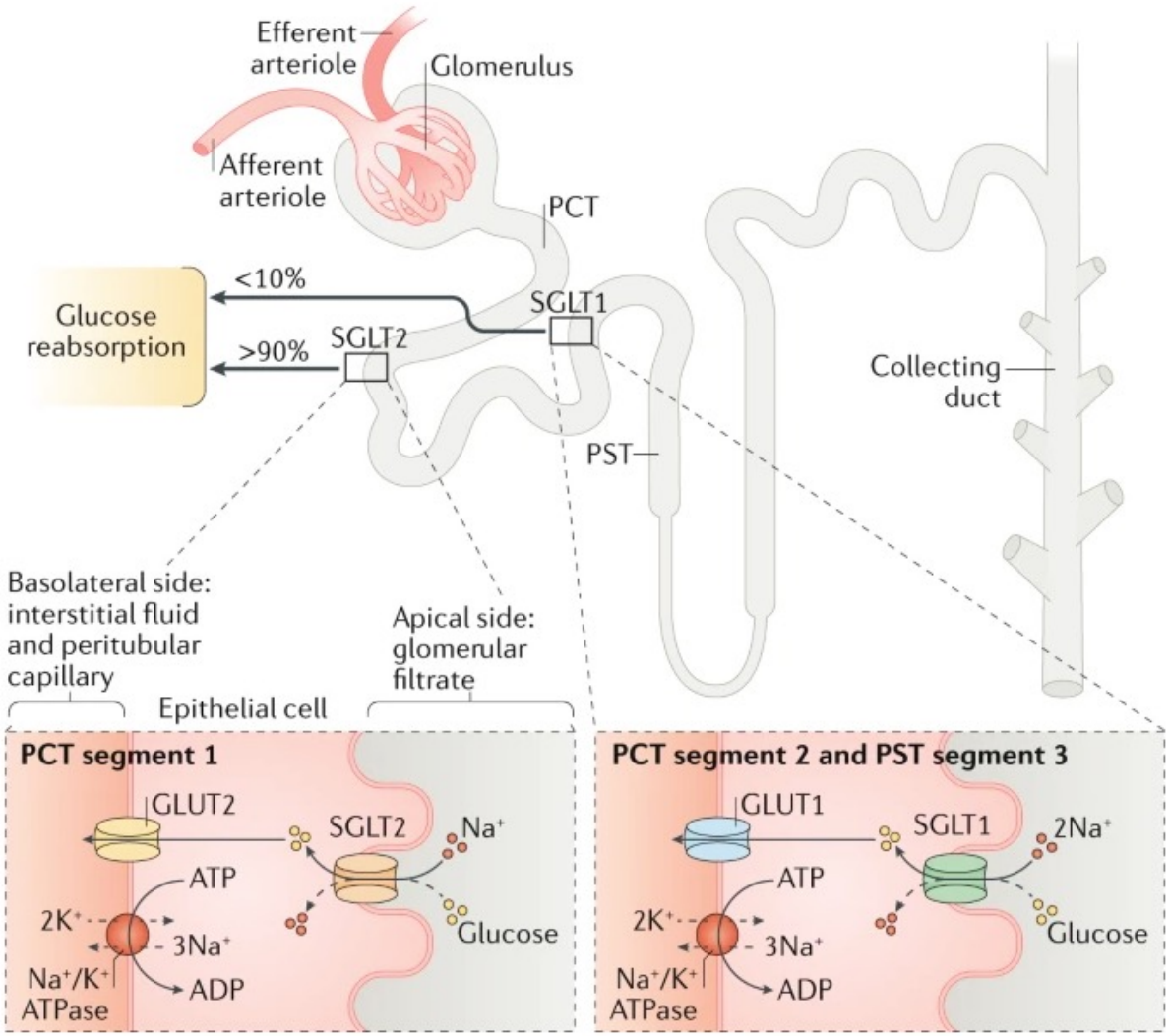
SGLT2i and CKD

September 7, 2023

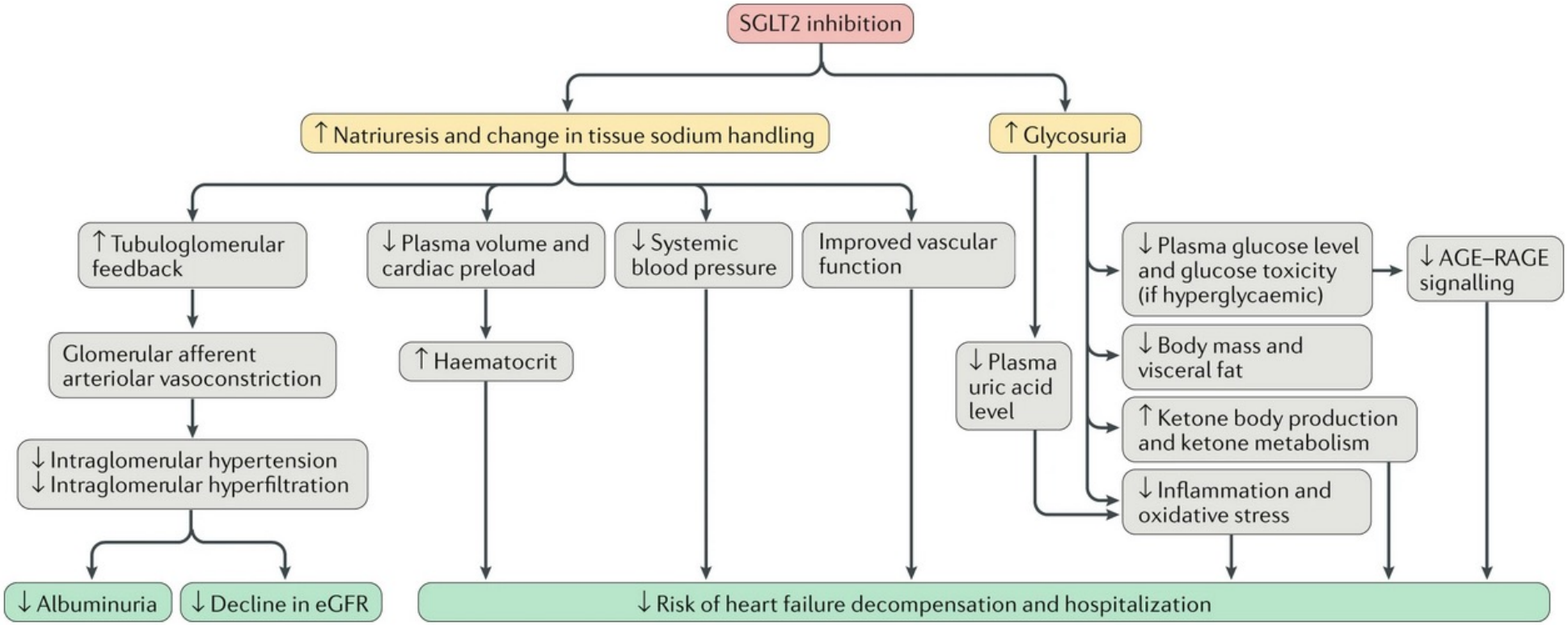
Objectives

- Review the mechanism of action
- Review the evidence
- Clinical use and application
- Questions and discussion

Mechanism of action of SGLT2i

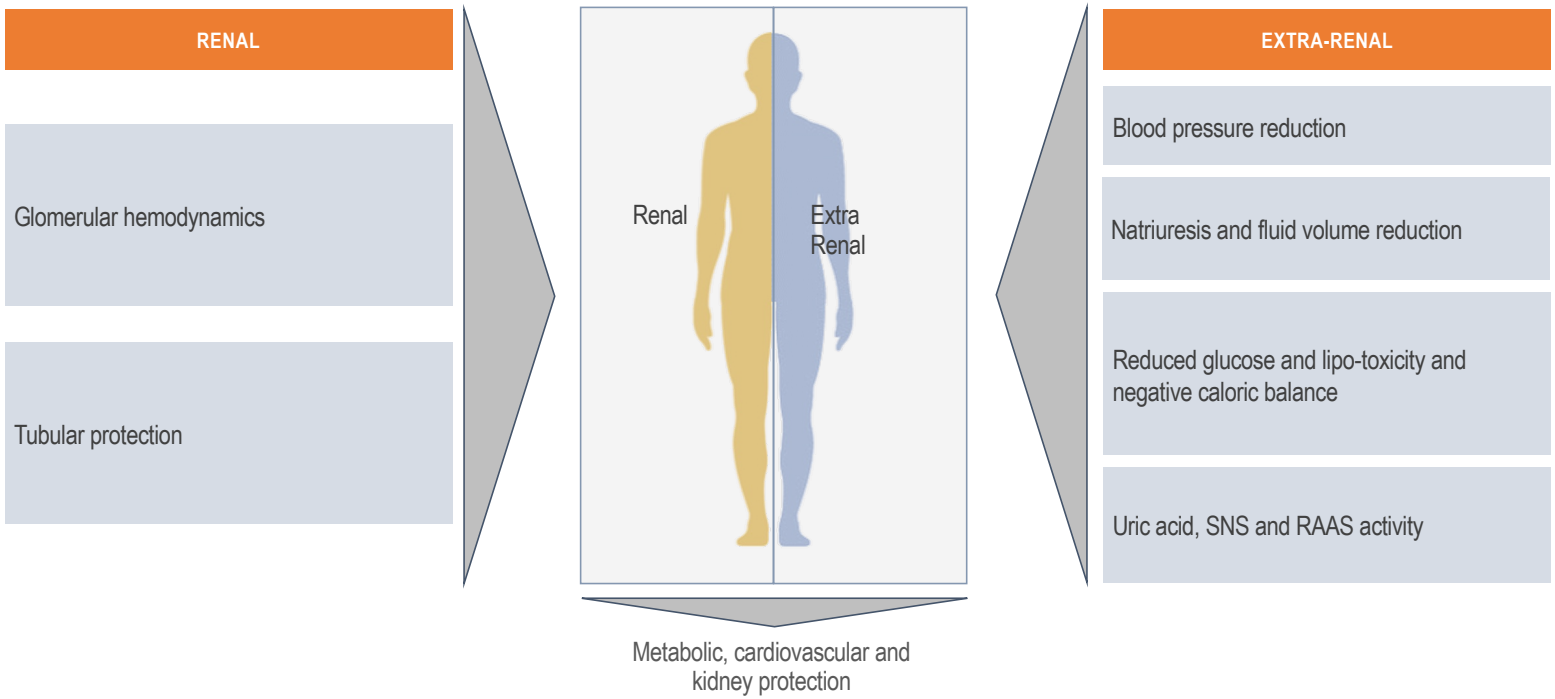


Cowie, M.R., Fisher, M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* **17**, 761–772 (2020). https://doi.org/10.1038/s41569-020-0406-8



