SGLT2 Inhibitors: A Nephrology Panacea

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OHSU CME Distinguished Lecture

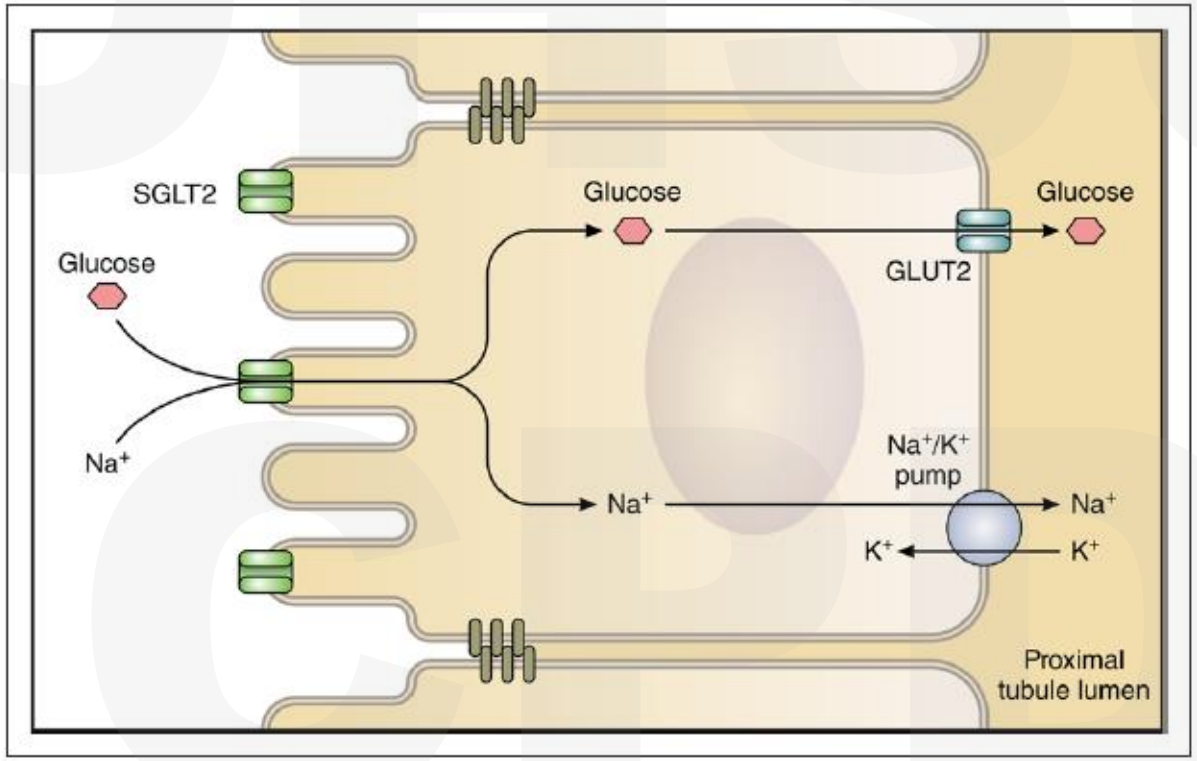
May 8th, 2025

Outline

- SGLT2 inhibitors mechanism of action
- Diabetic Nephropathy
- Proteinuric CKD
- Heart Failure
- Hyponatremia
- Hypomagnesemia
- Kidney stones

Background

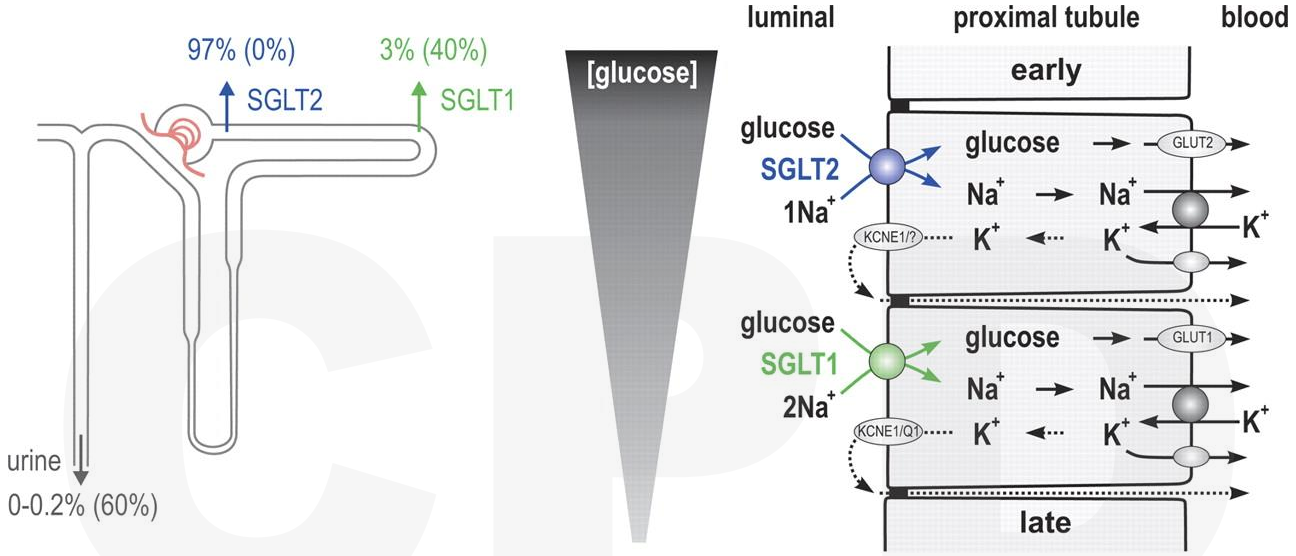
- SGLT2 inhibitors block the Na-Glucose cotransporter in the proximal tubule



Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016 Sep 6;134(10):752-72.

Background

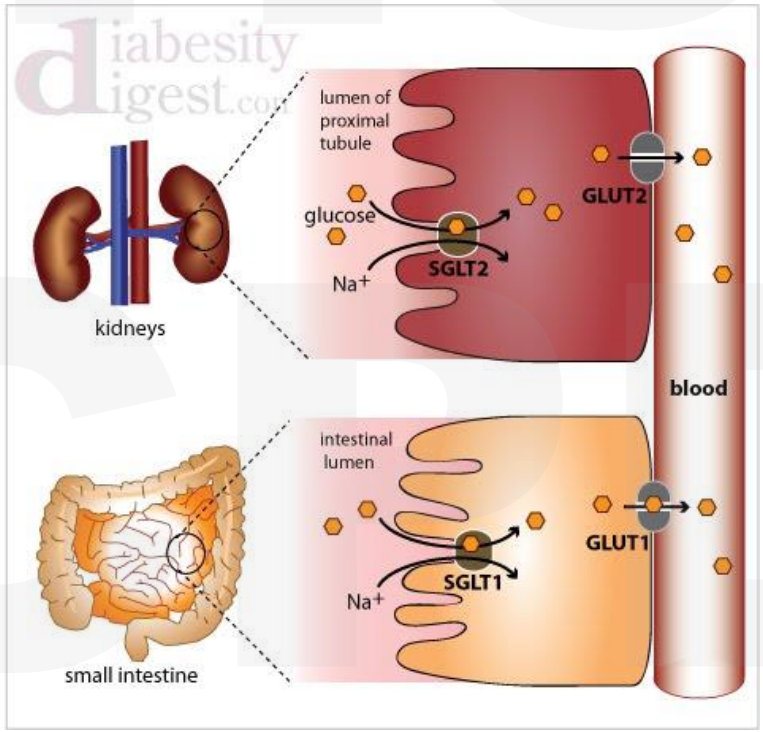
- SGLT2 (high capacity, low affinity) in the early proximal tubule resorbs ~90% of the filtered glucose in euglycemia
- SGLT1 (high affinity, low capacity) absorbs the other ~10%



Volker Vallon *Molecular determinants of renal glucose reabsorption*. Focus on "Glucose transport by human renal Na^+/d-glucose cotransporters SGLT1 and SGLT2" American Journal of Physiology - Cell Physiology Published 28 December 2010 Vol. 300 no. 1, C6-C8

Background

- SGLT1 is also present in the small intestines
  - Need selective inhibitors of SGLT2 to prevent intestinal glucose malabsorption and severe diarrhea



Scheen AJ. Pharmacokinetic and pharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor.Clin Pharmacokinet. 2014 Mar;53(3):213-25.

