



SGLT2 inhibitors: how they work and when not to use them

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Relevant Financial Disclosure(s)

Ramon Bonegio, MBBCh/PhD

- I have nothing to disclose



Objectives



- Review the role of sodium glucose transporters (SGLT) in the kidney
- Understand the pharmacology of the SGLT2 inhibitors and how they protect the kidney in diabetes and heart failure
- Gain an appreciation for when and why SGLT2 inhibitors should sometimes be avoided

Outline



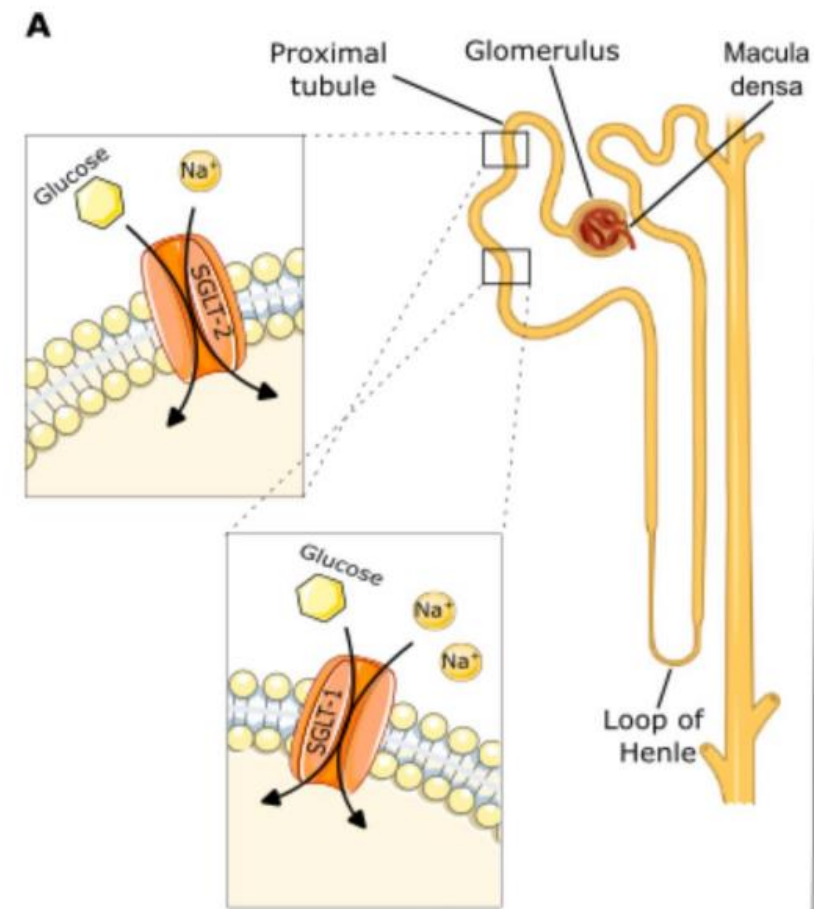
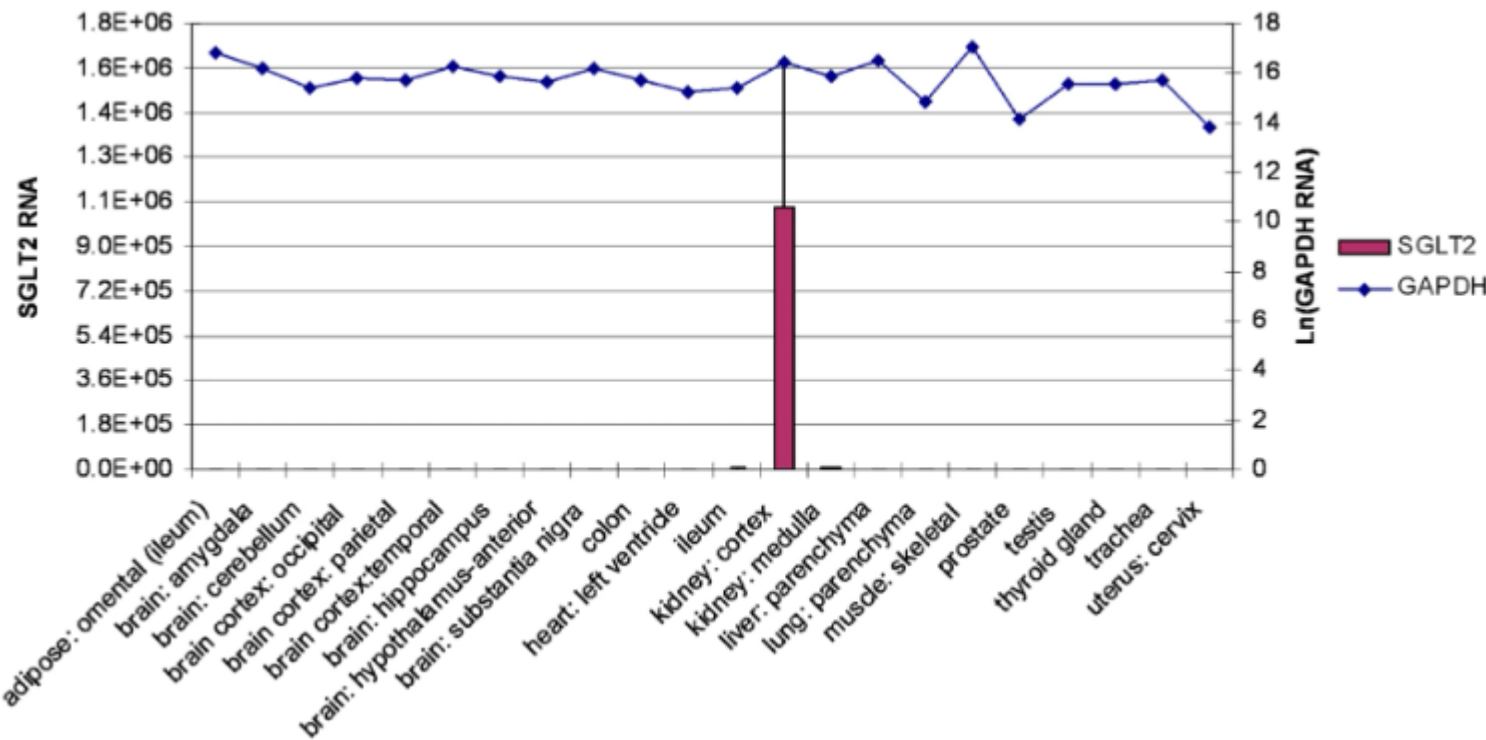
- Clinical case for consideration
- SGLT2 biology
- The pharmacology of SGLT2 inhibitors
- Important contra-indications to consider when “floxinating”

A rare clinical cautionary tale



- Mr. JM is a 76-year-old Navy Veteran with a history of type 2 diabetes, hypertension, Parkinsonism with autonomic dysfunction, and prostate cancer s/p external beam radiation
- He is following a nephrologist because of CKD stage 4 (eGFR 29 ml/min) with albuminuria (ACR 422 mg/g).
 - Receiving Semaglutide, Losartan, and Dapagliflozin for renal protection
 - HbA1c 6.8%
 - BP well controlled at home and averaging 127/64 mmHg

