

# SGLT2Is in CKD: A New KDIGO Guideline 2023

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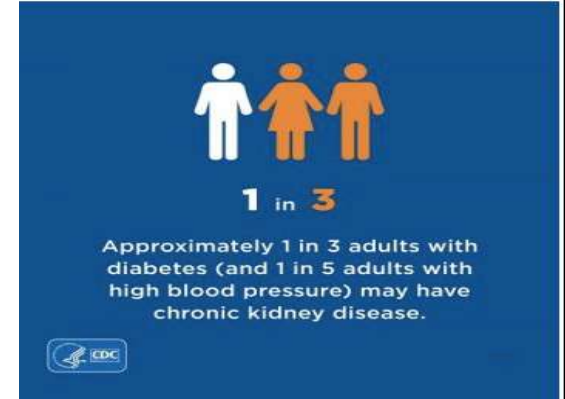
**CDC** Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™

### Kidney Facts

-Kidney diseases are the 9th leading cause of death in the United States.

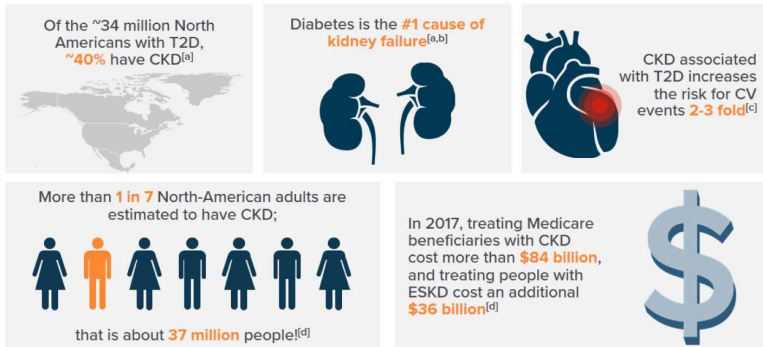
- Approximately 1 of 3 adults with diabetes has chronic kidney disease.

- Every 24 hours, 160 people with diabetes begin treatment for kidney failure.