Background

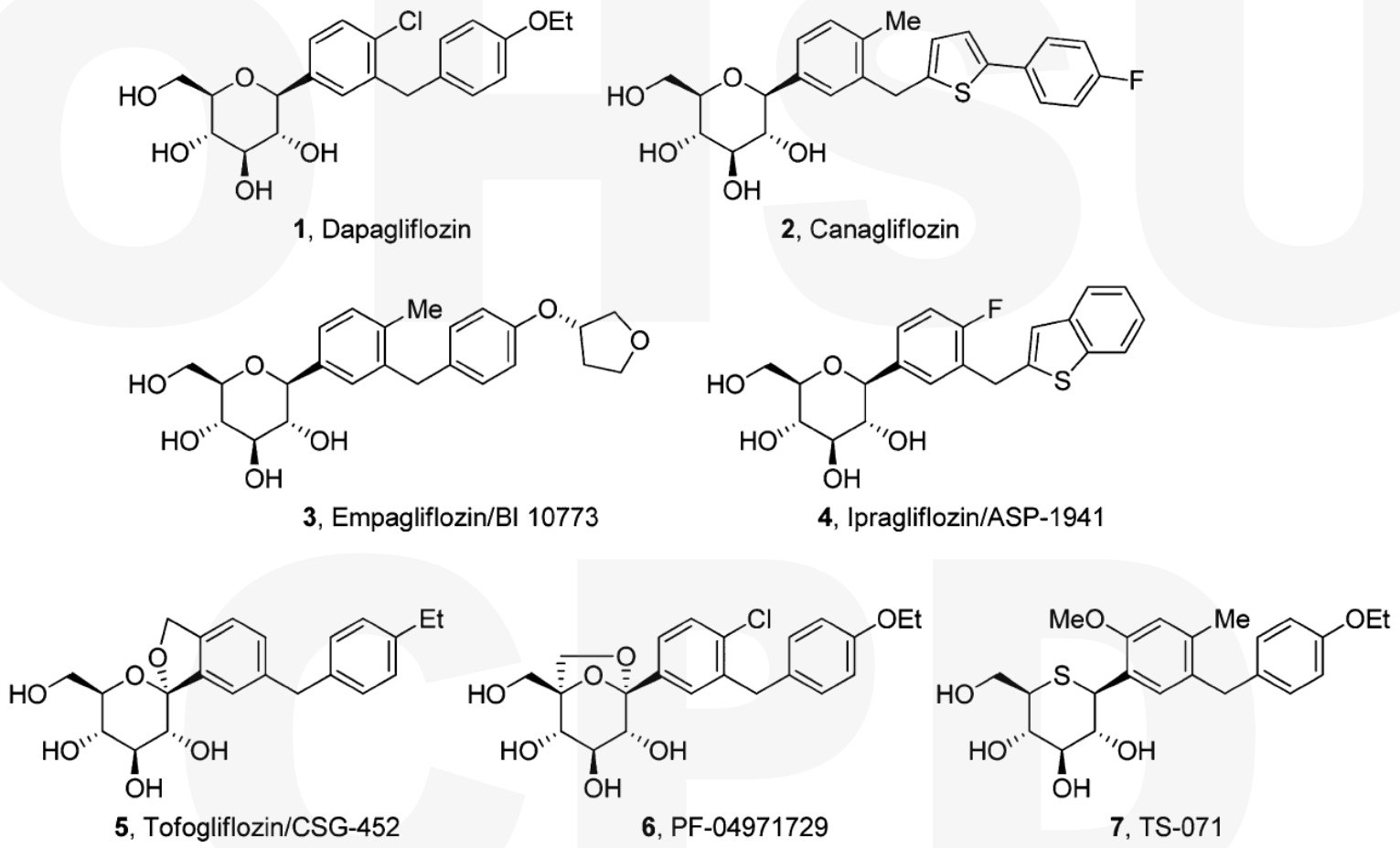


FIG. 1. SGLT2 inhibitors in late-stage clinical trials.

Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016 Sep 6;134(10):752-72.

Metabolism and Excretion

- All these medications are competitive, reversible and highly selective inhibitors SGLT2
- SGLT2 inhibitors are metabolized mostly by glucoronidation by both the liver and to a lesser degree the kidney
- Inactive Metabolites is excreted mainly by the kidney (~70%)
- Very small amount of freely filtered urinary excreted parent compound in normal subjects (1%)

Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2.Clin Pharmacokinet. 2014 Jan;53(1):17-27.

Urinary Glucose Excretion

- In clinical trials, SGLT2 inhibitors only inhibit 30-50% (50-80 gm/day) of the filtered glucose load despite inhibiting 100% of the transporter activity in vitro

- Unclear if this is from incomplete blockade of SGLT2 *in vivo*, clearance of the medication or increased activity of SGLT1

Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? Diabetes. 2012 Sep;61(9):2199-204.

Tubuloglomerular Feedback

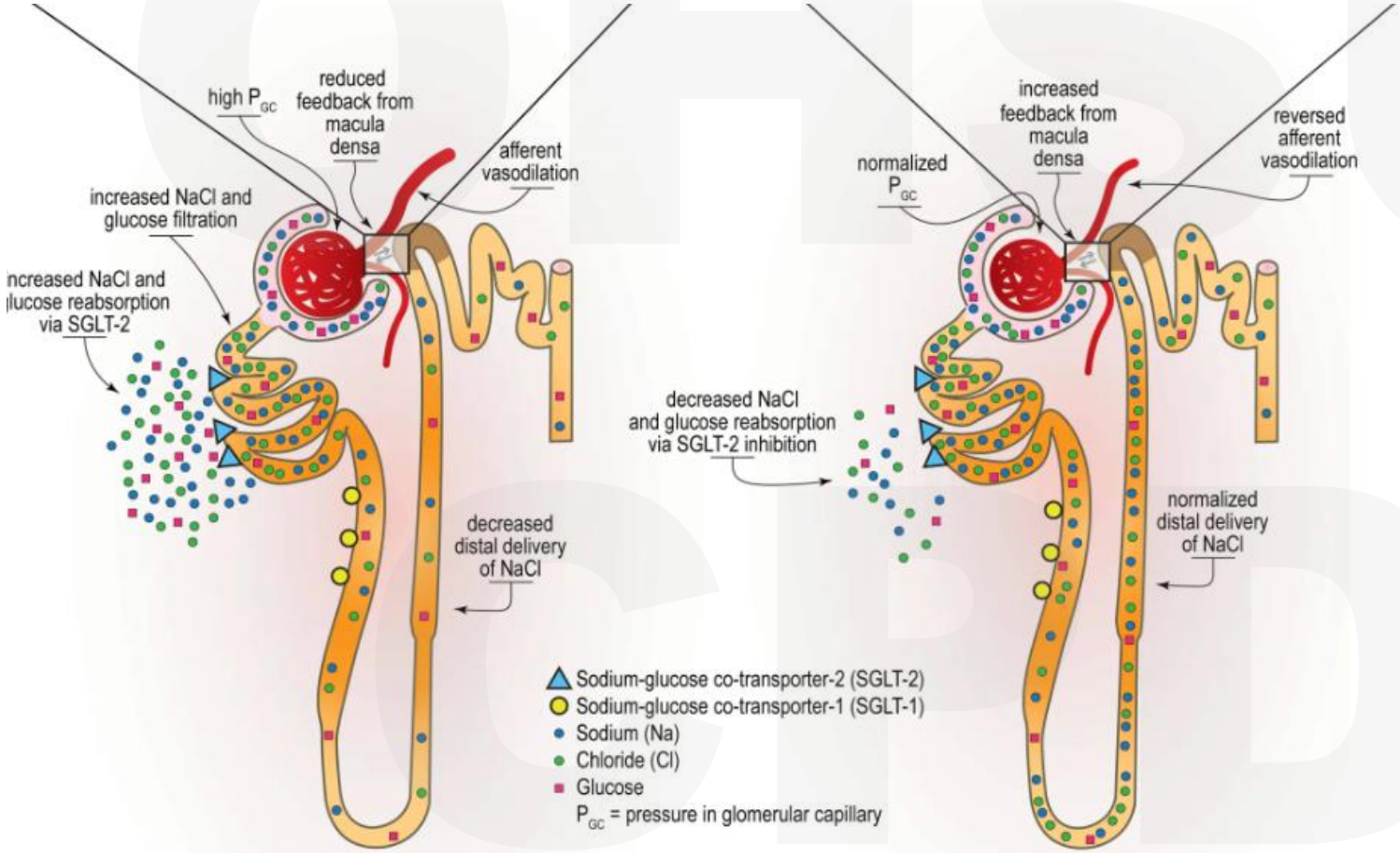


Figure 1 from Tuttle et al, *AJKD* © National Kidney Foundation and American Diabetes Association

Diabetic Nephropathy

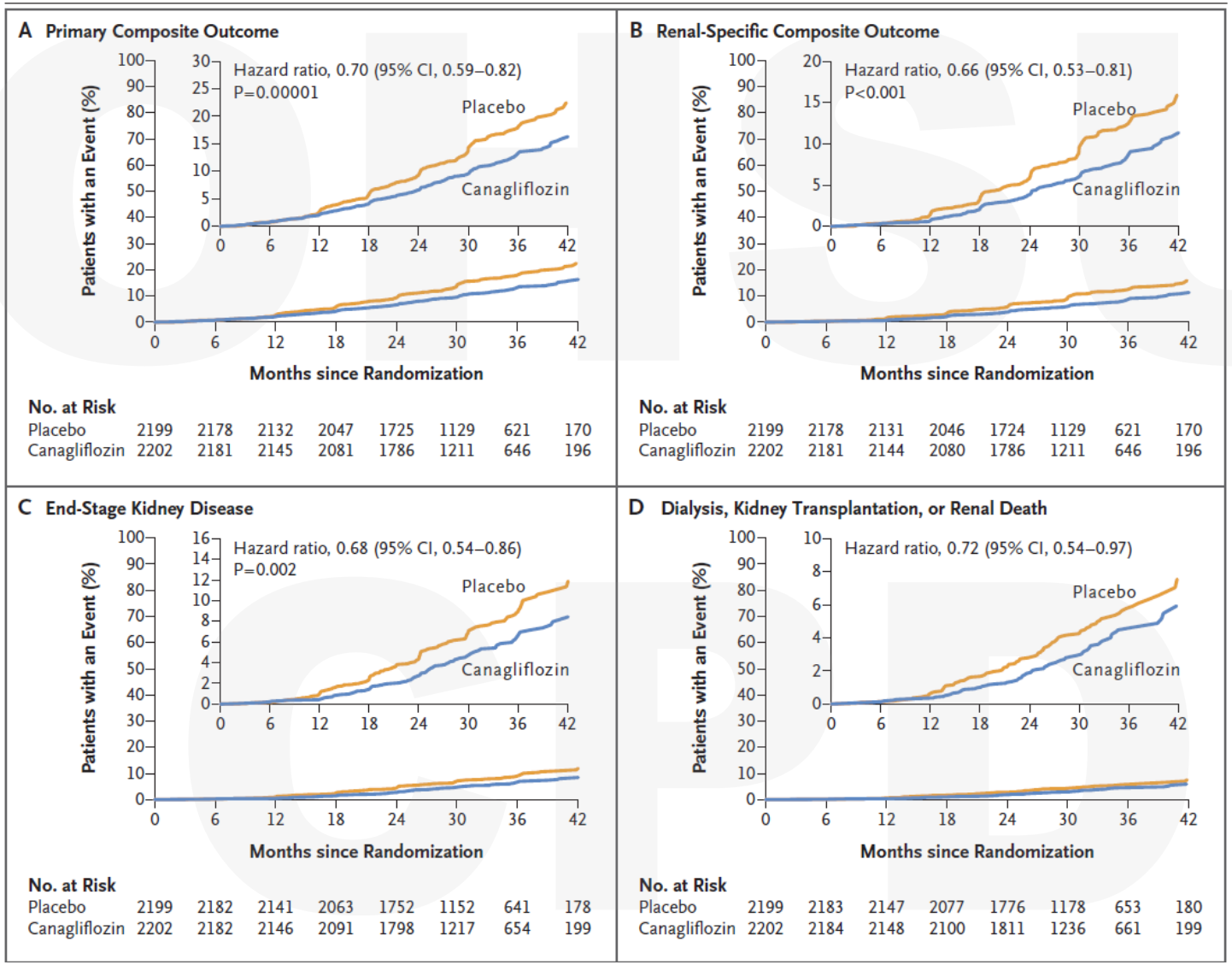
- Timeline of breakthroughs in treating the most common glomerular disease