SGLT2 transporters are expressed in the kidney



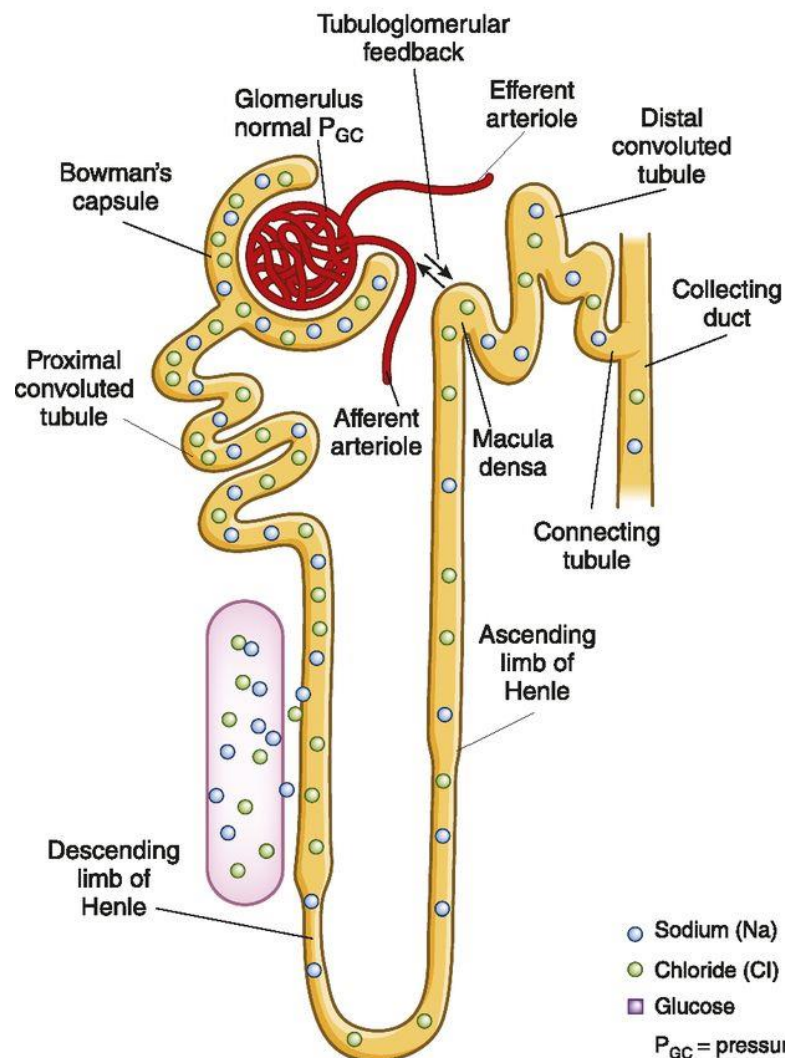
Chen et al Quantitative PCR tissue expression profiling of the human SGLT2 gene and related family members, Diabetic Therapy 2010

Hoehlschen et al Cardiovascular Diabetology 2023

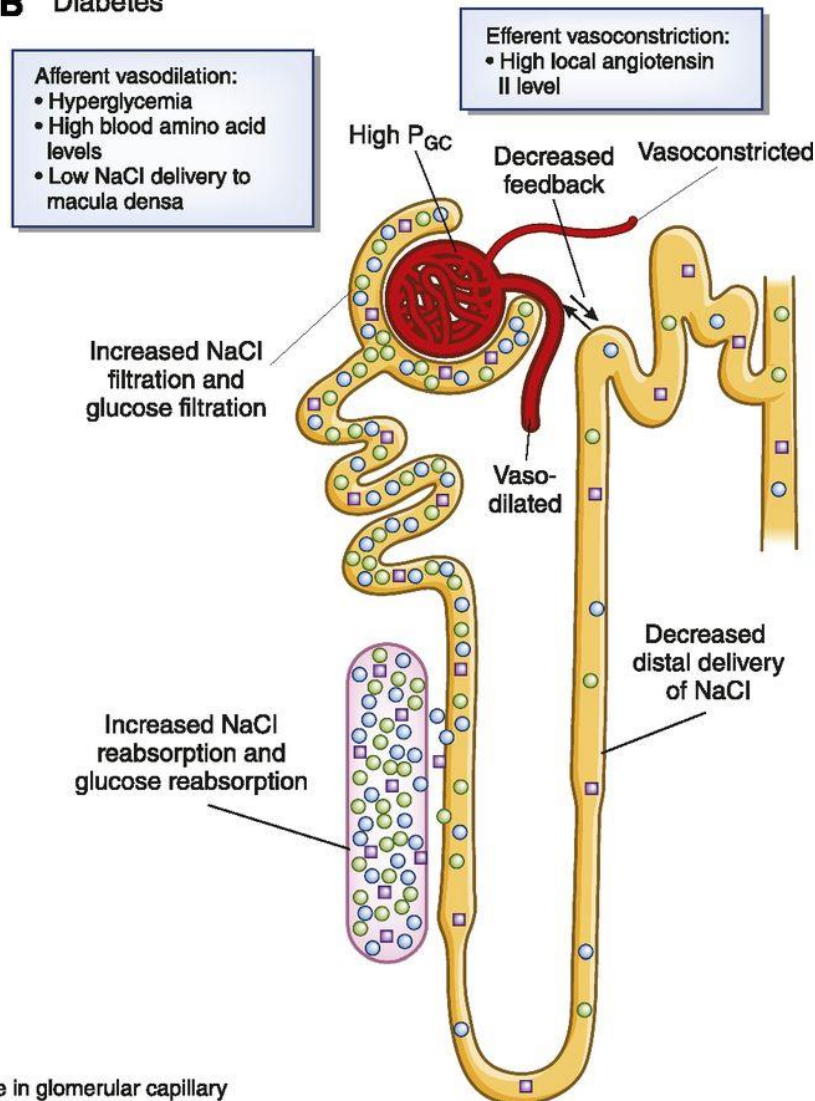


NORMAL AND DIABETIC RENAL HEMODYNAMICS.

