SGLT2is in Current treatment of CKD

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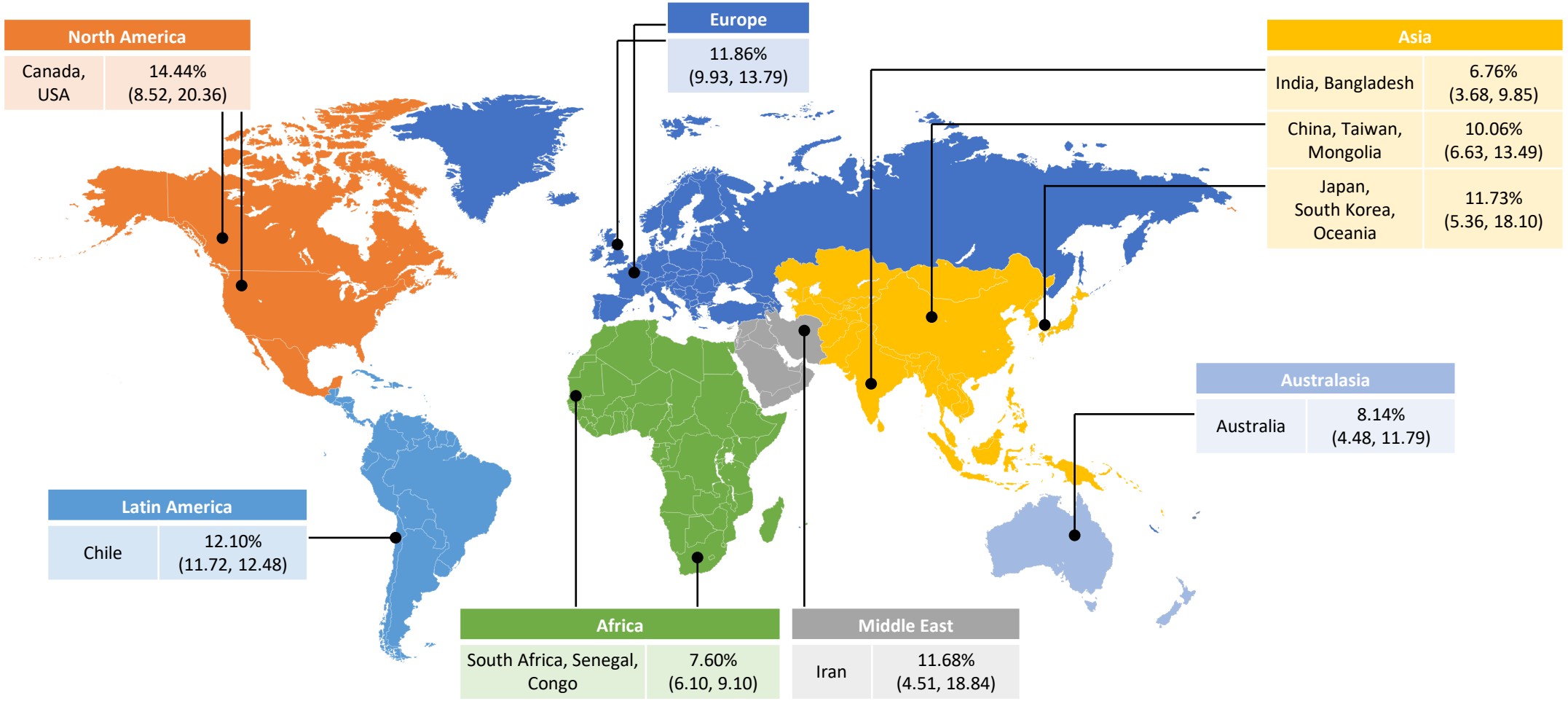
Disclosures:

Honoraria, Consultations and advisory boards

Astellas, Astra, Genesis, GSK, Menarini, Novagem, Rafarm, Αλέκτωρ Φαρμακευτική, Sanofi

A staggering ~840 million people worldwide are affected by CKD[1]

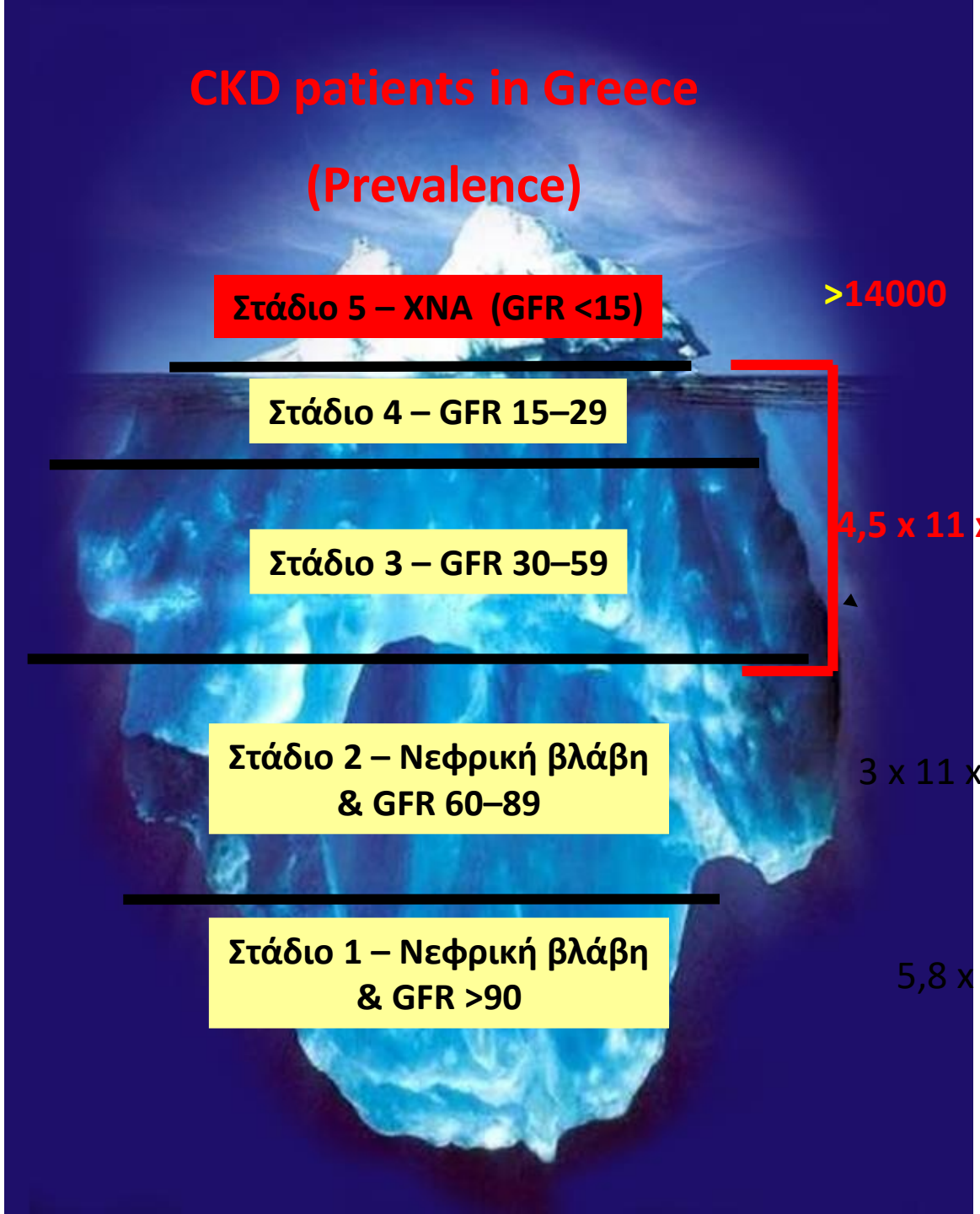
Meta-analysis estimating the global prevalence of CKD (stages 3–5)[2,a]



[a]Global prevalence reported as percentage with 95% confidence intervals.

CKD = chronic kidney disease.

1. Jager KJ et al. *Nephrol Dial Transplant.* 2019;34:1803-1805; 2. Hill NR et al. *PLoS One.* 2016;11:e0158765.



>14000

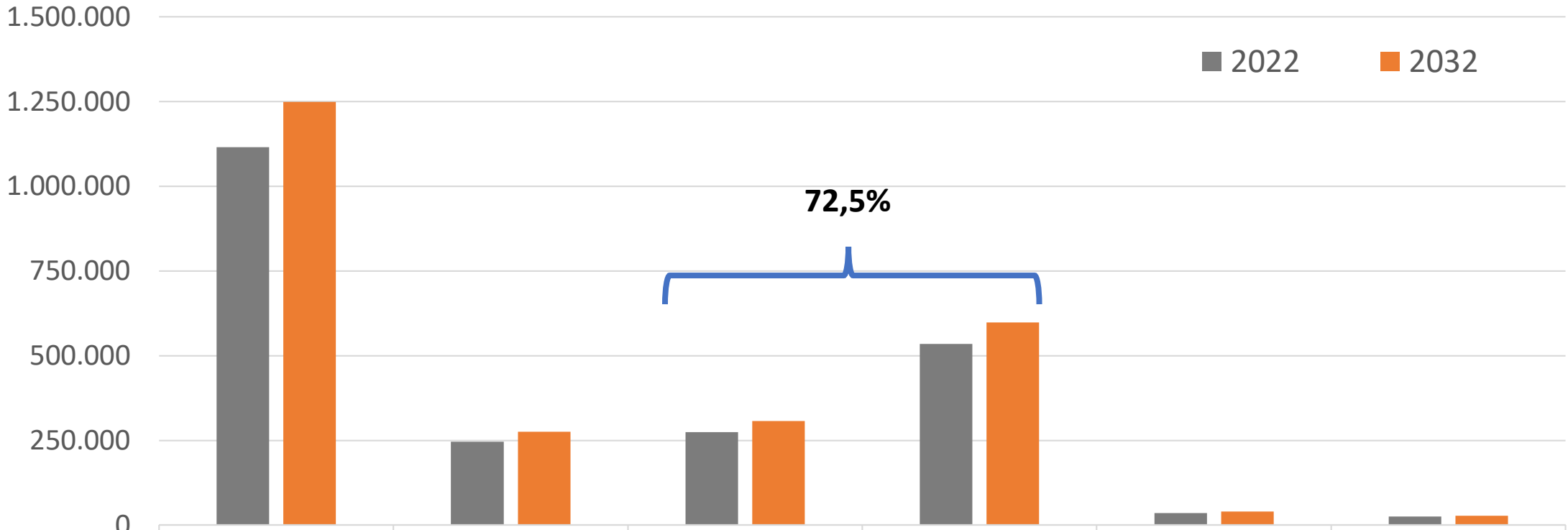
4,5 x 11 x 10^6=490000

3 x 11 x 10^6 = 330000

5,8 x 11 x 10^6= 630000

Total CKD patients>1000000

Prevalence & 10-year forecast

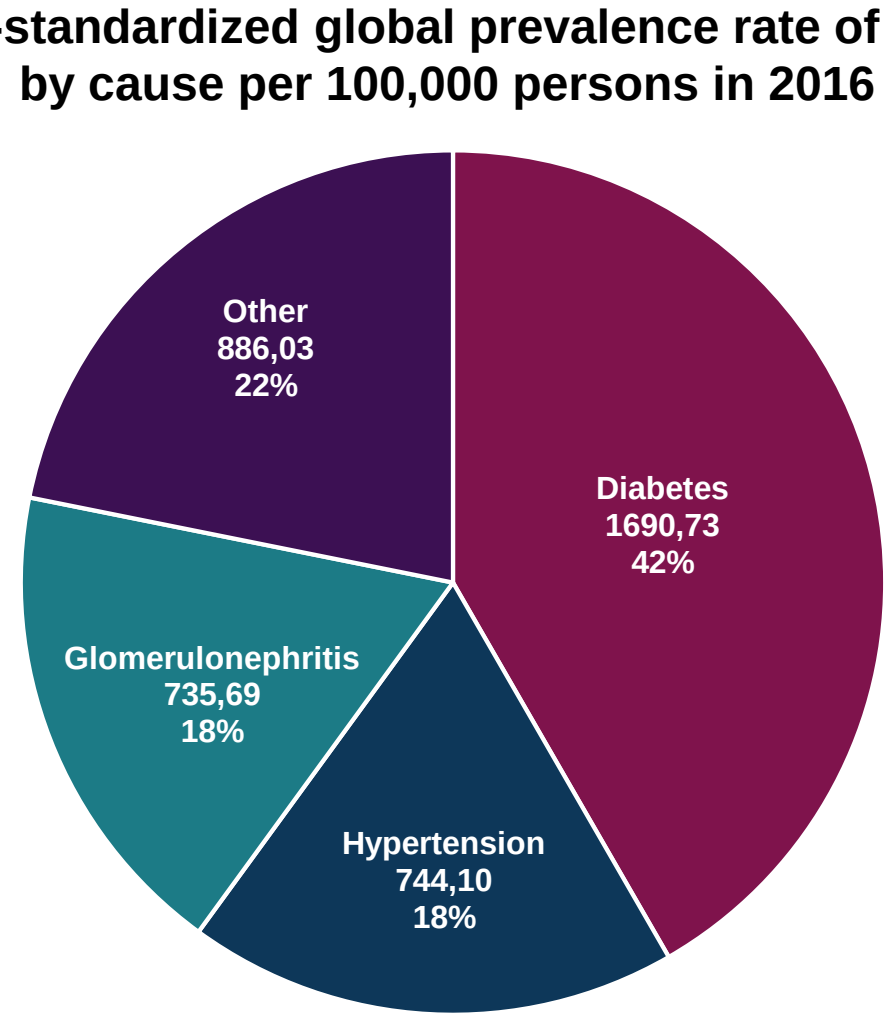


	XNN	Στάδιο 1	Στάδιο 2	Στάδιο 3	Στάδιο 4	Στάδιο 5
2022	1.115.991	245.888	274.500	534.694	35.765	25.144
2032	1.249.475	275.299	307.333	598.649	40.043	28.151

References: GBD 2020; Hill et al. (2016); ERA-EDTA registry 2021; Teruel et al. (2015); Provenzano et al. (2018); Loutradis et al. (2015)

Stafylas P et al. 2022

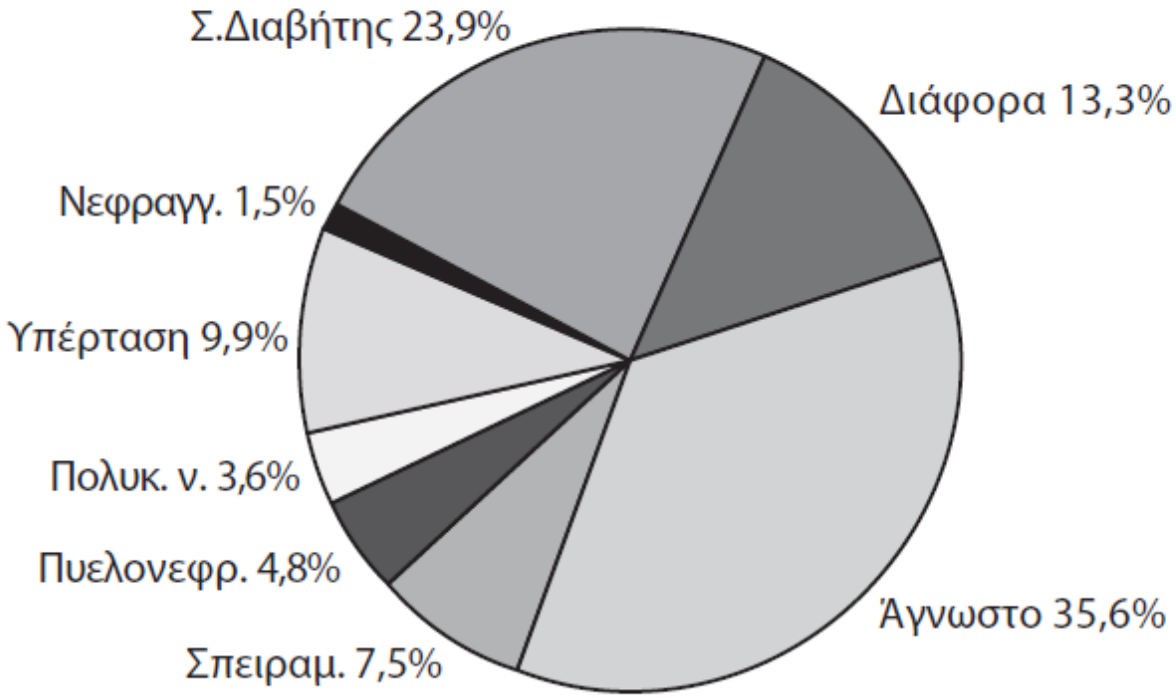
The causes of CKD are diverse, with diabetes and hypertension responsible for more than half of all cases



CKD = chronic kidney disease.

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

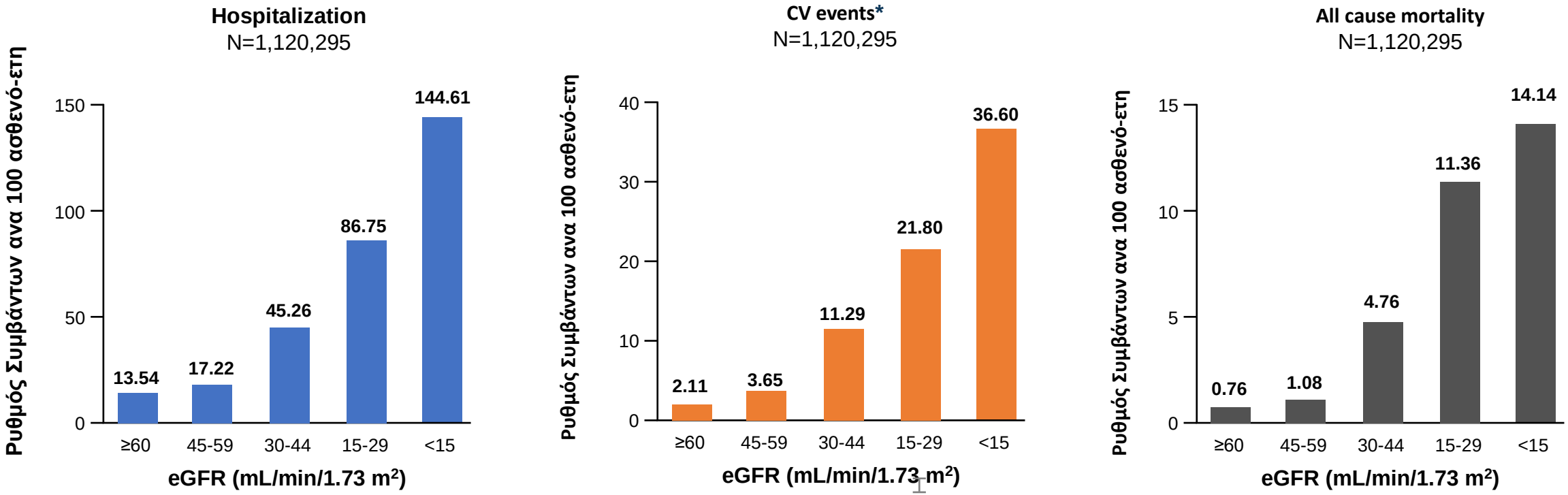
ESKD in Greece



Εικόνα 6. *Νέοι ασθενείς (%) σε ΘΥΝΛ, έτους 2020, ανά ομάδα αιτίων ΧΝΝ.*

Papadaki O et al, Hell Nephrol 2023

Kidney function and survival [1]

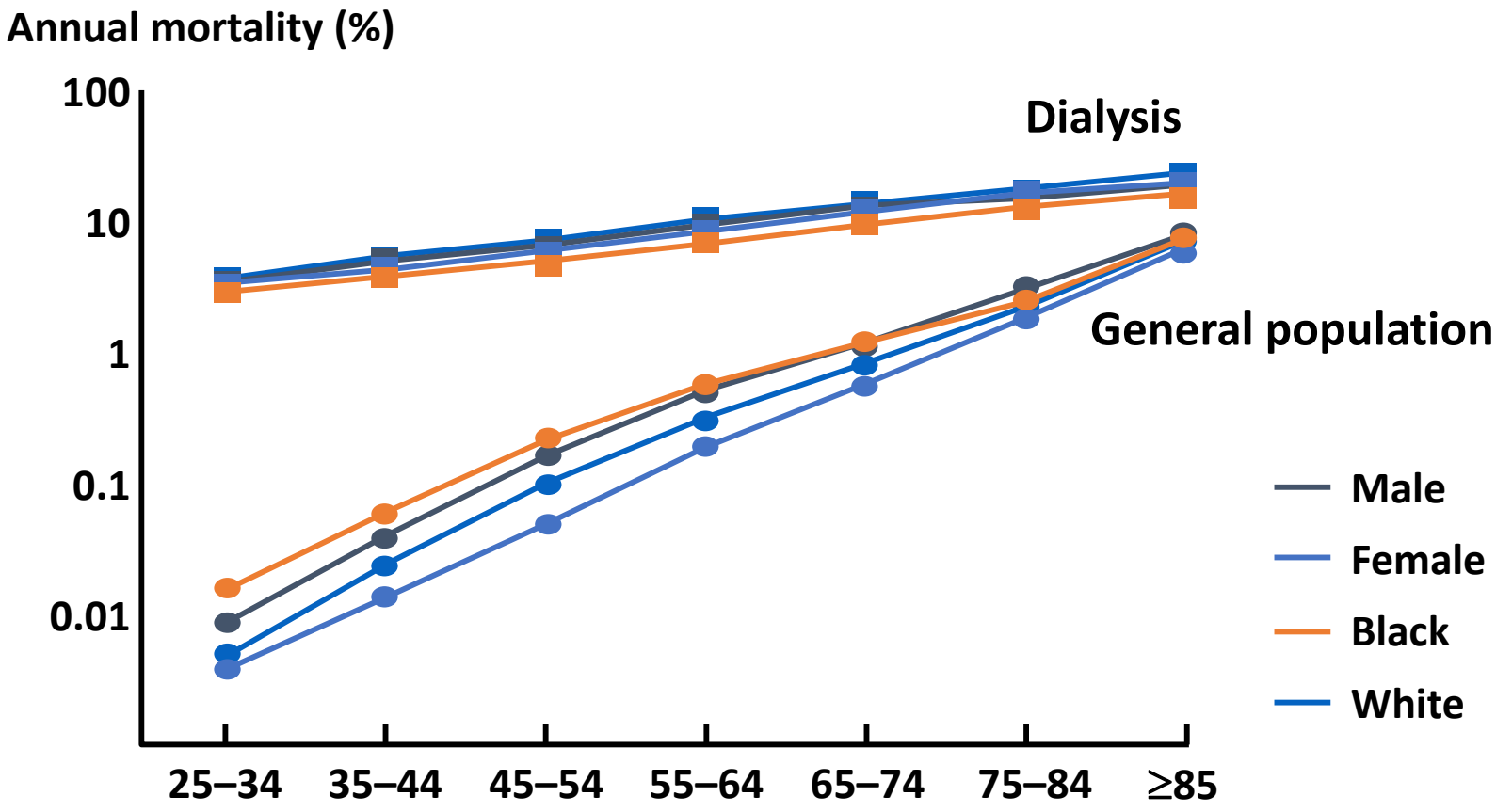


*Καρδιαγγειακά Συμβάματα ορίστηκαν ως νοσηλεία για στεφανιαία νόσο, καρδιακή ανεπάρκεια, ισχαιμικό Αγγειακό Εγκεφαλικό Επεισόδιο ή Περιφερική Αγγειακή Νόσο.

[1]ΧΝΝ: Χρόνια Νεφρική Νόσος; eGFR = εκτιμώμενος ρυθμός σπειραματικής διήθησης

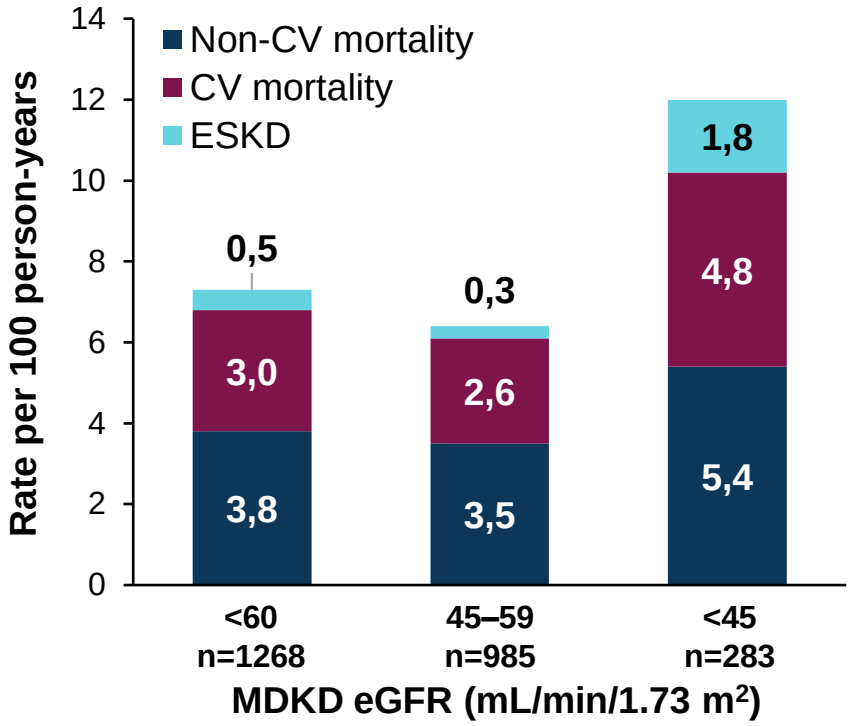
1.Go A, et al. *N Engl J Med.* 2004;351:1296-1305.

Cardiovascular Mortality in the General Population and in ESRD Treated by Dialysis



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)

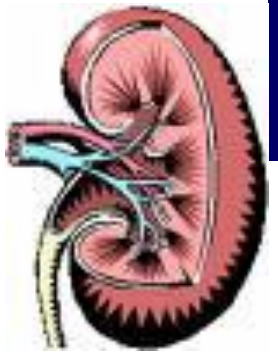
Kidney decline is associated with increased risk of CV mortality

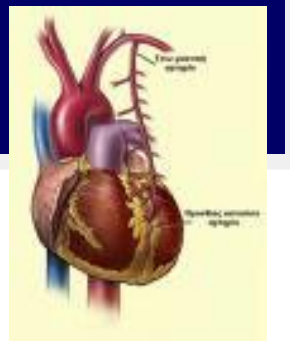
[a]Each cell represents a pooled RR from a meta-analysis, colors reflect the ranking of adjusted RR. Bold numbers indicate statistical significance ($p<0.05$); [b]Incidence rate of 4.5/1000 person-years. Results are adjusted for covariates and compared to the reference cell.

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.

Evolution of CKD and CVD is parallel



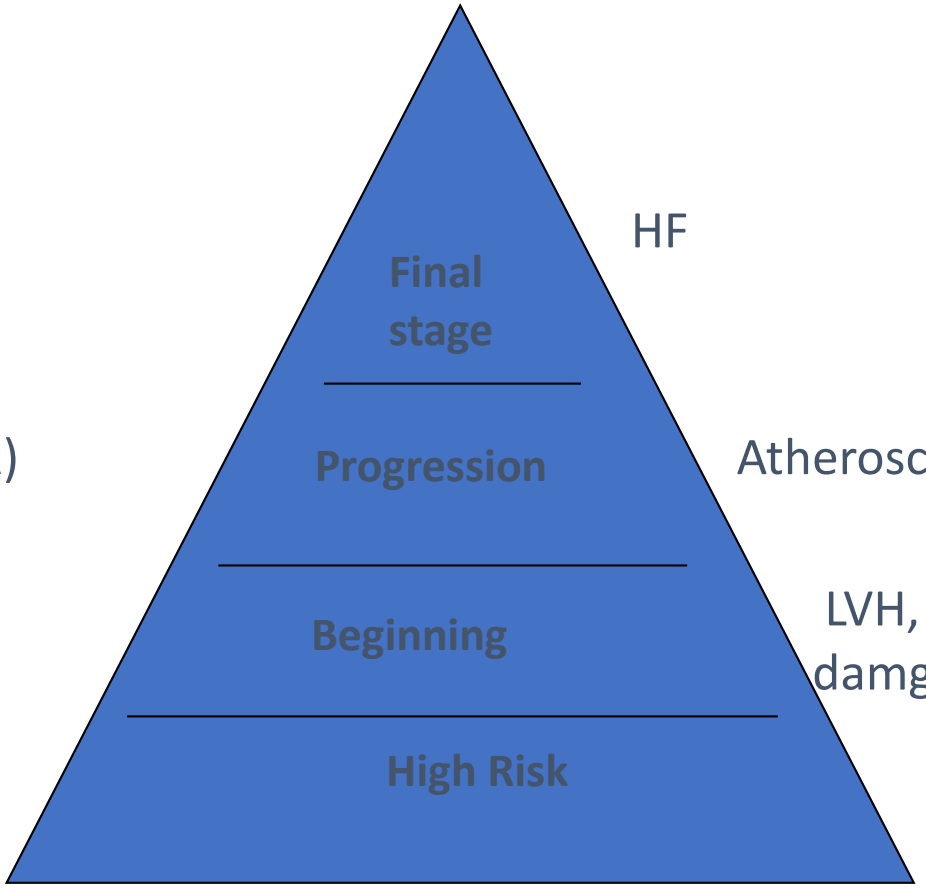


ESKD

CKD (GFR)

Albuminuria

Age, DM, Hypertension



HF

Atherosclerosis

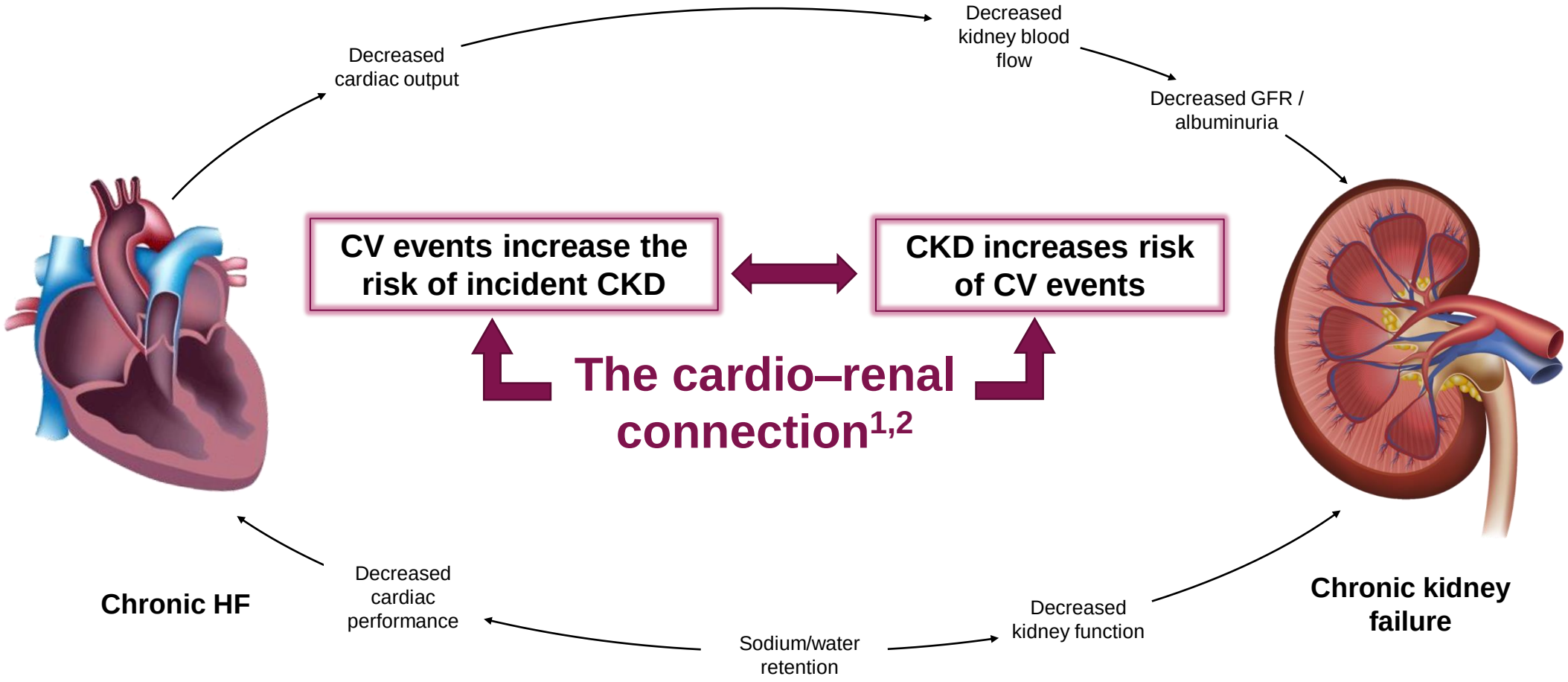
LVH, endothelial damge

CKD

CVD

Sarnak MJ, AJKD 2000, 35(Suppl 1): 117-131

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

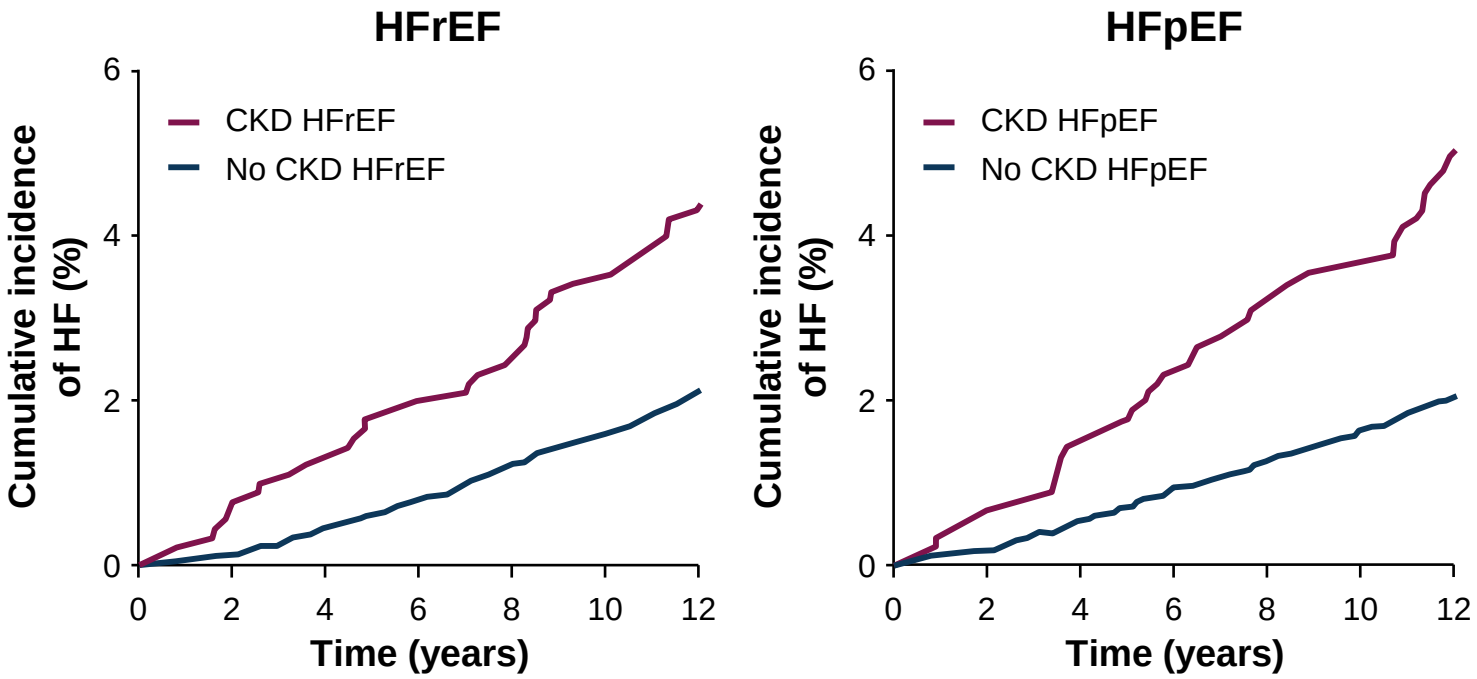


CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GFR = glomerular filtration rate; HF = heart failure.

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.

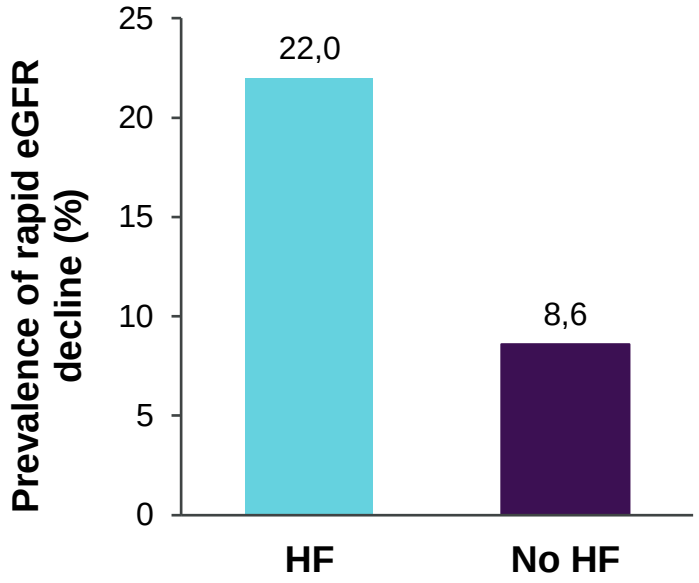
CKD and HF are interconnected: CKD is associated with increased risk of HF and conversely HF is associated with risk of eGFR decline

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

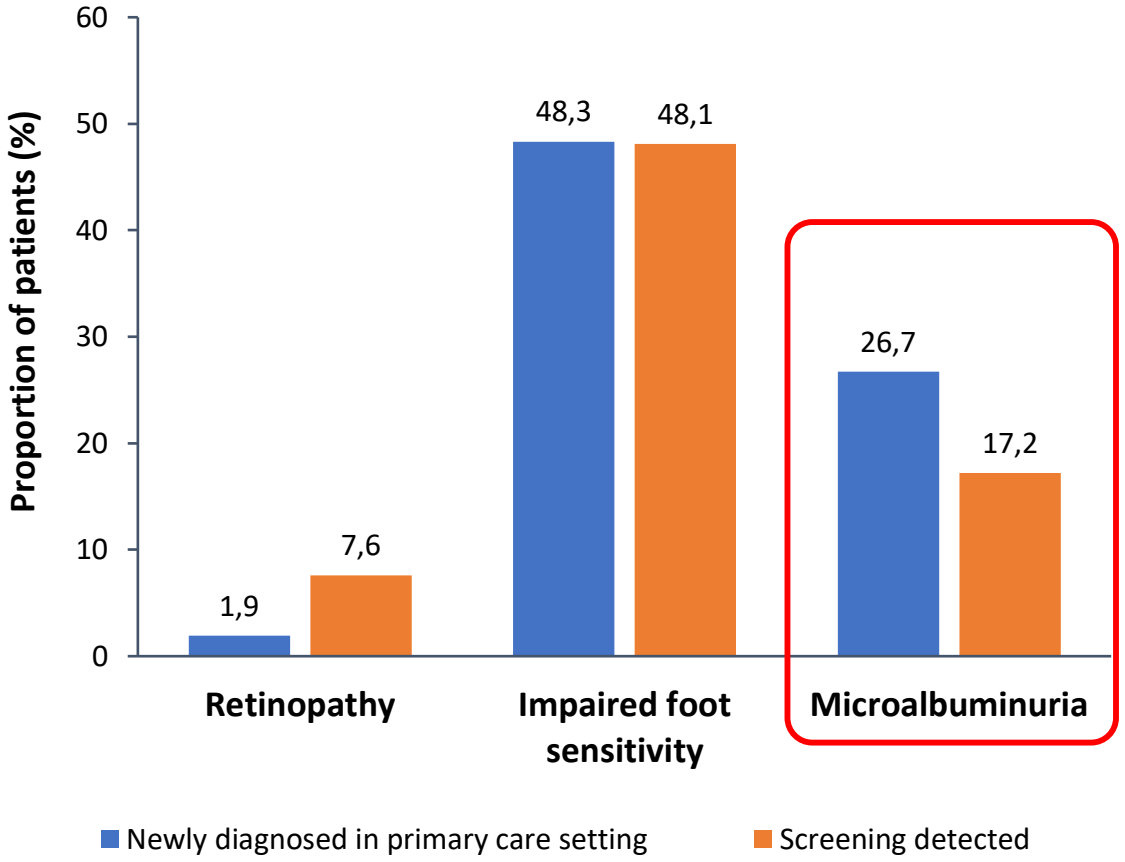
[a]Rapid rate of eGFR decline was defined as slopes steeper than −5 mL/min/1.73 m^2/year.

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.

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

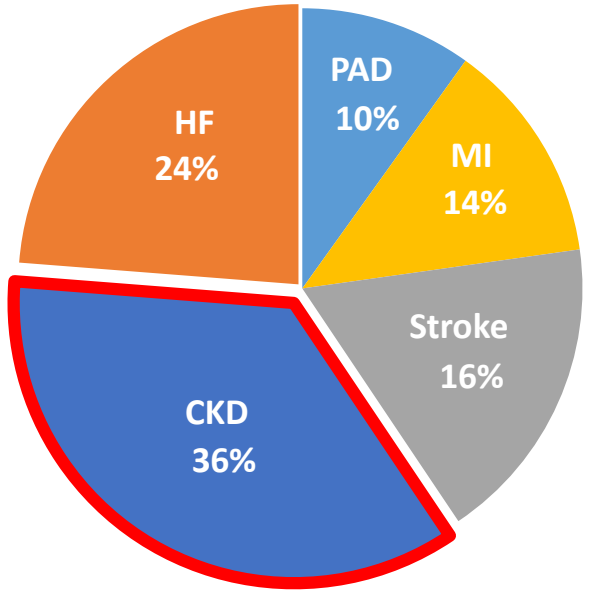
Prevalence of microvascular complications at time of T2D diagnosis[1]



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.

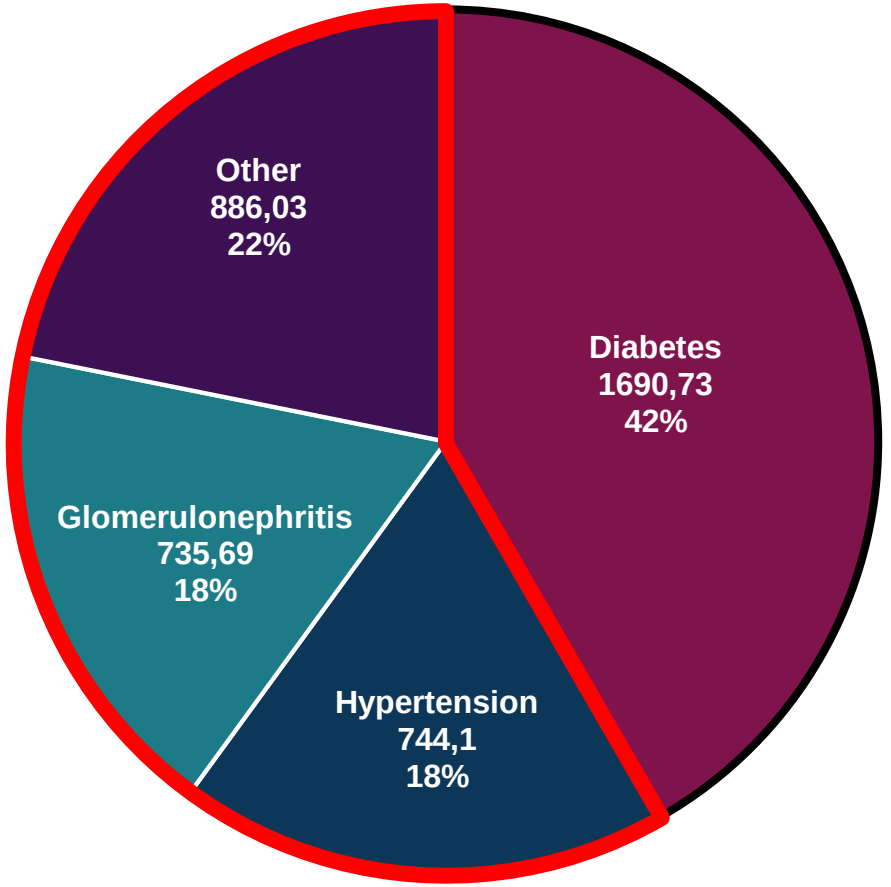
CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; MI = myocardial infarction; PAD = peripheral artery disease; T2D = type 2 diabetes.

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.

Mortality and CV risks are elevated, regardless of CKD etiology

Hypertensive nephropathy

>3×

Greater risk of CV events and mortality[1,a]

70% of patients received an ACE inhibitor/ARB

IgA nephropathy

53%

Increased mortality risk[2,b]

74% of patients received an ACE inhibitor/ARB

Diabetic nephropathy

~6×

Greater risk of CV events and mortality[1,a]

76% of patients received an ACE inhibitor/ARB

[a]Compared with primary renal disease defined by primary glomerulonephritis and tubulointerstitial nephritis; [b]Data compared with the general population.

1. Nakayama M et al. *Hypertens Res.* 2011;34(10):1106-1110; 2. Jarrick S et al. Article and online supplemental material. *J Am Soc Nephrol*. 2019;30(5):866-876.

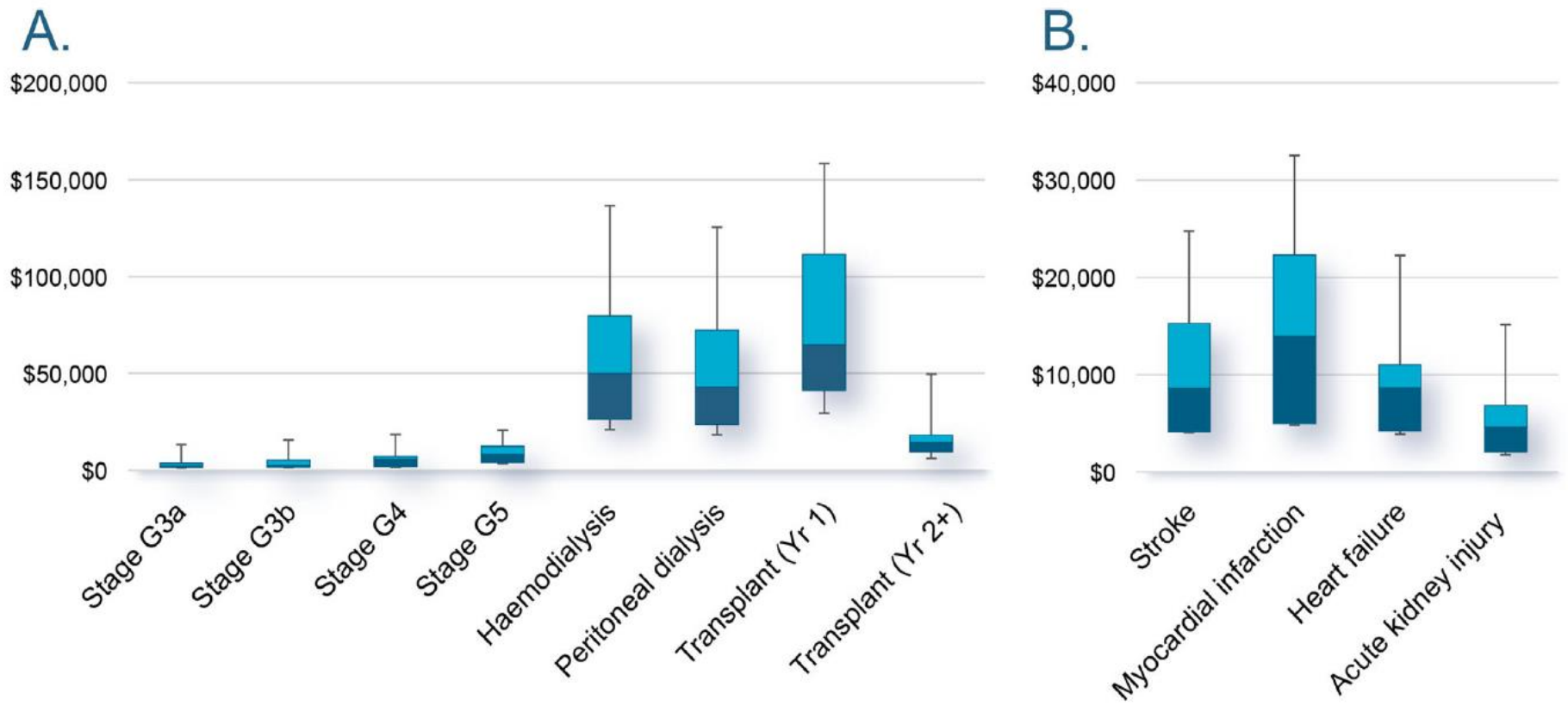
CKD cost (I)

Table 1. Kidney Failure in the United States

	2005 Estimates		2020 Projections
Mortality	85,000	Death rate was 7 times greater in persons ≥ 65 y treated by dialysis than in those in the general Medicare population	125,000*
Incidence	105,000	Most cases caused by diabetes (44%) or hypertension (27%)	151,000†
Prevalence	478,000	Including > 335,000 living on dialysis therapy and > 141,000 with a kidney transplant	785,000
Costs	$20 billion	Total Medicare expenditures for ESRD represented > 6% of total Medicare budget	$54 billion

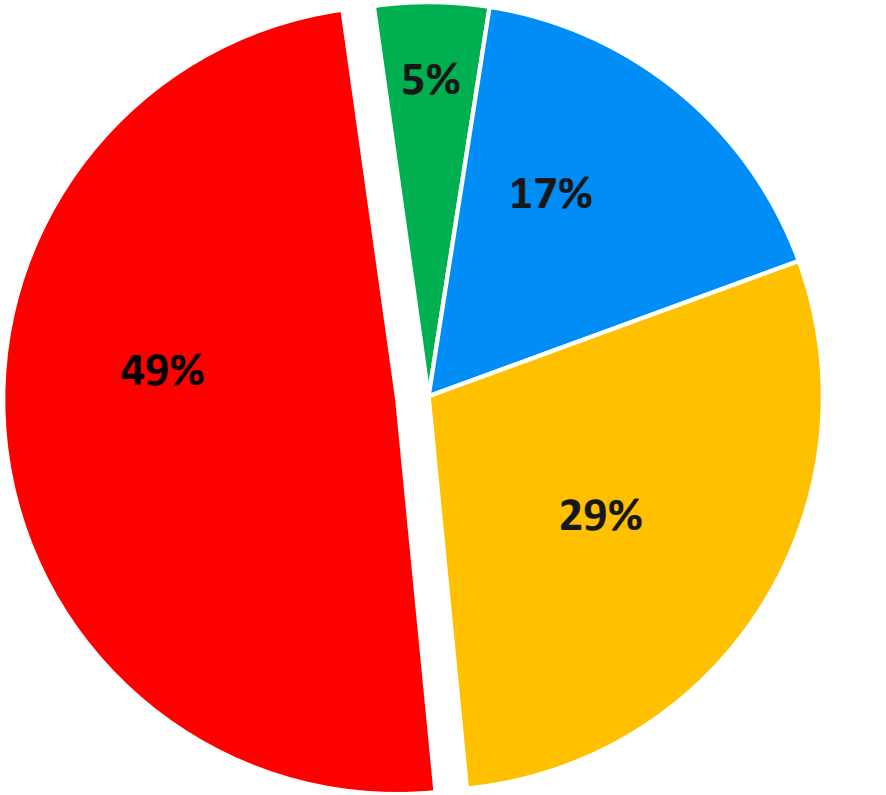
Levey AS et al, Am J Kidney Dis 2009

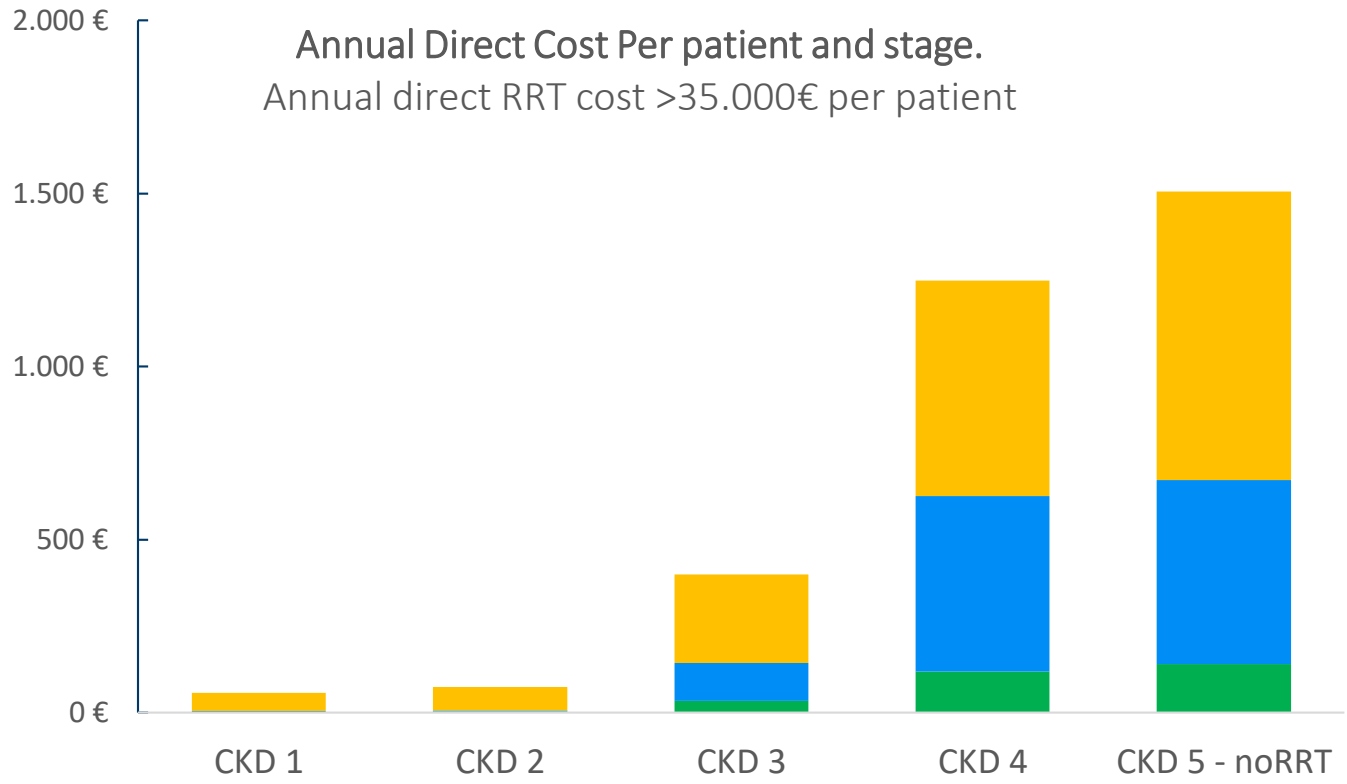
CKD cost (II)



Jha V et al. Adv Ther 2023

The direct annual cost of CKD in Greece is approx. 850 million euros



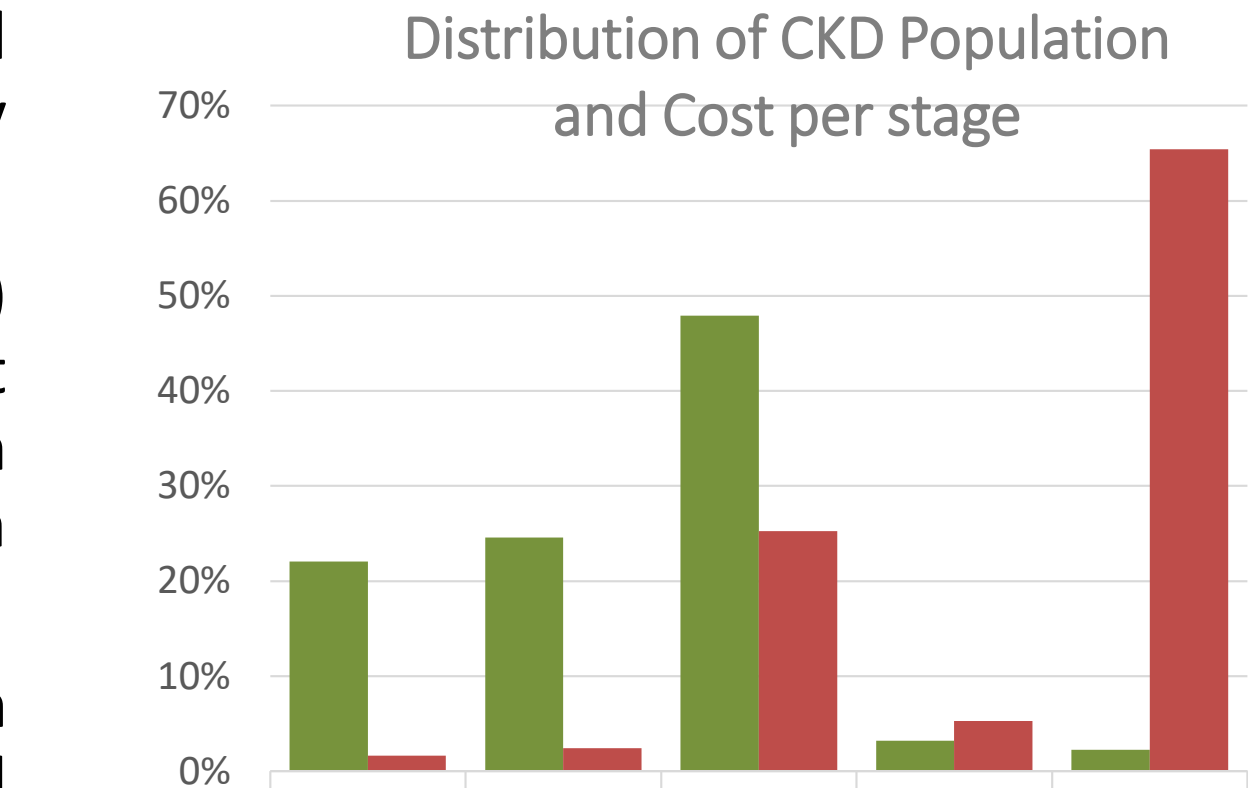


Abbreviations: CKD – Chronic Kidney Disease; RRT – Renal Replacement Therapy (includes haemodialysis, peritoneal dialysis, kidney transplantations)

Stafylas P et al. 2022

Cost of ESKD in Greece

- CKD is creating a high and growing clinical and economic burden, largely driven by the RRT cost.
- About 2% of the CKD population (stage 5) spend about 65% of the total CKD budget or more than 4% of the total public health expenditure, higher than other European countries.
- There is an urgent need for public health strategies aiming at early detection and management of CKD.



	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5
Population	22%	25%	48%	3%	2%
Cost	2%	2%	25%	5%	65%

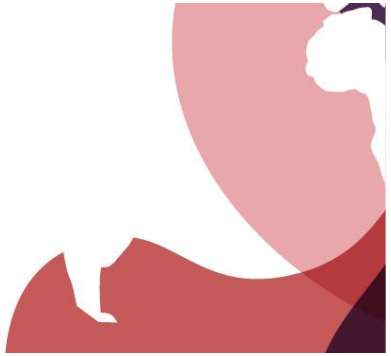
Stafylas P et al. 2022

KIDNEY HEALTH
FOR EVERYONE
EVERYWHERE

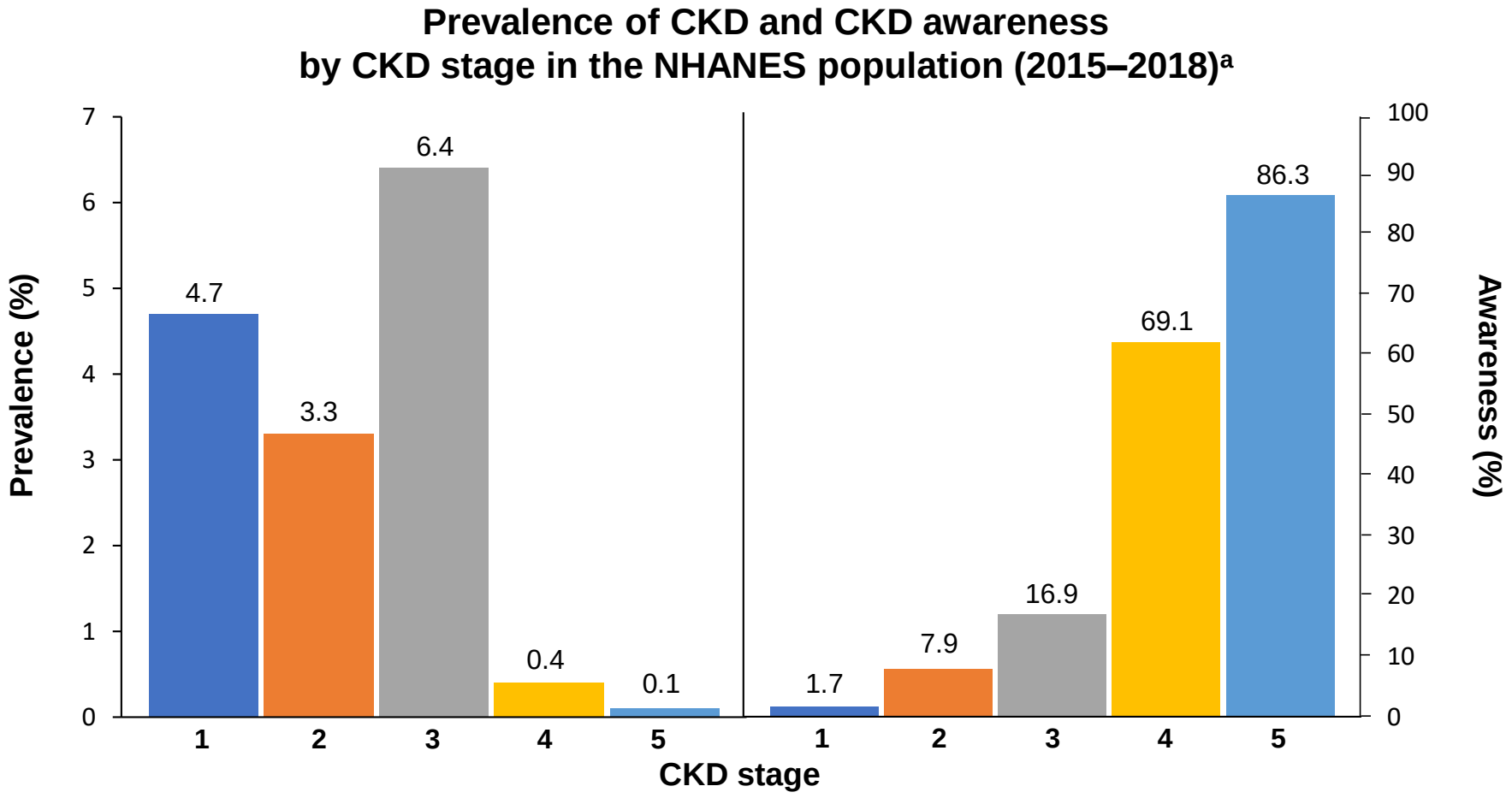
Despite the growing burden of kidney disease worldwide, kidney health disparity and inequity are still widespread. Early diagnosis, prevention and delay of progression are sustainable options to reduce costs and consequences of kidney diseases for individuals and countries. Yet, barriers to available, accessible, adequate and quality kidney care persist.

World Kidney Day

World Kidney Day is a joint initiative of ISN IFKF International Federation of Kidney Foundations



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

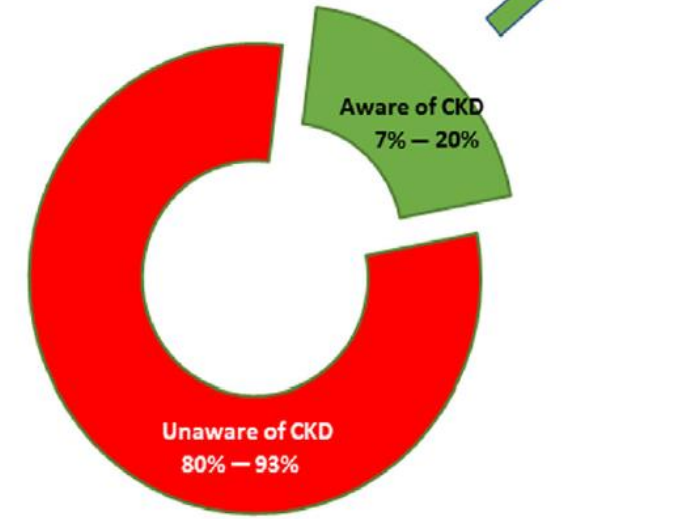


[a]Awareness was assessed as those who reported being told that they had kidney disease.

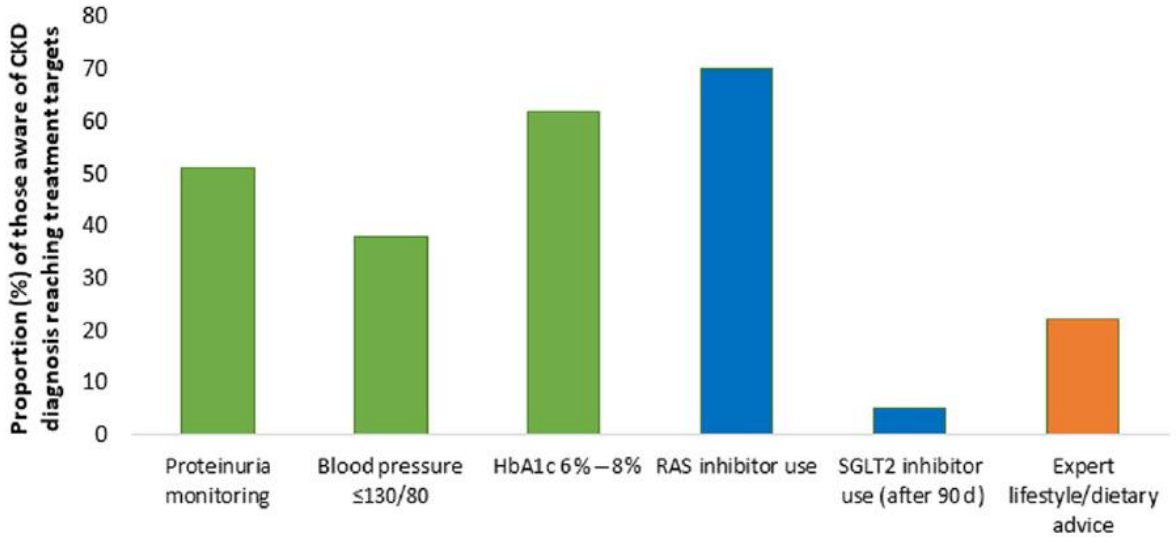
CKD = chronic kidney disease; NHANES = National Health and Nutrition Examination Survey.

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

Proportion of people with CKD who are aware of their diagnosis and are receiving appropriate guideline-recommended care

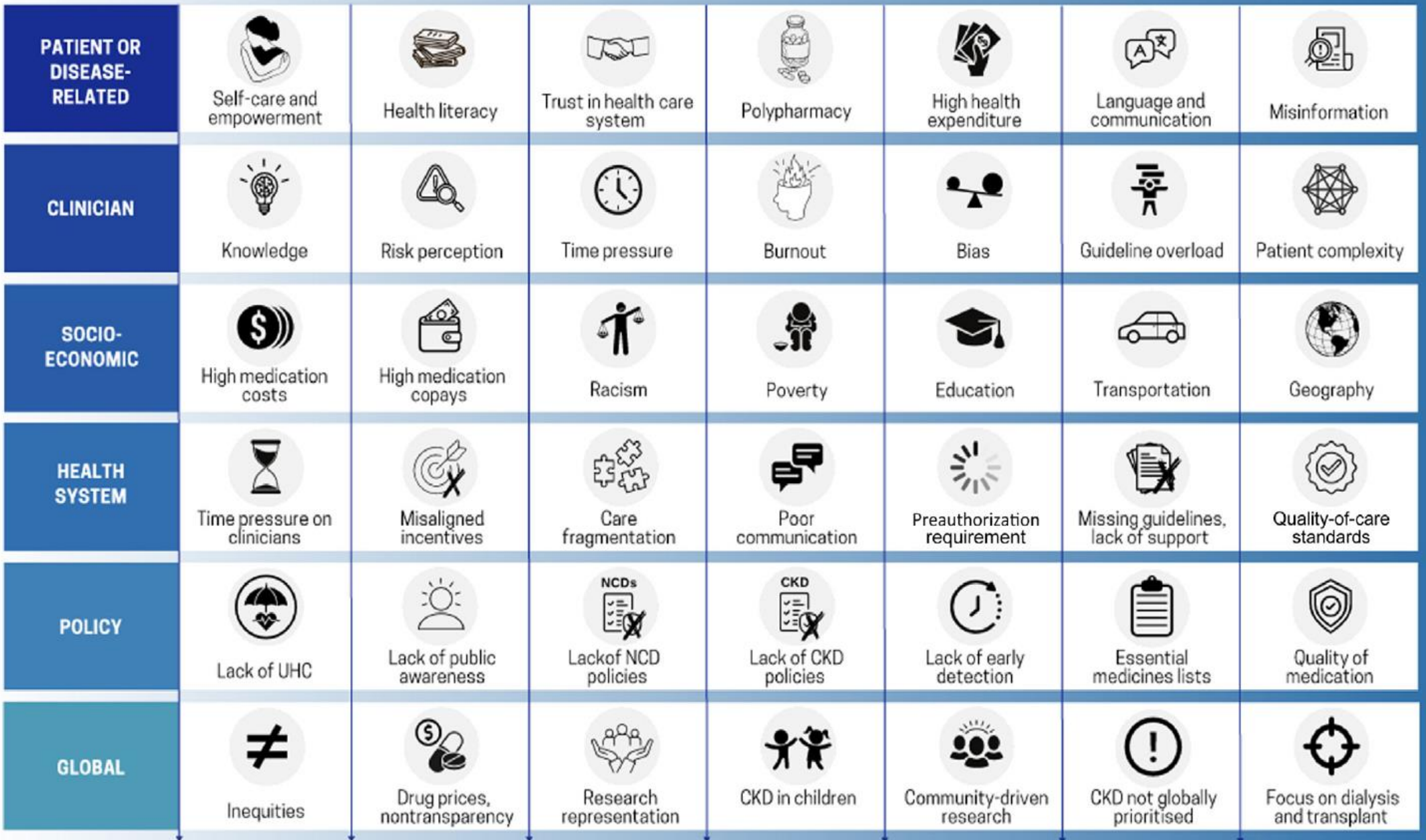


Proportion of people with CKD aware of their diagnosis



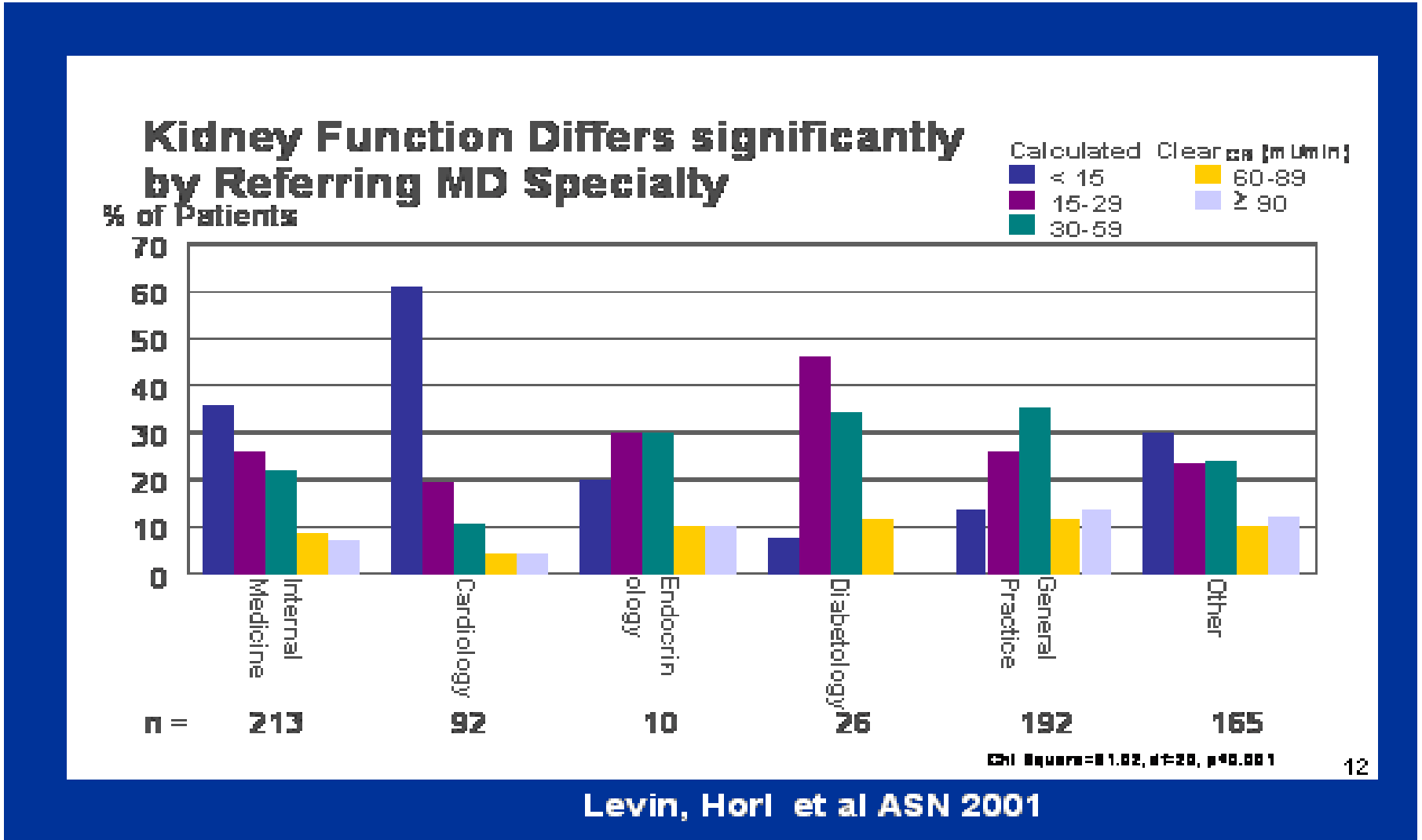
Lyckx V et al. 2024

BARRIERS TO APPROPRIATE MEDICATION PRESCRIBING AND USE IN CKD



Lyckx V et al. 2024

Renal function at time of referral



Mind the gap in kidney care: translating what we know into what we do

OPEN

Valerie A. Luyckx[1,2,3,18], Katherine R. Tuttle[4,5,18], Dina Abdellatif[6], Ricardo Correa-Rotter[7], Winston W.S. Fung[8], Agnès Haris[9], Li-Li Hsiao[2], Makram Khalife[10,19], Latha A. Kumaraswami[11], Fiona Loud[10,19], Vasundhara Raghavan[10,19], Stefanos Roumeliotis[12], Marianella Sierra[10,19], Ifeoma Ulasi[13], Bill Wang[10,19], Siu-Fai Lui[14], Vassilios Liakopoulos[15] and Alessandro Balducci[16]; for the World Kidney Day Joint Steering Committee[17]

[1]*Department of Public and Global Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland;*
[2]*Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston,*

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.

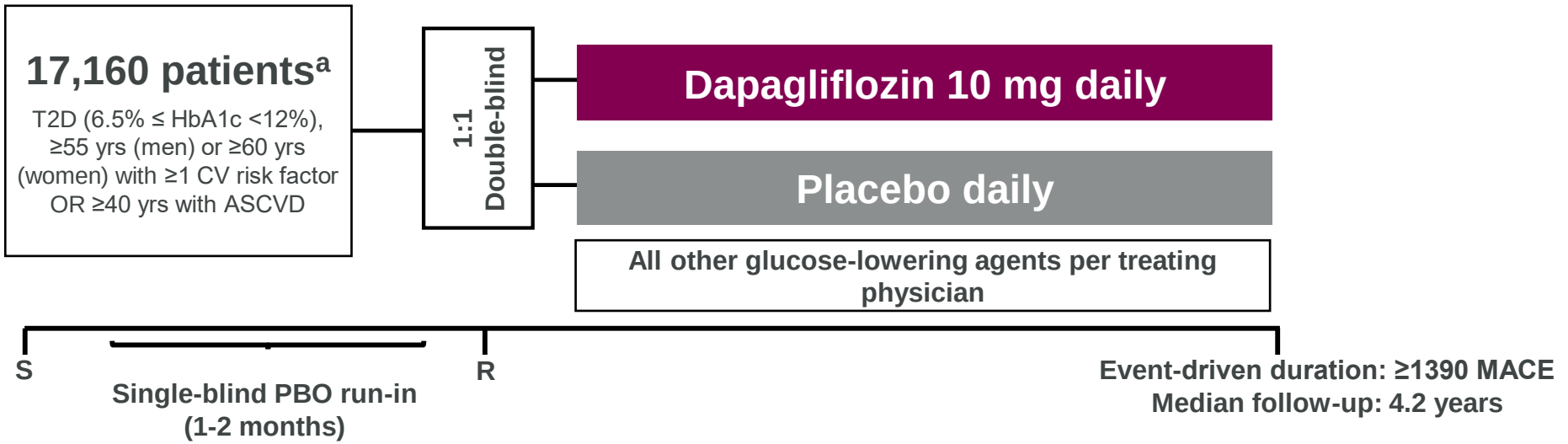
CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced 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.

DECLARE-TIMI 58:

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

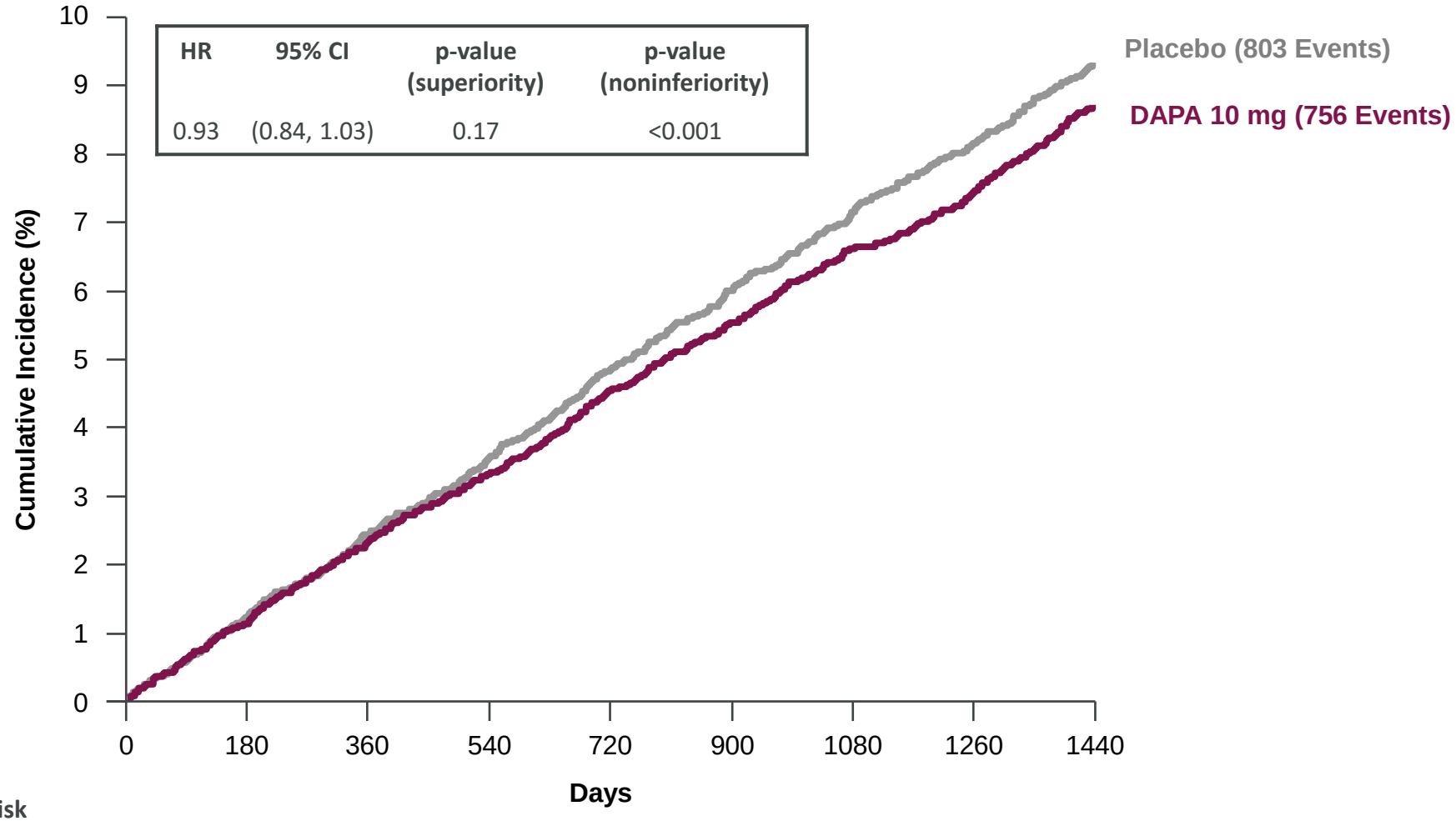
Additional safety endpoints

- 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.

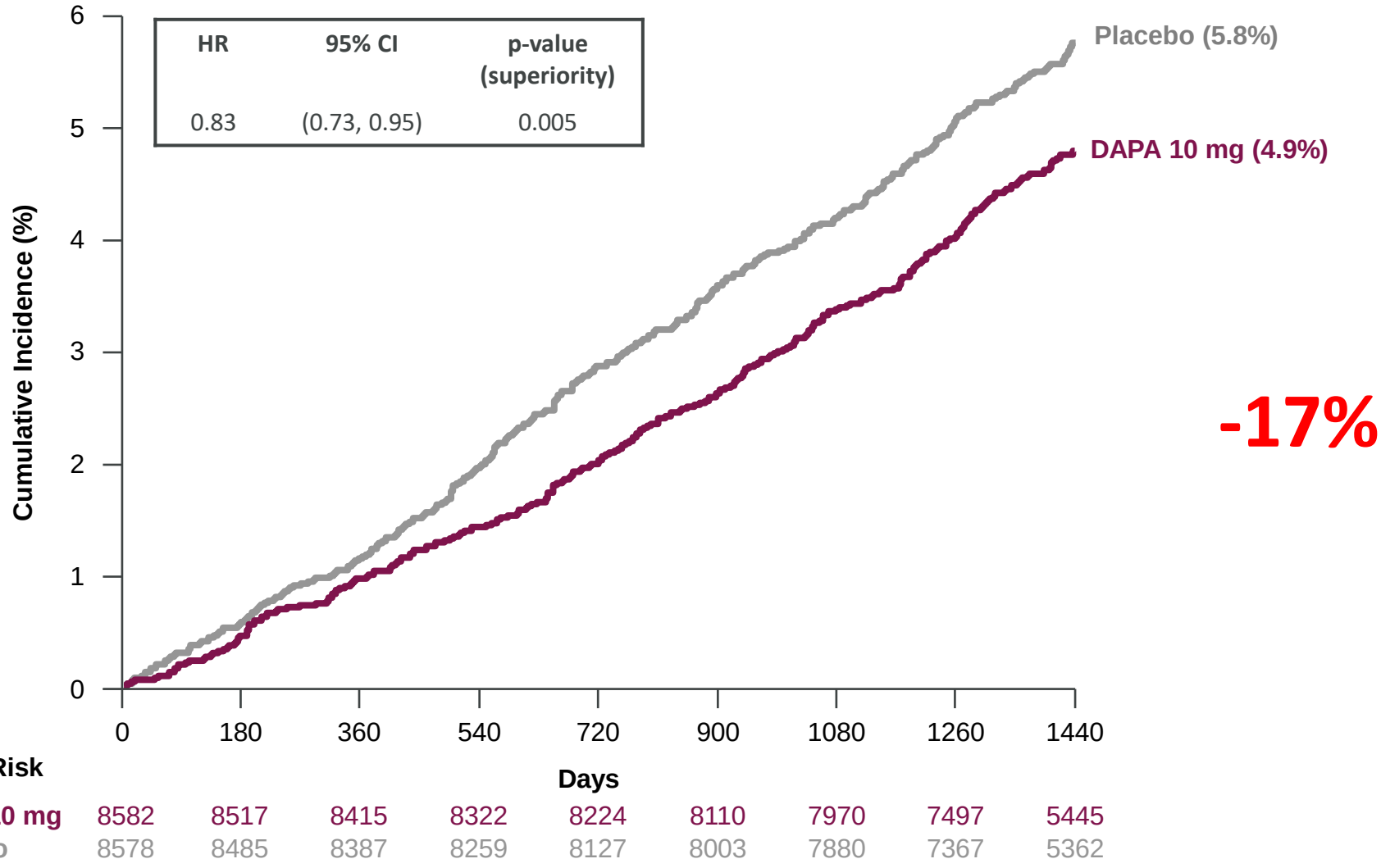
Primary Endpoint: MACE



DAPA = dapagliflozin; HR = hazard ratio; MACE = major adverse cardiovascular events.

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

Primary Endpoint: Composite of hHF or CV Death

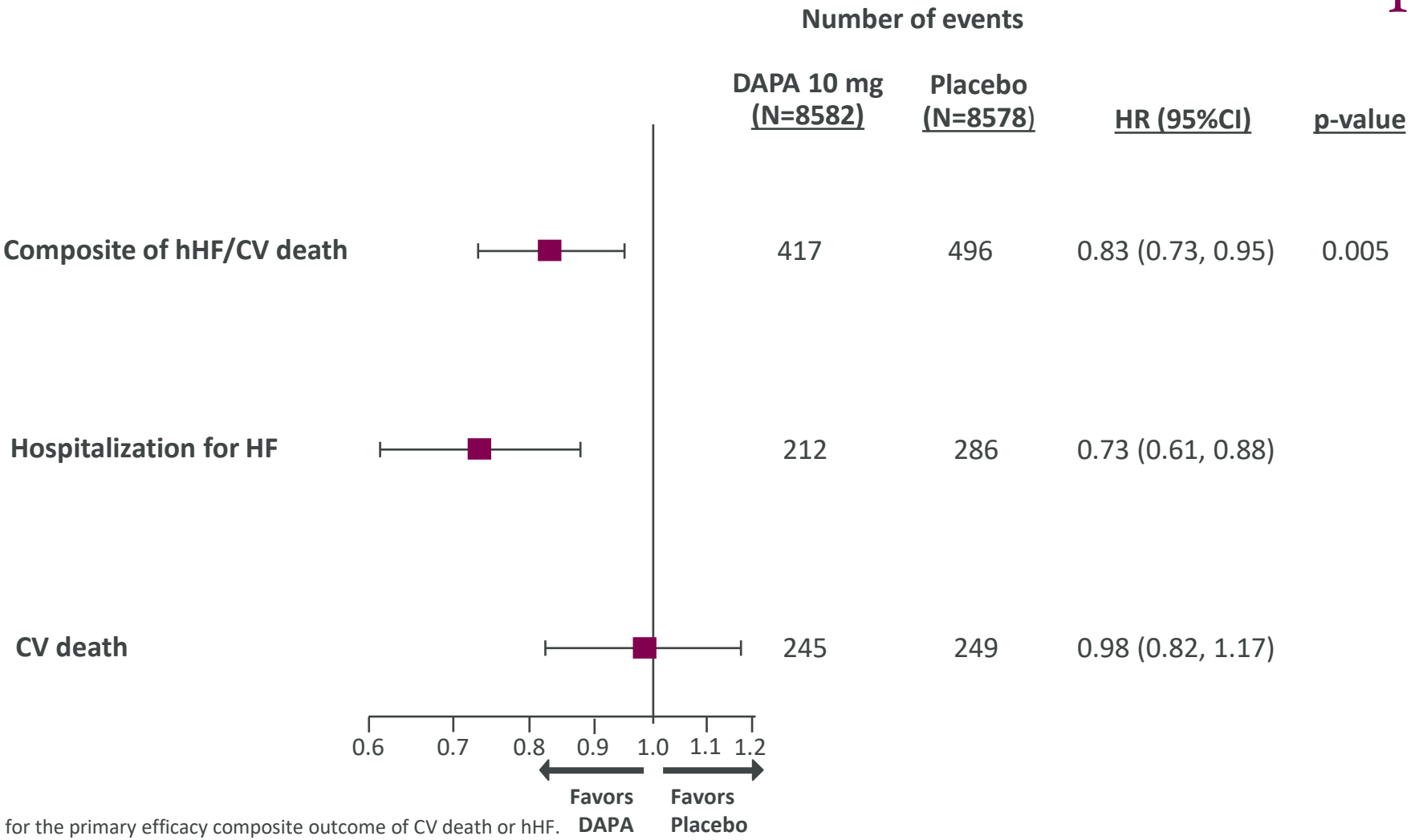


-17%

CV = cardiovascular; DAPA = dapagliflozin; hHF = hospitalization for heart failure; HR = hazard ratio.

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

Primary Endpoint: Composite of hHF or CV Death and the Individual Components



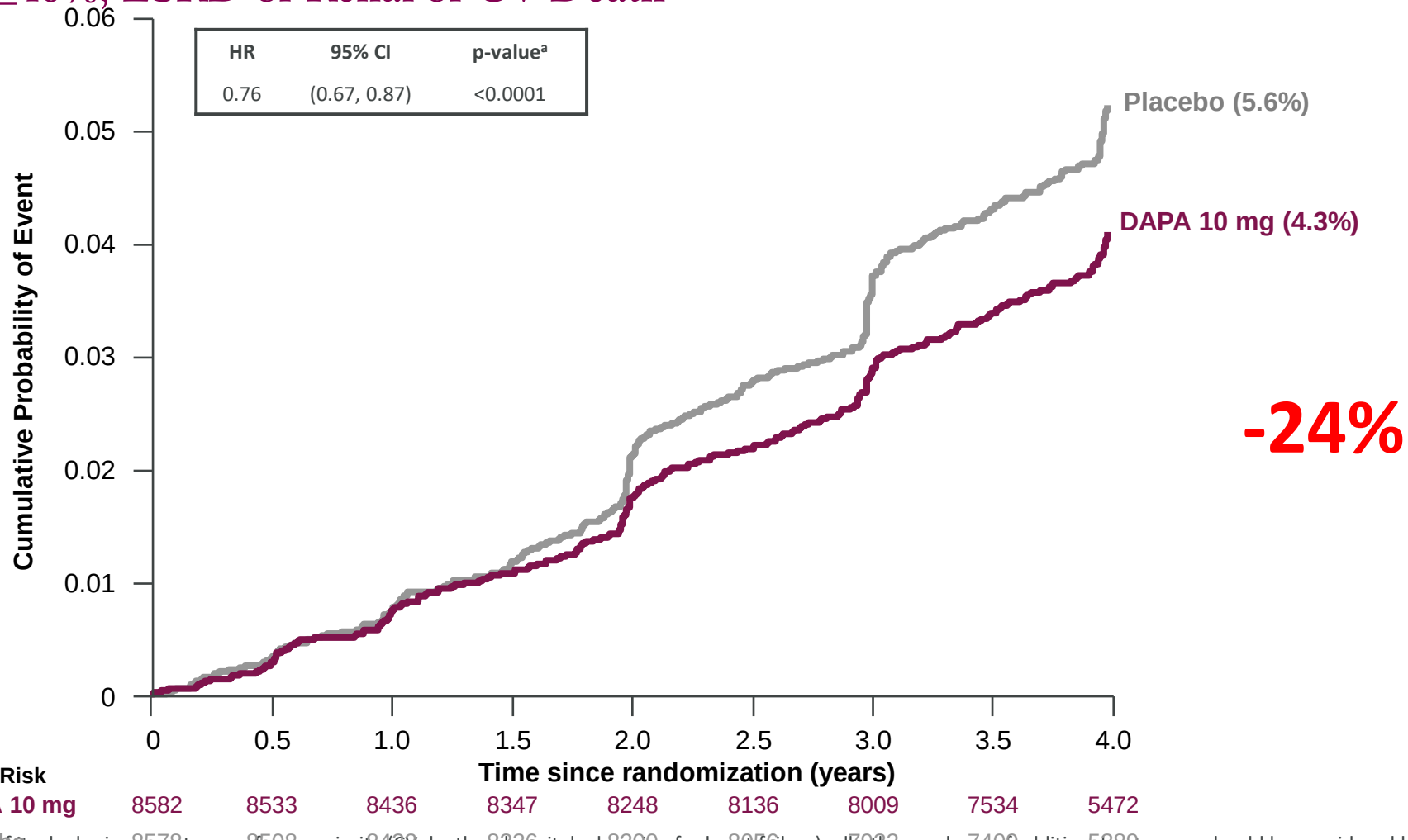
Two-sided p-value is shown for the primary efficacy composite outcome of CV death or hHF.

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

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

Cardiorenal Composite Secondary Outcome[1,2]

Decrease eGFR ≥40%, ESRD or Renal or CV Death



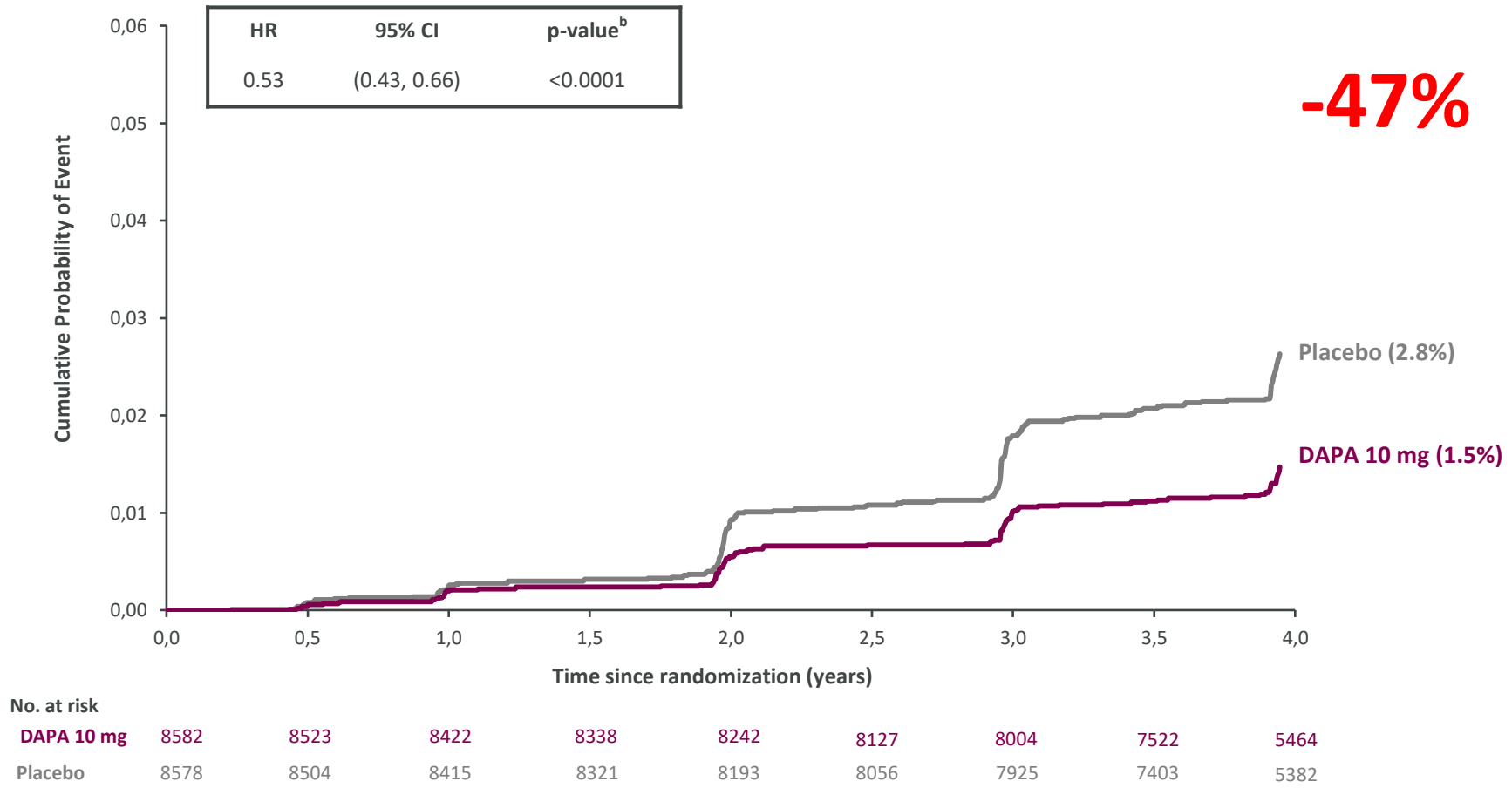
[a]Because the trial met only one of its dual primary outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only. No. at risk is the number of subjects at risk at the beginning of the period.

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

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.

Renal-specific Outcome[a]

Decrease eGFR ≥40%, ESRD or Renal Death



[a]Prespecified exploratory endpoint; [b]Because the trial met only one of its dual primary outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only. No. at risk is the number of subjects at risk at the beginning of the period.

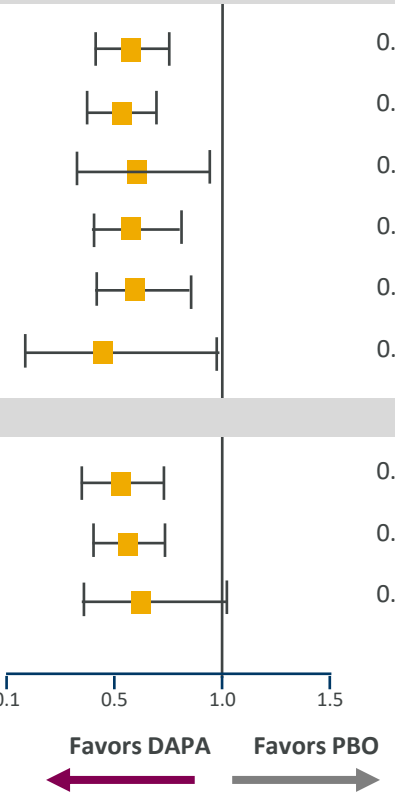
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio.

Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7:606-617.

Renal-specific Outcome[a] by Subgroup:

Decrease eGFR ≥40%, ESRD or Renal Death

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate (4 years)	n/N (%)	KM Event Rate (4 years)	Hazard Ratio (95% CI)	Interaction P value
Baseline CV disease or risk factor						
Established CVD	65/3474 (1.9)	1.9%	118/3500 (3.4)	3.2%	0.55 (0.41-0.75)	0.72
Multiple risk factors	62/5108 (1.2)	1.2%	120/5078 (2.4)	2.3%	0.51 (0.37-0.69)	
History of heart failure	27/852 (3.2)	3.3%	48/872 (5.5)	5.4%	0.58 (0.36-0.92)	0.78
No history of heart failure	100/7730 (1.3)	1.3%	190/7706 (2.5)	2.3%	0.52 (0.41-0.66)	
History of hypertension	122/7769 (1.6)	1.6%	222/7658 (2.9)	2.7%	0.54 (0.43-0.67)	0.41
No history of hypertension	5/813 (0.6)	0.5%	16/920 (1.7)	1.8%	0.36 (0.13-0.98)	
Baseline renal function						
eGFR ≥90 mL/min/1.73 m^2	41/4137 (1.0)	1.0%	79/4025 (2.0)	2.0%	0.50 (0.34-0.73)	0.87
eGFR 60-<90 mL/min/1.73 m^2	65/3838 (1.7)	1.6%	121/3894 (3.1)	2.8%	0.54 (0.40-0.73)	
eGFR <60 mL/min/1.73 m^2	21/606 (3.5)	3.8%	38/659 (5.8)	5.8%	0.60 (0.35-1.02)	



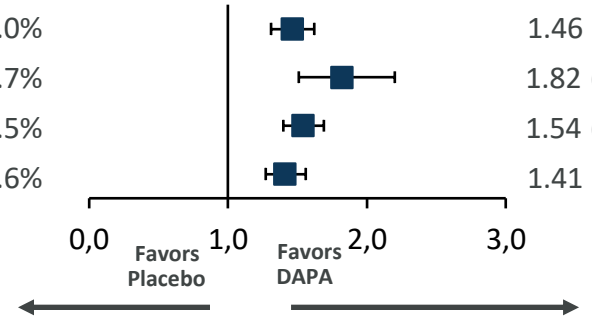
[a]Prespecified exploratory outcome.

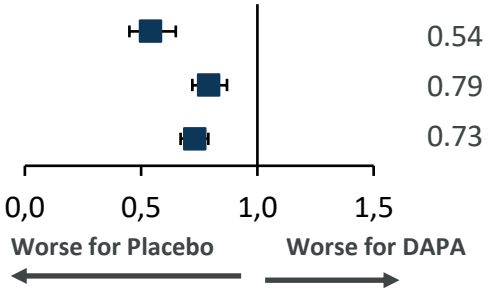
CVD = cardiovascular disease; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; KM = Kaplan Meier; PBO = placebo.

Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7:606-617.

Dapagliflozin had a Favorable Effect on Albuminuria Across Baseline UACR Categories, Including Patients with Normal Albumin Excretion[1,2]

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.9%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.1%	175/575 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.0%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.5%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001
Deterioration from baseline						
Normo/Micro to Macro	181/7836 (2.3)	2.3%	330/7838 (4.2)	4.2%	0.54 (0.45, 0.65)	<0.0001
Normo to Micro/Macro	772/5819 (13.3)	13.3%	959/5825 (16.5)	16.3%	0.79 (0.72, 0.87)	<0.0001
Normo to Micro/Macro or Micro to Macro	928/7836 (11.8)	11.9%	1243/7838 (15.9)	15.8%	0.73 (0.67, 0.79)	<0.0001





Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

DAPA = dapagliflozin; KM = Kaplan-Meier; Macro = macroalbuminuria; Micro = microalbuminuria; ; Normo = normoalbuminuria; UACR = urinary albumin-to-creatinine ratio.

1. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA. 244-OR. 2. Mosenzon O et al. *Diabetes Care*. 2021;44:1-11.

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.

Summary: DECLARE Renal Outcomes

- Dapagliflozin appears to reduce the risk for the onset and progression of renal dysfunction and kidney disease in T2D[1]
- **Dapagliflozin reduced the risk for the renal-specific outcome by 47% compared to placebo[1]**
- **Benefit of dapagliflozin on the renal-specific outcome is consistent regardless of baseline eGFR, degree of proteinuria or ACEi/ARB use[1]**
- **The progressive decline in eGFR was attenuated over 4 years with dapagliflozin, including in patients with normal renal function or mild renal impairment[1]**
- The prevalence of fast decline was less in the dapagliflozin arm regardless of prespecified subgroups[2]
- Dapagliflozin increased the likelihood that patients transitioned from a worse to better albuminuria classification; **dapagliflozin decreased the likelihood of worsening albuminuria[3,4]**

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

1. Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7:606-617; 2. Raz I et al. Presented at ADA 80th Scientific Sessions Virtual Meeting; June 12-16, 2020; 3. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR; 4. Mosenzon O et al. *Diabetes Care*. 2021;44:1-11.

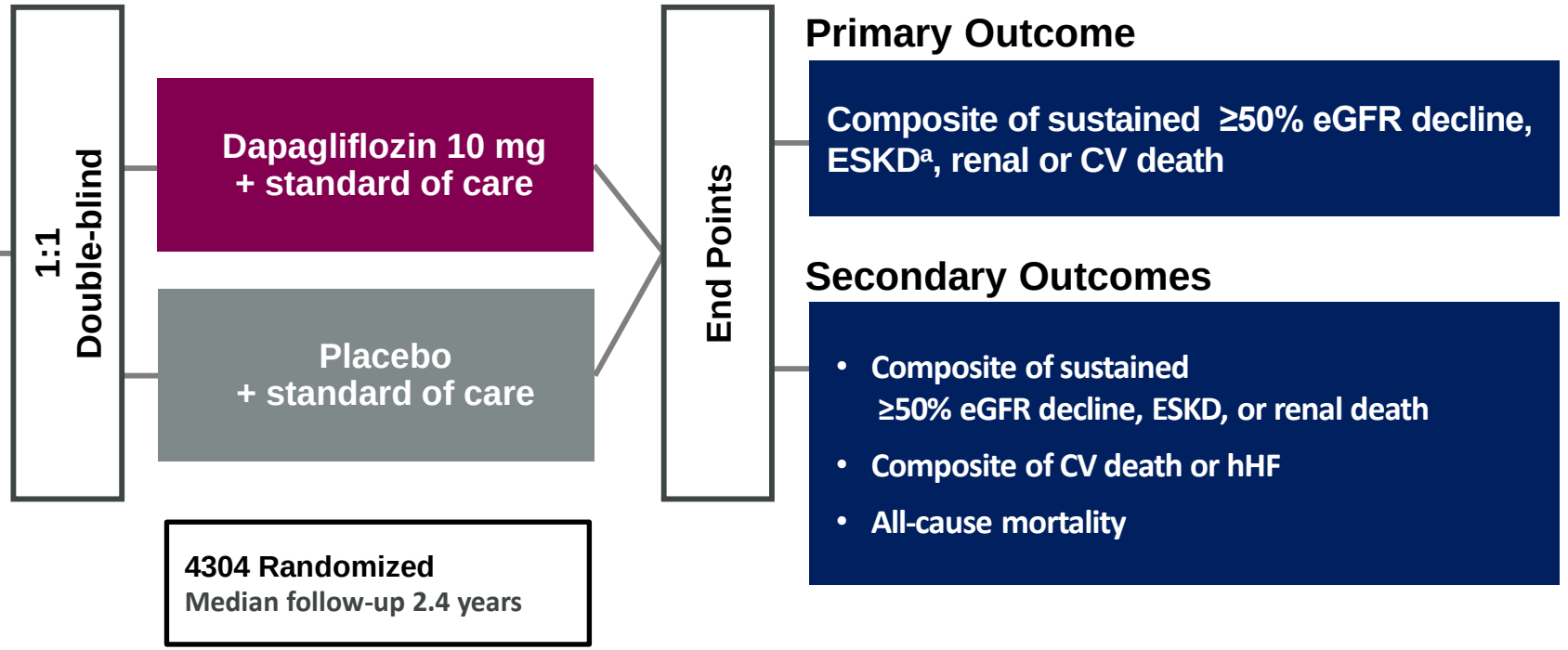
DAPA-CKD:

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

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

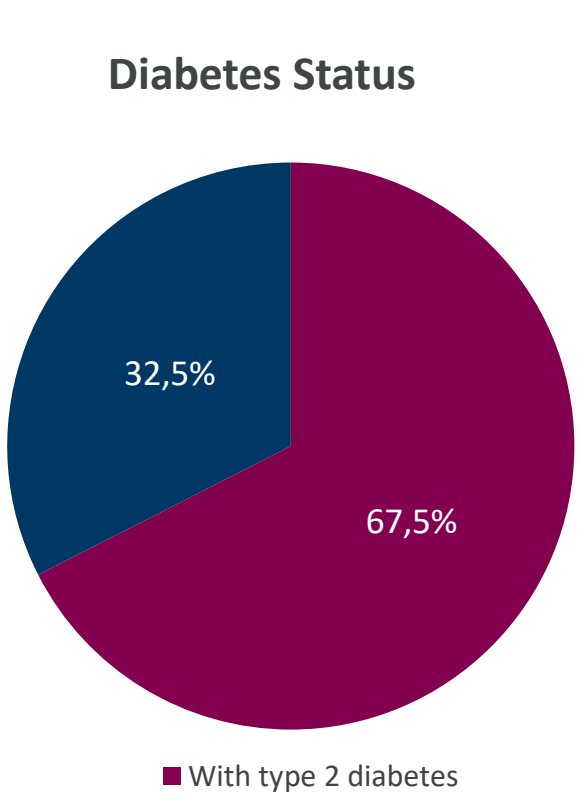


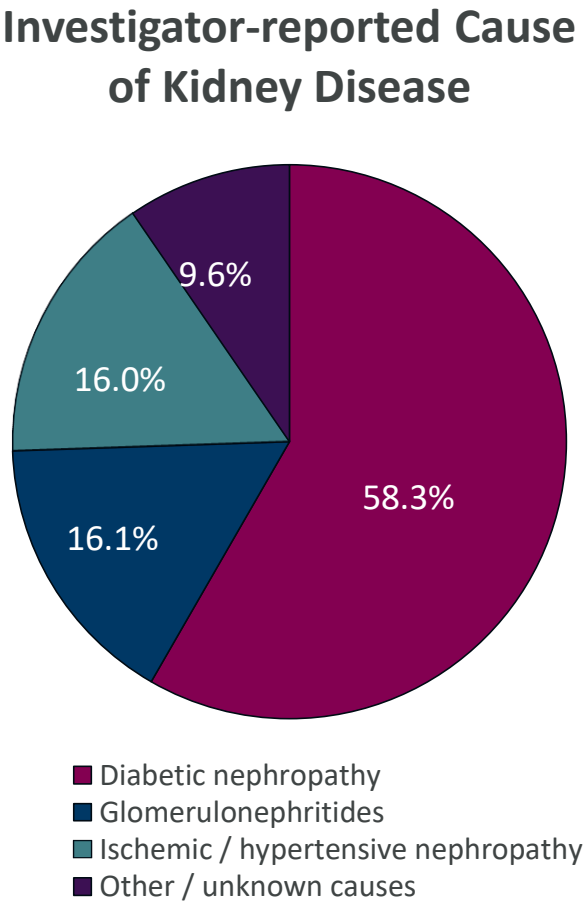
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

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.

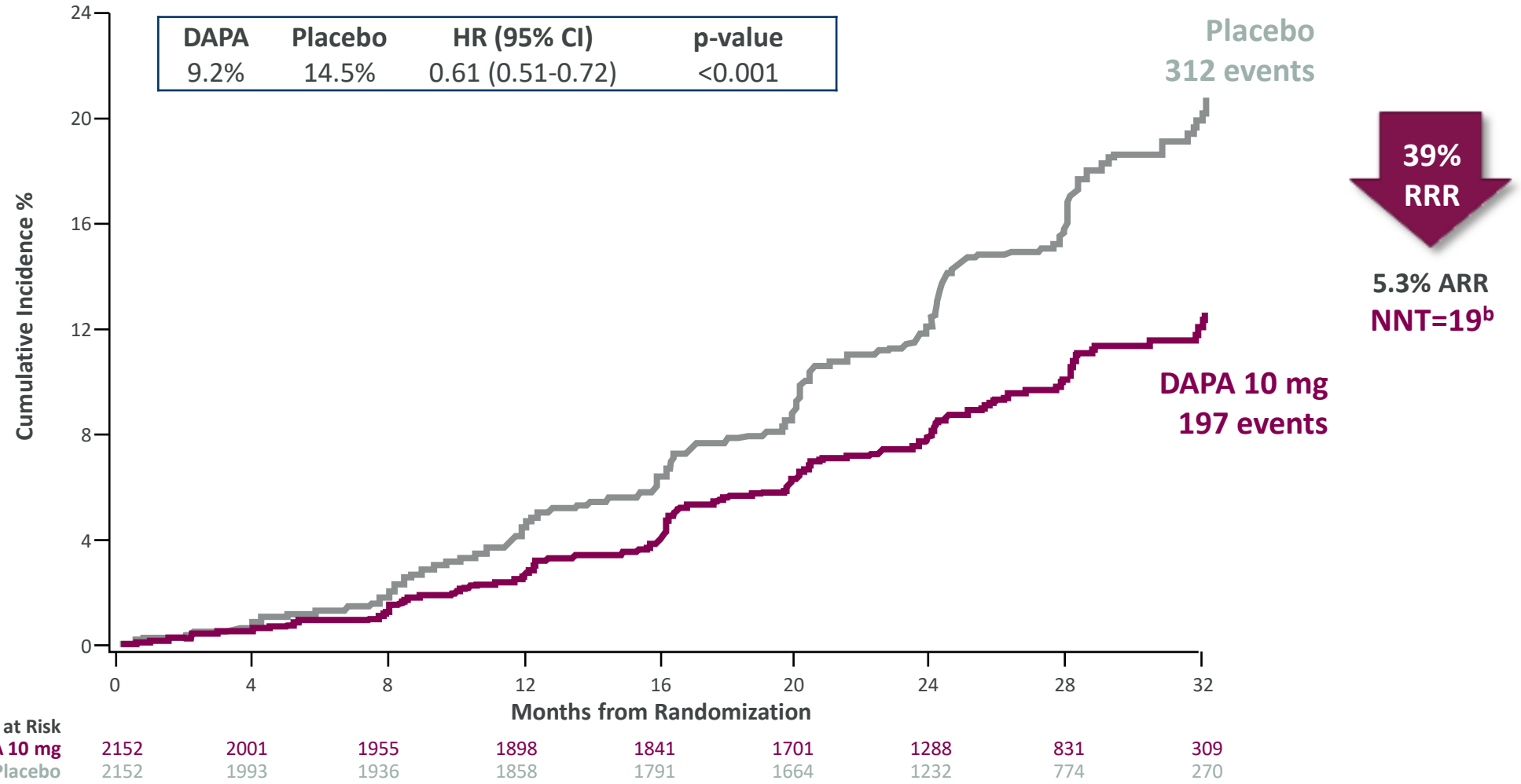
Diabetes Status and Investigator-reported Cause of Kidney Disease at Baseline





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

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



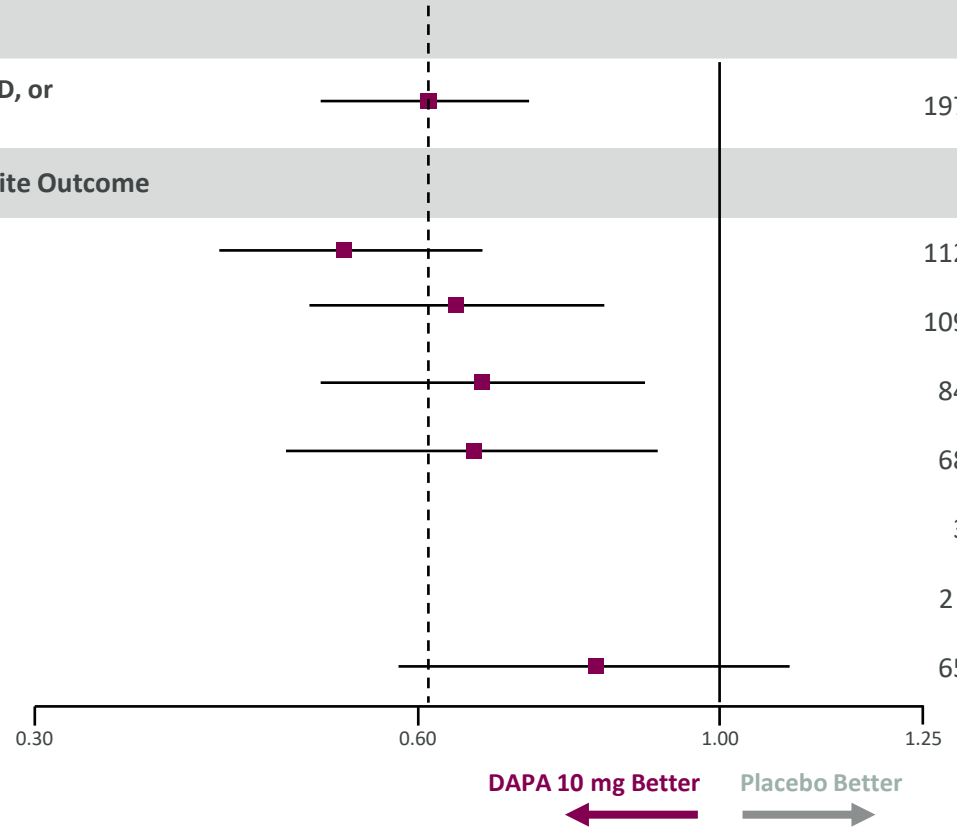
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2];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



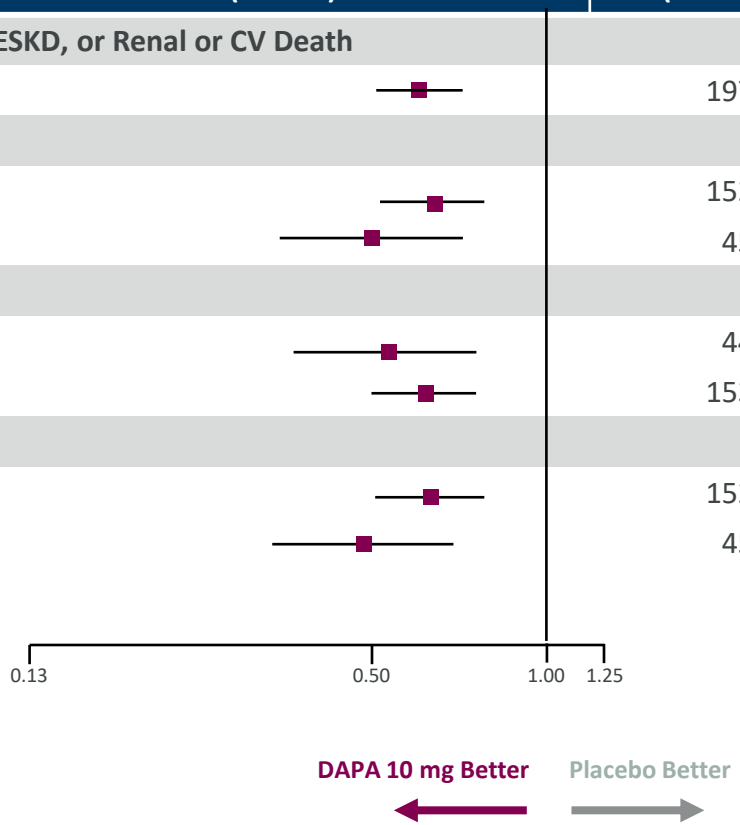
[a]There were 69 endpoint events for dapagliflozin and 100 endpoint events for placebo for the combined chronic dialysis and renal transplantation endpoint (HR 0.66; 95% CI 0.49, 0.90).

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				
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)	

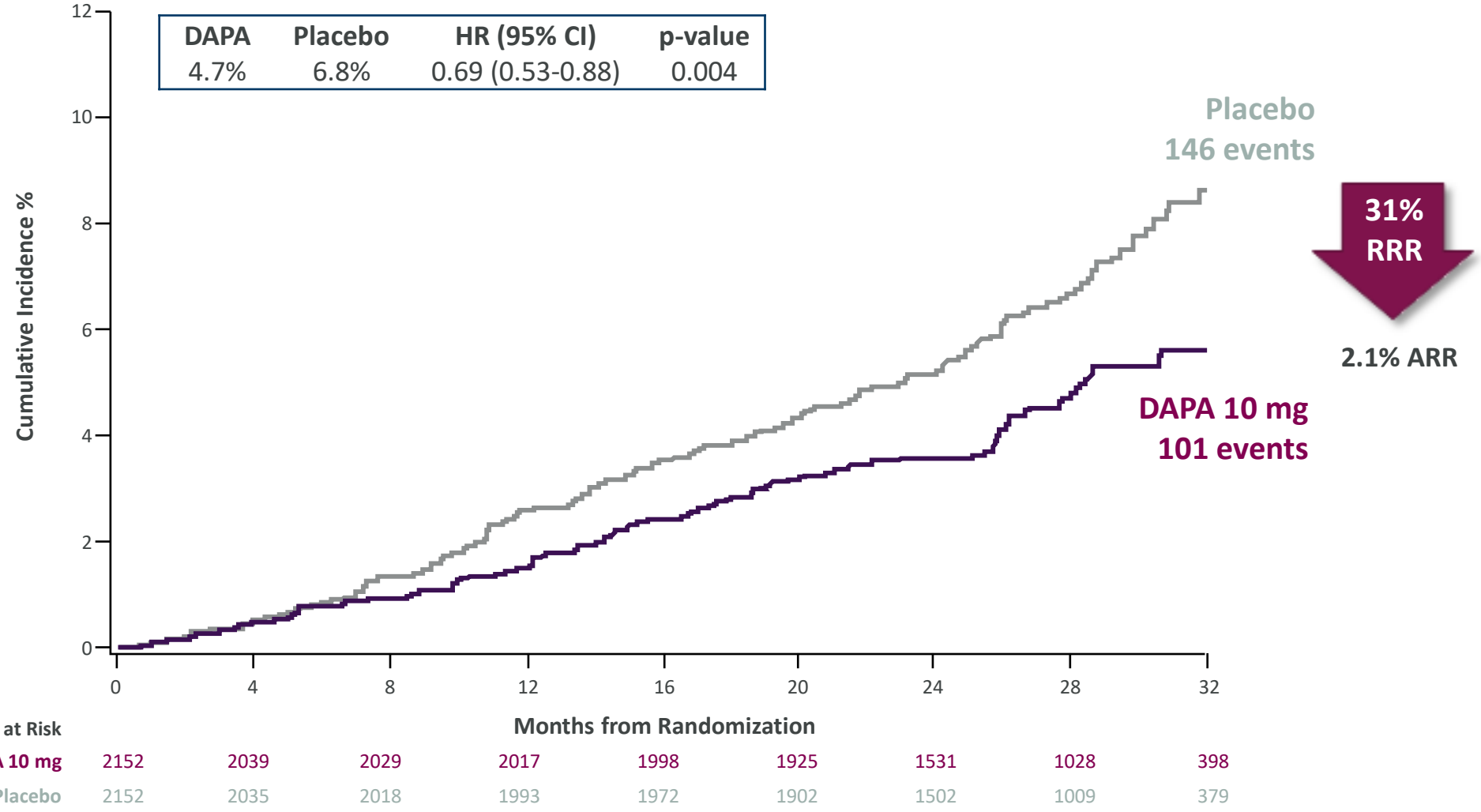


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

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

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

DAPA	Placebo	HR (95% CI)	p-value
4.7%	6.8%	0.69 (0.53-0.88)	0.004

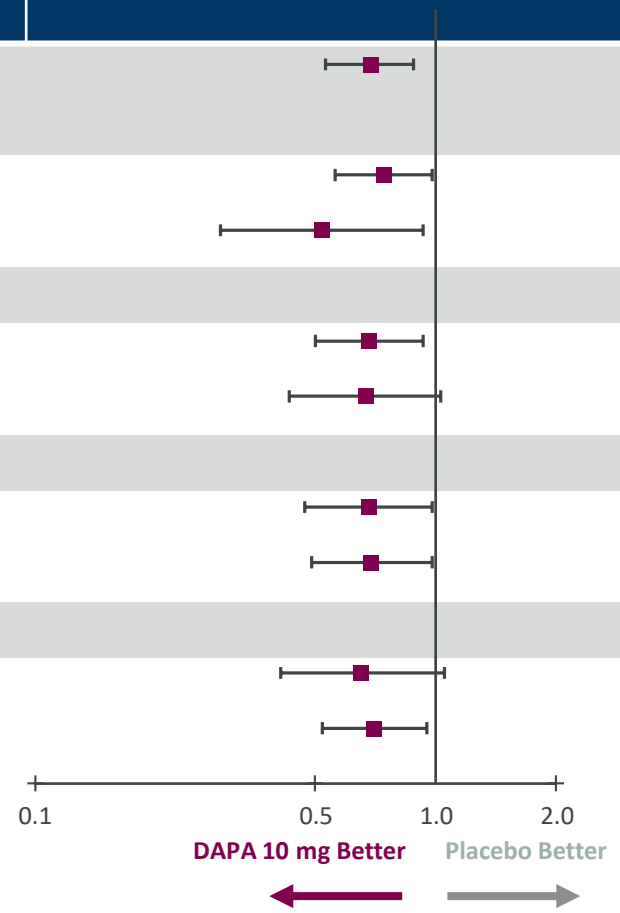


ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

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 Outcome – All-cause Mortality: Treatment Benefit Consistent Across Prespecified Subgroups[1]

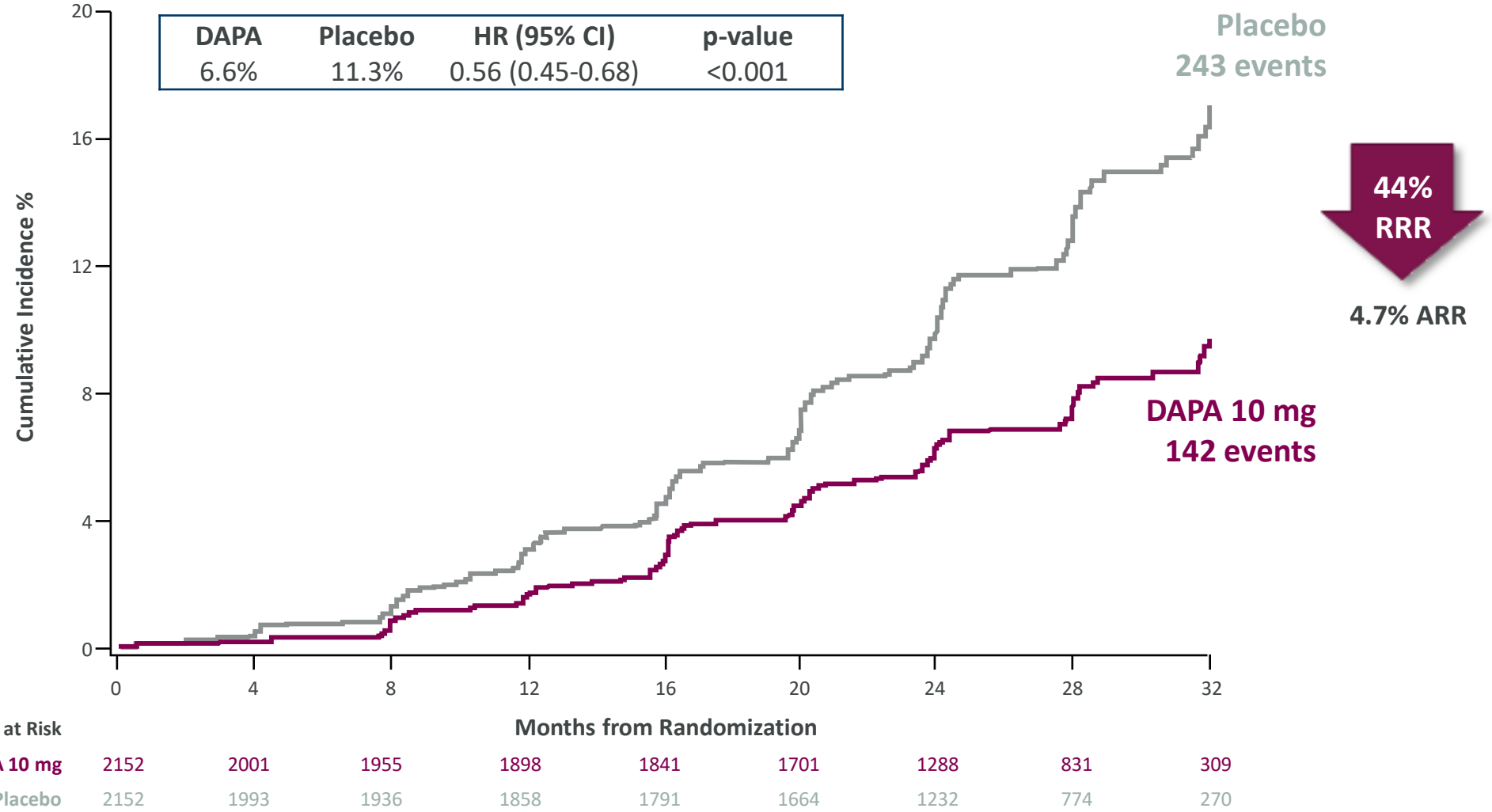
	No. of Patients/Total No.		Events per 100 Patient-years		Hazard Ratio (95% CI)	p-value for Interaction
	DAPA	Placebo	DAPA	Placebo		
Overall	101/2152	146/2152	2.2	3.2	0.69 (0.53, 0.88)	
Type 2 Diabetes						
Yes	84/1455	113/1451	2.6	3.5	0.74 (0.56, 0.98)	0.250
No	17/697	33/701	1.2	2.3	0.52 (0.29, 0.93)	
eGFR						
<45 mL/min/1.73m^2	67/1272	94/1250	2.5	3.6	0.68 (0.50, 0.93)	0.963
≥45 mL/min/1.73m^2	34/880	52/902	1.7	2.6	0.67 (0.43, 1.03)	
Urinary Albumin-to-creatinine Ratio						
≤1000	46/1104	70/1121	1.9	2.7	0.68 (0.47, 0.98)	0.915
>1000	55/1048	76/1031	2.4	3.5	0.69 (0.49, 0.98)	
Systolic Blood Pressure						
≤130	29/793	42/749	1.7	2.7	0.65 (0.41, 1.05)	0.825
>130	72/1359	104/1403	2.4	3.4	0.70 (0.52, 0.95)	



DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate.

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

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.

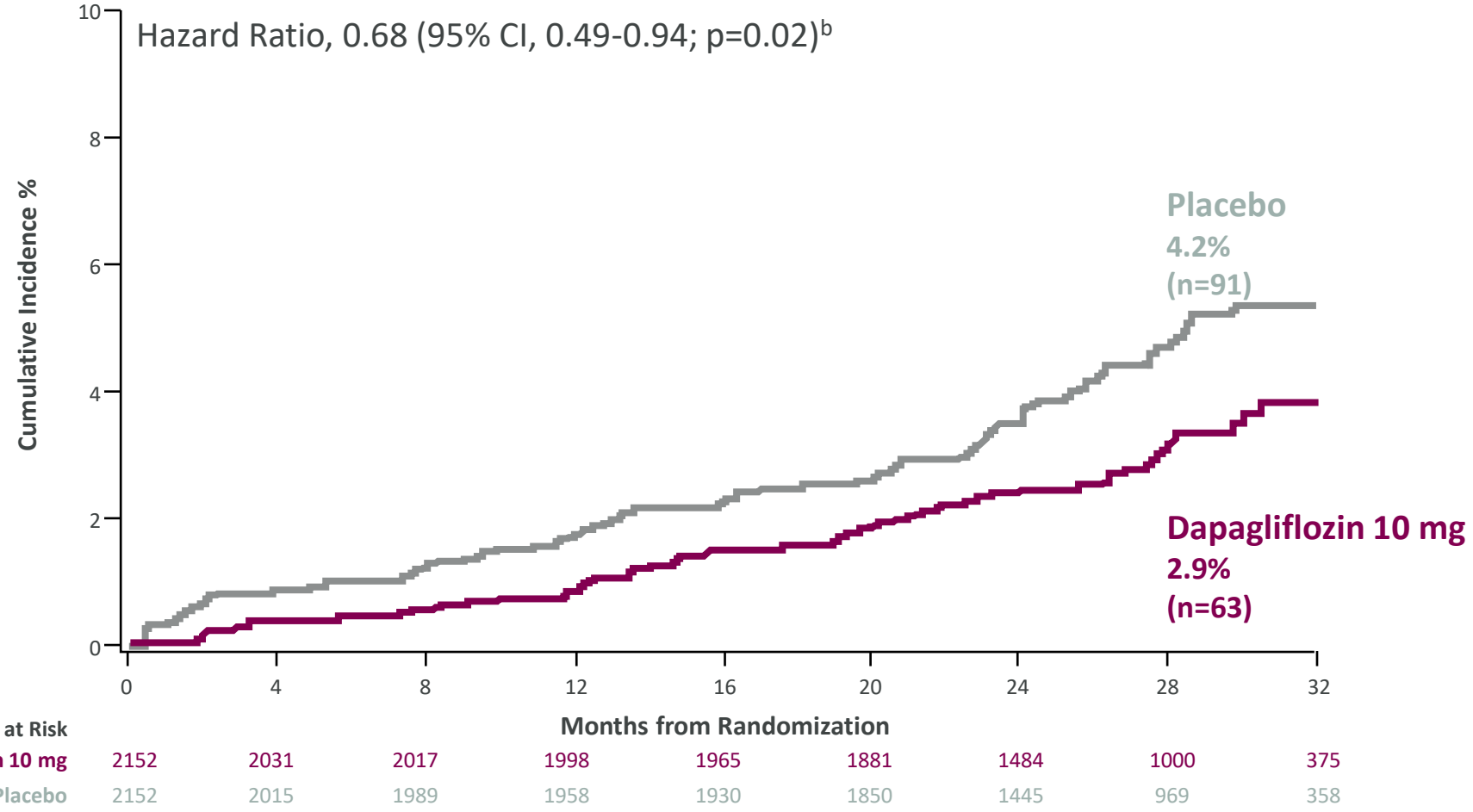
Safety Outcomes[1]

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]



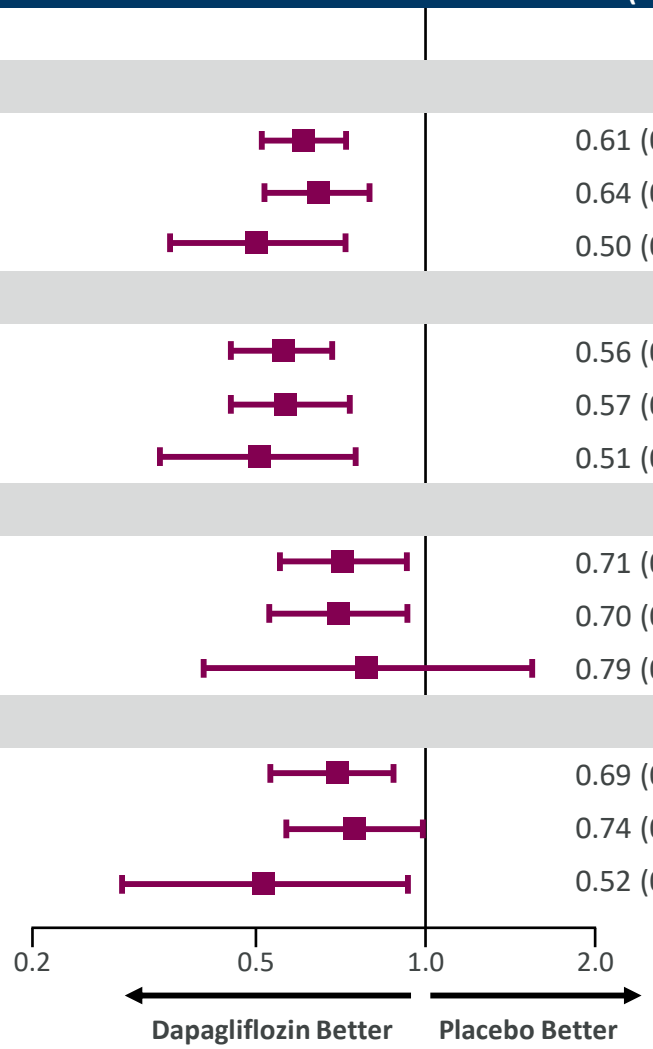
[a]Pre-specified exploratory endpoint. Defined as doubling of serum creatinine since last central laboratory result. Referred to as "abrupt decline" in the publication; [b]Subdistribution HR, 0.69; 95% CI, 0.50 to 0.95; p=0.02 using the Fine-Gray model which accounted for the competing risk of death.

AKI = acute kidney injury; CI = confidence interval.

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

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)	



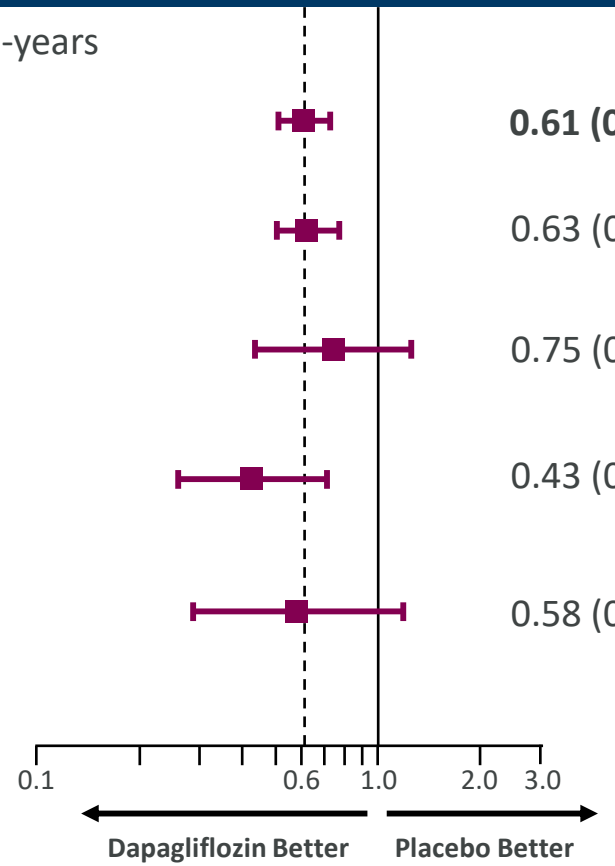
CV = cardiovascular; hHF = hospitalization for heart failure; T2D = type 2 diabetes.

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

Primary Outcome According to Underlying Cause of Kidney Disease

Composite outcome of sustained ≥50% eGFR decline, ESKD, or renal or cardiovascular death

Primary Outcome	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patents/total no.		Events[a]/100 patient-years			
Overall	**197/2152**	**312/2152**	**4.6**	**7.5**	**0.61 (0.51, 0.72)**	
Diabetic nephropathy	139/1271	207/1239	5.4	8.5	0.63 (0.51, 0.78)	0.53
Ischemic/hypertensive nephropathy	24/324	35/363	3.8	4.9	0.75 (0.44, 1.26)	
Glomerulonephritis	22/343	49/352	3.4	7.5	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	2.9	5.5	0.58 (0.29, 1.19)	



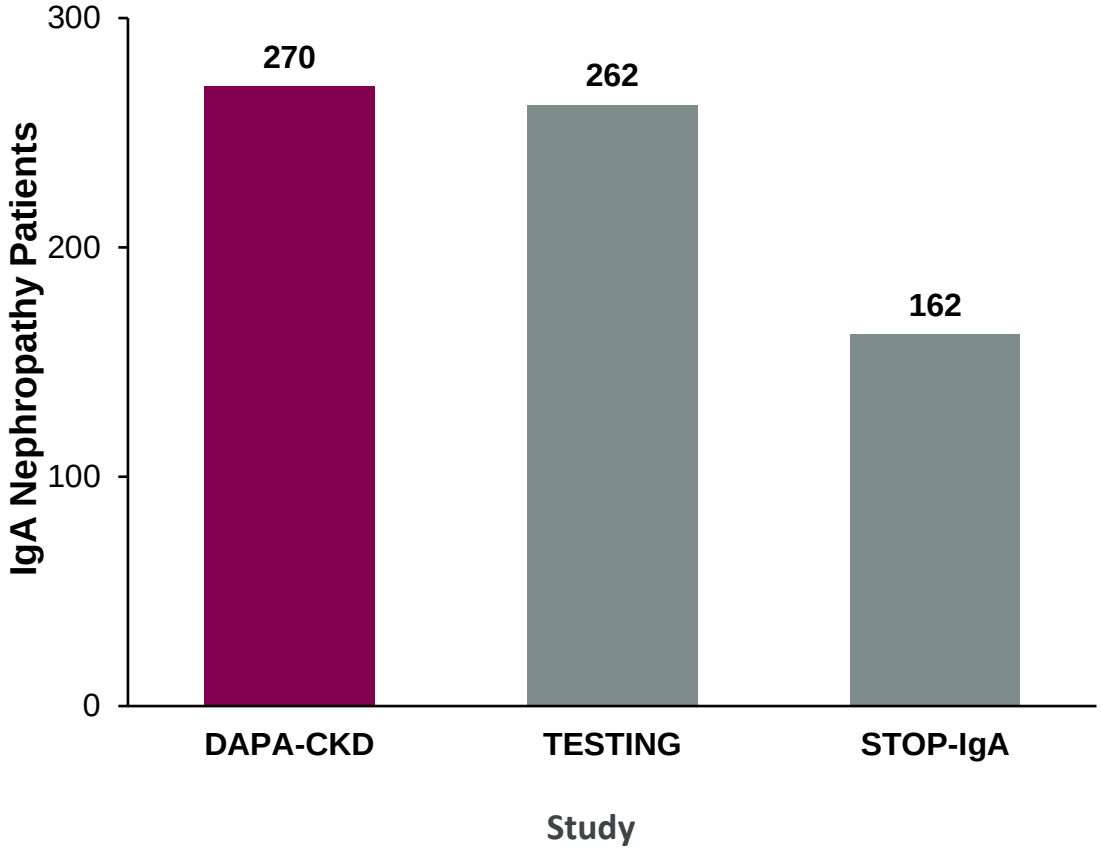
[a] Event data are numbers of patients with an outcome event/total patients.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.

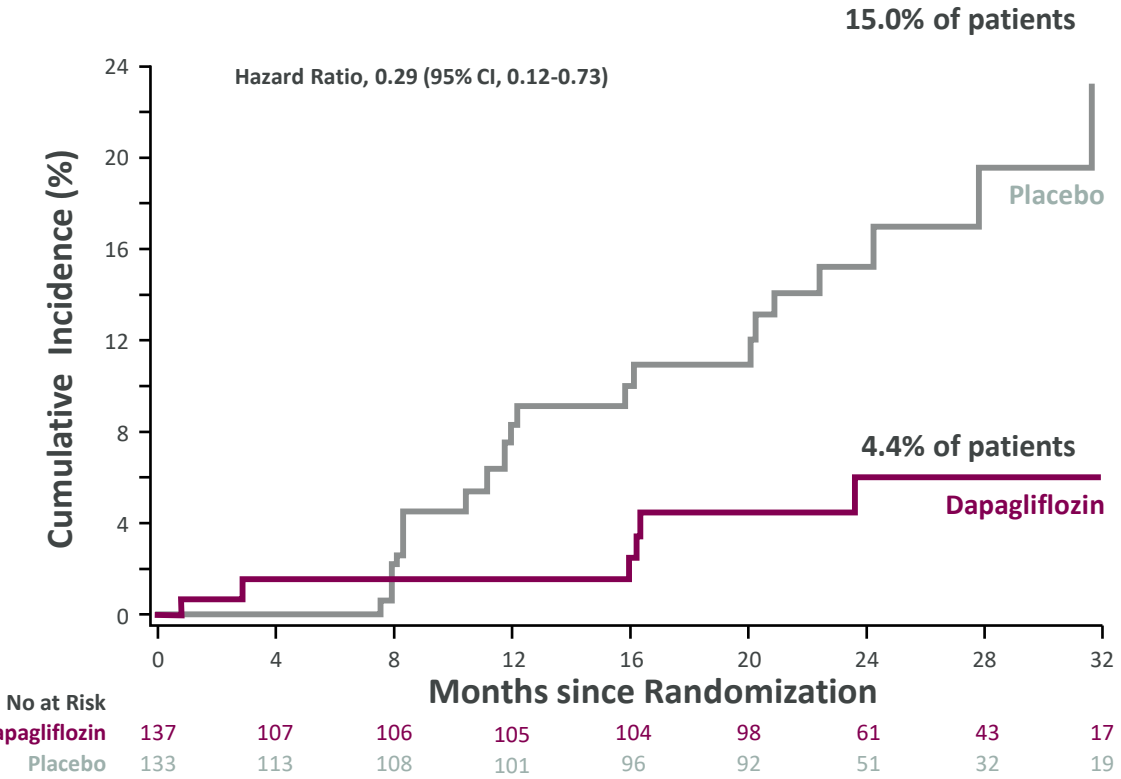
Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31.

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]

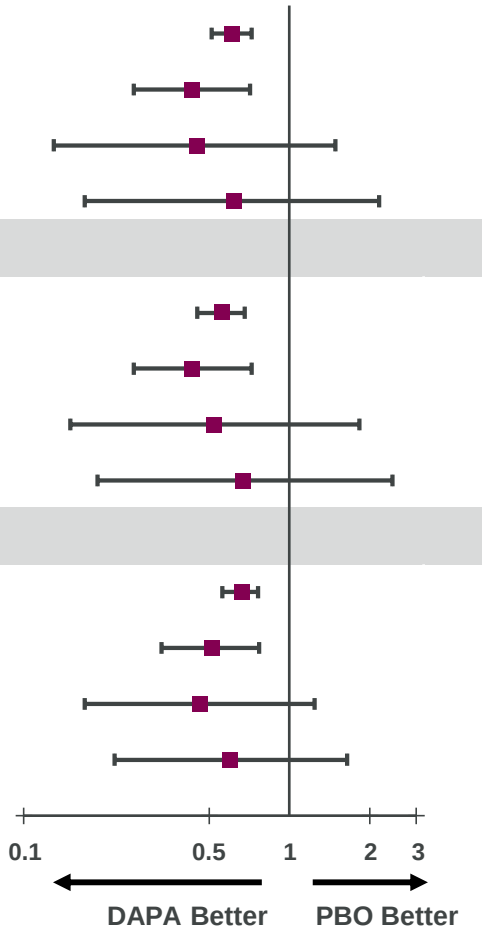


CKD = chronic kidney disease; IgA = immunoglobulin A

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.

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)



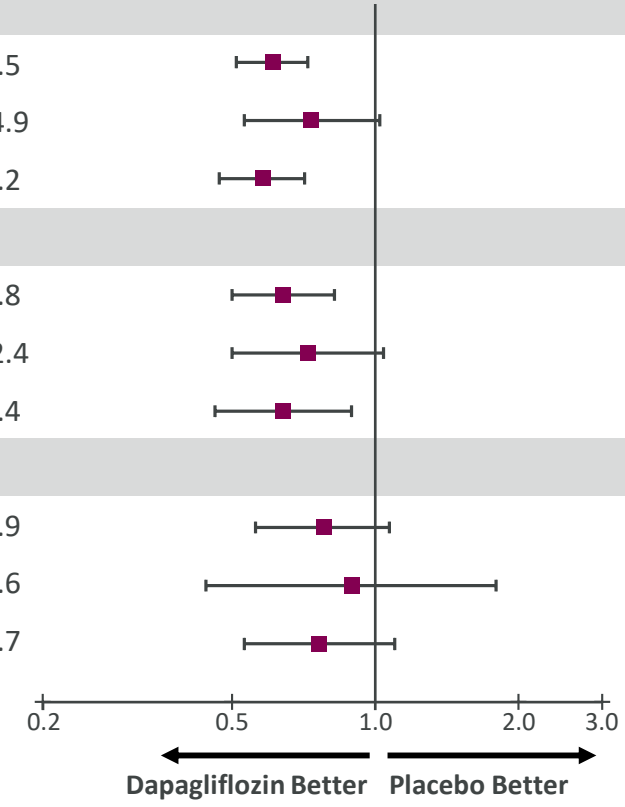
[a]Includes patients with biopsy-confirmed FSGS (n=104) and those classed as FSGS but without biopsy confirmation (n=11).

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

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)	



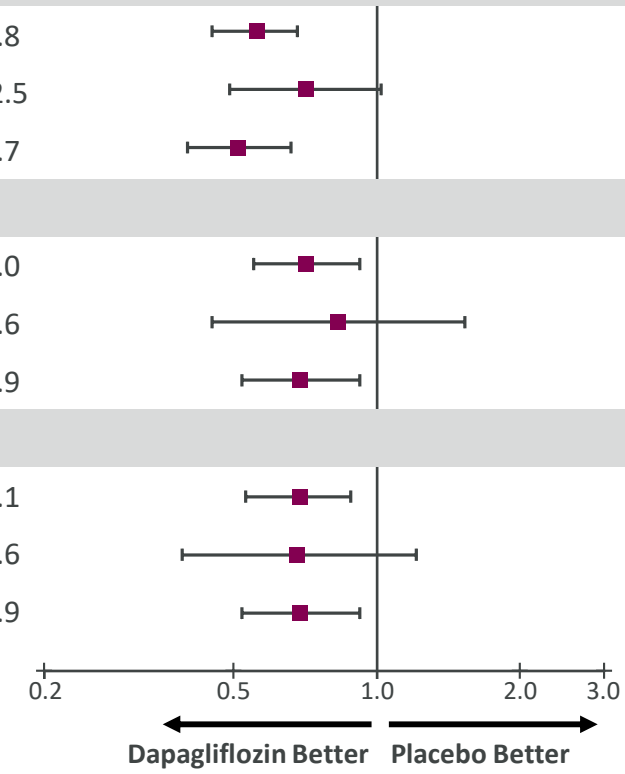
NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2

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

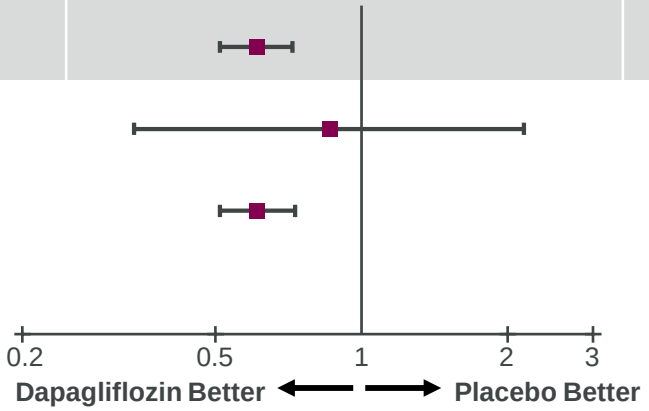
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of patients/ total no.		Events/100 patient-years			
Kidney composite outcome: ≥50% eGFR decline, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	9.2	12.5	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.

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)	



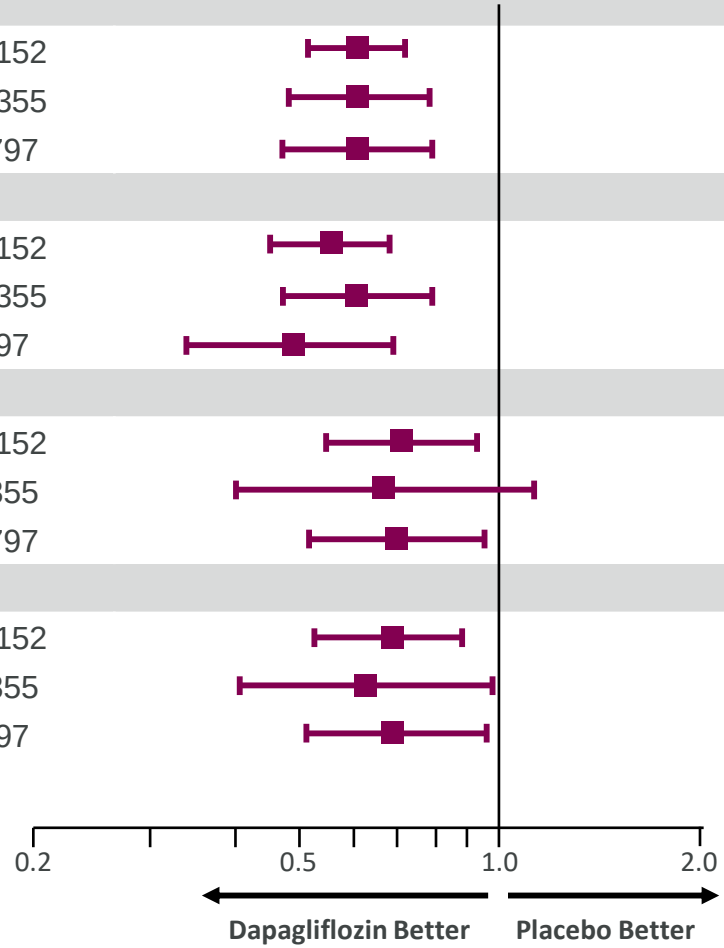
[a]Sustained ≥50% eGFR decline, ESKD, renal death, or CV death.

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 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.

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.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