Antonio Cardarelli
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

Outcome cardiovascolari e renali nel paziente con cardiopatia ischemica trattato con SGLT2i

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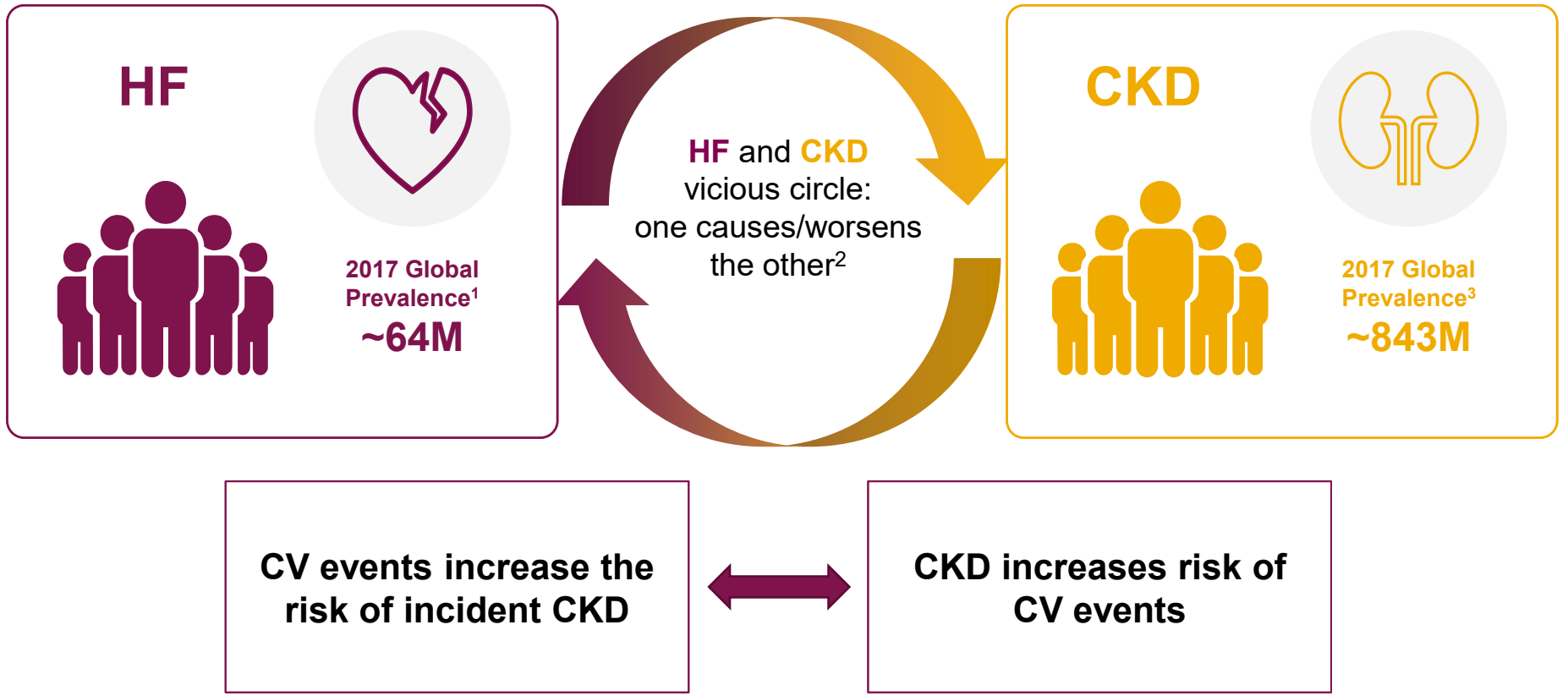
The Cardio-Renal Syndrome

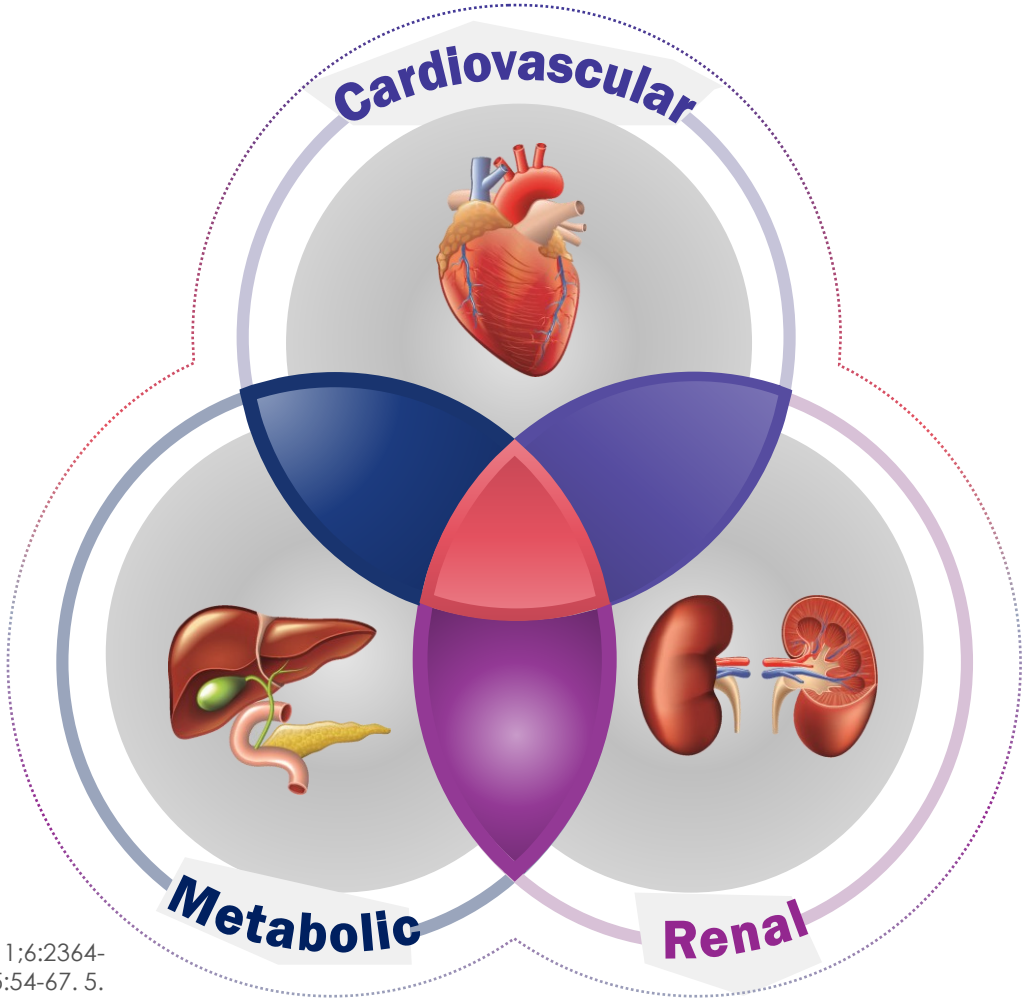


CKD = chronic kidney disease; HF = heart failure; M = million

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Ronco C et al. *J Am Coll Cardiol.* 2008;52:1527-1539; 3. Jager KJ et al. *Nephrol Dial Transplant*. 2019;34:1803-1805

Dysfunction of the heart, kidneys, or metabolism may contribute to the dysfunction of the others[1,2]

- Disorders affecting the CRM systems share many of the same risk factors[3]
- Dysfunction in one system can set off a cascade of multisystem dysfunction[4]
- This can lead to interrelated diseases such as T2DM, CV disease, HF, and CKD, which in turn lead to an increased risk of CV death[5]

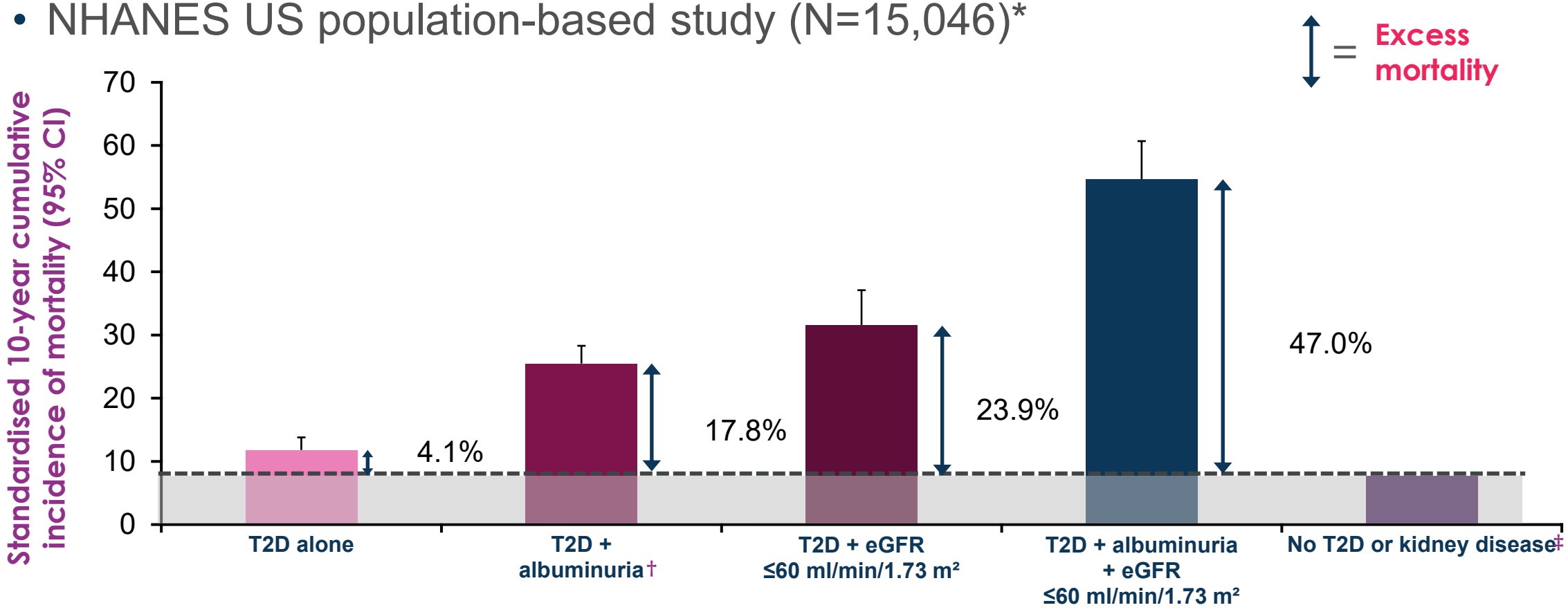


CV, cardiovascular; HF, heart failure; T2DM, type 2 diabetes mellitus.