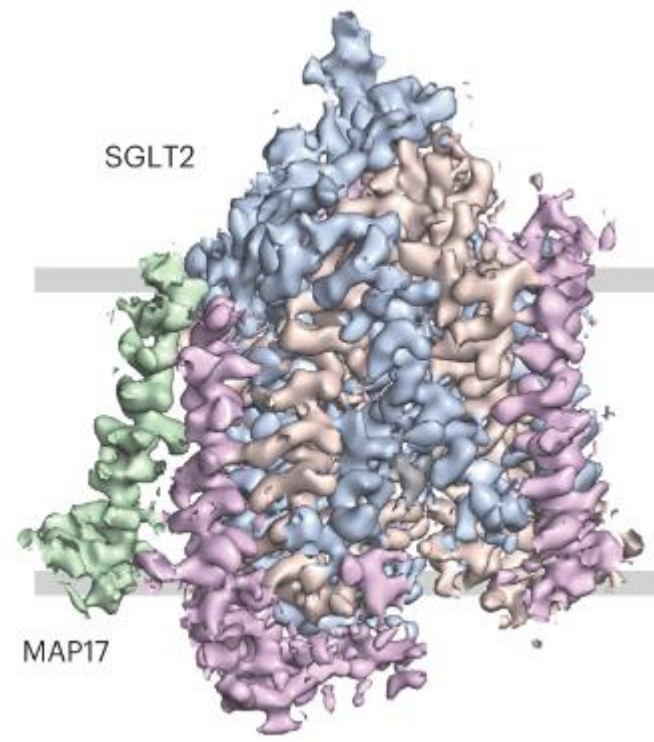
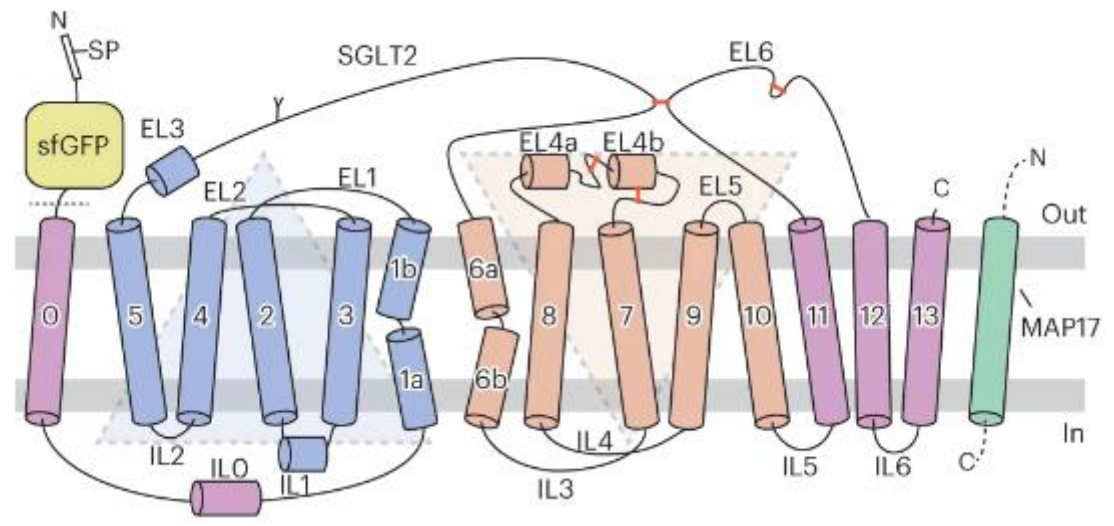
A Normal



B Diabetes



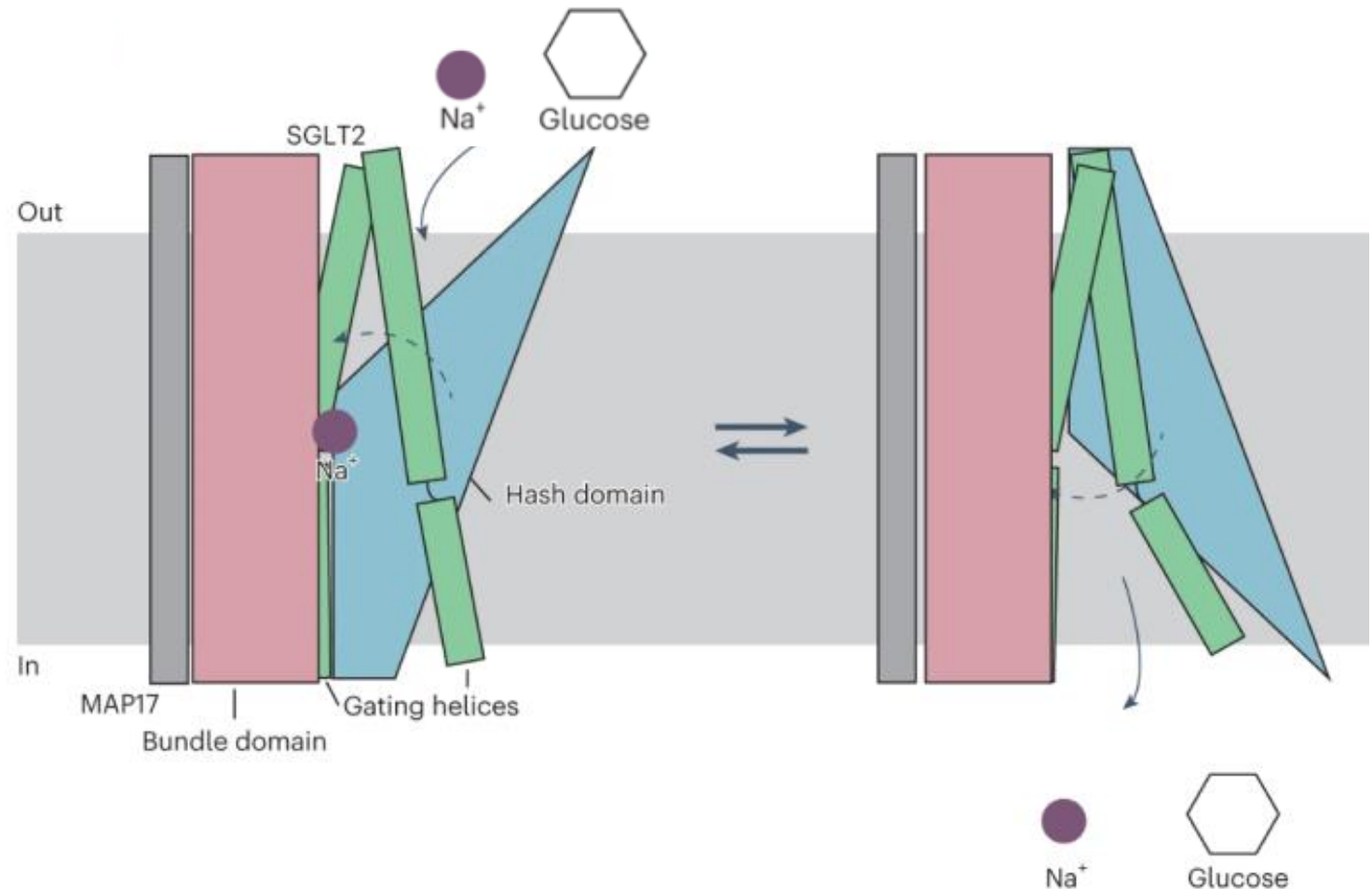
SGLT2 transporters a heterodimer of SGLT2 and MAP17



