SGLT2-inhibitors

Beskikbaar in Suid Afrika (Aug 2023)

DAPAGLIFLOZIN:	EMPAGLIFLOZIN:
Forxiga	Jardiance
Duforzig	
Daglif	
Sagalatin	

DAPAGLIFLOZIN PLUS METFORMIN:	EMPAGLIFLOZIN PLUS METFORMIN:
Synglutra	Synjardy
Xigduo (Dapagliflozin with Metformin XR)	

Dapagliflozin internationally:

eGFR < 25 mL/min/1.73 m^2: starting treatment with dapagliflozin is not recommended; treatment may be continued if eGFR falls below this unless dialysis is commenced. 01 Sept 2022

NPS MedicineWise

https://www.nps.org.au › radar › articles › dapagliflozin-...

New PBS listing: Dapagliflozin for chronic kidney disease

Current consensus:

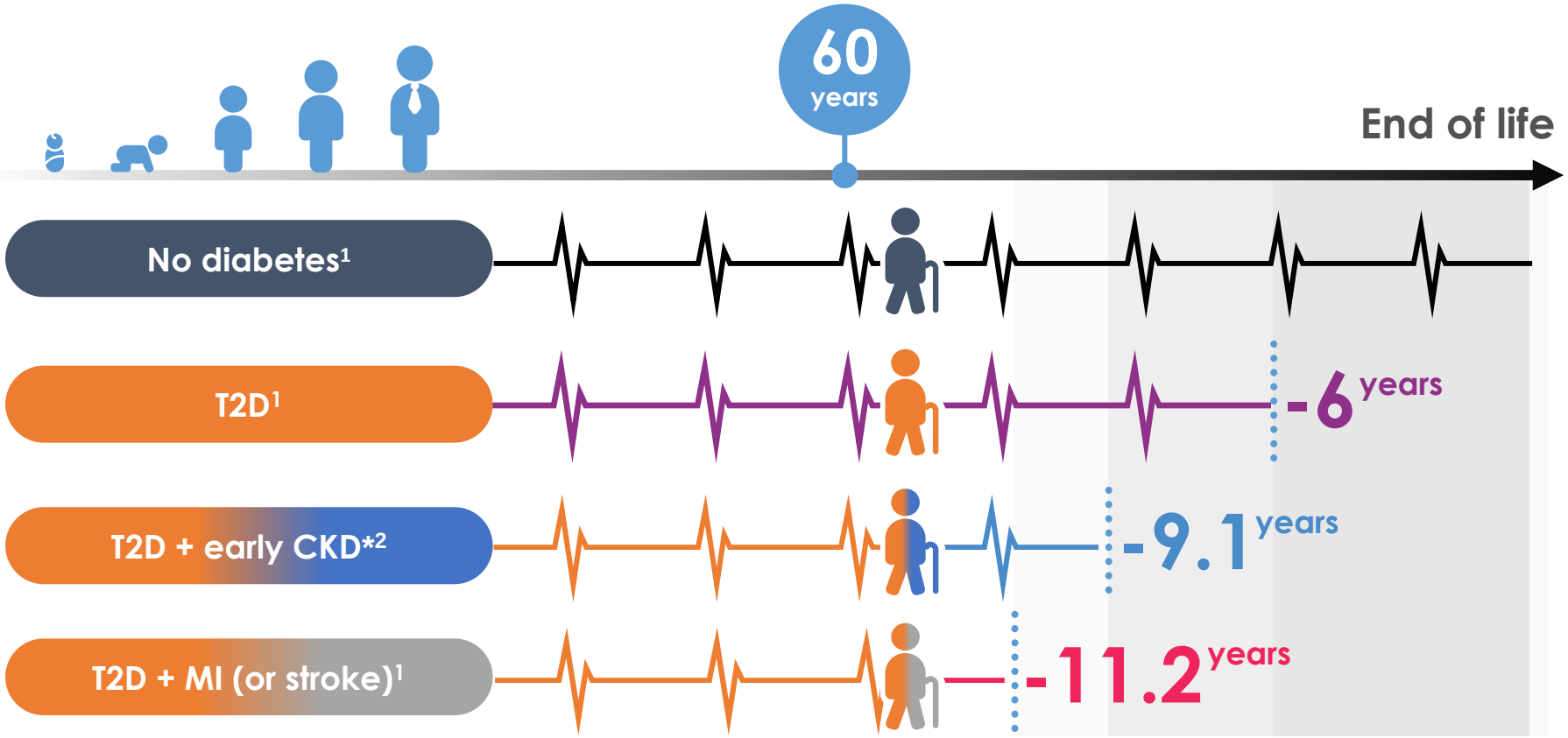
Initiating SGLT2 inhibitors should generally be avoided among patients with an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2 (although they can likely be continued among patients whose eGFR ultimately falls below this threshold). 17 Jul 2023