Cowie, M.R., Fisher, M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* **17**, 761–772 (2020). https://doi.org/10.1038/s41569-020-0406-8

Renal and Extrarenal Mechanism of Action by SGLT2i



RAAS, renin-angiotensin-aldosterone system; SNS, Sympathetic nervous system

Leoncini G, Russo E, Bussalino E, Barnini C, Viazzi F, Pontremoli R. SGLT2is and Renal Protection: From Biological Mechanisms to Real-World Clinical Benefits. *Int J Mol Sci*. 2021;22(9):4441. doi:10.3390/ijms22094441

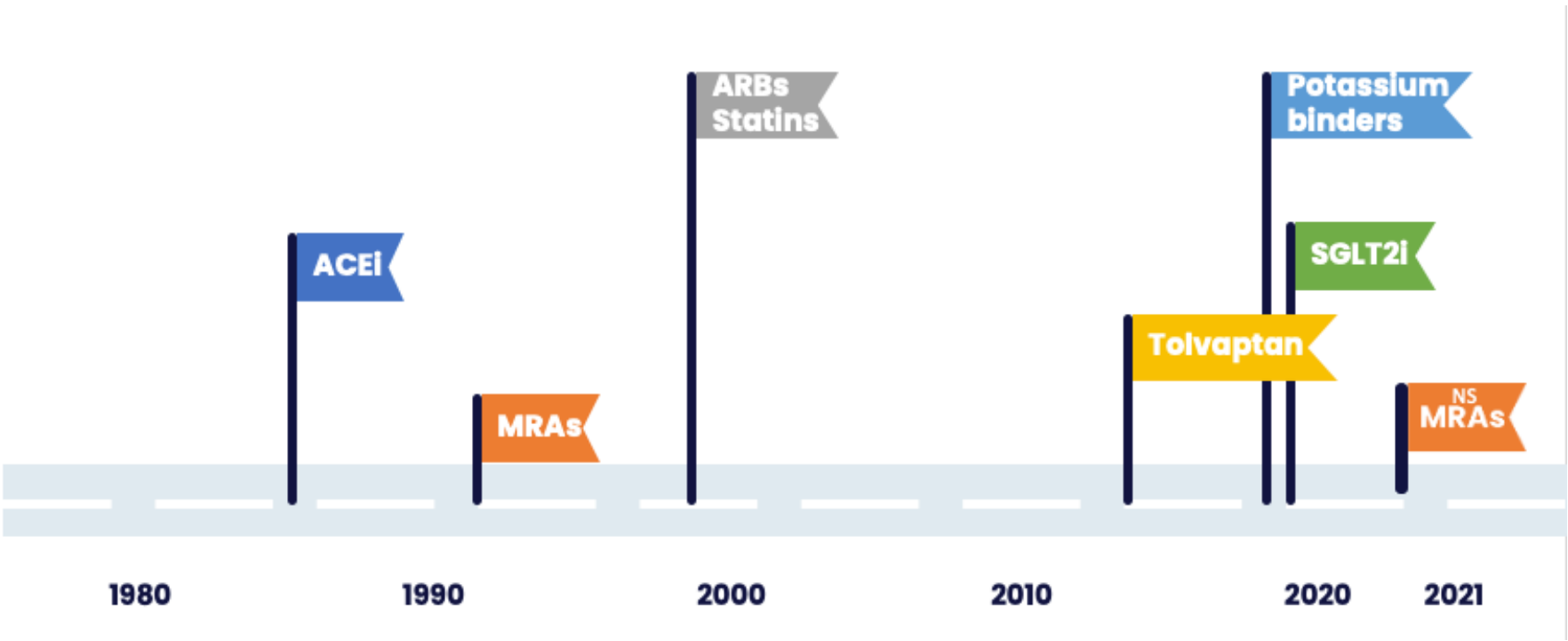
Take home message #1

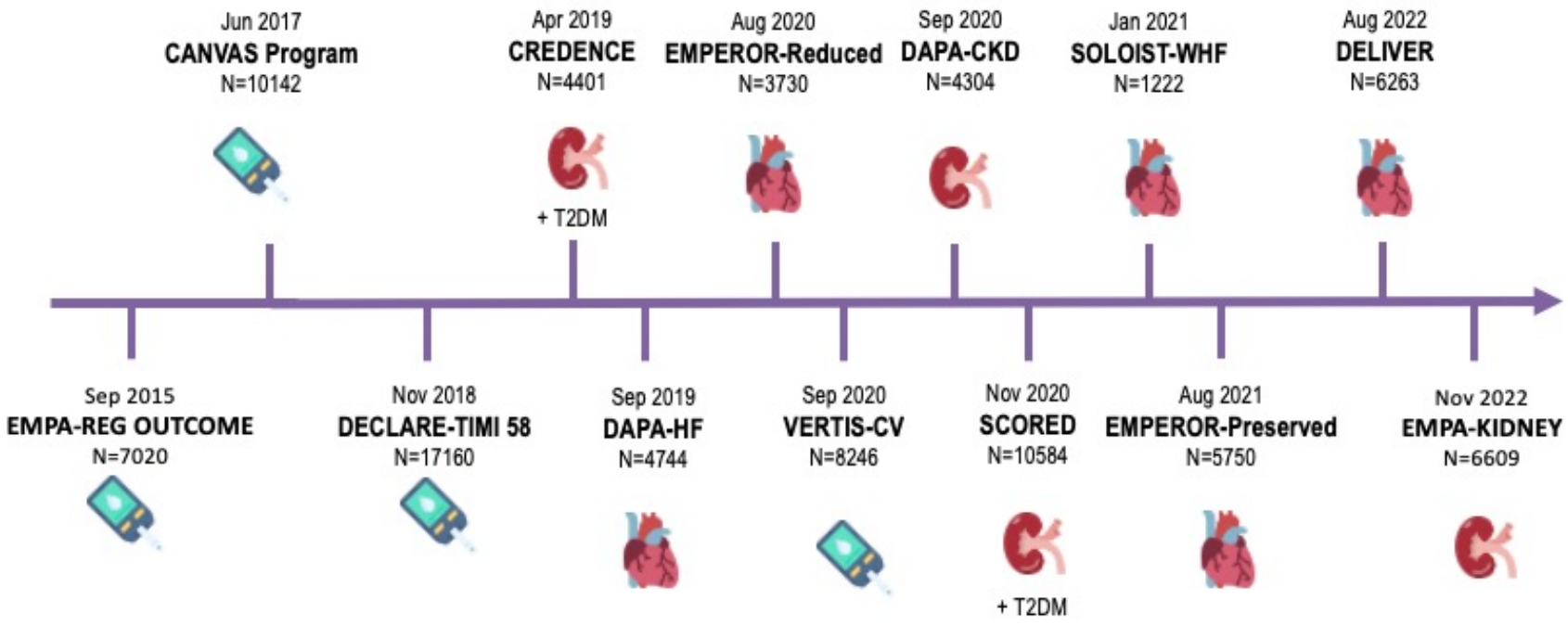
- Main mechanism of action of SGLT2i is thought to be derived from increased glucosuria and natriuresis

- This results in
  - Lower BP
  - Volume control
  - Weight loss

  - Impacting cardiovascular and kidney health

Review of evidence


ACEi
MRAs
ARBs
Statins
Potassium
binders
SGLT2i
Tolvaptan
NS
MRAs
1980
1990
2000
2010
2020
2021


Jun 2017
CANVAS Program
N=10142
Apr 2019
CREDENCE
N=4401
+ T2DM
Aug 2020
EMPEROR-Reduced
N=3730
Sep 2020
DAPA-CKD
N=4304
Jan 2021
SOLOIST-WHF
N=1222
Aug 2022
DELIVER
N=6263
Sep 2015
EMPA-REG OUTCOME
N=7020
Nov 2018
DECLARE-TIMI 58
N=17160
Sep 2019
DAPA-HF
N=4744
Sep 2020
VERTIS-CV
N=8246
Nov 2020
SCORED
N=10584
+ T2DM
Aug 2021
EMPEROR-Preserved
N=5750
Nov 2022
EMPA-KIDNEY
N=6609

CREDENCE Trial

Canagliflozin 100 mg

Inclusion/Baseline Criteria[1]

≥30 years
Canagliflozin n=2202
Placebo n=2199

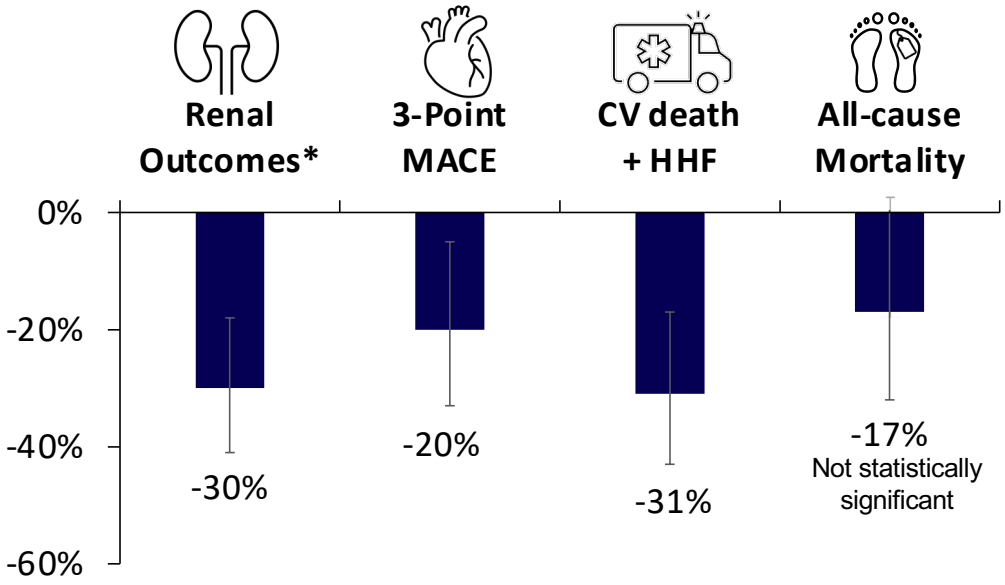
≥30 to <90 mL/min/1.73 m²
eGFR

>33.9 to ≤565.6 mg/mmol
UACR

Confirmed T2D
A1C ≥6.5% to ≤12.0%

ACEi/ARB use **99.9%**
Mean A1C **8.3%**
Mean sBP **140.0 mmHg**

Key outcomes[2]



*Primary composite outcome: end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death

