SGLT2i and Kidney
a new hope for slowing the loss of kidney function in CKD

Dr Guillen A MA .
Epicura Nephrologie
WKD 2022

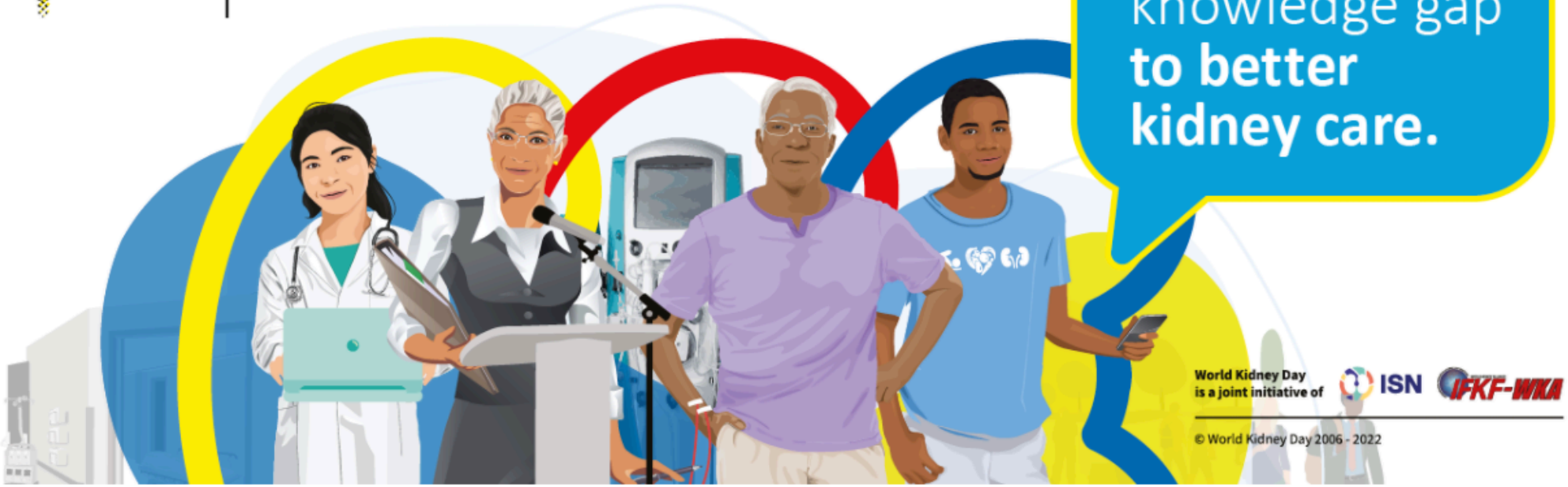
World Kidney Day

10 MARCH 2022

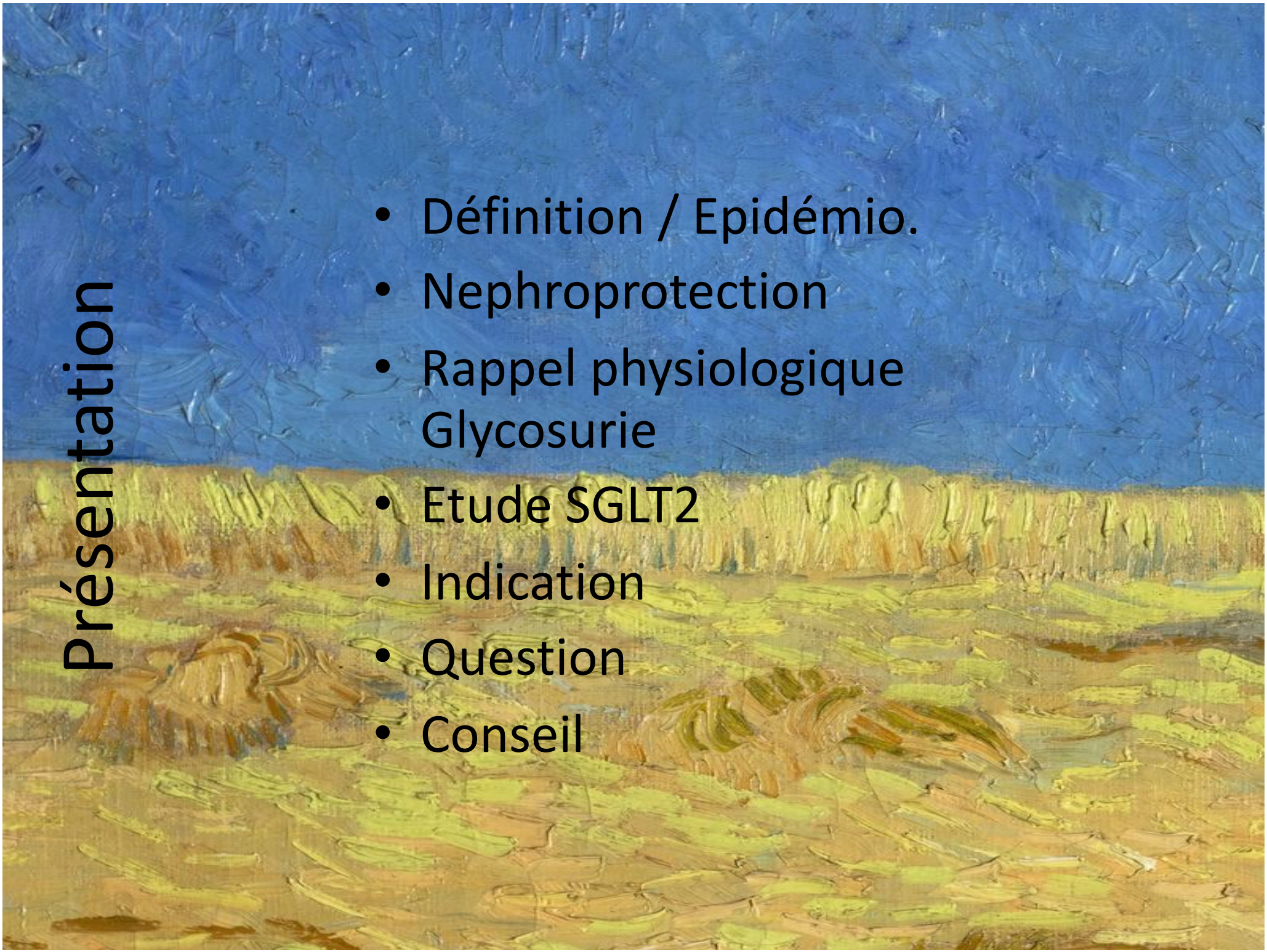
Kidney Health for All

#worldkidneyday #kidneyhealthforall

www.worldkidneyday.org



World Kidney Day is a joint initiative of ISN IFKF-WKA


Présentation
• Définition / Epidémio.
• Nephroprotection
• Rappel physiologique Glycosurie
• Etude SGLT2
• Indication
• Question
• Conseil

Maladie rénale chronique

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

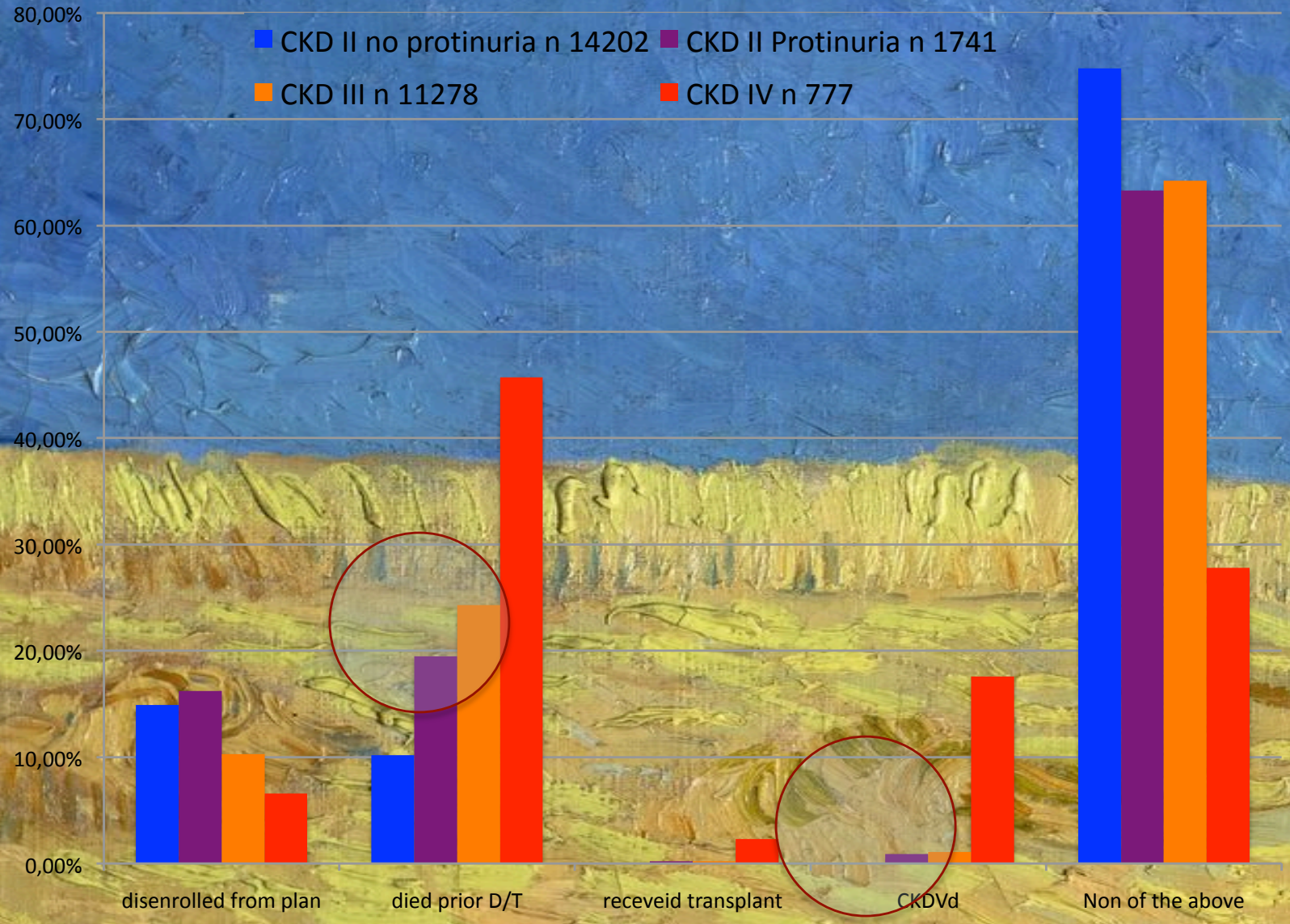
CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

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

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.
GFR, glomerular filtration rate.

Effets de la protéinurie



Douglas et al. Longitudinal Folow up and outcomes among a Population with KD in a Large Managed Care Organization. Arch Inter Med 2004 ; 164 : 659-663

Maladie rénale chronique

DIAGNOSTIC

- Constitutionnelle
- Fonctionnelle non-eGFR

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

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GFR, glomerular filtration rate.

Mortalité

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization.

Alan Go et al. N Engl J Med 2004;351:1296-305.

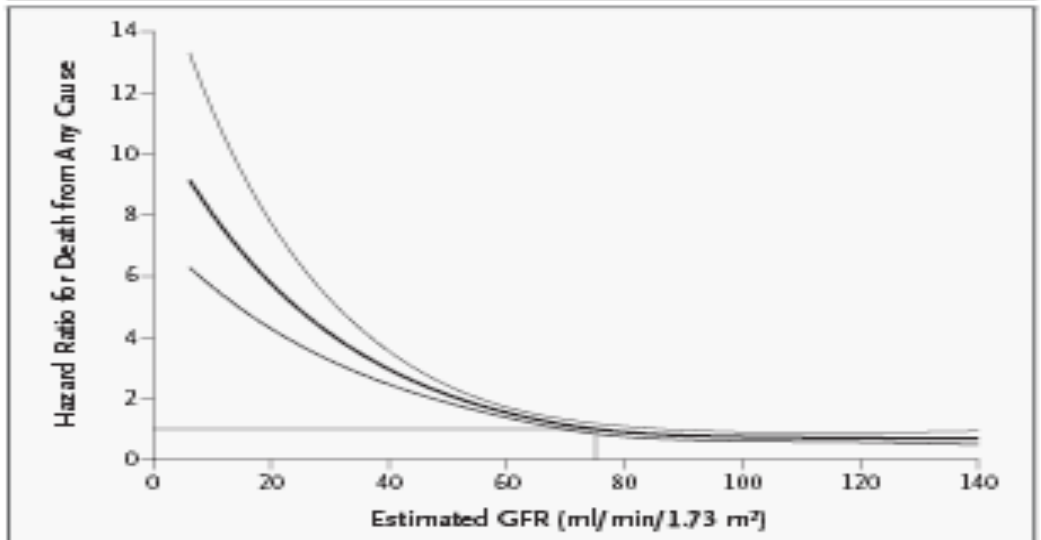


Figure 4. Unadjusted Hazard Ratio for Death from Any Cause, According to the Estimated GFR at Baseline.

The estimated hazard ratio (middle curve) is shown with the 95 percent confidence limits (upper and lower curves).

