SGLT2 inhibitors in Diabetic Nephropathy

Shahrzad Ossareh- M.D.

Professor in Medicine- Nephrologist

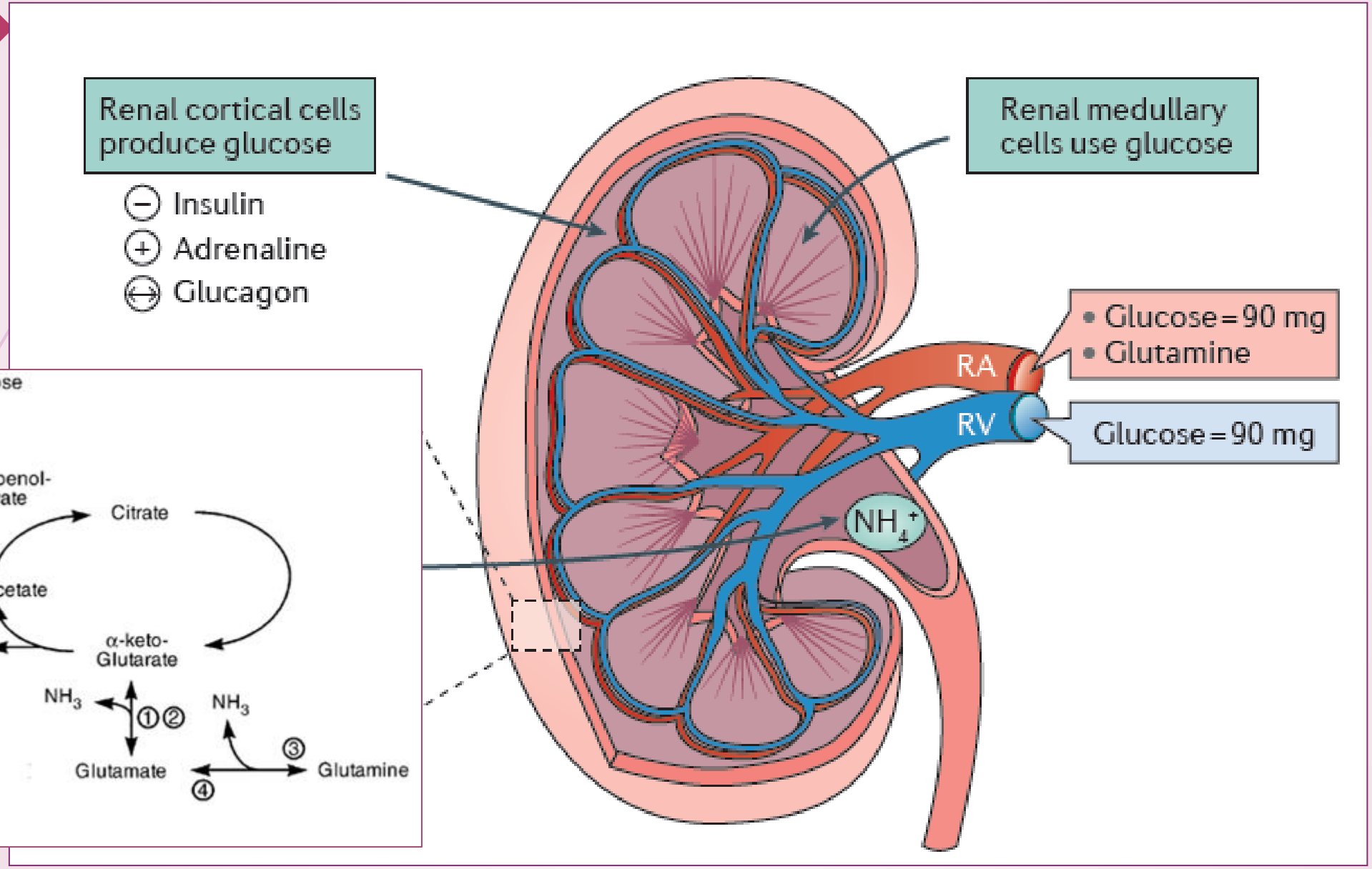
IUMS- HKC

- Glucose produced by the kidney is primarily derived from renal cortical cells, whereas glucose utilization within the kidney is primarily by renal medullary cells.

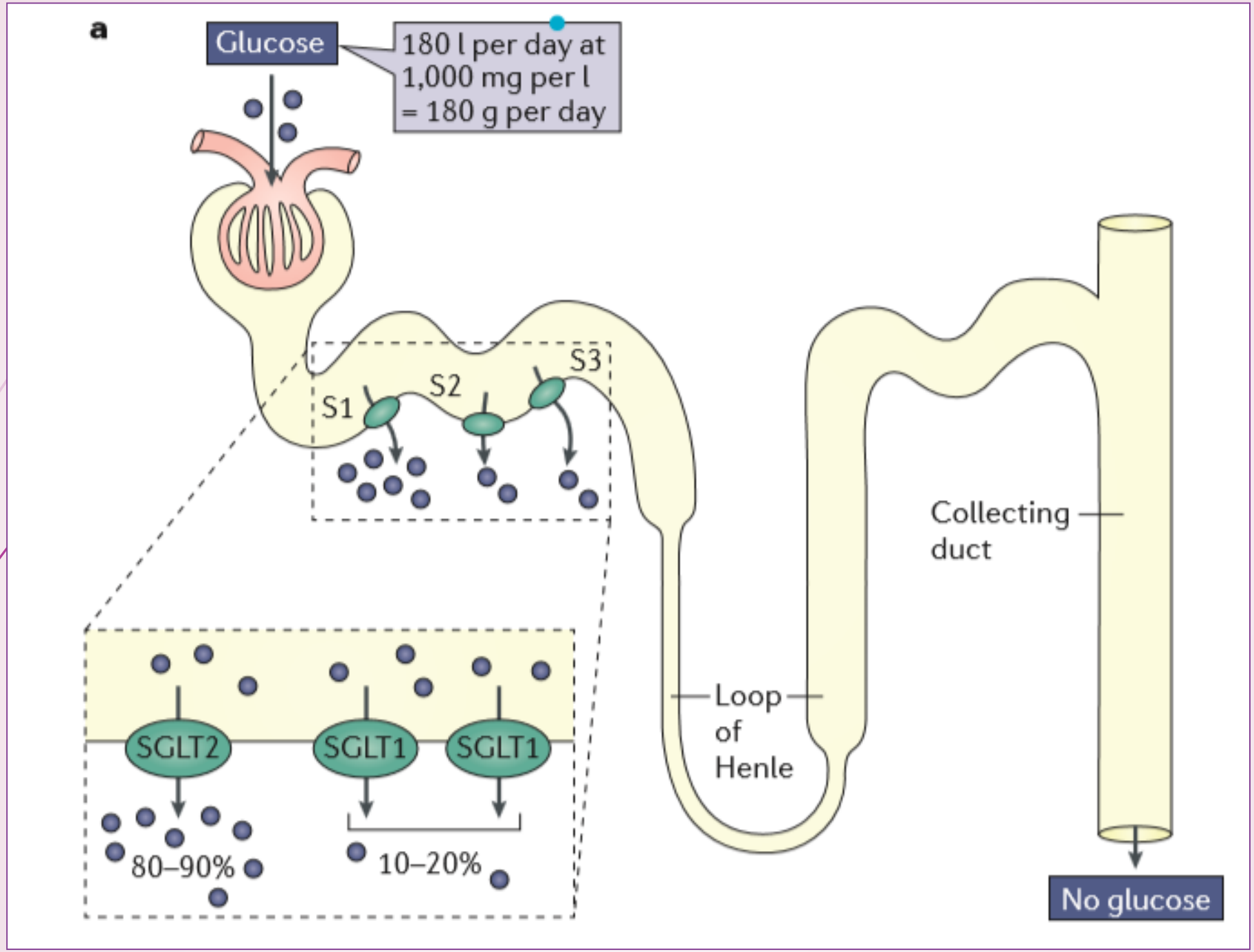
- SGLT2 inhibitors are unique as they target the transport of glucose in the kidney, preventing glucose reabsorption and inducing glucosuria to lower plasma glucose levels.

DeFronzo RA, . Nat Rev Nephrol.2017 13(1):11

Role of the kidneys in glucose hemostasis

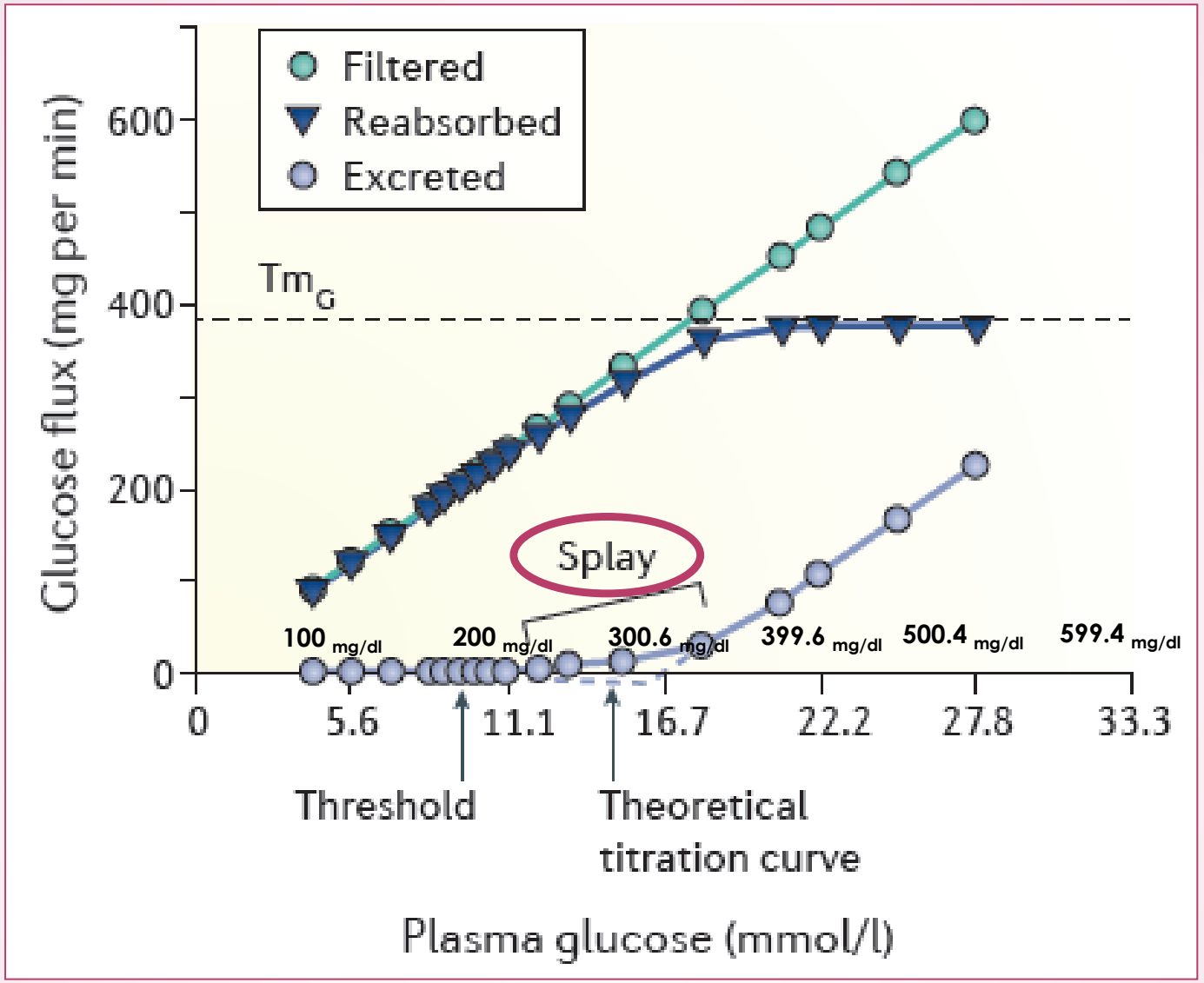


DeFronzo RA, . Nat Rev Nephrol.2017 13(1):11



DeFronzo RA, . Nat Rev Nephrol.2017 13(1):11

Splay



DeFronzo RA, . Nat Rev Nephrol.2017

- Splay is the difference between urine threshold (the amount of a substance required in the kidneys before it appears in the urine) and saturation or T_M; Or splay is the concentration difference between a substance's maximum renal reabsorption vs. appearance in the urine. https://en.wikipedia.org/wiki/Splay_(physiology)#cite_note-EssentialsMedical-1