Credence Trial was the first to show benefit of SGLT2 inhibitors in progression of renal disease

- Double blind randomized controlled trial comparing canagliflozin 100 mg daily to placebo in 4401 patients
- Inclusion criteria
  - Type 2 DM
  - HgbA1c of 6.5 to 12
  - eGFR of 30-90 ml/min
  - Urinary albuminuria of 300 to 5000 mg/day
  - Already on a stable dose of an ACEI/ARB

Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.

SGLT2-I decreased rates of ESRD



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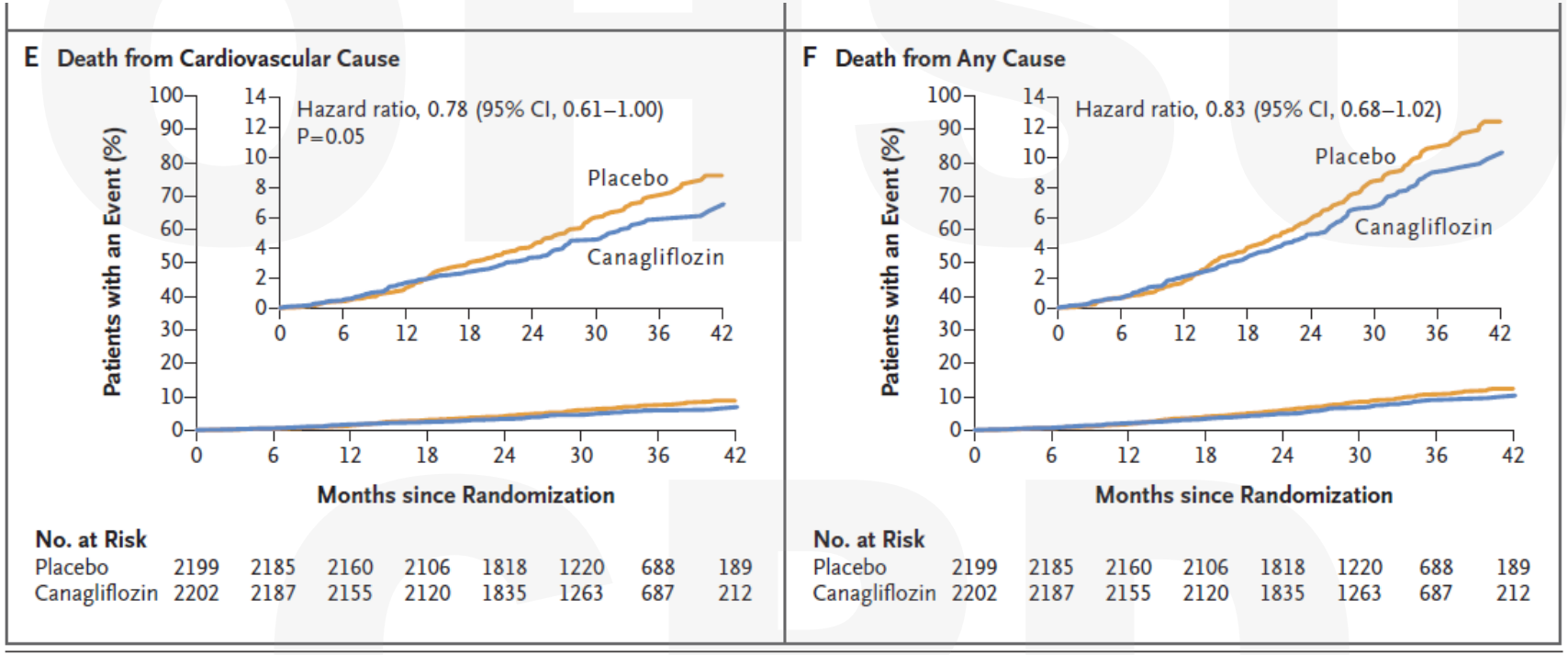
SGLT2-I decreased Mortality



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CREDENCE Summary

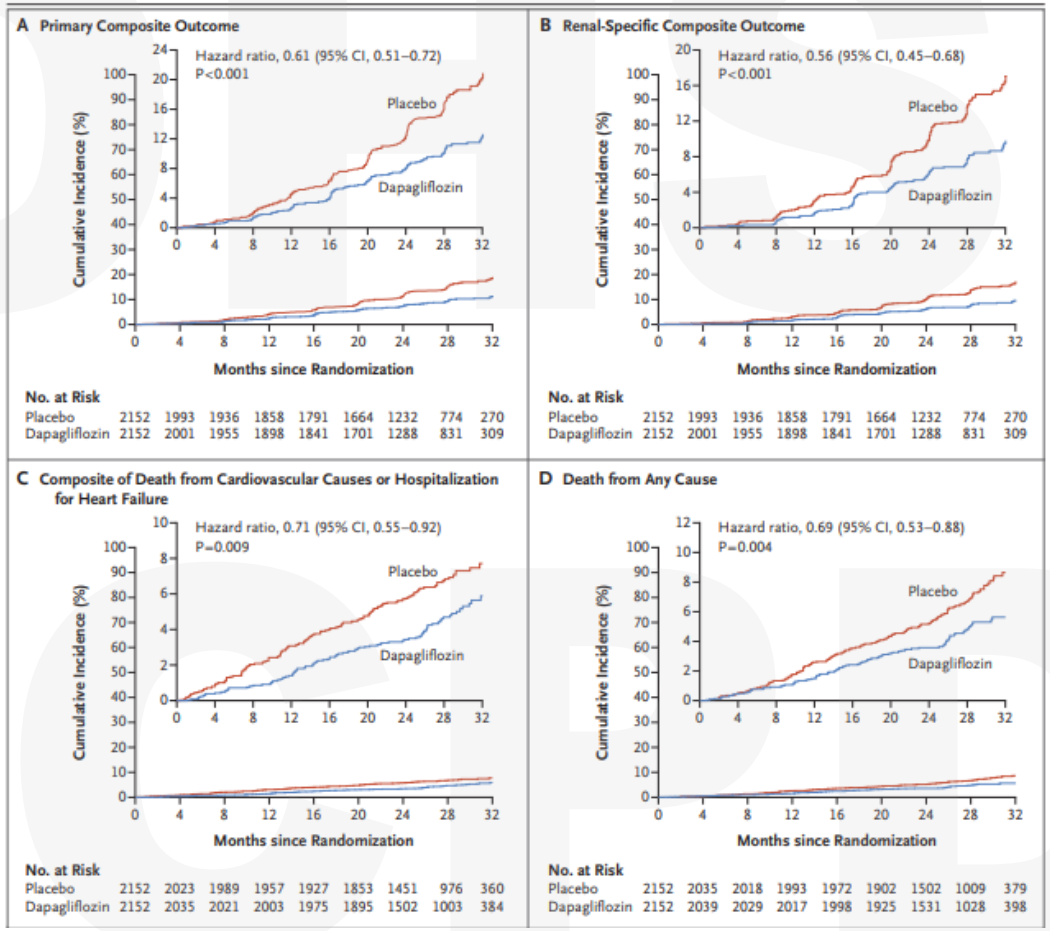
- Canagliflozin had a NNT of 22 for the composite end point
- This was in patients already on stable ACEI therapy
- Major side effects are polyuria and genital infections

DAPA CKD Showed Benefit in non-diabetic proteinuric patients

- Randomized trial of 4304 participants
  - eGFR 25 to 75
  - UAC of 200 to 5000
  - Primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. doi: 10.1056/NEJMoa2024816. Epub 2020 Sep 24. PMID: 32970396.

Dapagliflozin decreased renal events and mortality



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SGLT2-I also reduced CV events in patients with heart failure with preserved EF (HFpEF)

- Randomized trial of 5988 patients
- Class II-IV heart failure and an ejection fraction of more than 40%
- Empagliflozin (10 mg once daily) or placebo

Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.

