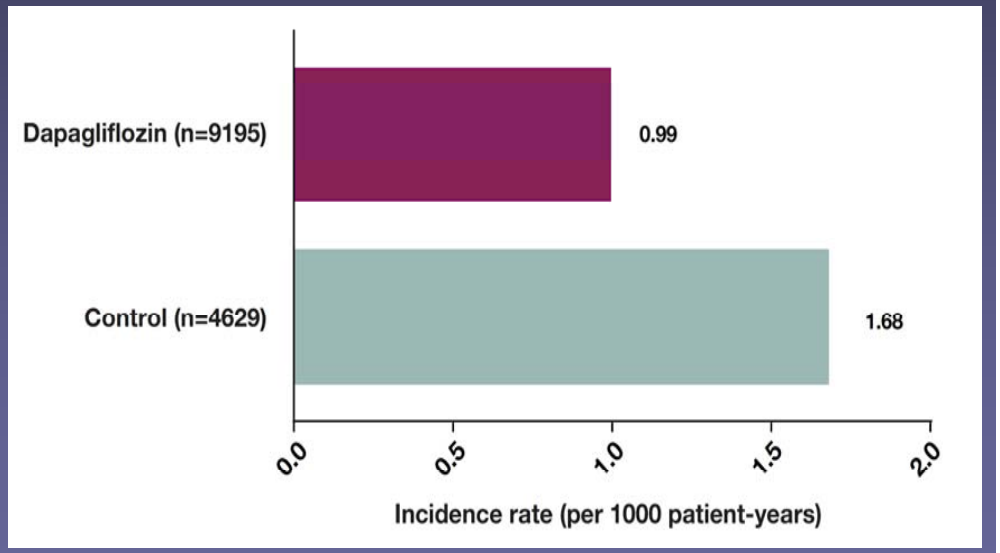
SGLT2 inhibitors and amputations: FDA Adverse Event Reporting System



Fadini et al. Lancet Diab Endo 2017

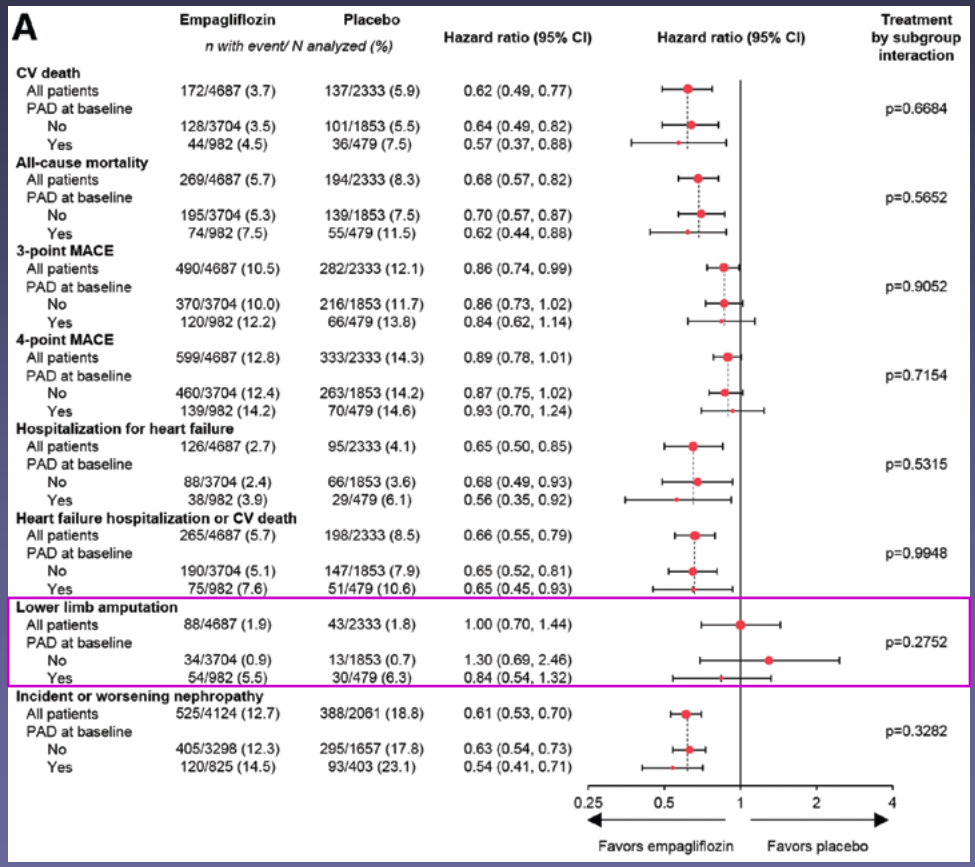
Events of amputation: dapagliflozin clinical trial program





Jabbour S, et al. WCIRDC 2016 Poster 119

CV outcomes, all-cause mortality, lower limb amputation, and incident or worsening nephropathy by peripheral artery disease at baseline



A	Empagliflozin	Placebo	Hazard ratio (95% CI)	Treatment by subgroup interaction
	n with event/ N analyzed (%)			
CV death				
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
PAD at baseline				p=0.6684
No	128/3704 (3.5)	101/1853 (5.5)	0.64 (0.49, 0.82)	
Yes	44/982 (4.5)	36/479 (7.5)	0.57 (0.37, 0.88)	
All-cause mortality				
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)	
PAD at baseline				p=0.5652
No	195/3704 (5.3)	139/1853 (7.5)	0.70 (0.57, 0.87)	
Yes	74/982 (7.5)	55/479 (11.5)	0.62 (0.44, 0.88)	
3-point MACE				
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)	
PAD at baseline				p=0.9052
No	370/3704 (10.0)	216/1853 (11.7)	0.86 (0.73, 1.02)	
Yes	120/982 (12.2)	66/479 (13.8)	0.84 (0.62, 1.14)	
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All patients	599/4687 (12.8)	333/2333 (14.3)	0.89 (0.78, 1.01)	
PAD at baseline				p=0.7154
No	460/3704 (12.4)	263/1853 (14.2)	0.87 (0.75, 1.02)	
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All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)	
PAD at baseline				p=0.5315
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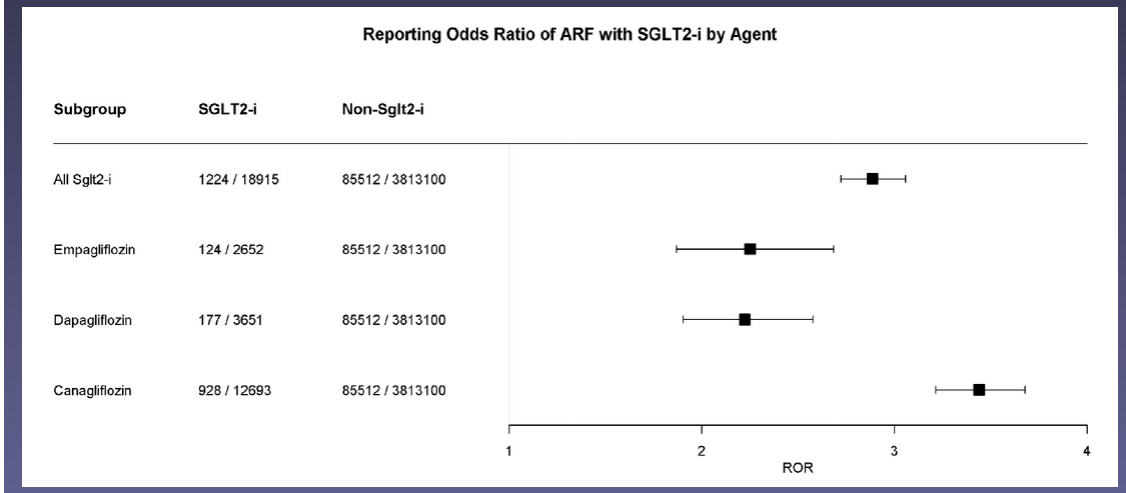
Yes	120/825 (14.5)	93/403 (23.1)	0.54 (0.41, 0.71)	

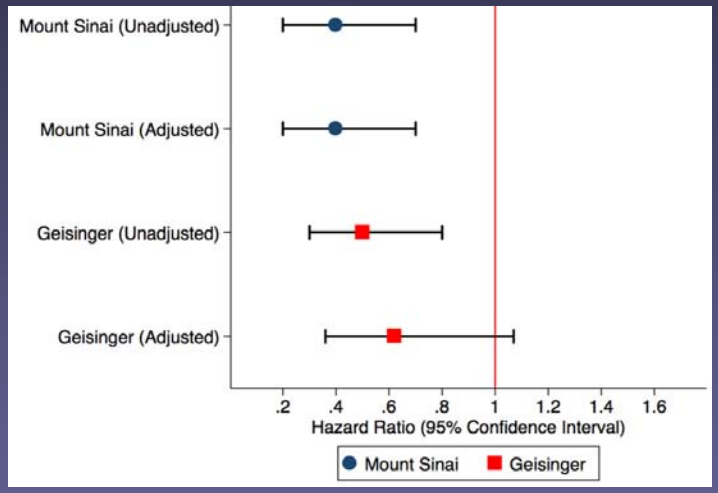
Verma et al. Circulation 2017

No signal AKI in EMPA-REG OUTCOME, CANVAS Program – how about "real world"

US FAERS Data (more NSAID, RAASi use)



US Propensity Score Data



Increase in AKI risk

Decrease in risk

- Sick day advice to patients (e.g. "SADMANS") – avoid hypovolemia, ketoacidosis

Perlman et al. Nutrition, Metabolism & Cardiovascular Diseases 2017;27:1108e1113
Nadkarni et al. Diab Care 2017

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 01 November 2017
doi: 10.3389/fphar.2017.00780