TABLE IV

Effect of insulin on T_{mG} and the ratio of glomerular filtration rate (GFR) to T_{mG}

Group	Patient	T_{mG}, *mgm. per min.*			GFR/T_{mG}		
		Control	Insulin	Δ	Control	Insulin	Δ
Diabetic	1	415	352	−63	0.29	0.37	+0.08
	2	514	496	−18	0.28	0.32	+0.04
	3	402	361	−41	0.26	0.29	+0.03
	4	377	314	−63	0.30	0.36	+0.06
	5	619	539	−80	0.26	0.28	+0.02
	6	450	427	−23	0.31	0.29	−0.02
	7	438	394	−44	0.27	0.32	+0.05
	8	271	197	−74	0.34	0.41	+0.07
	9	419	401	−18	0.28	0.30	+0.02
	10	461	420	−41	0.26	0.27	+0.01
	11	495	445	−50	0.28	0.31	+0.03
	12	226	204	−22	0.29	0.22	−0.27
	Average	424	379	−45	0.27	0.31	+0.04
Non-Diabetic	13	330	216	−114	0.44	0.57	+0.13
	14	372	396	+24	0.34	0.32	−0.02
	15	470	416	−54	0.32	0.35	+0.03
	16	402	404	+2	0.36	0.36	−0.00

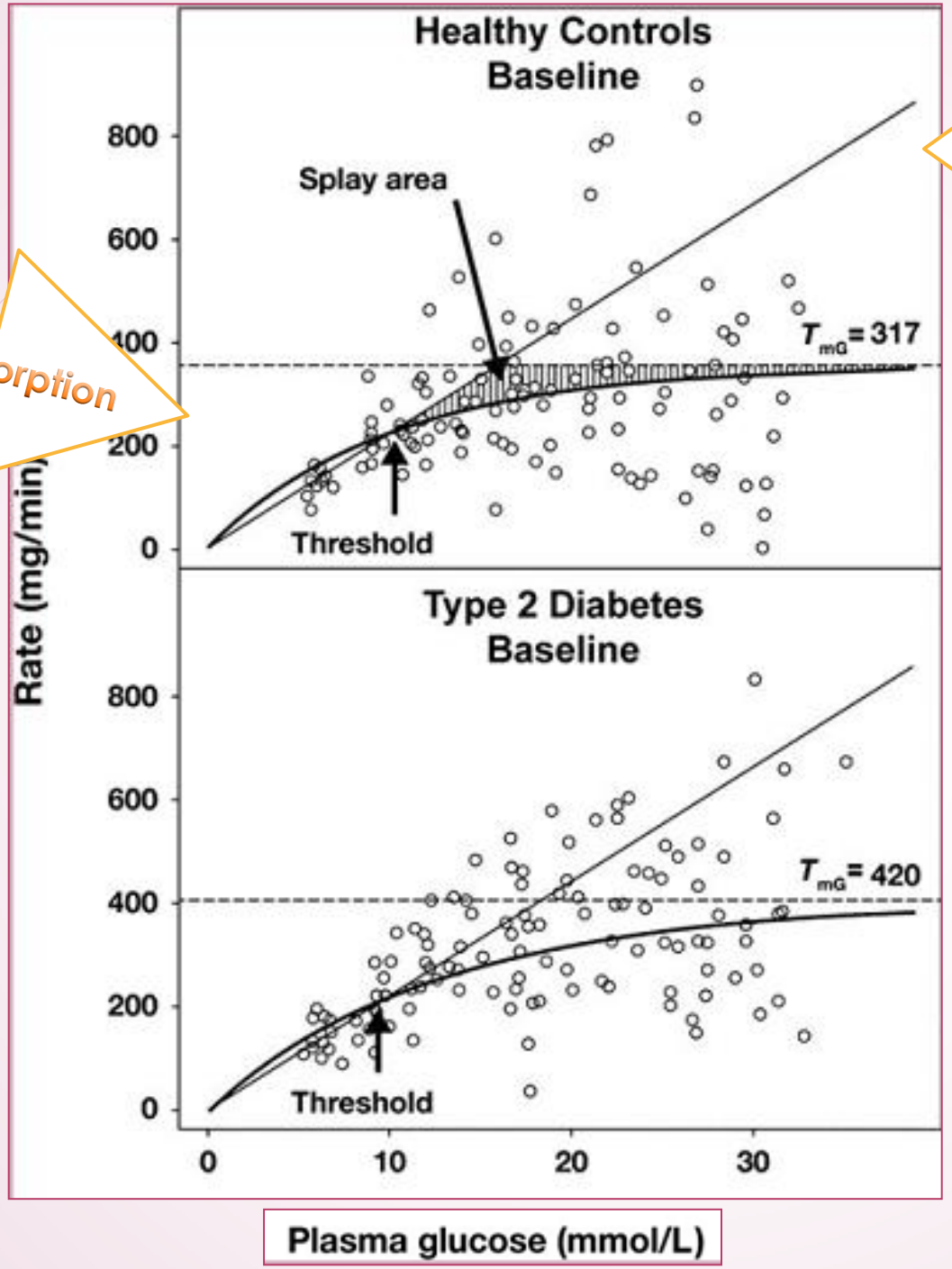
J Clin Invest. 1951;30(2):125-129

- Generally SGLT2 inhibitors can induce glucosuria by one of 3 mechanisms:

1. Lowering TmG;
2. Reducing the threshold for glucosuria;
3. Increasing splay.

DeFronzo RA, . Nat Rev Nephrol. 2017

Predicted rate of reabsorption

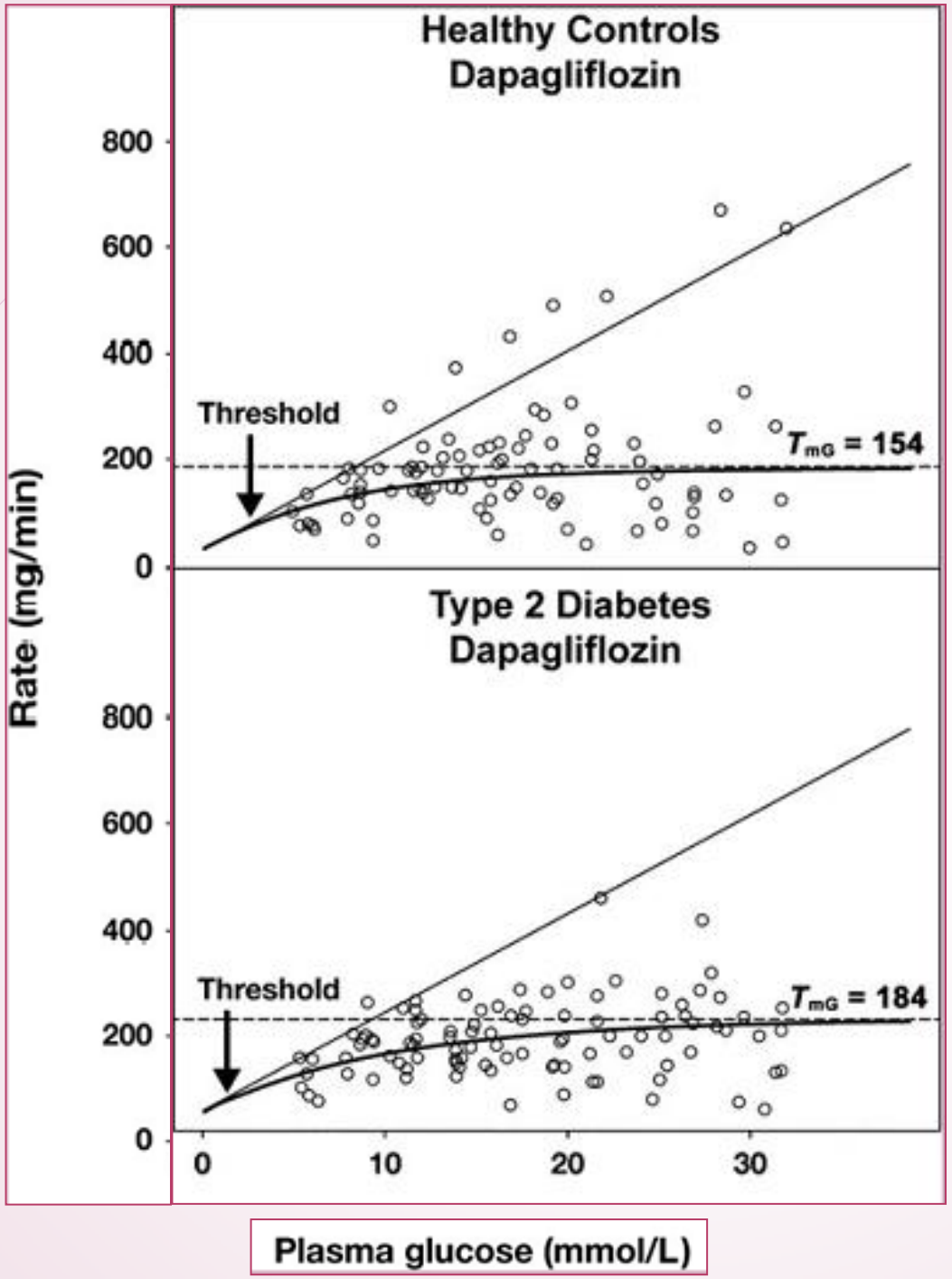


Glucose filtration

At baseline, type 2 diabetic subjects had elevated TmG, splay, and threshold compared with controls.

DeFronzo RA. Diabetes care. 2013

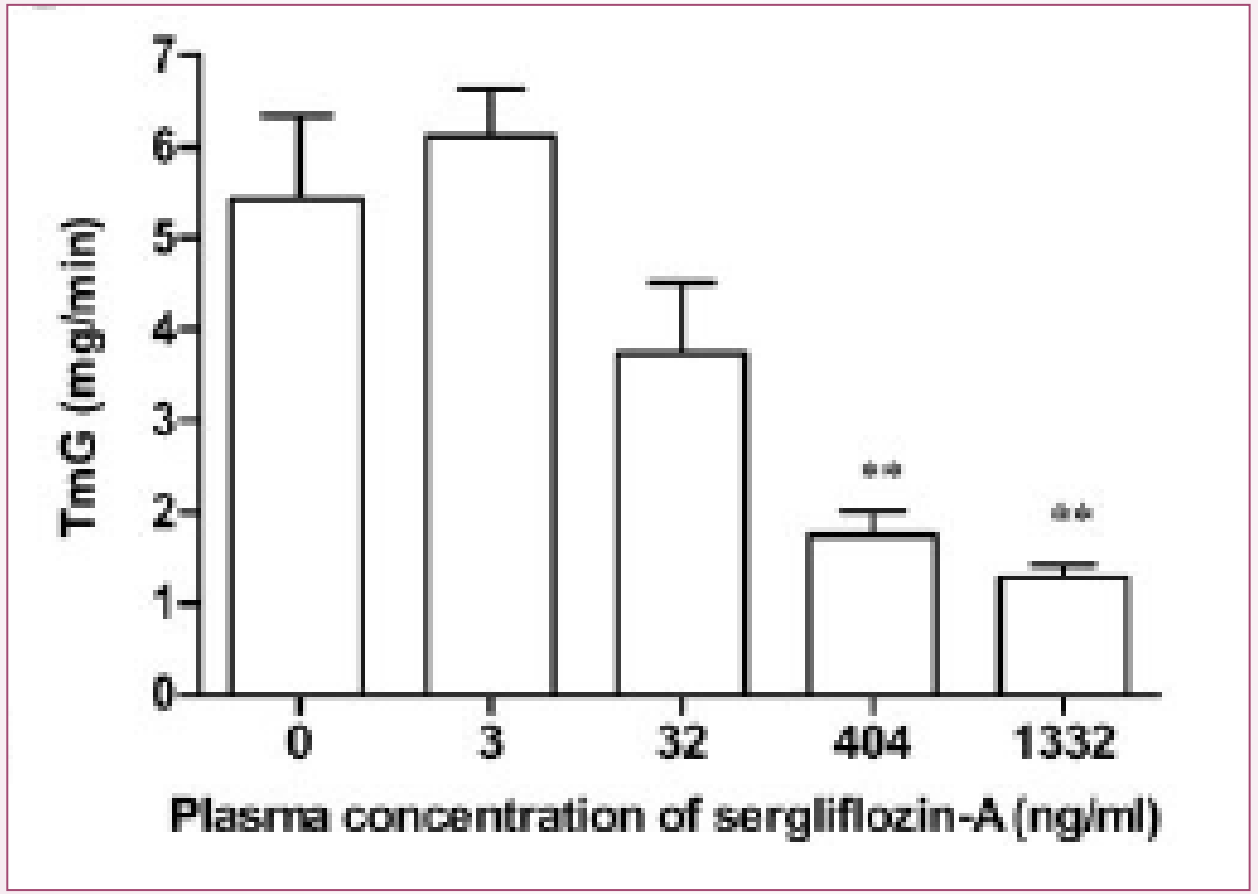
Empagliflozin has the same effect (reduction of TmG, splay and threshold)



