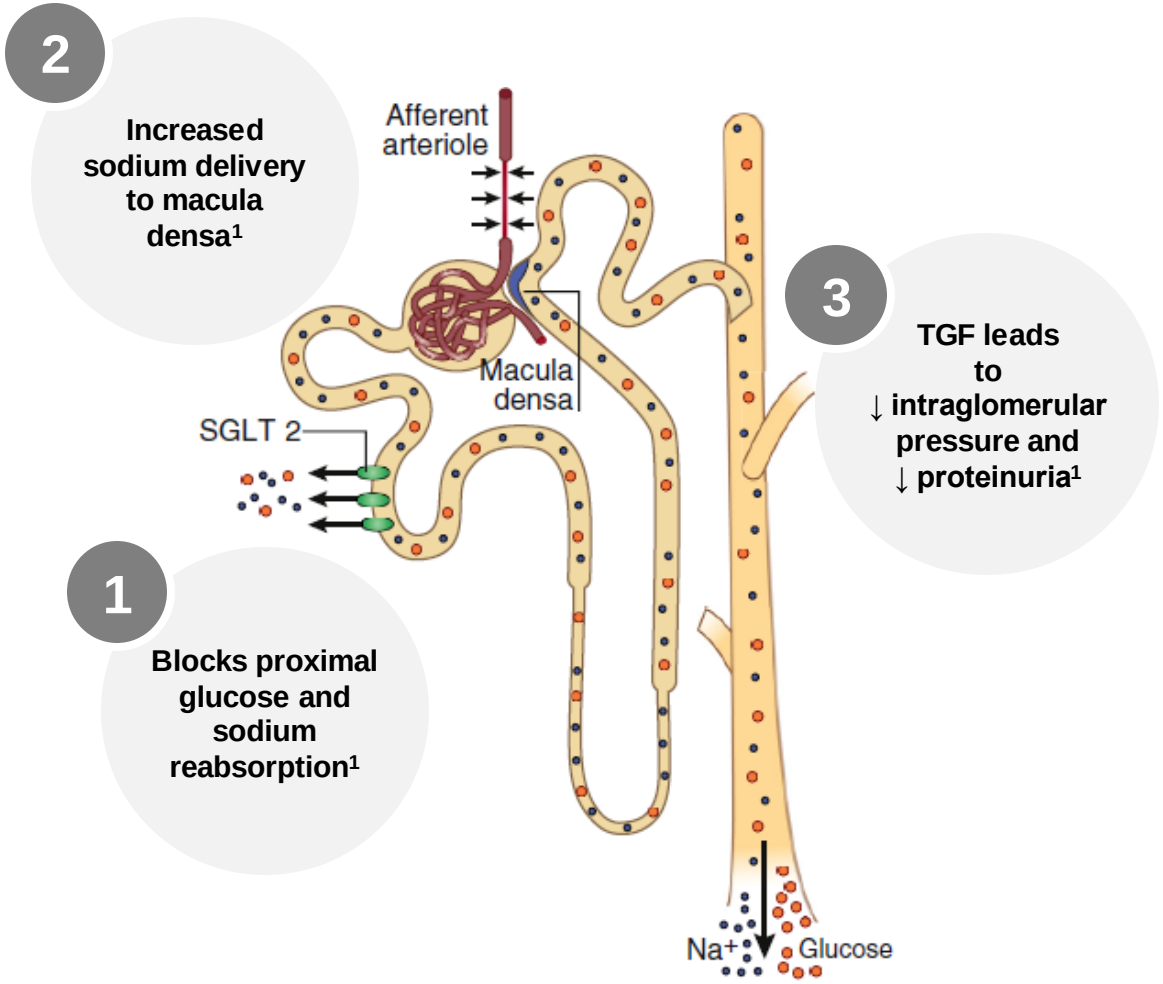
Mechanism of Action

SGLT2 Inhibition has a Number of Potential Direct and Downstream Effects which may Result in Beneficial Effects on Kidney Function[1]



As CKD progresses elevated intraglomerular pressure is a common feature and driver of several CKD etiologies[2,3]