1. García-Donaire JA, et al. *Int J Nephrol*. 2011;2011:975782. 2. Thomas G, et al. *Clin J Am Soc Nephrol*. 2011;6:2364-2373. 3. Sarafidis PA, et al. *J Cardiometab Syndr*. 2006;1:58-65. 4. Ronco C, et al. *Contrib Nephrol*. 2010;165:54-67. 5. Leon BM, et al. *World J Diabetes*. 2015;6:1246-1258.

The coexistence of T2D and kidney disease is associated with increased mortality

- NHANES US population-based study (N=15,046)*

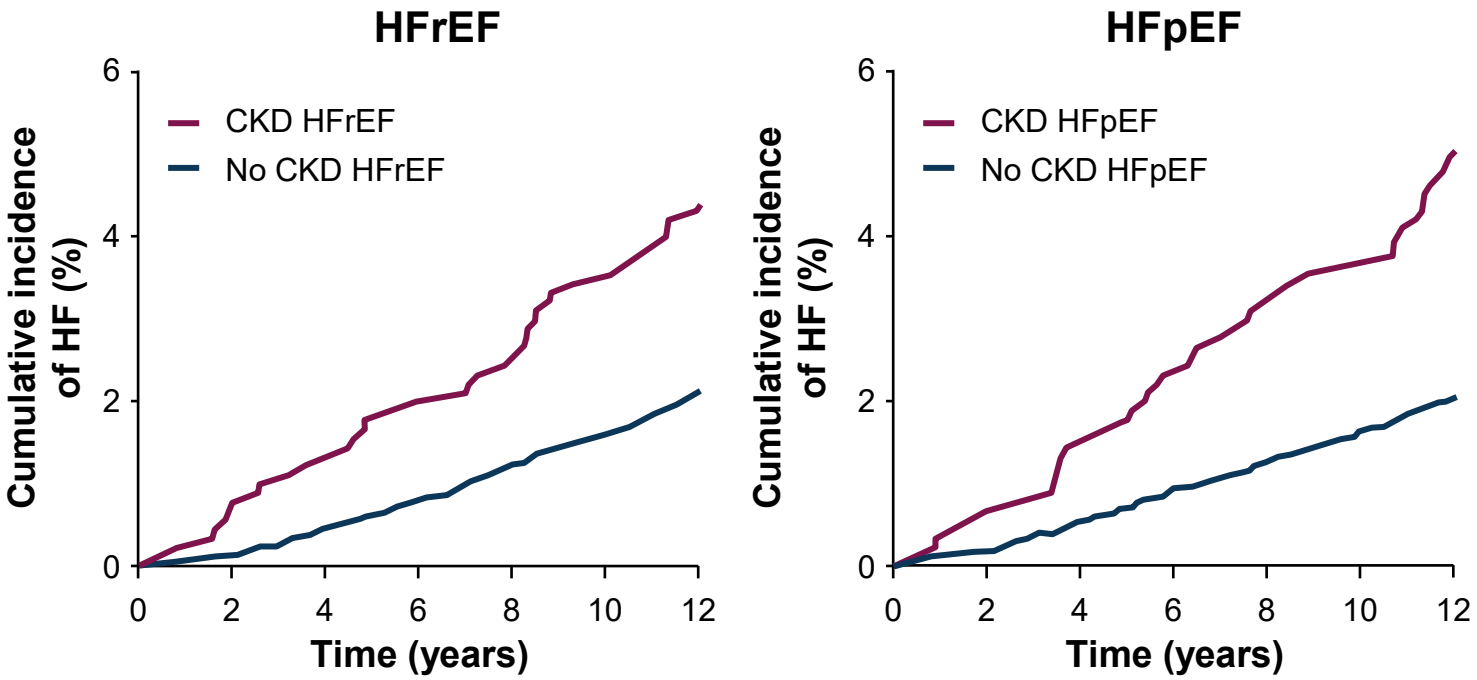


Percentages indicate absolute excess mortality above the reference group (individuals with no T2D or kidney disease). *Adults aged ≥20 years with diabetes participating in NHANES from 1988 to 2014; †Albuminuria defined as urinary albumin/creatinine ratio ≥30 mg/g; ‡Kidney disease defined as albuminuria (urinary albumin/creatinine ratio ≥30 mg/g), impaired GFR (eGFR ≤60 ml/min/1.73 m2) or both. (e)GFR, (estimated) glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; NR, not reported; T2D, type 2 diabetes

Afkarian M *et al. J Am Soc Nephrol* 2013;24:302

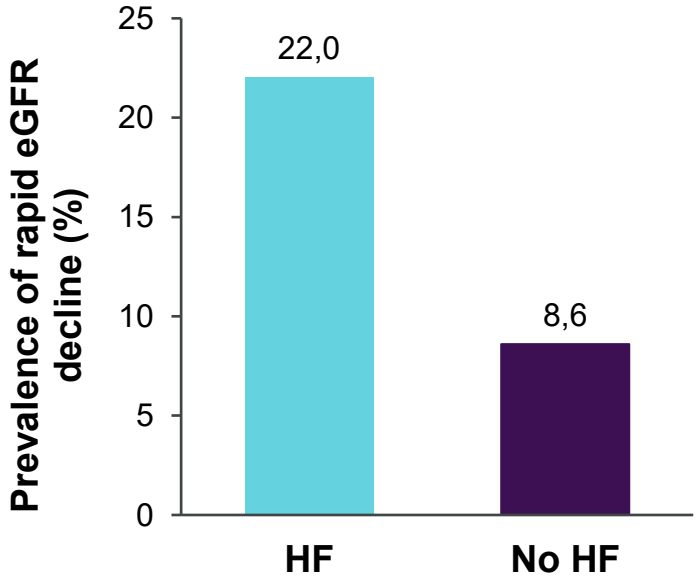
CKD and HF Are Interconnected: CKD Is Associated With Increased Risk of HF and Conversely HF Is Associated With Risk of eGFR Decline

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.

Presence of CKD is commonly associated with the development of fatal CV outcomes

- Older patients[a] with CKD are 6 times more likely to die of CV disease than to advance to ESKD and dialysis[b]

[a] ≥65 years of age. [b] During median 9.7 years of follow-up. KRT, kidney replacement therapy.
Dalrymple L, et al. *J Gen Intern Med*. 2011;26:379-385.

Diagnosis of CKD relies on assessment of kidney damage and/or function

Early-stage kidney disease is usually asymptomatic, requiring laboratory tests for detection[1]

Guideline-recommended laboratory tests to evaluate and stage kidney disease include[2]

eGFR
Index of kidney function

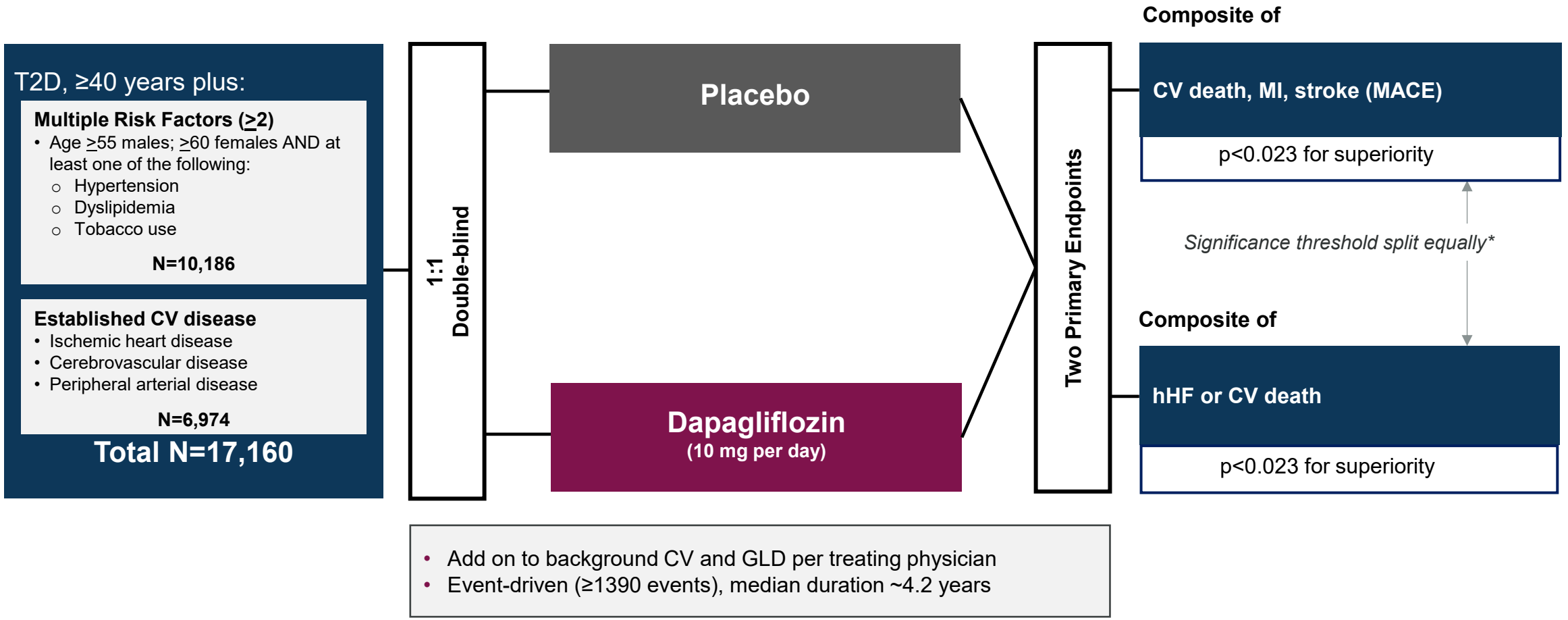
Albuminuria (UACR)
Marker of kidney damage

UACR and eGFR should be assessed annually in all patients with T2D regardless of treatment, and twice annually in patients with UACR >30mg/g and/or eGFR <60 ml/min/1.73 m^2 [2 3]

Clinical diagnosis of CKD is defined as UACR >30 mg/g and eGFR <60 ml/min/1.73 m^2 which persists for >3 months[4]

1. Levey AS, *et al. JAMA* 2015;313:837; 2. ISN-KDIGO Early CKD Screening. 2022. https://www.theisn.org/initiatives/ckd-early-screening-intervention/#Quick-Guide-and-Infographics (accessed Jan 2023); 3. American Diabetes Association *Diabetes Care 2022;45(Supplement_1):S3;* 4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group *Kidney Int Suppl* 2013;3:1

