New kids on the block: GLP-1 agonists and SGLT2 inhibitors

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GLP-1 agonists and
SGLT2 inhibitors:

In this talk we will discuss these medications in reference to cardiovascular health and CKD.

These drugs are “overnight successes” that took years to develop (e.g. exenatide – Byetta - released 2005)

FDA requires new DM drugs to look at CV disease impact

Serendipity - The CVD and CKD benefits of these medications could not be predicted

GLP-1 RA

Incretins - gut hormones released after a meal

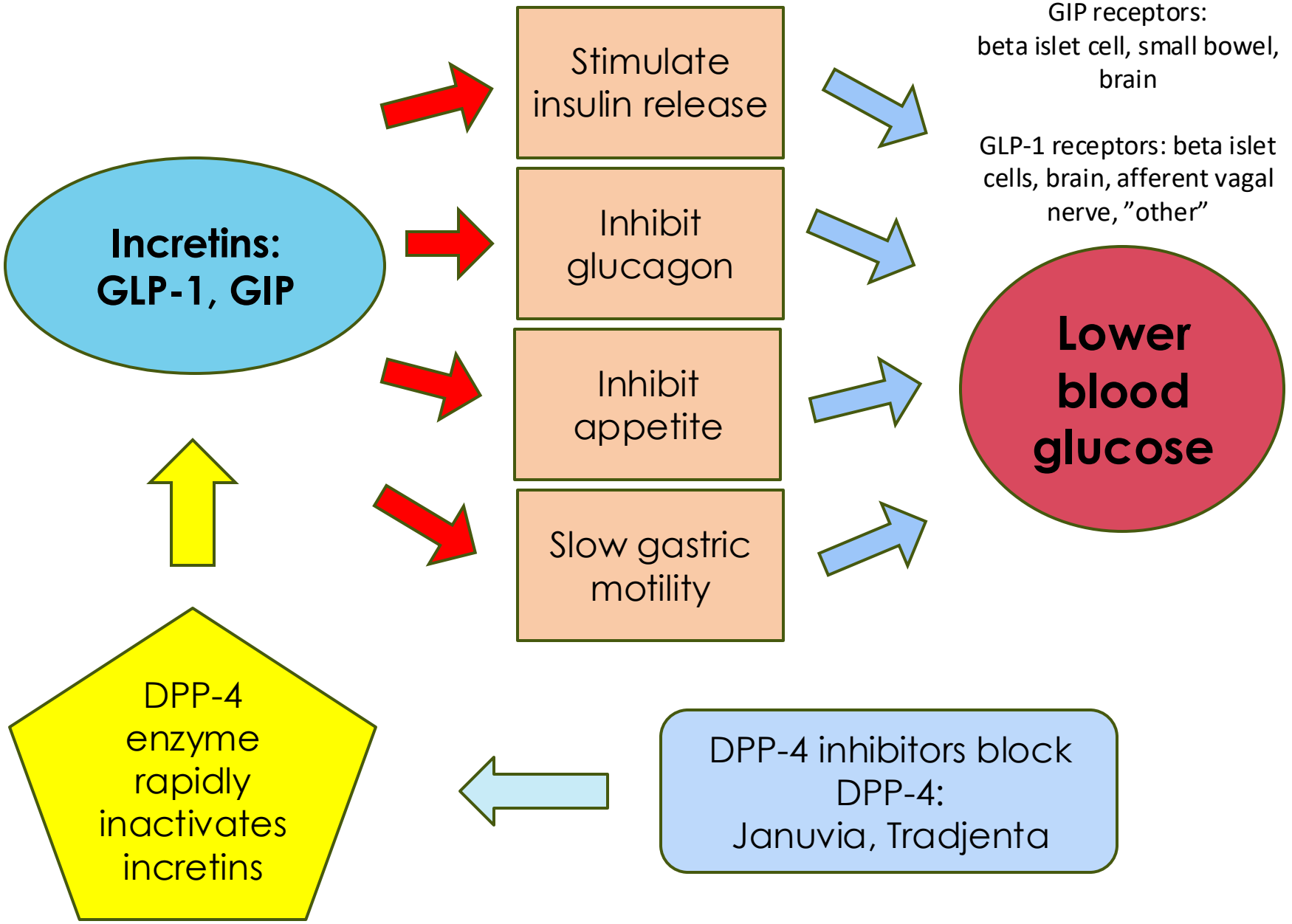
GLP-1 – glucagon-like peptide-1

GIP – glucose-dependent insulinotropic polypeptide

Origin:

GLP-1 is made by L-cells of the small bowel with interaction via microbiome

GIP is made from enteroendocrine K-cells in the upper small intestine, also with microbiome interactions


Incretins:
GLP-1, GIP
Stimulate insulin release
Inhibit glucagon
Inhibit appetite
Slow gastric motility
GIP receptors:
beta islet cell, small bowel, brain
GLP-1 receptors: beta islet cells, brain, afferent vagal nerve, "other"
Lower blood glucose
DPP-4 enzyme rapidly inactivates incretins
DPP-4 inhibitors block DPP-4:
Januvia, Tradjenta

GLP-1 is a transient compound

GLP-1 RA are peptide *receptor agonists*
Each generation with improved half-lives and receptor affinity.

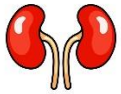
AHA and KDIGO (renal advisory board) remind us the benefits of GLP-1 RA **are NOT group effects** but vary by medication.

Each needs to prove their worth.
For example, exenatide (Byetta) avg weight loss 2.5- 3 kg after 24 weeks, no CVD risk reduction.

SUMMARY OVERVIEW of GLP-1 RA

 **CVD:**

Meta-analysis of 99,592 patients (21 trials) found that MACE , CV death and CVA reduced by 13% (NNT = 66)
(Mattia Galli, et al, J AM Coll Cardiol, 2025)

 **CKD:**

Meta-analysis of 8 trials shows 15-19% risk reduction in CKD (GFR loss, progression to ESRD<, kidney-related death, albuminuria). Albuminuria reduction was driving force

Semaglutide (FLOW study was a CKD study) – 24% reduction in kidney failure, >50% GFR loss, death from CKD or CVD over 3.4 years

Tirzepatide (SUMMIT, SURPASS-4 trials) – 42% reduction vs insulin, mostly studied CKD III

GLP-1 RA FDA approved for CVD ❤ reduction:

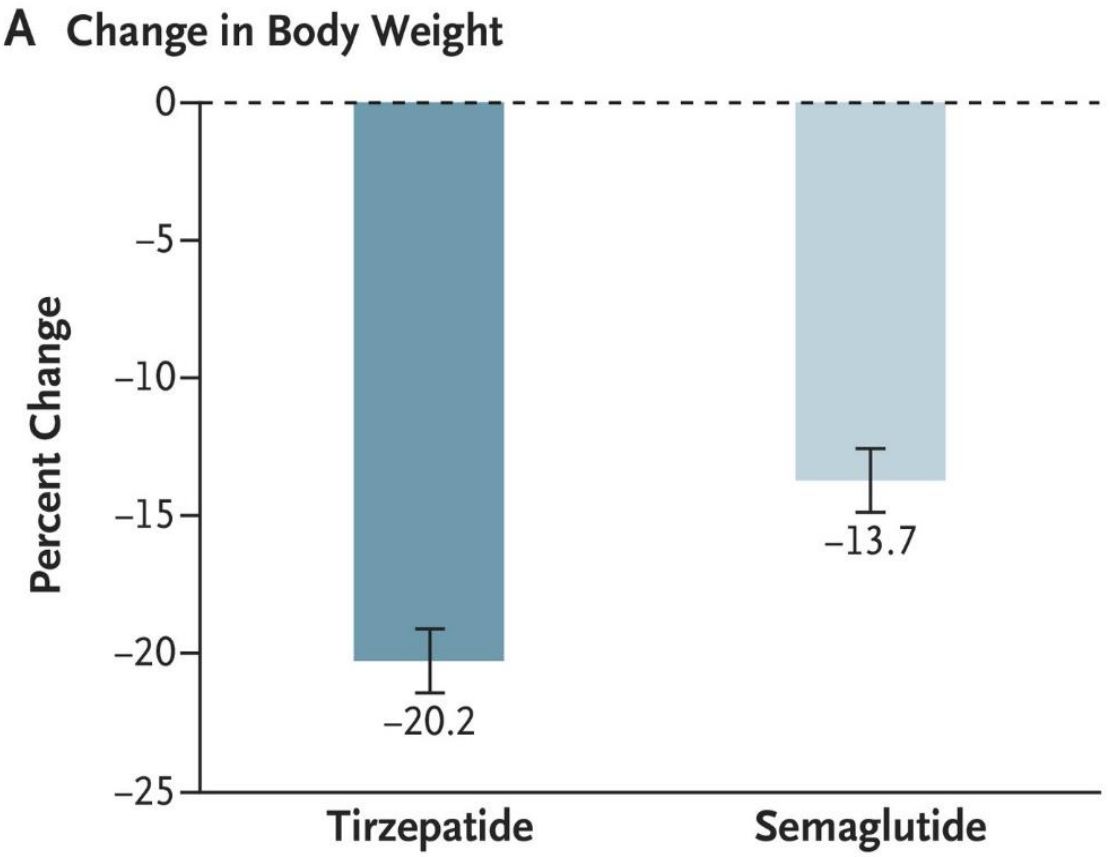
liraglutide (Victoza)
LEADER trial – CV reduction 13% vs 14.9% placebo over 3.8 years

dulaglutide (Trulicity)
REWIND trial, 12% reduction – many primary prevention

semaglutide (Ozempic / Wegovy)
SUSTAIN-6 trial, 26% reduction in MACE in obese diabetics
SELECT trial –non diabetic BMI > 27 kg/m2, 20% reduction over 40 months

tirzepatide (Mounjaro / Zepbound) ? - not yet FDA approved; GLP-1 / GIP combination, several real-world experience to suggest success

The Battle of the Heavyweights: Semaglutide vs Tirzepatide



Tirzepatide as Compared with Semaglutide for the Treatment of Obesity: Louis J. Aronne, M.D., et al. **N Engl J Med 2025;393:26-36** VOL. 393 NO. 1

The Battle of the Heavyweights: Semaglutide vs Tirzepatide

Weight loss may not translate into CVD risk reduction:

CVD reduction:

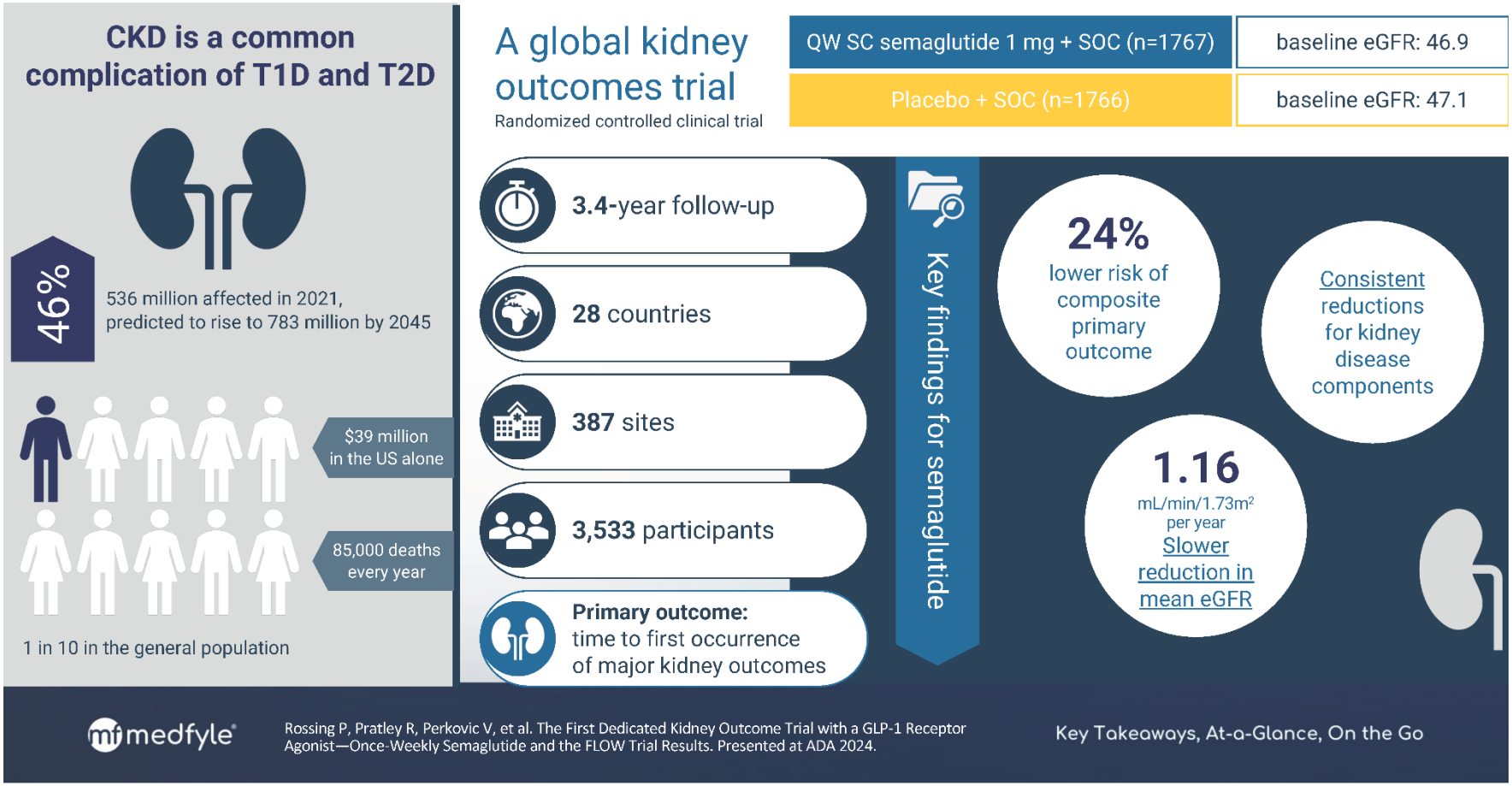
Surpass – CVOT trial:
Tirzepatide (with superior weight loss) was shown non-inferior to dulaglutide (Trulicity) but not superior