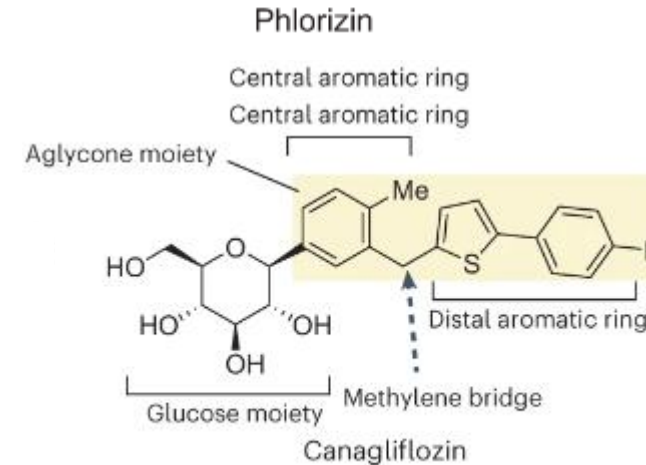
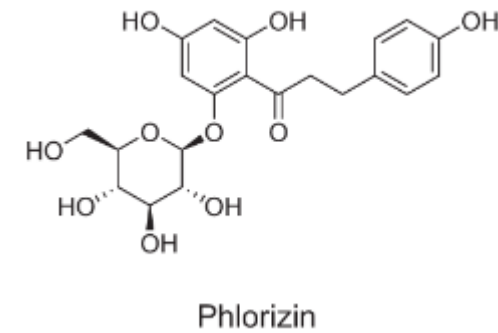
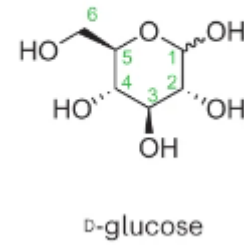
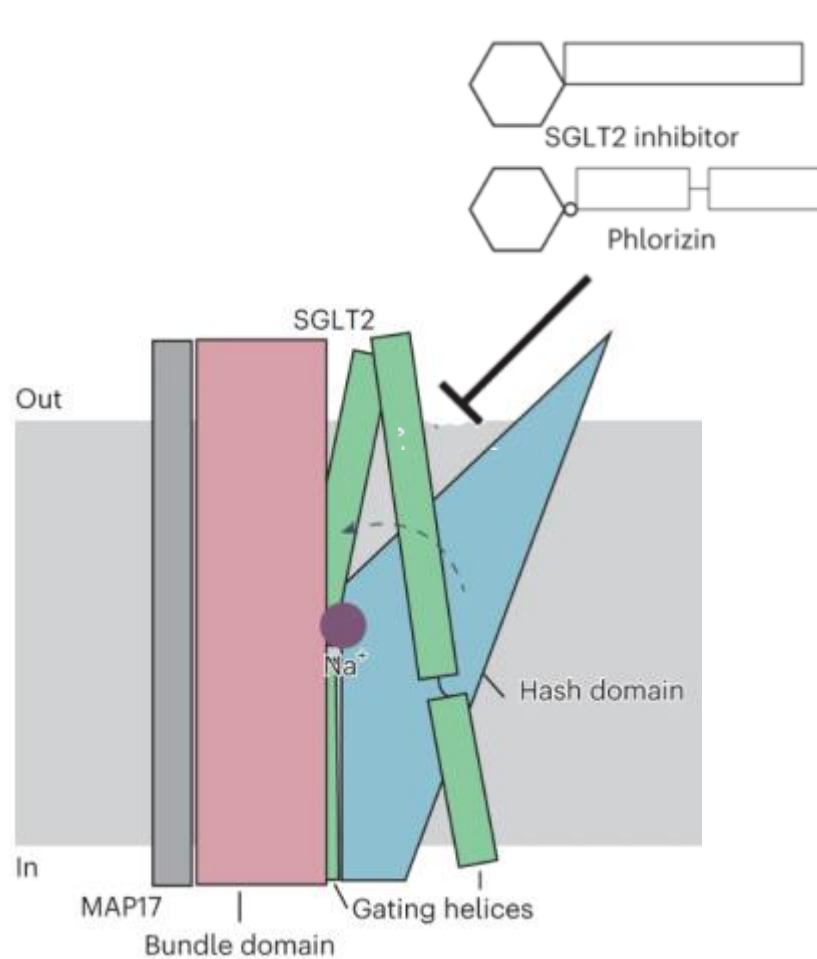
SGLT2 transporter move glucose into cells



- SGLTs have two parts
- An Immobilized scaffold and a rocking bundle that opens outwards or inwards
- The rocking bundle is though to oscillate between an outward facing conformation and inward facing conformation
- Sodium, which is at relatively high concentration outside can bind to the rocking bundle and this allows the substrate (glucose) to engage
- When the bundle rocks to the inward facing conformation, sodium and glucose dissociate into the cell
- SGLT1 (gut and kidney) is higher affinity and binds 2 Na for every glucose while SGLT2 transports 1 Na per glucose



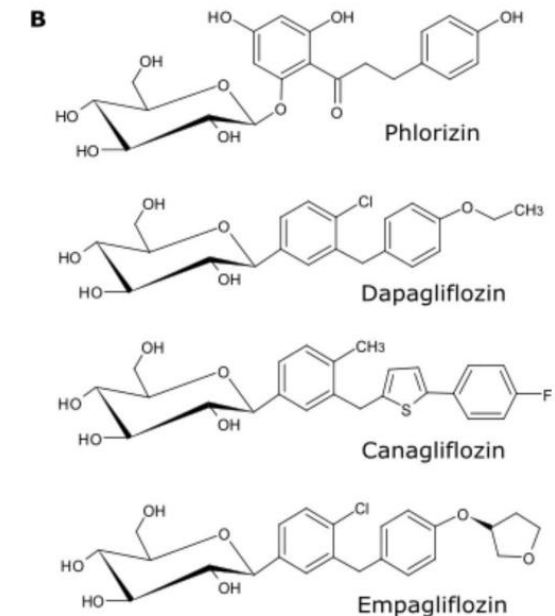
SGLT2 transporter move glucose with sodium using a



Multiple SGLT2 inhibitors are now available

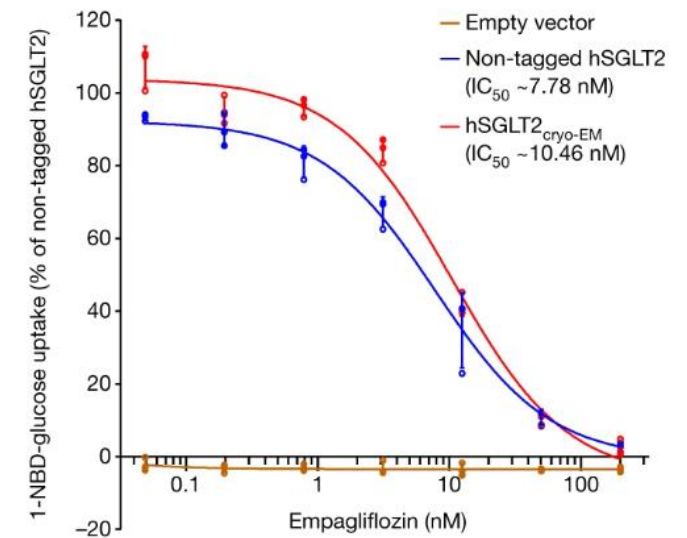
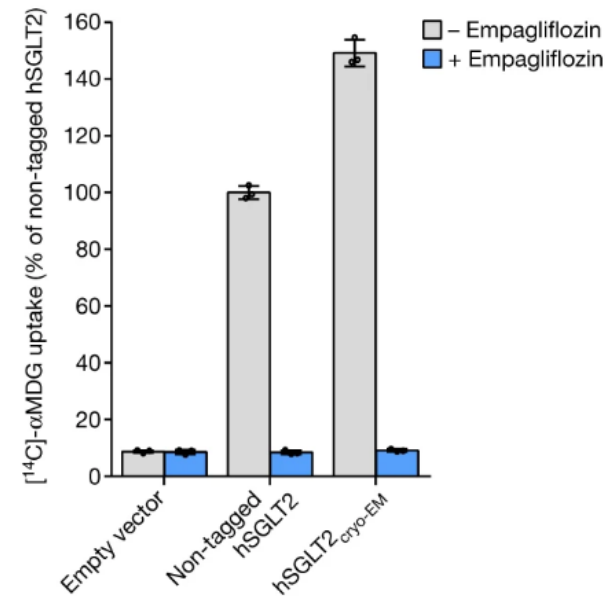
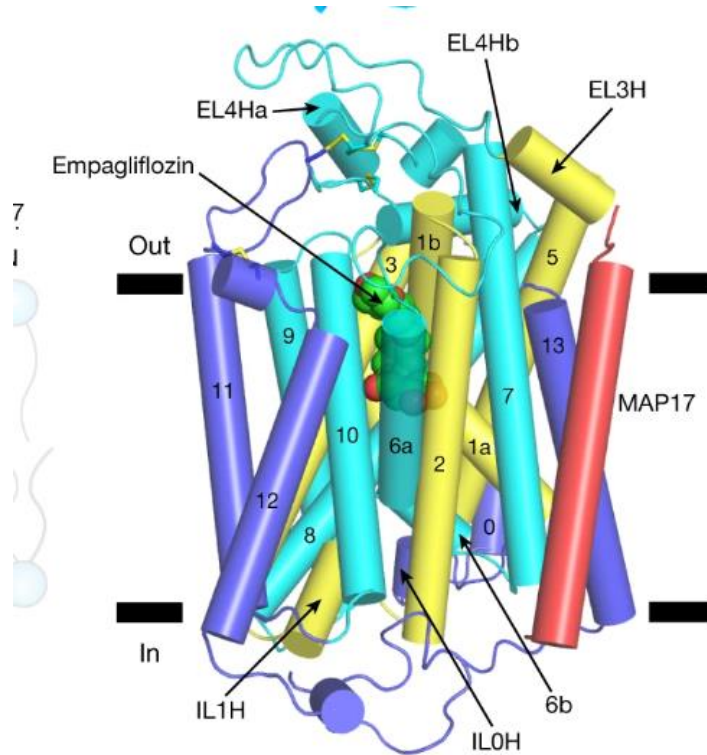