DECLARE: A CV Safety Assessment of Dapagliflozin in a Broad CV Risk Population with Type 2 Diabetes[1-2]

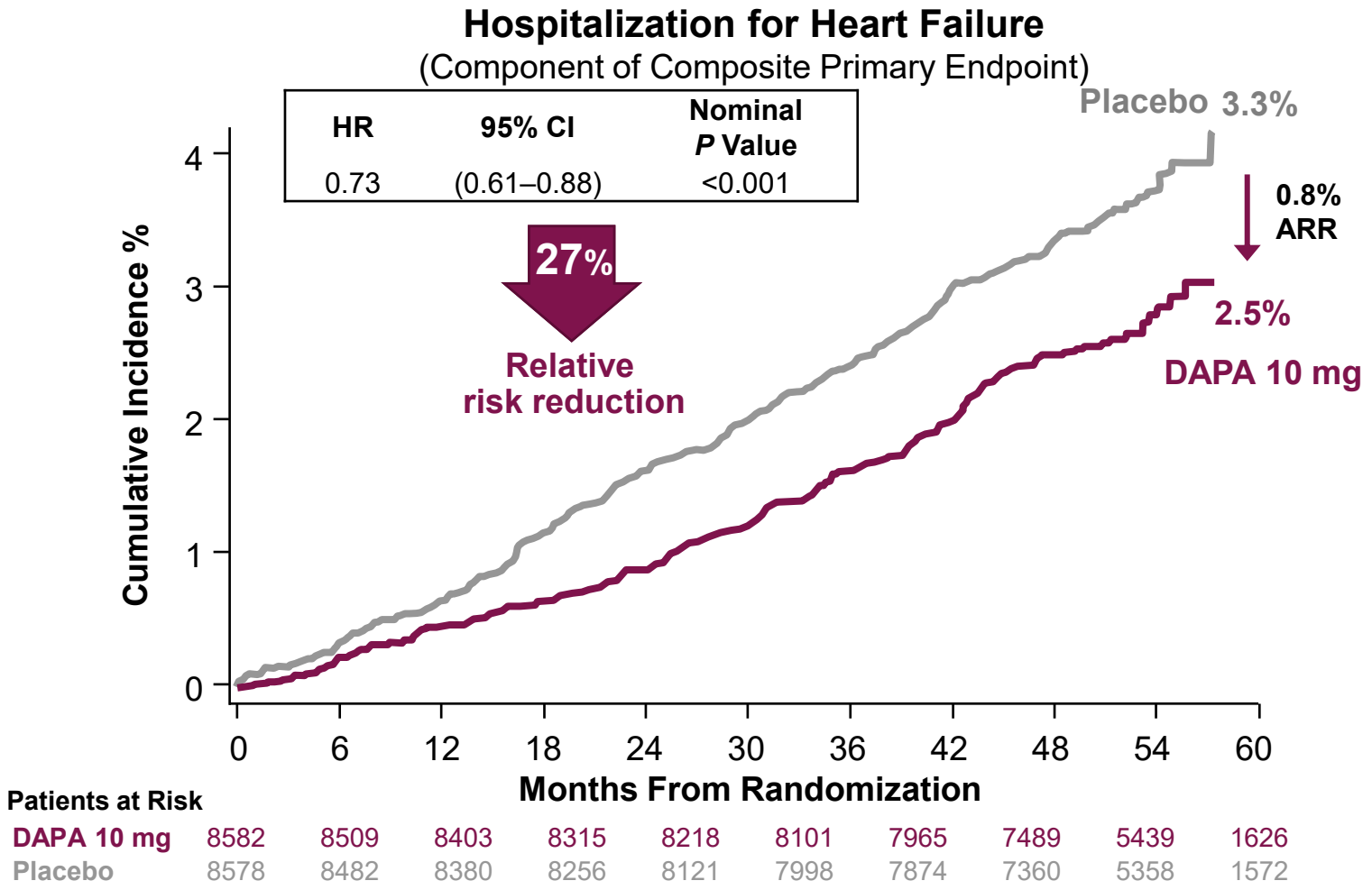


*If non-inferiority established, alpha split equally between two primary endpoints

CV = cardiovascular; GLD = glucose-lowering drug; hHF = hospitalization for heart failure; MACE = major adverse cardiovascular event; MI = myocardial infarction; T2D = type 2 diabetes.

1. Wiviott SD, et al. *Am Heart J*. 2018; 200:83-89. 2. Wiviott SD et al. *New Engl J Med.* 2019;380:347-357.

DECLARE : Dapagliflozin Reduced the Risk for Heart Failure Hospitalization in Patients With T2D and Multiple CV Risk Factors or Established CV Disease[1,2]

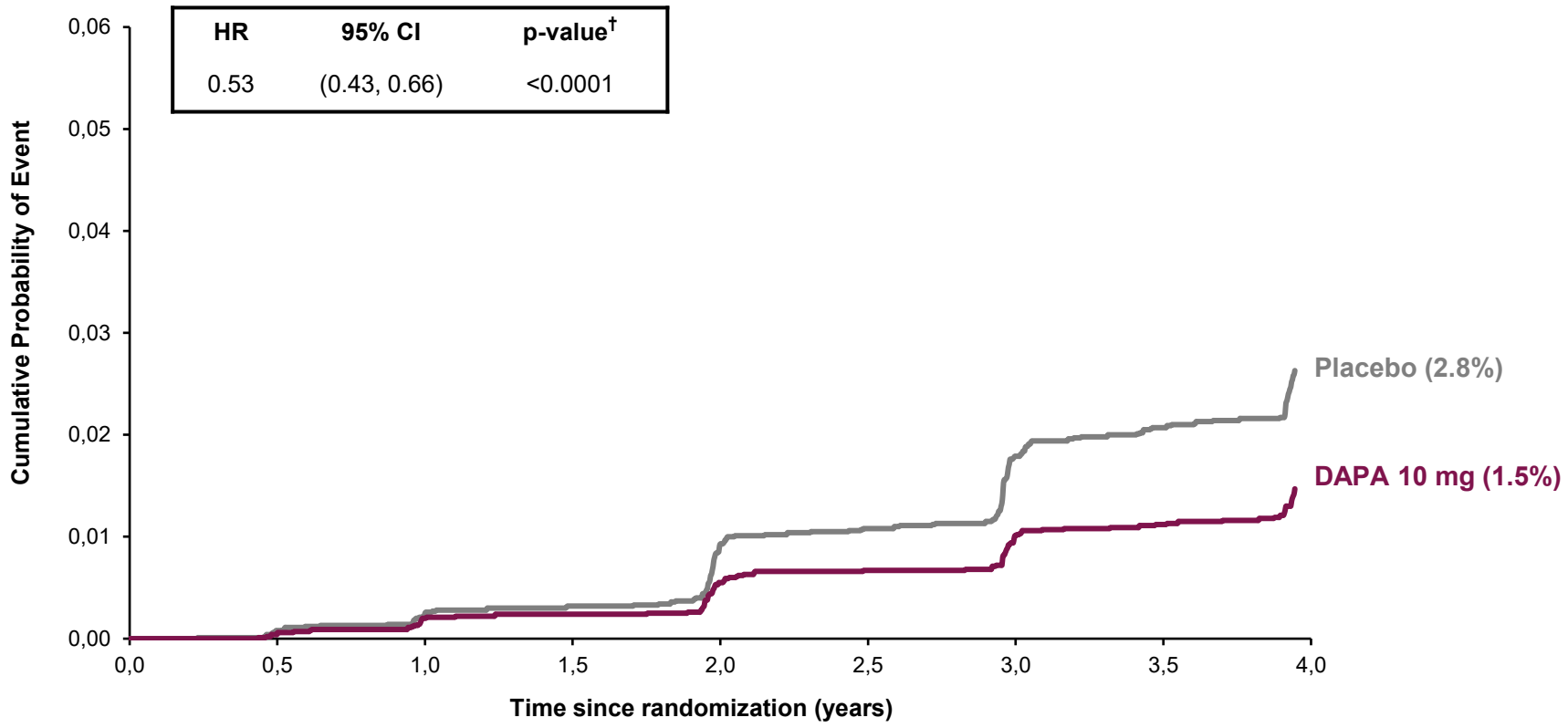


ARR=absolute risk reduction; CI=confidence interval; CV=cardiovascular; DAPA=dapagliflozin; HR=hazard ratio; T2D=type 2 diabetes.

1. Data on File, REF-62129. AZPLP. 2. FARXIGA® (dapagliflozin) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020.

DECLARE : Renal-specific Outcome*

Decrease eGFR ≥40%, ESRD or Renal Death



*Prespecified exploratory endpoint; †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.

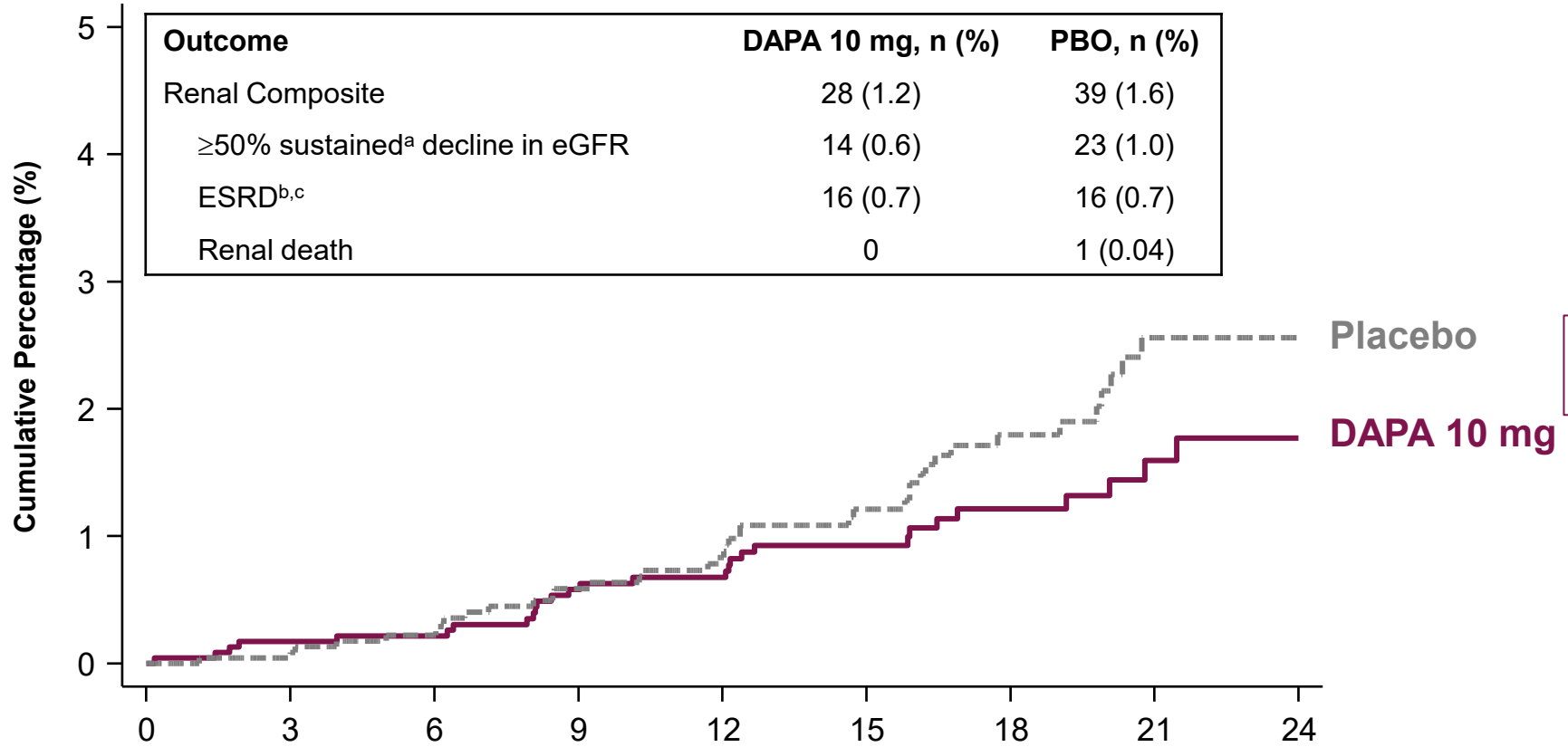
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio.