Check for updates

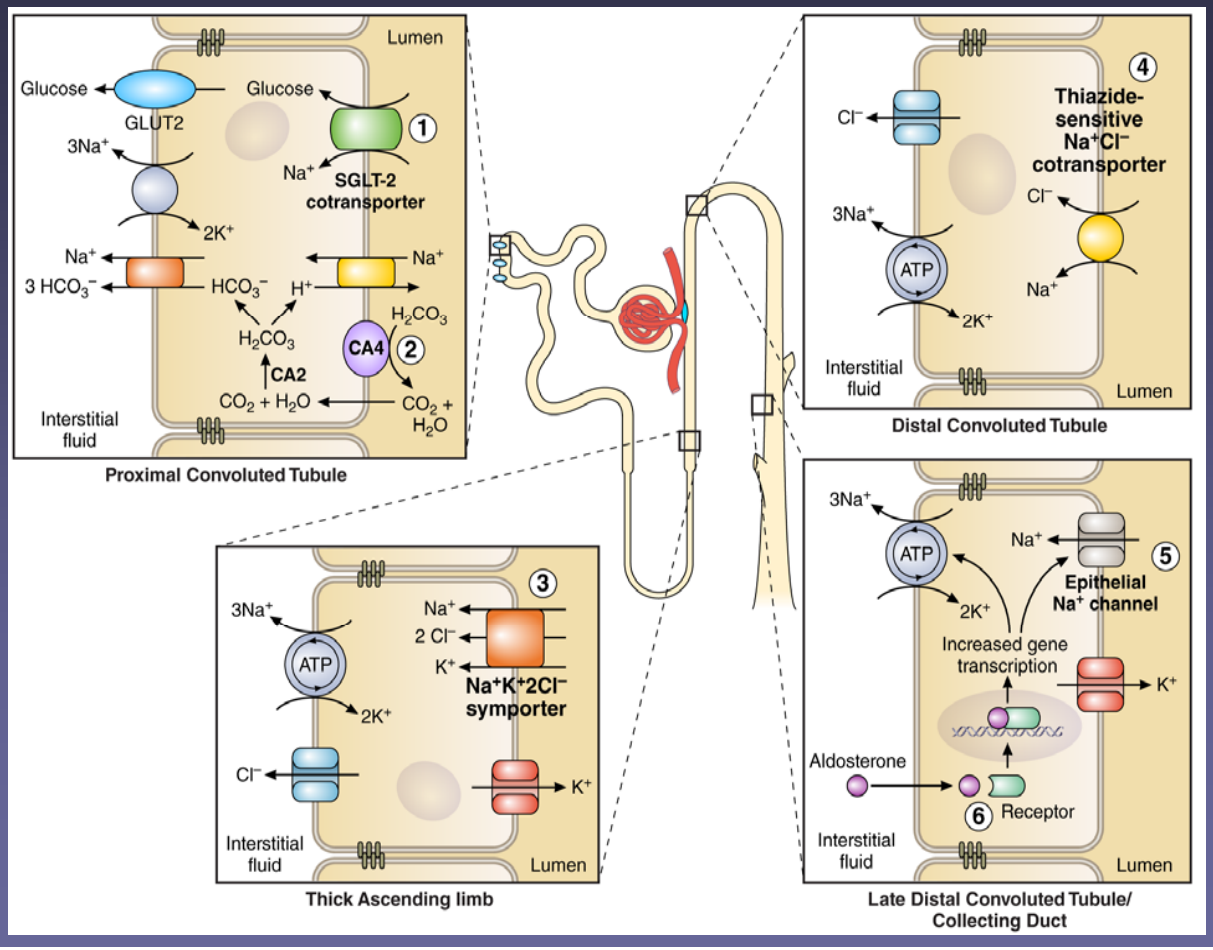
Saxagliptin Attenuates Albuminuria by Inhibiting Podocyte Epithelial-to-Mesenchymal Transition via SDF-1α in Diabetic Nephropathy

Yun-peng Chang, Bei Sun, Zhe Han, Fei Han, Shao-lan Hu, Xiao-yu Li, Mei Xue, Yang Yang, Li Chen, Chun-jun Li and Li-ming Chen**

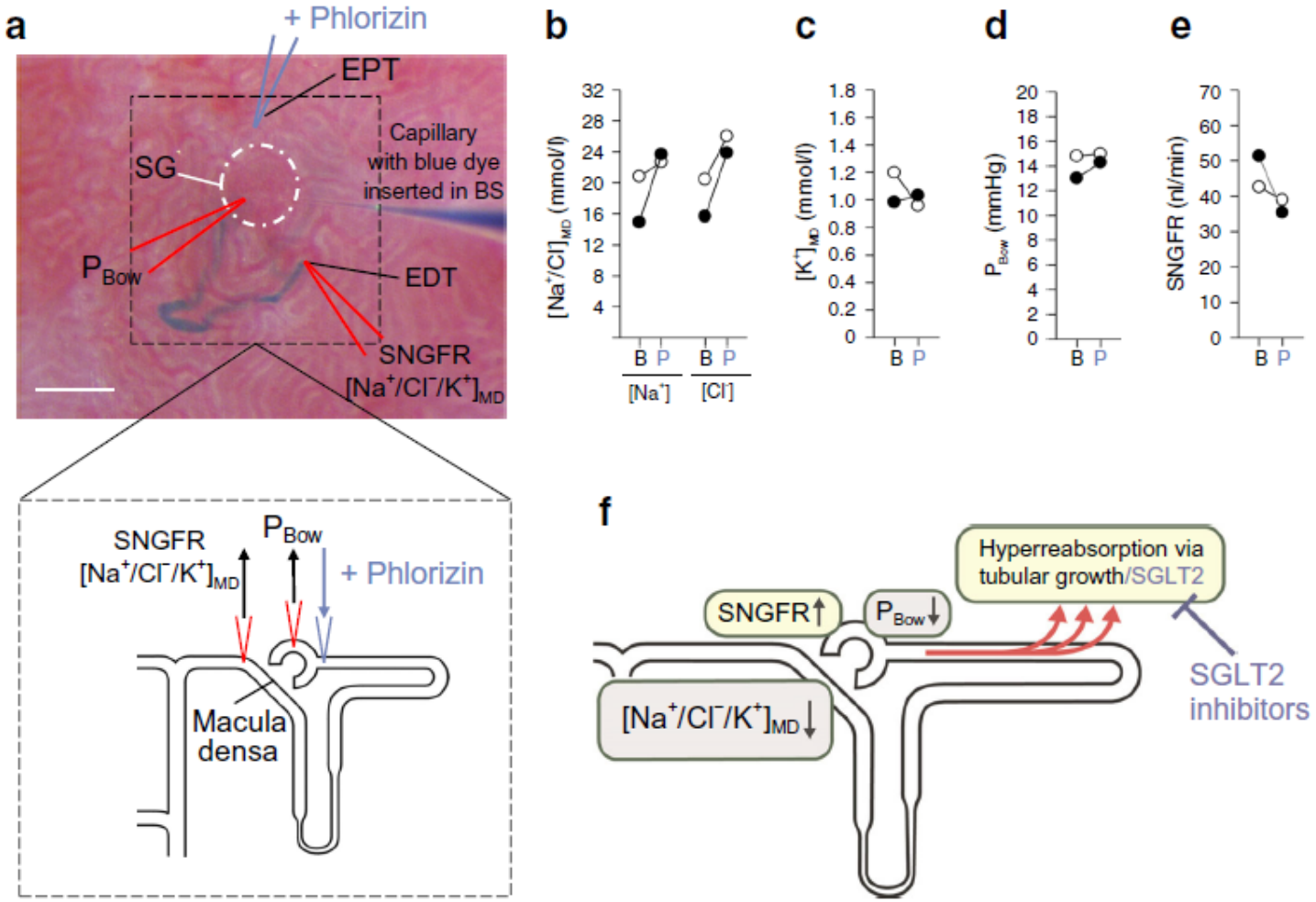
Key Laboratory of Hormones and Development (Ministry of Health), Tianjin Key Laboratory of Metabolic Diseases, Tianjin Metabolic Diseases Hospital and Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin, China

Chang et al. Frontiers in Pharmacology 2017
Takashima et al. *Kidney Int* 2016;90:783–796

Why don’t other diuretics impact tubuloglomerular feedback?



Rajasekeran/Cherney/Lovshin.
Curr Opin Nephrol Hypertens 2017



Vallon et al. Diabetologia 2017;60:215-225

Use of Canagliflozin in Kidney Transplant Recipients for the Treatment of Type 2 Diabetes: A Case Series

Harindra Rajasekeran,[1,2] S. Joseph Kim,[1,3,4] Carl J. Cardella,[1,3] Jeffrey Schiff,[1,3,5] Mark Cattral,[5,6] David Z.I. Cherney,[1,2] and Sunita K.S. Singh[1,3,5]

Diabetes Care 2017;40:e75–e76 | https://doi.org/10.2337/dc17-0237

Baseline characteristic	SPKTR ($N = 4$)	KTR ($N = 6$)
Age at time of canagliflozin initiation, years	49.4 ± 8.9	61.6 ± 12.6
Female sex	2 (50)	1 (17)
PTDM	4 (100)	4 (67)
Prior DM therapy	3 (75)	5 (83)
Time from transplant to canagliflozin treatment, years	3.5 ± 3.9	4.4 ± 3.3
Time on canagliflozin treatment, months	5.6 ± 3.4	10.1 ± 4.2
Hemoglobin A_{1c}, %	7.4 ± 1.1	8.6 ± 1.4
Hemoglobin A_{1c}, mmol/mol	57 ± 12.0	70 ± 15.3
eGFR, mL/min/1.73 m^2	60 ± 14	78 ± 18.2
Serum creatinine, μmol/L	108.3 ± 21.6	90.2 ± 22.9
ACEi therapy	1 (25)	0 (0)
ARB therapy	0 (0)	2 (50)
Diuretic therapy	3 (75)	2 (50)
Calcium channel blocker therapy	4 (100)	3 (75)
α-Adrenergic antagonist therapy	1 (25)	1 (25)
Beta blocker therapy	4 (100)	2 (50)

