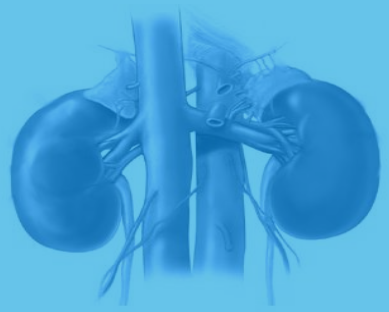
SGLT2-inhibition:

A New Strategy to Protect the Heart and the Kidney?



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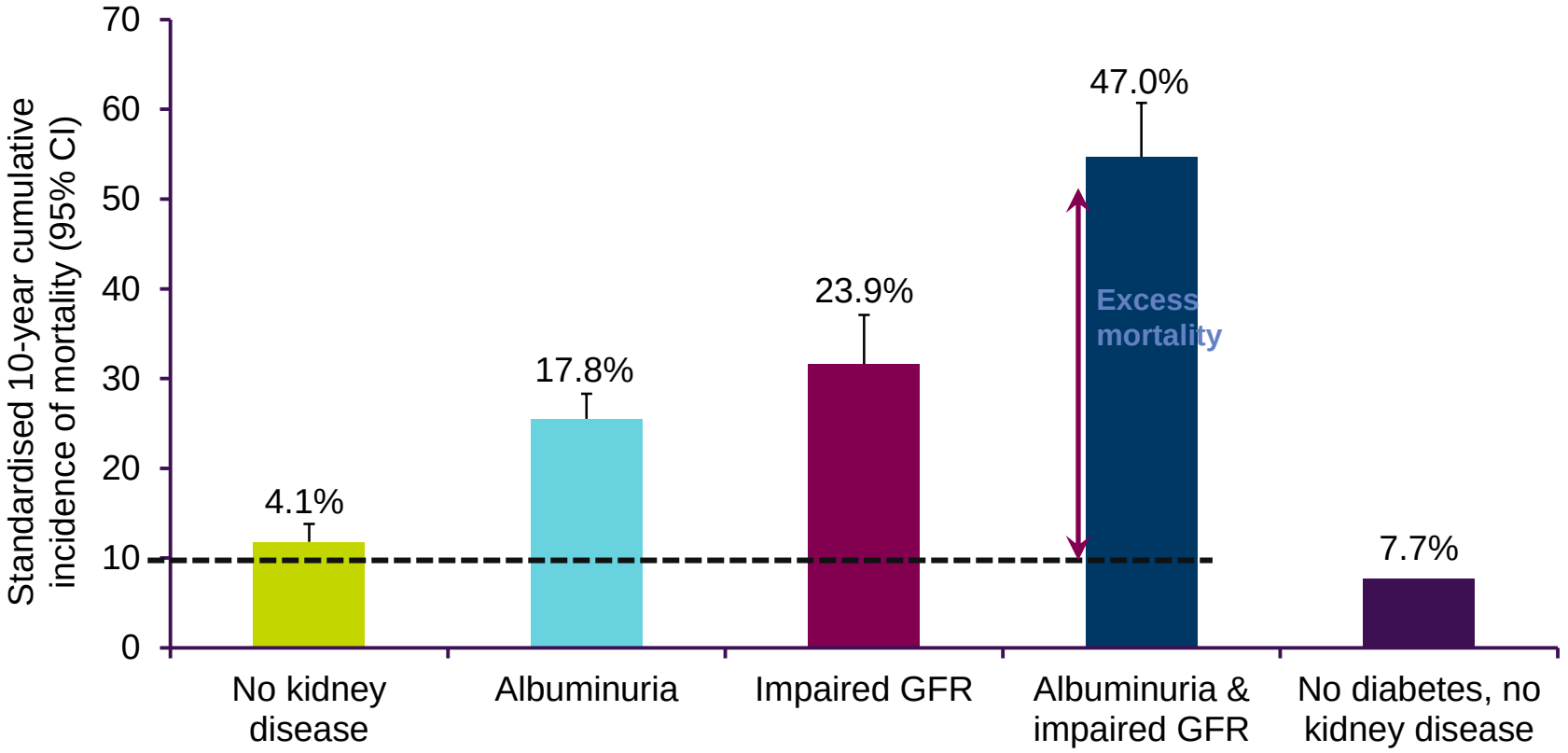
Disclosures: Consultancy for Abbvie, Astellas, Astra Zeneca, Boehringer Ingelheim, Janssen, Merck, ZS-Pharma. All honoraria paid to institution

Mortality is more frequent present in diabetes and kidney disease than those without

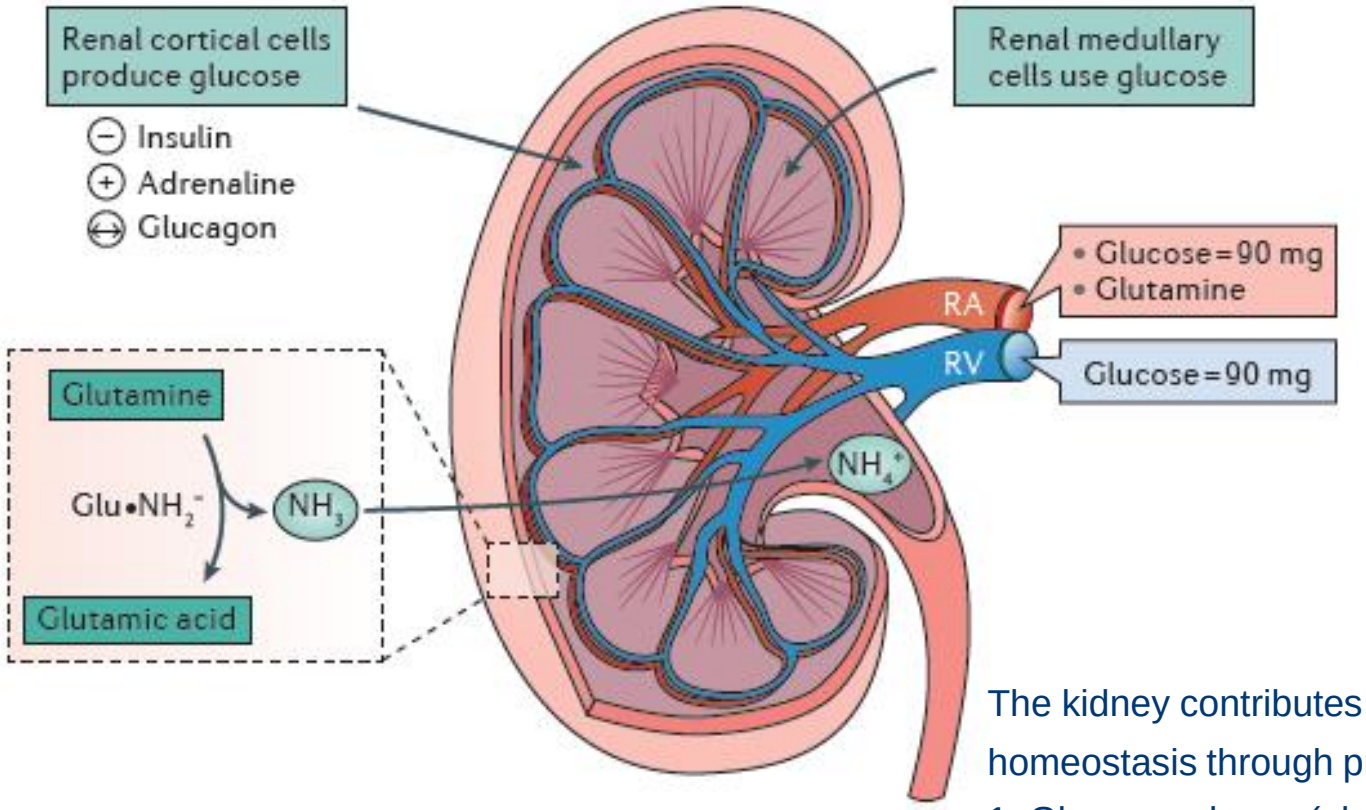


Percentages indicate absolute excess mortality above the reference group (individuals with no diabetes or kidney disease)
*No diabetes and no kidney disease; GFR, glomerular filtration rate; T2D, type 2 diabetes
Afkarian M *et al. J Am Soc Nephrol* 2013;24:302

Potential approaches and trials testing additive renal (cardiovascular) protection (on top of ACEi or ARB)

- ACEi+ARB (**VA NEPHRON-D**; prematurely *stopped* for safety; renal)
- ACEi + ARB (**HALT-PKD**; *no effect*; renal)
- ACEi/ARB + DRI (**ALTITUDE**; prematurely *stopped* for safety; CV/renal)
- Low Protein Diet (**MDRD**; completed, no additive effect?)
- Erythropoietin (**TREAT**; completed; no effect CV/renal)
- GAG's (**SUN-Overt**; prematurely *stopped*; no effect renal)
- GAG's (**SUN-Micro**; completed; no effect renal)
- ET-A (Avosentan) (**ASCEND**; prematurely *stopped* for safety; renal)
- Statins (**SHARP**; completed; no renal effect?; CV/renal)
- Pentoxifylline (**PREDIAN**; completed; eGFR protection)
- Nrf2 (Bardoxolone) (**BEACON**; *stopped* for safety; renal/CV outcome)
- Carbon Absorption (AST-120) (**CAP-KD**; completed no effect; renal outcome)
- Nrf2 (Bardoxolone) (**Japanese study**; ongoing; renal outcome)
- ET-A (Atrasentan) (**SONAR**; ongoing; renal outcome)
- SGLT2 (canagliflozin) (**CREDENCE**; starting; renal/CV outcome)
- SGLT2 (empagliflozin) (**EMPA-REG**; completed; CV and renal protection)
- Uric acid (allopurinol) (**PERL**; ongoing; renal outcome)
- GLP-1 mimetic (Liraglutide) (**LEADER**; ongoing; CV and renal outcome)
- DPP-4 (Linagliptin) (**CARMELINA**; ongoing; CV and renal)
- Pyridorin (**PIONEER**; ongoing, renal outcome)
- AngII/NEPi (LCZ696) (?)
- Prostacyclin (Beraprost) (**CASSIOPEIR**; ongoing; renal outcome; ASN submission)
- MCA (spironolactone) (**PRIORITY**; ongoing; renal outcome)
- MCA (fineronone) (**FIGARO** and **FIDELIO-DKD**; ongoing; renal/CV outcome)

The kidney plays an important role in glucose production and utilization

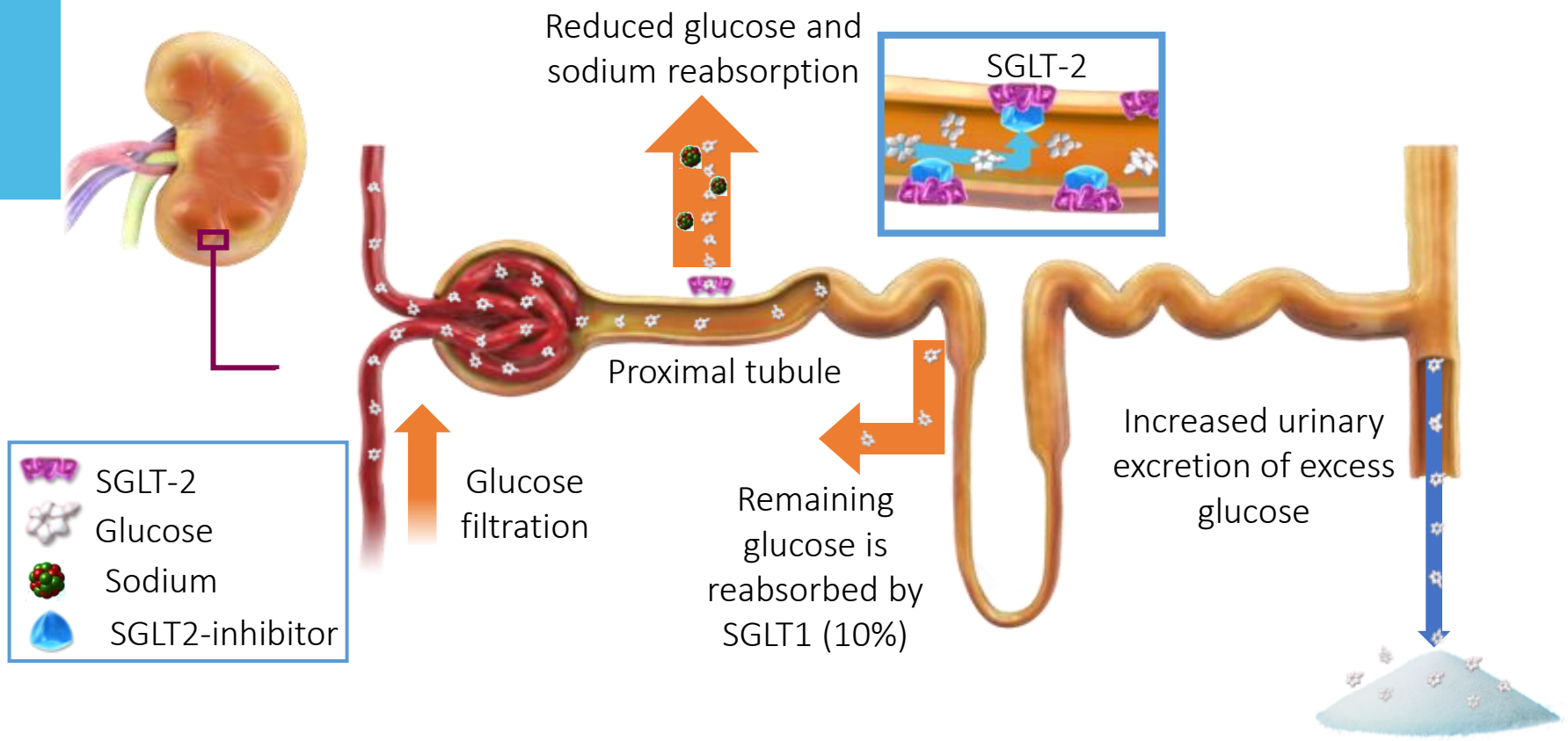


The kidney contributes to glucose homeostasis through processes of:

1. Glucose release (gluconeogenesis)
2. Glucose utilisation for energy needs
3. Glucose filtration and reabsorption

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

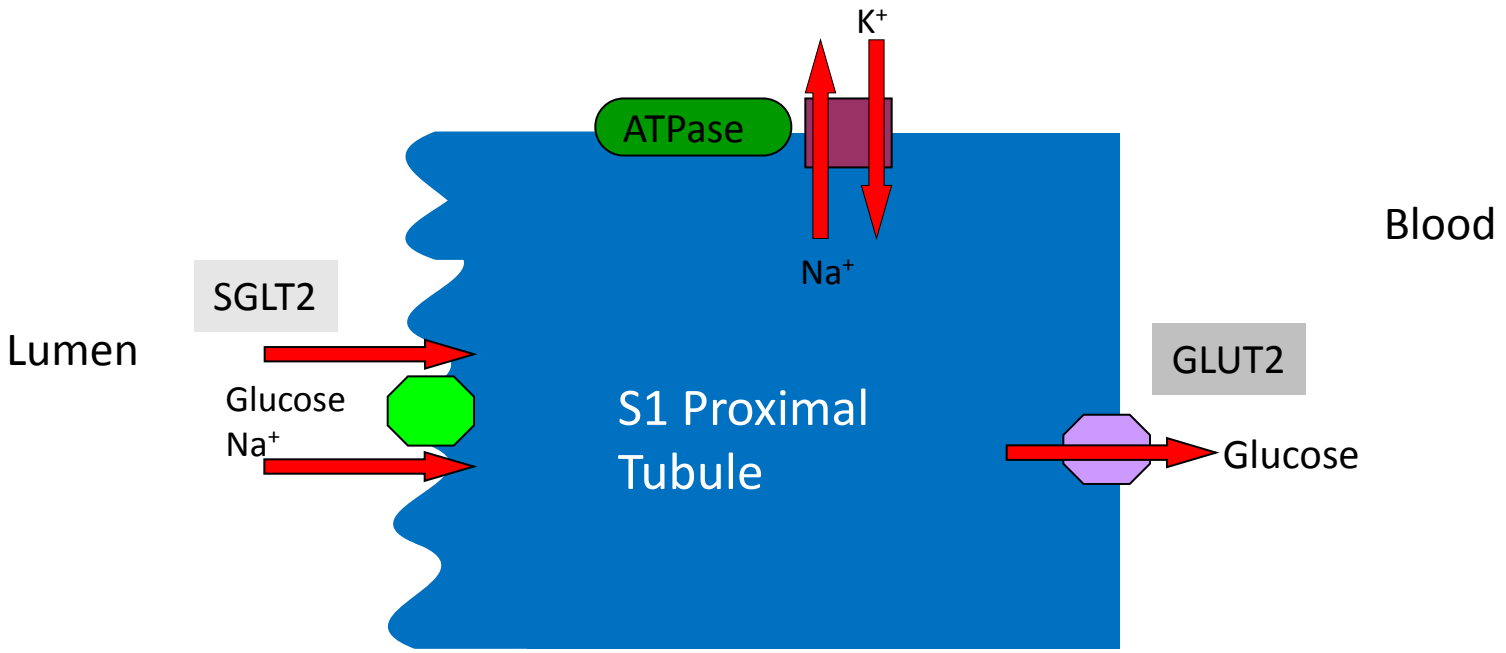
The role of SGLT2 inhibitors in glucose reabsorption



- By inhibiting SGLT2, these drugs remove excess glucose in the urine and lower HbA_{1c}[1]
- SGLT-2 inhibitors act on natriuretic mechanisms and are associated with a decrease in intracellular Na^+ concentration & Na^+ /K ATPase activity

1. Marsenic O. *Am J Kidney Dis* 2009;**53**:875–85;

SGLT2 Mediates Glucose Reabsorption in the Kidney

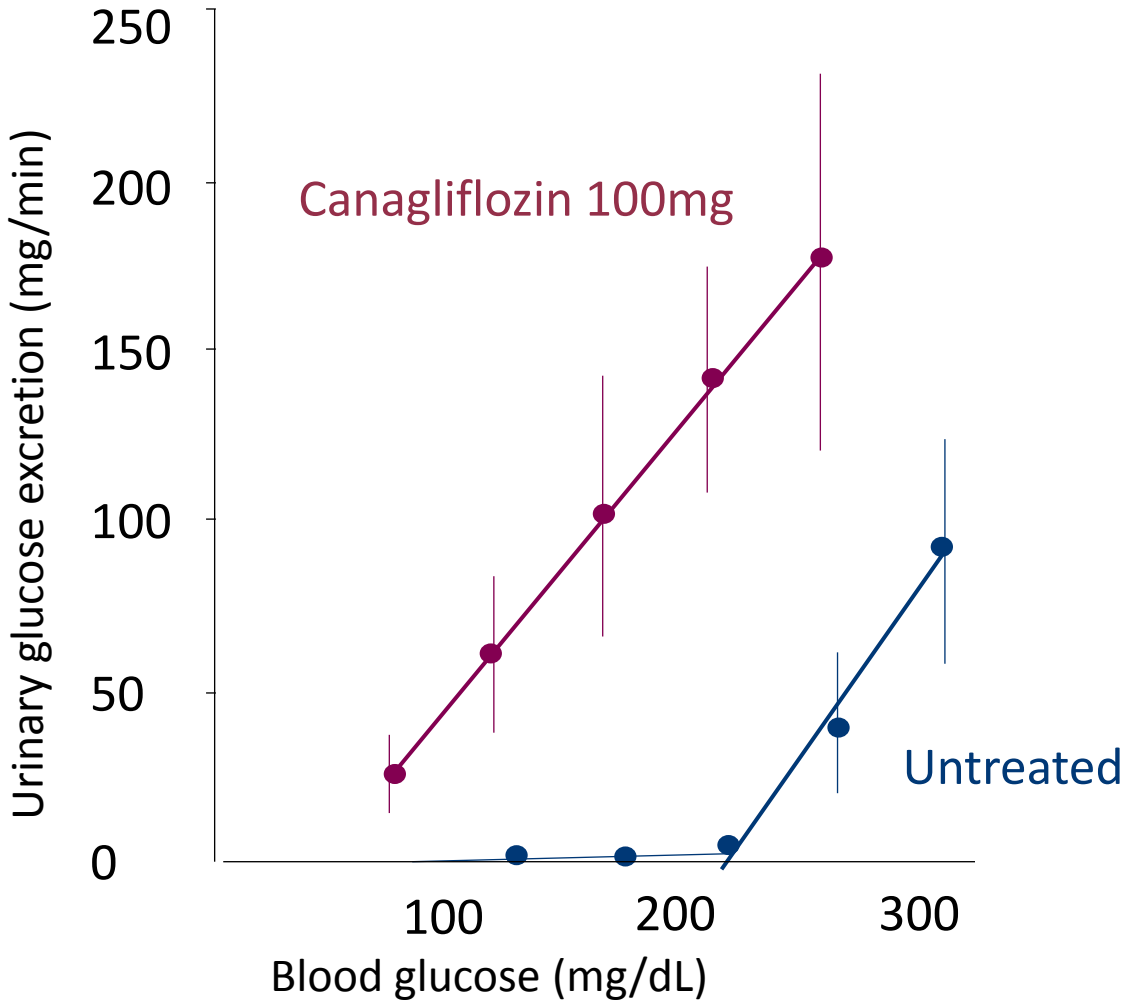


SGLT2: Major transporter of glucose in the kidney[1-3]

- Co-transports Na+ and glucose at 2:1 stoichiometry
- Responsible for majority of renal glucose reabsorption in the proximal tubule

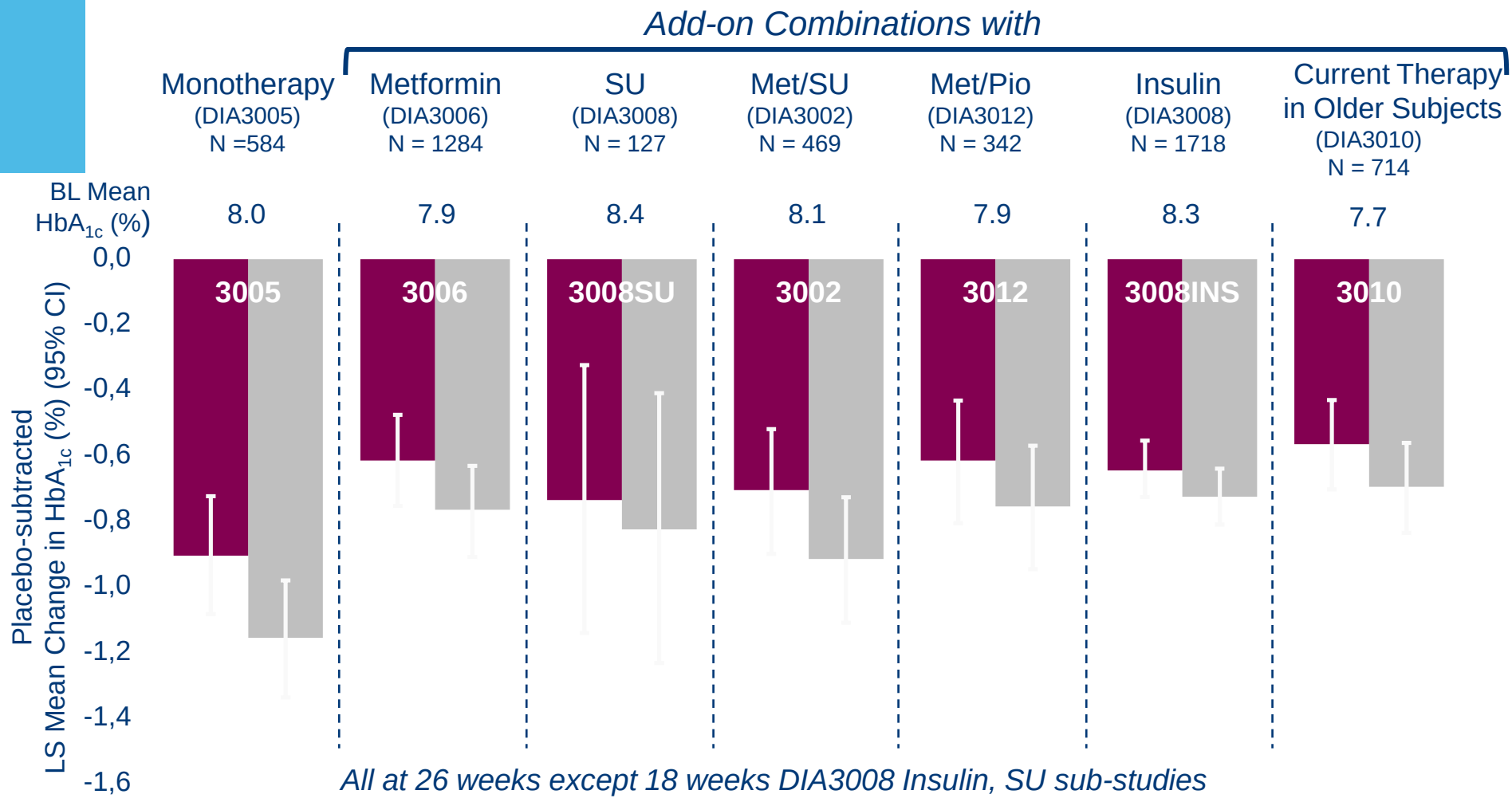
1. Hediger and Rhoads. *Physiol Rev*. 1994;74:993; 2. Magen et al. *Kidney Int.* 2005;67:34;
3. Kanai et al. *J Clin Invest*.1994;93:397.