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

Secondary Endpoint: Worsening Renal Function

Renal composite of ≥50% sustained[a] decline in eGFR, ESRD[b], or renal death

Outcome	DAPA 10 mg, n (%)	PBO, n (%)
Renal Composite	28 (1.2)	39 (1.6)
≥50% sustained[a] decline in eGFR	14 (0.6)	23 (1.0)
ESRD[b,c]	16 (0.7)	16 (0.7)
Renal death	0	1 (0.04)



Number at Risk

DAPA 10 mg	2372	2294	2226	2141	2008	1570	1153	622	223
Placebo	2370	2276	2200	2117	1975	1537	1132	600	215

[a]Defined as ≥28 days; [b]ESRD consisted of sustained eGFR below 15 mL/min/1.73 m^2, sustained dialysis or kidney transplantation; [c]Sustained eGFR <15 mL/min/1.73 m^2 occurred in 1 patient (0.04%) in the dapagliflozin group and no patients in the placebo group; chronic dialysis treatment occurred in 16 patients (0.7%) in the dapagliflozin group and 16 patients (0.7%) in the placebo group; no patients in either group received a renal transplant.

Jhund PS et al. *Circulation*. 2021;143:298-309.

DAPA-CKD enrolled a diverse population of patients with CKD, including various etiologies

DAPACKD

The **first trial** to study the cardiorenal effects of an SGLT2 inhibitor in patients with CKD, with and without T2D[1,a]

N=4304

1:1 randomization

- **DAPA 10 mg**
- **Placebo**

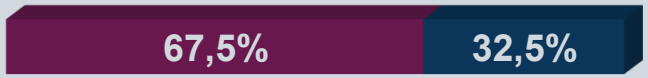
Median follow-up time: 2.4 years

eGFR range[2,b]
25-75 mL/min/1.73 m²
- eGFR ≥45: 41%
- eGFR <45: 59%

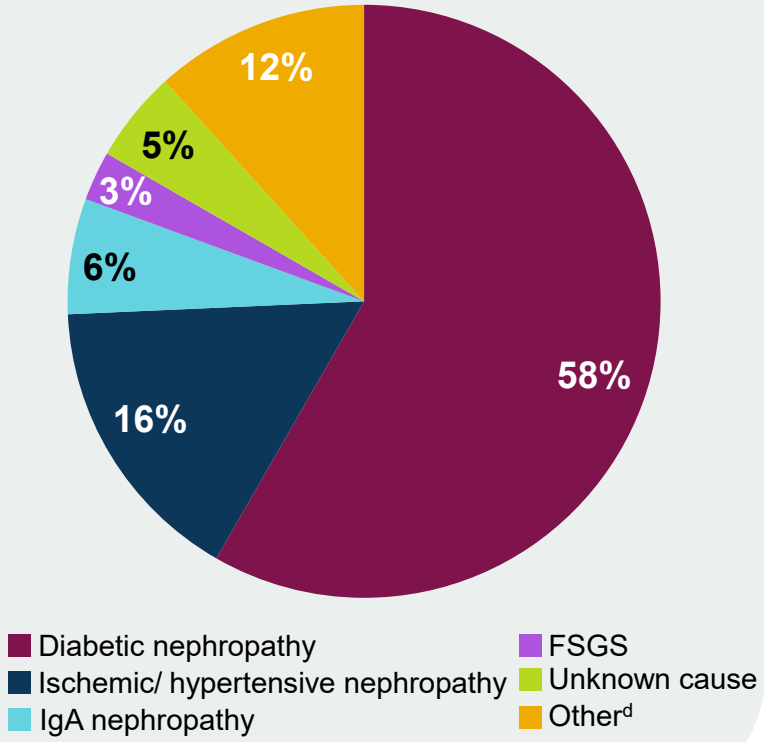
UACR range[1]
≥200 to ≤5000 mg/g

DAPA therapy could continue following dialysis initiation[3,4,c]

Patients with and without T2D



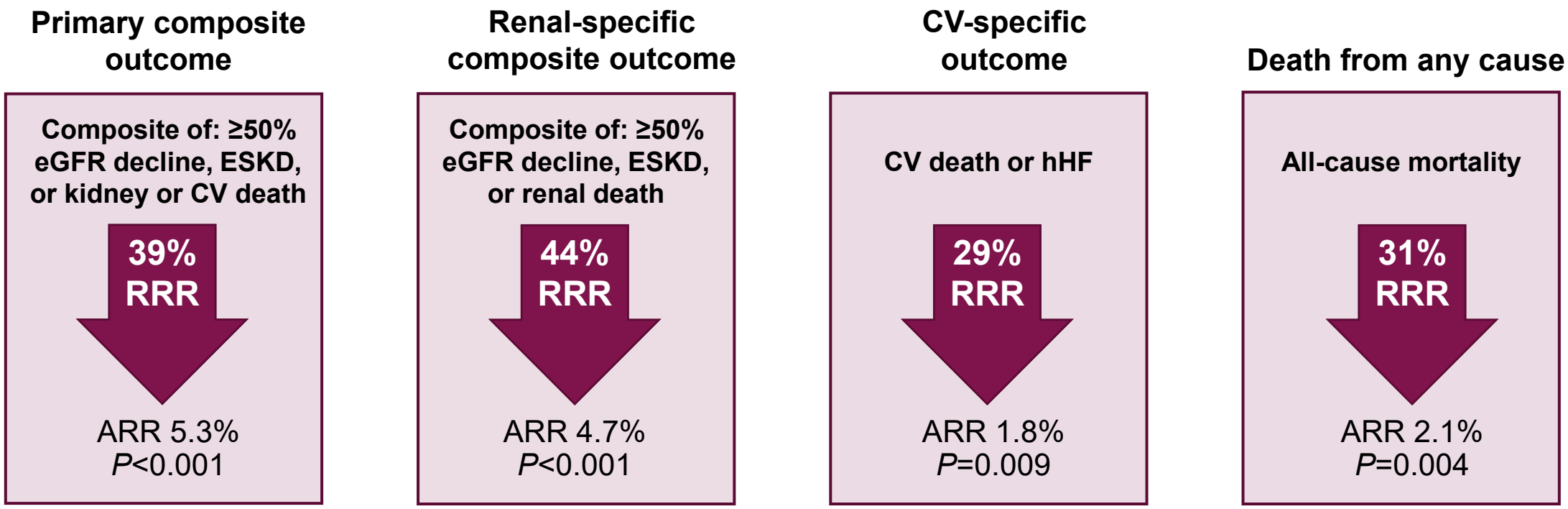
Cause of kidney disease[2]



[a]All patients were required to be on a stable dose of an ACE inhibitor or ARB for at least 4 weeks before screening, if not medically contraindicated. Patients with T1D, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis were excluded; [b]Patients were permitted to continue with dapagliflozin therapy if eGFR fell to <25 mL/min/1.73 m² over the course of the study; [c]At the investigators discretion; [d]'Other' included patients with chronic pyelonephritis, chronic interstitial nephritis, and other causes.

1. Heerspink HJL et al. *N Engl J Med*. 2020:383(15):1436-1446; 2. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35(10):1700-1711; 3. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35(2):274-282; 4. Heerspink HJL et al. *Eur Heart J*. 2021;42(13):1216-1227.

Dapagliflozin is the first and only SGLT2 inhibitor for patients with CKD, with and without T2D, to improve cardiorenal outcomes and reduce mortality

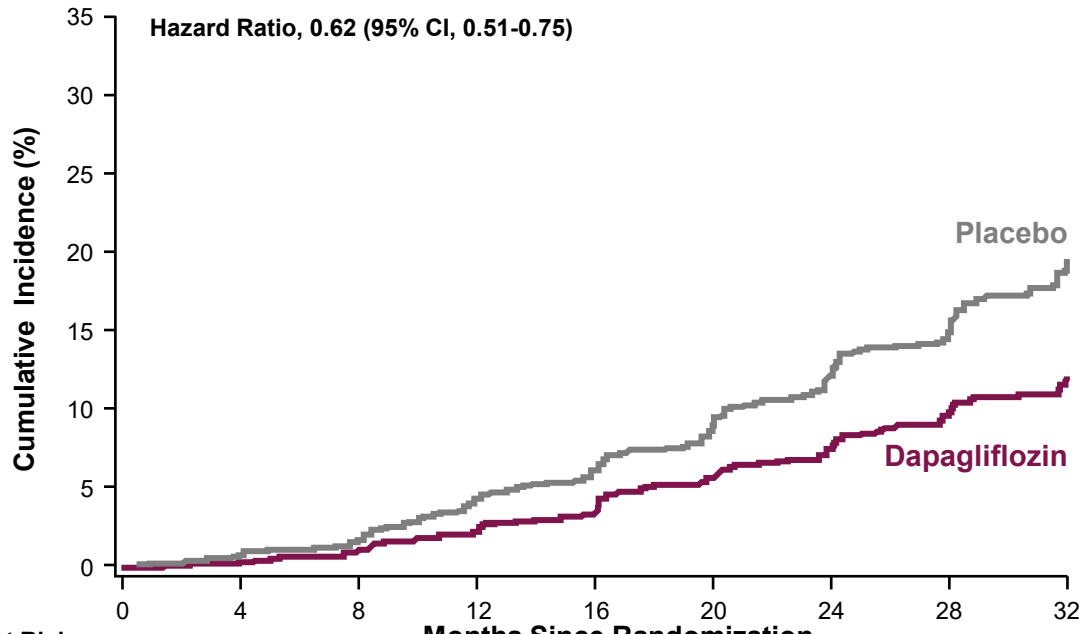


ARR = absolute risk reduction; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF, hospitalization for heart failure; RRR = relative risk reduction; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes.