1. Jardine MJ, et al. Am J Nephrol. 2017;46(6):462-472.
2. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.

DAPA-CKD Trial

Dapagliflozin 10 mg

Inclusion/Baseline Criteria[1]

≥18 years
Dapagliflozin n=2152
Placebo n= 2152

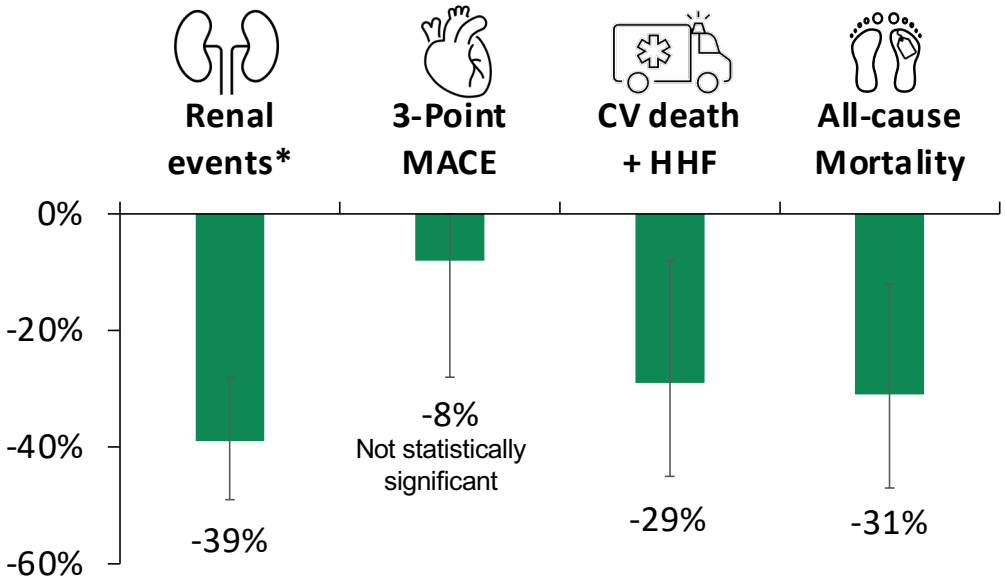
≥25 to ≤75 mL/min/1.73 m²
eGFR

>22.6 to ≤565 mg/mmol
UACR

68% with T2D

ACEi/ARB use **97%**
Mean sBP **137.4 mmHg**

Key outcomes[2,3]



*Primary composite outcome: sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

1. Wheeler et al. Nephrol Dial Transplant 2020;35: 1700–1711
2. Heerspink et al. N Engl J Med 2020; 383:1436-1446.
3. McMurray et al. Circulation. 2020; ePub ahead of print: 10.1161/CIRCULATIONAHA.120.051675

EMPA-KIDNEY Trial

Empagliflozin 10 mg

Inclusion/Baseline Criteria[1]

≥18 years
Empagliflozin n=3304
Placebo n= 3305

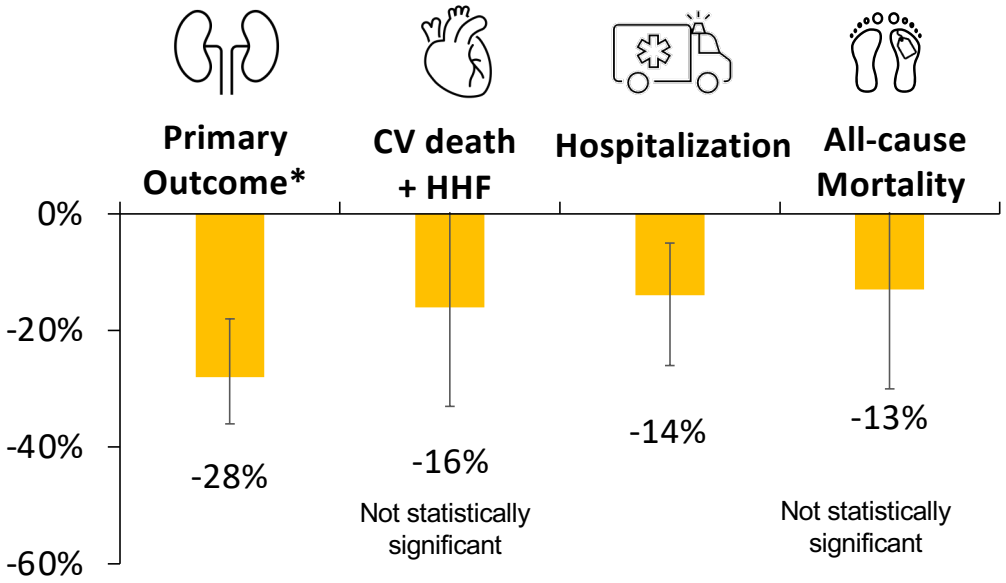
≥20 to <45 mL/min/1.73 m²
OR
≥45 to <90 mL/min/1.73 m²
≥22.6 mg/mmol

46.2% with T2D

ACEi/ARB use **85.7%**
Mean sBP **136.4 mmHg**

1. Herrington et al. N Engl J Med 2023; 388(2):117-127

Key outcomes[1]



*Primary composite outcome: progression of kidney disease (dialysis or kidney transplant, sustained decrease in eGFR <10 mL/min, sustained decrease from baseline in eGFR by at least 40%, death from renal causes) or death from cardiovascular causes

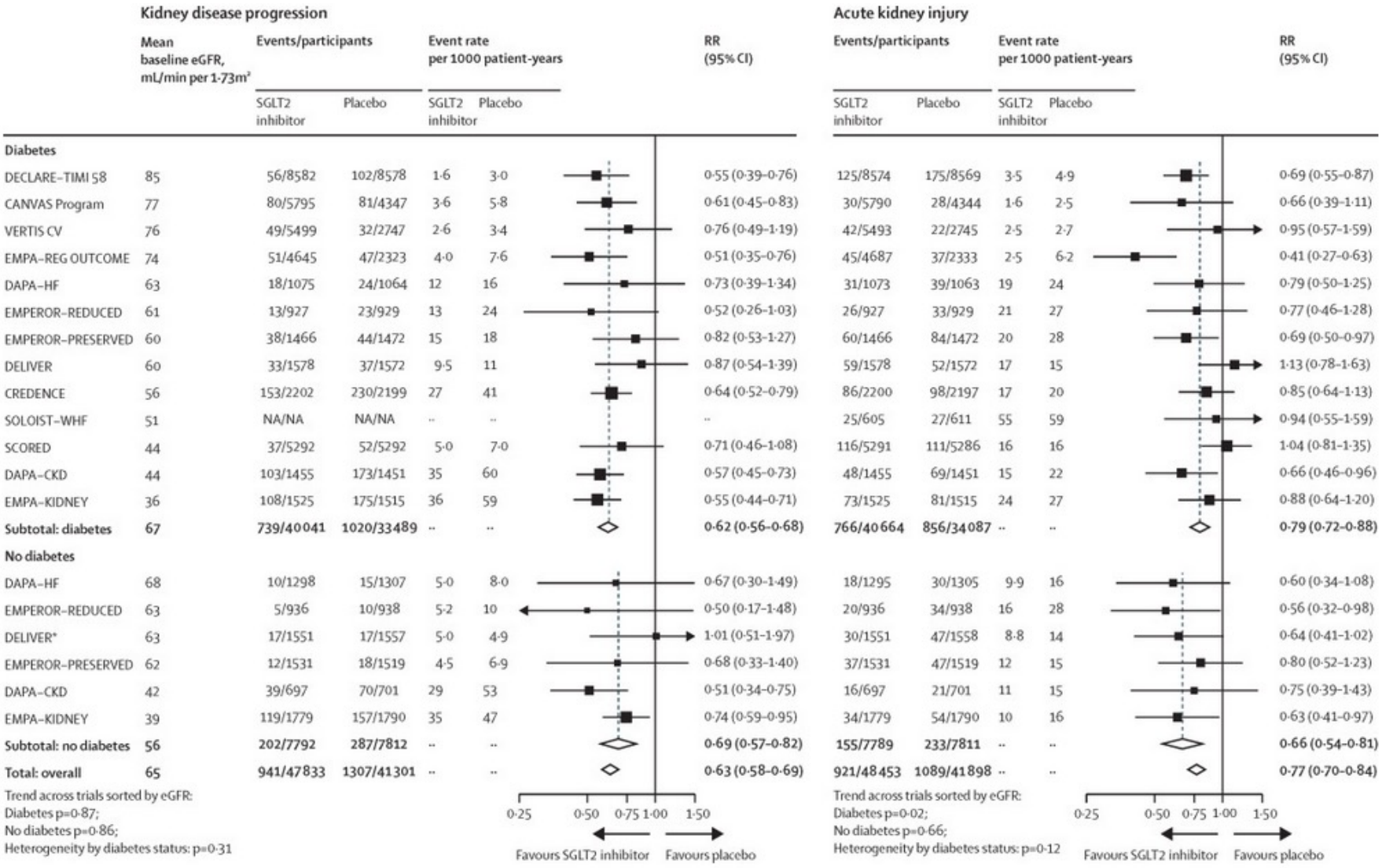
Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

The Nuffield Department of Population Health Renal Studies Group † •
and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium † • Show footnotes

SMART-C

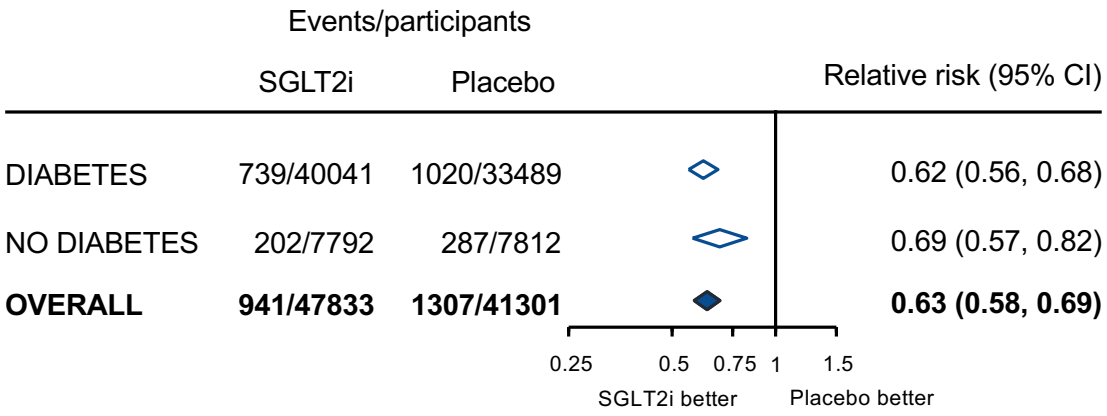
Population	Trials	Mean eGFR, ml/min/1.73m^2 (range)	Median follow-up, years (range)	Number (%) without diabetes	Total participants
Type 2 diabetes & high CV risk	4	74-85	2.4-4.2	0 (0%)	42,568
Heart failure	5	51-66	0.8-2.2	10,985 (50%)	21,947
Chronic kidney disease (CKD)	4	37-56	1.3-2.6	4968 (19%)	25,898
TOTAL	**13**			**15,953 (18%)**	**90,413**

Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.



Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.

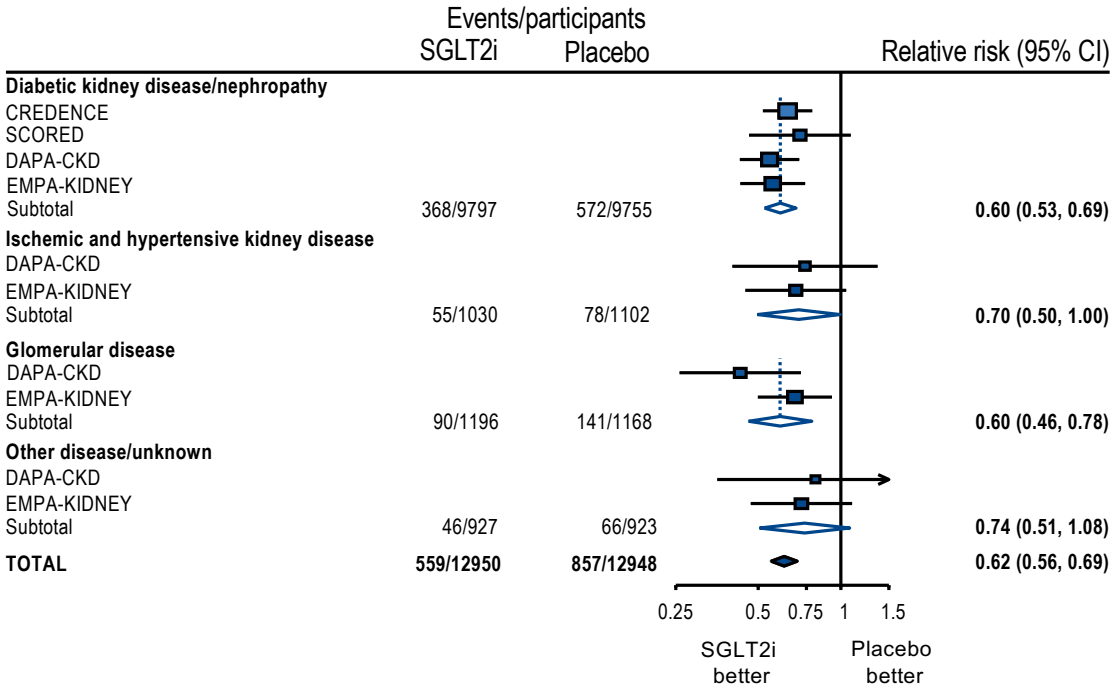
Kidney disease progression is attenuated



Heterogeneity by diabetes status: p=0.31

Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.

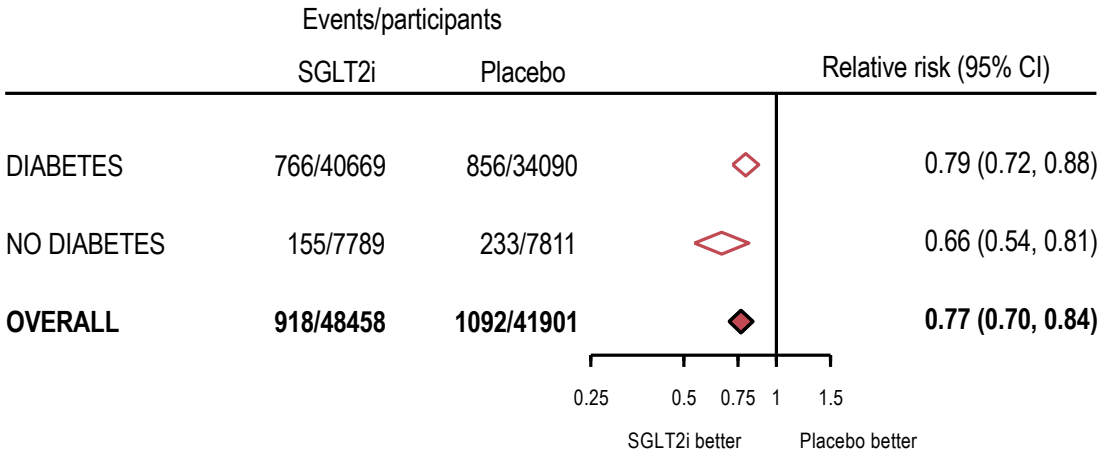
Kidney disease progression is attenuated irrespective of cause



Heterogeneity across groups of primary kidney disease: p=0.67

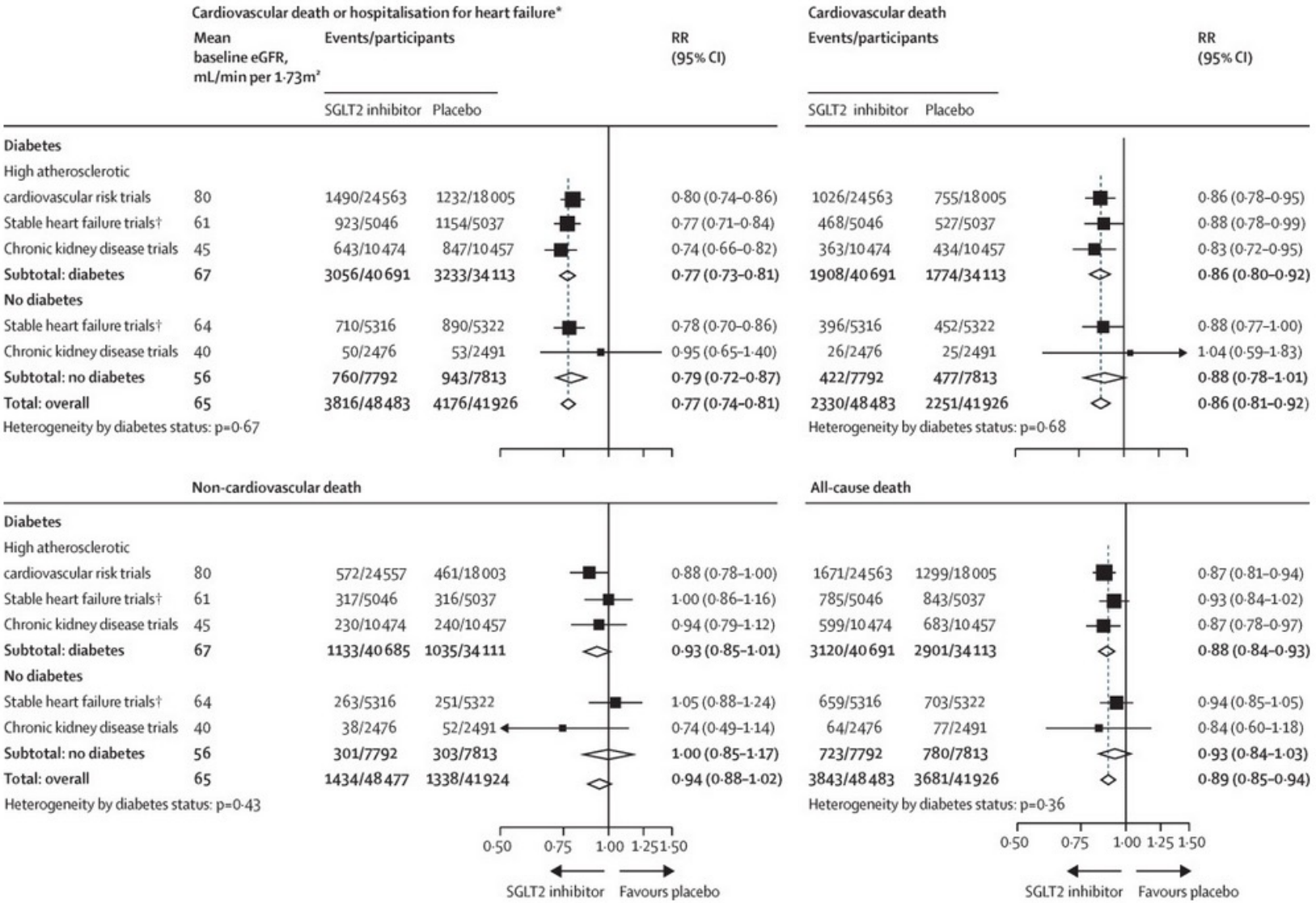
Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.

Acute kidney injury is reduced



Heterogeneity by diabetes status: p=0.12

Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.



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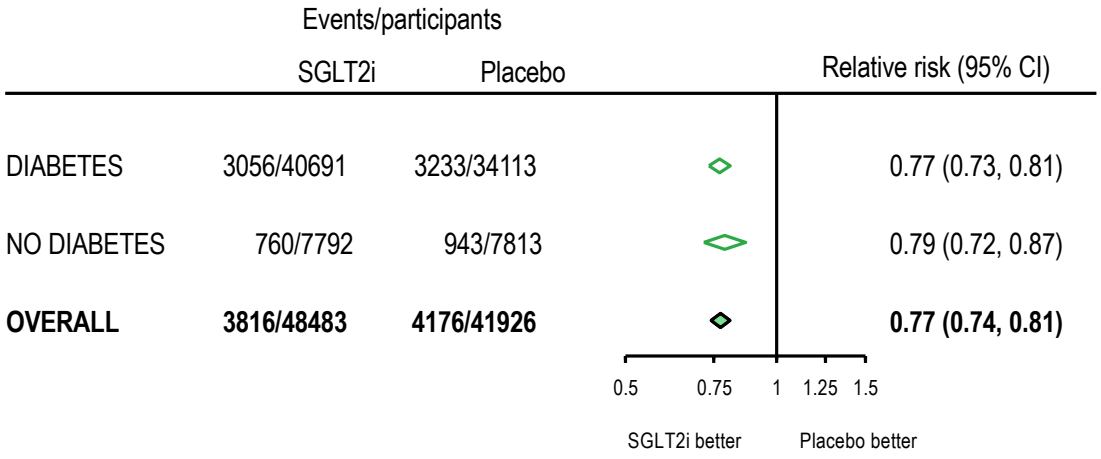
CV death or hospitalization for heart failure is reduced