Dapagliflozin <u>reduced</u> the **TmG** and **splay** in both groups. However, the most significant effect of dapagliflozin was a reduction of the **renal threshold** for glucose excretion in type 2 diabetic and control subjects

DeFronzo RA. Diabetes care. 2013

Sergliflozin reduced TmG without altering threshold or splay in diabetic rodents.



Katsuno K. J Pharmacol Exp Ther. 2007

- Dapagliflozin
- Canagliflozin
- Empagliflozin

have been approved by the FDA & European Medicines Agency

- Tofogliflozin
- Luseogliflozin
- Ipragliflozin

have been approved in Japan.

- Remogliflozin
- Ertugliflozin
- Sotagliflozin

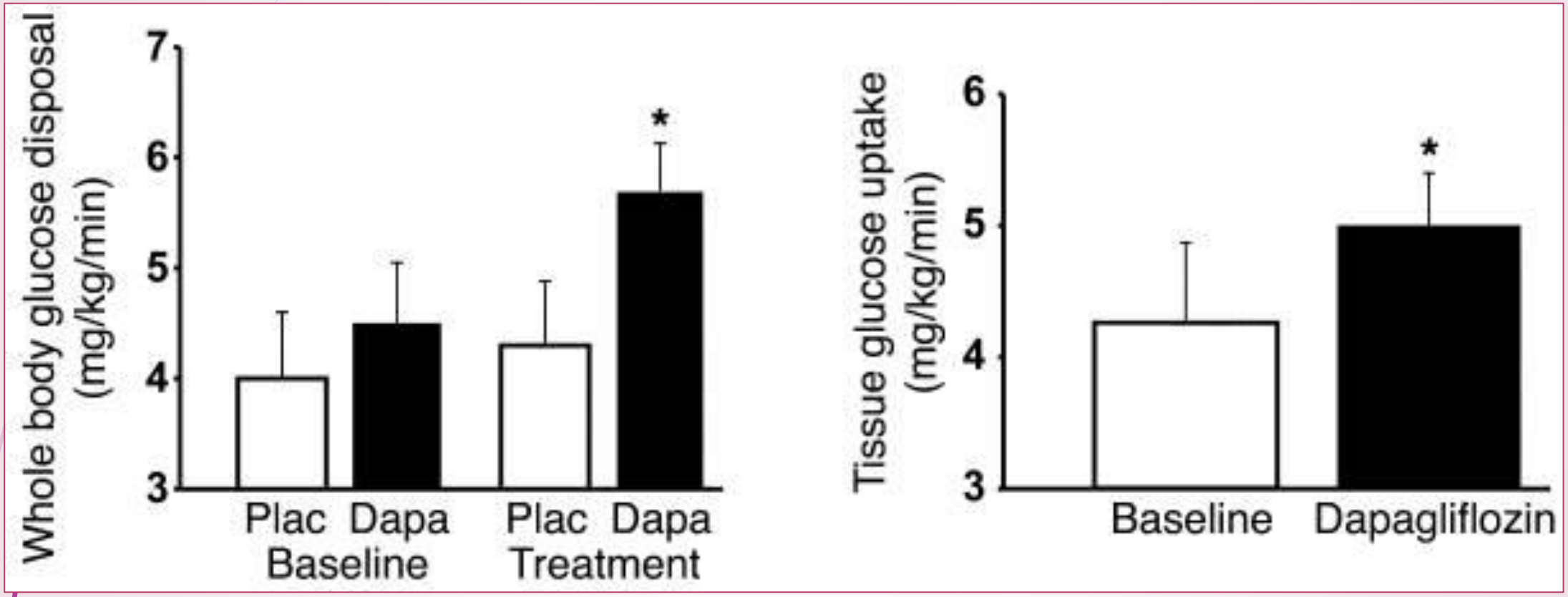
Are under development

Mechanism of improved glycemic control By SGLT2 Inhibitors

- By increasing the removal of plasma glucose by augmenting glucose excretion.
- By ameliorating glucotoxicity, which leads to improved insulin sensitivity in peripheral tissues (including muscles) and enhanced β cell function.

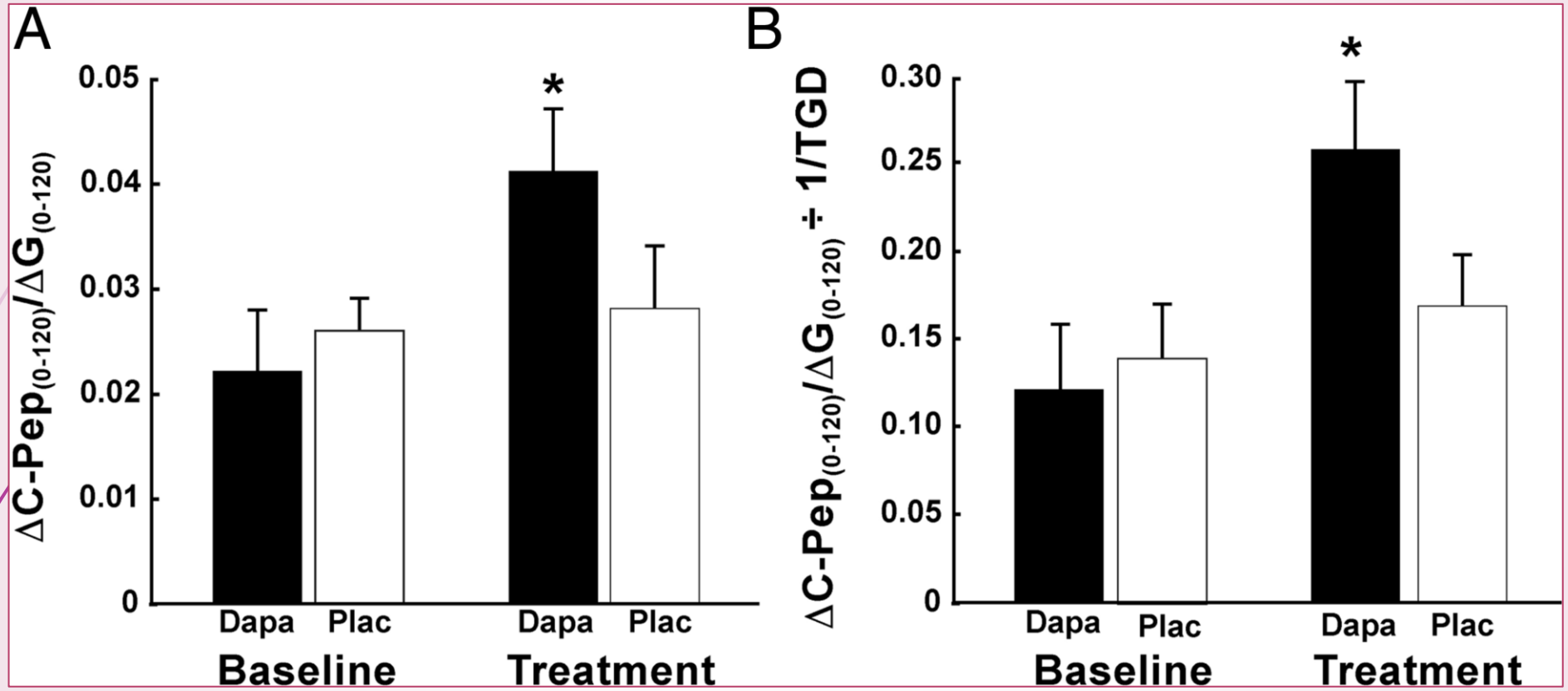
DeFronzo RA, . Nat Rev Nephrol. 2017

Effect of dapagliflozin on tissue sensitivity to insulin



Merovci, AJ. Clin. Invest. 124, 509–514 (2014)

Effect of dapagliflozin on β-cell function



A. Insulin secretion

B. β-cell function

Merovci, AJ. Clin. Endocrinol. Metab. 100, 1927–1932 (2015)

Effect on extracellular fluid volume & blood pressure

- SGLT2 inhibition is associated with mild negative salt and water balance and a durable decrease in extracellular fluid and plasma volumes.
- The natriuretic effect of SGLT2 inhibition dissipates after 2–3 days and sodium and fluid balance is re-established, albeit with a ~7% reduction in plasma volume.

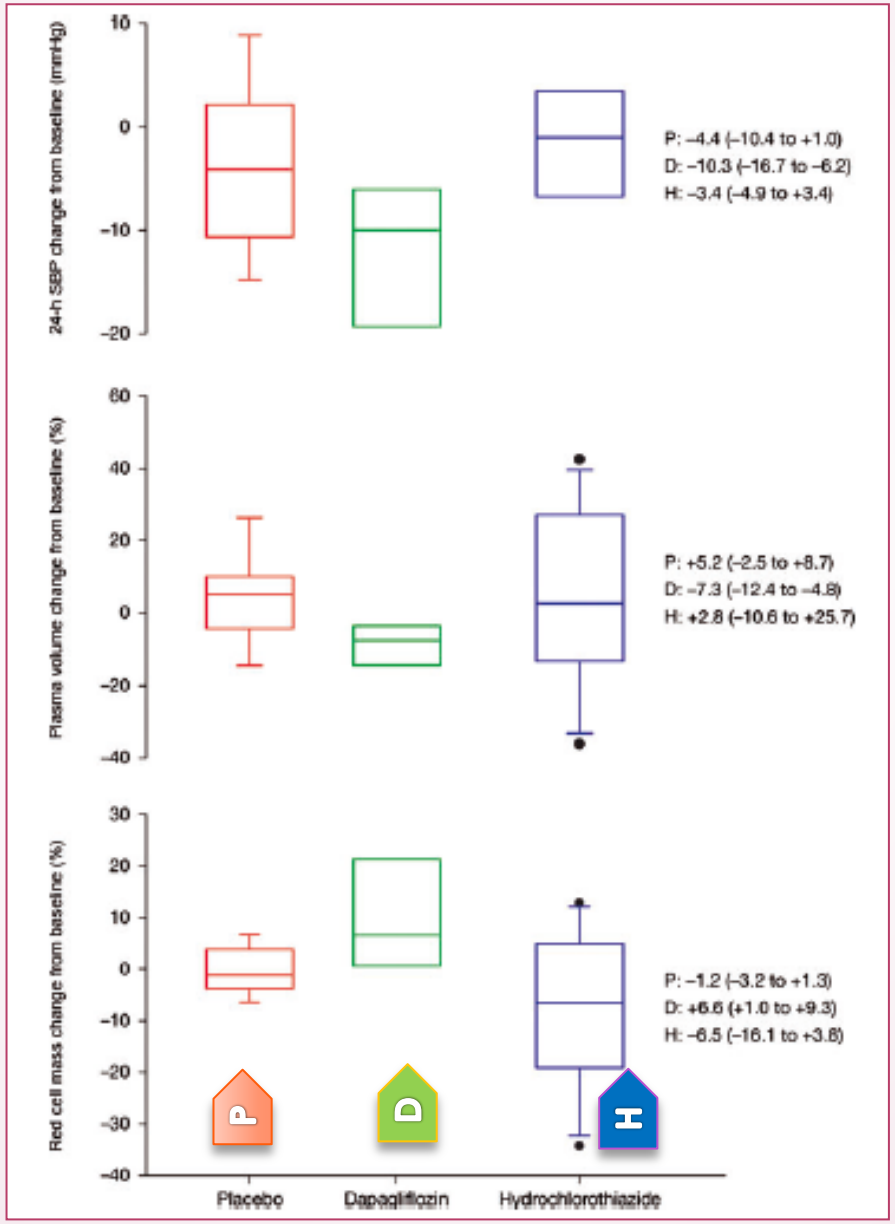
DeFronzo RA, . Nat Rev Nephrol. 2017

Median change in 24-h SBP, and median % change in plasma volume and red cell mass with Dapa vs. HCTZ

24-h SBP

plasma volume

red cell mass



5–6 mmHg decrease in SBP and 1–2 mmHg decrease in DBP during 1-2 wks

Transient increases in reticulocyte count & serum erythropoietin concentrations.