SGLT2-i	Dose (mg/d)	Bioavailability	T _{1/2} (hr)	IC50 (nM) (SGLT2/SGLT1)	Excretion (% Renal/GI)
Phlorizin		<10			
Dapagliflozin	5-10	~78%	13	1.2/1,400 (~1,200-fold)	75/21
Canagliflozin	100-300	~ 65%	13	2.7/710 (~250-fold)	33/50
Empagliflozin	10-25	~75%	13	3.1/8,300 (~2,500-fold)	55/40



- Several newer agents with less specificity for SGLT2 are under investigation

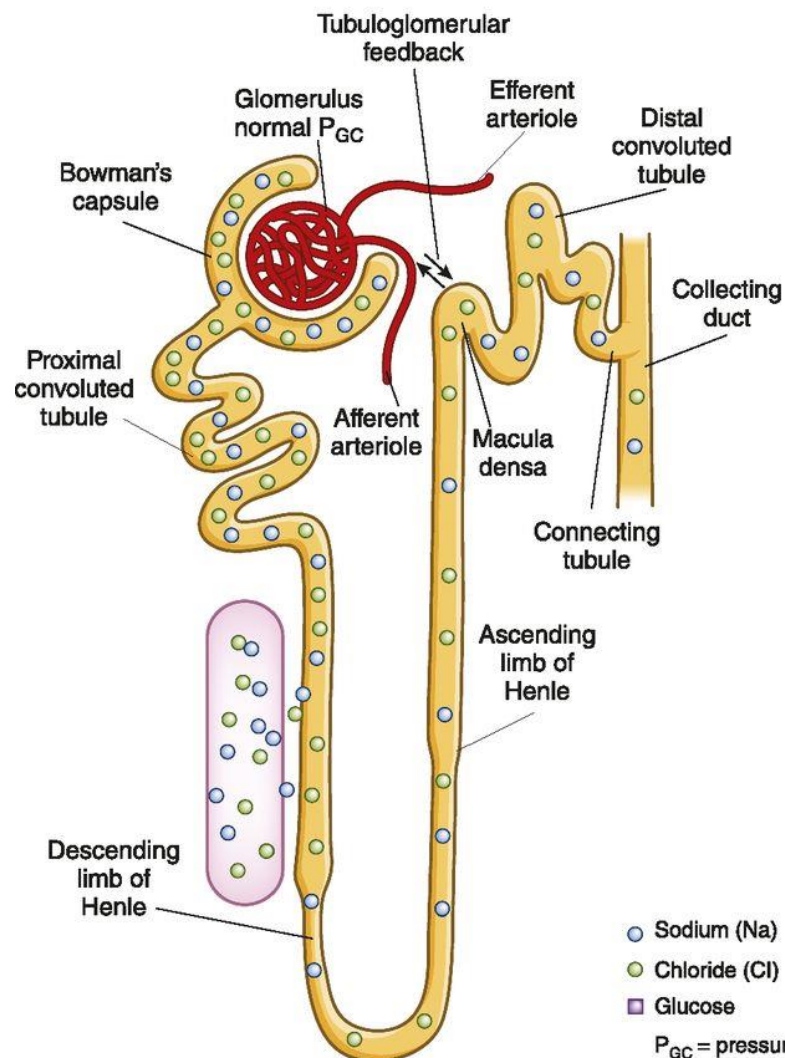
Effective inhibition of SGLT2 with Phlorizin derivatives



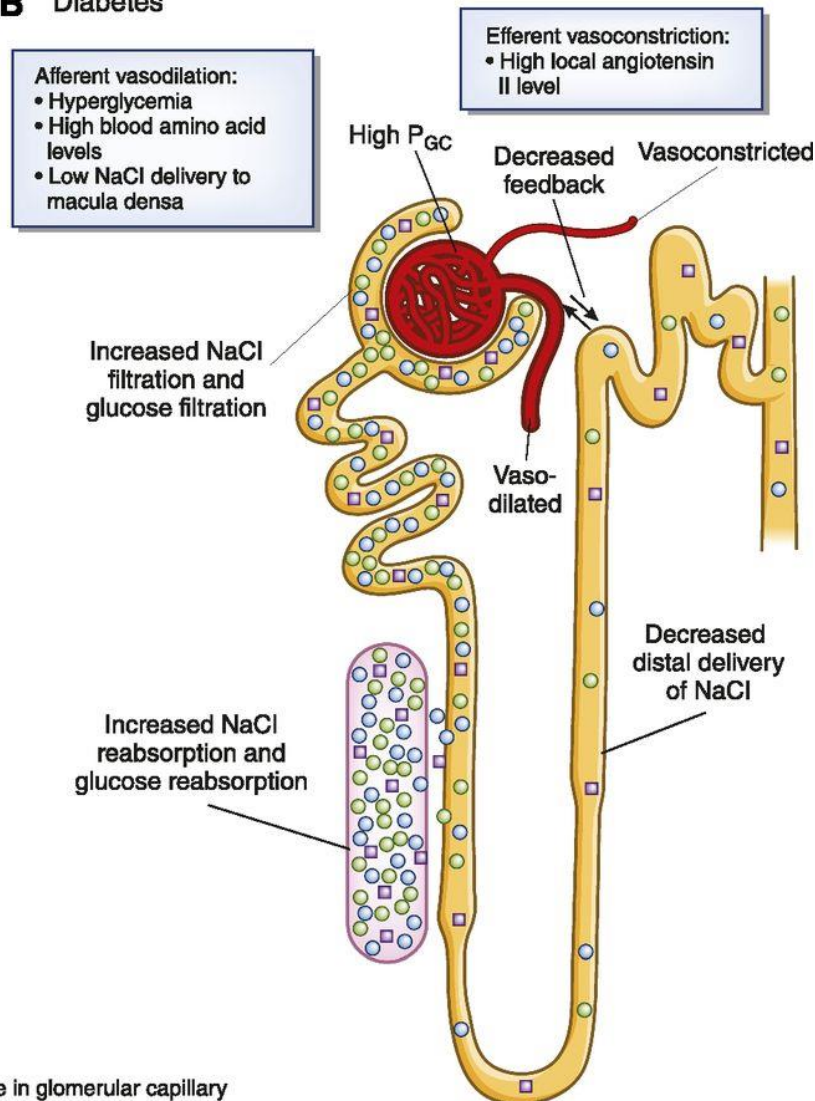


NORMAL AND DIABETIC RENAL HEMODYNAMICS.