SGLT2 inhibitors decrease the glucose excretion threshold



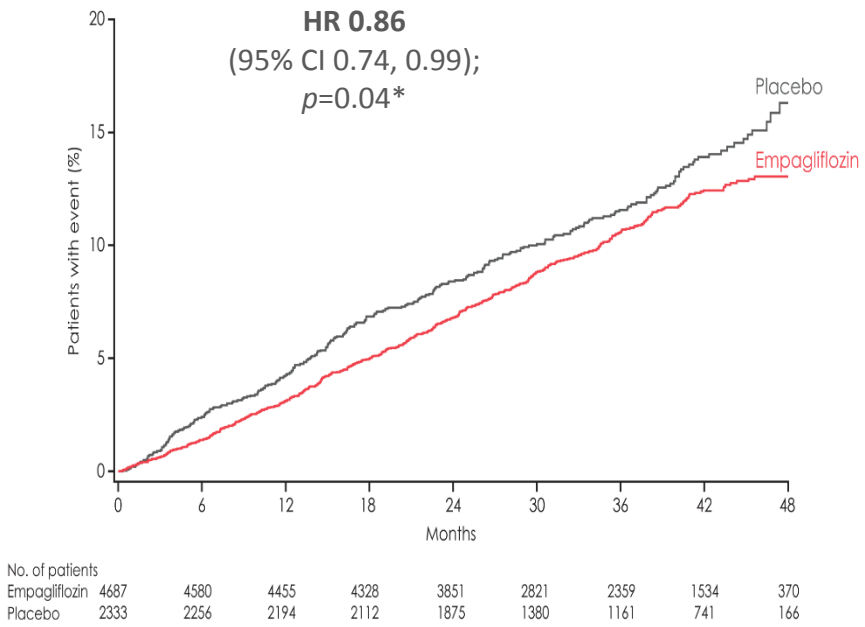
Polidori D et.al. Con Endorinol Metab 2013;98:E867-E871

SGLT2 decreases HbA1c on top of other diabetic medications

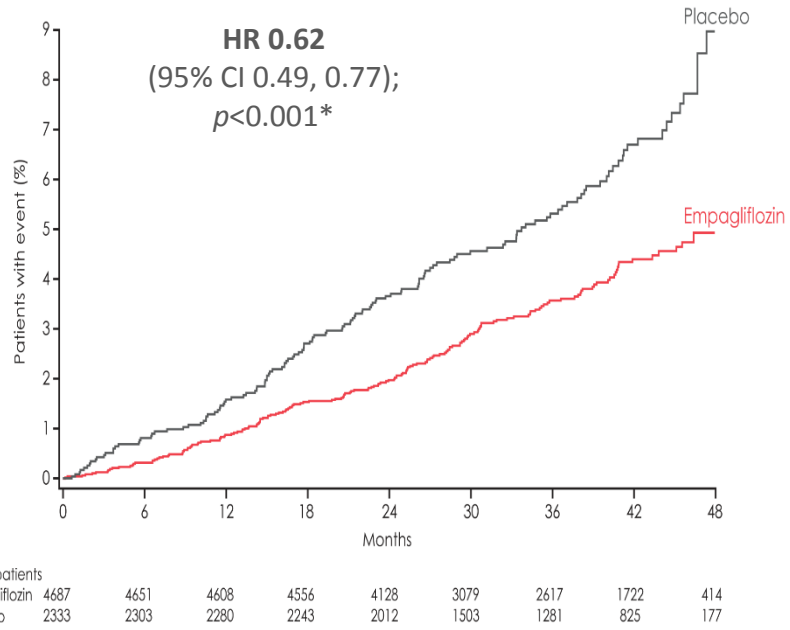


EMPAREG: Empagliflozin is cardioprotective in patients with type 2 diabetes and established CV disease

Primary CV endpoint



CV death endpoint

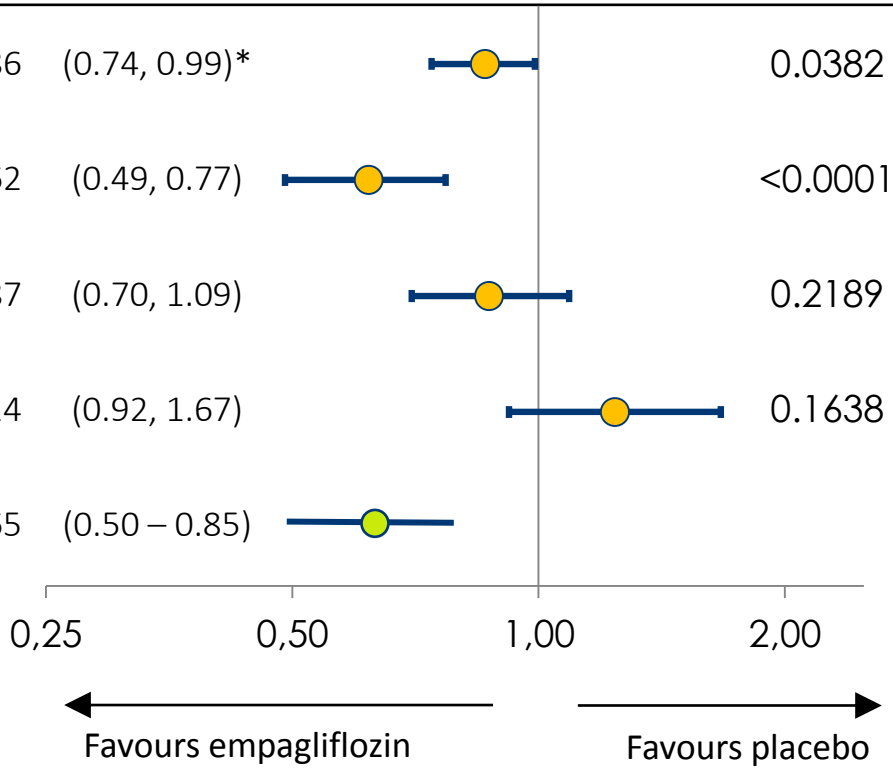


- Primary CV endpoint composite of non-fatal MI, stroke or CV-death
- Patients were randomly assigned to empa 10 mg, empa 25 mg or placebo. Shown are the combined 10 and 25 mg doses versus placebo

Zinman B et.al. N Engl J Med. 2015 Nov 26;373(22):2117-28

EMPAREG: Empagliflozin is cardioprotective in patients with type 2 diabetes and established CV disease

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638
Heart Failure	95/4687	126/2333	0.65	(0.50 – 0.85)	

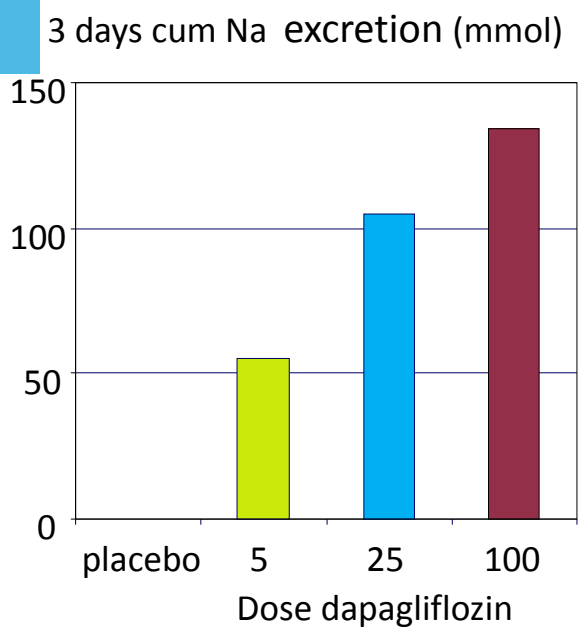


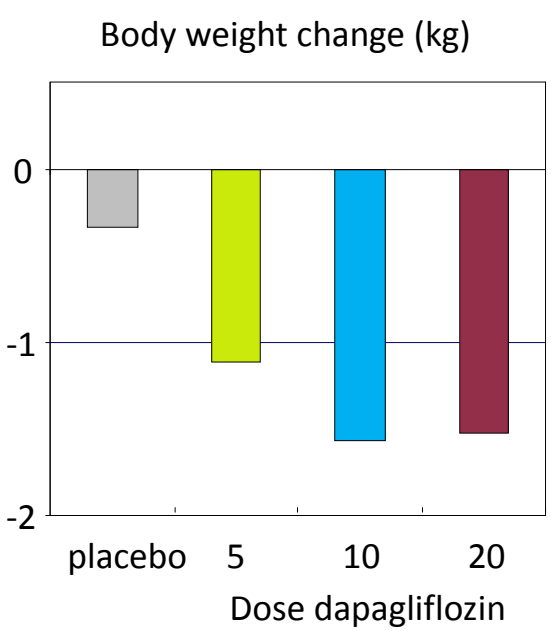
Zinman B et.al. N Engl J Med. 2015 Nov 26;373(22):2117-28

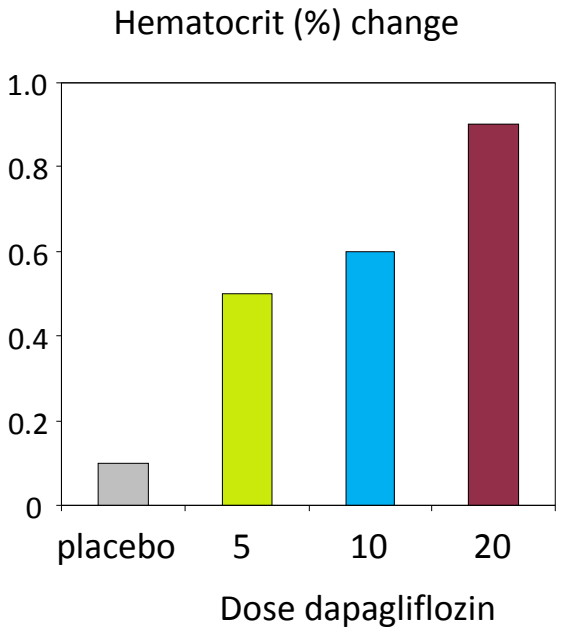
What could be the mechanisms of clinical benefit?

- Clinical benefit of SGLT2 inhibitors could be explained by:
  1. Metabolic effects
     - Improved β-cell function/ tissue insulin sensitivity
     - Decrease in β-cell glucotoxicity
     - Body weight loss
       - effects on visceral
       - subcutaneous fat
  2. Diuretic / Natriuretic effects
  3. Renal effects

SGLT2 inhibitors: Proximal tubular diuretics?