Lambers Hearspink HJ. Diabetes Obes Metab. 2013

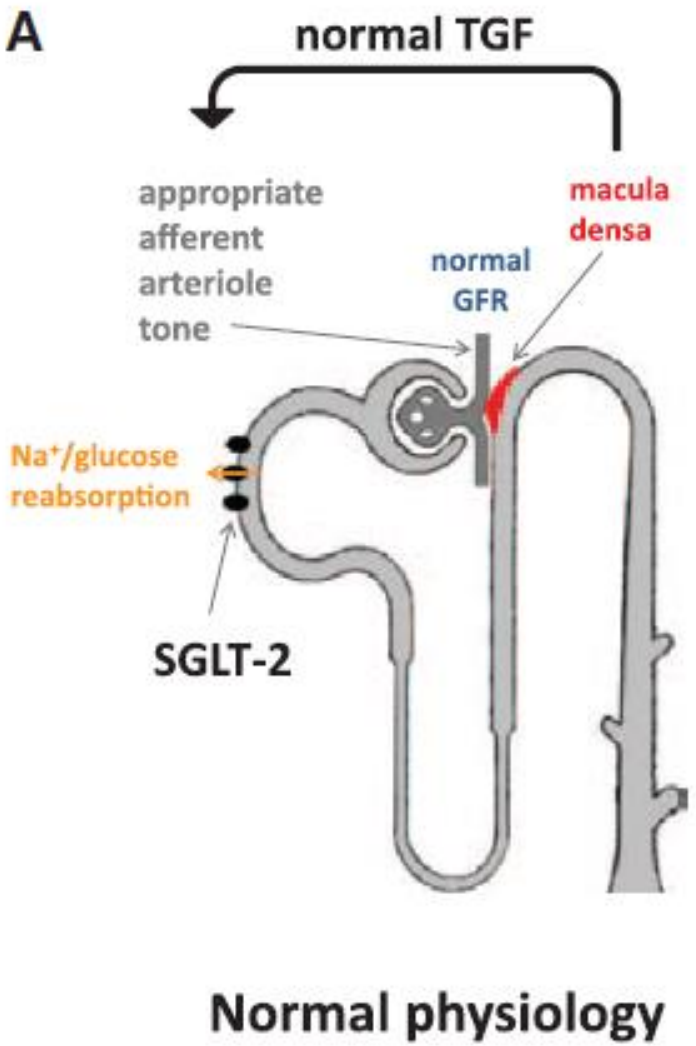
Effect on extracellular fluid volume & blood pressure

- Over a period of 6–12 months other factors are also likely contribute to the sustained reduction in blood pressure:

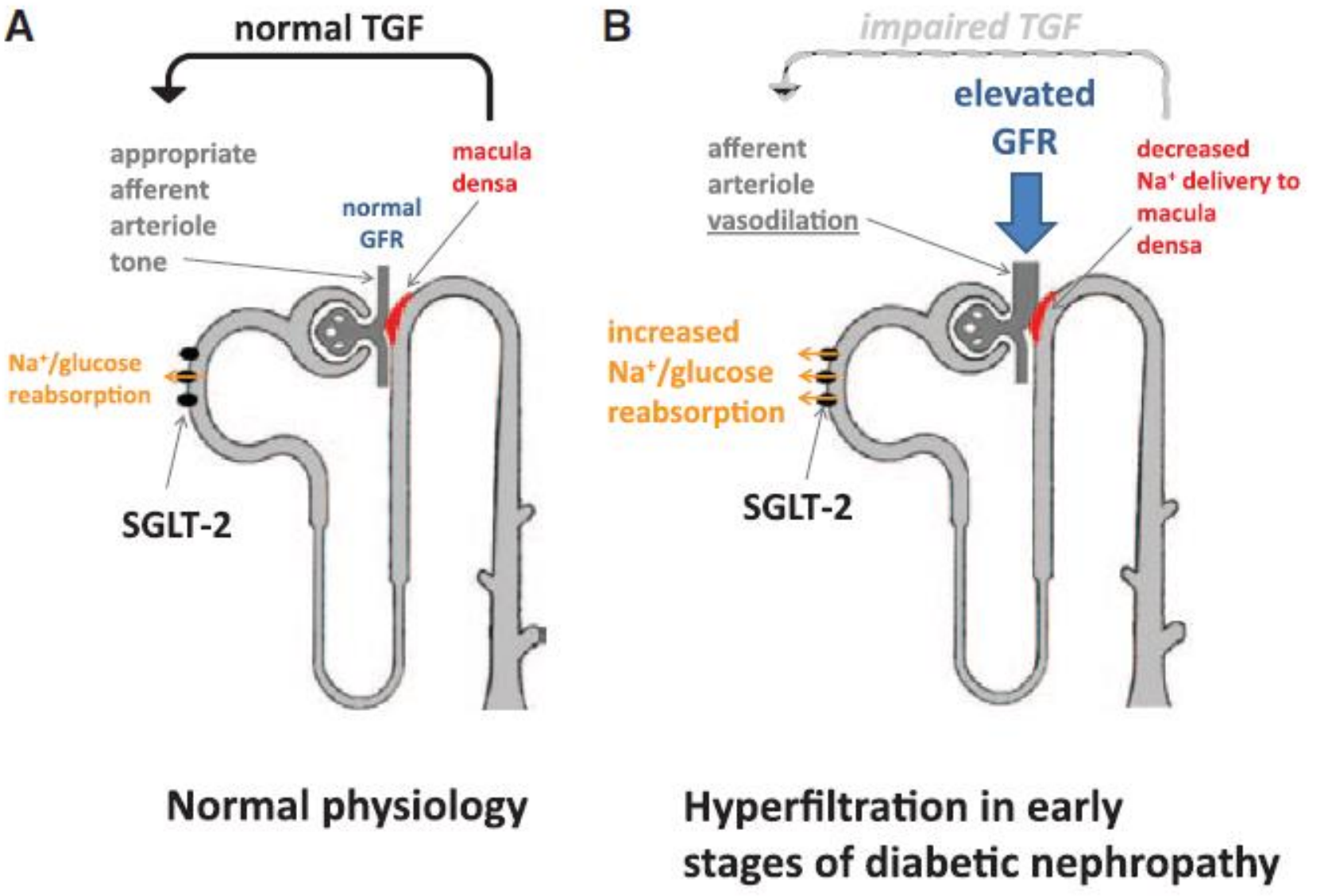
1. Weight loss
2. Alterations in the renin– angiotensin–aldosterone system (Via increase in Ang 1-7 through action of ACE-2) [Nat Rev Cardiol. 2014]
3. Reduced plasma uric acid levels
4. Decreased proteinuria

DeFronzo RA, . Nat Rev Nephrol. 2017

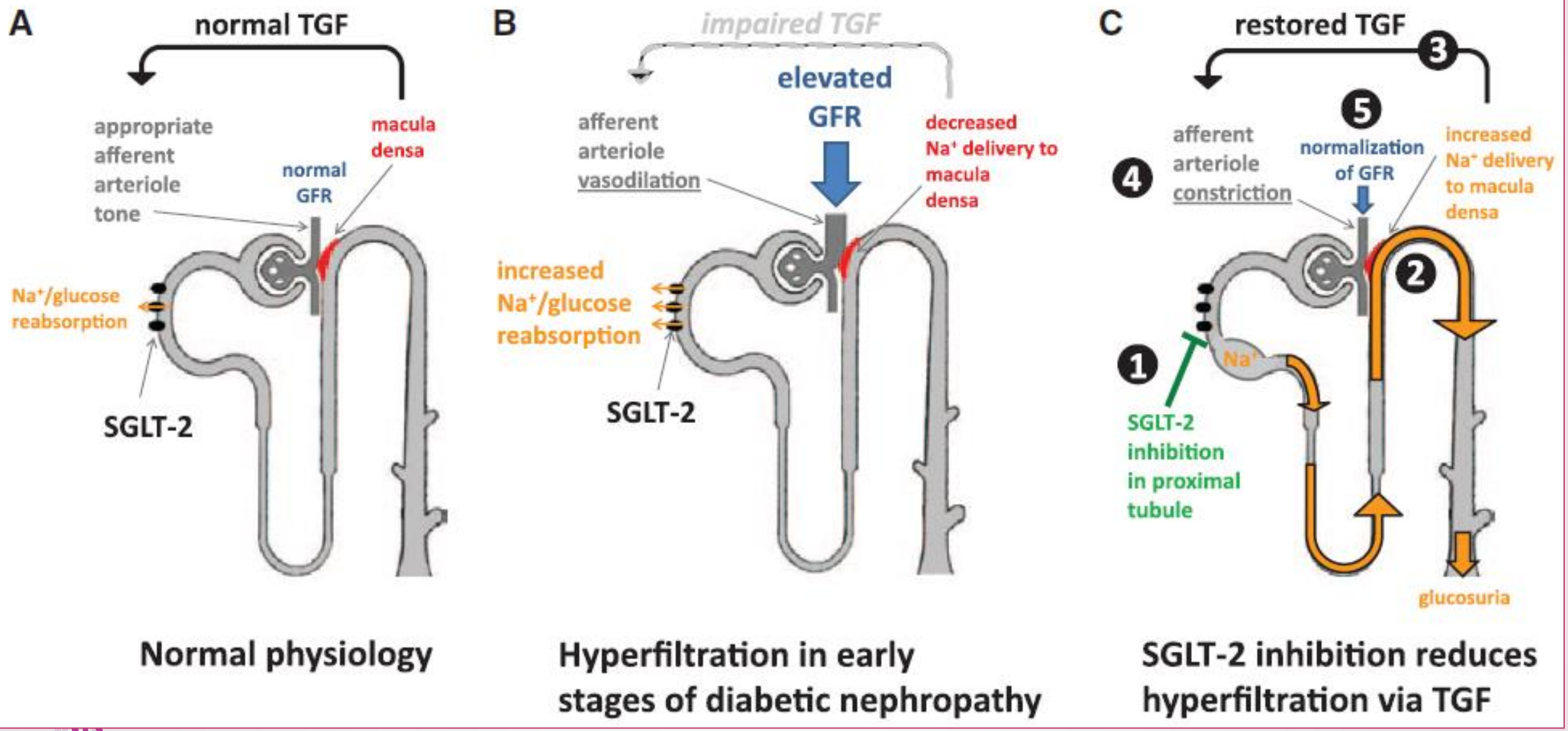
- A growing body of evidence suggests that SGLT2 inhibition might afford renal protection and prevent the development of diabetic nephropathy.