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

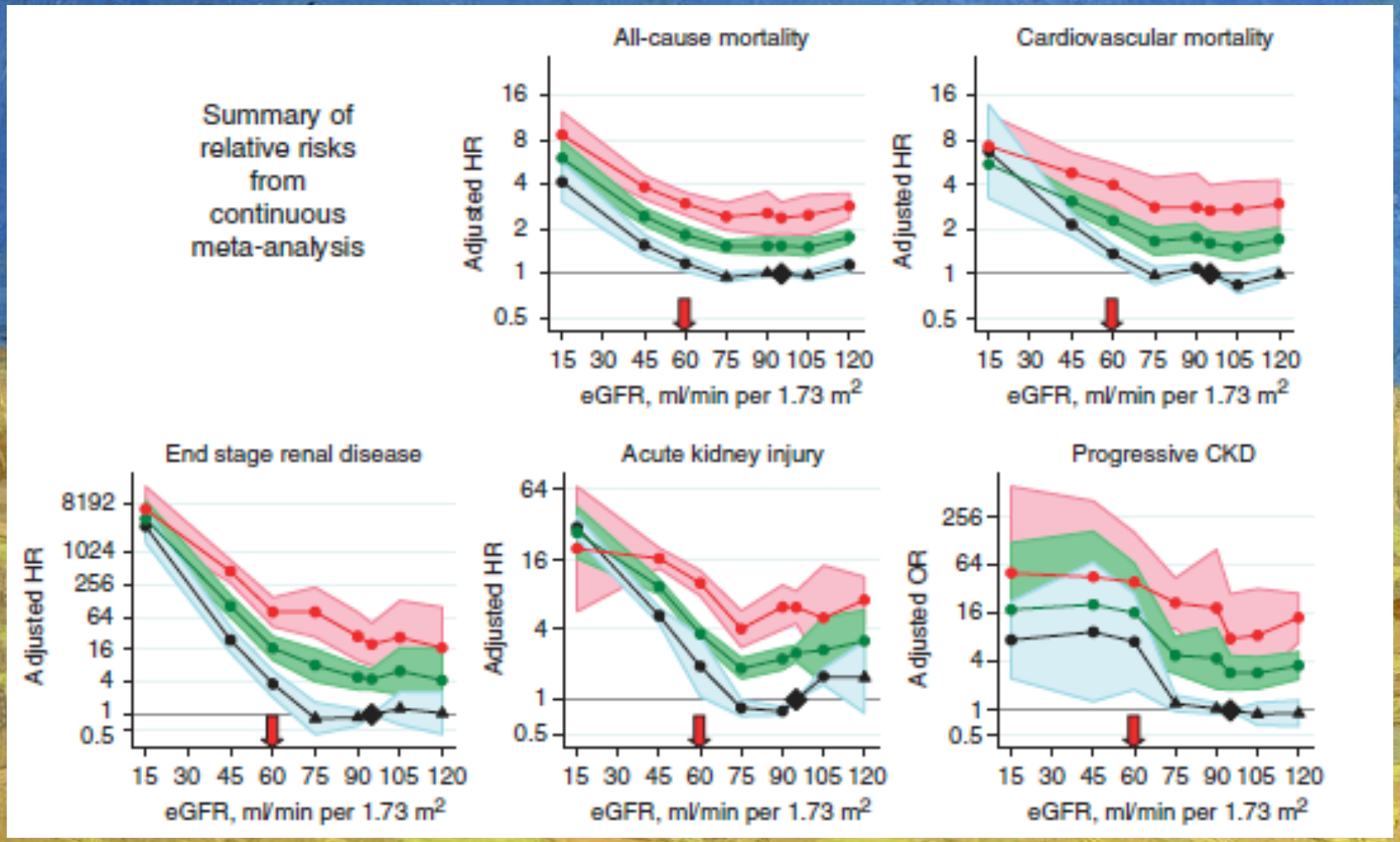
* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

† This group served as the reference group.

- We estimated the longitudinal glomerular filtration rate (GFR) among 1,120,295 adults within a large, integrated system of health care delivery in whom serum creati- nine had been measured between 1996 and 2000 and who had not undergone dialysis or kidney transplantation

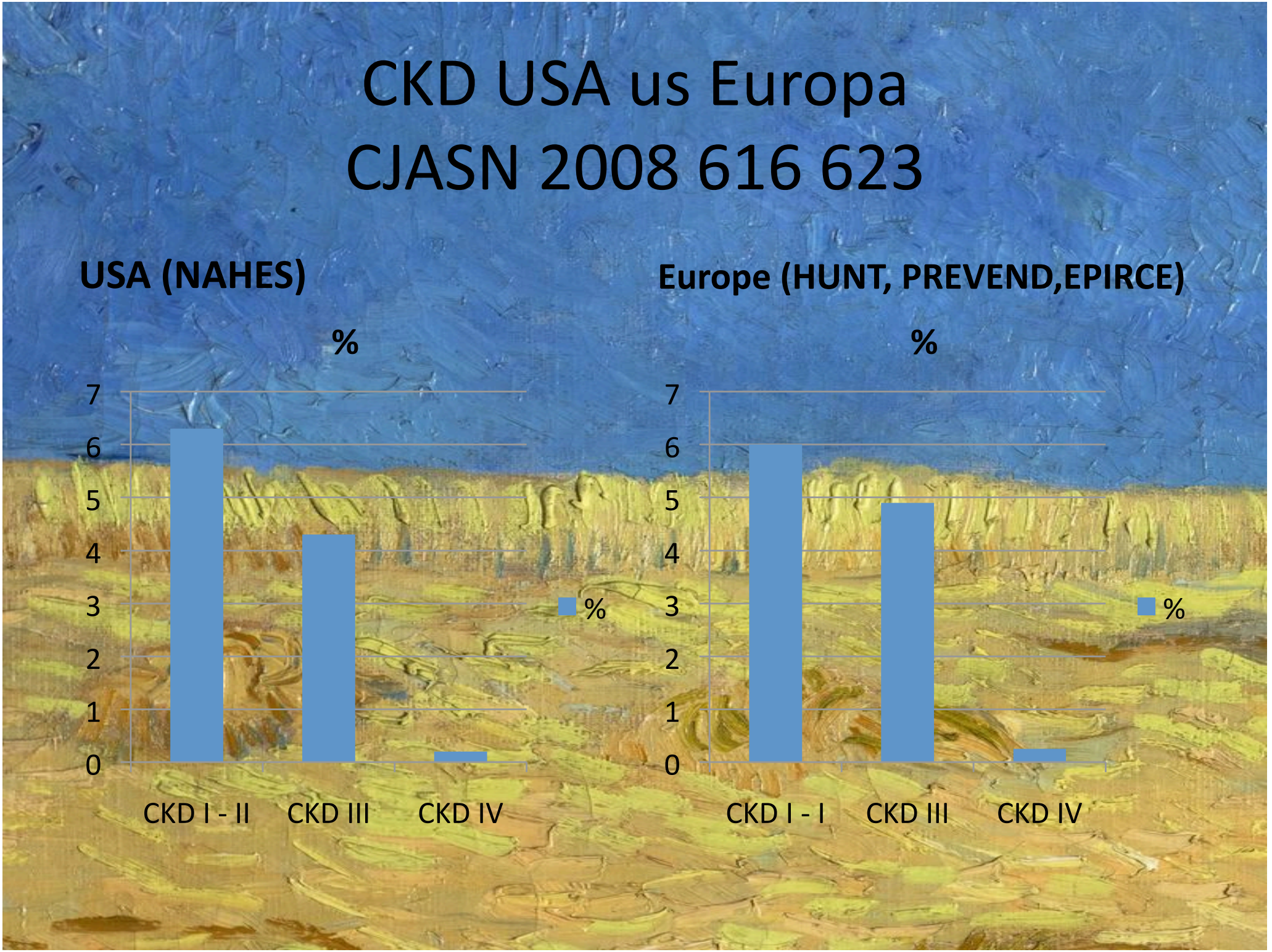
Patient n° 1

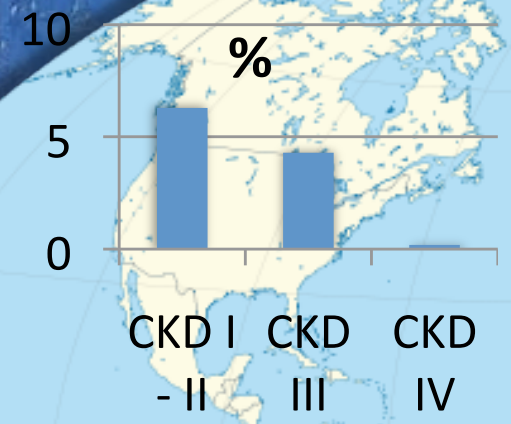
The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report

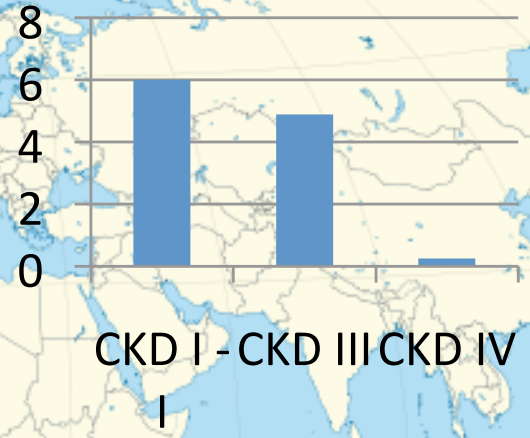


Kidney International (2011) **80**, 17–28

CKD USA us Europa
CJASN 2008 616 623







→ Semblables pays industrialisés

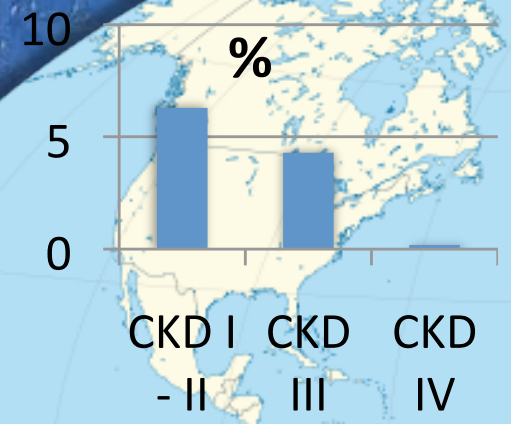
→ 10% CKD.

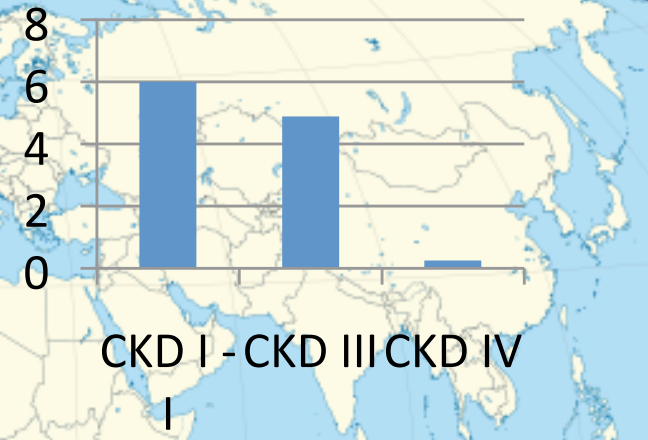
→ ! 55 – 85 ! > 65 ans : 15 % ?

→ majoration cout mortalité morbidité

World Kidney Day
12 March 2015

Cout





→ Hospitalisation pour CVD

→ Cout traitement HTA/ANEMIE/CVD

→ Cout Dialyse

→ Cout maladie oncologique et infectiologie

Maladie rénale chronique
Peut on la ralentir ?

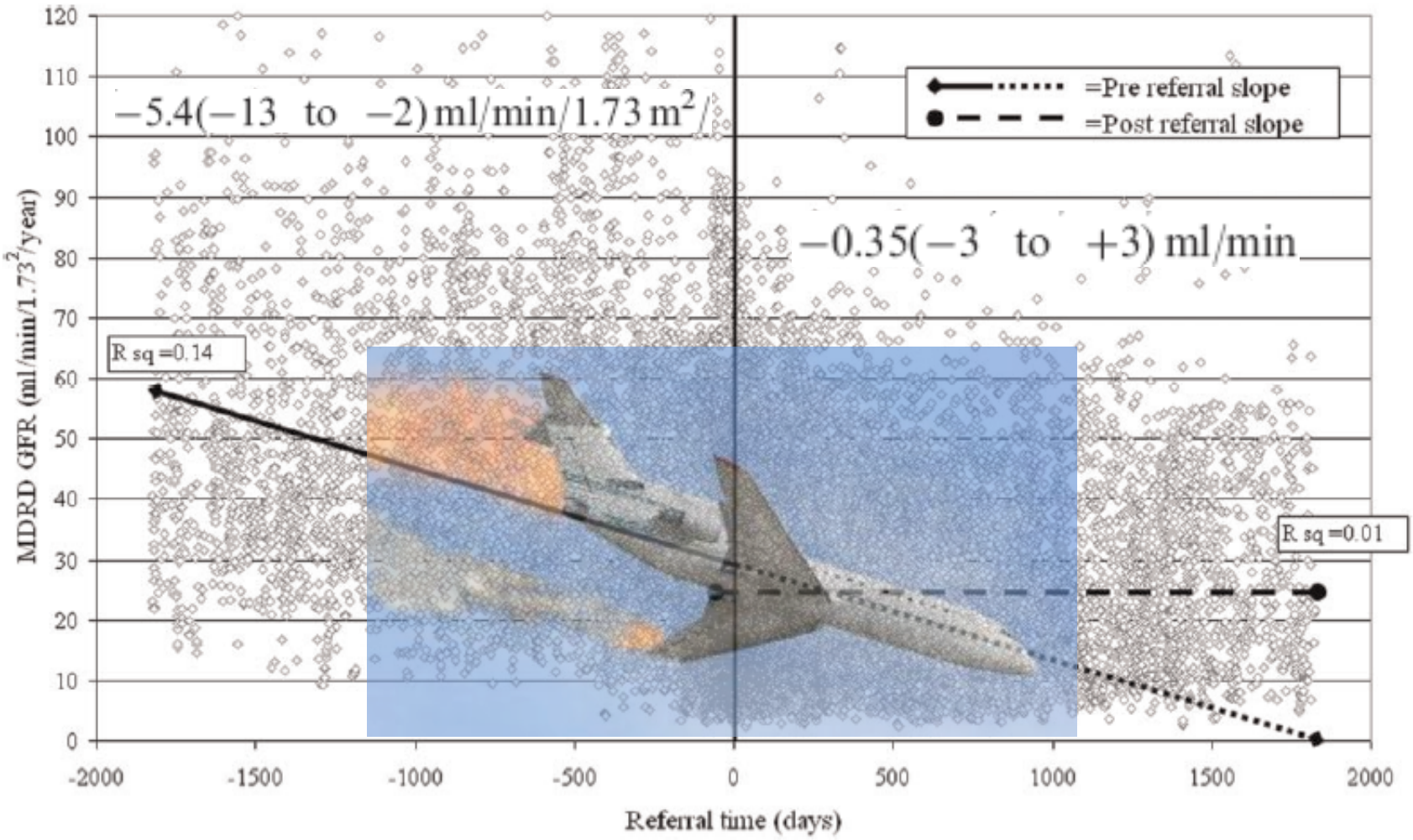


Fig. 1. Decline in MDRD GFR in the 5 years prior to and following nephrology referral with regression lines of summary pre- and post-referral GFR slopes (each point is a single GFR measure).