uptodate.com

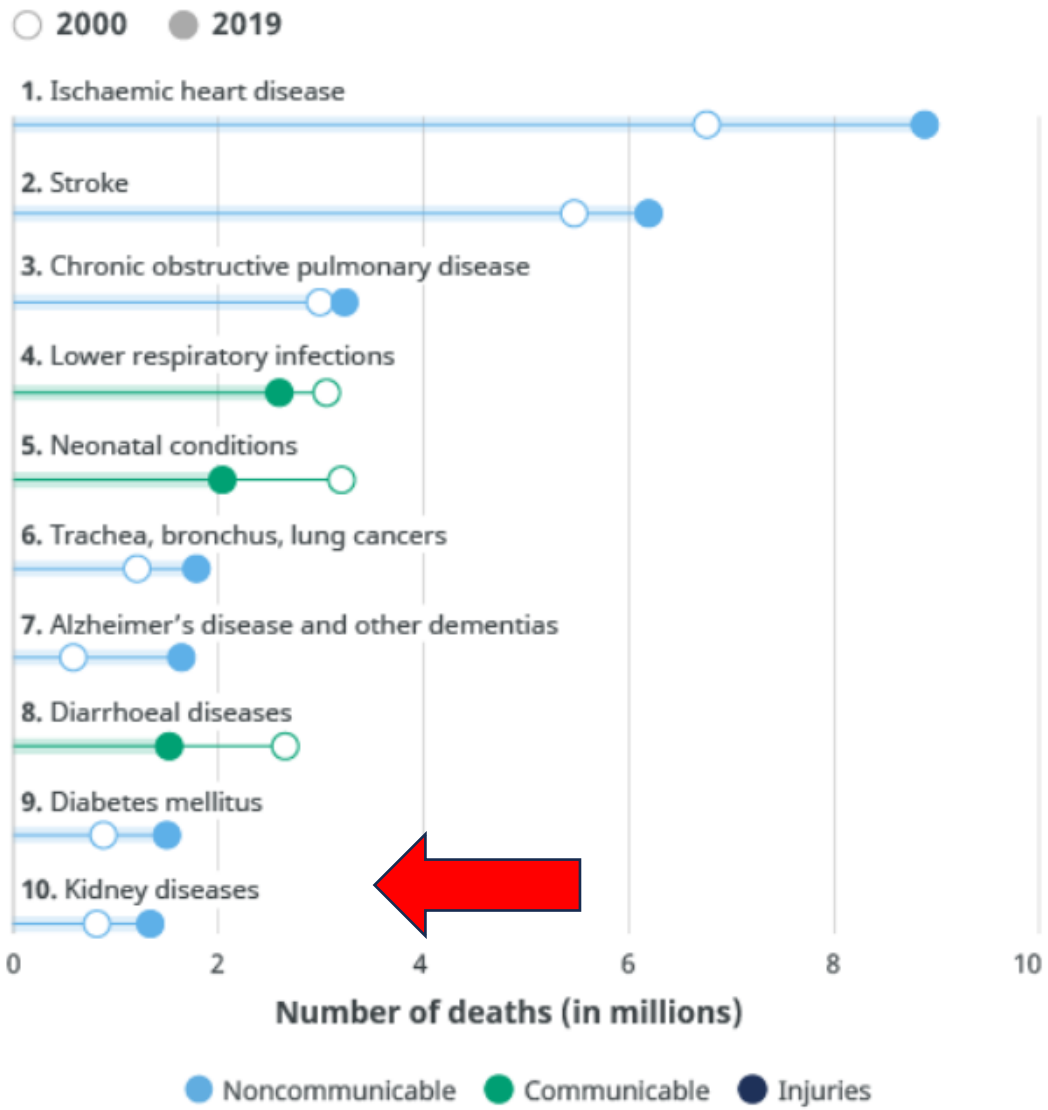
https://www.uptodate.com › contents › print

Treatment of diabetic kidney disease - UpToDate

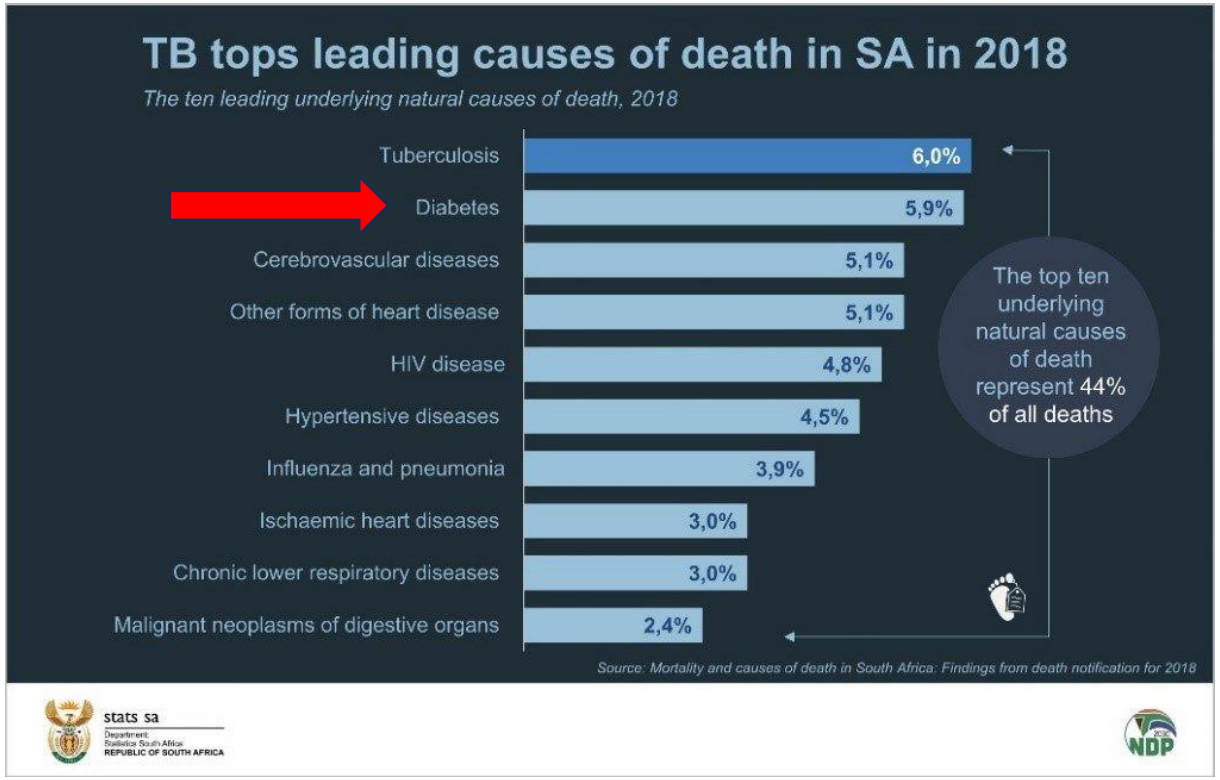
Conditions of the CardioRrenalMetabolism systems are among the leading causes of premature death