A Normal



B Diabetes



A rare clinical cautionary tale

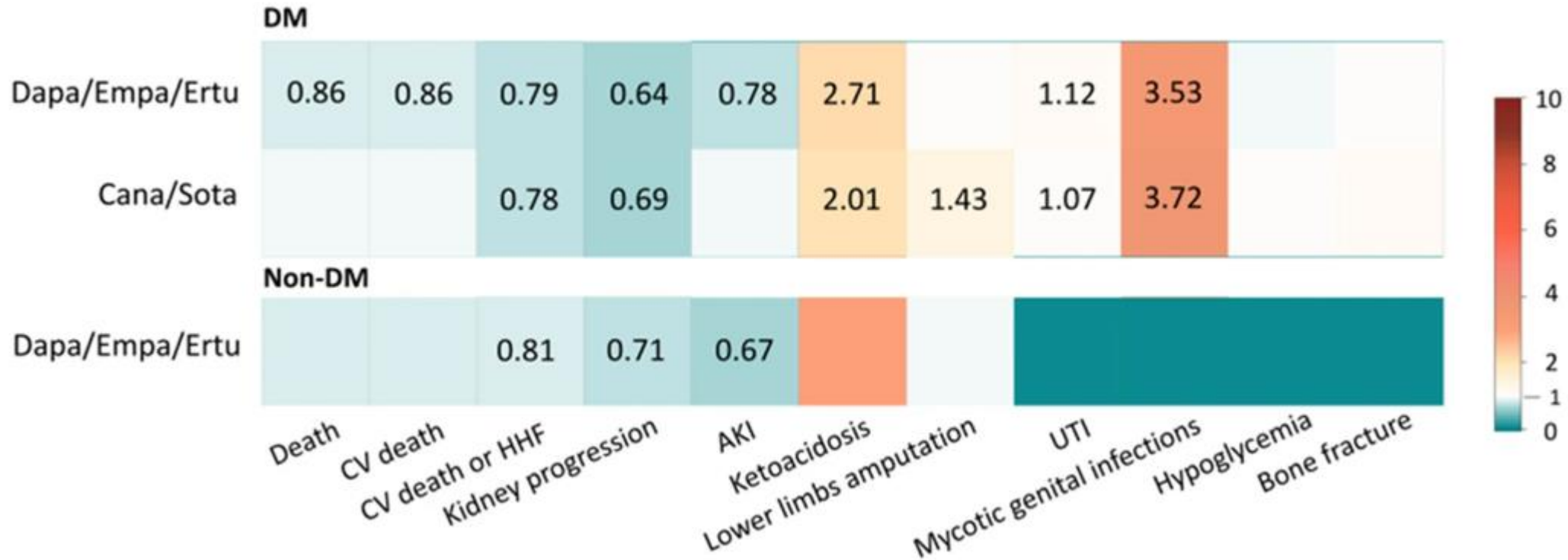


As expected, Mr. JM had glycosuria

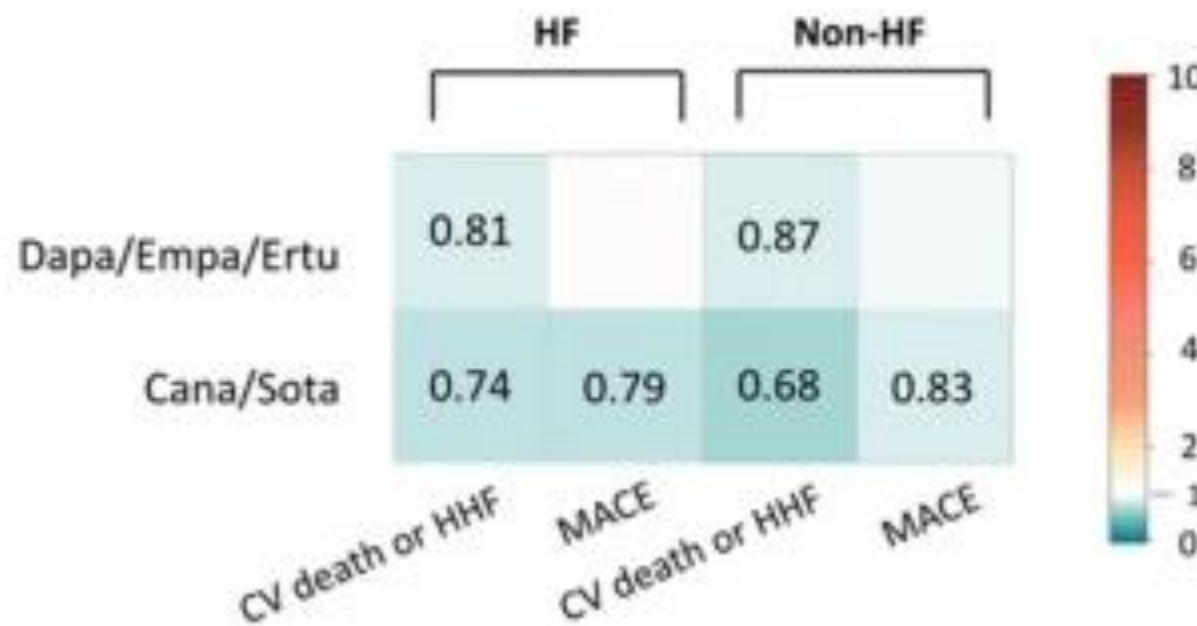
Dipstick	Result
pH	7
SG	1.009
Protein	30 mg/dL
Glucose	1000mg/dL
Ketones	Neg
Blood	Small
Bilirubin	Neg
Nitrites	Neg
Leukocytes	Large
RBC/HPF	5/HPF
WBC/HPF	>100/HPF with clumps