STEER trial: Reports from European Society of Cardiology Congress, September 2025 : semaglutide superior to tirzepatide (obesity and non diabetic use) *(not published)

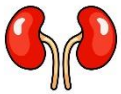
SELECT – Wegovy improved MACE within 3 months of a cardiac event , prior to significant weight reduction.
Hazard reduction 63% vs control in the first 3 months.
(so start ASAP post MI)

Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes, Perkovic et al, NEJM: 2024: 391:109-121

FLOW: the first dedicated kidney outcomes trial with a GLP-1RA



* versus placebo: slower GFR loss - GFR 3.3 ml/min better after 2 years, albuminuria reduced 40%, CVD events 18% lower, death of any cause 20% lower



CKD improvements

Semaglutide (non diabetics with obesity):

- SELECT trial - 22% relative risk reduction in albuminuria, eGFR decline of 50%, kidney failure or death due to kidney – hazard ratio 0.78
- Only 21% Select had eGFR < 60 – so main goal was CKD development / not progression
- Benefits occurred independent of weight loss (as also in FLOW study)

Tirzepatide:

Surpass-4 trial post hoc analysis

- Reduced GFR decline, UACR reduced ~ 7% vs 24% increase with insulin use (Lancet Diabetes Endocrinol, Nov 2022, Heerspink, et al.)
- Not powered for hard endpoints

Mechanisms of GLP-1 RA effects on CKD & CV disease risk reduction:

Weight loss
DM control
BP control
Lipid control

GLP-1 receptors in the heart and kidney (GIP not):

- Cardiomyocytes especially at the SA node but also ventricles
- Renal vascular smooth muscles and mesangial cells of the glomerulus.
- mTOR pathway inhibition -> reduces collagen expression
- Downregulates angiotensin II, upregulates AT2 receptors and downregulates AT1 receptors. May slow angiotensin- induced fibrosis.
- Improves glucose use of cardiomyocytes in ischemia – shifts from fatty acid use that occurs in DM and ischemia.

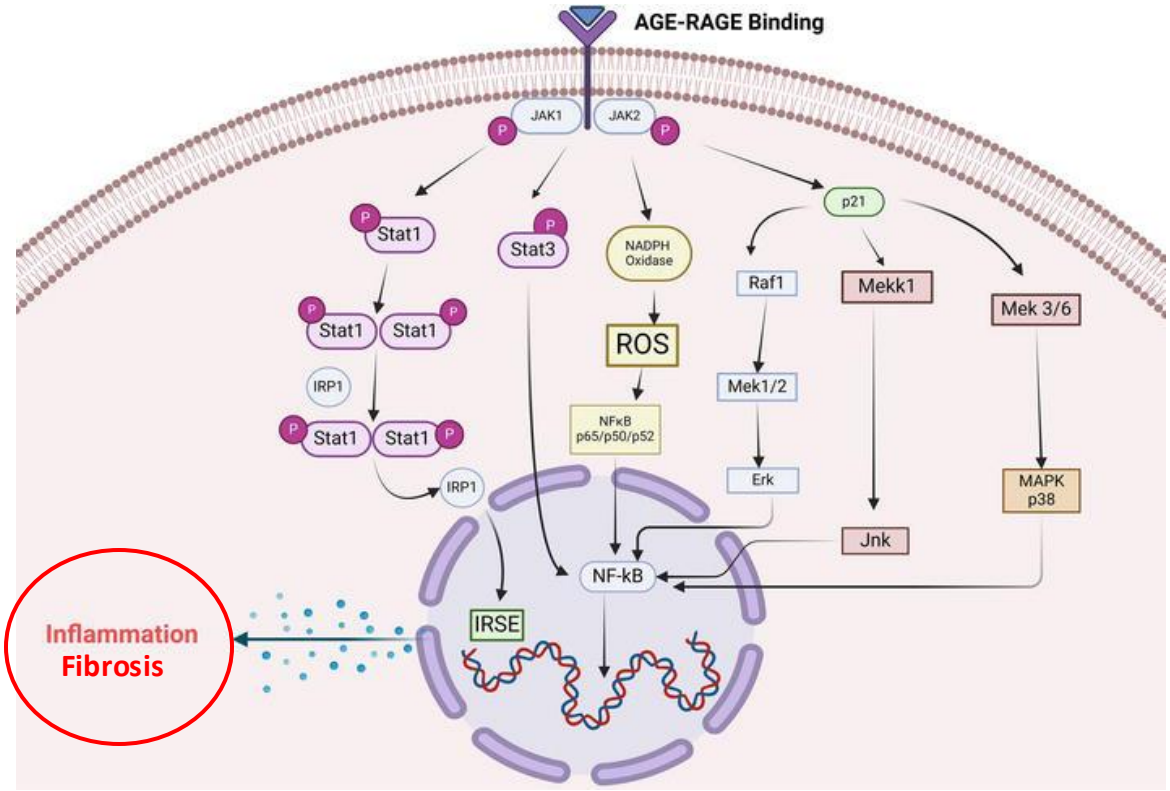
GLP-1 RAs inhibit the RAGE (Receptor of AGE)

