INHIBITEURS DU SGLT2 ET REINS

DR LUC RADERMACHER

NEPHROLOGIE
IMMUNO-INFECTIOLOGIE
MÉDECINE INTERNE
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PLAN

- Effets rénaux directs et indirects des iSGLT2
- La révolution de l'étude Dapa-CKD
- Indications néphrologiques

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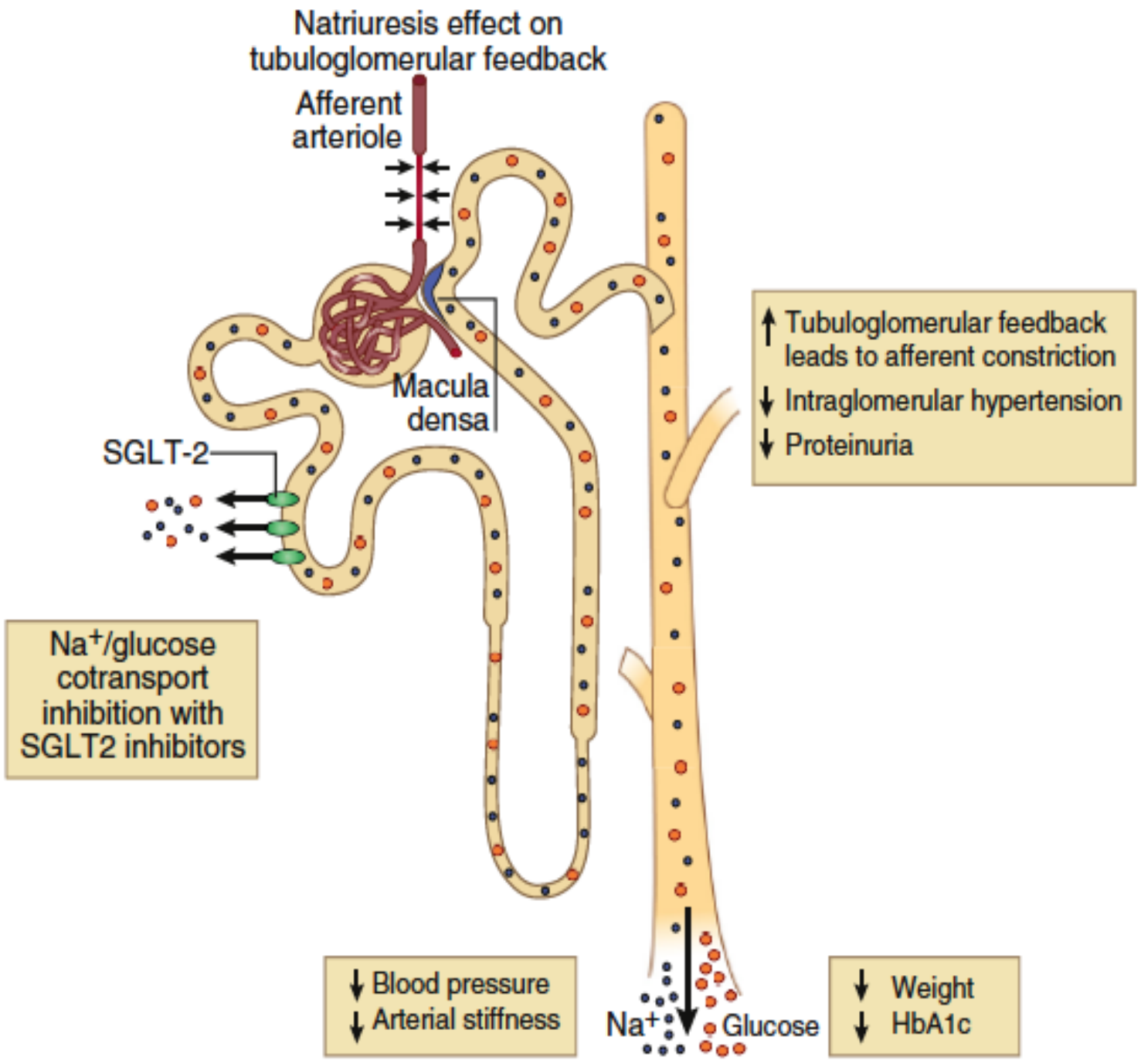

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

N Engl J Med. 2020 Oct 8;383(15):1436-1446.

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 maximum tolerated 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 max tolerated 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

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

[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.