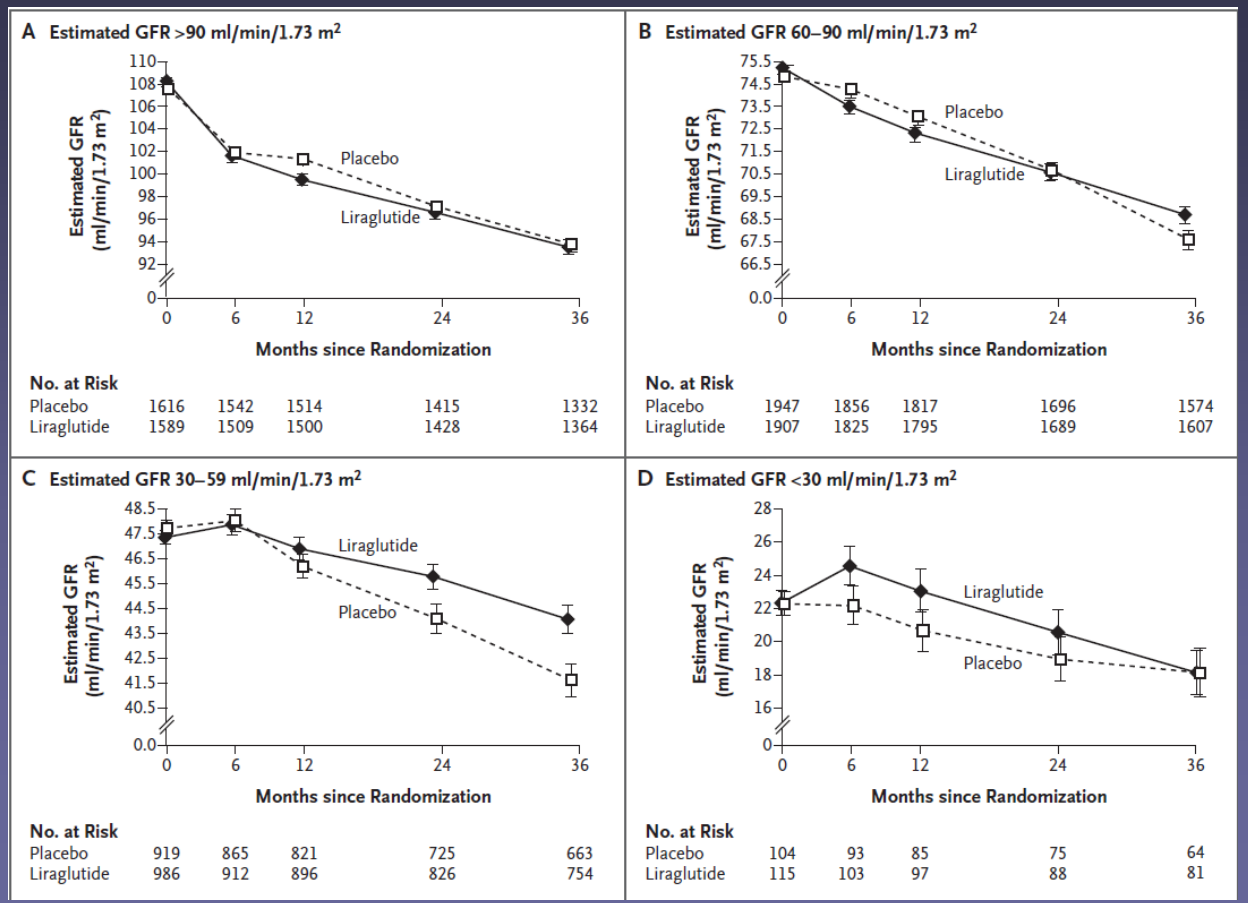
Rajasekeran et al.
Diabetes Care 2017

Effects on metabolic and hemodynamic parameters

Parameter over follow-up	Mean (SD) change	*P* value
Hemoglobin A_{1c}, % ($N = 9$)	−0.84 (1.2)	0.07
Hemoglobin A_{1c}, mmol/mol ($N = 9$)	−9.2 (13.1)	0.07
Weight, kg ($N = 8$)	−2.14 (2.8)	0.07
Serum sodium, mmol/L ($N = 10$)	0.6 (2.2)	0.4
Serum potassium, mmol/L ($N = 10$)	0.2 (0.5)	0.2
Systolic blood pressure, mmHg ($N = 8$)	−6.5 (10.8)	0.13
Diastolic blood pressure, mmHg ($N = 8$)	−4.8 (12)	0.3
Hematocrit, % ($N = 10$)	1.6 (2.5)	0.08
Serum creatinine, μmol/L ($N = 10$)	9.7 (14.6)	0.06
eGFR, mL/min/1.73 m^2 ($N = 10$)	−4.3 (12.2)	0.3

Rajasekeran et al. Diabetes Care 2017

Liraglutide and Renal Outcomes in Type 2 Diabetes



Mann et al. NEJM 2017

Overview of Study Procedures – NATRIURETIC (n=36, T2D)

Recruitment: pre-study preparation (controlled Na^+/protein diet for 7 days); 24-h urine collection (protein, Na^+, urea, creatinine) 1 day prior to Day 1. Li^+CO_3 300 mg at 22:00 h on the evening prior to Day 1.

↓

Day 1: 07:45 h: Admit to Renal Physiology Unit, euglycemic clamp (4-6 mmol/L)

↓

13:00 h: Baseline plasma levels of RAAS mediators, norepinephrine, epinephrine. Spot urine sample for adenosine, urinary RAAS markers

↓

13:00-15:00 h: Urinary Na^+ and Li^+ clearance parameters, cardiovascular and renal function

↓

End of Study Day 1 – allocation to treatment arm (SGLT2i vs. GLP1RA), with safety telephone visit after 2 days of treatment. Clinic visit 2 weeks later to assess for adverse events. Continue to treatment allocation for 6 weeks for repeat physiological assessments (Day 2)

↓

Day 2: Repeat all physiological assessments for Day 1. Combo (described in the protocol) for 6 weeks.

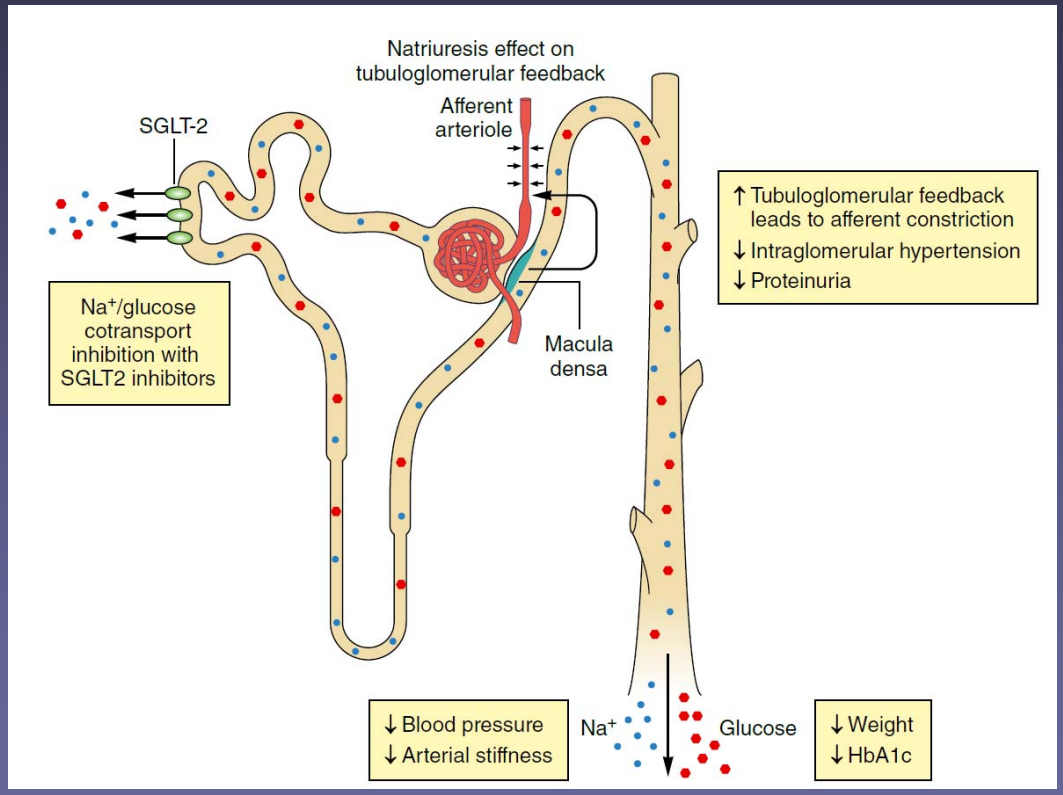
↓

Days 3: Return to the Renal Physiology Laboratory at 12 weeks for physiological assessments

↓

End of Treatment Phase, followed by 1-week washout, with telephone calls and final clinic visit to readjust insulin doses, antihyperglycemic agents if needed

The "Tubular Hypothesis": Diabetes and SGLT2 inhibition



Heerpsink//Cherney. Kidney International 2018 (in press)

CARMELINA: study design

Aim: to assess the CV and renal safety of linagliptin vs placebo in patients with T2D at high risk of CV and kidney events

Main inclusion criteria

1. Adults (≥18 years old) with T2D*
2. HbA1c 6.5–10.0%
3. BMI ≤45 kg/m^2 and high CV risk
4. High risk of CV events (albuminuria [UACR >30 mg/g] and previous macrovascular disease and/or impaired renal function with predefined UACR)

Main exclusion criteria

1. T1D
2. Prior treatment with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT2 inhibitors for ≥7 days
3. eGFR <15 ml/min/1.73 m^2 and/or need for maintenance dialysis

Primary outcome: time to first occurrence of primary composite endpoint:

- **CV death**
- **Non-fatal MI**
- **Non-fatal stroke**

Secondary outcome: time to the first occurrence of any of the following adjudicated components:

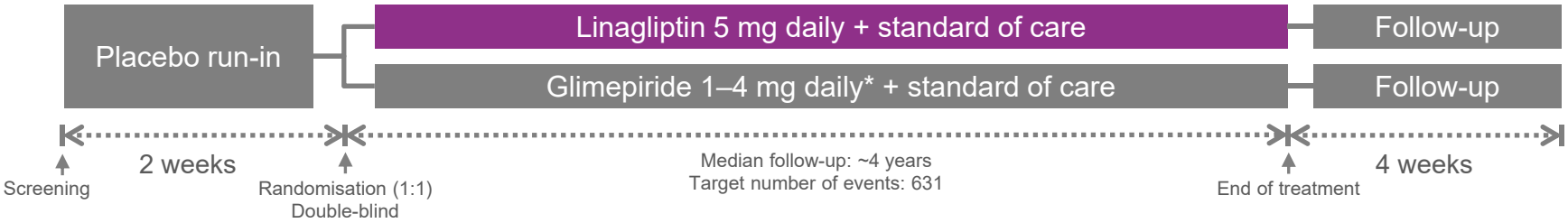
- **Renal death**
- **Sustained end-stage renal disease**
- **Sustained loss of eGFR ≥40%**

*≥20 years of age for Japan. BMI, body mass index; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter-2; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Rosenstock J *et al. ADA* 2017; poster P1284; ClinicalTrials.gov NCT01897532 (Accessed July 2017)

CAROLINA: study design

Aim: to assess the CV safety of linagliptin vs glimepiride in patients with T2D at high risk of CV events



Main inclusion criteria

1. T2D with HbA1c 6.5−8.5% (treatment naïve) or 6.5−8.5% (on treatment)
2. High risk of CV events defined as ≥1 of the following: previous CV complications; evidence of end-organ damage, e.g. albuminuria; age ≥70 years; and/or ≥2 specified traditional CV risk factors

Main exclusion criteria

1. T1D
2. Any history and/or current treatment with insulin or other glucose-lowering therapies (e.g. GLP-1 receptor agonists, DPP-4 inhibitors)
3. BMI >45 kg/m^2
4. Age <40 or >85 years

Primary endpoint: time to first occurrence of primary composite endpoint:

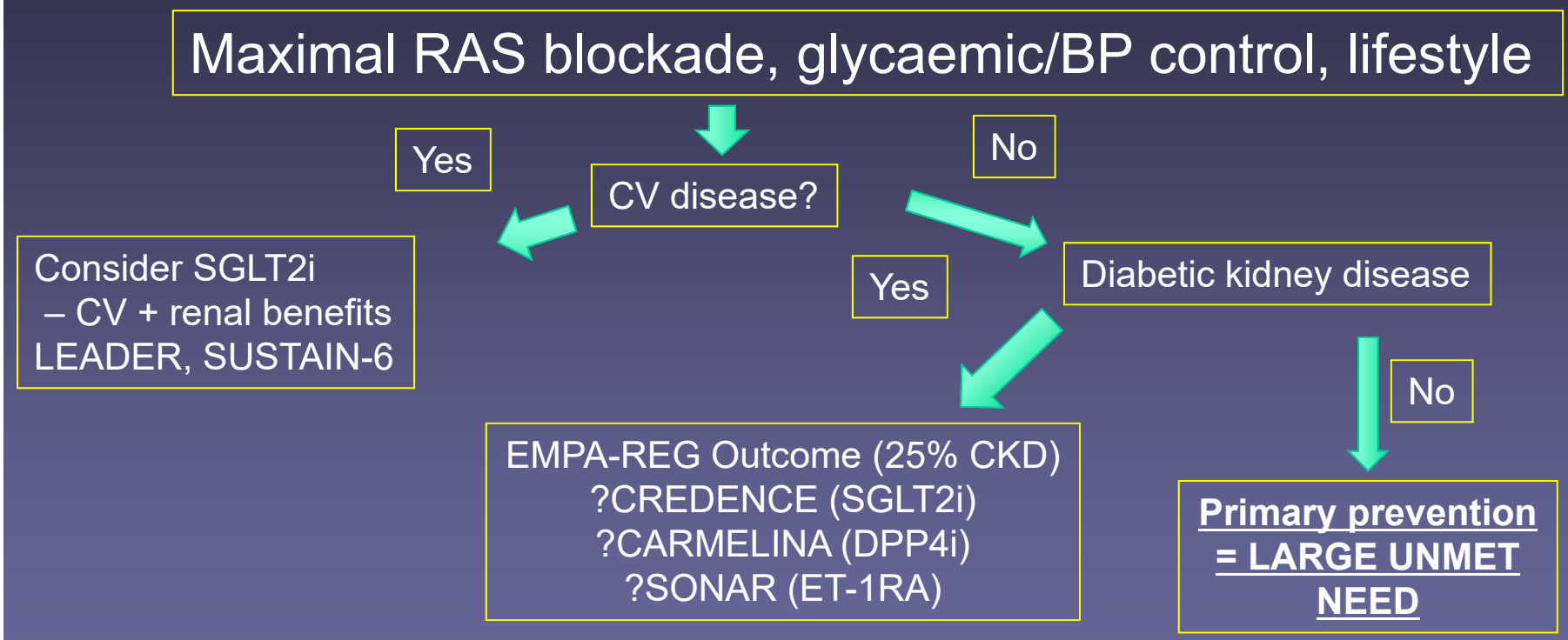
- **CV death**
- **Non-fatal MI**
- **Non-fatal stroke**

Key secondary endpoints:

- **4P-MACE (composite of 3P-MACE plus time to first occurrence of hospitalisation for unstable angina)**
- **Proportion of patients on treatment and maintaining HbA1c ≤7.0% at final visit**

***Starting dose of 1 mg/day up-titrated to a potential maximum of 4 mg/day every 4 weeks for the first 16 weeks. Visit schedule after this period: 16 weeks. At any point in the study course the dose can be up- or down- titrated if needed. 3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; BMI, body mass index; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like ppeptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes. Marx N *et al. Diabetes Vasc Dis Res* 2015;12:164; ClinicalTrials.gov NCT01243424 (accessed July 2017)**

How does this impact management of Type 2 diabetes?



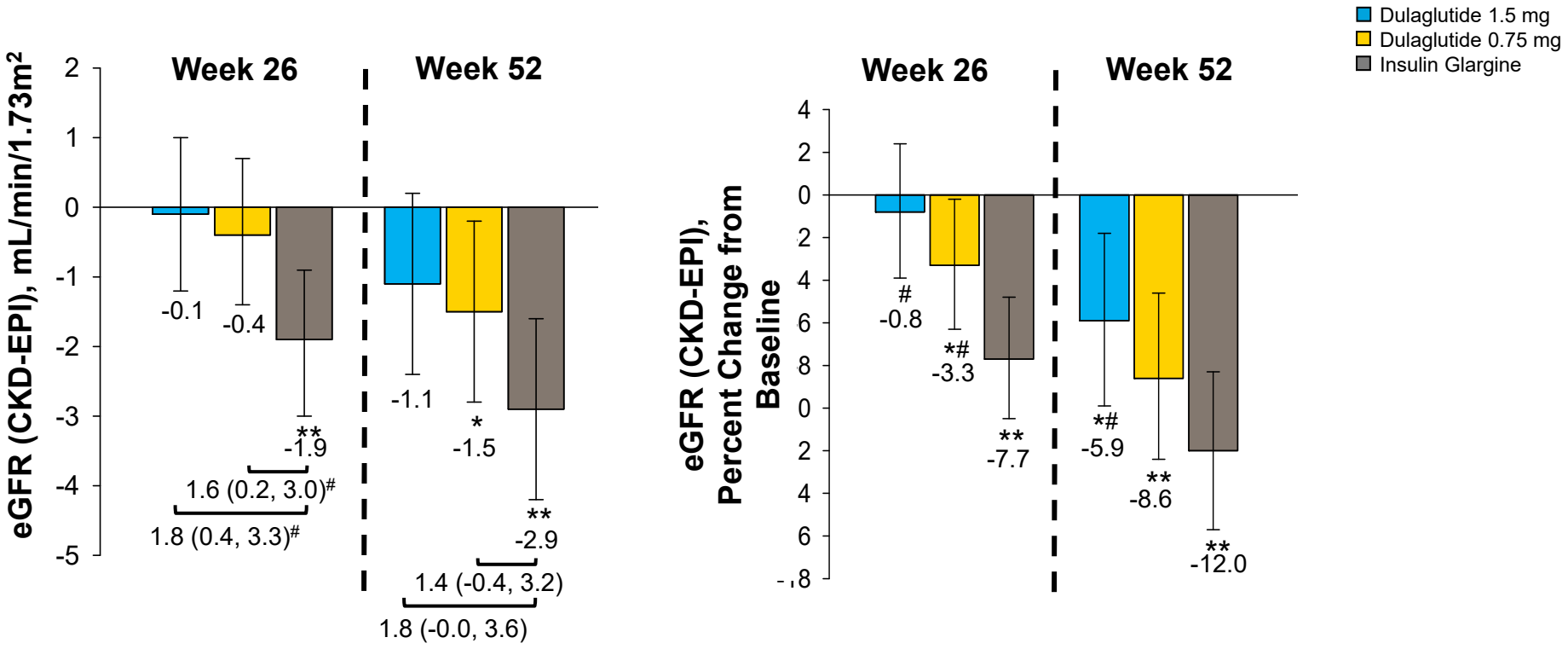
CKD, chronic kidney disease; CV, cardiovascular; RAS, renin–angiotensin system; SGLT2i, sodium–glucose co-transporter 2 inhibitor

Goldenberg R, et al. *Can J Diabetes* 2016;40:193–195

Non-glycemic effects of SGLT2i and DPP4i alone/combination

	SGLT2i	DPP4i	Combination
Renal parameters			
Renal hemodynamics	↓glomerular hypertension	↔	↓glomerular hypertension
Albuminuria	↓30-50%	↓10-20%	↓↓
Inflammation	↓MCP-1, IL-6, NF-κβ, ROS	↓inflammatory, ROS	↓↓
Natriuresis	↑Proximal natriuresis	↑Distal natriuresis	↑↑
Blood pressure	↓4-6 mmHg	↔	↓
Cardiovascular events			

AWARD-7:
Lesser eGFR Decline with Dulaglutide

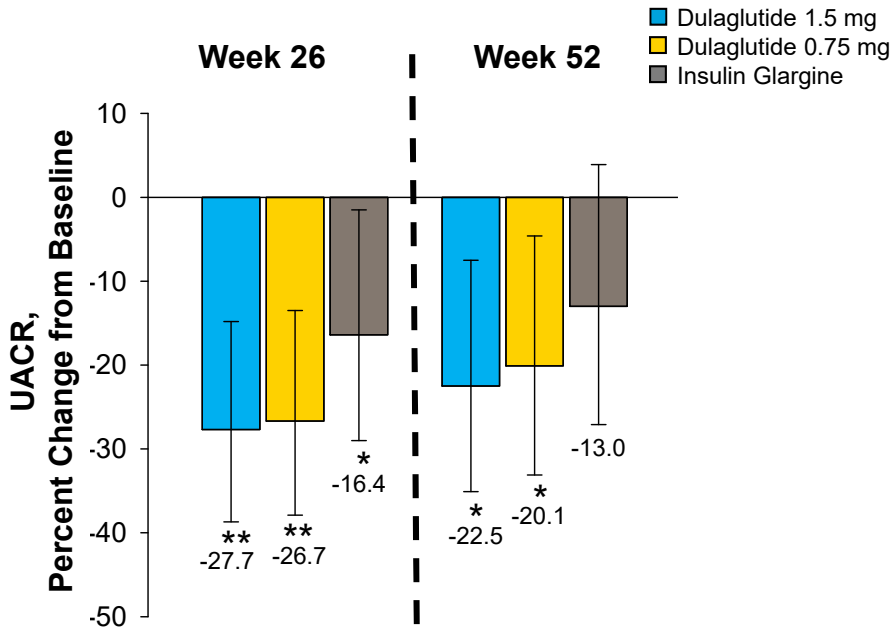


Data presented as change from baseline [LSM (95%CI)]; safety population; MMRM analysis; *p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. insulin glargine.

Tuttle et al. ASN 2017

AWARD-7: Albuminuria Reduction

Baseline UACR, mg/g		
Group	**n**	**Mean/Median**
Dulaglutide 1.5 mg	192	779/214
Dulaglutide 0.75 mg	189	842/234
Insulin Glargine	194	920/196

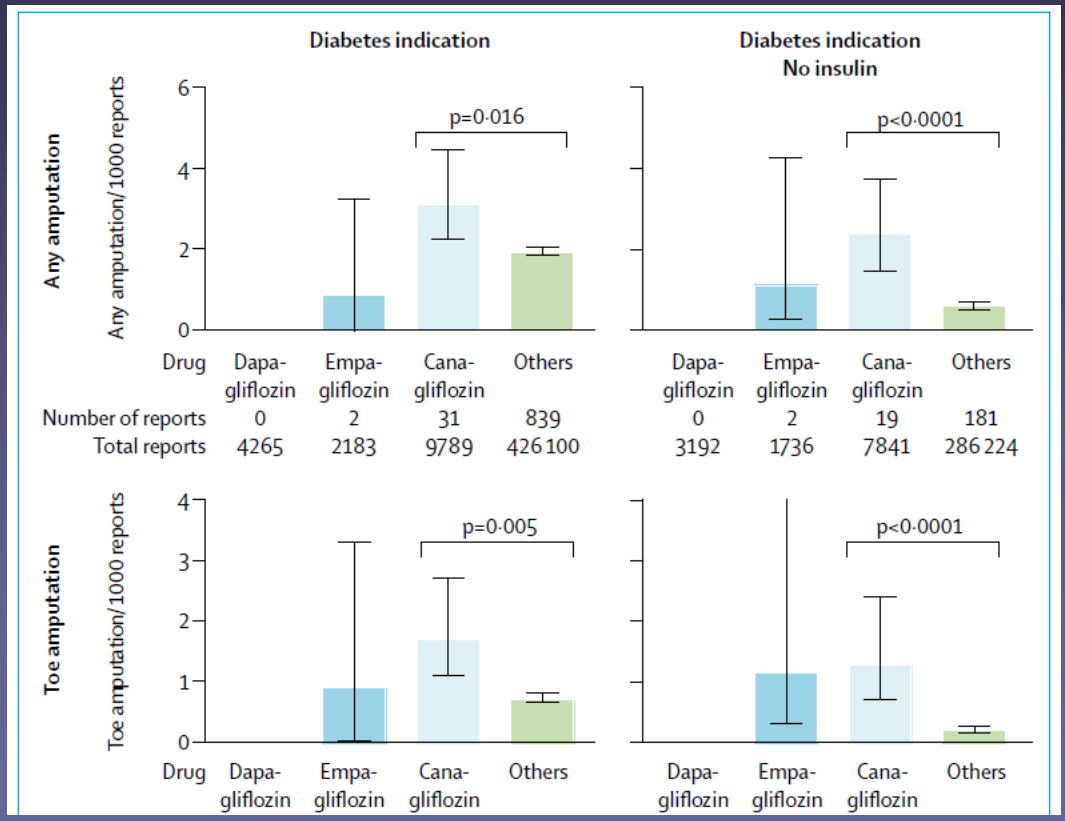


- Dulaglutide treatment is associated with larger decrease in UACR but with no significant differences between treatment groups

Data presented as % change from baseline [LSM (95% CI)]; safety population, MMRM analysis; *p<0.05 and **p<0.001 vs. baseline.