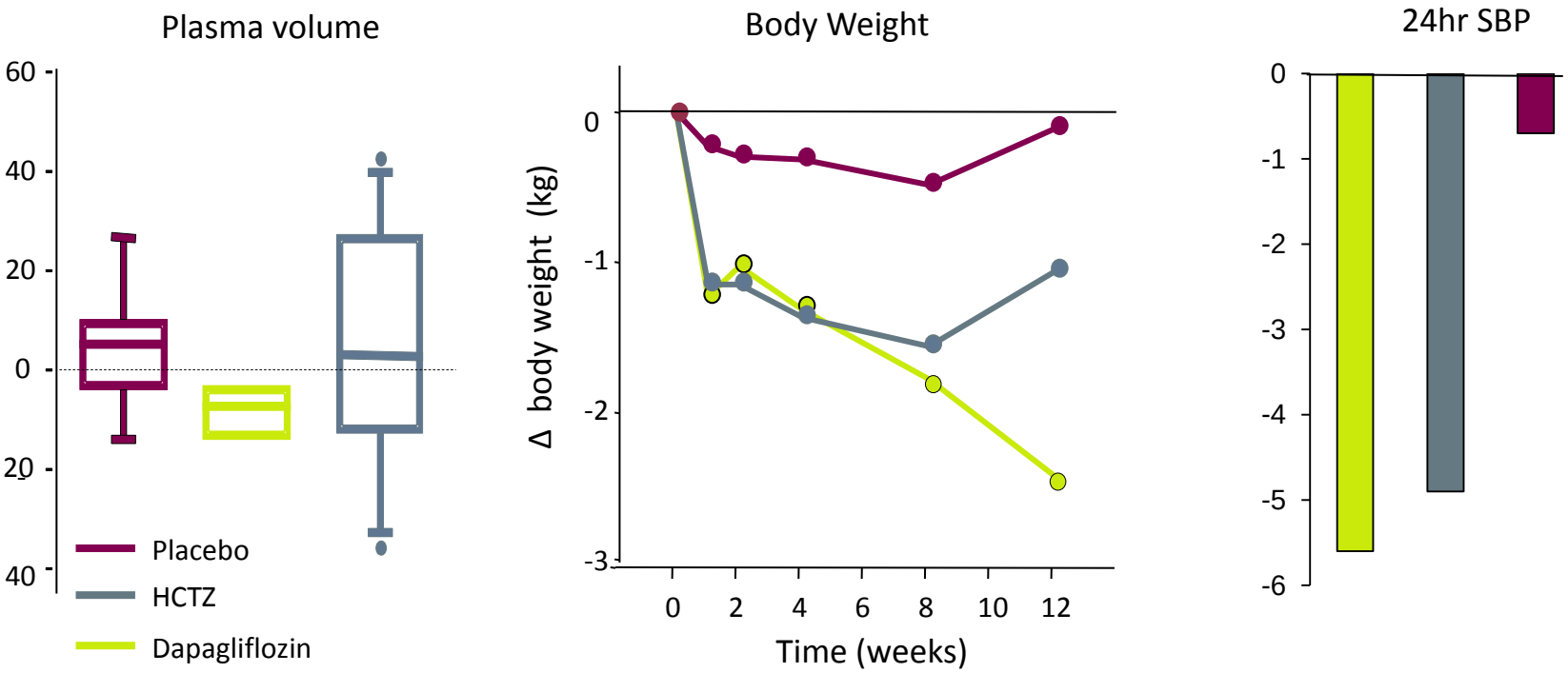






Heerspink et al. World Congress Nephrology 2011

Dapagliflozin diuretic effects: lower plasma volume, body weight, and 24-hr blood pressure



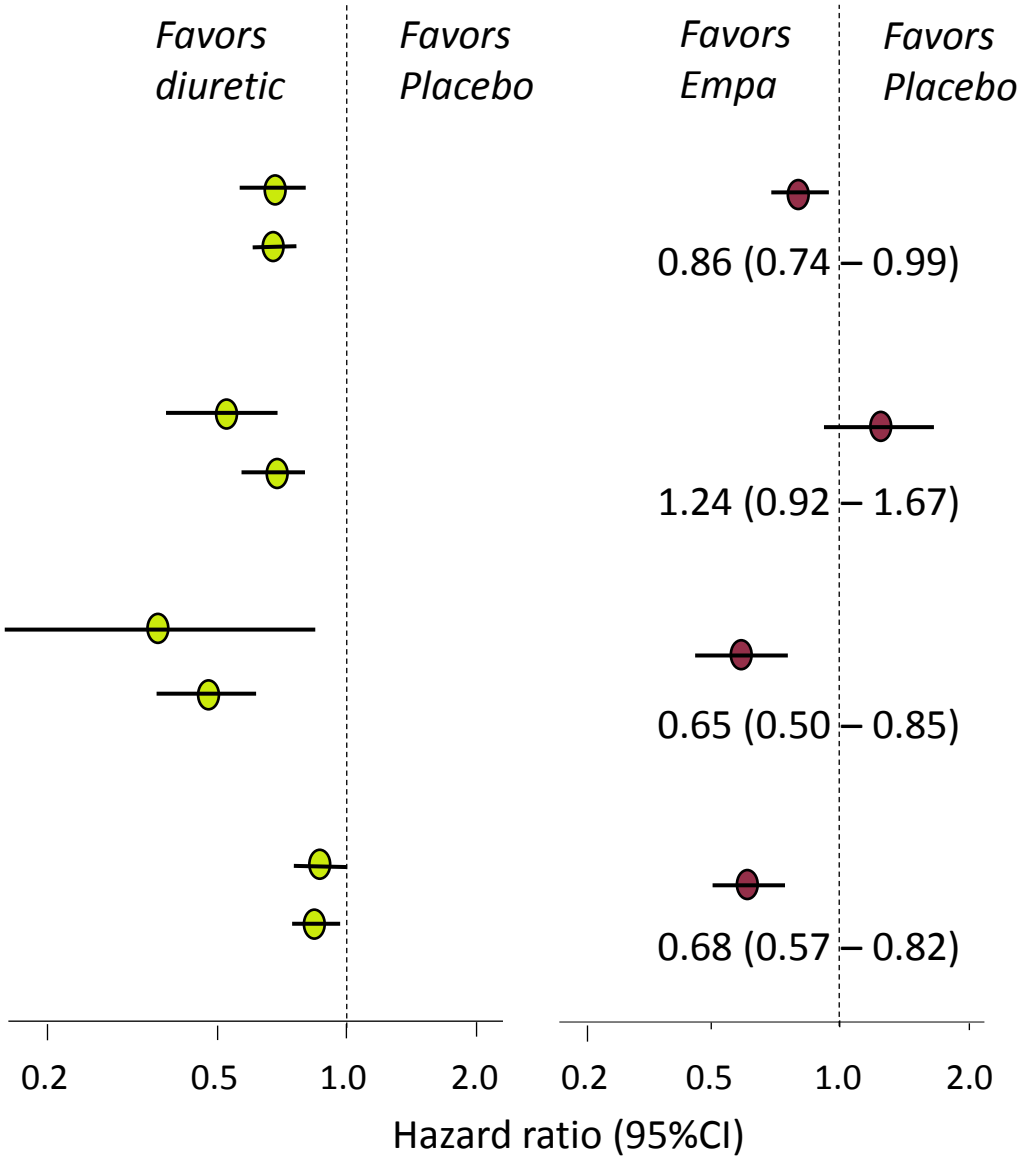
- Dapagliflozin reduces plasma volume compared to placebo or HCTZ as measured by ^{51}Cr Albumin
- Reductions in body weight during the initial 4 weeks paralleled reductions in body weight during HCTZ

Abbreviations: HCTZ, hydrochlorothiazide, SBP, systolic blood pressure

*Heerspink et al. Diabetes Obesity Metabolism 2013;*15(9):853-62

Meta-analysis of diuretic effects on CV outcomes

Cardiovascular events	**RR (95% CI)**
Thiazide-type	0.67 (0.56 – 0.81)
Thiazide-like	0.67 (0.60 – 0.75)
Cerebrovascular events	
Thiazide-type	0.52 (0.38 – 0.69)
Thiazide-like	0.68 (0.57 – 0.80)
Heart Failure	
Thiazide-type	0.36 (0.16 – 0.84)
Thiazide-like	0.47 (0.36 – 0.61)
All-cause Mortality	
Thiazide-type	0.86 (0.75 – 1.00)
Thiazide-like	0.84 (0.74 – 0.96)

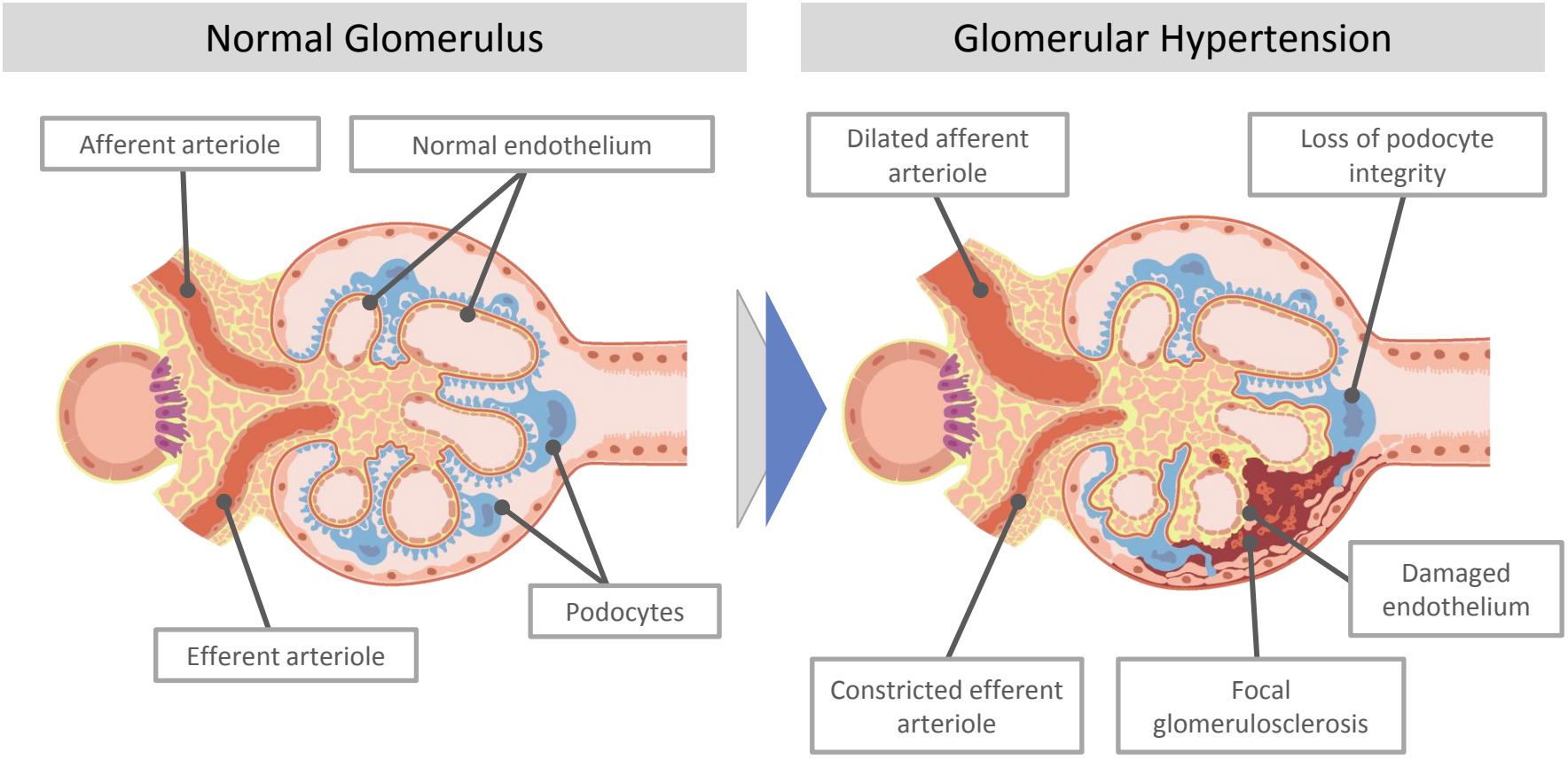


Olde Egberink et.al. Hypertension 2015

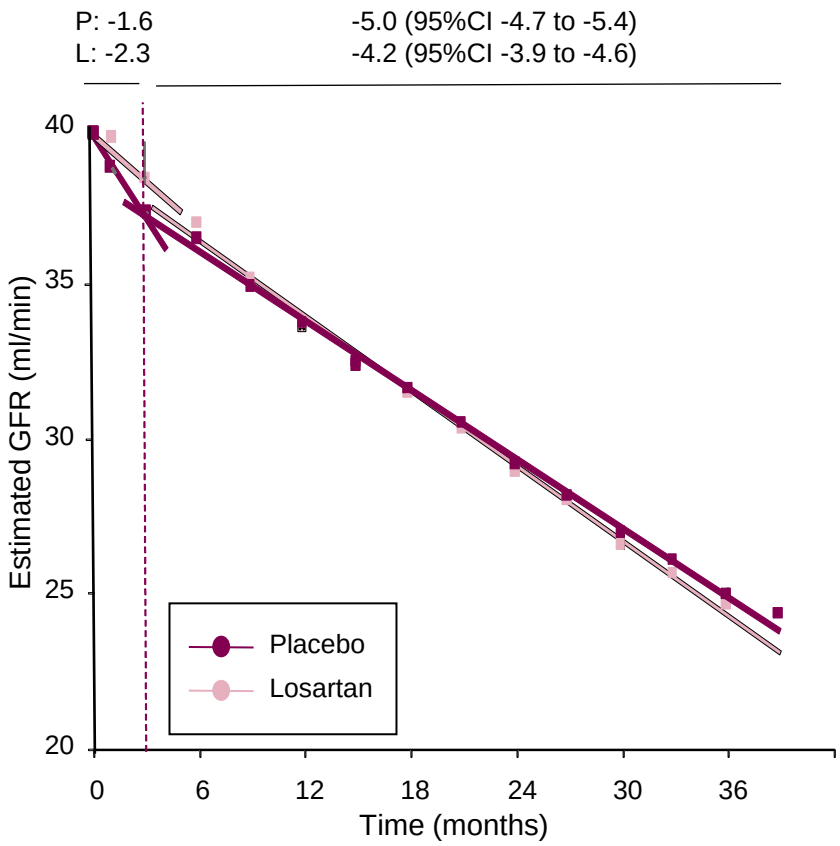
What could be the mechanisms of clinical benefit?