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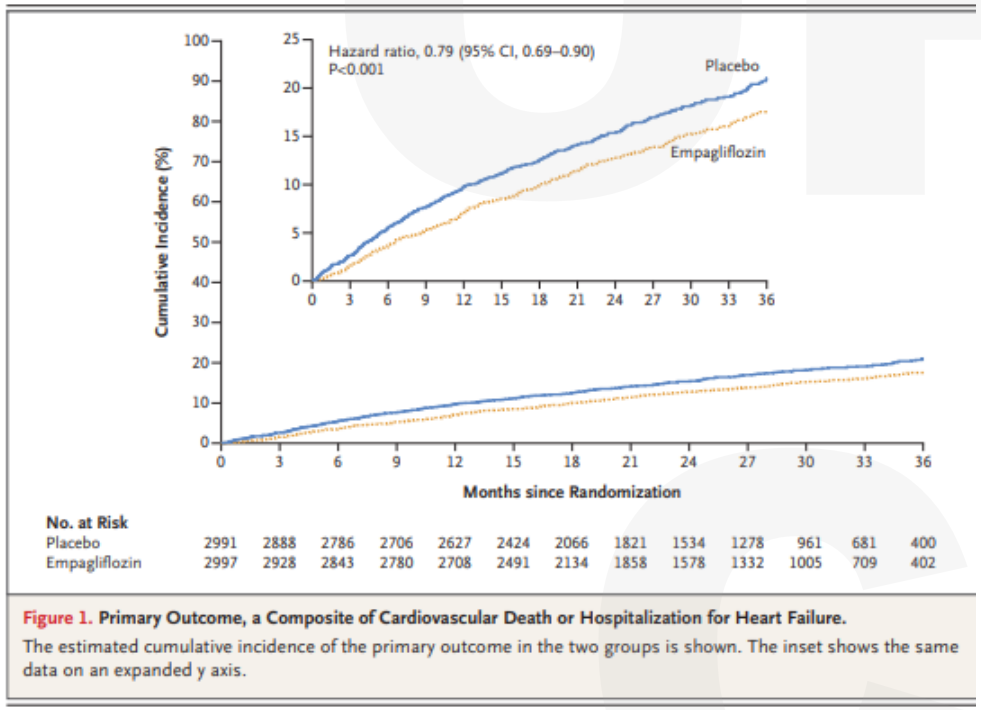


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

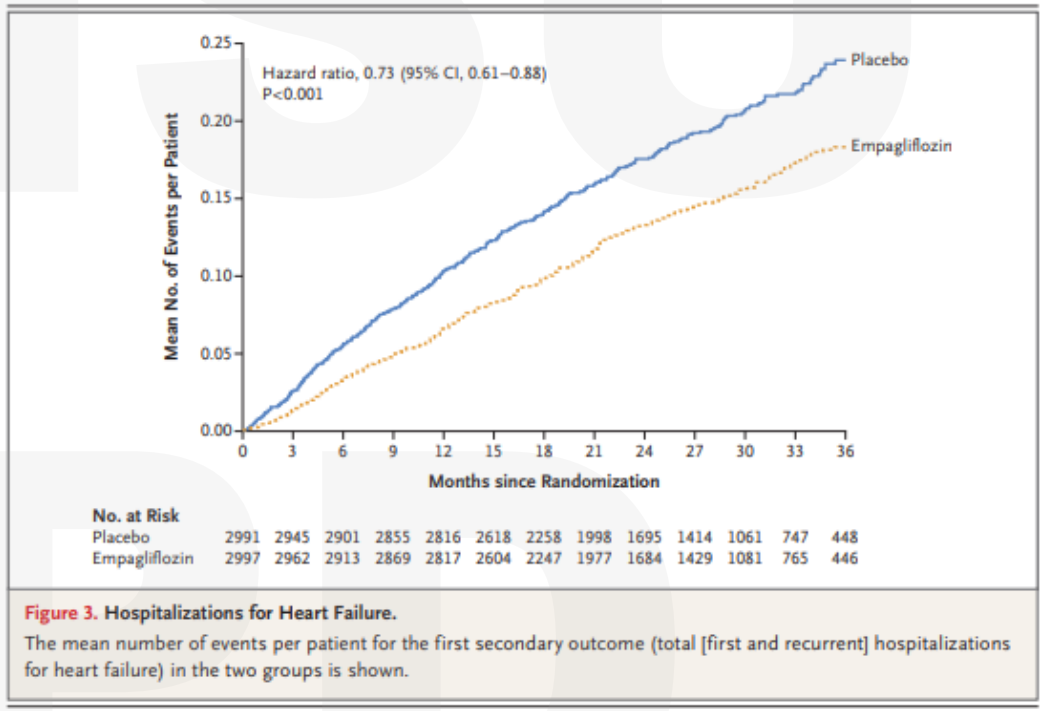


Figure 3. Hospitalizations for Heart Failure.
The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

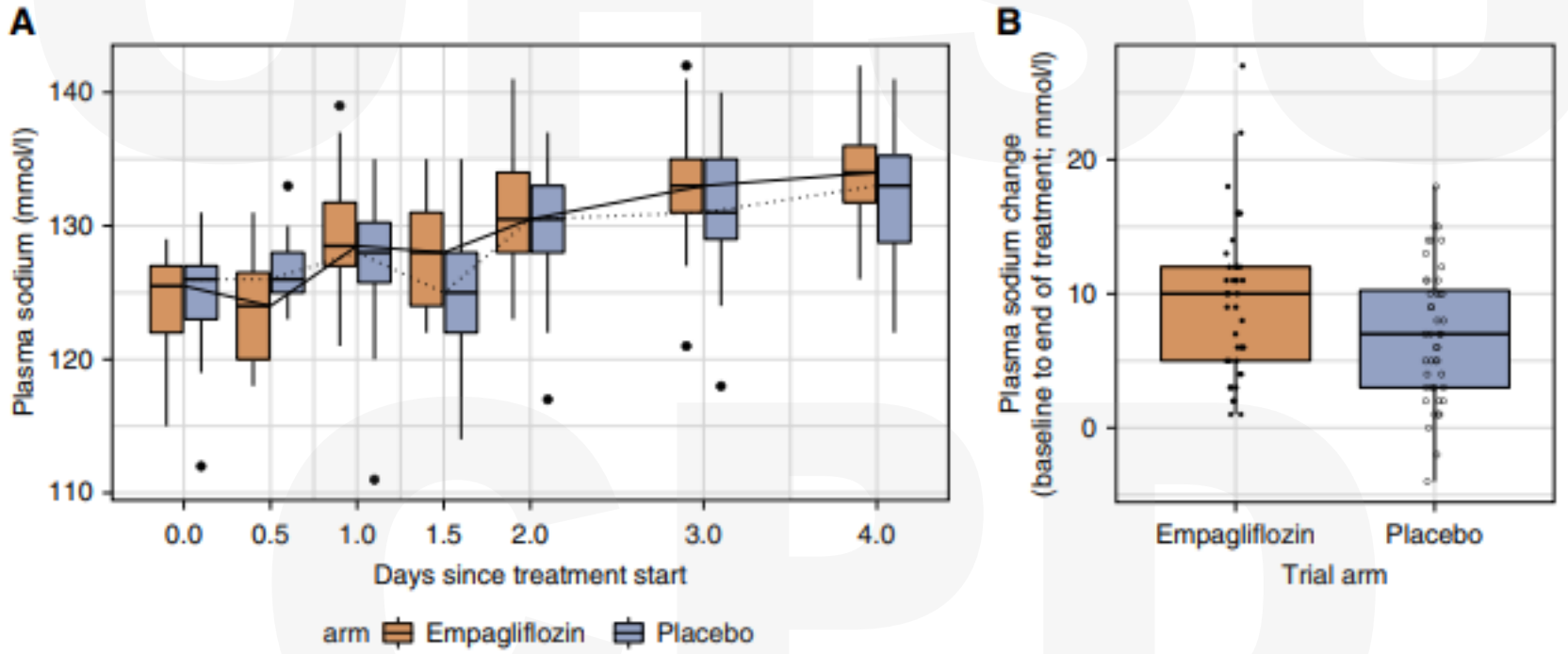
Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.

SGLT2-I can improve Hyponatremia in SIAD

- Randomized 88 hospitalized patients with SIAD-induced hyponatremia <130 mmol/L
  - All had standard fluid restriction of <1000 ml/24 h
  - Randomized to once-daily dose of oral empagliflozin or placebo for 4 days

Refardt J, Imber C, Sailer CO, Jeanloz N, Potasso L, Kutz A, Widmer A, Urwyler SA, Ebrahimi F, Vogt DR, Winzeler B, Christ-Crain M. A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis. J Am Soc Nephrol. 2020 Mar;31(3):615-624. doi: 10.1681/ASN.2019090944. Epub 2020 Feb 4. PMID: 32019783; PMCID: PMC7062212.