Heterogeneity by diabetes status: p=0.67

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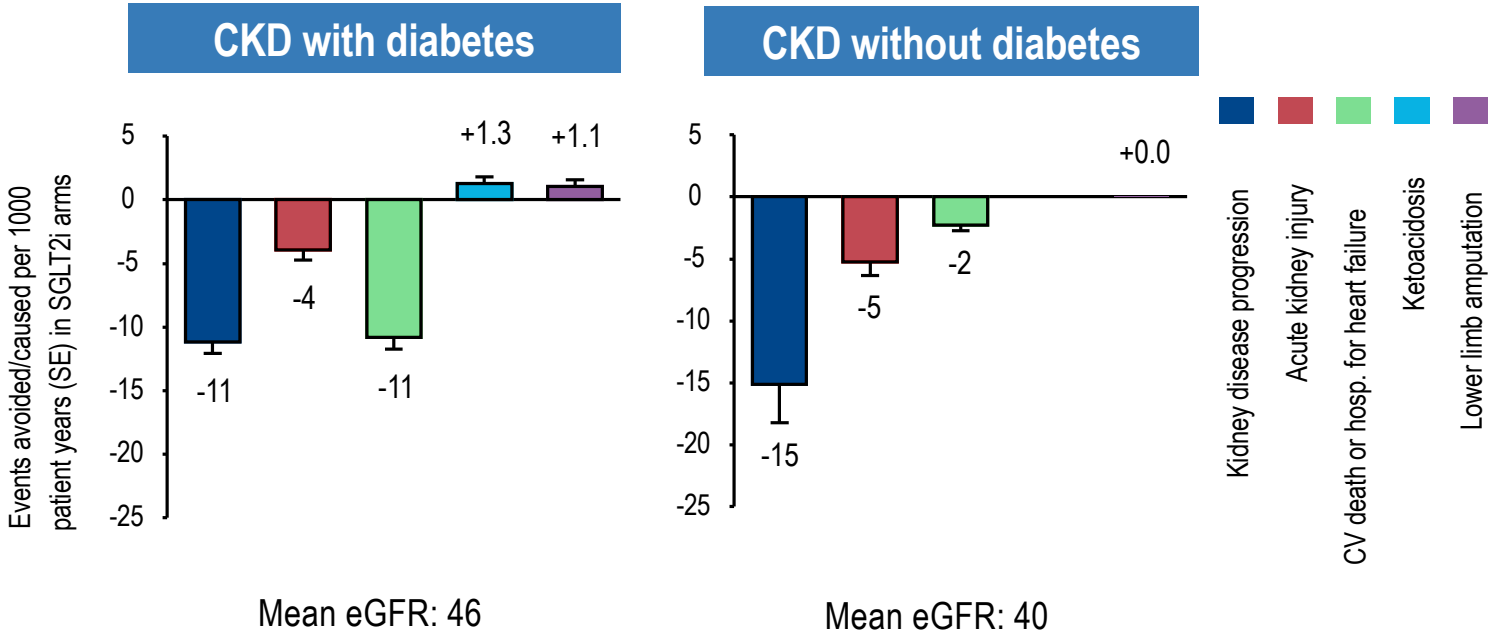
Predicted absolute effects per 1000 patient years



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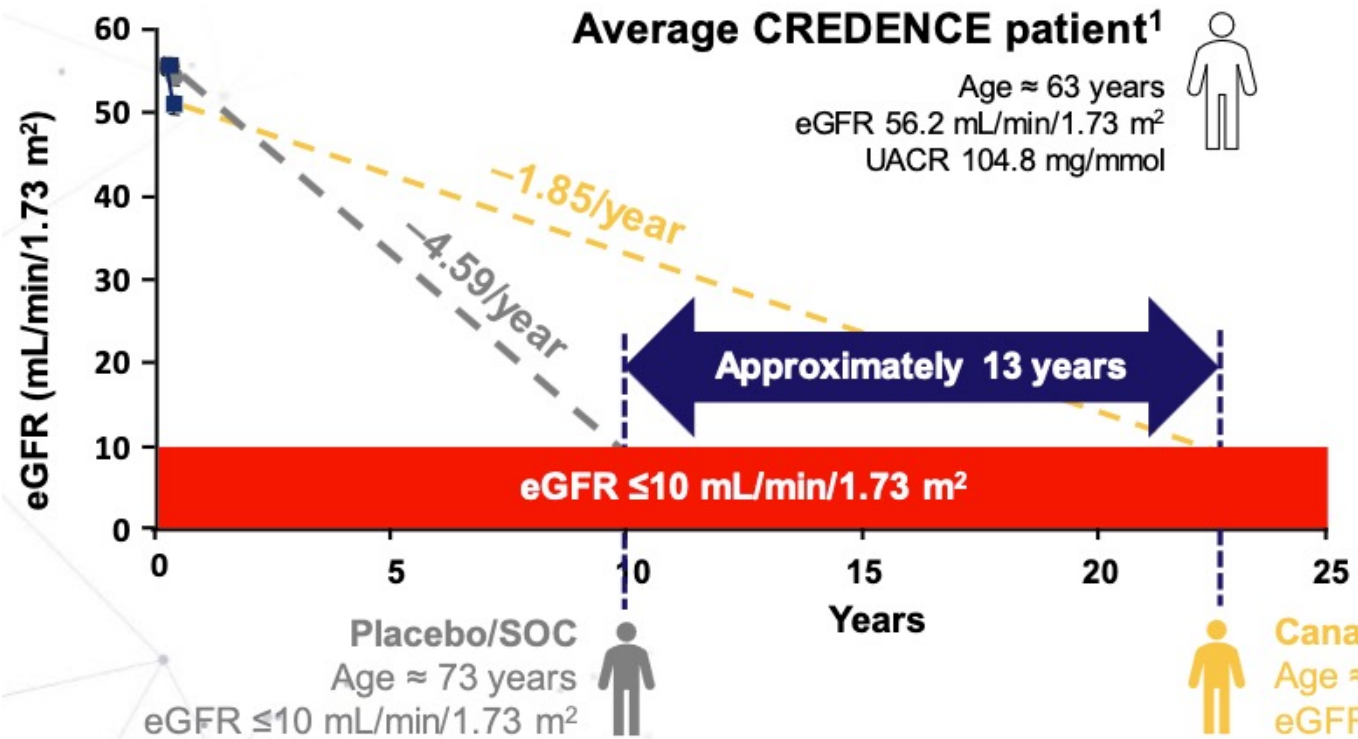


Estimated cost savings for 13-year delay of dialysis[2]

$502,554
(peritoneal)

to

$834,782
(in-center hemodialysis)

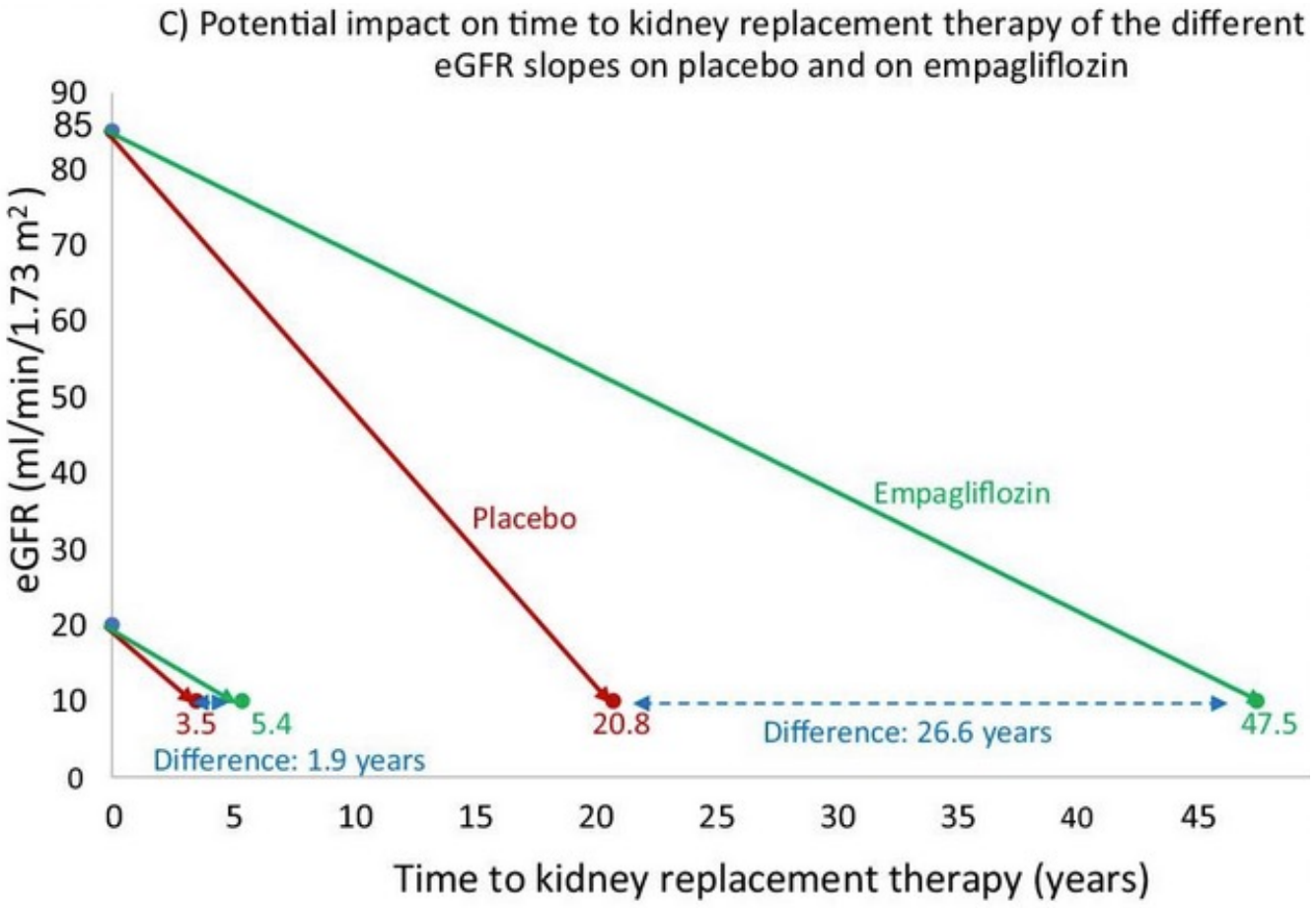
Projections are based on eGFR slopes from week 3 to end of treatment (chronic phase) and assume linear progression of eGFR decline

- Calculated as [(eGFR at start of chronic phase – 10 mL/min/1.73 m²) / chronic eGFR slope]

eGFR at start of chronic phase (3-week time point): Canagliflozin 100 mg/SOC 52.28 mL/min/1.73 m2, Placebo/SOC 55.45 mL/min/1.73 m2

Figure adapted from: Durkin & Blais. Diabetes Ther. 2020 Dec 18. doi: 10.1007/s13300-020-00953-4.

1. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
2. Beaudry et al. Clin J Am Soc Nephrol. 2018;13(8):1197-1203.



Beatriz Fernández-Fernandez and others, EMPA-KIDNEY: expanding the range of kidney protection by SGLT2 inhibitors, *Clinical Kidney Journal*, Volume 16, Issue 8, August 2023, Pages 1187–1198, https://doi.org/10.1093/ckj/sfad082

Take home message #2

- SGLT2i reduces kidney disease progression, cardiovascular complications, death, and keeps patients out of hospital

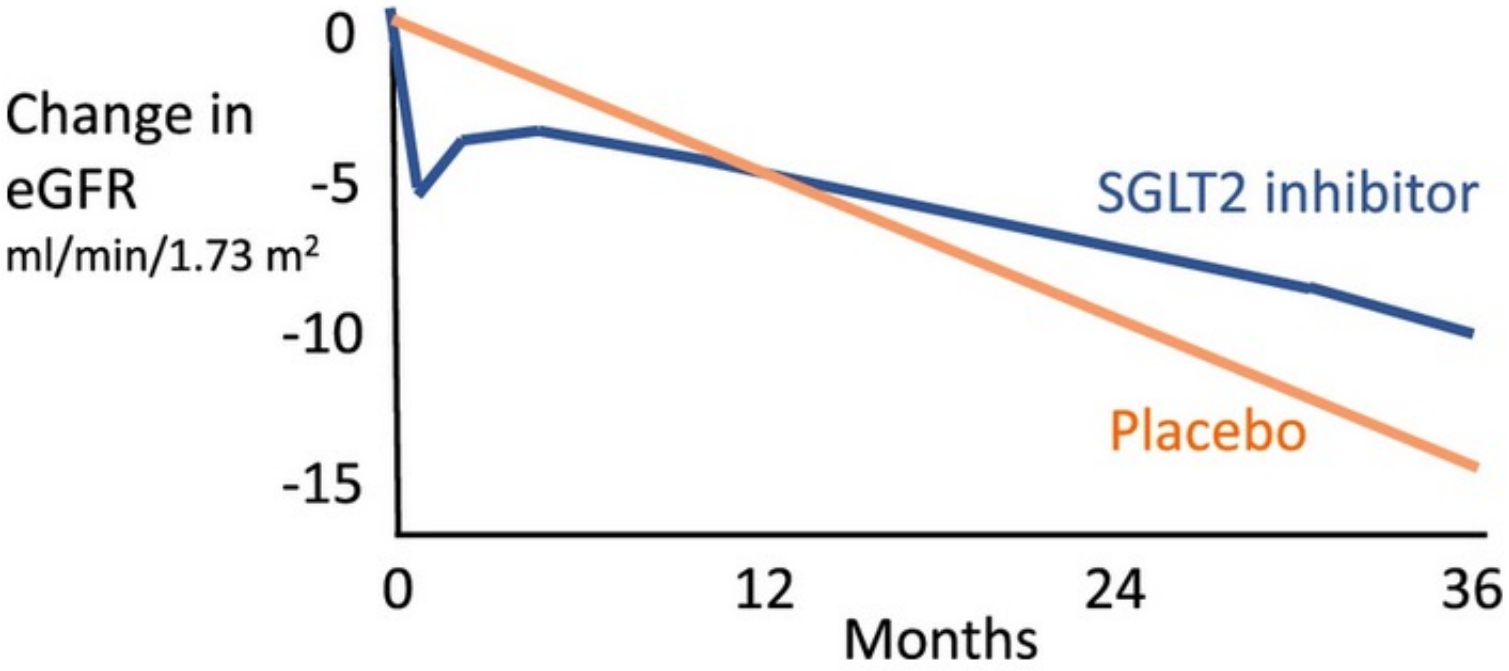
Clinical applications

eGFR dip

Adverse reactions

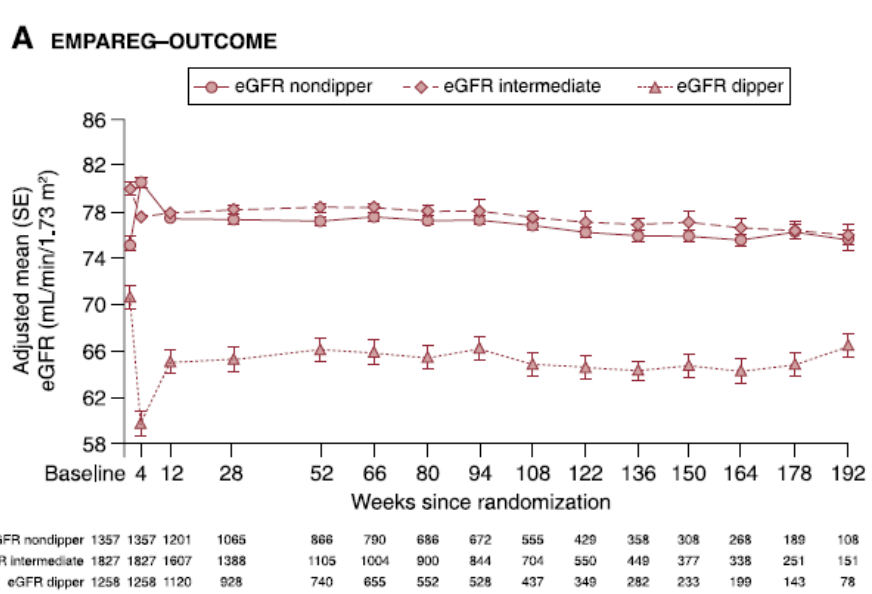
Interaction with other medications

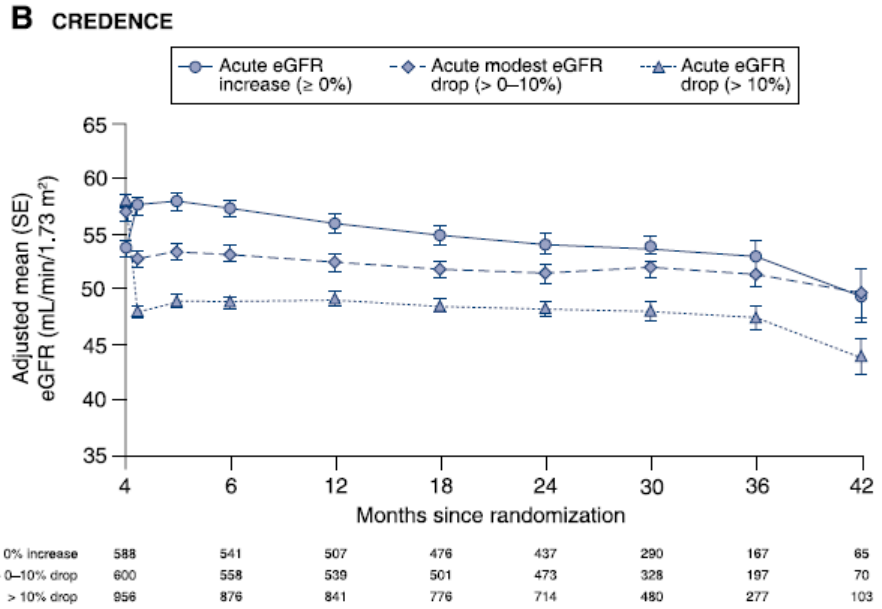
What is the ‘dip’?



Trial Name	Agent Studied	Primary Outcomes	Observed Early Drop in eGFR
CREDENCE (8)	Canagliflozin	Reduction in the composite risk of ESKD, doubling serum creatinine level, or death from renal or cardiovascular causes (HR, 0.70; 95% CI, 0.59 to 0.82), compared with placebo.	5 ml/min per 1.73 m^2
DAPA-CKD (9)	Dapagliflozin	Reduction in the risk of 50% eGFR decline, ESKD, or death from renal or cardiovascular causes (HR, 0.61; 95% CI, 0.51 to 0.72), compared with placebo.	4 ml/min per 1.73 m^2
EMPEROR-Reduced (5)	Empagliflozin	Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR, 0.75; 95% CI, 0.65 to 0.86), compared with placebo.	4 ml/min per 1.73 m^2
EMPA-REG Outcome (11)	Empagliflozin	Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo.	3–4 ml/min per 1.73 m^2
CANTATA-SU (12)	Canagliflozin	Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM ($P<0.01$ for each canagliflozin group versus glimepiride).	3–6 ml/min per 1.73 m^2

Meraz-Muñoz AY, Weinstein J, Wald R. eGFR Decline after SGLT2 Inhibitor Initiation: The Tortoise and the Hare Reimagined. Kidney360. 2021 Mar 26;2(6):1042-1047. doi: 10.34067/KID.0001172021





Heerspink HJL, Cherney DZI. Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation. Clin J Am Soc Nephrol. 2021 Aug;16(8):1278-1280. doi: 10.2215/CJN.02480221

eGFR dip with SGLT2i

- Common within first 14-28 days
- Usually <30% eGFR dip from baseline
- If >30% dip identified, repeat blood work and consider alternatives

- Should **NOT** stop SGLT2i due to ‘dip’

- No need to measure eGFR/creatinine after starting SGLT2i if the only purpose is to ‘check renal function’

No blood work after initiating SGTL2i?