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

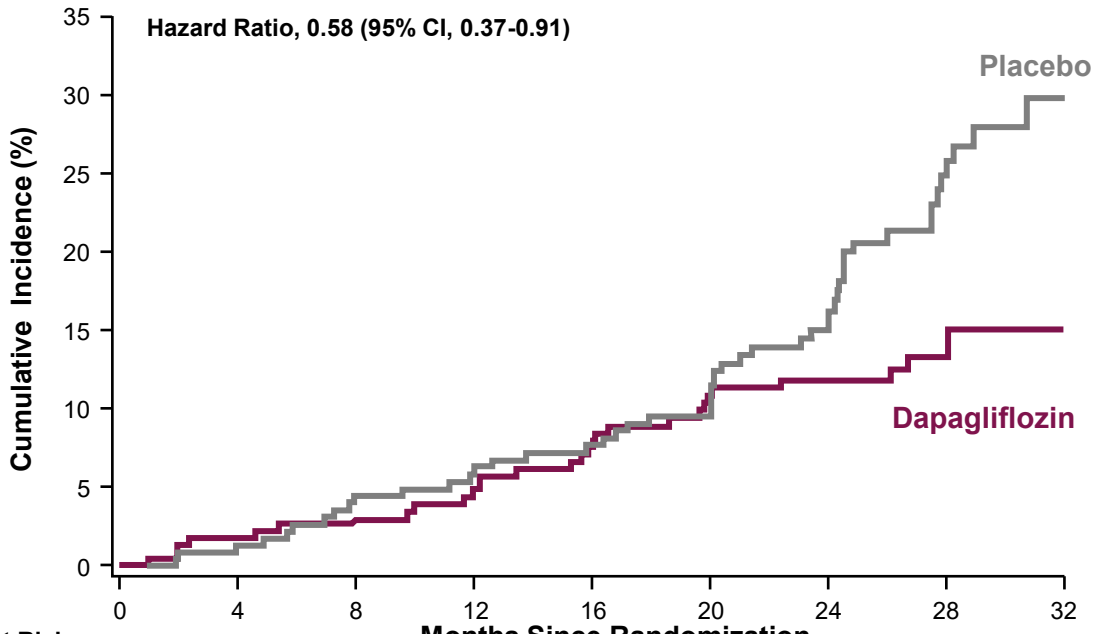
DAPA-CKD Primary Composite Outcome of Sustained ≥50% eGFR Decline, ESKD, or Renal or Cardiovascular Death by Baseline History of HF

No History of Heart Failure



No at Risk									
Dapagliflozin	1917	1773	1732	1683	1638	1517	1143	735	278
Placebo	1919	1769	1720	1651	1594	1477	1090	693	239

History of Heart Failure (10.9%)



No at Risk									
Dapagliflozin	235	228	223	215	203	184	145	96	31
Placebo	233	224	216	207	197	187	142	81	31

p-interaction=0.59

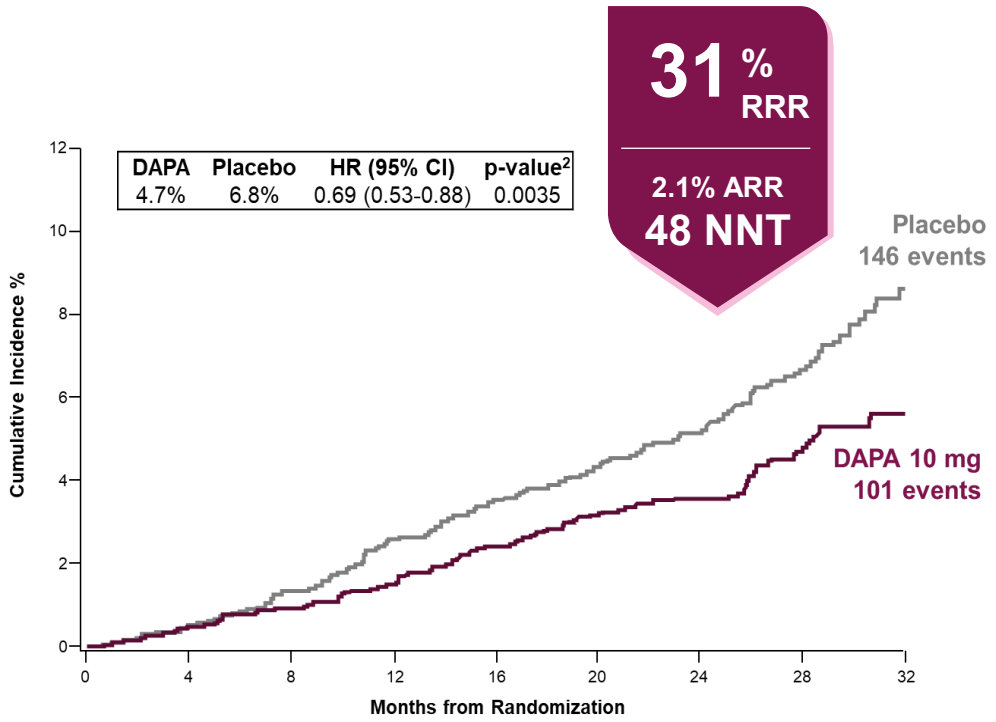
eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; HF = heart failure.

McMurray JJV et al. Published online ahead of print August 23, 2021. *JACC Heart Fail.* 2021. doi: 10.1016/j.jchf.2021.06.017.

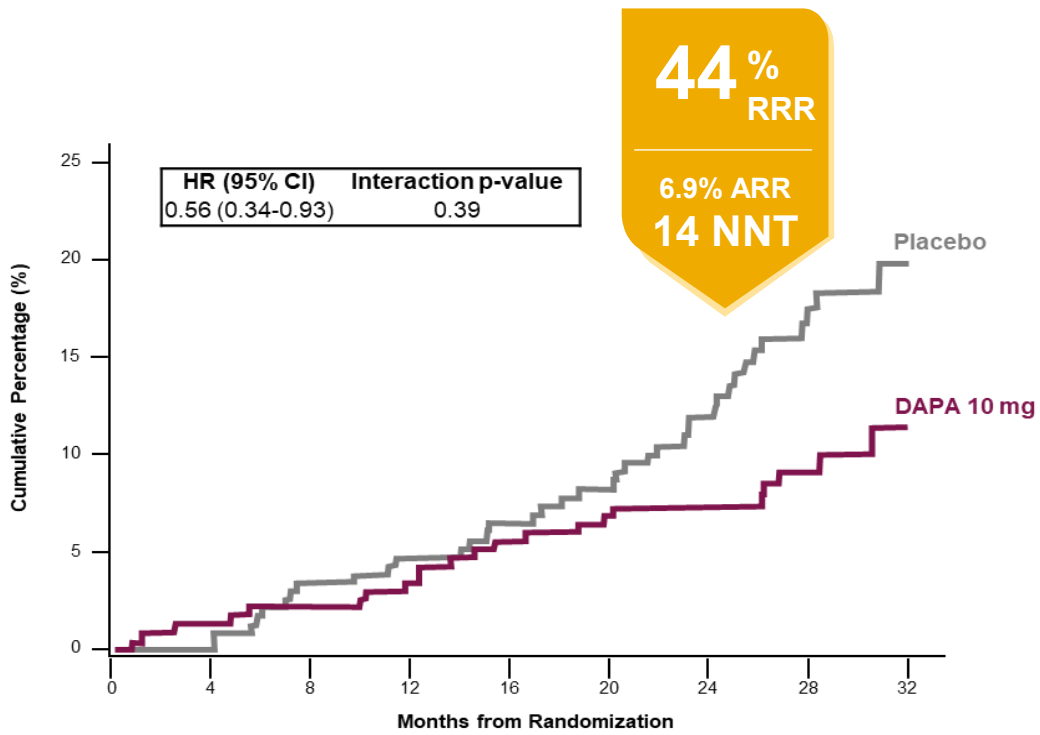
Dapagliflozin in CKD patients: efficacy on All-Cause Mortality

All-Cause Mortality

Patients with CKD



Patients with CKD and HF



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. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020. 2. McMurray JJV, Wheeler DC, Stefánsson BV, et al. Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure [published correction appears in JACC Heart Fail. 2022 Jun;10(6):446-447]. JACC Heart Fail. 2021;9(11):807-820. doi:10.1016/j.jchf.2021.06.017

EMPA-KIDNEY was designed to investigate whether empagliflozin reduces the risk of kidney disease progression or CV death in patients with CKD

Phase III randomized double-blind placebo-controlled trial

Population: Designed to assess the effects of empagliflozin in a broad range of patients (~6000) with chronic kidney disease (CKD) at risk of progression, including many patients without diabetes, and patients with low levels of proteinuria

Trial design

EMPA-KIDNEY

Evidence of CKD at risk of kidney disease progression

- Empagliflozin 10 mg once daily + standard of care†
- Placebo once daily + standard of care†

Event driven: 1070 primary outcomes: 90% power at p<0.05 to detect an 18% relative risk reduction

Outcomes

Composite primary outcome

Kidney disease progression OR **CV death**

Kidney function loss defined as:
- Sustained reduction of ≥40% eGFR decline
- Sustained eGFR <10 ml/min/1.73 m^2

End-stage kidney disease
- Defined as initiation of chronic dialysis or kidney transplant

Renal death

Key secondary outcomes‡

- All-cause hospitalization
- First occurrence of hospitalization for heart failure or CV death
- All-cause mortality

*Between 15 May 2019 and 16 April 2021, 6609 patients were randomized; †Guideline-directed medical therapy; ‡Other outcomes prespecified
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

EMPA-KIDNEY: key inclusion and exclusion criteria[1]