AGE: advanced glycosylated endproducts

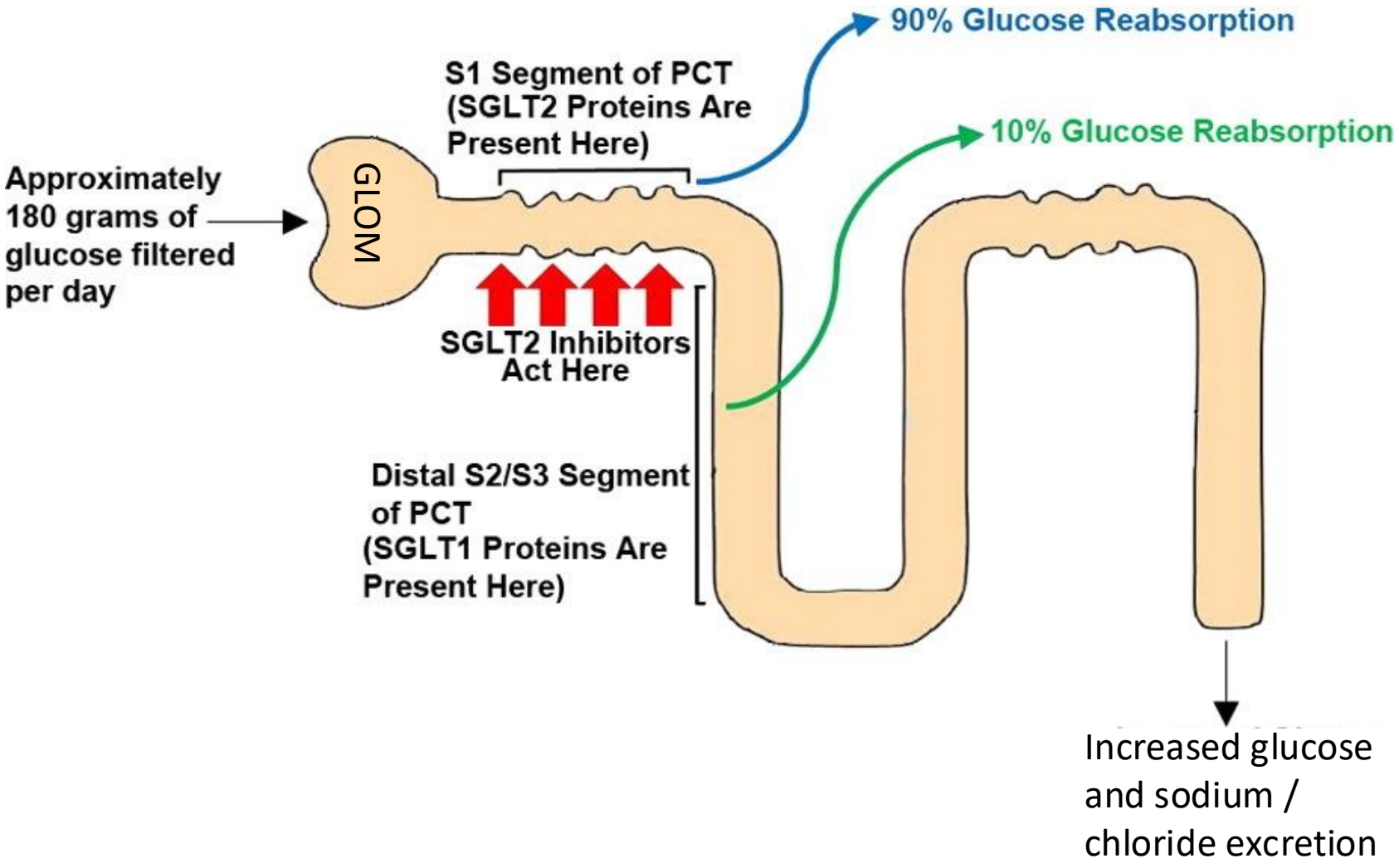
(aka Amadori products – proteins and lipids that are glycated)