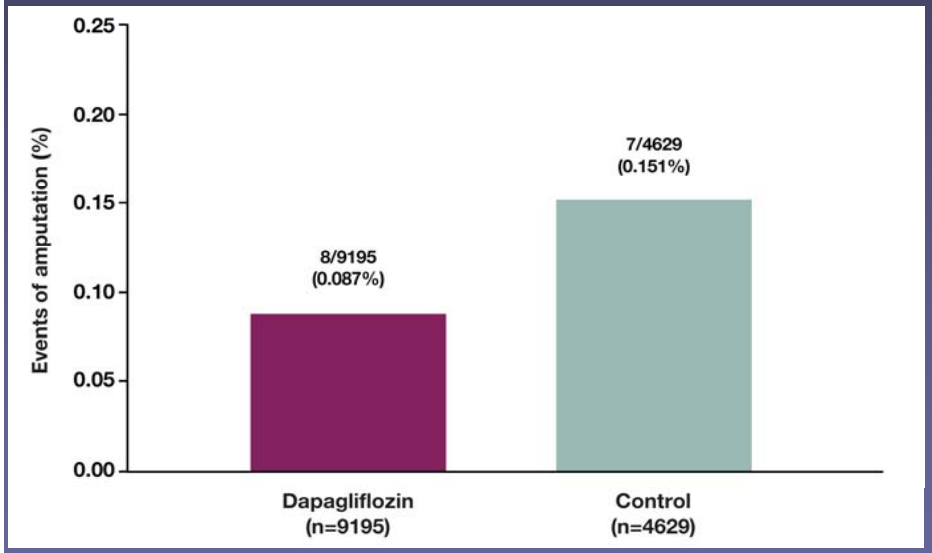
Tuttle et al. ASN 2017

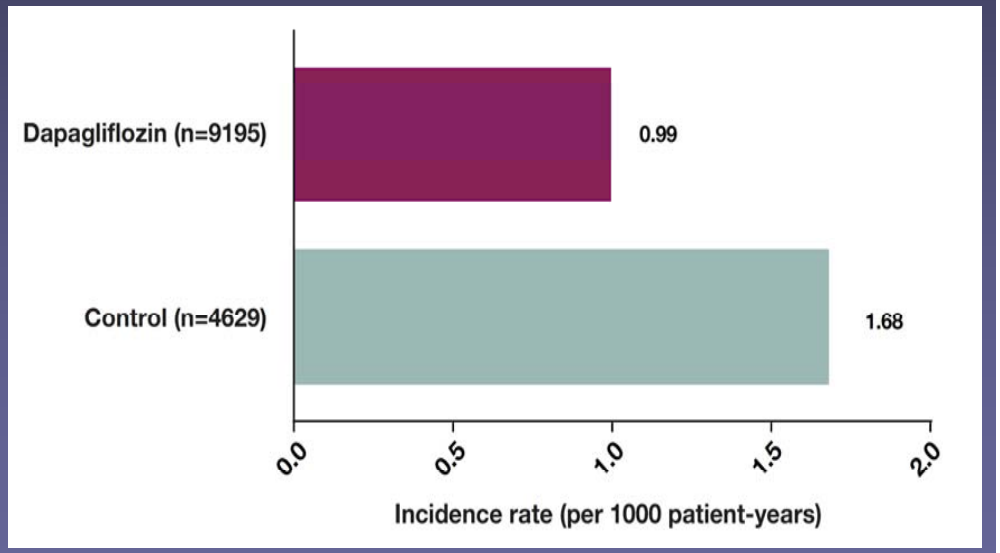
SGTL2 inhibitors and amputations in the US FDA Adverse Event Reporting System.



Fadini et al. Lancet Diabetes Endocrinol. 2017 Sep;5(9):680-681

Events of amputation in the dapagliflozin clinical trial program





Jabbour S, et al. WCIRDC 2016 Poster 119

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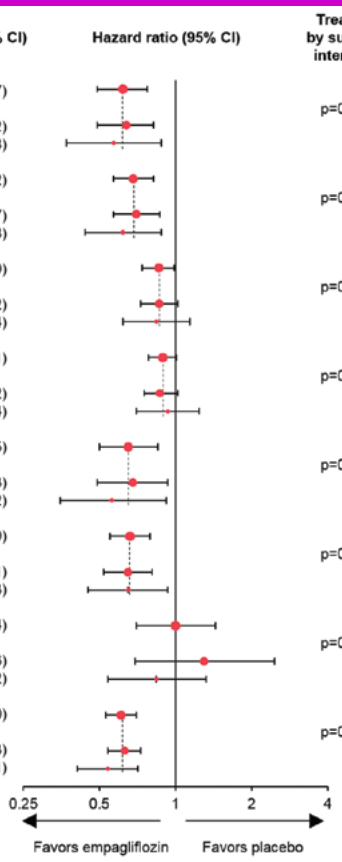
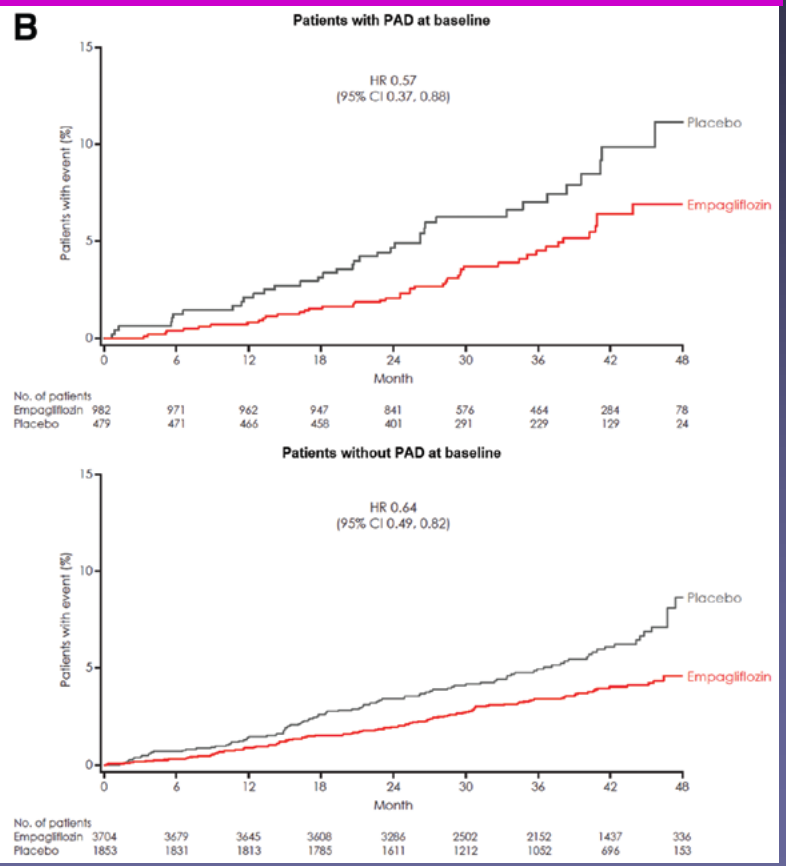


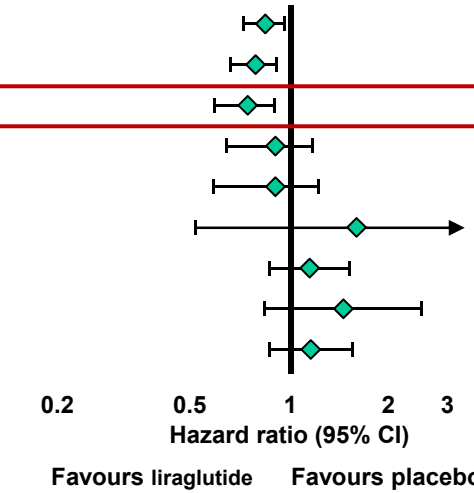
B



Verma et al. Circulation 2017

LEADER: Time to first microvascular endpoints

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
		4668	100	4672	100
Microvascular endpoint	0.84 (0.73, 0.97)	355	7.6	416	8.9
Renal event	0.78 (0.67, 0.92)	268	5.7	337	7.2
New onset of persistent macroalbuminuria[a]	0.74 (0.60, 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine[b]	0.88 (0.66, 1.18)	87	1.9	97	2.1
Need for continuous renal-replacement therapy	0.87 (0.61, 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52, 4.87)	8	0.2	5	0.1
Eye event	1.15 (0.87, 1.52)	106	2.3	92	2.0
Vitreous haemorrhage	1.45 (0.84, 2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87, 1.55)	100	2.1	86	1.8



Similar observations with semaglutide (SUSTAIN-6)

Marso SP, et al. *N Eng J Med* 2016;375:311–322

Acknowledgments

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- UHN Research Team
- Bruce Perkins
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  - Marko Skrtic, MD PhD
  - Harindra Rajasekeran MSc(C)
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  - Bernard Zinman
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  - Silvio Inzucchi