Demographics and Baseline Characteristics

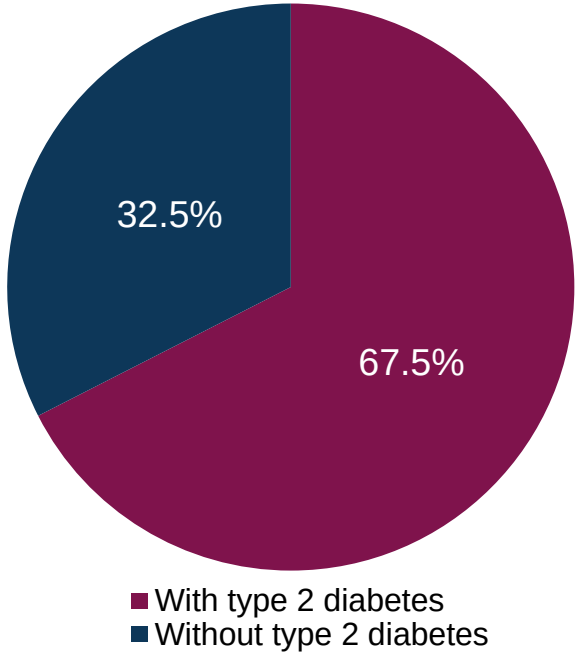
	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
Age, years, mean	61.8	61.9
Gender, female, %	32.9	33.3
Race[a], %		
White	52.2	54.2
Black or African-American	4.8	4.0
Asian	34.8	33.4
Other	8.1	8.4
Weight, kg	81.5	82.0
Body mass index, kg/m^2	29.4	29.6
Current smoker, %	13.2	14.0
Blood pressure, mmHg, mean		
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.

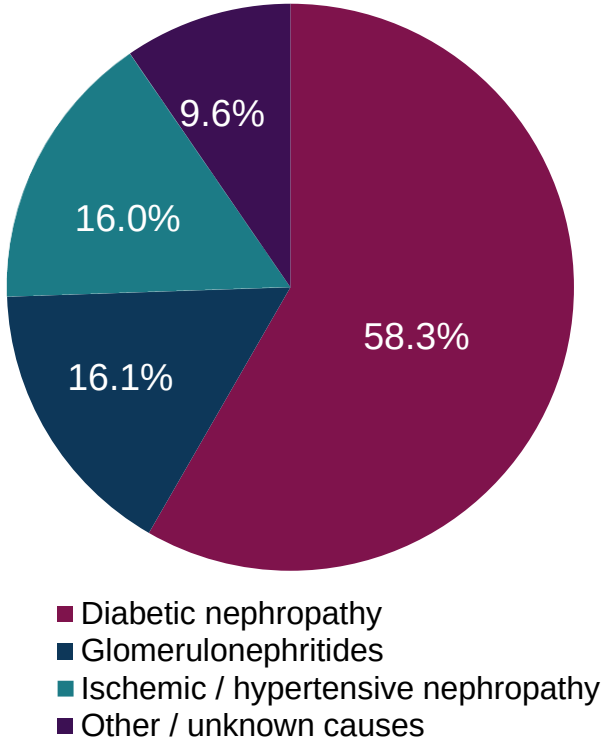
Demographics and BL Characteristics by Diabetes Status