GLP-1 RA

Decrease receptor expression
Promote cell shedding or receptor



Sodium Glucose Transporter -2 Inhibitors

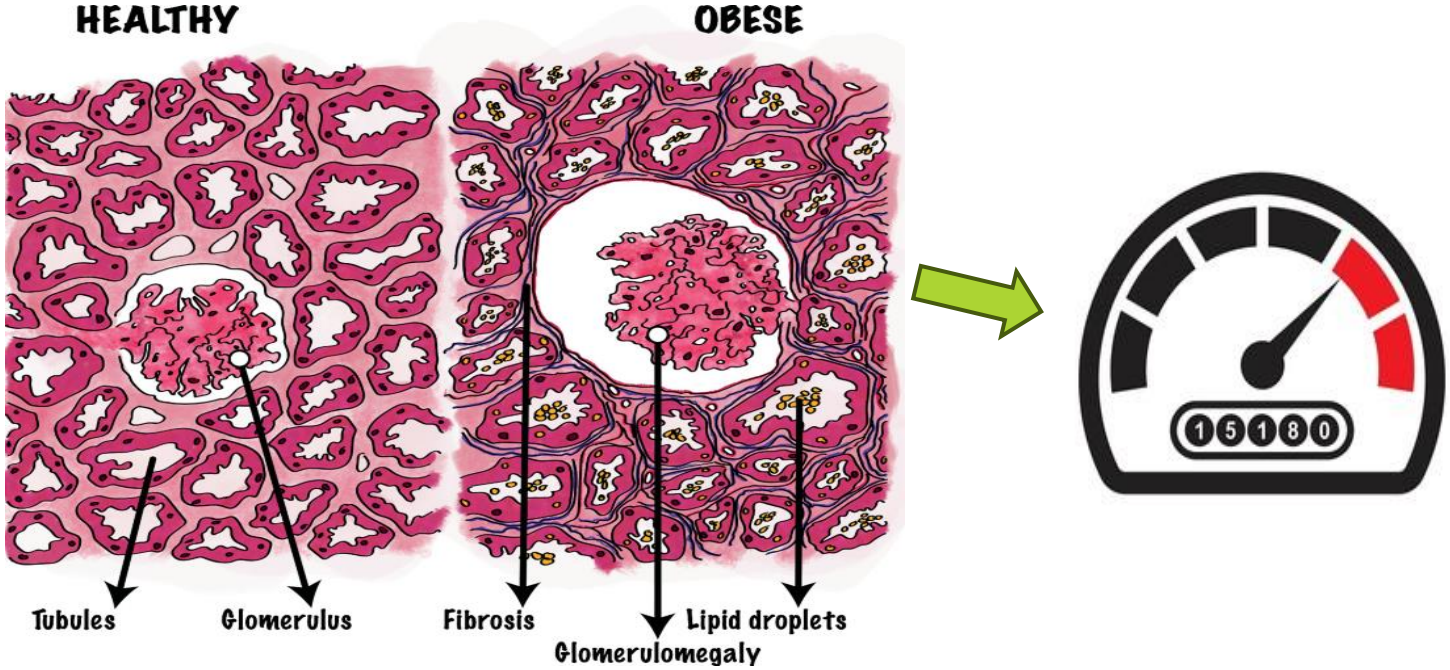


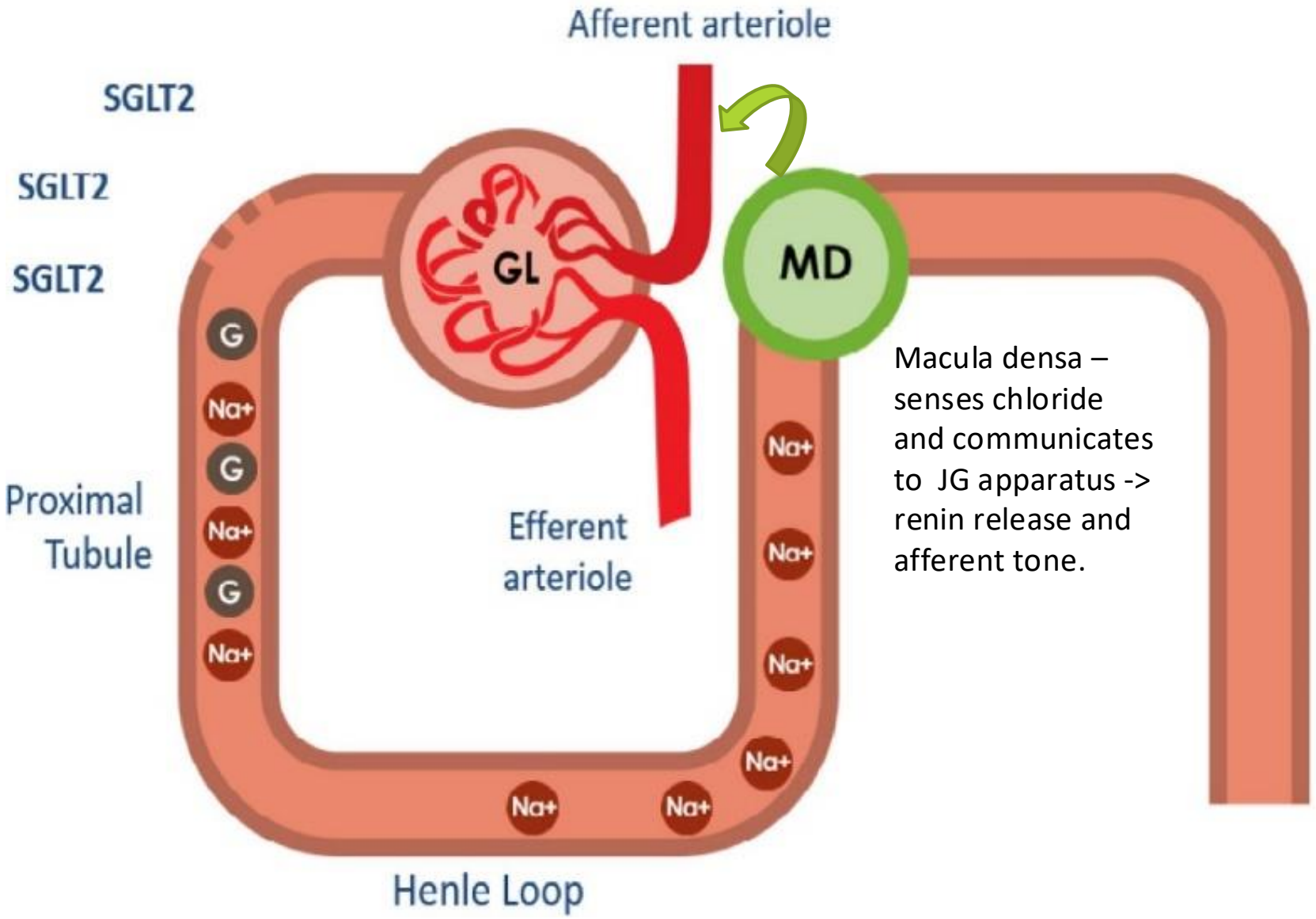
- SGLT2i create an osmotic diuresis and a sodium losing state.
- These effects do not seem to have a “braking” phenomenon as traditional diuretic therapy
- Addition of SGLT2 I to loop diuretic increases natriuesis by > 35%
- Intravascular depletion DOES NOT activate RAAS

Glomerular Hyperfiltration -> CKD

<u>Clinical states:</u>
Obesity
Poor nephron development (prematurity), loss of a kidney as a child
Nephron loss of CKD (remaining nephrons work harder = ablative nephropathy)
DM with hyperglycemia – via SGLT2 receptors

