Updates in Diabetes and Chronic Kidney Disease

Natalie Sweiss, MD, FASN

Hot Topics in Medicine Webinar Series

2023

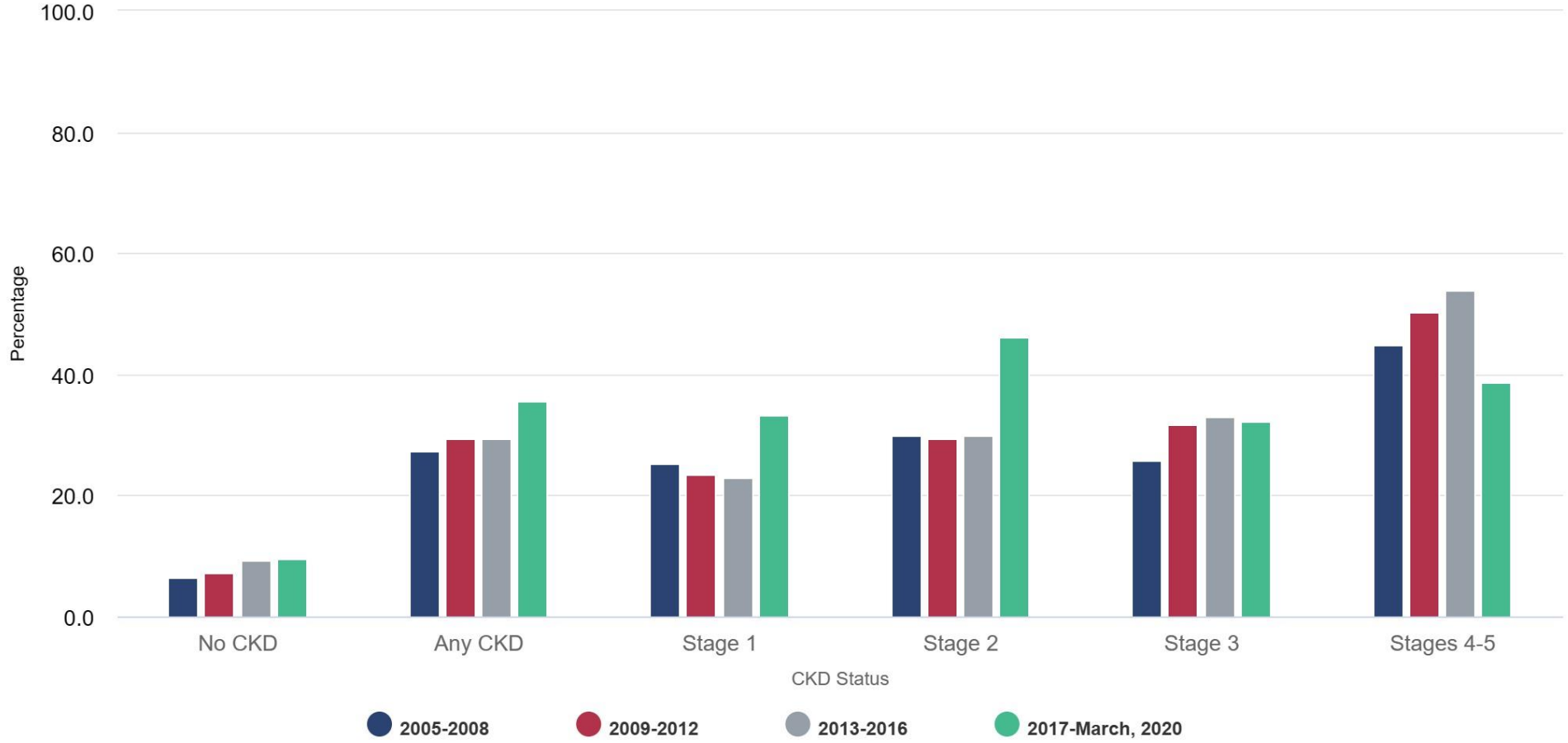
To Review

- Impact of DM and CKD
- Advancements
- Best Practices for Clinic
- Future Directions

- No disclosures

CKD caused by DM

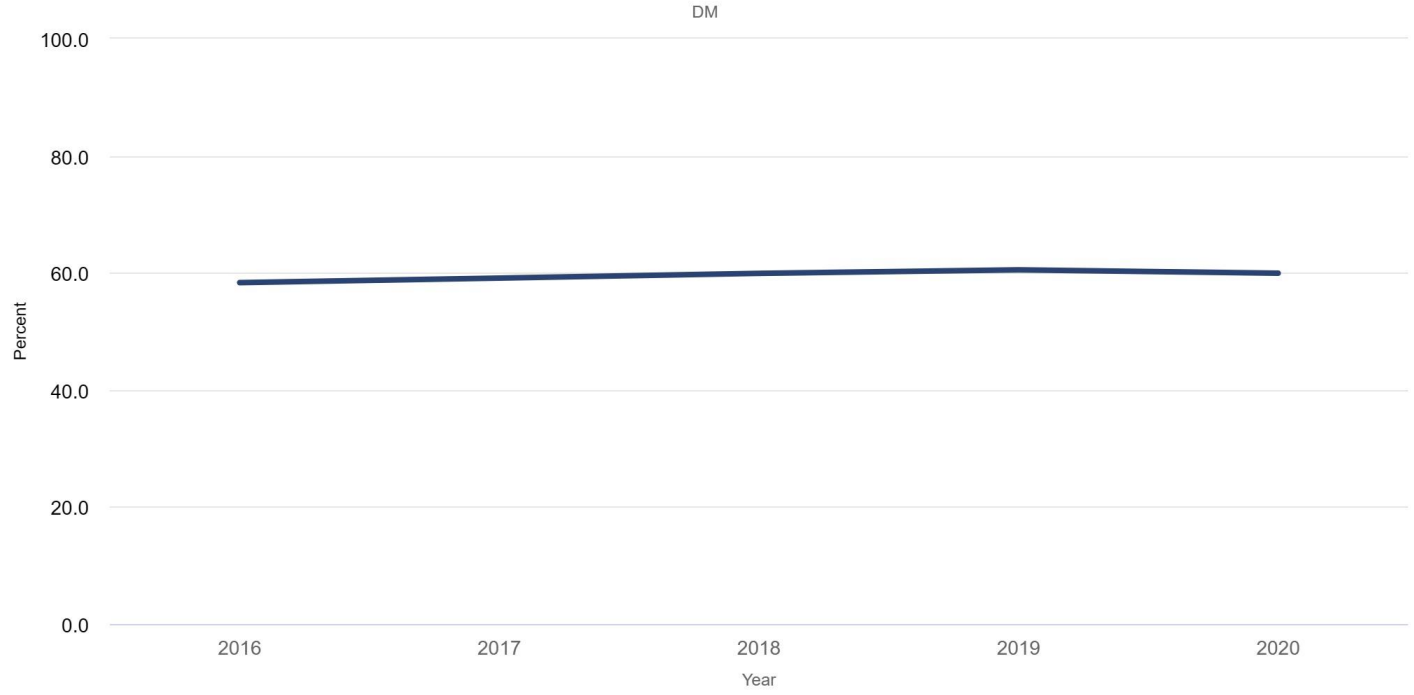
Figure 1.5 Prevalence of diabetes mellitus by CKD status in U.S. adults



Data Source: 2022 United States Renal Data System Annual Data Report

DM in ESKD

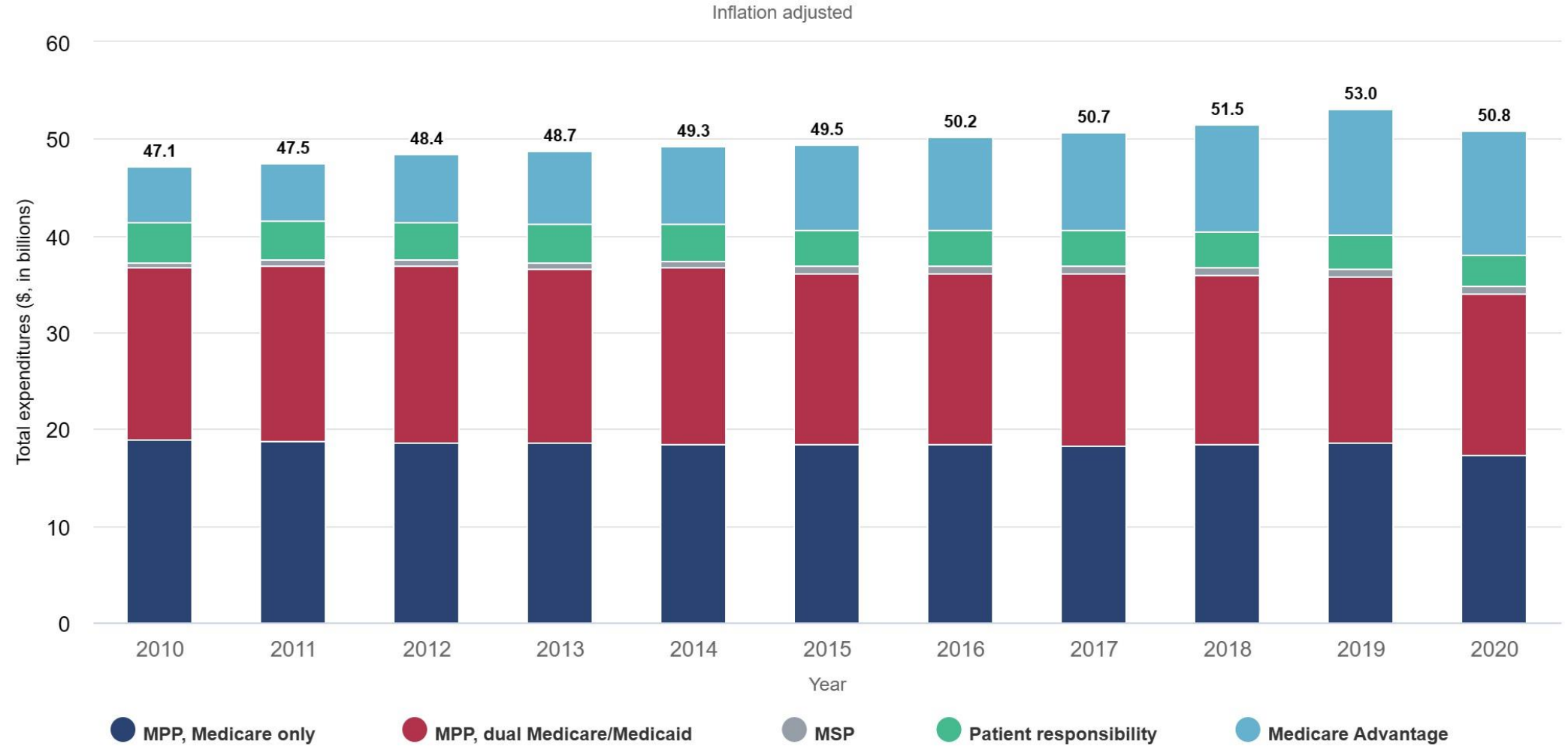
Figure 1.18 Comorbid conditions of incident ESRD patients, 2016-2020



Data Source: 2022 United States Renal Data System Annual Data Report

Cost of ESKD

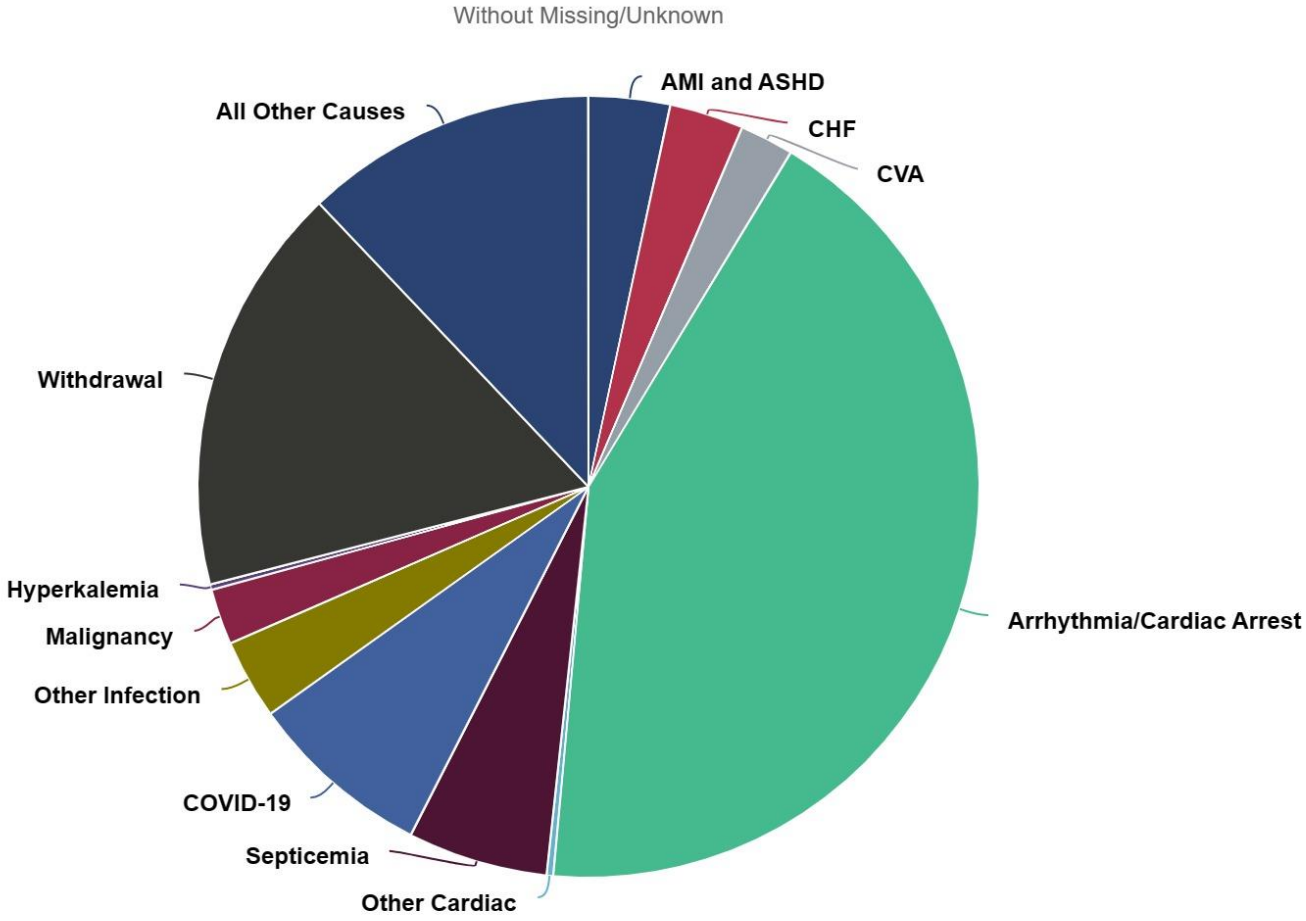
Figure 9.1 Total spending for Medicare beneficiaries with ESRD, 2010-2020