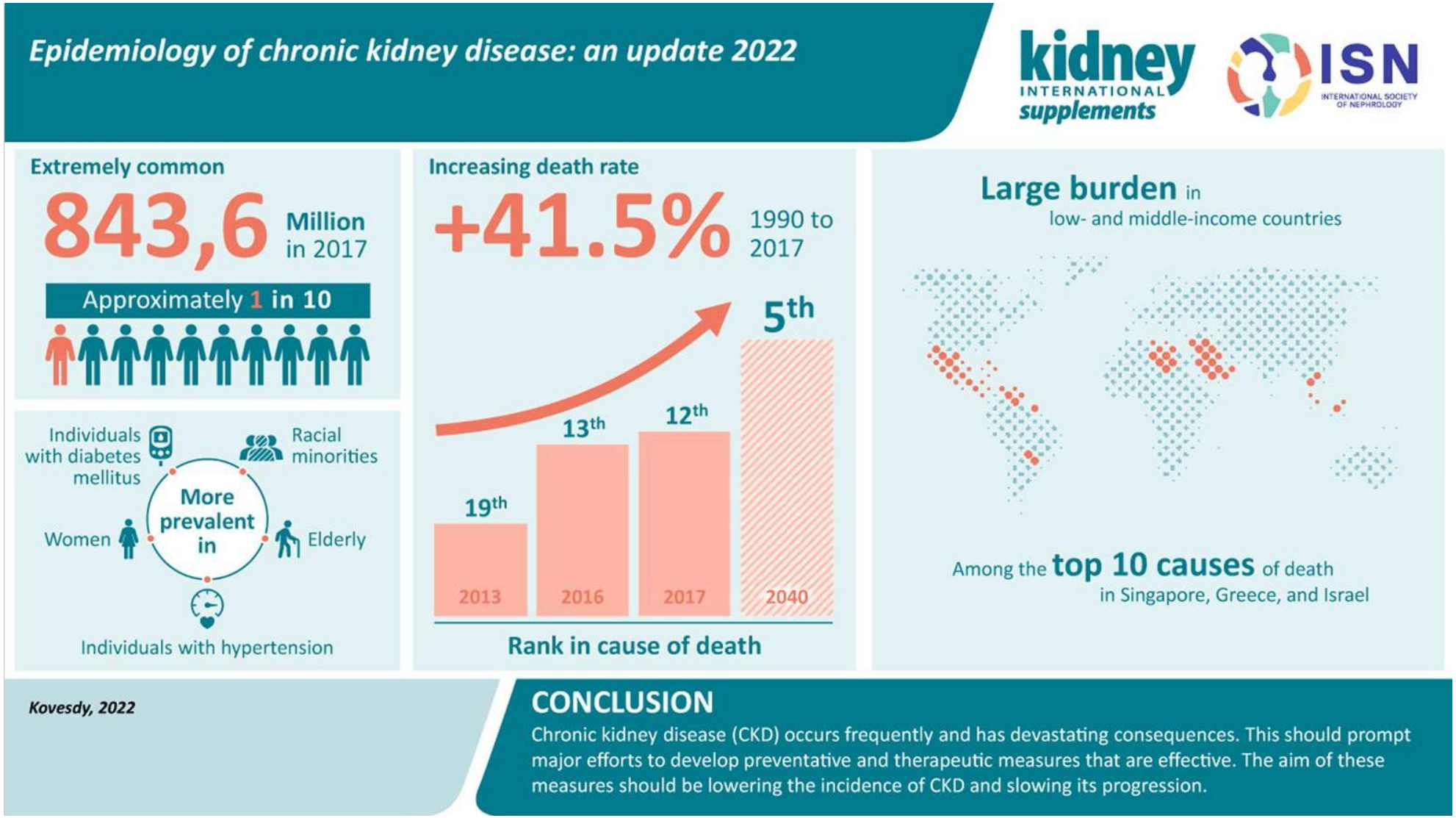
Leading causes of death globally



Source: WHO Global Health Estimates.



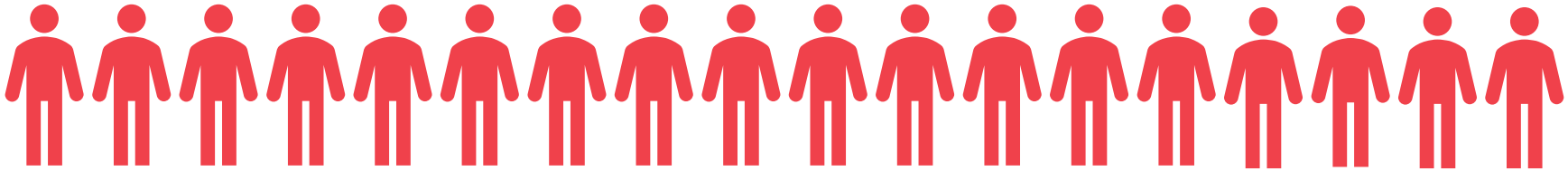
We need to create a different future for our Chronic Kidney Disease (CKD) pts



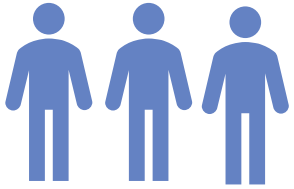
Presence of CKD is commonly associated with the development of fatal CV comorbidities