Cherney DZI. Circulation. 2014;129:587-597

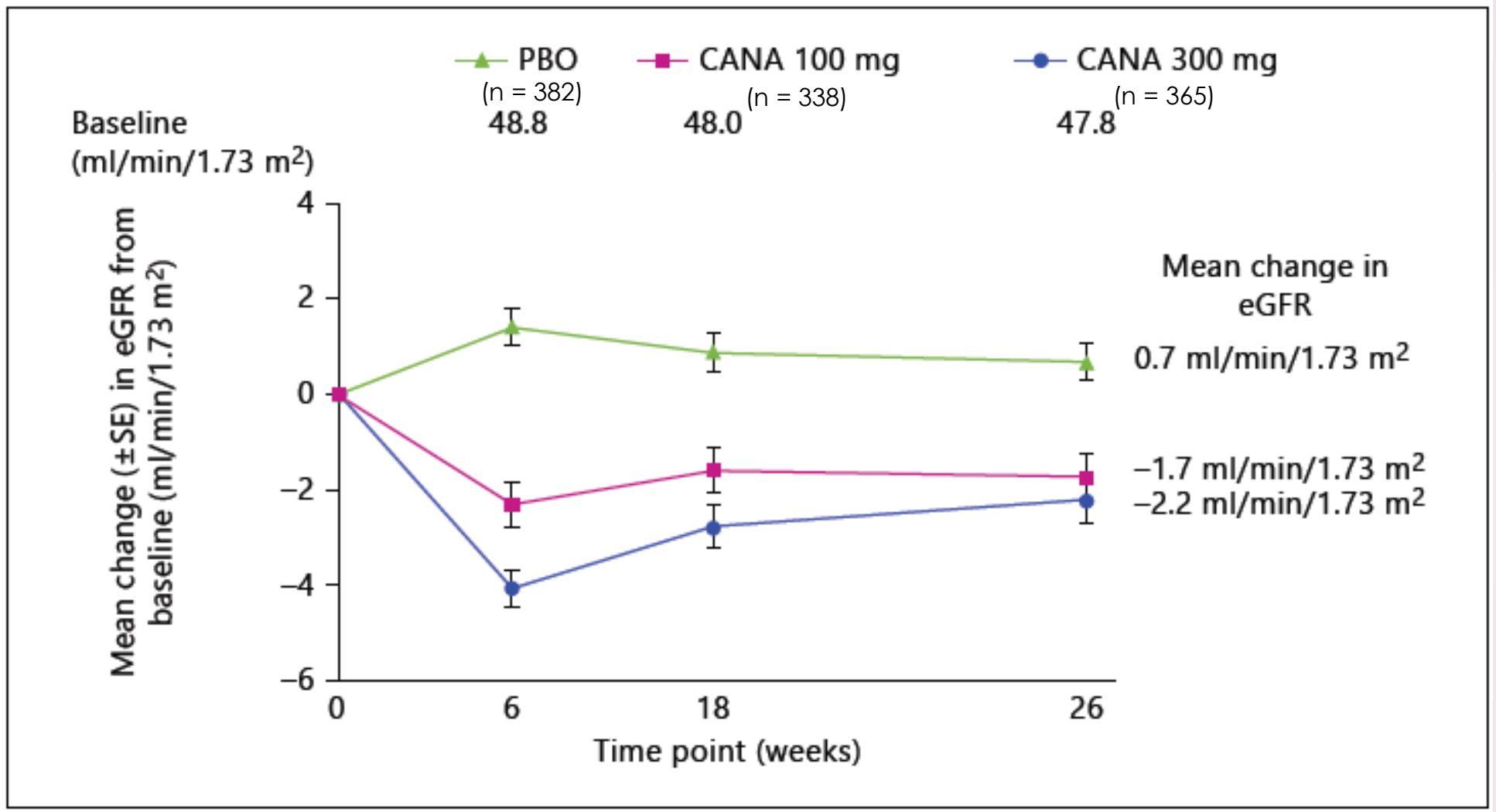


Cherney DZI. Circulation. 2014;129:587-597



Cherney DZI. Circulation. 2014;129:587-597

Assessment of Kidney Function



Changes in eGFR among **all stage 3 CKD participants**. PBO = Placebo; CANA = canagliflozin; SE = standard error. Note: Data are reported regardless of rescue medication and up to within 2 days after the last dose of study drug.

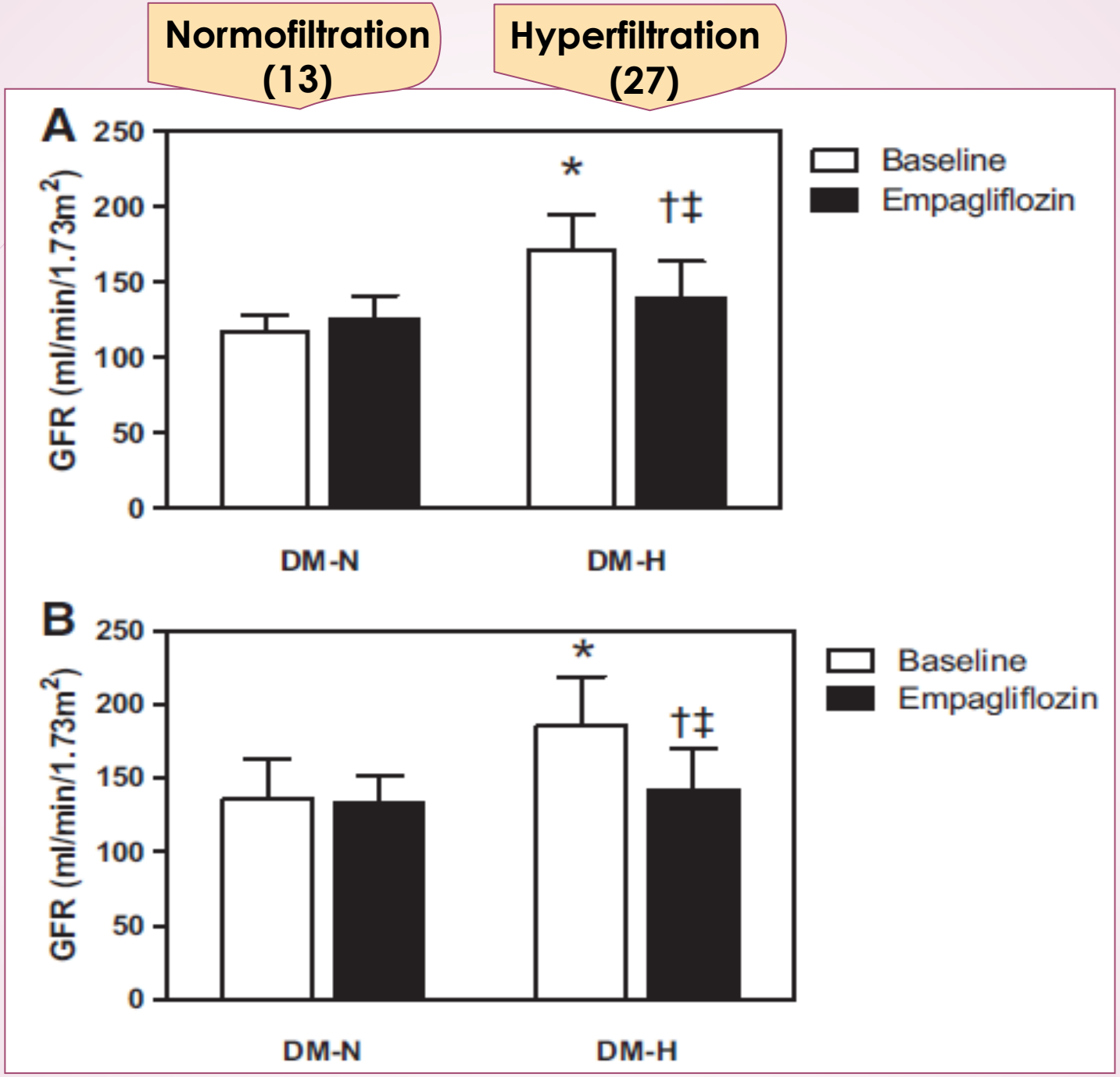
Yamout H. Am J Nephrol 2014;40:64–74

- The modest reduction in plasma volume following initiation of SGLT inhibitor therapy is associated with a small decline in GFR (~4–5 ml/min per 1.73m^2), which tends to return to baseline within 6–12 months of initiating therapy.

Yamout H. Am J Nephrol 2014;40:64–74

Euglycemia

Hyperglycemia



8 wks of Empa
2 wks of F/U afterwards

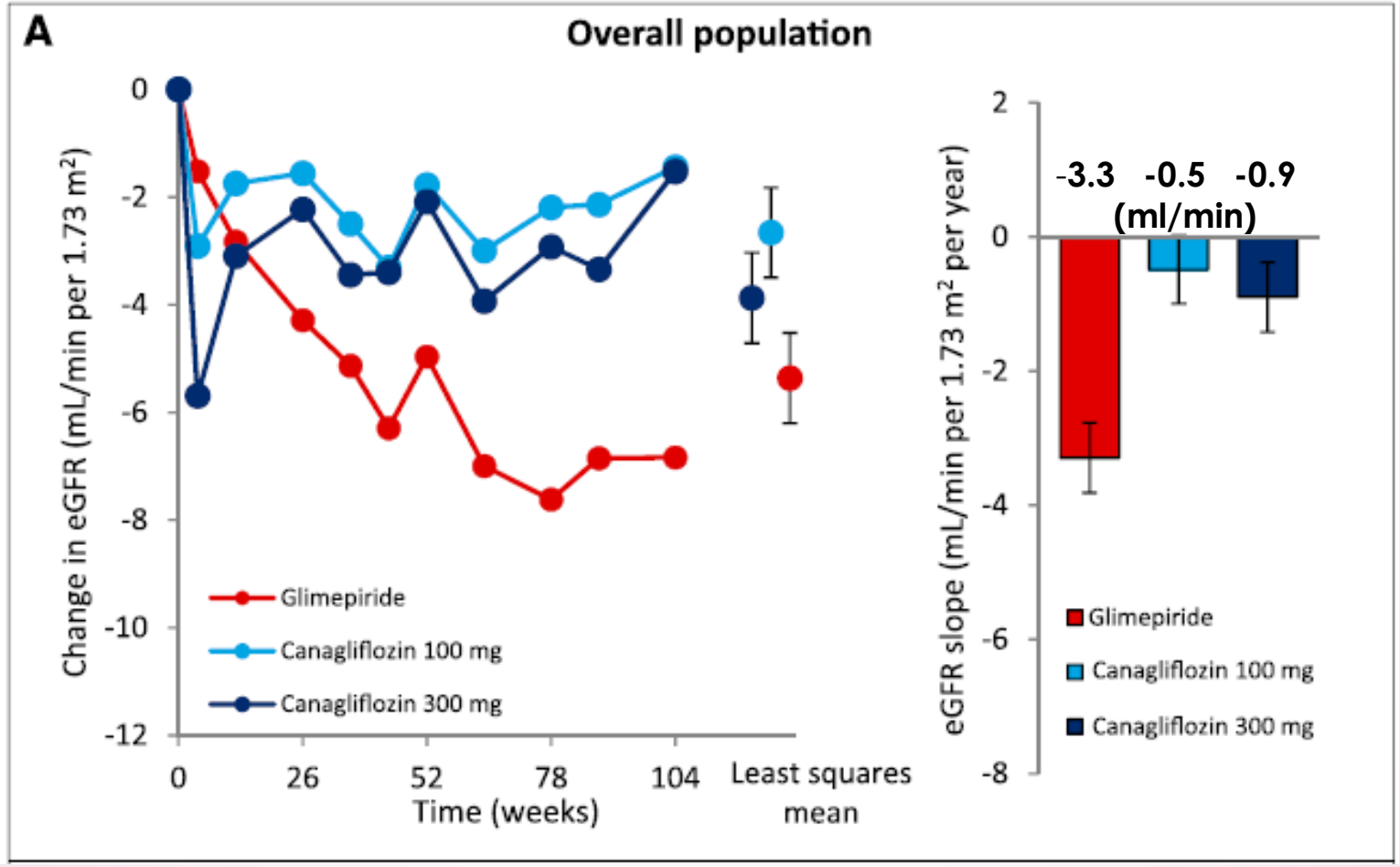
Cherney DZI. Circulation. 2014;129:587-597