Tubuloglomerular feedback restoration with SGLT2i:

- Inhibits proximal glucose reabsorption[1]
- Blocks proximal sodium reabsorption[1]
- Leads to increased distal delivery of sodium to the macula densa[1]
- TGF restoration resulting in decreased glomerular hyperfiltration and hydrostatic pressure[1,4,5]

Additional downstream effects:[1]

- Decreased urinary albumin excretion may reduce pro-inflammatory pathway activation and direct tubular toxicity
- Improved cardiac function and increased hematocrit concentration may result in increased oxygen delivery to the kidney and improvements in renal hypoxia

Na = sodium; SGLT2 = sodium–glucose co-transporter 2; TGF = tubuloglomerular feedback.

1. Heerspink HJL et al. *Kidney Int*. 2018;94:26-39; 2. Helal I et al. *Nat Rev Nephrol*. 2012;8:293-300; 3. Palatini P. *Nephrol Dial Transplant*. 2012;27:1708-1714. 4. Schefold JC et al. *Nat Rev Nephrol*. 2016;12:610-623; 5. Zelniker TA et al. *J Am Coll Cardiol*. 2018;72:1845-1855.

Potential Effects By Which SGLT-2 Inhibition Improves Renal Outcomes

SGLT-2 INHIBITION

Reduce Glomerular Pressure[1]
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity[3]
↓SNS activity[4]

Inflammation/Fibrosis Reductions[1,2]
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal Workload and Hypoxia[1,2]
↓Solute transport
↓Oxygen demand

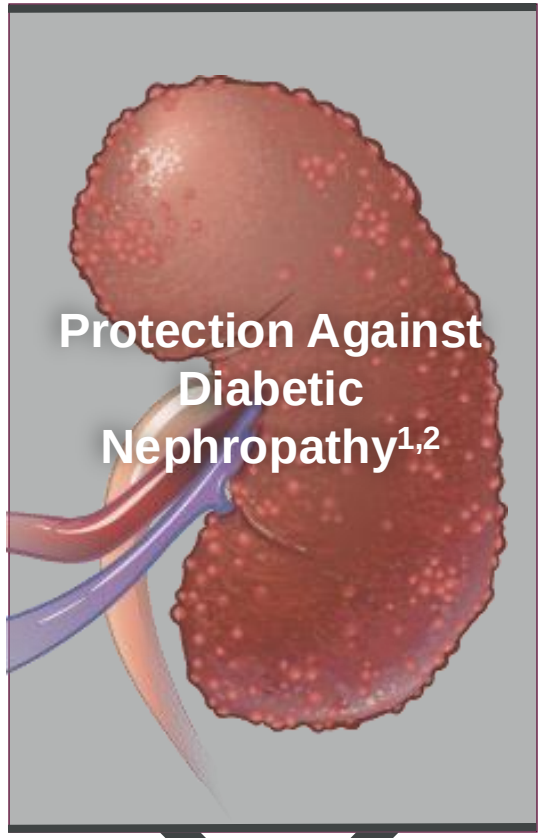
CLINICAL EFFECTS

Stabilization of eGFR[2]

↓Blood Pressure[1]

↓Tubular/Glomerular Injury[1,2]
↓Albuminuria

↓Renal Ischemic Injury[1]
↑Hb/hematocrit[2]

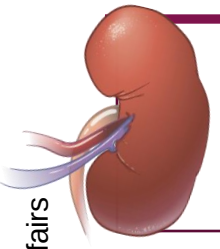


Preserved Renal Function[2]

eGFR=estimated glomerular filtration rate; Hb=hemoglobin; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

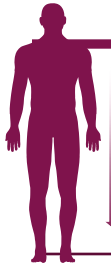
1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 4. Sano M. *J Cardiol*. 2018;71(5):471-476.