Data Source: 2022 United States Renal Data System Annual Data Report

Mortality in ESKD

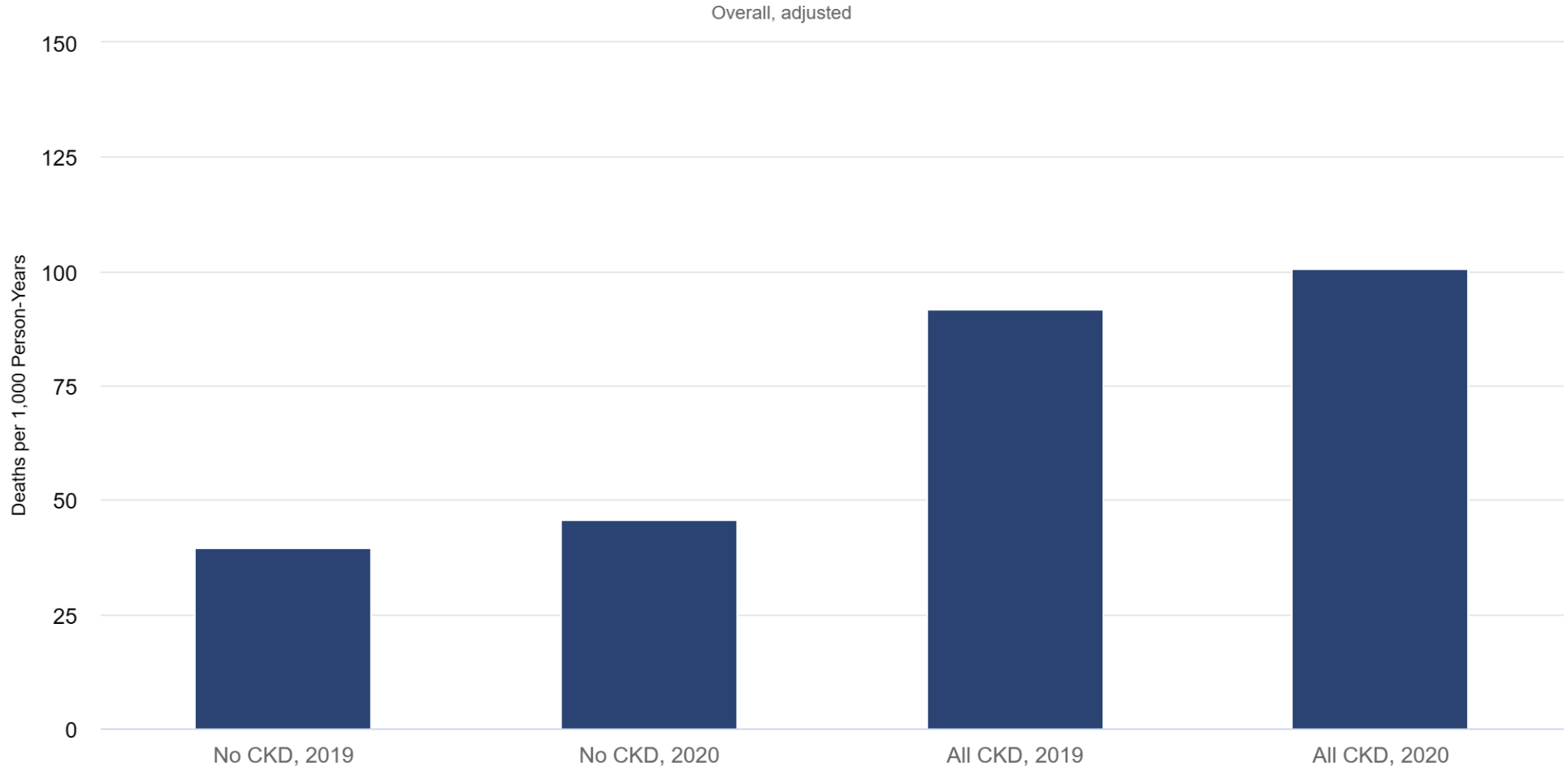
Figure 6.6a Percentages of cause-specific mortality, with and without inclusion of missing and unknown causes of death, in patients with ESRD receiving hemodialysis, who died in 2020



Data Source: 2022 United States Renal Data System Annual Data Report

Mortality in CKD

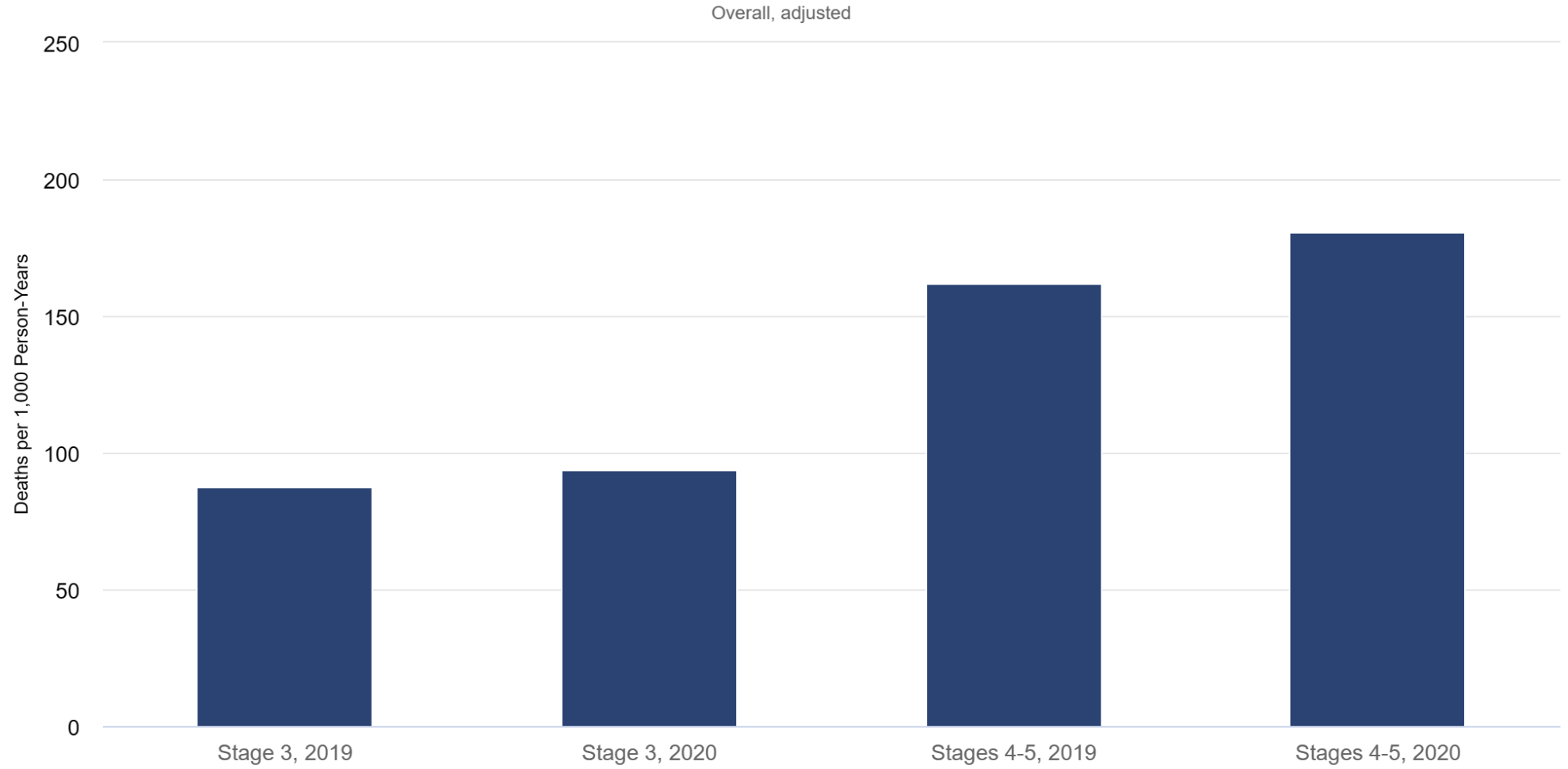
Figure 3.2a All-cause mortality rate in older adults, by CKD status and demographics, 2019 and 2020



Data Source: 2022 United States Renal Data System Annual Data Report

Mortality as CKD progresses

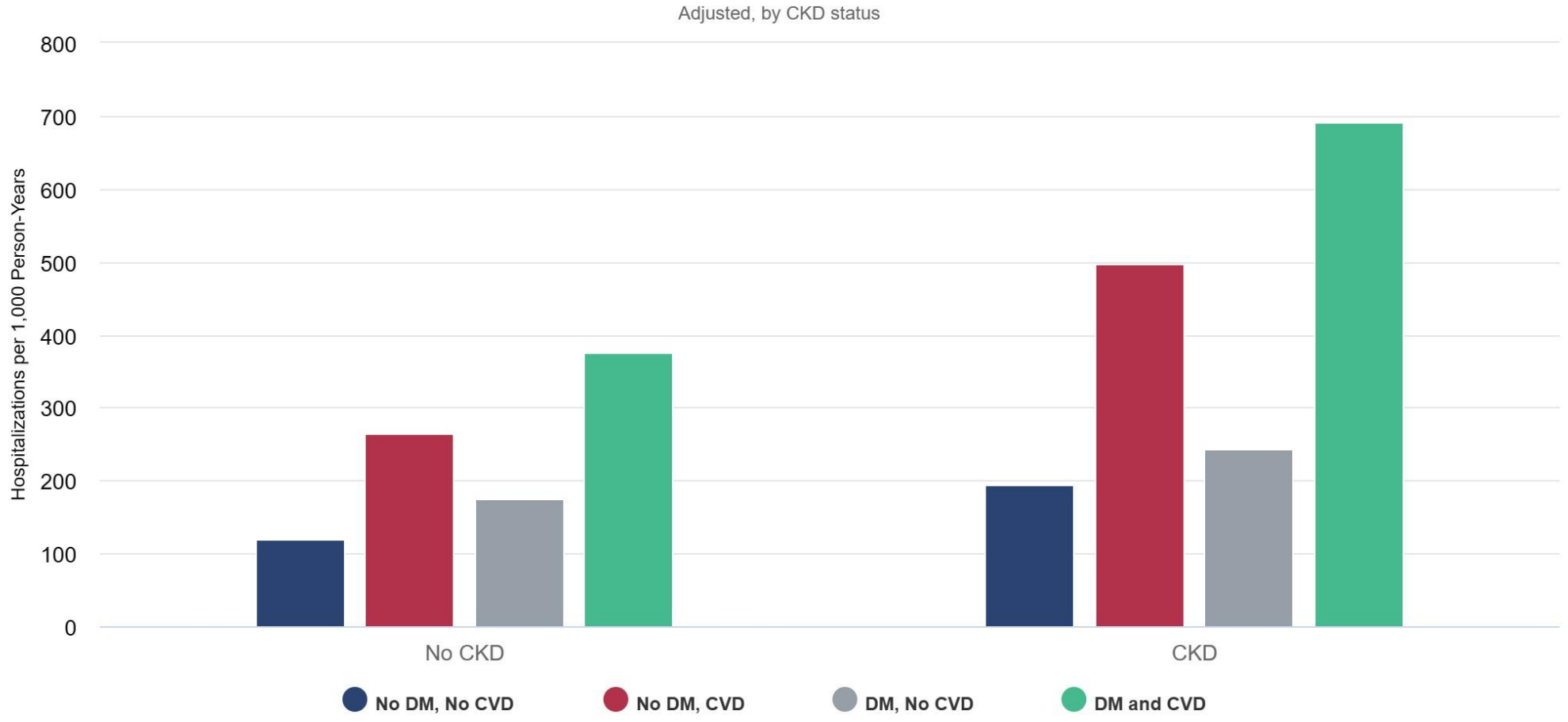
Figure 3.2b All-cause mortality rate in older adults, by CKD stage and demographics, 2019 and 2020



Data Source: 2022 United States Renal Data System Annual Data Report

The addition of DM and CV with CKD

Figure 3.6 All-cause hospitalization rates in older adults, by presence of diabetes mellitus and cardiovascular disease, 2020



Data Source: 2022 United States Renal Data System Annual Data Report

Treatment of DM and CKD

- Hyperglycemia
- HTN
- HLP
- Obesity
- Diet
- Smoking
- ACEi, ARB (and previously both!)

The early days

J Am Soc Nephrol. 1999 Dec;10(12):2569-76. doi: 10.1681/ASN.V10122569.

Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption

V Vallon [1], K Richter, R C Blantz, S Thomson, H Osswald

Affiliations + expand

PMID: 10589696 DOI: 10.1681/ASN.V10122569

Abstract

An increase in Na+/glucose cotransport upstream to the macula densa might contribute to the increase in single nephron GFR (SNGFR) in early diabetes mellitus by lowering the signal of the tubuloglomerular feedback, i.e., the luminal Na+, Cl-, and K+ concentration sensed by the macula densa. To examine this issue, micropuncture experiments were performed in nephrons with superficial glomeruli of streptozotocin-induced diabetes mellitus in rats. First, in nondiabetic control rats, ambient early distal tubular concentrations of Na+, Cl-, and K+ were about 21, 20, and 1.2 mM, respectively, suggesting collection sites relatively close to the macula densa. Second, glomerular hyperfiltration in diabetic rats was associated with a reduction in ambient early distal tubular concentrations of Na+, Cl-, and K+ by 20 to 28%, reflecting an increase in fractional reabsorption of these ions up to the early distal tubule. Third, in diabetic rats, early proximal tubular application of

SGLT2-inhibitors

Am J Physiol Renal Physiol 304: F156–F167, 2013.
First published November 14, 2012; doi:10.1152/ajprenal.00409.2012.

Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus

Volker Vallon,[1,2,3] Michael Rose,[3] Maria Gerasimova,[3] Joseph Satriano,[1,3] Kenneth A. Platt,[4] Hermann Koepsell,[5] Robyn Cunard,[3,1] Kumar Sharma,[1,3] Scott C. Thomson,[1,3] and Timo Rieg[1,3]

[1]Department of Medicine, University of California, San Diego, California; [2]Department of Pharmacology, University of California, San Diego, California; [3]Veterans Affairs, San Diego Healthcare System, San Diego, California; [4]Lexicon Pharmaceuticals, Woodlands, Texas; and [5]Institute for Anatomy and Cell Biology, University of Würzburg, Würzburg, Germany

Submitted 20 July 2012; accepted in final form 8 November 2012

Vallon V, Rose M, Gerasimova M, Satriano J, Platt KA, Koepsell H, Cunard R, Sharma K, Thomson SC, Rieg T. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. *Am J Physiol Renal Physiol* 304: F156–F167, 2013. First published November 14, 2012; doi:10.1152/ajprenal.00409.2012.—The Na-glucose cotransporter SGLT2 mediates high-capacity glucose uptake in the early proximal tubule and SGLT2 inhibitors are developed as new antidiabetic drugs. We used gene-targeted Sglt2 knockout ($Sglt2^{-/-}$) mice to elucidate the contribution of SGLT2 to blood glucose control, glomerular hyperfiltration, kidney growth, and markers of renal growth and injury at 5 wk and 4.5 mo after induction of low-dose streptozotocin (STZ) diabetes. The absence of SGLT2 did not affect renal mRNA expression of glucose transporters SGLT1, NaGLT1, GLUT1, or GLUT2 in response to STZ. Application of STZ increased blood glucose levels to a lesser extent in $Sglt2^{-/-}$ vs. wild-type (WT) mice (~300 vs. 470 mg/dl) but increased glucosuria and food and fluid intake to similar levels in both genotypes. Lack of SGLT2 prevented STZ-induced glomerular hyperfiltration but not the increase in kidney weight. Knockout of SGLT2 attenuated the STZ-

The bulk of tubular glucose uptake across the apical membrane of the kidney occurs in the early proximal tubule and is mediated by the high-capacity SGLT2 whereas the low-capacity SGLT1 (SLC5A1) is thought to "cleanup" most of the remaining luminal glucose in further distal parts of the proximal tubule (for review see Refs. 28, 47). In accordance, recent studies directly localized SGLT2 and SGLT1 protein expression in the brush border membrane of the early and later sections of the proximal tubule, respectively (1, 41). Micropuncture studies in knockout mice directly showed that SGLT2 is responsible for all glucose reabsorption in the early proximal tubule and, overall, is the major pathway of glucose reabsorption in the kidney (41). In comparison, mice lacking SGLT1 have only a minor reduction in fractional renal glucose reabsorption (12). In accordance with these studies in mice, individuals with gene mutations in SGLT1 have little or no glucosuria, whereas those with mutations in SGLT2 have persistent renal glucosuria (28).