Quelques bases dans la MRC

Dépistage

Dépister la MRC dans les populations à risque

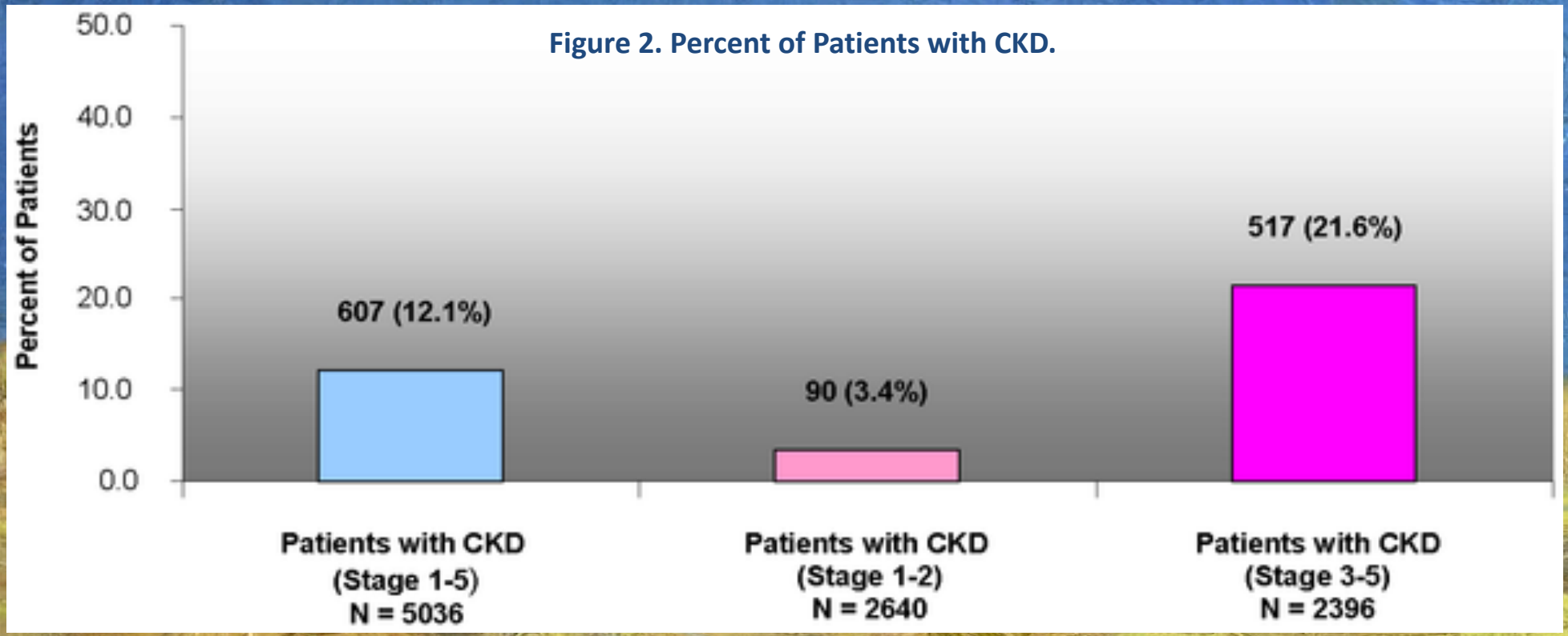
Un certain nombre de personnes ont une probabilité importante d'avoir une atteinte rénale et doivent donc être l'objet d'un dépistage systématique. Le dépistage doit porter sur les 2 indicateurs que sont le DFG estimé et le ratio albuminurie/créatininurie afin d'identifier les stades précoces de la MRC.

Facteurs de risque

- *Diabète*
- *Hypertension*
- *Obésité > 30 kg/m²*
- *Maladie cardiovasculaire*
- *Personnes âgées > 60 ans*
- *Antécédents familiaux d'insuffisance rénale chronique*
- *Uropathies obstructives*
- *Maladies de système*
- *Médicaments néphrotoxiques*
- *Bas poids de naissance (<2,5 kg)*
- *Épisodes d'insuffisance rénale aiguë*

Le dépistage est il bien réalisé ?

Figure 2. Percent of Patients with CKD.



Szczech LA, Stewart RC, Su HL, DeLoskey RJ, Astor BC, et al. (2014) Primary Care Detection of Chronic Kidney Disease in Adults with Type-2 Diabetes: The ADD-CKD Study (Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease). PLOS ONE 9(11): e110535. https://doi.org/10.1371/journal.pone.0110535
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0110535

HYPERTENSION

Global Science. Local Change.

KDIGO is *the* global nonprofit organization developing and implementing evidence-based clinical practice guidelines in kidney disease.

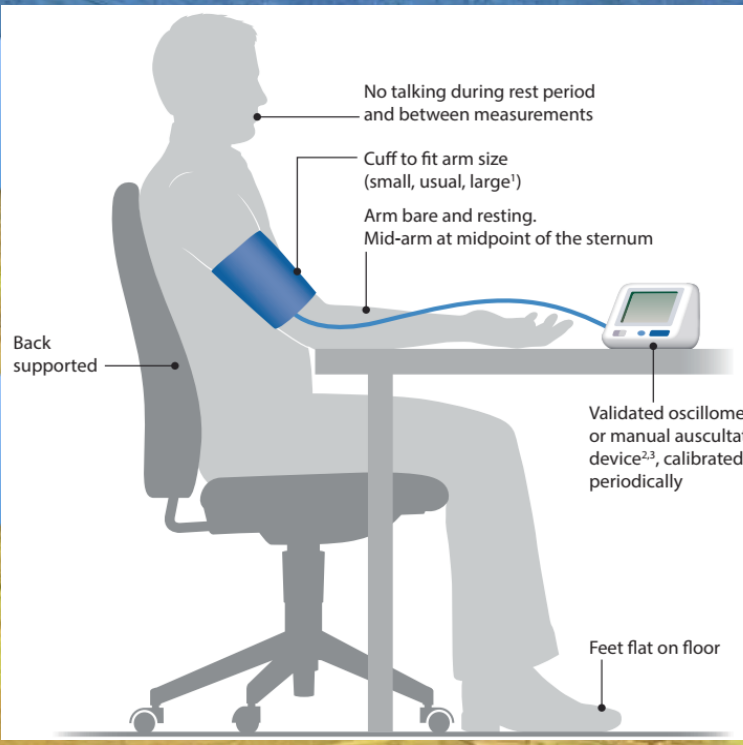
GO TO ALL GUIDELINES

< 120 /80

- Prudence.

... 130 / 80

- Objectif.



- Quiet room (no talking by patient or observer)
- No smoking, caffeine, or exercise for ≥30 min before measurement
- Empty bladder
- Note the time of most recent BP medication taken before measurements
- Relax for >5 min
- At first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings
- Separate repeated measurements by 1–2 minutes
- Use an average of ≥2 readings obtained on ≥2 occasions
- Provide patients with the SBP/DBP readings verbally and in writing

[1]Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used

[2]See validated electronic devices lists at www.stridebp.org

[3]For auscultatory readings, either the stethoscope diaphragm or bell may be used. Use a palpated radial pulse obliteration pressure to estimate SBP, then inflate the cuff 20–30 mm Hg above this level for auscultatory determination of BP level. Deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds

Rationale for Target SBP <120 mm Hg in CKD

- For most patients with CKD, a cardiovascular event is a more likely outcome than ESKD.[1]
- SPRINT confirmed cardiovascular and survival benefits in non-diabetic CKD.[2]
- ACCORD showed marked reduction in stroke in diabetes, but only included 401 patients with eGFR <60 ml/min/1.73m^2; nonetheless, benefits of SBP <120 mm Hg in the standard glycemia arm similar to those seen in SPRINT.[3,4]
- Meta-analyses demonstrate reduction of CV risk proportional to BP lowering, though some show lower proportional risk reduction in the presence of CKD and of DM.[5,6,7]

[1]O'Hare J Am Soc Nephrol 2007;18: 2758. [2]Cheung JASN 2017; 28: 2812. [3]Papademetriou Am J Nephrol 2016; 43: 271. [4]Tsuijimoto Hypertension 2018;72;323. [5]BPLTC BMJ 2013;347:f5680; [6]Ettehad Lancet 2016;387:435; [7]Malhotra JAMA Int Med 2017;177:1498

Blood Pressure Management in Patients with CKD, with or without Diabetes, not Receiving Dialysis

Recommendation 3.1.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, using standardized office BP measurement (2B).

This recommendation is weak according to GRADE because there is less certainty that the benefits outweigh the harms in the following scenarios:

- CKD G4 and G5
- Diabetes
- Individuals with SBP 120-129 mm Hg
- Patients with very low baseline diastolic BP, particularly in the presence of coronary artery disease
- Specific etiology of CKD
- Severely increased proteinuria
- Older age
- Younger age
- Very frail
- "White coat" hypertension

Individualization is KEY

Potential Implications

Potential implications of the 2021 KDIGO blood pressure guideline for adults with chronic kidney disease in the United States

2021 KDIGO Guideline

What's new for adults with CKD and high BP?

- Recommends treatment to SBP <120 mmHg using standardized office BP measurement
- Recommends ACEi/ARBs for adults with albuminuria and high BP (SBP ≥120 mmHg)

Current Study Goals

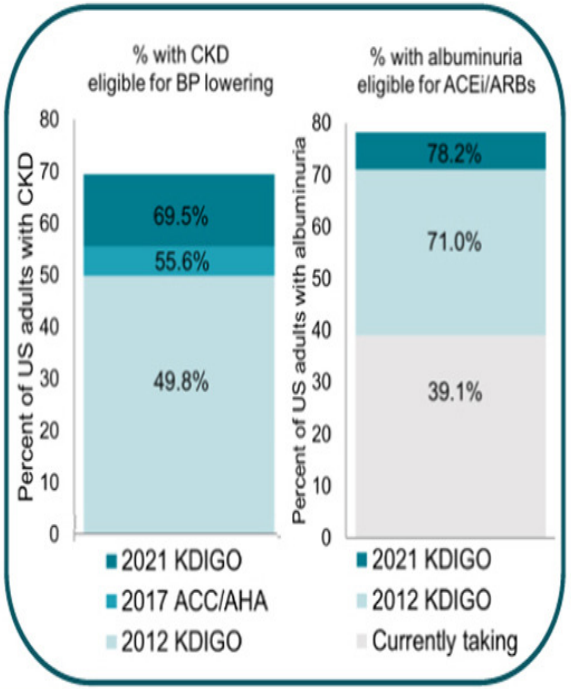
Determine potential implications of 2021 KDIGO guideline compared to:

- 2012 KDIGO guideline
- 2017 ACC/AHA guideline

Data Source

- National Health and Nutrition Examination Survey 2015-2018
- N=9,419 adults aged ≥20 years with CKD
- BP based on mean of up to 3 standardized measurements

Results



CONCLUSION:

Based on the 2021 KDIGO guideline, 69.5% of US adults with CKD are eligible for BP lowering. Among those with albuminuria, 78.2% are eligible but only 39.1% take ACEi/ARBs.

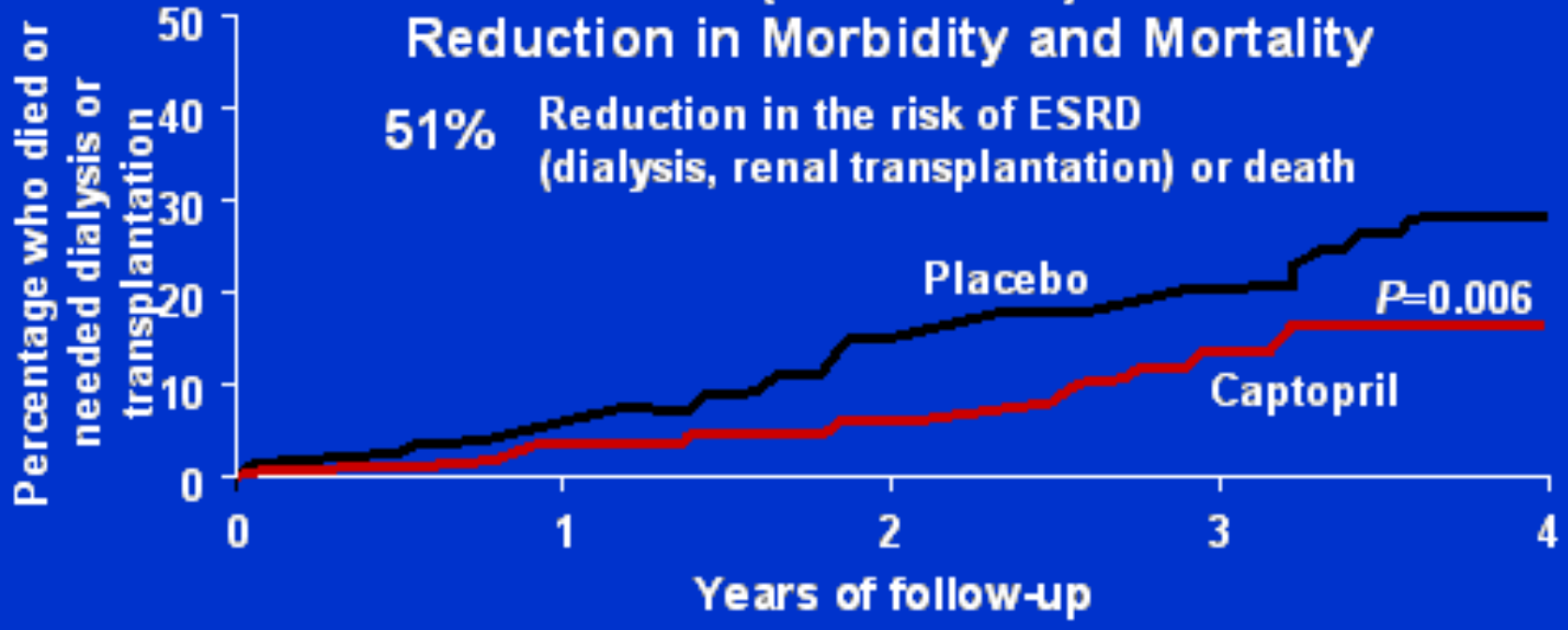
kidney INTERNATIONAL ISN

Foti, 2021

Kidney International 2021 99686-695DOI: (10.1016/j.kint.2020.12.019)

Effect of ACE Inhibition on Diabetic Kidney Disease

- 48% reduction in the risk of doubling of serum creatinine (*P*=0.007)



Lewis et al. N Engl J Med. 1993;329:1456.