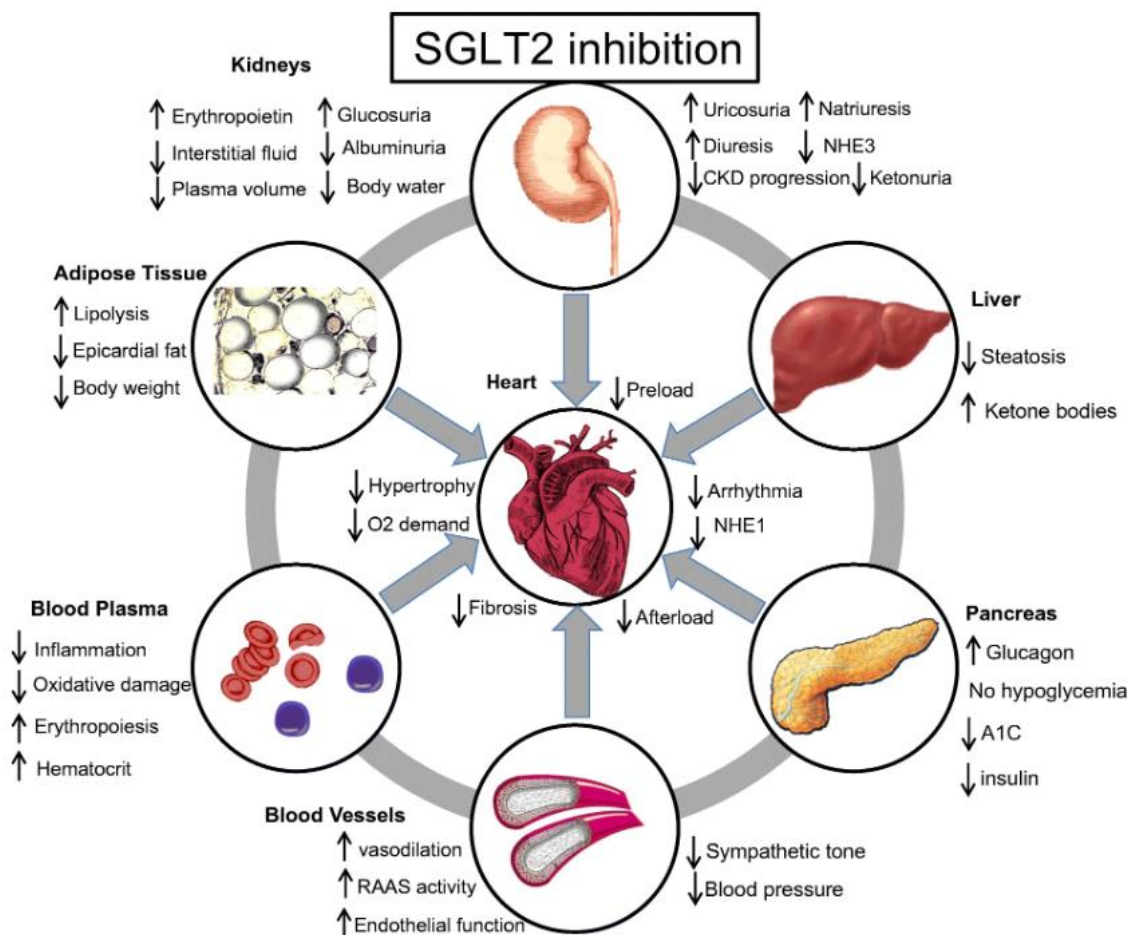
“FloxiNation” has significant benefits



“FloxiNation” with non-selective SGLTi might be better for heart failure



“Floxination” with non-selective SGLTi might be better for heart failure



A schematic representation of the different mechanisms implicated in the cardiovascular benefits of SGLT2 inhibitors

Before “floxination”



Do not start if

Patient have type 1 diabetes

Patient is hypotension or hypovolemia or has acute kidney injury

- Consider decreasing the dose of other diuretics
 - We stop thiazides and half to dose of loop diuretics unless the patient is overloaded

Education

- Monitor BP, weight and glucose carefully
 - We decrease insulin by 10-20% in well-controlled diabetics
 - Call if weight decreasing or glucose running low
- Follow the “sick day” rule and stop the SGLT2 inhibitor 3-4 days prior to scheduled surgery or fasting
- Avoid keto- or very low carb diets that could increase the risk of ketoacidosis
- Inform your doctor
 - If you develop urinary symptoms or have itching, redness or a genital discharge
 - If you notice a new leg wound or breakdown of the skin below the knees

Anticipating common issue after SGLT2 inhibition



Symptom	New-onset LUTS prevalence, %	
	Patients with autonomic neuropathy	Patients without autonomic neuropathy
Pollakiuria	43.8	73.6
Nocturia	25.0	50.0
HbA1c at approximately 4.5 months	7.2	7.8

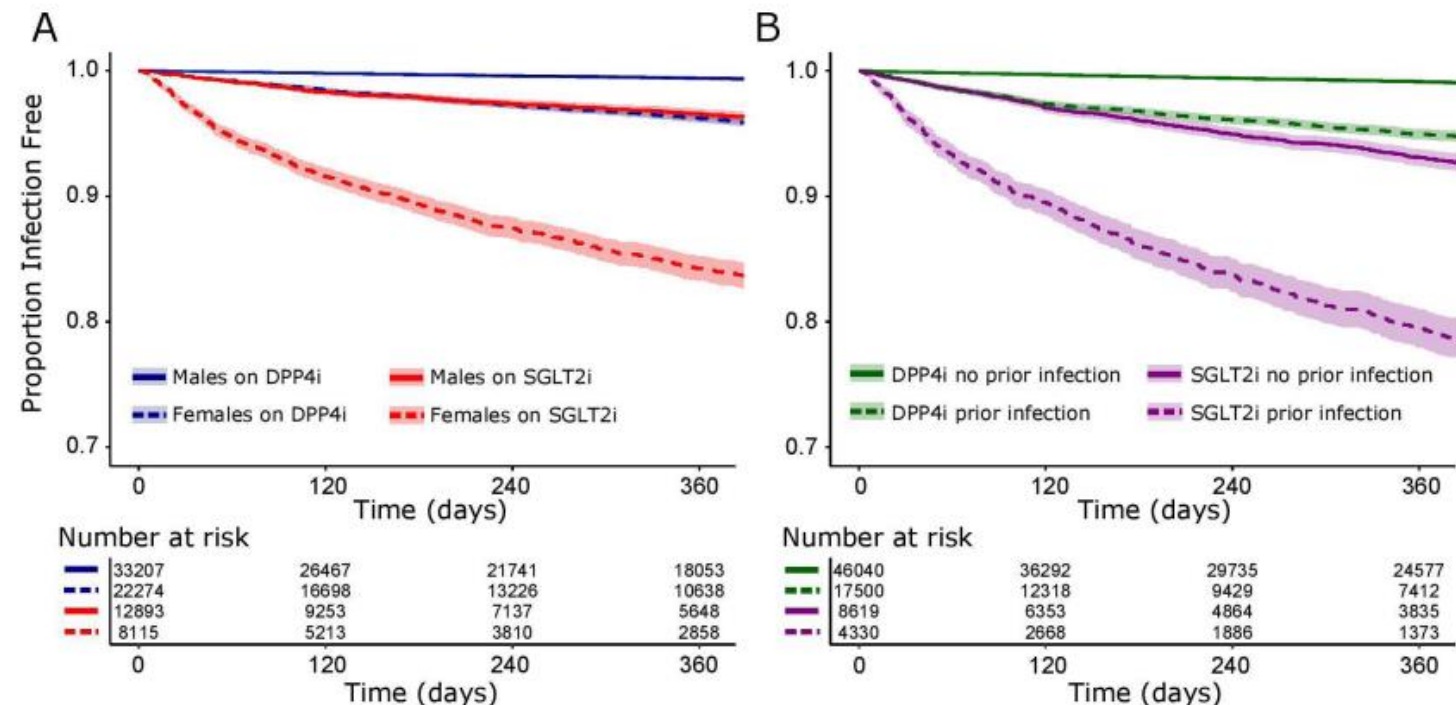
Chilelli NC, Bax G, Bonaldo G *et al.* Lower urinary tract symptoms (LUTS) in males with type 2 diabetes recently treated with SGLT2 inhibitors-overlooked and overwhelming? A retrospective case series. *Endocrine* 2018; **59**: 690-3.