SGLT2-I can improve Hyponatremia in SIAD



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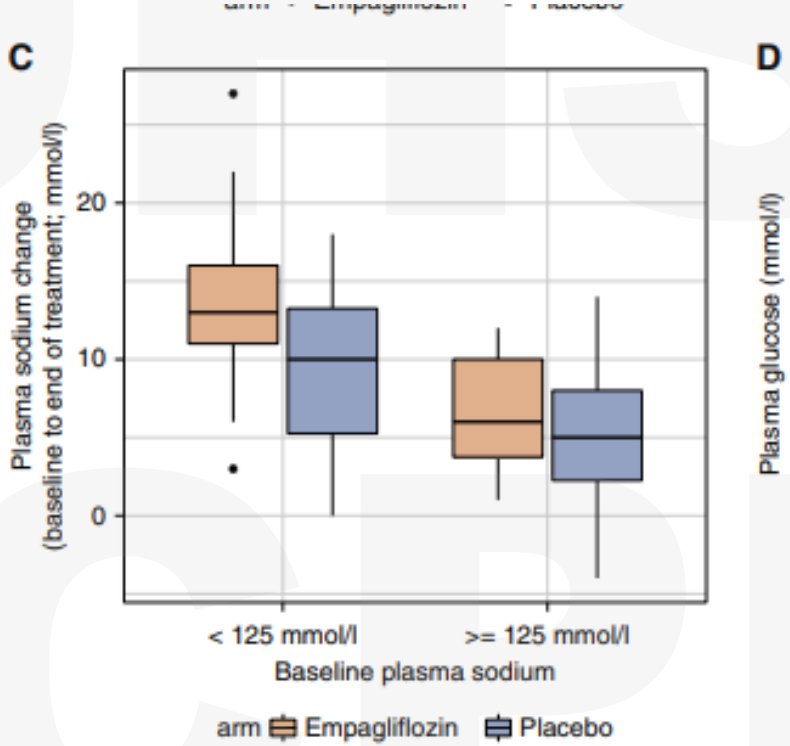
SGLT2-I particularly effective for lower Serum Na patients



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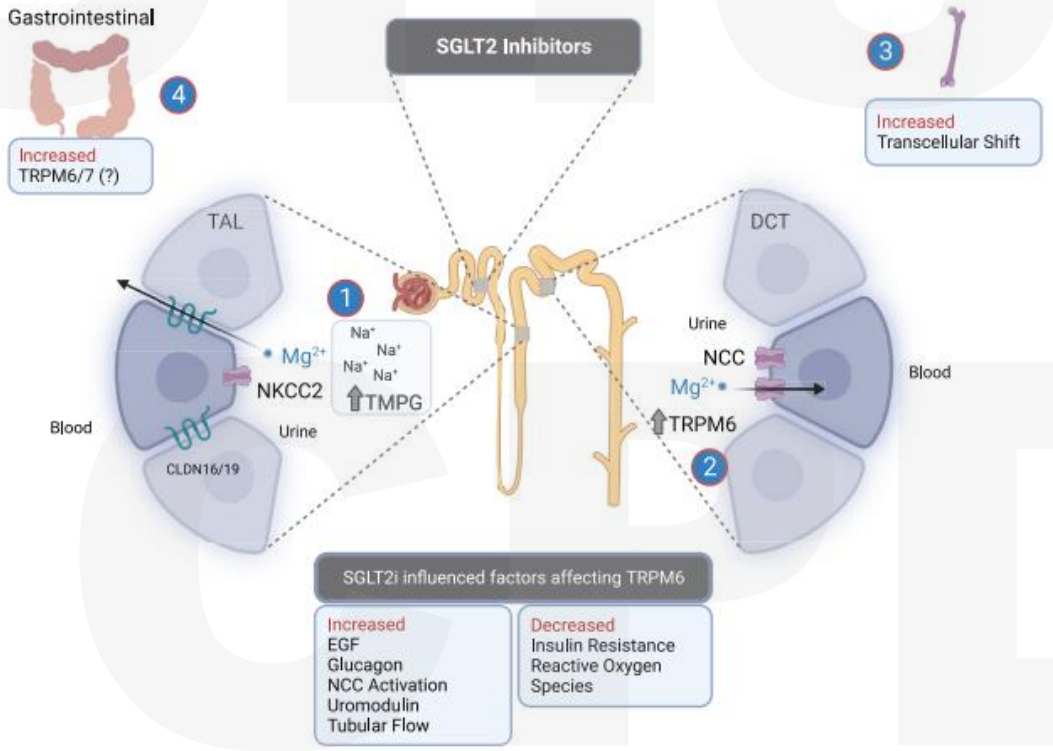
Hypomagnesemia and SGLT2-I

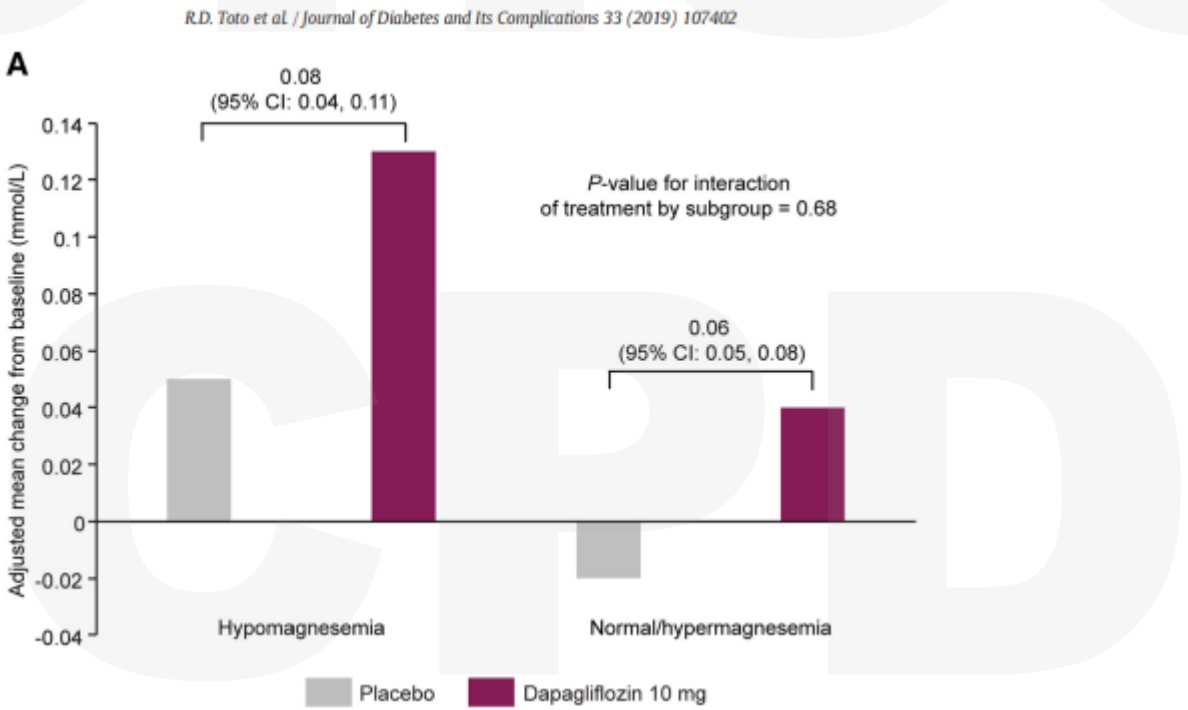
- SGLT2- I appear to increase Mg resorption in the tubule



Shah CV, Sparks MA, Lee CT. Sodium/Glucose Cotransporter 2 Inhibitors and Magnesium Homeostasis: A Review. Am J Kidney Dis. 2024 May;83(5):648-658. doi: 10.1053/j.ajkd.2023.11.006. Epub 2024 Feb 17. PMID: 38372686.

Less data for hypoMg but also also less treatments for hypoMg

- A post-hoc analysis of 4398 patients from 10 studies showed an increase in Mg on the patients on SGLT2-I



Toto RD, Goldenberg R, Chertow GM, Cain V, Stefánsson BV, Sjöström CD, Sartipy P. Correction of hypomagnesemia by dapagliflozin in patients with type 2 diabetes: A post hoc analysis of 10 randomized, placebo-controlled trials. J Diabetes Complications. 2019 Oct;33(10):107402. doi: 10.1016/j.jdiacomp.2019.06.007. Epub 2019 Jul 2. PMID: 31375422.

Kidney Stones

Urinary Inhibitors

- Citrate is major inhibitor of calcium stones

$$[Ca^{2+}]_{aq} + [Oxalate^{2-}]_{aq} \rightleftharpoons [CaOxalate]_{s}$$

$$[Ca^{2+}]_{aq} + [Citrate^{2-}]_{aq} \rightleftharpoons [CaCitrate]_{aq}$$

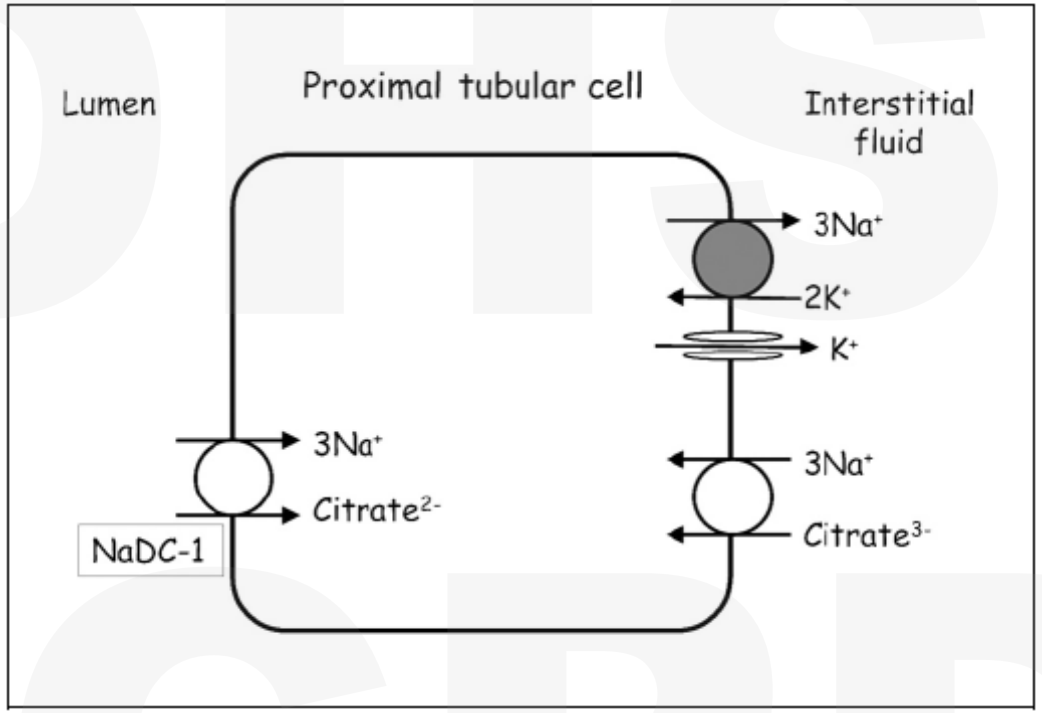
- Citrate binds significant portion of free calcium making it unavailable for stone formation