- Clinical benefit of SGLT2 inhibitors could be explained by:
  1. Metabolic effects
  2. Diuretic / Natriuretic effects
  3. Renal effects
     - Restore tubulo-glomerular feedback
     - Reduction Intraglomerular Pressure
     - Reduction Albuminuria

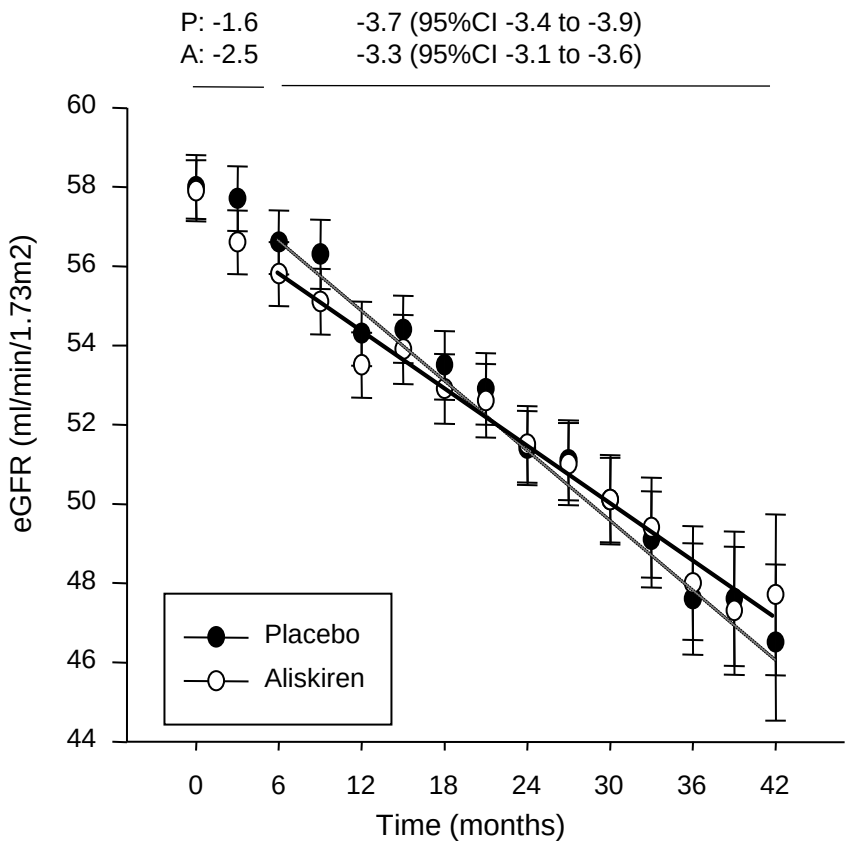
High intraglomerular pressure causes renal damage



Acute reduction in GFR during RAAS inhibition associated with subsequent stabile renal function



RENAAL: Type 2 diabetes and nephropathy randomized to losartan 100 mg/d or placebo.

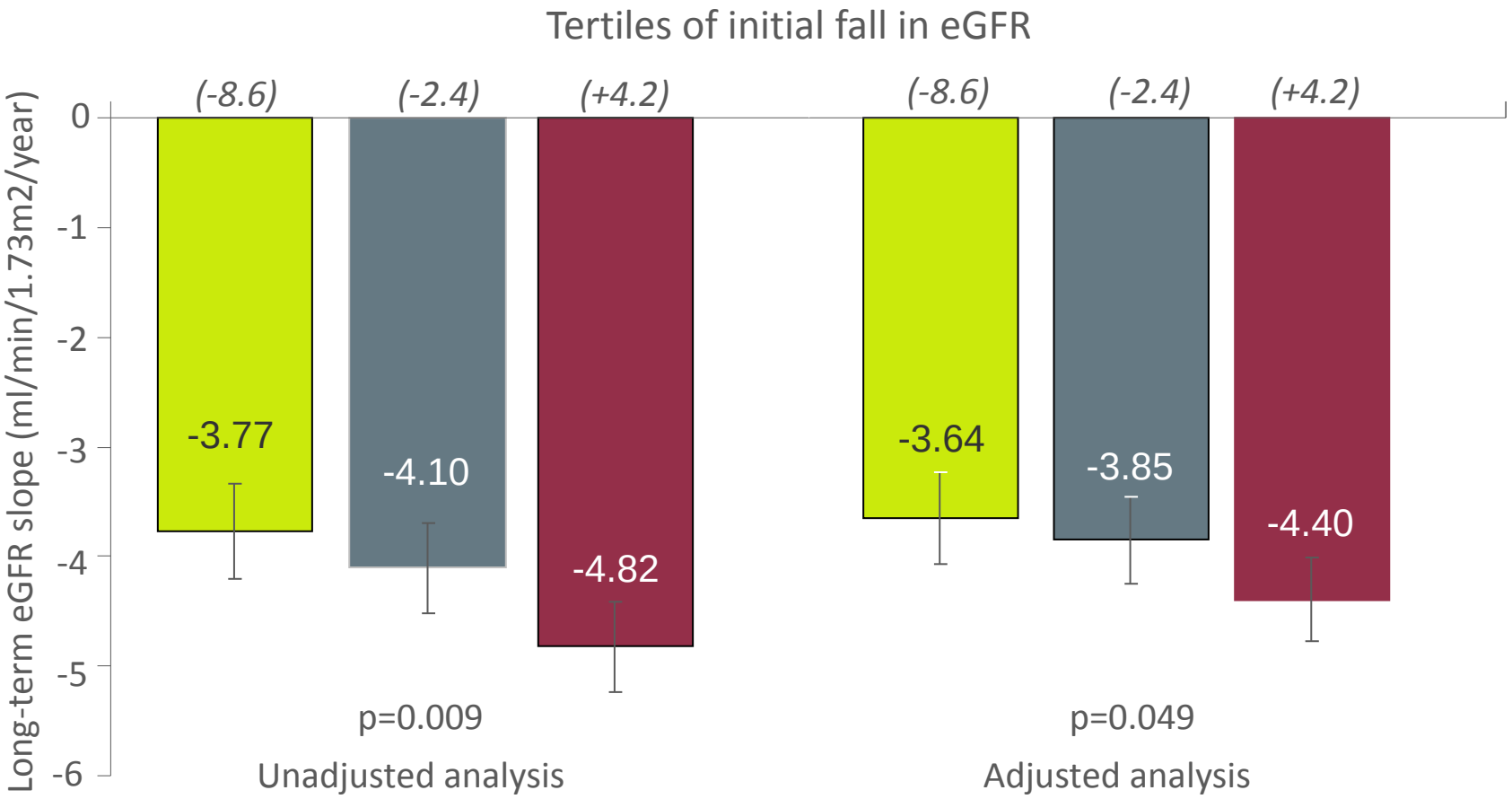


ALTITUDE: Selection of patients with type 2 diabetes and nephropathy randomized to aliskiren 300 mg/d or placebo on top of ACEI or ARB.

Holtkamp et al. Kidney Int 2011:

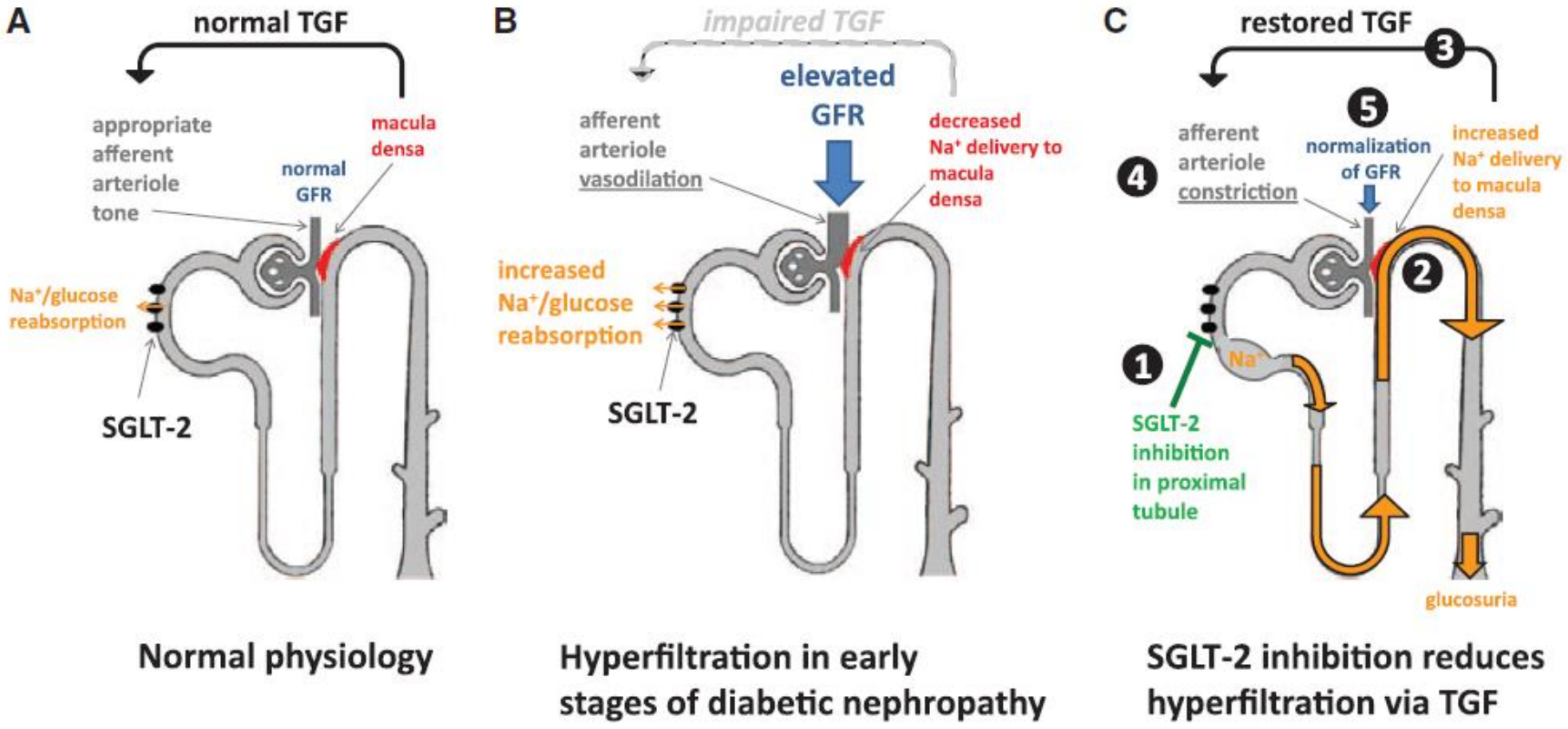
Heerspink et.al. Lancet Diabetes & Endocrinology 2016

Initial fall in eGFR is associated with less renal function decline during prolonged follow-up