Older patients* with CKD are 6 times more likely to die of CV disease than to advance to ESKD and dialysis†

Deaths due to CV disease



Progression to ESKD/RRT



CKD = CHRONIC KIDNEY DISEASE

*≥65 years of age; †During 9.7 years of median follow-up
RRT, renal replacement therapy
Dalrymple L *et al. J Gen Intern Med* 2011;26:379

Chronic kidney disease: high unmet medical need

CKD affects approximately **1 in 10 adults, or about 850 million people**[1-3]

CKD affects up to **50% of patients** with T2D globally,[4] and about **20%** of patients with CKD **also have HF**[5]

An estimated **1.2 million people die** each year from CKD[3]

CKD is a **major global health burden** because of its **high prevalence** and **associated risk of ESKD, CV disease and premature death**[1]

CKD represents a significant economic burden, accounting for ~US$84 billion in Medicare spending, with an additional ~US$36 billion for ESKD (2017)[6]

Current treatment options in CKD (Rx Cause)

- Blood glucose target is individualised for each patient with the HbA1c target ranging from <6.5% to <8.0%[1,3]
- Multifactorial and intensive glucose control may reduce kidney function decline[2]

- ACEi or ARB is recommended in patients with hypertension and albuminuria[1,3]
- SGLT2i recommended for patients with T2D and CKD, with eGFR >30mL/min/1.73m2[3]

- Blood pressure target <130/80 mmHg[4]
- First-line antihypertensive drug treatment should be a once-daily, generic ACEi[4]
- Limit salt intake to <5g of sodium chloride per day[3,5]

- Consider lowering dietary protein intake in patients with an eGFR <60 ml/min/1.73 m^2 based on underlying disease and degree of proteinuria[3,5]

- Treatment of other secondary complications of CKD, e.g. hyperkalaemia, metabolic acidosis, anaemia, volume overload, mineral-bone disorders, dyslipidemia[5]
- Avoid nephrotoxic drugs (e.g. NSAIDs), stop smoking[5]

Verskeie studies sedert 2015 met mees onlangse een Jan 2023

EMPA-KIDNEY's double-blind placebo-controlled design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with chronic kidney disease (CKD) at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

Adults with CKD-EPI estimated GFR (eGFR):

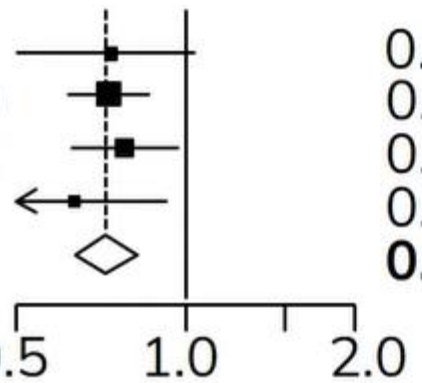
20 to <45 mL/min/1.73 m^2; or

45 to <90 mL/min/1.73 m^2 with a urinary ACR of ≥200 mg/g (≥22.6 mg/mmol)

Excluded patients with polycystic kidney disease or transplant

Primary outcome by kidney function (post-hoc)

eGFR mL/min/1.73m²	No. of events / participants: Empagliflozin	Placebo	Hazard ratio (95% CI)
< 20	47/123	64/131	0.73 (0.50–1.06)
≥ 20 < 30	200/1008	253/1020	0.74 (0.61–0.89)
≥ 30 <45	140/1467	175/1461	0.78 (0.62–0.97)
≥ 45	45/706	66/693	0.64 (0.44–0.93)
All participants			**0.72 (0.64–0.82)**



Trend P value= 0.81

Metanalysis: SMART-C collaboration

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**

Lancet 2022; 400: 1788–801

Published Online November 6, 2022 https://doi.org/10.1016/S0140-6736(22)02074-8

See Comment page 1745

*Members are listed at the end of the Article (see Writing committee and SMART-C steering committee); affiliations are listed in the appendix (pp 24–25)

Correspondence to: Assoc Prof William Herrington, Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health,

Summary

Background Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease. None of the trials recruiting patients with and without diabetes were designed to assess outcomes separately in patients without diabetes.

Methods We did a systematic review and meta-analysis of SGLT2 inhibitor trials. We searched the MEDLINE and Embase databases for trials published from database inception to Sept 5, 2022. SGLT2 inhibitor trials that were double-blind, placebo-controlled, performed in adults (age ≥18 years), large (≥500 participants per group), and at least 6 months in duration were included. Summary-level data used for analysis were extracted from published reports or provided by trial investigators, and inverse-variance-weighted meta-analyses were conducted to estimate treatment effects. The main efficacy outcomes were kidney disease progression (standardised to a definition of a sustained ≥50% decrease in estimated glomerular filtration rate [eGFR] from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure), acute kidney injury, and a composite of cardiovascular death or hospitalisation for heart failure. Other outcomes were death from cardiovascular and non-cardiovascular disease considered separately, and the main safety outcomes were ketoacidosis and lower limb amputation. This study is registered with PROSPERO, CRD42022351618.

SMART-C Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

	eGFR mL/min/1.73m²	uACR mg/g	Diabetes	Differences in kidney disease composite outcome definitions*
CREDENCE	Mean: 56 Inclusion: 30-90	Median: 927 Inclusion: 300-5000	100%	Sustained **doubling of serum creatinine**
DAPA-CKD	Mean: 43 Inclusion: 25-75	Median: 949 Inclusion: 200-5000	68%	Sustained **≥50% eGFR decline**
SCORED	Median: 45 Inclusion: 25-60	Median: 74 Inclusion: not required	100%	Sustained **≥50% eGFR decline**
EMPA-KIDNEY	Mean: 37 Inclusion: 20-90	Median: 329 Inclusion: not required if eGFR<45; ≥200 if eGFR 45-90	46%	Sustained **≥40% eGFR decline**

*All include maintenance dialysis, transplant, sustained low eGFR (<15 or <10). All include renal, cardiovascular death except SCORED.