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

Diabetes Status



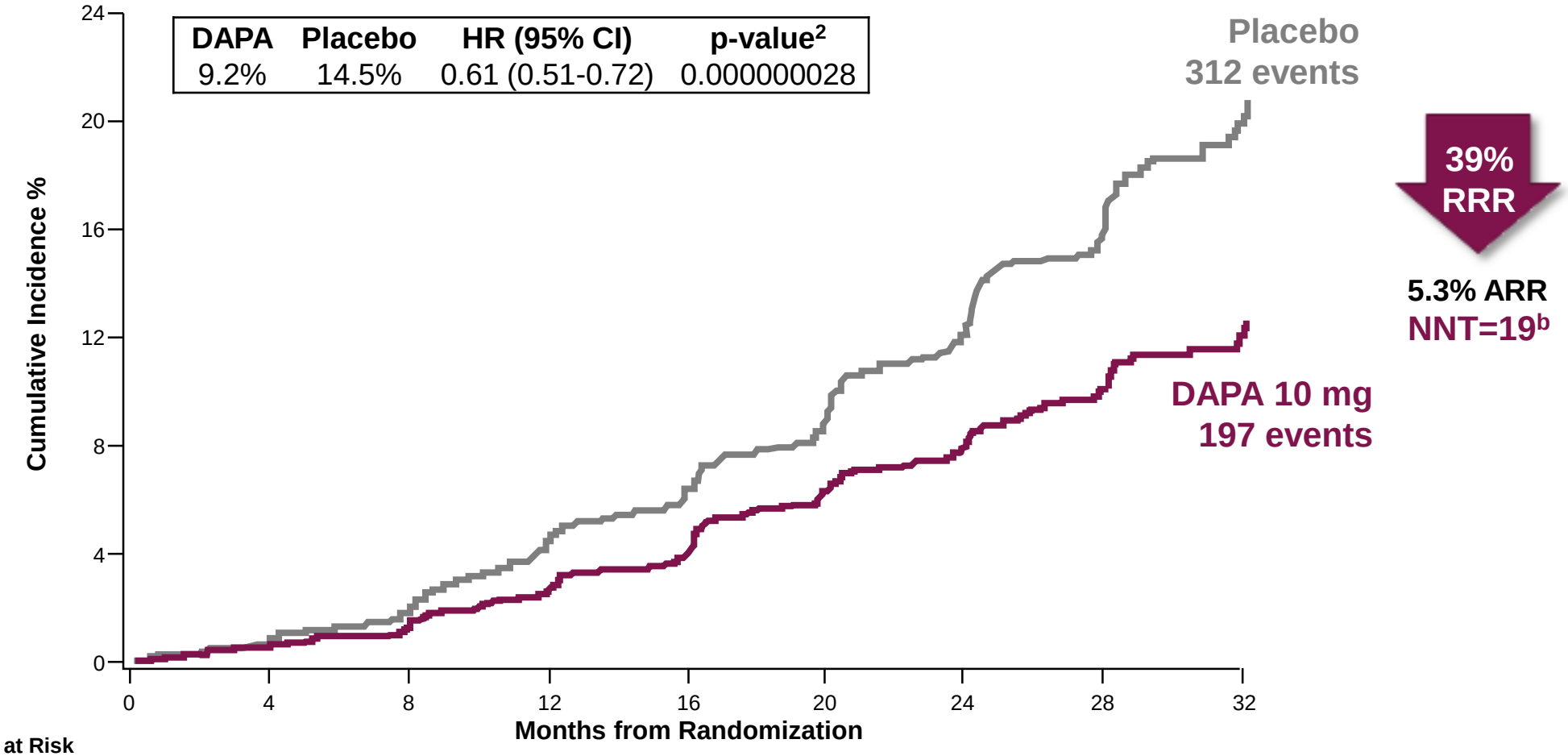
Investigator-reported Cause of Kidney Disease



CKD Etiologies

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]



N at Risk									
DAPA 10 mg	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

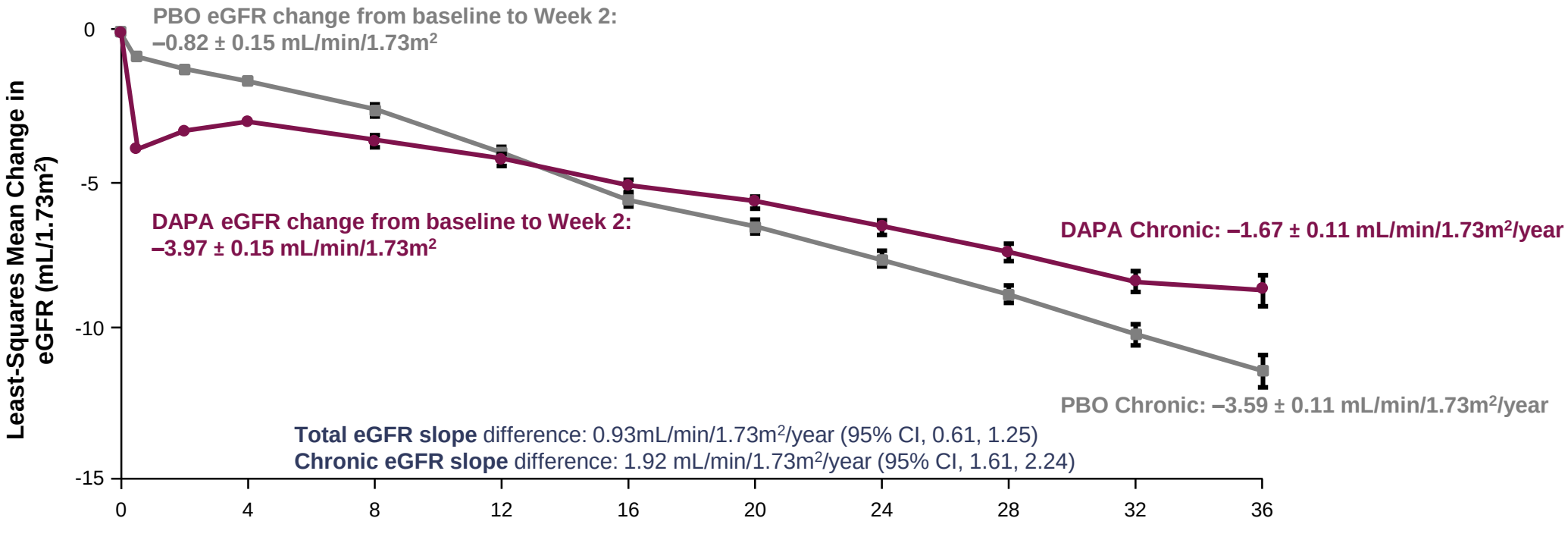
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[3]; [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. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;

3. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Change from Baseline in eGFR[1,2]

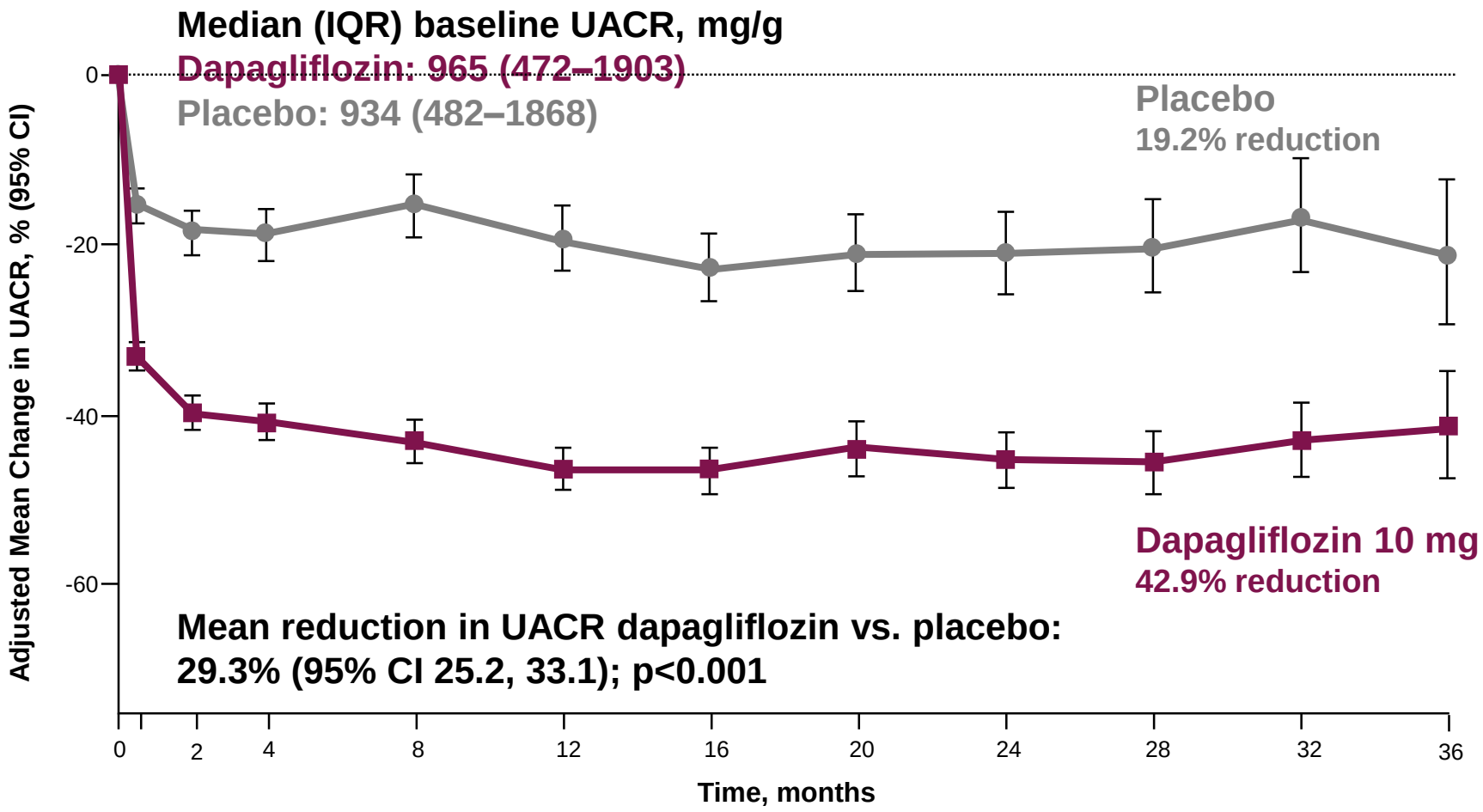


No. of Patients											
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157

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

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Toto R. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

Change in Albuminuria in the Overall Population



Dapagliflozin	2152	2085	2047	2048	1943	1884	1843	1778	1631	1172	692	233
Placebo	2152	2090	2054	2033	1909	1854	1818	1748	1581	1135	640	229

CI = confidence interval; IQR = interquartile range; UACR = urinary albumin-to-creatinine ratio

Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

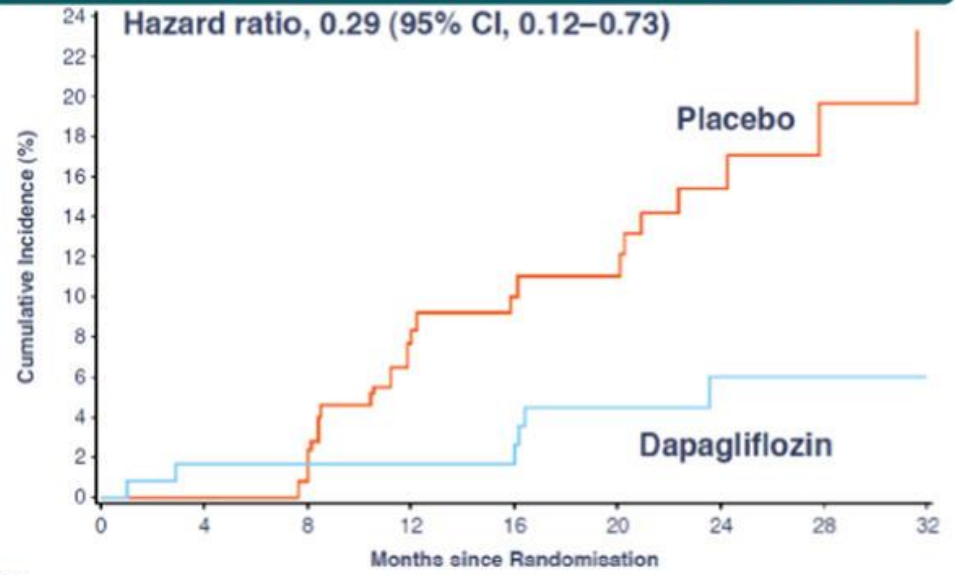
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

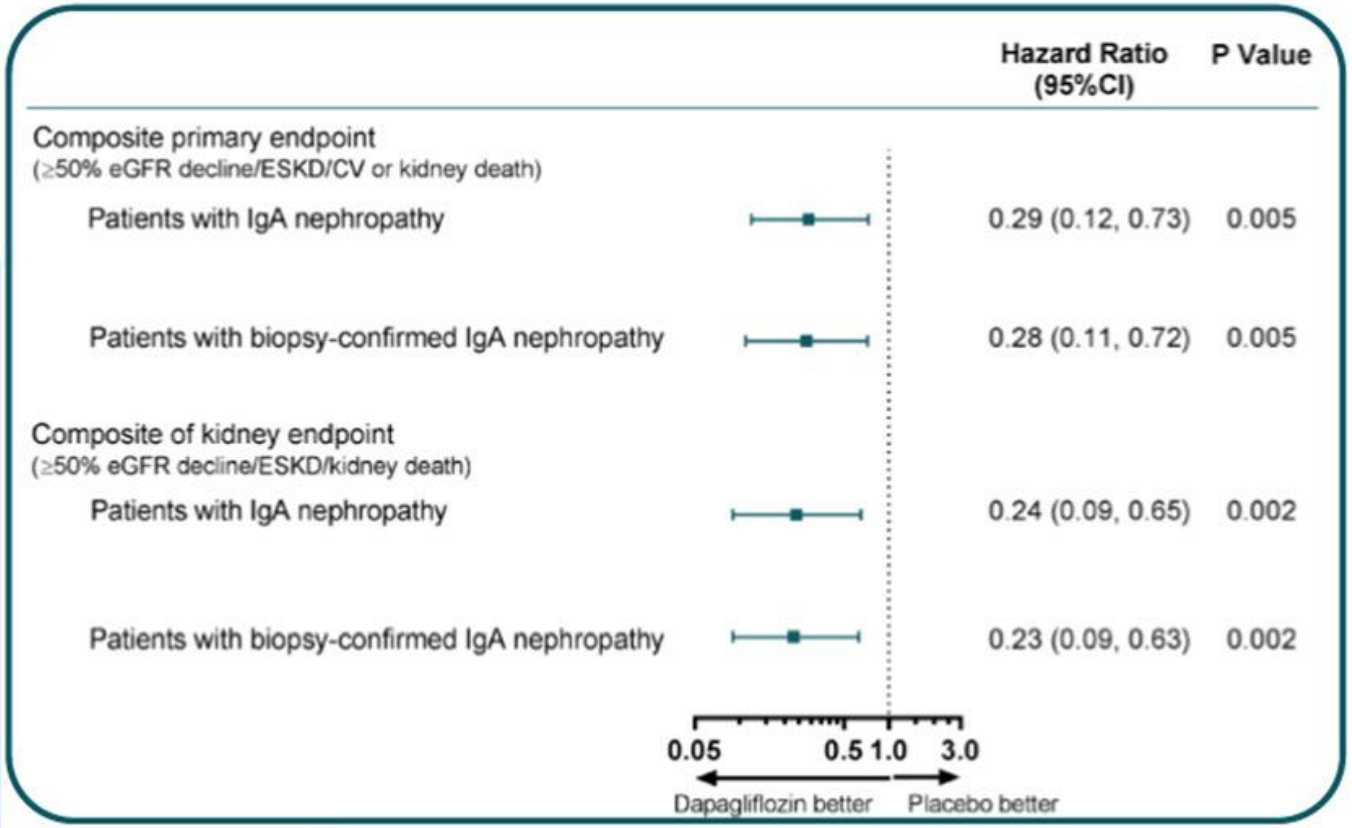
⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**