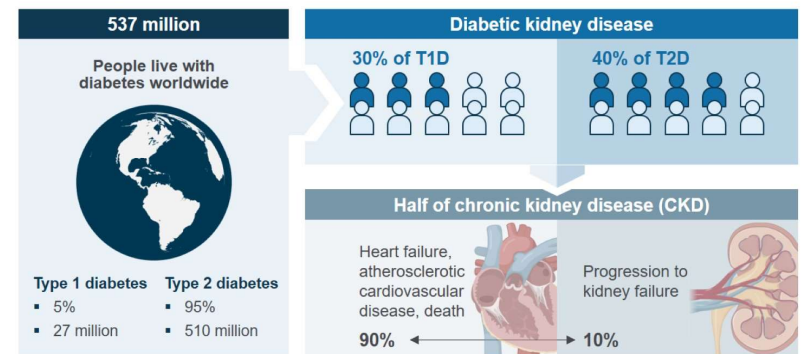
## CKD in Patients With T2D

Epidemiological Situation and Human Economic Burden



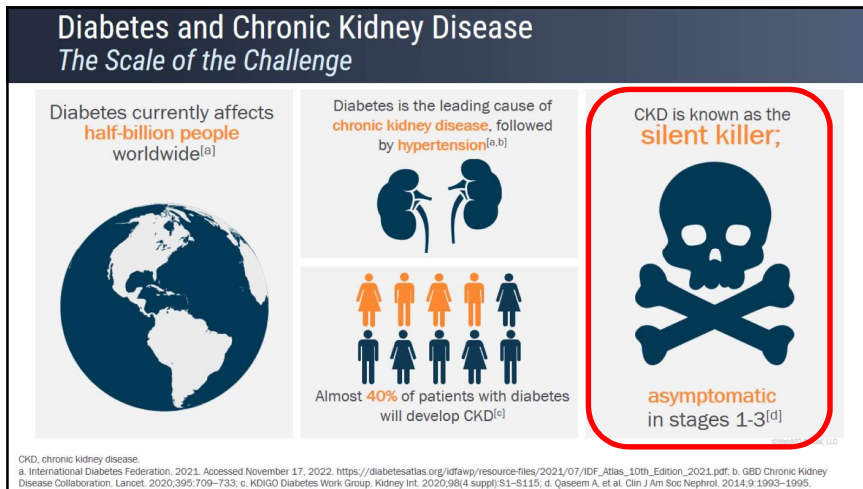
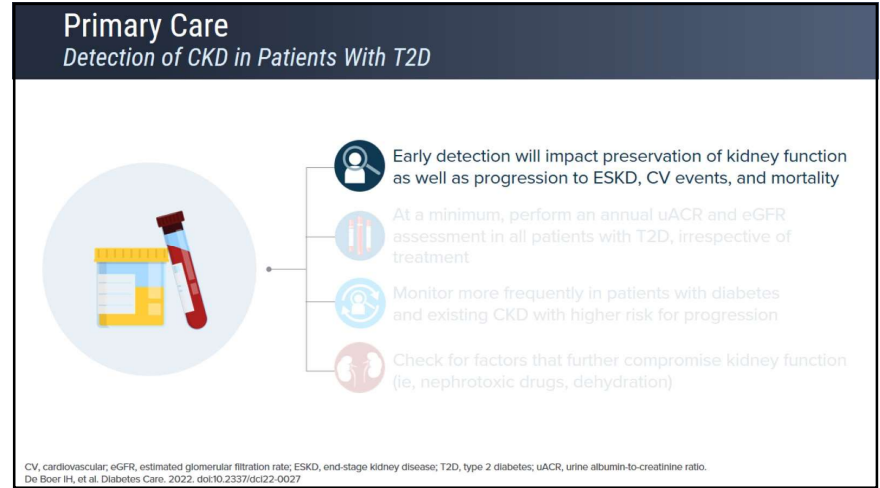
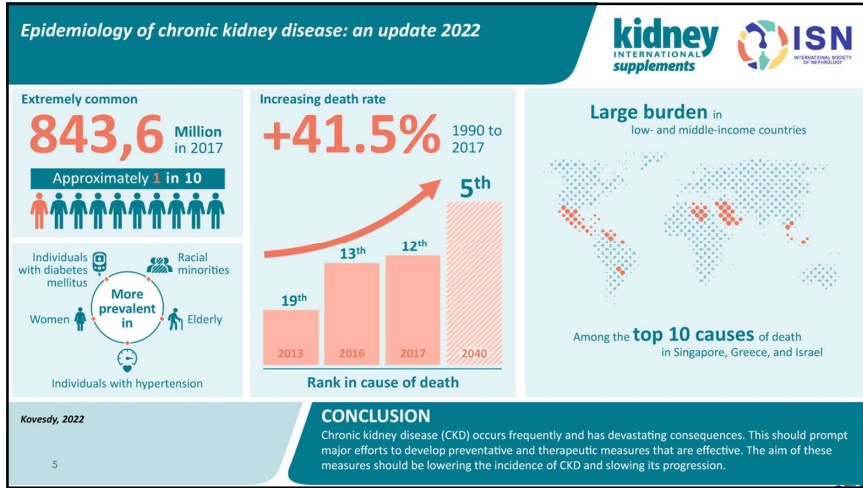
CKD, chronic kidney disease; CV, cardiovascular; ESKD, end stage kidney disease; T2D, type 2 diabetes.  
a. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>; b. <https://www.kidney.org/news/newsroom/factsheets/Diabetes-And-CKD>; c. Chen SC and Tseng CH. Rev Diabet Stud. 2013;10:88-100; d. CDC. Updated March 4, 2021. <https://www.cdc.gov/kidneydisease/prevention-risk/CKD-common-serious-costly.html>

## The Enormity of Diabetes and CKD



Tuttle KR, et al. Clin J Am Soc Nephrol. 2022;17:1092-1103.