Expansion of Cortical Interstitium Is Limited by Converting Enzyme Inhibition in Type 2 Diabetic patients with Glomerulosclerosis

DANIEL J. CORDONNIER,* NICOLE PINEL,§ CLAIRE BARRO,CLAIRE MAYNARD,* PHILIPPE ZAOUI,* SERGE HALIMI,*BRUNO HURAULT DE LIGNY,† YVES REZNIC,† DOMINIQUE SIMON,‡RUDOLF W. BILOUS,FOR THE DIABIOPSIES GROUPa

J Am Soc Nephrol 10: 1253–1263, 1999

Table 4. Longitudinal renal function[a]

Group	Mean BP (mmHg)		Creatinine Clearance (ml/min)		Proteinuria[b] (mg/24 h)		Urine Na (mmol/24 h)	
	M0	M24	M0	M24	M0	M24	M0	M24
Placebo (n = 10)	109 ± 12	108 ± 10	119 ± 54	102 ± 53	547 (191,1567)	881 (239,3242)	145 ± 75	120 ± 68
Perindopril (n = 9)	101 ± 12	96 ± 11	124 ± 23	109 ± 31	668 (226,1369)	436 (187,1016)	202 ± 136	171 ± 88

[a] Results are given as mean ± SD. M, month.
[b] $P < 0.05$ *versus* respective baseline values between groups. Results are expressed as geometric mean and antilog of the 95% confidence interval of the mean.

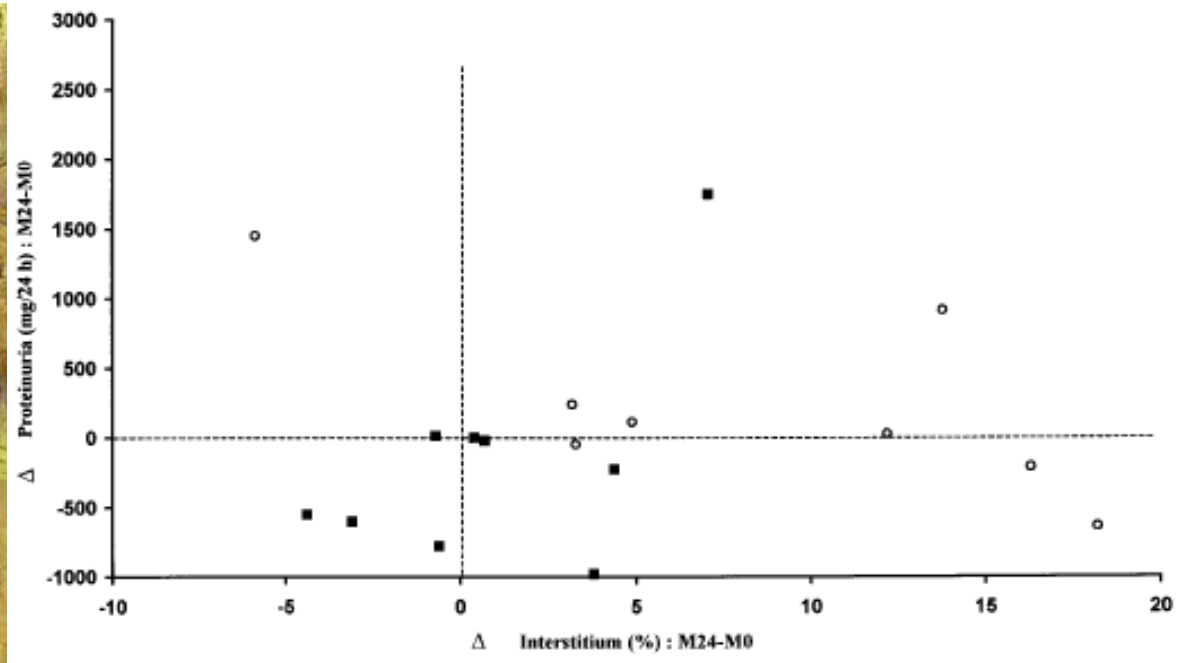
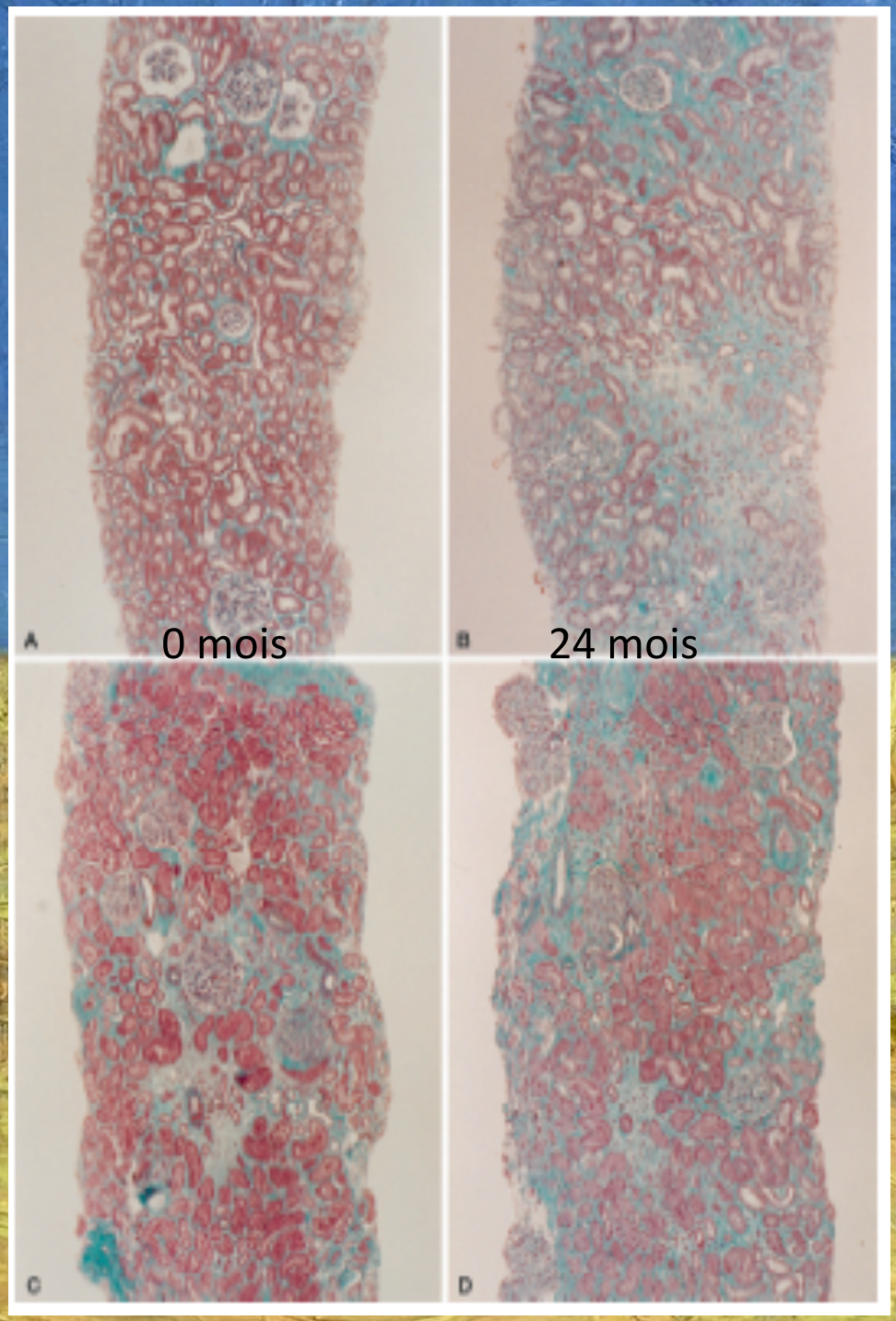


Figure 3. Individual changes at 24 mo from baseline in mean cortical interstitium fractional volume (x-axis) and in proteinuria (y-axis) for Perindopril (■) and placebo (○) groups.