Key inclusion criteria*

- Age ≥18 years or at 'full age' as required by local regulation
- **Evidence of CKD** at risk of kidney disease progression, defined by ≥3 months before and at the time of screening visit
  - **eGFR ≥45 to <90 ml/min/1.73 m^2 with UACR A2–A3 (≥200 mg/g) , or**
  - **eGFR ≥20 to <45 ml/min/1.73 m^2**
- Clinically appropriate doses of single-agent RAS-inhibition with either ACEi or ARB unless either is not tolerated or not indicated
- Neither requires an SGLT2 or SGLT1/2 inhibitor, nor that such treatment is inappropriate

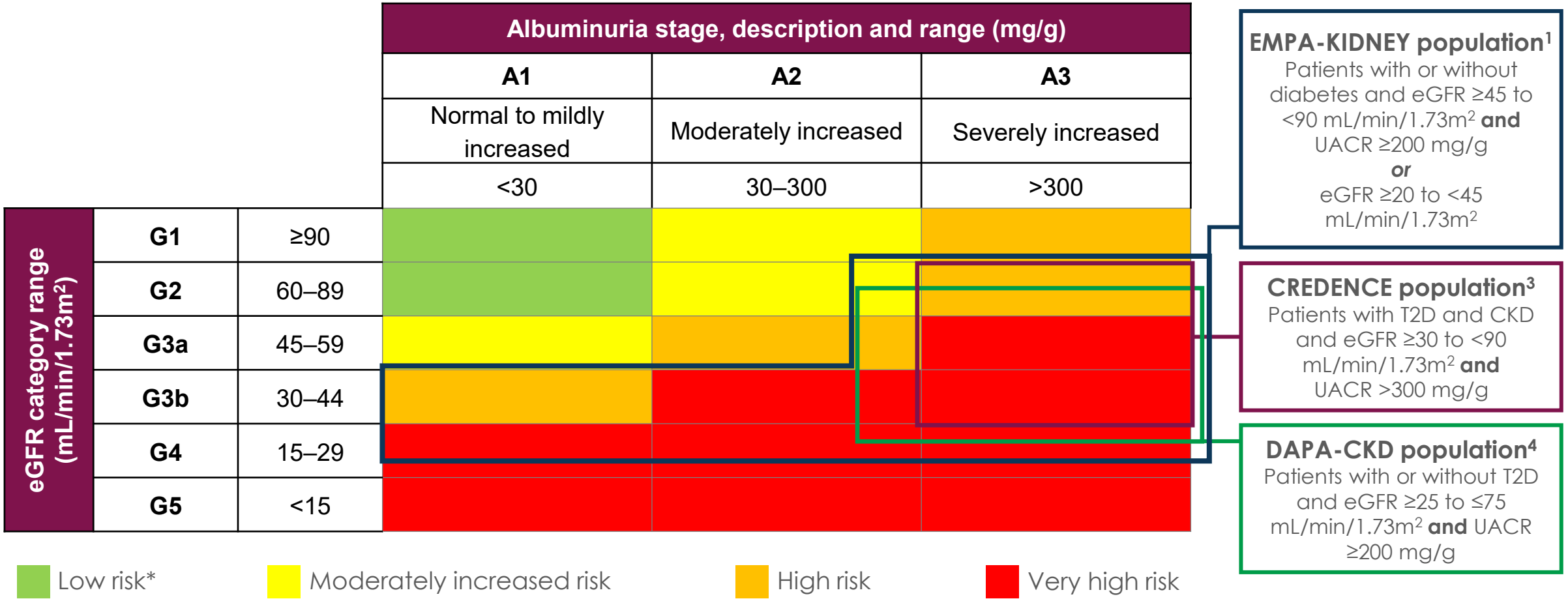
Key exclusion criteria*

- Currently receiving an SGLT2 or dual SGLT1/2 inhibitor
- T2D and prior atherosclerotic CV disease with eGFR >60 ml/min/1.73 m^2
- Receiving dual RAS-inhibition (two of ACEi, ARB, DRI)
- Any IV immunosuppression therapy in the last 3 months or anyone currently on >45 mg prednisolone (or equivalent)
- **Maintenance dialysis, functioning kidney transplant or scheduled living donor transplant**
- **Polycystic kidney disease**
- T1D†

eGFR calculated using CKD-EPI formula
*For full details, refer to publication supplement; †As of January 2020, the protocol was amended to allow currently enrolled patients with T1D to continue in the study and limit screening of new patients with T1D due to a sponsor decision. At that time, the Data Monitoring Committee (DMC) did not report any safety concerns in patients with T1D
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DRI, direct renin inhibitor; IV, intravenous; UACR, urine albumin-to-creatinine ratio; RAS, renin–angiotensin system; SGLT, sodium-glucose co-transporter; T1D, type 1 diabetes; T2D, type 2 diabetes
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

EMPA-KIDNEY enrolled a CKD population with a broad range of eGFR, with and without albuminuria[1]

Prognosis of CKD by eGFR and albuminuria categories[2]



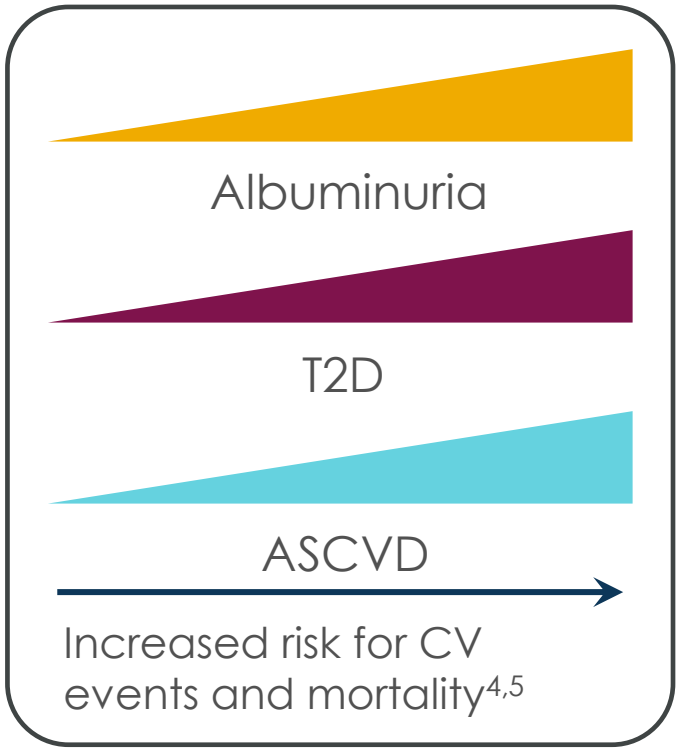
*If no other markers of kidney disease, no CKD.

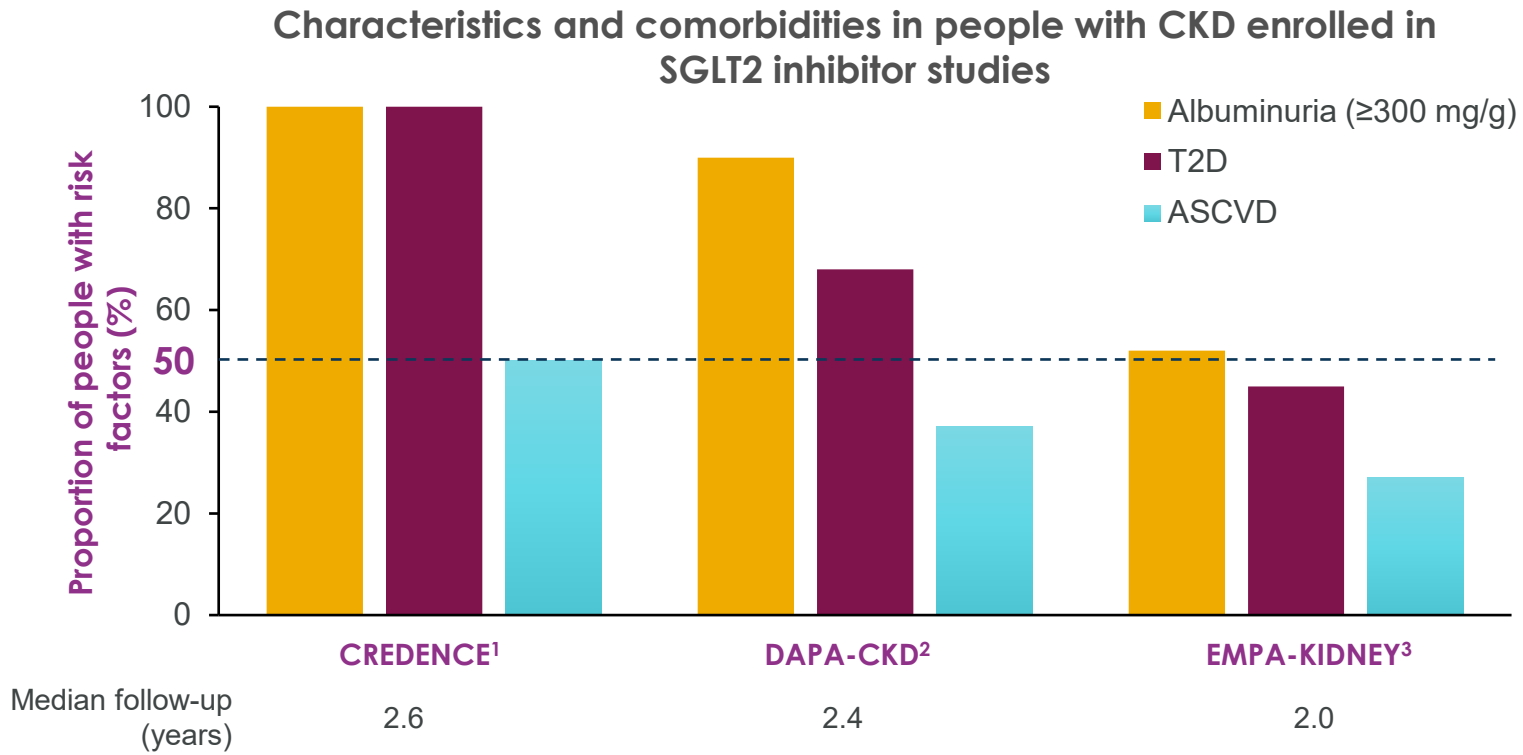
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; T2D, type 2 diabetes.

1. The EMPA-KIDNEY Collaborative Group. *N Engl J Med*. 2023 Jan 12;388(2):117-127. 2. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1–150. 3. Perkovic V, *et al. N Engl J Med*. 2019; 380:2295-2306 4. Wheeler DC, *et al. Nephrol Dial Transplant* 2020;35:1700.