	Normofiltration Group (13)			Hyperfiltration Group (27)		
	Baseline	EMPA	*P* Value	Baseline	EMPA	*P* Value
Renal hemodynamic function						
Effective renal plasma flow	706±157	688±101	0.74	1051±251	748±144	<0.01
Filtration fraction	0.195±0.024	0.196±0.019	0.95	0.185±0.046	0.192±0.032	0.40
Renal blood flow	1117±240	1140±154	0.79	1633±430	1193±227	<0.01
Renal vascular resistance	0.078±0.015	0.073±0.012	0.37	0.054±0.015	0.072±0.015	<0.01
Plasma biochemistry						
Plasma angiotensin II, pmol/L	2.6±2.4	4.2±4.0	0.17	2.3±2.5	3.6±3.0	0.03
Plasma aldosterone, pmol/L	27±4	47±32	0.04	29±8	50±43	0.03
Plasma renin activity, ng/mL/hr	0.317±0.281	0.368±0.389	0.36	0.328±0.273	0.356±0.241	0.61
Plasma nitric oxide, μmol/L	40±23	42±20	0.73	46±20	28±23	<0.01

- Decrease in body weight, HBA1C & daily Insulin intake, despite increase in carbohydrate intake
- Mild increase in HCT
- No change in urine Alb/Cr, serum Na, K, Ca, Mg, Cl, P, HCO_3, EPO, liver enzymes, LDH, CK, lipase, lipid profiles & uric acid.

Cherney DZI. Circulation. 2014;129:587-597

Canagliflozin slows the progression of eGFR decline in patients with type 2 diabetes compared with glimepiride

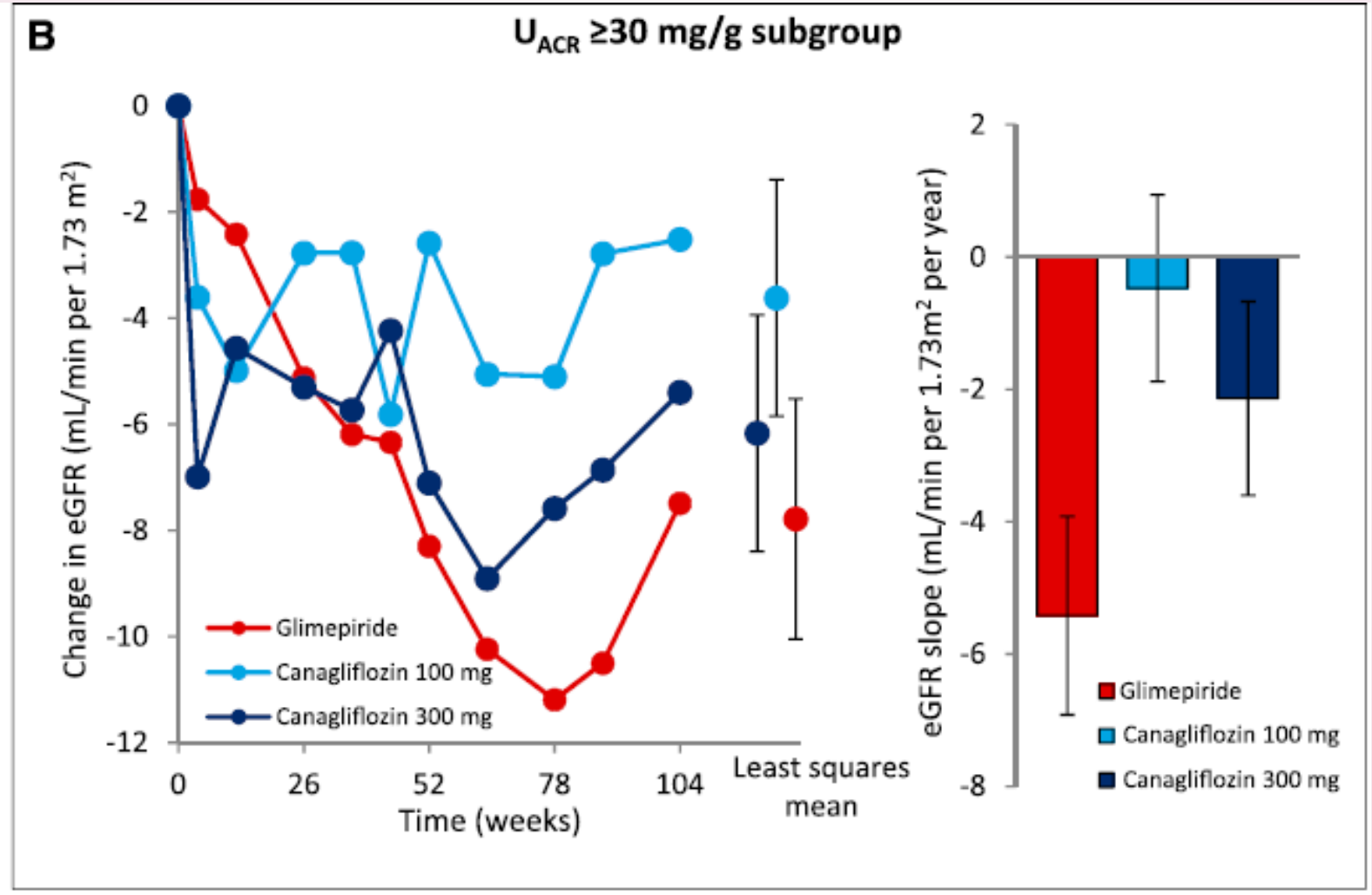


- Clinical trial in 1450 patients with T2DM receiving metformin & randomly assigned to either OD
- canagliflozin100 mg,
- canagliflozin 300 mg,
- glimepiride uptitrated to 6–8 mg.
- End points: annual change in eGFR & albuminuria in 2 years of F/U.

(A) Changes in eGFR in the canagliflozin and glimepiride treatment arms in the overall population, and the rate of eGFR decline per year.

Lambers Heerspink HJ. J Am Soc Nephrol, 2017

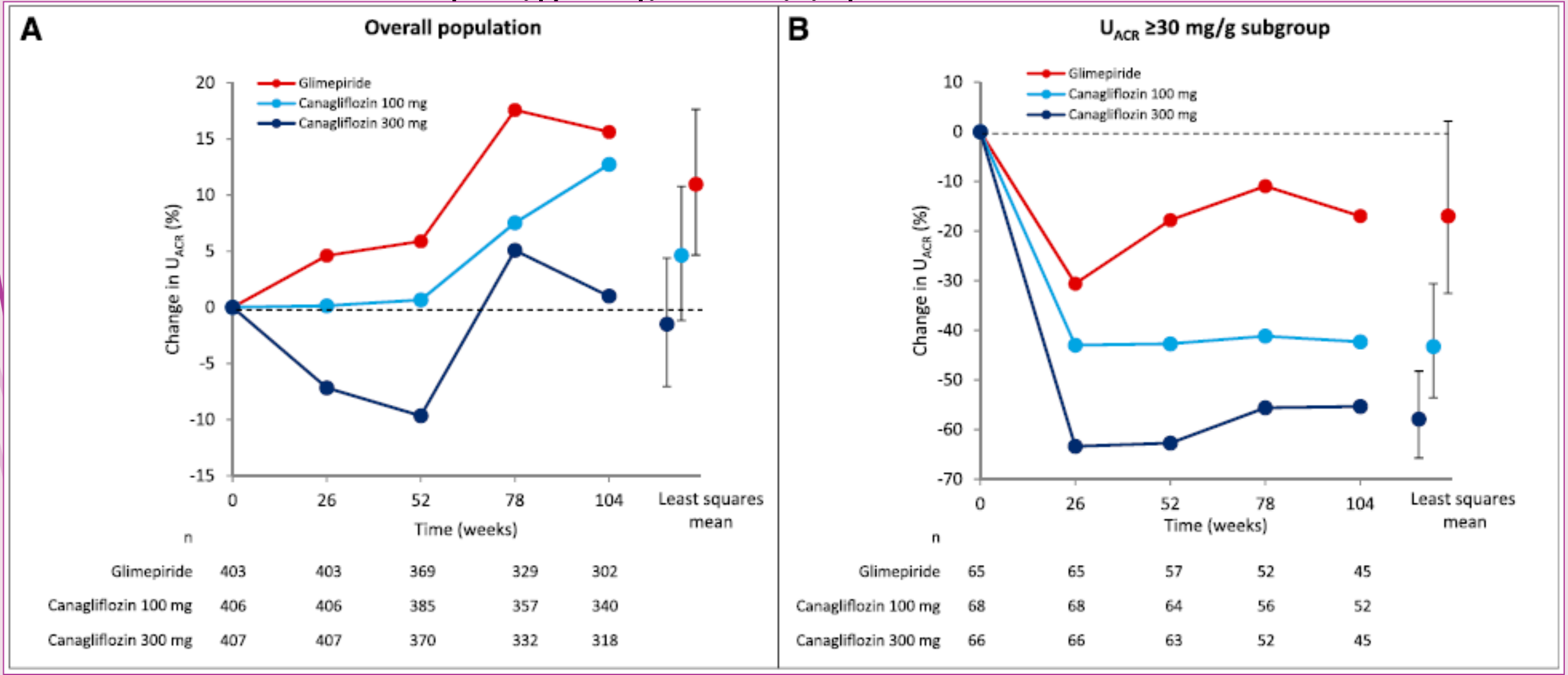
Canagliflozin slows the progression of eGFR decline in patients with type 2 diabetes compared with glimepiride



(B) Changes in eGFR in the canagliflozin and glimepiride treatment arms in patients with UACR≥30 mg/g, and the rate of eGFR decline per year in patients with UACR ≥ 30 mg/g.

Lambers Heerspink HJ. J Am Soc Nephrol, 2017

Canagliflozin slows the progression of eGFR decline in patients with type 2 diabetes