Placebo

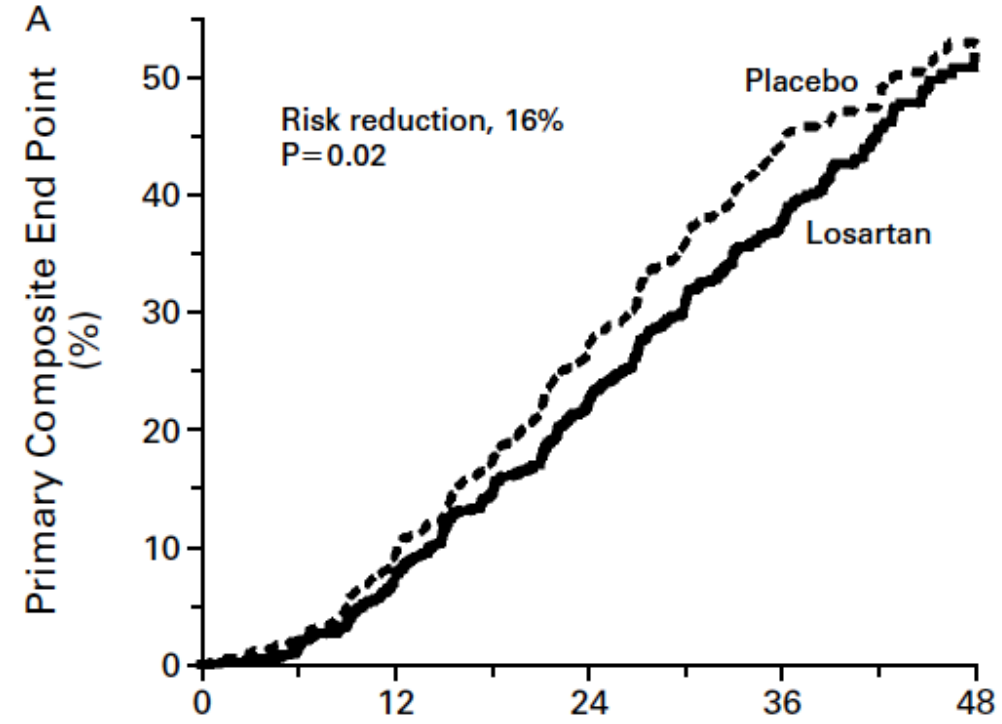
Perindopril

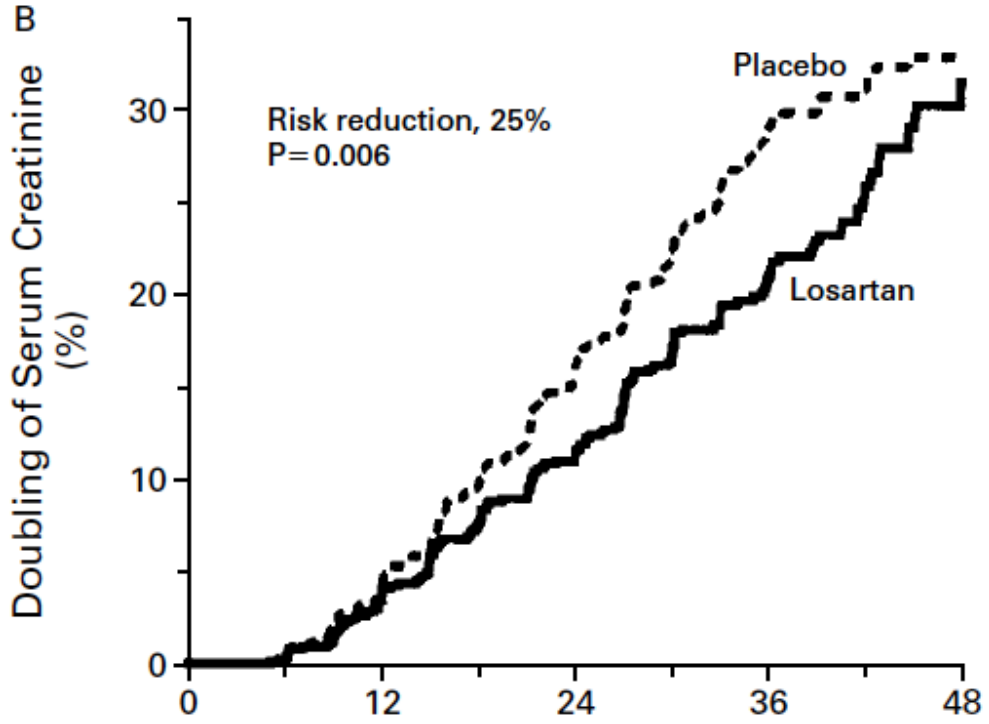


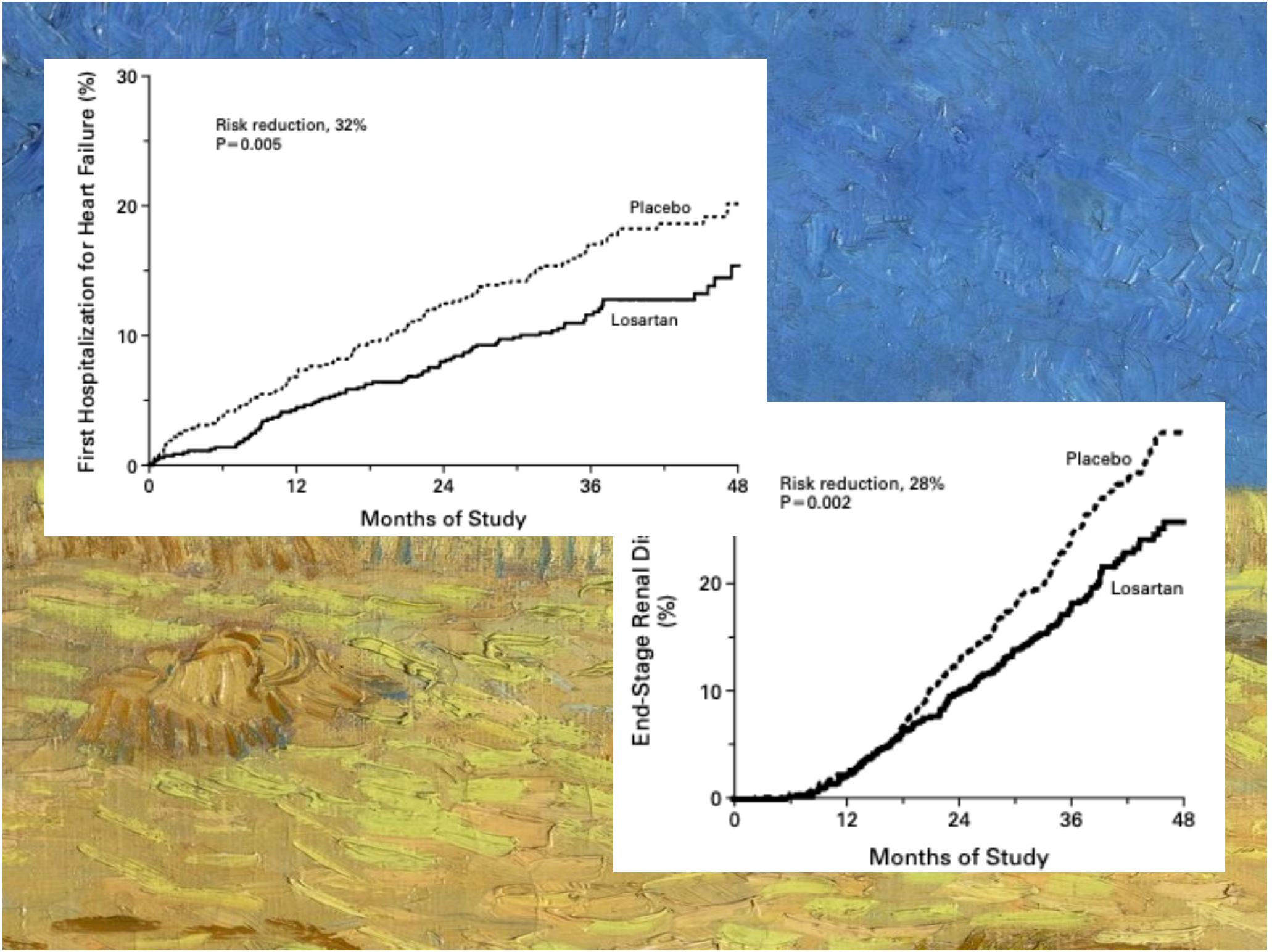
EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

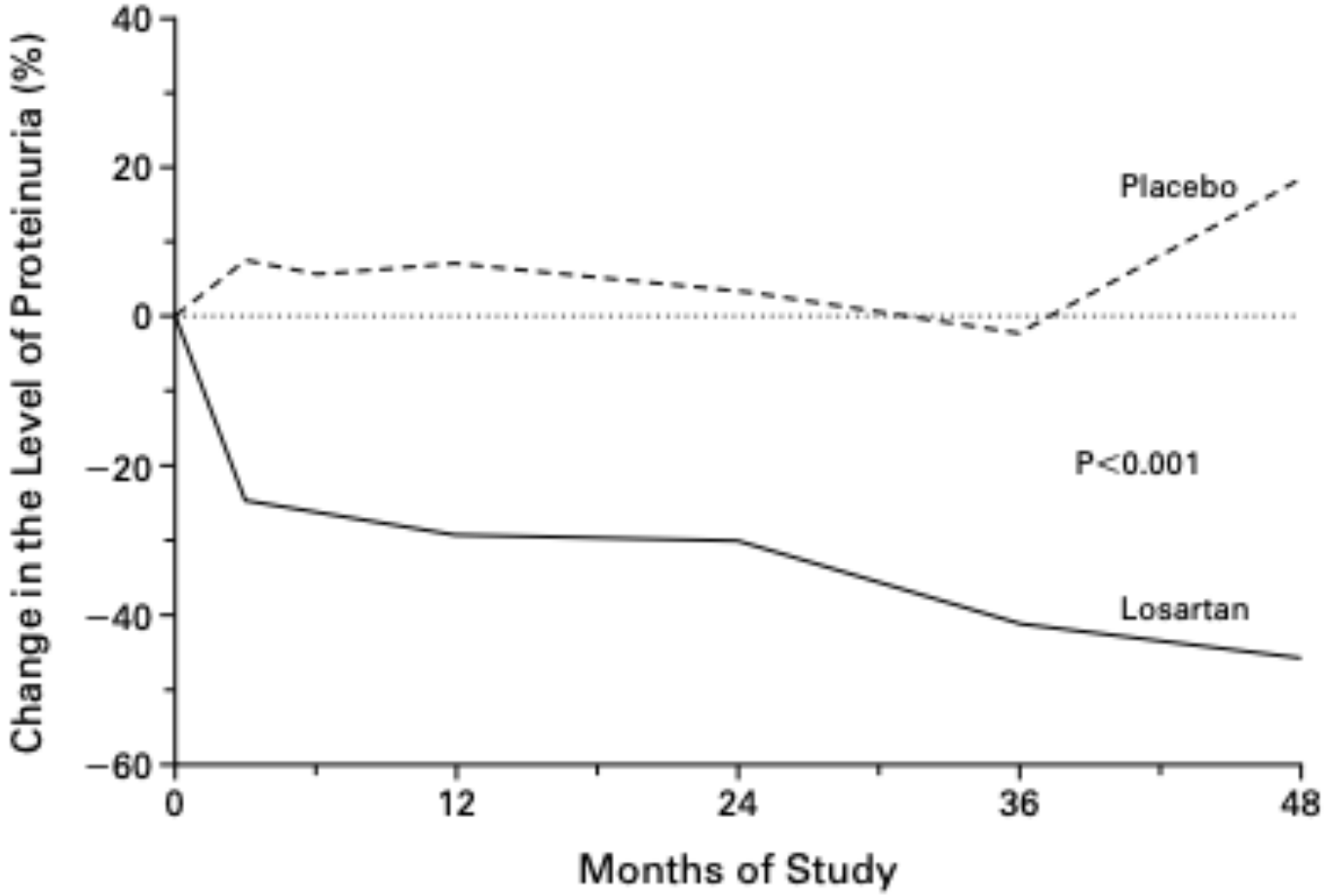
BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

N Engl J Med, Vol. 345, No. 12 · September 20, 2001 · www.nejm.org · 861






First Hospitalization for Heart Failure (%)
30
20
10
0
Risk reduction, 32%
P=0.005
Placebo
Losartan
0
12
24
36
48
Months of Study
End-Stage Renal Di
(%)
20
10
0
Risk reduction, 28%
P=0.002
Placebo
Losartan
0
12
24
36
48
Months of Study



No. at Risk					
Placebo	762	632	529	390	130
Losartan	751	661	558	438	167

Figure 3. Median Changes from Base Line in the Level of Proteinuria.

Proteinuria was measured as the urinary albumin-to-creatinine ratio in a first morning specimen. The mean follow-up time was 3.4 years.

20 ans d'observation …

- → IEC /ARBS
  - Diminution 15-20 %
    - Progression
    - ESRD
    - Mortalité
- Albuminurie diminué de 30 % = - 24 % ESRD (REASSURE) , également diminution HF/CVD
- EMA & FDA accepte
    - - 30 % albuminurie / six mois
    - Réduction de pente 0,5 – 1 sur 2-3 ans