SMART-C

Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

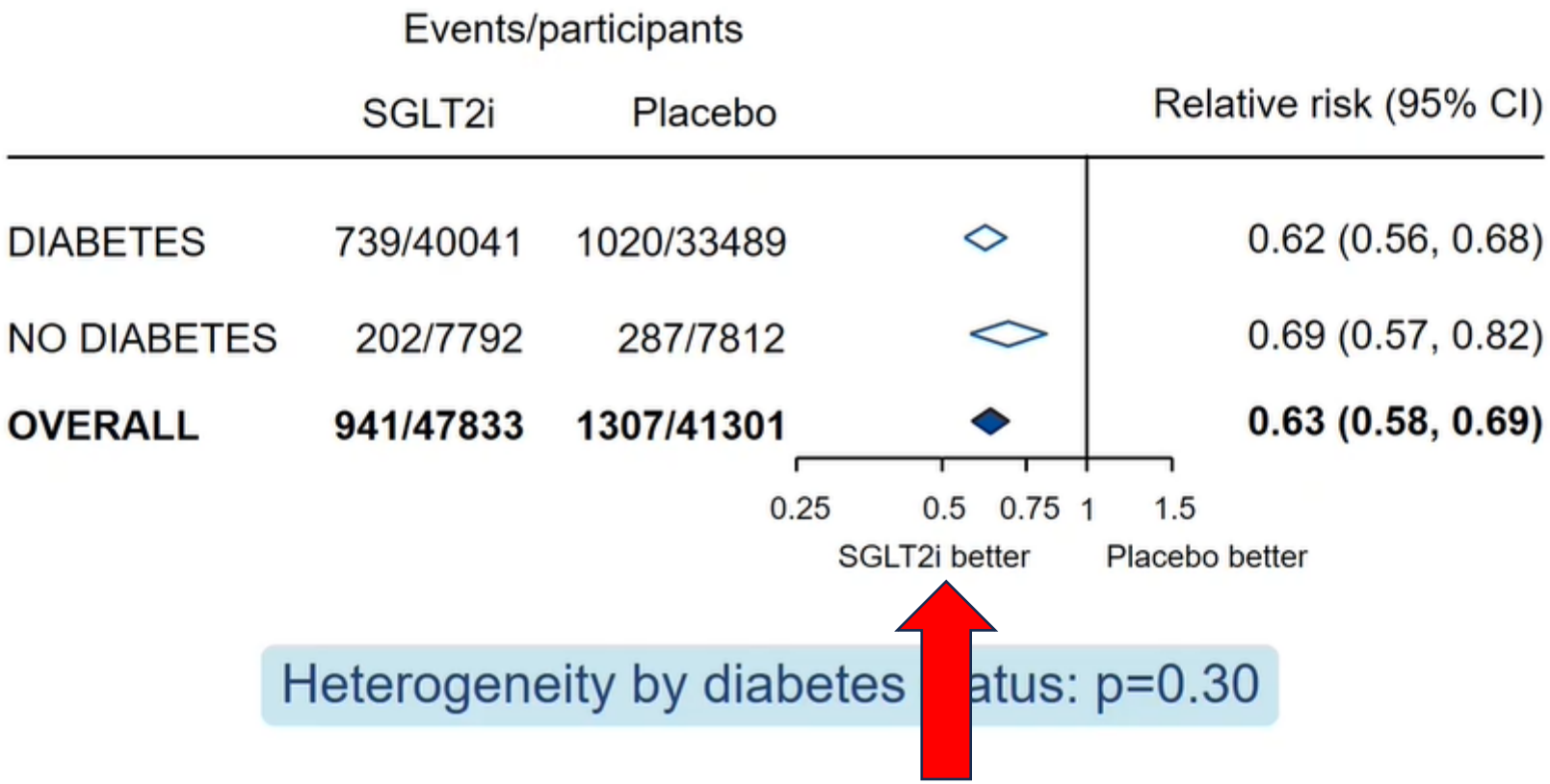
Aims

- Collaborative meta-analysis of the effects of SGLT2 inhibitors on:
  - A common composite kidney disease progression outcome
  - Acute kidney injury events

- Main aim: comparing findings in patients with versus without diabetes
- Subsidiary aims:
  a) Any effect modification by:
     - Baseline eGFR (at a trial level); or
     - By primary kidney diagnosis (CKD trials only)
  b) Predicted absolute benefits and harms in patients with & without diabetes

Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

Kidney disease progression

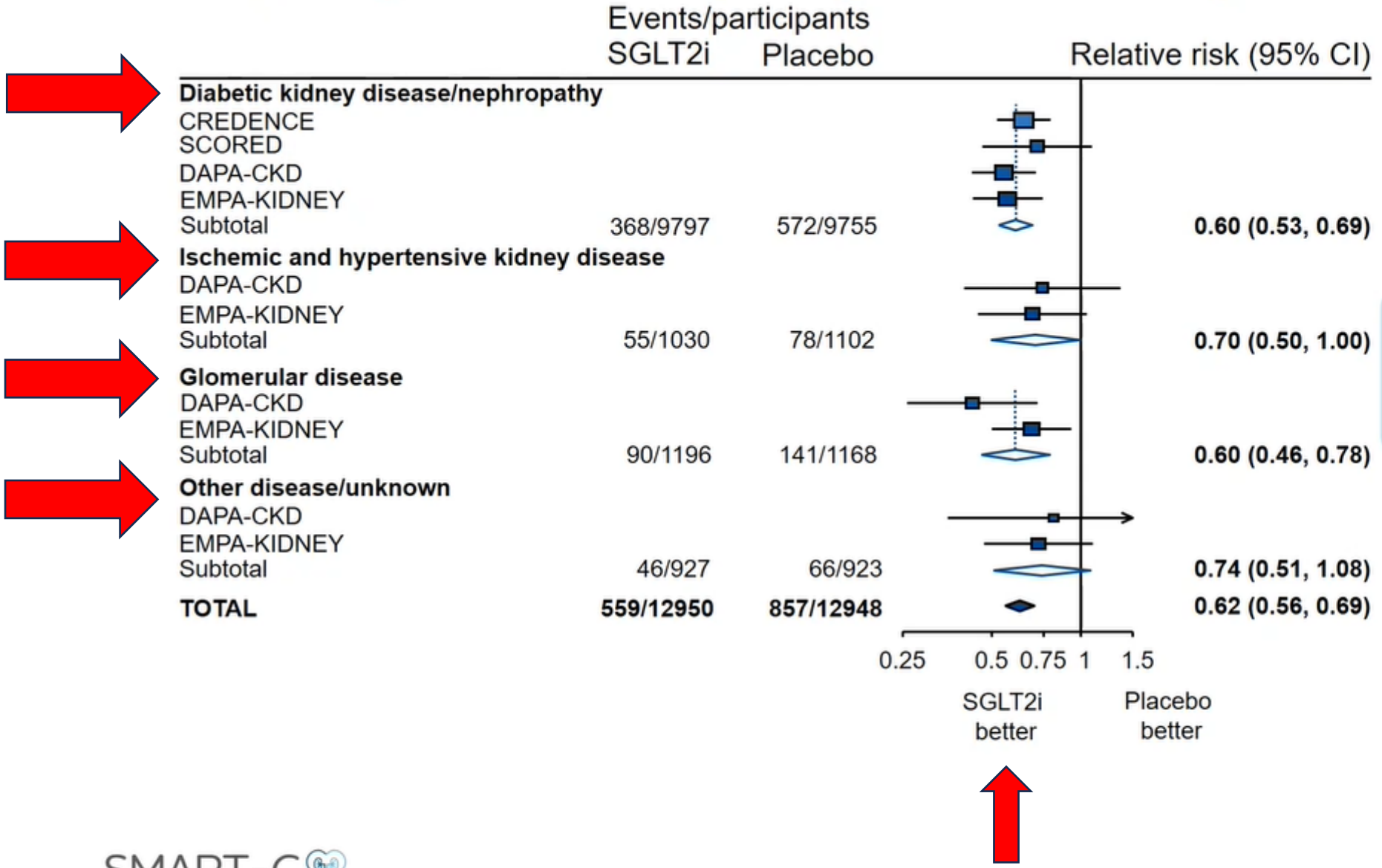


Heterogeneity by diabetes status: p=0.30

SMART-C

Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

Kidney disease progression: by DIAGNOSIS

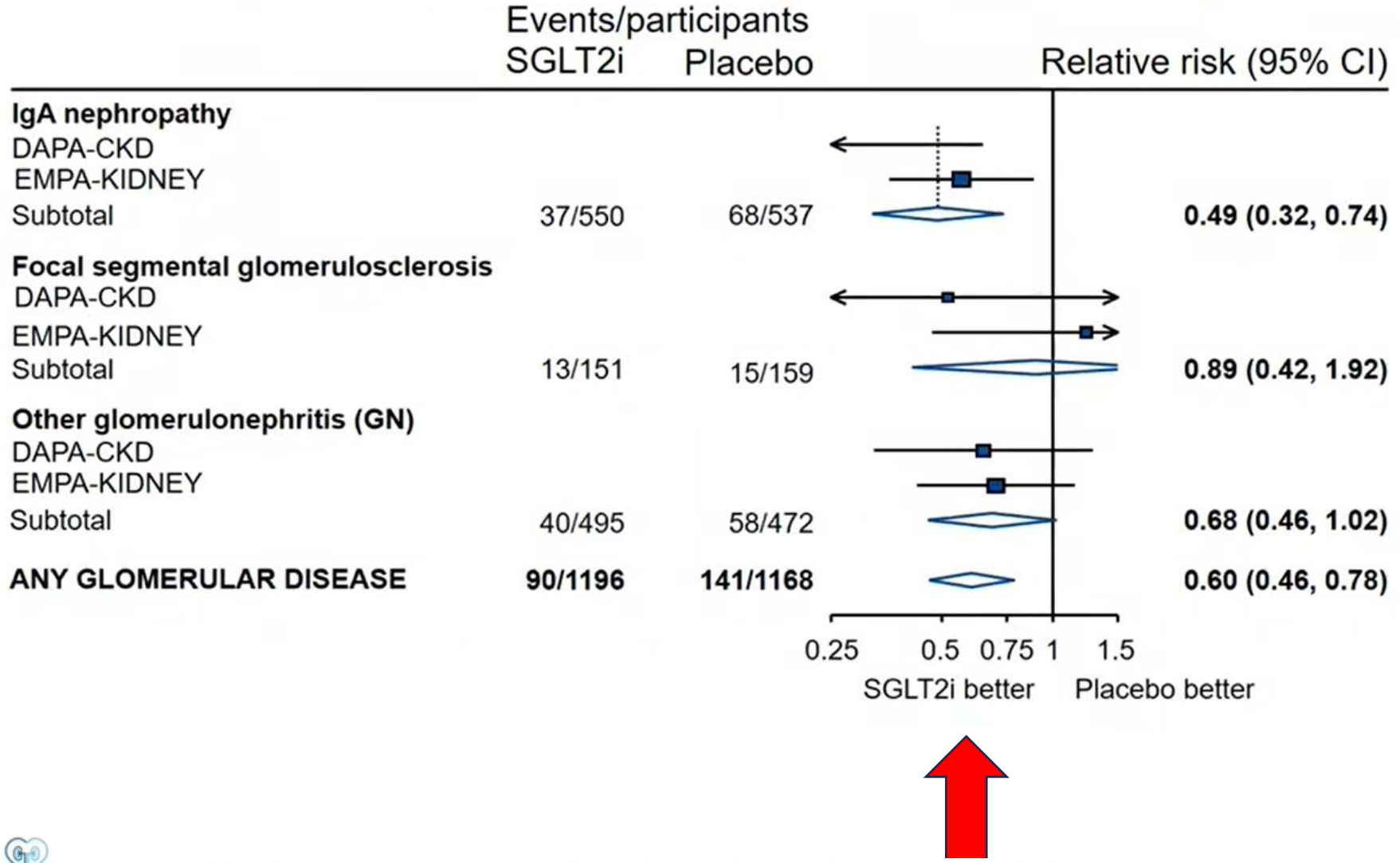


Heterogeneity across groups of primary kidney disease: p=0.67

SMART-C

Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

Kidney disease progression: by GN



SMART-C

Publication: NDPH Renal Studies Group & SMART-C. The Lancet. 6th Nov 2022.

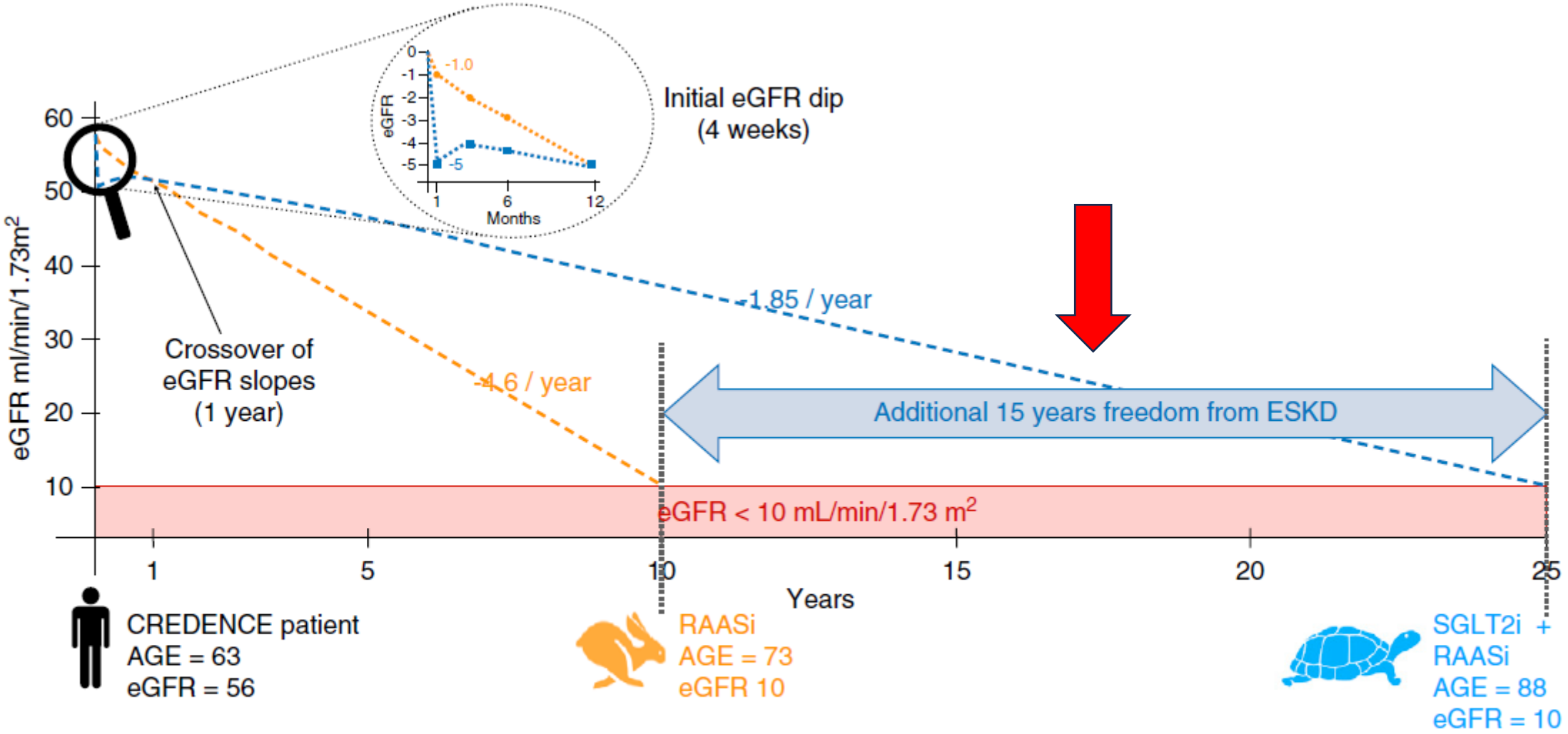


Figure 1. **SGLT2is may delay ESKD by 15 years.** A typical patient included in CREDENCE would lose 4.6 ml/min per year of eGFR if treated with RAASi only, reaching ESKD in 10 years. However, if canagliflozin is added to his treatment, he would only lose 1.85 ml/min per year of eGFR, delaying ESKD by 15 years. RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

SGLT-2 inhibitors are recommended for patients with type 2 diabetes and CKD who have estimated glomerular filtration rates (eGFRs) ≥20 mL/minute/1.73 m^2. (The previous guideline-recommended eGFR threshold was ≥30 mL/minute.) 17 Jan 2023

NEJM Journal Watch

https://www.jwatch.org › 2023/01/17 › updated-kdigo-g...