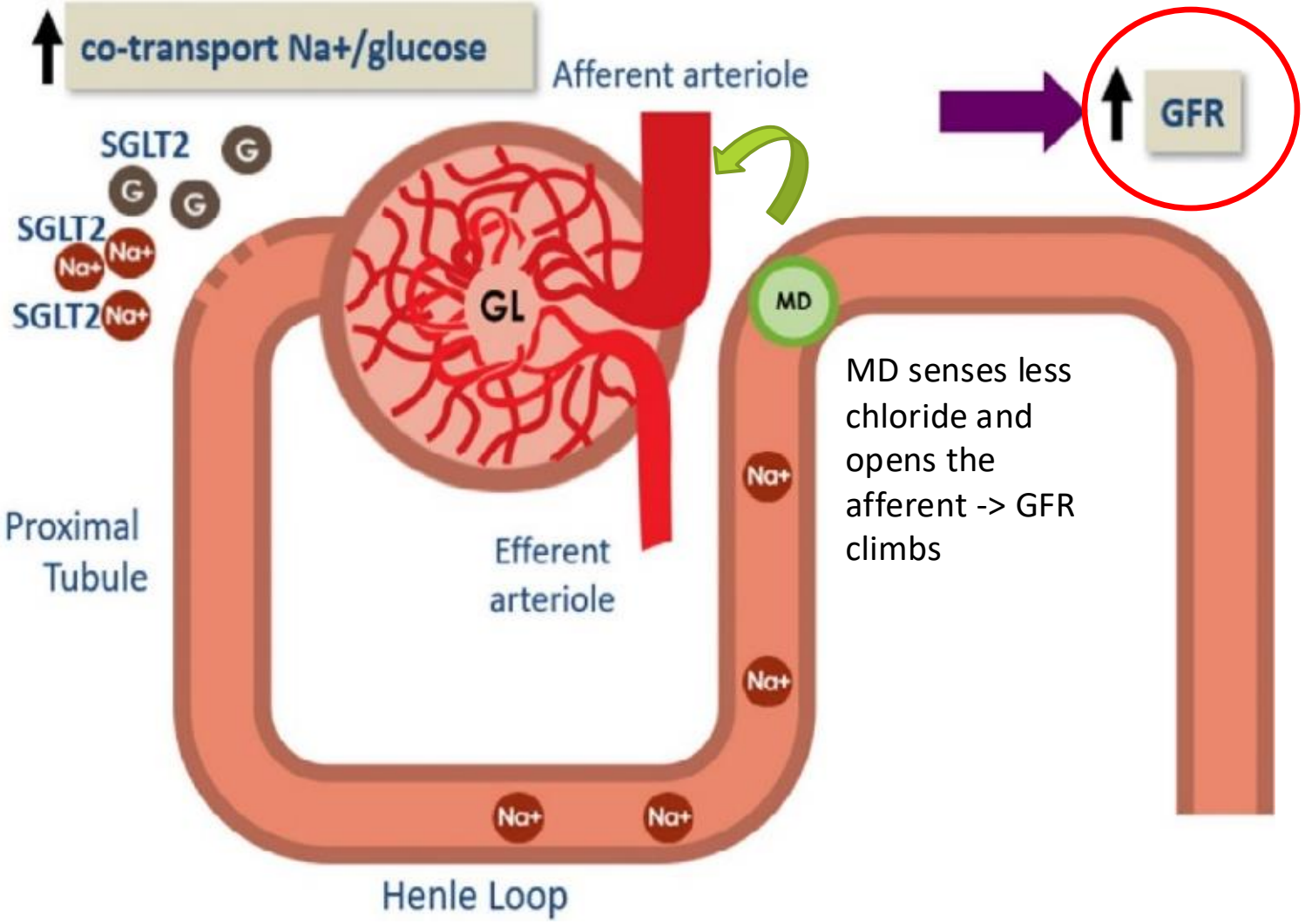
Anatomical change: glomerulomegaly

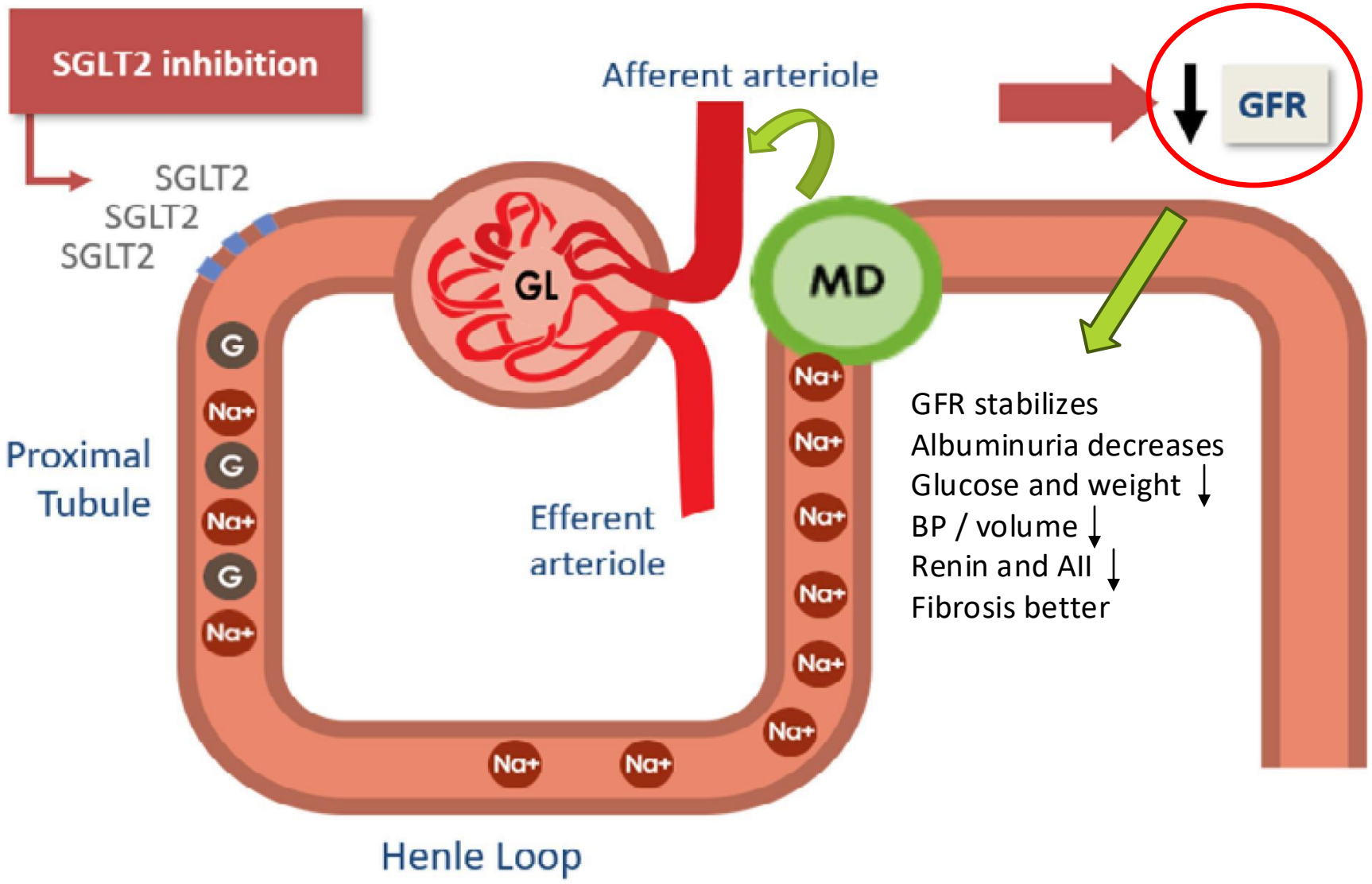


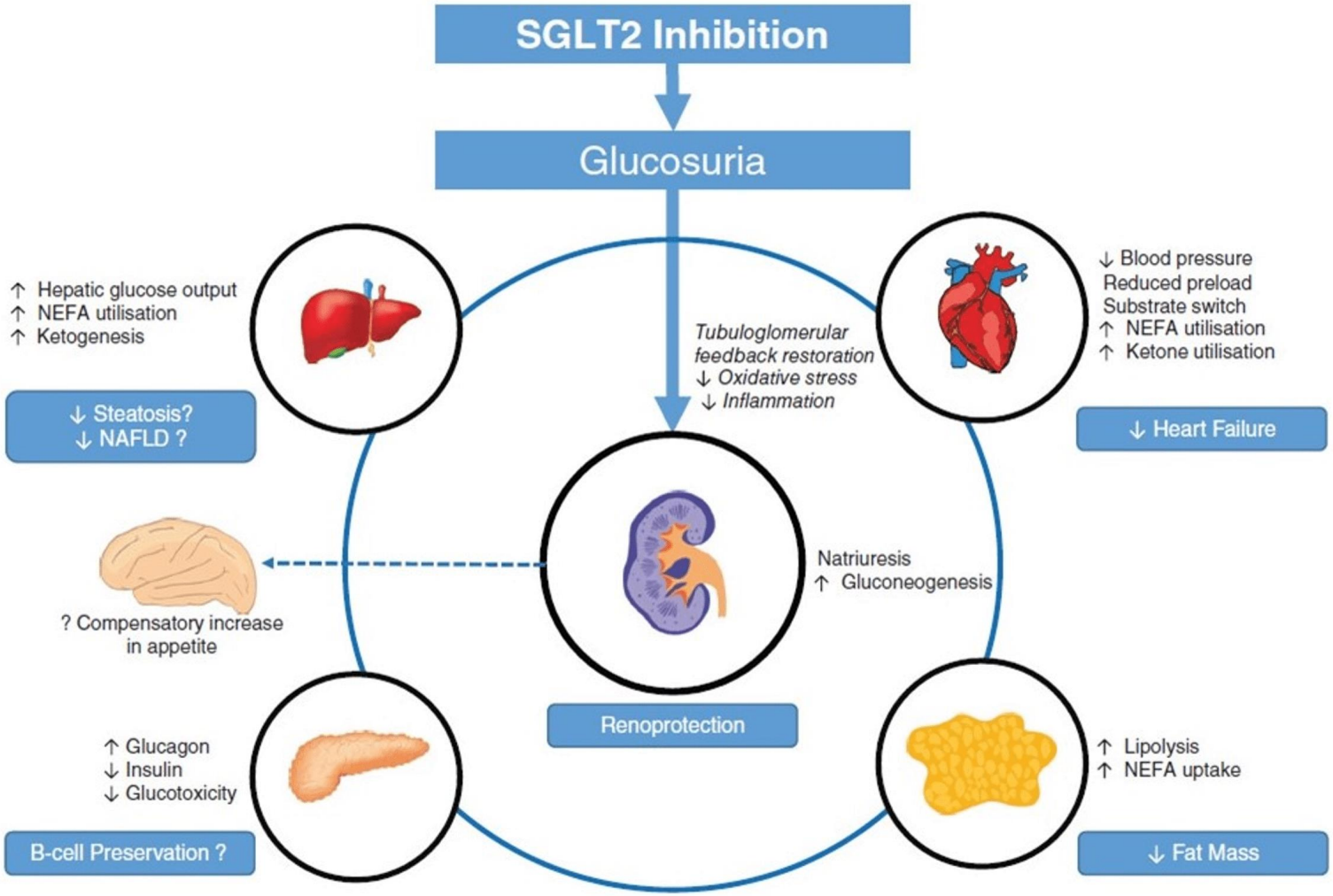


Macula densa – senses chloride and communicates to JG apparatus -> renin release and afferent tone.

Diabetes causes hyperfiltration and glomerular injury




SGLT2 inhibition
Afferent arteriole
GFR
SGLT2
SGLT2
SGLT2
GL
MD
G
Na+
G
Na+
G
Na+
Proximal Tubule
Efferent arteriole
Na+
Na+
Na+
Na+
Na+
Na+
Na+
Na+
GFR stabilizes
Albuminuria decreases
Glucose and weight
BP / volume
Renin and AII
Fibrosis better
Henle Loop

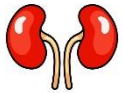

SGLT2 Inhibition
Glucosuria
↑ Hepatic glucose output
↑ NEFA utilisation
↑ Ketogenesis
↓ Steatosis?
↓ NAFLD ?
Tubuloglomerular
feedback restoration
↓ Oxidative stress
↓ Inflammation
↓ Blood pressure
Reduced preload
Substrate switch
↑ NEFA utilisation
↑ Ketone utilisation
↓ Heart Failure
? Compensatory increase
in appetite
Natriuresis
↑ Gluconeogenesis
Renoprotection
↑ Glucagon
↓ Insulin
↓ Glucotoxicity
B-cell Preservation ?
↑ Lipolysis
↑ NEFA uptake
↓ Fat Mass

SGLT2i Trials

 Improvement in MACE, including CV death, HF hospitalizations (diabetics and non-diabetics)