GLP-1 receptor agonist

Am J Physiol Renal Physiol 304: F137–F144, 2013.
First published September 26, 2012; doi:10.1152/ajprenal.00064.2012.

CALL FOR PAPERS | *Integrative Aspects of Renal Endocrinology*

Glucagon-like peptide-1 receptor stimulation increases GFR and suppresses proximal reabsorption in the rat

Scott C. Thomson, Ali Kashkouli, and Prabhleen Singh
Department of Medicine, University of California and Veterans Affairs San Diego Healthcare System, San Diego, California

Submitted 7 February 2012; accepted in final form 25 September 2012

Thomson SC, Kashkouli A, Singh P. Glucagon-like peptide-1 receptor stimulation increases GFR and suppresses proximal reabsorption in the rat. *Am J Physiol Renal Physiol* 304: F137–F144, 2013. First published September 26, 2012; doi:10.1152/ajprenal.00064.2012.—The incretin hormone glucagon-like peptide-1 (GLP-1) is released from the gut in response to fat or carbohydrate and contributes to negative feedback control of blood glucose by stimulating insulin secretion, inhibiting glucagon, and slowing gastric emptying. GLP-1 receptors (GLP-1R) are also expressed in the proximal tubule, and possibly elsewhere in the kidney. Presently, we examined the effect of a GLP-1R agonist on single-nephron glomerular filtration rate (GFR; *SNGFR*), proximal reabsorption (*Jprox*), tubuloglomerular feedback (TGF) responses, and urine flow rate in hydropenic male Wistar and Wistar-Froemter rats. Micropuncture and whole-kidney data were obtained before and during infusion of the GLP-1 agonist exenatide (1 nmol/h iv). *SNGFR* and *Jprox* were measured by late proximal collection at both extremes of TGF activation, which was achieved by perfusing Henle's loop at 0 or 50 nl/min. Primary changes in *Jprox* were revealed by analysis of covariance for *Jprox* with *SNGFR* as a covariate. Effects on TGF

liraglutide) are peptide agonists of the GLP-1 receptor (GLP-1R) and are resistant to degradation by DPP-4 (33).

While most of the incretin literature focuses on glucose metabolism, a handful of publications suggest that activating GLP-1R might affect renal hemodynamics or salt handling. GLP-1R is expressed in cultured monolayers of proximal tubule cells, where activation by GLP-1 inhibits sodium transport (24). GLP-1R is expressed in human renal arteries (17). GLP-1R mRNA is found in rat glomeruli and proximal tubules (5), and recombinant GLP-1 infusion vasodilates the rat kidney (5), more so with intact renal nerves (21). DPP-4, an enzyme that rapidly degrades GLP-1, is expressed in proximal tubule brush border, where it associates with Na/H exchanger 3 (NHE3) (13) and where its expression (both mRNA and protein) is augmented by a high-fat diet (34). Recombinant GLP-1 is also natriuretic in the rat (4), and continuous infusion in Dahl salt-sensitive rats accelerates the return to salt balance following an increase in sodium intake (36). Sustained expo-

FDA

Dated: December 11, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–30154 Filed 12–18–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–D–0118]

Guidance for Industry on Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

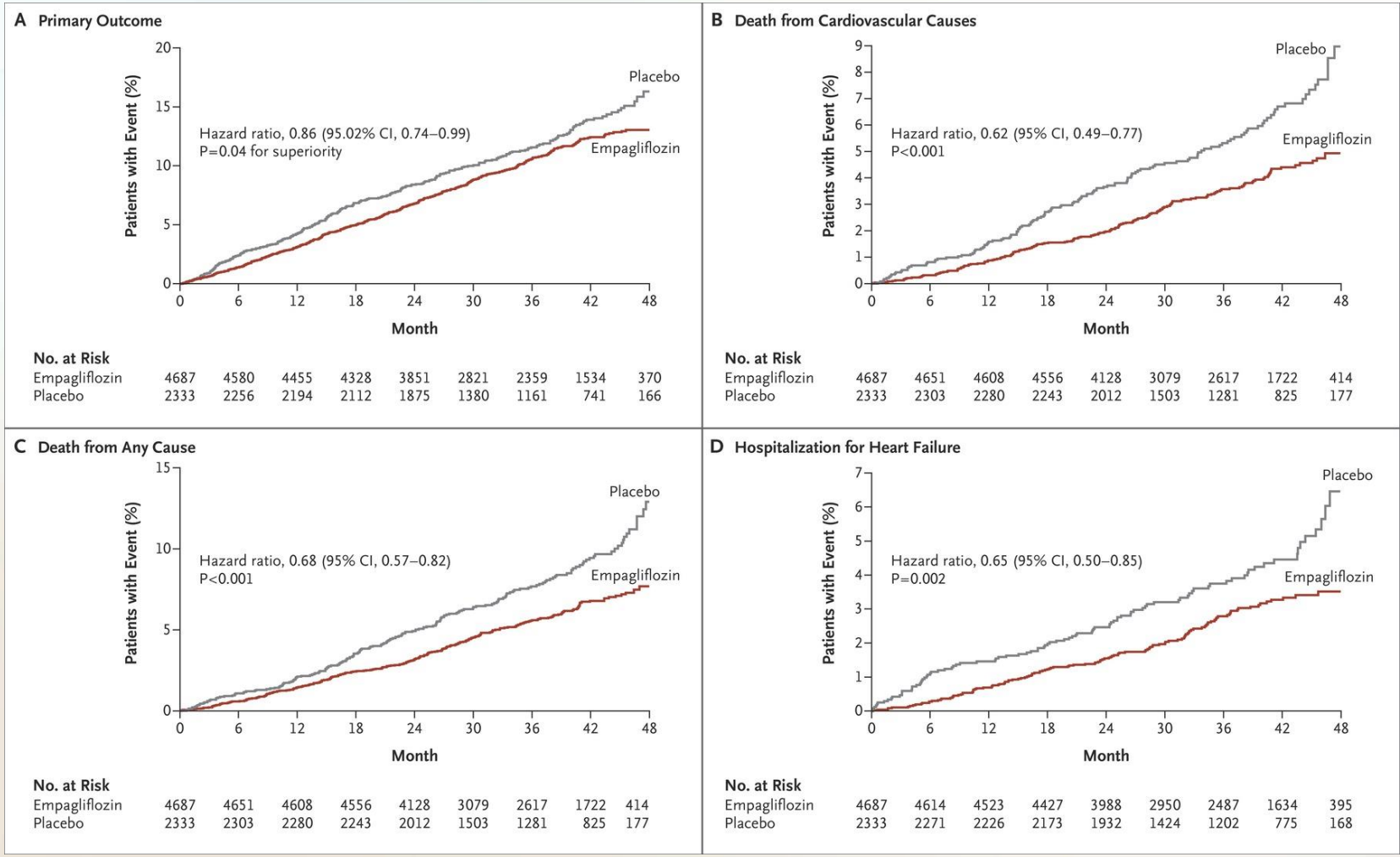
SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled ''Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.'' This guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk. We are issuing this guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered by all sponsors who have ongoing drug development programs for type 2 diabetes.

DATES: Submit written or electronic comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit

Early Trials – EMPA Reg, CANVAS

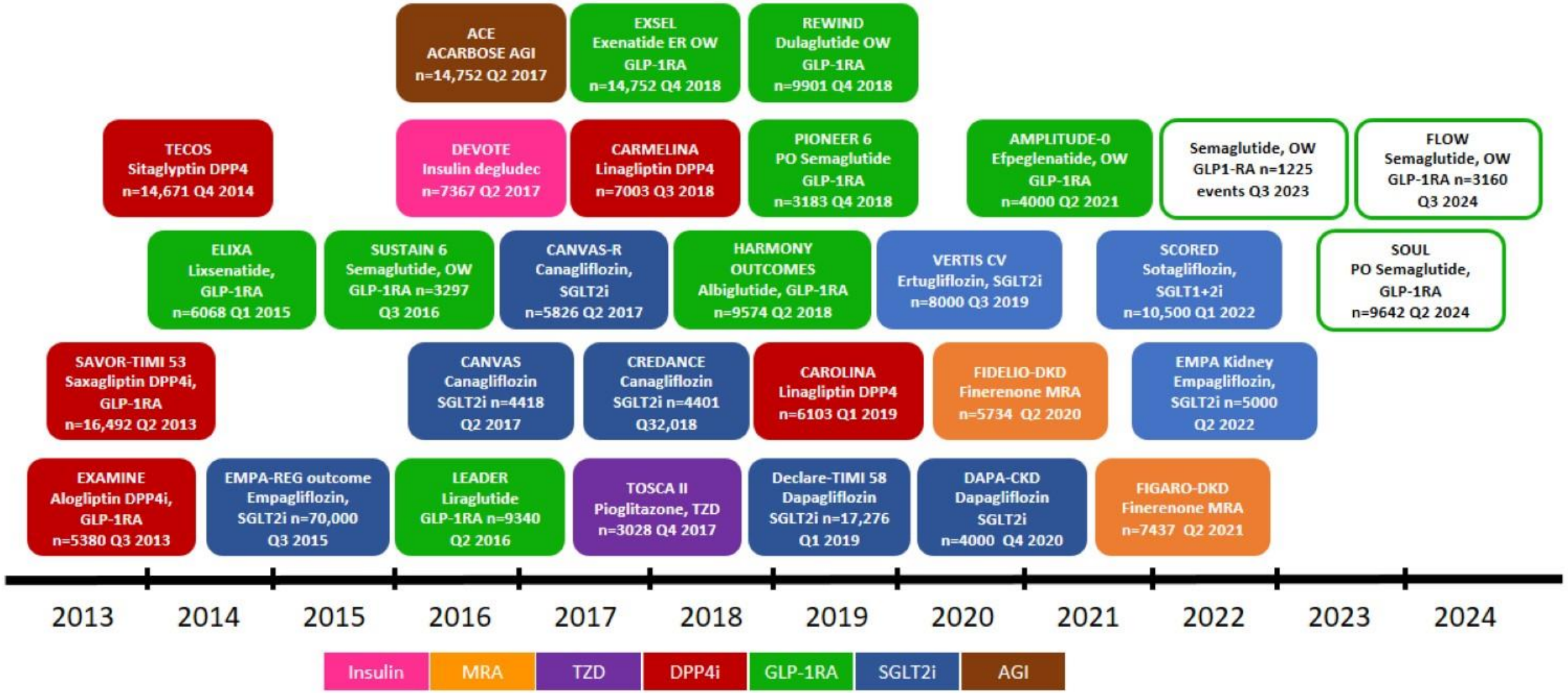
- EMPA Reg
  - HR 0.61 (0.53-0.70) 95% CI
- CANVAS Program
  - HR 0.6 (0.47-0.77) 95% CI



The Age of Advancement

- Finding ways to blunt the development of kidney disease and cardiovascular morbidity and mortality in diabetic patients (and beyond)

Cardiovascular outcome trials with type 2 diabetes and CKD



AGI, alpha glucosidase inhibitor; CKD, chronic kidney disease; DDP4, dipeptidyl-peptidase 4; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; OW, once weekly; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione.

Slide courtesy of Kieran McCafferty, Closing the Loop with SGLT2 inhibitors for CKD Management, ERA Congress 2022

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

American Diabetes Association

DIABETES NEWS AND RESEARCH

AA

Revised ADA Guidelines Include SGLT2 Inhibitors for Type 2 Diabetes Patients

BY ERIC SEABORG | APR 2020

SGLT2 inhibitors were designed to lower glucose, but clinical trials uncovered unexpected cardiovascular and renal benefits. Updated guidelines from the American Diabetes Association now recommends SGLT2 inhibitors in type 2 diabetes patients to lower glucose.

The evidence is clear that SGLT2 inhibitors should be added to the drug regimen of many type 2 diabetes patients, according to recent revisions of the American Diabetes Association's standards of care for diabetes.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors interfere with glucose reuptake in the proximal tubules of the kidneys, increasing urinary excretion of glucose and thereby lowering glucose in the bloodstream. The drugs were brought to market with the thought that lowering

ACC with similar updates

ACC Releases Updated Guidance on Use of SGLT2 Inhibitors, GLP-1RAs to Reduce CV Risk in Patients With Type 2 Diabetes

Aug 05, 2020

ACC News Story

Share via: 37 Print Font Size A A A

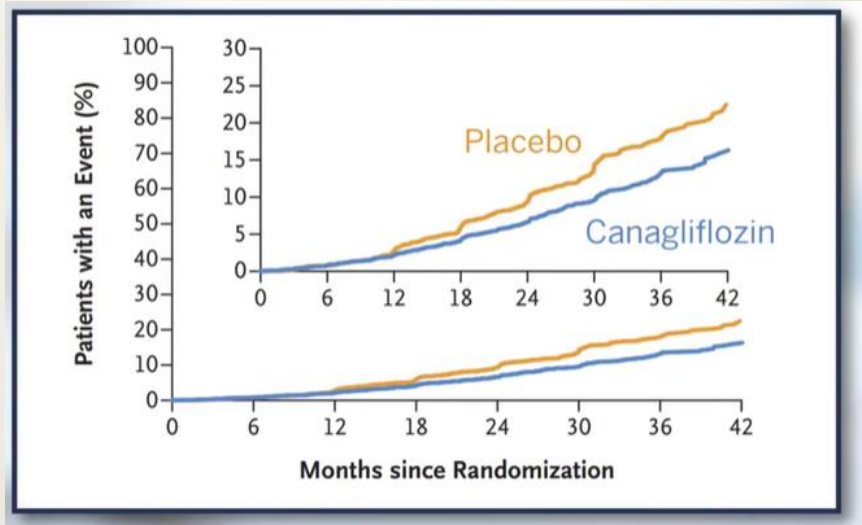
The ACC on Aug. 5 released the *2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes* in the *Journal of the American College of Cardiology*. The document provides practical guidance for cardiologists to initiate and monitor the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1RAs) with the goal of reducing cardiovascular risk in patients with type 2 diabetes.

Led by Writing Committee Co-Chairs **Sandeep R. Das, MD, MPH, FACC**, and **Brendan M. Everett, MD, MPH, FACC**, the new document updates the *2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease*. Specifically, the document provides treatment algorithms for SGLT2 inhibitors and GLP-1RAs that clinicians can use with established risk-factor modification guidelines to prevent major adverse cardiovascular events in patients with type 2 diabetes. The authors stress that the document should be applied in the context of guideline-directed diabetes care and is "intended to facilitate clinical decision-making."

Cardiovascular specialists have a key role in optimizing care for patients, particularly in screening for type 2 diabetes in patients with or at high risk of cardiovascular disease; aggressively treating cardiovascular risk factors; and incorporating newer glucose-lowering agents with evidence for improving cardiovascular outcomes into routine practice, the document notes.