Holtkamp et al. Kidney Int 2011

SGLT2 inhibitors restore tubulo-glomerular feedback

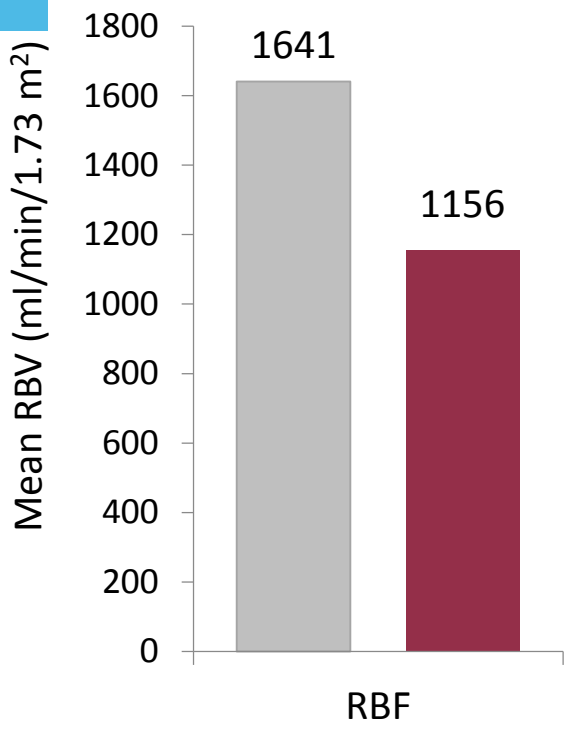


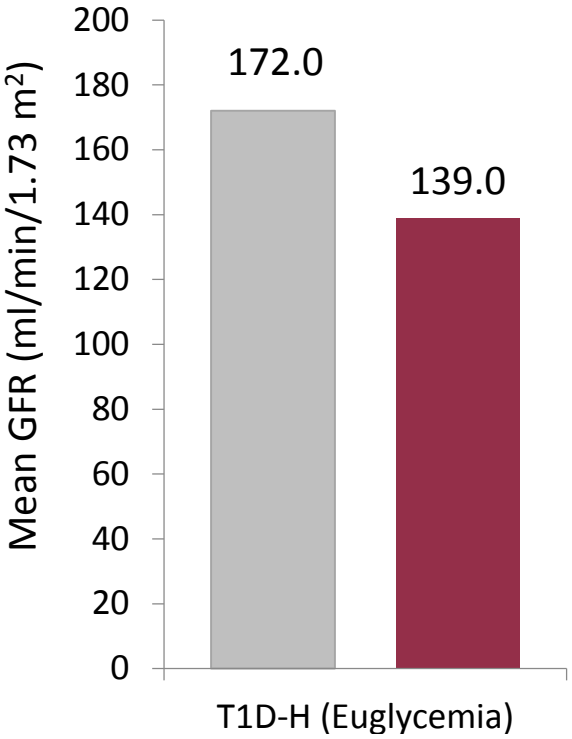
GFR, glomerular filtration rate; SGLT, sodium–glucose cotransporter; TGF, tubuloglomerular feedback

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

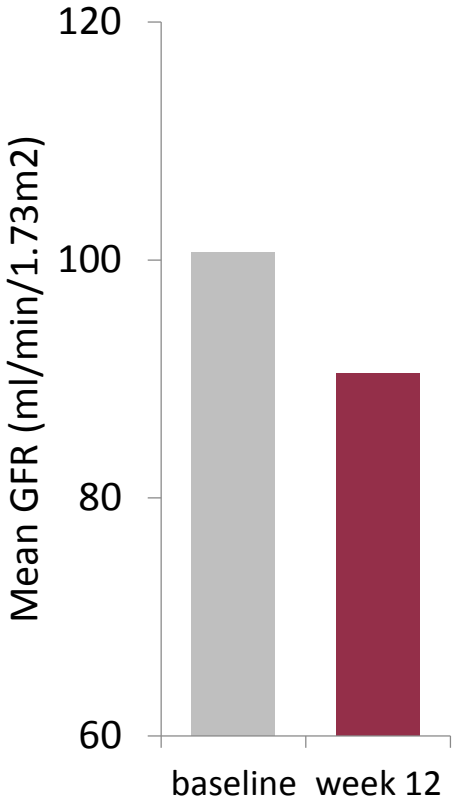
SGLT2 inhibitors decrease RPF and GFR

Type 1 diabetes





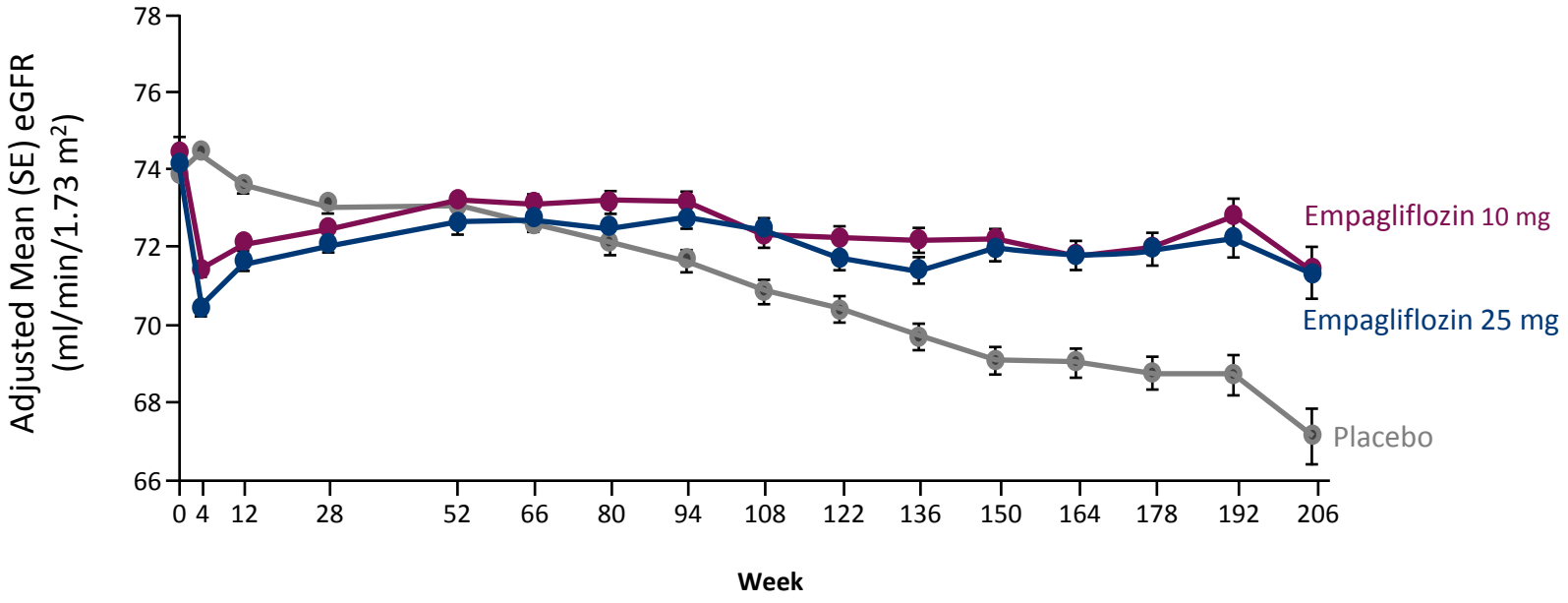
Type 2 diabetes



Cherney D et al. Circulation 2014:129;587-99

Heerspink et.al. DOM 2013: 15:853-62

EMPAREG: Empagliflozin slows eGFR decline over time

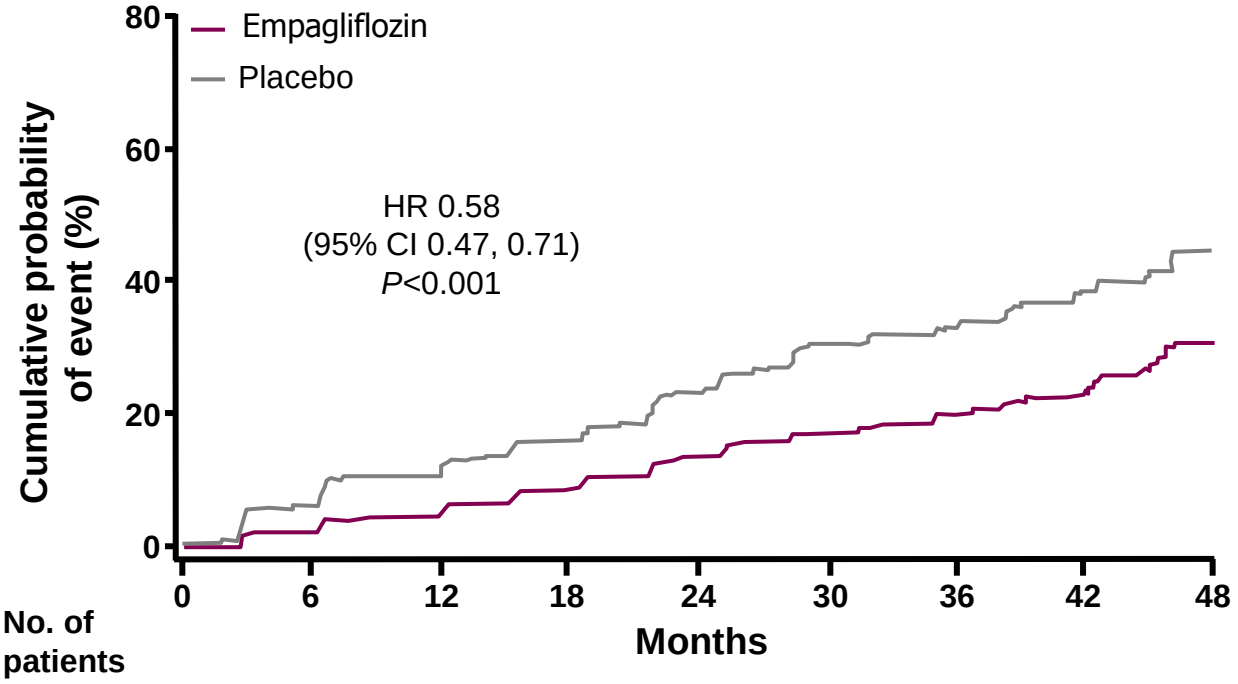


Placebo	2223	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448	171
Empa 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513	193
Empa 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524	216

Wanner C et.al. N Engl J Med. 2016 Jul 28;375(4):323-34

EMPAREG: Empagliflozin reduces renal risk in patients with type 2 diabetes and established CV disease

In patients with eGFR (MDRD) <60 mL/min/1.73 m^2 and/or macroalbuminuria (UACR >300 mg/g) at baseline, **empagliflozin reduced the risk of incident or worsening nephropathy**

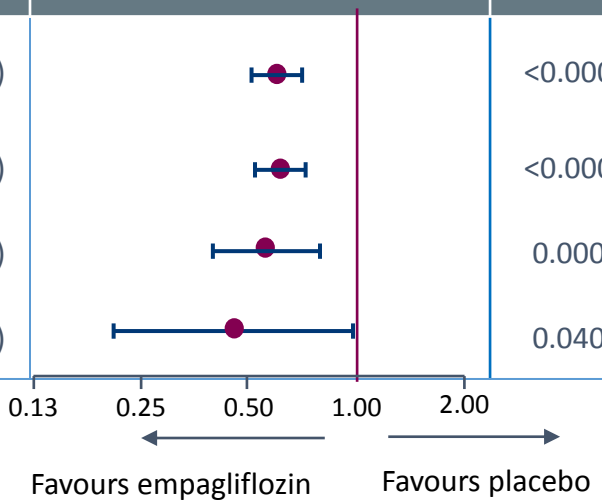


No. of patients									
Empagliflozin	998	952	895	836	694	516	420	273	69
Placebo	507	462	425	377	302	206	172	102	23

Wanner C et.al. N Engl J Med. 2016 Jul 28;375(4):323-34

EMPAREG: Empagliflozin reduces renal risk

	N With Event/N Patients					*P*-value
	Empagliflozin	Placebo	HR	(95% CI)		
New onset/worsening of nephropathy	525/4124	388/2061	0.61	(0.53, 0.70)		<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62	(0.54, 0.72)		<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56	(0.39, 0.79)		0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45	(0.21, 0.97)		0.0409



* Accompanied by estimated glomerular filtration rate (MDRD) ≤45 mL/min/1.73 m^2.

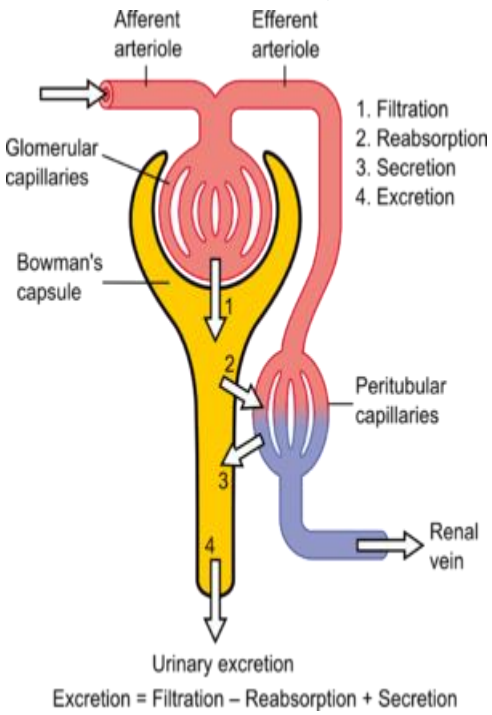
Wanner C et.al. N Engl J Med. 2016 Jul 28;375(4):323-34

RAAS and SGLT2 inhibitors reduce intraglomerular pressure through different mechanisms

SGLT2i ↑ tubuloglomerular feedback, ↑ afferent arteriole tone and ↓intraglomerular pressure

Initial ↓ in eGFR followed by stabilization
↓ albuminuria

Renal Protection
(to be determined)



ACEi and ARB ↓ efferent arteriole tone and ↓ intraglomerular pressure

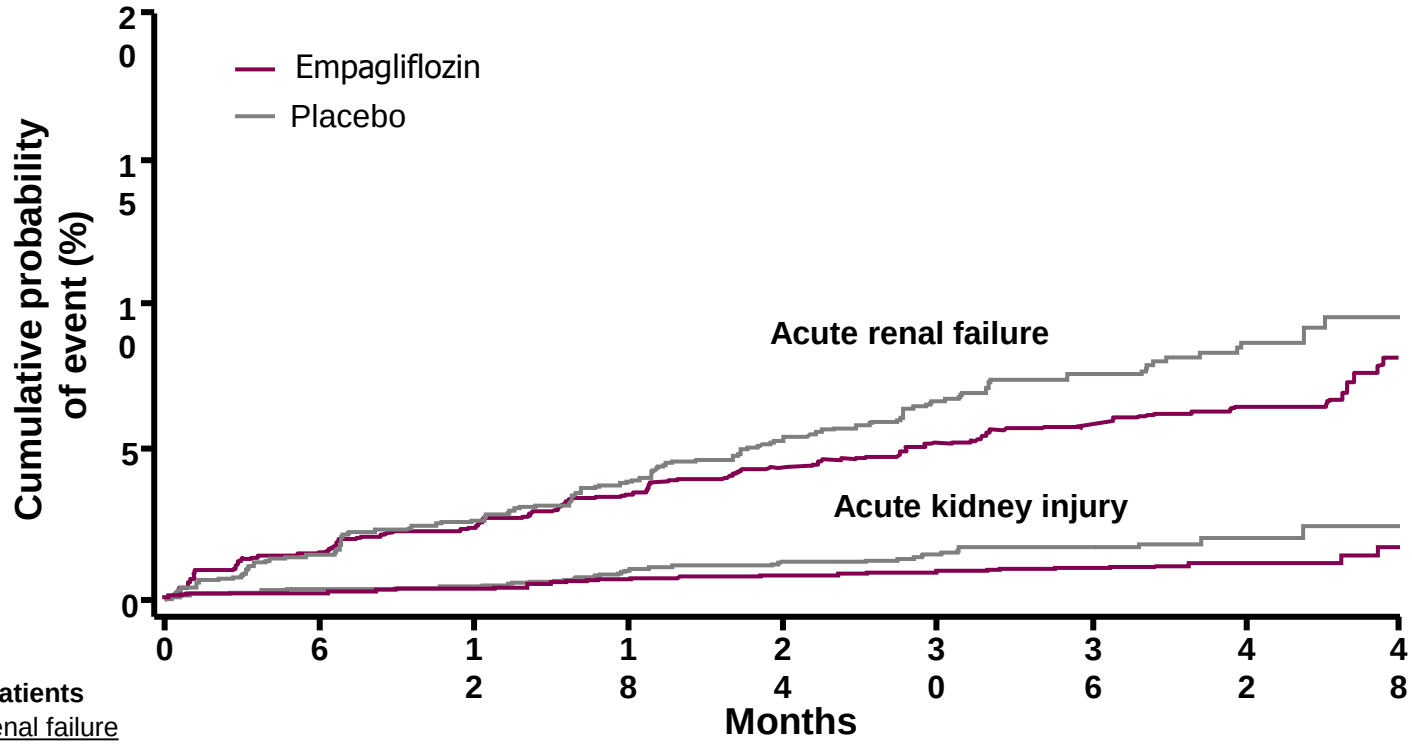
Initial ↓ in eGFR followed by stabilization
↓ albuminuria

Renal Protection

Increased intraglomerular pressure and hyperfiltration are key steps in the progression of diabetic kidney disease

EMPAREG: Empagliflozin reduces risk of AKI

Empagliflozin had **a protective effect against** acute renal failure and acute kidney failure vs placebo

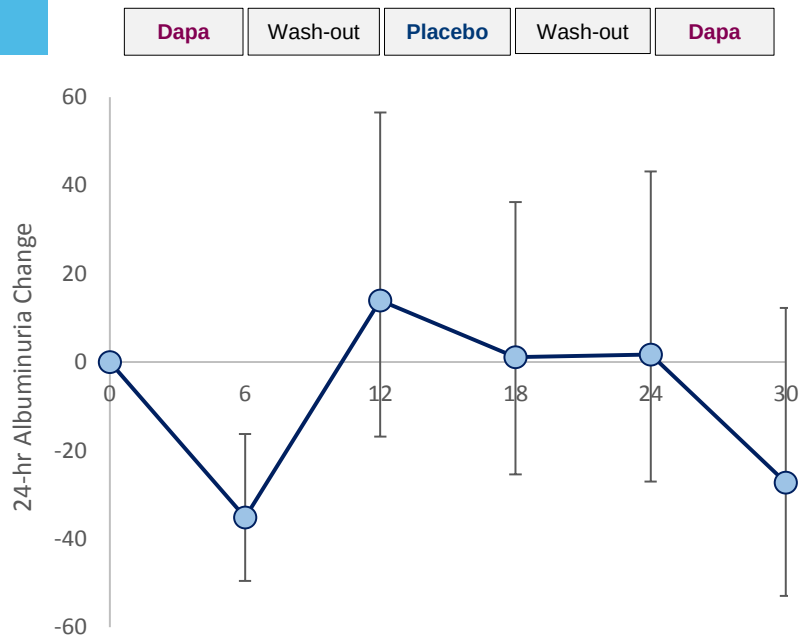


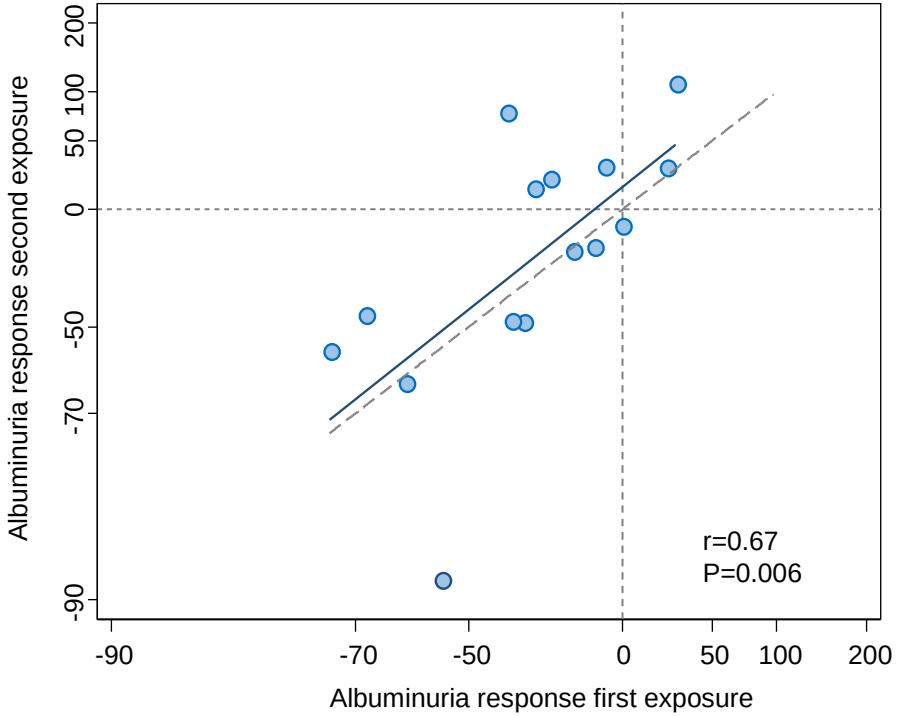
No. of patients									
Acute renal failure									
Empagliflozin	4687	4359	4159	3937	3398	2463	1897	975	268
Placebo	2333	2167	2031	1889	1588	1133	866	403	108
Acute kidney injury									
Empagliflozin	4687	4415	4238	4037	3505	2545	1965	1014	279
Placebo	2333	2194	2078	1944	1653	1178	902	427	111

CI, confidence interval; HR, hazard ratio;

Wanner C, et al. Presented at the 52nd EASD Annual Meeting 2016. Munich, Germany; 16th September 2016; OP S44.3

IMPROVE: Dapagliflozin consistently reduces albuminuria in type 2 diabetes and micro/macroalbuminuria





Petrykiv S. et.al. Submitted

Summary of Product Characteristics

Dapagliflozin

Use in patients with renal impairment

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension,

Canagliflozin

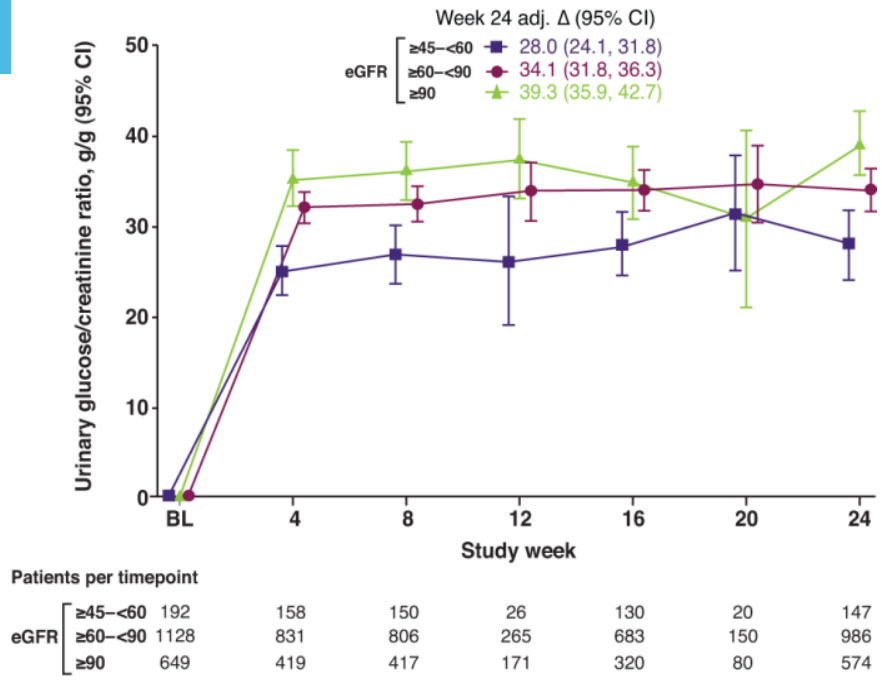
Renal impairment

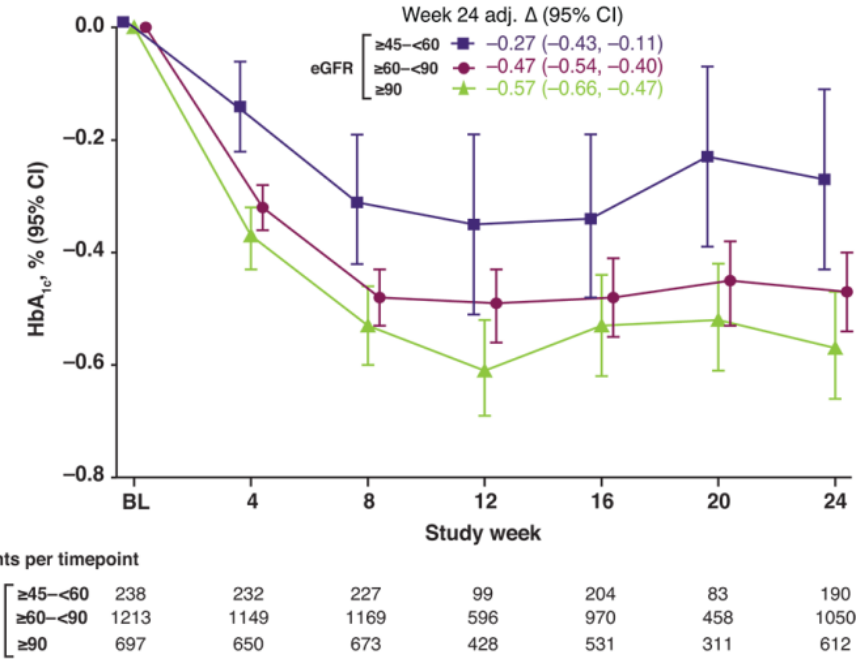
For patients with an eGFR 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2 or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).

Glycemic effects of dapagliflozin is blunted in patients with renal impairment

Placebo-adjusted change from baseline over time with dapagliflozin in HbA1c in the overall population

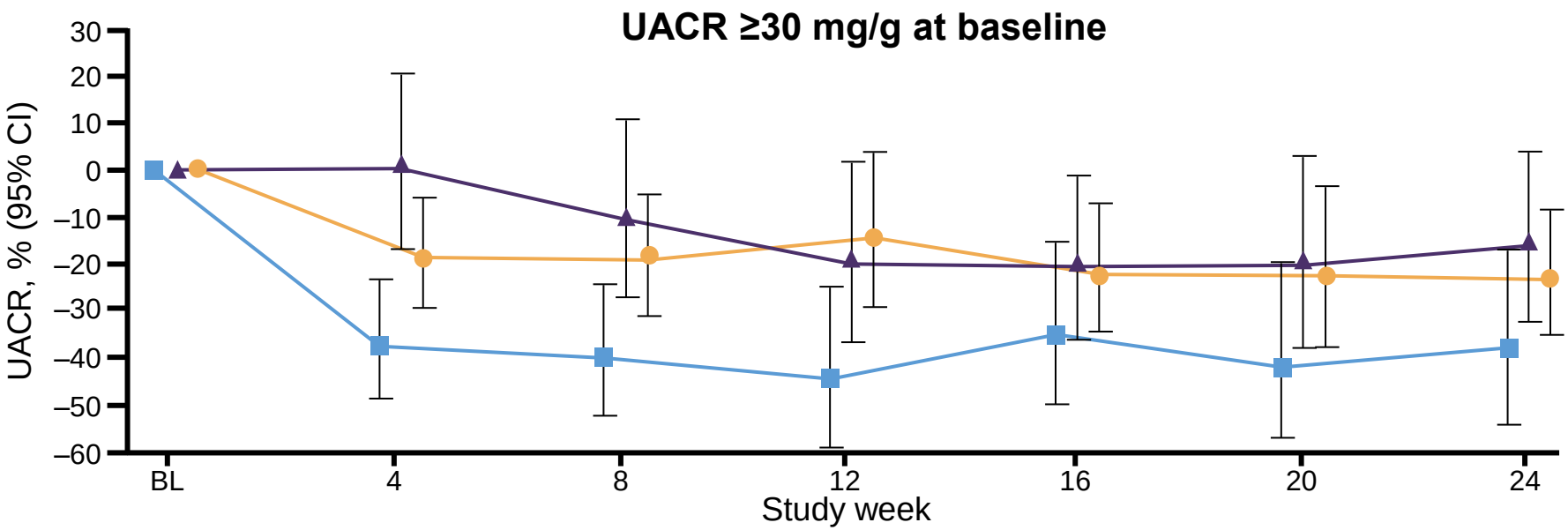




Excludes data after rescue. Adj., adjusted; BL, baseline; CI, confidence interval.

Petrykiv S. et.al. CJASN provisionally accepted

Albuminuria lowering effect persists in patients with renal impairment



eGFR							
≥45–<60, n	90	88	82	40	74	36	71
≥60–<90, n	310	306	293	126	269	105	261
≥90, n	175	173	168	94	145	77	150

eGFR subgroup (mL/min/1.73 m²)	Mean UACR		
	Baseline (SD)	Week 24 adjusted Δ (%)	95% CI
≥45–<60	211 (370)	–38.3	–54.4, –16.6
≥60–<90	206 (350	–23.3	–35.5, –8.7
≥90	170 (248)	–16.1	–32.3, 3.8

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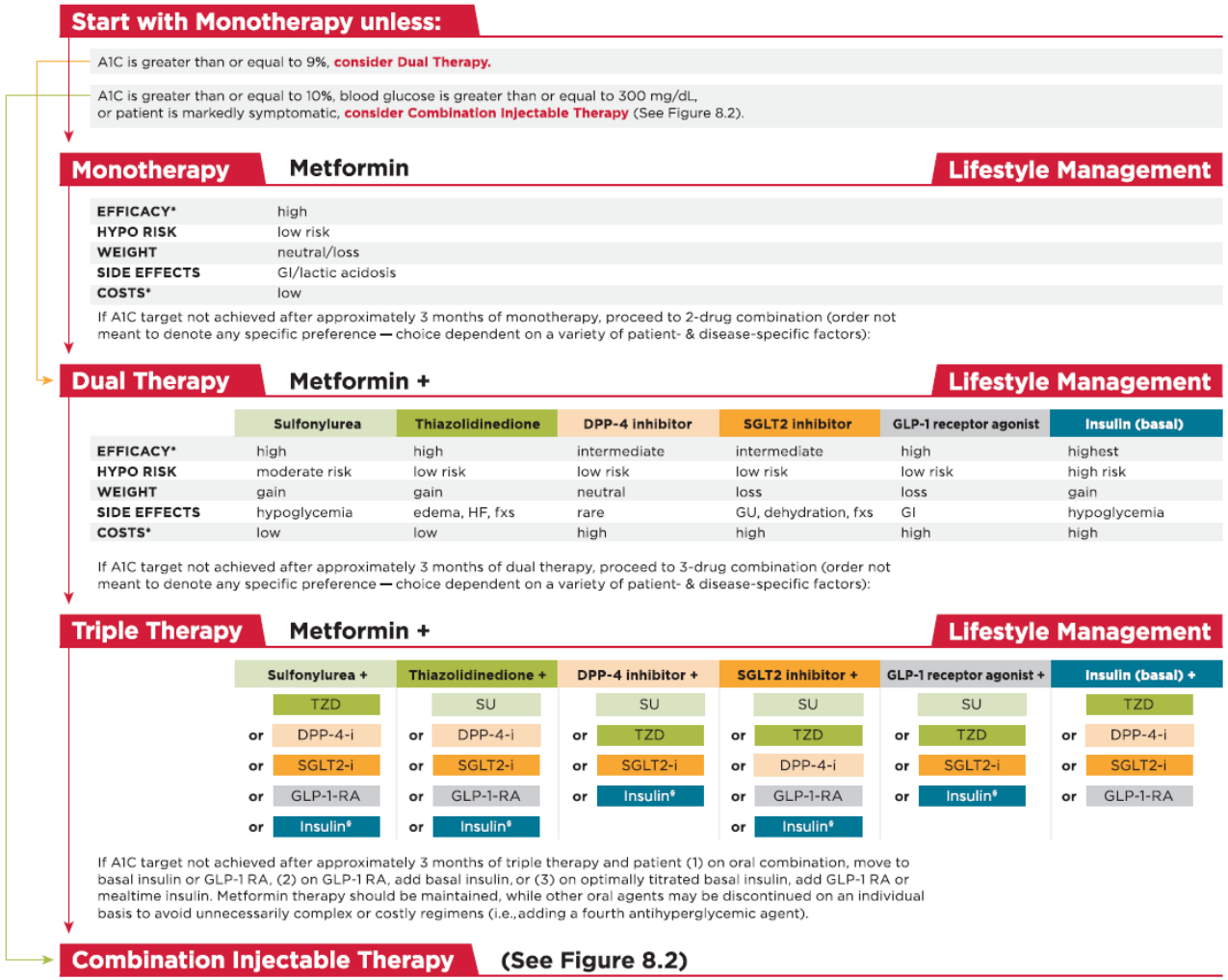
Clinical implications: Individualize treatment



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Metformin** **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy **Metformin +** **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

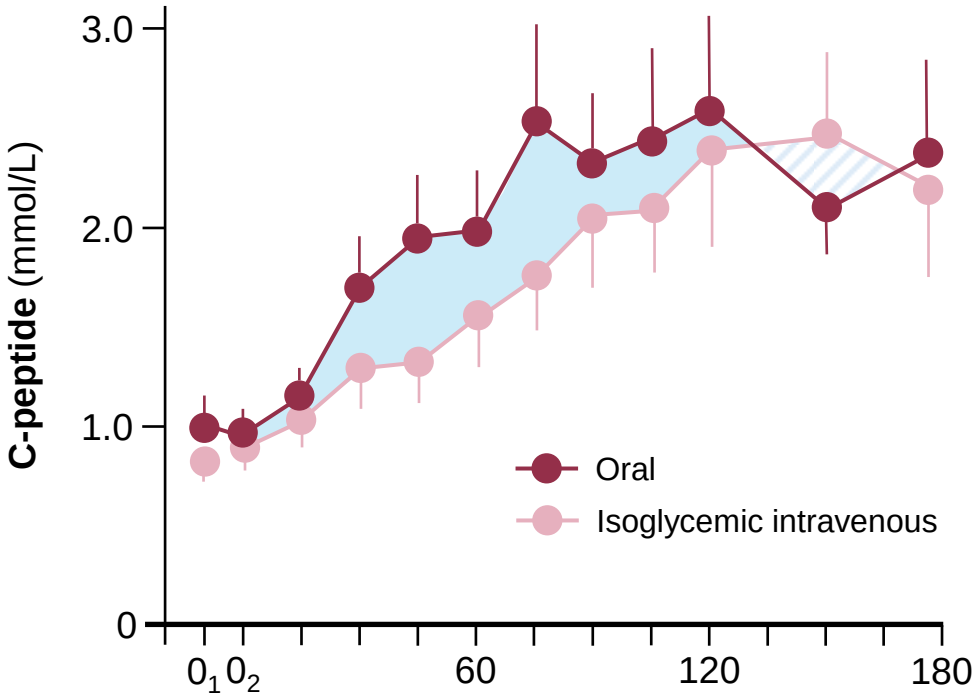
In patient with longstanding diabetes and established atherosclerotic cardiovascular disease empagliflozin or liraglutide should be considered as they have shown to reduce cardiovascular events

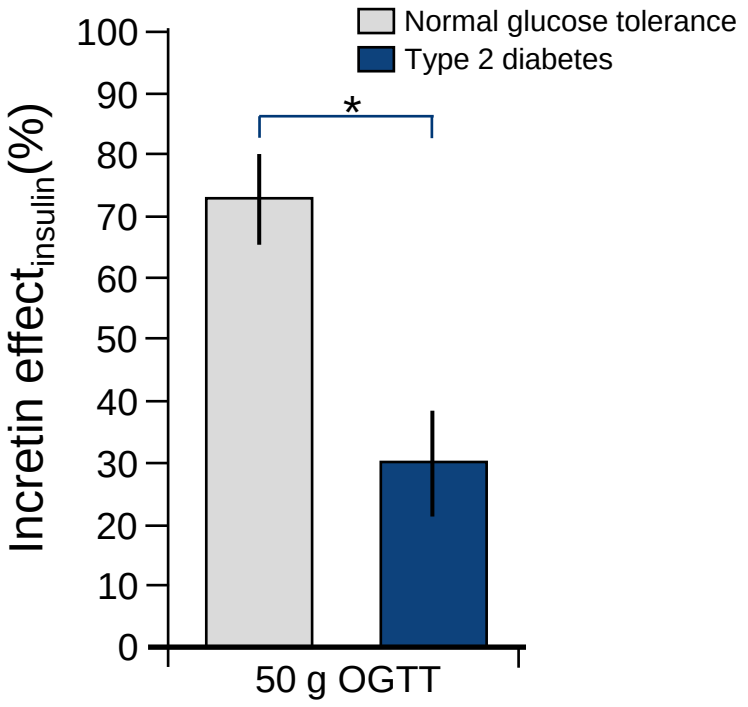
ADA standard of care guideline; Diabetes Care 2017; Supplement 1; S1-S135

Conclusions

- SGLT2 inhibitors form a new class of oral glucose lowering agents
- These drugs have multiple pleiotropic effects
- The alleged renoprotective effects are mediated by
  - Restoring tubulo-glomerular feedback,
  - Inducing natriuresis/diuresis
  - Lowering renal glucotoxicity
- Glucose lowering efficacy in patients with CKD is diminished but albuminuria, blood pressure, body weight lowering effects persists
- Hard outcome outcome trials are needed to definitely proof the renoprotective effects

The “incretin effect” is reduced or absent in type 2 diabetes patients





- A dysfunctional incretin system is part of the pathogenesis of type 2 diabetes
- Enhancement of incretin action was pursued as an interesting therapeutic solution

Nauck MA. *Diabetologia* 1986;29(1):46-52.
Nauck MA. *Lancet Diabetes Endocrinol* 2016;4(6):525-36.

Jørgensen MB. *Kidney Week 2016*. **TH-PO445**

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