Urinary Citrate Handling

- Citrate is freely filtered
- Reabsorbed in proximal tubule
  - 65-90% of filtered load
  - Amount appears to be pH dependent
  - Accounts of ~10% of renal oxidative metabolism
- No evidence for secretion
- Urinary citrate level influenced little by plasma level so changes appear due to changes in reabsorbed amount

Hamm LL. Renal handling of citrate. Kidney Int. 1990 Oct;38(4):728-35

Urinary Citrate Handling

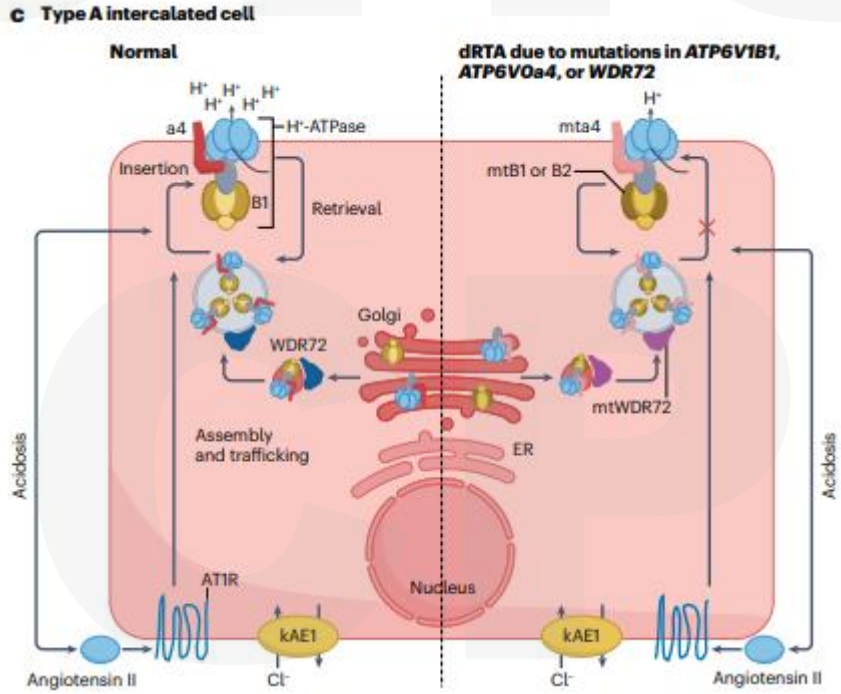


- Reabsorbed
  - With Na
  - As $Citrate^{2-}$ on luminal side

Unwin RJ, Capasso G, Shirley DG. An overview of divalent cation and citrate handling by the kidney. Nephron Physiol. 2004;98(2):p15-20.

Distal RTA

- Classic dRTA phenotype includes metabolic acidosis, hypokalemia and hypocitraturia resulting in CaP stones and nephrocalcinosis
- Generally diagnosed early related to labs/symptoms
- Defect in the H+-ATPase structure or trafficking



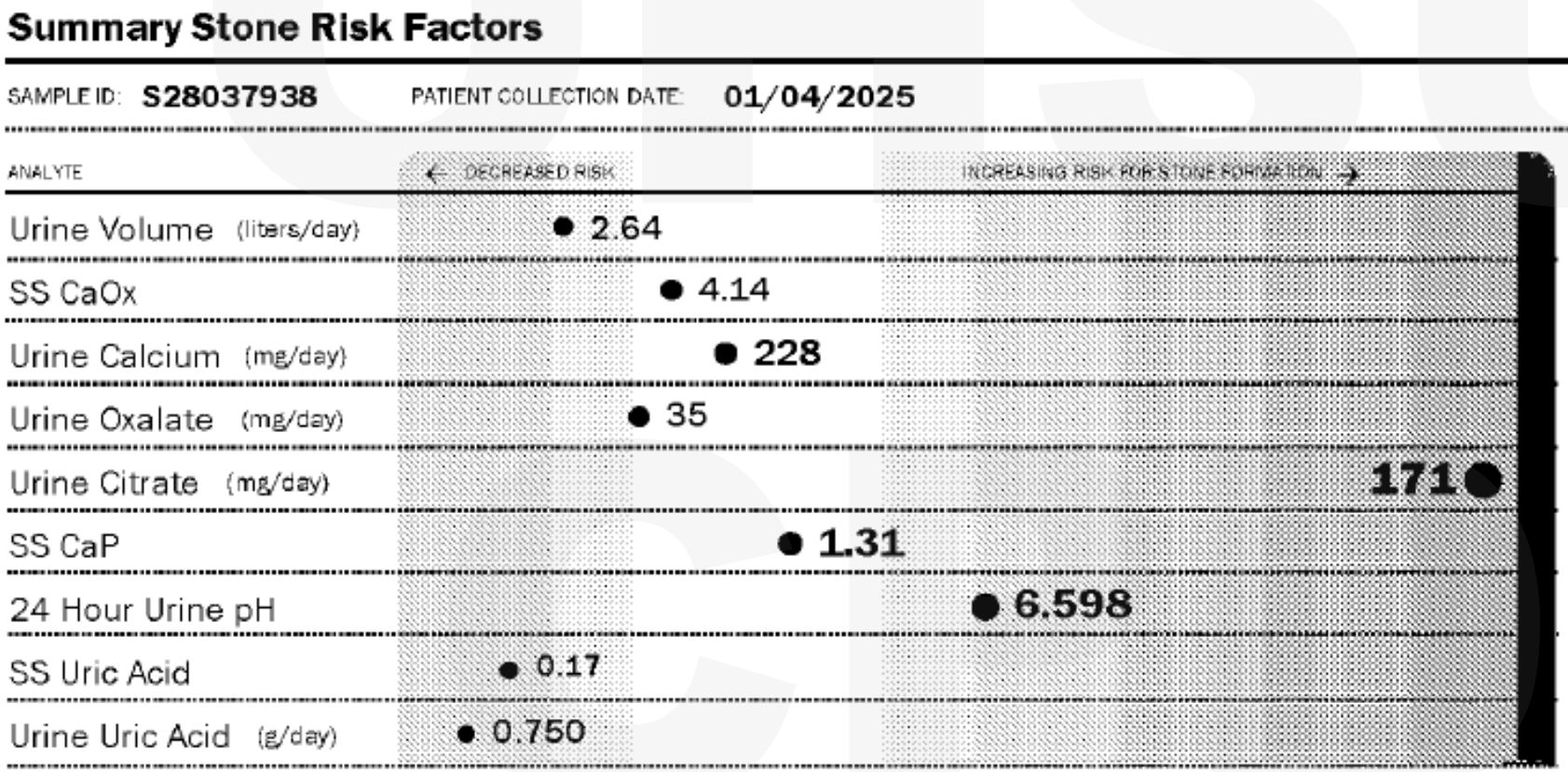
Wagner, C.A., Unwin, R., Lopez-Garcia, S.C. *et al.* The pathophysiology of distal renal tubular acidosis. *Nat Rev Nephrol* **19**, 384–400 (2023).

Incomplete dRTA

- Largely urinary abnormalities – high urine pH, hypocitraturia without serum abnormalities
- Frequently diagnosed related to stones or nephrocalcinosis on imaging
- First described in 1959 in 3 patients with nephrocalcinosis but no metabolic acidosis who were unable to maximally acidify the urine by a 1-day ammonium chloride acid–loading test (0.1 g of NH_4Cl/kg body weight)
- Makes up about 25% of stone clinic referrals here

Fuster DG, Moe OW. Incomplete Distal Renal Tubular Acidosis and Kidney Stones. Adv Chronic Kidney Dis. 2018 Jul;25(4):366-374. doi: 10.1053/j.ackd.2018.05.007. PMID: 30139463; PMCID: PMC7932558.