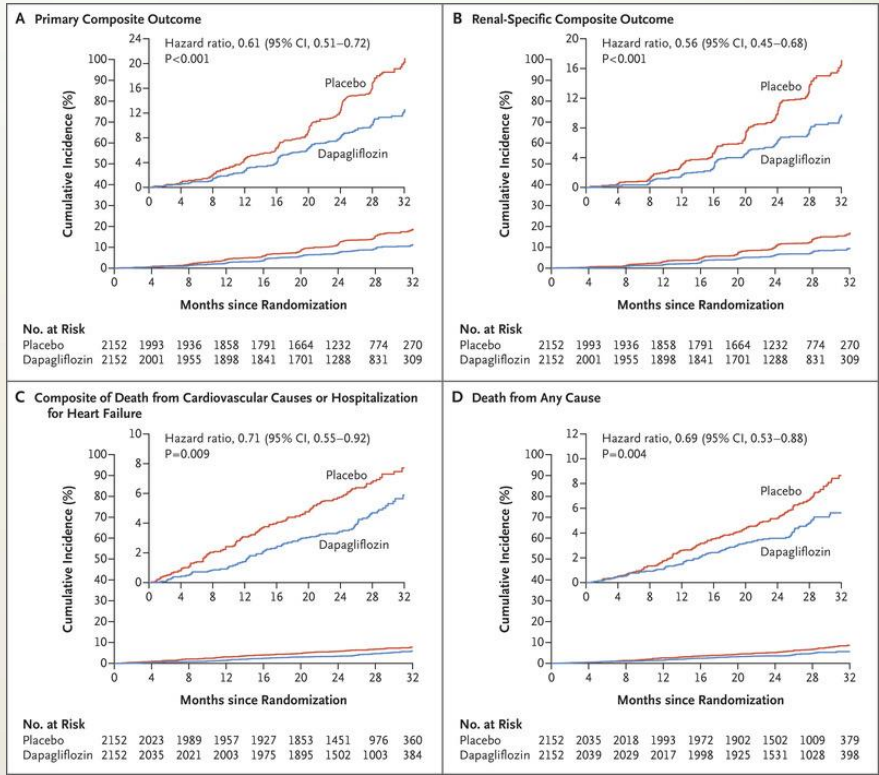
SGLT2 inhibitor Trials - CREDENCE

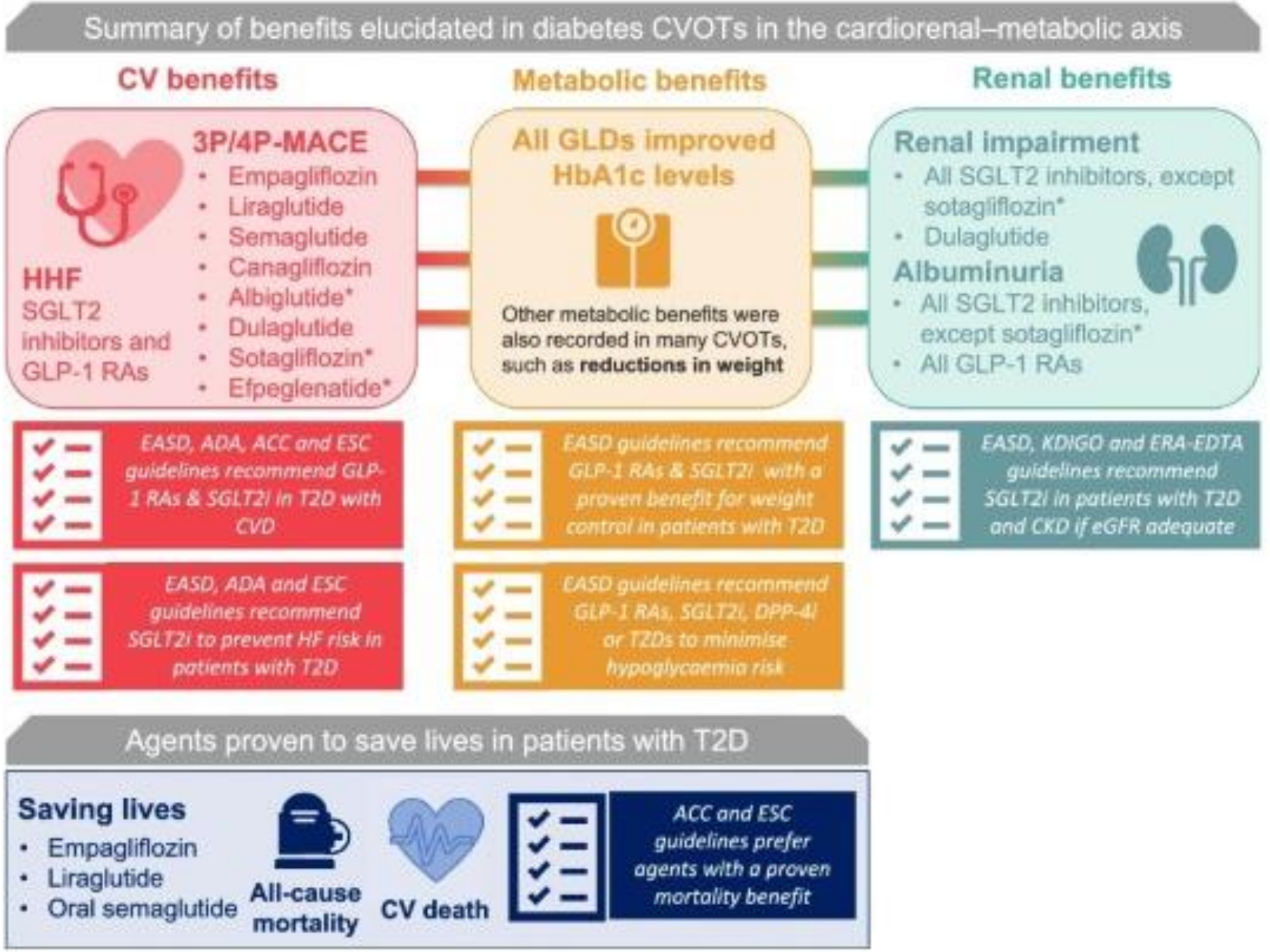
- CREDENCE
  - First RCT trial for kidney outcomes in **albuminuric CKD with T2DM**
  - Canagliflozin 100 mg daily vs placebo (and RAASb)
  - **eGFR 30-90 ml/min**
  - **UACR 300-5000 mg/g**
  - Primary outcome: doubling of Cr, ESKD, death from CV or renal cause
  - Stopped early
  - 30% relative risk reduction in 2.6 years
  - 34% relative risk reduction in kidney specific events



SGLT2 inhibitor Trials – DAPA CKD

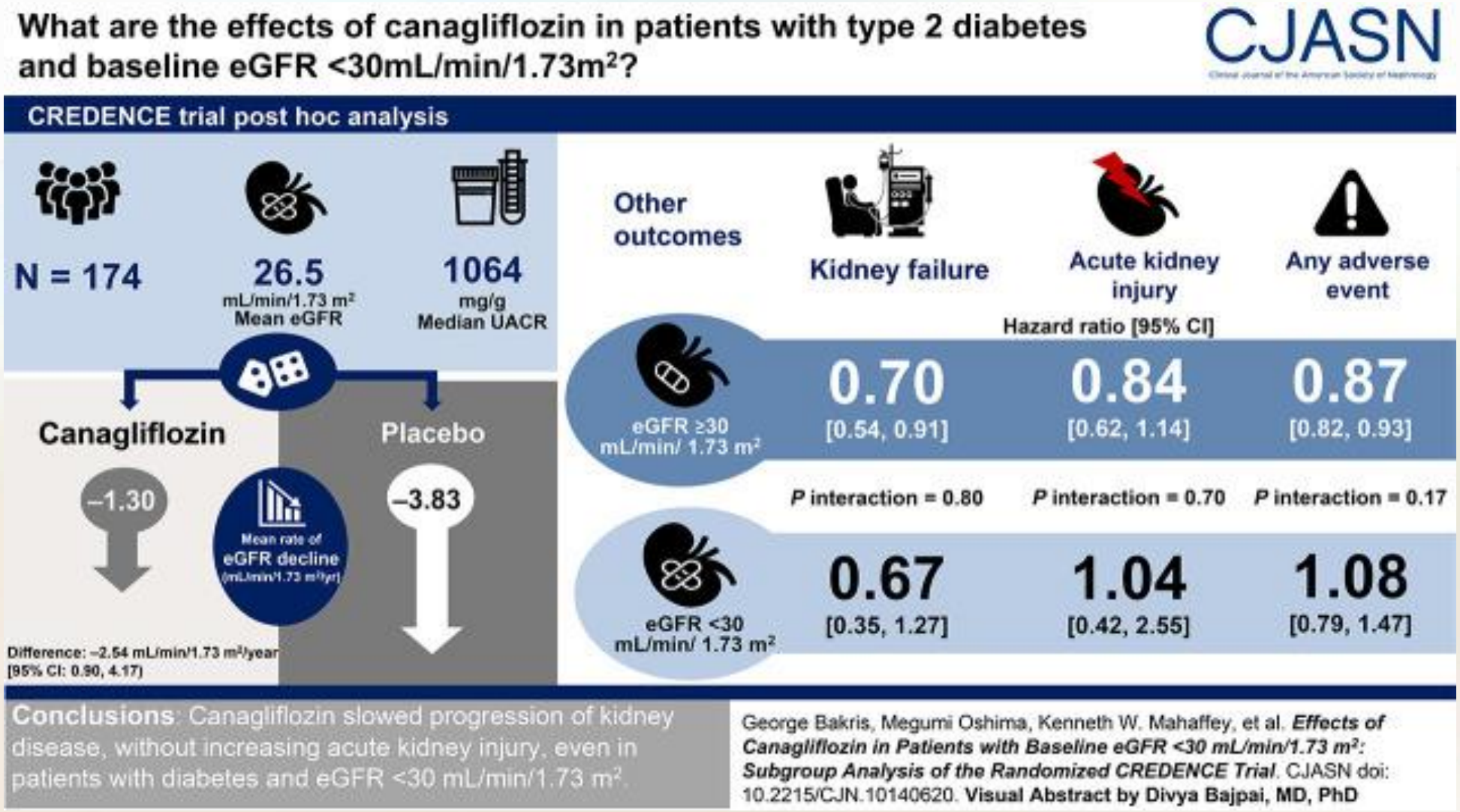
- **CKD pts – with and without T2DM (1/3 without!)**
- **eGFR 25-75 ml/min**
- **UACR 200-5000 mg/g**
- Dapa 10 mg vs placebo
- Sustained decline of 50% eGFR, ESKD, death
- Stopped early
- 39% reduction of primary composite outcome
  after 2.4 years – regardless of T2DM
- Kidney specific outcome – 44% risk reduction
- 29% RRR composite of death, hospitalization for HF
- 31% relative risk reduction in all cause mortality



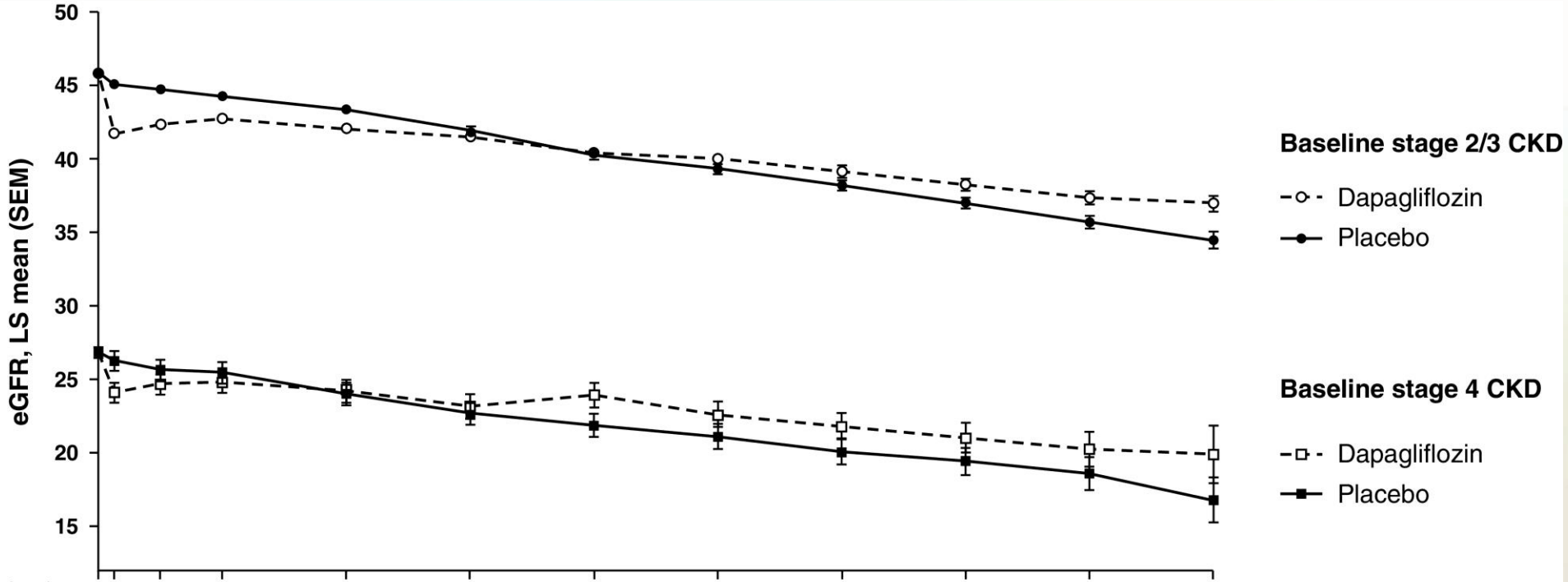

Summary of benefits elucidated in diabetes CVOTs in the cardiorenal–metabolic axis
CV benefits
Metabolic benefits
Renal benefits
3P/4P-MACE
Empagliflozin
Liraglutide
Semaglutide
Canagliflozin
Albiglutide*
Dulaglutide
Sotagliflozin*
Efpeglenatide*
HHF
SGLT2 inhibitors and GLP-1 RAs
All GLDs improved HbA1c levels
Other metabolic benefits were also recorded in many CVOTs, such as reductions in weight
Renal impairment
All SGLT2 inhibitors, except sotagliflozin*
Dulaglutide
Albuminuria
All SGLT2 inhibitors, except sotagliflozin*
All GLP-1 RAs
EASD, ADA, ACC and ESC guidelines recommend GLP-1 RAs & SGLT2i in T2D with CVD
EASD guidelines recommend GLP-1 RAs & SGLT2i with a proven benefit for weight control in patients with T2D
EASD, KDIGO and ERA-EDTA guidelines recommend SGLT2i in patients with T2D and CKD if eGFR adequate
EASD, ADA and ESC guidelines recommend SGLT2i to prevent HF risk in patients with T2D
EASD guidelines recommend GLP-1 RAs, SGLT2i, DPP-4i or T2Ds to minimise hypoglycaemia risk
Agents proven to save lives in patients with T2D
Saving lives
Empagliflozin
Liraglutide
Oral semaglutide
All-cause mortality
CV death
ACC and ESC guidelines prefer agents with a proven mortality benefit

Are vou a Flozinator?