Lambers Heerspink HJ. J Am Soc Nephrol, 2017

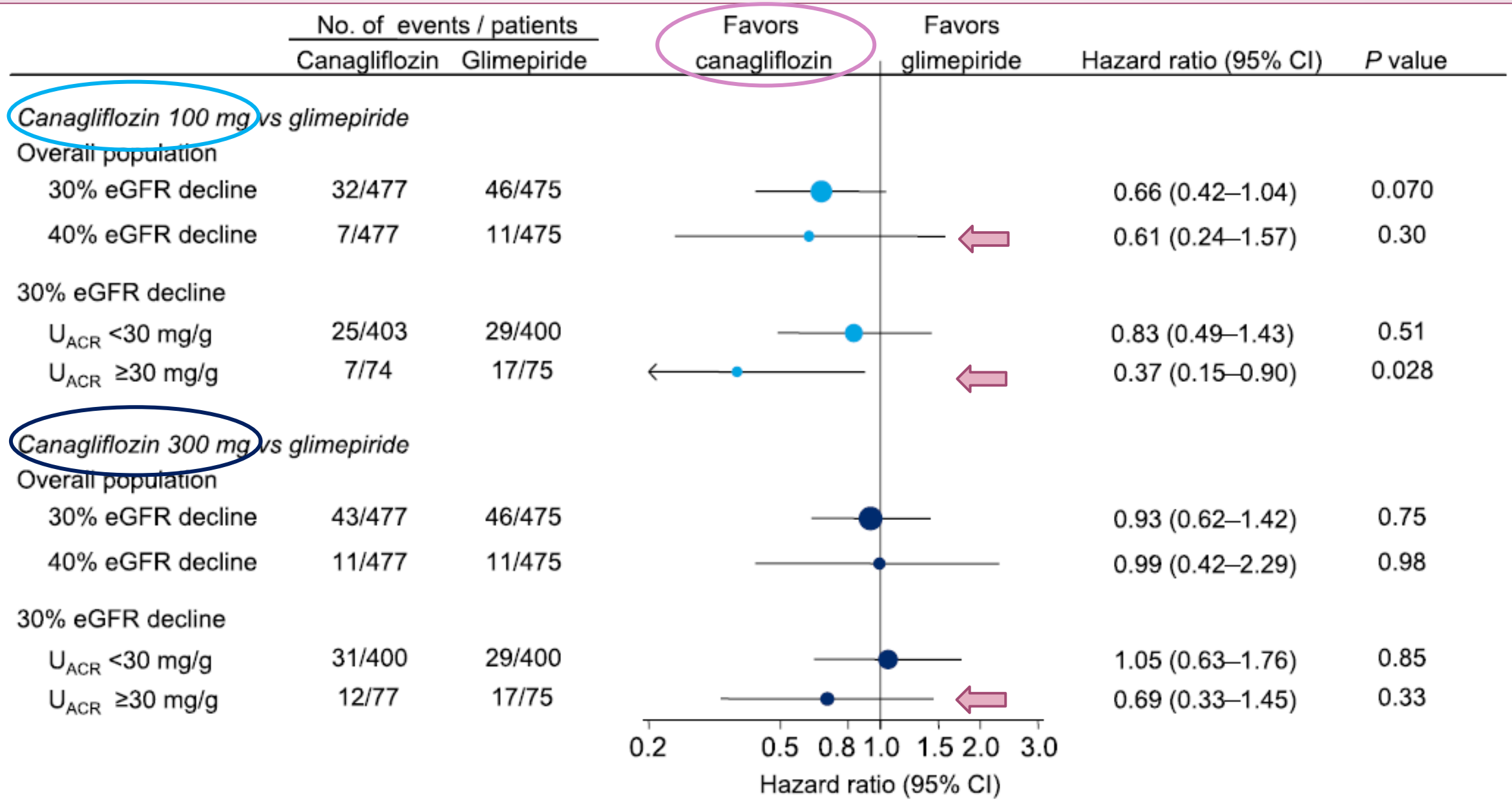


Figure 2. eGFR decline >30% or >40% was generally less frequent with canagliflozin compared with glimepiride.

Lambers Heerspink HJ. J Am Soc Nephrol, 2017

EMPA-REG outcome

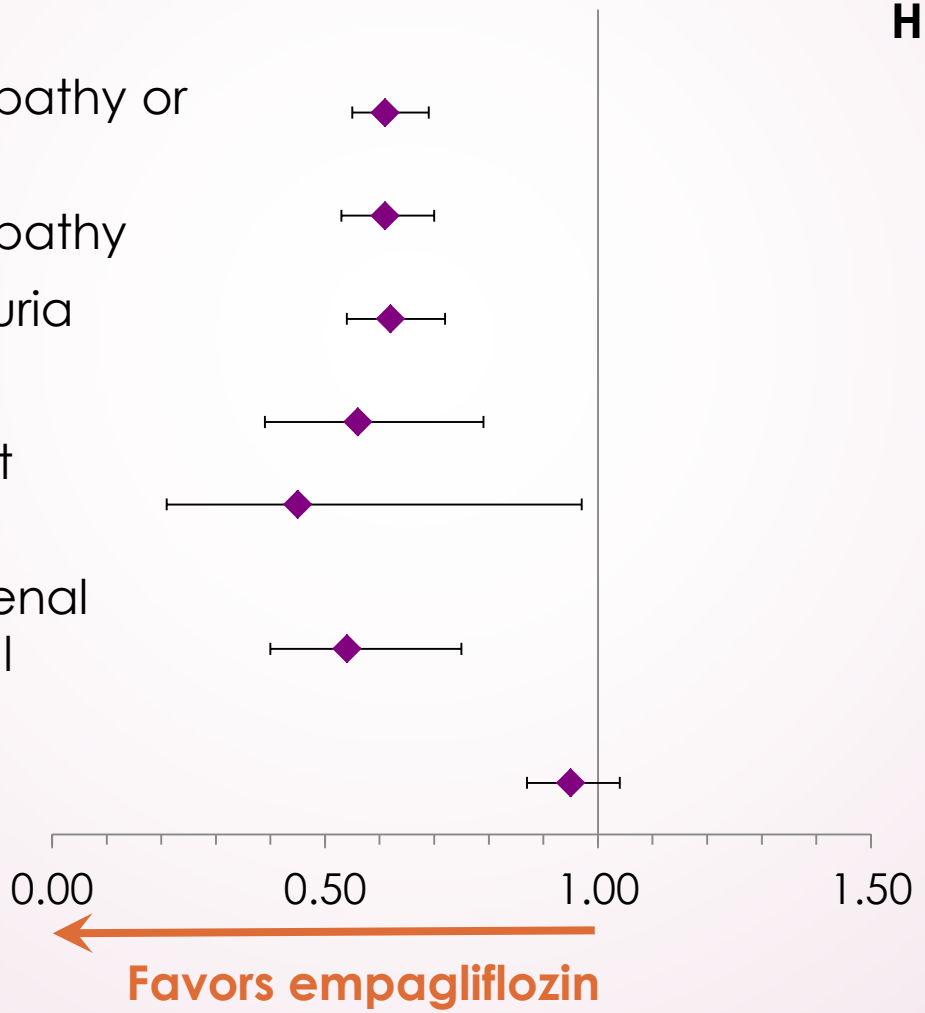
(Empagliflozin cardiovascular Outcome event trial in type 2 diabetes mellitus patients)

Wanner C, et al. N Engl J Med. 2016 Jun 14

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)

Empagliflozin: n=4687 **Placebo: n=2333**



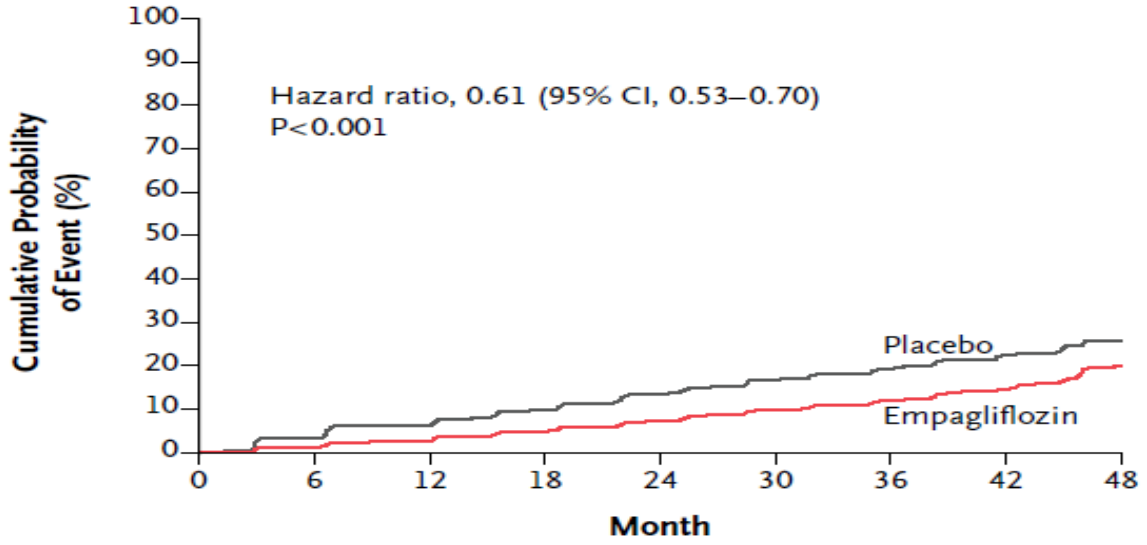
	Hazard ratio (95% CI)	*P* value
Incident or worsening nephropathy or CV death	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	0.61 (0.53-0.70)	<0.001
Progression to macroalbuminuria	0.62 (0.54-0.72)	<0.001
Doubling of SCr + eGFR ≤45	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	0.45 (0.21-0.97)	0.04
Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death	0.54 (0.40-0.75)	<0.001
Incident albuminuria*	0.95 (0.87-1.04)	0.25

Wanner C, et al. N Engl J Med. 2016 Jun 14

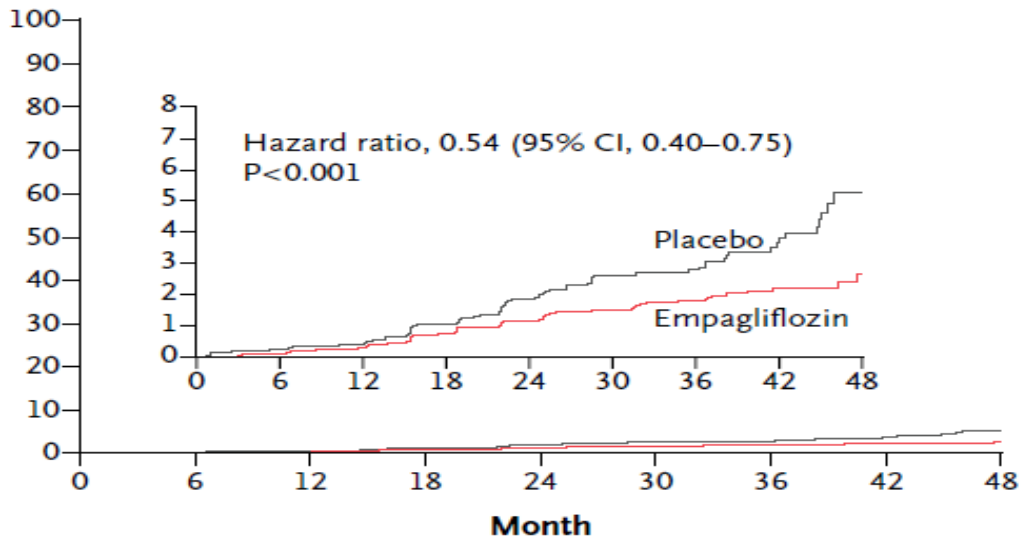
Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)

Incident or Worsening Nephropathy



Post-hoc Renal Composite Outcome*



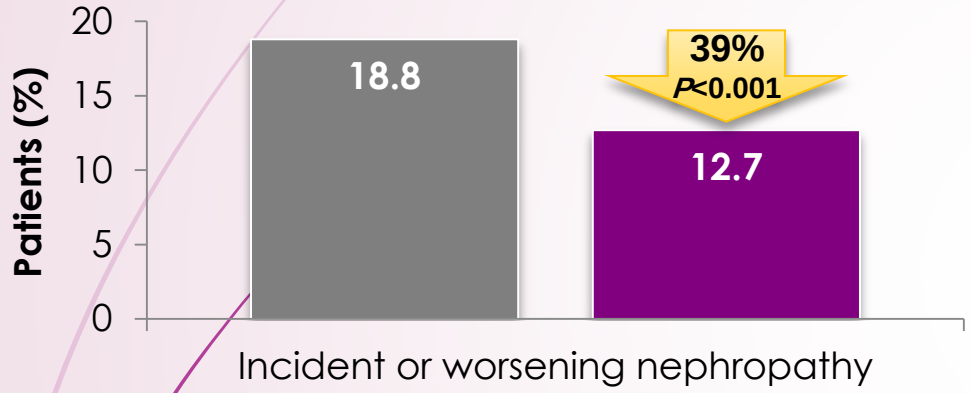
No. at Risk																	
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2061	1946	1836	1703	1433	1016	833	521	106	2323	2229	2146	2047	1771	1289	1079	680	144