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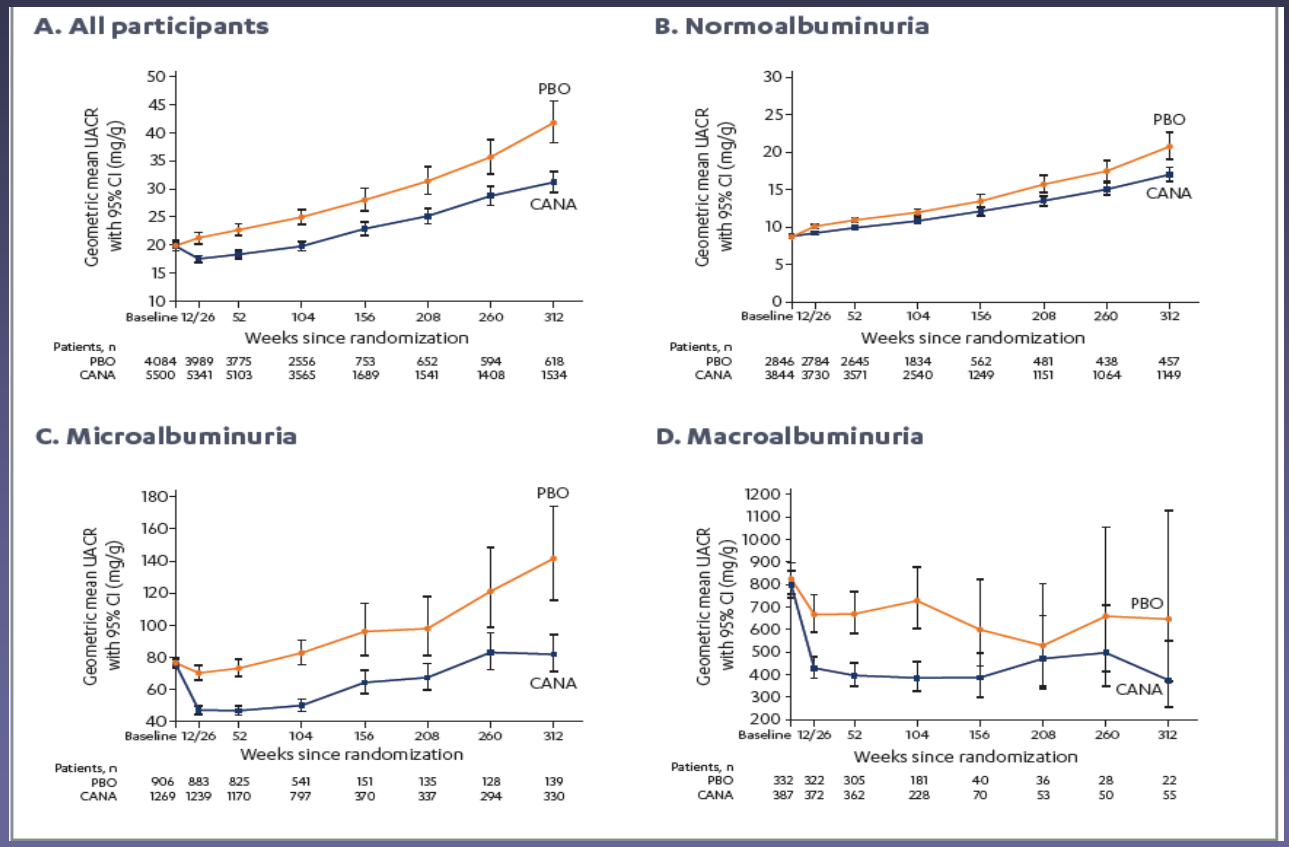
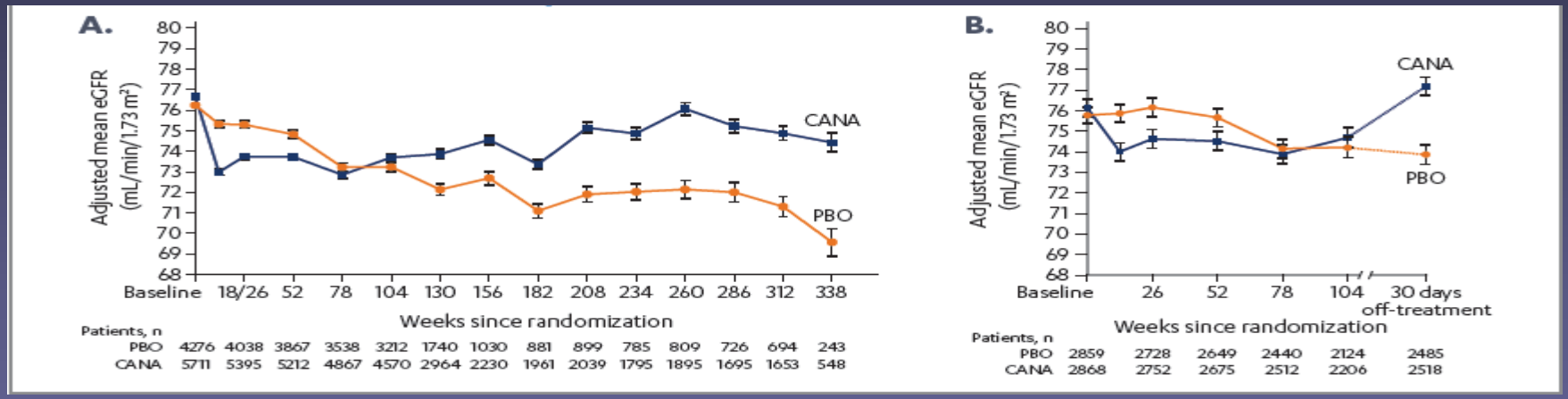
UACR according to baseline albuminuria level



Perkovic et al. ASN poster, 2017

Effects of CANA on (A) eGFR over time in the CANVAS Program and (B) eGFR over time and after a median of 30 days off-treatment in CANVAS-R.



Perkovic et al. ASN poster, 2017

A multifactorial intervention strategy is recommended in DKD

Glucose — HbA1c target individualised, but generally ~7%[1]

Coca SG *et al. Arch Intern Med* 2012;172:761
Zoungas S *et al. N Engl J Med* 2014;371:1392

BP — Target of <130/80 mmHg[2]

de Galan B *et al. J Am Soc Nephrol* 2009;20:883

ACEi/ ARB — Use ACEi or ARBs

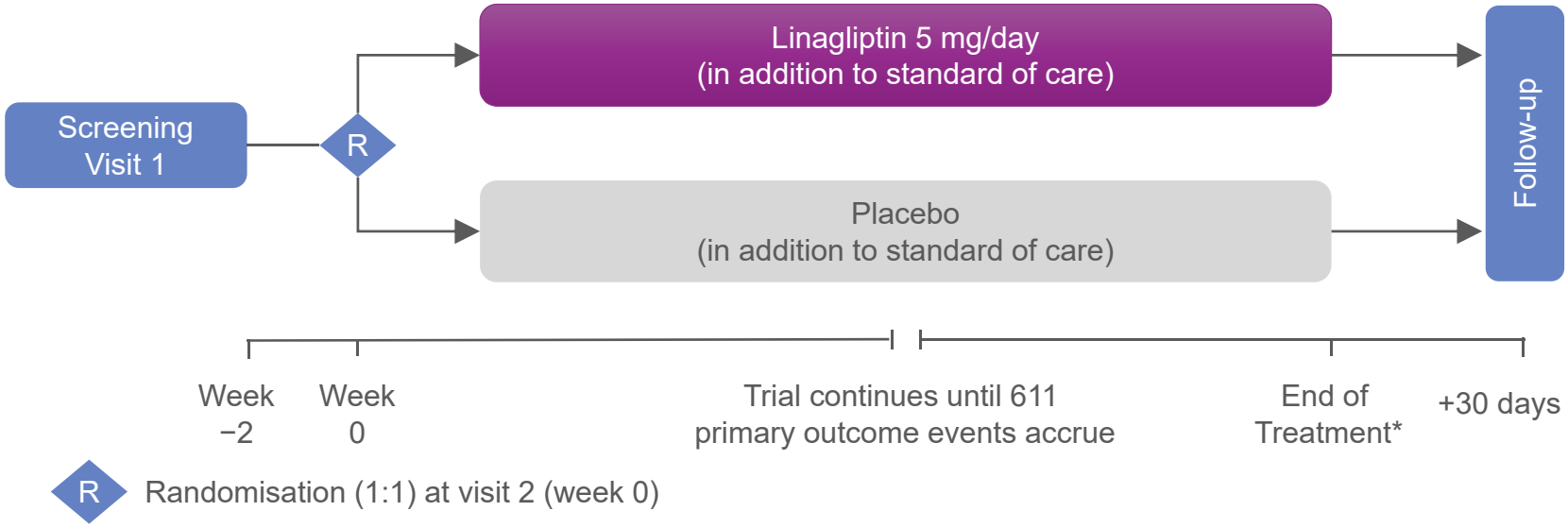
Lipids — Lipid-lowering recommended to reduce risk of atherosclerotic events; statins likely ineffective in dialysis patients

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; DKD, diabetic kidney disease; HbA1c, glycated haemoglobin

1. National Kidney Foundation. *Am J Kidney Dis* 2012;60:850; 2. NICE. Clinical guideline: Type 2 diabetes (CG87), May 2009

CARMELINA® trial design

- Multi-national, randomised, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov: NCT01897532)



- The protocol also encourages the investigators and patients' HCPs to treat all CV risk factors (e.g. lipid levels, blood pressure, albuminuria, hyperglycaemia, smoking) according to an optimal level of local/regional standard of care

CV, cardiovascular; HCP, healthcare provider. *Patients who stop treatment early are observed until study end (not just until their treatment stop + 30 days).

Source: Perkovic V *et al.* EASD 2017; Poster 779

CARMELINA

Key inclusion criteria

Patients with documented diagnosis of T2DM at high risk of CV events defined as:

Age ≥18 years

HbA1c of ≥6.5% and ≤10.0%

BMI ≤45 kg/m^2

and/or

Albuminuria (UACR >30 mg/g*) and previous macrovascular disease, defined as ≥1 of the following:

- Confirmed history of MI
- Advanced CAD†
- High-risk single-vessel CAD
- History of ischaemic or haemorrhagic stroke
- Presence of carotid artery disease
- Presence of peripheral artery disease

Impaired kidney function with or without albuminuria

- eGFR:15−<45 ml/min/1.73 m^2
- eGFR ≥45−75 ml/min/1.73 m^2 with UACR >200 mg/g creatinine or >200 mg/l or >200 µg/min or >200 mg/24 h

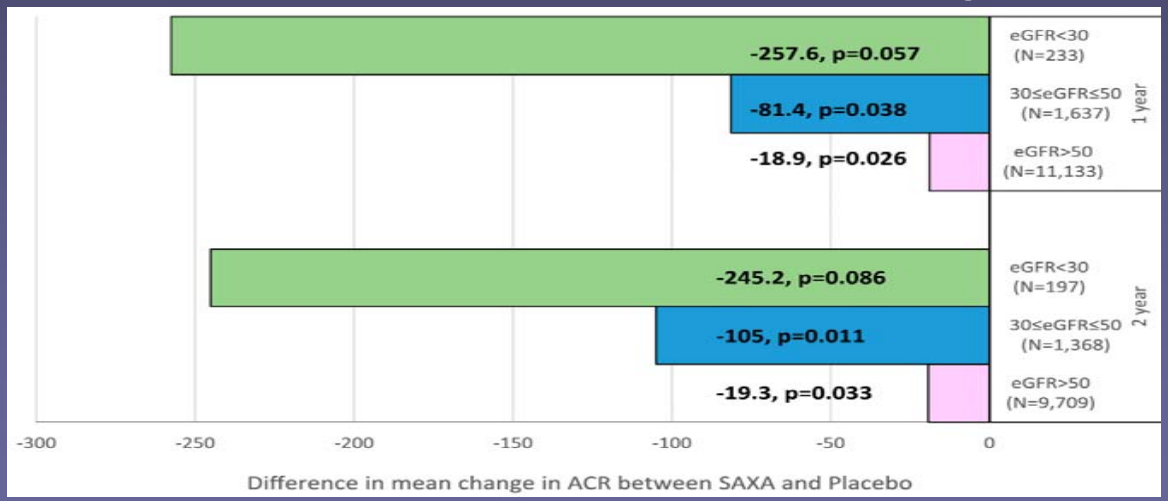
BMI, body-mass index; CAD, coronary artery disease; CT, computed tomography; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MI, myocardial infarction; MRI, magnetic resonance imaging; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio. *Albuminuria was also defined as ≥30 µg albumin/min or ≥30 mg albumin/24 h. †Any 1 of the following: ≥50% narrowing of the luminal diameter in ≥2 major coronary arteries by coronary angiography, MRI angiography or CT angiography; left main stem coronary artery with ≥50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography; prior percutaneous or surgical revascularization of ≥2 major coronary arteries ≥2 months prior to Visit 1 (screening); the combination of prior percutaneous or surgical revascularization of 1 major coronary artery ≥2 months prior to Visit 1, and ≥50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography of ≥1 additional major coronary artery.