Evidence Supports Glycemic and Non-glycemic Effects of SGLT-2i

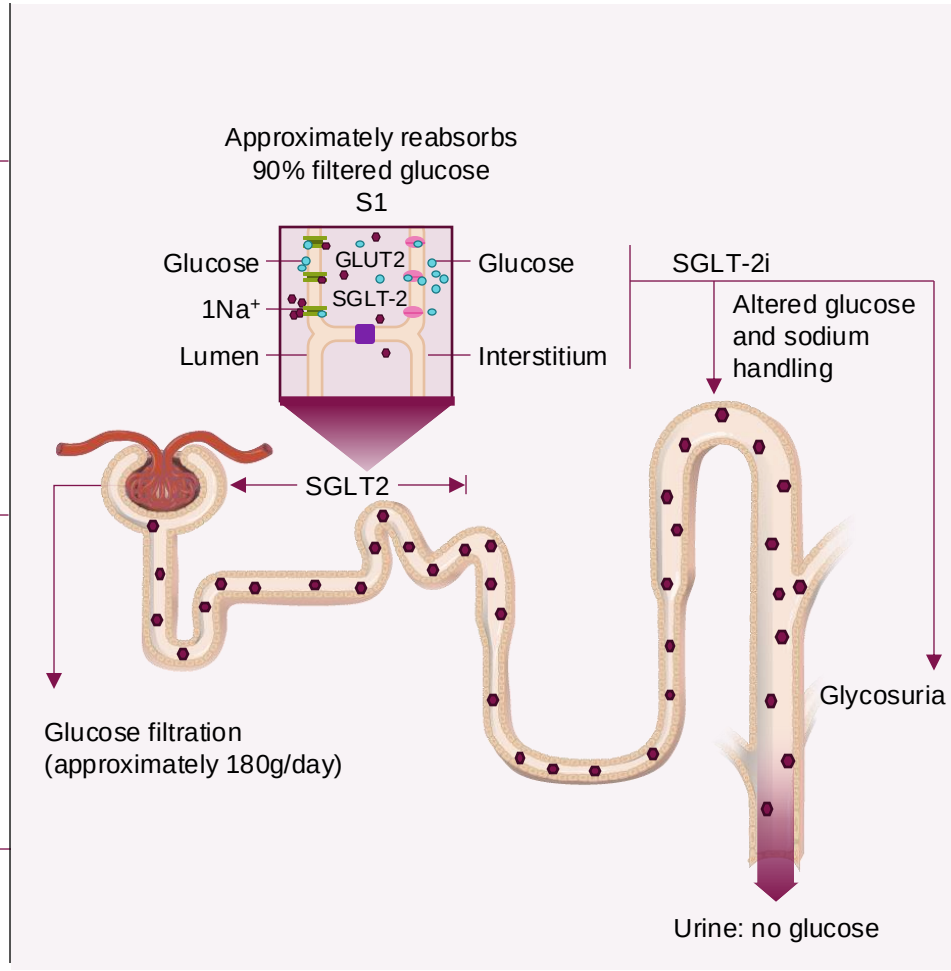


- Decreased glucose and sodium reabsorption[1,2]
- Increased delivery of sodium to the distal tubule[1]

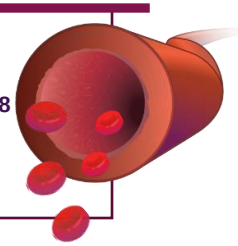
- Decreased plasma glucose[3,4]
- Increased β-cell function[3,4]



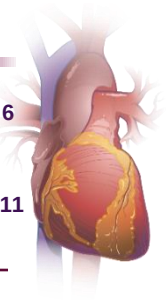
- Decreased body weight[5,6]
- Decreased fat mass[5,6]
- Increased insulin sensitivity[7]



- Decreased blood pressure[7]
- Decreased plasma volume[6,8]
- Increased hematocrit[6]



- Decreased preload and afterload[6]
- Increased cardiac efficiency[9,10]
- Decreased cardiac remodeling[10,11]

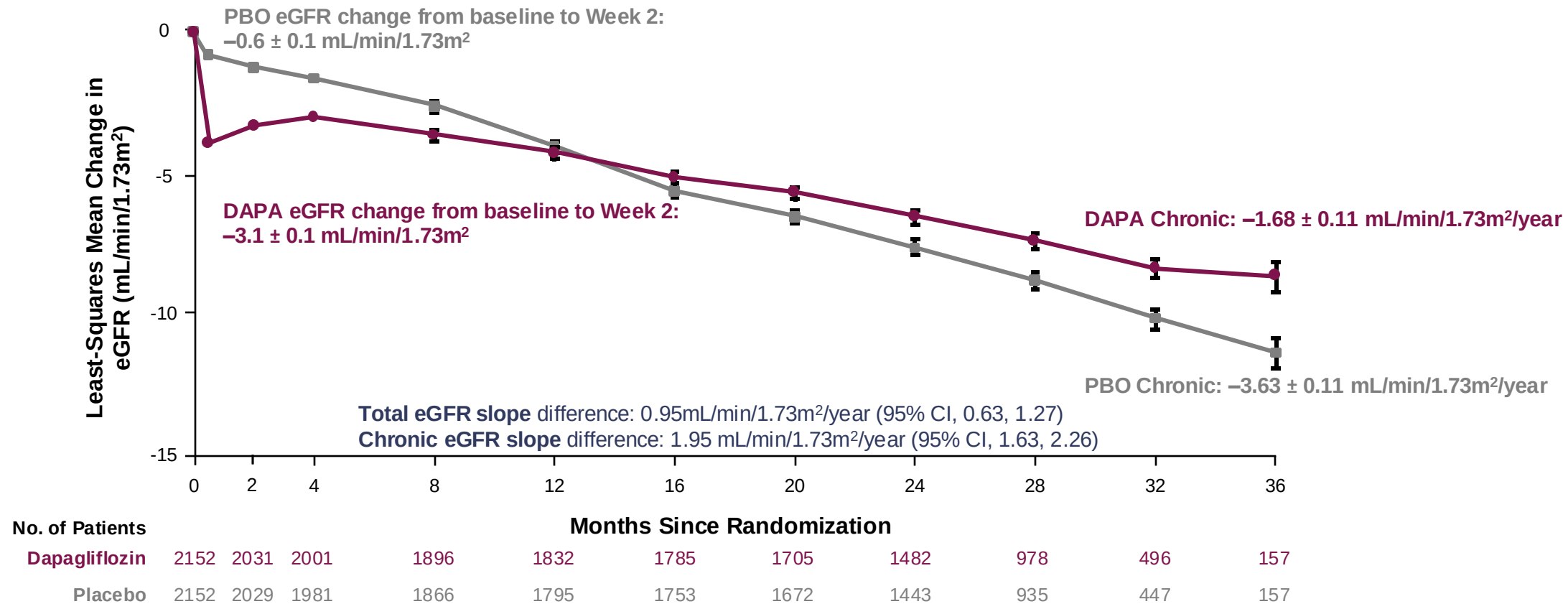


Potential mechanisms by which SGLT-2 inhibition reduces risk for heart failure hospitalization are not fully understood and research is under way

Dapagliflozin is not indicated for weight loss or hypertension.

1. FARXIGA® (dapagliflozin) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020. 2. Eickhoff MK, et al. *J Clin Med*. 2019;8(6);779. 3. Merovci A, et al. *J Clin Endocrinol Metab*. 2015;100(5):1927-1932. 4. Kaneto H, et al. *J Diabetes*. 2017;9(3):219-225. 5. Bolinder J, et al. *J Clin Endocrinol Metab*. 2012;97(3):1020-1031. 6. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 7. Kalra S, et al. *Indian J Endocrinol Metab*. 2017;21(1):210-230. 8. Lambers Heerspink HJ, et al. *Diabetes Obes Metab*. 2013;15(9):853-862. 9. Verma S, et al. *JACC Basic Transl Sci*. 2018;3(5):575-587. 10. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 11. Lee TM, et al. *Free Radic Biol Med*. 2017;104:298-310.

DAPA-CKD: After Initial Decrease in eGFR, Annual Change in Mean eGFR Was Less With Dapagliflozin Compared With Placebo[1,2]

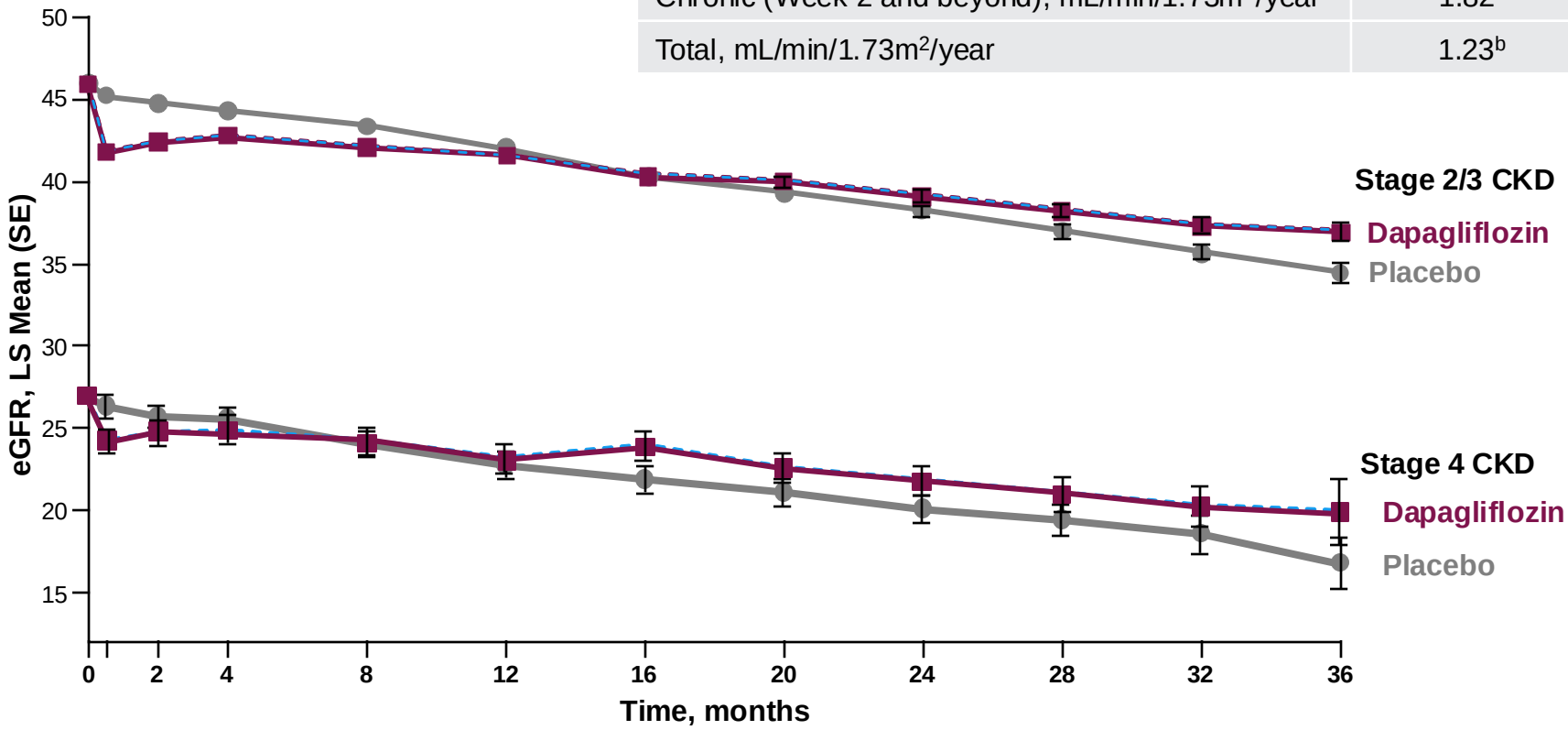


BL = baseline; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL et al. *Lancet Diabetes Endocrinol*. 2021;9(11):743-754., 3Konishi H, et al. J Endocrinol Metab 2018;8:106–112; 4. Cherney DZI, et al. Lancet Diabetes Endocrinol 2020;8:582–593

DAPA-CKD: Initial Decrease in eGFR Was Proportional to the Baseline eGFR

Between-group slope difference[a]	Stage 4 CKD	Stage 2/3 CKD
Acute (2 weeks), mL/min/1.73m^2/2 weeks	-1.42[b]	-2.56
Chronic (Week 2 and beyond), mL/min/1.73m^2/year	1.82[c]	1.95
Total, mL/min/1.73m^2/year	1.23[b]	0.89



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.

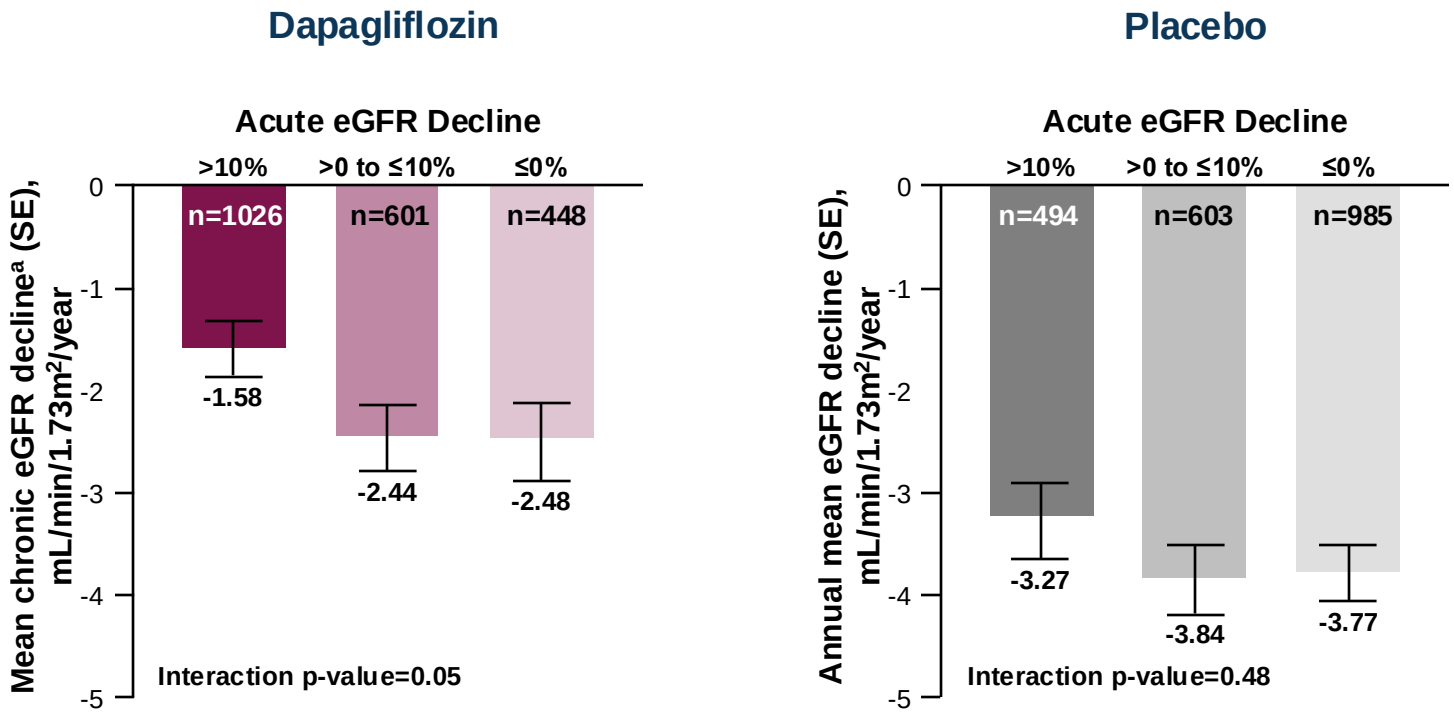
[a]Dapagliflozin vs placebo; [b]p=0.005 vs PBO; [c]p<0.0001 vs PBO.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LS = least squares.

Chertow GM et al. *J Am Soc Nephrol.* 2021;32(9):2352-2361.

DAPA-CKD: Dapagliflozin Slowed Chronic eGFR Decline[a] Versus Placebo, Regardless of Magnitude of Acute eGFR Decline

Chronic eGFR decline[a] by acute eGFR decline category



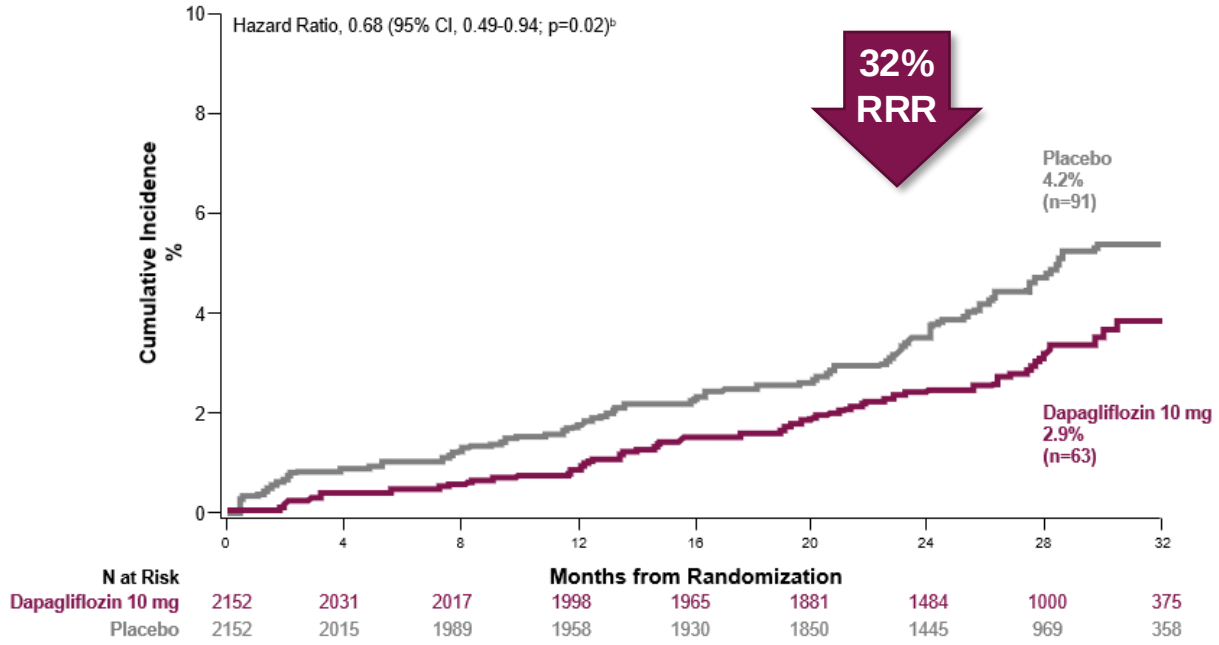
A >10% acute eGFR decline with dapagliflozin was associated with greater attenuation of chronic eGFR decline and no increased risk of primary[b] or secondary renal-specific outcomes[c]

[a]Rate of change from Month 2 to end of treatment; [b]Composite of sustained ≥50% eGFR decline, ESKD, renal or CV death; [c]Composite of sustained ≥50% eGFR decline, ESKD, or renal death.

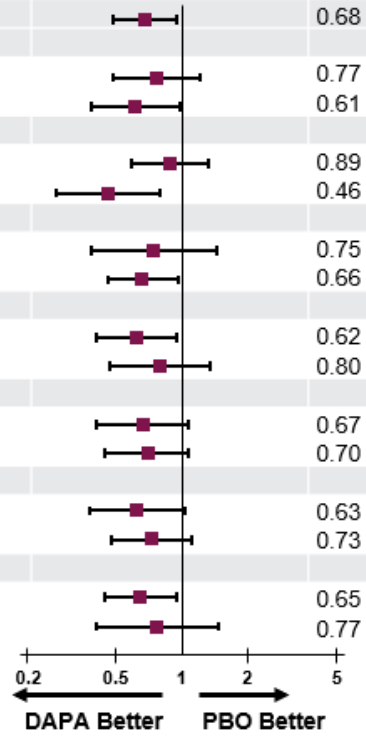
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; SE = standard error.

Jongs N et al. *J Am Soc Nephrol*. 2022;33(11):2094-2107.

DAPA-CKD: Dapagliflozin Reduced the Risk of Acute Kidney Injury Compared With Placebo



	Events/100 patient years		Hazard ratio (95% CI)	P value for interaction
	DAPA	PBO		
Overall	1.4	2.0	0.68 (0.49-0.94)	
Age (years)				**0.45**
≤65	1.3	1.7	0.77 (0.49-1.21)	
>65	1.5	2.4	0.61 (0.39-0.98)	
Gender				**0.05**
Male	1.4	1.6	0.89 (0.59-1.33)	
Female	1.3	2.8	0.46 (0.27-0.79)	
T2D				**0.77**
No	1.1	1.5	0.75 (0.39-1.43)	
Yes	1.5	2.2	0.66 (0.46-0.96)	
eGFR				**0.49**
<45 mL/min/1.73 m^2	1.4	2.3	0.62 (0.41-0.94)	
≥45 mL/min/1.73 m^2	1.3	1.7	0.80 (0.47-1.34)	
UACR				**0.86**
≤1000 mg/g	1.2	1.8	0.67 (0.41-1.07)	
>1000 mg/g	1.6	2.2	0.70 (0.45-1.08)	
Diuretic use				**0.66**
No	1.0	1.5	0.63 (0.38-1.04)	
Yes	1.9	2.6	0.73 (0.48-1.11)	
Heart failure				**0.71**
No	1.1	1.7	0.65 (0.45-0.95)	
Yes	3.3	4.3	0.77 (0.41-1.47)	



There was no heterogeneity in the effect of dapagliflozin on AKI based on age, diabetes status, baseline eGFR, degree of albuminuria, diuretic treatment, or presence of heart failure

1.Heerspink HJL et al. *Kidney Int*. 2022;101(1):174-184, 2. Konishi H, et al. J Endocrinol Metab 2018;8:106–112, 3. Cherney DZI, et al. Lancet Diabetes Endocrinol 2020;8:582–5931. , 4.Van Bommel EJ, et al. Clin J Am Soc Nephrol 2017;12:700–710; 5. Seidu S, et al. Prim Care Diabetes 2018;12:265–283; 6. Cherney DZ, et al. Circulation 2014;129:587–597; 7. Heerspink HJL, et al. Diabetes Care 2011;34(Suppl. 2):S325–S329

2024 KDIGO Evaluation and Management of CKD Guideline: Summary of SGLT2 Inhibitor Use

- **SGLT2i** is recommended in patients with T2D, CKD, and an eGFR ≥20 mL/min/1.73 m^2 (1A)[a]

  Practice Point:[b,c]

  - *Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 mL/min/1.73 m^2, unless it is not tolerated or KRT is initiated*
  - *It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis)*

- **SGLT2i** is recommended in adults with CKD for the following (1A):[a]
  - eGFR ≥20 mL/min/1.73 m^2 with UACR ≥200 mg/g, or
  - Heart failure, irrespective of level of albuminuria

***Practice Point*:[b]**

- ***SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy***

- **SGLT2i** is suggested in adults with eGFR ≥20 to 45 mL/min/1.73 m^2 with UACR <200 mg/g (2B)[a]

[a]Level 1 = "We recommend" and Grade A = High certainty of evidence. Level 2 = "We suggest" and Grade B = Moderate certainty ofevidence; [b]This is a practice point - a consensus-based statement that represents the expert judgment of the Work Group and is not graded. It should be considered as expert guidance and used by clinicians as they see fit to inform the care of patients; [c]The 2024 KDIGO Guideline highlights that these practice points from the 2022 KDIGO Diabetes Management in CKD Guideline are also relevant for people with CKD without diabetes.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; KRT = kidney replacement therapy; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2D = type 2 diabetes; UACR = urine albumin-to-creatinine ratio.

KDIGO CKD Work Group. *Kidney Int.* 2024;105(4S): S117-S314.

AstraZeneca

Ad uso esclusivo del Medical Affairs