Composite primary endpoint in patients with IgA nephropathy (n=270)



No. at Risk

Dapagliflozin	137	107	106	105	104	98	61	43	17
Placebo	133	113	108	101	96	92	51	32	19



IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

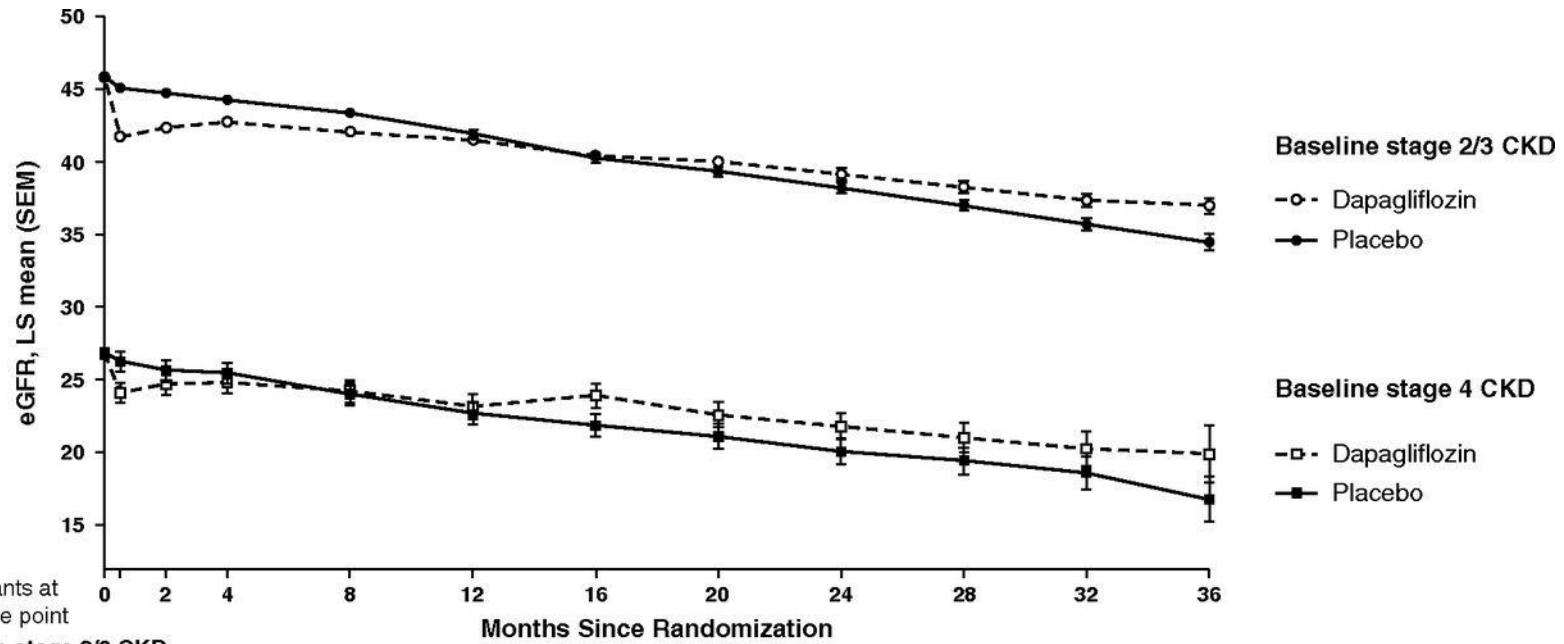
CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

kidney INTERNATIONAL ISN

Wheeler et al, 2021

LS mean change in eGFR over the study in those with baseline stage 4 or stages 2/3 CKD. On the basis of the two-slope model.



Participants at each time point	0	2	4	8	12	16	20	24	28	32	36
Baseline stage 2/3 CKD											
Dapagliflozin	1859	1762	1733	1643	1594	1558	1493	1302	864	450	148
Placebo	1821	1723	1691	1594	1539	1509	1449	1245	811	394	140
Baseline stage 4 CKD											
Dapagliflozin	293	269	268	253	238	227	212	180	114	46	9
Placebo	331	306	290	272	256	244	223	198	124	53	17