Source: Perkovic V *et al.* EASD 2017; Poster 779

CARMELINA

Renal effects of DPP-4 inhibitors

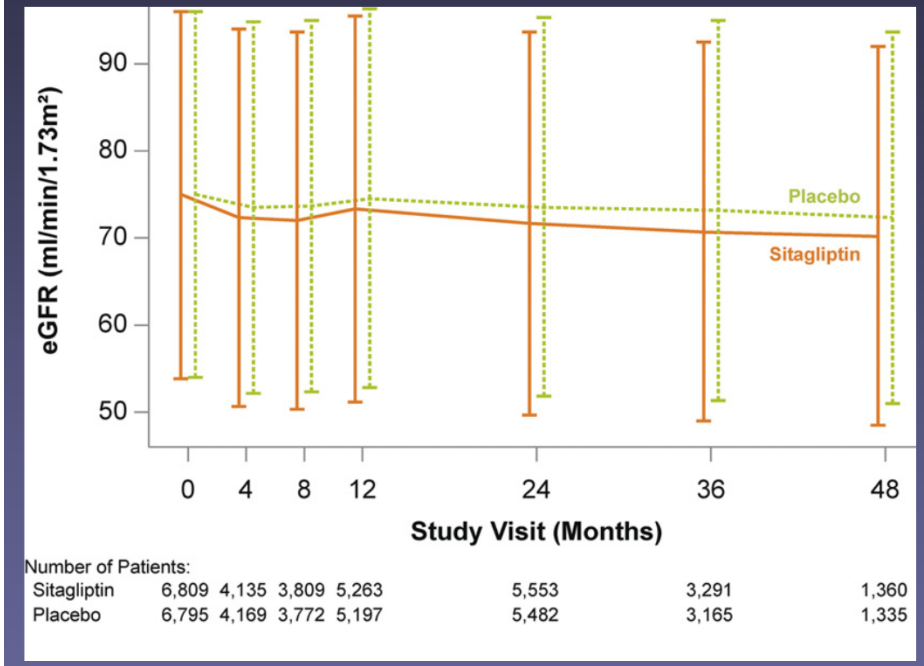
- SAVOR-TIMI 53 (saxagliptin)
  - No meaningful eGFR differences
  - No differences in "hard" renal outcomes
  - Decrease in UACR unrelated to changes in HbA1c

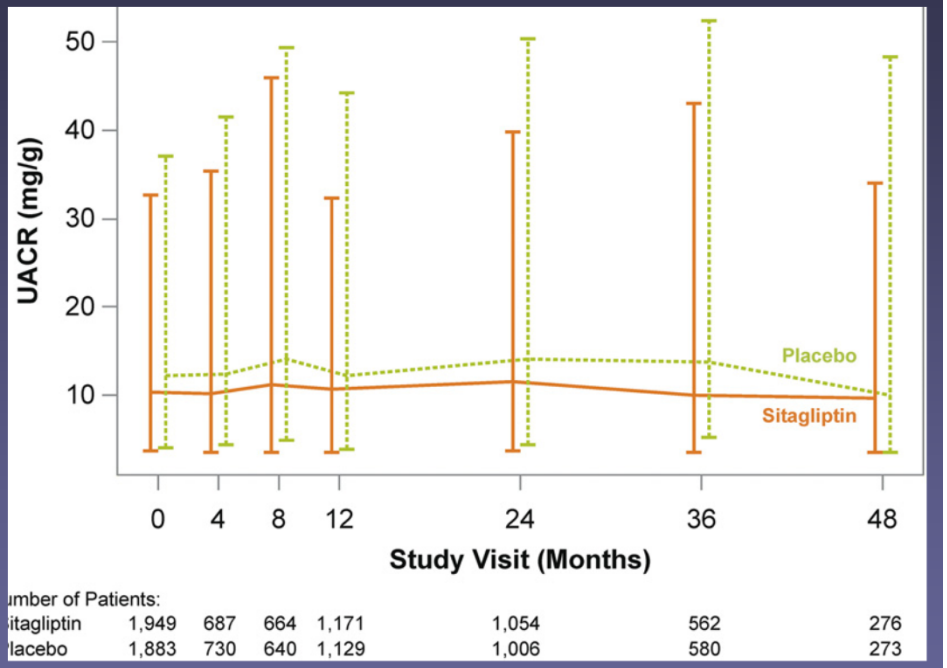


ACR, albumin:creatinine ratio; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate

Green JB, et al. *N Engl J Med* 2015;373:232–242; White W, et al. *N Engl J Med* 2013;369:1327–1335; Scirica BM, et al. *N Engl J Med* 2013;369:1317–1326; Mosenzon O, et al. *Diabetes Care* 2017;40:69–76

Effects of DPP-4 inhibitors: CV and renal outcomes





- TECOS: no clinically significant impact on cardiovascular or CKD outcomes in any eGFR category

Cornel et al. Diabetes Care 2016

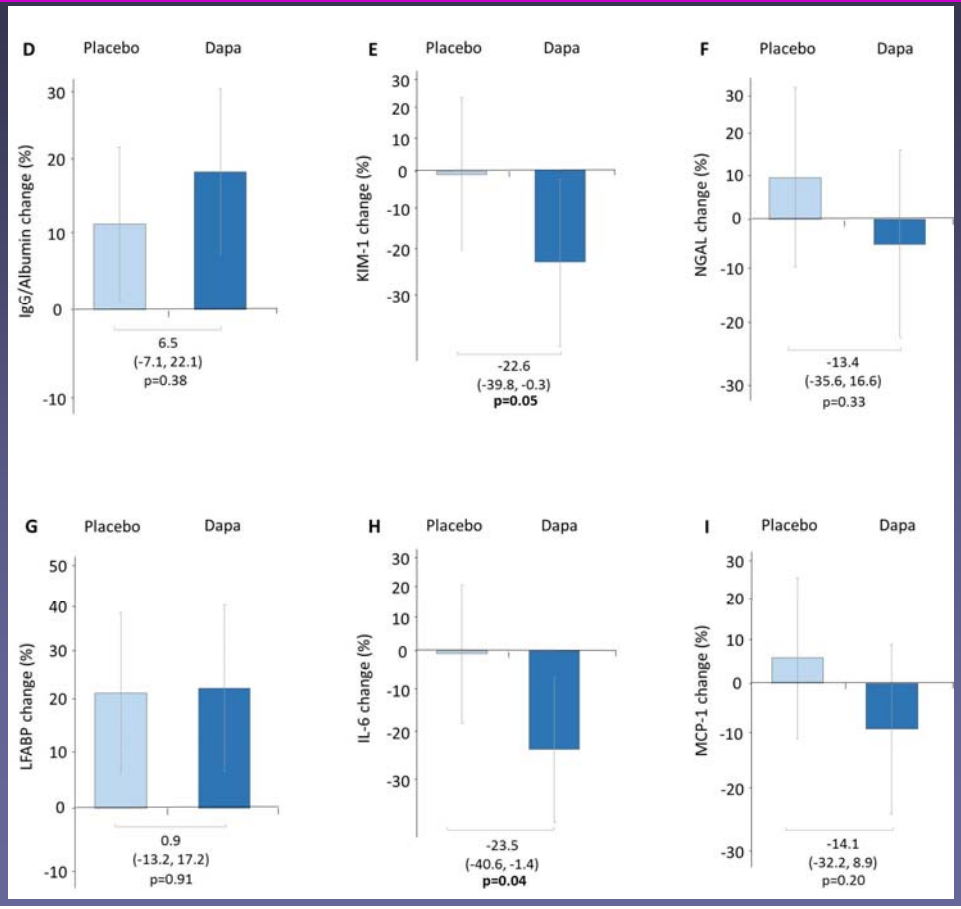
Table 1. Baseline Characteristics for the CANVAS Program[8,*]

	CANA (n = 5795)	PBO (n = 4347)
Age, y	63.2 (8.3)	63.4 (8.2)
Female, n (%)	2036 (35.1)	1597 (36.7)
Drug therapy, n (%)		
Statin	4329 (74.7)	3270 (75.2)
Antithrombotic	4233 (73.0)	3233 (74.4)
RAAS inhibitor	4645 (80.2)	3471 (79.8)
Beta-blocker	3039 (52.4)	2382 (54.8)
Diuretic	2536 (43.8)	1954 (45.0)
Body mass index, kg/m^2	31.9 (5.9)	32.0 (6.0)
HbA1c, %	8.2 (0.9)	8.2 (0.9)
eGFR, mL/min/1.73 m^{2,†}	76.7 (20.3)	76.2 (20.8)
eGFR ≥90 mL/min/1.73 m^2, n (%)	1419 (24.5)	1057 (24.3)
eGFR ≥60 to <90 mL/min/1.73 m^2, n (%)	3265 (56.4)	2360 (54.3)
eGFR ≥45 to <60 mL/min/1.73 m^2, n (%)	812 (14.0)	673 (15.5)
eGFR ≥30 to <45 mL/min/1.73 m^2, n (%)	287 (5.0)	239 (5.5)
eGFR ≥15 to <30 mL/min/1.73 m^2, n (%)	9 (0.2)	17 (0.4)
eGFR <15 mL/min/1.73 m^2, n (%)	2 (<0.1)	0
UACR, mg/g, median (IQR)[‡]	12.4 (6.7-40.9)	12.1 (6.6-43.9)
Normoalbuminuria, n (%)	4012 (69.9)	2995 (69.8)
Microalbuminuria, n (%)	1322 (23.0)	944 (22.0)
Macroalbuminuria, n (%)	406 (7.1)	354 (8.2)

RAAS, renin-angiotensin-aldosterone system; IQR, interquartile range; SD, standard deviation.
*Data are mean (SD) unless otherwise specified.
†eGFR measurements are based on 5794 participants in the CANA group and 4346 in the PBO group.
‡UACR measurements are based on 5740 participants in the CANA group and 4293 in the PBO group.

Perkovic et al. ASN poster, 2017

Effects on inflammatory markers in humans



Dekkers et al. ASN 2017

Figure 4. Effects of CANA on renal outcomes.