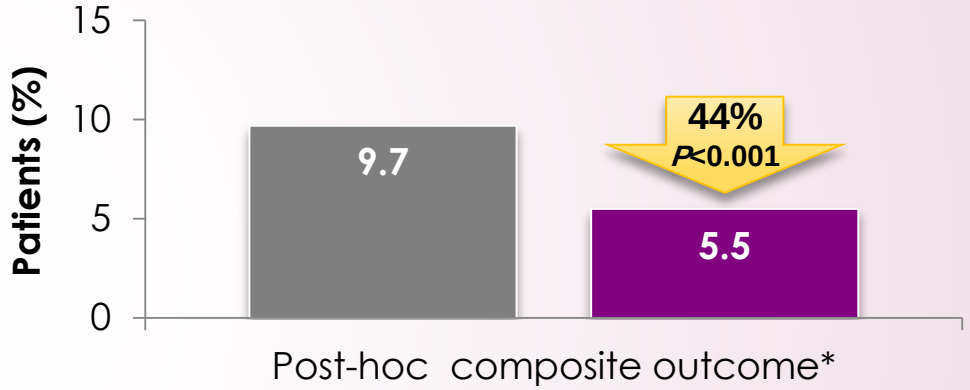
***Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease**

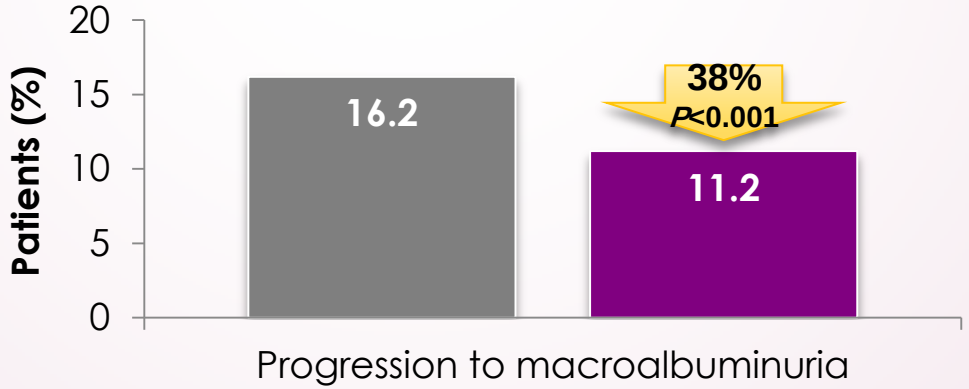
Wanner C, et al. N Engl J Med. 2016 Jun 14

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)







***Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease**

Wanner C, et al. N Engl J Med. 2016 Jun 14

Patients with established chronic kidney disease (CKD) at baseline:

Empagliflozin reduced the risk of:

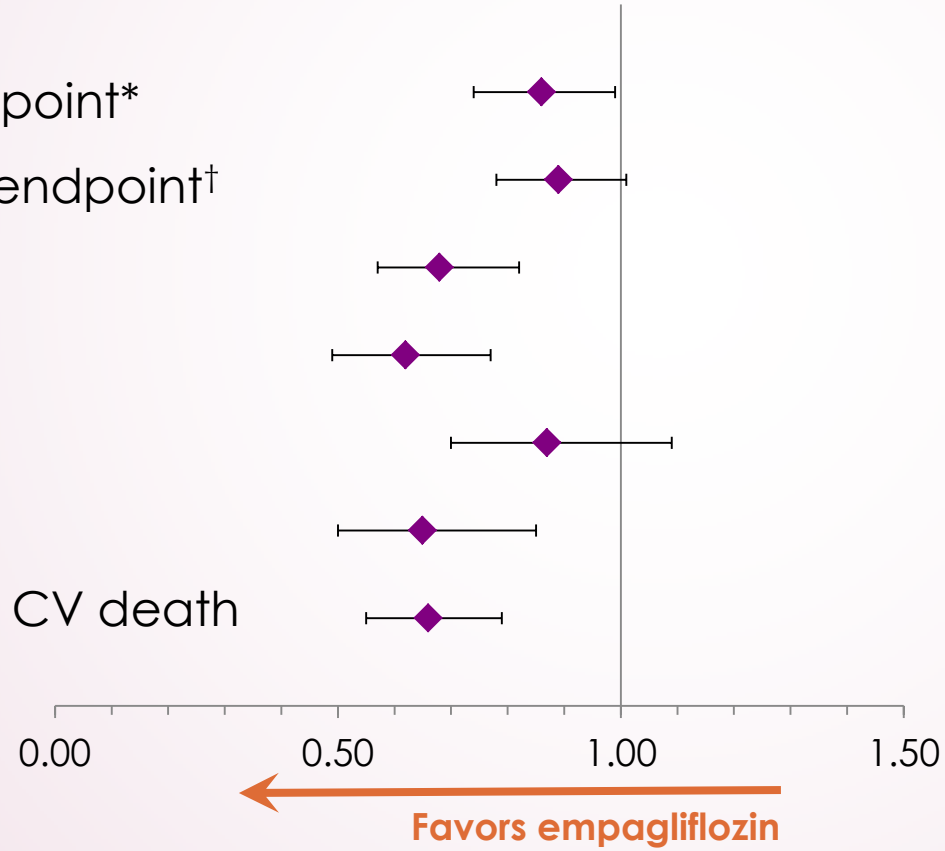
- CV death by 29% vs. placebo (HR 0.71, 95% CI 0.52-0.98)
- All-cause mortality by 24% (HR 0.76, 95% CI 0.59-0.99)
- Hospitalization for heart failure by 39% (HR 0.61, 95% CI 0.42-0.87)
- All-cause hospitalization by 19% (HR 0.81, 95% CI 0.72-0.92)

Zinman B, et al. N Engl J Med. 2015

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

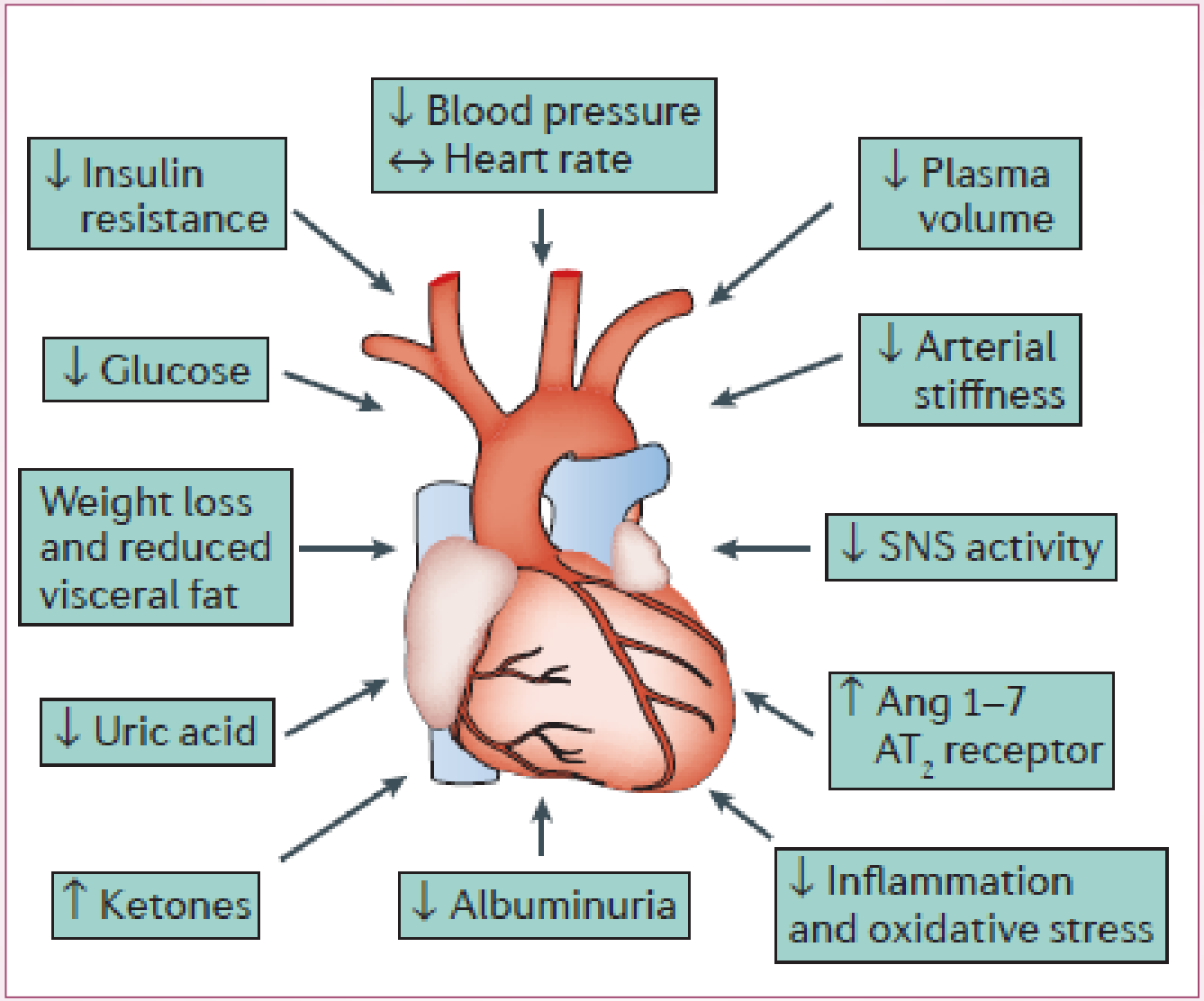
Empagliflozin: n=4687 **Placebo: n=2333**



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

Zinman B, et al.N Engl J Med. 2015



Potential mechanisms for the beneficial effect of empagliflozin on cardiovascular outcomes

DeFronzo RA, . Nat Rev Nephrol.2017 13(1):11

Major Adverse Effects

- Genital mycotic infection which occurs in 7–8% of women and 1–2% of men, primarily uncircumcised males
- A small, statistically insignificant increase in urinary tract infections and cases of urosepsis have also been reported
- Reduced intravascular volume (hypotension, reduced GFR)
- Hyperkalaemia with canagliflozin but not others
- Hypoglycaemia is uncommon unless SGLT2 inhibitors are used with sulfonylureas or insulin
- Rare cases of ketoacidosis
- FDA warning also about toe amputations with canagliflozin

DeFronzo RA, . Nat Rev Nephrol.2017 13(1):11

Conclusions

1. SGLT2 inhibitors effectively reduce HbA1c directly by promoting glucosuria and indirectly by reducing glucotoxicity
2. Improved β-cell function and enhanced insulin sensitivity
3. Decrease body weight
4. Decrease in blood pressure
5. A reduction in intraglomerular pressure and normalization of hyperfiltration
6. Effective in preventing and/or slowing the progression of diabetic nephropathy
7. A significant reduction in the risk of worsening or incident nephropathy among patients with T2DM at high cardiovascular risk.
8. The reduction in a composite of cardiovascular events, including cardiovascular mortality, and hospitalizations for heart failure with empagliflozin
9. A good safety profile

- Because of their unique mechanism of action on the kidney, they can be used as an initial therapy in drug-naive patients with T2DM or as an add-on therapy to any other antidiabetic agent, including insulin.
- Combination with ACE-I or ARBs should be considered to prevent the adverse effects associated with Ang increase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- *Are the EMPA-REG OUTCOME results generalizable or a class effect?*
- *All three approved SGLT2 inhibitors have similar effects on HbA1c, blood pressure, body weight, and other metabolic and haemodynamic parameters.*
- *Using a predictive model, dapagliflozin has been projected to reduce the risk of myocardial infarction, cardiovascular death, and all-cause death over a period of 20 years;*
- *however, only the results of CANVAS-R and DECLARE will determine whether canagliflozin and dapagliflozin also reduce cardiovascular events.*
- *In the meantime, evidence-based medicine dictates that empagliflozin should be the SGLT2 inhibitor of choice for patients at high cardiovascular risk who are similar to those in the EMPA-REG OUTCOME study.*
- *No data are available to determine whether any of the three FDA-approved SGLT2 inhibitors will have a cardiovascular or renal protective effect in patients with T2DM without a high risk cardiovascular profile.*
- *Consequently, physicians should feel comfortable using any approved SGTL2 inhibitor in these patients, since these agents reduce HbA1c, blood pressure, and body weight to a similar extent.*