- This is predicated on the concepts that:

1. AKI risk is not increased
2. eGFR dipping is not associated with kidney injury
3. SGLT2i do not cause electrolyte abnormalities
   - i.e. no need to check K as with ACEi or ARBs

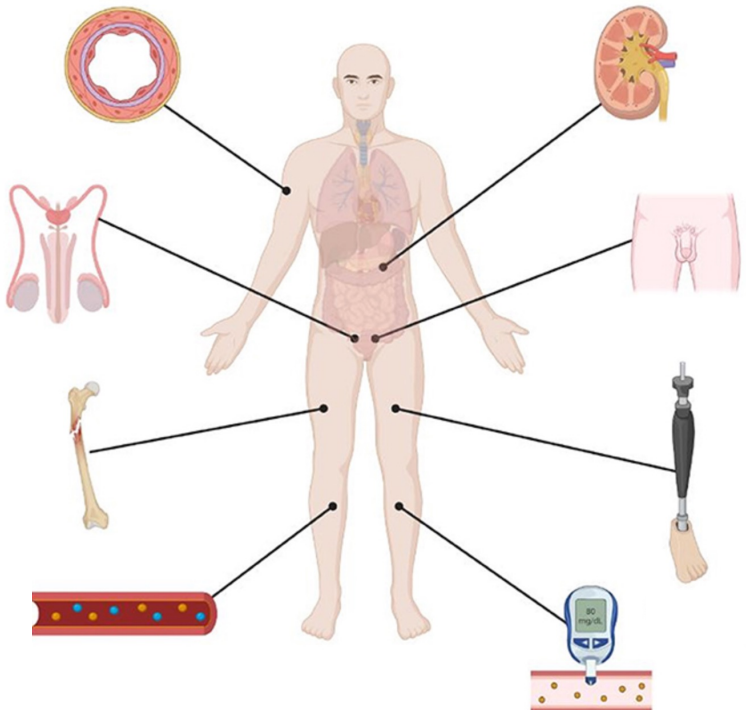
Patients can safely have the next set of blood work at subsequent scheduled appointment – routine blood work*

Heerspink HJL, Cherney DZI. Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation. Clin J Am Soc Nephrol. 2021 Aug;16(8):1278-1280. doi: 10.2215/CJN.02480221

Take home message #3

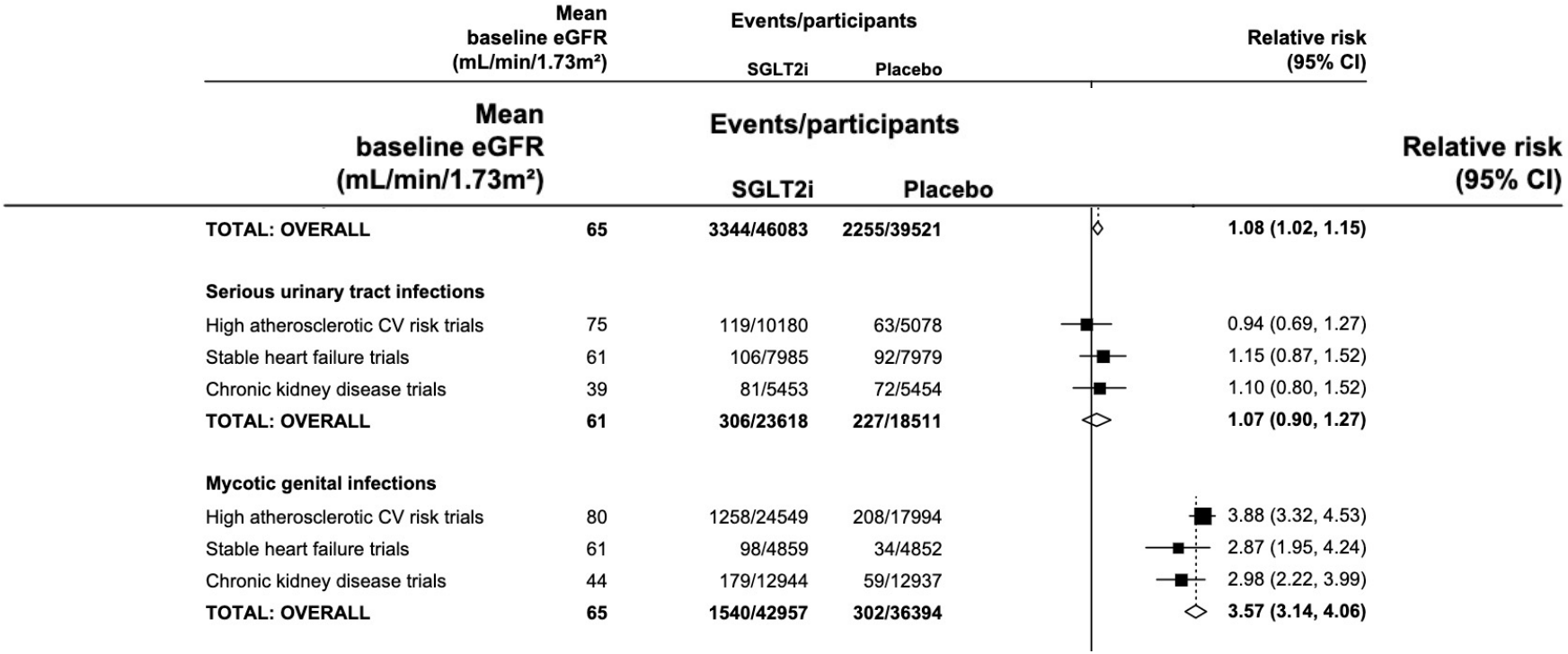
- eGFR dip is expected after initiating SGLT2i and this should not lead to discontinuation of SGLT2i

Other potential side effects



Mascolo A, Di Napoli R, Balzano N, Cappetta D, Urbanek K, De Angelis A, Scisciola L, Di Meo I, Sullo MG, Rafaniello C, Sportiello L. Safety profile of sodium glucose co-transporter 2 (SGLT2) inhibitors: A brief summary. Front Cardiovasc Med. 2022 Sep 21;9:1010693.

Mycotic genital infections: relative risks are higher but **absolute risk remains low**



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Mycotic genital infections - males vs females

Adverse Event	Incidence		Event Rate		HR (95% CI)	*P* Value	*P* for Interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo			
Mycotic genital infections							
Female	22/761	10/731	12.6	6.1	2.10 (1.00-4.45)	0.05	0.04
Male	28/1,439	3/1,466	8.4	0.9	9.30 (2.83-30.60)	0.0002	

Yi TW, Smyth B, Di Tanna GL, Arnott C, Cardoza K, Kang A, Pollock C, Agarwal R, Bakris G, Charytan DM, de Zeeuw D, Heerspink HJL, Neal B, Wheeler DC, Cannon CP, Zhang H, Zinman B, Perkovic V, Levin A, Mahaffey KW, Jardine M; CREDENCE Trial Investigators. Kidney and Cardiovascular Effects of Canagliflozin According to Age and Sex: A Post Hoc Analysis of the CREDENCE Randomized Clinical Trial. Am J Kidney Dis. 2023 Jul;82(1):84-96.e1. doi: 10.1053/j.ajkd.2022.12.015.

Advice for patients re: mycotic genital infections

- Genital hygiene advice reduces the number of genital infections and increases adherence to SGLT2i (6/125 vs 51/125)[1]
  - Rinse genital region with water after every void and before going to bed

- Treatment with topical or PO anti-fungal

1. SCOTT M. WILLIAMS, SYED HARIS AHMED; 1224-P: Improving Compliance with SGLT2 Inhibitors by Reducing the Risk of Genital Mycotic Infections: The Outcomes of Personal Hygiene Advice. *Diabetes* 1 June 2019; 68 (Supplement_1): 1224–P. https://doi.org/10.2337/db19-1224-P

Take home message #4

- Mycotic genital infections occur more frequently in those on SGLT2i than placebo, and more commonly in females than males, but is preventable and treatable.
- The absolute risk for mycotic genital infections remains low: it is NOT a frequent complication

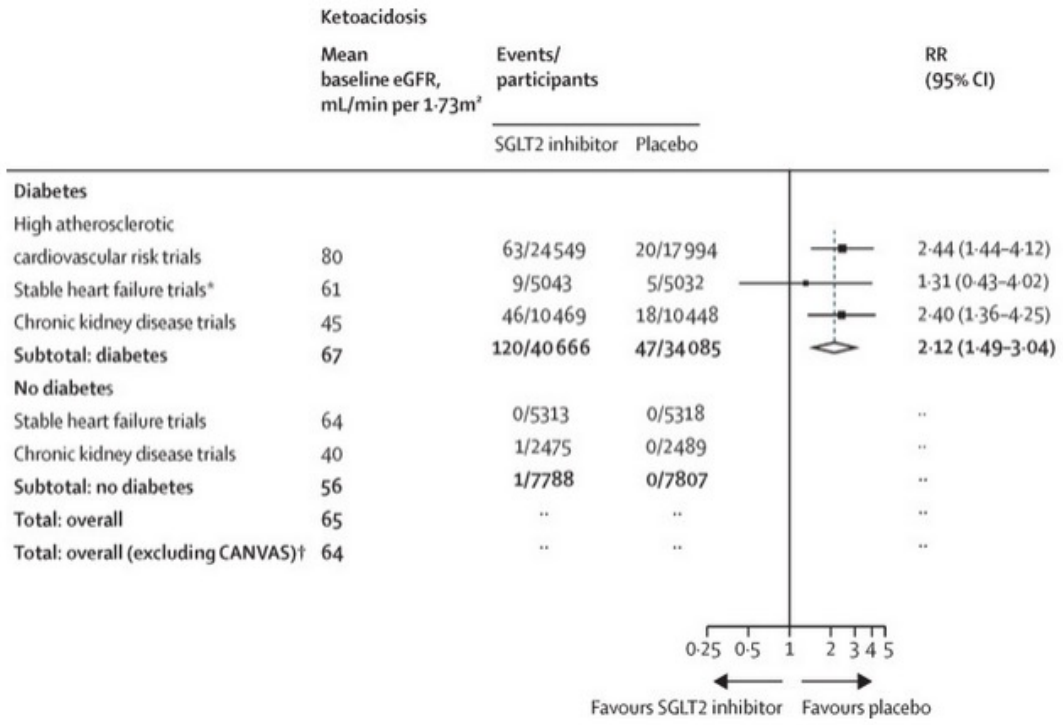
Ketoacidosis

- Uncommon side effect, does not occur without precipitating event
  - Remains an important potential issue in patients with diabetes
- Risk among patients without diabetes is minimal with only 1 event in 30,000 participant years of follow up[1]

- Clinical symptoms of precipitating event may exacerbate other symptoms:
  - abdominal pain, nausea, vomiting, weakness, fast breathing, excessive thirst, or drowsiness
- Labs: elevated anion gap and normal serum glucose

Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.