SGLT2i


What are the effects of canagliflozin in patients with type 2 diabetes and baseline eGFR <30mL/min/1.73m²?
CJASN
CREDENCE trial post hoc analysis
N = 174
26.5
mL/min/1.73 m²
Mean eGFR
1064
mg/g
Median UACR
Canagliflozin
Placebo
–1.30
–3.83
Mean rate of eGFR decline
Difference: –2.54 mL/min/1.73 m²/year
[95% CI: 0.90, 4.17)
Other outcomes
Kidney failure
Acute kidney injury
Any adverse event
Hazard ratio [95% CI]
eGFR ≥30 mL/min/ 1.73 m²
0.70 [0.54, 0.91]
0.84 [0.62, 1.14]
0.87 [0.82, 0.93]
P interaction = 0.80
P interaction = 0.70
P interaction = 0.17
eGFR <30 mL/min/ 1.73 m²
0.67 [0.35, 1.27]
1.04 [0.42, 2.55]
1.08 [0.79, 1.47]
Conclusions: Canagliflozin slowed progression of kidney disease, without increasing acute kidney injury, even in patients with diabetes and eGFR <30 mL/min/1.73 m².
George Bakris, Megumi Oshima, Kenneth W. Mahaffey, et al. Effects of Canagliflozin in Patients with Baseline eGFR <30 mL/min/1.73 m²: Subgroup Analysis of the Randomized CREDENCE Trial. CJASN doi: 10.2215/CJN.10140620. Visual Abstract by Divya Bajpai, MD, PhD

DAPA CKD – CKD Stage 4



Participants at each time point

Baseline stage 2/3 CKD											
Dapagliflozin	1859	1762	1733	1643	1594	1558	1493	1302	864	450	148
Placebo	1821	1723	1691	1594	1539	1509	1449	1245	811	394	140
Baseline stage 4 CKD											
Dapagliflozin	293	269	268	253	238	227	212	180	114	46	9
Placebo	331	306	290	272	256	244	223	198	124	53	17

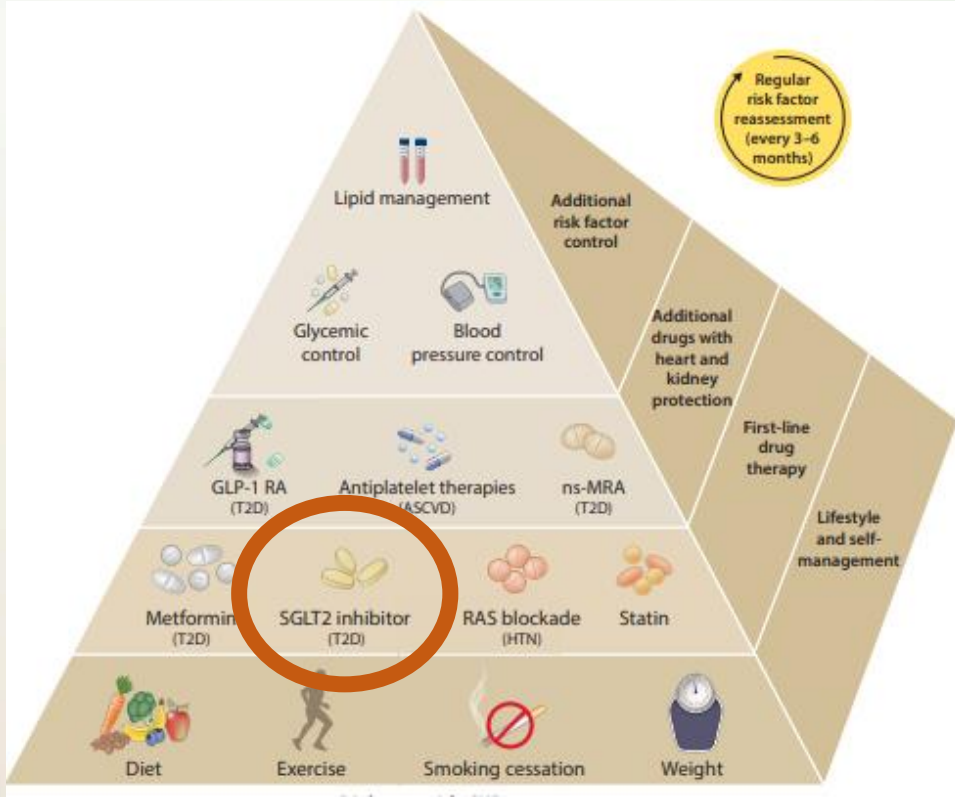
KDIGO DM in CKD Guidelines 2022

- Nutrition, exercise, smoking cessation, weight control
- ACEi/ARB with HTN and albuminuria
- Statin with T1DM/ T2DM and CKD
  - moderate intensity for primary prevention
  - high intensity for secondary prevention or multiple atherosclerotic cardiovascular disease (ASCVD)
- Metformin forT2DM, CKD eGFR >30
  - If eGFR 30-44 or If 45-59 higher risk of LA: 1,000 mg daily

KDIGO DM in CKD Guidelines 2022

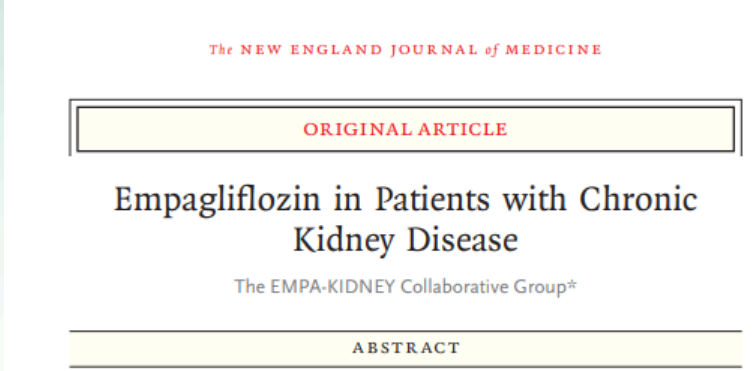
- A sodium–glucose cotransporter-2 inhibitor (SGLT2i) with proven kidney or cardiovascular benefit is recommended for patients with T2D, CKD, and eGFR ≥20 ml/min/1.73 m^2.

- Don’t stop the SGLT2i despite renal disease progression



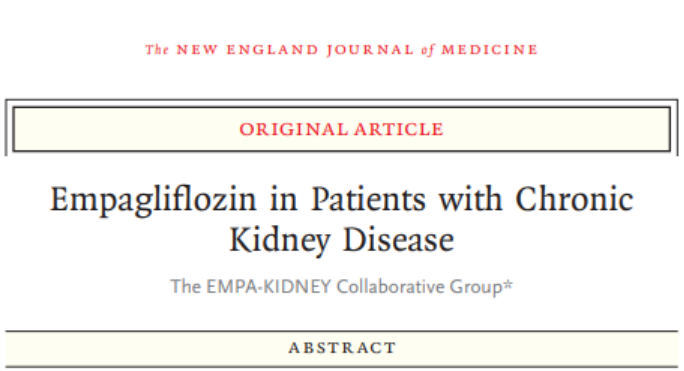
https://kdigo.org/wp-content/uploads/2022/10/KDIGO-2022-Clinical-Practice-Guideline-for-Diabetes-Management-in-CKD.pdf

EMPA Kidney



- Randomized, multi-center, placebo controlled
- Empagliflozin 10 mg daily
- **GFR 20-45 ml/min without UACR requirement**
- **45-90 with UACR >200 mg/g (limited to a third of patients)**
- **T2DM or no DM**
- Initial recruitment included T1DM, then modified
- RAASi if appropriate
- Exclusions: PCKD, s/p kidney transplant, ketoacidosis last 5 yrs, any IS in the last 3 months (except equivalent of ≤10 mg of pred/day)
- Excluded: T2DM with prior atherosclerotic disease with eGFR >60 ml/min

EMPA Kidney


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

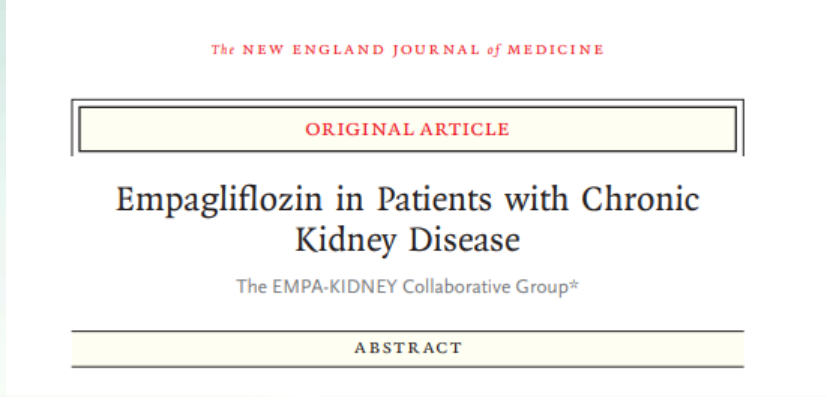
Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

- 15 weeks of run in phase
  - RAASb eval, eGFR eval
- Randomization
  - **eGFR checked 2 months later** (not 2-3 weeks like in CREDENCE or DAPA CKD)
- Primary outcome – composite of progression of kidney disease and cardiovascular death
  - Progression of kidney disease: ESKD, transplant, eGFR <10 ml/min, sustained decrease from baseline of >40% (vs 50% in DAPA CKD, vs Cr doubling in CREDENCE)
- Secondary outcomes – composite of hospitalization for HF, CV death, any hospitalization, any death

EMPA Kidney


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

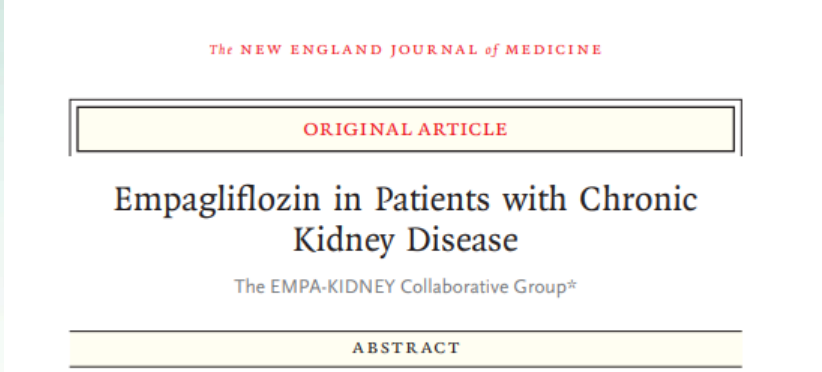
The EMPA-KIDNEY Collaborative Group*

ABSTRACT

- 2019-2021
  - Once randomized if eGFR dropped below 20 they were still included (7 weeks into run-in)
- 33% females
- <4% black
- 73% did not have cardiovascular disease
- 85% on RAASb
- 31% with DKD (25% with glomerular disease)

- Stopped early after meeting efficacy outcomes
- Follow up 2 years – 99% of patients were accounted for

EMPA Kidney


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

- Primary outcomes: Progression of CKD or CV death
- 13.1% of empagliflozin group vs 16.9% of placebo
- 28% risk reduction

- Progression of CKD alone
  - 29% relative risk reduction
- CV death events (overall small)
  - 1.8% of empa vs 2.1% placebo

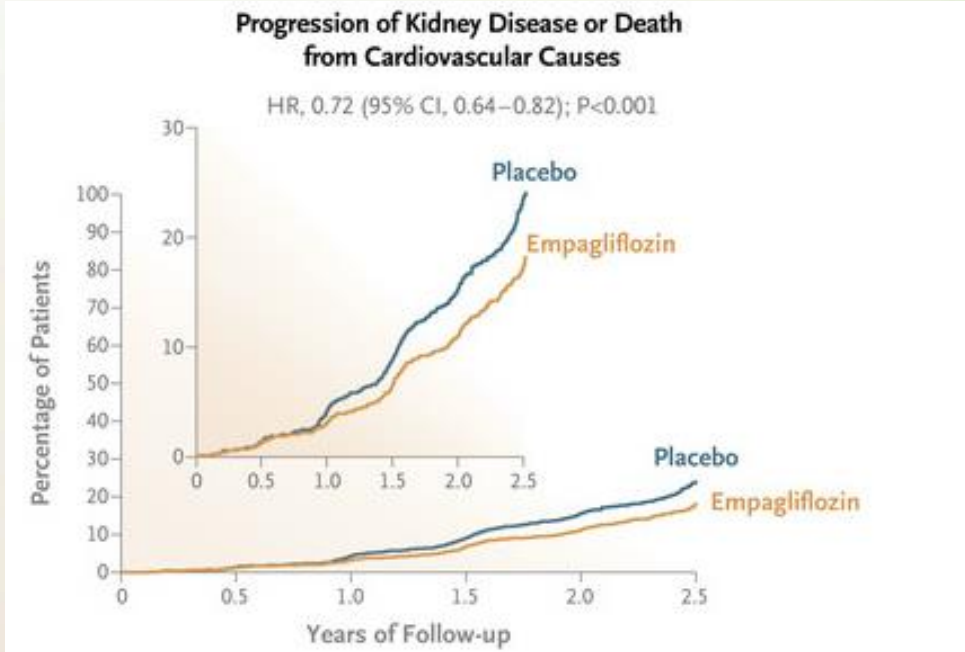


Table 2. Primary, Secondary, and Safety Outcomes.

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21
Other secondary outcomes						
Progression of kidney disease	384 (11.6)	6.09	504 (15.2)	8.09	0.71 (0.62–0.81)	
Death from cardiovascular causes	59 (1.8)	0.91	69 (2.1)	1.06	0.84 (0.60–1.19)	
End-stage kidney disease or death from cardiovascular causes§	163 (4.9)	2.54	217 (6.6)	3.40	0.73 (0.59–0.89)	
Safety outcomes						
Serious urinary tract infection	52 (1.6)	0.81	54 (1.6)	0.84	0.94 (0.64–1.37)	
Serious genital infection	1 (<0.1)	0.02	1 (<0.1)	0.02	—	
Serious hyperkalemia	92 (2.8)	1.44	109 (3.3)	1.72	0.83 (0.63–1.09)	
Serious acute kidney injury	107 (3.2)	1.67	135 (4.1)	2.11	0.78 (0.60–1.00)	
Serious dehydration	30 (0.9)	0.46	24 (0.7)	0.37	1.25 (0.73–2.14)	
Liver injury	13 (0.4)	0.20	12 (0.4)	0.19	1.09 (0.50–2.38)	
Ketoacidosis¶	6 (0.2)	0.09	1 (<0.1)	0.02	—	
Lower-limb amputation	28 (0.8)	0.43	19 (0.6)	0.29	1.43 (0.80–2.57)	
Bone fracture	133 (4.0)	2.09	123 (3.7)	1.93	1.08 (0.84–1.38)	
Severe hypoglycemia‖	77 (2.3)	1.20	77 (2.3)	1.21	1.00 (0.73–1.37)	
Symptomatic dehydration**	83 (2.5)	1.30	76 (2.3)	1.19	1.10 (0.81–1.51)	

* Hazard ratios were not calculated for outcomes with fewer than 10 events.
† Key secondary outcomes were prespecified to be adjusted for multiple testing with the use of the Hochberg step-up procedure with a familywise error rate of 0.029.
‡ The analysis of hospitalizations for any cause included the first and all subsequent events, so only the rates are shown; 1611 hospitalizations occurred among 960 patients in the empagliflozin group, and 1895 hospitalizations occurred among 1035 patients in the placebo group.
§ End-stage kidney disease was defined as the initiation of maintenance dialysis or receipt of a kidney transplant.
¶ Ketoacidosis occurred in one patient (in the empagliflozin group) without diabetes at baseline.
‖ Severe hypoglycemia was defined as a low blood glucose level causing severe cognitive impairment and warranting assistance from another person for recovery.
** Symptomatic dehydration was defined as symptoms attributed by patients to dehydration, such as feeling faint or fainting.