Updated KDIGO Guideline for Managing Diabetes in Patients ...

https://www.jwatch.org/na55698/2023/01/17/updated-kdigo-guideline-managing-diabetes-patients-with

The KDIGO 2020 guideline recommended SGLT2 inhibitors for patients with kidney disease and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2 (1). The updated guideline now recommends initiation of SGLT2 inhibitor therapy in those with an eGFR of at least 20 mL/min/1.73 m^2 (Appendix Figure). 10 Jan 2023

ACP Journals

https://www.acpjournals.org › doi

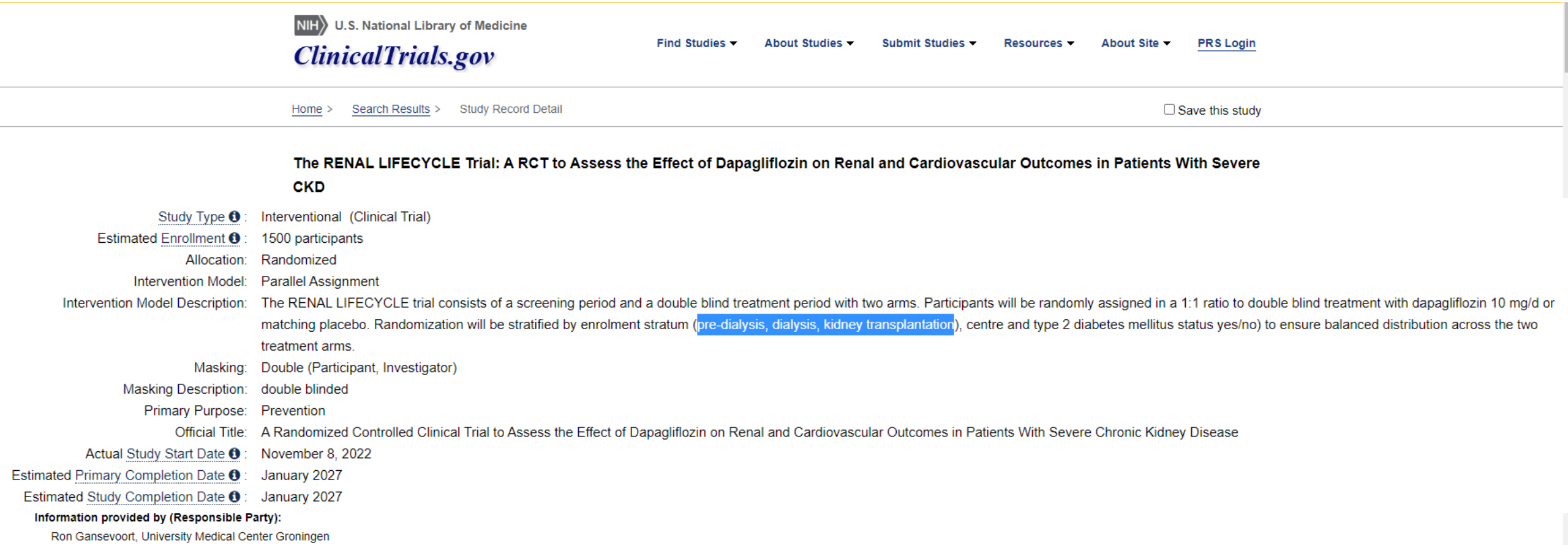
Synopsis of the KDIGO 2022 Clinical Practice Guideline Update

https://www.acpjournals.org/doi/10.7326/M22-2904#:~:text=The%20KDIGO%202020%20guideline%20recommended,m2%20(Appendix%20Figure)

Discussion

The updated KDIGO 2022 guideline advocates a layered approach to care, starting with a foundation of lifestyle interventions and first-line pharmacotherapy demonstrated to improve clinical outcomes (1). To this, other therapies are added to reduce risk for adverse outcomes and to control risk factors for CKD progression and cardiovascular events, such as blood pressure, glycemia, and lipids. Although other guidelines have suggested viewing multifactorial therapy as "pillars" of care (24–26), the KDIGO layered approach includes the preference for starting new treatments one at a time and then reassessing response and residual risk to further refine therapy. To maximize the tolerability of combination treatments, the guideline recommends the serial introduction of medications that improve intrarenal hemodynamics (such as RAS inhibitors, SGLT2 inhibitors, MRAs, diuretics, and other antihypertensive medications). Ongoing monitoring is critical to ensuring that each patient ultimately receives the optimal therapeutic regimen.

LIFECYCLE TRIAL = 1500 patients ongoing study (expected 2027/2028)



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The RENAL LIFECYCLE Trial: A RCT to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe CKD

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	1500 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	The RENAL LIFECYCLE trial consists of a screening period and a double blind treatment period with two arms. Participants will be randomly assigned in a 1:1 ratio to double blind treatment with dapagliflozin 10 mg/d or matching placebo. Randomization will be stratified by enrolment stratum (pre-dialysis, dialysis, kidney transplantation), centre and type 2 diabetes mellitus status yes/no) to ensure balanced distribution across the two treatment arms.
Masking:	Double (Participant, Investigator)
Masking Description:	double blinded
Primary Purpose:	Prevention
Official Title:	A Randomized Controlled Clinical Trial to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe Chronic Kidney Disease
Actual Study Start Date :	November 8, 2022
Estimated Primary Completion Date :	January 2027
Estimated Study Completion Date :	January 2027

Information provided by (Responsible Party):
Ron Gansevoort, University Medical Center Groningen

THIS STUDY WILL GIVE MORE ANSWERS ON
1) 500 patients with eGFR < 15ml/min
2) 500 patients with transplanted kidney
3) 500 patients on haemodialysis