Ketoacidosis: relative risks are higher but **absolute risk remains low**



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Take home message #5

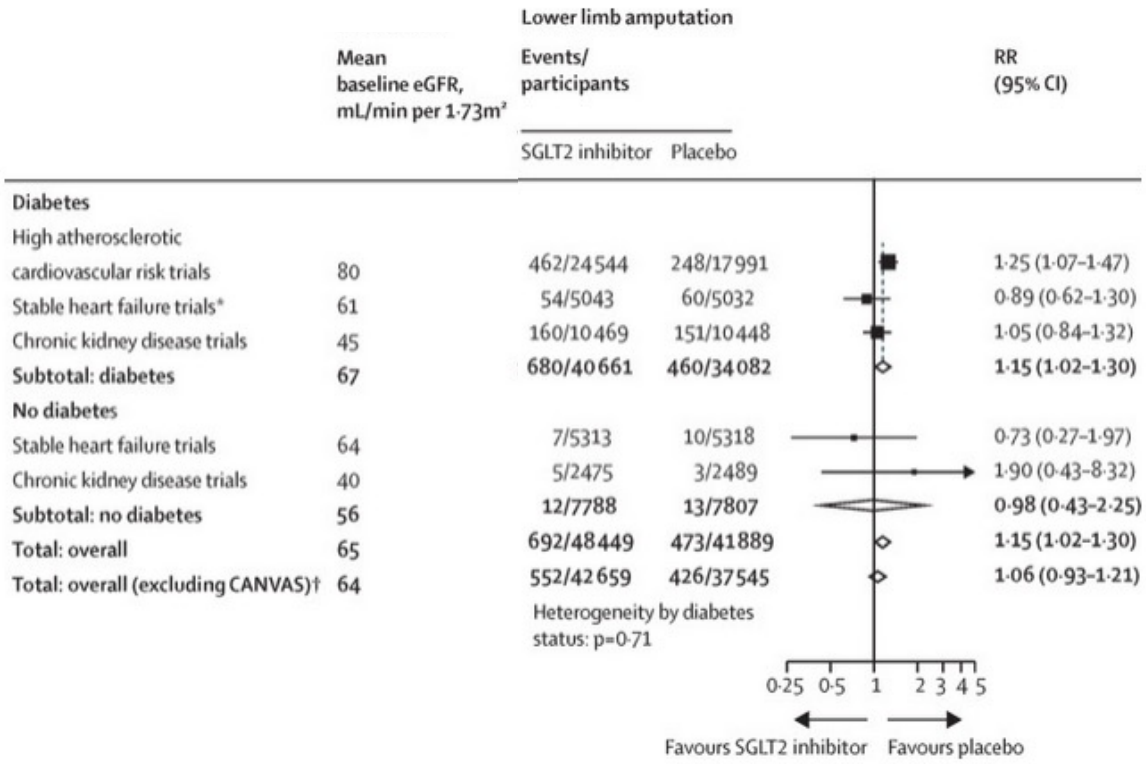
- Euglycemic DKA is rare but a potential adverse effect of SGLT2i and should be considered during times of acute illness/stress

Lower limb amputation

- In one trial (CANVAS) patients with diabetes allocated to canagliflozin had a doubling in risk of lower-limb amputation, mostly at the level of the toe or metatarsal
  - 6.3 vs 3.4 events per 1,000-patient years; HR, 1.97; 95% CI, 1.41-2.75

- Not noted in other trials with canagliflozin (CREDENCE)

Lower limb amputation



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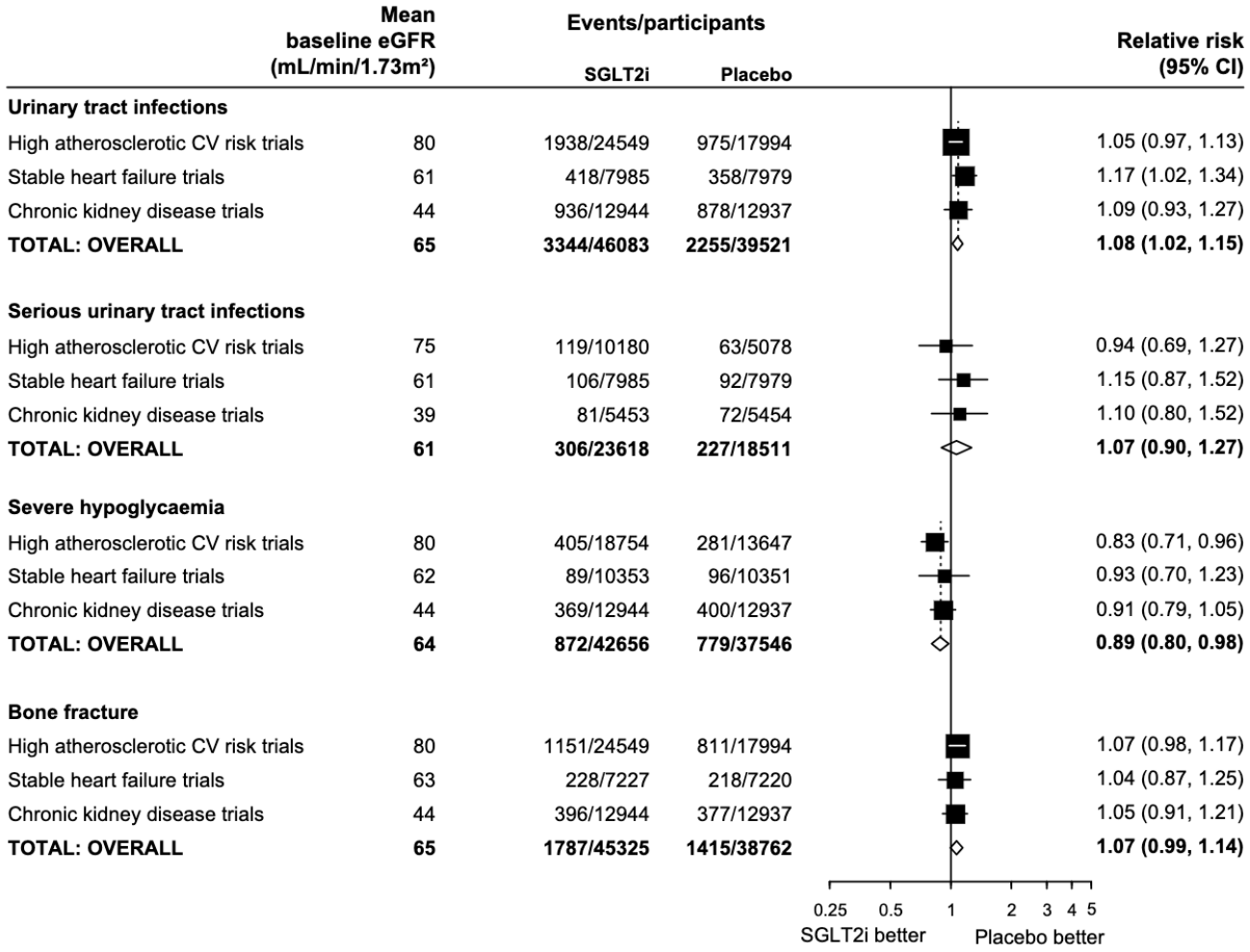
Take home message #6

- There is no consistent data to support increased risk of lower limb amputation. Good clinical practice for people with DM would be to do regular foot examinations, irrespective of medication use.



Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.

Take home message #7

- SGLT2i do not increase the risks for UTI, severe hypoglycemia, and bone fracture

Medication considerations

- Many patients with CKD are on multiple concurrent medications and SGLT2i may interact with them
  - Diuretics
  - Anti-glycemic agents

Diuretic effects of SGLT2i

- There is a diuretic effect with SGLT2i due to its mechanism of action
- Approximately an increase of ~500mL/24hr with SGLT2i + loop diuretic vs loop diuretic alone[1]
- Monitor for signs of volume depletion, hypotension

1. Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination With Loop Diuretics in Patients With Type 2 Diabetes and Chronic Heart Failure
The RECEDE-CHF Trial

Take home message #8

- SGLT2i exert a diuretic effect so in patients who are not clinically volume overloaded, decreasing thiazide or loop diuretic dosage could be considered

Hypoglycemia

- SGLT2i agents only lower plasma glucose levels by blocking the reabsorption of filtered glucose, which is reduced as plasma levels fall

- The glucose-lowering effect of SGLT2i is somewhat attenuated in patients with eGFR <60 ml/min (but should be considered when eGFR >45 ml/min) and minimal when eGFR is <30 ml/min[1,2]

- If the blood glucose level is well controlled or there is a history of severe hypoglycemia prior to initiating SGLT2i, consider weaning/stopping sulfonylurea and meglitinides, and consider reducing insulin by 10-20%

1. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep. 2022 May 5;7(7):1463-1476. doi: 10.1016/j.ekir.2022.04.094.
2. Cherney DZI, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, Broedl UC, Lund SS. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int. 2018 Jan;93(1):231-244. doi: 10.1016/j.kint.2017.06.017.

Take home message #9

- Consider adjusting anti-glycemic medications when initiating SGLT2i in those with preserved GFR (eGFR >45mL/min)
- Note that the glucose lowering impact in those with GFR < 45 is less, and below 30 ml/min, almost none.

Sick day and periprocedural advice

- BC Provincial Academic Detailing Service

Strategies aimed at addressing the risk of DKA have been proposed.

Table 2: Proposed strategies to address the risk of DKA[2,3,8,10,12]	
Acute Serious Illness	▪ hold SGLT2i at onset of illness ▪ restart when feeling well and able to eat and drink
Major Surgery	▪ hold 3 days before surgery ▪ restart after acute phase response and physiological stress has resolved, and is feeling well and able to eat and drink
Bariatric Surgery	▪ hold SGLT2i during preoperative low-carbohydrate diet ▪ reassess postoperatively
Low Intake of Carbohydrates	▪ hold until normal diet resumes
Excess Intake of Alcohol	▪ stop immediately ▪ reassess at later date

Take home message #10

- SGLT2i are considered a medication worthy of ‘sick day’ rules, and they should be held 3 days prior to major surgery. Need to ensure that they are restarted afterwards.

- No harm to stopping during acute illness/surgery

Summary

1. Main mechanism of action of SGLT2i is increased glucosuria and natriuresis which leads to improved BP, volume, and weight control
2. SGLT2i reduces kidney disease progression, cardiovascular complications, death, and keeps patients out of hospital
3. eGFR dip is expected after initiating SGLT2i and this should not lead to discontinuation of SGLT2i
4. Mycotic genital infections are rare, but more frequent in females than males, but is preventable and treatable. The absolute risk remains low and it is not a frequent complication
5. Euglycemic DKA is rare but a potential adverse effect of SGLT2i and should be considered during times of acute illness/stress

Summary

6. There is no consistent data to support increased risk of lower limb amputation. Good clinical practice for people with DM would be to do regular foot examinations, irrespective of medication use.
7. SGLT2i do not increase the risks for UTI, severe hypoglycemia, and bone fracture
8. SGLT2i exert a diuretic effect so in patients who are not clinically volume overloaded, decreasing thiazide or loop diuretic dosage could be considered
9. Consider adjusting anti-glycemic medications when initiating SGLT2i in those with preserved GFR (>45 ml/min)
10. SGLT2i are considered a medication worthy of ‘sick day’ rules, and they should be held 3 days prior to major surgery. Need to ensure that they are restarted afterwards.