The EMPA-KIDNEY population has the lowest CV risk compared with other SGLT2 inhibitor studies in people with CKD[1-3]

Albuminuria, ASCVD and T2D independently increase the risk for CV events and mortality in people with CKD[4,5]



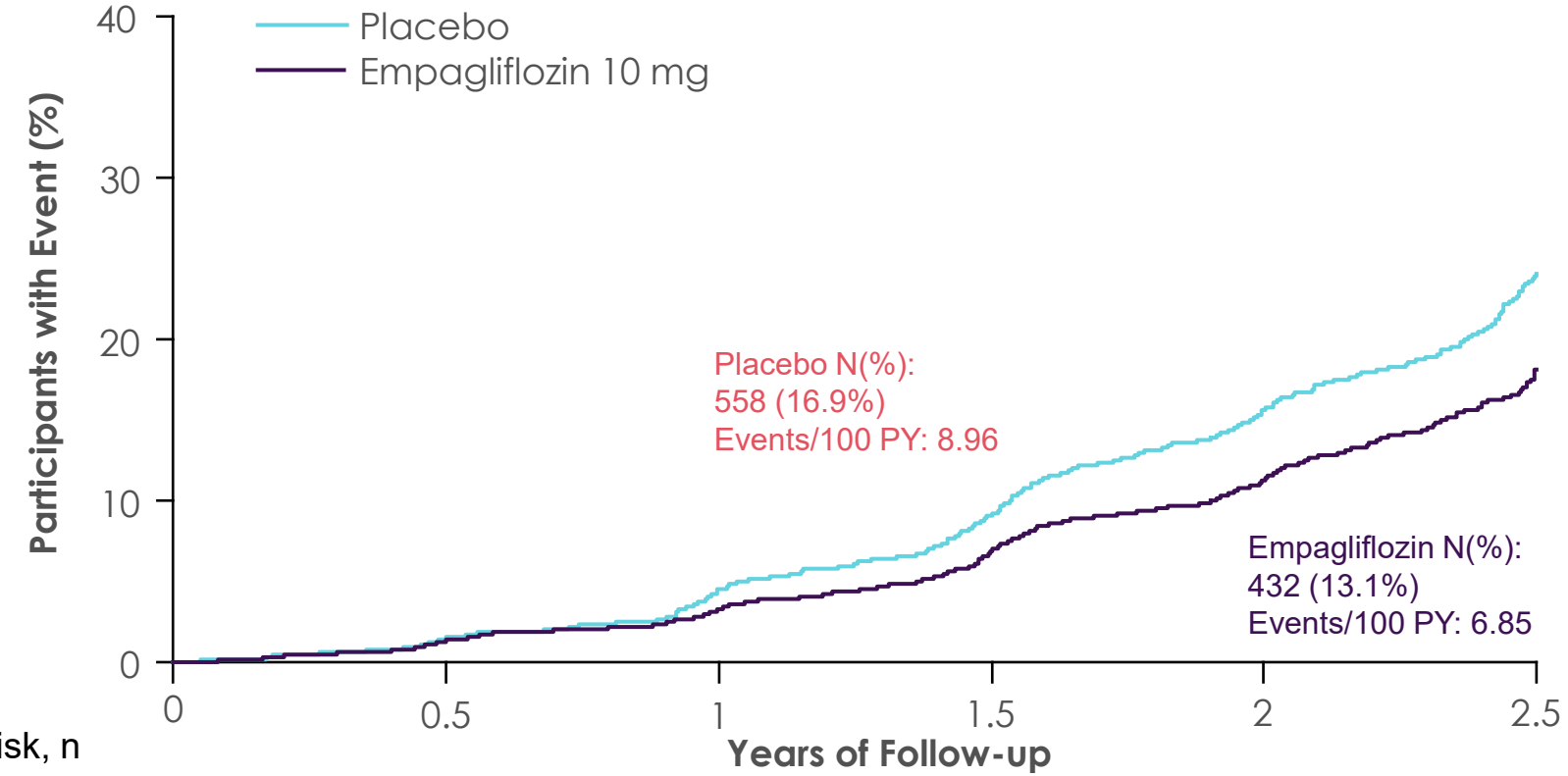


Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. Perkovic V *et al. N Engl J Med* 2019;380:2295; 2. Wheeler DC *et al. Nephrol Dial Transplant* 2020;35:1700; 3. The EMPA-KIDNEY Collaborative Group. *Nephrol Dial Transplant* 2022;37:1317; 4. de Boer IH *et al. Diabetes Care* 2022;45:3075; 5. American Diabetes Association. *Diabetes Care* 2023;46:S1

Primary composite outcome
Kidney disease progression or CV death[1]



HR 0.72
(95% CI 0.64, 0.82)
P < 0.001

RRR 28%

NNT=28*

Patients at risk, n

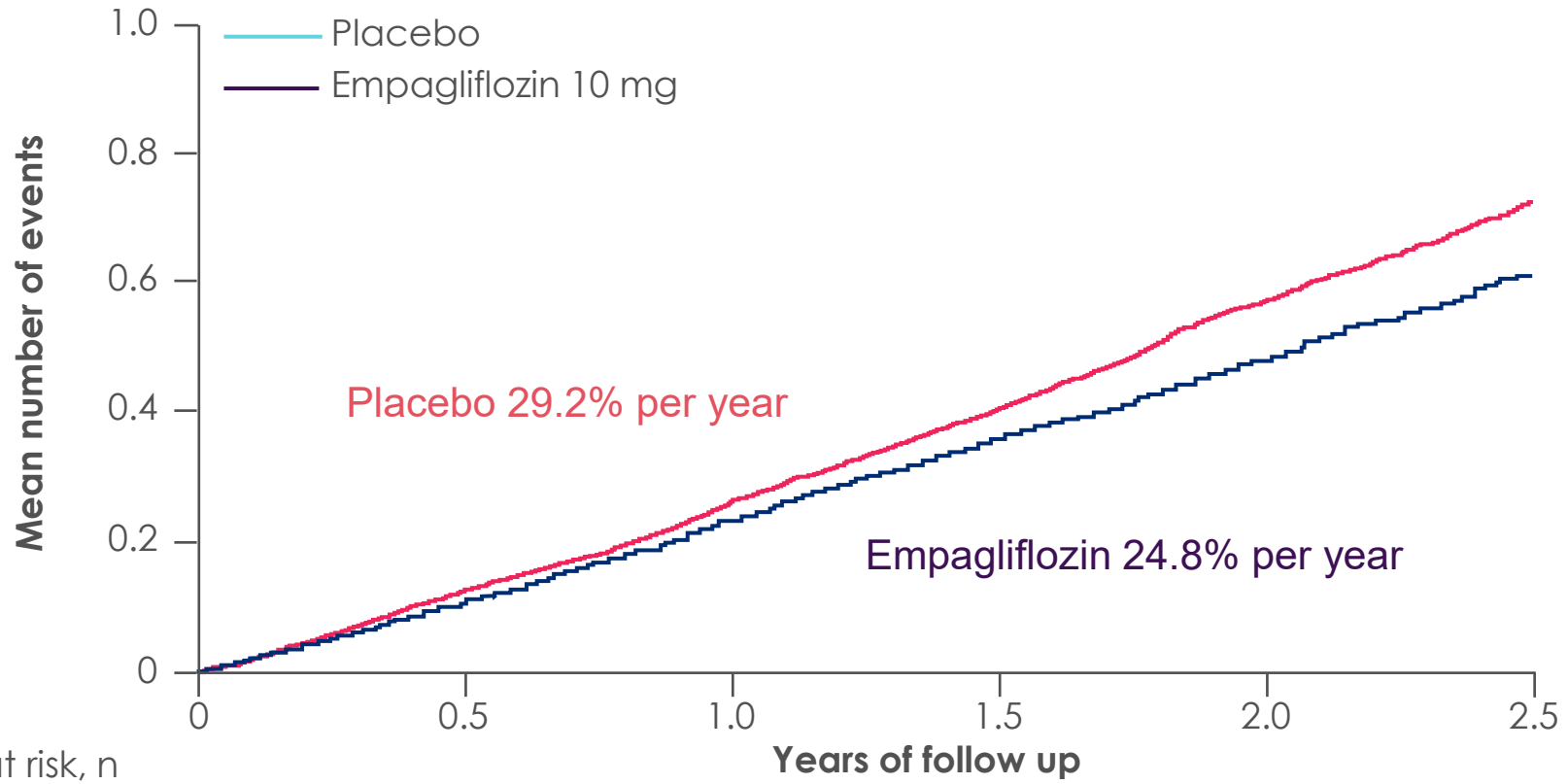
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

ARR: 3.6%†

*NNT: 28 (95% CI 19, 53) per 2 years at risk[2]; †ARR for the primary composite outcome of kidney disease progression or CV death is 3.6% per patient year at risk. Figure adapted from Figure 1 of reference.
Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization
ARR, absolute risk reduction; CV, cardiovascular, eGFR, estimated glomerular filtration rate; NNT, number needed to treat; PY, patient years; RRR, relative risk reduction; UACR, urine albumin-to-creatinine ratio

1. eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

Key secondary outcome: All-cause hospitalization (first and recurrent)[1]



HR 0.86
(95% CI 0.78, 0.95)
P=0.003

RRR 14%

Patients at risk, n

Placebo	3305	3283	3241	2500	1705	775
Empagliflozin	3304	3283	3245	2493	1719	798

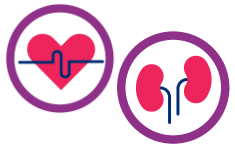
Key secondary outcomes were prespecified to be adjusted for multiple testing using the Hochberg "step-up" procedure with a family-wise error rate of 0.029; semi-parametric joint frailty model was used. The analysis of hospitalizations for any cause included the first and all subsequent events, so only the rates are shown; 1611 hospitalizations occurred among 960 patients in the empagliflozin group, and 1895 hospitalizations occurred among 1035 patients in the placebo group

eGFR, estimated glomerular filtration rate; RRR, relative risk reduction; UACR, urine albumin-to-creatinine ratio

1. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233;

Efficacy results: overview of confirmatory outcomes

Composite primary outcome



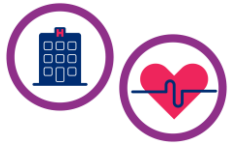
CV death or kidney disease progression (first)

RRR 28%
P<0.001

Key secondary outcomes

All-cause hospitalization (first and recurrent)

RRR 14%
P=0.003



HHF or CV death (first)