SGLT2 inhibitors and urinary infections



Mycotic and other infections

- SGLT2-I increases fungal (HR 3.5-4) but not bacterial infections in those with DM2
- Major risk
 - Female sex
 - Prior infection < 5 years
 - Diabetes
- Contributors
 - Personal hygiene
 - Circumcision
 - BMI>30
- Most mild (local or 1 dose Rx)
- HR 1.58 of d/cing SGLT2i



SGLT2 inhibitors and when they should be avoided



Severe infections - Severe fungal infection, xanthogranulomatous pyelonephritis, emphysematous pyelonephritis, and Fournier's gangrene

- Monitor for this in patients with history of infection or asymptomatic bacteriuria
- Major risk
 - Diabetes with poor control (HbA1c > 9%)
 - Urinary obstruction, incomplete voiding, urinary reflux
 - Neurogenic bladder
 - Urinary tract foreign body
 - Pregnancy
 - Immunosuppression
 - Trials pending in kidney transplant patients
- Minor risk – uncircumcised, genital piercing

A rare clinical cautionary tale



He is also following with urology because of his prostate cancer, which is currently in remission, and lower urinary tract symptoms

- He complains of both storage difficulties (urgency, polyuria, frequency, and nocturia x 4) and voiding difficulties (dribbling and straining)
- He has episodes of incontinence and is intermittently catheterizing to avoid incontinence episodes
- Has had several episodes of urinary tract infections in the last few months – treated with Bactrim and Ceftriaxone and Cefpodoxime

A rare clinical cautionary tale



- He presented complaining of symptoms of another urinary tract infection and was discovered to have acute kidney injury (creatinine 2.3 mg/dL > 6.7 mg/dL)
 - Urine culture sent
 - Initiated on Ceftriaxone IV
 - Dapagliflozin and Losartan held and he was given IV fluids
- Over several days renal function improved and the creatinine decreased from 6.7 mg/dL to 3.2 mg/dL
- Ultrasound revealed a left sided hydronephrosis



A rare clinical cautionary tale



Culture grew candida albicans > 100,000 CFU

Antibiotic	MIC (ug/ml)	MBC (ug/ml)
AMPHOTERICIN B	1	Sensitive
MICAFUNGIN	0.03	Sensitive
FLUCONAZOLE	>64	Resistant
POSACONAZOLE	>16	Probable resistance
ISAVUCONAZOLE	>16	Probable resistance
5-FLUOROCYTOSINE	0.125	Probable resistance



SGLT2 inhibitors and ketoacidosis



- Low insulin + High glucagon >> Ketogenesis
- SGLT2 inhibitors reportedly increase glucagon production especially during fasting or stress
- Glycosuria often blunts the hyperglycemia (euglycemic <250 mg/dL)

- Stop SGLT2 inhibitors 3-4 days prior to major surgery and 1-2 days prior to day surgery
- Stop inhibition in fasting or critically ill

- Admit and treat seriously if it does occur

SGLT2 inhibitors and kidney failure



Acute renal failure

- AKI was not a major finding of clinical trials
- Most patients do have a rise in creatinine after starting

Chronic kidney disease stage 5 or ESRD

- Solid evidence for benefit for eGFR > 45
- Good evidence for benefit for eGFR > 25
- New research in advanced CKD
 - De la Flor et al Efficacy and Safety of the Use of SGLT2 Inhibitors in Patients on Incremental Hemodialysis: Maximizing Residual Renal Function, Is There a Role for SGLT2 Inhibitors? Biosciences 2023
 - St. Peter and Calvin Extending SGLT2 Inhibitor Use for People Undergoing Dialysis? CJASN 2023
 - Barretto et al Pharmacokinetic Properties of Dapagliflozin in Hemodialysis and Peritoneal Dialysis Patients CJASN 2023



SGLT2 inhibitors in Pregnancy



- There is a relative paucity about the safety of SGLT2 inhibitors during pregnancy
- In animal studies
 - > No documented teratogenicity in the first trimester
 - > Canagliflozin was associated with delayed ossification of bones
 - > Exposure in the 2-3rd trimester resulted in dilation of the renal pelvis
 - > SGLT2 inhibitors were excreted in breast milk and affected neonatal growth



SGLT2 inhibitors in Pregnancy



- In human case reports
 - Twenty-two pregnancies reported on empagliflozin > 4 health births
 - Twenty-nine pregnancies reported on canagliflozin > 8 normal births
 - Twenty-one pregnancies reported on dapagliflozin > 1 health birth
 - Human case reports with increased prematurity, renal dysplasia, hydrocephalus and encephalocele, and spontaneous abortions
 - Euglycemic ketoacidosis is a rare complication of pregnancy

SGLT2 inhibitors should be avoided and/or stopped during pregnancy and lactation based on limited animal and human data



A rare clinical cautionary tale



- A nephrostomy was placed to decompress the left kidney
- The Veteran refused systemic Amphotericin B treatment +/- nephrectomy for fear of inducing renal failure
- Was started on Micafungin (that does not penetrate the urinary space) and Ampho B was given via the nephrostomy.
- The Veteran failed to clear the infection and suffered recurrent episodes of AKI
- After several months on anti-fungal treatment he developed fungemia and acute blindness in the right eye thought to be a septic embolism
- He again refused Ampho B systemically and elected hospice care



Summary



- Reviewed the physiology of SGLT2 transporters and SGLT2 inhibitors
- Reviewed benefits of SGLT2 inhibition in diabetics and non-diabetics
- Cautionary tail
 - Infection is a major risk
 - Most infections are not serious but be careful in immunosuppressed patients and those with urologic disease
- When woul

Summary continued



- Avoid in pregnancy, around the time of surgery and in the critically ill
- Most of the documented benefit is in those with heart failure or kidney disease stage 3-4
- SGLT2 inhibitors seem to be better tolerated in non-diabetic
- Some experimental use in patients with ESRD and advanced kidney disease for volume control or heart protection

References



1. Chen et al Quantitative PCR tissue expression profiling of the human SGLT2 gene and related family members, Diabetic Therapy 2010
2. Hoehlschen et al Redox-driven cardioprotective effects of sodium-glucose co-transporter-2 inhibitors: comparative review, Cardiovascular Diabetology 2023
3. Alicic et al Diabetic Kidney Disease: Challenges, Progress, and Possibilities CJASN 2017
4. Hiraizumi et al Transport and inhibition mechanisms of the human SGLT2-MAP17 glucose transporter, Nature Structural & Mol. Biol 2023
5. Garcia-Ropero et al The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments, Expert Op. on Drug Met.&Tox. 2018
6. Habtemariam The molecular pharmacology of phloretin Biomedicines 2023
7. Niu et al Structural basis of inhibition of the human SGLT2-MAP17 glucose transporter, Nature 2021
8. Chen et al Impact of SGLT2 inhibitors on patient outcome: A network meta-analysis Cardiovascular Diabetology 2023
9. Wojcik and Warden Mechanisms and Evidence for Heart Failure Benefits from SGLT2 inhibitors Curr. Cardio. Reports 2019
10. Chilelli NC, Bax G, Bonaldo G et al. Lower urinary tract symptoms (LUTS) in males with type 2 diabetes recently treated with SGLT2 inhibitors-overlooked and overwhelming? A retrospective case series. Endocrine 2018; 59: 690–3.
11. McGovern et al Risk Factors for genital infection in people initiating SGLT2 inhibitors and their impact on discontinuation BMJ Open Diabetes Research & Care 2020
12. Bonkat G, Pickard R, Bartoletti R et al. EAU Guidelines on Urological Infections 2018. In: European Association of Urology Guidelines. 2018 Edition. Vol presented at the EAU Annual Congress Copenhagen 2018. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2018
13. Chandreshaker et al Sodium glucose-linked transport protein 2 inhibitors: An overview of genitourinary and perioperative implications, Int. J. Urol. 2021
14. Muller et al Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes:a systematic review of the evidence Front. Endo. 2023



Questions?

Contact Information: