Reducing all-cause mortality as a treatment goal in all CKD patients
Feasible or not?

Myrto Giannopoulou MD, PhD
Renal Consultant
Evagelismos Hospital, Athens

Disclosures

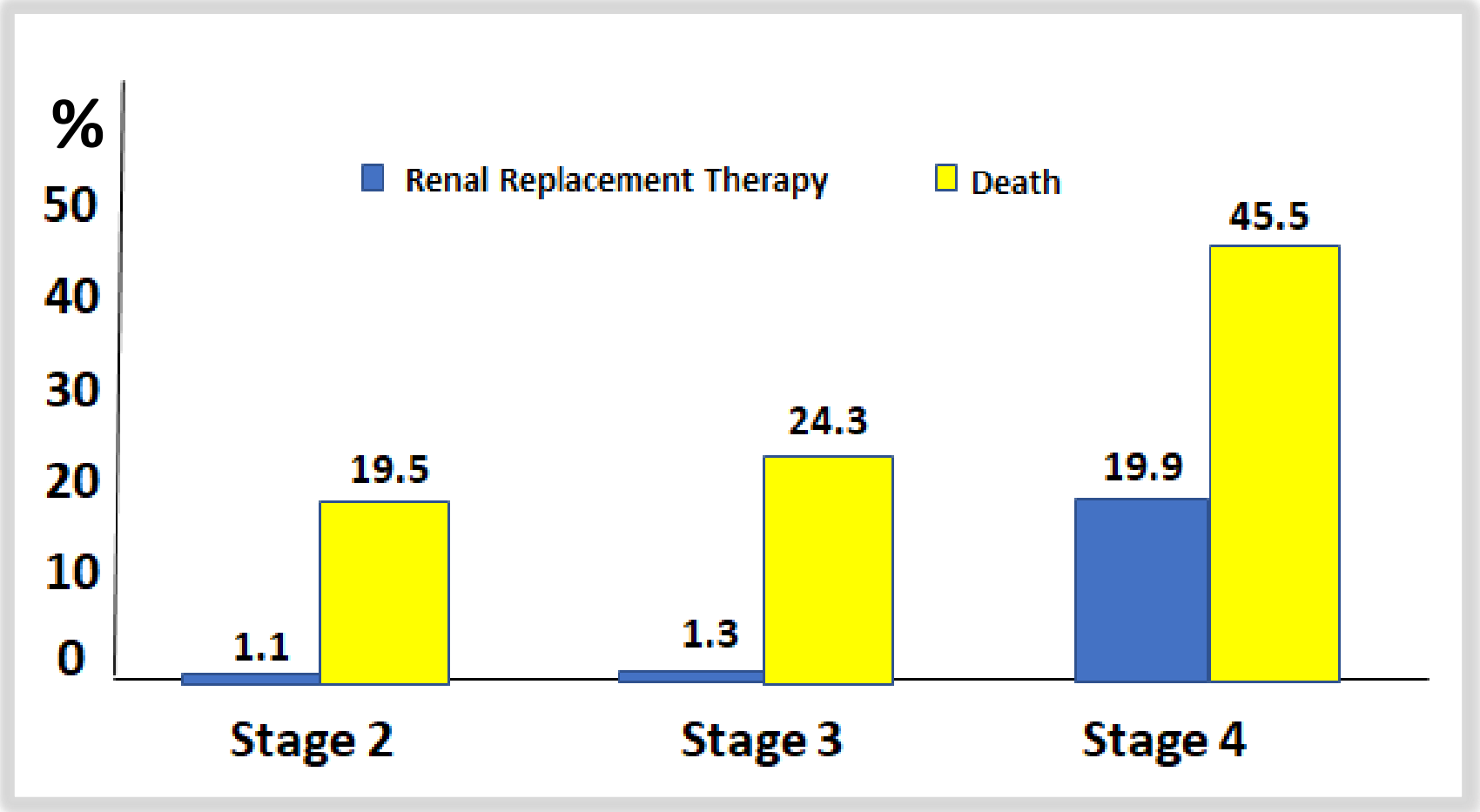
- For this talk I have received honoraria from Astra Zeneca
- I have previously received honoraria from other companies (Amgen, Astellas, GSK, Genesis)

ORIGINAL INVESTIGATION

Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization

Douglas S. Keith, MD; Gregory A. Nichols, MBA, PhD; Christina M. Gullion, PhD; Jonathan Betz Brown, MPP, PhD; David H. Smith, RPh, PhD

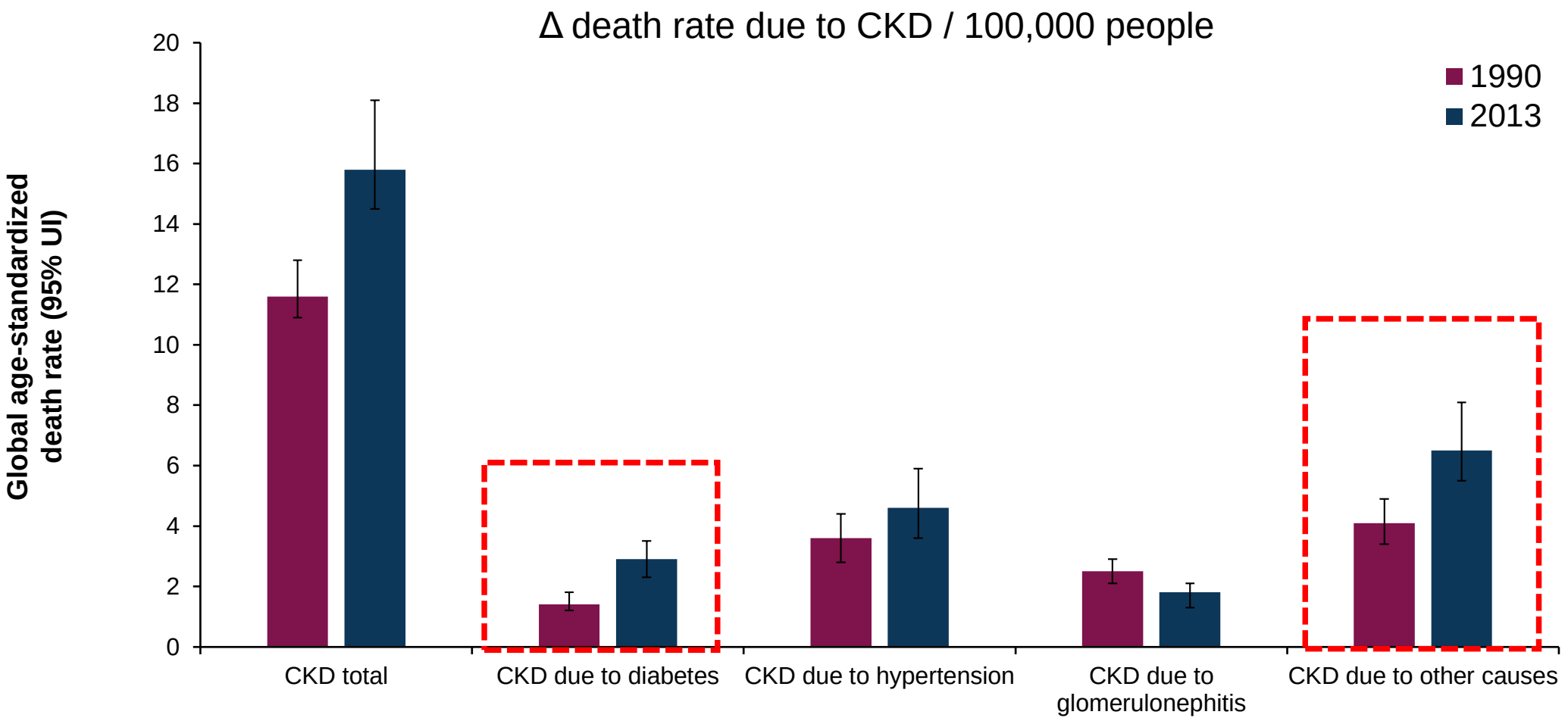
5 year outcome follow up (n=27,998)



Arch Intern Med. 2004 Mar 22;164(6):659-63

Mortality burden of CKD has been rising in the diabetic and in the non diabetic CKD population

1990 -2013



Jager KJ et al. Nephrol Dial Transplant. 2017;32(supp 2):ii121–ii128

Epidemiology of CKD

General population

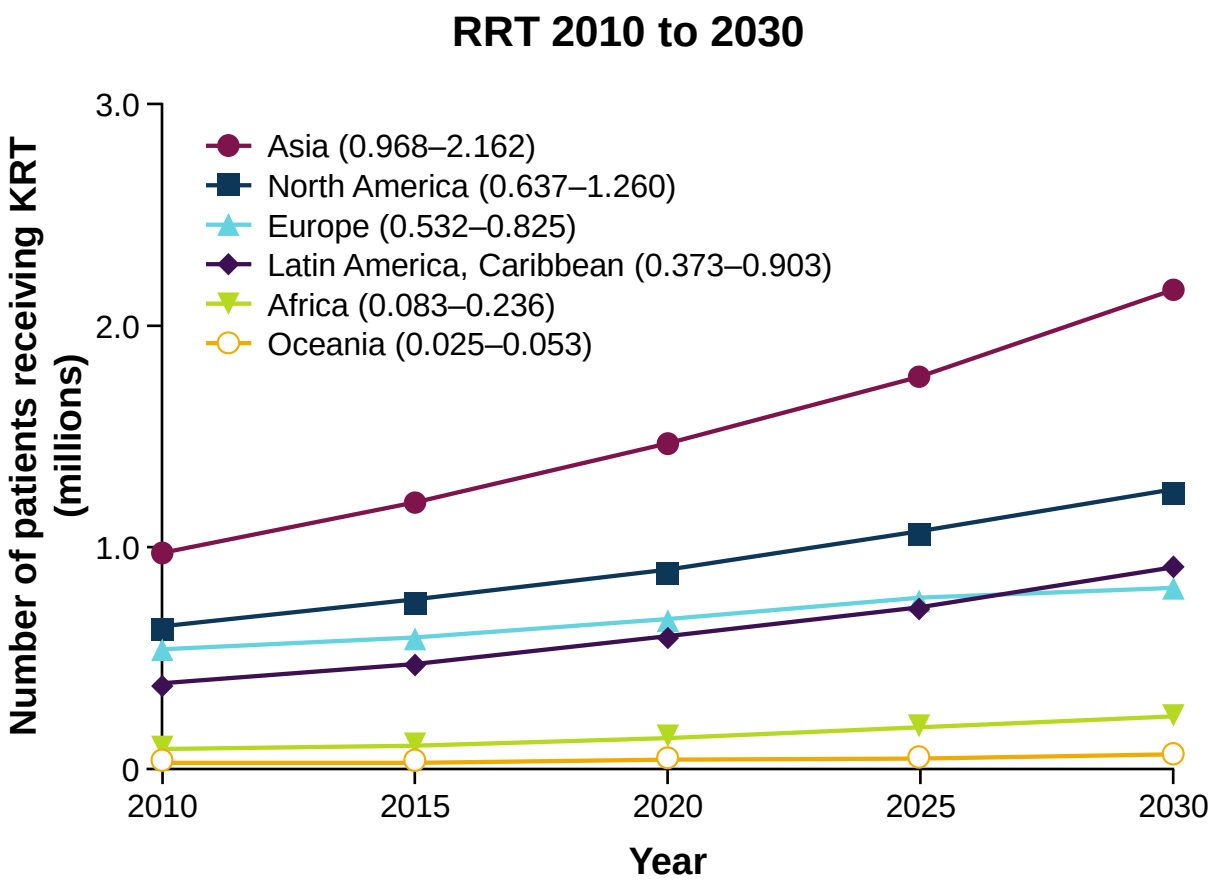
843,6 **Million in 2017**

Approximately **1** in **10**

These data should prompt major efforts to develop preventive and therapeutic measures

C.P. Kovesdy Kidney International Supplements (2022) 12, 7-11

Rates of RRT and CKD mortality are projected to rise substantially on a global scale

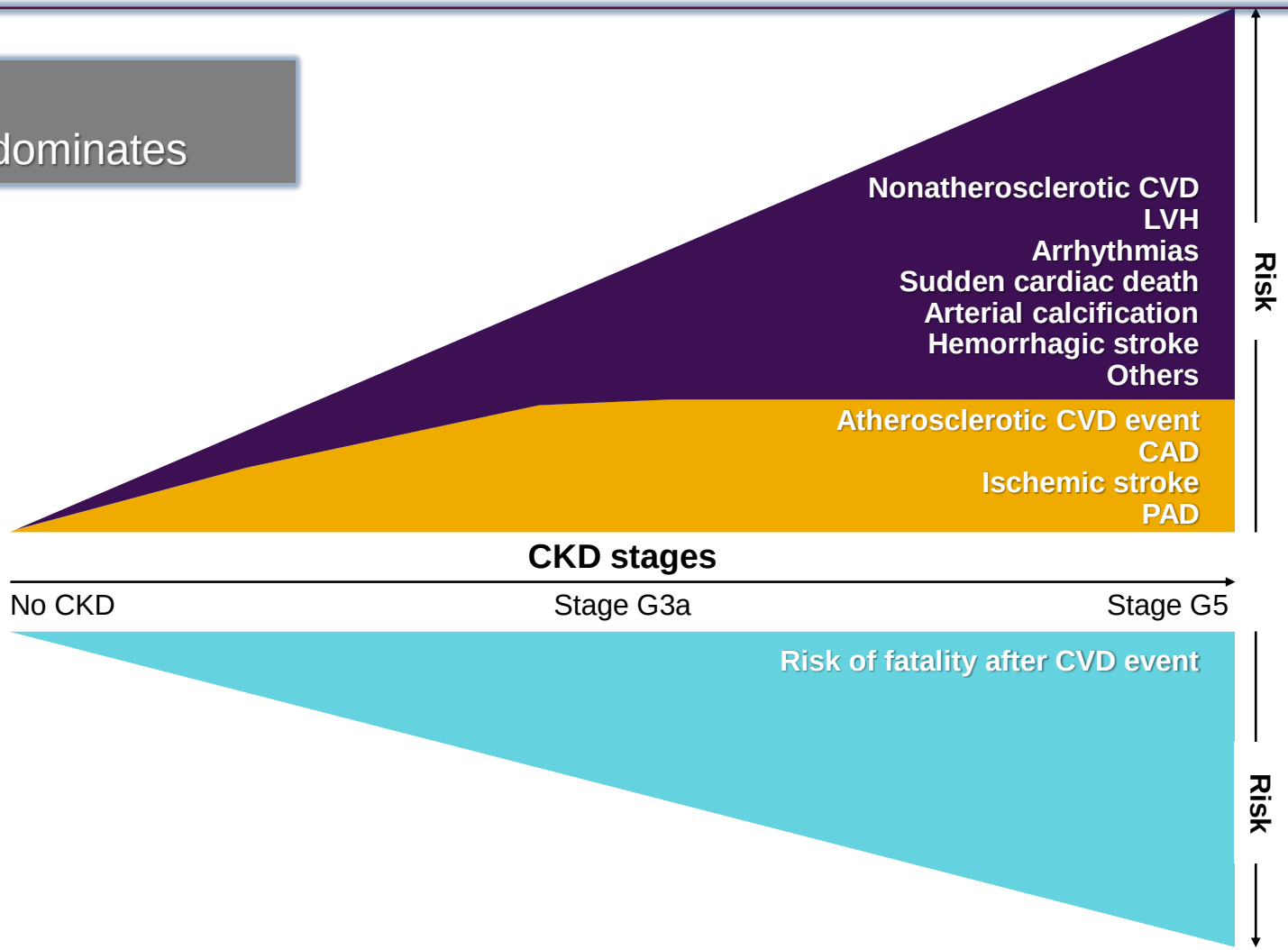


The number receiving RRT is estimated to increase to more than 5 million by 2030

Liyanage T et al. Lancet. 2015;385:1975–1982
Foreman KJ et al. Lancet. 2018;392:2052–2090

Risk of CVD and CV mortality increase with progression of CKD

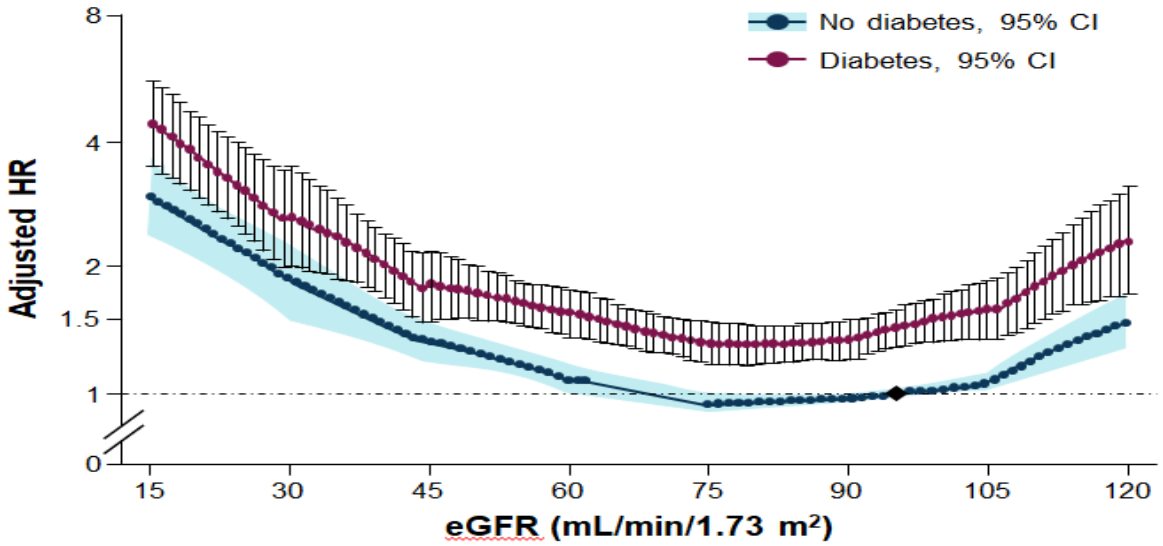
In later CKD stages,
nonatherosclerotic risk dominates



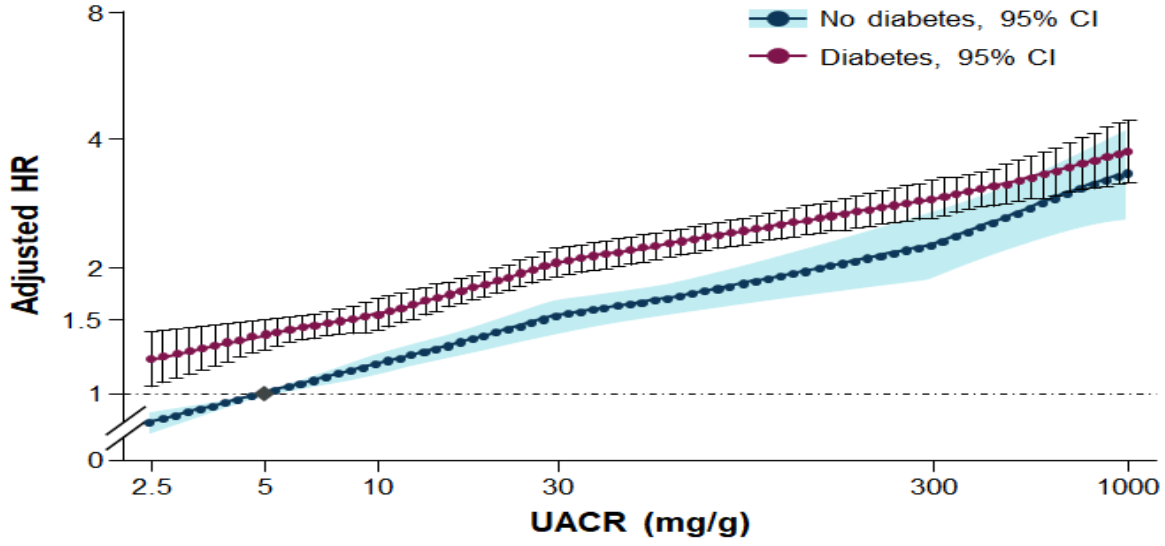
Sarnak MJ et al. J Am Coll Cardiol. 2019;74:1823–1838

Reduced eGFR and albuminuria lead to increased risk for CV mortality

CV mortality risk in CKD in diabetics and non diabetics



Mortality risk based on UACR in diabetics and non diabetics



Fox CS et al. Lancet. 2012;380:1662–1673

CV risks and mortality are elevated, regardless of CKD etiology

Hypertensive nephropathy

>3×

Greater risk of CV events and mortality

70% of patients received an ACE inhibitor/ARB

IgA nephropathy

53%

Increased mortality risk

74% of patients received an ACE inhibitor/ARB

Diabetic nephropathy

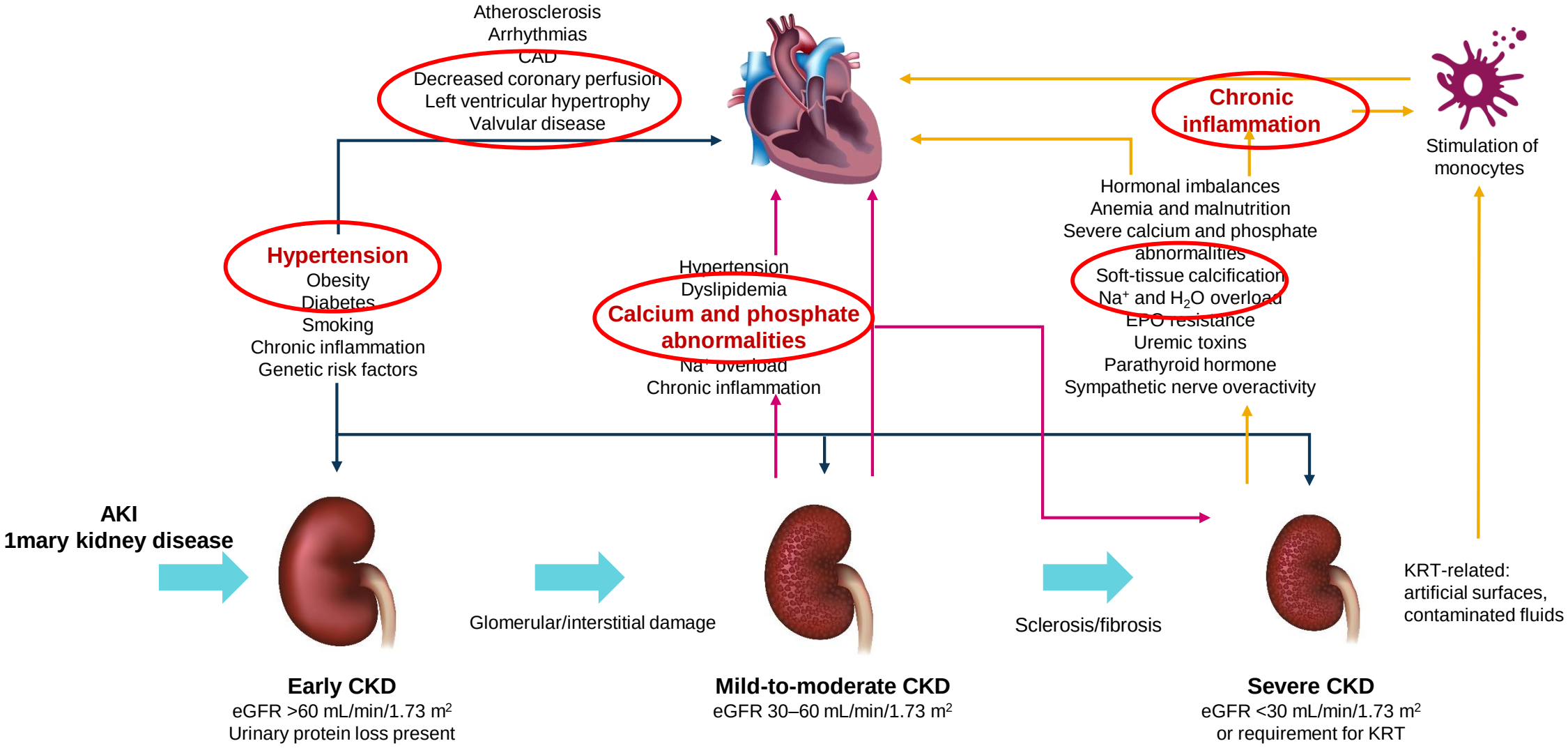
~6×

Greater risk of CV events and mortality

76% of patients received an ACE inhibitor/ARB

Hypertens Res. 2011;34(10):1106-1110
J Am Soc Nephrol. 2019;30(5):866-876.

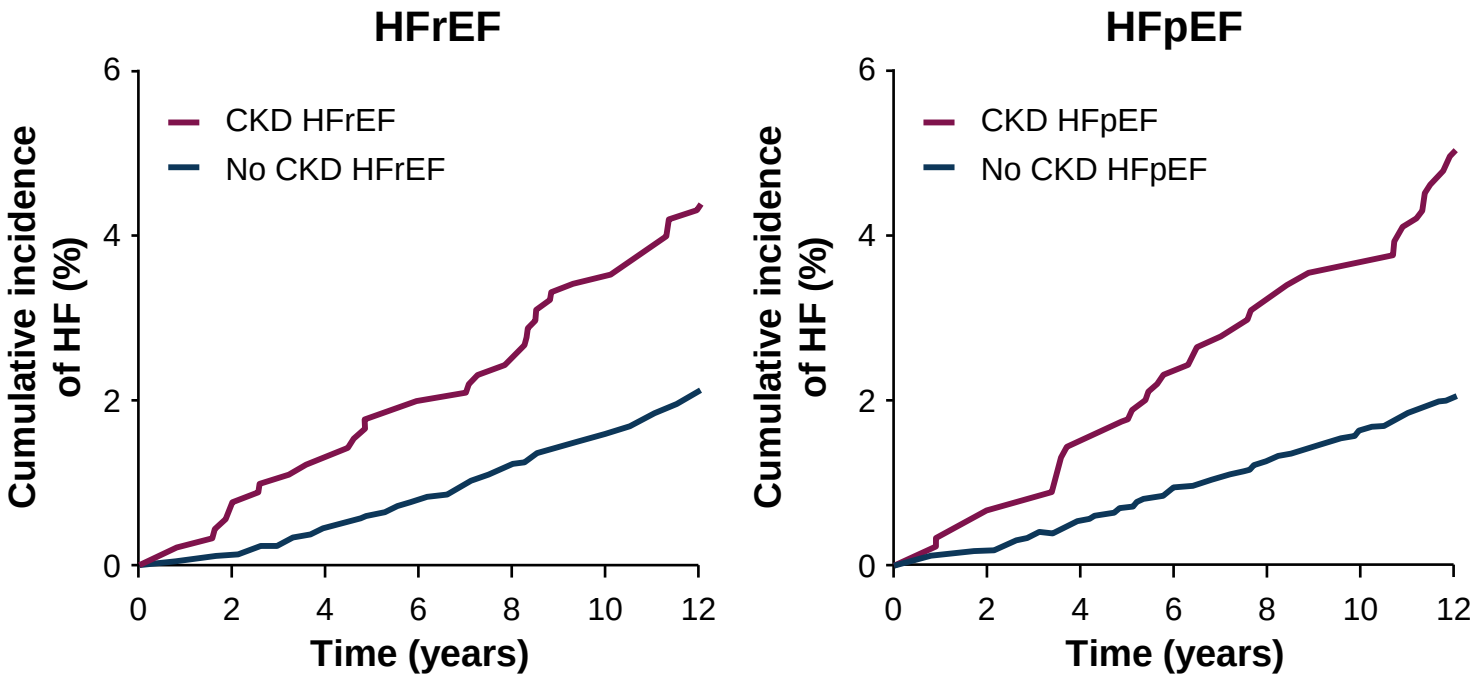
Pathophysiological interactions underlying cardiorenal disease



Lancet. 2013;382:339–352

CKD and HF are interconnected: CKD is associated with increased risk of HF and conversely HF is associated with risk of eGFR decline

Incidences of HF are higher in those with CKD than those without

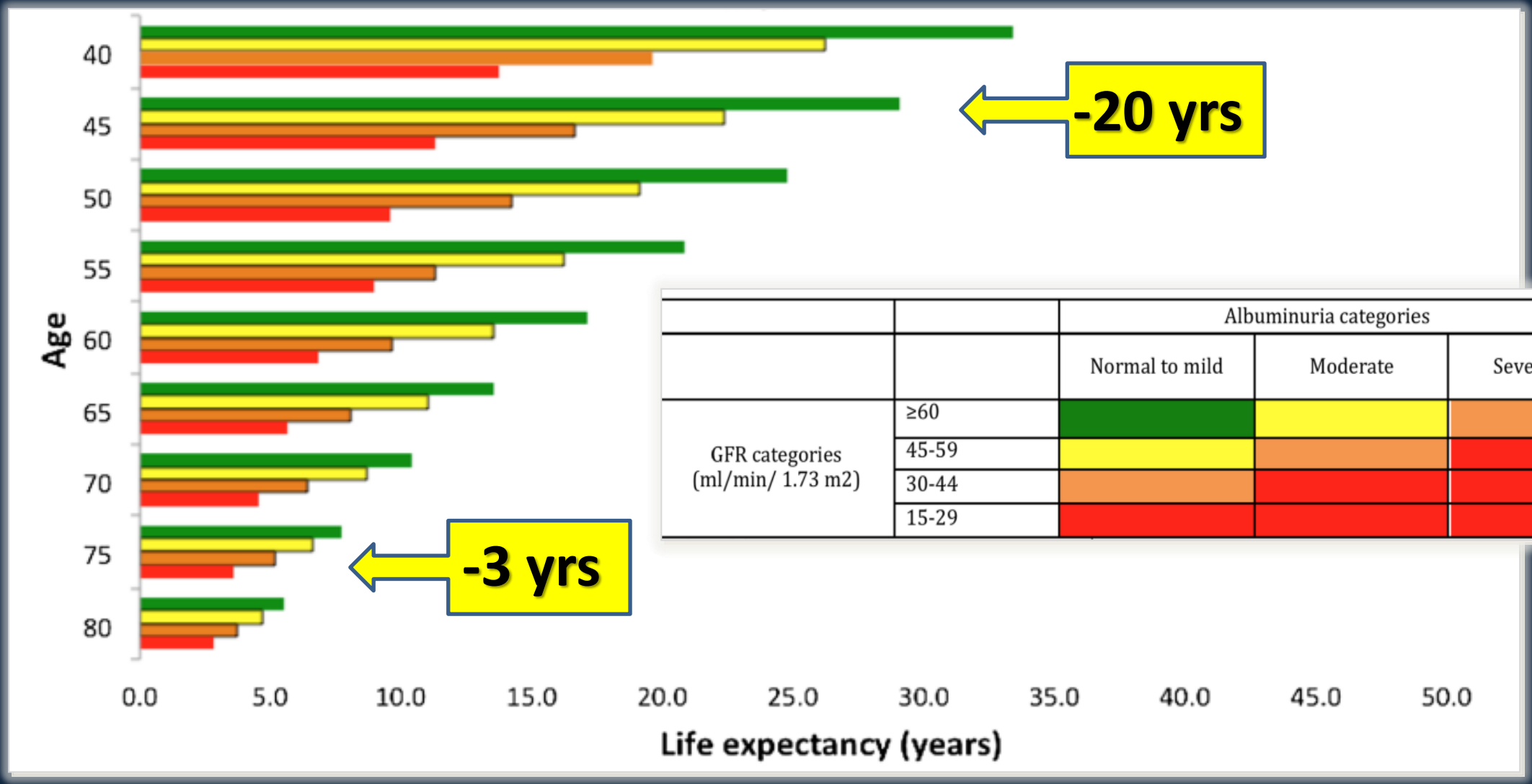


CKD is associated with incident HF

HF is associated with rapid decline in eGFR

Nayor M et al. Eur J Heart Fail. 2017;19:615–623
Circ Heart Fail. 2017;10:e003825.

Unmet need for effective treatment of CKD



		Albuminuria categories		
		Normal to mild	Moderate	Severe
GFR categories (ml/min/ 1.73 m2)	≥60			
	45-59			
	30-44			
	15-29			

Kidney Int Suppl (2011). 2013; 3:19–62.

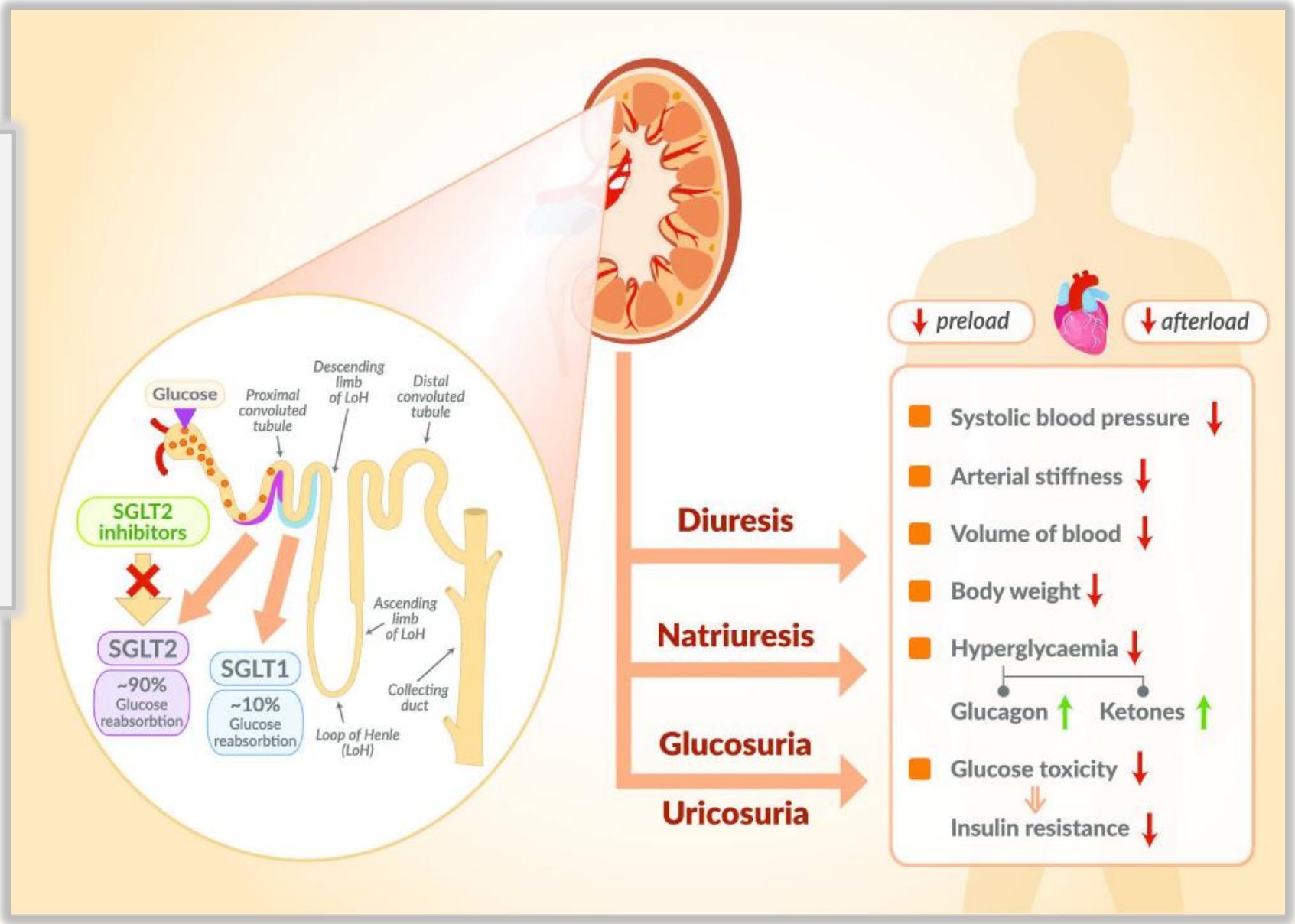
Can J Kidney Health Dis. 2014 Dec 19;1:33

Mechanisms of action of SGLT2 inhibitors

↑ Sodium to distal nephron
↑Afferent Vasoconstriction
↓Intraglomerular P
↓Glomerular hyperfiltration

↓SNS activity
↓Inflammation

↑erythropoesis
↓O_2 needs



Heart Fail Rev. 2021; 26(3): 603–622

Overview of placebo-controlled clinical outcome trials assessing SGLT2 inhibitors (CVOTs)

National Kidney Foundation classification of CKD

GFR Stages				Albuminuria categories		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90	CANVAS EMPA-REG DECLARE TIMI		
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

3 point MACE (CV death, MI or stroke)

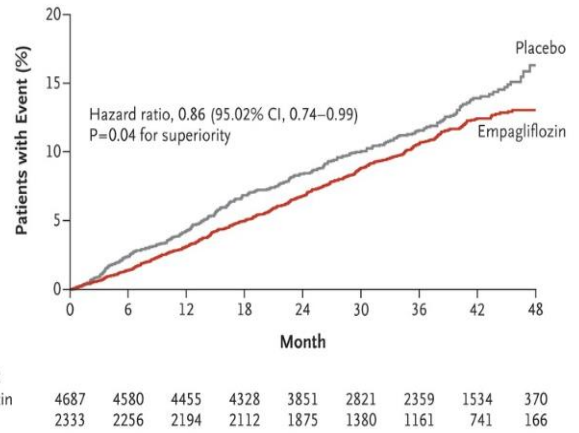
Kidney International (2020) 98, S1–S115

CVOTs: *3 point MACE (CV death, MI or stroke)*

combined end point of heart failure hospitalization or CV death

EMPA-REG OUTCOME

Empagliflozin

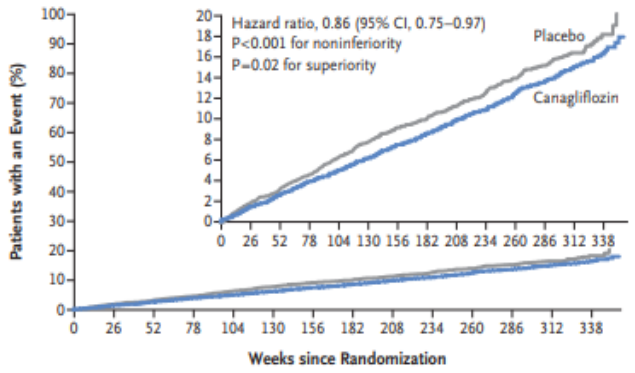


No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

N Engl J Med 2015;373:2117-2128

CANVAS program

Canagliflozin

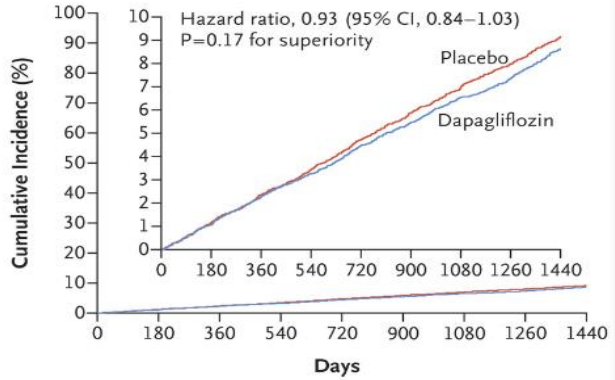


No. at Risk															
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

N Engl J Med 2017;377:644-65

DECLARE TIMI

Dapagliflozin



No. at Risk									
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

N Engl J Med 2019; 380:347-357

SGLT2i in non diabetic animals with kidney disease or risk factor s for renal function decline

References	Design	Main outcomes	Conclusion
Zhang *et al.* [52]	53 Sprague Dawley rats were assigned to sham surgery + vehicle, sham surgery + DAPA or subtotal nephrectomy (SNx) + vehicle SNx + DAPA Treatment period: 12 weeks	DAPA versus vehicle: no change in SBP, 24-h proteinuria excretion, and GFR; no effect on glomerulosclerosis, tubulointerstitial fibrosis and TGF-β1 mRNA overexpression	No renoprotective effects in a non-diabetic rat model, representing glomerular hyperfiltration
Ma *et al.* [53]	20 C57BL/6N mice were assigned to high oxalate diet + vehicle or high oxalate diet + EMPA	EMPA versus vehicle: no effect on calcium oxalate crystal deposition; no effect on GFR decline, plasma creatinine and BUN; no	No renoprotective effects in a non-diabetic mouse model with progressive CKD due
Cassis *et al.* [54]	Unilateral nephrectomy was performed and C57BL/6N mice were assigned to control group ($n = 12$), bovine serum albumin (BSA) injections + vehicle ($n = 9$), BSA + DAPA ($n = 8$) or BSA + lisinopril ($n = 8$) Treatment period: 23 days	DAPA and lisinopril reduced SBP. No effects on BW and mGFR decline. DAPA and lisinopril reduced UACR by 63 and 72%, respectively. DAPA attenuated glomerular lesions, macrophage infiltration and podocyte loss. DAPA limited cytoskeletal remodelling *in vitro*	DAPA reduced proteinuria, glomerular lesions and limited podocyte loss in non-diabetic proteinuric mice
Jaikumkao *et al.* [56]	Obese Wistar rats were assigned to control group ($n = 6$), high-fat diet (HFD) ($n = 6$), HFD + metformin ($n = 6$) or HFD + DAPA ($n = 6$) Treatment period: 4 weeks	DAPA reduced renal hyperfiltration, microal buminuria and expression of antioxidant enzyme superoxide dismutase, increased antioxidant glutathione, suppressed markers of inflammation and fibrosis and suppressed the expression of endoplasmic reticulum stress and renal pro-apoptotic proteins	DAPA decreased renal hyperfiltration, microalbuminuria and markers for renal inflammation, tubulointerstitial fibrosis and apoptosis in a prediabetic rat model

Nephrol Dial Transplant. 2020 Jan; 35(Suppl 1): i33–i42.

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3 point MACE (CV death, MI or stroke)

Kidney International (2020) 98, S1–S115

DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

DAPACKD

Objective To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a stable dose of an ACEi or ARB

Key Inclusion Criteria
- ≥18 years of age
- eGFR 25-75 mL/min/1.73m^2
- UACR 200- 5000 mg/g
- Stable dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria
- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled

1:1 Double-blind

- Dapagliflozin 10 mg + standard of care
- Placebo + standard of care

4304 Randomized
Median follow-up 2.4 years

End Points

Primary Outcome
Composite of sustained ≥50% eGFR decline, ESKD[a], renal or CV death

Secondary Outcomes
- Composite renal outcome of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

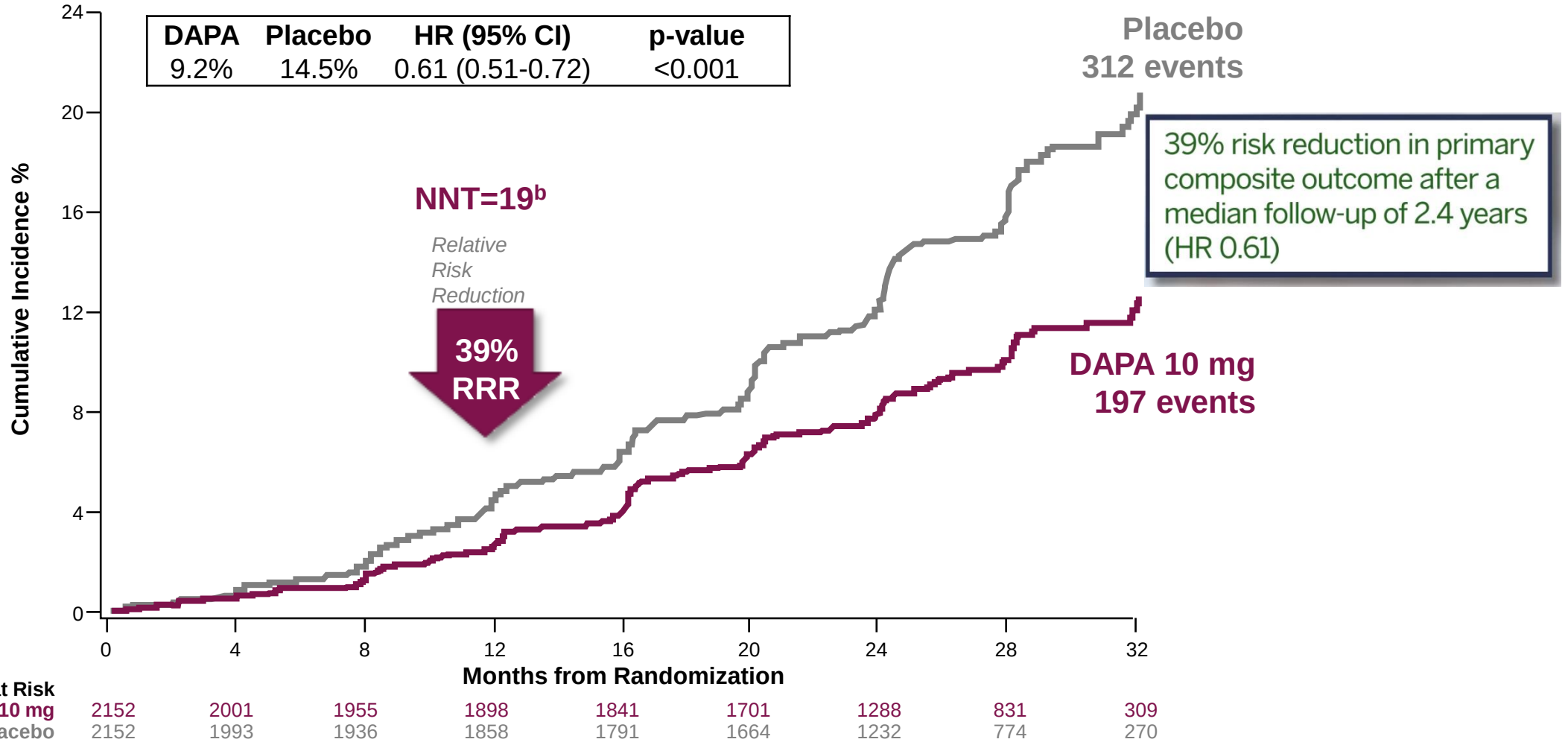
median follow-up was 2.4 years.2

1/3 of pnts did NOT have T2DM

1. Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446; 2.Wheeler DC et al, Lancet Diabetes Endocrinol 2021; 9:22-31

Primary Composite Outcome: Sustained ≥50% eGFR decline, ESKD, renal or CV Death

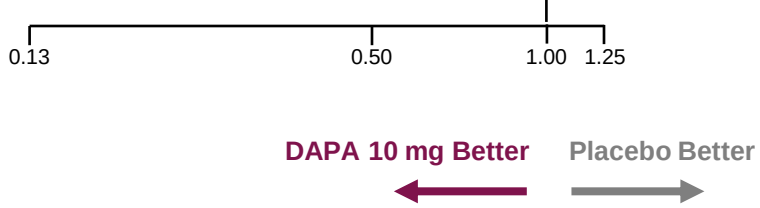
DAPA	Placebo	HR (95% CI)	p-value
9.2%	14.5%	0.61 (0.51-0.72)	<0.001



1. Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446; 2.Wheeler DC et al, Lancet Diabetes Endocrinol 2021; 9:22-31

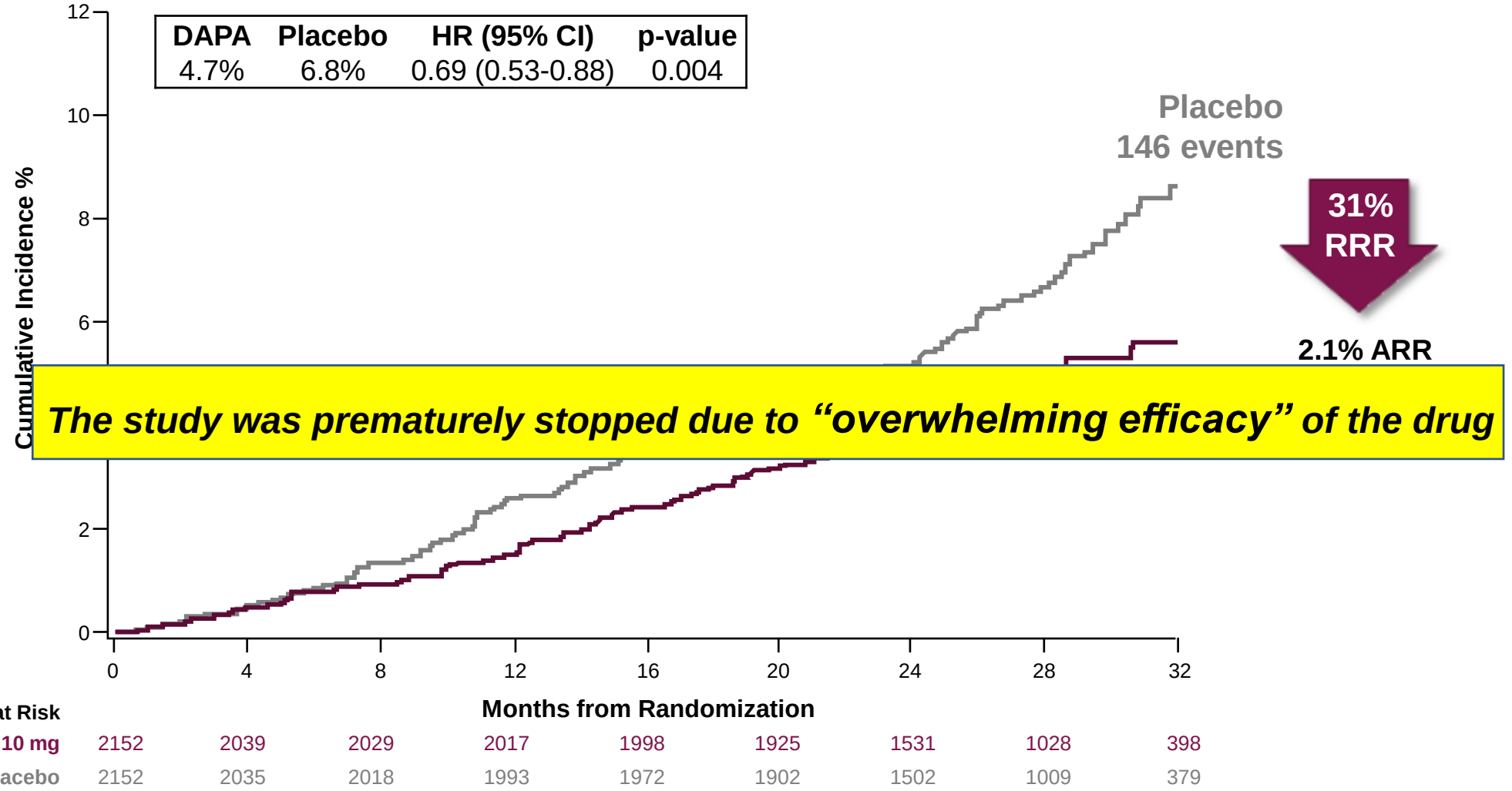
Primary Composite Outcome: (Sustained ≥50% eGFR decline, ESKD, renal or CV Death) Stable treatment benefit across subgroups

	Number of Events				
HR (95% CI)	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction[2]
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24[2]
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



1. Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446; 2.Wheeler DC et al, Lancet Diabetes Endocrinol 2021; 9:22-31

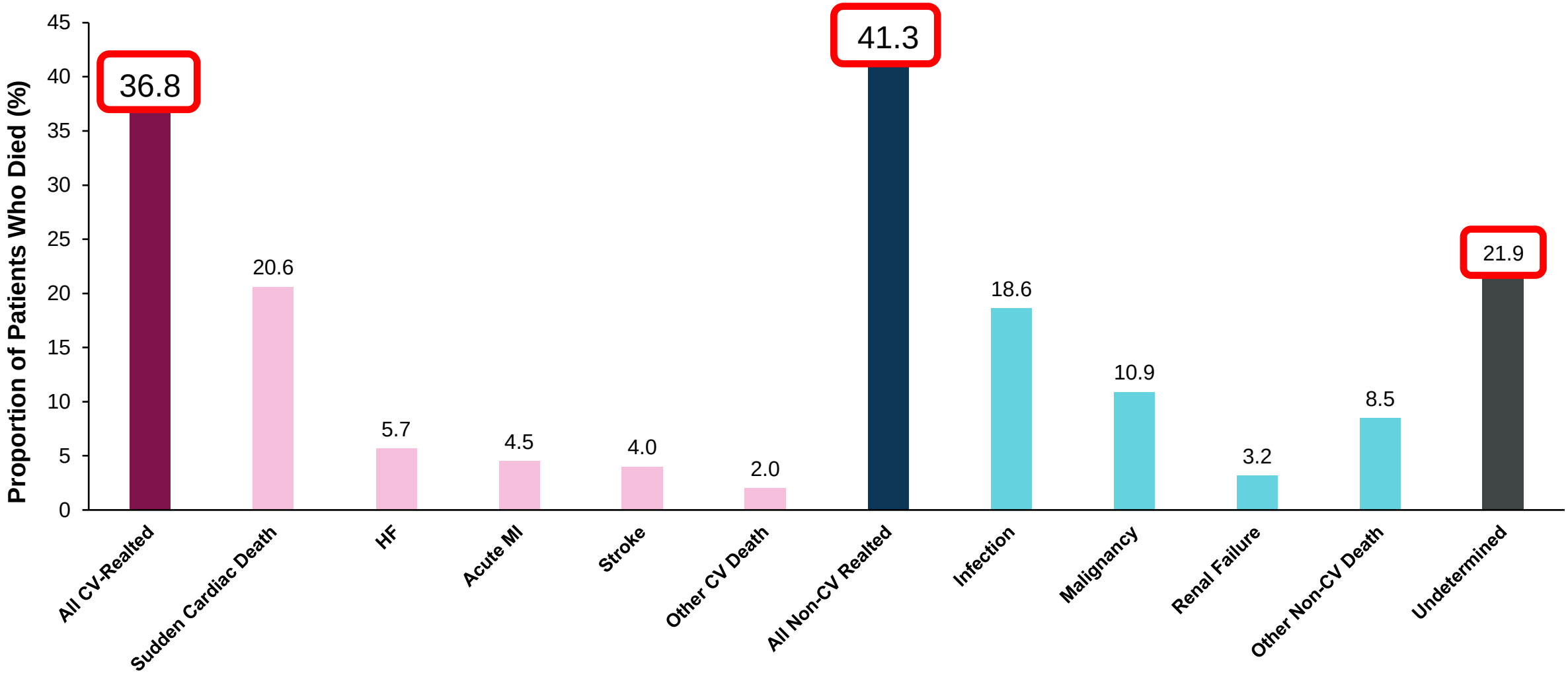
Secondary Outcome: All-cause Mortality



1. Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446; 2.Wheeler DC et al, Lancet Diabetes Endocrinol 2021; 9:22-31

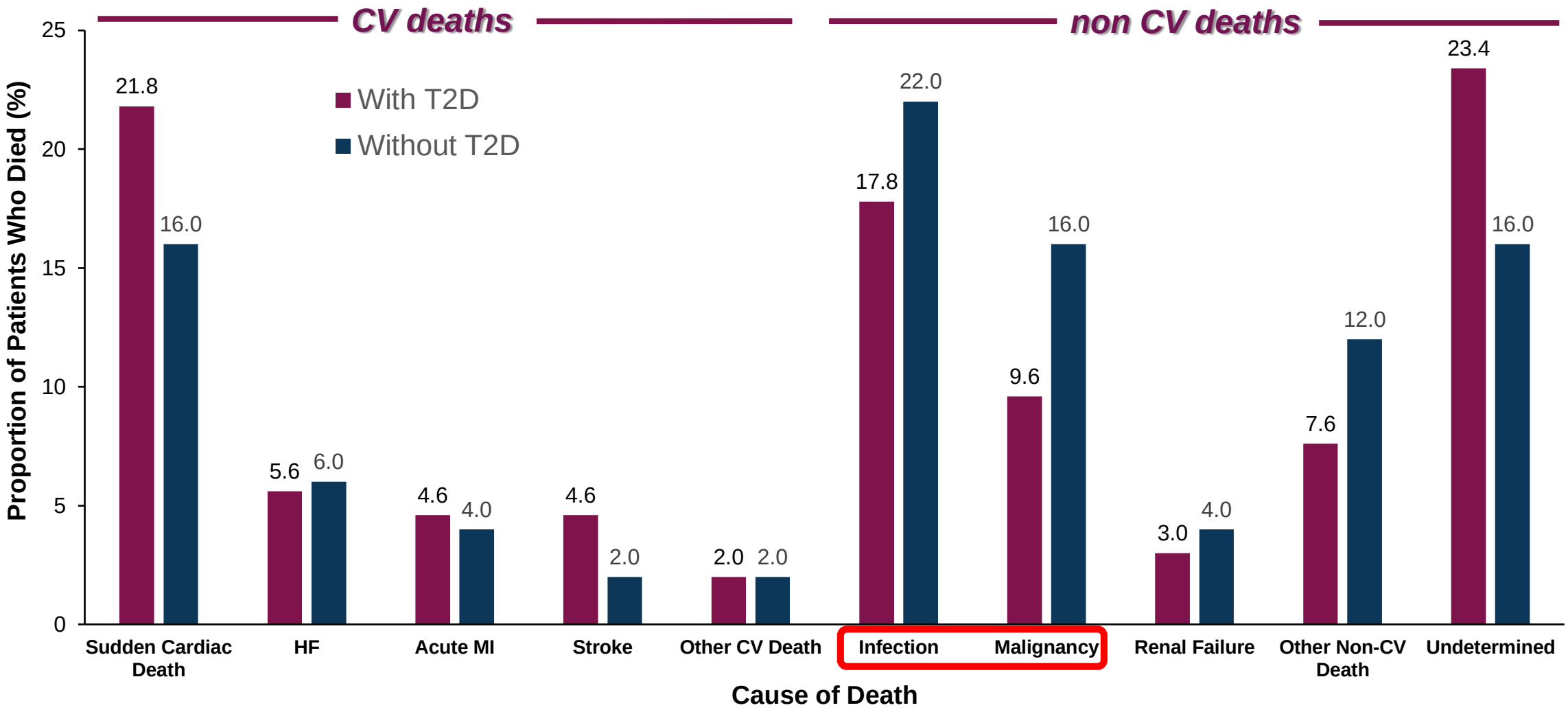
Main Causes of Death in DAPA-CKD

247 (5.7%) participants died



Eur Heart J. 2021 Mar 31;42(13):1216-1227

Main Causes of Death in diabetic and non diabetic population of DAPA-CKD



Eur Heart J. 2021 Mar 31;42(13):1216-1227

All-Cause Mortality in Patients Who Did and Did Not Reach Chronic Dialysis

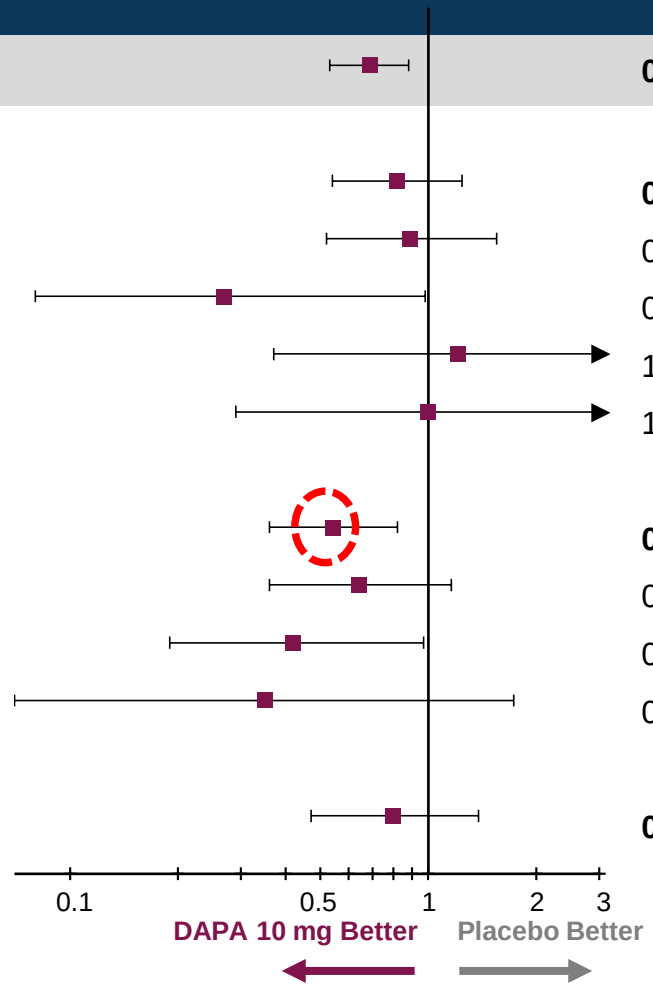
	Dapagliflozin		Placebo		Total	
	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)
Overall mortality	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	247/4304 (5.7)	2.6
Without chronic dialysis, n	2084		2053		4137	
All-cause mortality	**89** (4.3)	1.9	**121** (5.9)	2.6	**210** (5.1)	2.2
With chronic dialysis, n	68		99		**167**	
All-cause mortality	**12** (17.6)	8.6	**25** (25.3)	13.4	**37** (22.2)	11.4

Eur Heart J. 2021 Mar 31;42(13):1216-1227

Dapagliflozin significantly prolonged survival in patients with CKD with and without T2DM

	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P Value
	No. of patients/total no.			
All-cause mortality	**101/2152**	**146/2152**	**0.69 (0.53, 0.88)**	**0.003**
CV death	**41/2152**	**50/2152**	**0.82 (0.54, 1.24)**	**0.338**
Sudden cardiac death	24/2152	27/2152	0.89 (0.52, 1.55)	
Heart failure	3/2152	11/2152	0.27 (0.08, 0.98)	
Acute MI	6/2152	5/2152	1.21 (0.37, 3.96)	
Stroke	5/2152	5/2152	1.00 (0.29, 3.74)	
Non-CV death	**36/2152**	**66/2152**	**0.54 (0.36, 0.82)**	**0.003**
Infection	18/2152	28/2152	0.64 (0.36, 1.16)	
Malignancy	8/2152	19/2152	0.42 (0.19, 0.97)	
Renal failure	2/2152	6/2152	0.35 (0.07, 1.73)	
Undetermined	**24/2152**	**30/2152**	**0.80 (0.47, 1.38)**	**0.426**

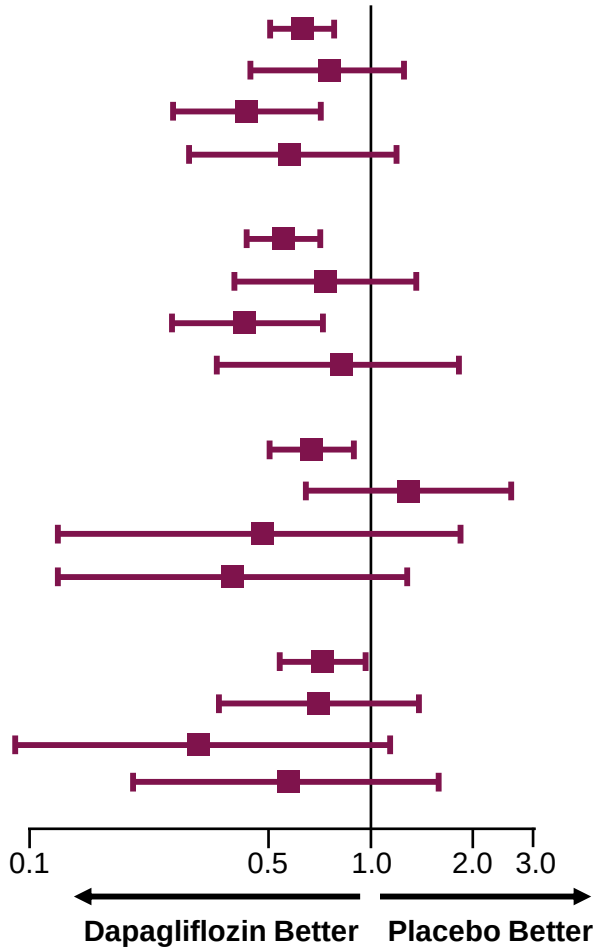
41% ↓



Eur Heart J. 2021 Mar 31;42(13):1216-1227

Primary and Secondary Outcomes by Underlying Cause of Kidney Disease

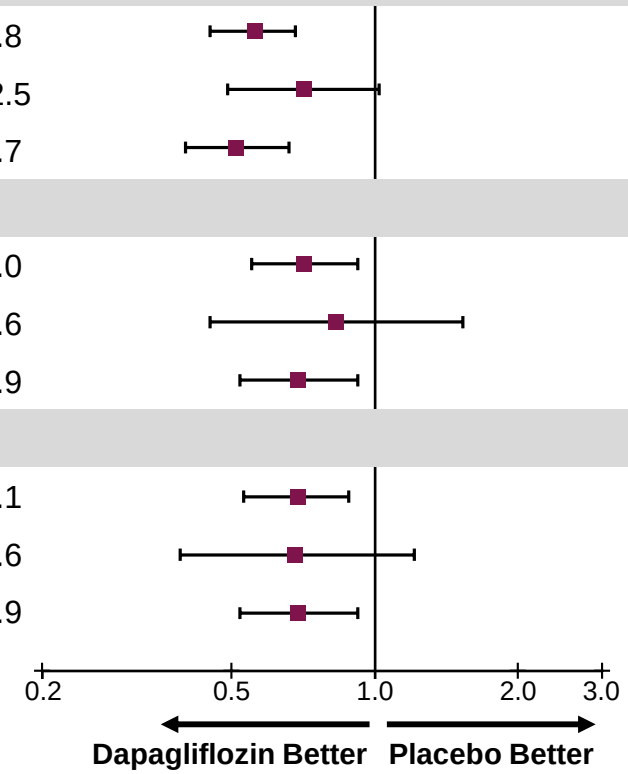
	Dapagliflozin 10 mg Events[a]	Placebo Events[a]	Hazard Ratio (95% CI)	P-value for Interaction
Primary outcome[b]				
Diabetic nephropathy	139/1271	207/1239	0.63 (0.51, 0.78)	0.53
Ischemic/hypertensive CKD	24/324	35/363	0.75 (0.44, 1.26)	
Glomerulonephritis	22/343	49/352	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	0.58 (0.29, 1.19)	
Renal-specific outcomes[c]				
Diabetic nephropathy	93/1271	157/1239	0.55 (0.43, 0.71)	0.67
Ischemic/hypertensive CKD	18/324	26/363	0.74 (0.40, 1.36)	
Glomerulonephritis	21/343	46/352	0.43 (0.26, 0.72)	
Other/unknown	10/214	14/198	0.81 (0.35, 1.83)	
CV death or hHF				
Diabetic nephropathy	76/1271	107/1239	0.67 (0.50, 0.90)	0.24
Ischemic/hypertensive CKD	17/324	15/363	1.29 (0.64, 2.60)	
Glomerulonephritis	3/343	7/352	0.48 (0.12, 1.84)	
Other/unknown	4/214	9/198	0.39 (0.12, 1.28)	
All-cause mortality				
Diabetic nephropathy	78/1271	104/1239	0.72 (0.54, 0.97)	0.55
Ischemic/hypertensive CKD	14/324	22/363	0.70 (0.36, 1.37)	
Glomerulonephritis	3/343	11/352	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	0.57 (0.20, 1.61)	



Lancet Diabetes Endocrinol. 2021;9:22–31

Secondary Outcomes According to CKD Stage

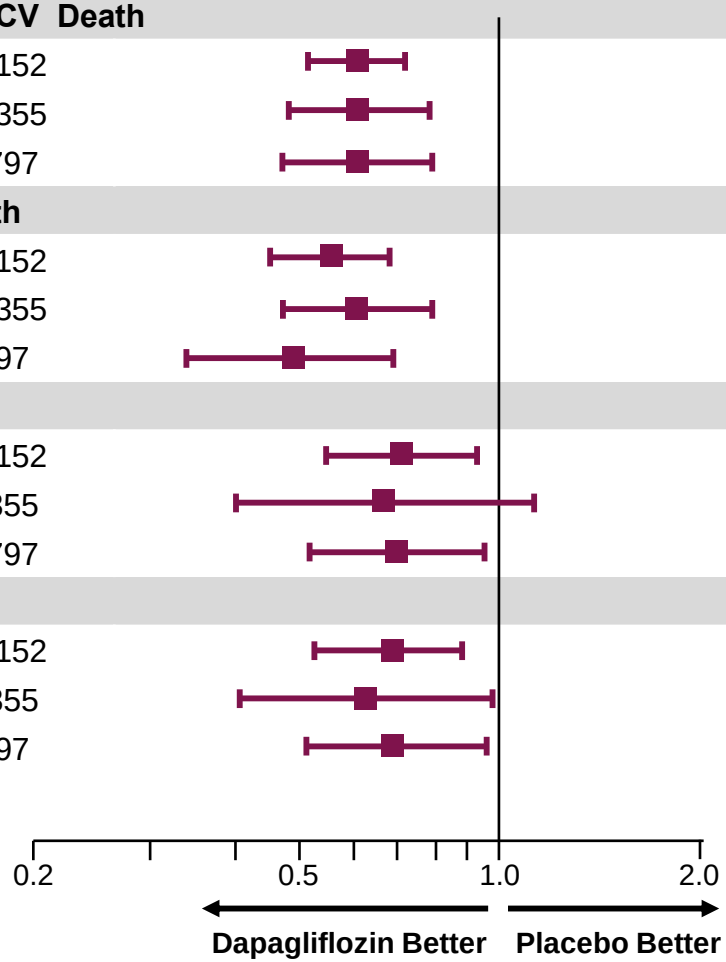
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients/ total no.		Events/100 patient-years			
Kidney composite outcome: ≥50% eGFR decline, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	9.2	12.5	0.71 (0.49, 1.02)	0.13
Stage 2/3	93/1859	170/1821	2.5	4.7	0.51 (0.40, 0.66)	
CV death or heart failure hospitalization						
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
Stage 4	18/293	24/331	2.9	3.6	0.83 (0.45, 1.53)	0.63
Stage 2/3	82/1859	114/1821	2.0	2.9	0.69 (0.52, 0.92)	
All-cause death						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	3.0	4.6	0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	2.0	2.9	0.69 (0.52, 0.92)	



J Am Soc Nephrol. 2021;32:2352-2361.

Primary and Secondary Outcomes by Baseline CVD

	Dapagliflozin 10 mg Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Primary Outcome: eGFR Decline ≥50%, ESKD, Renal Death, or CV Death				
Overall[1]	197/2152	312/2152	0.61 (0.51, 0.72)	
Without CVD[2]	106/1339	175/1355	0.61 (0.48, 0.78)	0.90
With CVD[2]	91/813	137/797	0.61 (0.47, 0.79)	
Secondary Outcome: eGFR Decline ≥50%, ESKD, or Renal Death				
Overall[1]	142/2152	243/2152	0.56 (0.45, 0.68)	
Without CVD[2]	93/1339	154/1355	0.61 (0.47, 0.79)	0.29
With CVD[2]	49/813	89/797	0.49 (0.34, 0.69)	
Secondary Outcome: CV Death or hHF				
Overall[1]	100/2152	138/2152	0.71 (0.55, 0.92)	
Without CVD[2]	24/1339	36/1355	0.67 (0.40, 1.13)	0.88
With CVD[2]	76/813	102/797	0.70 (0.52, 0.94)	
Secondary Outcome: All-cause Mortality				
Overall[1]	101/2152	146/2152	0.69 (0.53, 0.88)	
Without CVD[2]	33/1339	53/1355	0.63 (0.41, 0.98)	0.71
With CVD[2]	68/813	93/797	0.70 (0.51, 0.95)	

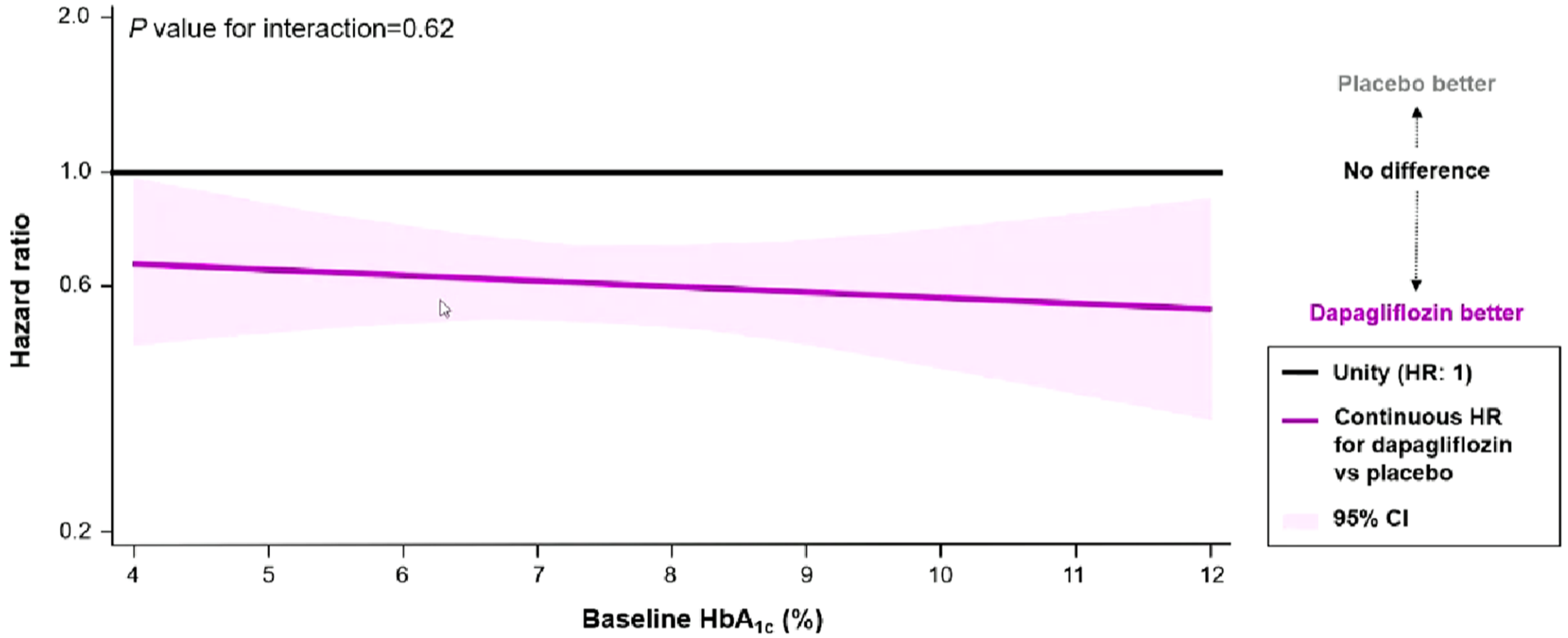


N Engl J Med 2020;383:1436-1446
Circulation. 2021;143:438–448.

1mary and 2ndary outcomes of DAPA CKD

Primary	HR (95% CI)	*P* value		
1. eGFR ≥50%, ESKD, or death from renal causes or CV causes	0.61 (0.51, 0.72)	<0.001	✔	39% ↓RRR
Secondary				
2. eGFR decline ≥50%, ESKD, or death from renal causes	0.56 (0.45, 0.68)	<0.001	✔	44% ↓RRR
3. Composite of CV death or hHF	0.71 (0.55, 0.92)	0.009	✔	29% ↓RRR
4. Death from any cause *A signal not been seen in other trials*	0.69 (0.53, 0.88)	0.004	✔	31% ↓RRR

DAPA CKD: Benefit of dapagliflozin on the 1mary outcome across a range of HbA1C



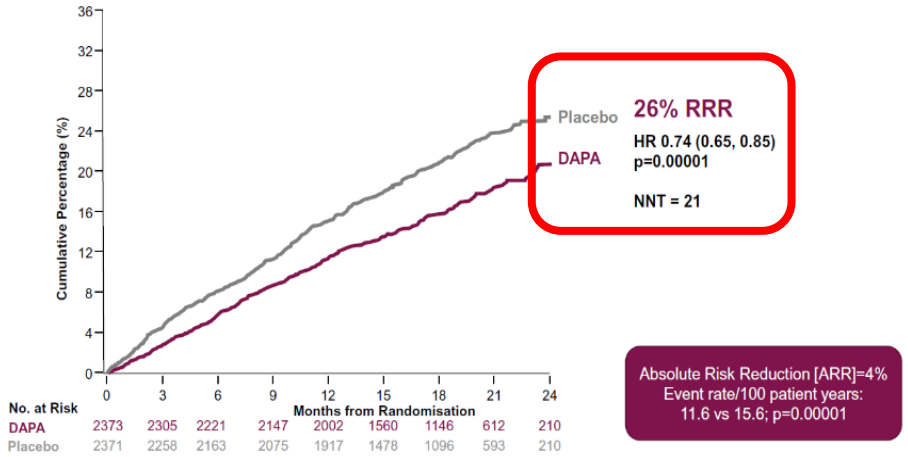
Diabetes Care 2021;44:1894-1897

DAPA-HF trial

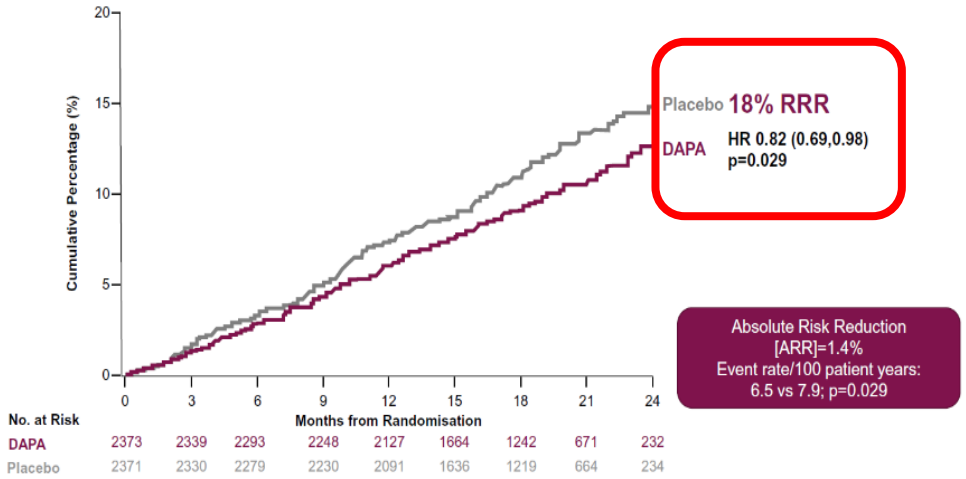
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., et al., for the DAPA-HF Trial Committees and Investigators*

Primary Endpoint: CV Death or hHF or an Urgent HF Visit



Component of Primary Endpoint: Cardiovascular Death



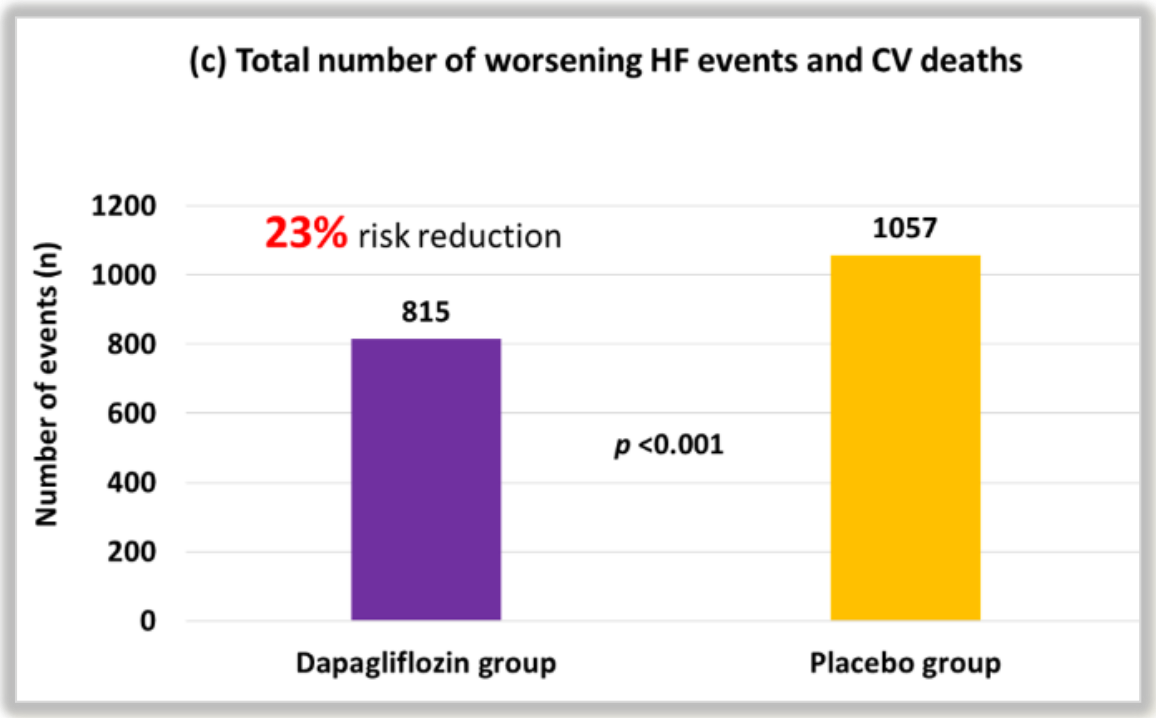
N Engl J Med 2019; 381:1995-2008

DELIVER

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Brian Claggett, Ph.D., Rudolf A. de Boer, M.D., David DeMets, Ph.D., Adrian F. Hernandez, M.D., Silvio E. Inzucchi, M.D. Mikhail N. Kosiborod, M.D., Carolyn S.P. Lam, M.D., Felipe Martinez, M.D., Sanjiv J. Shah, M.D., Akshay S. Desai, M.D., et al., for the DELIVER Trial Committees and Investigators*

N=6263 NYHA II-IV EF>40



N Engl J Med 2022; 387:1089-1098

How can SGLT2i also preserve kidney function in patients with kidney diseases due to causes other than diabetes mellitus?

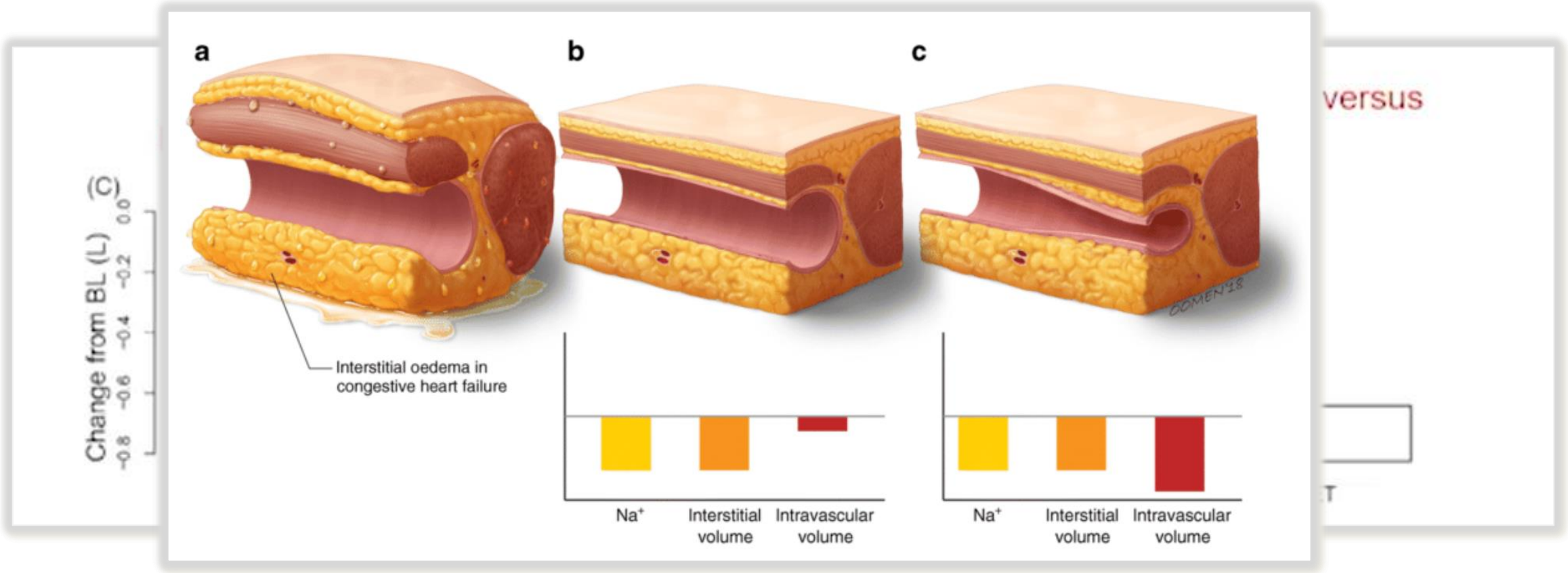
And how do you then explain its benefit in heart failure – seen in non-diabetic patients as well?

••••

There's no tubuloglomerular feedback involved in the Frank-Starling curve

If it's merely the natriuretic effect at play – why don't we see those kinds of benefits with other natriuretics?

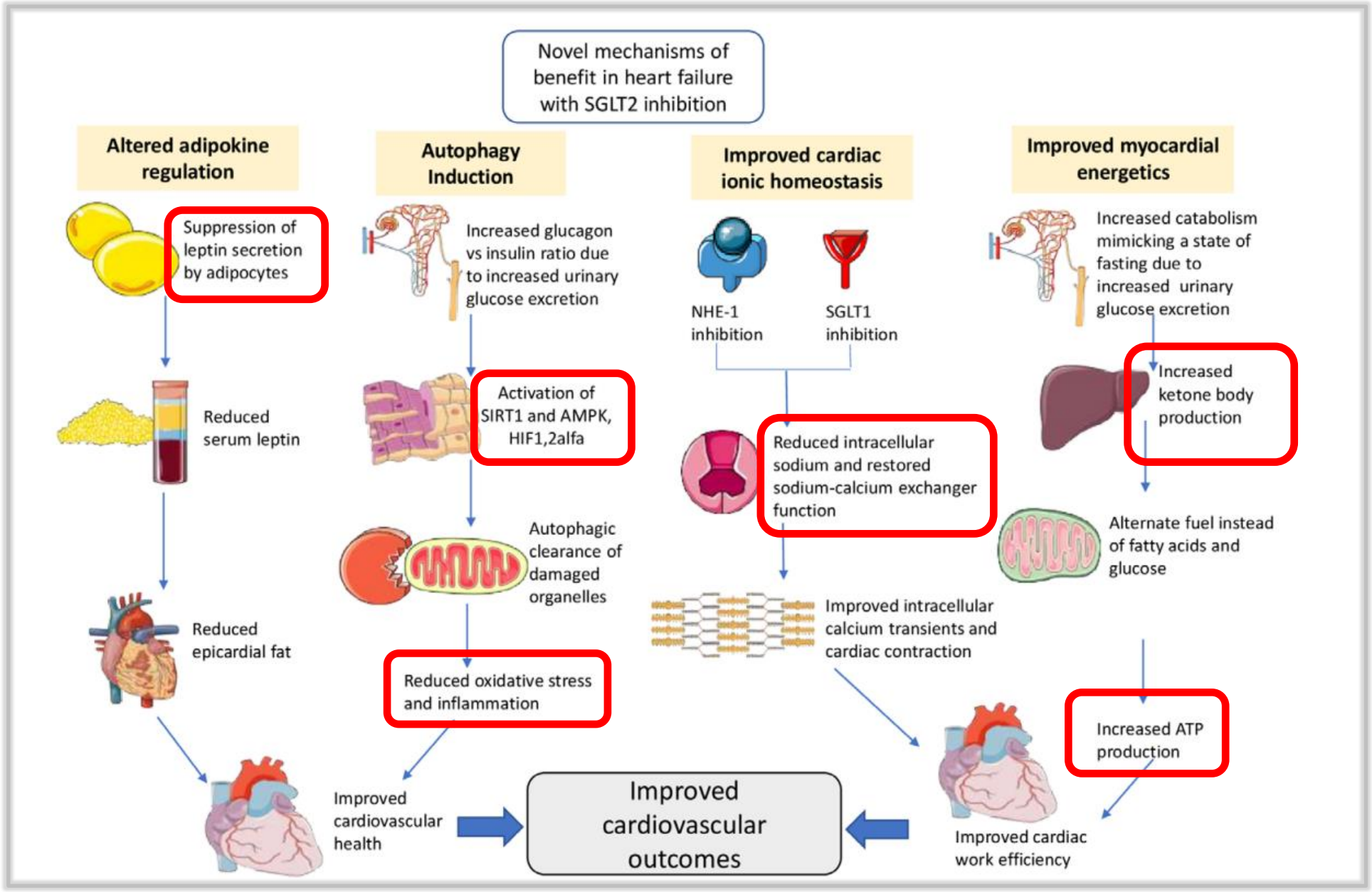
SGLT2 inhibitors vs diuretics: Differential regulation of interstitial vs intravascular compartment



This may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics

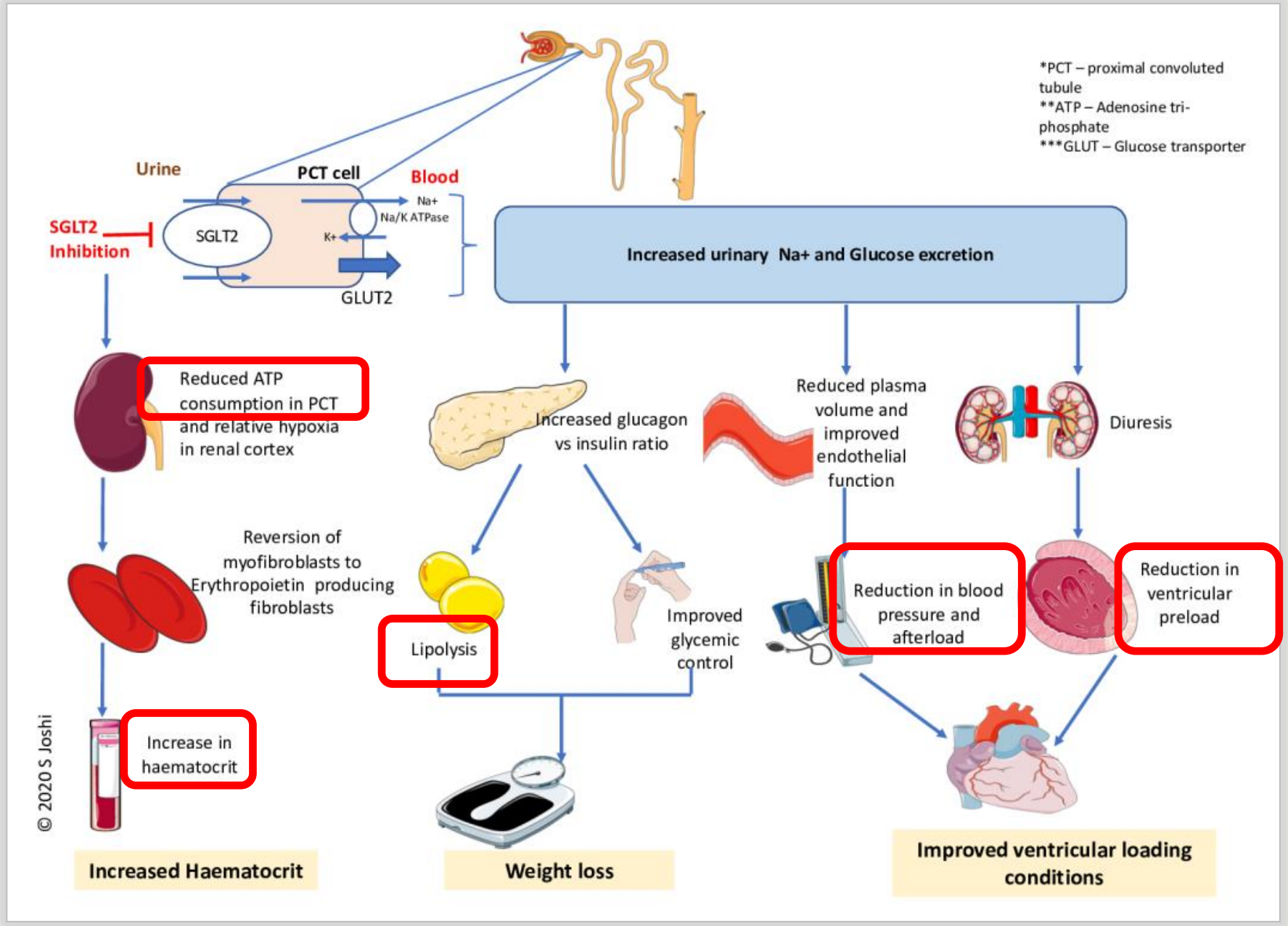
Diabetes Obes Metabol 2018;20:479-487
Diabetologia. 2018 Oct;61(10):2108-2117

Novel mechanisms of cardioprotective benefit with SGLT2 inhibition



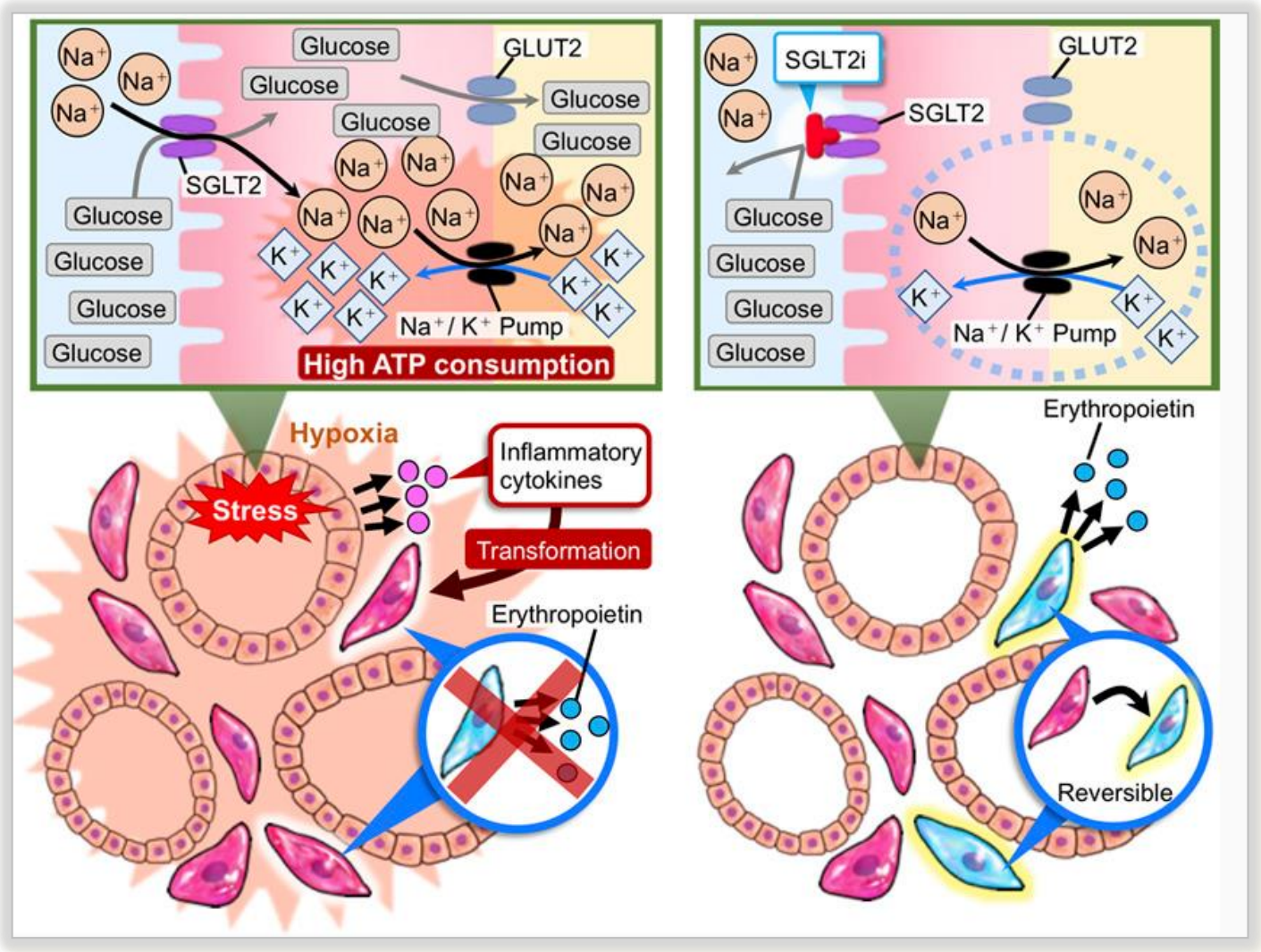
Heart 2021;107:1032–1038

Mechanisms of action of SGLT2 inhibitors



Heart 2021;107:1032–1038

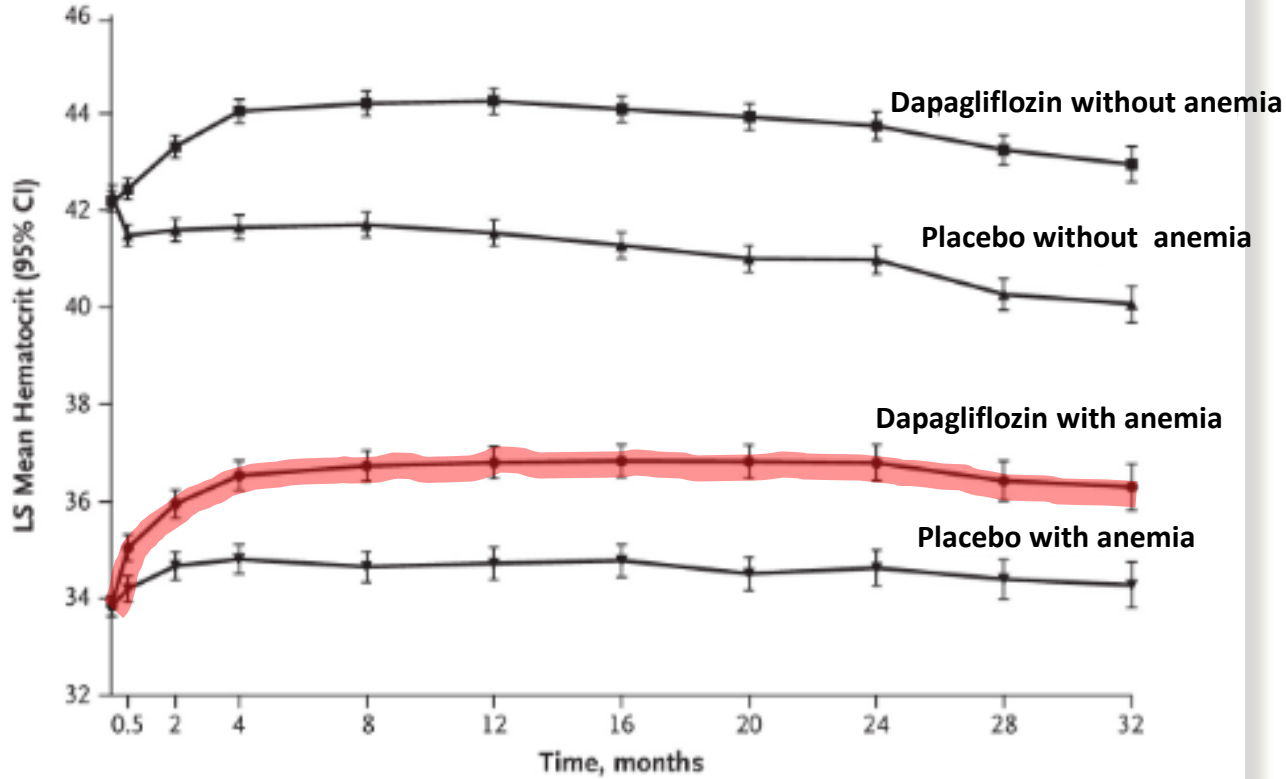
Possible mechanism by which SGLT2i increase erythropoietin production



Circulation. 2019 Apr 23;139(17):1985-1987

Placebo → 29.4% anemia was corrected

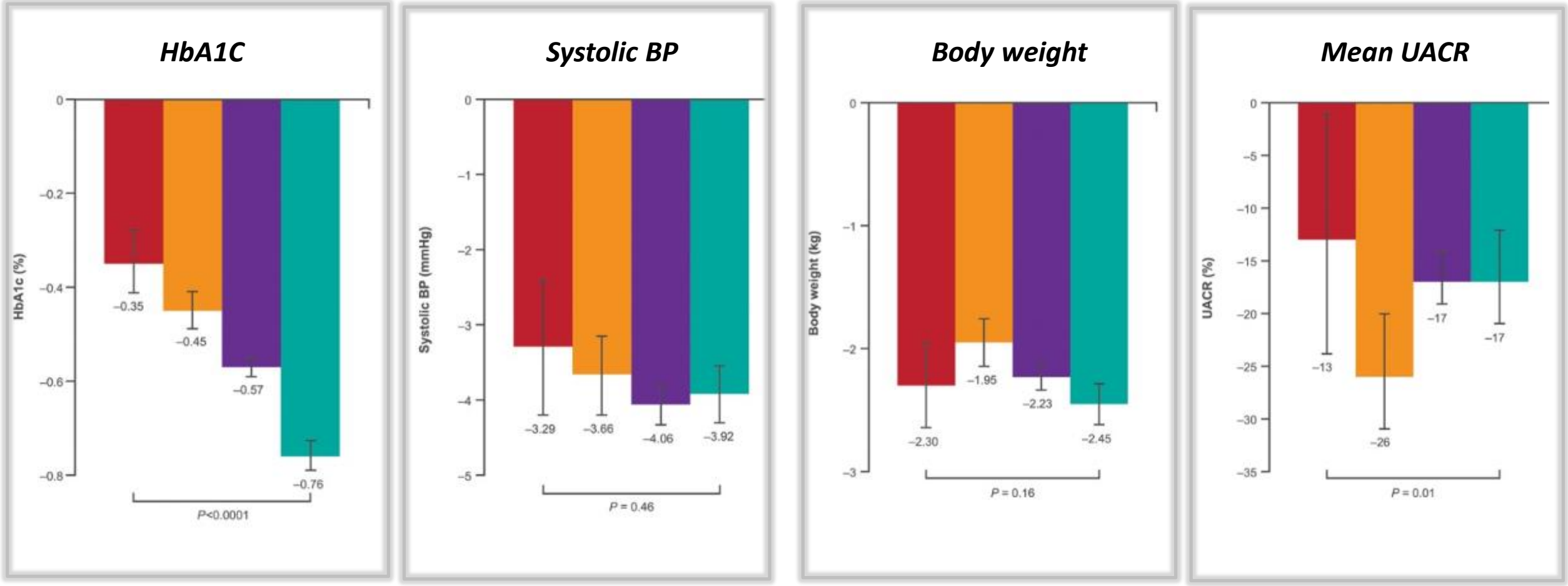
Dapagliflozin → 53.3% anemia was corrected



Participants at each time point										
Without anemia										
Dapagliflozin (n=1289 at BL)	1217	1219	1204	1145	1106	1096	1059	962	682	401
Placebo (n=1287 at BL)	1243	1224	1205	1141	1107	1095	1054	943	646	354
With anemia										
Dapagliflozin (n=858 at BL)	811	796	803	762	743	721	679	600	409	212
Pacebo (n=858 at BL)	826	793	792	739	706	691	649	588	408	228

Published May 19, 2023 NEJM Evid 2023;2(6) DOI: 10.1056/EVIDoa2300049

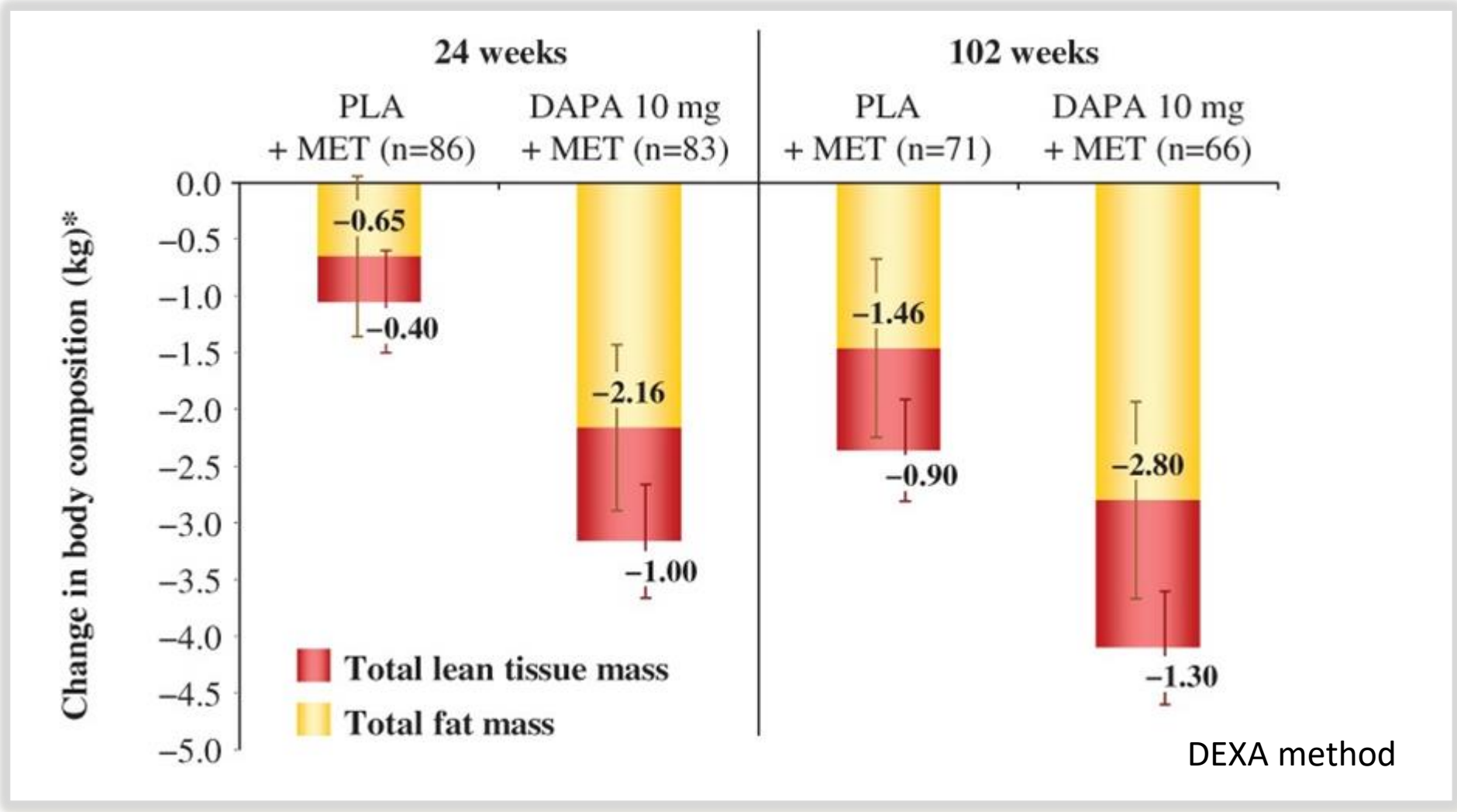
Changes in parameters with canagliflozin compared to placebo in participants with different levels of kidney function



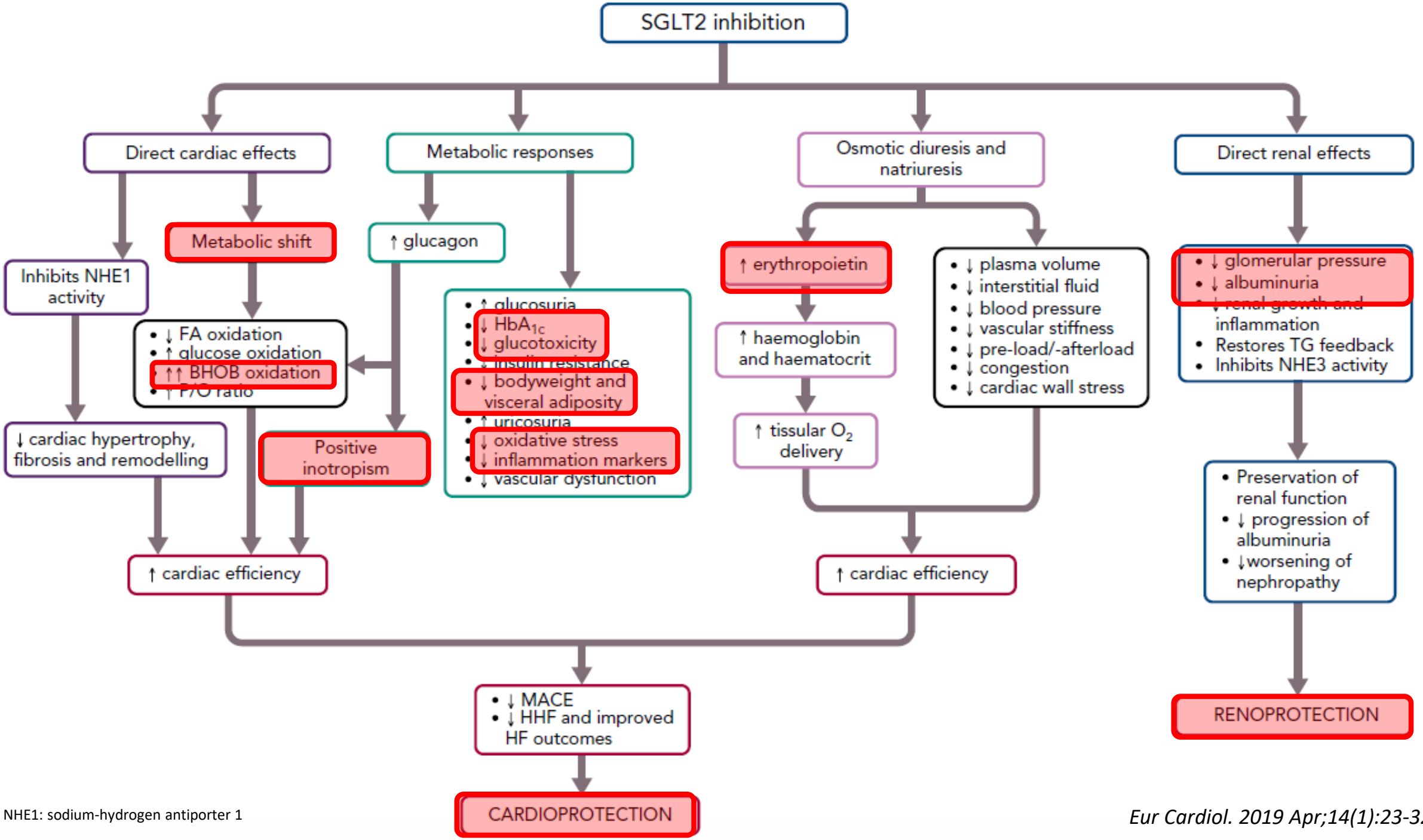
Circulation. 2018 Oct 9; 138(15): 1537–1550.

Dapagliflozin reduces weight and body fat mass over 2 years in patients with T2DM

randomized, double-blind, placebo-controlled study (NCT00855166)



Diabetes Obes Metab. 2014 Feb;16(2):159-69.



NHE1: sodium-hydrogen antiporter 1

Eur Cardiol. 2019 Apr;14(1):23-32

2023 KDIGO CKD Guideline: SGLT2 Inhibitors in CKD

Preview presented at the 60th ERA Congress June 15-18 2023

- Recommendation 3.6.1: We recommend treating patients with **type 2 diabetes** (T2D), CKD, and an **eGFR ≥20 ml/min per 1.73 m2 with an SGLT2i** (1A).

- Recommendation 3.6.2: We recommend treating adults with CKD and heart failure or eGFR ≥20 ml/min per 1.73 m2 with urine albumin-to-creatinine ratio (ACR) ≥200 mg/g with an SGLT2i (1A).

Unmet needs….

✓ at present unclear whether SGLT2 inhibition will be effective in preventing clinically relevant outcomes and be sufficiently safe in patients with severe CKD that are not included in the present label

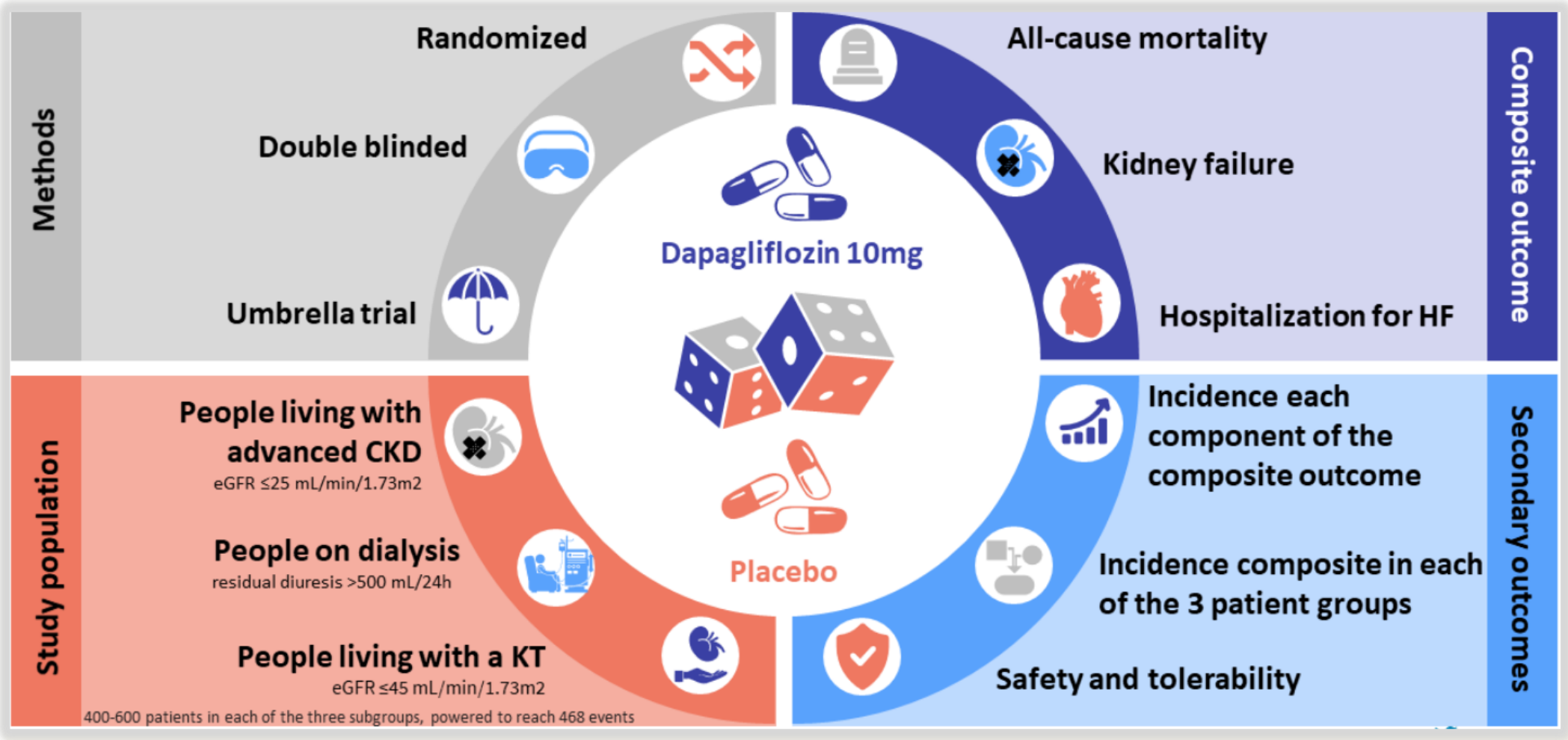
The RENAL LIFECYCLE Trial: Not just another FLOZIN trial

RENAL LIFECYCLE TRIAL

- Dapagliflozin 10 mg versus placebo
- At least 1500 patients
  (1) an eGFR , 25 ml/min per 1.73 m2
  (2) dialysis patients with residual diuresis > 500 ml/24-hour
  (3) kidney transplant recipients with an eGFR ≤ 45 ml/min per 1.73 m^2
- 1mary end point is a composite end point of kidney failure, heart failure hospitalization, or all-cause mortality
- Completion: in 4 years

Clin J Am Soc Nephrol. 2023 Jun 14. doi: 10.2215/CJN.0000000000000221. Online ahead of print.

The RENAL LIFESTYLE TRIAL (NCT05374291) : RCT to assess the effect of Dapagliflozin on renal and cardiovascular outcomes in people living with severe CKD



Completion in 4 years

DAPA-CKD (Dapagliflozin) :

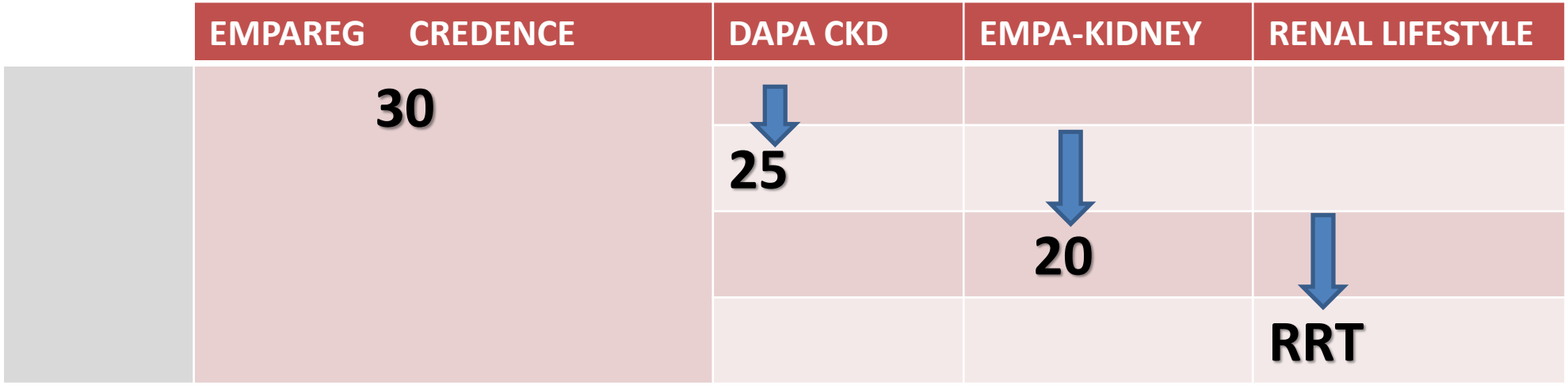
1. ***Reduction in risk of all-cause mortality in CKD*** *(mainly in the non CV events)*
2. ***Improvement in kidney disease outcomes, being equally effective in diabetic and in the nondiabetic CKD patients***

“The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases.”

Sir William Osler

one of the "Big Four" founding professors of Johns Hopkins Hospital

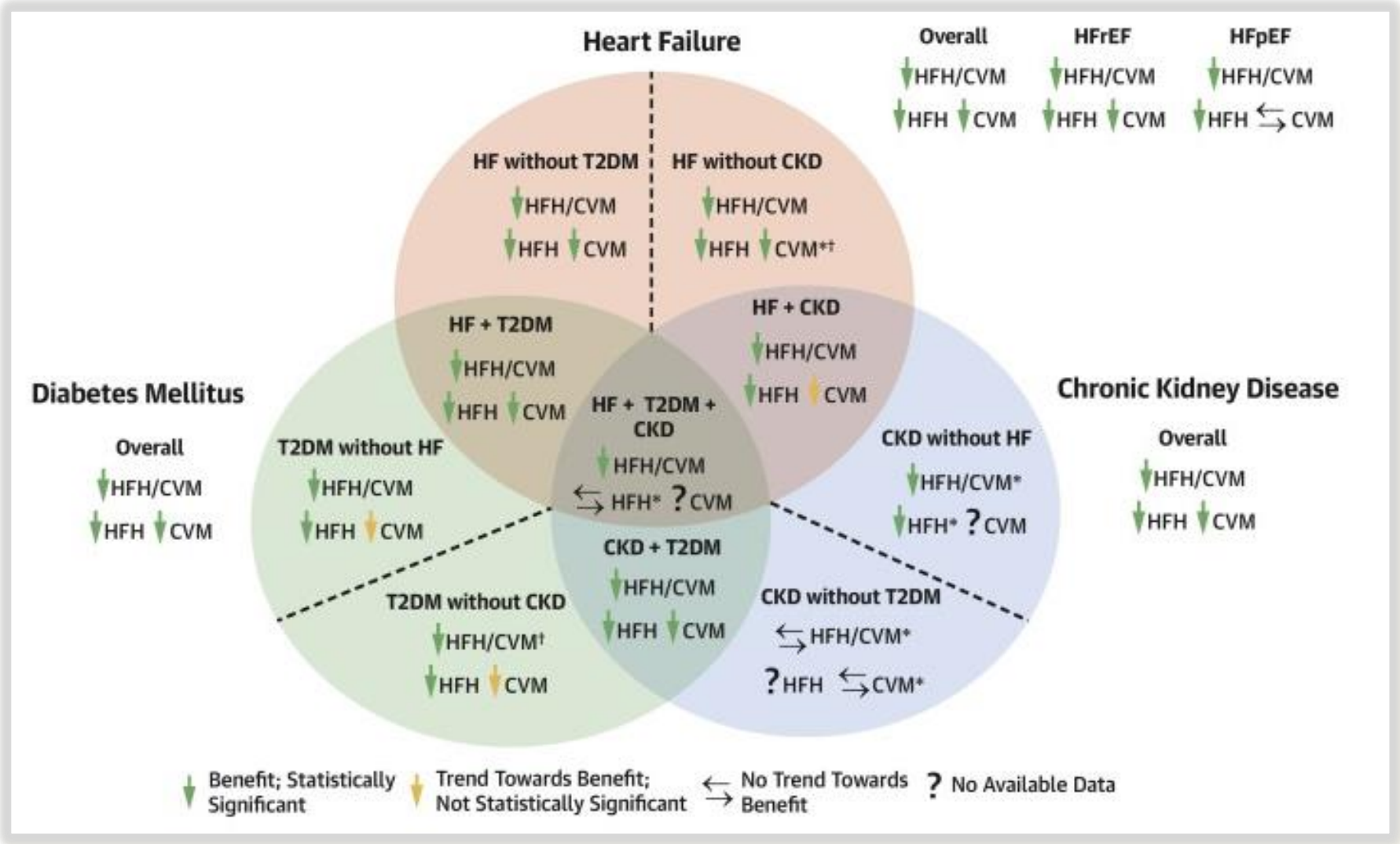
How low can we go ….
for GFR with respect to initiating SGLT2i?



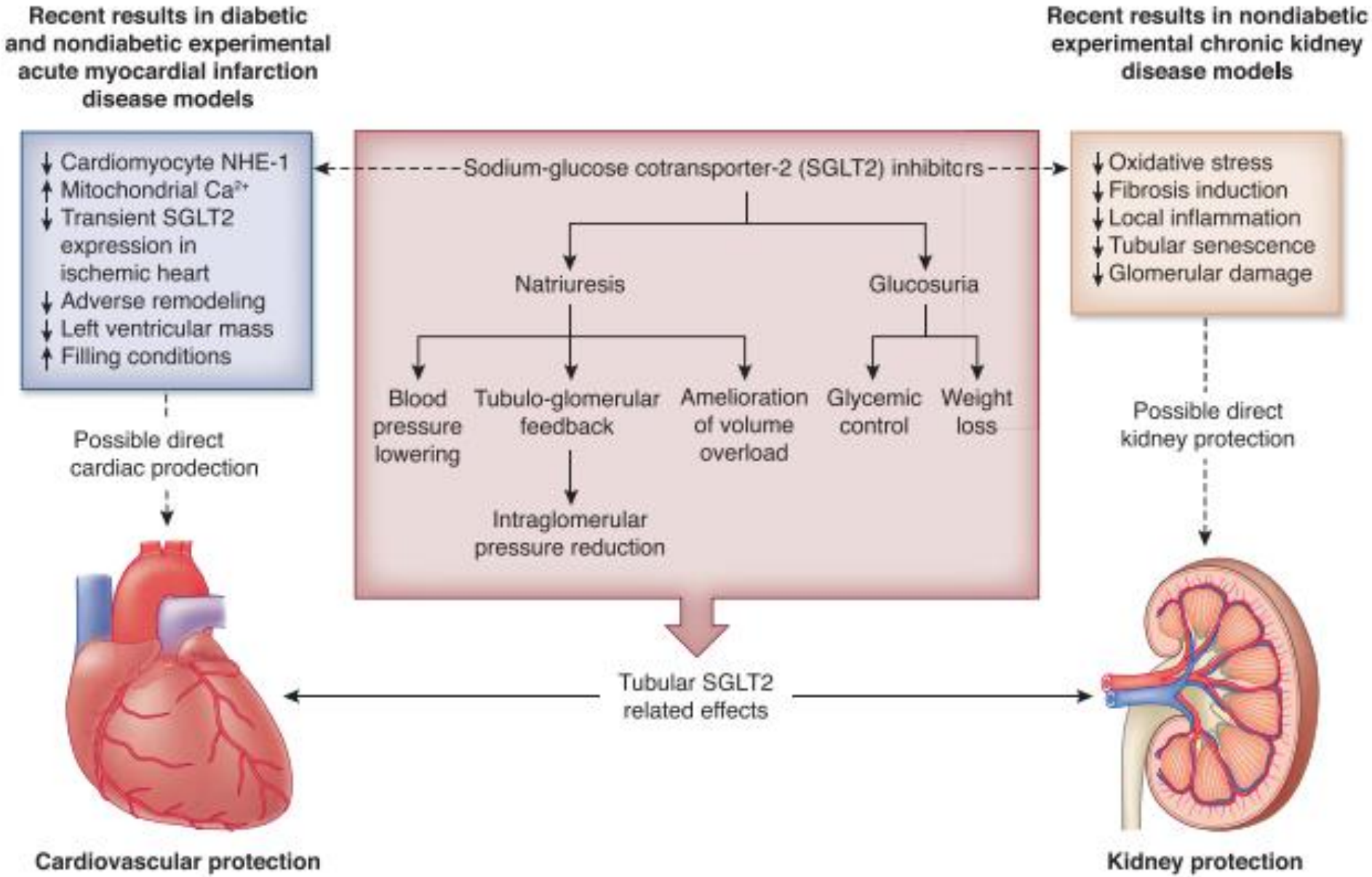
- < 20 ml/min/1.73m2 → similar concerns as starting RAS blockade in CKD 4 or 5
- Is it too late? It might be too late for kidney disease - but will starting these drugs at low GFR still help with heart failure and CV benefit?

- Both in CREDENCE and in DAPA-CKD, the drugs were continued all the way down to dialysis - and hence this practice definitely has support. There is no need to stop at a GFR threshold once they are started.

Effect of SGLT2 Inhibitors on Cardiovascular Outcomes Across Various Patient Populations

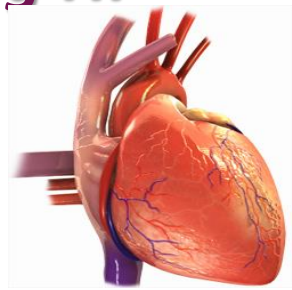


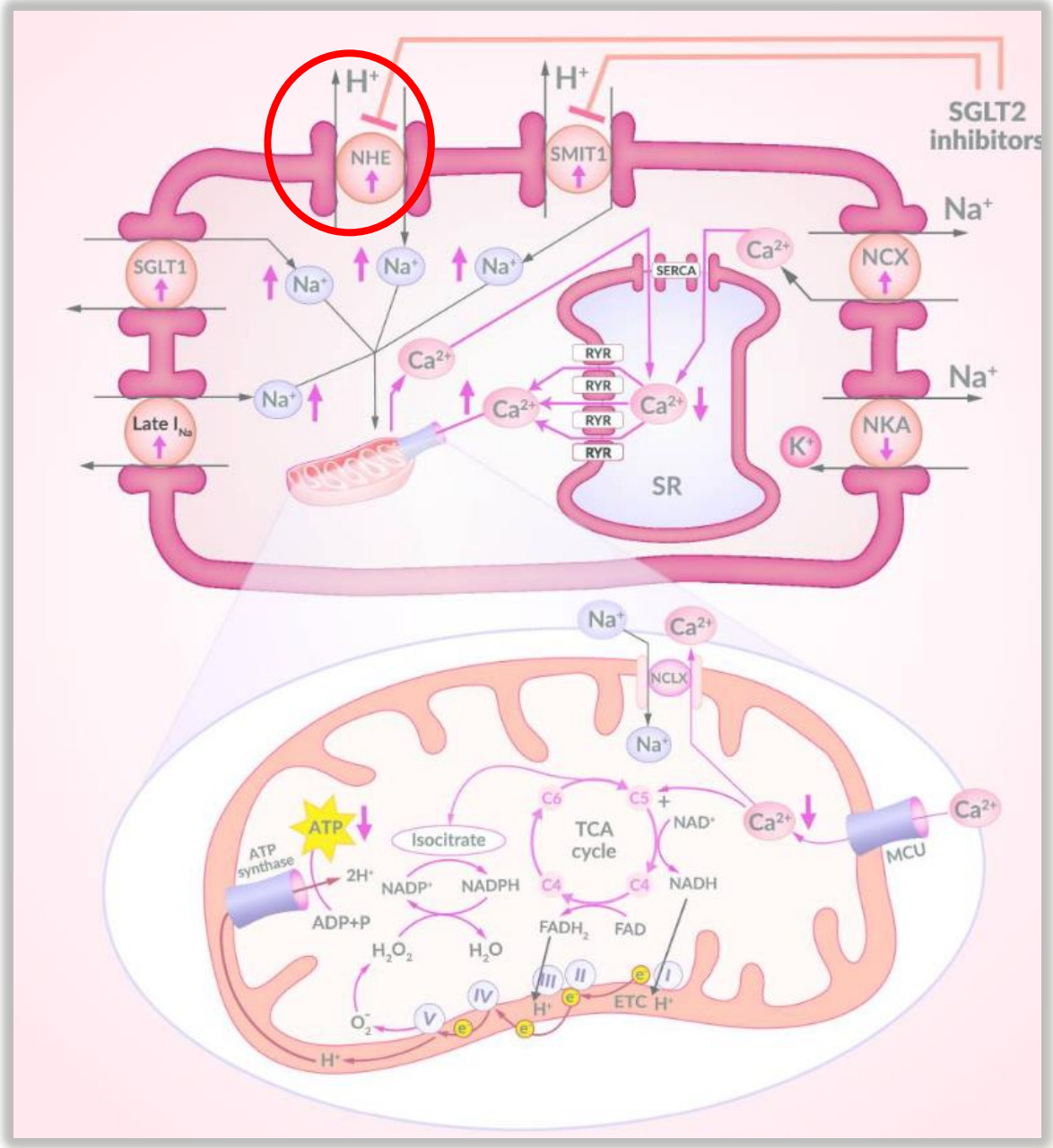
J Am Coll Cardiol. 2023 Jun 27;81(25):2377-2387



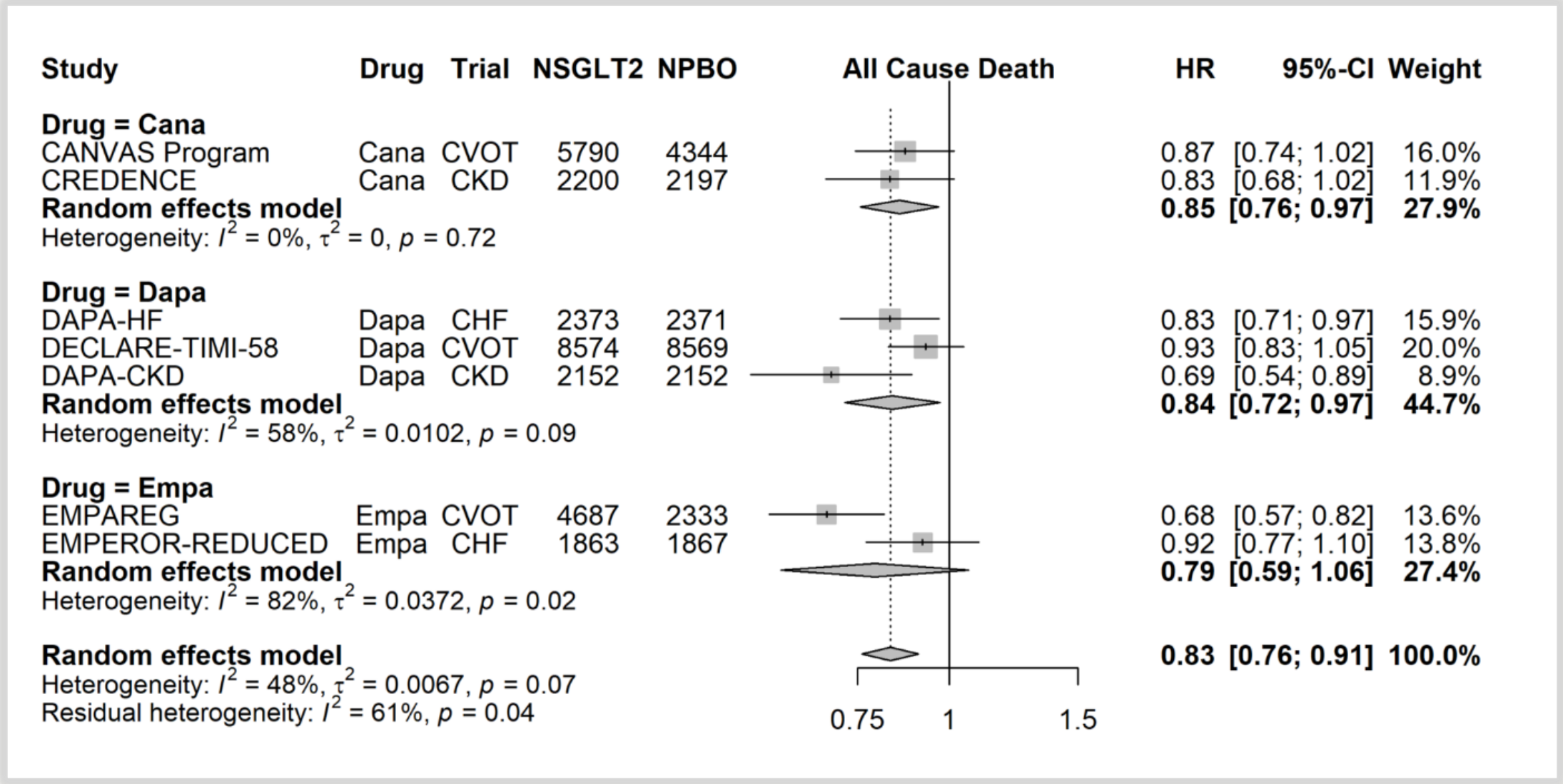
J Am Coll Cardiol. 2023 Jun 27;81(25):2377-2387

SGLT2i reduce the influx of sodium into cardiomyocyte increase during HF





Heart Fail Rev. 2021; 26(3): 603–622


Study
Drug
Trial
NSGLT2
NPBO
All Cause Death
HR
95%-CI
Weight
Drug = Cana
CANVAS Program Cana CVOT 5790 4344 0.87 [0.74; 1.02] 16.0%
CREDENCE Cana CKD 2200 2197 0.83 [0.68; 1.02] 11.9%
Random effects model 0.85 [0.76; 0.97] 27.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.72
Drug = Dapa
DAPA-HF Dapa CHF 2373 2371 0.83 [0.71; 0.97] 15.9%
DECLARE-TIMI-58 Dapa CVOT 8574 8569 0.93 [0.83; 1.05] 20.0%
DAPA-CKD Dapa CKD 2152 2152 0.69 [0.54; 0.89] 8.9%
Random effects model 0.84 [0.72; 0.97] 44.7%
Heterogeneity: I^2 = 58%, τ^2 = 0.0102, p = 0.09
Drug = Empa
EMPAREG Empa CVOT 4687 2333 0.68 [0.57; 0.82] 13.6%
EMPEROR-REDUCED Empa CHF 1863 1867 0.92 [0.77; 1.10] 13.8%
Random effects model 0.79 [0.59; 1.06] 27.4%
Heterogeneity: I^2 = 82%, τ^2 = 0.0372, p = 0.02
Random effects model 0.83 [0.76; 0.91] 100.0%
Heterogeneity: I^2 = 48%, τ^2 = 0.0067, p = 0.07
Residual heterogeneity: I^2 = 61%, p = 0.04
0.75
1
1.5

DELIVER: Dapagliflozin in Heart Failure with Mildly Reduced and Preserved Ejection Fraction

Purpose:
To evaluate whether SGLT2 inhibitors (dapagliflozin) are effective in patients with heart failure and more than 40% left ventricular ejection fraction.

Trial Design: This was an international, multicenter, parallel-group, event-driven, randomized, double-blind, placebo-controlled study. N=6,263 patients with heart failure and a left ventricular ejection fraction of more than 40% were randomized in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo.

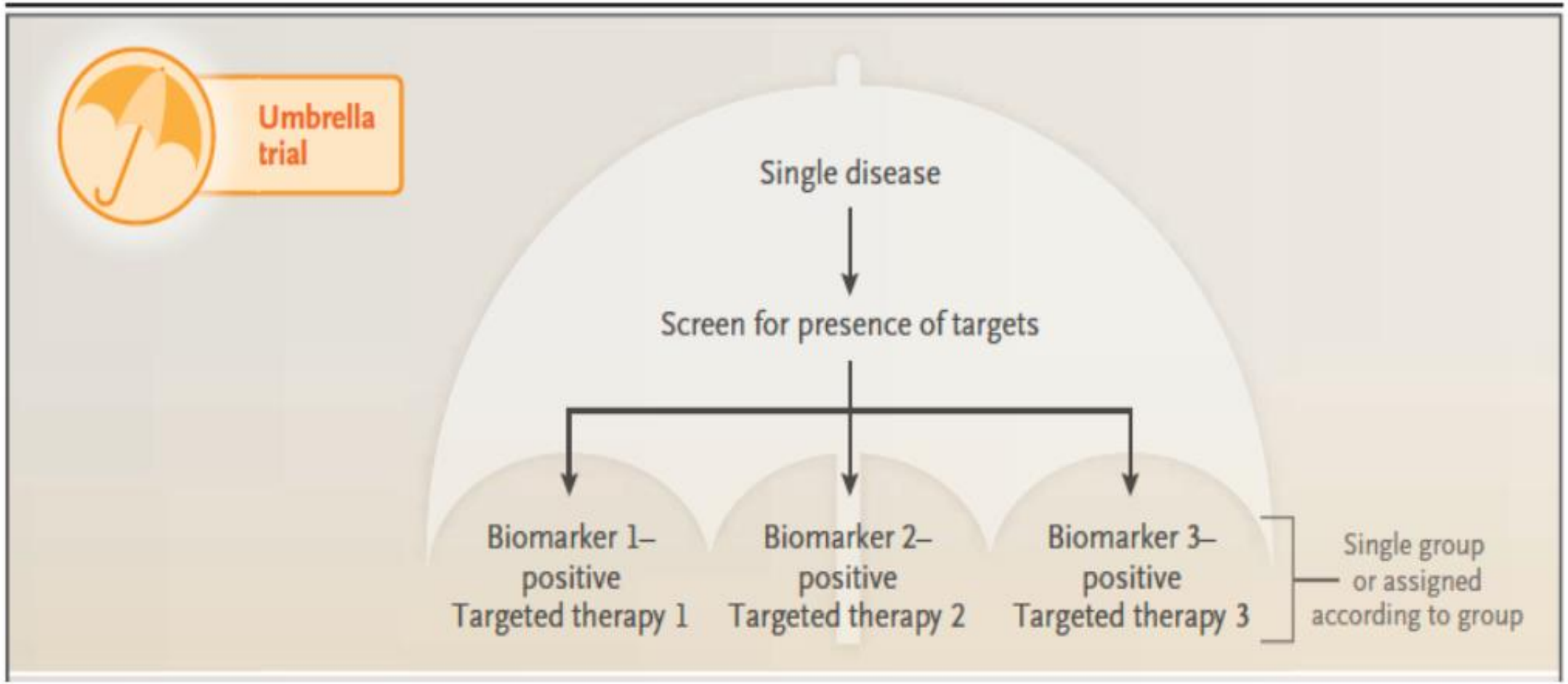
Primary Endpoint: Time-to-event analysis of a composite of worsening heart failure (defined as unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death [over a median of 2.3 years].

Other Endpoints: Total number of worsening heart failure events and cardiovascular death, death from any cause, and change in total symptoms score of KCCQ at 8 months.

Results	Dapagliflozin	Placebo	P-value
Primary Composite Outcome – no.(%): Time to first occurrence of: 1) CV death; 2) Hospitalization for HF; 3) Urgent visit for HF	512 (16.4)	610 (19.5)	< 0.001
Total # of worsening HF events + Death	815	1057	< 0.001
Death from any cause – no. (%)	497 (15.9)	526 (16.8)	NA
Change in total symptom score of KCCQ at 8 months	Win ratio, 1.11; 95% CI, 1.03-1.21; P=0.009		
Results: Among individuals with heart failure and a mildly reduced or preserved ejection fraction, dapagloflozin reduced the combined risk of worsening heart failure or cardiovascular death.			

Results reflect the data available at the time of presentation.

Presented by: Dr. Scott Solomon for the DELIVER Investigators


Umbrella trial
Single disease
Screen for presence of targets
Biomarker 1–positive Targeted therapy 1
Biomarker 2–positive Targeted therapy 2
Biomarker 3–positive Targeted therapy 3
Single group or assigned according to group

https://www.cfrjournal.com/video-index/hfa-23-deliver-phase-iii-trial

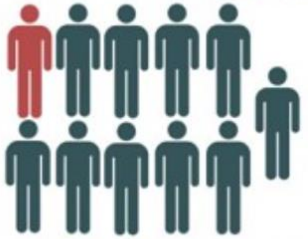
https://pace-cme.org/2019/09/24/cardioprotective-mechanisms-of-sglt2-inhibitors-what-do-cardiologists-need-to-know/

http://www.nephjc.com/news/dapa-ckd

International Diabetes Federation

Number of diabetics will rise to 642 million by 2040

1 in 11 adults have diabetes



415 million worldwide

1 in 3 adult diabetics have chronic kidney disease

138 million

No current test that can predict diabetic kidney disease

Kidney disease is one of the major complications of diabetes

North America & Caribbean (NAC)

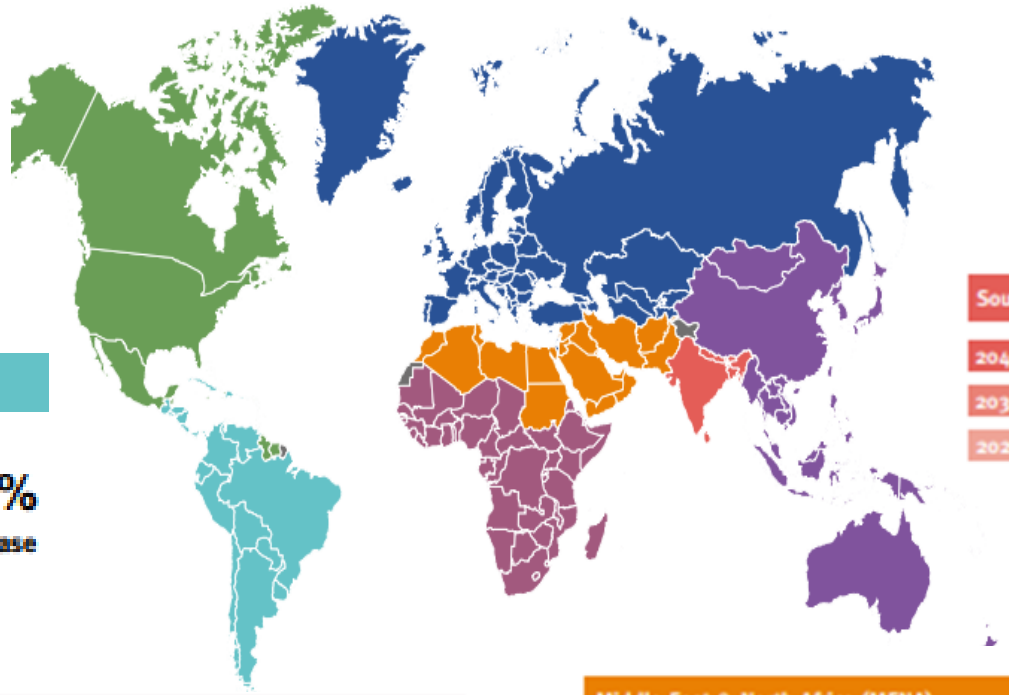
2045	63 million
2030	57 million
2021	51 million

24% increase

Europe (EUR)

2045	69 million
2030	67 million
2021	61 million

13% increase



South & Central America (SACA)

2045	49 million
2030	40 million
2021	32 million

50% increase

South-East Asia (SEA)

2045	152 million
2030	113 million
2021	90 million

68% increase

Western Pacific (WP)

2045	260 million
2030	238 million
2021	206 million

27% increase

Africa (AFR)

2045	55 million
2030	33 million
2021	24 million

134% increase

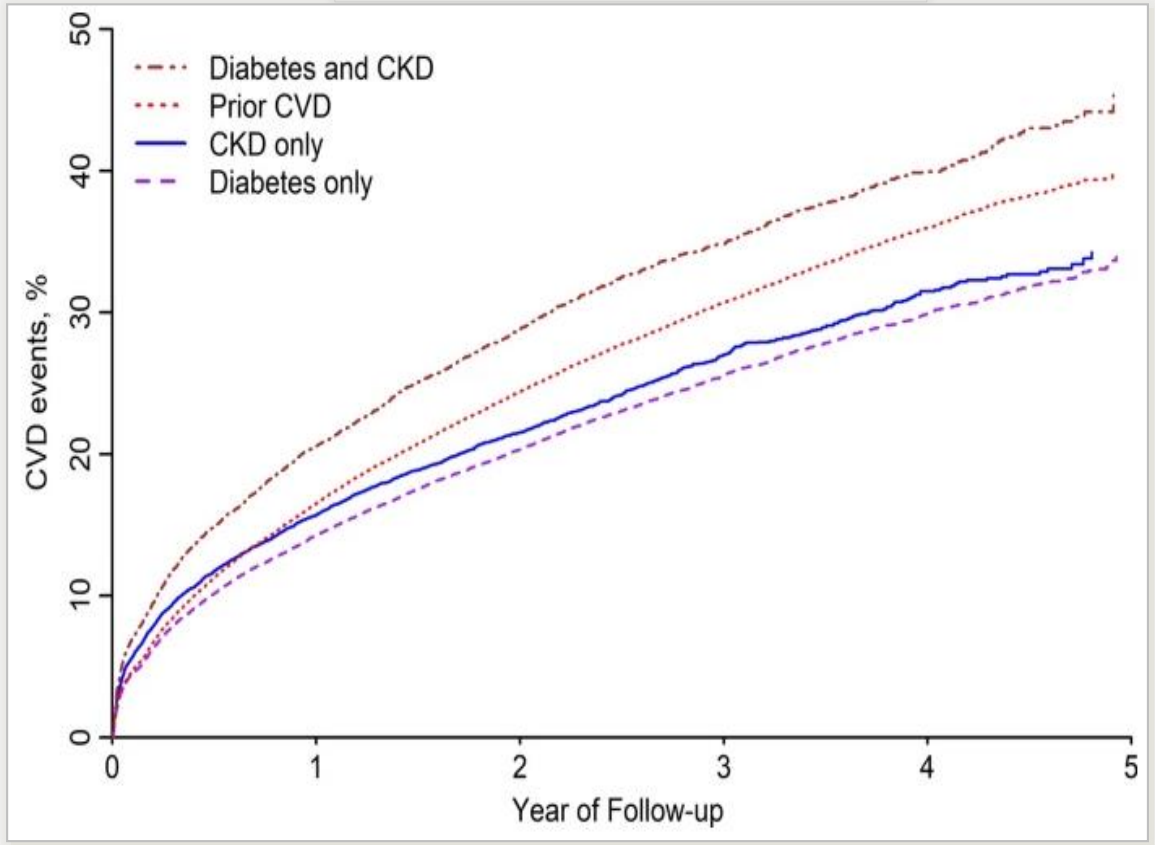
Middle East & North Africa (MENA)

2045	136 million
2030	95 million
2021	73 million

87% increase

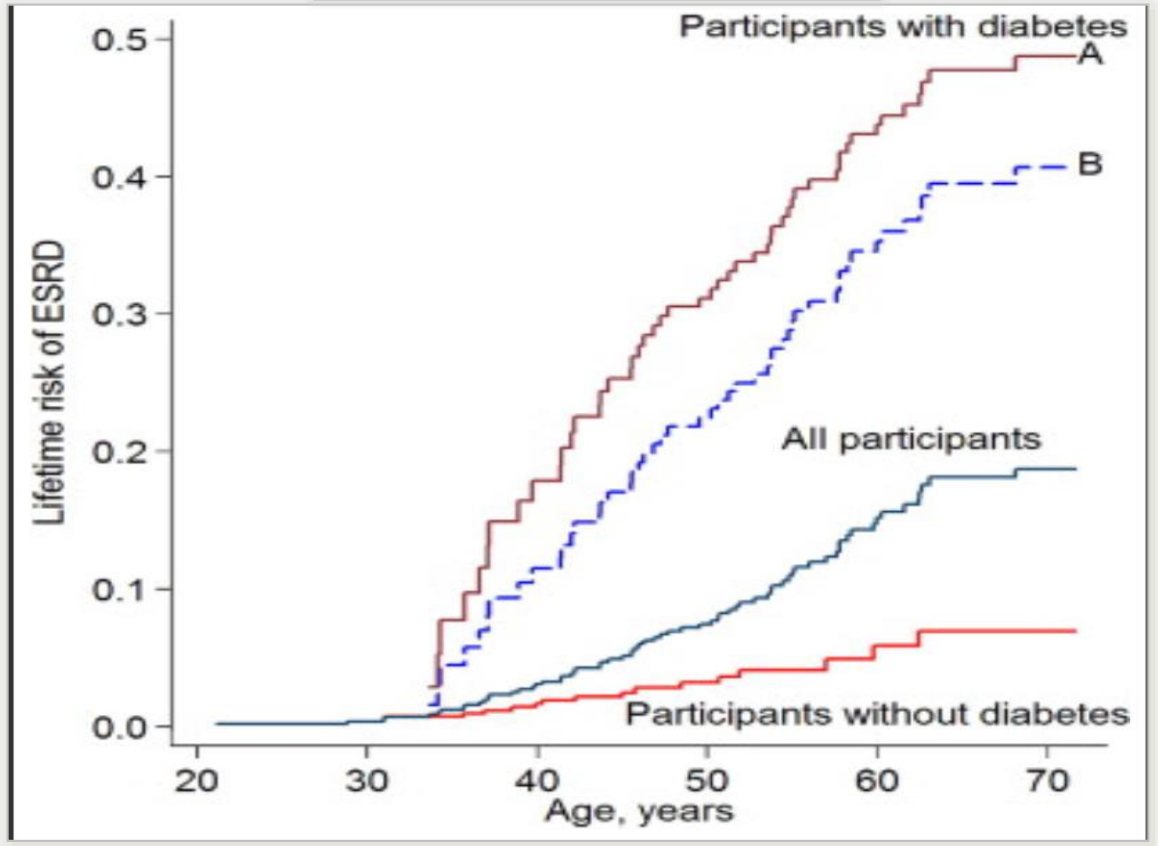
Type II DM

↑ 2-3X risk for CVD



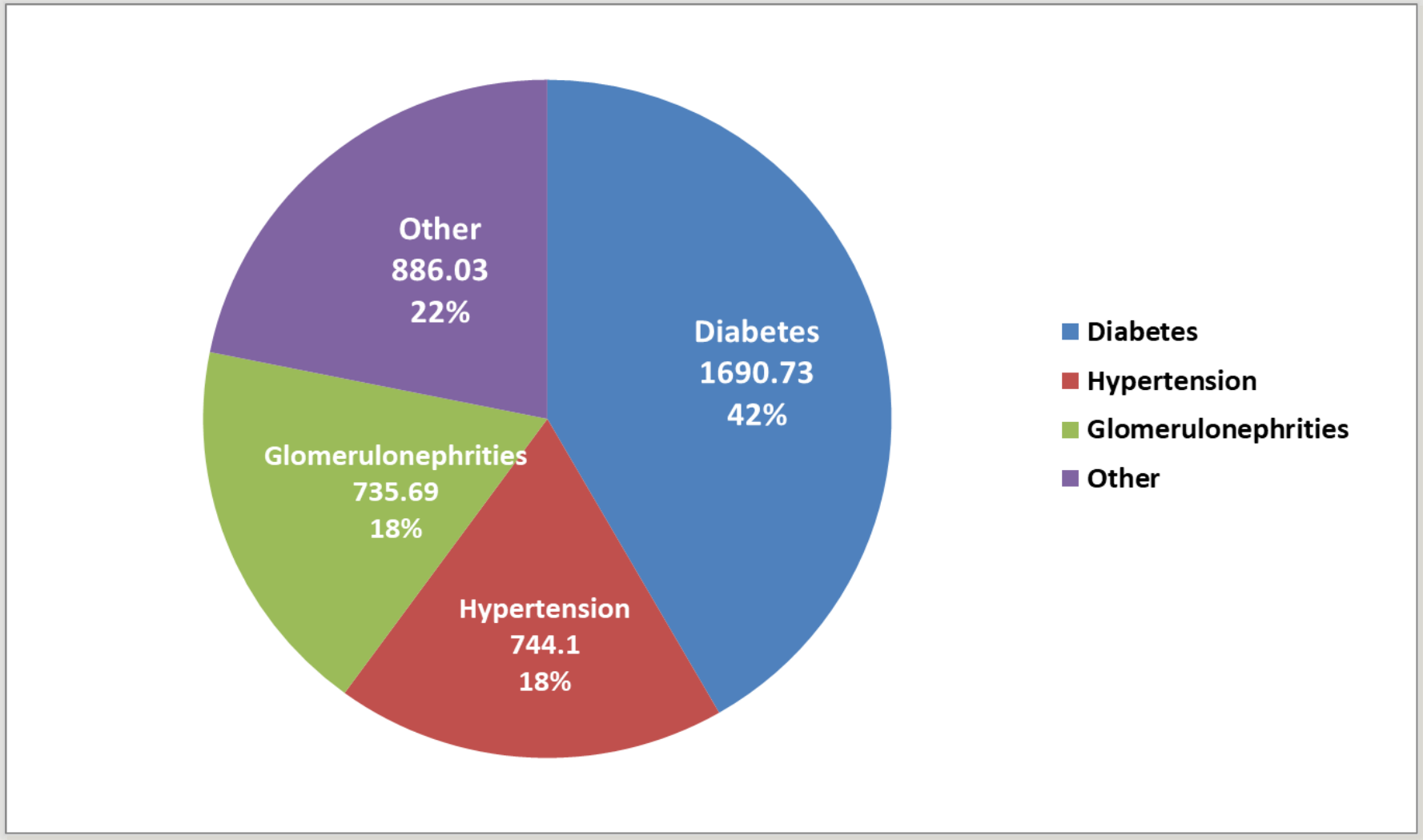
World J Diabetes 2016 October 15; 7(18): 449-461
Cardiovasc Diabetol. 2021 Mar 1;20(1):58

↑ 10X risk for ESKD



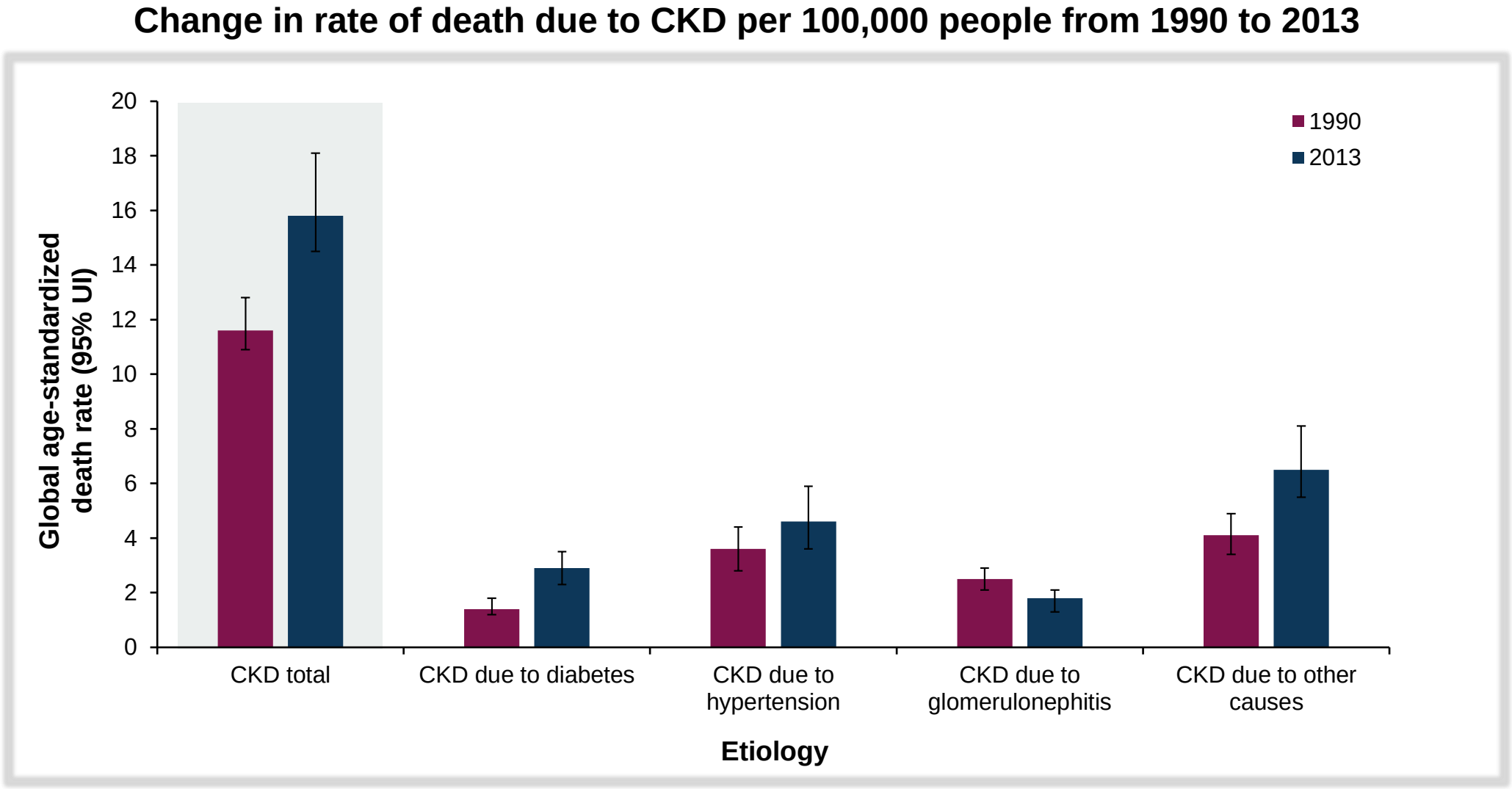
Am J Kidney Dis. 2013;62(4):844-846

Age-standardized global prevalence rate of CKD



Xie Y et al. Kidney Int. 2018; 567-581

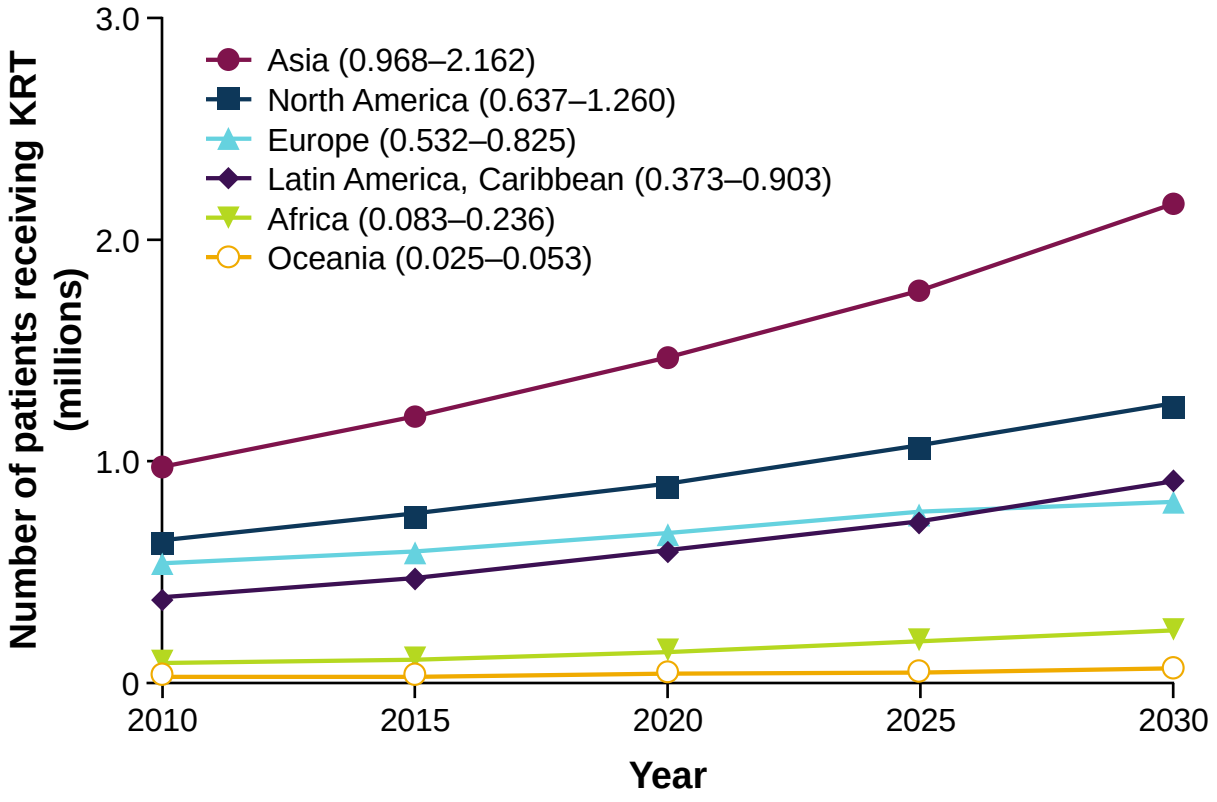
The mortality burden of CKD has been rising since 1990



Jager KJ et al. Nephrol Dial Transplant. 2017;32(supp 2):ii121–ii128

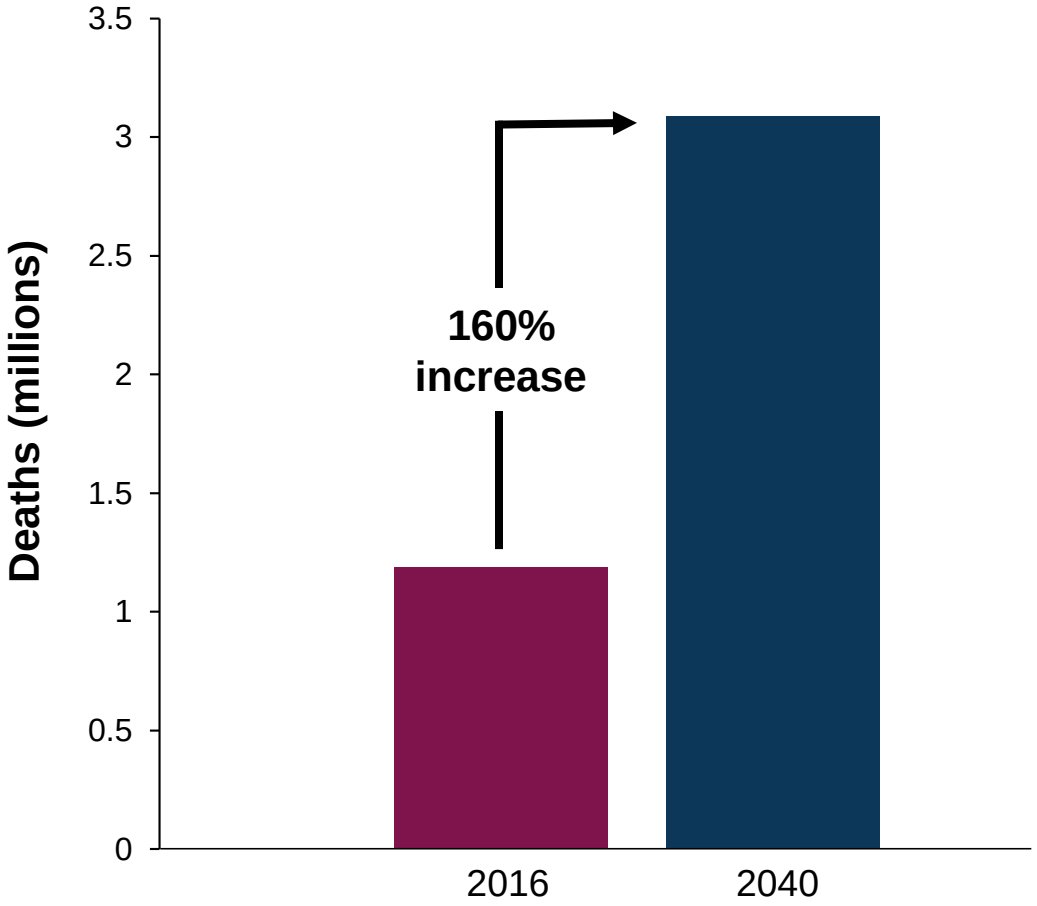
Furthermore, rates of KRT and mortality due to CKD are projected to rise substantially on a global scale

Estimated number of patients undergoing KRT from 2010 to 2030 worldwide[1]



The number receiving KRT is estimated to increase to more than 5 million by 2030[1]

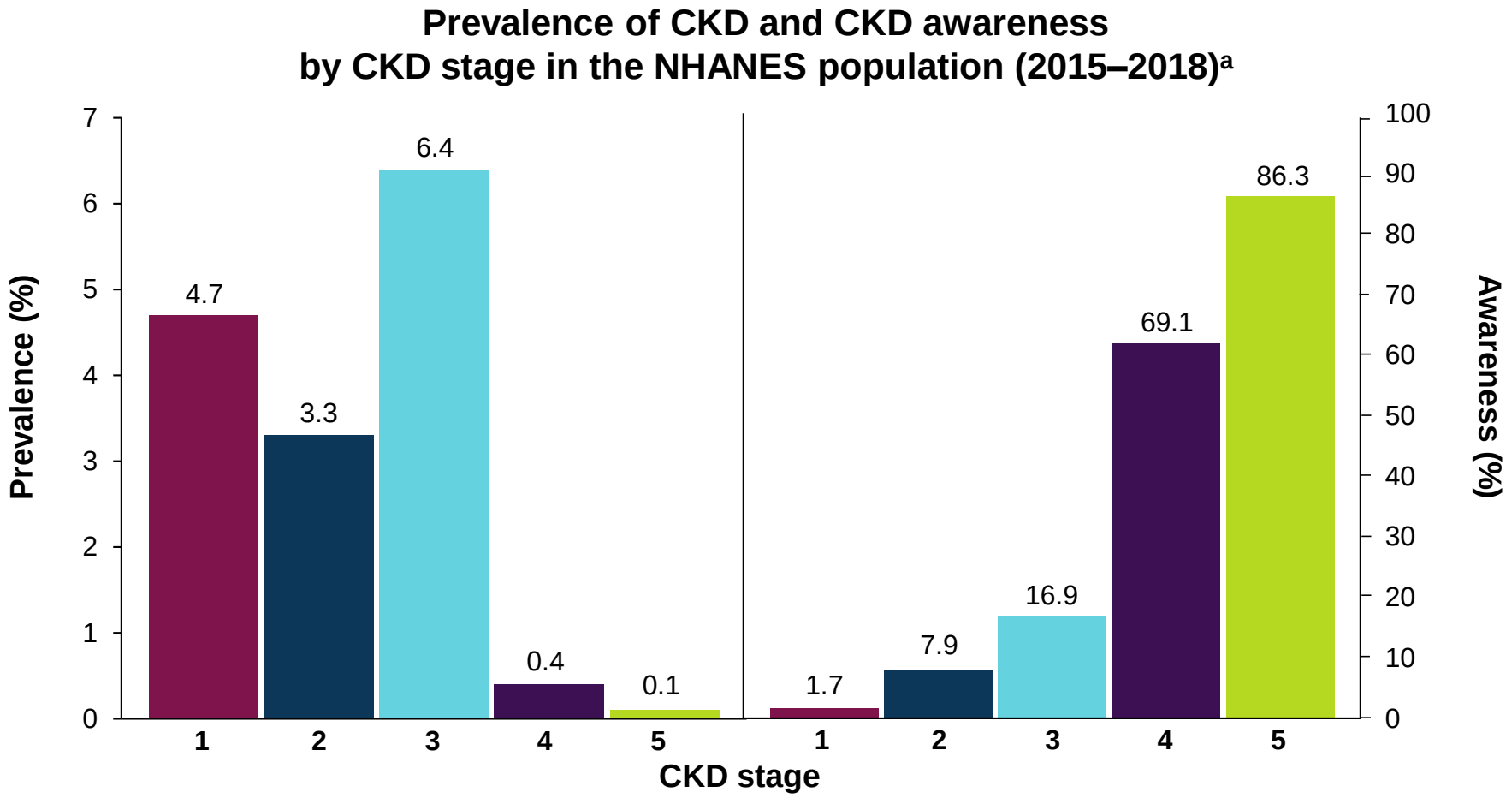
CKD deaths in 2016 and forecast for 2040[2]



CKD = chronic kidney disease; KRT = kidney replacement therapy.

1. Liyanage T et al. *Lancet.* 2015;385:1975–1982; 2. Foreman KJ et al. *Lancet.* 2018;392:2052–2090.

Among those diagnosed with CKD stages 1–3, the percentage of patients aware of their CKD is low



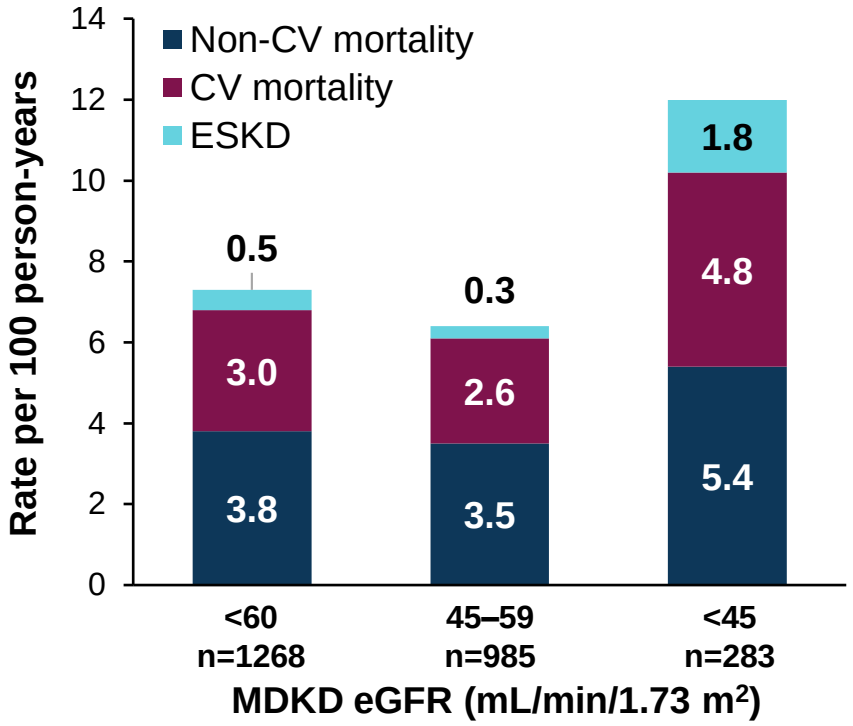
[a]Awareness was assessed as those who reported being told that they had kidney disease.

CKD = chronic kidney disease; NHANES = National Health and Nutrition Examination Survey.

USRDS. 2020 Annual data report: CKD in the general population. https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population.

Death is more likely than progression to ESKD in patients with CKD

ESKD, CV, and non-CV mortality[1]



Relative risk of CV mortality[2]

Categorical meta-analysis[a]

Increasing kidney damage

Decreasing kidney function

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref[b]	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Leading causes of death in CKD:[3]

- CV events
- non-CV causes (e.g. cancer, infection)

Kidney decline is associated with increased risk of CV mortality

[a]Each cell represents a pooled RR from a meta-analysis, colors reflect the ranking of adjusted RR. Bold numbers indicate statistical significance ($p<0.05$); [b]Incidence rate of 4.5/1000 person-years. Results are adjusted for covariates and compared to the reference cell.

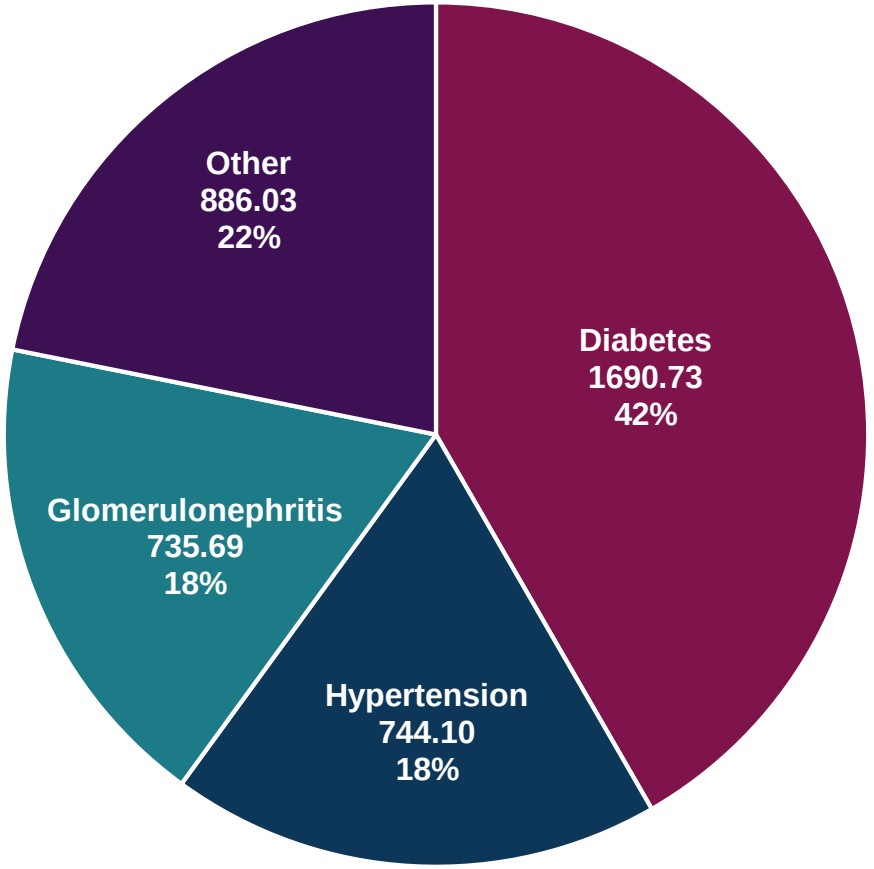
ACR = albumin:creatinine ratio; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; MDKD = modified diet in kidney disease; RR = risk reduction.

1. Dalrymple LS et al. *J Gen Intern Med.* 2010;26:379–385; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150; 3. Thompson S et al. *J Am Soc Nephrol.* 2015;26:2504–2511.

Disease pathology and progression

The causes of CKD are diverse, with diabetes and hypertension responsible for more than half of all cases

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016

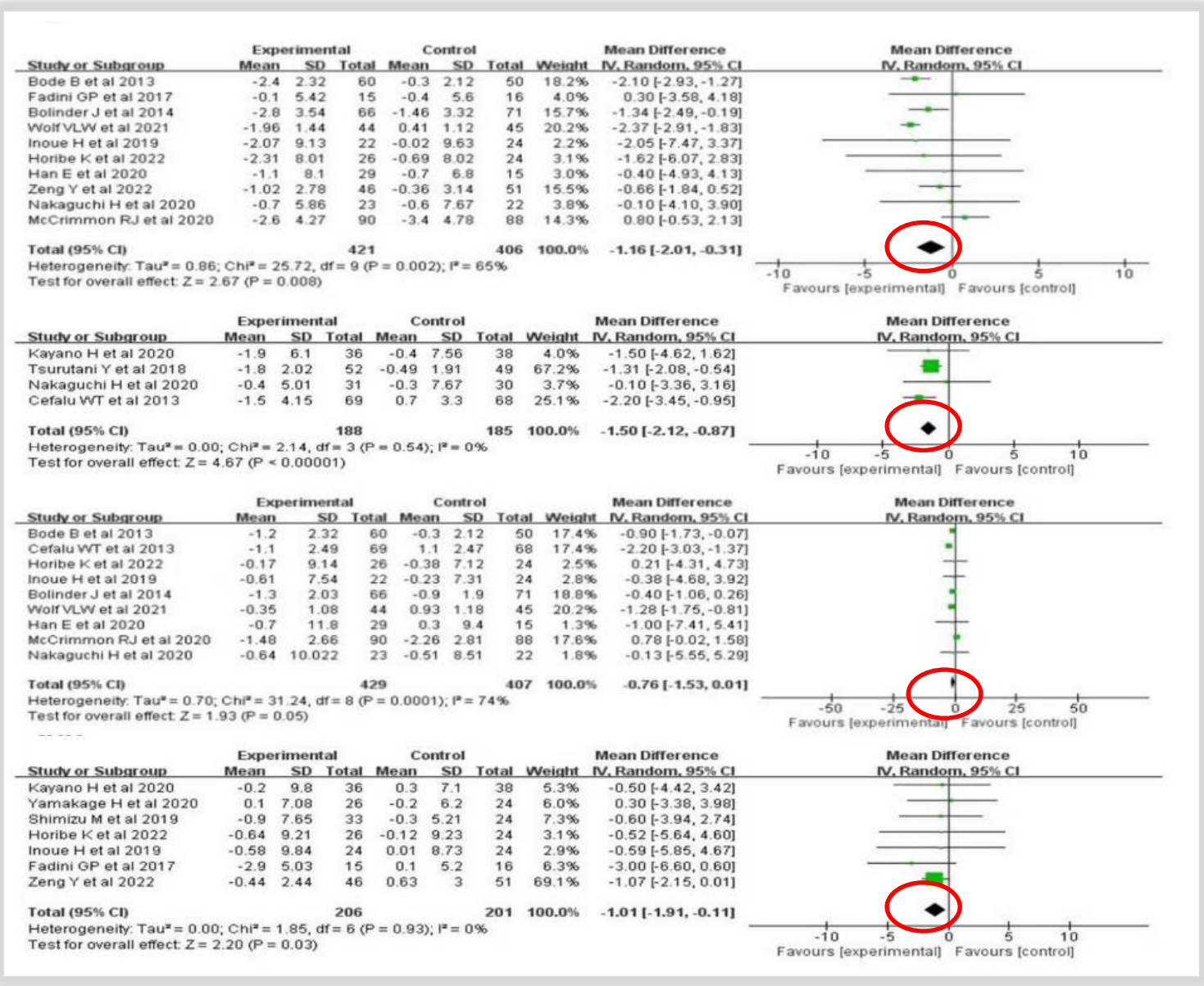


CKD = chronic kidney disease.

Xie Y et al. *Kidney Int.* 2018;94:567–581.

Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials

- *18 RTCs*
- *1430 participants*



Fat mass

Percentage body fat

Lean mass

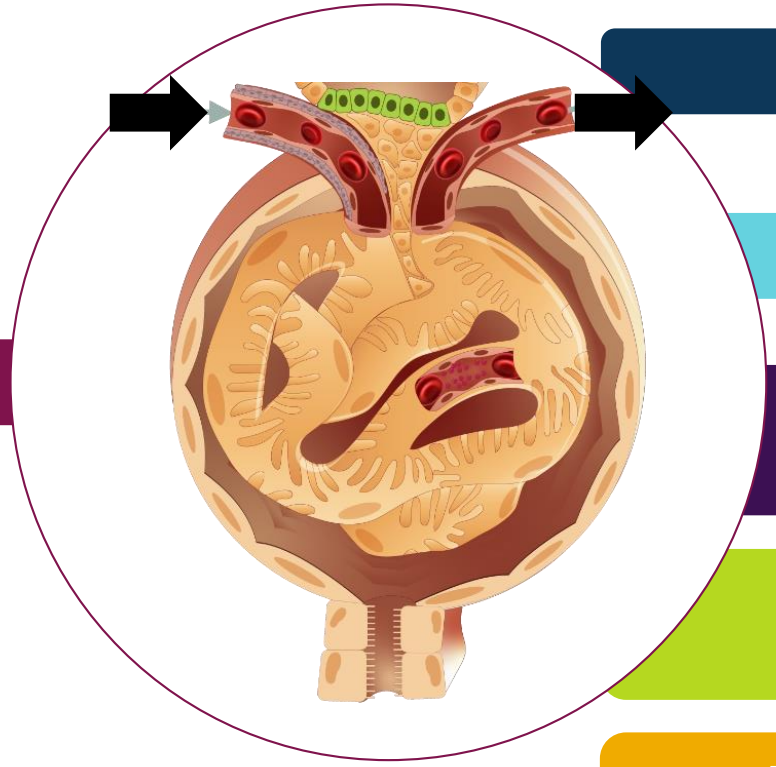
Skeletal muscle mass *(→the risk of sarcopenia)*

PLoS One. 2022 Dec 30;17(12):e0279889

Kidney hyperfiltration is a common feature and driver of disease progression across CKD etiologies

Diabetes

Diabetic nephropathy[1]



Nondiabetes

Hypertensive nephrosclerosis[2]

IgA nephropathy[3]

Focal segmental glomerulosclerosis[4]

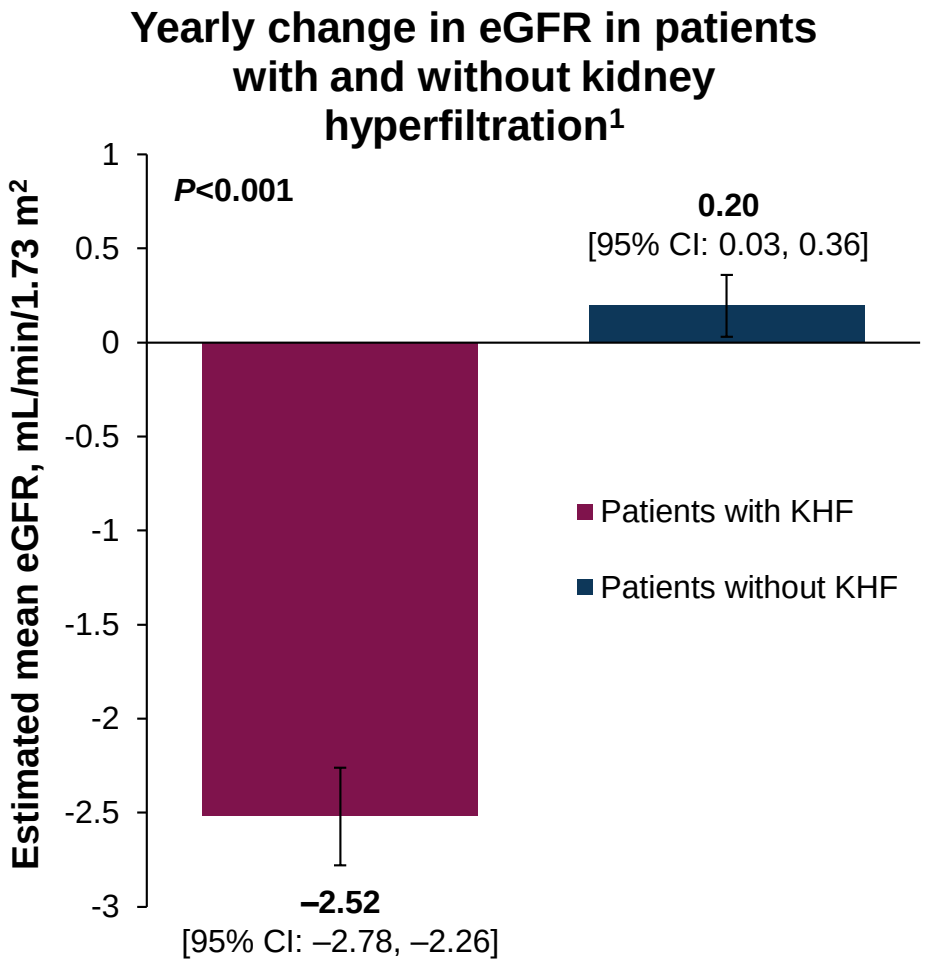
Obesity[1]

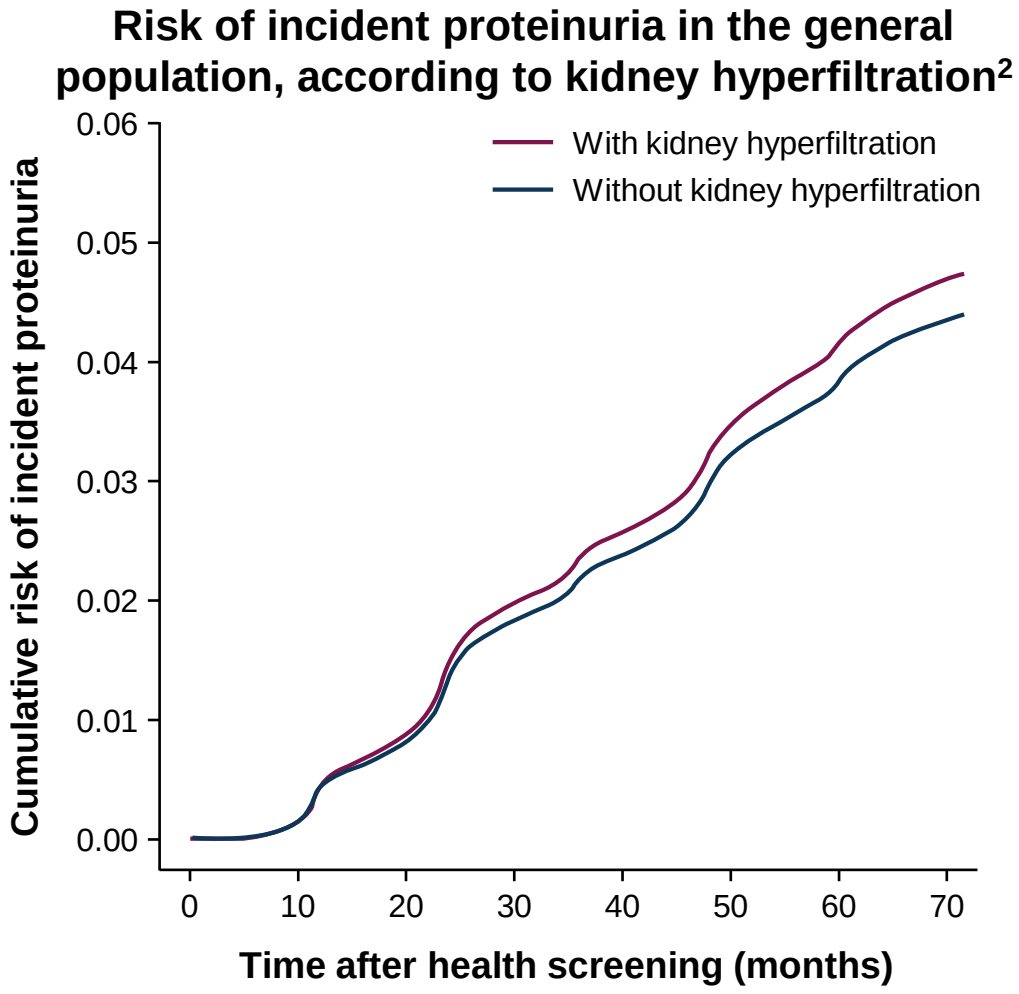
Autosomal dominant polycystic kidney disease[1]

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis; IgA = immunoglobulin A.

1. Helal I et al. *Nat Rev Nephrol.* 2012;8:293–300; 2. Palatini P. *Nephrol Dial Transplant.* 2012;27:1708–1714; 3. Coppo R. *Nephrol Dial Transplant.* 2019;34:1832–1838; 4. Rosenberg AZ et al. *Clin J Am Soc Nephrol.* 2017;12:502–517.

Kidney hyperfiltration drives eGFR decline and increases the risk of proteinuria

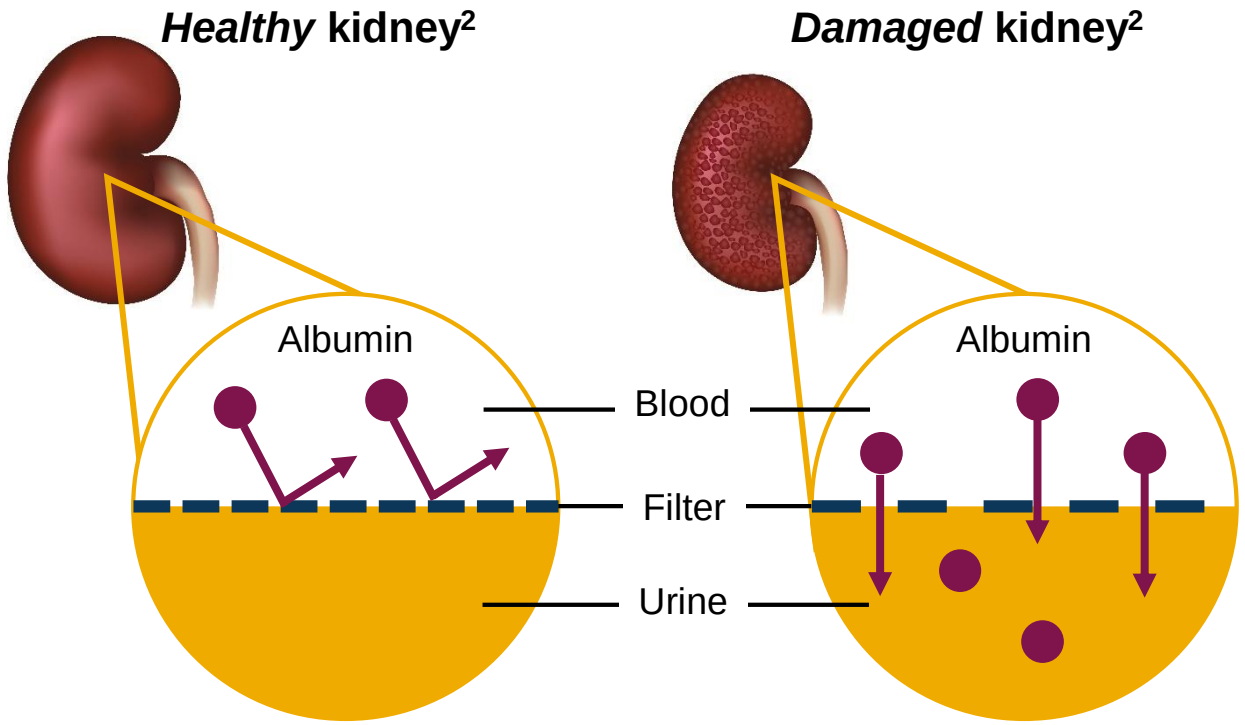




CI = confidence interval; eGFR = estimated glomerular filtration rate; KHF = kidney hyperfiltration.

1. Park M et al. *J Am Soc Nephrol.* 2015;26:1426–1433; 2. Lee SM et al. *PLoS One.* 2018;13:e0195784.

Damage to the glomerular filtration barrier leads to development of albuminuria[1]



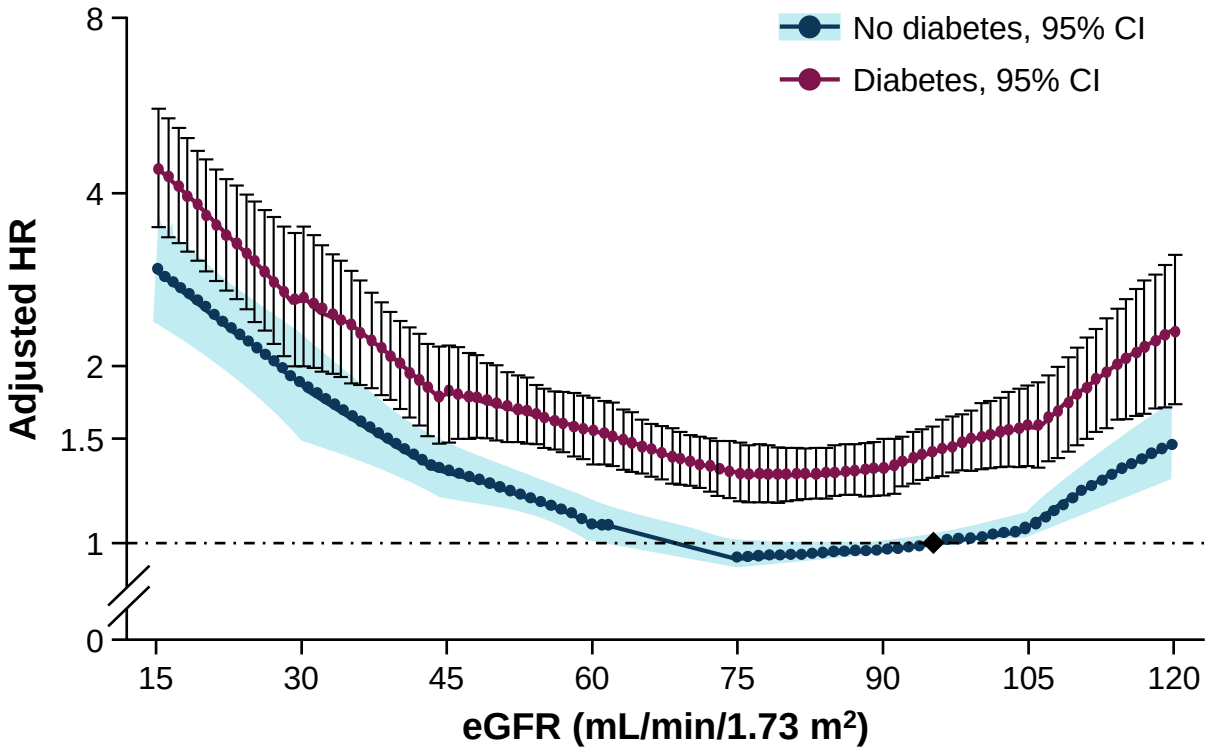
Albuminuria is a dynamic and fluctuating condition that may precede macroalbuminuria with structural changes[3,4]

CKD = chronic kidney disease.

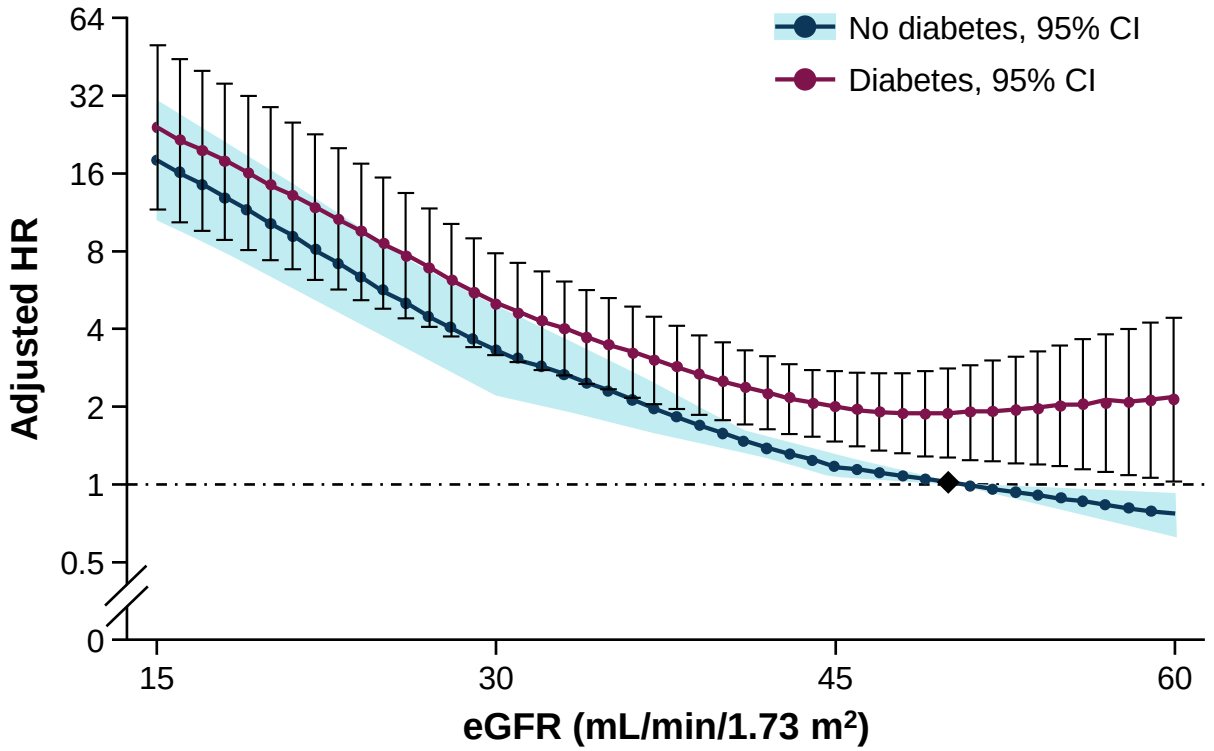
1. D'Amico G et al. *Kidney Int.* 2003;63:809–825; 2. Adapted from National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis/albuminuria-albumin-urine; 3. Gaede P et al. *Nephrol Dial Transplant.* 2004;19:2784–2788; 4. Looker HC et al. *J Am Soc Nephrol.* 2019;30:1049–1059.

Declining eGFR is associated with an increased risk of progression to ESKD and mortality

Risk of all-cause mortality according to eGFR in individuals with and without diabetes[a–c]



Risk of ESKD according to baseline eGFR in individuals with and without diabetes[b–d]



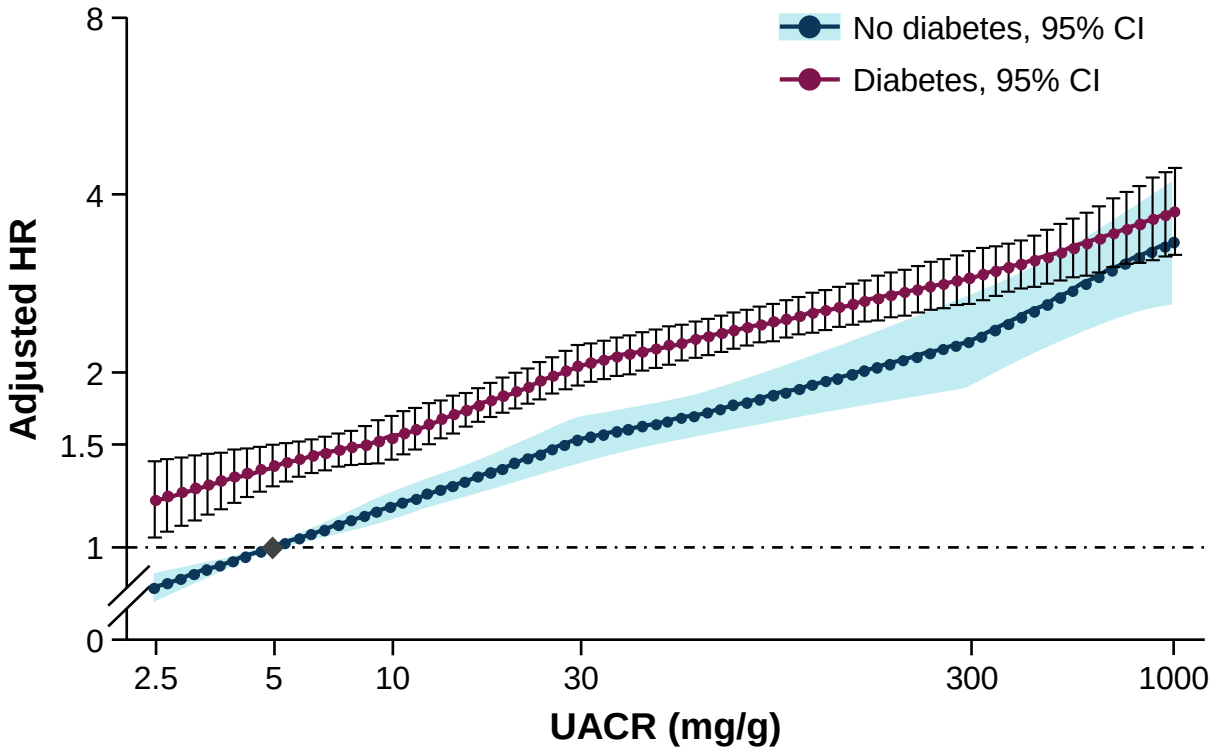
[a]Reference point: (diamond, eGFR of 95 mL/min/1.73 m^2 in the no diabetes group) for both individuals with and without diabetes to show the main effect of diabetes on risk; [b]HRs were adjusted for age, sex, race, smoking, history of CVD, serum total cholesterol concentration, BMI, and albuminuria (log UACR, log UPCR, or categorical dipstick proteinuria [negative, trace, 1+, ≥2+]); [c]Blue and purple circles denote $P<0.05$ as compared with the reference (diamond); [d]eGFR of 50 mL/min/1.73 m^2 used as the reference point (diamond) in diabetes and no diabetes groups.

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; UACR = urine albumin:creatinine ratio; UPCR = urine protein:creatinine ratio.

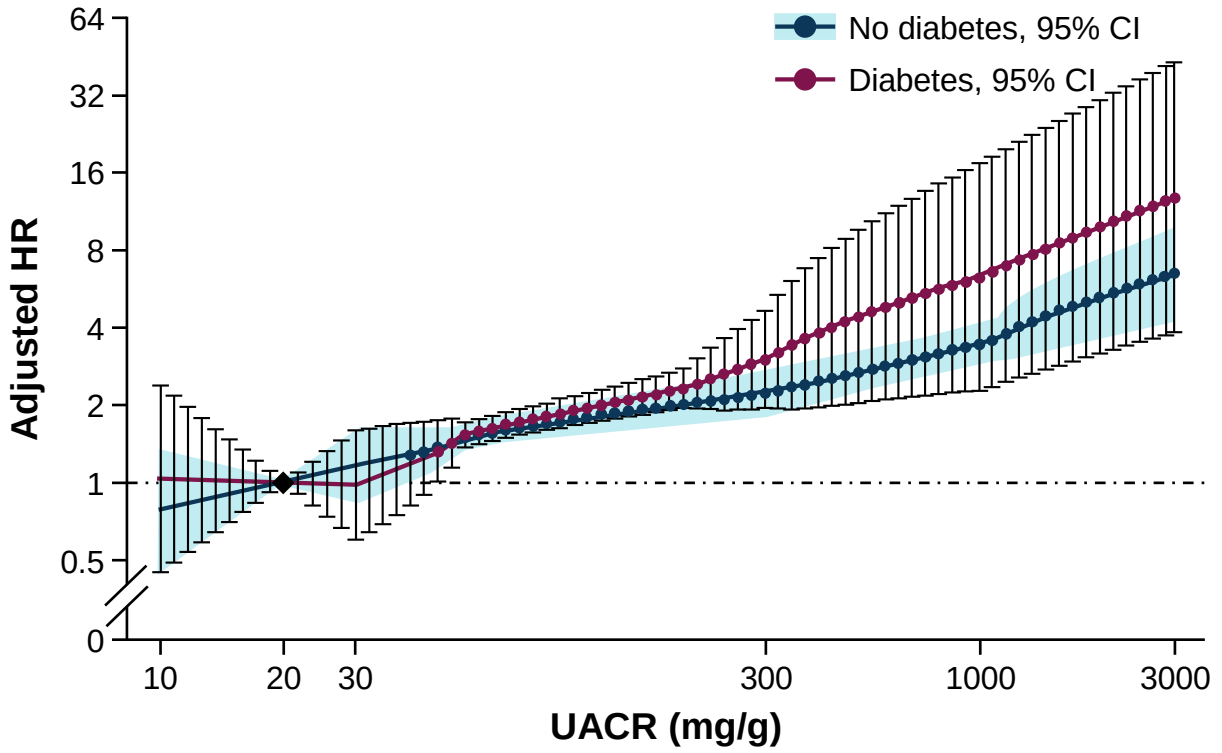
Fox CS et al. *Lancet.* 2012;380:1662–1673.

…which is also the case with albuminuria

Risk of all-cause mortality according to UACR in individuals with and without diabetes[a–c]



Risk for ESKD in populations with CKD, stratified by UACR and diabetes status[b–e]

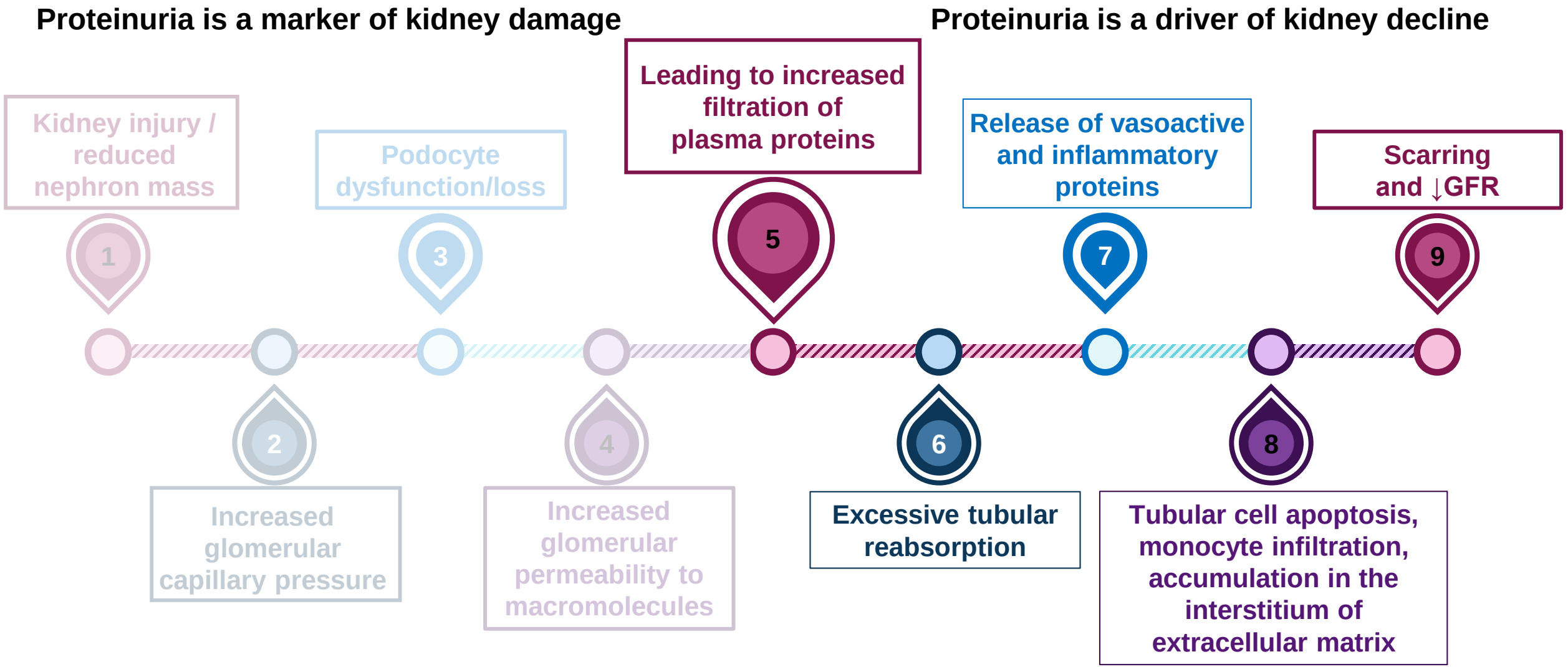


[a]Reference point (diamond) is UACR of 5 mg/g in the no diabetes group, for both individuals with and without hypertension, to show the main effect of diabetes on risk; [b]HRs were adjusted for age, sex, race, smoking, history of CVD, serum total cholesterol concentration, BMI, and eGFR; [c]Blue and purple circles denote $P<0.05$ as compared with the reference (diamond); [d]CKD defined as eGFR of <60 mL/min/1.73 m^2; [e]Reference point (diamond) is UACR of 20 mg/g.

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; UACR = urine albumin:creatinine ratio.

Fox CS et al. *Lancet.* 2012;380:1662–1673.

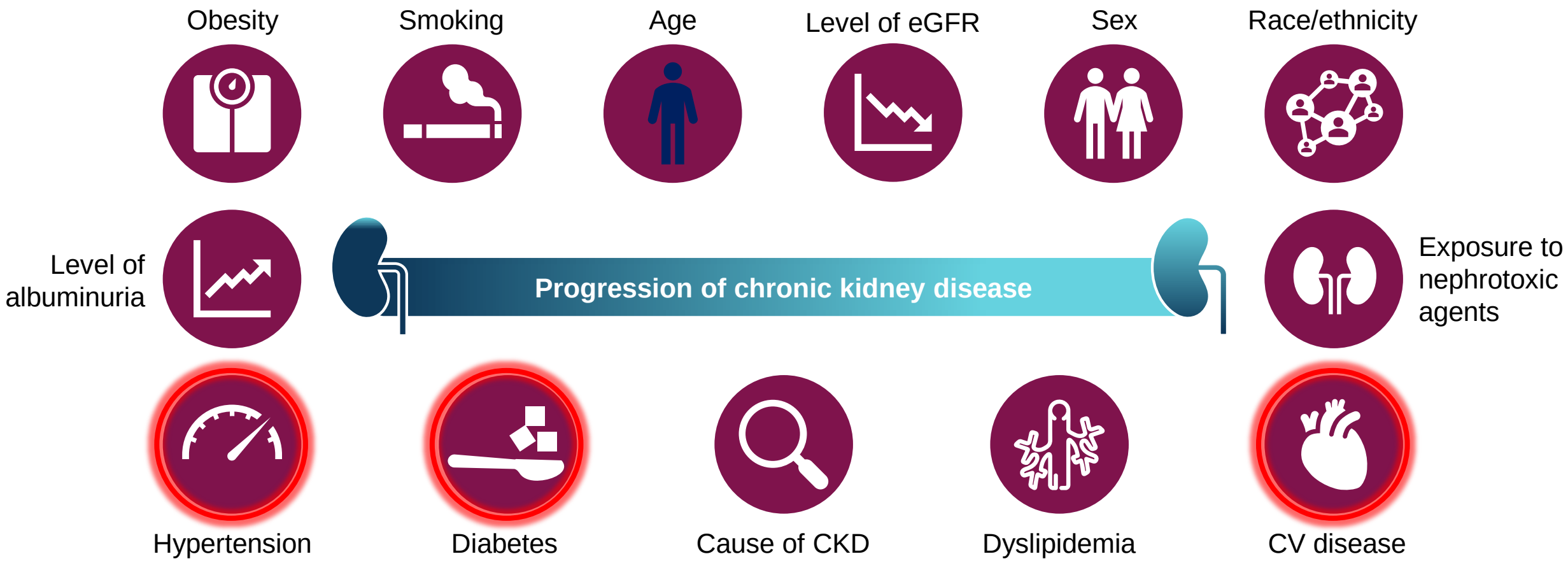
Proteinuria plays a crucial pathogenic role in the loss of kidney function and also serves as a marker of kidney damage



GFR = glomerular filtration rate.

Cravedi P et al. *Br J Clin Pharmacol.* 2013;76:516–523

Nonetheless, multiple factors affect the progression of kidney disease[1]



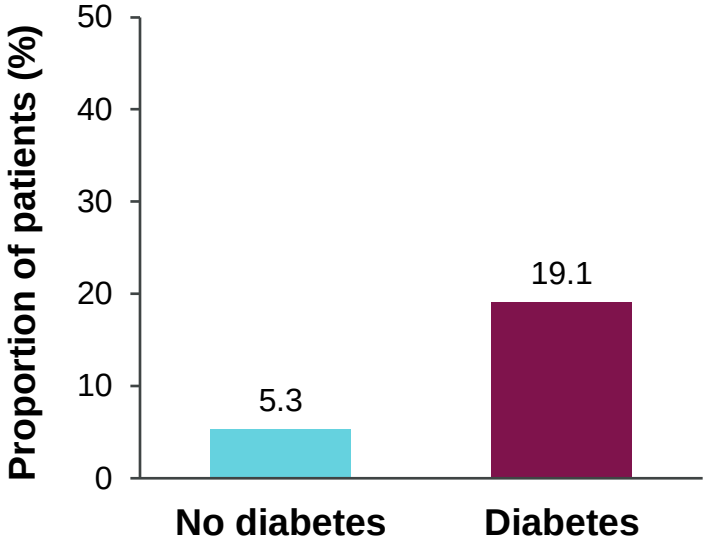
Screening for CKD in persons with hypertension, diabetes, or CVD should be prioritized and screening for CKD in other high-risk individuals should be individualized based on comorbidities, environmental exposures, or genetic risk factors[2]

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150; 2. Shlipak MG et al. *Kidney Int.* 2021;99:34–47.

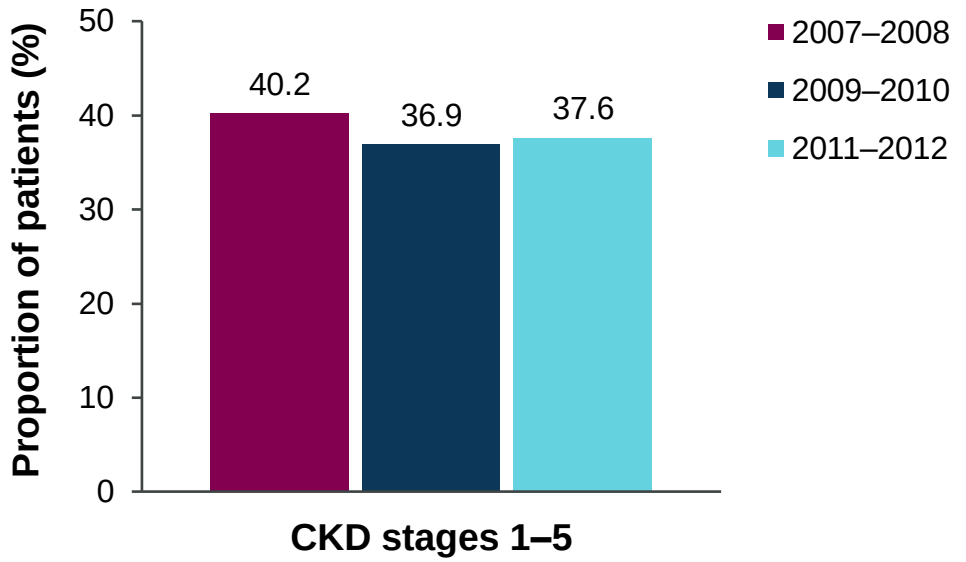
Diabetes is a strong risk factor for CKD

Prevalence of CKD stages 3–4[a]
2011–2012



Prevalence of CKD is **three times higher** in patients with diabetes[1]

Prevalence of CKD stages 1–5 in patients with T2D[b]
2007–2012



The prevalence of CKD in patients with T2D has been **consistent over time**[2]

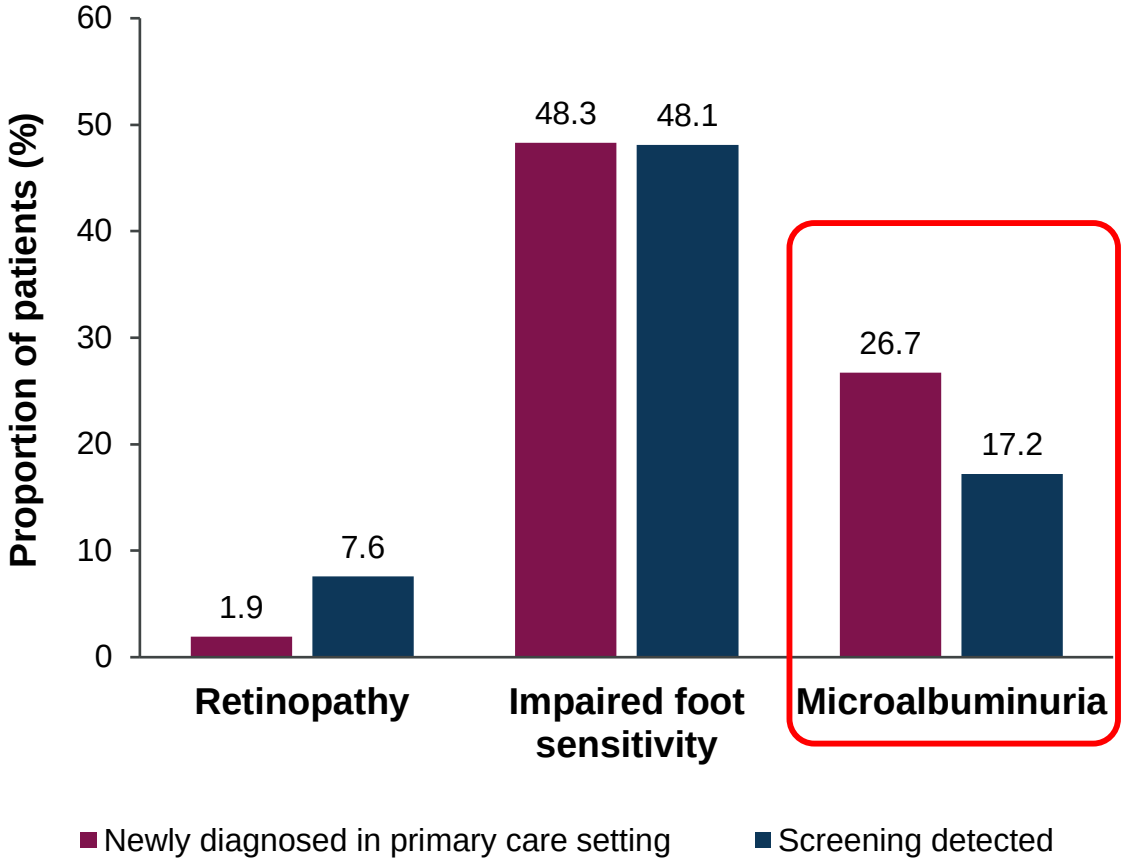
[a]CKD was defined as eGFR of 15–59 mL/min/1.73 m^2 (stages 3–4); [b]CKD stages were defined as: stage 1, eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g; stage 2, eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g; stage 3a, eGFR 45–59 mL/min/1.73 m^2; stage 3b, eGFR 30–44 mL/min/1.73 m^2; stage 4, eGFR 15–29 mL/min/1.73 m^2; stage 5, eGFR <15 mL/min/1.73 m^2.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes; UACR = urine albumin:creatinine ratio.

1. Murphy D et al. *Ann Intern Med.* 2016;165:473–481; 2. Wu B et al. *BMJ Open Diabetes Res Care.* 2016;4:e000154.

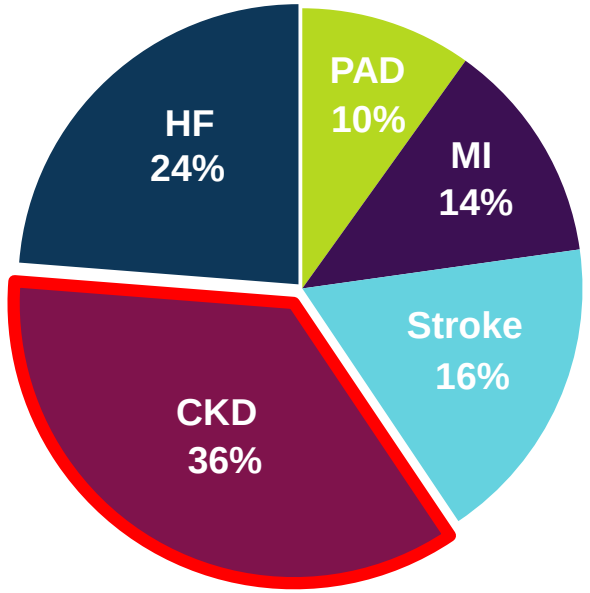
Kidney complications occur early in T2D, highlighting the need for early management of kidney risk

Prevalence of microvascular complications at time of T2D diagnosis[1]



First comorbidity identified in CV-free patients with T2D[2]

137,081 patients (18% of total CV-free patient population)[a]
Mean follow-up: 4.5 years



[a]Retrospective analysis of data from >1.1 million patients with T2D including population data from England and the Netherlands, claims data from Germany and Japan, and full population data from Norway and Sweden.

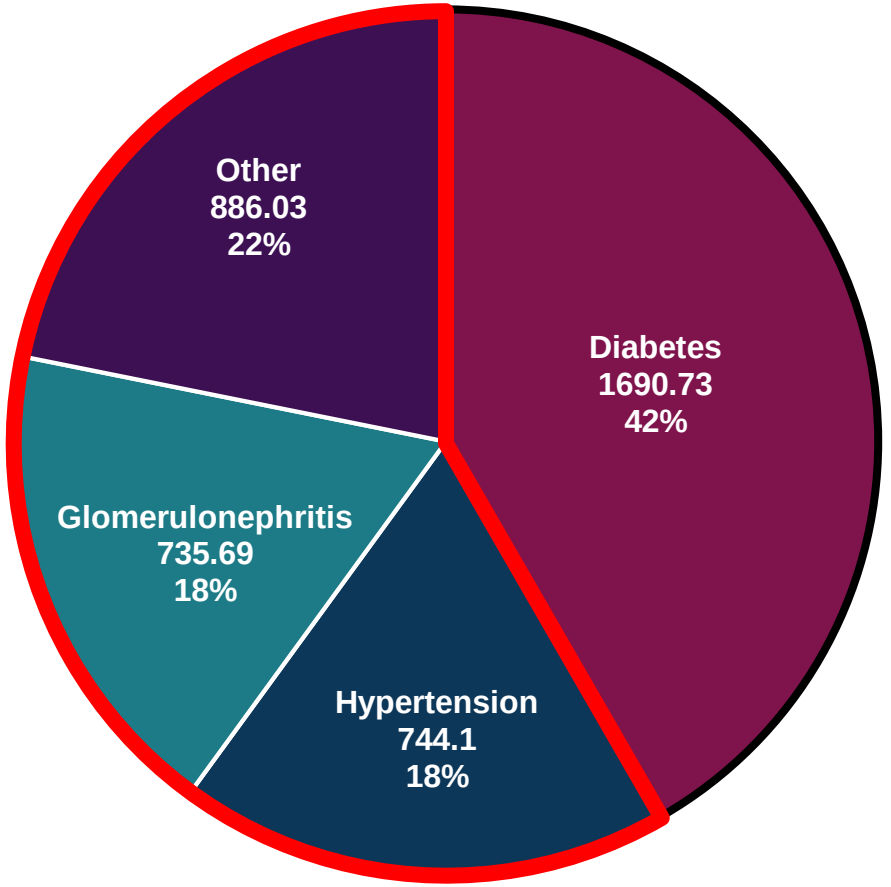
CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; MI = myocardial infarction; PAD = peripheral artery disease; T2D = type 2 diabetes.

1. Spijkerman AM et al. *Diabetes Care.* 2003;26:2604–2608; 2. Birkeland KI et al. *Diabetes Obes Metab.* 2020;22:1607–1618.

Nonetheless, the majority of CKD cases are nondiabetic

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016

Nondiabetic kidney disease
(58%)



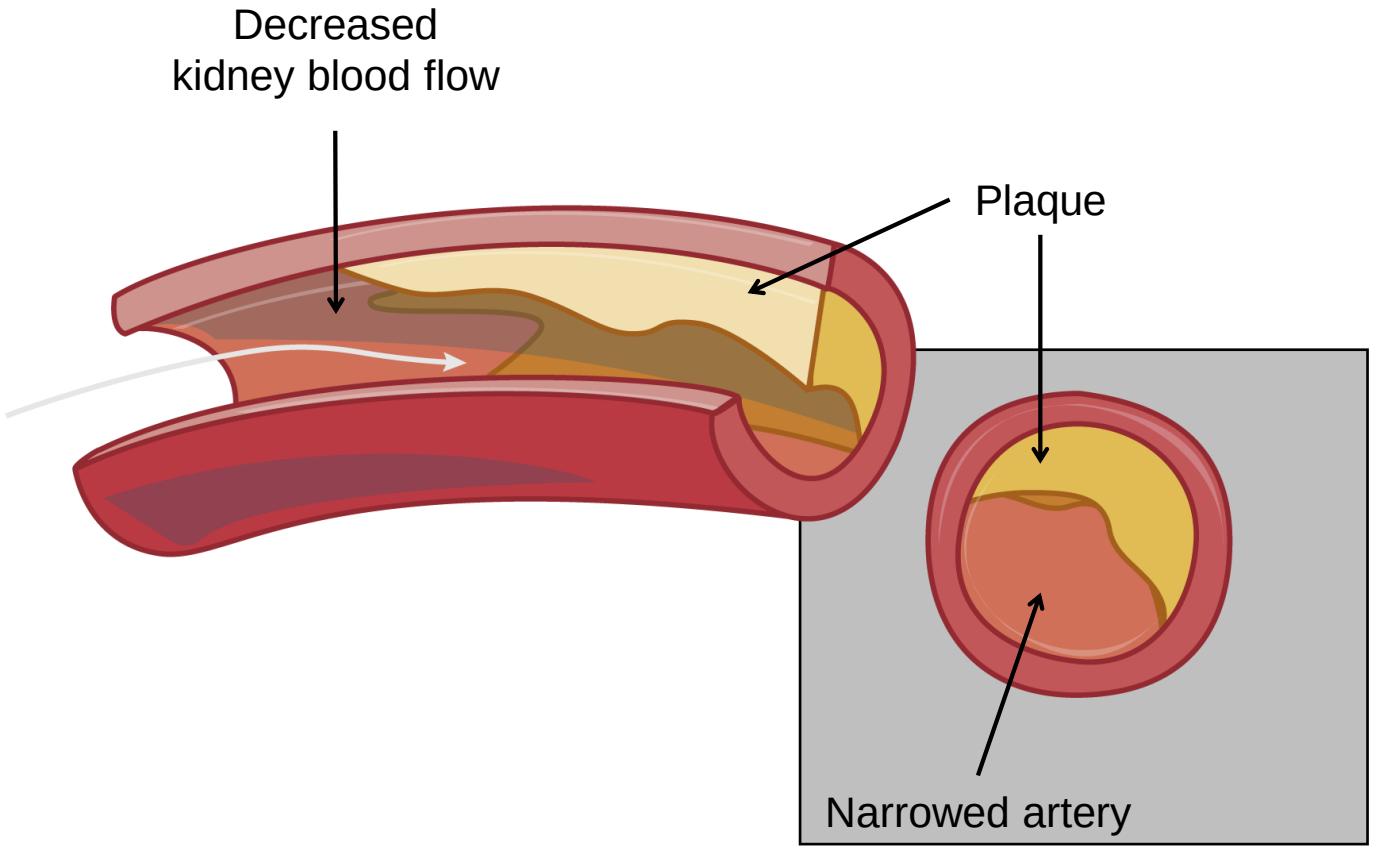
Diabetic kidney disease
(42%)

CKD = chronic kidney disease.

Xie Y et al. *Kidney Int.* 2018;94:567–581.

Hypertensive/ischemic CKD manifests following dysfunction in large vessels

- Namely kidney artery stenosis – involves the narrowing of kidney arteries, usually due to atherosclerosis[1]
- Kidney artery stenosis results in reduction of kidney blood flow and GFR, and causes secondary hypertension via activation of RAAS[1,2]

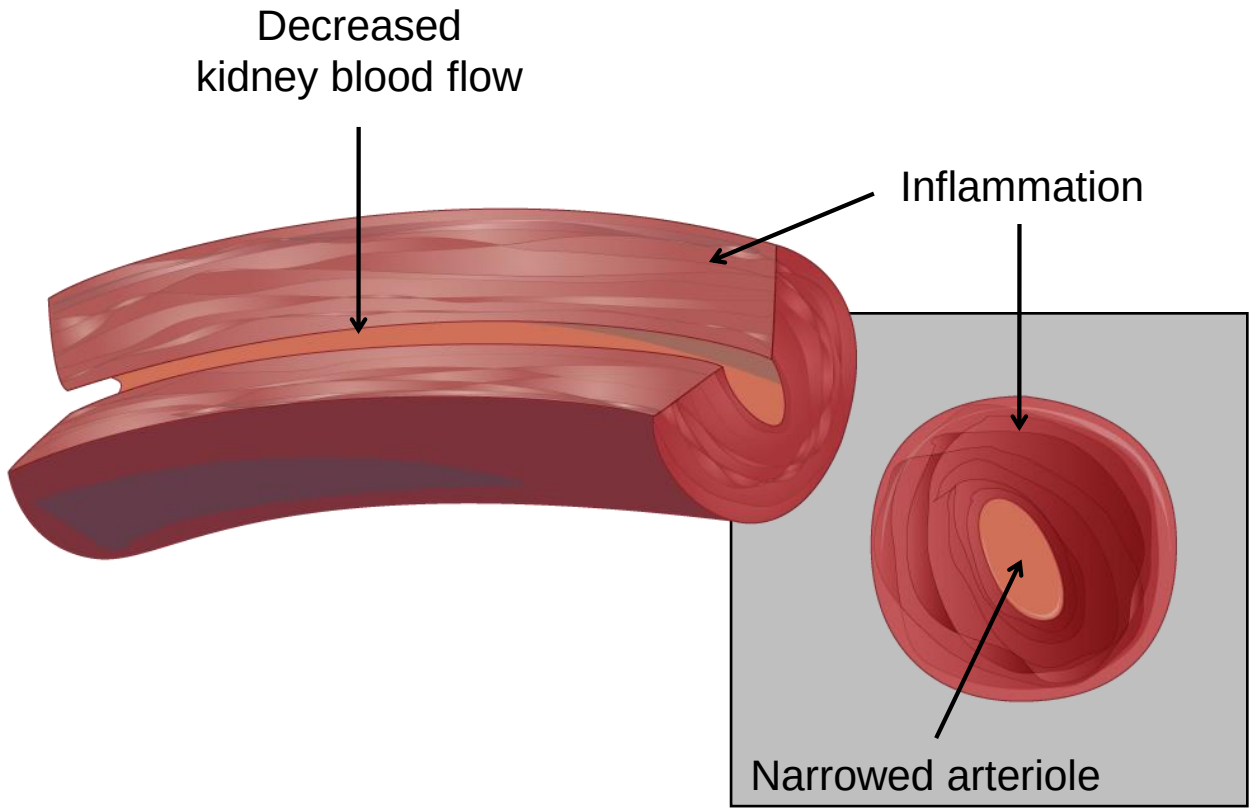


CKD = chronic kidney disease; GFR = glomerular filtration rate; RAAS = renin–angiotensin–aldosterone system.

1. Tafur-Soto JD et al. *Cardiol Clin.* 2015;33:59–73; 2. van den Born BJ et al. Macrovascular involvement in diabetes: Renal artery stenosis. In: Roelofs JJ, Vogt L (eds.). *Diabetic Nephropathy*. Cham, Switzerland: Springer International Publishing AG; 2019;337–355.

Glomerulonephritis manifests following dysfunction in small vessels

Manifesting as glomerulonephritis, involves the induction of inflammatory responses and subsequent necrosis and fibrosis of glomerular epithelial cells; these diseases are classified as both vascular and glomerular NDKD



NDKD = nondiabetic kidney disease.

Jennette JC et al. *Clin J Am Soc Nephrol.* 2017;12:1680–1691.

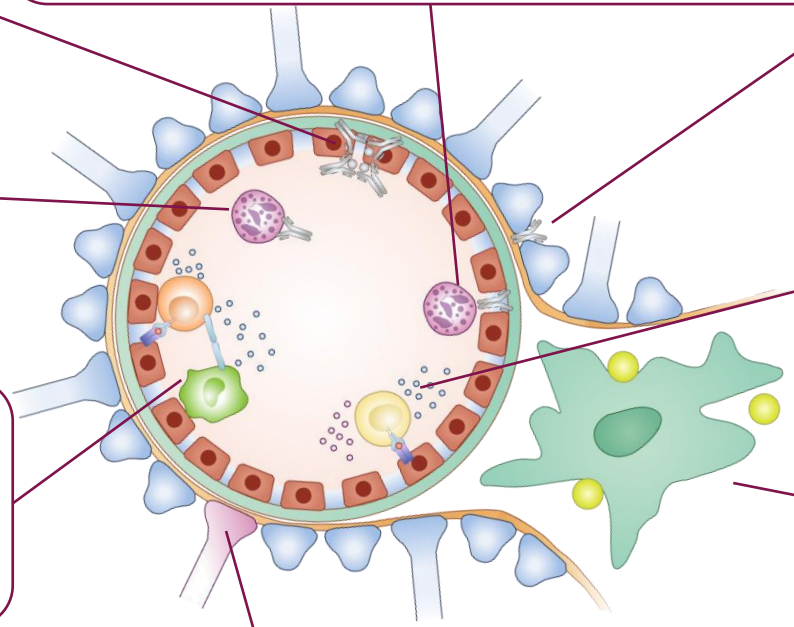
Glomerular NDKD develops from inflammatory responses caused by autoimmune disorders, systemic infection, malignancies, and obesity

Infection-mediated glomerulonephritis:
- Circulating immune complexes lodged between endothelial cells[1]

Autoimmune antiglomerular basement membrane glomerulonephritis:
- Autoantibodies bound to the glomerular basement membrane induce inflammation[1]

Membranous nephropathy:
- Autoantibodies lodge in, or are presented by podocytes, inducing inflammation[1]

Autoimmune ANCA vasculitis:
- ANCA activates neutrophils, enabling recruitment in the glomerulus, inducing inflammation[1]



Glomerulonephritis:
- $CD8^+$ activation induces inflammation and cell death[1]

Glomerulonephritis:
- $CD4^+$ activation induces inflammation
- In progressive glomerulonephritis, $CD4^+$ accumulates[2]

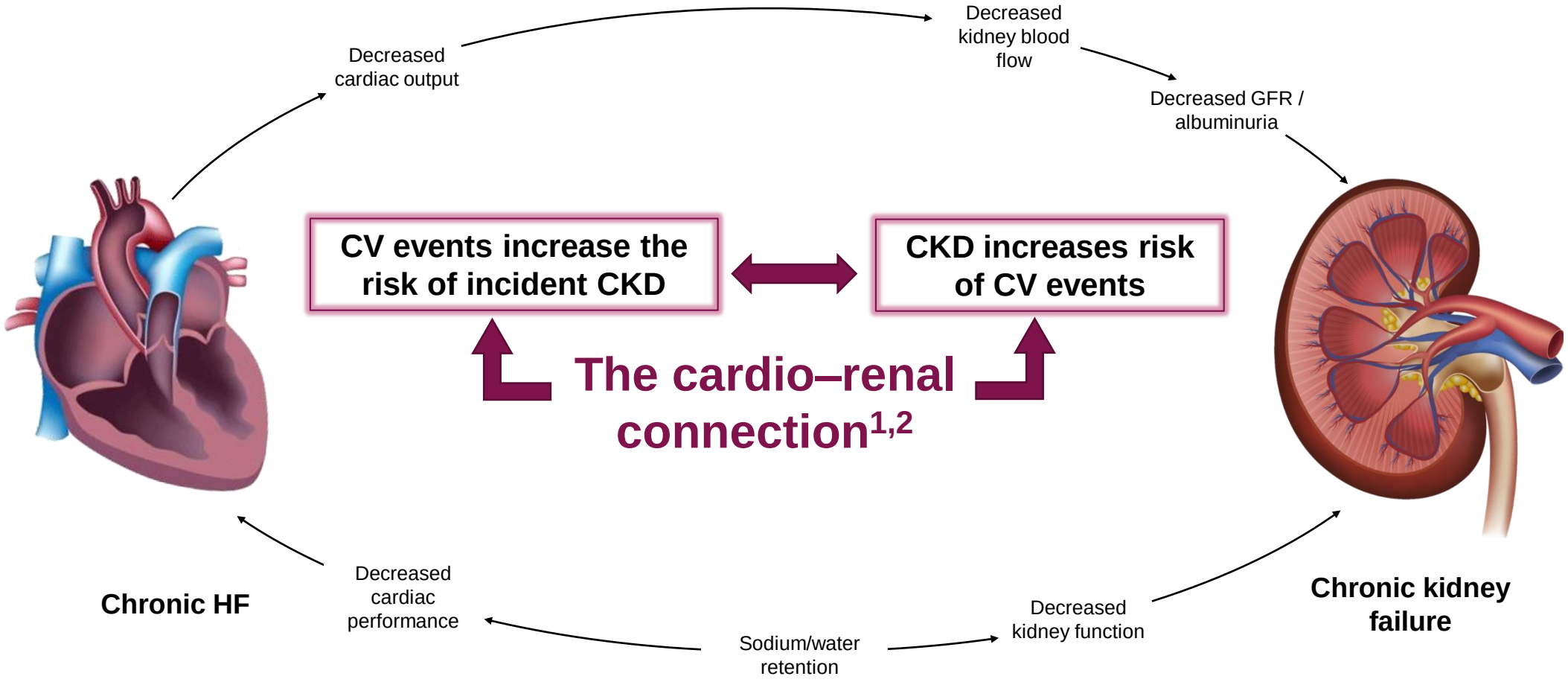
Autoimmune IgA nephropathy:
- Results in mesangial cell expansion[3]

Obesity-related glomerulosclerosis:
- Glomerular hypertension/hypertrophy and microvascular stretching lead to podocyte loss and glomerulosclerosis[4]

ANCA = anti-neutrophil cytoplasmic antibody; CD = cluster of differentiation; IgA = immunoglobulin A; NDKD = nondiabetic kidney disease.

1. Kitching AR et al. *Clin J Am Soc Nephrol.* 2016;11:1664–1674; 2. Summers SA et al. *J Am Soc Nephrol.* 2009;20:2518–2524; 3. Suzuki H et al. *J Am Soc Nephrol.* 2011;22:1795–1803; 4. Praga M et al. *Nephron.* 2017;136:273–276.

There is a close and specific association between cardiac and kidney physiology

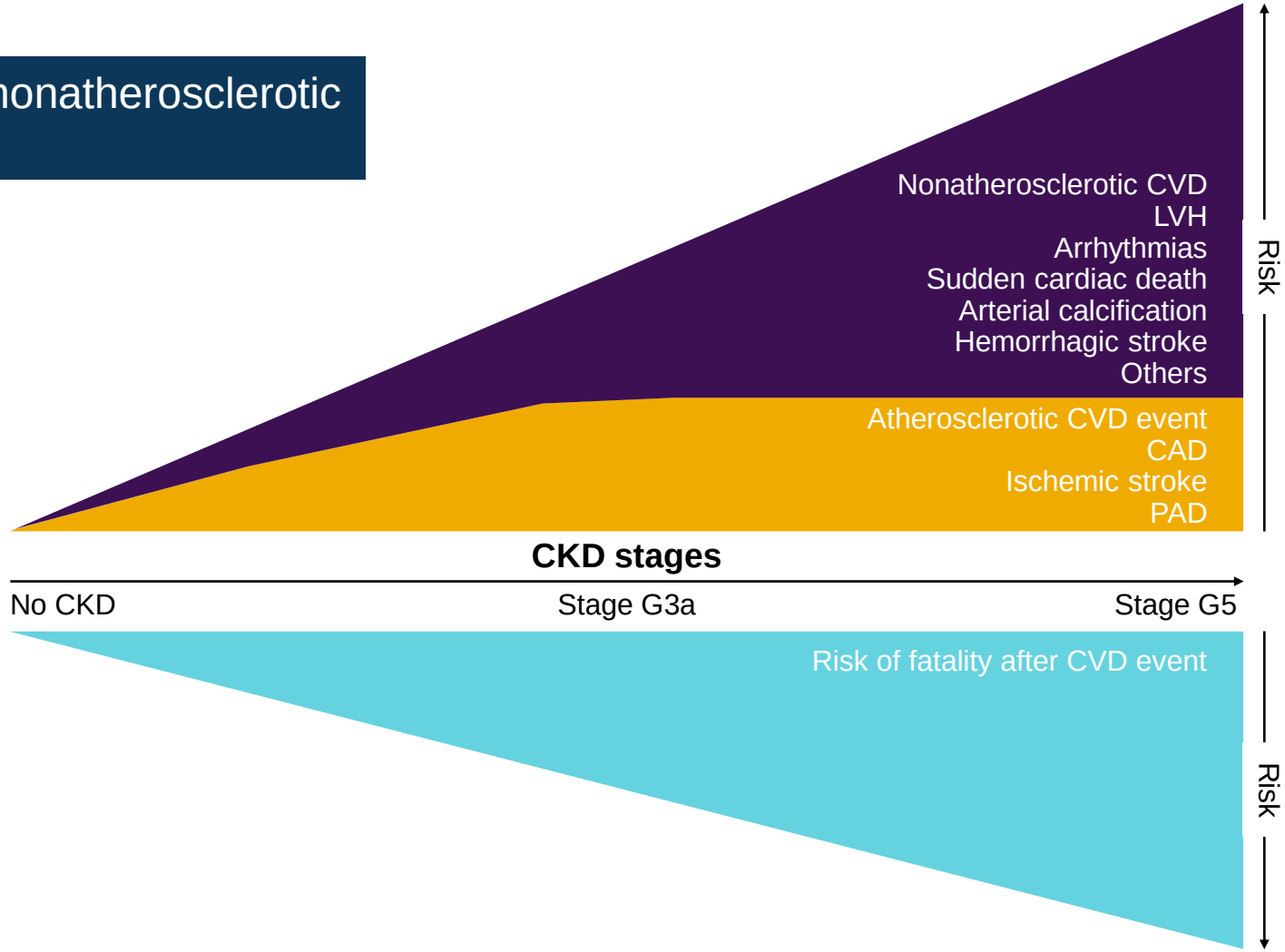


CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GFR = glomerular filtration rate; HF = heart failure.

1. Damman K et al. *J Am Coll Cardiol.* 2014;63:853–871; 2. Metra M et al. *Eur Heart J.* 2012;33:2135–2143.

Risk of CVD and CV mortality increase with progression of CKD

- In later CKD stages, nonatherosclerotic risk dominates

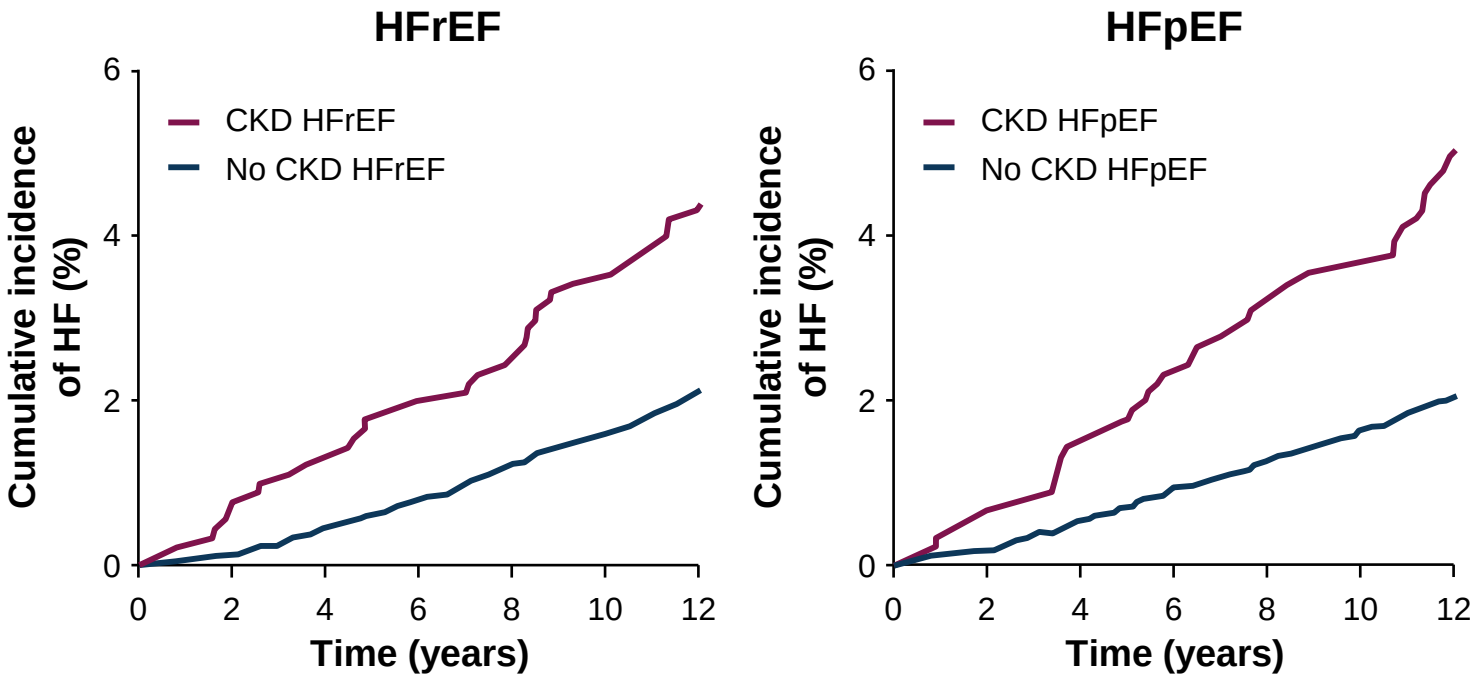


CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; LVH = left ventricular hypertrophy; PAD = peripheral artery disease.

Sarnak MJ et al. *J Am Coll Cardiol.* 2019;74:1823–1838.

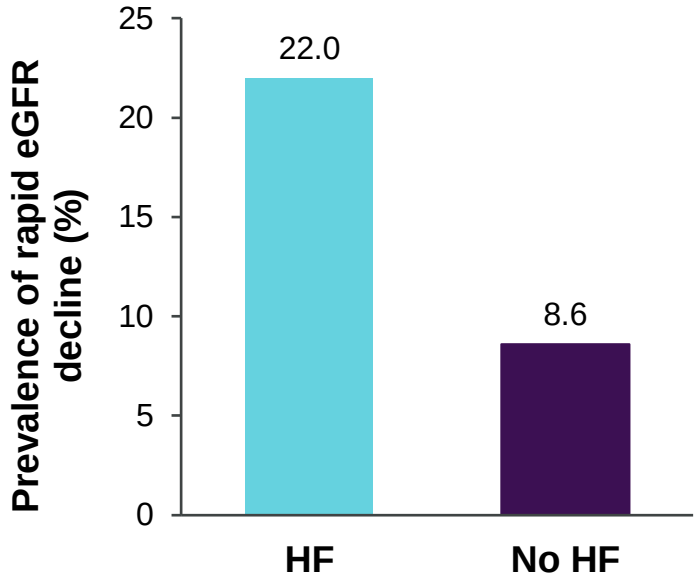
CKD and HF are interconnected: CKD is associated with increased risk of HF and conversely HF is associated with risk of eGFR decline

Incidences of HF are higher in those with CKD than those without[1]



CKD is associated with incident HF

HF is associated with rapid decline in eGFR[2,a]



HF is associated with the risk of kidney function decline

[a]Rapid rate of eGFR decline was defined as slopes steeper than −5 mL/min/1.73 m^2/year.

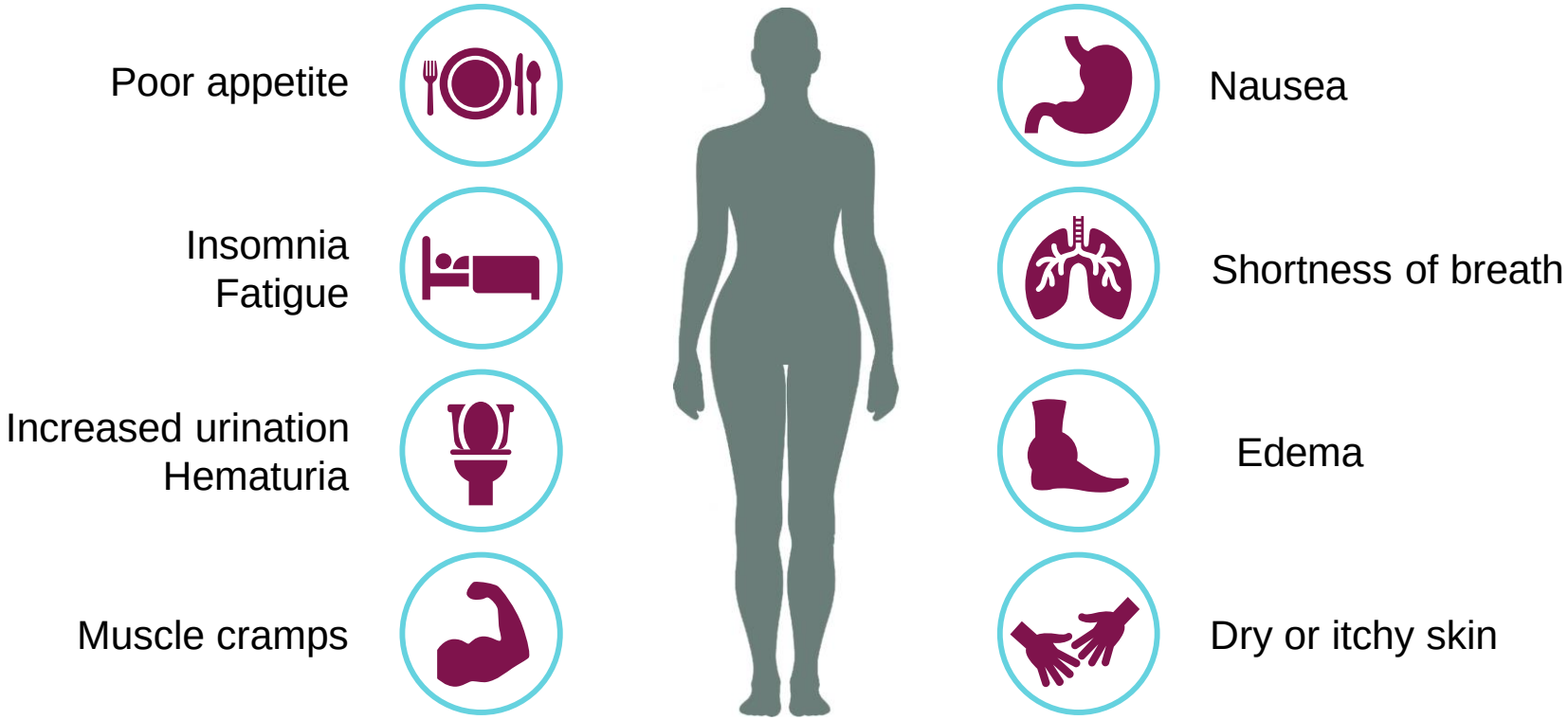
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

1. Nayor M et al. *Eur J Heart Fail.* 2017;19:615–623; 2. George LK et al. *Circ Heart Fail.* 2017;10:e003825.

Screening and monitoring CKD

CKD = chronic kidney disease.

Signs and symptoms of CKD[1,2]



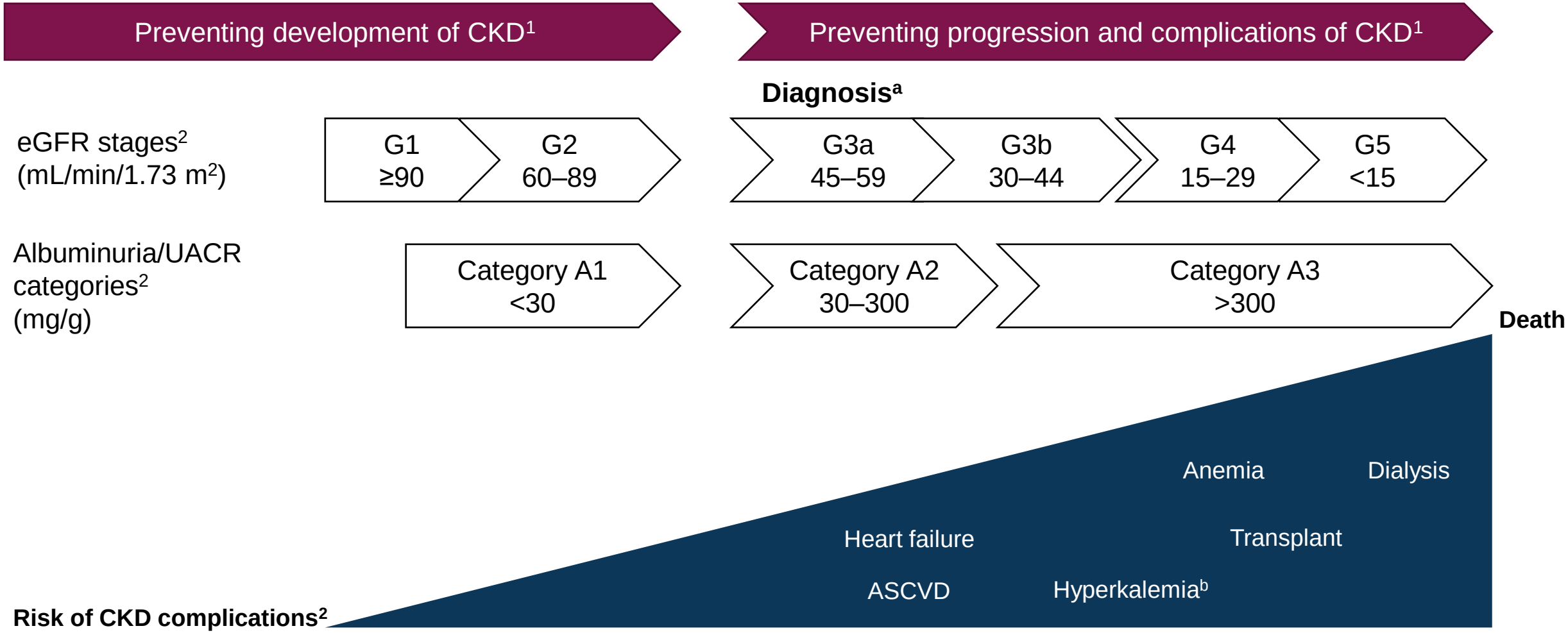
Early CKD can be asymptomatic

Identifying early stage CKD is often difficult

CKD = chronic kidney disease.

1. National Kidney Foundation. https://www.kidney.org/news/ekidney/august14/10_Signs_You_May_Have_Kidney_Disease; 2. Webster AC et al. *Lancet.* 2017;389:1238–1252.

CKD is associated with a variety of comorbidities, the prevalence and severity of which increase with worsening CKD



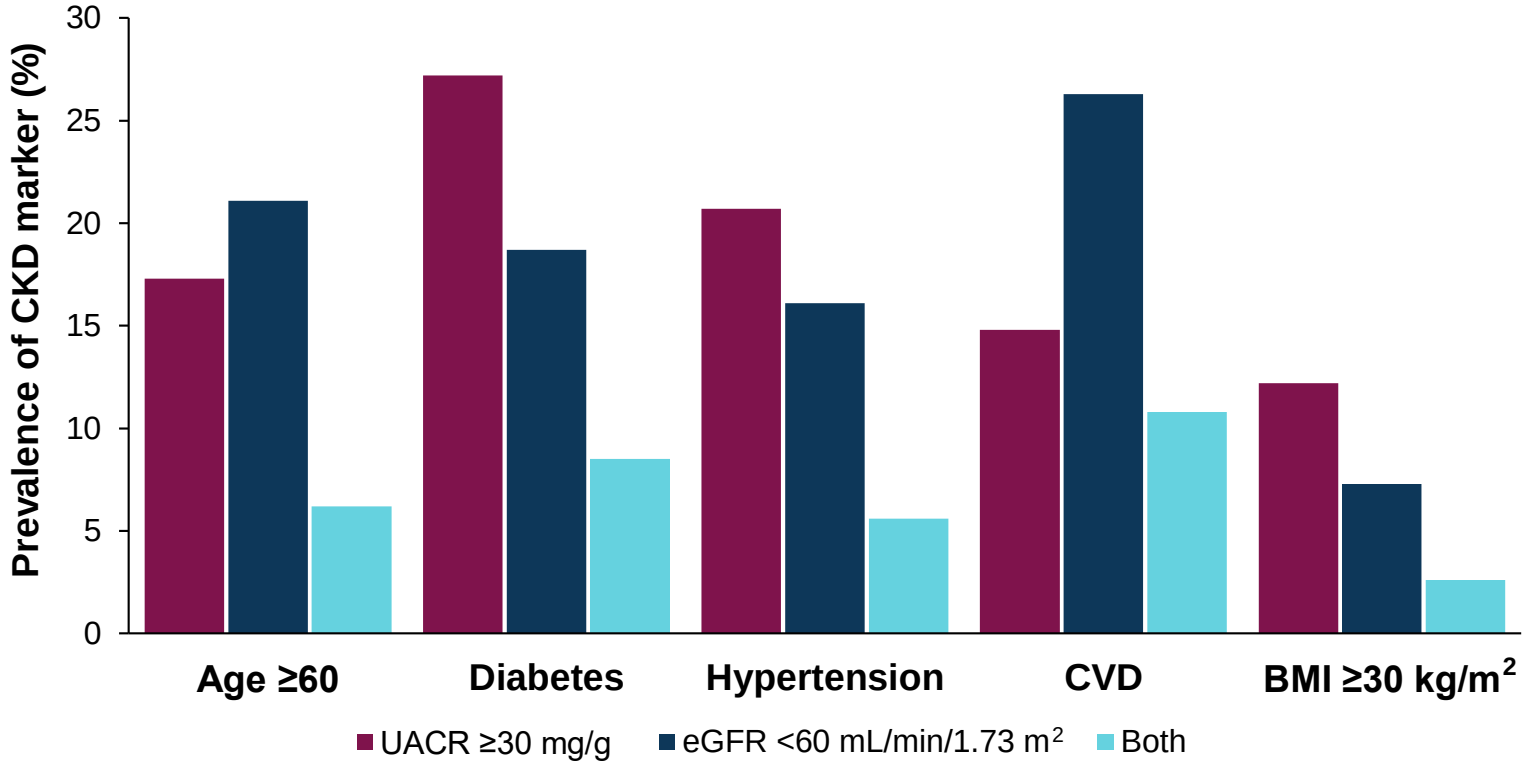
[a]In the absence of evidence or kidney damage, neither G1 nor G2 meet the criteria for CKD; [b]Risk particularly with lower eGFR when aldosterone antagonists are used in addition to an ACE inhibitor or ARB in patients with HF.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF,= heart failure; UACR = urine albumin:creatinine ratio.

1. Levey AS et al. *Am J Kidney Dis.* 2009;53:522–535; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

Urine albumin and estimated glomerular filtration rate are the two key markers for CKD

Distribution of CKD markers in patients with diabetes, hypertension, self-reported CVD, and obesity
NHANES 2013–2016



BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey; UACR = urine albumin:creatinine ratio.

USRDS. 2018 Annual data report: CKD the general population. https://www.usrds.org/media/1723/v1_c01_genpop_18_usrds.pdf.

However, eGFR measurements do not always lead to CKD diagnosis and UACR testing is underutilized[1–3]

Electronic health records from 39 US healthcare organizations[2]

976,299 patients with eGFR <60 mL/min/1.73 m^2

80.7%

received no UACR testing over three years

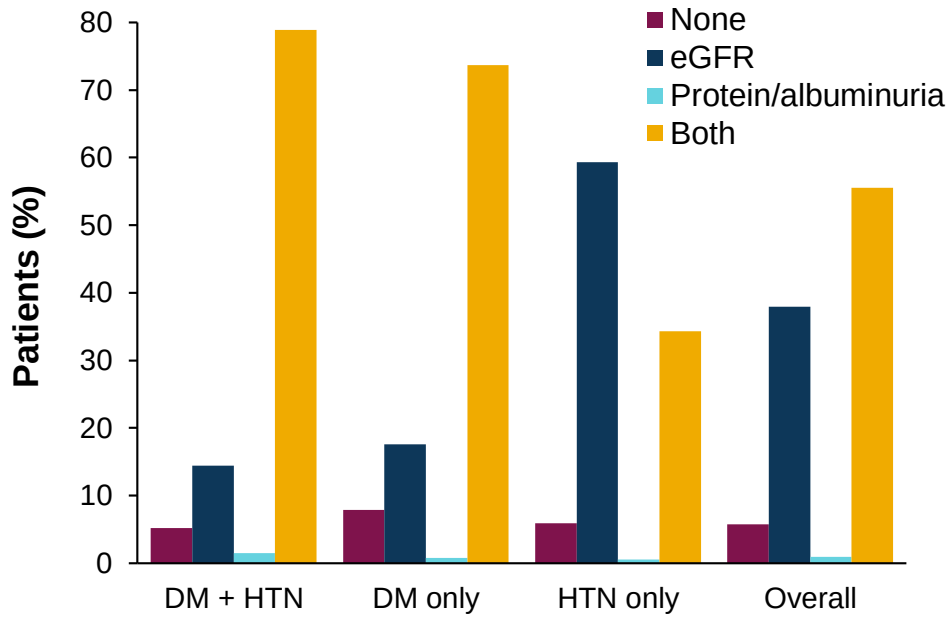
Primary care setting[3]

270,170 patients at risk of CKD due to DM, HTN, or both

Although **93.4%** of patients were tested for eGFR[a]

Only **56.4%** of patients were tested for protein/albuminuria[b]

Percentage of patients that received CKD testing by comorbidities[3]



Protein/albuminuria testing is lower in patients with hypertension compared with those with diabetes

[a]Patients tested for eGFR includes those tested for eGFR only and those tested for both eGFR and protein/albuminuria; [b]Patients tested for protein/albuminuria includes those tested for protein/albuminuria only and those tested for both protein/albuminuria and eGFR.

CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; UACR = urine albumin:creatinine ratio.

1. Tuttle KR et al. *JAMA* Netw Open. 2019;2:e1918169; 2. Naranjo FS et al. *Kidney360*. 2021;2(3):415-424; 3. Bansal S et al. *Kidney360.* 2020;1:904–915.

Assessment of kidney function and damage

Ideal CKD screening should consist of a dual assessment of eGFR and UACR[1]

Kidney function

- **Decreased eGFR**
  - eGFR <60 mL/min/1.73 m^2 (stage 3a–5)[2]
  - Addition of cystatin C measurement to creatinine measurement may enhance accuracy of eGFR assessment[1]
  - Diagnostic confirmation and staging should ideally include both creatinine and cystatin C for accurate eGFR measurements[1]

Kidney damage[2]

- **Albuminuria[2]**
  - AER ≥ 30 mg/24 h
  - UACR ≥ 30 mg/g [≥ 3 mg/mmol]
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Diagnosis of CKD requires two abnormal measurements at least 3 months apart

AER = albumin excretion rate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin:creatinine ratio.

1. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

Categories of kidney function and damage

eGFR

GFR category	GFR (mL/min/1.73 m^2)	Kidney function
G1[a]	≥90	Normal or high
G2[a]	60–89	Mildly decreased[b]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Albuminuria

Albuminuria category[c]	AER (mg/24 h)	ACR[d] (mg/mmol)	ACR[d] (mg/g)	Albumin in urine
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased[b]
A3	>300	>30	>300	Severely increased[e]

CKD is classified based on cause, GFR category and albuminuria category

[a]Does not fulfill the criteria for CKD in the absence of evidence of kidney damage; [b]Relative to young adult level; [c]Note that where albuminuria measurement is not available, urine reagent strip results can be substituted; [d]Approximate equivalent; [e]Including nephrotic syndrome (albumin excretion usually >2200 mg/24 h [ACR >2220 mg/g; >220 mg/mmol]).

ACR = albumin:creatinine ratio; AER = albumin excretion rate; CKD = chronic kidney disease; GFR = glomerular filtration rate.

Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

Monitoring of CKD should increase as kidney function declines

Recommended frequency of monitoring
(number of times per year)
by GFR and albuminuria category[1]

Green: low risk (if no other markers of kidney disease, no CKD)
Yellow: moderately increased risk
Orange: high risk
Red: very high risk

GFR categories (mL/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	>90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decrease	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Individuals with normal GFR, but with severely increased albuminuria (>300 mg/g), are still at risk for decline in renal function[2]

KDIGO recommends referral to a nephrologist for advanced CKD

CKD screening and risk stratification must consist of a dual assessment of eGFR and UACR[3]

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; UACR = urine albumin:creatinine ratio.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int Supp.l* 2013;3:1–150; 2. Perkins BA et al. *J Am Soc Nephrol.* 2007;18:1353–1361; 3. Shlipak MG et al. *Kidney Int.* 2021;99:34–47.

Guidelines recommend routine screening and intervention for CKD in patients with cardiorenal–metabolic disease

KDIGO[1,2]

- Persons with hypertension, diabetes, or CVD should be screened for CKD
- CKD screening should also be implemented in other high-risk individuals and populations based on comorbidities, environmental exposures, and genetic risk factors
- Initiation, frequency, and cessation of CKD screening should be individualized based on kidney and CV risk profiles and individual preference
- Public health policies should include screening of these high-risk populations

NICE[3]

- Test for CKD using eGFRcreatinine[a] and ACR in people with:
  - Diabetes
  - Hypertension
  - Acute kidney injury
  - CVD (ischemic heart disease, chronic HF, peripheral or cerebral vascular disease)
  - Structural renal tract disease, recurrent renal calculi, or prostatic hypertrophy
  - Multisystem disease with possible kidney involvement, e.g. systemic lupus erythematosus
  - Family history of ESKD or hereditary kidney disease
  - Opportunistic detection of hematuria

American Diabetes Association[4]

- At least once yearly, assess urinary albumin (spot urinary ACR) and eGFR in patients with:
  - T1D with duration of ≥5 years
  - T2D
  - Comorbid hypertension

[a]eGFRcreatinine refers to an eGFR calculated using the CKD-EPI creatinine equation, from a patients serum creatinine, age, sex and race.[5]

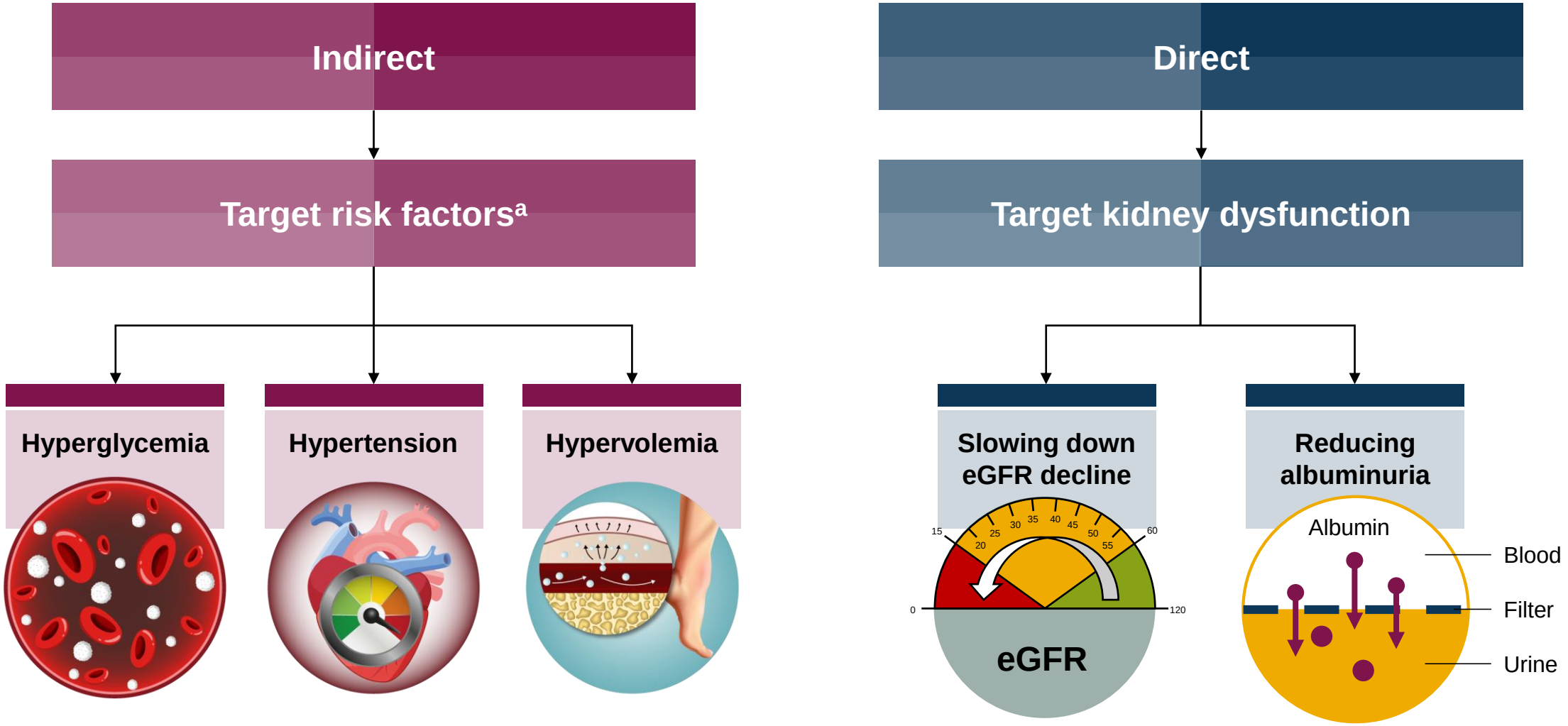
ACR = albumin:creatinine ratio; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; KDIGO = Kidney Disease: Improving Global Outcomes; NICE = UK National Institute for Health and Care Excellence; T1D = type 1 diabetes; T2D = type 2 diabetes.

1. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150; 3. UK National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management (CG182). 2014; 4. American Diabetes Association. *Clin Diabetes.* 2019;37:11–34; 5. Levey AS et al. *Ann Intern Med*. 2009;150:604–612.

Management of CKD

CKD = chronic kidney disease.

Effective treatment of CKD includes both direct and indirect approaches



[a]This is not an exhaustive list of treatable risk factors.

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

Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115.

According to the 2012 KDIGO CKD guideline, there are certain lifestyle modifications that are recommended for those with CKD

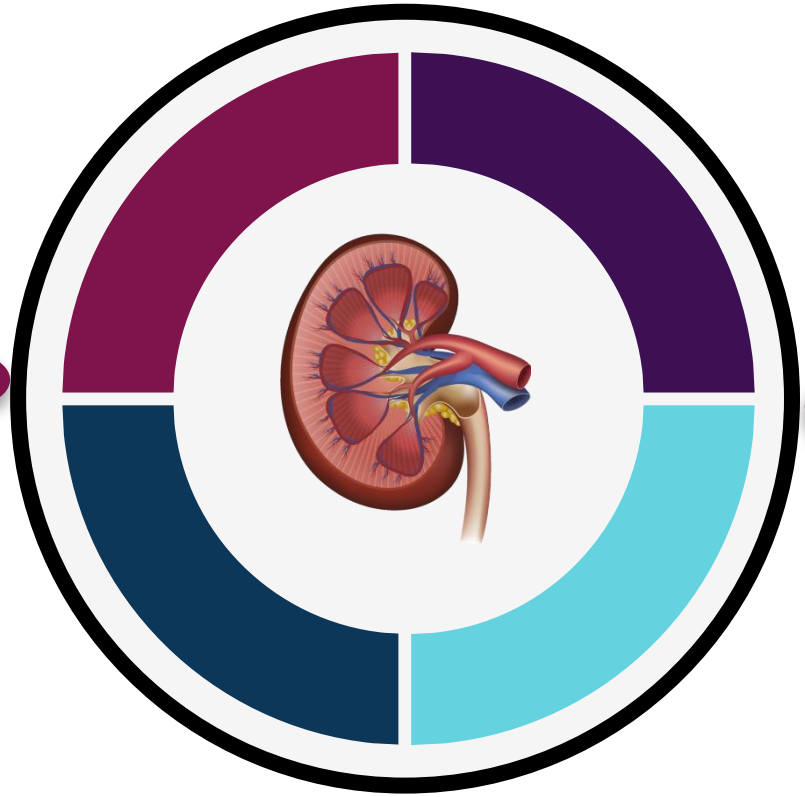
KDIGO recommend the following lifestyle modifications for those with CKD:

Protein intake

- Lower protein intake to 0.8 g/kg/day in adults with diabetes or without diabetes and eGFR <30 mL/min/1.73m^2 with appropriate education
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression

Lifestyle

Should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20–25, according to country-specific demographics) and stop smoking



Salt intake

Lower salt intake to less than 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated

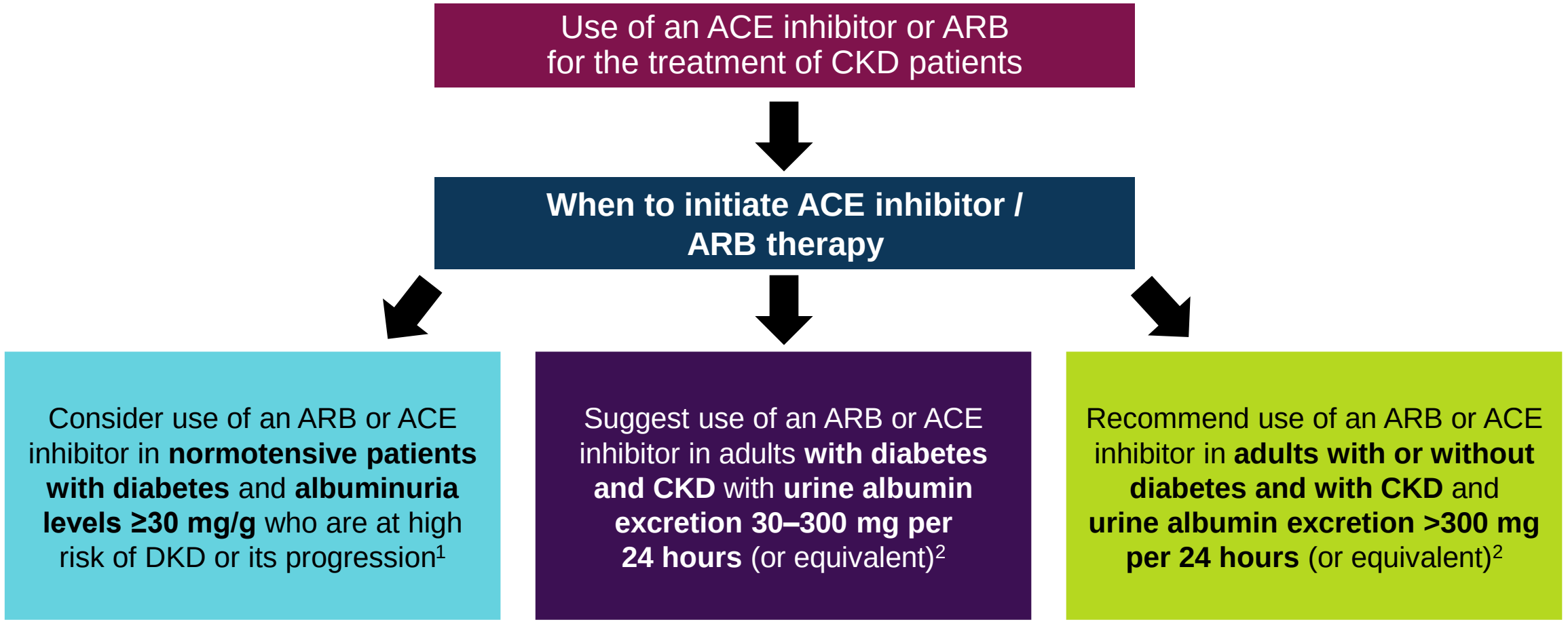
Additional dietary advice

Should receive dietary advice and information in th context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated

BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes.

Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

KDIGO guidelines recommend the use of ACE inhibitors / ARBs in albuminuria patients irrespective of diabetes and BP status



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; DKD = diabetic kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

Guidelines accept combination of ACE inhibitors/ARBs with β blockers and Ca^{2+} channel blockers, but caution against aldosterone antagonist add-ons

Coadministration of β blockers and calcium-channel blockers with ACE inhibitor or ARBs is acceptable[1]

Due to the risk of hyperkalemia, aldosterone antagonists should be used with caution in CKD patients[2–3]

National Kidney Foundation KDOQI KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; GFR = glomerular filtration rate.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2012;2:338–414; 2. Taler SJ et al. *Am J Kidney Dis.* 2013;62:201–213; 3. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2012;3:1–150

Summary

Summary

- The global burden of CKD continues to rise while diagnosis and patient awareness of the disease remains low[1–2]
- Diabetes, hypertension, and glomerulonephritis are the most common singular causes of CKD[3]
- Patients with hypertension, diabetes, and CVD are considered to be high risk for CKD and should be screened using eGFR and UACR[4]
- Risk of CV events and mortality are elevated in patients with CKD, independent of diabetes status or CKD etiology[5-7]
- The risk of mortality increases as CKD progresses, and is more likely than progression to ESKD[7,8]
- Guidelines recommend multifactorial interventional approaches for the management of CKD patients, including glycemic, blood pressure, and lipid management[9]

CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

1. Foreman KJ et al. *Lancet.* 2018;392:2052–2090; 2. USRDS. 2020 Annual data report: CKD in the general population. https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population; 3. Xie Y et al. *Kidney Int.* 2018;94:567–581; 4. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 5. Nakayama M et al. *Hypertens Res.* 2011;34(10):1106-1110; 6. Jarrick S et al. Article and online supplemental material. *J Am Soc Nephrol*. 2019;30(5):866-876; 7. Fox CS et al. *Lancet*. 2012;380:1662–1673; 8. Dalrymple LS et al. *J Gen Intern Med*. 2010;26:379–385; 9. Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115.

ACT on Chronic Kidney Disease
Accelerate Change Together

Dapagliflozin in Chronic Kidney Disease
Table of Contents

Renal Outcomes Trial

DAPA-CKD

Cardiovascular Outcomes Trial

DECLARE-TIMI 58

DAPA-CKD: Study Design

DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

DAPACKD

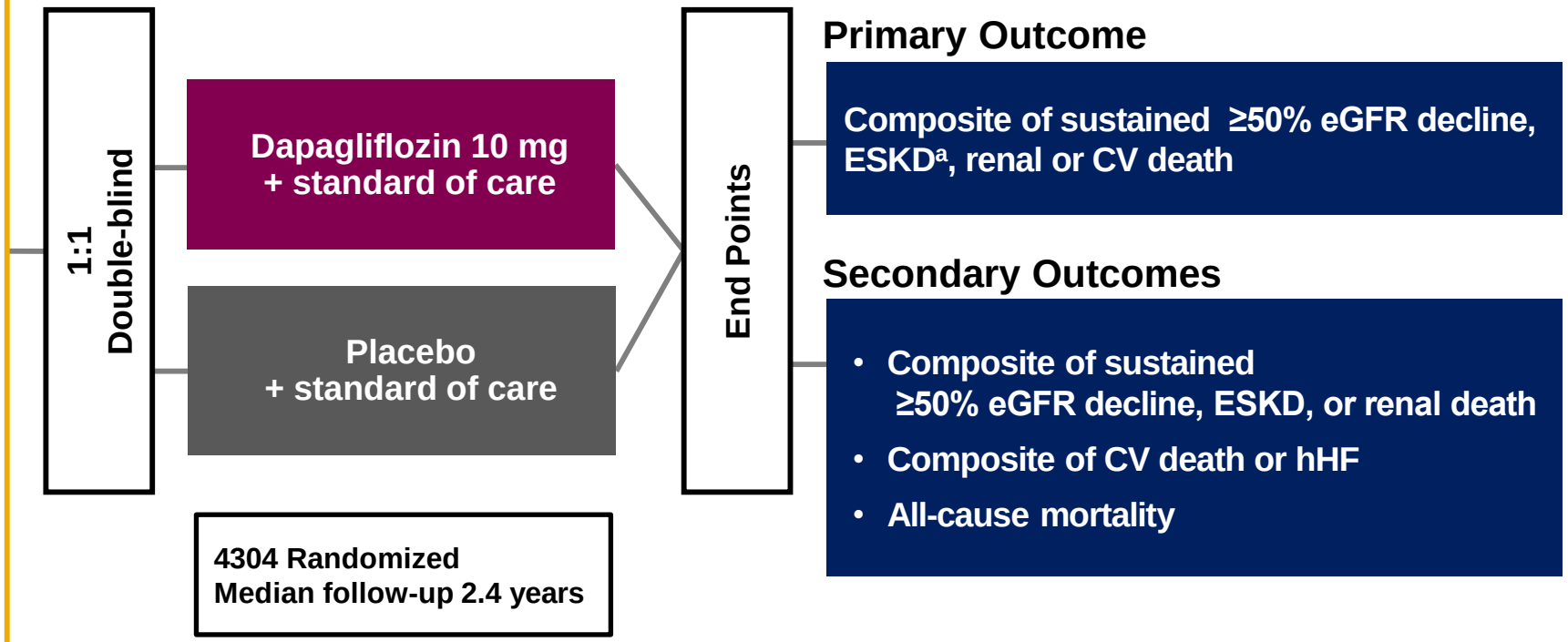
Objective To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a stable dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Countries Participating in DAPA-CKD[1,2]

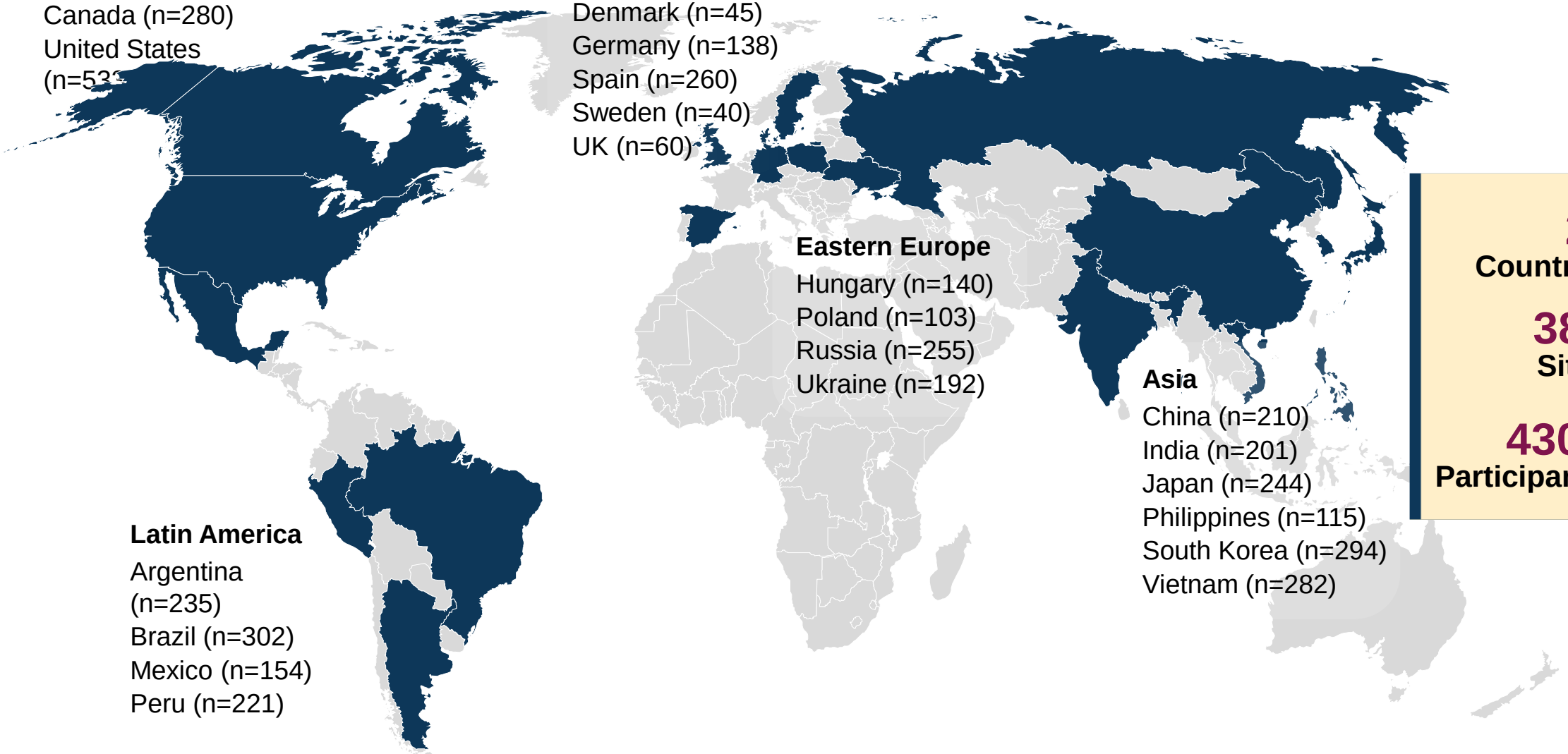
North America
Canada (n=280)
United States (n=53

Western Europe
Denmark (n=45)
Germany (n=138)
Spain (n=260)
Sweden (n=40)
UK (n=60)

Eastern Europe
Hungary (n=140)
Poland (n=103)
Russia (n=255)
Ukraine (n=192)

Asia
China (n=210)
India (n=201)
Japan (n=244)
Philippines (n=115)
South Korea (n=294)
Vietnam (n=282)

Latin America
Argentina (n=235)
Brazil (n=302)
Mexico (n=154)
Peru (n=221)



21 Countries

386 Sites

4304 Participants

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

DAPA-CKD:
Baseline Characteristics

Demographics and Baseline Characteristics

	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
Age, years, mean	61.8	61.9
Gender, female, %	32.9	33.3
Race[a], %		
White	52.2	54.2
Black or African-American	4.8	4.0
Asian	34.8	33.4
Other	8.1	8.4
Weight, kg	81.5	82.0
Body mass index, kg/m^2	29.4	29.6
Current smoker, %	13.2	14.0
Blood pressure, mmHg, mean		
Systolic blood pressure	136.7	137.4
Diastolic blood pressure	77.5	77.5
Hemoglobin, g/L	128.6	127.9
Serum potassium, mEq/L	4.6	4.6

[a]Race was reported by the investigators; the designation 'other' includes Native Hawaiian or other Pacific Islander; American Indian or Alaska Native and Other.
BL = baseline.
Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Renal Characteristics

	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
eGFR, mL/min/1.73m^2, mean	43.2	43.0
eGFR ≥60 mL/min/1.73m^2, %	10.9	10.2
eGFR 45 to <60 mL/min/1.73m^2, %	30.0	31.7
eGFR 30 to <45 mL/min/1.73m^2, %	45.5	42.7
eGFR <30 mL/min/1.73m^2, %	13.6	15.4
UACR, mg/g, median	965	934
UACR >1000 mg/g, %	48.7	47.9

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Medical History and Baseline Medications

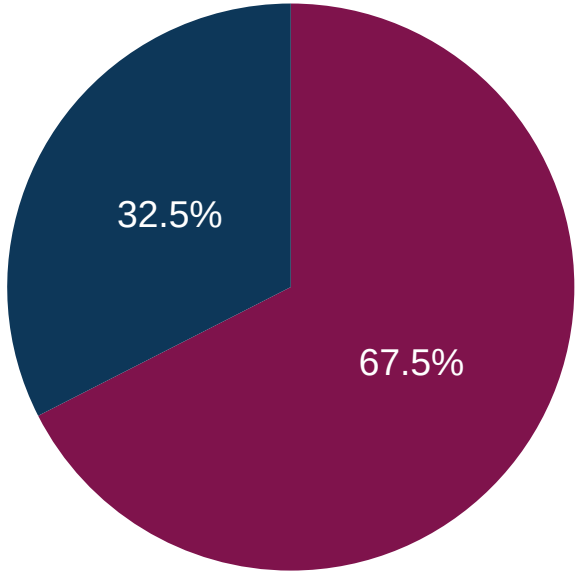
	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
Type 2 diabetes, %	67.6	67.4
CV disease, %	37.8	37.0
Heart failure, %	10.9	10.8
Prior medication, %		
ACEi	31.3	31.6
ARB	67.1	66.3
Diuretic	43.1	44.3
Statin	64.8	65.0

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BL = baseline; CKD = chronic kidney disease; CV = cardiovascular.

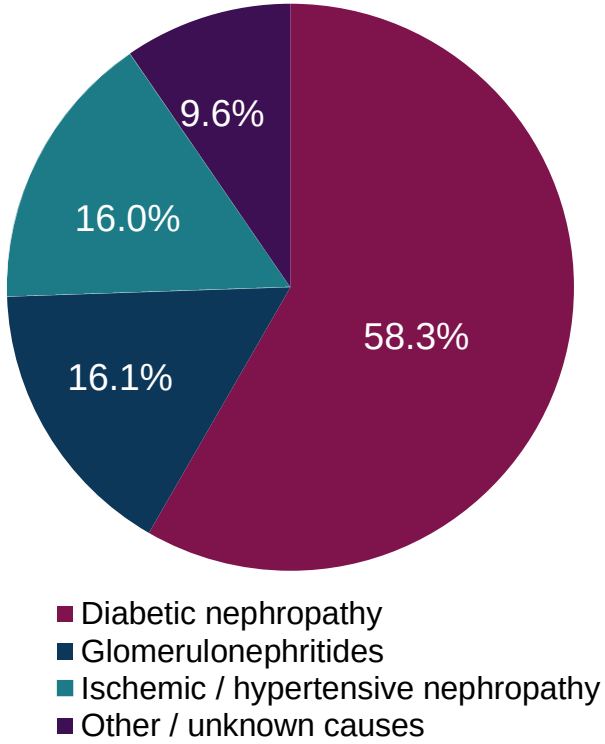
Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Diabetes Status and Investigator-reported Cause of Kidney Disease at Baseline

Diabetes Status



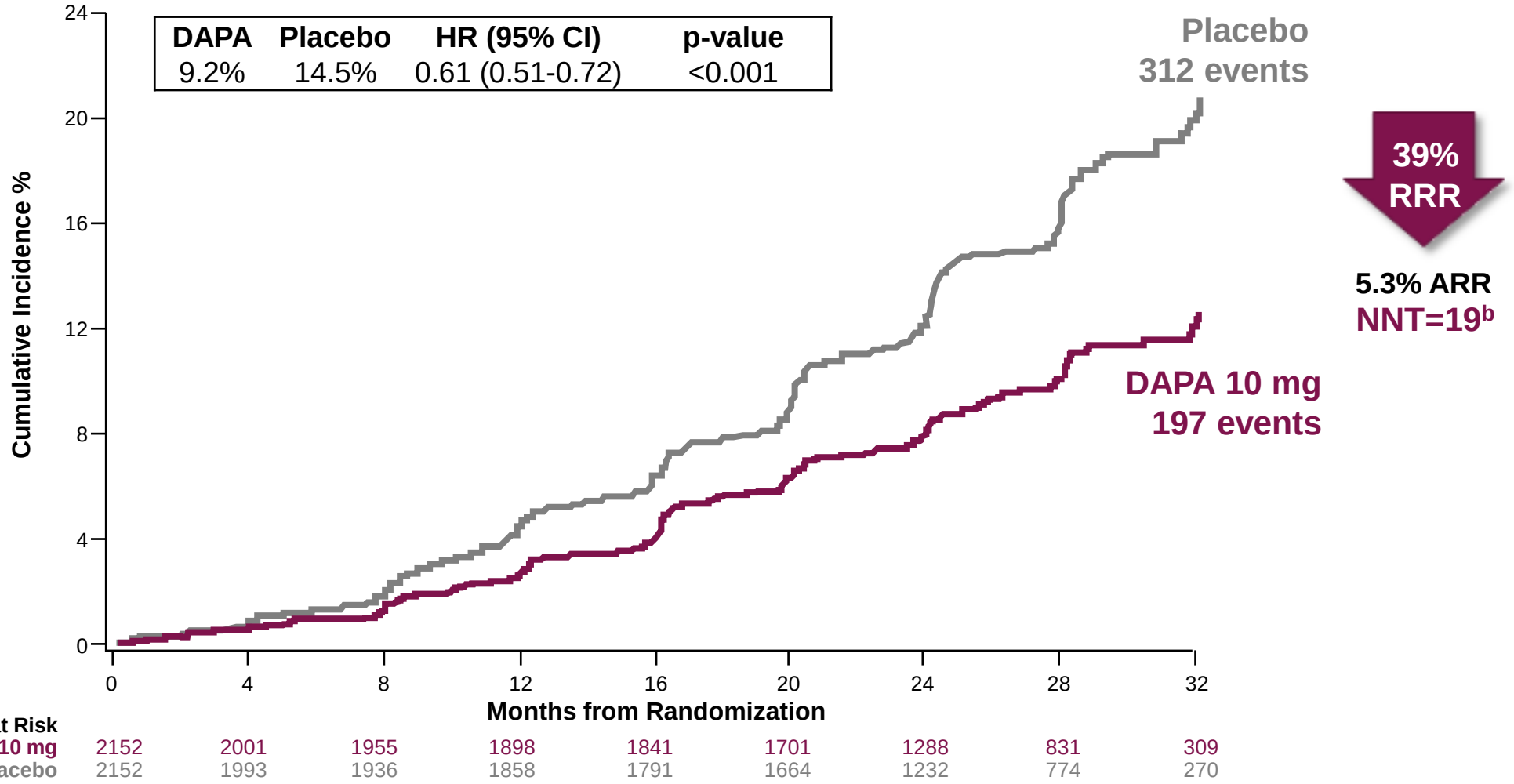
Investigator-reported Cause of Kidney Disease



Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

DAPA-CKD:
Primary Endpoint

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a,1]



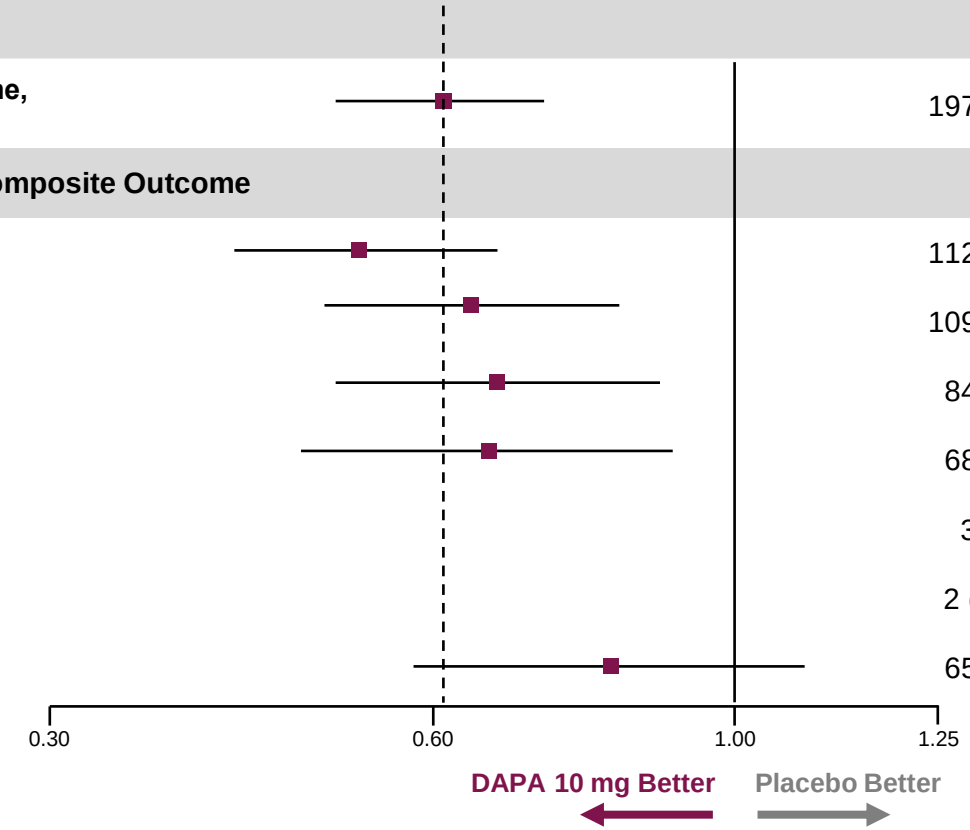
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]; [b]95% CI, 15 to 27.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Primary Composite Outcome: All Components Contributed to the Observed Treatment Effect[1]

	Number of Events (%)				
	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	<0.001
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112 (5.2)	201 (9.3)	0.53	(0.42, 0.67)	
ESKD	109 (5.1)	161 (7.5)	0.64	(0.50, 0.82)	
eGFR <15mL/min/1.73m^2	84 (3.9)	120 (5.6)	0.67	(0.51, 0.88)	
Chronic Dialysis[a]	68 (3.2)	99 (4.6)	0.66	(0.48, 0.90)	
Transplantation[a]	3 (0.1)	8 (0.4)	NC		
Renal Death	2 (<0.1)	6 (0.3)	NC		
CV Death	65 (3.0)	80 (3.7)	0.81	(0.58, 1.12)	

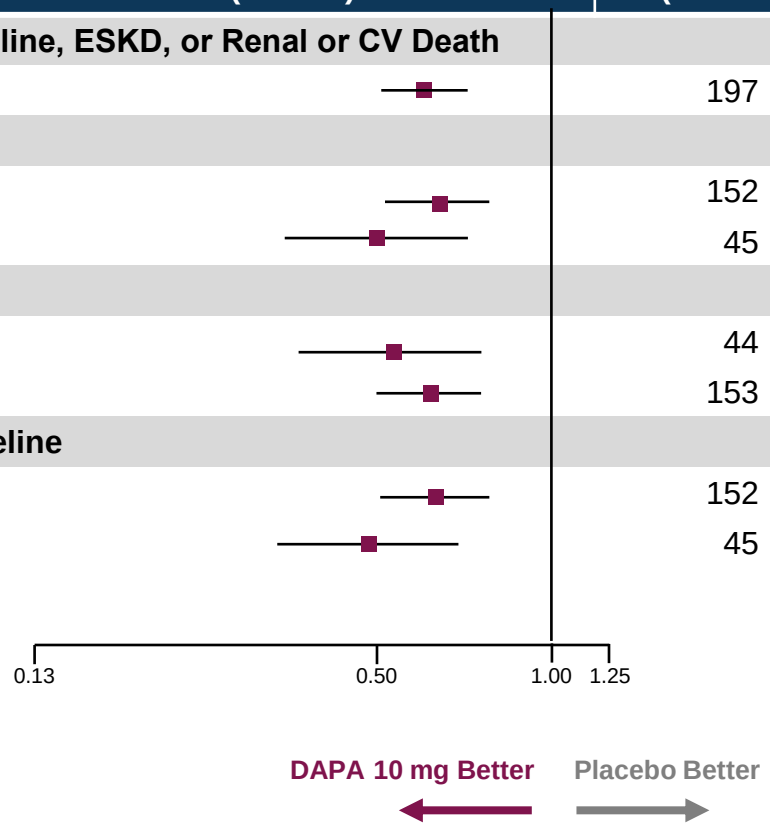


[a]There were 69 endpoint events for dapagliflozin and 100 endpoint events for placebo for the combined chronic dialysis and renal transplantation endpoint (HR 0.66; 95% CI 0.49, 0.90).
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446;

Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups[1]

	Number of Events				
	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction[2]
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24[2]
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	

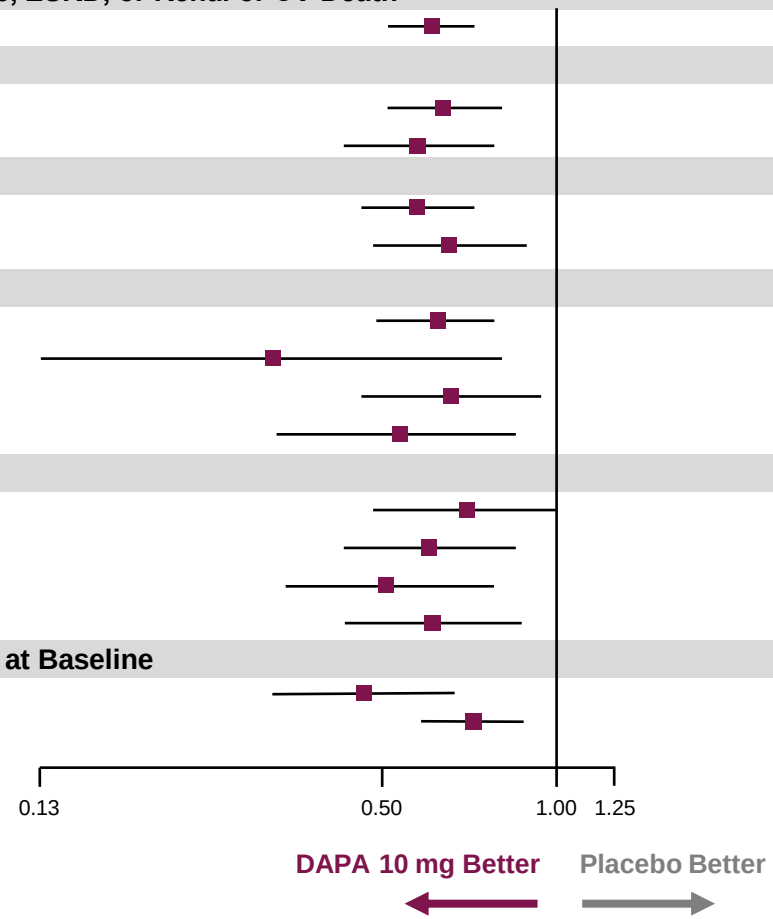


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2.Wheeler DC et al, Lancet Diabetes Endocrinol 2021; 9:22-31

Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups[1]

	Number of Events				
	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
Age (years)					
≤65	122	191	0.64	(0.51, 0.80)	
>65	75	121	0.58	(0.43, 0.77)	
Gender					
Male	126	209	0.57	(0.46, 0.72)	
Female	71	103	0.65	(0.48, 0.88)	
Race					
White	110	174	0.62	(0.49, 0.79)	
Black	7	14	0.33	(0.13, 0.81)	
Asian	53	77	0.66	(0.46, 0.93)	
Other	27	47	0.54	(0.33, 0.86)	
Geographic Region					
Asia	50	69	0.70	(0.48, 1.00)	
Europe	57	89	0.60	(0.43, 0.85)	
North America	35	69	0.51	(0.34, 0.76)	
Latin America	55	85	0.61	(0.43, 0.86)	
Systolic Blood Pressure (mmHg) at Baseline					
≤130	46	96	0.44	(0.31, 0.63)	
>130	151	216	0.68	(0.56, 0.84)	

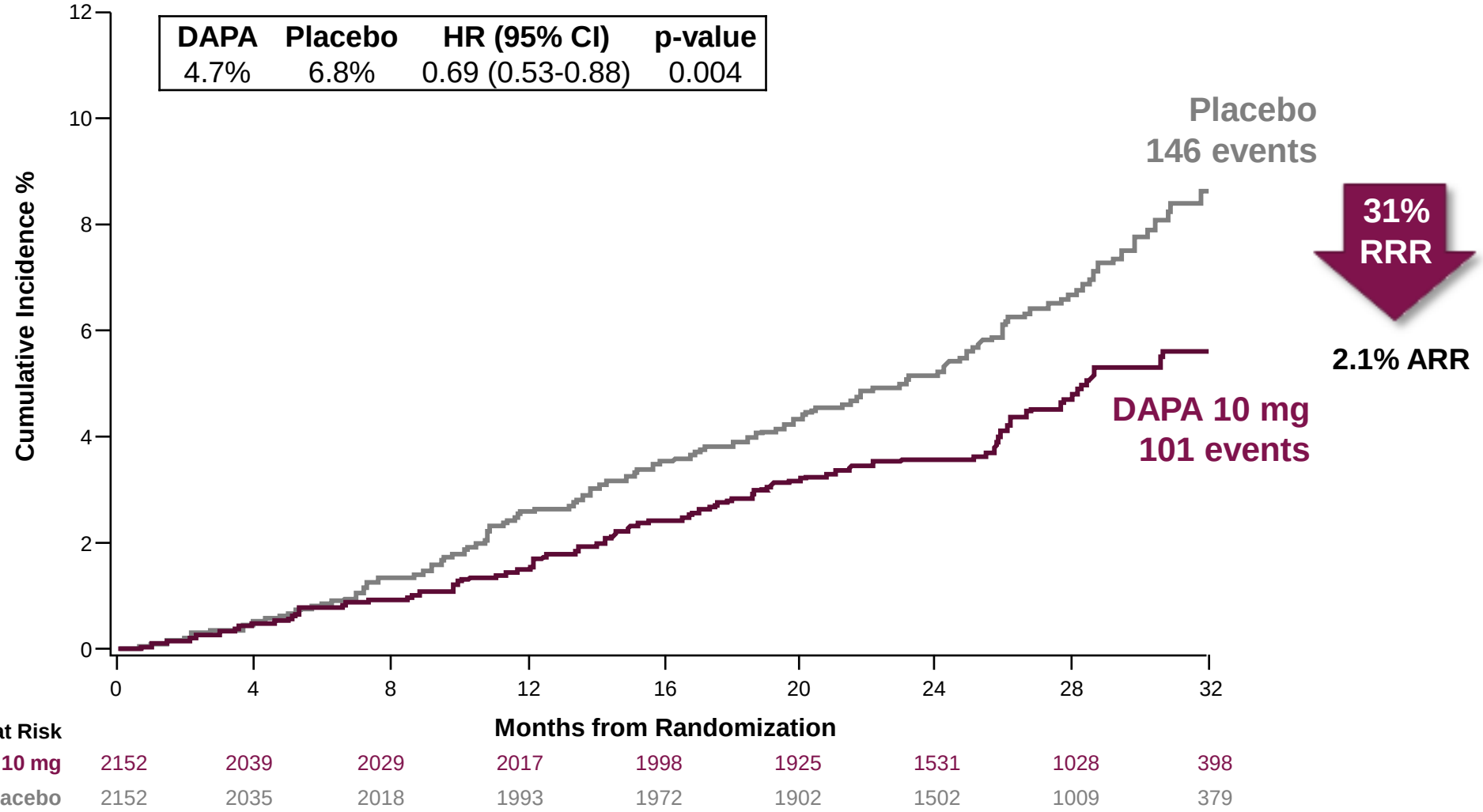


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446;

DAPA-CKD:
Secondary and Exploratory Endpoints

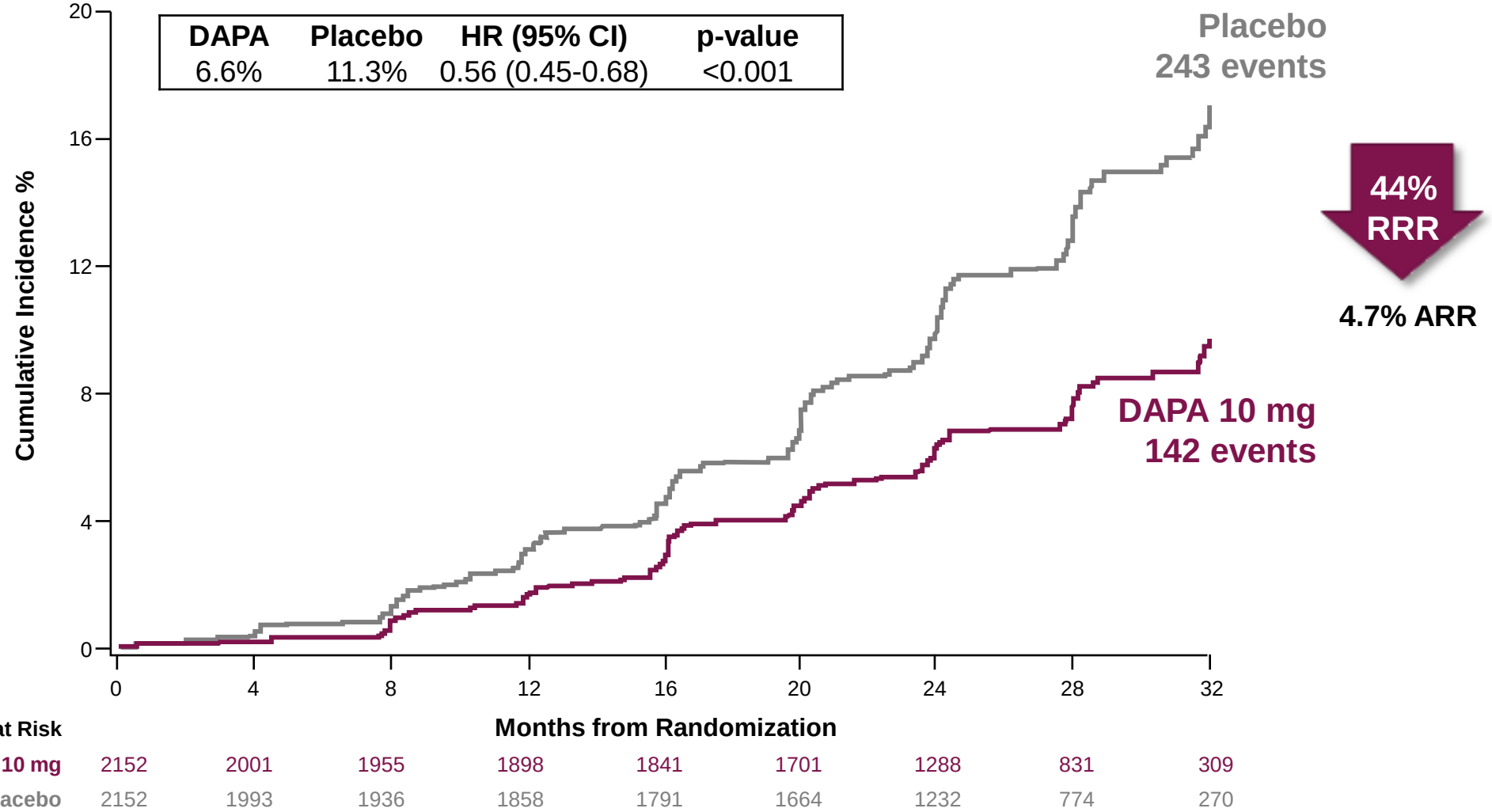
Secondary Outcome: All-cause Mortality[1,2]



ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Secondary Renal-Specific Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a,1]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

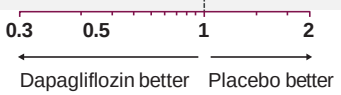
ARR = absolute risk reduction; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446;.2. Heerspink HJL et al. N Nephrol Dial Transplant. 2020;35:274–282.

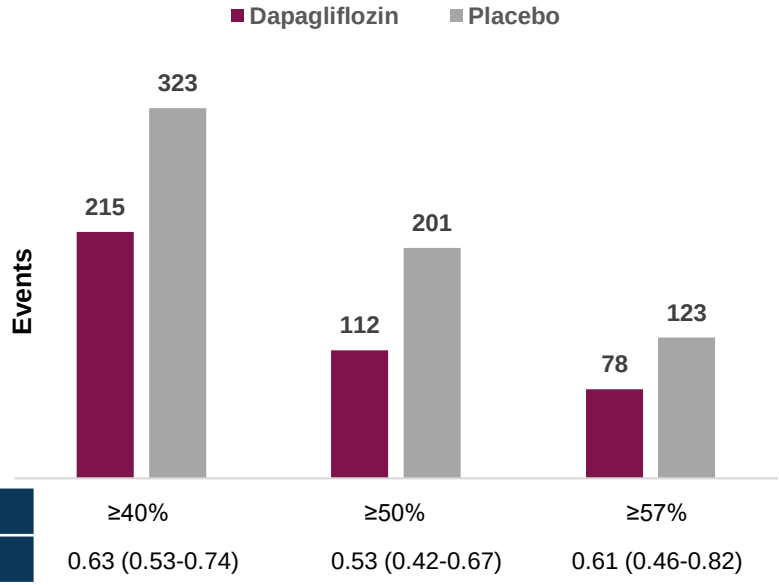
Reductions in the Renal-Specific Outcome With Dapagliflozin Were Similar Across Different eGFR Thresholds

Renal-Specific Outcome Across Different eGFR Decline Thresholds

	Dapagliflozin n/N	Placebo n/N	HR (95% CI)
≥40% eGFR decline, ESKD, or kidney death			
Overall	235/2152	345/2152	0.64 (0.54-0.76)
With T2D	173/1455	248/1451	0.66 (0.54-0.80)
Without T2D	62/697	97/701	0.58 (0.42-0.80)
≥50% eGFR decline, ESKD, or kidney death			
Overall	142/2152	243/2152	0.56 (0.45-0.68)
With T2D	103/1455	173/1451	0.57 (0.45-0.73)
Without T2D	39/697	70/701	0.51 (0.34-0.75)
≥57% eGFR decline, ESKD, or kidney death			
Overall	120/2152	192/2152	0.59 (0.47-0.75)
With T2D	88/1455	134/1451	0.64 (0.49-0.83)
Without T2D	32/697	58/701	0.50 (0.32-0.77)



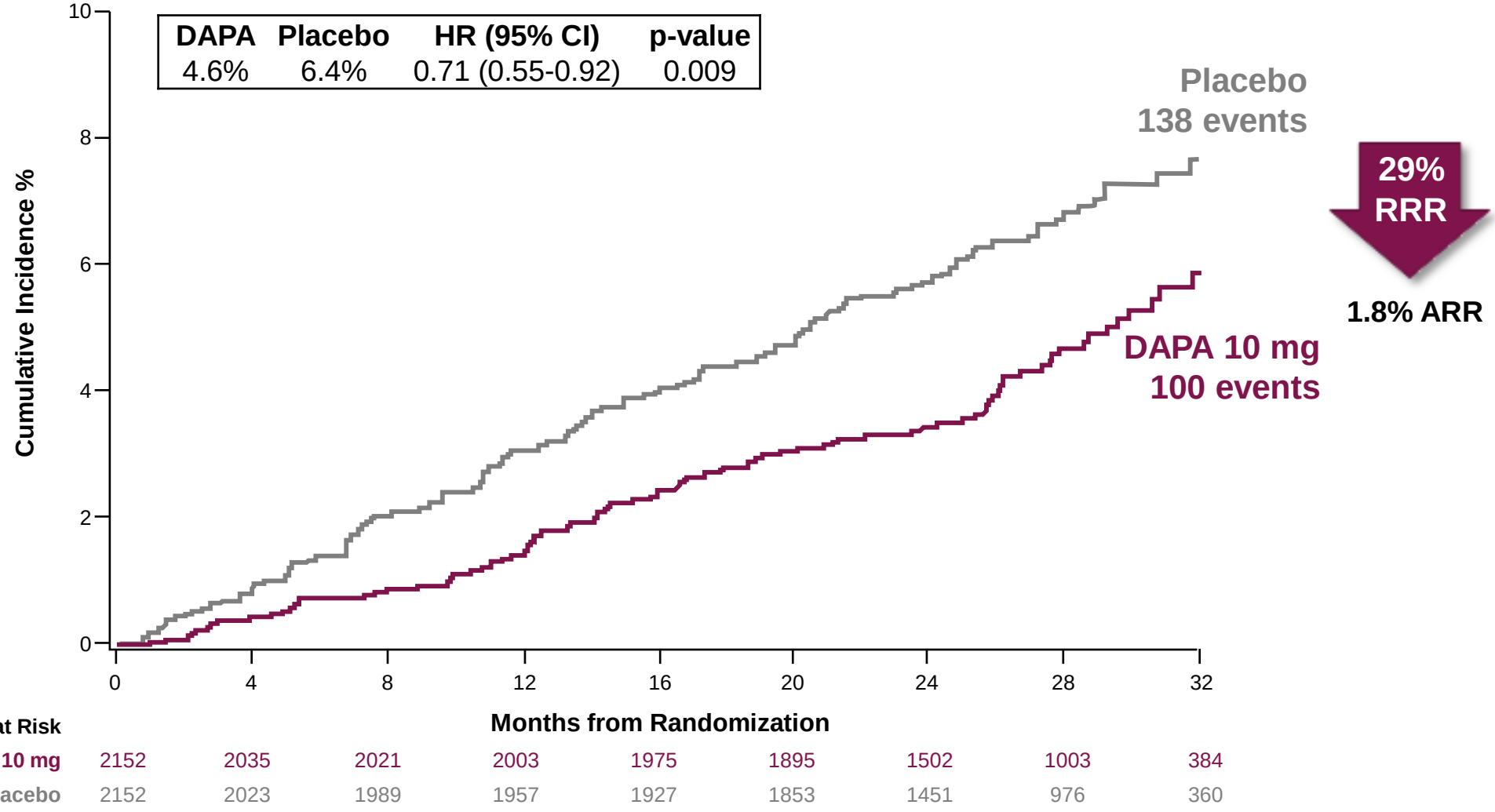
Events of eGFR Decline by Threshold



eGFR = estimated glomerular filtration rate; HR = hazard ratio; ESKD = end-stage kidney disease; T2D = type 2 diabetes.

Jongs N et al. Poster presented at: ASN Kidney Week; November 3-6, 2022; Orlando, FL. Poster SA-PO886.

Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure

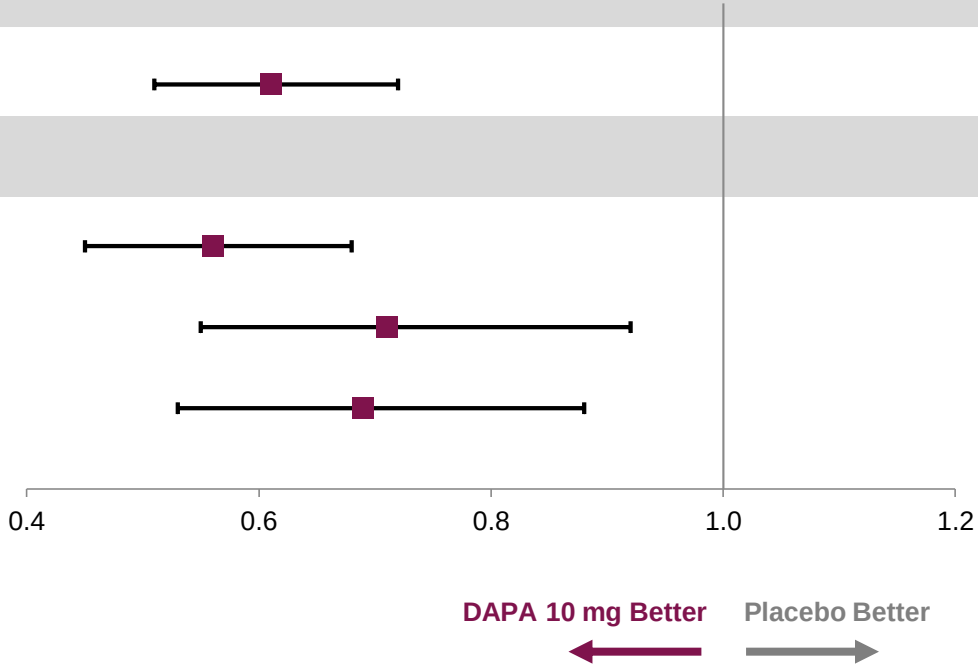


ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Statistical Significance Achieved for the Primary and All Secondary Outcomes[1,2]

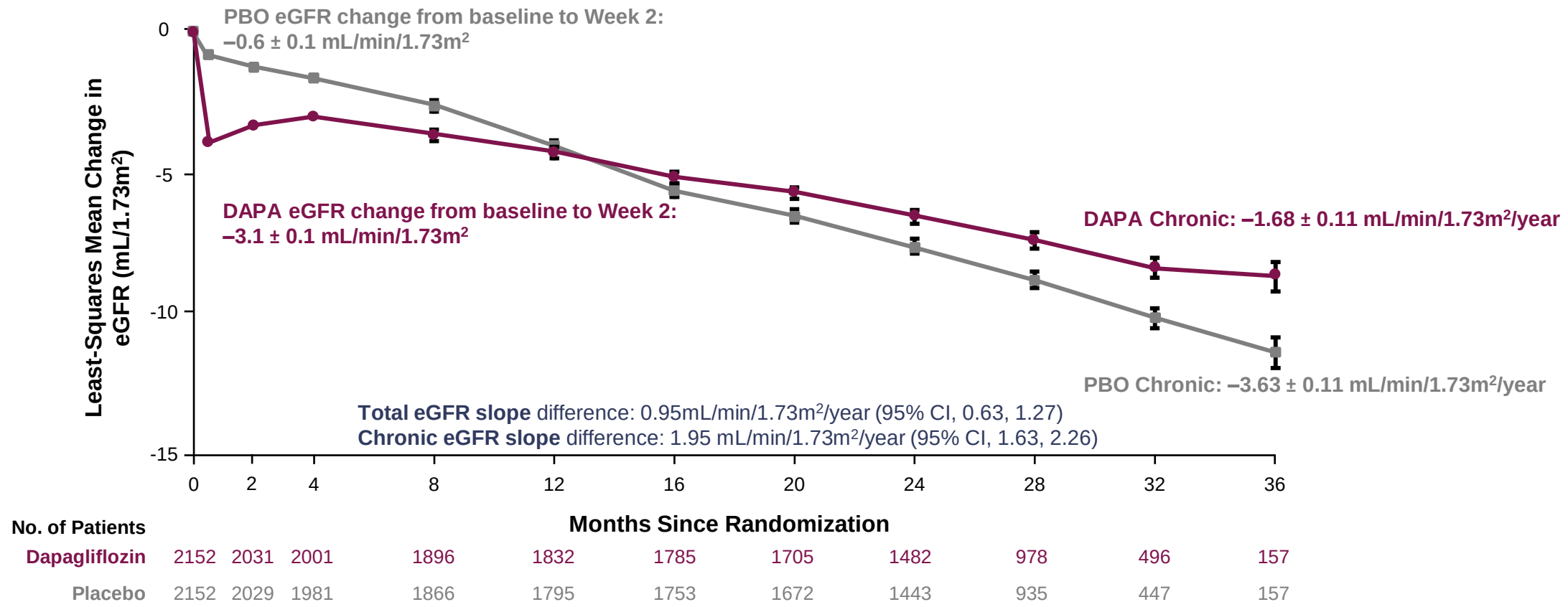
	Number of Events (%)				
HR (95% CI)	DAPA 10 mg (n=2152)	Placebo (n=2152)	Hazard Ratio	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, and Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	<0.001
Secondary Outcomes					
Composite of ≥50% eGFR Decline, ESKD, or Renal Death	142 (6.6)	243 (11.3)	0.56	(0.45, 0.68)	<0.001
Composite of CV Death or Hospitalization for HF	100 (4.6)	138 (6.4)	0.71	(0.55, 0.92)	0.009
All-cause mortality	101 (4.7)	146 (6.8)	0.69	(0.53, 0.88)	0.004



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Summary of Product Characteristics Dapagliflozin 10mg (February 2023)

Change From Baseline in eGFR in the Overall Population[1,2]



BL = baseline; CKD = chronic kidney disease; 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;9:743-754.

DAPA-CKD:
Safety

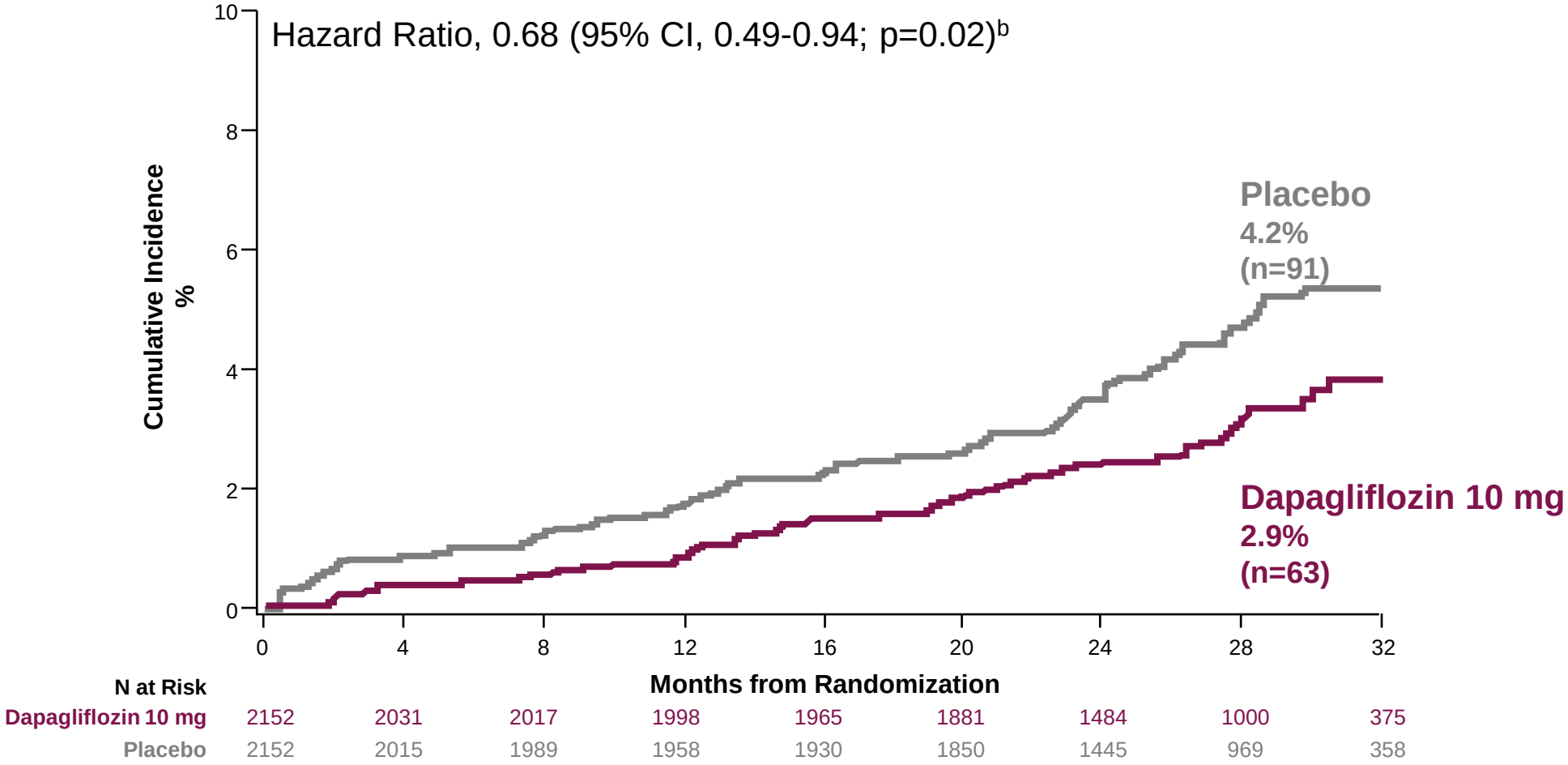
Safety Outcomes[1]

Safety Outcomes[a], n (%)	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	
Discontinuation of study drug	274 (12.7)	309 (14.4)	
Discontinuation due to adverse event	118 (5.5)	123 (5.7)	
Any serious adverse event	633 (29.5)	729 (33.9)	
Adverse events of interest			
Amputation[b]	35 (1.6)	39 (1.8)	
Any definite or probable diabetic ketoacidosis	0	2 (0.1)	
Fracture[c]	85 (4.0)	69 (3.2)	
Renal-related adverse event[c]	155 (7.2)	188 (8.7)	
Major hypoglycemia[d]	14 (0.7)	28 (1.3)	
Volume depletion[c]	127 (5.9)	90 (4.2)	
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)	
Fournier's Gangrene	0	1(<0.1)	

[a]Safety outcomes reported in participants on and off treatment; [b]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma;
[c]Based on pre-defined list of preferred terms; [d]Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446;

Cumulative Incidence of AKI[a]



[a]Pre-specified exploratory endpoint. Defined as doubling of serum creatinine since last central laboratory result. Referred to as “abrupt decline” in the publication;
[b]Subdistribution HR, 0.69; 95% CI, 0.50 to 0.95; p=0.02 using the Fine-Gray model which accounted for the competing risk of death.

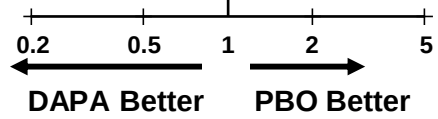
AKI = acute kidney injury; CI = confidence interval.

Heerspink HJL et al. *Kidney Int*. 2022;101:174-184.

AKI by Baseline Subgroups[a]

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

	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)	



[a]Pre-specified exploratory endpoint. Defined as doubling of serum creatinine since last central laboratory result.

AKI = acute kidney injury; CI = confidence interval; DAPA= dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL et al. *Kidney Int*. 2022;101:174-184.

DAPA-CKD Subgroup Analysis
T2D Status

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to baseline T2D status.[1]

T2D = type 2 diabetes.

Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31

Demographics and Baseline Characteristics by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	Dapagliflozin 10 mg (n=1455)	Placebo (n=1451)	Dapagliflozin 10 mg (n=697)	Placebo (n=701)
Age (years), mean (SD)	64.1 (9.8)	64.7 (9.5)	56.9 (14.6)	56.0 (14.6)
Female sex, n (%)	494 (34)	471 (32)	215 (31)	245 (35)
Race, n (%)				
White	751 (52)	790 (54)	373 (54)	376 (54)
Black or African American	76 (5)	61 (4)	28 (4)	26 (4)
Asian	481 (33)	451 (31)	268 (38)	267 (38)
Other	147 (10)	149 (10)	28 (4)	32 (5)
Weight (kg), mean (SD)	83.2 (20.9)	83.8 (21.2)	77.9 (17.8)	78.3 (19.9)
BMI, kg/m^2, mean	30.3[2,a]		27.9[2,b]	
Current smoker, n (%)	195 (13)	200 (14)	88 (13)	101 (14)
Blood pressure (mmHg), mean (SD)				
Systolic	138.8 (17.6)	139.6 (17.1)	132.3 (16.4)	132.9 (16.9)
Diastolic	76.5 (10.4)	76.5 (9.9)	79.6 (10.9)	79.6 (10.8)
Hemoglobin (g/L), mean (SD)	126.3 (17.8)	125.6 (18.0)	133.4 (17.9)	132.7 (17.2)
Serum potassium (mmol/L), mean (SD)	4.7 (0.6)	4.7 (0.6)	4.6 (0.5)	4.6 (0.5)

[a] n=2899; [b] n=1397.

BMI = body mass index; T2D = Type 2 diabetes.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Renal Characteristics by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	**Dapagliflozin 10 mg (n=1455)**	**Placebo (n=1451)**	**Dapagliflozin 10 mg (n=697)**	**Placebo (n=701)**
Serum creatinine, mg/dL, mean	1.6[2]		1.8[2]	
eGFR (mL/min/1.73m²)	44.0 (12.6)	43.6 (12.6)	41.7 (11.5)	41.8 (11.9)
eGFR ≥60 mL/min/1.73m², n (%)	179 (12)	169 (12)	55 (8)	51 (7)
eGFR 45 to <60 mL/min/1.73m², n (%)	450 (31)	468 (32)	196 (28)	214 (31)
eGFR 30 to <45 mL/min/1.73m², n (%)	636 (44)	603 (42)	343 (49)	316 (45)
eGFR <30 mL/min/1.73m², n (%)	190 (13)	211 (15)	103 (15)	120 (17)
UACR (mg/g), median (IQR)	1024.5 (472.5-2111.0)	1004.5 (493.3-2017.0)	870.5 (472.0-1533.5)	841.5 (458.5-1554.5)
UACR 30-300 mg/g (Stage A2), %	10.6[2]		9.7[2]	
UACR >300 mg/g (Stage A3), %	89.4[2]		90.3[2]	
UACR >1000 mg/g, n (%)	741 (51)	732 (50)	307 (44)	299 (43)

eGFR = estimated glomerular filtration rate; IQR = interquartile range; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Medical History and Baseline Medications by Diabetes Status at Baseline (All Randomized Patients)

	Type 2 Diabetes		Without Type 2 Diabetes	
Characteristic[1]	Dapagliflozin 10 mg (n=1455)	Placebo (n=1451)	Dapagliflozin 10 mg (n=697)	Placebo (n=701)
HbA1c (%), mean (SD)	7.8 (1.7)	7.8 (1.6)	5.6 (0.4)	5.6 (0.4)
HbA1c (mmol/mol), mean (SD)	62 (18.6)	62 (17.5)	38 (4.4)	38 (4.4)
Obese (BMI ≥30 kg/m²), %	49.4[2]		34.3[2]	
Hypertension, %	98.3[2]		90.5[2]	
Any history of CV disease, %	44.1[2]		23.5[2]	
Myocardial infarction, %	11.0[2]		5.1[2]	
Stroke, %	7.9[2]		4.9[2]	
Heart failure, n (%)	177 (12)	184 (13)	58 (8)	49 (7)
Prior medication, n (%)				
ACE inhibitor	451 (31)	443 (31)	222 (32)	238 (34)
ARB	984 (68)	974 (67)	460 (66)	452 (64)
Diuretic	718 (49)	747 (51)	210 (30)	207 (30)
Statin	1039 (71)	1043 (72)	356 (51)	356 (51)
Metformin (biguanides)[c]	629 (44)	613 (43)	-	-
SU derivative[c]	389 (27)	385 (27)	-	-
DPP4 inhibitor[c]	364 (25)	378 (26)	-	-
GLP-1 analog[c]	63 (4)	59 (4)	-	-
Insulin[a]	814 (56)	784 (54)	-	-

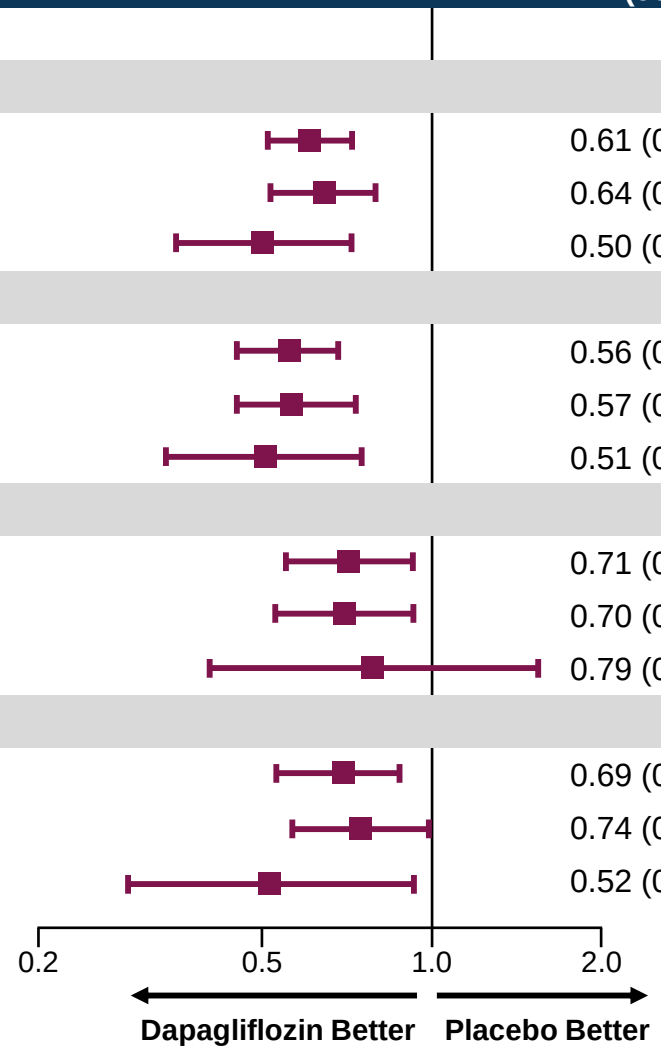
[a]Dapagliflozin n=1444; placebo n=1442.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; DPP4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

Primary and Secondary Outcomes by Diabetes Status

	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients with event/total no. patients			
Primary outcome				0.24
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
With type 2 diabetes	152/1455	229/1451	0.64 (0.52, 0.79)	
Without type 2 diabetes	45/697	83/701	0.50 (0.35, 0.72)	
Renal-specific outcome				0.57
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
With type 2 diabetes	103/1455	173/1451	0.57 (0.45, 0.73)	
Without type 2 diabetes	39/697	70/701	0.51 (0.34, 0.75)	
CV death or hHF				0.78
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
With type 2 diabetes	85/1455	119/1451	0.70 (0.53, 0.92)	
Without type 2 diabetes	15/697	19/701	0.79 (0.40, 1.55)	
All-cause mortality				0.25
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
With type 2 diabetes	84/1455	113/1451	0.74 (0.56, 0.98)	
Without type 2 diabetes	17/697	33/701	0.52 (0.29, 0.93)	

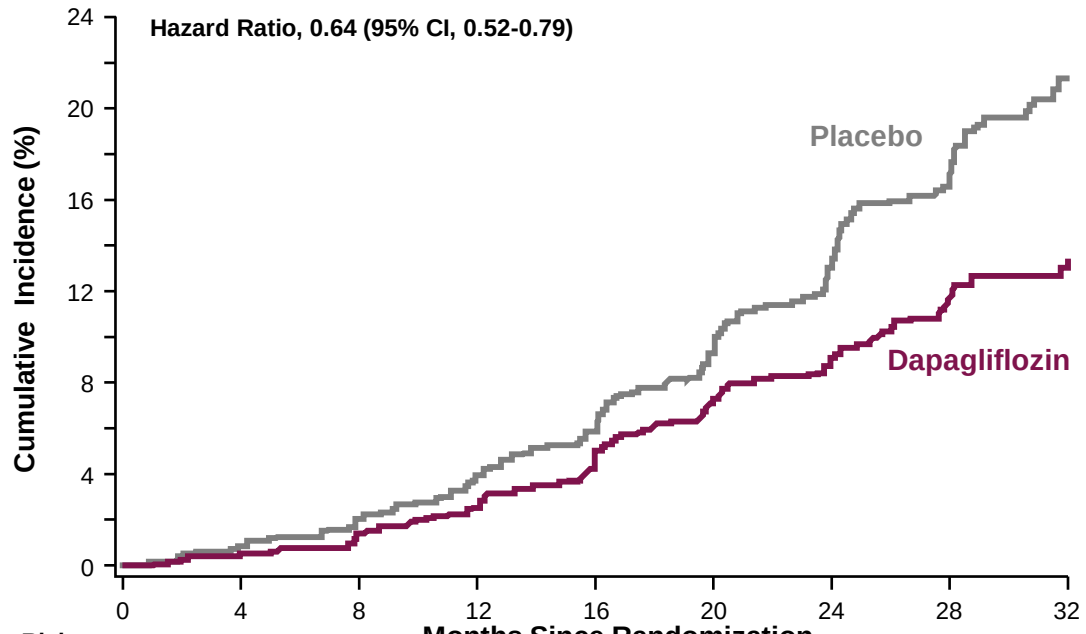


CV = cardiovascular; hHF = hospitalization for heart failure; T2D = type 2 diabetes.

Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

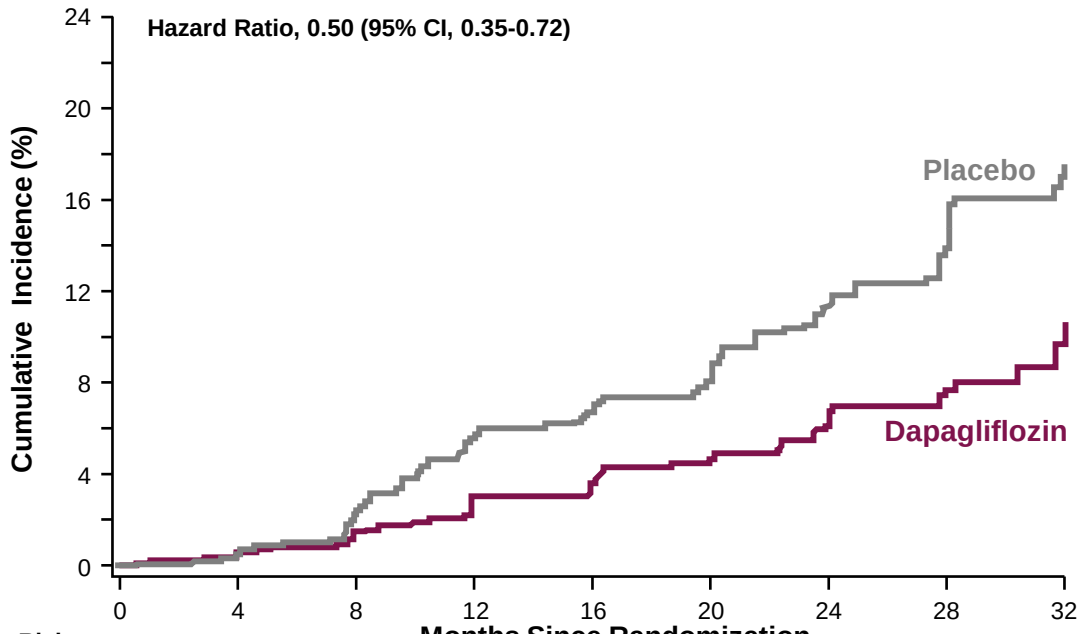
Primary Outcome (Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a]) by Diabetes Status

Patients With T2D



No at Risk									
Dapagliflozin	1455	1383	1349	1307	1262	1155	910	580	215
Placebo	1451	1360	1321	1275	1224	1130	868	545	190

Patients Without T2D



No at Risk									
Dapagliflozin	697	618	606	591	579	546	378	251	94
Placebo	701	633	615	583	567	534	364	229	80

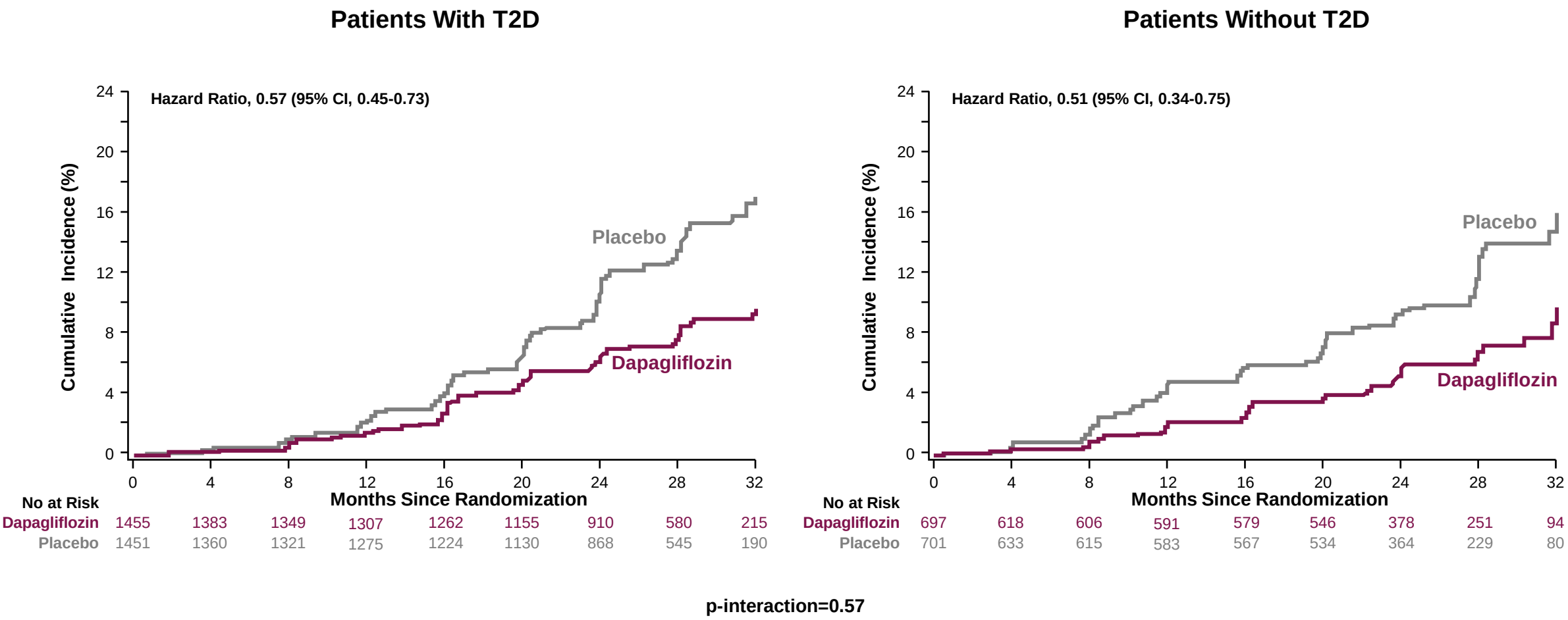
p-interaction=0.24

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

CV= cardiovascular; ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Secondary Renal-Specific Composite Outcome (Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a]) by Diabetes Status



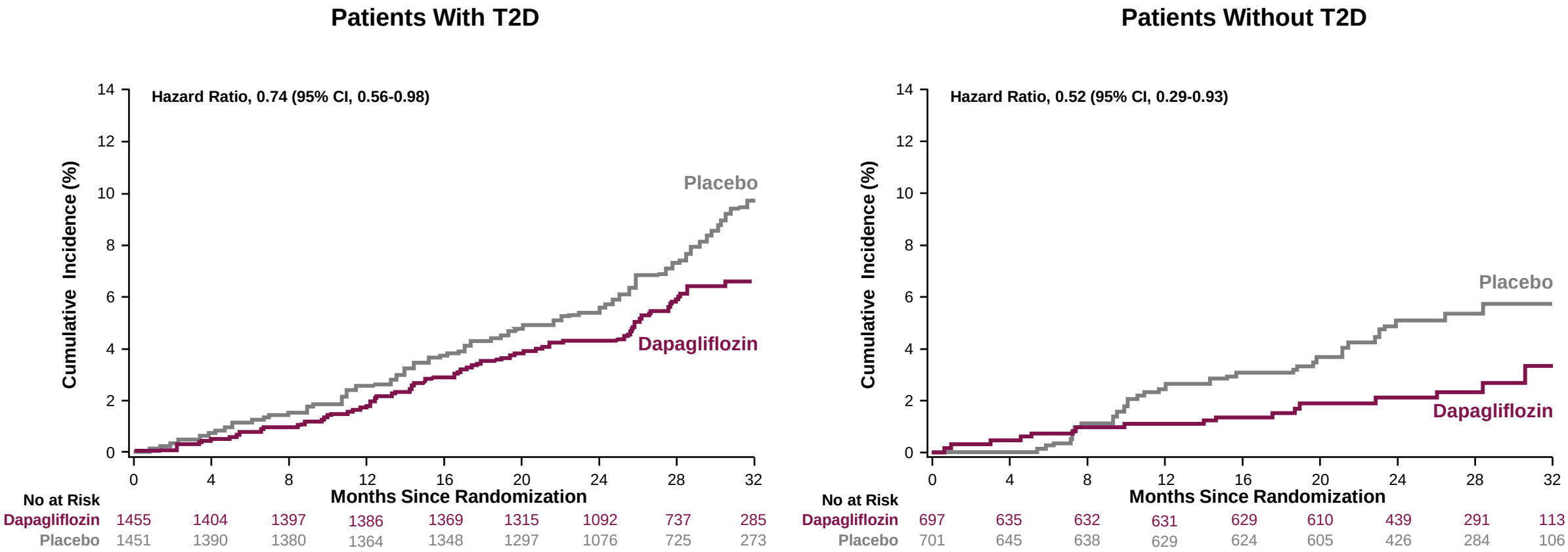
p-interaction=0.57

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2]

ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Secondary Outcome (All-Cause Mortality) by Diabetes Status



p-interaction=0.25

T2D = type 2 diabetes

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

Safety by Diabetes Status

Safety outcomes[a], %	With T2D			Without T2D			
	Dapagliflozin 10 mg (n=1453)	Placebo (n=1450)	Odds Ratio (95% CI)	Dapagliflozin 10 mg (n=696)	Placebo (n=699)	Odds Ratio (95% CI)	p-interaction
Discontinuation due to AE	6	6	0.86 (0.63, 1.17)	5	4	1.26 (0.77, 2.09)	0.20
Any serious AE[b]	33	39	0.79 (0.68, 0.92)	22	24	0.88 (0.68, 1.12)	0.48
AE of special interest							
Amputation[c]	2	3	0.92 (0.57, 1.46)	0	<1%	NA	0.26
Any definite or probable DKA	0	<1%	NA	-	-	-	NA
Fracture[d]	4	4	1.28 (0.89, 1.87)	3	3	1.12 (0.59, 2.15)	0.72
Renal-related adverse event[d]	8	10	0.80 (0.62, 1.03)	5	6	0.85 (0.53, 1.35)	0.83
Major hypoglycemia[e]	1	2	0.49 (0.25, 0.93)	-	-	-	1.00
Volume depletion[d]	6	5	1.31 (0.96, 1.81)	5	3	1.90 (1.09, 3.41)	0.27

[a]Safety analysis set; [b]Includes death; [c]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; [d]Based on pre-defined list of preferred terms; [e]AE with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

AE = adverse event; DKA = diabetic ketoacidosis; NA = not applicable; T2D = type 2 diabetes.

Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

DAPA-CKD Subgroup Analysis
Etiology

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to the underlying cause of kidney disease

Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

Baseline Characteristics by Underlying Cause of Kidney Disease

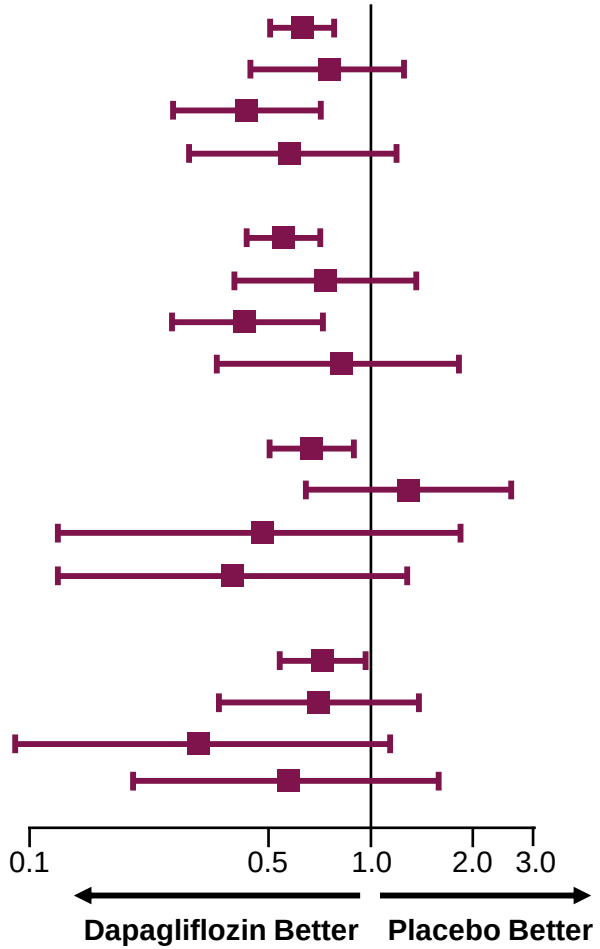
Characteristic	Diabetic Nephropathy		Ischemic / Hypertensive CKD		Glomerulonephritis		Other / Unknown	
	DAPA (n=1271)	PBO (n=1239)	DAPA (n=324)	PBO (n=363)	DAPA (n=343)	PBO (n=352)	DAPA (n=214)	PBO (n=198)
Age, years, mean	64.2	65.0	64.2	63.1	51.9	51.7	59.6	58.4
Sex, female, %	34.2	33.0	26.9	27.5	34.1	38.9	32.7	35.4
Race, %								
White	51.7	54.6	54.6	54.5	48.1	50.0	58.4	58.6
Black or African American	5.2	4.0	7.7	8.0	1.7	0.9	3.3	3.0
Asian	32.2	30.1	32.1	30.0	47.2	46.6	34.6	36.4
Other	10.9	11.4	5.6	7.4	2.9	2.6	3.7	2.0
Weight, kg, mean	82.9	83.4	82.7	83.5	77.2	77.2	78.1	79.6
Blood pressure, mmHg, mean	139.1/76.4	139.8/76.2	137.9/79.6	139.5/79.5	128.8/79.0	128.6/78.2	133.9/78.6	134.6/80.7
eGFR, mL/min/1.73m^2, mean	44.2	43.5	42.0	42.0	42.9	42.8	40.2	41.7
UACR, mg/g, median	1056.0	1037.5	801.0	711.0	975.0	981.2	794.5	841.0

CKD = chronic kidney disease; DAPA = dapagliflozin 10 mg; eGFR = estimated glomerular filtration rate; PBO = placebo; UACR = urinary albumin-to-creatine ratio.

Wheeler DC et al. Article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

Primary and Secondary Outcomes by Underlying Cause of Kidney Disease

	Dapagliflozin 10 mg Events[a]	Placebo Events[a]	Hazard Ratio (95% CI)	P-value for Interaction
Primary outcome[b]				
Diabetic nephropathy	139/1271	207/1239	0.63 (0.51, 0.78)	0.53
Ischemic/hypertensive CKD	24/324	35/363	0.75 (0.44, 1.26)	
Glomerulonephritis	22/343	49/352	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	0.58 (0.29, 1.19)	
Renal-specific outcomes[c]				
Diabetic nephropathy	93/1271	157/1239	0.55 (0.43, 0.71)	0.67
Ischemic/hypertensive CKD	18/324	26/363	0.74 (0.40, 1.36)	
Glomerulonephritis	21/343	46/352	0.43 (0.26, 0.72)	
Other/unknown	10/214	14/198	0.81 (0.35, 1.83)	
CV death or hHF				
Diabetic nephropathy	76/1271	107/1239	0.67 (0.50, 0.90)	0.24
Ischemic/hypertensive CKD	17/324	15/363	1.29 (0.64, 2.60)	
Glomerulonephritis	3/343	7/352	0.48 (0.12, 1.84)	
Other/unknown	4/214	9/198	0.39 (0.12, 1.28)	
All-cause mortality				
Diabetic nephropathy	78/1271	104/1239	0.72 (0.54, 0.97)	0.55
Ischemic/hypertensive CKD	14/324	22/363	0.70 (0.36, 1.37)	
Glomerulonephritis	3/343	11/352	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	0.57 (0.20, 1.61)	



[a]Event data are numbers of patients with an outcome event/total patients; [b]Sustained ≥50% eGFR decline, ESKD, renal or CV death; [c]Sustained ≥50% eGFR decline, ESKD, or renal death; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

Adverse Events by Kidney Disease Diagnosis at Baseline[1]

Etiology, n	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	Odds Ratio (95% CI)	P-value for interaction
Diabetic nephropathy	1269	1239		
Hypertensive CKD	324	362		
Glomerulonephritis	343	351		
IgA nephropathy[2]	137	133		
FSGS[3]	45	58		
Other / Unknown	213	197		
Outcome, n (%)				
Discontinuation due to adverse event, n (%)				0.0352
Diabetic nephropathy	71 (5.6)	82 (6.6)	0.84 (0.60, 1.16)	
Hypertensive CKD	17 (5.2)	18 (5.0)	1.06 (0.53, 2.10)	
Glomerulonephritis	16 (4.7)	20 (5.7)	0.81 (0.41, 1.59)	
IgA nephropathy[2]	6 (4.4)	7 (5.3)		
FSGS[3]	3 (6.7)	3 (5.2)		
Other / Unknown	14 (6.6)	3 (1.5)	4.55 (1.46, 19.96)	
Any serious adverse event, n (%)[a]				0.1363
Diabetic nephropathy	427 (33.6)	492 (39.7)	0.77 (0.65, 0.91)	
Hypertensive CKD	94 (29.0)	108 (29.8)	0.96 (0.69, 1.34)	
Glomerulonephritis	64 (18.7)	91 (25.9)	0.66 (0.46, 0.94)	
IgA nephropathy[2]	22 (16.1)	34 (25.6)		
FSGS[3]	9 (20.0)	16 (27.6)		
Other / Unknown	48 (22.5)	38 (19.3)	1.22 (0.76, 1.97)	

[a]Includes death.

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis; IgA = immunoglobulin A.

1. Wheeler DC et al. Article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Wheeler DC et al. *Kidney Int*. 2021;100:215-224; 3. Wheeler DC et al. Online ahead of print. *Nephrol Dial Transplant*. 2021.

DAPA-CKD Subgroup Analysis
IgA Nephropathy

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed in patients with CKD due to IgA Nephropathy

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Baseline Characteristics in Patients with IgA Nephropathy

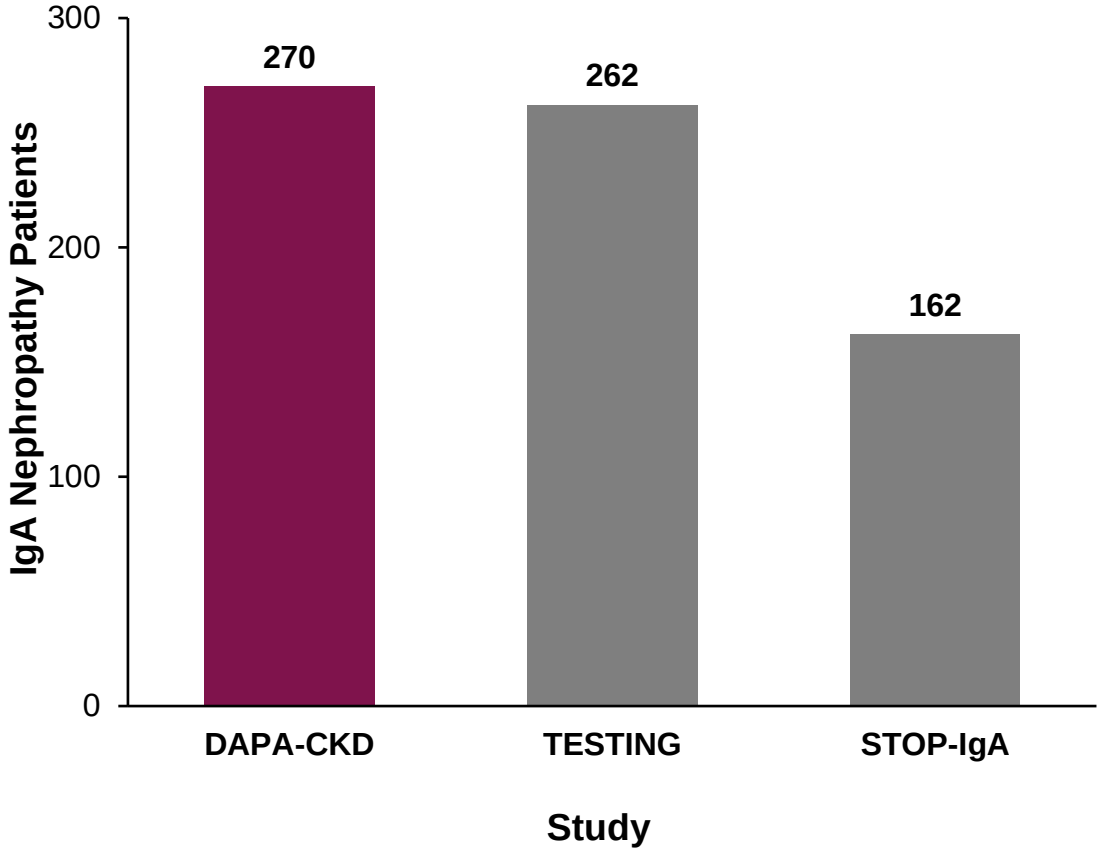
Characteristic	Dapagliflozin (n=137)	Placebo (n=133)	Total (n=270)
Age (years), mean (SD)	52.2 (13.1)	50.1 (13.1)	51.2 (13.1)
Female sex, n (%)	44 (32.1)	44 (33.1)	88 (32.6)
Race, n (%)			
White	54 (39.4)	54 (40.6)	108 (40.0)
Black	0 (0)	1 (0.8)	1 (0.4)
Asian	82 (59.9)	77 (57.9)	159 (58.9)
Other	1 (0.7)	1 (0.8)	2 (0.7)
Weight (kg), mean (SD)	75.1 (15.4)	78.7 (20.2)	76.8 (18.0)
Blood pressure (mmHg), mean (SD)			
Systolic	127.7 (16.2)	127.0 (13.9)	127.4 (15.1)
Diastolic	78.7 (11.8)	79.5 (10.1)	79.1 (11.0)
eGFR (mL/min/1.73m^2), mean (SD)	44.3 (12.4)	43.2 (12.0)	43.8 (12.2)
UACR (mg/g), median (Q1–Q3)	889.5 (557.5-1472.0)	902.5 (500.5-1633.0)	900 (539.6-1515.0)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	38 (14.1)
IgA nephropathy confirmed by previous biopsy, n (%)	129 (94)	125 (94)	254 (94)

IgA = immunoglobulin A; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio

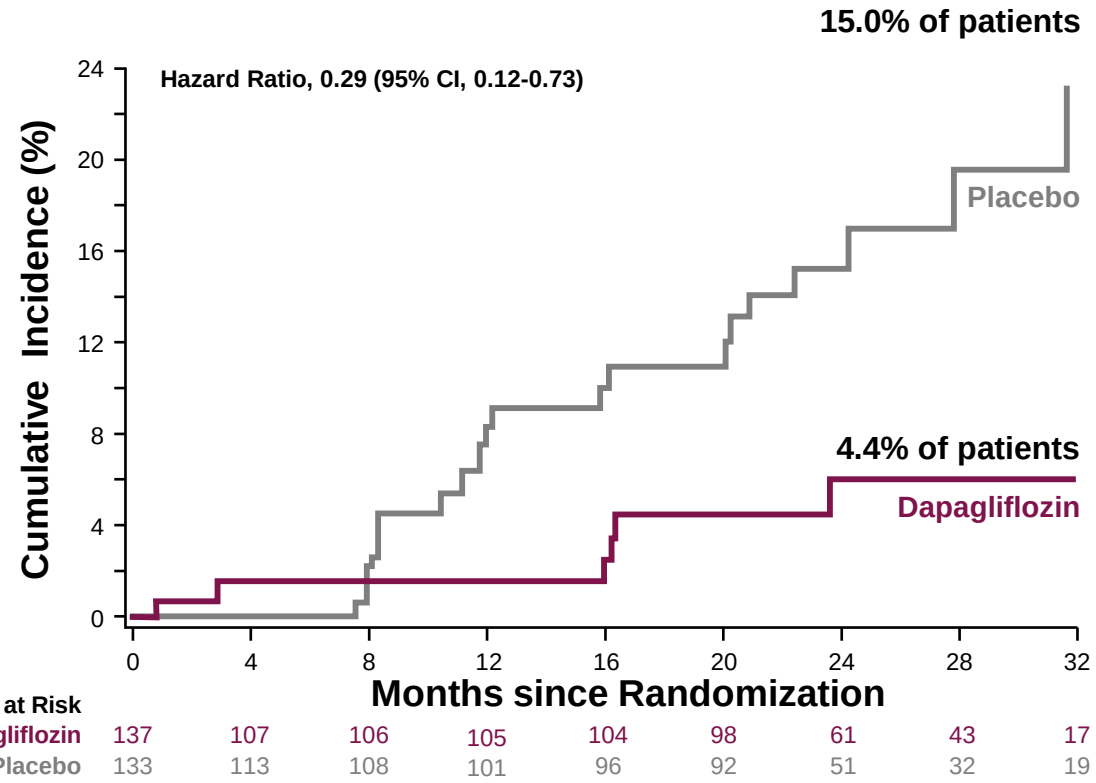
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Further Exploring the Effect of Dapagliflozin by Causes Of Kidney Disease in DAPA-CKD – IgA Nephropathy

Number of participants with IgA nephropathy in clinical trials[1]



Primary outcome in participants with IgA nephropathy[2,3]

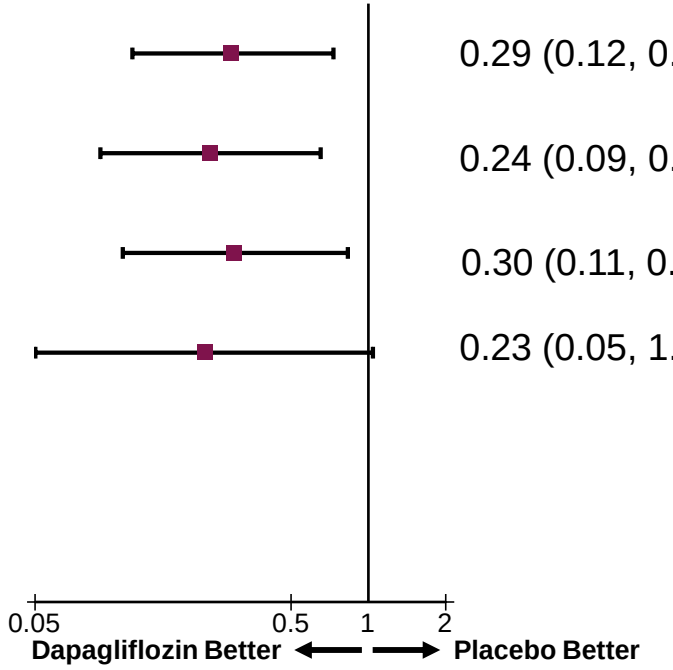


CKD = chronic kidney disease; IgA = immunoglobulin A

1. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711; 2. Wheeler DC et al. Article and supplementary appendix. *Lancet Diabetes Endocrinol.* 2021;9:22–31;
3. Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Key Endpoints in Patients with IgA Nephropathy

	No. of patients/total no.		Events/100 patient-years		Hazard Ratio (95% CI)	p-value
	Dapagliflozin	Placebo	Dapagliflozin	Placebo		
Primary endpoint[a]	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	0.005
Kidney-specific endpoint[b]	5/137	20/133	2.1	8.8	0.24 (0.09, 0.65)	0.002
ESKD[c]	5/137	16/133	2.1	6.9	0.30 (0.11, 0.83)	0.014
Composite endpoint of chronic dialysis, kidney transplant and kidney death	2/137	10/133	0.8	4.0	0.23 (0.05, 1.04)	NC



[a]Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney or cardiovascular cause; [b]Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney cause; [c]Maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after 28 days.

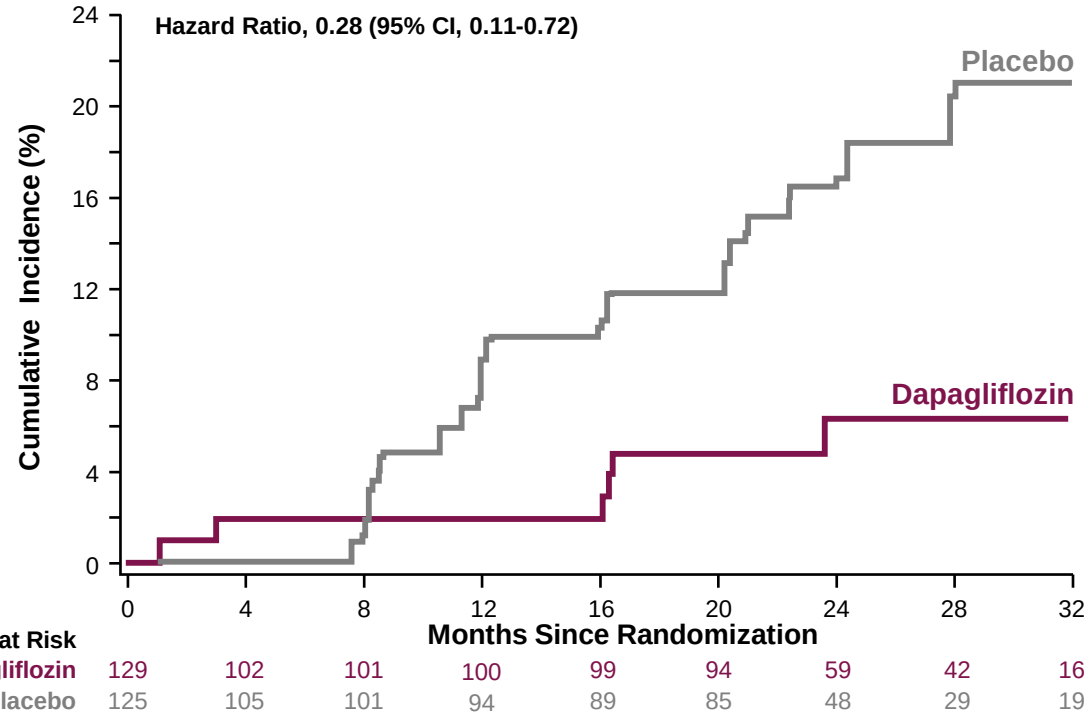
eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; IgA = immunoglobulin A.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Outcomes in Patients with IgA Nephropathy Confirmed With a Biopsy

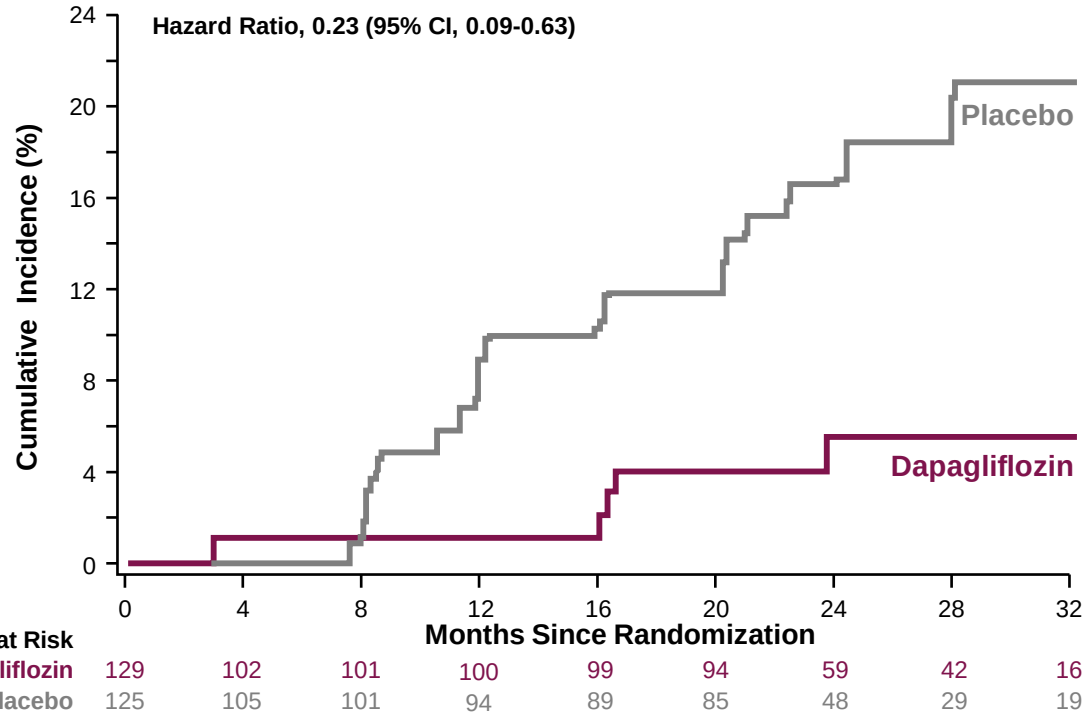
Diagnosis of IgA nephropathy was confirmed by previous biopsy in 254 (94%) patients

Primary Outcome[a]



No at Risk									
Dapagliflozin	129	102	101	100	99	94	59	42	16
Placebo	125	105	101	94	89	85	48	29	19

Kidney-specific Outcome[b]



No at Risk									
Dapagliflozin	129	102	101	100	99	94	59	42	16
Placebo	125	105	101	94	89	85	48	29	19

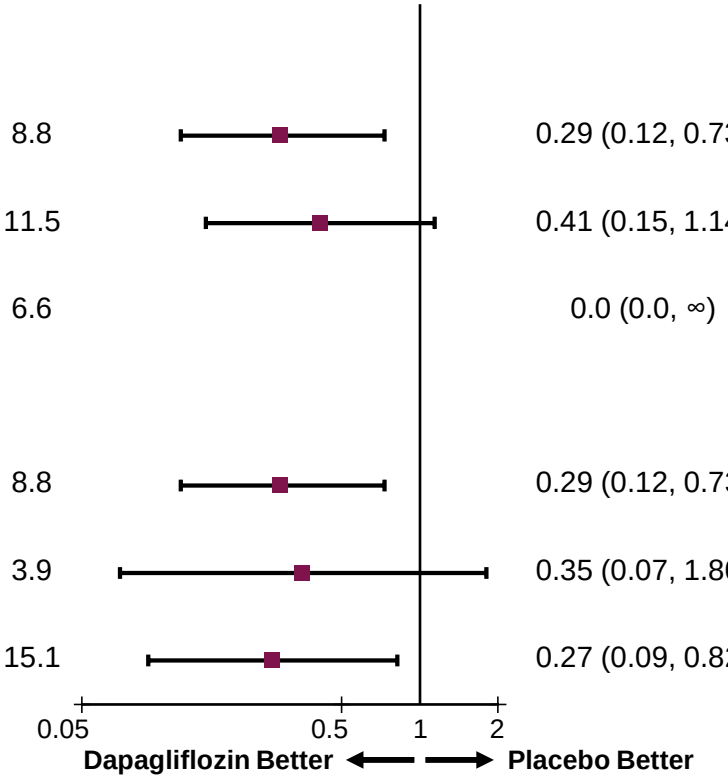
[a]Composite of sustained ≥50% decline in eGFR, onset of ESKD[c], or death from a kidney or cardiovascular cause; [b]Composite of sustained ≥50% decline in eGFR, onset of ESKD[c], or death from a kidney cause; [c]Maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after 28 days.

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; IgA = immunoglobulin A.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Primary composite endpoint by pre-specified baseline eGFR and UACR subgroups in patients with IgA nephropathy

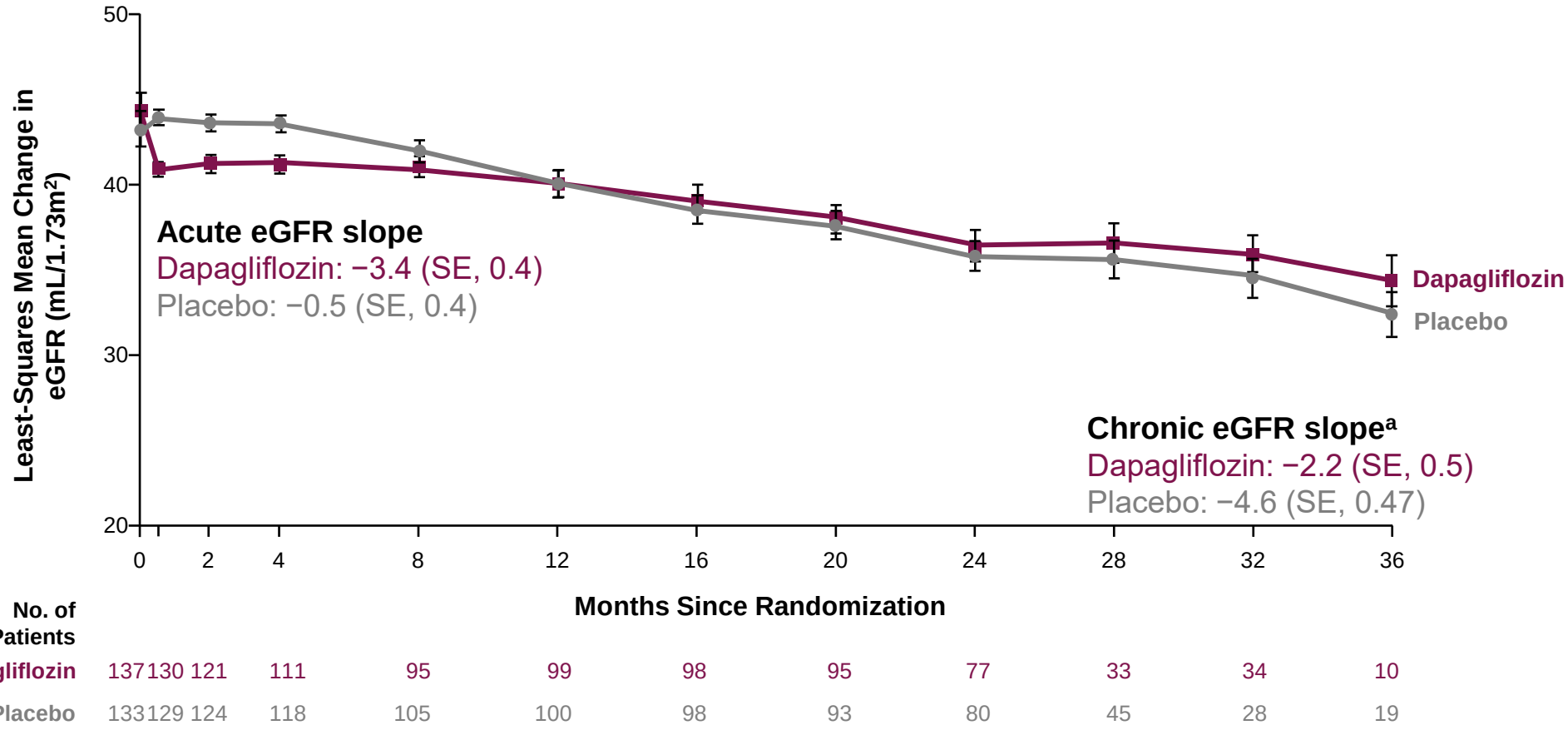
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	Absolute risk difference (95% CI)
	No. of participants/total no.		Events/100 patient years			
eGFR						
Overall	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
<45 mL/min/1.73m^2	6/76	12/70	4.8	11.5	0.41 (0.15, 1.14)	-9.2 (-20.0, 1.5)
≥45 mL/min/1.73m^2	0/61	8/63	0.0	6.6	0.0 (0.0, ∞)	NC
UACR						
Overall	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
≤1000 mg/g	2/77	5/73	1.5	3.9	0.35 (0.07, 1.80)	-4.3 (-11.0, 2.5)
>1000 mg/g	4/60	15/60	4.0	15.1	0.27 (0.09, 0.82)	-18.3 (-31.0, -5.7)



eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; NC = not calculable; UACR = urinary albumin-to-creatinine ratio

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Changes Over Time in eGFR Trajectory in Patients With IgA Nephropathy



No. of Patients											
Dapagliflozin	137	130	121	111	95	99	98	95	77	33	34	10
Placebo	133	129	124	118	105	100	98	93	80	45	28	19

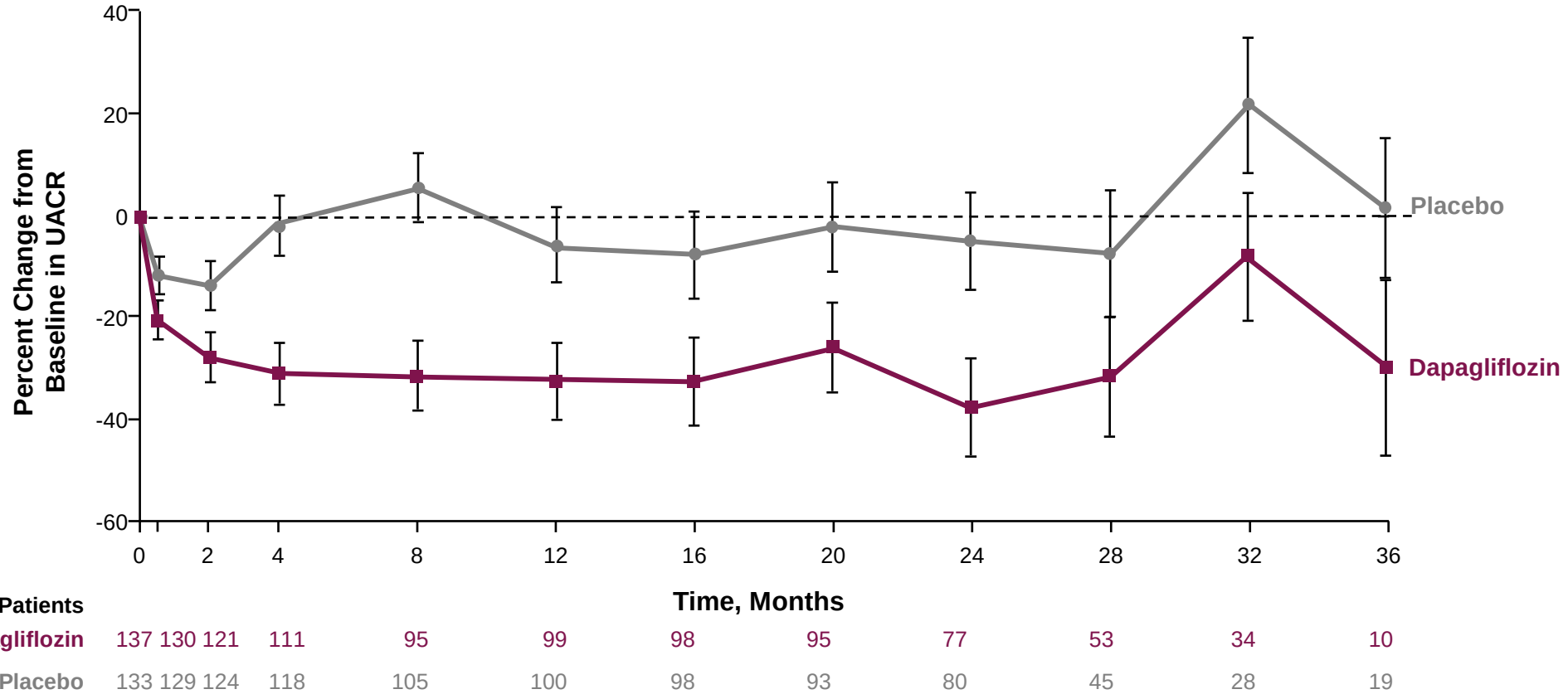
Error bars represent standard error.

[a]Chronic eGFR slope defined as annual mean change with DAPA vs PBO from week 2.

eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; SE = standard error.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Changes Over Time in UACR in Patients With IgA Nephropathy[a]



Mean difference[b]: −26 (95% CI, −37 to −14; p<0.001)

[a]Error bars represent standard error; [b]Dapagliflozin versus placebo.
eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; UACR = urinary albumin-to-creatinine ratio.
Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

Safety outcomes

Safety outcomes	Dapagliflozin (n=137)	Placebo (n=133)
Adverse events leading to discontinuation of the study drug, n (%)	6 (4.4)	7 (5.3)
Serious adverse event,[a] n (%)	22 (16.1)	34 (25.6)

[a]Includes death.

IgA = immunoglobulin A.

Wheeler DC et al. *Kidney Int*. 2021;100:215-224.

DAPA-CKD Subgroup Analysis
FSGS

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed in patients with CKD due to FSGS

CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis.

Wheeler DC et al. Online ahead of print. *Nephrol Dial Transplant*. 2021.

Baseline Characteristics in the Biopsy-Confirmed FSGS Subgroup

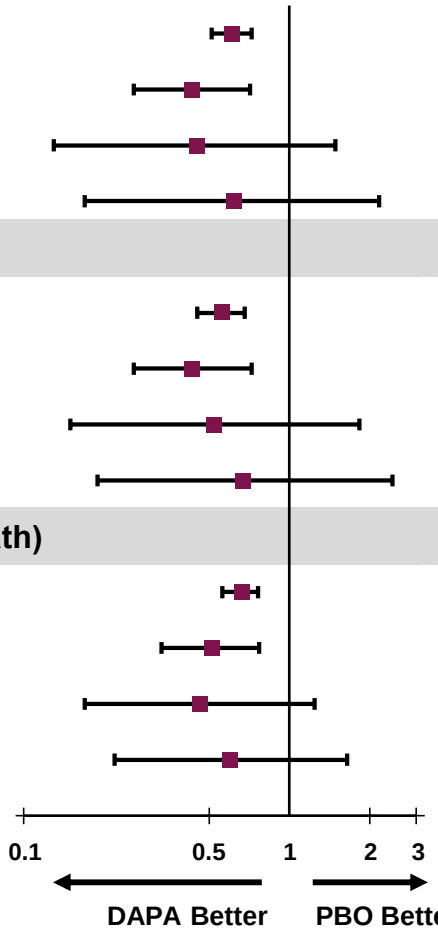
Characteristic	Dapagliflozin (n=45)	Placebo (n=59)	Total (n=104)
Age, years, mean	52.2	55.4	54.0
Sex, female, %	28.9	35.6	32.7
Race, %			
White	62.2	50.8	55.8
Black or African-American	11.1	3.4	6.7
Asian	17.8	37.3	28.8
Other	8.9	8.5	8.7
Weight, kg, mean	89.9	81.7	85.3
BMI, kg/m^2, mean	30.7	28.7	29.6
Blood pressure, mmHg, mean	127/76	129/76	128/76
eGFR, mL/min/1.73m^2, mean	40.3	43.2	41.9
UACR, mg/g, median	997	1410	1248
Type 2 diabetes, %	11.1	25.4	19.2
Prior medications, %			
ACE inhibitor	37.8	35.6	36.5
ARB	62.2	61.0	61.5

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; FSGS = focal segmental glomerulosclerosis; UACR = urinary albumin-to-creatinine ratio.

Wheeler DC et al. Online ahead of print. *Nephrol Dial Transplant*. 2021.

Outcomes in Patients With FSGS

	DAPA (n/N)	PBO (n/N)	Hazard Ratio (95% CI)
Primary composite outcome (sustained ≥50% eGFR decline, ESKD, or renal or CV death)			
Overall	197/2152	312/2152	0.61 (0.51, 0.72)
Glomerulonephritis	22/343	49/352	0.43 (0.26, 0.71)
FSGS[a]	4/53	9/62	0.45 (0.13, 1.49)
Biopsy-confirmed FSGS	4/45	7/59	0.62 (0.17, 2.17)
Renal-specific composite outcome (sustained ≥50% eGFR decline, ESKD, or renal death)			
Overall	142/2152	243/2152	0.56 (0.45, 0.68)
Glomerulonephritis	21/343	46/352	0.43 (0.26, 0.72)
FSGS[a]	4/53	7/62	0.52 (0.15, 1.83)
Biopsy-confirmed FSGS	4/45	6/59	0.67 (0.19, 2.44)
Post hoc exploratory composite outcome (sustained ≥40% eGFR decline, ESKD, or renal or CV death)			
Overall	287/2152	414/2152	0.66 (0.56, 0.76)
Glomerulonephritis	34/343	63/352	0.51 (0.33, 0.78)
FSGS[a]	6/53	13/62	0.46 (0.17, 1.24)
Biopsy-confirmed FSGS	6/45	11/59	0.60 (0.22, 1.65)



[a]Includes patients with biopsy-confirmed FSGS (n=104) and those classed as FSGS but without biopsy confirmation (n=11).

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis; PBO = placebo.

Wheeler, David C et al. "Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial." *Nephrology, dialysis, transplantation :* vol. 37,9 (2022): 1647-1656. doi:10.1093/ndt/gfab335

Safety Outcomes

Safety outcomes, n (%)	Dapagliflozin (n=45)	Placebo (n=58)
Adverse events leading to discontinuation of the study drug	3 (6.7)	3 (5.2)
Any serious adverse event[a]	9 (20.0)	16 (27.6)

- No cases of major hypoglycemia or diabetic ketoacidosis were reported.

[a]Includes death.

Wheeler, David C et al. “Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial.” Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association vol. 37,9 (2022): 1647-1656. doi:10.1093/ndt/gfab335

DAPA-CKD Subgroup Analysis
Stage 4 CKD

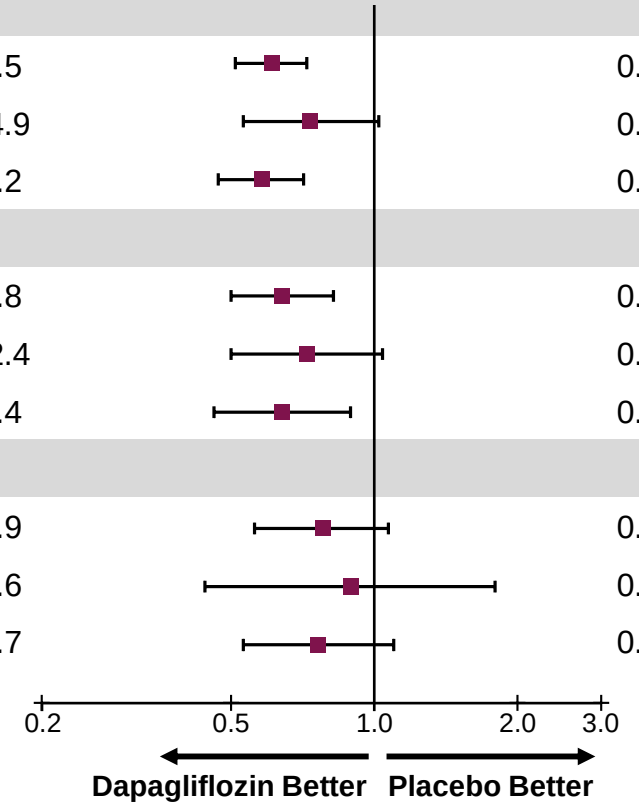
In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed by stage of CKD, including Stage 4 CKD (<30 ml/min/1.73m^2)

CKD = chronic kidney disease.

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

Primary Outcome According to CKD Stage

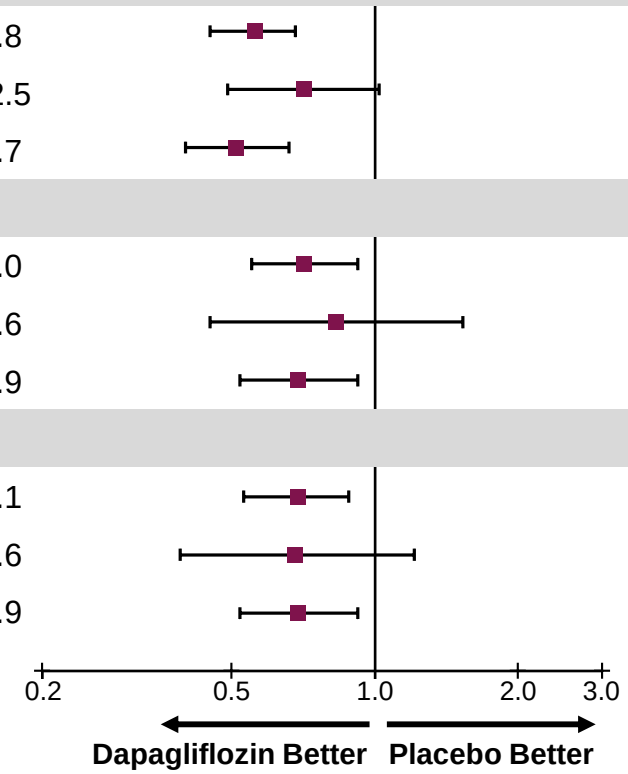
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	p-value for Interaction
	No. of patients/total no.		Events/100 patient-years			
Primary outcome: ≥50% eGFR decline, ESKD, kidney or CV death						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
Stage 4	59/293	87/331	11.1	14.9	0.73 (0.53, 1.02)	0.22
Stage 2/3	138/1859	225/1821	3.7	6.2	0.58 (0.47, 0.71)	
ESKD						
Overall	109/2152	161/2152	2.5	3.8	0.64 (0.50, 0.82)	
Stage 4	49/293	72/331	9.2	12.4	0.72 (0.50, 1.04)	0.64
Stage 2/3	60/1859	89/1821	1.6	2.4	0.64 (0.46, 0.89)	
Kidney or CV death						
Overall	67/2152	86/2152	1.4	1.9	0.78 (0.56, 1.07)	
Stage 4	14/293	18/331	2.3	2.6	0.89 (0.44, 1.79)	0.74
Stage 2/3	53/1859	68/1821	1.3	1.7	0.76 (0.53, 1.09)	



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.
Chertow GM et al. *J Am Soc Nephrol*. 2021;32:2352-2361.

Secondary Outcomes According to CKD Stage

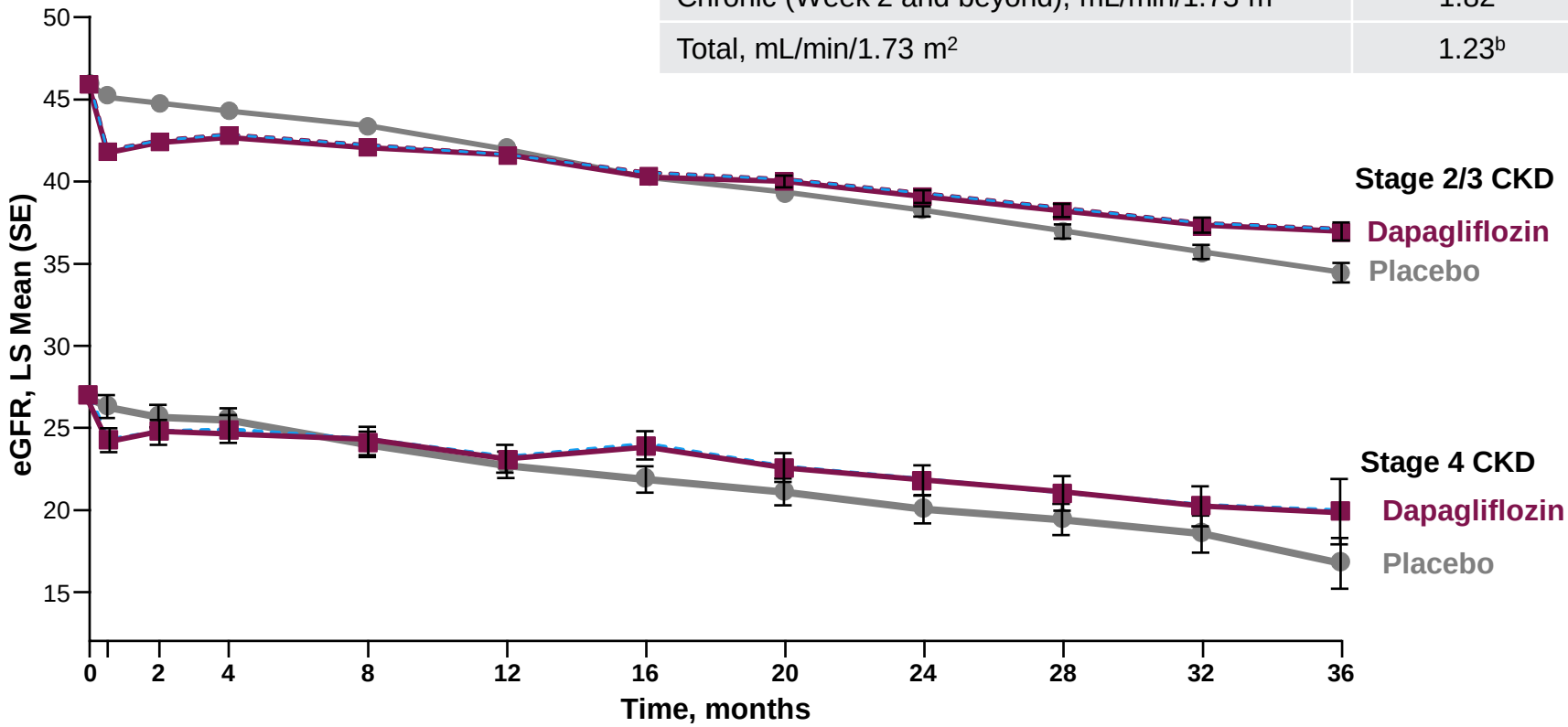
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients/ total no.		Events/100 patient-years			
Kidney composite outcome: ≥50% eGFR decline, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	9.2	12.5	0.71 (0.49, 1.02)	0.13
Stage 2/3	93/1859	170/1821	2.5	4.7	0.51 (0.40, 0.66)	
CV death or heart failure hospitalization						
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
Stage 4	18/293	24/331	2.9	3.6	0.83 (0.45, 1.53)	0.63
Stage 2/3	82/1859	114/1821	2.0	2.9	0.69 (0.52, 0.92)	
All-cause death						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	3.0	4.6	0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	2.0	2.9	0.69 (0.52, 0.92)	



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.
Chertow GM et al. *J Am Soc Nephrol*. 2021;32:2352-2361.

eGFR Decline Over the Study by Baseline CKD Stage

Between-group slope difference[a]	Stage 4 CKD	Stage 2/3 CKD
Acute (2 weeks), mL/min/1.73 m^2	-1.42[b]	-2.56
Chronic (Week 2 and beyond), mL/min/1.73 m^2	1.82[c]	1.95
Total, mL/min/1.73 m^2	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; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; NA = not available; PBO = placebo.

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

Safety Outcomes According to CKD Stage

Safety outcomes	Stage 4 CKD			Stage 2/3 CKD			
	DAPA % (n/N)	PBO % (n/N)	OR (95% CI)	DAPA % (n/N)	PBO % (n/N)	OR (95% CI)	P-Interaction
Discontinuation due to adverse event	9.6 (28/293)	10.9 (36/331)	0.87 (0.51-1.45)	4.8 (90/1856)	4.8 (87/1818)	1.01 (0.75-1.37)	0.61
Any serious adverse event[a]	34.5 (101/293)	41.7 (138/331)	0.74 (0.53-1.02)	28.7 (532/1856)	32.5 (591/1818)	0.83 (0.72-0.96)	0.49
Adverse events of interest							
Amputation[b]	1.0 (3/293)	1.2 (4/331)	0.85 (0.17-3.87)	1.7 (32/1856)	1.9 (35/1818)	0.89 (0.55-1.45)	0.95
Any definite or probable DKA	0	0.3 (1/331)	NC	0	0.1 (1/1818)	NC	NC
Fracture[c]	3.8 (11/293)	4.5 (15/331)	0.82 (0.36-1.81)	4.0 (74/1856)	3.0 (54/1818)	1.36 (0.95-1.95)	0.26
Renal related adverse events	14.7 (43/293)	13.3 (44/331)	1.12 (0.71-1.77)	6.0 (112/1856)	7.9 (144/1818)	0.75 (0.58-0.96)	0.13
Major hypoglycaemia[d]	0.7 (2/293)	2.4 (8/331)	0.28 (0.04-1.12)	0.6 (12/1856)	1.1 (20/1818)	0.59 (0.28-1.18)	0.37
Volume depletion	4.8 (14/293)	4.5 (15/331)	1.06 (0.50-2.24)	6.1 (113/1856)	4.1 (75/1818)	1.51 (1.12-2.04)	0.39

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

[a]Includes death; [b]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; [c]Based on pre-defined list of preferred terms; [d]Adverse event with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

CKD = chronic kidney disease; DAPA = dapagliflozin; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; NC = not calculated; PBO = placebo.

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

DAPA-CKD Subgroup Analysis
Baseline UACR

In a prespecified secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed for the primary and secondary outcomes stratified by UACR at baseline (≤1000 mg/g, >1000 to ≤3500 mg/g, >3500 mg/g)[1,2]

UACR = urinary albumin-to-creatine ratio.

1. Waijer SW et al. Article and supplementary material. *Diabetologia.* 2022;65(7):1085-1097;

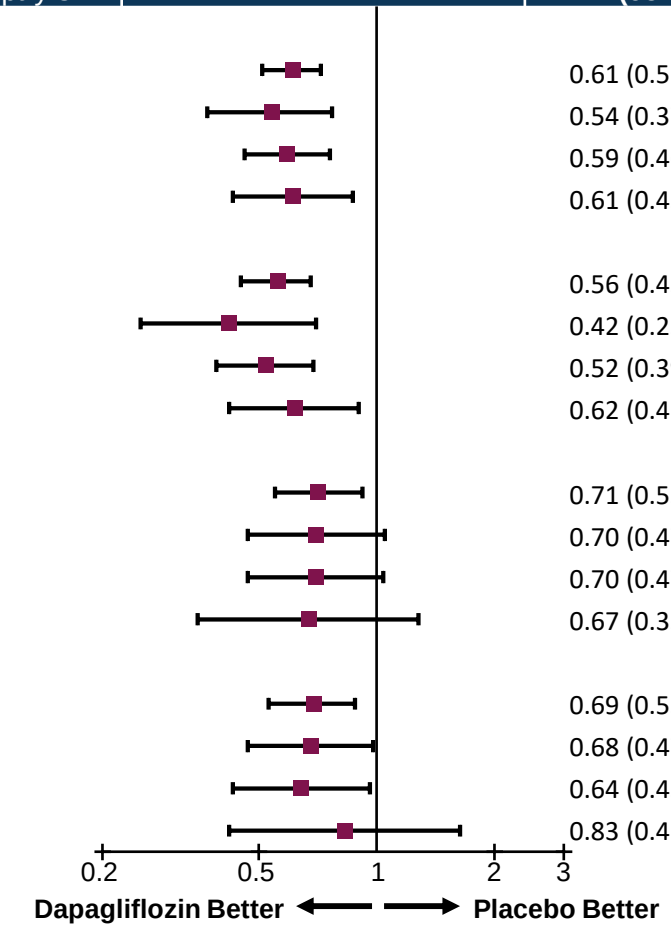
Patient Characteristics by Baseline UACR

Characteristic	UACR Categories			p-value[a]
	≤1000 mg/g (n=2225)	>1000 to ≤3500 mg/g (n=1764)	>3500 mg/g (n=315)	
Mean age, years	62.7	61.0	60.1	<0.001
Female sex, %	32.5	32.9	38.4	0.11
Race, %				<0.001
White	55.6	51.9	43.5	
Black	4.7	4.2	3.8	
Asian	34.2	34.5	31.1	
Other	5.5	9.3	21.6	
Mean blood pressure, mmHg	134/76	139/79	145/80	<0.001
Mean eGFR, mL/min/1.73m²	44.0	42.5	40.6	<0.001
Median UACR, mg/g	488	1744	4127	<0.001
Mean HbA1c, %	7.0	7.1	7.6	<0.001
Type 2 diabetes, %	64.4	68.2	85.4	<0.001
History of CVD, %	36.6	37.9	40.0	0.43

[a]Across the 3 strata of baseline UACR (≤113.0 mg/mmol [≤1000 mg/g], >113.0 to ≤395.5 mg/mmol [>1000 to ≤3500 mg/g] and >395.5 mg/mmol [>3500 mg/g]).
CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatine ratio.
Waijer SW et al. Article and supplementary material. *Diabetologia.* 2022;65(7):1085-1097.

Primary and Secondary Outcomes by Baseline UACR

	Dapagliflozin Events/100 pt-yrs	Placebo Events/100 pt-yrs	Hazard Ratio (95% CI)	Interaction p-value
Primary outcome: eGFR decline ≥50%, ESKD, or kidney or CV death				
Overall	4.6	7.5	0.61 (0.51 to 0.72)	
UACR ≤1000 mg/g	1.9	3.7	0.54 (0.37 to 0.77)	
UACR >1000 to ≤3500 mg/g	5.6	9.3	0.59 (0.46 to 0.76)	0.93
UACR >3500 mg/g	18.7	31.2	0.61 (0.43 to 0.87)	
Secondary outcome: eGFR decline ≥50%, ESKD, or kidney death				
Overall	3.3	5.8	0.56 (0.45 to 0.68)	
UACR ≤1000 mg/g	0.9	2.3	0.42 (0.25 to 0.70)	
UACR >1000 to ≤3500 mg/g	4.1	7.7	0.52 (0.39 to 0.69)	0.59
UACR >3500 mg/g	16.7	27.7	0.62 (0.42 to 0.90)	
Secondary outcome: CV death or hHF				
Overall	2.2	3.0	0.71 (0.55 to 0.92)	
UACR ≤1000 mg/g	1.7	2.5	0.70 (0.47 to 1.05)	
UACR >1000 to ≤3500 mg/g	2.2	3.2	0.70 (0.47 to 1.04)	0.98
UACR >3500 mg/g	4.8	7.0	0.67 (0.35 to 1.28)	
Secondary outcome: All-cause mortality				
Overall	2.2	3.1	0.69 (0.53 to 0.88)	
UACR ≤1000 mg/g	1.9	2.9	0.68 (0.47 to 0.98)	
UACR >1000 to ≤3500 mg/g	2.0	3.1	0.64 (0.43 to 0.96)	0.83
UACR >3500 mg/g	4.7	5.7	0.83 (0.42 to 1.63)	

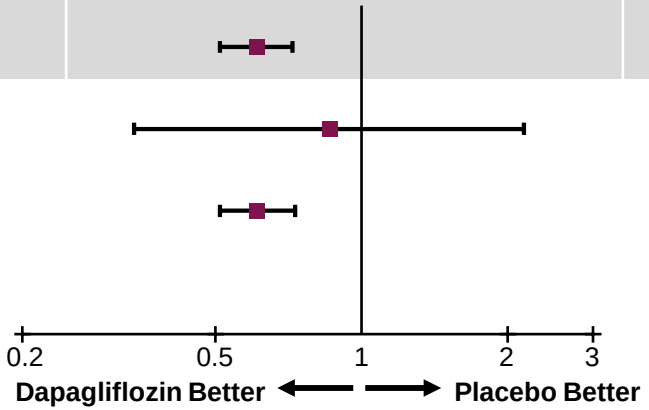


CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; pt-yrs = patient-years; UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Article and supplementary material. *Diabetologia.* 2022;65(7):1085-1097.

Primary Composite Outcome[a] in Patients With UACR ≤300 mg/g and >300 mg/g

	n/N		Events/100 pt-yrs			
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	Interaction p-value
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
UACR ≤300 mg/g	9/240	9/205	1.8	2.1	0.86 (0.34, 2.16)	0.38
UACR >300 mg/g	188/1912	303/1947	5.0	8.1	0.61 (0.51, 0.73)	

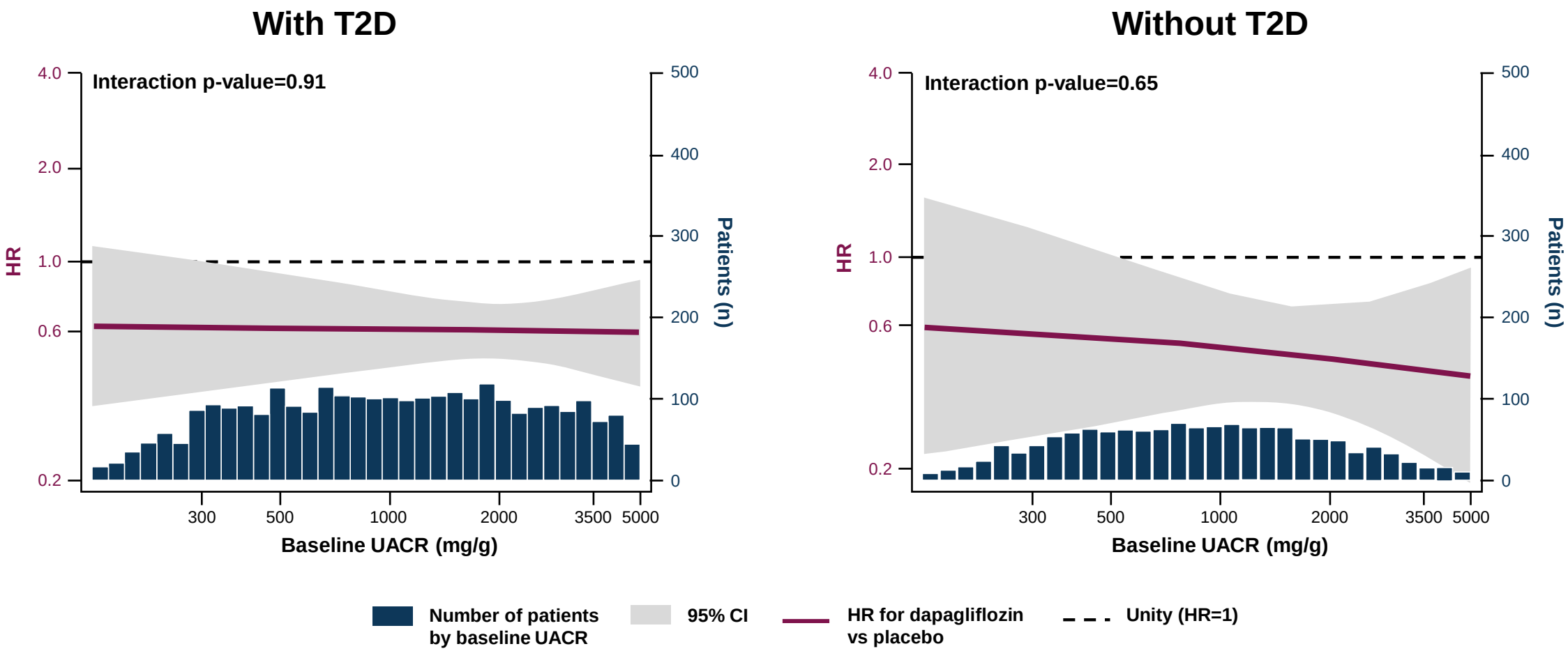


[a]Sustained ≥50% eGFR decline, ESKD, renal death, or CV death.

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; pt-yrs = patient-years; UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. Article and supplementary material. *Diabetologia.* 2022;65(7):1085-1097.

Primary Composite Outcome[a] Across Baseline UACR Levels in Patients With and Without T2D



[a]Sustained ≥50% eGFR decline, ESKD, renal death, or CV death.

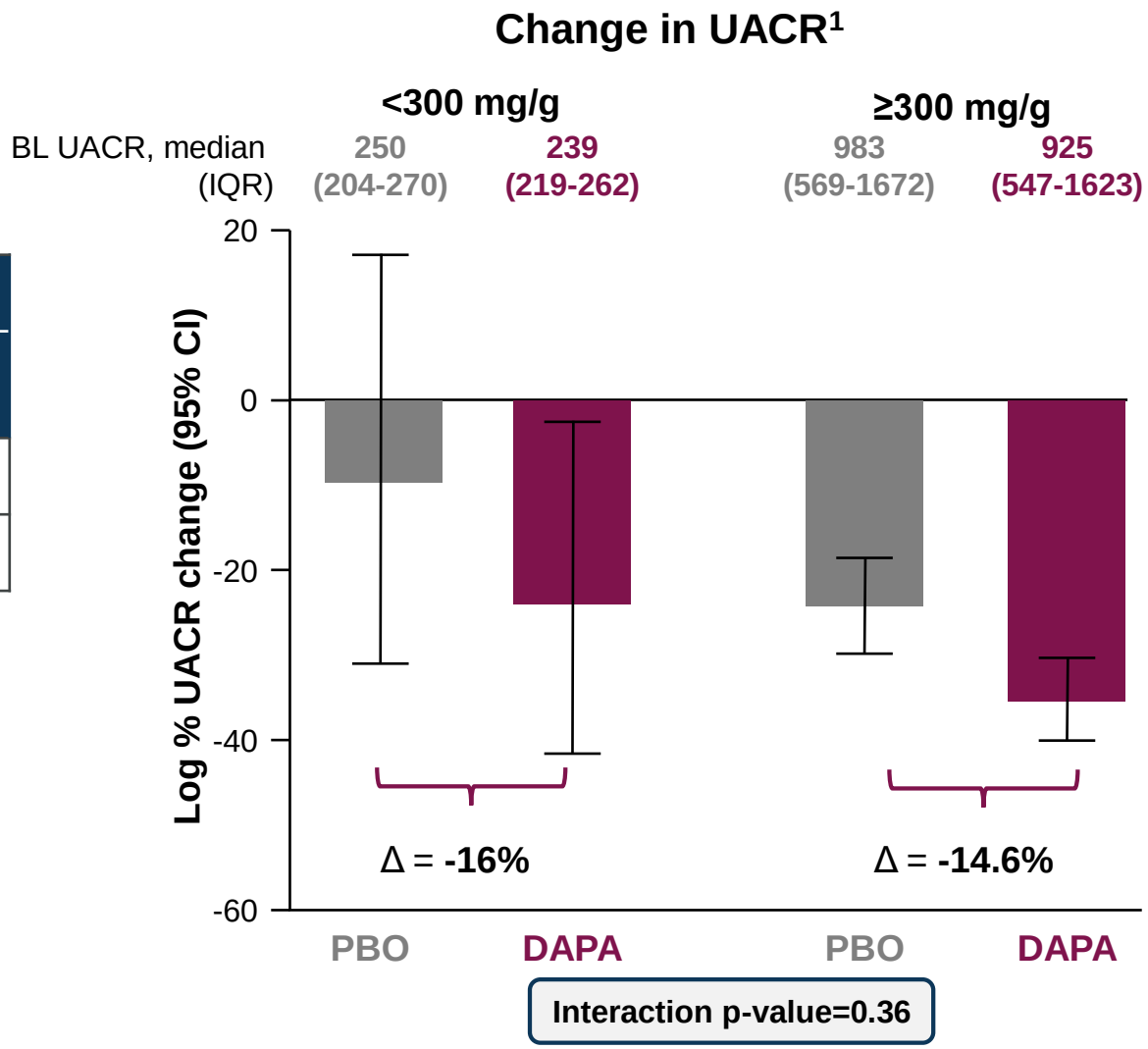
CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatine ratio.

Waijer SW et al. *Diabetologia.* 2022;65(7):1085-1097.

Dapagliflozin Consistently Slowed eGFR Decline and Reduced UACR in Patients Without T2D Who Had UACR <300 mg/g

Attenuation of Chronic eGFR Decline With DAPA Versus PBO[1]	
UACR 30 to <300 mg/g (n=136)	UACR ≥300 mg/g (n=1262)
1.8 mL/min/1.73m^2/year	1.2 mL/min/1.73m^2/year
Interaction p-value=0.62	

In 24 patients without T2D who had UACR 30-200 mg/g, DAPA slowed chronic eGFR decline compared with PBO[2,a]



[a]Difference between DAPA and PBO in chronic eGFR slope of 1.41 mL/min/1.73m^2/year.

Δ = difference between DAPA and PBO; BL = baseline; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; IQR = interquartile range; PBO = placebo; T2D = type 2 diabetes; UACR = urinary albumin-to-creatine ratio.

1. Heerspink HJL et al. Online ahead of print. *Clin J Am Soc Nephrol*. 2022; 2. Heerspink HJL et al. Poster presented at: ASN Kidney Week; November 3-6, 2022; Orlando, FL. Poster SA-PO885.

Adverse Events by Baseline UACR

	Dapagliflozin (%)	Placebo (%)	Odds ratio (95% CI)	Interaction p-value
Discontinuation due to adverse event				
Overall	5.5	5.7	0.97 (0.74 to 1.26)	
UACR ≤1000 mg/g	5.0	4.5	1.12 (0.76 to 1.66)	
UACR >1000 to ≤3500 mg/g	5.3	6.1	0.87 (0.58 to 1.30)	0.48
UACR >3500 mg/g	9.6	12.8	0.71 (0.35 to 1.46)	
Any serious adverse event[a]				
Overall	29.5	33.9	0.81 (0.72 to 0.93)	
UACR ≤1000 mg/g	25.8	30.7	0.78 (0.65 to 0.95)	
UACR >1000 to ≤3500 mg/g	31.7	35.5	0.85 (0.69 to 1.03)	0.79
UACR >3500 mg/g	42.2	48.6	0.77 (0.49 to 1.22)	

[a]Includes death

UACR = urinary albumin-to-creatine ratio

1. Waijer SW et al. *Diabetologia.* 2022;65(7):1085-1097;

DAPA-CKD Subgroup Analysis
Baseline History of CVD

In a secondary analysis from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed according to baseline history of CVD

CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Characteristics by Baseline CVD History

	Baseline cardiovascular disease (n= 1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	n = 813	**n = 797**	**n = 1339**	**n = 1355**
Age – years	66.5	66.2	59	59.4
Male sex - no (%)	587 (72.2)	548 (68.8)	856 (63.9)	888 (65.5)
Race – no. (%)				
White	539 (66.3)	523 (65.6)	585 (43.7)	643 (47.5)
Black or African American	37 (4.6)	43 (5.4)	67 (5)	44 (3.2)
Asian	180 (22.1)	173 (21.7)	569 (42.5)	545 (40.2)
Other	57 (7.0)	58 (7.3)	118 (8.8)	123 (9.1)
Heart rate – beats/min = pulse	71.6	70.7	73.7	74.1
Systolic Blood Pressure – mmHg	138.8	139.7	135.5	136.1
HbA1c – %	7.4	7.4	6.9	6.8
Hemoglobin – g/dL	130.1	127.9	127.7	127.9
Current smoker – no. (%)	97 (11.9)	117 (14.7)	186 (13.9)	184 (13.6)
Body-mass index – Kg/m^2	30.3	30.9	28.8	28.9
Obese (body-mass index ≥30 Kg/m^2) – no. (%)	415 (51.0)	435 (54.6)	526 (39.3)	541 (39.9)
eGFR – ml/min/1.73m^2 of body-surface area	43.3	43.0	43.2	42.9
eGFR category				
≥60 ml/min/1.73m^2 – no. (%)	94 (11.6)	88 (11.0)	140 (10.5)	132 (9.7)
45-59 ml/min/1.73m^2 – no. (%)	233 (28.7)	254 (31.9)	413 (30.8)	428 (31.6)
30-44 ml/min/1.73m^2 – no. (%)	388 (47.7)	322 (40.4)	591 (44.1)	597 (44.1)
<30 ml/min/1.73m^2 – no. (%)	98 (12.1)	133 (16.7)	195 (14.6)	198 (14.6)
Median UACR (IQR) – mg/g	1012 (446-1956)	944 (473-1825)	937 (487-1856)	933 (488-1911)

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; IQR = interquartile range; UACR = urinary albumin-to-creatine ratio.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Medical History by Baseline CVD History

	Baseline cardiovascular disease, n (%) (n= 1610)		No baseline cardiovascular disease, n (%) (n=2694)	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
	n = 813	n = 797	n = 1339	n = 1355
Any atherosclerotic cardiovascular disease	663 (81.5)	666 (83.6)	-	-
Hypertension	803 (98.8)	788 (98.9)	1262 (94.2)	1268 (93.6)
Heart failure	235 (28.9)	233 (29.2)	-	-
Atrial fibrillation or flutter	115 (14.1)	112 (14.1)	-	-
Angina	201 (24.7)	204 (25.6)	-	-
Myocardial infarction	185 (22.8)	207 (26.0)	-	-
Coronary artery bypass grafting	74 (9.1)	102 (12.8)	-	-
Percutaneous coronary intervention	145 (17.8)	149 (18.7)	-	-
Stroke	144 (17.7)	154 (19.3)	-	-
Transient ischemic attack	41 (5.0)	38 (4.8)	-	-
Peripheral artery disease	154 (18.9)	171 (21.5)	-	-
Amputation	59 (7.3)	50 (6.3)	36 (2.7)	36 (2.7)
Type 2 diabetes	640 (78.7)	641 (80.4)	815 (60.9)	810 (59.8)

CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Baseline Therapy by Baseline CVD History

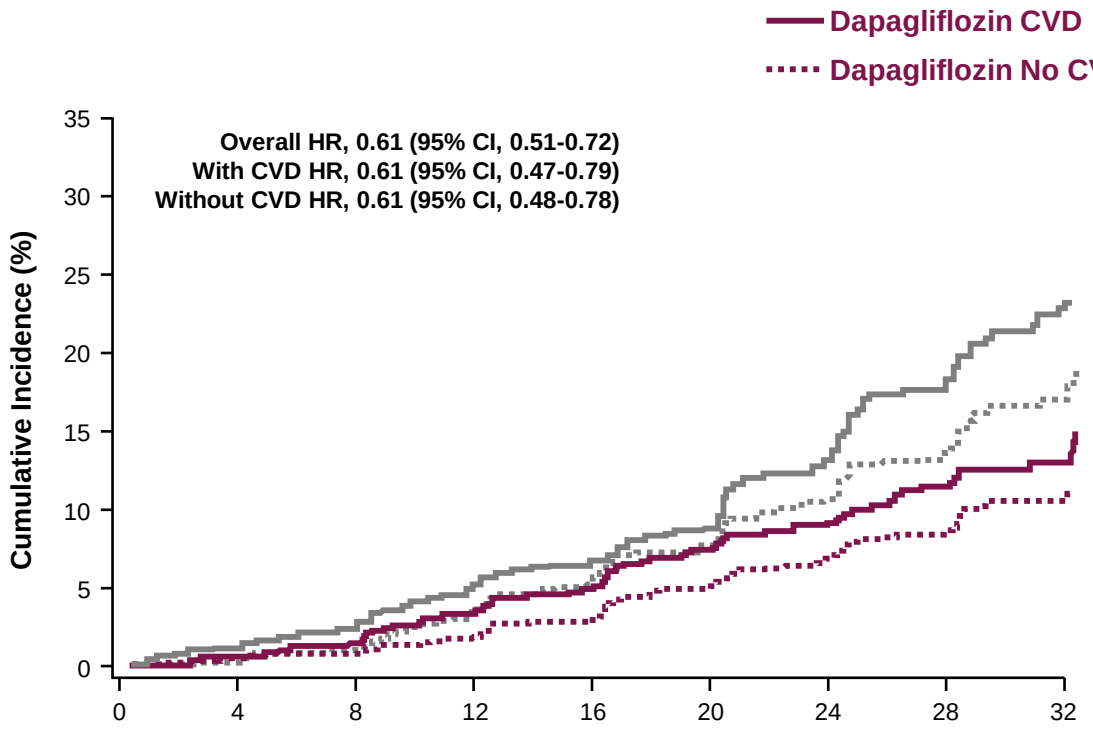
	Baseline cardiovascular disease (n= 1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	n = 813	**n = 797**	**n = 1339**	**n = 1355**
Device therapy – no (%)				
Implantable cardioverter-defibrillator	8 (1.0)	6 (0.8)	-	-
Cardiac resynchronization therapy	2 (0.2)	4 (0.5)	-	-
Pacemaker	27 (3.3)	28 (3.5)	-	-
Cardiovascular and renal medication – no (%)				
Beta-blocker	495 (60.9)	474 (59.5)	351 (26.2)	360 (26.6)
Diuretic	437 (53.8)	443 (55.6)	491 (36.7)	511 (37.7)
Mineralocorticoid receptor antagonist	65 (8.0)	74 (9.3)	44 (3.3)	46 (3.4)
ACE inhibitor, ARB or other RAS blocker	798 (98.2)	761 (95.5)	1296 (96.8)	1319 (97.3)
Antiplatelet	577 (71.0)	547 (68.6)	375 (28.0)	381 (28.1)
Statin	622 (76.5)	609 (76.4)	773 (57.7)	790 (58.3)
Other lipid lowering therapy	132 (16.2)	115 (14.4)	188 (14.0)	210 (15.5)
Glucose-lowering medication – no (%)				
Biguanide	272 (33.5)	274 (34.4)	362 (27.0)	342 (25.2)
Sulfonylurea	158 (19.4)	156 (19.6)	232 (17.3)	230 (17.0)
DPP-4 inhibitor	133 (16.4)	145 (18.2)	231 (17.3)	233 (17.2)
GLP-1 receptor agonist	30 (3.7)	23 (2.9)	33 (2.5)	36 (2.7)
Insulin	382 (47.0)	367 (46)	432 (32.3)	417 (30.8)

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CVD = cardiovascular disease; DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon like peptide-1; RAS = renin-angiotensin system.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

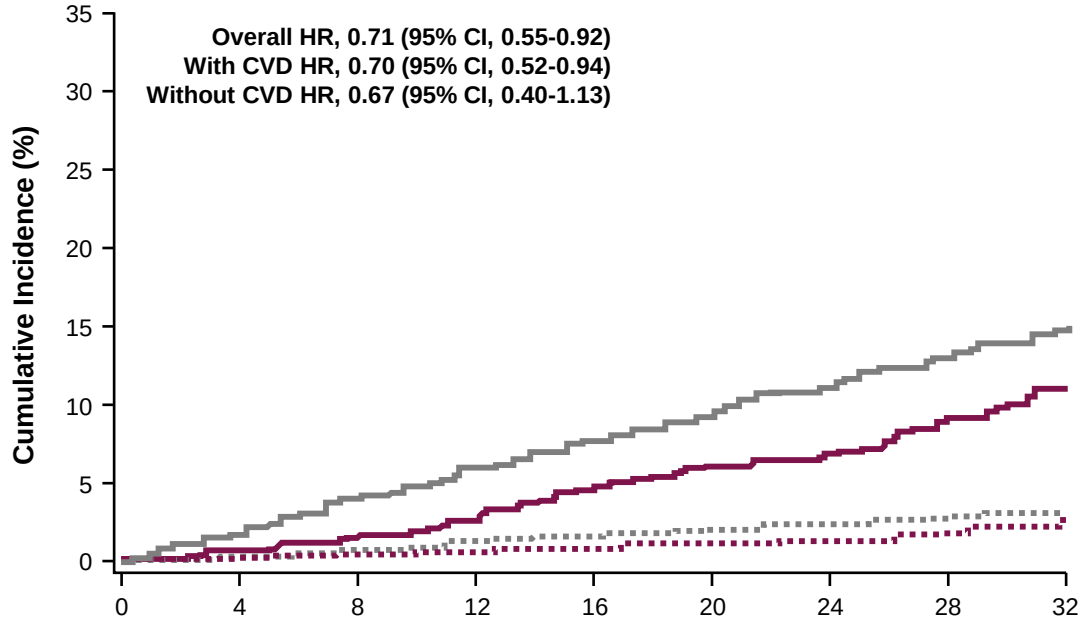
Outcomes by Baseline CVD

Primary Endpoint
eGFR Decline ≥50%, ESKD, Renal Death, or CV Death



No at Risk									
Dapagliflozin/CVD	813	780	760	736	710	650	510	326	124
Dapagliflozin/No CVD	1339	1221	1195	1162	1131	1051	778	505	185
Placebo/CVD	797	757	734	703	677	626	470	289	94
Placebo/No CVD	1355	1236	1202	1155	1114	1038	762	485	176

Secondary Endpoint
hHF or CV Death



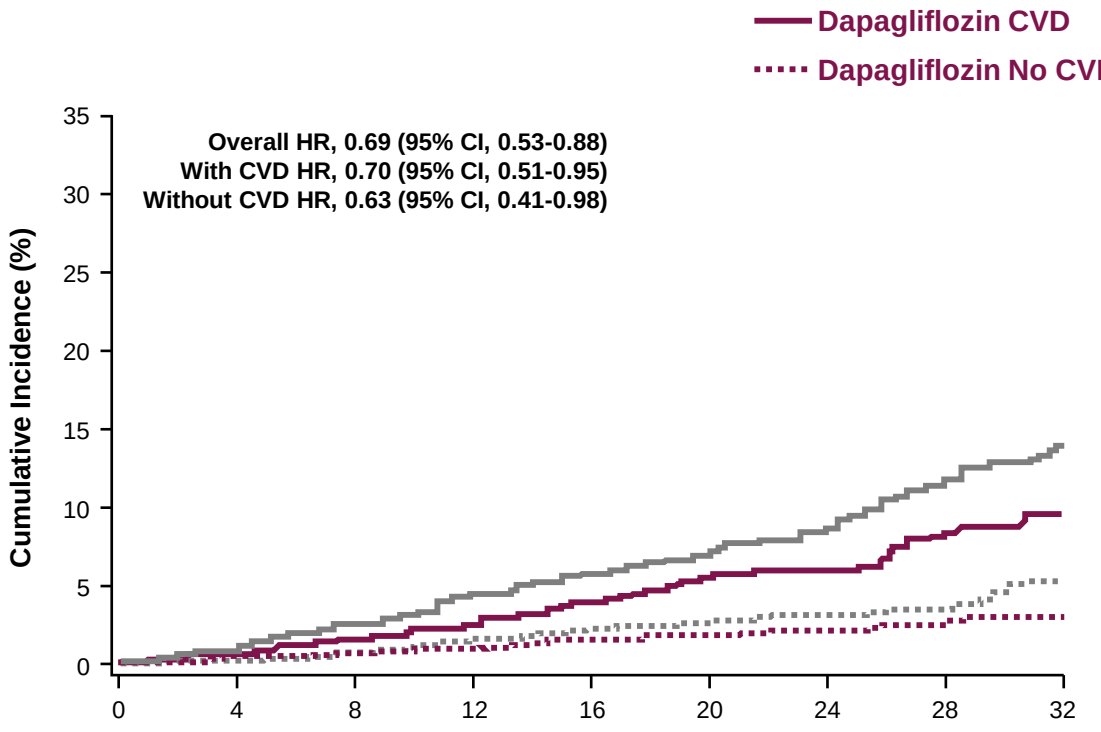
No at Risk									
Dapagliflozin/CVD	813	787	779	767	747	712	581	384	150
Dapagliflozin/No CVD	1339	1248	1242	1236	1228	1183	921	619	234
Placebo/CVD	797	761	740	721	703	671	531	366	124
Placebo/No CVD	1355	1262	1249	1236	1224	1182	920	610	236

CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

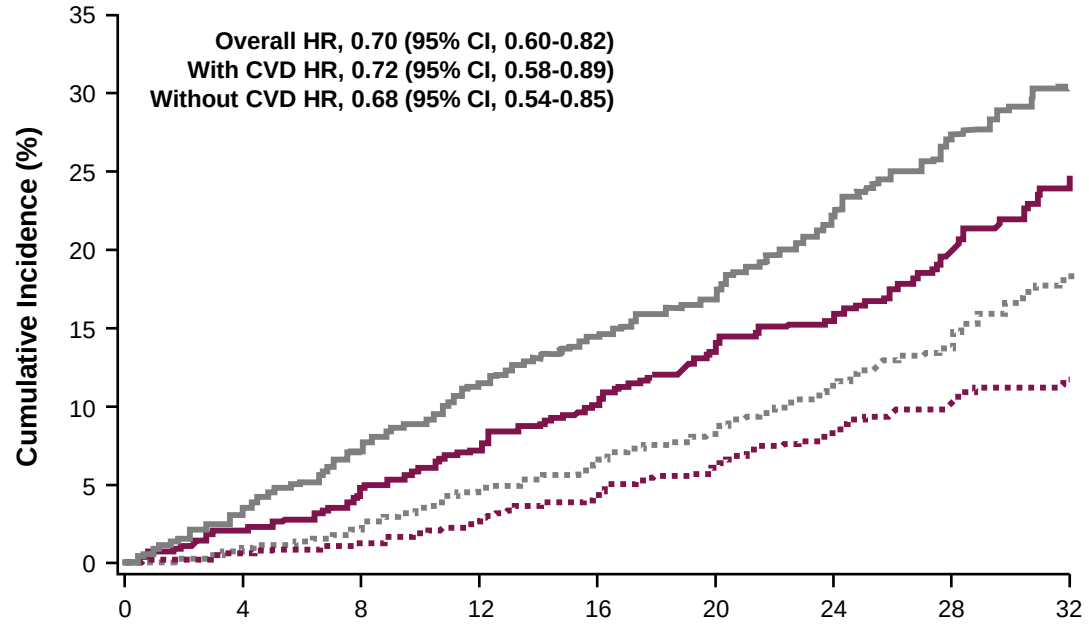
Outcomes by Baseline CVD

Secondary Endpoint
All-cause Mortality



No at Risk									
Dapagliflozin/CV	813	790	783	776	764	731	600	403	160
Dapagliflozin/No CV	1339	1249	1246	1241	1234	1194	931	625	238
Placebo/CV	797	770	759	745	734	702	566	386	137
Placebo/No CV	1355	1265	1259	1248	1238	1200	936	623	242

***Post Hoc* Endpoint**
MI, Stroke, hHF, ESKD, or Death



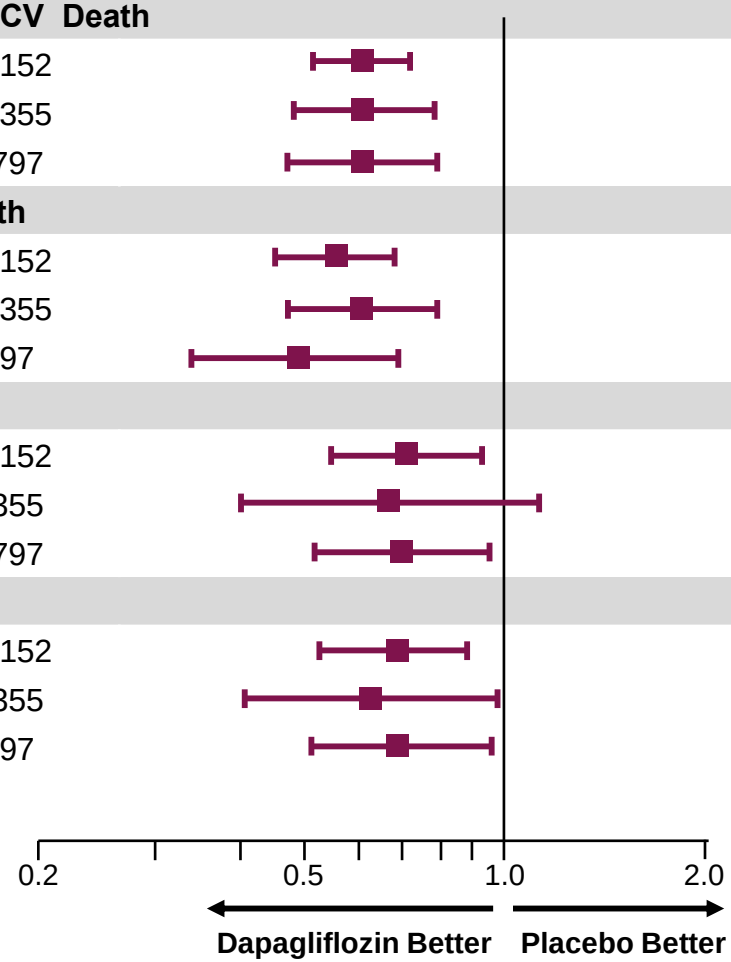
No at Risk									
Dapagliflozin/CV	813	771	747	715	687	627	493	305	114
Dapagliflozin/No CV	1339	1219	1194	1158	1127	1050	776	504	187
Placebo/CV	797	743	706	669	637	595	448	276	84
Placebo/No CV	1355	1231	1195	1151	1119	1041	772	490	188

CV = cardiovascular; CVD = cardiovascular disease; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Primary and Secondary Outcomes by Baseline CVD

	Dapagliflozin 10 mg Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Primary Outcome: eGFR Decline ≥50%, ESKD, Renal Death, or CV Death				
Overall[1]	197/2152	312/2152	0.61 (0.51, 0.72)	
Without CVD[2]	106/1339	175/1355	0.61 (0.48, 0.78)	0.90
With CVD[2]	91/813	137/797	0.61 (0.47, 0.79)	
Secondary Outcome: eGFR Decline ≥50%, ESKD, or Renal Death				
Overall[1]	142/2152	243/2152	0.56 (0.45, 0.68)	
Without CVD[2]	93/1339	154/1355	0.61 (0.47, 0.79)	0.29
With CVD[2]	49/813	89/797	0.49 (0.34, 0.69)	
Secondary Outcome: CV Death or hHF				
Overall[1]	100/2152	138/2152	0.71 (0.55, 0.92)	
Without CVD[2]	24/1339	36/1355	0.67 (0.40, 1.13)	0.88
With CVD[2]	76/813	102/797	0.70 (0.52, 0.94)	
Secondary Outcome: All-cause Mortality				
Overall[1]	101/2152	146/2152	0.69 (0.53, 0.88)	
Without CVD[2]	33/1339	53/1355	0.63 (0.41, 0.98)	0.71
With CVD[2]	68/813	93/797	0.70 (0.51, 0.95)	

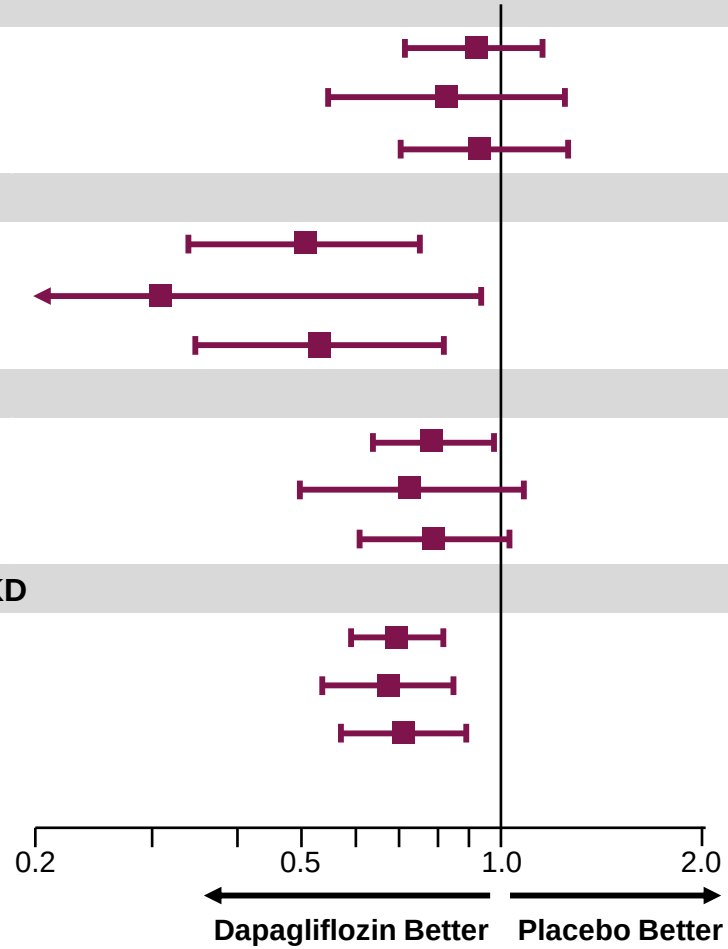


CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure.

1. Heerspink HJL. Et al. *N Engl J Med* 2020;383:1436-1446; 2. McMurray JJV et al. *Circulation*. 2021;143:438–448.

Prespecified and *Post Hoc* Exploratory Outcomes by CV Disease

	Dapagliflozin 10 mg Events	Placebo Events	Hazard Ratio (95% CI)	p-value Interaction
Prespecified Outcome: CV Death, MI, or Stroke				
Overall	132/2152	143/2152	0.92 (0.72, 1.16)	
Without CVD	41/1339	50/1355	0.83 (0.55, 1.25)	0.61
With CVD	91/813	93/797	0.94 (0.71, 1.26)	
Prespecified Outcome: First hHF				
Overall	37/2152	71/2152	0.51 (0.34, 0.76)	
Without CVD	4/1339	13/1355	0.31 (0.10, 0.94)	0.35
With CVD	33/813	58/797	0.54 (0.35, 0.82)	
***Post Hoc* Outcome: CV Death, MI, Stroke, or hHF**				
Overall	158/2152	195/2152	0.79 (0.64, 0.98)	
Without CVD	44/1339	60/1355	0.73 (0.50, 1.08)	0.72
With CVD	114/813	135/797	0.80 (0.62, 1.03)	
***Post Hoc* Outcome: All-cause Mortality, MI, Stroke, hHF, or ESKD**				
Overall	274/2152	376/2152	0.70 (0.60, 0.82)	
Without CVD	118/1339	177/1355	0.68 (0.54, 0.85)	0.77
With CVD	156/813	199/797	0.72 (0.58, 0.89)	



CV = cardiovascular; CVD = cardiovascular disease; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; MI = myocardial infarction.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Safety by Baseline CVD History

		Dapagliflozin 10 mg No CVD n = 1337 CVD n = 812 Number (%)	Placebo No CVD n = 1352 CVD n = 797 Number (%)	P value for interaction
Any serious AE	No CVD	287 (21.5)	371 (27.4)	0.09
	CVD	346 (42.6)	358 (44.9)	
AE leading to study drug discontinuation	No CVD	73 (5.5)	70 (5.2)	0.36
	CVD	45 (5.5)	53 (6.6)	
Amputation	No CVD	10 (0.7)	15 (1.1)	0.40
	CVD	25 (3.1)	24 (3.0)	
Fracture	No CVD	44 (3.3)	44 (3.3)	0.15
	CVD	41 (5.0)	25 (3.1)	
Renal adverse event	No CVD	76 (5.7)	99 (7.3)	0.61
	CVD	79 (9.7)	89 (11.2)	
Volume depletion	No CVD	75 (5.6)	46 (3.4)	0.20
	CVD	52 (6.4)	44 (5.5)	
Major hypoglycemia[a]	No CVD	3 (0.2)	13 (1.0)	0.12
	CVD	11 (1.4)	15 (1.9)	

Definite or probable ketoacidosis occurred in 2 patients without CV disease randomly allocated to placebo; there were no cases of ketoacidosis in the dapagliflozin group.

[a]The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

AE = adverse event; CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

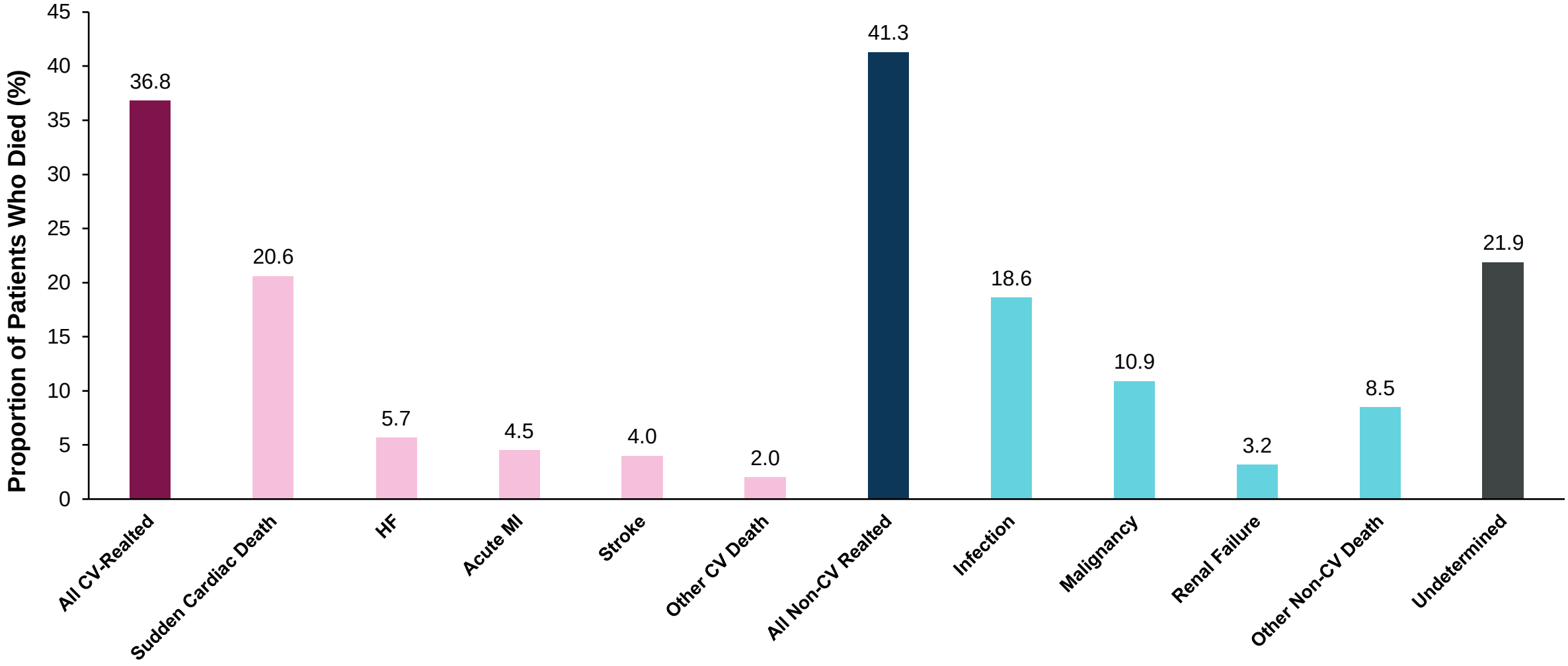
DAPA-CKD Subgroup Analysis
Causes of Mortality

A secondary analysis assessed the causes of death in DAPA-CKD patients, and assessed the effects of dapagliflozin on CV and non-CV causes of death in these patients

CV = cardiovascular.

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

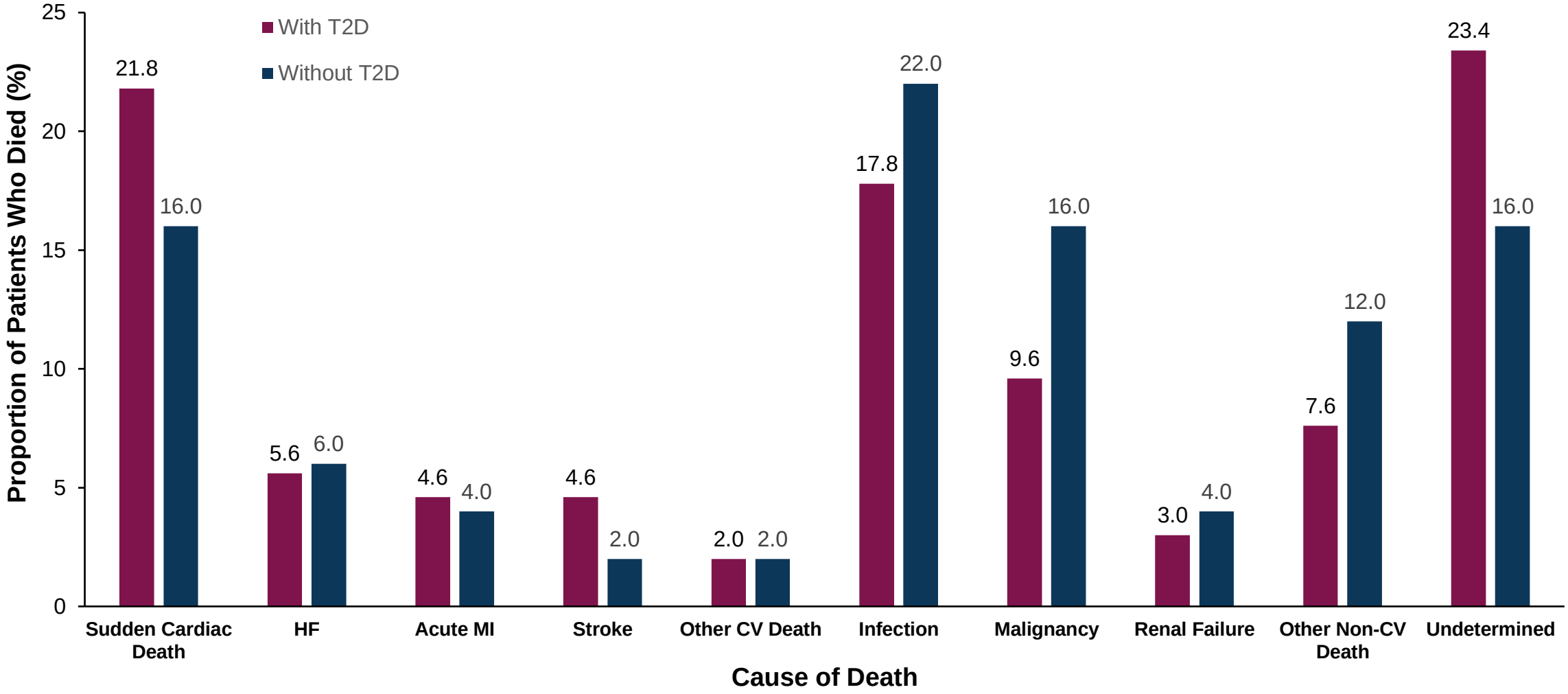
Main Causes of Death in DAPA-CKD



CV = cardiovascular; HF = heart failure; MI = myocardial infarction.

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

Main Causes of Death in DAPA-CKD by T2D Status

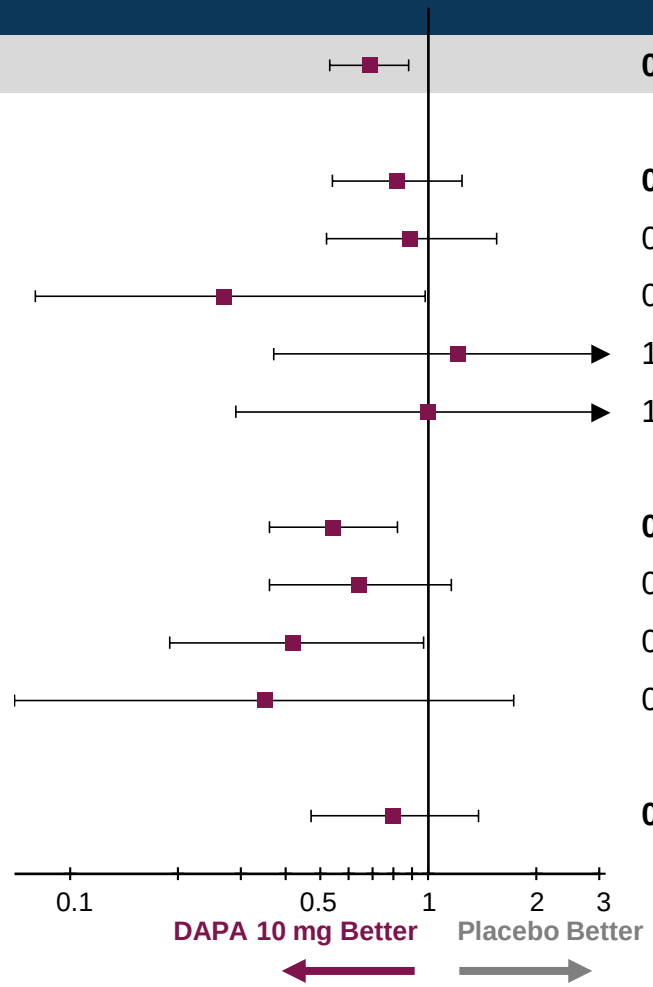


CV = cardiovascular; HF = heart failure; MI = myocardial infarction; T2D = type 2 diabetes.

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

Effect of Dapagliflozin on CV Death and Non-CV Death

	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P Value
	No. of patients/total no.			
All-cause mortality	**101/2152**	**146/2152**	**0.69 (0.53, 0.88)**	**0.003**
CV death	**41/2152**	**50/2152**	**0.82 (0.54, 1.24)**	**0.338**
Sudden cardiac death	24/2152	27/2152	0.89 (0.52, 1.55)	
Heart failure	3/2152	11/2152	0.27 (0.08, 0.98)	
Acute MI	6/2152	5/2152	1.21 (0.37, 3.96)	
Stroke	5/2152	5/2152	1.00 (0.29, 3.74)	
Non-CV death	**36/2152**	**66/2152**	**0.54 (0.36, 0.82)**	**0.003**
Infection	18/2152	28/2152	0.64 (0.36, 1.16)	
Malignancy	8/2152	19/2152	0.42 (0.19, 0.97)	
Renal failure	2/2152	6/2152	0.35 (0.07, 1.73)	
Undetermined	**24/2152**	**30/2152**	**0.80 (0.47, 1.38)**	**0.426**



CV = cardiovascular; DAPA= dapagliflozin; MI = myocardial infarction; No. = number.

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

All-Cause Mortality in Patients Who Did and Did Not Reach Chronic Dialysis

	Dapagliflozin		Placebo		Total	
	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)	n (%)	Event rate (100 pt-yrs)
Overall mortality	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	247/4304 (5.7)	2.6
Without chronic dialysis, n	2084		2053		4137	
All-cause mortality	89 (4.3)	1.9	121 (5.9)	2.6	210 (5.1)	2.2
With chronic dialysis, n	68		99		167	
All-cause mortality	12 (17.6)	8.6	25 (25.3)	13.4	37 (22.2)	11.4

Heerspink HJL et al. *Eur Heart J*. 2021;42:1216-1227.

DAPA-CKD
Effect on Anemia

In a prespecified analysis from DAPA-CKD, the effect of dapagliflozin versus placebo on anemia was assessed in patients with CKD, with or without T2D

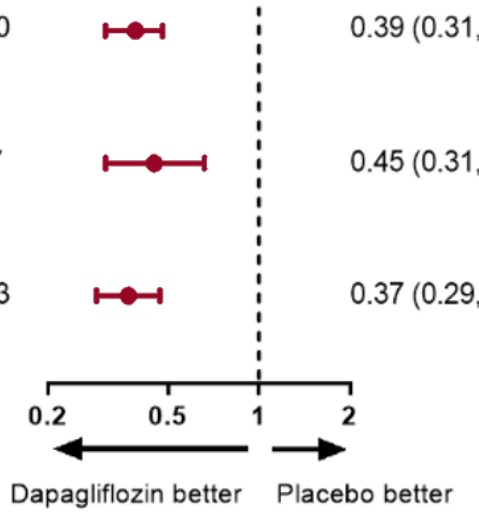
CKD = chronic kidney disease; T2D = type 2 diabetes.

Heerspink HJL et al. Presented at: ASN Kidney Week; November 3-6, 2022; Orlando, FL.

Effect of Dapagliflozin on Anemia

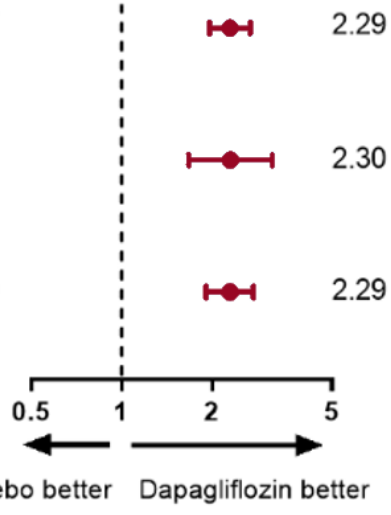
Patients Without Anemia at Baseline

	Incidence of anemia, n		Hazard ratio (95% CI)	P-interaction
	Dapagliflozin n=1264	Placebo n=1267		
Overall population	131	300	0.39 (0.31, 0.48)	
Without type 2 diabetes	39	87	0.45 (0.31, 0.66)	0.35
With type 2 diabetes	92	213	0.37 (0.29, 0.47)	



Anemia Correction in Patients With Anemia at Baseline

	Correction of anemia, n		Hazard ratio (95% CI)	P-interaction
	Dapagliflozin n=831	Placebo n=841		
Overall population	443	247	2.29 (1.96, 2.68)	
Without type 2 diabetes	116	57	2.30 (1.67, 3.17)	0.93
With type 2 diabetes	327	190	2.29 (1.91, 2.74)	



- **Dapagliflozin** significantly **increased** absolute **hematocrit by 2.3%** compared with placebo over a median follow-up of 2.4 years
- **Dapagliflozin consistently reduced** the risk of **renal and CV outcomes** in patients **with and without anemia** at baseline

Note: Anemia was defined as hematocrit levels <39% in males or <36% in females.
CV = cardiovascular.
Heerspink HJL et al. Presented at: ASN Kidney Week; November 3-6, 2022; Orlando, FL.

DAPA-CKD: Summary

Summary

- **DAPA-CKD[1],** the first dedicated renal outcomes trial to assess the efficacy and safety of an SGLT-2 inhibitor in patients with CKD with and without T2D, demonstrated:

39% RRR
for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)

31% RRR
all-cause mortality

44% RRR
for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)

29% RRR
for the composite of CV death or hospitalization for heart failure

- Consistent clinical benefits in patients with CKD across major subgroups including in patients **with and without T2D,** and by baseline eGFR and UACR categories
- Dapagliflozin was well-tolerated for the treatment of CKD (in patients with and without T2D) and data **confirm the known safety profile**
- **DAPA-CKD** builds upon the evidence for dapagliflozin in the prevention of hHF and worsening of renal disease in **DECLARE[2]** and reduction in the risk of worsening HF and CV death in **DAPA-HF[3]**

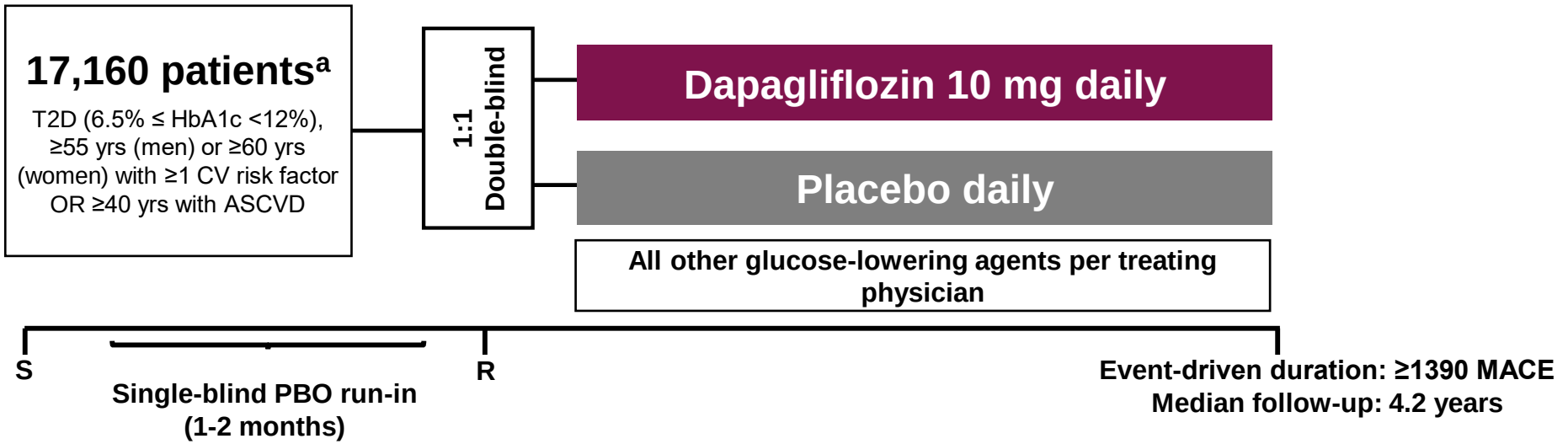
CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; hHF = hospitalization for heart failure; RRR = relative risk reduction; SGLT-2 = sodium glucose co-transporter 2; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446. 2. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357. 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008.

DECLARE-TIMI 58:
Study Design and Baseline Renal Characteristics

A Multinational, Randomized, Double-blind, Placebo-controlled, Phase IIIb Cardiovascular Outcomes Trial

Study Design[1,2,3,4]



Primary safety endpoint

- Composite of CV death, nonfatal MI, or nonfatal ischemic stroke (MACE)

Primary efficacy endpoints

- MACE
- Composite of hospitalization for heart failure or CV death

Secondary endpoints

- Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESKD and/or renal or CV death)
- All-cause mortality

Prespecified exploratory renal endpoints

- Renal-specific composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESKD and/or renal death)
- Development of new onset albuminuria
- Development of new onset macroalbuminuria
- Regression of albuminuria

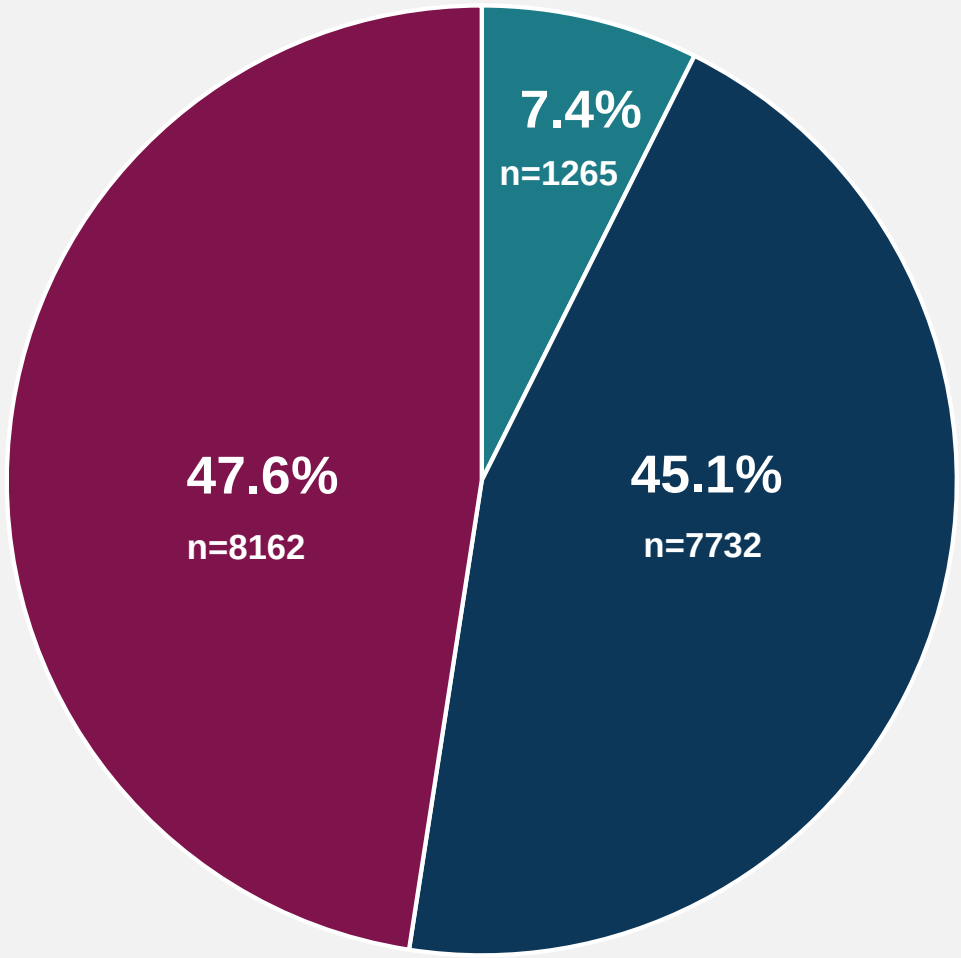
Additional safety endpoints

- Malignancies[b] (eg, bladder cancer)
- Liver events[b]
- DKA events[b]
- Amputations
- Fractures

[a]A total of 17,190 patients were randomized; however, 30 patients were excluded from all analyses because of significant good clinical practice violations at a single site for a different trial; [b]Blinded adjudication of events.
ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HbA1c = glycated hemoglobin; MACE = major adverse cardiovascular events; MI = myocardial infarction; PBO = placebo; R = randomization; S = screening; T2D = type 2 diabetes; yrs = years.

1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Wiviott SD et al. *Am Heart J*. 2018;200:83-89; 3. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 4. Wiviott SD et al. Protocol. *N Engl J Med*. 2019;380:347-357.

Distribution of eGFR Categories Among the Overall Population



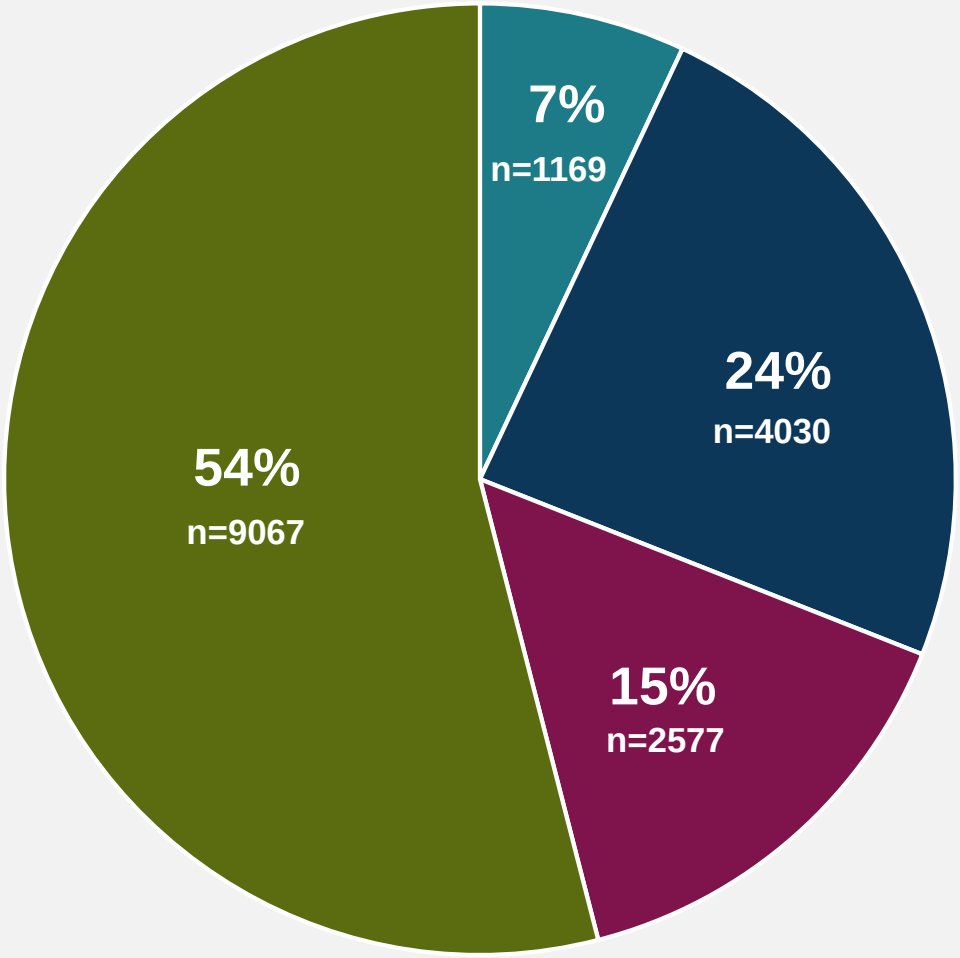
Baseline eGFR Category

- **<60 mL/min/1.73m²**
- **60 to <90 mL/min/1.73m²**
- **≥90 mL/min/1.73m²**

UACR,[a] n (%)	eGFR ≥90 mL/min/1.73m² (N=8026)	eGFR 60 to <90 mL/min/1.73m² (N=7582)	eGFR <60 mL/min/1.73m² (N=1234)
<30 mg/g	5691 (70.9)	5267 (69.5)	686 (55.6)
30 to 300 mg/g	1887 (23.5)	1761 (23.2)	381 (30.9)
>300 mg/g	448 (5.6)	554 (7.3)	167 (13.5)

[a]UACR was not measured at baseline for all patients, so N values are smaller for UACR group than for the overall population
eGFR = estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration equation; UACR = urinary albumin-to-creatinine ratio.
Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617.

Distribution of UACR Categories Among the Overall Population



Baseline UACR Category

- >300 mg/g
- ≥30 to ≤300 mg/g
- >15 to <30 mg/g
- ≤15 mg/g

eGFR, n (%)	UACR ≤15 mg/g (N=9067)	UACR >15 to <30 mg/g (N=2577)	UACR ≥30 to ≤300 mg/g (N=4030)	UACR >300 mg/g (N=1169)
<60 mL/min/1.73 m^2	508 (5.6)	178 (6.9)	381 (9.5)	167 (14.3)
60 to <90 mL/min/1.73 m^2	4156 (45.8)	1111 (43.1)	1761 (43.7)	554 (47.4)
≥90 mL/min/1.73 m^2	4403 (48.6)	1288 (50.0)	1887 (46.8)	448 (38.3)

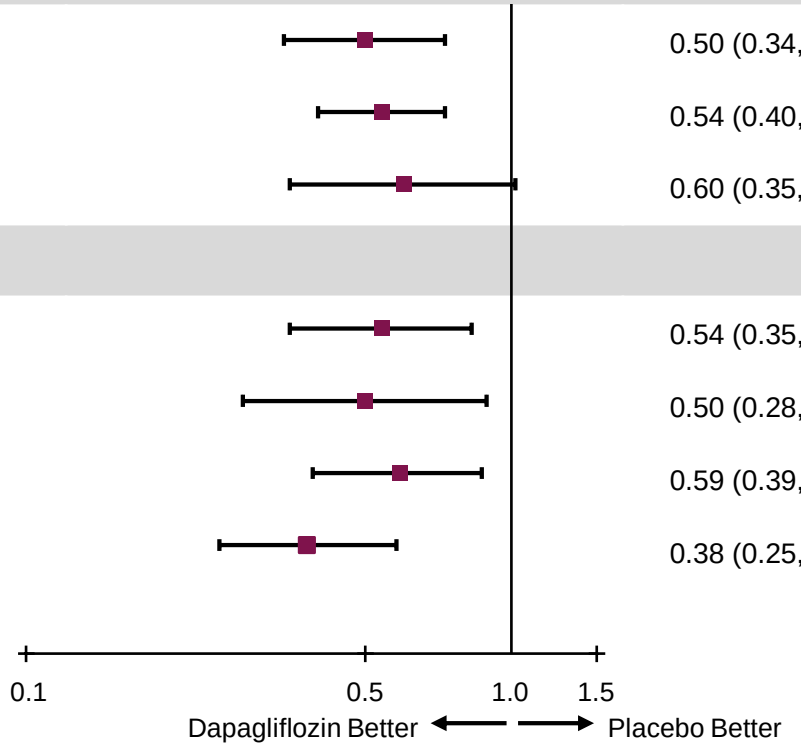
eGFR = estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration equation; UACR = urinary albumin-to-creatinine ratio.

Mosenzon O et al. *Diabetes Care*. 2021;44(8):1805-1815.

DECLARE-TIMI 58:
Outcomes by eGFR or UACR

Benefit of Dapagliflozin on the Renal-specific Outcome[a] Was Consistent Regardless of Baseline eGFR or UACR

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate (4 years)	n/N (%)	KM Event Rate (4 years)	Hazard Ratio (95% CI)	Interaction P-Value
Baseline eGFR[1]						
≥90 mL/min/1.73m^2	41/4137 (1.0%)	1.0%	79/4025 (2.0%)	2.0%	0.50 (0.34, 0.73)	
60 to <90 mL/min/1.73m^2	65/3838 (1.7%)	1.6%	121/3894 (3.1%)	2.8%	0.54 (0.40, 0.73)	0.87
<60 mL/min/1.73m^2	21/606 (3.5%)	3.8%	38/659 (5.8%)	5.8%	0.60 (0.35, 1.02)	
Baseline UACR[2]						
≤15 mg/g	33/4538 (0.7%)	0.7%	60/4529 (1.3%)	1.3%	0.54 (0.35, 0.83)	
>15 to <30 mg/g	17/1281 (1.3%)	1.3%	35/1296 (2.7%)	2.4%	0.50 (0.28, 0.89)	
≥30 to ≤300 mg/g	39/2017 (1.9%)	2.0%	66/2013 (3.3%)	3.3%	0.59 (0.39, 0.87)	0.4801
>300 mg/g	31/594 (5.2%)	4.8%	75/575 (13%)	12.8%	0.38 (0.25, 0.58)	



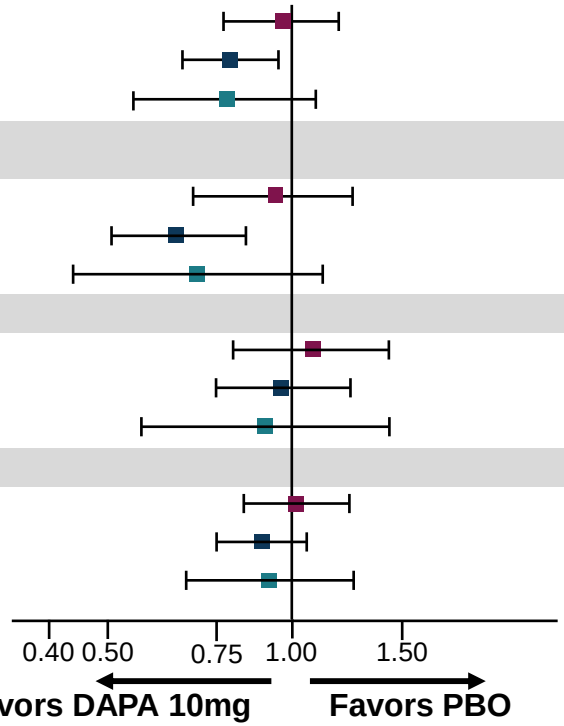
[a]Prespecified exploratory composite outcome (≥40% eGFR decline, ESKD, or renal death).

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KM = Kaplan-Meier; UACR = urinary albumin-to-creatinine ratio.

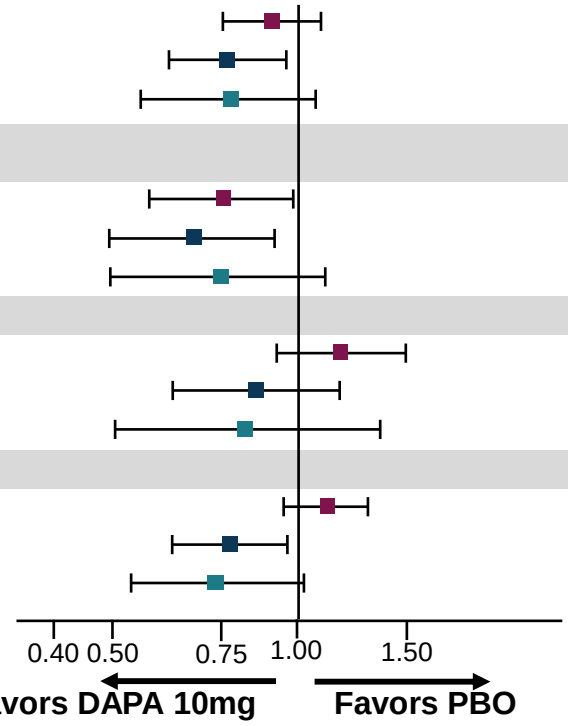
1. Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617; 2. Mosenzon O et al. *Diabetes Care*. 2021;44(8):1805-1815.

Effect of Dapagliflozin on Additional Outcomes Was Generally Consistent Regardless of Baseline eGFR or UACR

Subgroup	Events	Hazard Ratio (95% CI)	Interaction p-value
CV Death/hHF			
eGFR ≥90	326		
eGFR 60-<90	451		0.37
eGFR <60	136		
hHF			
eGFR ≥90	170		
eGFR 60-<90	251		0.19
eGFR <60	77		
CV Death			
eGFR ≥90	180		
eGFR 60-<90	242		0.79
eGFR <60	72		
ACM			
eGFR ≥90	403		
eGFR 60-<90	538		0.61
eGFR <60	158		



Subgroup	Events	Hazard Ratio (95% CI)	Interaction p-value
CV Death/hHF			
UACR <30	453		
UACR 30-<300	303		0.47
UACR ≥300	143		
hHF			
UACR <30	224		
UACR 30-<300	169		0.86
UACR ≥300	96		
CV Death			
UACR <30	262		
UACR 30-<300	162		0.20
UACR ≥300	63		
ACM			
UACR <30	588		
UACR 30-<300	343		0.007
UACR ≥300	151		



ACM = all-cause mortality; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; hHF = hospitalization for heart failure; PBO = placebo; UACR = urinary albumin-to creatinine ratio.

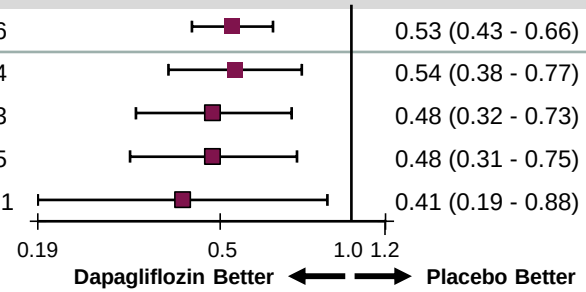
Zelniker TA et al. Article and supplementary appendix. *JAMA Cardiol*. 2021;6(7):801-810.

DECLARE-TIMI 58:
Outcomes by KDIGO Risk Category

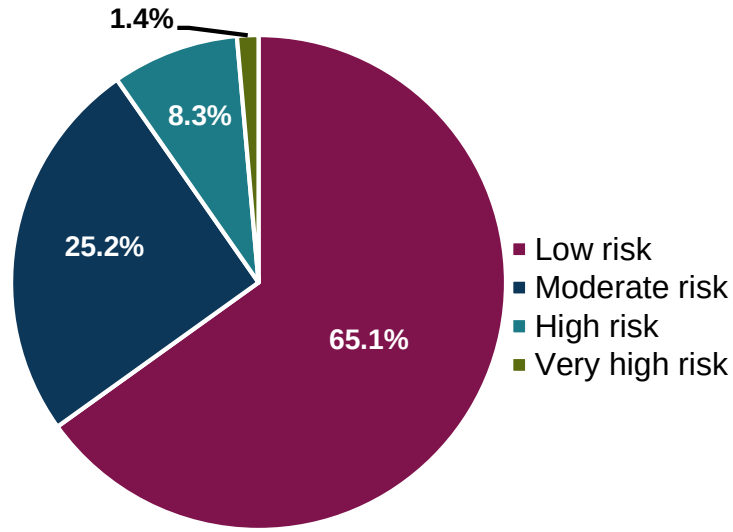
Dapagliflozin Prevented Diabetic Kidney Disease in Patients With Low KDIGO Risk

Dapagliflozin consistently reduced the risk of the renal-specific outcome[a] across KDIGO risk categories[b]

	Dapagliflozin		Placebo			Hazard Ratio (95% CI)	Interaction p-value
	n/N (%)	KM, %	n/N (%)	KM, %			
Renal-specific composite outcome[a]							
Overall	127/8582 (1.5)	1.5	238/8578 (2.8)	2.6		0.53 (0.43 - 0.66)	
Low risk	46/5485 (0.8)	0.8	85/5473 (1.6)	1.4		0.54 (0.38 - 0.77)	0.9681
Moderate risk	34/2124 (1.6)	1.6	69/2119 (3.3)	3.3		0.48 (0.32 - 0.73)	
High risk	30/706 (4.2)	3.9	60/697 (8.6)	8.5		0.48 (0.31 - 0.75)	
Very high risk	10/114 (8.8)	9.9	22/124 (17.7)	18.1		0.41 (0.19 - 0.88)	



Patient Distribution by KDIGO Risk Category[b]



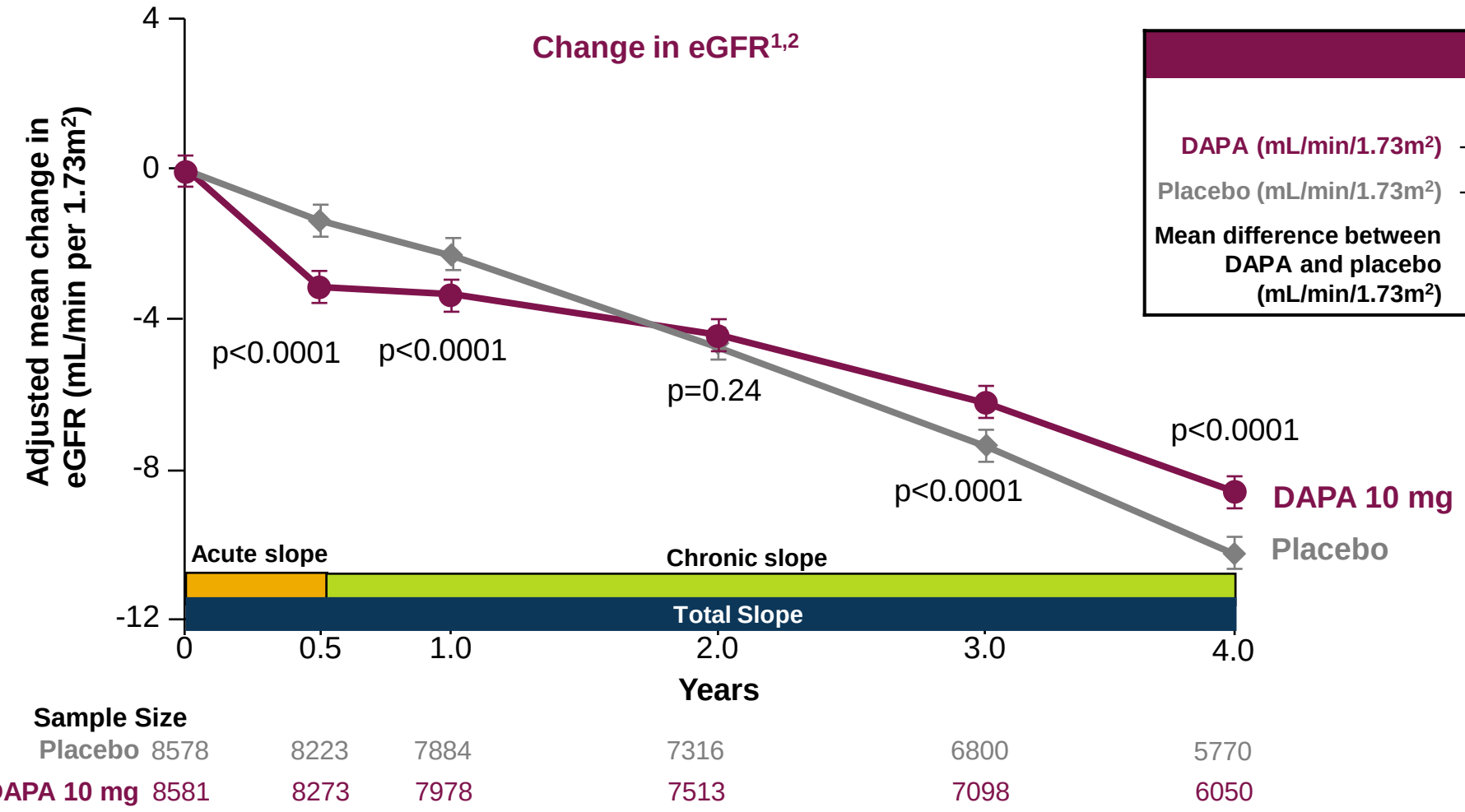
[a]Composite of ≥40% eGFR decline, ESKD, or renal death; [b]Low risk = eGFR ≥60 mL/min/1.73m^2 and UACR <30 mg/g. Moderate risk = eGFR 45 to <60 mL/min/1.73m^2 and UACR <30 mg/g; or eGFR ≥60 mL/min/1.73m^2 and UACR 30–300 mg/g. High risk = eGFR 30 to <45 mL/min/1.73m^2 and UACR <30 mg/g; or eGFR 45 to <60 mL/min/1.73m^2 and UACR >30-300 mg/g. Very high risk = eGFR <30 mL/min/1.73m^2 and UACR <30 mg/g; or eGFR <45 mL/min/1.73m^2 and UACR 30-300 mg/g; or eGFR <60 mL/min/1.73m^2 and UACR >30 mg/g.

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KDIGO = Kidney Disease Improving Global Outcomes; KM = Kaplan-Meier; UACR = urinary albumin-to-creatinine ratio.

Mosenzon O et al. *Diabetes Care.* 2022;45(10):2350-2359.

DECLARE-TIMI 58: Effect on eGFR

Change in eGFR Over Time



	Mean eGFR Slopes[2]		
	Acute	Chronic	Total
DAPA (mL/min/1.73m²)	-2.99/6 mo	-1.54/y	-1.78/y
Placebo (mL/min/1.73m²)	-1.15/6 mo	-2.55/y	-2.44/y
Mean difference between DAPA and placebo (mL/min/1.73m²)	NA	1.01/y p<0.0001	0.66/y p<0.0001

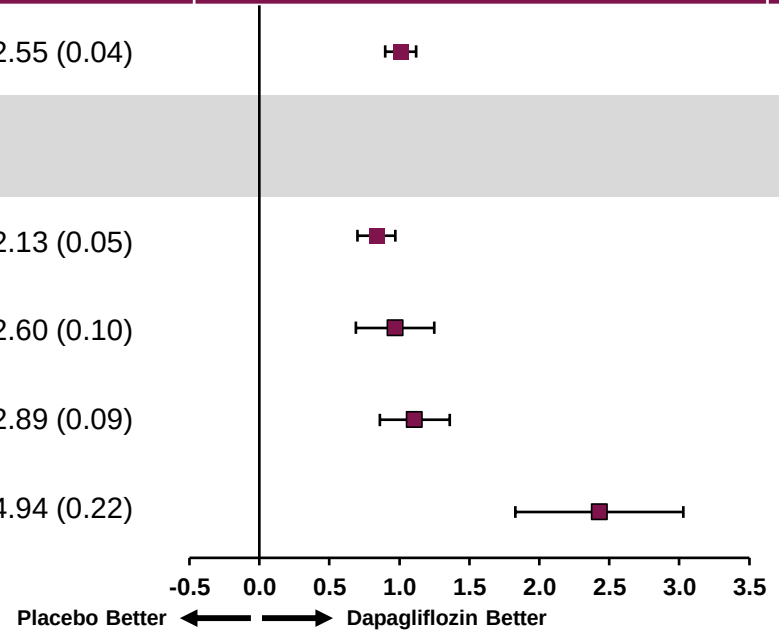
eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; total (baseline to 4 years) and chronic slopes (6 months to 4 years) are presented annually, and acute slope (baseline to 6 months) is presented by 6 months.[2]

DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; mo = months; NA = not available; y = year.

1. Mosenzon O et al. *Lancet Diabetes Endocrinol.* 2019;7(8):606-617; 2. Mosenzon O et al. *Diabetes Care.* 2022;45(10):2350-2359.

Acute and Chronic eGFR Slopes by Baseline UACR

	Acute Slope		Chronic Slope		Difference in Chronic Slope, Dapagliflozin-Placebo	
	Dapagliflozin LS Means (SE)	Placebo LS Means (SE)	Dapagliflozin LS Means (SE)	Placebo LS Means (SE)	Mean Difference (95% CI)	p-value
Overall	-2.99 (0.10)	-1.15 (0.10)	-1.54 (0.04)	-2.55 (0.04)	1.01 (0.90 – 1.12)	<0.0001
UACR, mg/g						
≤15	-2.46 (0.12)	-0.71 (0.13)	-1.29 (0.05)	-2.13 (0.05)	0.84 (0.70 – 0.97)	<0.0001
15-<30	-2.74 (0.24)	-0.90 (0.24)	-1.63 (0.10)	-2.60 (0.10)	0.97 (0.69 – 1.25)	<0.0001
30-300	-3.59 (0.21)	-1.74 (0.21)	-1.78 (0.09)	-2.89 (0.09)	1.11 (0.86 – 1.36)	<0.0001
>300	-5.48 (0.43)	-3.50 (0.43)	-2.51 (0.21)	-4.94 (0.22)	2.43 (1.83 – 3.03)	<0.0001

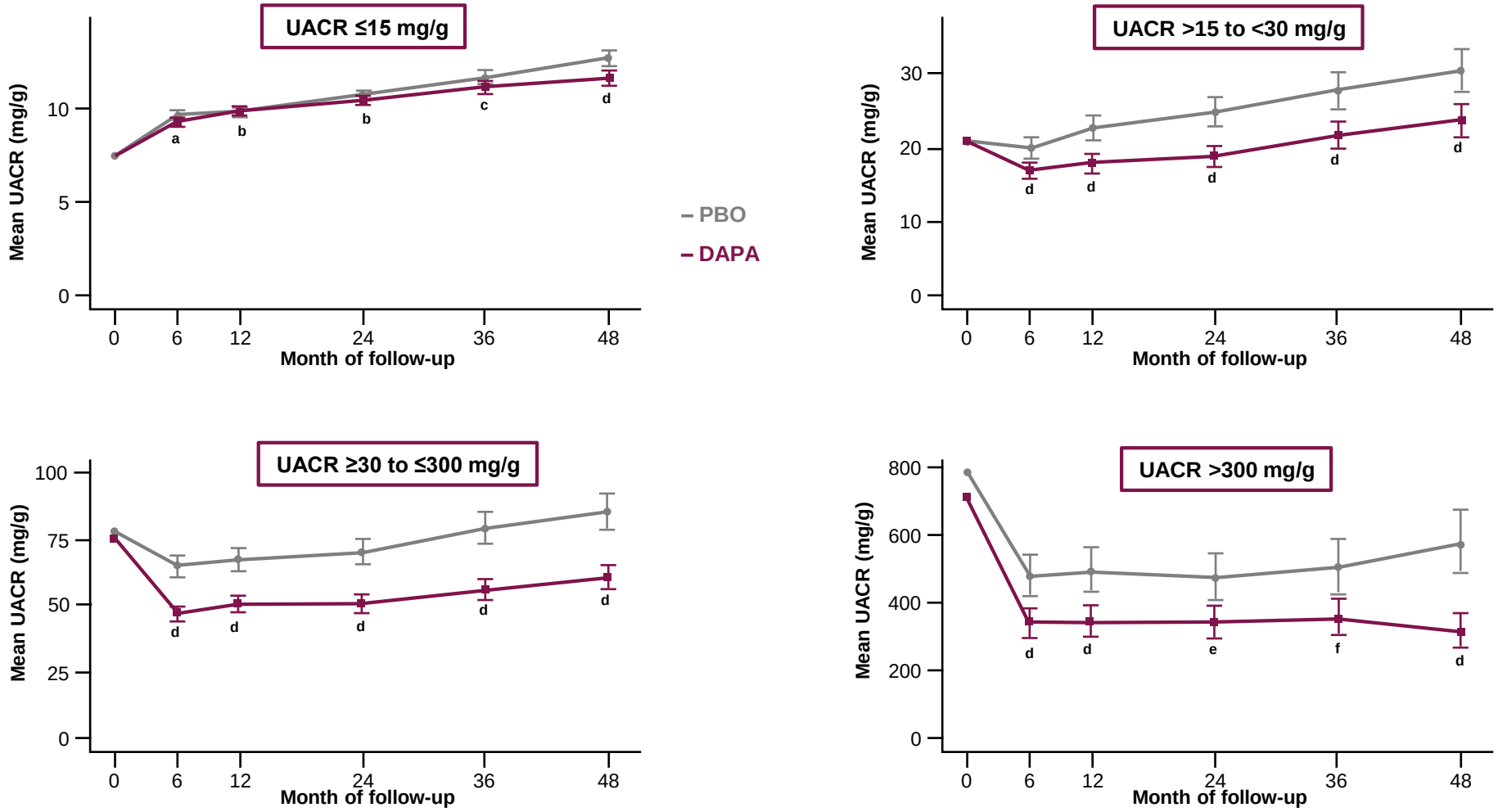


eGFR = estimated glomerular filtration rate; LS = least square; SE = standard error; UACR = urinary albumin-to-creatinine ratio.

Mosenzon O et al. *Diabetes Care.* 2022;45(10):2350-2359.

DECLARE-TIMI 58: Effect on Albuminuria

Effect of Dapagliflozin on UACR by Baseline UACR

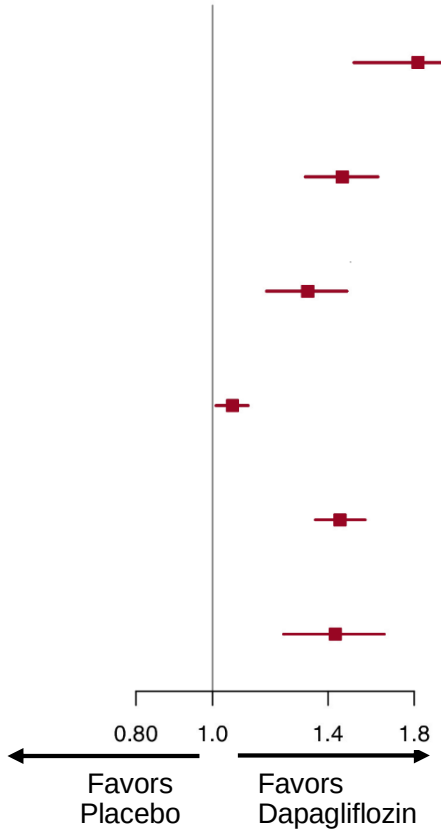


Mean UACR was significantly lower with DAPA compared with PBO at 4 years in all baseline UACR subgroups

Note: Shown are point estimates and 95% confidence intervals of geometric mean back-transformed to the original scale. [a]p=0.0033; [b]p>0.05; [c]p=0.0140; [d]p<0.0001; [e]p=0.0001; [f]p=0.0004.
DAPA= dapagliflozin; PBO = placebo; UACR = urinary albumin-to-creatinine ratio.
Mosenzon O et al. *Diabetes Care.* 2021;44(8):1805-1815.

Improvement in UACR Category from Baseline

	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	Cox p-value
UACR to ≤300 in patients with >300 at BL	282/594 (47.5)	175/575 (30.4)	1.82 (1.51, 2.20)	<0.0001
UACR to <30 in patients with 30 to 300 at BL	774/2017 (38.4)	576/2013 (28.6)	1.46 (1.31, 1.62)	<0.0001
UACR to ≤15 in patients with >15 to <30 at BL	618/1281 (48.2)	507/1296 (39.1)	1.32 (1.17, 1.48)	<0.0001
Stable UACR at ≤15 in patients with ≤15 at BL	3660/4538 (80.7)	3543/4529 (78.2)	1.06 (1.01, 1.11)	0.0195
UACR of at least 1-step improvement in patients with >15 at BL	1674/3892 (43.0)	1258/3884 (32.4)	1.45 (1.35, 1.56)	<0.0001
UACR of 2-step improvement in patients with ≥30 at BL	422/2611 (16.2)	301/2588 (11.6)	1.43 (1.23, 1.65)	<0.0001



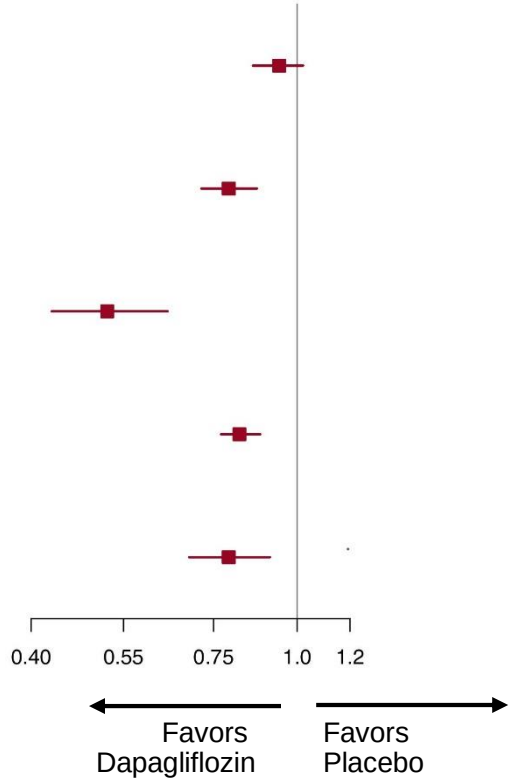
UACR measured as mg/g.

BL = baseline; UACR = urinary albumin-to-creatinine ratio.

Mosenzon O et al. *Diabetes Care*. 2021;44(8):1805-1815.

Deterioration In UACR Category from Baseline

	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	Cox p-value
UACR to >15 in patients with ≤15 at BL	1078/4538 (23.8)	1137/4529 (25.1)	0.94 (0.86, 1.02)	0.1319
UACR to ≥30 in patients with <30 at BL	772/5819 (13.3)	959/5825 (16.5)	0.79 (0.72, 0.87)	<0.0001
UACR to >300 in patients with 30 to 300 at BL	156/2017 (7.7)	284/2013 (14.1)	0.52 (0.43, 0.64)	<0.0001
UACR of at least 1-step deterioration in patients with ≤300 at BL	1630/7836 (20.8)	1931/7838 (24.6)	0.82 (0.77, 0.88)	<0.0001
UACR 2-step deterioration in patients with <30 at BL	385/5819 (6.6)	481/5825 (8.3)	0.79 (0.69, 0.91)	0.0007



UACR measured as mg/g.
BL = baseline; UACR = urinary albumin-to-creatinine ratio.
Mosenzon O et al. *Diabetes Care*. 2021;44(8):1805-1815.

DECLARE-TIMI 58:
Safety

AEs of Special Interest and Other Safety Events

Adverse Event	DAPA 10 mg (N=8574) n (%)	Placebo (N=8569)
Malignancy	481 (5.6)	486 (5.7)
Bladder cancer	26 (0.3)	45 (0.5)
Hepatic event	82 (1.0)	87 (1.0)
Major hypoglycaemia	58 (0.7)	83 (1.0)
Fracture	457 (5.3)	440 (5.1)
Acute kidney injury	125 (1.5)	175 (2.0)
Symptoms of volume depletion	213 (2.5)	207 (2.4)
Hypersensitivity reaction	32 (0.4)	36 (0.4)
Urinary tract infection	127 (1.5)	133 (1.6)
Genital infection*	76 (0.9)	9 (0.1)
Diabetic ketoacidosis event	27 (0.3)	12 (0.1)
Amputation	123 (1.4)	113 (1.3)
Fournier’s Gangrene	1 (0.01)	5 (0.06)

*leading to discontinuation of the trial regimen or considered to be serious AE

DAPA = dapagliflozin

Wiviott SD et al. *N Engl J Med.* 2019;380(4):347-357.

Cardiorenal and Mortality Benefits of Dapagliflozin Extend to Patients With CKD

	DECLARE TIMI-58	DAPA-HF	DELIVER	DAPA-CKD
	N = 17,160[1,2]	N = 4744[3,4]	N = 6263[5]	N = 4304[6]
Patient Population	**T2D**	**HFrEF with or without T2D**	**HFmrEF/HFpEF with or without T2D**	**CKD with or without T2D**
Mean eGFR	**85 mL/min/1.73 m²**	**66 mL/min/1.73 m²**	**61 mL/min/1.73 m²**	**43 mL/min/1.73 m²**
Primary Endpoint	• **hHF or CV death** 0.83 (0.73, 0.95) p=0.005	• **CV death or worsening HF[a]** 0.74 (0.65, 0.85) p<0.001	• **CV death or worsening HF[a]** 0.82 (0.73, 0.92) p<0.001	• **≥50% eGFR decline, ESKD, or renal or CV death** 0.61 (0.51, 0.72) p<0.001
Key Secondary Endpoints	• **eGFR decrease ≥40% to <60, ESKD or renal death** 0.53 (0.43, 0.66) p<0.0001[b]	• **All-cause mortality** 0.83 (0.71, 0.97) p=0.022[c]	• **Total[d] worsening HF[a] and CV death** 0.77 (0.67, 0.89) p<0.001	• **All-cause mortality** 0.69 (0.53, 0.88) p=0.004 • **CV death or hHF** 0.71 (0.55, 0.92) p=0.009

Pre-specified patient-level pooled analysis of DAPA-HF and DELIVER

N = 11,007[8]

Primary Endpoint	• **CV death** 0.86 (0.76, 0.97) p=0.01
Additional Endpoints	• **All-cause mortality** 0.90 (0.82, 0.99) p=0.03
	• **CV death or hHF** 0.78 (0.72, 0.86) p<0.001

Benefit was consistent across the full range of LVEF

Renal

CV

Mortality

[a]Includes hHF or urgent HF visit; [b]Because the trial met only one of its dual primary composite outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only; [c]Nominal p-value; [d]First or recurrent.

CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes.

1. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357; 2. Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7:606-617; 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008; 4. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France; 5. Solomon SD et al. *N Engl J Med. 2022*;387(12):1089-1098; 6. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 7. Jhund PS et al. *Nat Med*. 2022;28(9):1956-1964.

Περίληψη Χαρακτηριστικών Προϊόντος

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

4.1 Θεραπευτικές ενδείξεις

Σακχαρώδης διαβήτης τύπου 2

Το Forxiga ενδείκνυται για χρήση σε ενήλικες και παιδιά ηλικίας 10 ετών και άνω για τη θεραπεία του ανεπαρκώς ελεγχόμενου σακχαρώδη διαβήτη τύπου 2 ως συμπληρωματική θεραπεία στη δίαιτα και την άσκηση
- ως μονοθεραπεία, όταν η μετφορμίνη θεωρείται ακατάλληλη λόγω δυσανεξίας.
- επιπρόσθετα με άλλα φαρμακευτικά προϊόντα για τη θεραπεία του διαβήτη τύπου 2.

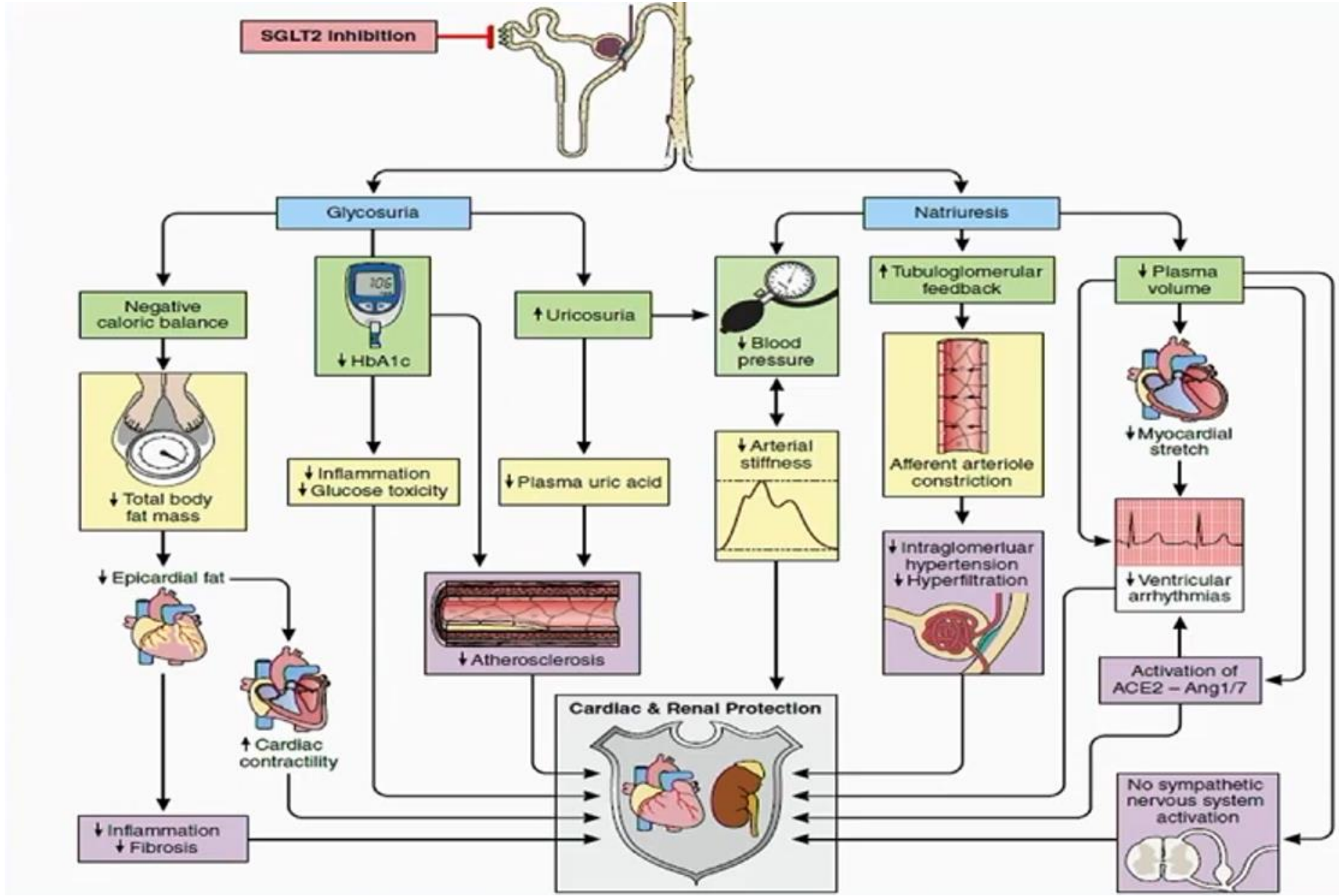
Για τα αποτελέσματα των μελετών σε σχέση με τον συνδυασμό των θεραπειών, τις επιδράσεις στον γλυκαιμικό έλεγχο, τα καρδιαγγειακά και νεφρικά συμβάντα και τους πληθυσμούς που μελετήθηκαν, βλέπε παραγράφους 4.4, 4.5 και 5.1.

Καρδιακή ανεπάρκεια

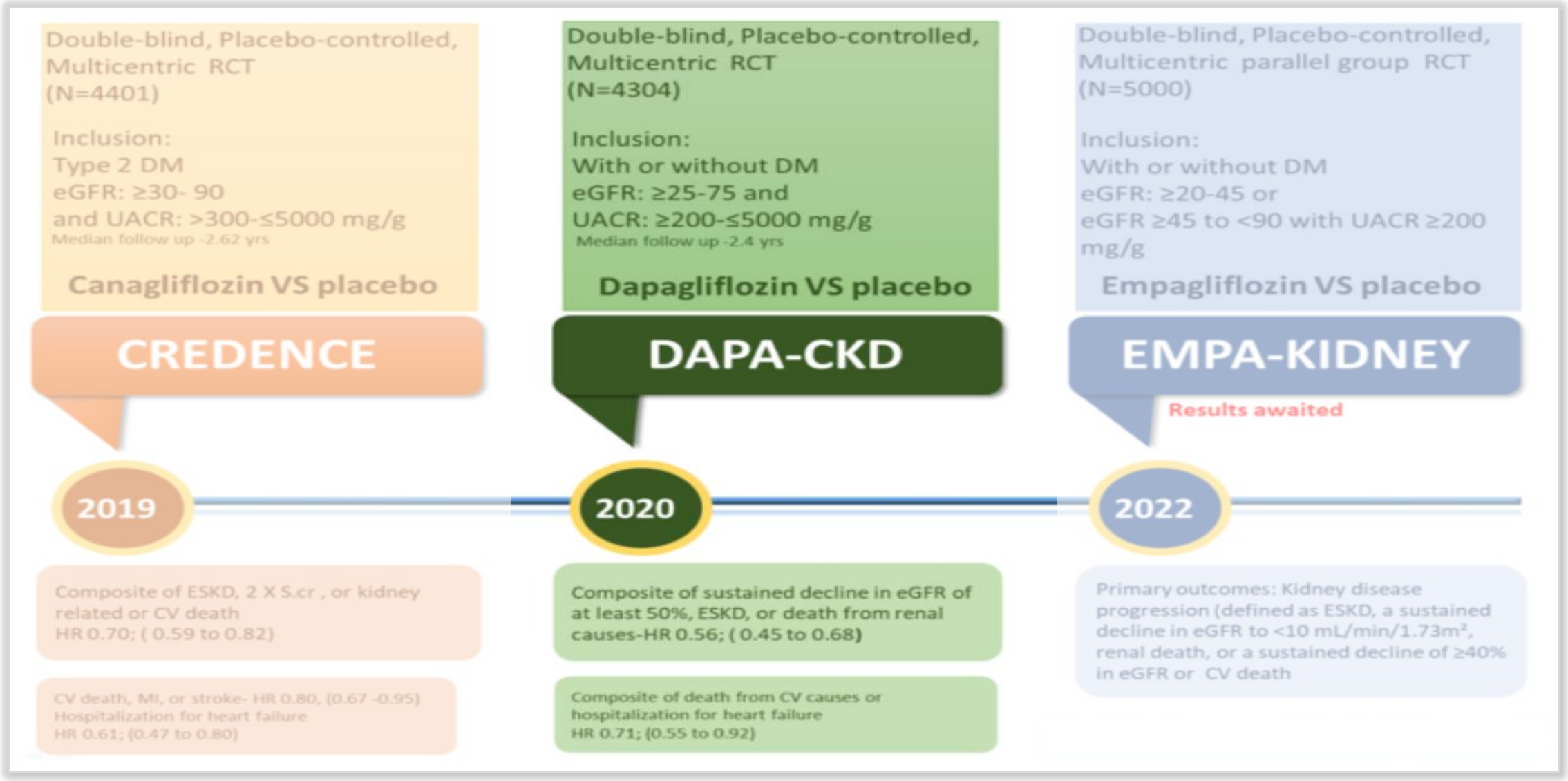
Το Forxiga ενδείκνυται για χρήση σε ενήλικες ασθενείς για τη θεραπεία της συμπτωματικής χρόνιας καρδιακής ανεπάρκειας

Χρόνια νεφρική νόσος

Το Forxiga ενδείκνυται για χρήση σε ενήλικες ασθενείς για τη θεραπεία της χρόνιας νεφρικής νόσου


SGLT2 Inhibition
Glycosuria
Natriuresis
Negative caloric balance
↓ Total body fat mass
↓ Epicardial fat
↑ Cardiac contractility
↓ Inflammation ↓ Fibrosis
↓ HbA1c
↓ Inflammation ↓ Glucose toxicity
↑ Uricosuria
↓ Plasma uric acid
↓ Atherosclerosis
↓ Blood pressure
↓ Arterial stiffness
↑ Tubuloglomerular feedback
Afferent arteriole constriction
↓ Intraglomerluar hypertension ↓ Hyperfiltration
↓ Plasma volume
↓ Myocardial stretch
↓ Ventricular arrhythmias
Activation of ACE2 – Ang1/7
Cardiac & Renal Protection
No sympathetic nervous system activation

SGLT2i trials in CKD with or without DM



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

DECLARE-TIMI 58 trial

17.169 ΣΔ2
≥55 ετών (άνδρες) ή ≥ 60 ετών
≥ 1 ΚΔ παράγοντα κινδύνου
Ή
≥40 ετών με εγκατεστημένη ΚΔ νόσο

60%

CKD=9.2%

Έκβαση	Dapagliflozin 10mg (N=8582)	Placebo (N=8.578)	HR (95% CI)
≥40% μείωση του eGFR <60ml/min/1.73m2, ΤΣΧΝΝ, ή θάνατος από νεφρικά αίτια, %	**1,5**	**2,8**	**0,53 (0,43 0,66)**

47%

N Engl J Med 2019; 380:1880-1882

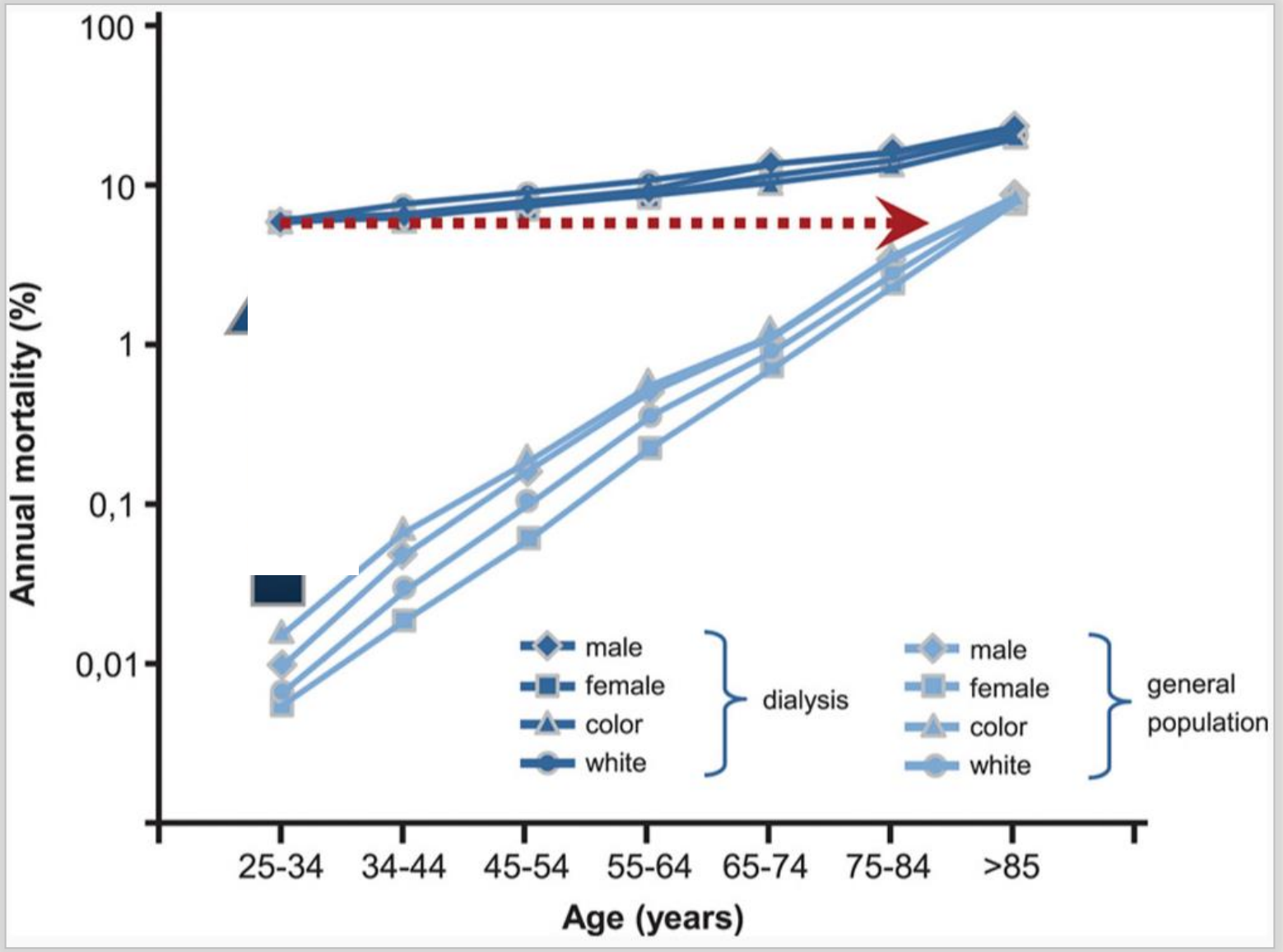
Progression of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mol	≥300 mg/g ≥30 mg/mmol
	G1	Normal to 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			

Green: low risk (if no other markers of kidney diseases, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 1: definition and classification of CKD.Kidney Int Suppl (2011). 2013; 3:19–62.

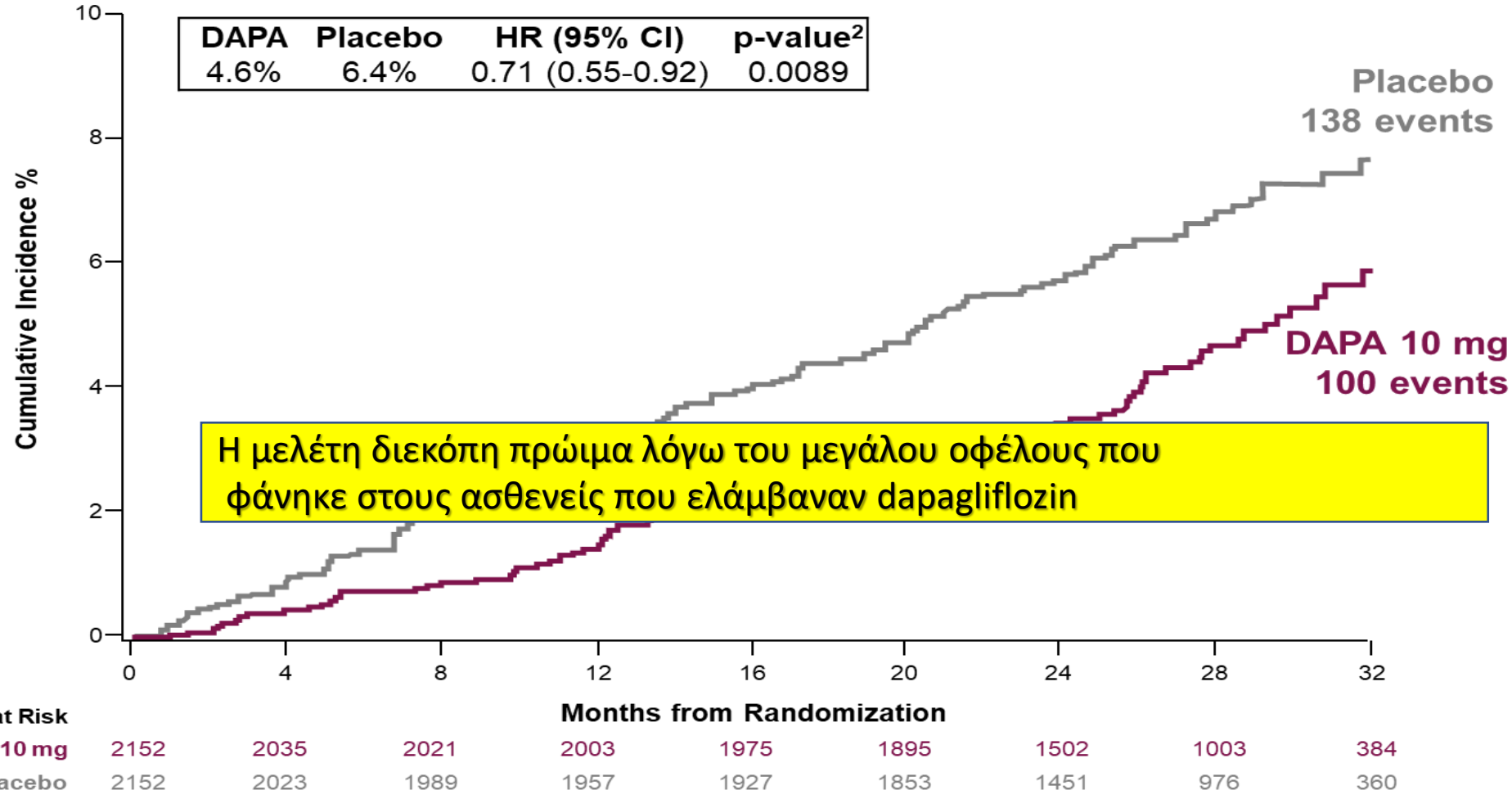
Cardiovascular mortality in the general population and in patients with end-stage kidney disease



Circulation. 2021;143:1157–1172

Epidemiology and burden of CKD

Σύνθετο δευτερεύον καταληκτικό σημείο: ΚΑ θάνατος ή νοσηλεία για καρδιακή ανεπάρκεια



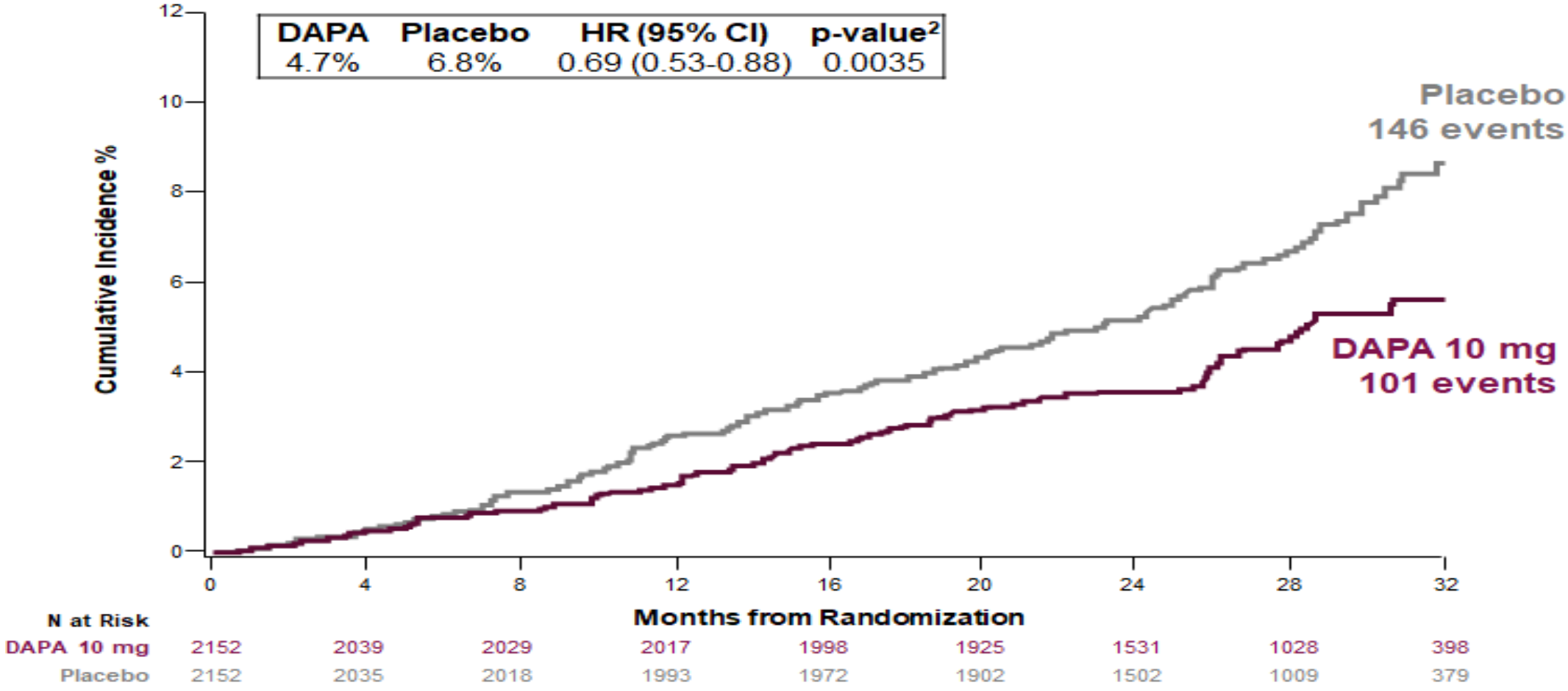
Η μελέτη διεκόπη πρώιμα λόγω του μεγάλου οφέλους που φάνηκε στους ασθενείς που ελάμβαναν dapagliflozin

29% RRR

1.8% ARR

Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446

Δευτερεύον καταληκτικό σημείο: Ολική θνησιμότητα

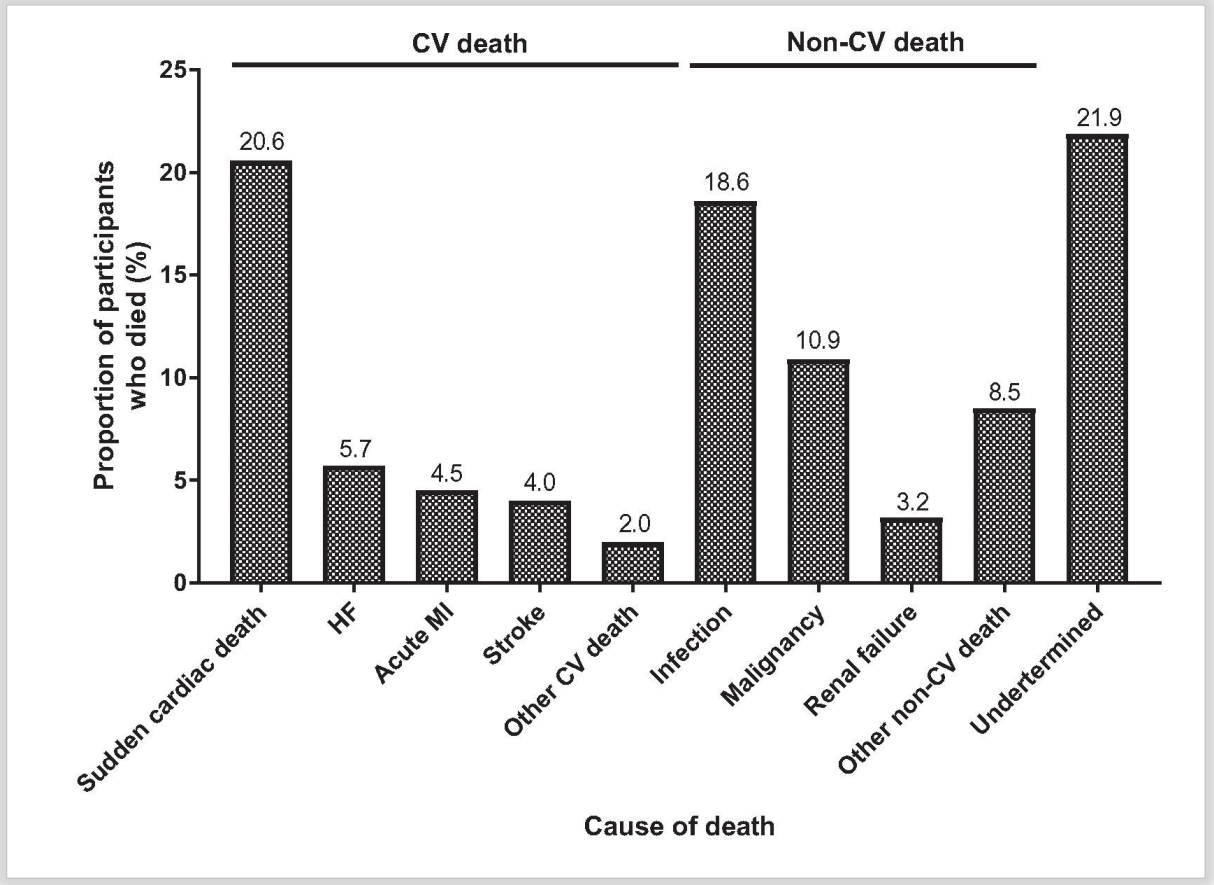


Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446

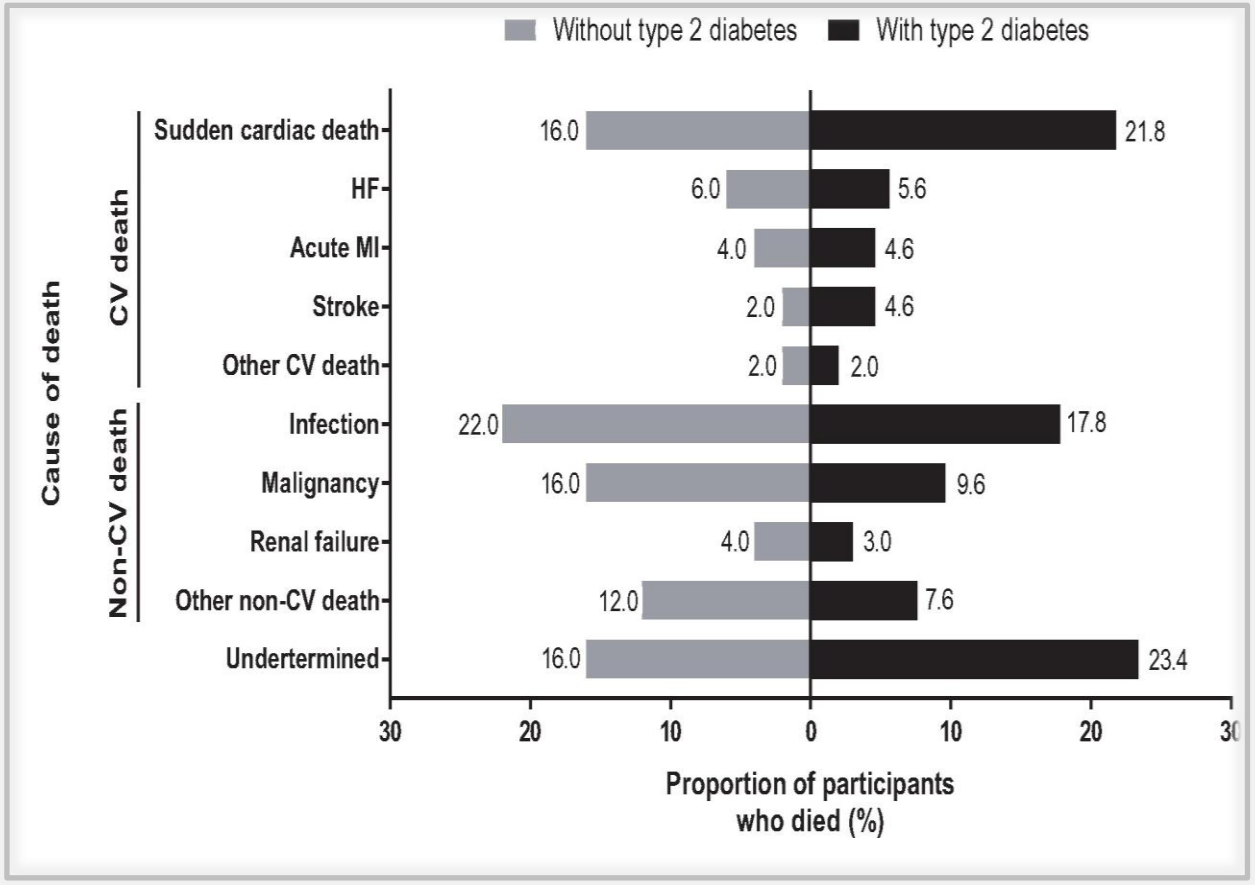
Ketone hypothesis

DAPA CKD trial

Cause of death in the overall population

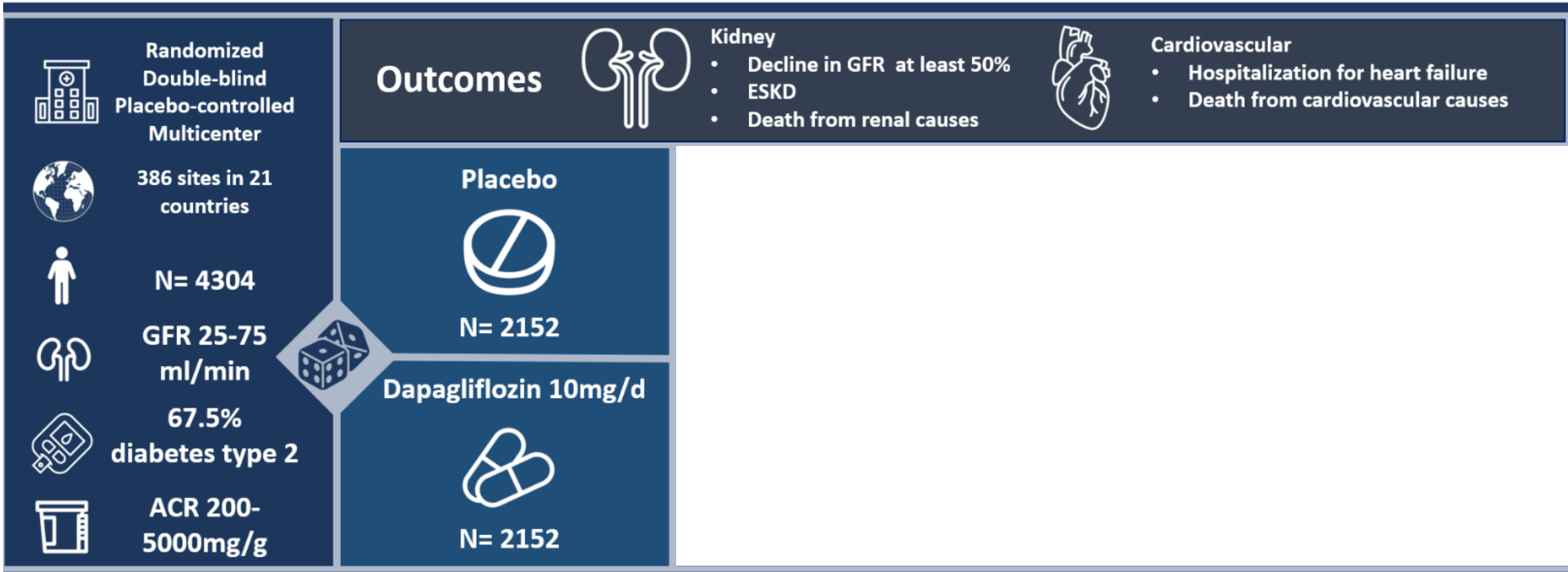


Cause of death in patients with or without Type 2 diabetes



Eur Heart J. 2021 Mar 31;42(13):1216-1227

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?



Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

N Engl J Med 2020; 383:1436-1446

Double-blind, Placebo-controlled, Multicentric RCT
(N=4304)

Inclusion:
With or without DM
eGFR: ≥25-75 and
UACR: ≥200-≤5000 mg/g
Median follow up -2.4 yrs

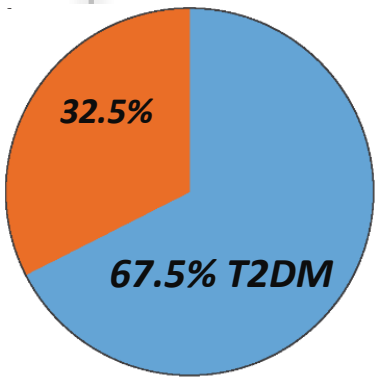
Dapagliflozin VS placebo

DAPA-CKD

2020

Composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal causes-HR 0.56; (0.45 to 0.68)

Composite of death from CV causes or hospitalization for heart failure
HR 0.71; (0.55 to 0.92)



N=2906

Double-blind, Placebo-controlled, Multicentric parallel group RCT
(N=5000)

Inclusion:
With or without DM
eGFR: ≥20-45 or
eGFR ≥45 to <90 with UACR ≥200 mg/g

Empagliflozin VS placebo

EMPA-KIDNEY

2022

Primary outcomes: Kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40% in eGFR or CV death

N Engl J Med. 2020;383(15):1436–1446.

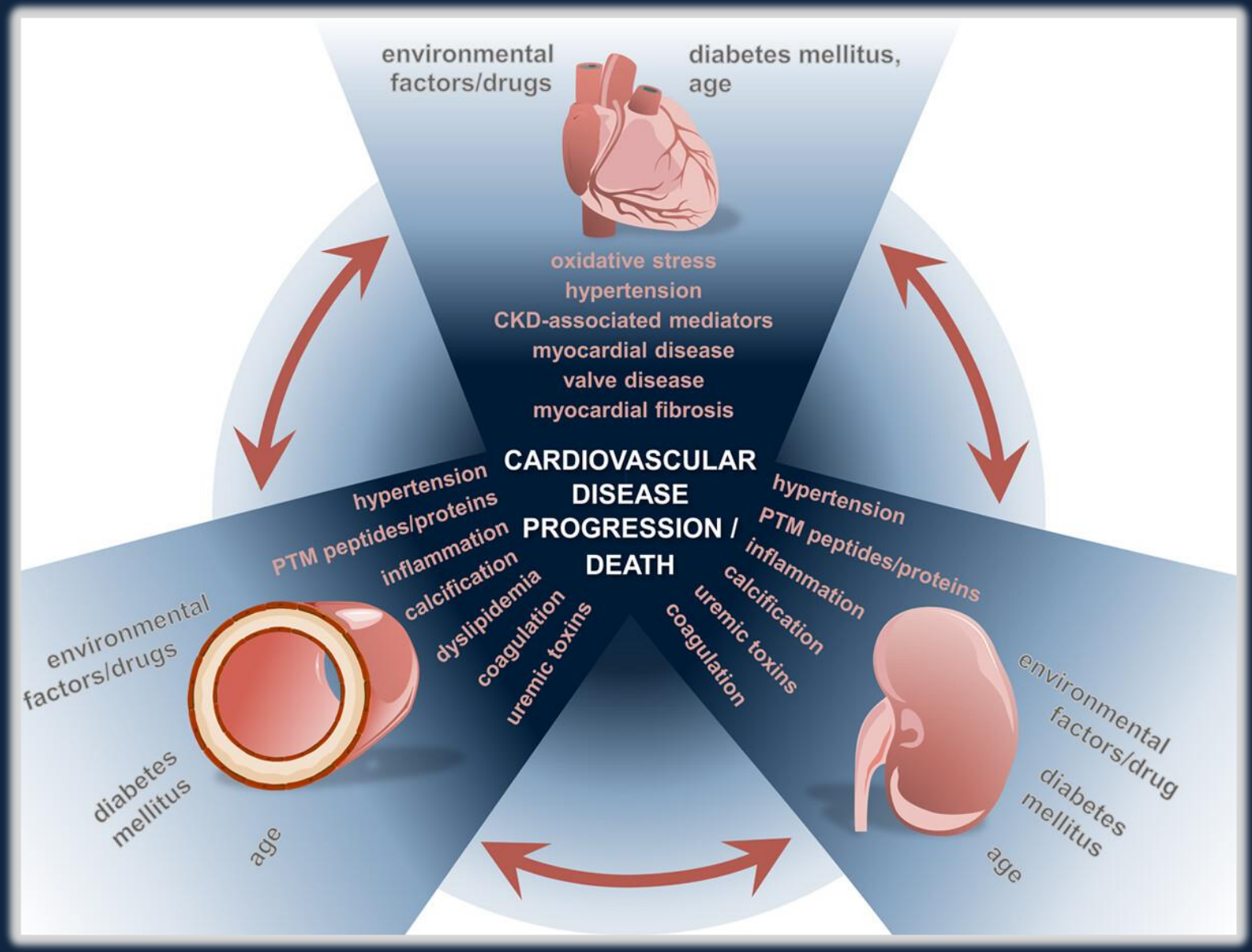
N Engl J Med. 2023;388(2):117–127

Effects of dapagliflozin on mortality in patients with chronic kidney disease: a pre-specified analysis from the DAPA-CKD randomized controlled trial

Hiddo J.L. Heerspink[1,2]*, C. David Sjöström[3], Niels Jongs[1], Glenn M. Chertow[4], Mikhail Kosiborod[2,5,6], Fan Fan Hou[7], John J.V. McMurray[8], Peter Rossing [9,10], Ricardo Correa-Rotter[11], Raisa Kurlyandskaya [12], Bergur V. Stefansson [3], Robert D. Toto[13], Anna Maria Langkilde[3], and David C. Wheeler [14,2]; for the DAPA-CKD Trial Committees and Investigators

Eur Heart J. 2021 Mar 31;42(13):1216-1227

Interaction of cardiovascular and chronic kidney disease



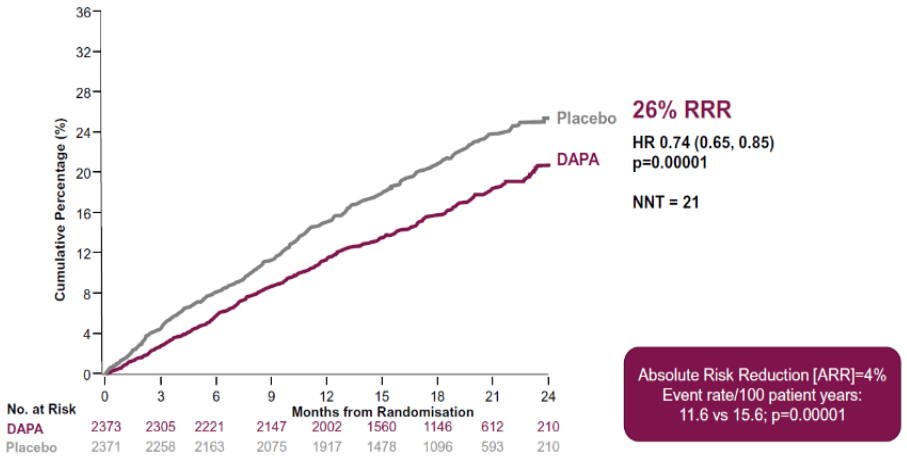
Circulation. 2021;143:1157–1172

DAPA-HF trial

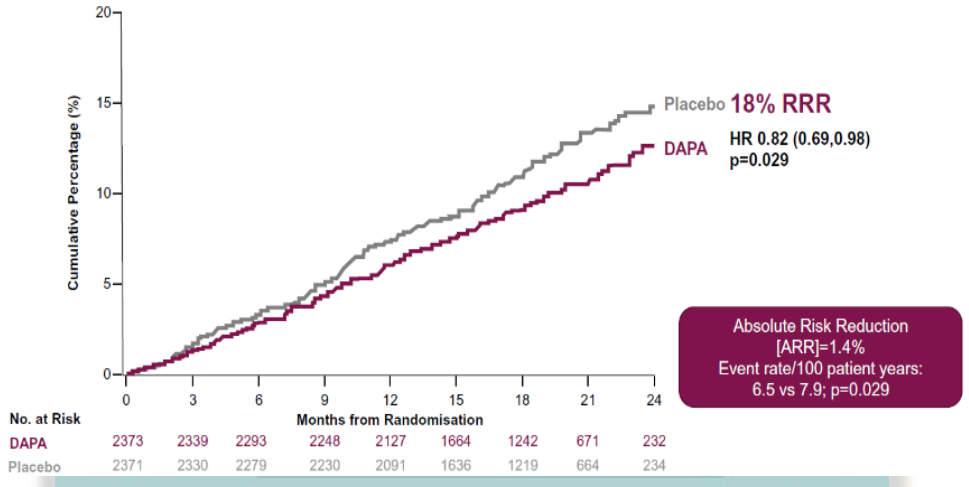
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., et al., for the DAPA-HF Trial Committees and Investigators*

Primary Endpoint: CV Death or hHF or an Urgent HF Visit



Component of Primary Endpoint: Cardiovascular Death



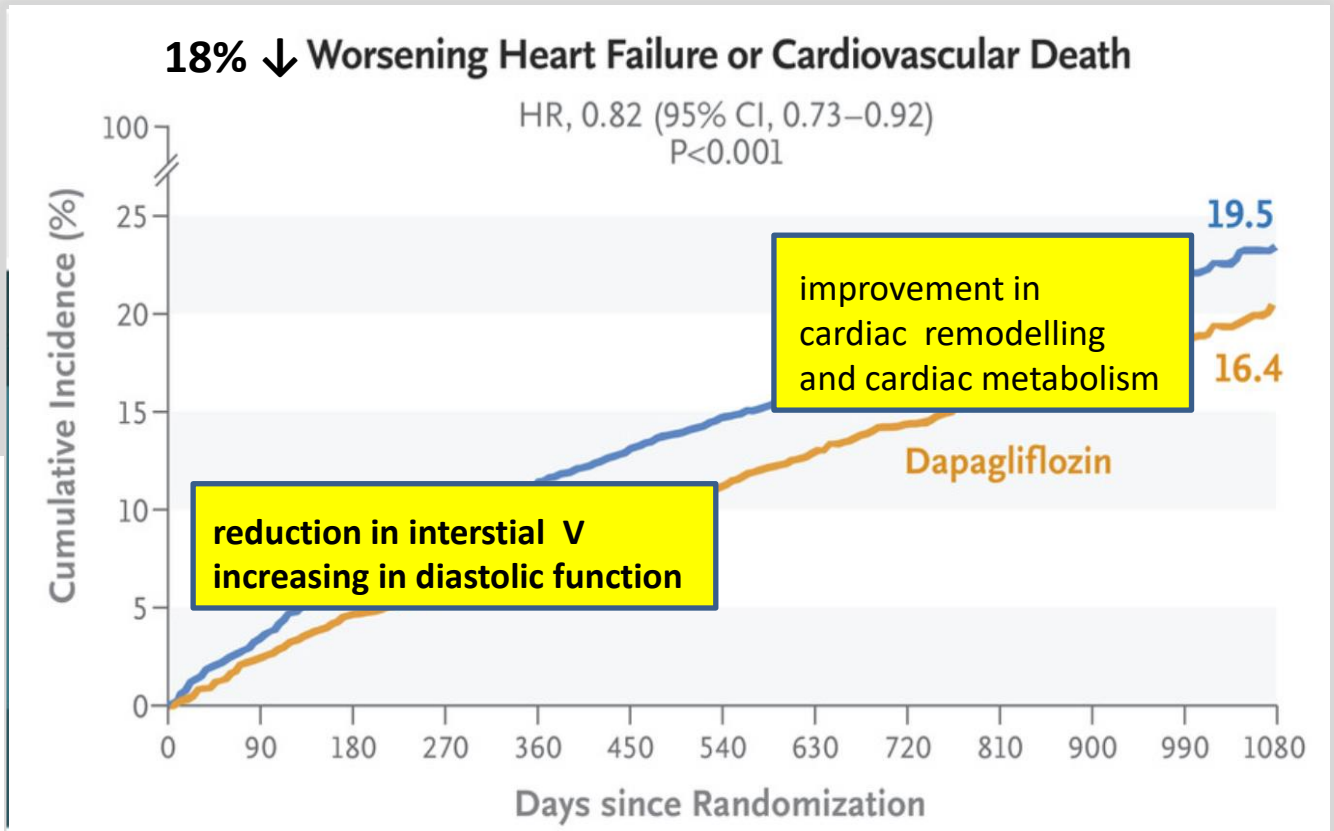
N Engl J Med 2019; 381:1995-2008

DELIVER

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Brian Claggett, Ph.D., Rudolf A. de Boer, M.D., David DeMets, Ph.D., Adrian F. Hernandez, M.D., Silvio E. Inzucchi, M.D. Mikhail N. Kosiborod, M.D., Carolyn S.P. Lam, M.D., Felipe Martinez, M.D., Sanjiv J. Shah, M.D., Akshay S. Desai, M.D., et al., for the DELIVER Trial Committees and Investigators*

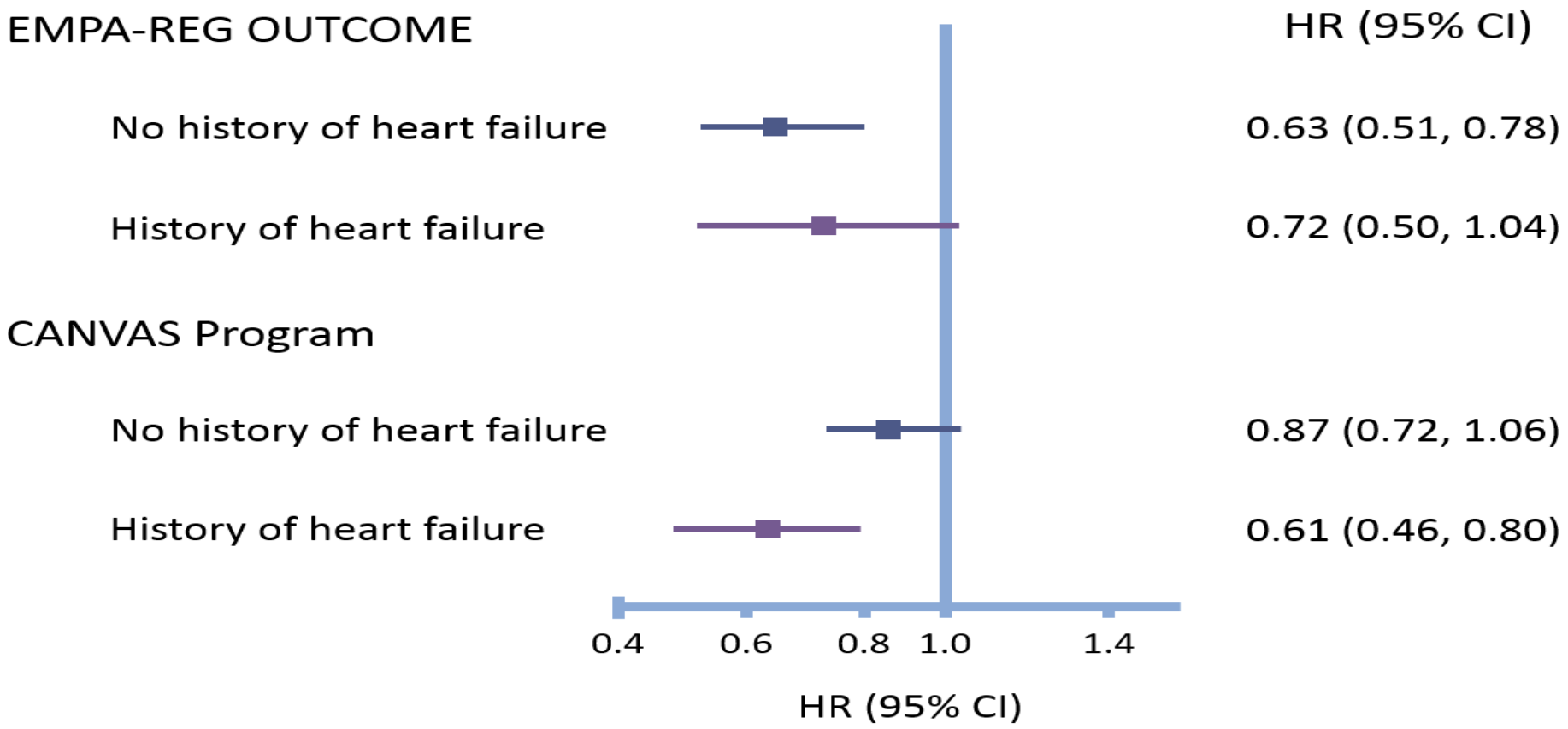
18% ↓ Worsening Heart Failure or Cardiovascular Death



Dapagliflozin was shown to reduce the risk of disease progression and cardiovascular death in patients with a mildly reduced or preserved ejection fraction as compared to a placebo and was associated with similar rates of adverse events to placebo.

N Engl J Med 2022; 387:1089-1098

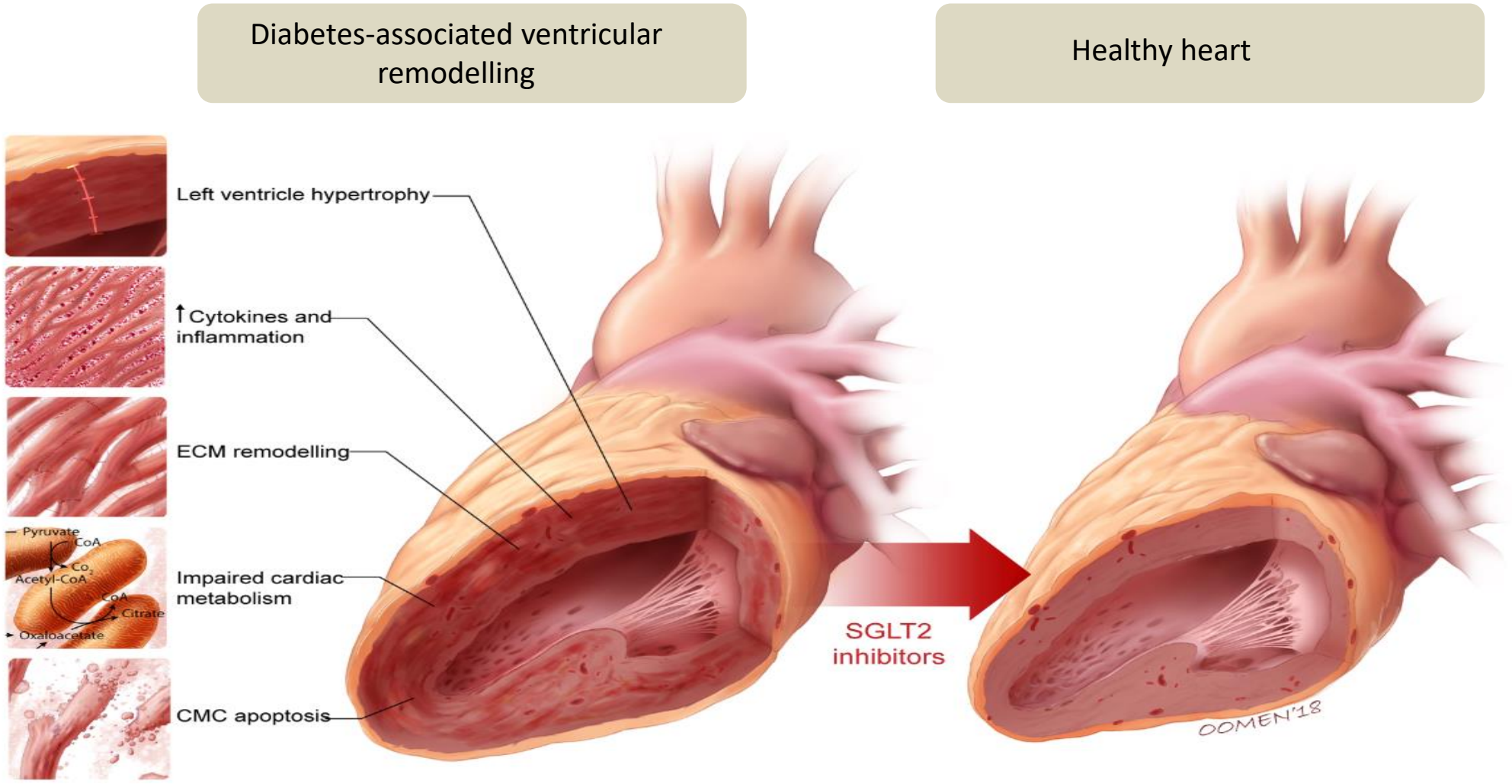
The cardiovascular benefits with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) in participants with and without a history of heart failure



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

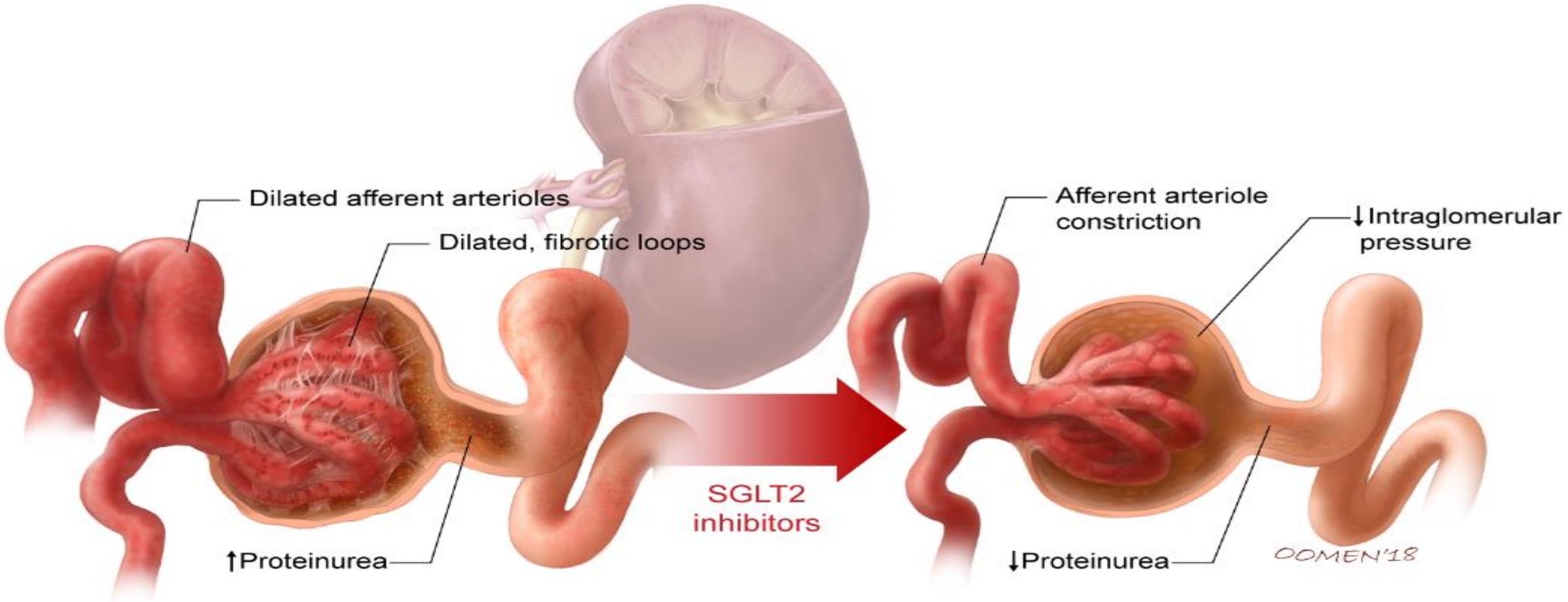
Cardiovascular protection by SGLT2 inhibitors



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

SGLT2 inhibitors improve ventricular loading conditions



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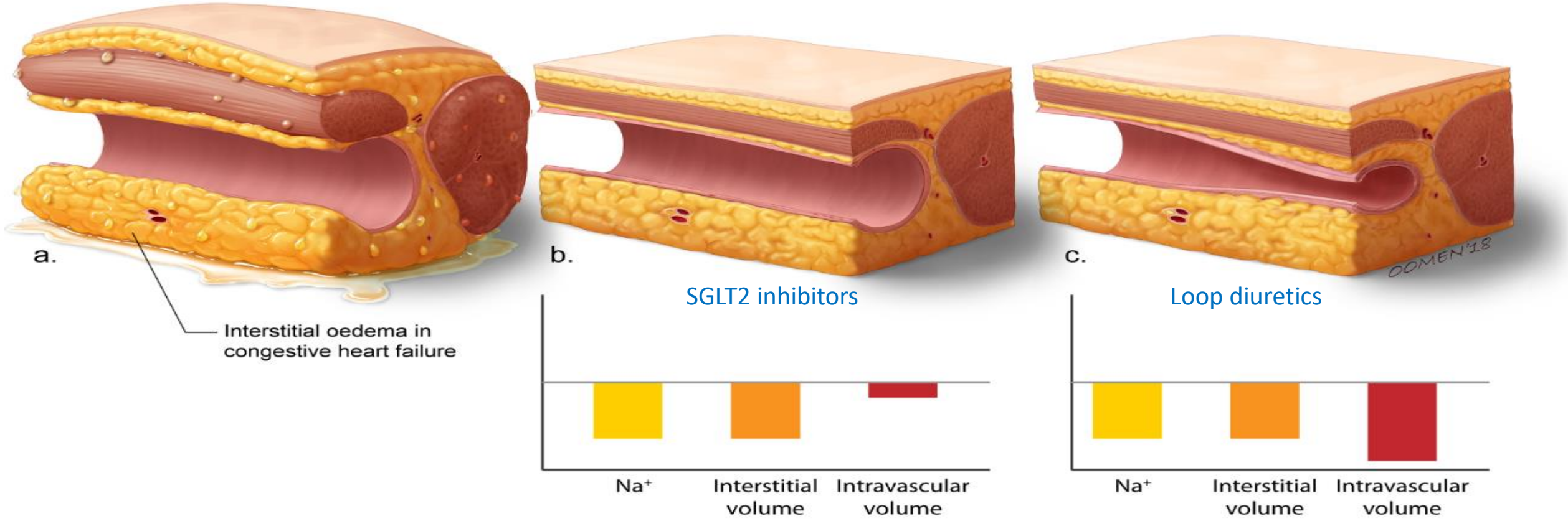
Diabetologia

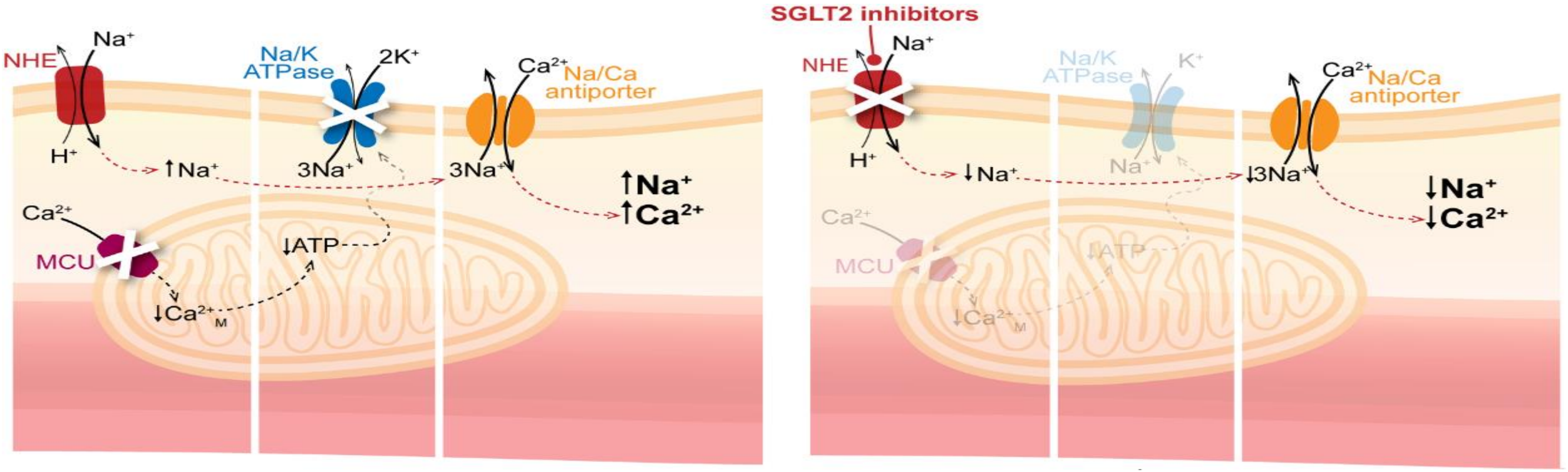
SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

SGLT2 inhibition and direct effects on Na+/H+ exchange in the myocardium



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

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