Glenn M. Chertow et al. JASN 2021;32:2352-2361

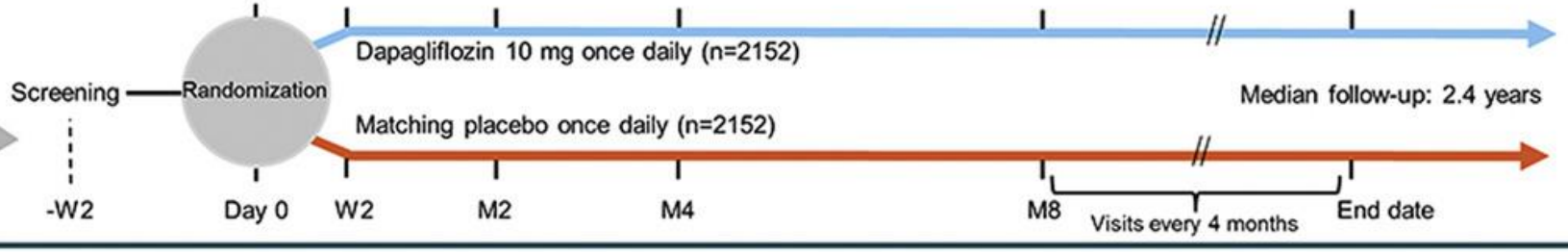
A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

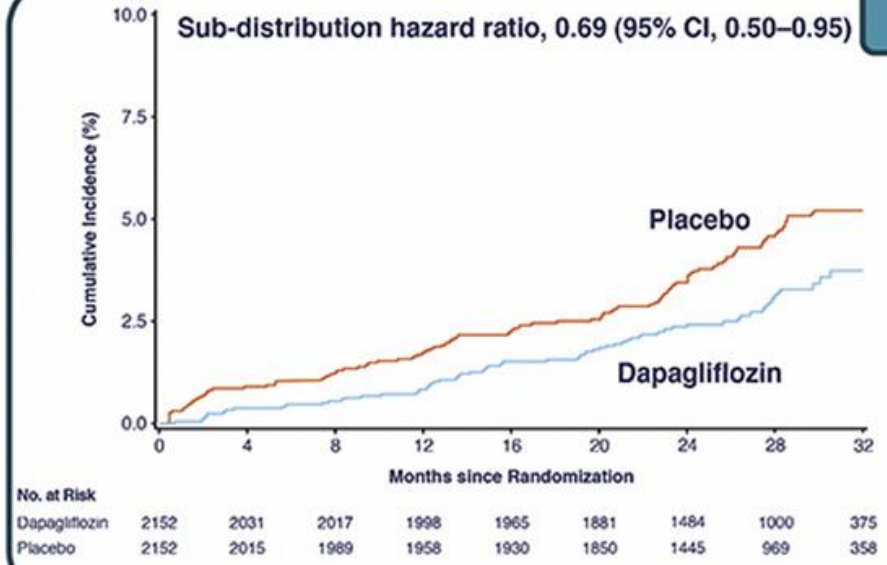
Study design

- eGFR 25–75 mL/min/1.73m^2
- UACR 200–5000 mg/g
- With/without type 2 diabetes
- Stable, maximally-tolerated ACEi/ARB dose



Outcomes

- Abrupt declines in kidney function, defined as a doubling of serum creatinine between two subsequent visits (median time-interval, 100 days)
- Investigator-reported SAEs of acute kidney injury (pre-defined list)



Results

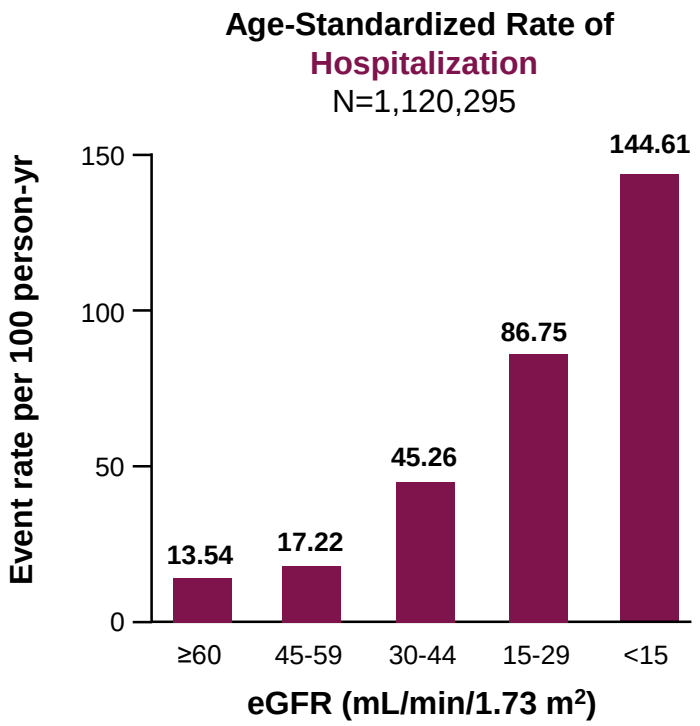
- **Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease with increased albuminuria (Figure)**
- **No heterogeneity in effect of dapagliflozin versus placebo across baseline subgroups**
- **SAEs of acute kidney injury occurred less frequently with dapagliflozin versus placebo**