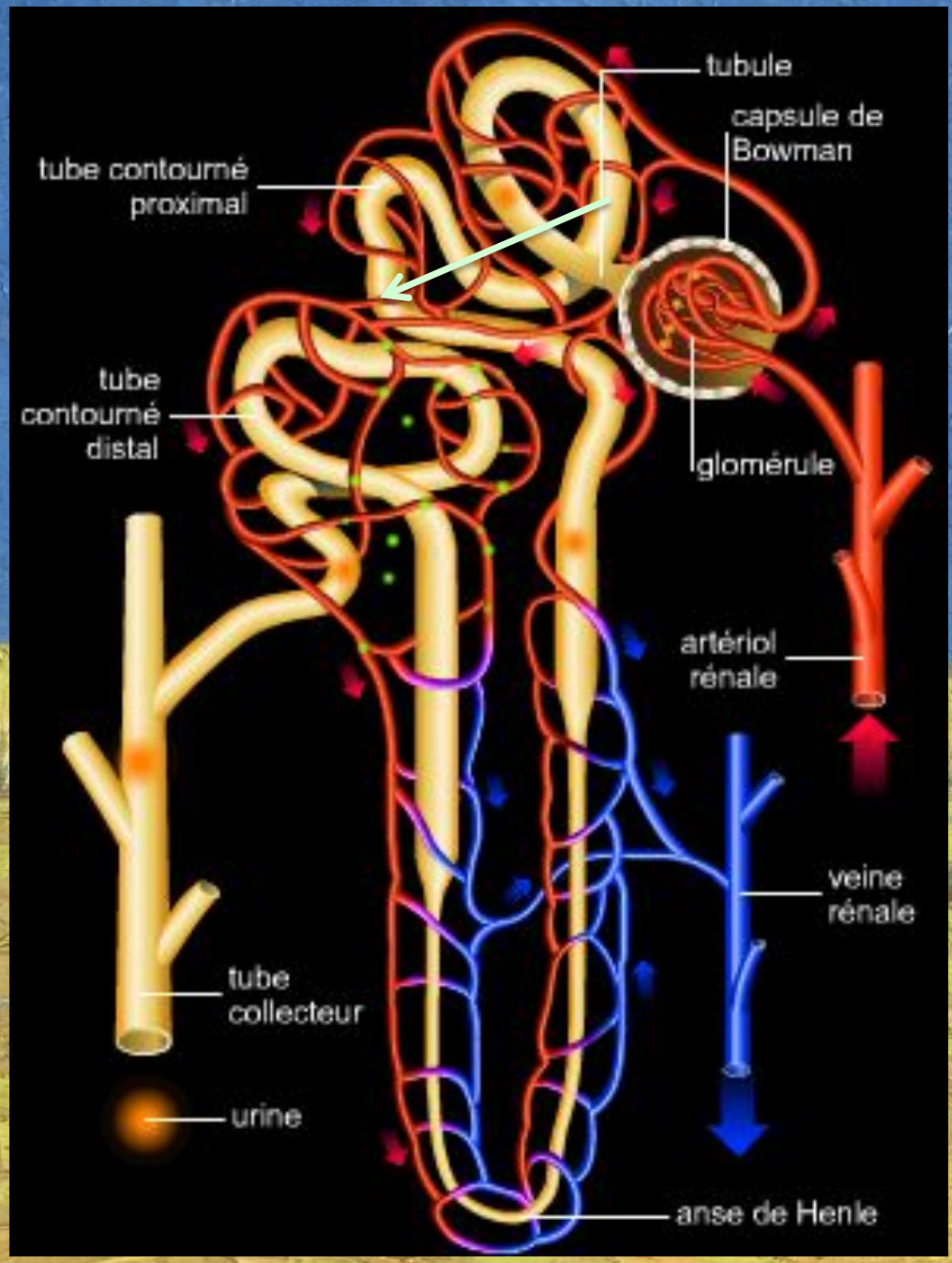
SGLT2 et REIN

(1) inhibition absorption Glu/Na

(2) Na stimule M/D

(3) Vasoconstriction a aff , vasodilatation a eff

(4) Diminution pression intraglomérulaire

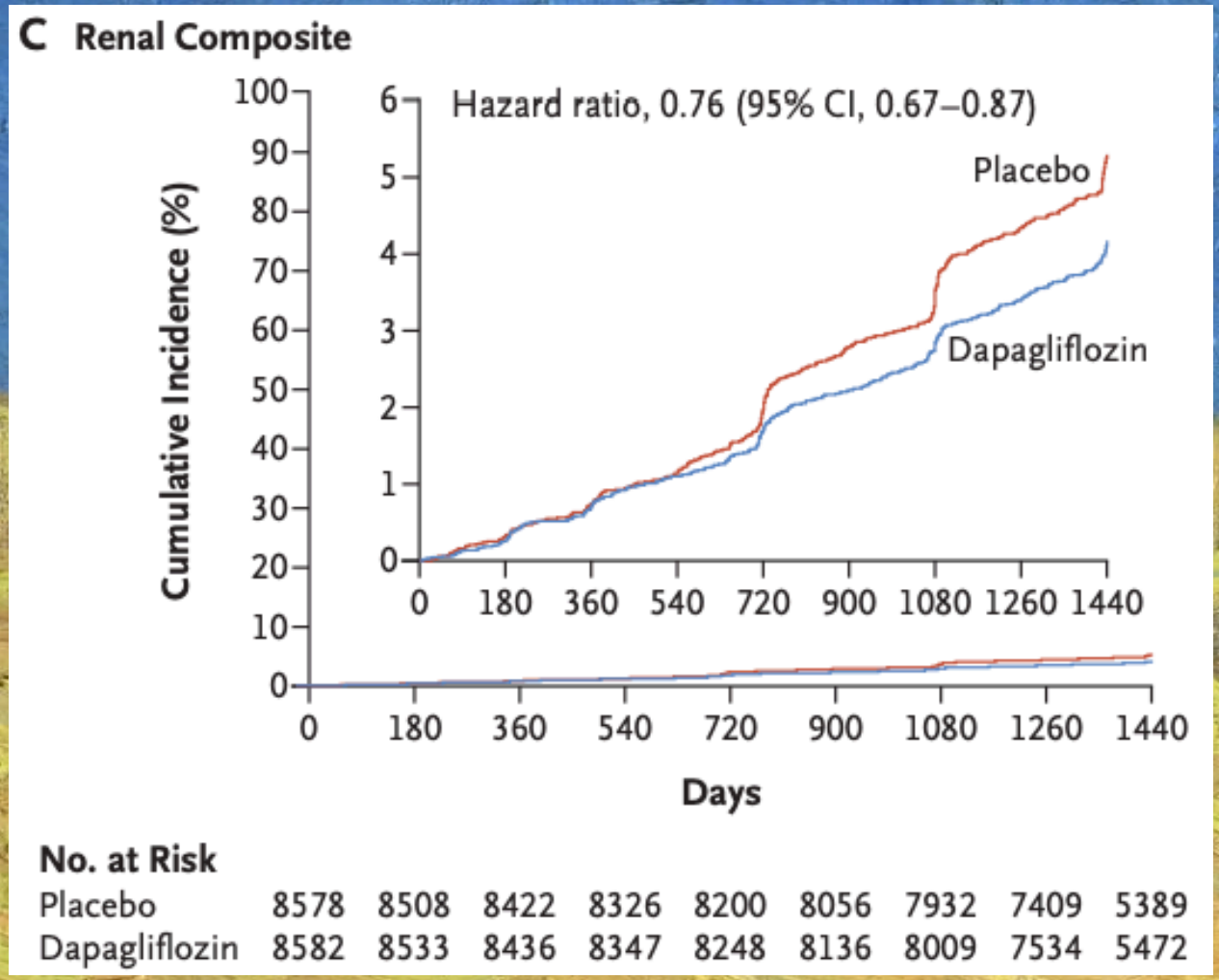


TRIAL Cardiovasculaire safety T2D => Renal Safety

CANVAS

EMPA REG

DECLARE TIMI 58



Renal trial

CREDENCE

- June 2019
- DKD

DAPA-CKD

- Oct 2020
- CKD /DKD

Empa-K

- June 2022
- CKD/DKD

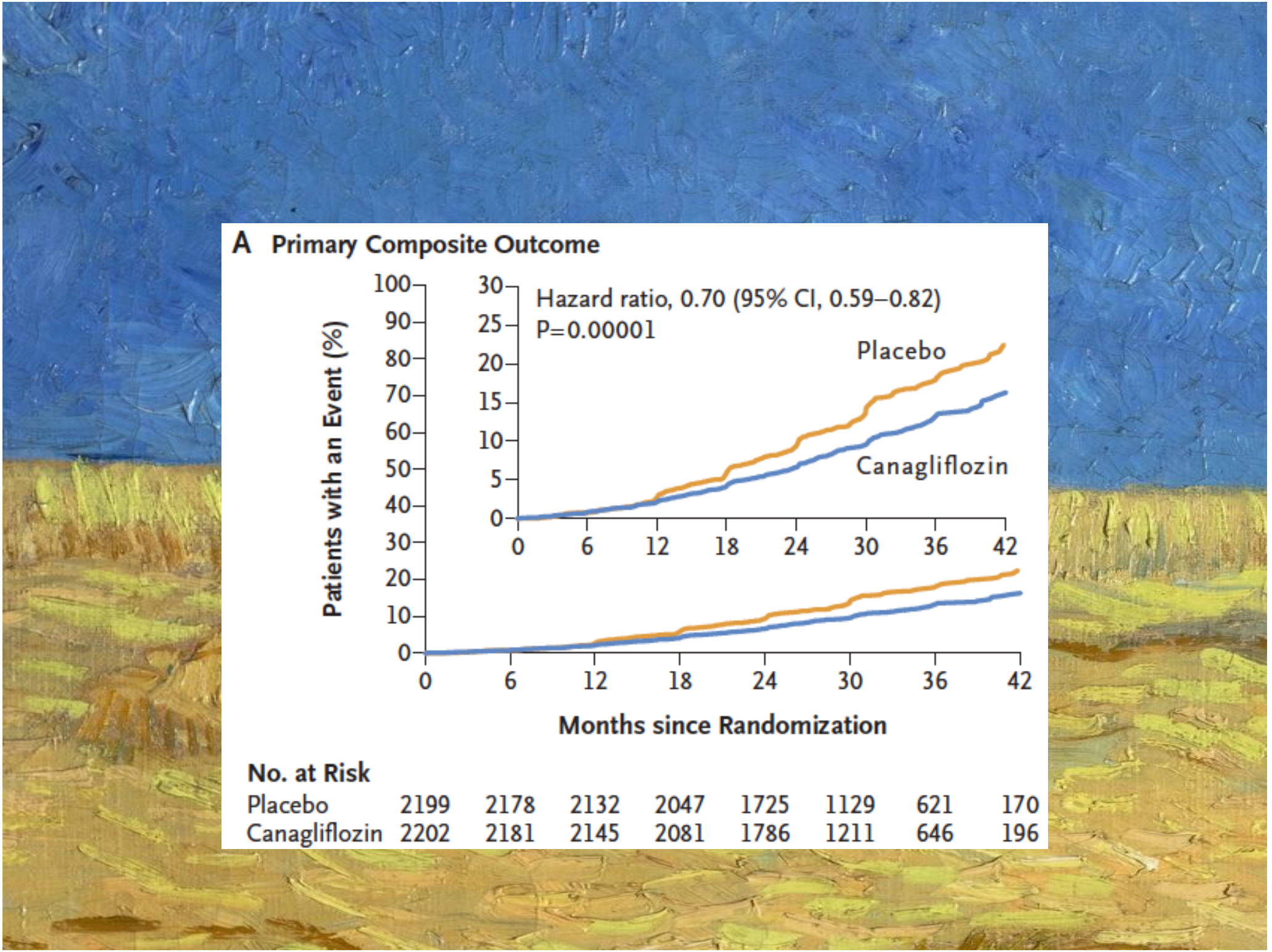
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

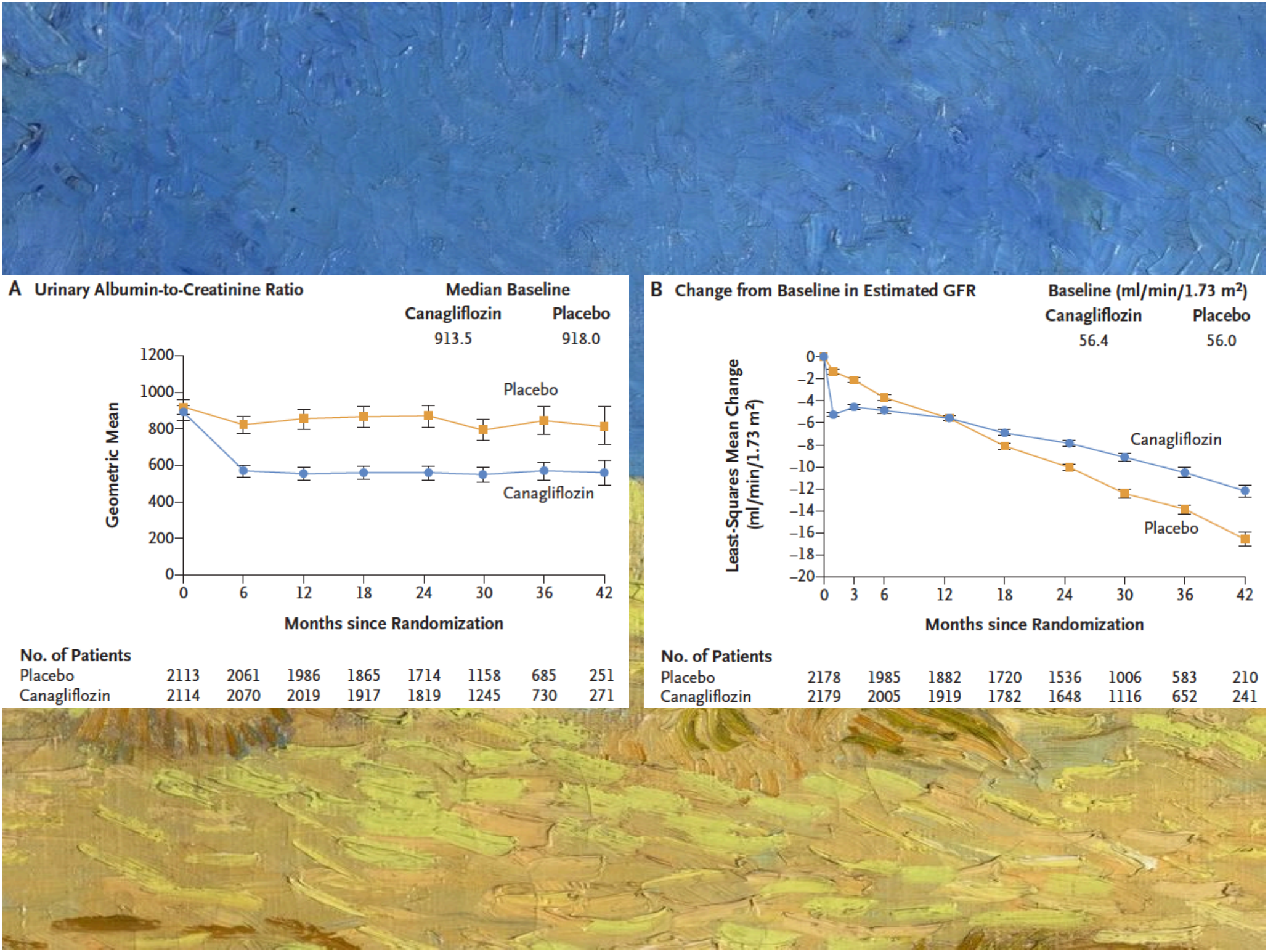
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N=2202)	Placebo (N=2199)	All Patients (N=4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

SAFE

Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA
Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA


A Primary Composite Outcome
Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P=0.00001
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2178 2132 2047 1725 1129 621 170
Canagliflozin 2202 2181 2145 2081 1786 1211 646 196


A Urinary Albumin-to-Creatinine Ratio
Median Baseline
Canagliflozin 913.5
Placebo 918.0
Geometric Mean
1200
1000
800
600
400
200
0
Placebo
Canagliflozin
0 6 12 18 24 30 36 42
Months since Randomization
No. of Patients
Placebo 2113 2061 1986 1865 1714 1158 685 251
Canagliflozin 2114 2070 2019 1917 1819 1245 730 271
B Change from Baseline in Estimated GFR
Baseline (ml/min/1.73 m²)
Canagliflozin 56.4
Placebo 56.0
Least-Squares Mean Change (ml/min/1.73 m²)
0
−2
−4
−6
−8
−10
−12
−14
−16
−18
−20
Canagliflozin
Placebo
0 3 6 12 18 24 30 36 42
Months since Randomization
No. of Patients
Placebo 2178 1985 1882 1720 1536 1006 583 210
Canagliflozin 2179 2005 1919 1782 1648 1116 652 241

DAPA CKD

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)

DAPA CKD

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

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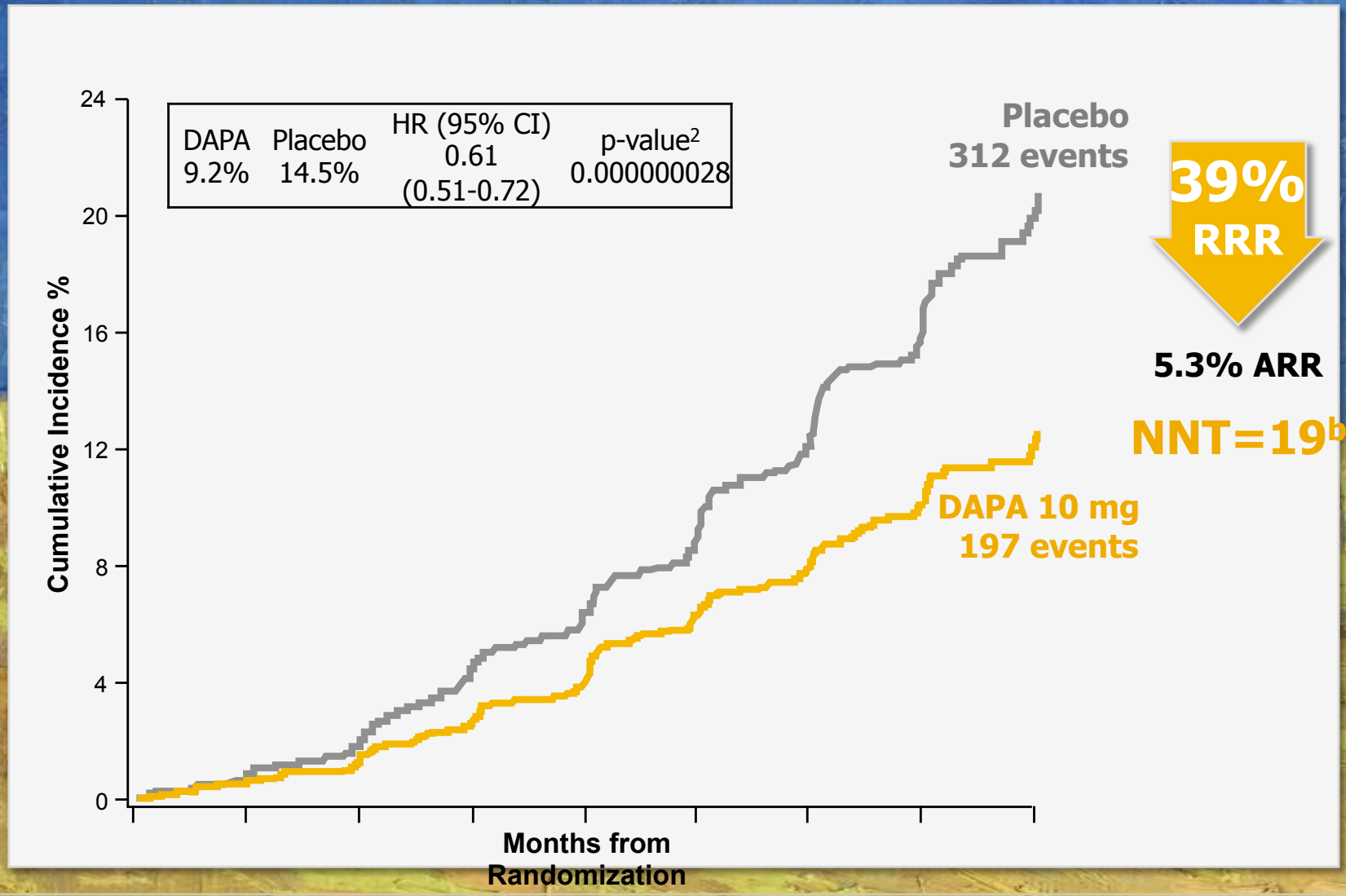
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