24 hour Urine Results in incomplete dRTA



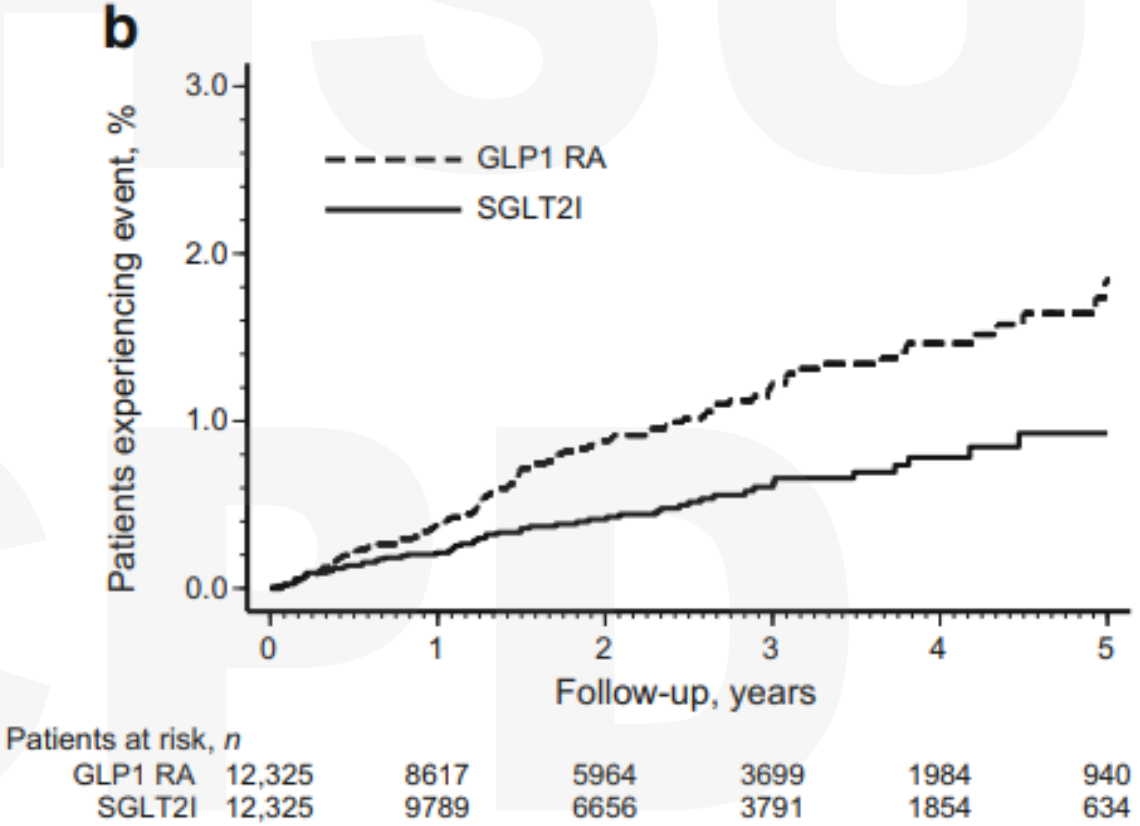
Stone Prevention for incomplete dRTA

- Generally use of K-citrate but
  - Doses of >60 mEq per day of K are needed to raise urinary citrate and that dose frequently causes GI issues
  - K-citrate increase urinary pH which increases CaP deposition risk

Fuster DG, Moe OW. Incomplete Distal Renal Tubular Acidosis and Kidney Stones. Adv Chronic Kidney Dis. 2018 Jul;25(4):366-374. doi: 10.1053/j.ackd.2018.05.007. PMID: 30139463; PMCID: PMC7932558.

In registry data, SGLT2 inhibitors decreased the risk of stone formation in diabetics

- Reviewed data from Danish Registry on new stone events on diabetic patients on SGLT2 vs GLP1 RA
- Event rate (new or recurrent) of 2.0 per 1000 person-years in SGLT2I initiators compared with 4.0 per 1000 person-years in GLP1 RA initiators



Kristensen KB, Henriksen DP, Hallas J, Pottegård A, Lund LC. Sodium-glucose cotransporter 2 inhibitors and risk of nephrolithiasis. Diabetologia. 2021 Jul;64(7):1563-1571. doi: 10.1007/s00125-021-05424-4. Epub 2021 Mar 13. PMID: 33715024.

Urinary Citrate increases without an increase in pH in Empagliflozin treated patients

- 40 patients had repeat 24 hour urine samples before and after 4 weeks of therapy with either Empagliflozin or Placebo

Table 1. Urinary parameters at baseline and after 4 weeks of treatment

Urinary Parameters	Placebo		Empagliflozin		Time	Treatment	Time × Treatment
	BL	4 wk	BL	4 wk			
Urinary Na, mmol/d	182±63	229±122	203±93	188±81	0.40	0.69	0.10
Urinary K, mmol/d	68±17	76±28	76±30	74±29	0.43	0.70	0.18
Urinary Cl, mmol/d	173±58	202±72	197±85	184±76	0.64	0.87	0.20
Urinary Ca, mmol/d	5.3±3.1	5.4±2.9	4.6±3.1	5.3±2.9	0.27	0.69	0.38
Urinary P, mmol/d	33±13	35±16	34±17	32±17	0.91	0.92	0.30
Urinary Mg, mmol/d	3.8±1.3	4.3±1.6	4.2±2.2	4.3±1.6	0.41	0.69	0.53
Urinary urate, μmol/d	4048±1417	4084±1393	4265±1940	4424±1876	0.68	0.62	0.79
Urinary oxalate, μmol/d	178±80	230±132	210±127	233±150	**0.05**	0.66	0.42
Urinary citrate , mmol/d	3±1	3.3±1.1	3.3±1.6	4.8±1.7	**<0.001**	**0.04**	**0.01**
Urinary sulfate, mmol/d	23±7.1	24±10	25±13	24±13	0.96	0.83	0.78
Urinary NH_4, mmol/d	74±23	80±33	83±38	77±33	>0.99	0.80	0.32
Urinary volume, mmol/d	1782±752	2790±1019	2103±944	2547±958	**<0.001**	0.89	0.06
Urinary pH							
Day	6.1±0.89	6.4±0.85	6.4±0.88	5.9±0.85	0.39	0.56	**0.004**
Night	5.8±0.6	6±0.55	6±0.76	5.6±0.56	0.39	0.70	**0.02**

Values are presented as mean ± SD in 24-hour urine collections except for pH, which is split for day and night collections. Data were analyzed by two-way mixed ANOVA, and *P* values are shown in the columns time, treatment, and time × treatment interaction. *P* values ≤0.05 are highlighted in bold. BL, baseline.

Harmacek D, Pruijm M, Burnier M, Muller ME, Ghajarzadeh-Wurzner A, Bonny O, Zanchi A. Empagliflozin Changes Urine Supersaturation by Decreasing pH and Increasing Citrate. J Am Soc Nephrol. 2022 Jun;33(6):1073-1075. doi: 10.1681/ASN.2021111515. Epub 2022 Apr 6. PMID: 35387874; PMCID: PMC9161803.

Sweetstone

- Randomized, double-blind, placebo-controlled, cross-over, single-center (Swiss) exploratory study

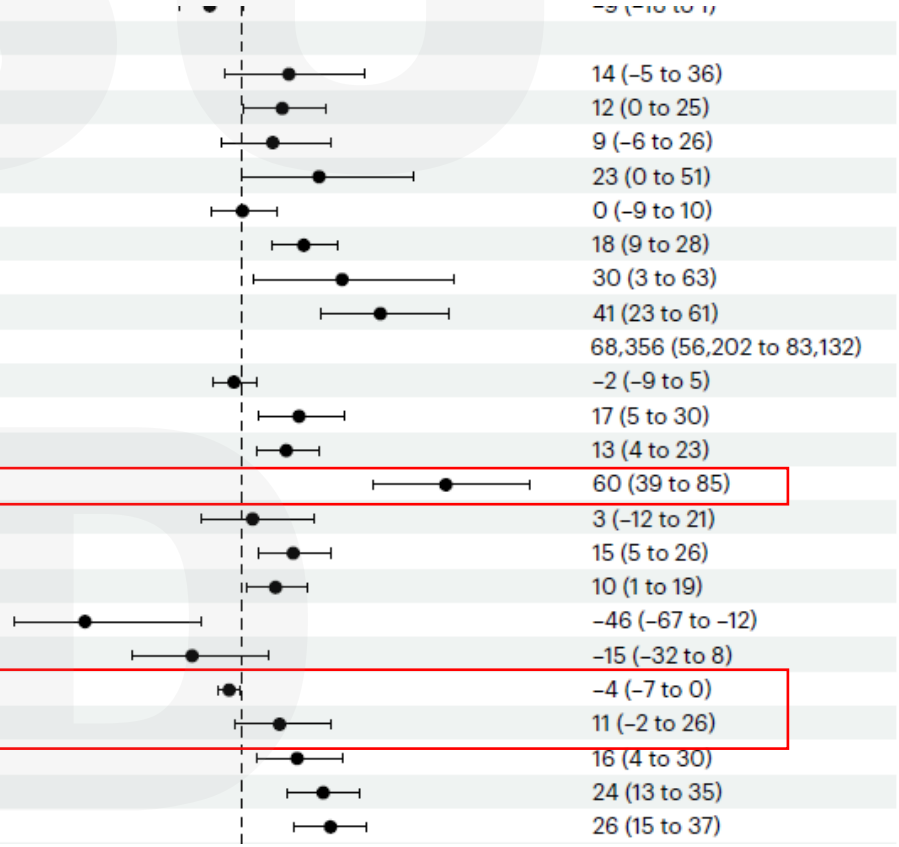
- Participants will be randomized in equal proportions into two groups
  - one group receiving 25mg empagliflozin and other placebo
  - Switch groups after 14 days

- Primary endpoint effect of empagliflozin on urinary supersaturation

Sweetstone

- Citrate increases likely accounts for the change in supersaturation in CaP as volume and pH were essentially unchanged