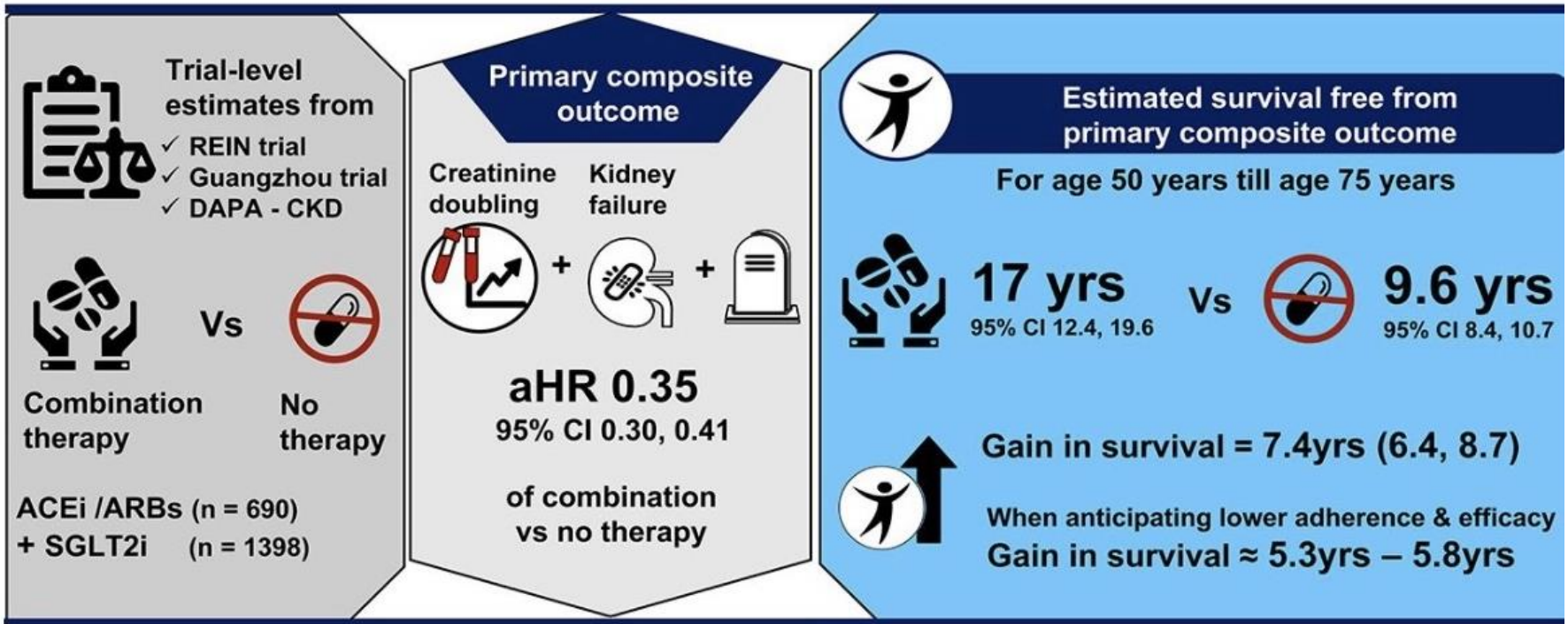
HFrEF: reduce risk of CV death, all cause mortality, HF admissions (DAPA-reduced trial)

HFpEF: reduce HF admissions, neutral benefit of death (DAPA- preserved trial)

 Improvement of GFR loss in diabetics and non-diabetics: CREDENCE, EMPA-REG, EMPEROR trials

Estimated lifetime benefit of combined RAAS and SGLT2 inhibitor therapy in albuminuric CKD without diabetes

CJASN
Clinical Journal of the American Society of Nephrology

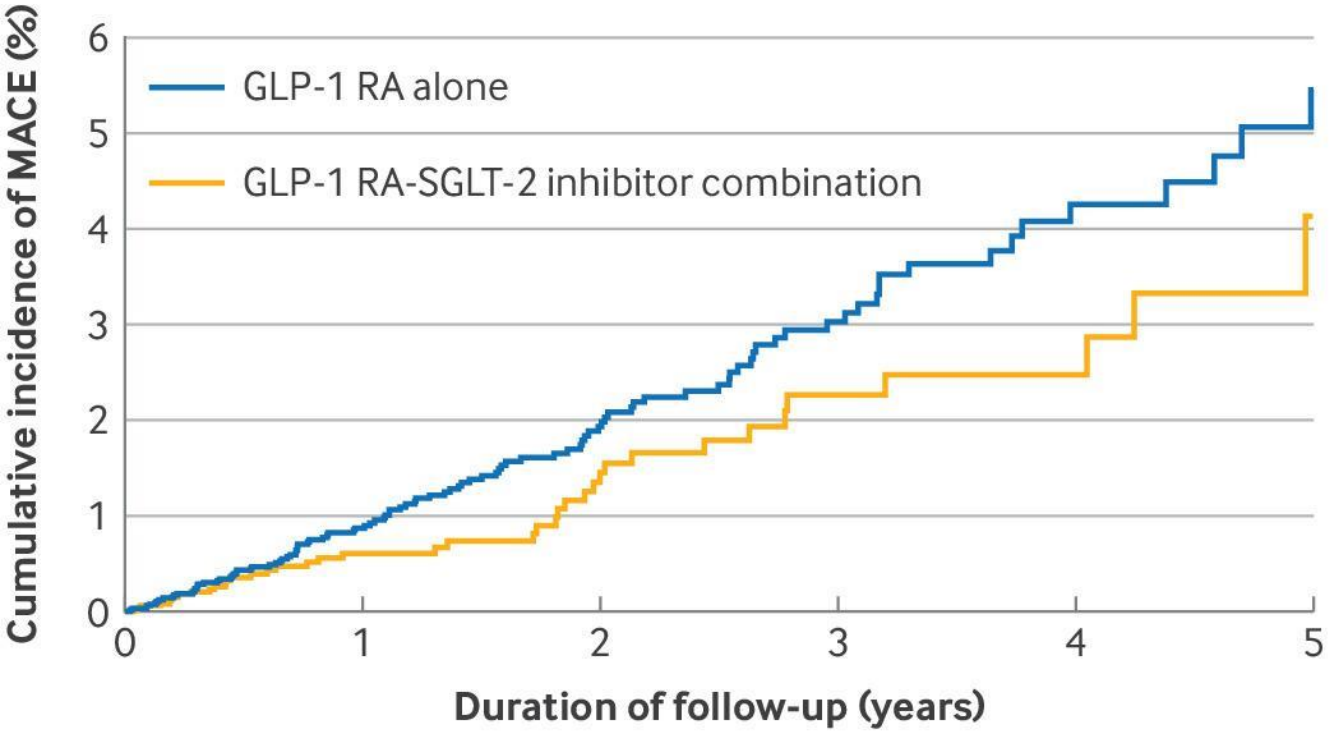


Conclusions: Treatment with the combination of ACE inhibitors/ARB and SGLT2 inhibitor in patients with albuminuric CKD without diabetes is expected to substantially increase kidney failure-free survival.

Priya Vart, Muthiah Vaduganathan, Niels Jongs, et al. ***Estimated Lifetime Benefit of Combined RAAS and SGLT2 Inhibitor Therapy in Patients with Albuminuric CKD without Diabetes***. CJASN doi: 10.2215/CJN.08900722. **Visual Abstract by Divya Bajpai, MD, PhD**

Combination Therapy: Is more….better?

Cumulative incidence curves of major adverse cardiovascular events (MACE) for glucagon-like peptide-1 (GLP-1) receptor agonist (RA)-sodium-glucose cotransporter-2 (SGLT-2) inhibitor combination versus GLP-1 RAs.



30% ⇩

(CKD: ⇩ 57% using both)

No at risk

GLP-1 RA alone					
6696	3798	1996	1072	532	242
GLP-1 RA-SGLT-2 inhibitor combination					
6696	1986	1000	519	259	114

Nikita Simms-Williams et al. BMJ 2024;385:bmj-2023-078242

Thank you