GLP1 Receptor Agonists - LEADER

- Liraglutide
  - T2DM, at least one CV condition
  - 3.8 years median follow up
  - Reduction in CV mortality, non-fatal MI, non-fatal stroke, all cause mortality
  - Microvascular event outcomes including nephropathy:
    - New persistent microalbuminuria, persistent doubling of the serum creatinine level, end-stage kidney disease, or death due to renal disease
    - 5.7 vs 7.2% with placebo HR 0.78 95% CI 0.67-0.92
    - results positive mainly due to the proteinuria findings

Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, Pocock S, Steinberg WM, Bergenstal RM, Mann JF, Ravn LS, Frandsen KB, Moses AC, Buse JB. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J. 2013 Nov;166(5):823-30.e5. doi: 10.1016/j.ahj.2013.07.012. Epub 2013 Oct 2. PMID: 24176437.

GLP1 Receptor Agonists – SUSTAIN-6

- Semaglutide
  - Pts with established CVD, heart failure, CKD or age ≥60 years with at least one cardiovascular risk factor
  - Primary outcome CV death, non-fatal MI, non-fatal stroke (HR 0.74; 95% CI 0.58-0.95, P<0.001 for non inferiority)
  - New or worsening nephropathy 3.8% vs 6.1% (HR 0.64)
  - Increase risk of retinopathy HR 1.76 -not seen in LEADER

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

LEADER & SUSTAIN 6
Post Hoc Analysis

- Effect of the Glucagon-Like Peptide-1 Receptor Agonists Semaglutide and Liraglutide on Kidney Outcomes in Patients With Type 2 Diabetes: Pooled Analysis of SUSTAIN 6 and LEADER
- Pooled data n=12k
- Albuminuria change, annual slope of eGFR rate change, timer to persistent eGFR reduction from baseline 30%, 40%, 50%, and 57%) .

Shaman AM, Bain SC, Bakris GL, Buse JB, Idorn T, Mahaffey KW, Mann JFE, Nauck MA, Rasmussen S, Rossing P, Wolthers B, Zinman B, Perkovic V. Effect of the Glucagon-Like Peptide-1 Receptor Agonists Semaglutide and Liraglutide on Kidney Outcomes in Patients With Type 2 Diabetes: Pooled Analysis of SUSTAIN 6 and LEADER. Circulation. 2022 Feb 22;145(8):575-585. doi: 10.1161/CIRCULATIONAHA.121.055459. Epub 2021 Dec 14. PMID: 34903039; PMCID: PMC8860212.

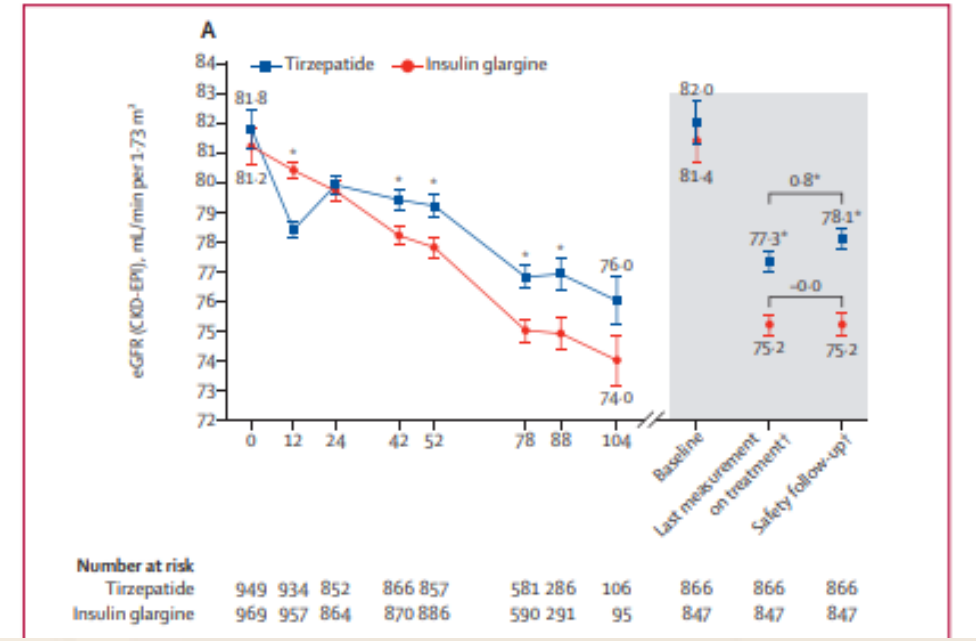
LEADER & SUSTAIN 6 Post Hoc Analysis

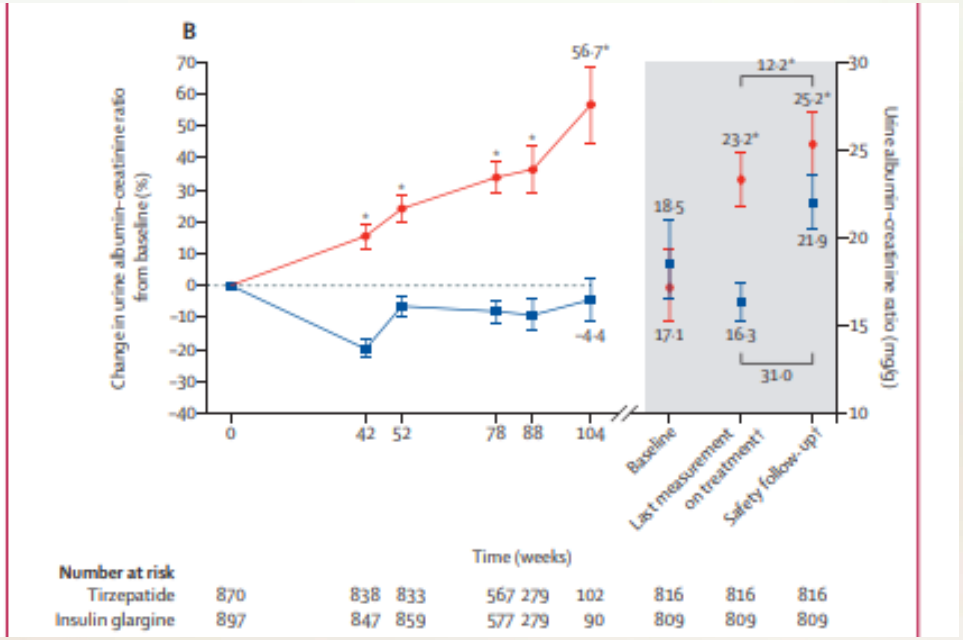
- By 2 years albuminuria decreased from baseline by 24% vs placebo
  - (95% CI, 20%-27%; *P*<0.001)
- With semaglutide 1.0 mg and liraglutide, eGFR slope decline was significantly slowed by 0.87 and 0.26 mL/min/1.73 m^2/y (*P*<0.0001 and *P*<0.001)
- Effects appeared larger in patients with baseline eGFR <60 versus ≥60
- Significantly lowered risk of persistent 40% and 50% eGFR reductions versus placebo (hazard ratio [HR], 0.86 [95% CI, 0.75-0.99]; *P*=0.039 and HR, 0.80 [95% CI, 0.66-0.97]; *P*=0.023, respectively)

Shaman AM, Bain SC, Bakris GL, Buse JB, Idorn T, Mahaffey KW, Mann JFE, Nauck MA, Rasmussen S, Rossing P, Wolthers B, Zinman B, Perkovic V. Effect of the Glucagon-Like Peptide-1 Receptor Agonists Semaglutide and Liraglutide on Kidney Outcomes in Patients With Type 2 Diabetes: Pooled Analysis of SUSTAIN 6 and LEADER. Circulation. 2022 Feb 22;145(8):575-585. doi: 10.1161/CIRCULATIONAHA.121.055459. Epub 2021 Dec 14. PMID: 34903039; PMCID: PMC8860212.

Tirzepatide - Mounjaro

- DGLP1/GIP dual agonist
- Very effective in weight loss – with or without diabetes
- Effective at reducing albuminuria





FLOW Trial – Stopped Early!

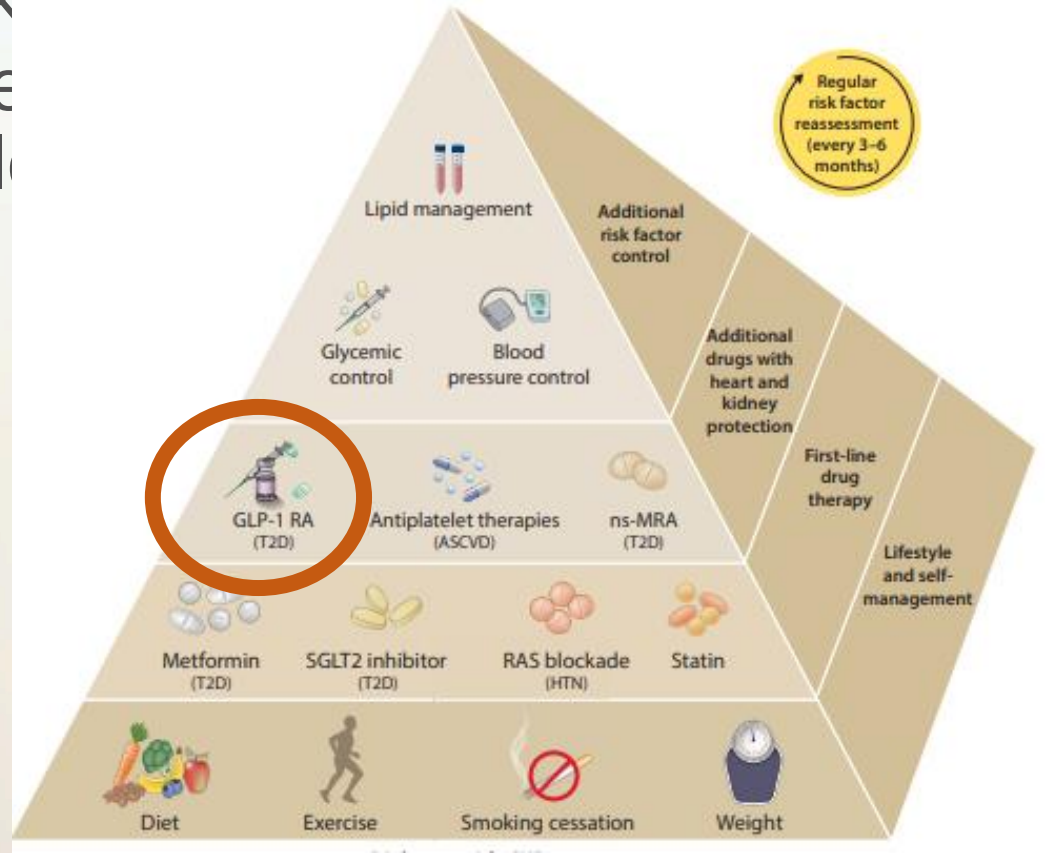
- Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease
- 3508 participants with T2DM
- eGFR 50-75 ml/min and UACR 300-5000 mg/g or
- eGFR 25-50 ml/min and UACR 100-5000 mg/g

- Composite primary outcome event defined as persistent eGFR decline of greater than or equal to 50 percentage from trial start, reaching ESRD, death from kidney disease or death from cardiovascular disease

https://clinicaltrials.gov/ct2/show/record/NCT03819153

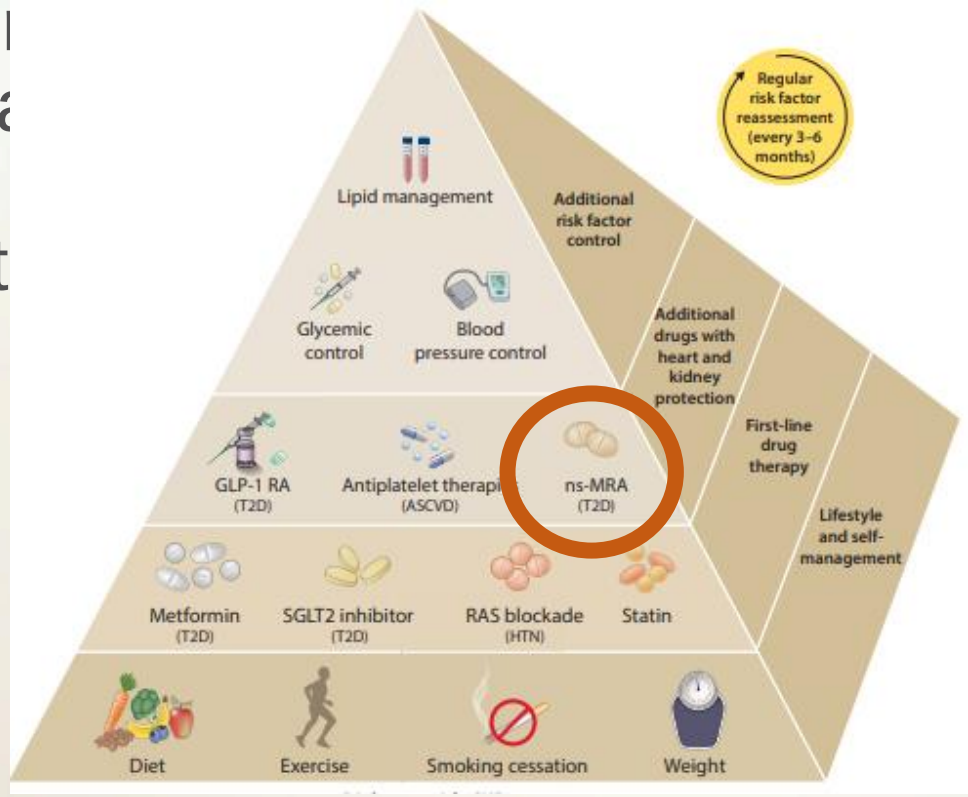
KDIGO DM in CKD Guidelines 2022

- A glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended for patients with T2D and CK
individualized glycemic targe
an SGLT2i or who are unabl



KDIGO DM in CKD Guidelines 2022

- A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2D, eGFR ≥25 ml/min/1.73 m^2, no
  concentration, and albuminuri
  ratio [ACR] ≥30 mg/g) despite
  dose of renin-angiotensin syst



Finerinone Trials

	FIDELIO-DKD	FIGARO-DKD
Drug	Finerenone	Finerenone
Total number of participants	5734	7437
% with CVD	45.4	44.7
eGFR and ACR criteria for enrollment	25–<60 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR 25–<75 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]	25–90 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR ≥60 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]
Mean eGFR at enrollment (ml/min per 1.73 m^2)	44	68
% with eGFR <60 ml/min per 1.73 m^2	88.4	38.2
Median ACR at enrollment (mg/g [mg/mmol])	850 [85.0]	309 [30.9]
% with ACR ≥300 mg/g (30 mg/mmol)	87.5	50.7
Follow-up time (median, yr)	2.6	3.4
Primary outcome	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF
Main secondary outcome	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death
Kidney composite outcome result	HR: 0.82; 95% CI: 0.73–0.93	HR: 0.87; 95% CI: 0.76–1.01
Cardiovascular composite outcome result	HR: 0.86; 95% CI: 0.75–0.99	HR: 0.87; 95% CI: 0.76–0.98

Figure 8 | Cardiovascular (CV) and kidney outcome trials for finerenone. ACR, albumin-creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Finerinone

- Risk of hyperkalemia

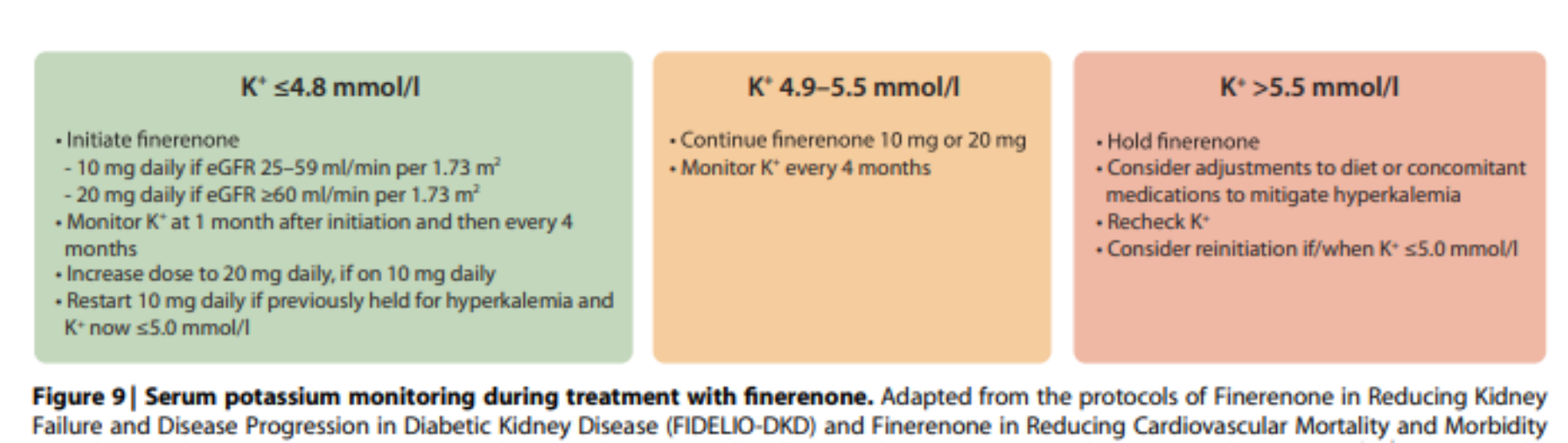


Figure 9 | Serum potassium monitoring during treatment with finerenone. Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity

What now?