Dapagliflozin significantly slowed progression of kidney disease and reduced the risk of adverse outcomes (sustained ≥ 50% egfr decline, ESKD, renal or CV death)[a,1]

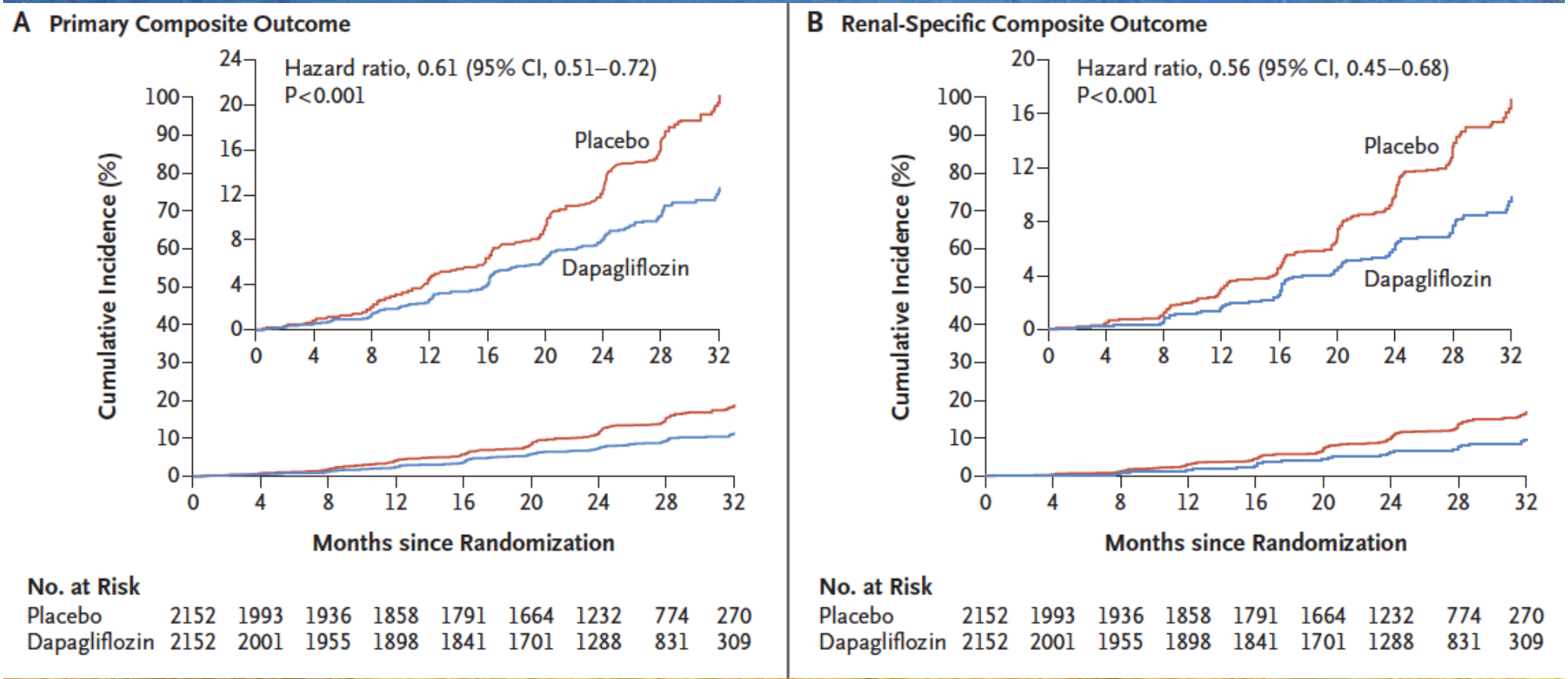


aESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.3; b95% 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.

DAPA CKD



No. at Risk

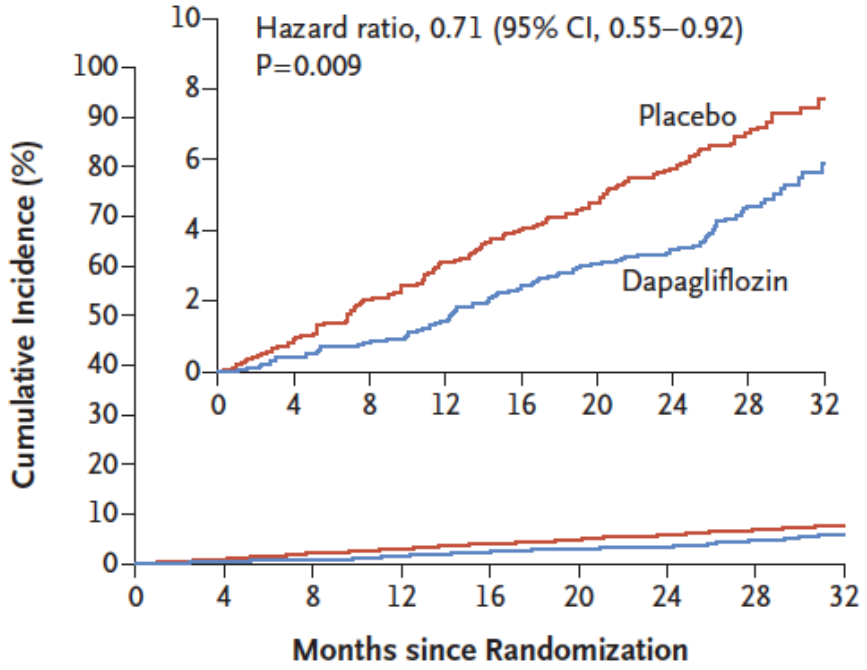
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

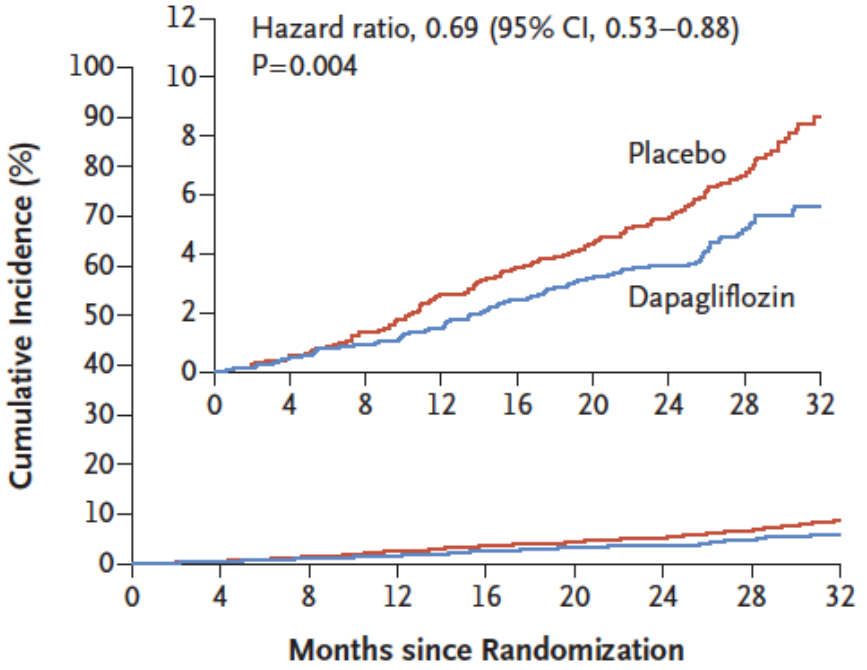
DAPA CKD

C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure



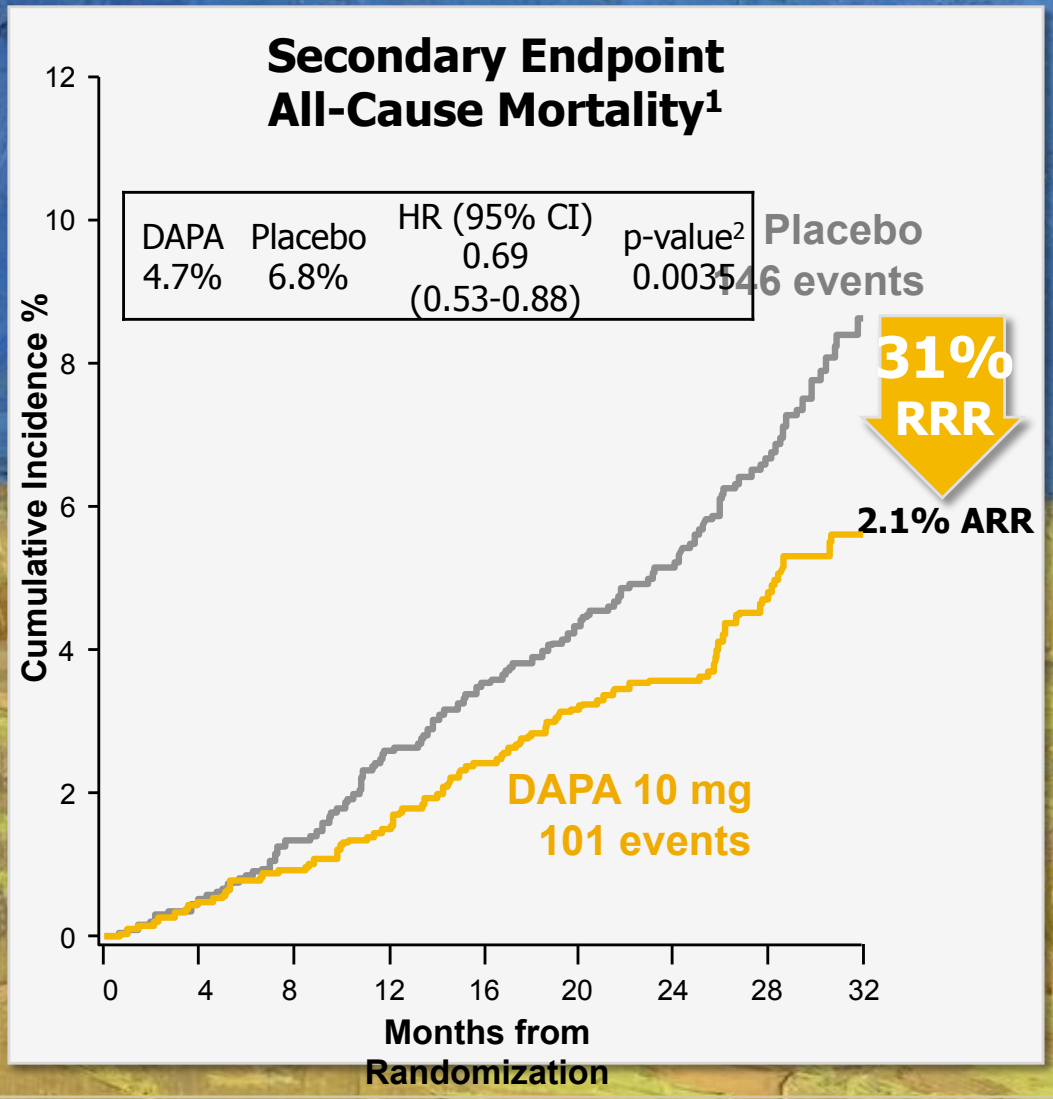
No. at Risk									
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384

D Death from Any Cause



No. at Risk									
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398

Dapagliflozin demonstrated a significant marked reduction in death from any cause.[1,2*]



All-cause mortality by causes of death and by dialysis initiation[3]