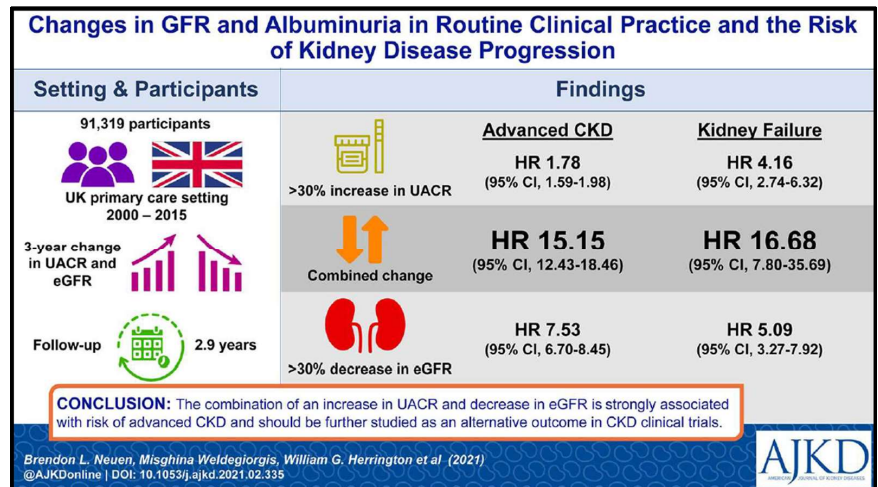
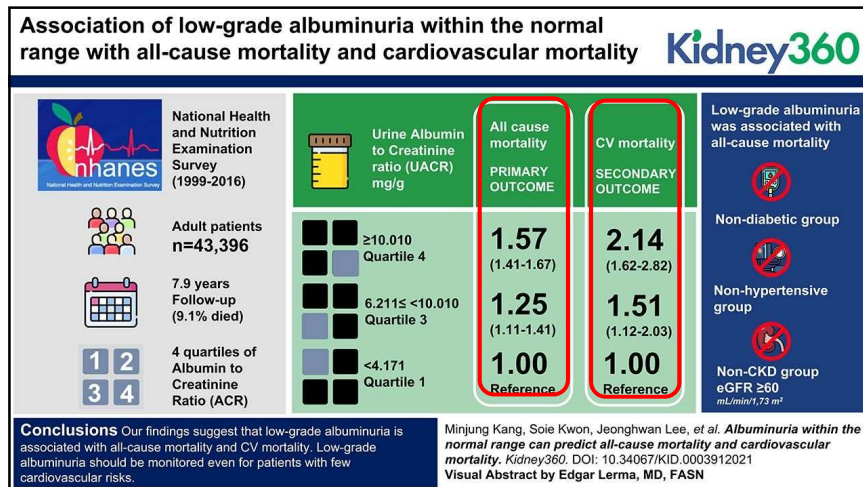
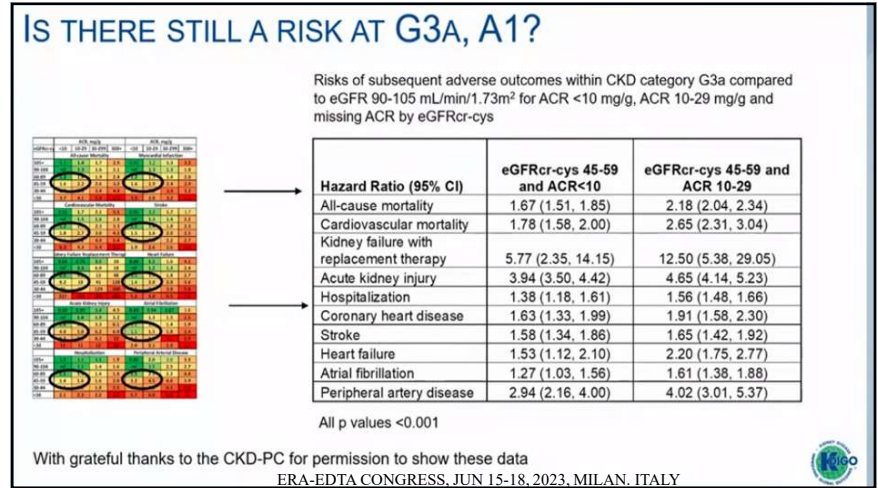
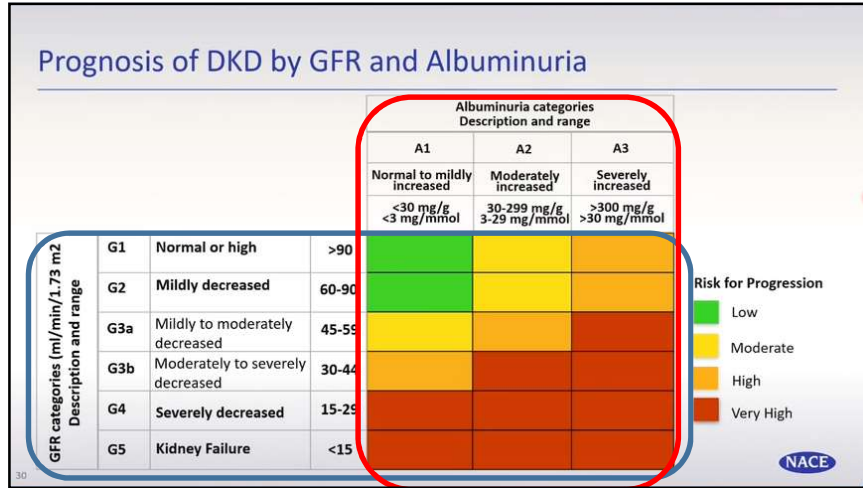
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### Prognosis of DKD by GFR and Albuminuria

GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1 Normal or high >90	G2 Mildly decreased 60-90	G3a Mildly to moderately decreased 45-59	G3b Moderately to severely decreased 30-44	G4 Severely decreased 15-29	G5 Kidney Failure <15	Albuminuria categories Description and range			Risk for Progression
							A1	A2	A3	
							Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-299 mg/g 3-29 mg/mmol	Severely increased >300 mg/g >30 mg/mmol	
							Low	Moderate	High	Very High

NACE





## KIDNEY FAILURE RISK EQUATION

- The KFRE was developed and initially validated in 8,391 adults from two Canadian provinces and validated in 721,357 individuals from 30 countries in 4 continents.
- In the validation study, cohorts from both general populations and nephrology clinic settings were included.
- Both the 4 variable and the 8 variable KFREs were accurate (pooled C statistics 0.90 at 2 years, and 0.88 at 5 years).
- Discrimination was excellent (C statistic >0.80 in 28/30 cohorts), and the use of a calibration factor improved calibration for some regions outside of North America.

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## Adult eGFR Calculator (NFK)

Serum Creatinine:   mg/dL  µmol/L

Serum Cystatin C:  mg/L

Age:  Years

Gender:  Male  Female

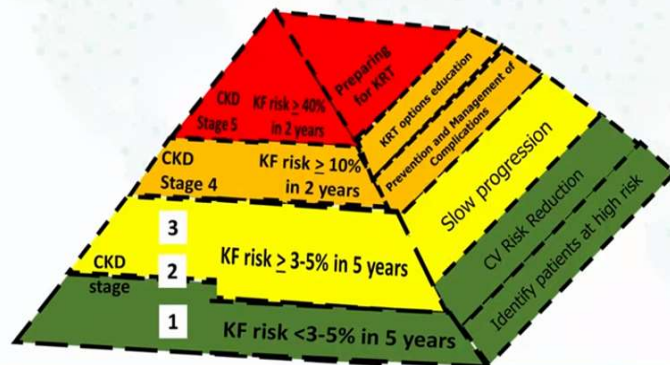
Standardized Assays:  Yes  No  Not Sure

Adjust for body surface area:  Yes  No  Not Sure

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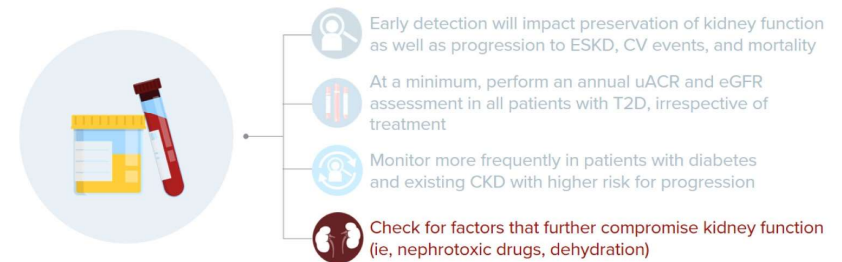
## THE ROLE OF RISK PROGNOSTICATION TOOLS

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## Primary Care

Detection of CKD in Patients With T2D



CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; T2D, type 2 diabetes; uACR, urine albumin-to-creatinine ratio.  
De Boer IH, et al. Diabetes Care. 2022. doi:10.2337/dci22-0027

# K DIGO (July 2023)

## 3.1. CKD treatment and risk modification

**Practice Point 3.1: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications (Figure 14).**

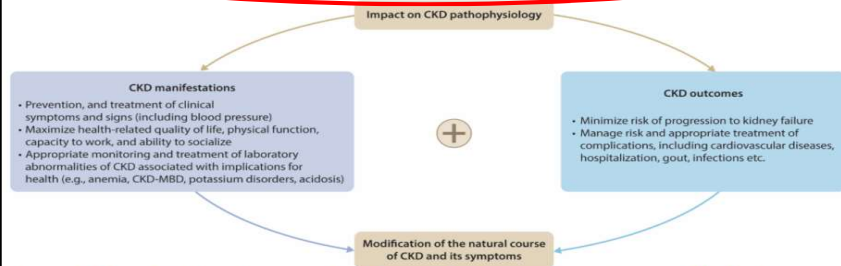
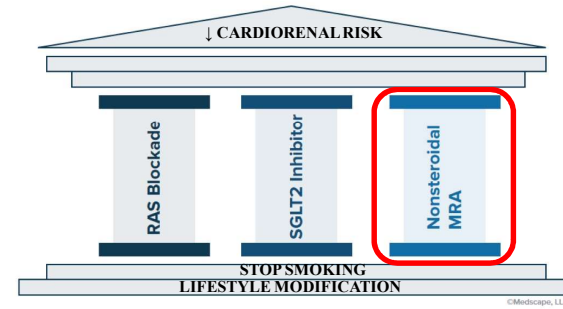


Figure 14. Chronic kidney disease (CKD) treatment and risk modification. CKD-MBD, chronic kidney disease-mineral and bone disorders

## 3 Pillars of Therapy to Reduce Cardiorenal Risk



NS-MRA, nonsteroidal mineralocorticoid antagonist; RAS, renin-angiotensin system.

## FIDELITY Pooled Analysis Efficacy Outcomes

Outcome	Finerenone (n=6819) n (%)	Placebo (n=6807) n (%)	HR (95% CI)	P value
eGFR ≥57% composite kidney outcome	360 (5.3)	465 (7.1)	0.77 (0.67, 0.88)	.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71, 0.99)	.039
ESKD*	151 (2.3)	188 (2.9)	<b>0.80 (0.64, 0.99)</b>	.040†
eGFR < 15 mL/min/1.73 m <sup>2</sup>	195 (3.0)	237 (3.6)	0.81 (0.67, 0.98)	.026†
≥ 5% decrease in eGFR from baseline	257 (3.9)	361 (5.5)	0.70 (0.60, 0.83)	<.00001
Renal death	2 (< 0.1)	4 (< 0.1)	0.53 (0.10, 2.91)	–

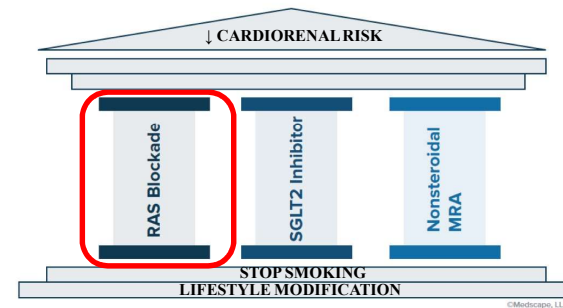
Outcome	Finerenone (n=6819) n (%)	Placebo (n=6807) n (%)	HR (95% CI)	P value
Composite CV outcome	825 (12.7)	939 (14.4)	0.86 (0.78, 0.95)	.0018
HHF	256 (3.9)	325 (5.0)	<b>0.78 (0.66, 0.92)</b>	.0030
CV death	322 (4.9)	364 (5.6)	0.88 (0.76, 1.02)	.092
Non-fatal MI	173 (2.7)	189 (2.9)	0.91 (0.74, 1.12)	.36
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82, 1.2)	.95

Finerenone significantly reduced the incidence of all components of the kidney composite outcome (except renal death\*)

The CV benefits of finerenone: primarily driven by reduction in HHF and CV death

Similar incidences of investigator-reported treatment-emergent adverse events were observed between treatment groups. Hyperkalemia-related adverse events occurred more frequently with finerenone (14.0%) vs placebo (6.9%), but no hyperkalemia-related adverse events were fatal and only a small proportion led to permanent treatment discontinuation [1.7% (incidence rate 0.66 per 100 patient-years) and 0.6% (incidence rate 0.22 per 100 patient-years), respectively] or hospitalization (0.9% and 0.2%, respectively).  
 CV, cardiovascular; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; MI, myocardial infarction.  
 \* ≥ 57% decrease in eGFR is equivalent to doubling of serum creatinine.  
 † Only 6 patients experienced renal death. \*\* Initiation of chronic dialysis for ≥ 90 days or kidney transplant.  
 ‡ Analysis for P value not prespecified. †† Confirmed by 2 eGFR measurements ≥ 4 weeks apart.  
 Agarwal R, et al. Eur Heart J. 2022;43:474–484.

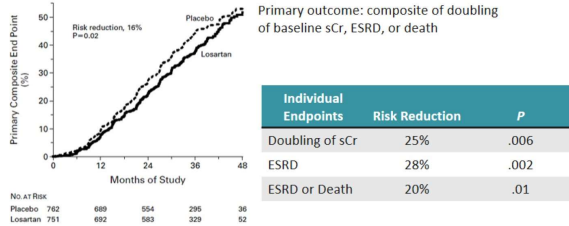
## 3 Pillars of Therapy to Reduce Cardiorenal Risk



NS-MRA, nonsteroidal mineralocorticoid antagonist; RAS, renin-angiotensin system.

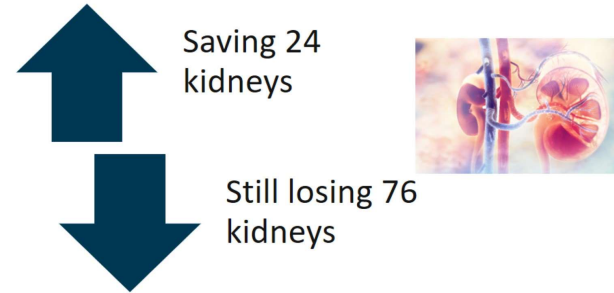
## RENAAL Trial

Double-blind RCT in 1513 patients with T2D and nephropathy on antihypertensive treatment\* randomized to losartan 50 to 100 mg once daily or placebo



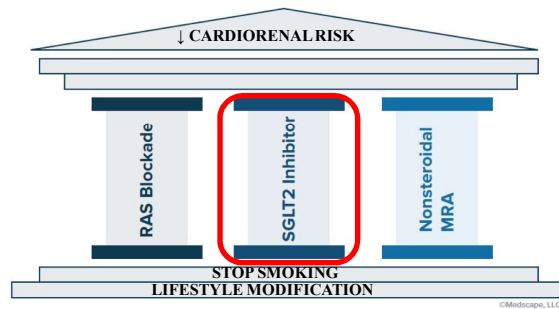
\*Conventional antihypertensive treatment at that time consisted of: calcium channel blockers, diuretics,  $\alpha$ -blockers,  $\beta$ -blockers, centrally-acting agents.  
Brenner BM, et al. *N Engl J Med*. 2001;345:861-869.

## There's Still More Work To Do!

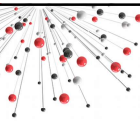


Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

## 3 Pillars of Therapy to Reduce Cardiorenal Risk



NS-MRA, nonsteroidal mineralocorticoid antagonist; RAS, renin-angiotensin system.



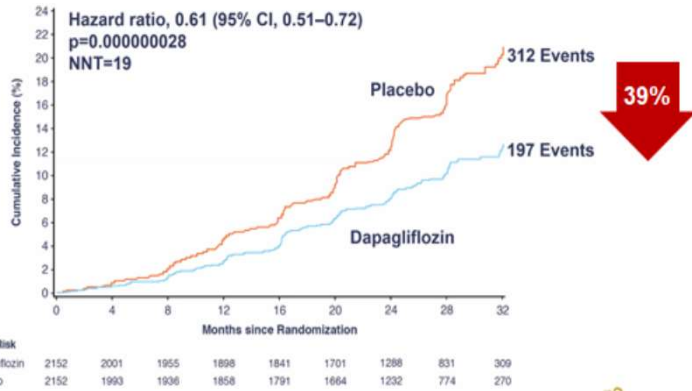
## Dapagliflozin in Patients with Chronic Kidney Disease DAPA-CKD

Hiddo L. Heerspink  
Department of Clinical Pharmacy and Pharmacology  
University Medical Center Groningen

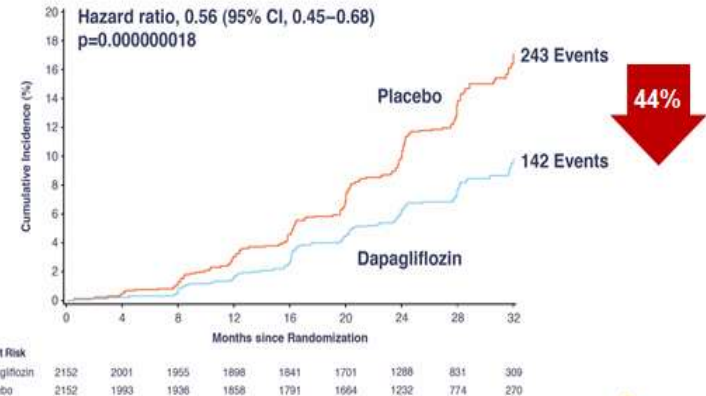


ESC Congress  
Amsterdam 2020

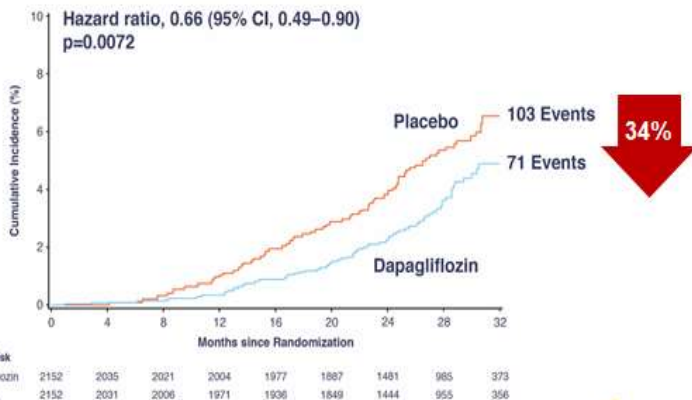
**Primary outcome:  
Sustained  $\geq 50\%$  eGFR decline, ESKD, renal or cardiovascular death**



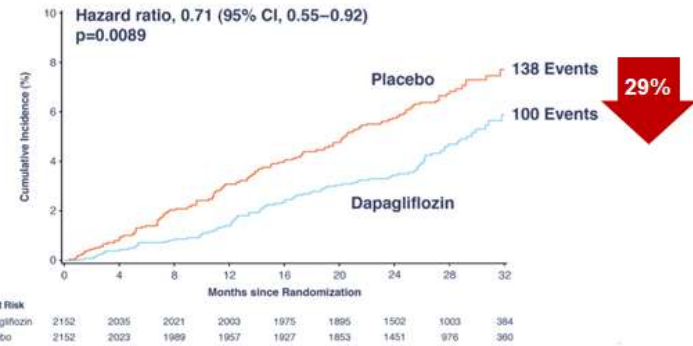
**Secondary outcome:  
Sustained  $\geq 50\%$  eGFR decline, ESKD, renal death**

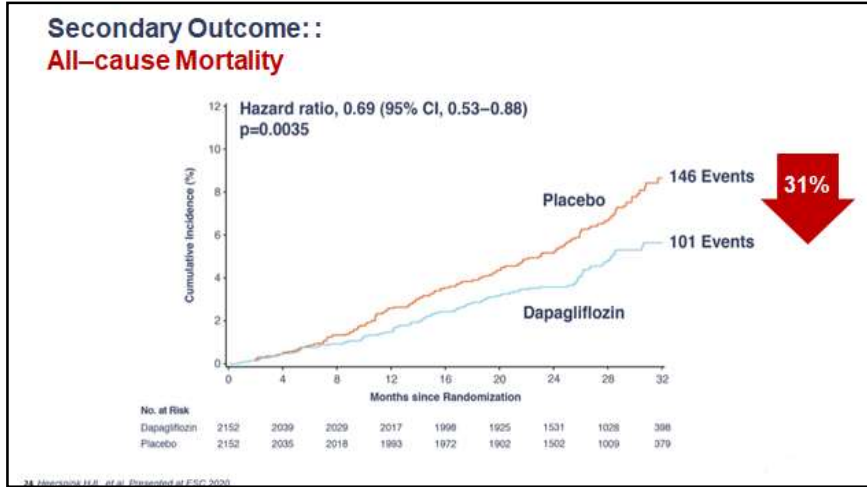


**Chronic dialysis, kidney transplantation, renal death**



**Secondary Outcome:  
CV Death/Hospitalization<sub>HF</sub>**





### EMPA KIDNEY ANNOUNCED IN 2022

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

#### Empagliflozin in Patients with Chronic Kidney Disease

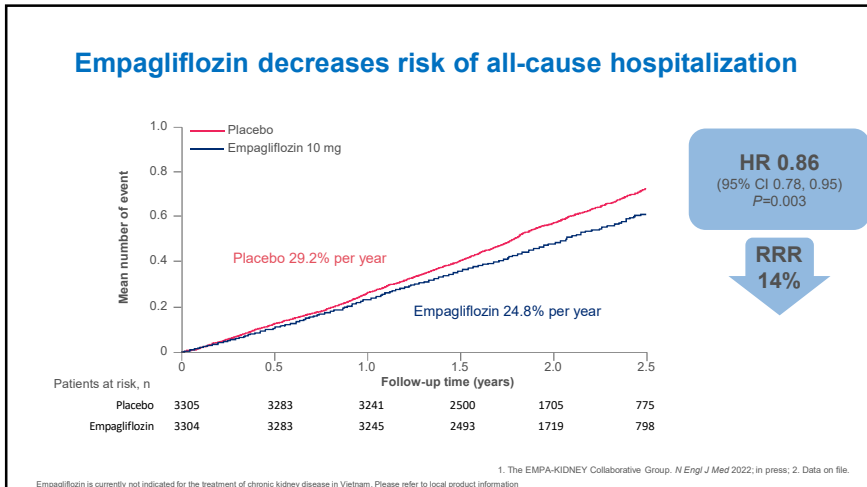
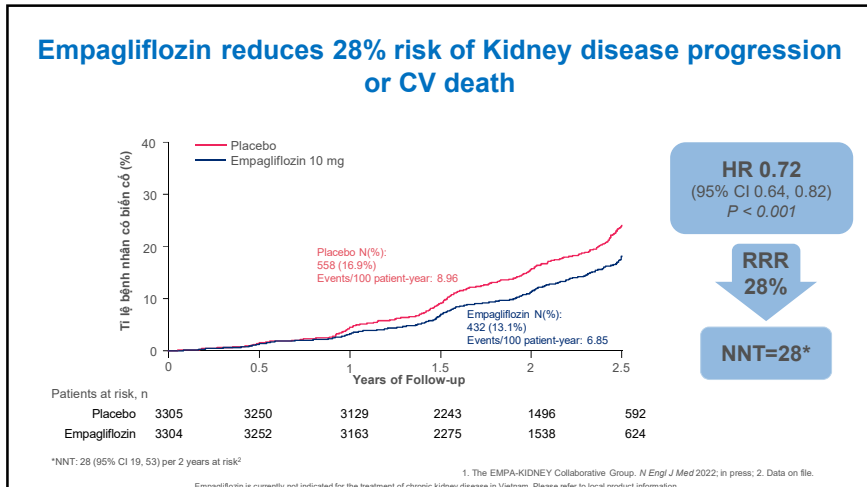
The EMPA-KIDNEY Collaborative Group\*

- Announced on March 16, the decision to stop the phase 3 trial is based on the recommendation of the trial's Independent Data Monitoring Committee and Eli Lilly and Company expects to present full results at an upcoming medical conference.
- Landmark trial was designed to include patients with mildly to severely reduced eGFR, with normal and increased levels of albumin, with and without diabetes, and with CKD attributable to a wide range of underlying causes.

**EMPA-KIDNEY To Be Stopped Early Due to 'Clear Positive Efficacy' with Empagliflozin**

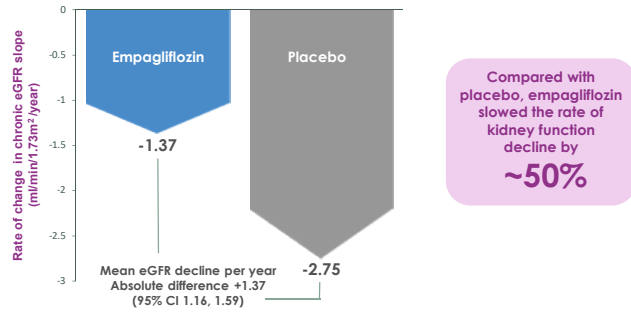
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1. <https://www.practicalcardiology.com/view/cardiology-month-in-review-march-2022?page=3>  
2. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; in press





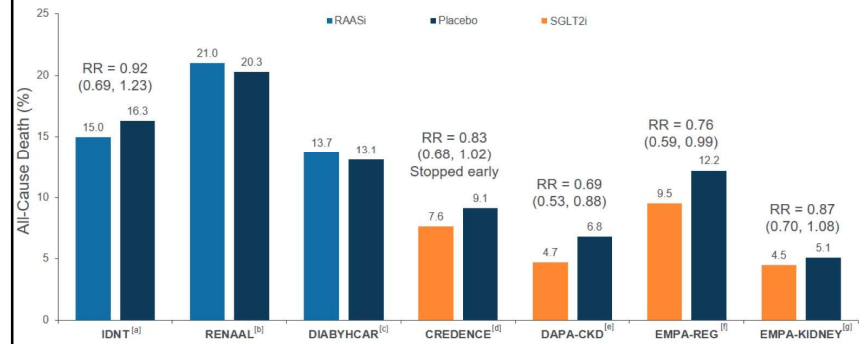
**Overall, compared with placebo, empagliflozin approximately halved the rate of progression of CKD\***



\*Mean annual rates of change in eGFR from 2 months to the final follow-up visit ('chronic slopes') by treatment allocation were estimated using shared parameter models. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117

Empagliflozin is currently not indicated for the treatment of chronic kidney disease in Vietnam. Please refer to local product information

**Patients With CKD**  
No Effect on Mortality With RAASi But Notable Reductions With SGLT2i



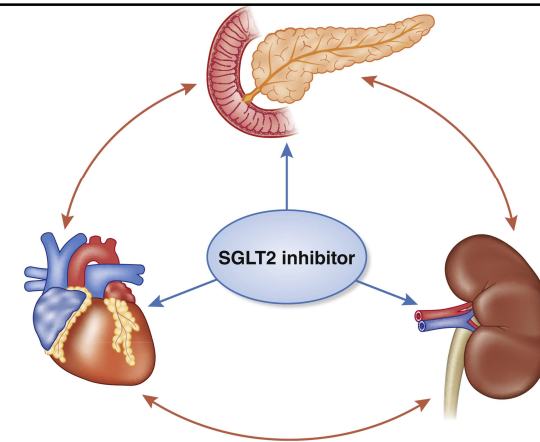
a. Lewis EJ, et al. *N Engl J Med*. 2001;345:851-860. b. Brenner BM, et al. *N Engl J Med*. 2001;345:861-869. c. Marre M, et al. *BMJ*. 2004;328:495. d. Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306. e. Heerspink HJL, et al. *Eur Heart J*. 2021;42:1216-1227. f. Wanner C, et al. *Circulation*. 2018;137:119-129. g. The EMPA-KIDNEY Collaborative Group. *Herrington WG, et al. N Engl J Med*. 2023;388:117-127

## K DIGO (July 2023)

**Recommendation 3.6.1:** We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR  $\geq 20$  ml/min per 1.73 m<sup>2</sup> with an SGLT2i (1A).

**Recommendation 3.6.2:** We recommend treating adults with CKD and heart failure or eGFR  $\geq 20$  ml/min per 1.73 m<sup>2</sup> with urine albumin-to-creatinine ratio (ACR)  $\geq 200$  mg/g with an SGLT2i (1A).

**Recommendation 3.6.3:** We suggest treating adults with eGFR  $\geq 20$  to 45 ml/min per 1.73 m<sup>2</sup> with urine ACR  $< 200$  mg/g with an SGLT2i (2B).



Masaomi Nangaku, et al (Oct 2020). More reasons to use SGLT2 inhibitors: EMPEROR-Reduced and DAPA-CKD. *KJ* Published: October 14, 2020 DOI: <https://doi.org/10.1016/j.kint.2020.10.002>