UC-Way Diabetes Pharmaceutical Use Algorithm: Emphasizing Cardiovascular and Renal Protection

- **Discuss lifestyle modificationswith patient, with focus on diet, weight loss, and exercise. Consult a nutritionist and / or diabetes educator**
- **Identify A1c goal, and strongly consider referral for diabetes education**
- **Initiate Non Osmoticmetformin for most patients**
- **Consider initiating an ACEi/ARB, Statin, andaspirin**

Established Cardiovascular Disease, (History of MI, CAD, Stroke/TIA, Heart Failure, PAD) or per clinical judgment

Preferred: GLP1RA or SGLT2i

GLP1RA
- Weekly: Dulaglutide, Semaglutide
- Daily: Liraglutide

OR

SGLT2i: **Preferred in Heart Failure**
- Empagliflozin, Dapagliflozin

If A1C > Target at 3 months
- Pts on GLP1RA, consider SGLT2i
- Pts on a SGLT2i, consider GLP1RA
- Sulfonylurea
- Basal Insulin

✗ Avoid TZD and Saxagliptin in heart failure

Chronic Kidney Disease

Regardless of starting A1c, recommend including GLP1RA and or SGLT2i; ensure on ACEi/ARB if no contraindications

Proteinuria and/or eGFR > 45
Preferred: SGLT2i
- Empagliflozin, Dapagliflozin, Canagliflozin

Alternative: GLP1 RA
- Weekly: Dulaglutide, Semaglutide
- Daily: Liraglutide, Oral Semaglutide

eGFR 25– 45
Preferred: SGLT2i
- Continue metformin if eGFR >30 with close monitoring
- **Refer to nephrology**, initiate SGLT2i in conjunction with nephrology

Alternative: GLP1 RA
- Weekly: Semaglutide, Dulaglutide
- Daily: Liraglutide, Oral Semaglutide

eGFR < 25
Preferred: GLP1 RA
- Weekly: Dulaglutide, Semaglutide
- Daily: Liraglutide, Oral Semaglutide
- **Refer to nephrology**
- Discontinue metformin
- Follow up with Nephrology for SGLT2 inhibitor continuation

If A1C > Target at 3 months

Alternative agents in CKD
- **DPP-4, if not on a GLP1RA**
- Insulin (monitor for hyperglycemia)
- Use SU with caution

Comorbid obesity (BMI > 30)
Insulin Resistance or
Preference to **avoid weight gain**

Preferred: GLP1RA
- Weekly: Dulaglutide, Semaglutide
- Daily: Liraglutide, Oral Semaglutide

If GLP1RA not possible, consider SGLT2i
- Empagliflozin, Dapagliflozin

If A1C > Target at 3 months
- Pts on GLP1RA consider SGLT2i
- Pts on SGLT2i consider GLP1RA
- DPP-4, if not on a GLP1RA

If A1C > Target at 3 months
- Sulfonylurea
- TZD
- Basal Insulin

Do not use DPP4 inhibitor with GLP1-RA

NO other comorbidities

Acceptable: Sulfonylurea
- Sulfonylurea: Glipizide preferred

If A1C > Target at 3 months
- TZD
- Basal Insulin

Additional Notes

Escalate to **max tolerated dose** before adding next agent

If guideline recommended therapies are not possible due to cost, **low-cost drug** classes include: **Sulfonylureas, TZDs**

Consider **INSULIN** if:
- Catabolic features are present: weight loss, ketosis
- HyperTG
- A1c > 10
- T1D is a possibility

Reassessment for **insulin de-escalation** when glycemic control is improved

UNIVERSITY OF CALIFORNIA HEALTH

Last updated March 2022

WD1237 (4-22)

UC-Way Diabetes: Pharmaceutical Use Algorithm is adapted from American Diabetes Association Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2022

Chronic Kidney Disease (CKD)

Early Identification and Intervention in Primary Care

CKD is underdiagnosed and undertreated in the community[1]

Early identification, risk stratification, and treatment can reduce the morbidity and mortality rates from CKD and its related complications, such as CVD[2]

Step 1 Identify individuals at risk

Main clinical risk factors for CKD:
- Hypertension
- Diabetes
- CVD
- Family history of CKD

Consider other factors:
- Systemic disease affecting the kidneys (e.g. SLE)
- Obesity
- Genetic risk factors (e.g. ADPKD)
- Environmental exposures to nephrotoxins
- Demographics – older age, race/ethnicity
- History of AKI

Step 2 Test high-risk adults to detect CKD
(not population-wide)

Evaluate kidney function – eGFR
- eGFR calculated based on serum creatinine and/or cystatin C

AND

Evaluate kidney damage – albuminuria
- **UACR or dipstick*** (if UACR is unavailable)

If UACR ≥30 mg/g (≥3 mg/mmol) **OR** eGFR <60 mL/min/1.73 m²

Re-test in 3 months

If UACR <30 mg/g (<3 mg/mmol) **AND** eGFR ≥60 mL/min/1.73 m²

Re-test at least once a year†

Step 3 Diagnose CKD

If low eGFR or high UACR are present for >3 months, **diagnose CKD**

Step 4 Stratify and treat
(also see Table 1)

Risk categories for CKD progression, morbidity, and mortality; monitoring frequency (number of check-ups per year in parentheses); and nephrology consultation[3]

eGFR categories (mL/min/1.73 m²) Description and range	Range	A1 <30 mg/g <3 mg/mmol	A2 30–299 mg/g 3–29 mg/mmol	A3 ≥300 mg/g ≥30 mg/mmol
		Albuminuria categories		
G1	≥90	Monitor (1)	Treat (1)	Treat & consult (3)
G2	60–89	Monitor (1)	Treat (1)	Treat & consult (3)
G3a	45–59	Treat (1)	Treat (2)	Treat & consult (3)
G3b	30–44	Treat (2)	Treat & consult (3)	Treat & consult (3)
G4	15–29	Treat & consult (3)	Treat & consult (3)	Treat & consult (4+)
G5	<15	Treat & consult (4+)	Treat & consult (4+)	Treat & consult (4+)

Low risk
Stable disease *OR* NO CKD in absence of other markers of kidney damage.‡
Requires measurements once a year or earlier in case of new symptoms / risk factors.

Moderately increased risk
Requires measurements at least once a year

High risk
Requires measurements at least twice a year

Very high risk
Treat in agreement with a nephrologist
Requires measurements at least three times a year
Requires the closest monitoring at least four times a year (every 1–3 months)

Adapted from de Boer *et al.* 2022[3]

Step 5 Nephrology consultation

Take action based on the risk categories for CKD progression, morbidity, and mortality, and monitoring frequency (see above).

Primary care practitioners should consult with a nephrologist while initiating treatment; some patients may be under the direct care of a nephrologist if indicated (see Table 3).

Table 1. Treat to slow CKD progression, reduce mortality risk, and manage comorbidities

Lifestyle modification	
Smoking cessation; regular exercise; well-balanced diet (avoid excessive protein intake and processed food, limit sodium intake <2 g/day)	
Medical treatment	
Treat diabetes, hypertension, and CVD: Optimise blood pressure and glycemic control	Ensure guideline-directed medical treatment to slow down CKD progression and reduce CVD risk: maximally tolerated doses of **ACEIs/ARBs, SGLT2 inhibitors, nonsteroidal MRAs** with proven benefits in renal and cardiovascular outcome trials for T2D; also consider **lipid-lowering therapy (statins)** and/or **antiplatelet therapy** (for patients with CKD at risk of atherosclerotic events)
Considerations	
Adjust dosing of medications based on eGFR; exercise caution when prescribing analgesics, antimicrobials, hypoglycemics, chemotherapeutics, or anticoagulants; avoid nephrotoxins (e.g. NSAIDs) and some contrast media	

Table 2. Monitor for CKD progression and comorbidities

CKD progression and comorbidities	What to monitor
CKD monitoring	eGFR, UACR, urinalysis (urine sediment)
CVD and dyslipidemia	Blood pressure, cardiovascular risk stratification, lipid status
Diabetes	Blood glucose, HbA1c

Identify CKD complications: anemia, mineral and bone disorders, metabolic acidosis, etc.

Table 3. Additional considerations for nephrology consultation

- Unexplained, progressive decline in eGFR ≥5 mL/min/1.73 m² over 12 months or sudden decline in eGFR over days to weeks
- Unexplained significant albuminuria/proteinuria or hematuria
- Persistent hyperkalemia, resistant hypertension (defined as uncontrolled hypertension on three antihypertensive agents, including a diuretic), recurring kidney stones, or hereditary kidney diseases (e.g. ADPKD)
- Other complications identified (anemia, mineral and bone disorders, metabolic acidosis, etc.)

Consultation with a nephrologist can be for identifying other treatable causes or for developing a treatment plan. Although some patients may be maintained further in nephrology care, most will return to primary care.

Consider using other KDIGO guidelines: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf; KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease https://kdigo.org/wp-content/uploads/2022/10/KDIGO-2022-Clinical-Practice-Guideline-for-Diabetes-Management-in-CKD.pdf; KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2021-BP-GL.pdf; KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2013-Lipids-Guideline-English.pdf

Footnotes
*If albuminuria is detected by dipstick, use UACR for quantification of urinary albumin excretion. †Re-test based on individual patient assessment, at least once a year. ‡Urine sediment abnormalities, electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy), or a history of kidney transplantation.

Abbreviations
ACEI, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; G, refers to the GFR category; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; SGLT2, sodium–glucose co-transporter-2; SLE, systemic lupus erythematosus; T2D, type 2 diabetes; UACR, urine albumin–creatinine ratio.

References
1. Sundström J *et al. Lancet Reg Health Eur* 2022; 20: 100438.
2. Shlipak MG *et al. Kidney Int* 2021; 99 (1): 34–47.
3. Adapted from de Boer IH et al. ADA/KDIGO Consensus Report: Diabetes Management in Chronic Kidney Disease. Diabetes Care 2022; In press by Adapted from de Boer IH et al. Kidney International (2022); https://kdigo.org/wp-content/uploads/2018/03/ADA-KDIGO-Consensus-Report-Diabetes-CKD-KI-2022.pdf.

PCDE endorses and supports the Clinical One Pager for Primary Care around Early Identification and Intervention of CKD.
This material has been commissioned and funded by AstraZeneca.

Chronic Kidney Disease (CKD)

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Step 1

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If UACR <30 mg/g (<3 mg/mmol)
AND
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Re-test at least once a year†

Step 3

Diagnose CKD

If low eGFR or high UACR are present for >3 months, **diagnose CKD**

Step 4

Stratify and treat

(also see Table 1)

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eGFR categories (mL/min/1.73 m²) Description and range	Albuminuria categories A1 <30 mg/g <3 mg/mmol	A2 30–299 mg/g 3–29 mg/mmol	A3 ≥300 mg/g ≥30 mg/mmol
≥90 G1	Monitor (1)	Treat (1)	Treat & consult (3)
60–89 G2	Monitor (1)	Treat (1)	Treat & consult (3)
45–59 G3a	Treat (1)	Treat (2)	Treat & consult (3)
30–44 G3b	Treat (2)	Treat & consult (3)	Treat & consult (3)
15–29 G4	Treat & consult (3)	Treat & consult (3)	Treat & consult (4+)
<15 G5	Treat & consult (4+)	Treat & consult (4+)	Treat & consult (4+)

Low risk

Stable disease *OR* NO CKD in absence of other markers of kidney damage.‡
Requires measurements once a year or earlier in case of new symptoms / risk factors.

Moderately increased risk

Requires measurements at least once a year

High risk

Requires measurements at least twice a year

Very high risk

Treat in agreement with a nephrologist

Requires measurements at least three times a year

Requires the closest monitoring at least four times a year (every 1–3 months)

Adapted from de Boer *et al.* 2022[3]

Step 5

Nephrology consultation

Take action based on the risk categories for CKD progression, morbidity, and mortality, and monitoring frequency (see above).

Primary care practitioners should consult with a nephrologist while initiating treatment; some patients may be under the direct care of a nephrologist if indicated (see Table 3).

Slow CKD, reduce mortality

- Lifestyle modification
  - Smoking cessation, regular exercise, well balanced diet
- Medical Treatment
  - BP and glycemic control
  - ACEi/ARB, SGLT2i, NS-MRA
- Consideration of renal dosing of other medications

Monitor for CKD Progression and Comorbidities

- CKD Monitoring
  - eGFR, UACR, UA
- CVD and dyslipidemia
  - BP, CV risk stratification, lipid status
- Diabetes
  - Blood glucose, HgbA1C

Additional Considerations

- Unexplained, **progressive decline** in eGFR > 5 ml/min or sudden decline in eGFR over days to weeks
- Unexplained significant **proteinuria or hematuria**
- Persistent **hyperkalemia, resistant hypertension** (uncontrolled on 3 anti-HTN agents including a diuretic), **recurring kidney stones or hereditary kidney diseases** (PKD)
- **Other complications**(anemia, mineral and bone disorders, metabolic acidosis, etc)

UTI Risk?

FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections

FDA Drug Safety Communication

UTI Risk – What UTI risk?