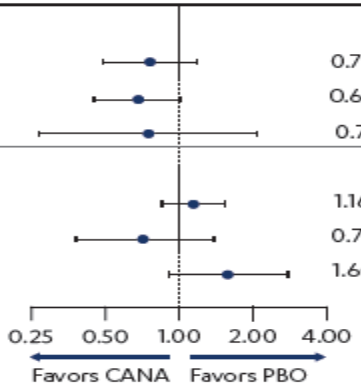
	Number of patients	CANA patients per 1000 patient-years	PBO patients per 1000 patient-years	Hazard ratio (95% CI)
New-onset microalbuminuria	1935	96.7	127.3	0.80 (0.73-0.87)
New-onset macroalbuminuria	636	15.1	27.6	0.58 (0.50-0.68)
dSCr, ESKD, or renal death	73	1.5	2.8	0.53 (0.33-0.84)
dSCr, ESKD, renal death, or new-onset macroalbuminuria	698	15.1	27.4	0.58 (0.50-0.67)
dSCr, ESKD, or renal or CV death	518	13.2	15.8	0.82 (0.68-0.97)
40% reduction in eGFR, ESKD, or renal death	249	5.5	9.0	0.60 (0.47-0.77)
40% reduction in eGFR, ESKD, renal death, or new-onset macroalbuminuria	847	18.6	33.3	0.57 (0.50-0.66)
40% reduction in eGFR, ESKD, or renal or CV death	679	16.9	21.6	0.77 (0.66-0.89)
40% eGFR reduction	239	5.3	8.7	0.60 (0.47-0.78)
dSCr	60	1.2	2.4	0.50 (0.30-0.84)
ESKD or renal death	21	0.4	0.8	0.56 (0.23-1.32)

Perkovic et al. ASN poster, 2017

Summary of renal safety.

Figure 5. Summary of renal safety.

	Number of patients	CANA patients per 1000 patient-years	PBO patients per 1000 patient-years	Hazard ratio (95% CI)
Serious AEs (CANVAS Program)				
Serious renal-related AEs	83	2.5	3.3	0.76 (0.49-1.19)
Serious acute kidney injury AEs	58	1.6	2.5	0.68 (0.45-1.02)
Serious hyperkalemia AEs	15	0.4	0.6	0.75 (0.27-2.11)
Serious and non-serious AEs (CANVAS alone)*				
Renal-related AEs	214	20.3	17.8	1.16 (0.86-1.56)
Acute kidney injury AEs	38	3.0	4.2	0.72 (0.38-1.39)
Hyperkalemia AEs	69	7.0	4.5	1.60 (0.92-2.81)



*For these AEs, the annualized incidence rates are reported based on the CANVAS study alone through January 7, 2014 since only serious AEs or AEs leading to discontinuation were collected after this time. In the CANVAS-R study, only serious AEs or AEs leading to discontinuation were collected for these events. Due to the differences in collection methodology, an integrated analysis of these AEs is not possible.

Perkovic et al. ASN poster, 2017

AWARD-7:
Baseline Characteristics

	DU 1.5 mg (N=192)	DU 0.75 mg (N=190)	Glargine (N=194)
Sex, women, n (%)	88 (45.8)	86 (45.3)	101 (52.1)
Age, years	64.7 ± 8.8	64.7 ± 8.6	64.3 ± 8.4
Duration of diabetes, years	17.6 ± 8.7	18.0 ± 8.8	18.7 ± 8.7
HbA1c, %	8.6 ± 0.9	8.6 ± 1.1	8.6 ± 1.0
HbA1c >8.5%, n (%)	96 (50.0)	91 (47.9)	81 (41.8)
Weight, kg	88.1 ± 16.1	90.9 ± 18.3	88.2 ±18.5
BMI, kg/m^2	32.1 ± 4.8	33.0 ± 5.5	32.4 ± 5.3
Daily total insulin dose, U/day	58.8 ± 30.1	56.6 ± 31.2	59.3 ± 34.2
Daily total insulin dose, U/kg/day	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3

Tuttle et al. ASN 2017

AWARD-7:
Baseline Characteristics Related to Kidney Disease

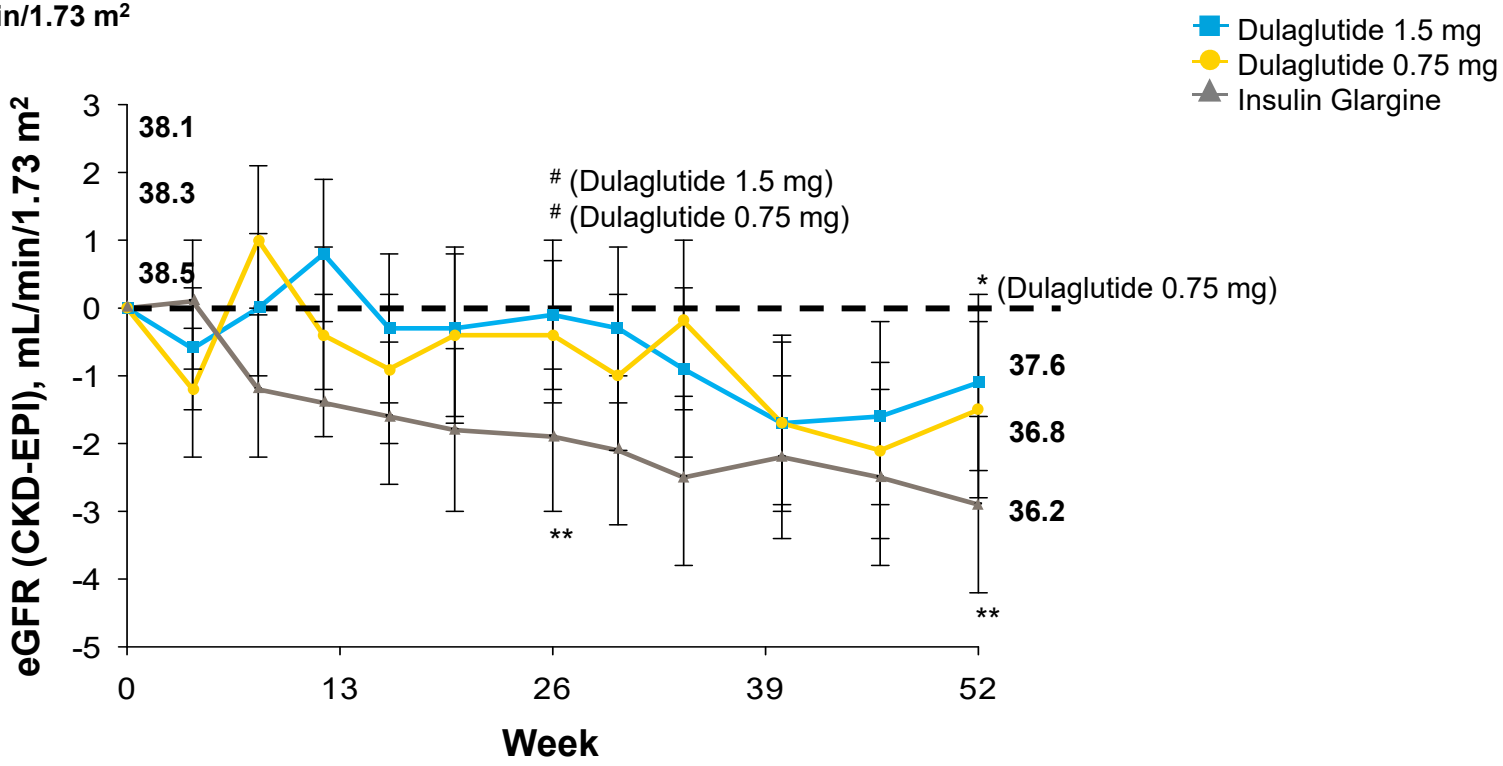
	DU 1.5 mg (N=192)	DU 0.75 mg (N=190)	Glargine (N=194)
Duration of CKD stage ≥3, years	4.2 ± 5.6	4.0 ± 4.9	3.5 ± 4.0
eGFR, mL/min/1.73m²	38.0 ± 13.3	38.4 ± 12.3	38.5 ± 13.0
60 ≤ Baseline eGFR <90	9 (4.7)	7 (3.7)	14 (7.2)
45 ≤ Baseline eGFR <60	53 (27.6)	53 (27.9)	51 (26.3)
30 ≤ Baseline eGFR <45	73 (38.0)	75 (39.5)	67 (34.5)
15 ≤ Baseline eGFR <30	55 (28.6)	55 (28.9)	61 (31.4)
Baseline eGFR <15	2 (1.0)	0 (0.0)	1 (0.5)
UACR, mg/g, mean (median)	779 (214)	842 (234)	920 (196)
Normal albuminuria (UACR <30)	34 (17.7)	44 (23.3)	48 (24.7)
Microalbuminuria (30 ≤ UACR ≤ 300)	74 (38.5)	61 (32.3)	56 (28.9)
Macroalbuminuria (UACR >300)	84 (43.8)	84 (44.4)	90 (46.4)

Data are mean ± SD or n (%) unless otherwise noted; safety population; CKD=chronic kidney disease; UACR=urinary albumin to creatinine ratio; baseline eGFR and UACR were determined by mean of values from 2 visits.

Tuttle et al. ASN 2017

AWARD-7:
Lesser eGFR Decline Over Time with Dulaglutide

Baseline eGFR = 38.3 mL/min/1.73 m²



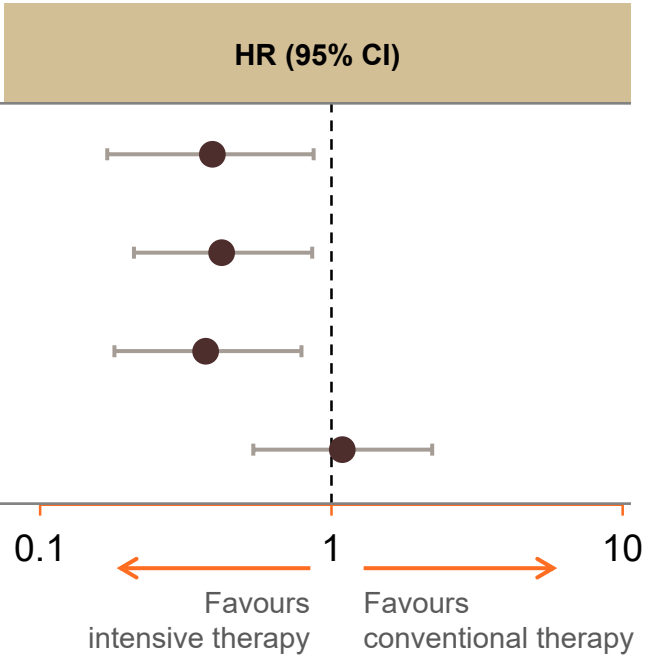
Data presented as LSM (95% CI); Safety population, MMRM analysis. *p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. insulin glargine. Note, only showing significance for weeks 26 and 52

Tuttle et al. ASN 2017

Intensified multifactorial intervention reduces risk of microvascular events

Steno-2 study: randomised controlled trial of intensified vs conventional multifactorial treatment in patients with T2D and microalbuminuria

Variable	Relative risk (95% CI)	*p*-value
Nephropathy	0.39 (0.17, 0.87)	0.003
Retinopathy	0.42 (0.21, 0.86)	0.02
Autonomic neuropathy	0.37 (0.18, 0.79)	0.002
Peripheral neuropathy	1.09 (0.54, 2.22)	0.66



n=80 for each group; average follow-up 7.8 years

HR, hazard ratio

Gaede P *et al*. *N Engl J Med* 2003;348:383