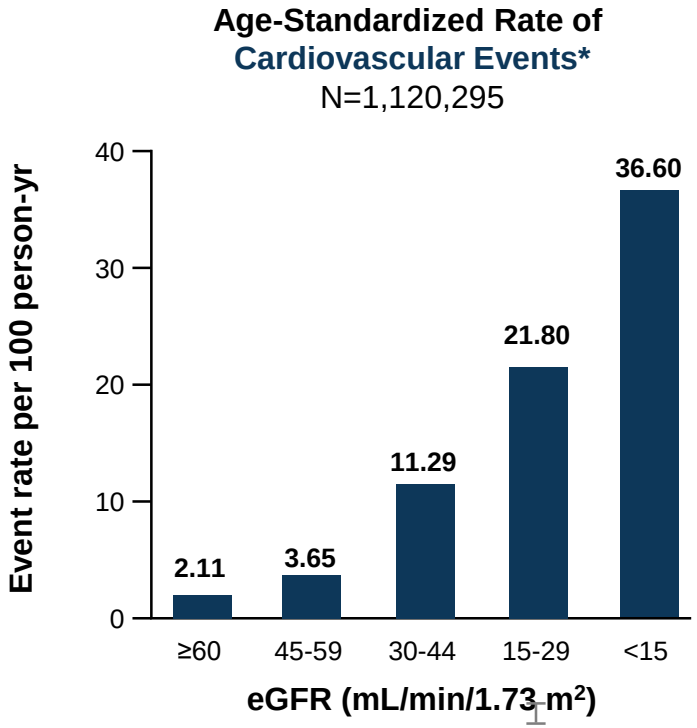
Heerspink et al, 2021

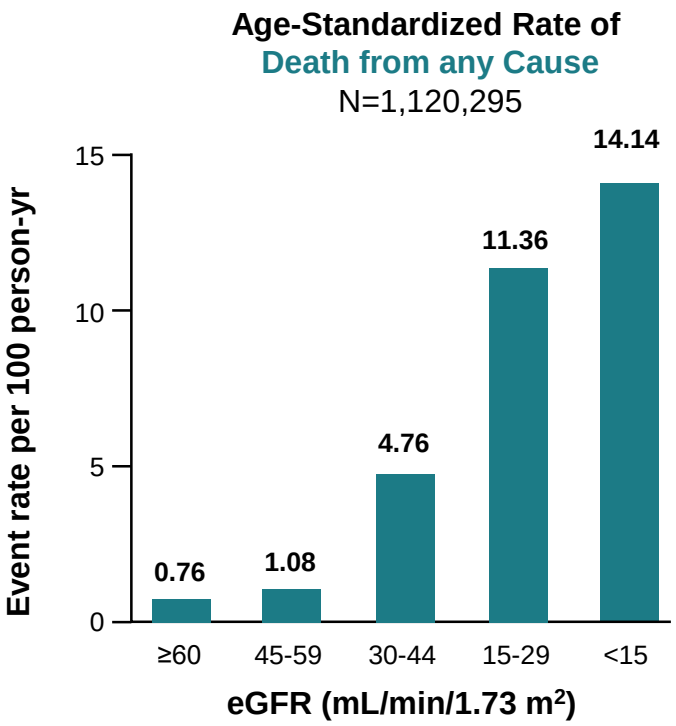
eGFR=estimated glomerular filtration rate; SAE=serious adverse event; UACR=urinary albumin-to-creatinine ratio

CONCLUSION: ***Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease and substantial albuminuria, with and without type 2 diabetes***

The Risk of Morbidity and Mortality Rises Sharply as CKD Progresses







*Cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

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

Kidney and Blood Pressure Research

Review Article

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From Proteinuria to Fibrosis: An Update on Pathophysiology and Treatment Options

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Quand utiliser un iSGLT2 en néphrologie

Le plus tôt possible pour toute IRC (Stade 2 – 4) avec protéinurie significative (> 200mg/g créat.) en ciblant surtout les pathologies à risque de progression :

- Néphropathie diabétique (type II) et hypertensive, idéalement même avant toute IR (Stade 1), si µalbuminurie.
- Syndrome métabolique (Néphropathie prédiabétique et HTA)
- Glomérulopathies (Néphropathie à IgA, GNEM, GN lésions minimes, HSF, …)
- Néphropathie tubulo-interstitielles.
- …etc…
- ADPKD, Néphropathie lupique et vascularite à ANCA **???**
- Avec IEC / ARA2
  - + Spironolactone / Finerenone
  - + Patiromer / Zirconium Cyclosilicate
  - + Bicarbonate / Veverimer

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Merci pour votre attention