Comparison	Study (Publication Yr)	Patients (*n*)	Outcome
Meta-analysis			
SGLT2i versus placebo	Puckrin *et al.* (2018) (10)	72 trials: 37,116	**Random-effects model risk ratio 1.03**; 95% CI, 0.96 to 1.11
			I^2 0%; 95% CI, 0 to 0
Randomized controlled trials			
Canagliflozin (100 mg) versus placebo	Perkovic *et al.* (2019) (5)	4397	**HR=1.08;** 95% CI, 0.9 to 1.29
Canagliflozin (all doses) versus placebo	Neal *et al.* (2017) (2)	4330	40 versus 37 participants with an event per 1000 patient-years; ***P*=0.38**
Dapagliflozin (10 mg) versus placebo	Heerspink *et al.* (2020) (6)	4298	**No difference reported; details unpublished**
	Wiviott *et al.* (2018) (3)	17,143	HR=0.93; 95% CI, 0.73 to 1.18; ***P*=0.54**
Empagliflozin (all doses) versus placebo	Wanner *et al.* (2016) (4)	7018	eGFR <60 ml/min per 1.73 m^2: **rate ratio 1.06;** 95% CI, 0.86 to 1.3
			eGFR ≥60 ml/min per 1.73 m^2: **rate ratio 0.92**; 95% CI, 0.8 to 1.07

Wiegley, Nasim1; So, Paolo Nikolai2. Sodium-Glucose Cotransporter 2 Inhibitors and Urinary Tract Infection: Is There Room for Real Concern?. Kidney360 3(11):p 1991-1993, November 24, 2022. | DOI: 10.34067/KID.0005722022

UTI Risk – What UTI Risk?

COMPARISON	STUDY (PUBLICATION YR)	PATIENTS (*N*)	OUTCOME
Meta-analysis			
SGLT2i versus active comparator	Puckrin *et al.* (2018) (10)	22 trials: 15,966	**Random-effects model risk ratio 1.08;** 95% CI, 0.93 to 1.25 I^2 22; 95% CI, 0 to 54
Retrospective cohort			
SGLT2i versus GLP1-RA	Varshney *et al.* (2021) (12)	474	**Composite genitourinary infection** (**HR=0.78**; 95% CI, 0.26 to 2.37)
SGLT2i versus DPP4i	Fisher *et al.* (2020) (13)	416,488	**Urosepsis (HR=0.58**; 95% CI, 0.42 to 0.8)
SGLT2i versus DPP4i or GLP1-RA	Dave *et al.* (2019) (11)	SGLT2i versus DPP4i: 123,752; SGLT2i versus GLP1-RA: 111,978	•Severe UTI:SGLT2i versus DPP4i: **HR=0.98**; 95% CI, 0.68 to 1.41 •SGLT2i versus GLP1-RA: **HR=0.72;** 95% CI, 0.53 to 0.99
			•Treated outpatient UTI:SGLT2i versus DPP4i: HR=0.96; 95% CI, 0.89 to 1.04 •SGLT2i versus GLP1-RA: HR=0.91; 95% CI, 0.84 to 0.99

Sick day rules?

Risk of ketoacidosis

Decreased risk of AKI

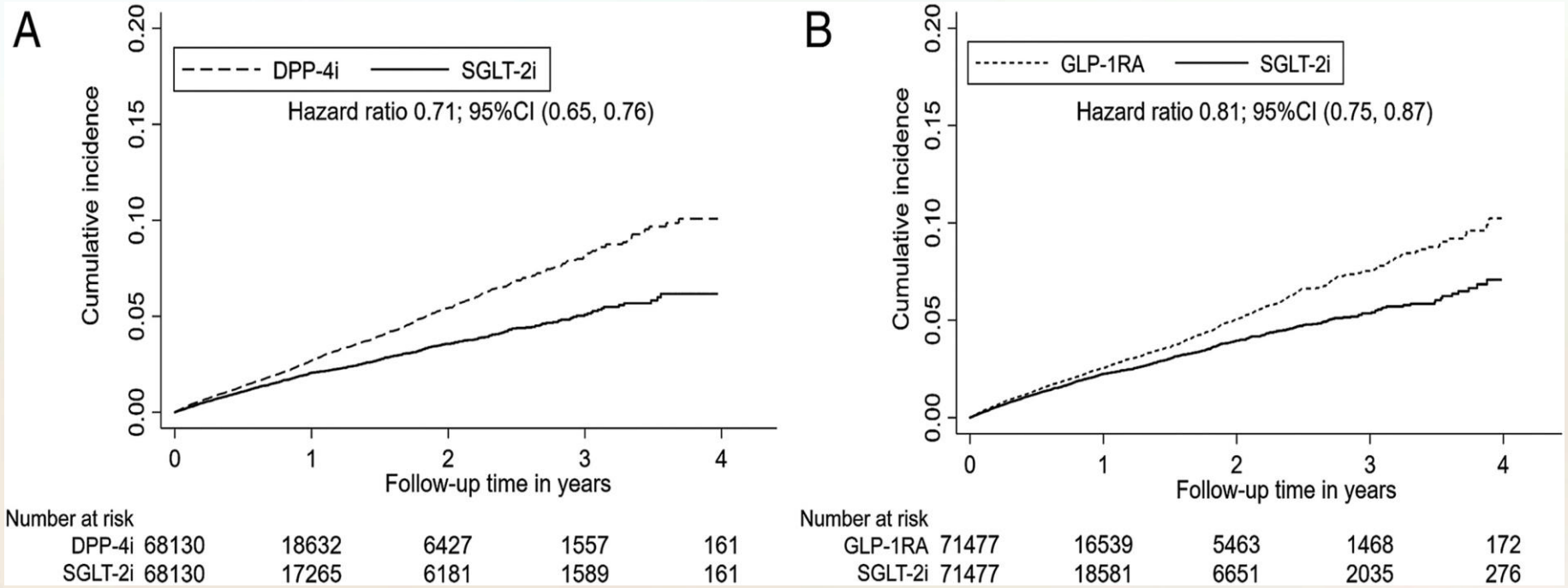
SGLT2 Inhibitors and the Risk of Acute Kidney Injury in Older Adults With Type 2 Diabetes

- >66 yrs with T2DM, Medicare
- New user of SGLT2i, DPP-4 inhibitor, GLP-1RA
- 68k vs 71k matched
- Mean age 72

American Journal of Kidney Diseases 2022 79858-867.e1DOI: (10.1053/j.ajkd.2021.09.015)

SGLT2 Inhibitors and the Risk of Acute Kidney Injury in Older Adults With Type 2 Diabetes

- The risk of AKI was lower in the SGLT2 inhibitor group than in the DPP-4 inhibitor group (HR, 0.71 [95% CI, 0.65-0.76]) or the GLP-1RA group (HR, 0.81 [95% CI, 0.75-0.87]).



American Journal of Kidney Diseases 2022 79858-867.e1DOI: (10.1053/j.ajkd.2021.09.015)

Sick day rules?

Risk of ketoacidosis

Decreased risk of AKI

Variability between SGLT2i

- FDA approved SGTL2i
  - Invokana® (canagliflozin)
  - Farxiga® (dapagliflozin)
  - Jardiance® (empagliflozin)
  - Steglatro® (ertugliflozin) – 15 mg better for glycemic control than dapa 10 and empa 25 mg daily
  - Brenzavvy™ (bexaglifloxin) – much lower cost

GoodRx

Jardiance	10mg (30 tablets)	$578.51	View prices
Farxiga	10mg (30 tablets)	$551.57	View prices
Steglatro	15mg (30 tablets)	$335.66	View prices
Invokana	100mg (30 tablets)	$590.03	View prices
Brenzavvy	20mg (30 tablets)	$46.25	View prices

FIND-CKD - Ongoing

- A Trial to Learn How Well Finerenone Works and How Safe it is in Adult Participants With Non-diabetic Chronic Kidney Disease
- 1600 pts with non-DM kidney disease
- Inclusion Criteria:
  - Urine albumin/creatinine ratio (UACR) of ≥ 200 but ≤ 3500 mg/g and estimated glomerular filtration rate (eGFR) ≥ 25 but < 90 mL/min/1.73m^2 at screening, and
  - Documentation of albuminuria/proteinuria in the participant's medical records at least 3 months prior to screening.
- Stable and maximum tolerated ACEI/ARB x 4 weeks
- K+ ≤ 4.8 mmol/L at screening

https://clinicaltrials.gov/ct2/show/NCT05047263

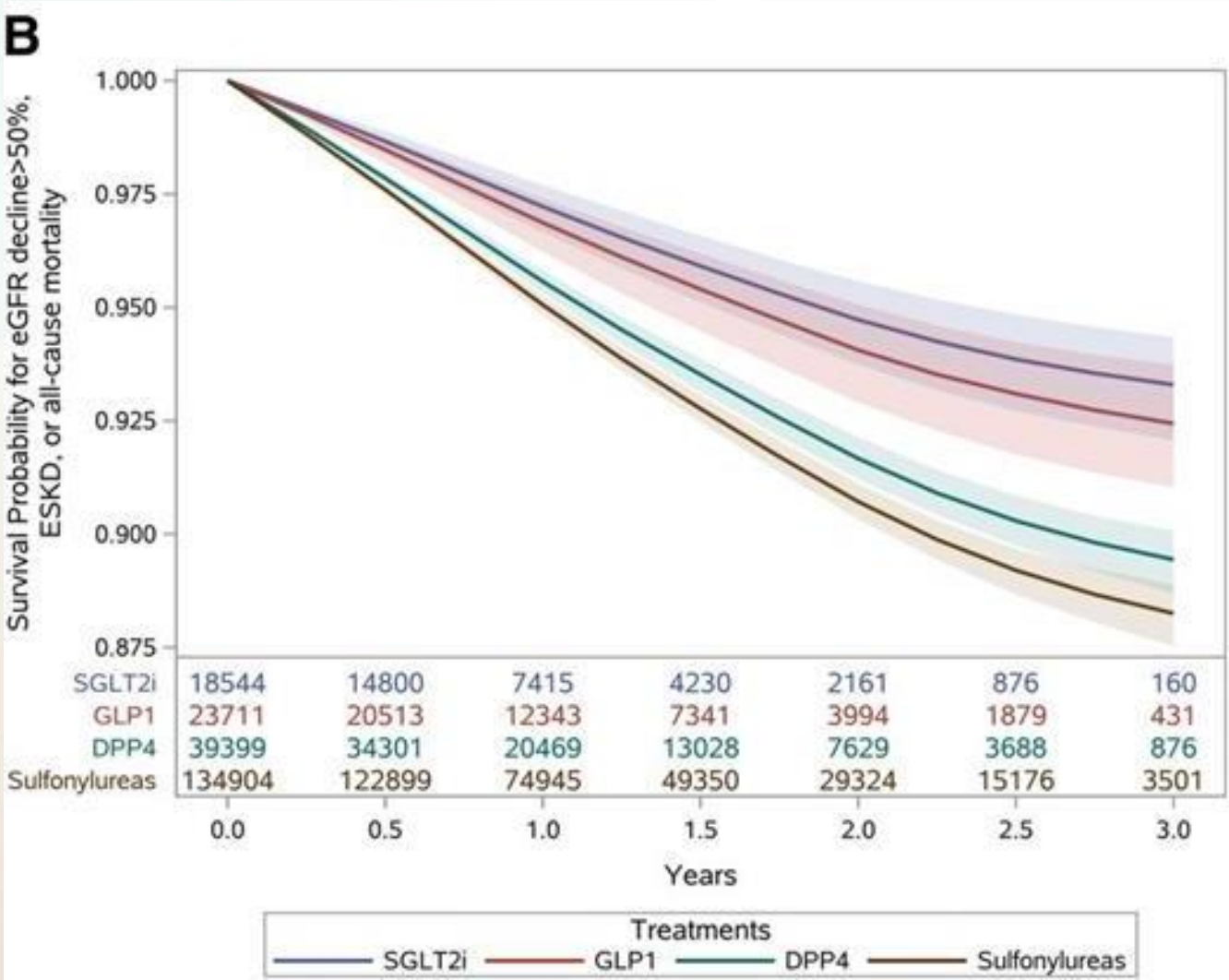
RENAL LIFECYCLE Trial - Ongoing

- RCT to access the effect of dapagliflozin on renal and cardiovascular outcomes in patients with severe CKD
- Enrolling now
- 500 dialysis patients
- 500 eGFR <20 ml/min
- 500 transplant patients

https://clinicaltrials.gov/ct2/show/NCT05374291

Real life effect

- SGLT2i, GLP1ra, DPP4, sulfonylureas on major adverse kidney events (MAKE) of eGFR decline >50%, ESKD or all cause mortality
- 216k with T2DM

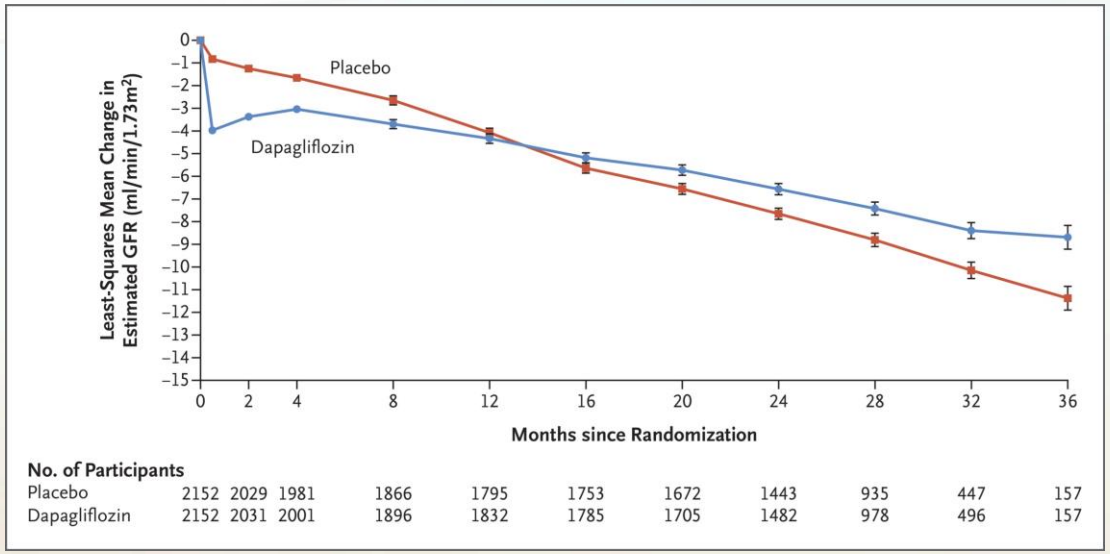


Yan Xie, Benjamin Bowe, Andrew K. Gibson, Janet B. McGill, Geetha Maddukuri, Yan Yan, Ziyad Al-Aly; Comparative Effectiveness of SGLT2 Inhibitors, GLP-1 Receptor Agonists, DPP-4 Inhibitors, and Sulfonylureas on Risk of Kidney Outcomes: Emulation of a Target Trial Using Health Care Databases. *Diabetes Care* 1 November 2020; 43 (11): 2859–2869.

It takes a village

- Routine clinic visits longer
- Communication with patients, pharmacists, endocrinology, cardiology and nephrology
- Insurance companies catching up to the data
- Patient education
- Nothing is free – it's appropriate to be aware of risks and changes in recommendations as new information comes out
- Share your knowledge

Thank you


Least-Squares Mean Change in Estimated GFR (ml/min/1.73m²)
0
−1
−2
−3
−4
−5
−6
−7
−8
−9
−10
−11
−12
−13
−14
−15
Placebo
Dapagliflozin
0 2 4 8 12 16 20 24 28 32 36
Months since Randomization
No. of Participants
Placebo 2152 2029 1981 1866 1795 1753 1672 1443 935 447 157
Dapagliflozin 2152 2031 2001 1896 1832 1785 1705 1482 978 496 157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