Secondary outcomes, urine					
Sodium (mmol per 24 h)	25	164.4 (132.3, 205.5)	25	184.6 (120.9, 253.0)	14 (–5 to 36)
Potassium (mmol per 24 h)	25	56.8 (42.8, 65.2)	25	60.4 (50.6, 68.4)	12 (0 to 25)
Chloride (mmol per 24 h)	25	151.0 (122.0, 184.0)	25	159.4 (108.0, 234.3)	9 (–6 to 26)
Calcium (mmol per 24 h)	25	6.2 (4.8, 8.3)	25	8.1 (6.3, 9.1)	23 (0 to 51)
Magnesium (mmol per 24 h)	25	4.1 (3.6, 5.0)	25	4.3 (3.3, 5.0)	0 (–9 to 10)
Phosphate (mmol per 24 h)	25	30.5 (21.1, 38.4)	25	35.2 (29.5, 42.9)	18 (9 to 28)
Osmolality (mosm kg^{-1})	22	509.5 (376.5, 640.0)	23	670.0 (522.5, 859.0)	30 (3 to 63)
Osmole excretion (mosm per 24 h)	22	882.9 (697.3, 978.9)	23	1,209.0 (940.5, 1,595.8)	41 (23 to 61)
Glucose (mmol per 24 h)	25	0.5 (0.3, 0.6)	25	289.2 (190.8, 389.2)	68,356 (56,202 to 83,132)
Creatinine (µmol per 24 h)	25	15,129.9 (12,019.4, 16,537.2)	25	15,685.2 (11,418.2, 17,679.1)	–2 (–9 to 5)
Urea (mmol per 24 h)	25	361.8 (284.2, 462.9)	25	384.0 (339.3, 584.5)	17 (5 to 30)
Uric acid (µmol per 24 h)	25	3,186.6 (2,573.3, 3,776.2)	25	4,334.0 (3,072.4, 5,143.2)	13 (4 to 23)
Citrate (mmol per 24 h)	25	3.2 (2.1, 3.9)	25	4.9 (3.3, 7.1)	60 (39 to 85)
Oxalate (µmol per 24 h)	25	513.7 (382.8, 599.1)	25	470.3 (356.4, 626.7)	3 (–12 to 21)
Sulfate (mmol per 24 h)	25	19.4 (14.1, 26.8)	25	24.7 (15.6, 29.8)	15 (5 to 26)
Ammonium (mmol per 24 h)	24	39.7 (20.6, 45.5)	24	42.2 (24.0, 50.0)	10 (1 to 19)
Bicarbonate (mmol per 24 h)	25	1.3 (0.5, 2.6)	25	0.9 (0.4, 1.7)	–46 (–67 to –12)
pCO_2 (mmHg)	25	38.0 (33.9, 57.0)	25	38.6 (27.1, 50.0)	–15 (–32 to 8)
Venous pH	25	5.8 (5.6, 6.4)	25	5.6 (5.5, 6.1)	–4 (–7 to 0)
Total volume per 24 h[d] (l)	25	1.8 (1.2, 2.5)	25	2.3 (1.4, 2.9)	11 (–2 to 26)
Titratable acid[e] (mEq per 24 h)	25	24.3 (16.6, 36.8)	25	33.2 (24.9, 35.8)	16 (4 to 30)
NGIA[e] (mEq per 24 h)	25	38.1 (26.9, 57.7)	25	49.9 (34.6, 63.6)	24 (13 to 35)
NAE[e] (mEq per 24 h)	24	62.1 (34.1, 80.4)	24	70.7 (53.2, 83.0)	26 (15 to 37)

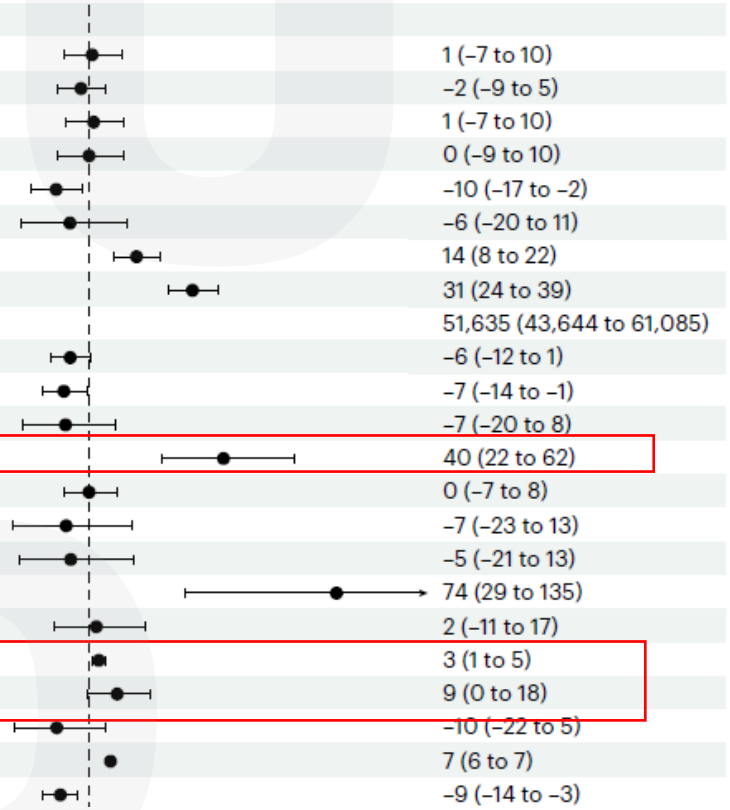


Secondary and exploratory outcomes in participants with calcium kidney stones.

Sweetstone

- In Uric Acid stone patients, citrate and pH increased while urine volume was stable and uric acid stones are very pH dependent

Secondary outcomes, urine					
Sodium (mmol per 24 h)	21	176.0 (150.7, 204.5)	21	195.2 (143.9, 204.4)	1 (–7 to 10)
Potassium (mmol per 24 h)	21	69.1 (49.1, 77.0)	21	62.6 (51.5, 73.6)	–2 (–9 to 5)
Chloride (mmol per 24 h)	21	163.6 (131.1, 187.5)	21	177.1 (136.4, 197.0)	1 (–7 to 10)
Calcium (mmol per 24 h)	21	4.6 (3.4, 6.4)	21	4.7 (3.3, 6.2)	0 (–9 to 10)
Magnesium (mmol per 24 h)	21	3.7 (3.1, 4.5)	21	3.4 (2.9, 4.1)	–10 (–17 to –2)
Phosphate (mmol per 24 h)	21	34.8 (28.7, 39.5)	21	32.3 (29.6, 37.6)	–6 (–20 to 11)
Osmolality (mosm kg^{-1})	21	622.0 (402.0, 784.0)	21	650.0 (575.0, 783.0)	14 (8 to 22)
Osmole excretion (mosm per 24 h)	21	967.2 (789.8, 1,041.1)	21	1,287.1 (1,085.0, 1,444.9)	31 (24 to 39)
Glucose (mosm per 24 h)	21	0.5 (0.4, 0.6)	21	267.7 (233.2, 311.5)	51,635 (43,644 to 61,085)
Creatinine (µmol per 24 h)	21	14,466.5 (12,456.0, 17,367.8)	21	13,530.0 (11,899.6, 15,896.8)	–6 (–12 to 1)
Urea (mmol per 24 h)	21	456.7 (372.7, 479.9)	21	417.9 (322.0, 469.5)	–7 (–14 to –1)
UA (µmol per 24 h)	21	4,307.6 (3,310.0, 4,680.3)	21	3,855.7 (3,120.9, 4,526.8)	–7 (–20 to 8)
Citrate (mmol per 24 h)	21	3.7 (2.3, 4.5)	21	4.2 (3.4, 5.6)	40 (22 to 62)
Oxalate (µmol per 24 h)	21	438.7 (375.2, 475.4)	21	411.8 (335.5, 575.7)	0 (–7 to 8)
Sulfate (mmol per 24 h)	21	22.4 (19.2, 29.4)	21	21.6 (17.9, 24.9)	–7 (–23 to 13)
Ammonium (mmol per 24 h	21	30.2 (25.3, 33.8)	21	31.3 (23.4, 35.9)	–5 (–21 to 13)
Bicarbonate (mmol per 24 h)	21	0.3 (0.2, 0.3)	21	0.5 (0.2, 0.8)	74 (29 to 135)
pCO_2 (mmHg)	21	26.7 (22.0, 35.3)	21	29.9 (24.2, 32.7)	2 (–11 to 17)
Venous pH	21	5.3 (5.2, 5.5)	21	5.6 (5.2, 5.6)	3 (1 to 5)
Total volume per 24 h[d] (l)	21	1.7 (1.3, 2.2)	21	1.9 (1.7, 2.1)	9 (0 to 18)
Titratable acid[e] (mEq per 24 h)	21	33.8 (27.9, 40.0)	21	31.1 (27.2, 37.1)	–10 (–22 to 5)
NGIA[e] (mEq per 24 h)	21	31.9 (24.4, 46.6)	21	36.7 (22.0, 49.9)	7 (6 to 7)
NAE[e] (mEq per 24 h)	21	63.4 (52.0, 78.6)	21	64.8 (52.0, 69.4)	–9 (–14 to –3)



Secondary and exploratory outcomes in participants with uric acid kidney stones.

Sweetstone

- Urine changes over 2 weeks may not be reflective of long-term changes for stone risk
- Supersaturation is not a hard endpoint so not clear this will translate into reduced stone events yet
- Promising new therapy

Summary

- SGLT2 inhibitors have been found to be useful treatments for numerous renal and renal adjacent issues
  - Diabetic Nephropathy
  - Proteinuric CKD
  - Heart Failure
  - Hyponatremia
  - Hypomagnesemia
  - Kidney stones
- Suspect there will be more trials to come for other electrolyte issues and long-term studies for Mg and Stones

Questions