P=0.15
RRR 16%

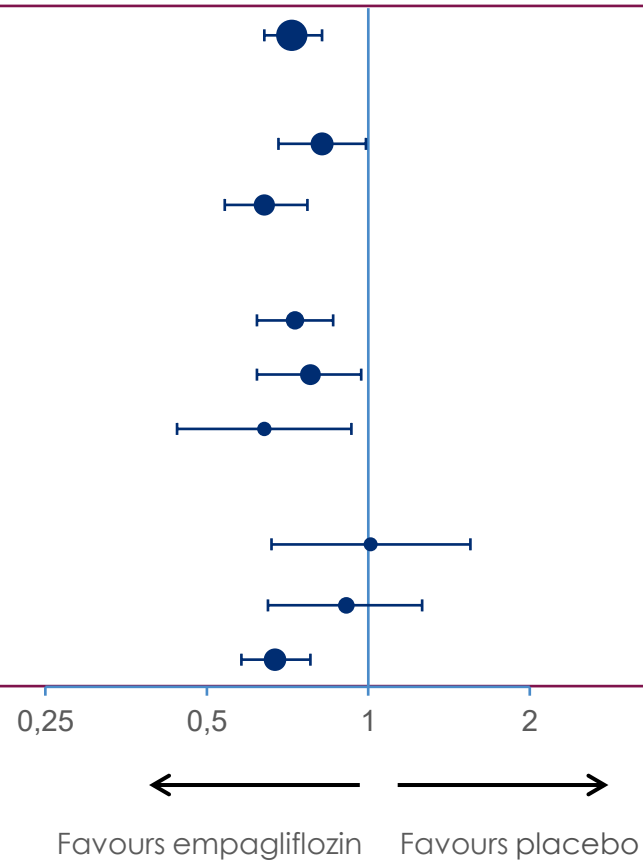
All-cause death

P=0.21
RRR 13%

Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m2, renal death or a sustained decline of ≥40% in eGFR from randomization.
Nominal results were statistically not significant. CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; RRR, relative risk reduction
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

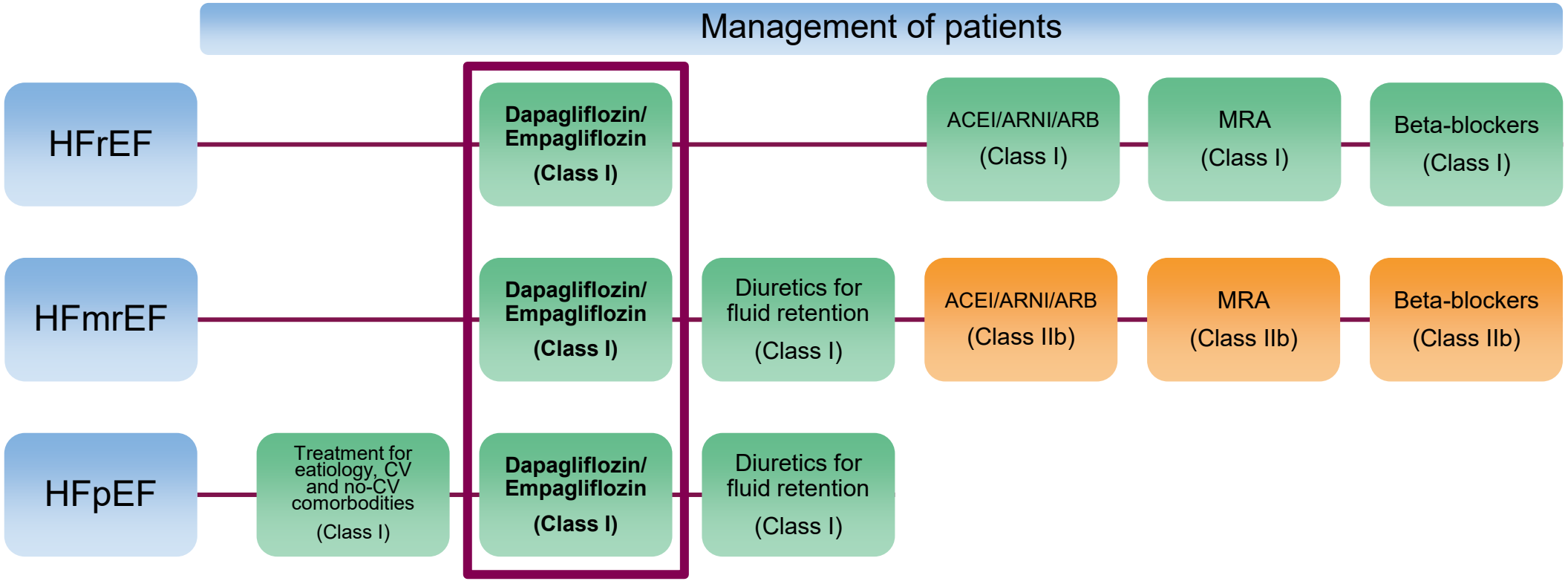
Subgroup analysis of primary endpoint: Key subgroups of interest

	Empagliflozin 10 mg	Placebo	
	n with event/N analysed		HR (95% CI)
Overall	432/3304	558/3305	0.72 (0.64, 0.82)
Baseline diabetes			
No	214/1779	252/1790	0.82 (0.68, 0.99)
Yes	218/1525	306/1515	0.64 (0.54, 0.77)
Baseline eGFR			
<30	247/1131	317/1151	0.73 (0.62, 0.86)
30 to <45	140/1467	175/1461	0.78 (0.62, 0.97)
≥45	45/706	66/693	0.64 (0.44, 0.93)
Baseline UACR, mg/g			
A1 (<30) normal to mildly increased	42/665	42/663	1.01 (0.66, 1.55)
A2 (30 to ≤300) moderately increased	67/927	78/937	0.91 (0.65, 1.26)
A3 (>300) severely increased	323/1712	438/1705	0.67 (0.58, 0.78)



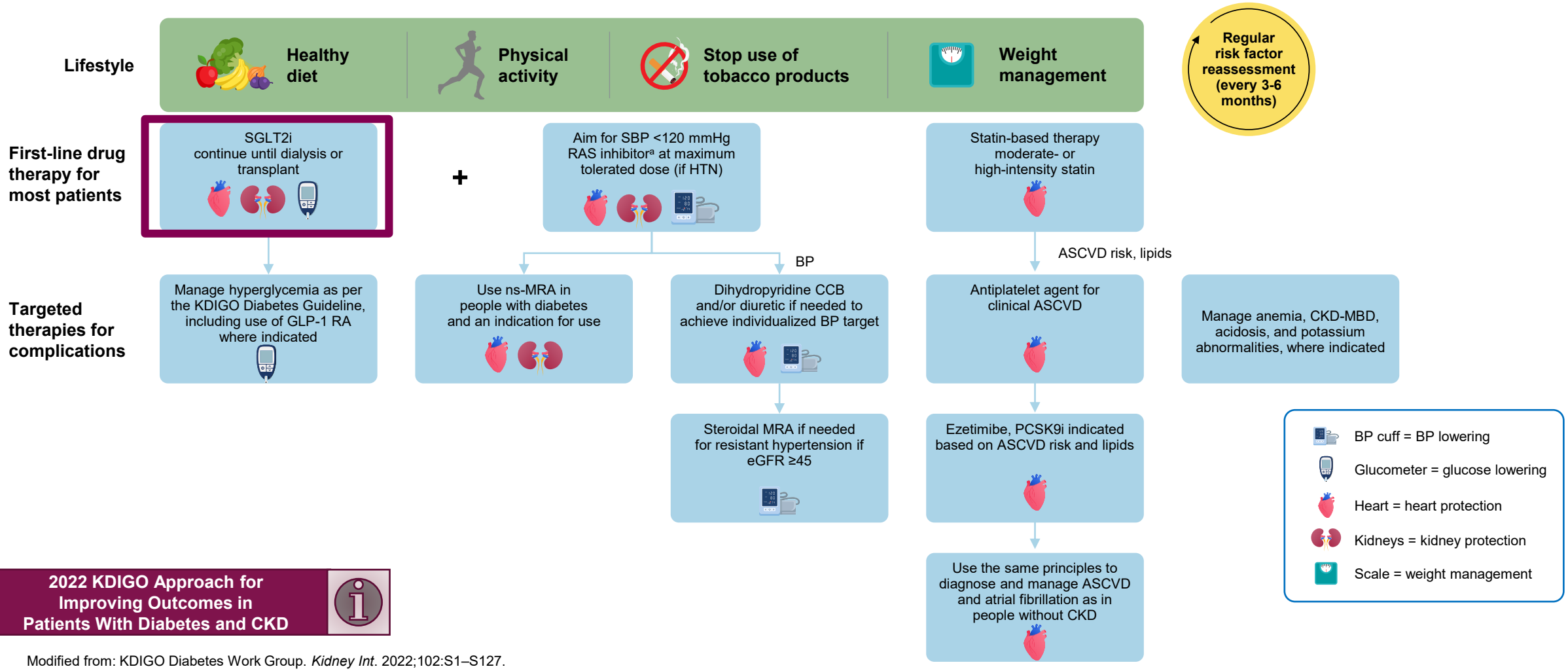
Primary outcome was kidney disease progression (defined as ESKD, sustained eGFR decline of ≥40% or to <10 ml/min/1.73m^2 or adjudicated renal death) or CV death. Events confirmed or unrefuted by adjudication are considered as an endpoint event
CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UACR, urinary albumin-to-creatinine ratio
The EMPA-KIDNEY Collaborative Group. *N Engl J Med 2022*; DOI: 10.1056/NEJMoa2204233

ESC Heart Failure Guidelines: Class IA Recommendation for SGLT2i in Patients With HF



Adapted from: McDonagh TA et al. Eur Heart J. 2021; McDonagh TA et al. Online ahead of print. Eur Heart J. 2023.

2024 KDIGO Evaluation and Management of CKD Guideline: Holistic Approach to CKD Treatment and Risk Modification



2022 KDIGO Approach for Improving Outcomes in Patients With Diabetes and CKD

Modified from: KDIGO Diabetes Work Group. *Kidney Int*. 2022;102:S1–S127.

[a]ACEi or ARB should be first-line therapy for BP control when albuminuria is present; otherwise dihydropyridine CCB or diuretic can also be considered. All 3 classes are often needed to attain BP targets.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium-channel blocker; CKD = chronic kidney disease; CKD-MBD = chronic kidney disease-mineral and bone disorder; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid-receptor antagonist; ns-MRA = nonsteroidal mineralocorticoid-receptor antagonist; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; RAS = renin-angiotensin system; SBP = systolic blood pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

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

THANKS FOR THE ATTENTION

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