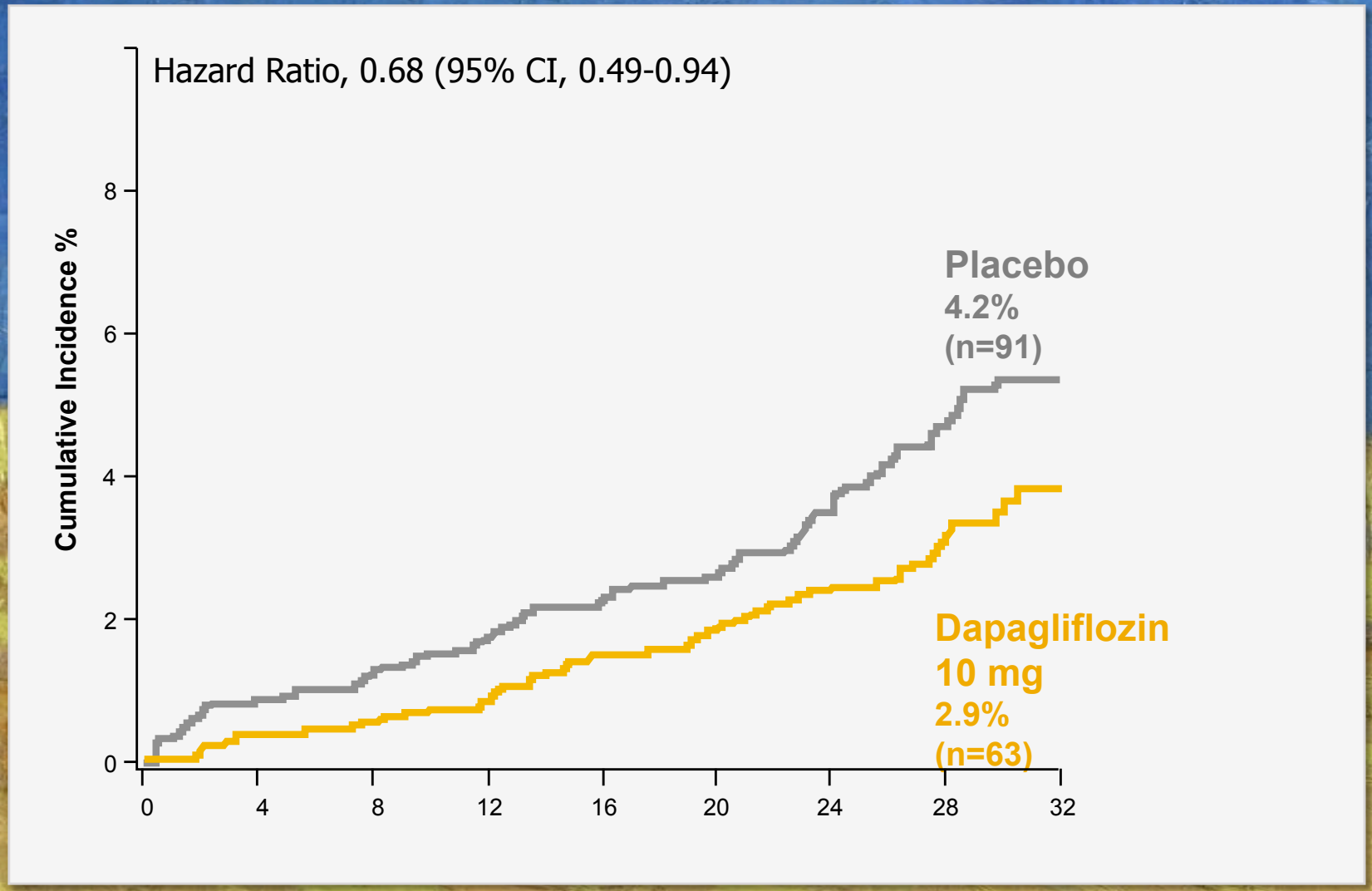
	DAPA	Placebo	Total
	n/N (%)	n/N (%)	n/N (%)
Overall mortality	101/2152 (4.7)	146/2152 (6.8)	247/4304 (5.7)
CV death	41/2152 (1.9)	50/2152 (2.3)	91/4304 (2.1)
Non-CV death	36/2152 (1.7)	66/2152 (3.1)	102/4304 (2.4)
Undetermined	24/2152 (1.1)	30/2152 (1.4)	54/4304 (1.3)
Overall mortality by dialysis initiation			
Without chronic dialysis	89/2084 (4.3)	121/2053 (5.9)	210/4137 (5.1)
With chronic dialysis	12/68 (17.6)	25/99 (25.3)	37/167 (22.2)

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; RRR = relative risk reduction

The DAPA-CKD trial was stopped early due to efficacy benefit. Because of the unplanned early stop, this secondary endpoint is considered nominal.

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. Eur Heart J. 2021;42:1216-1227.

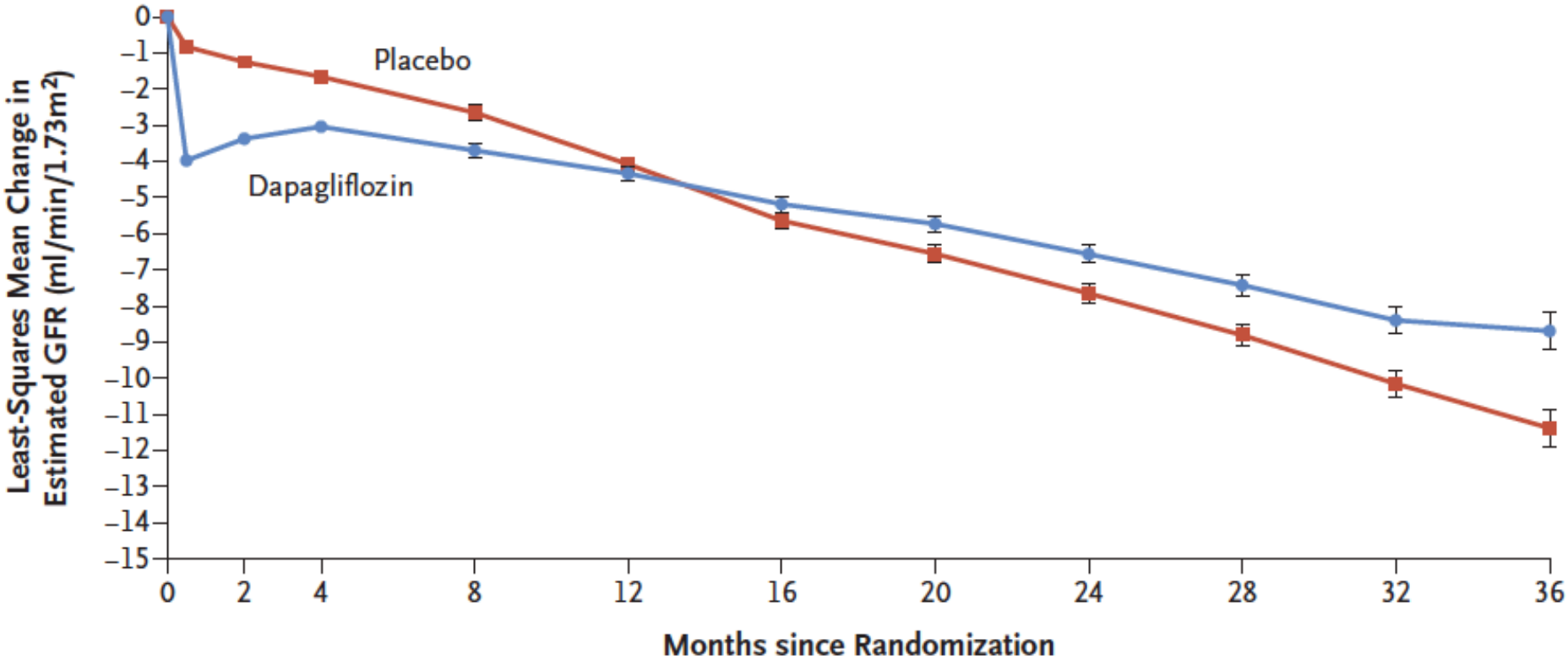
In a prespecified analysis, dapagliflozin reduced the risk of AKI versus placebo



AKI = acute kidney injury; CI = confidence interval

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

DAPA CKD

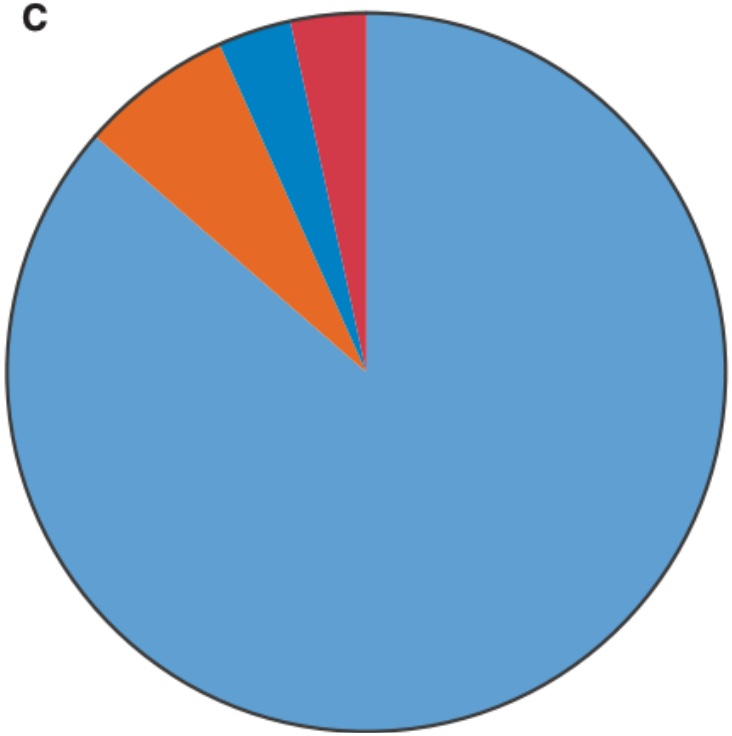


No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

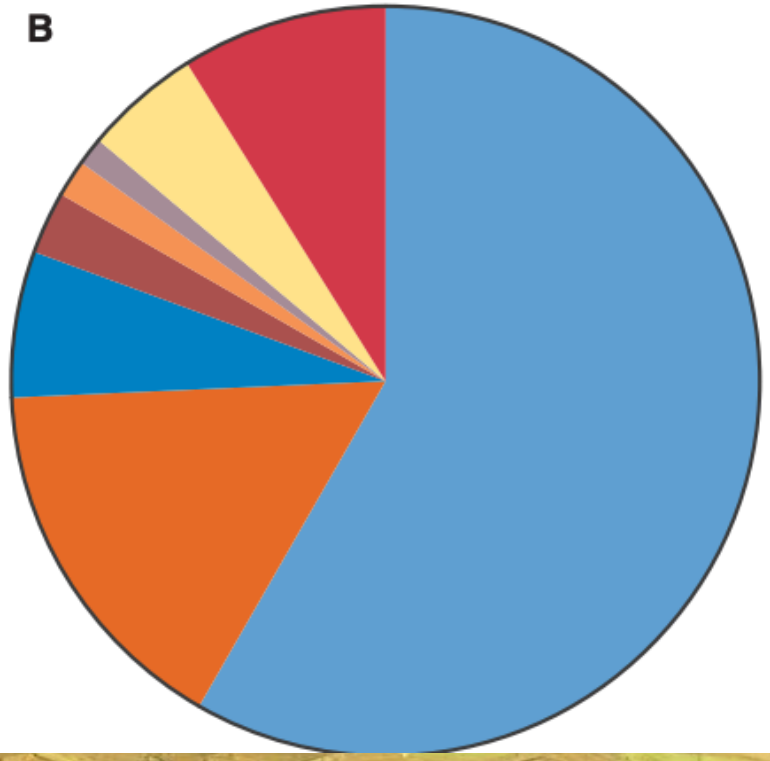
DAPA CKD ETIOLOGIE

C



- 86.4% Diabetic Nephropathy
- 6.9% Ischaemic/Hypertensive Nephropathy
- 3.3% Glomerulonephritis
- 3.4% Other

B



- 58.3% Diabetic Nephropathy
- 16.0% Ischaemic/Hypertensive Nephropathy
- 6.3% IgA Nephropathy
- 2.7% Focal Segmental Glomerulosclerosis
- 1.6% Chronic Pyelonephritis
- 1.2% Chronic Interstitial Nephritis
- 5.0% Unknown Cause
- 8.9% Other

DAPA CKD IgA

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy
David C. Wheeler et al. KI Avril 2021

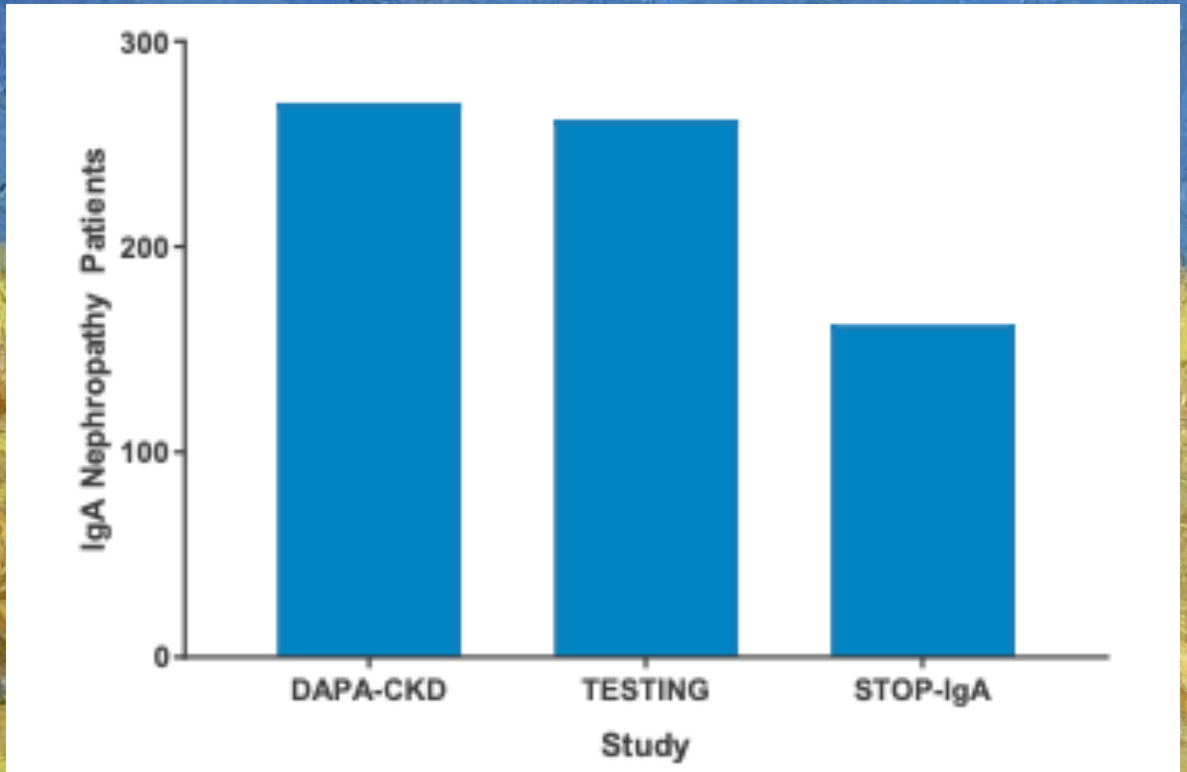


FIGURE 3: Number of participants with IgAN in clinical trials [18, 19].

DAPA CKD IgA

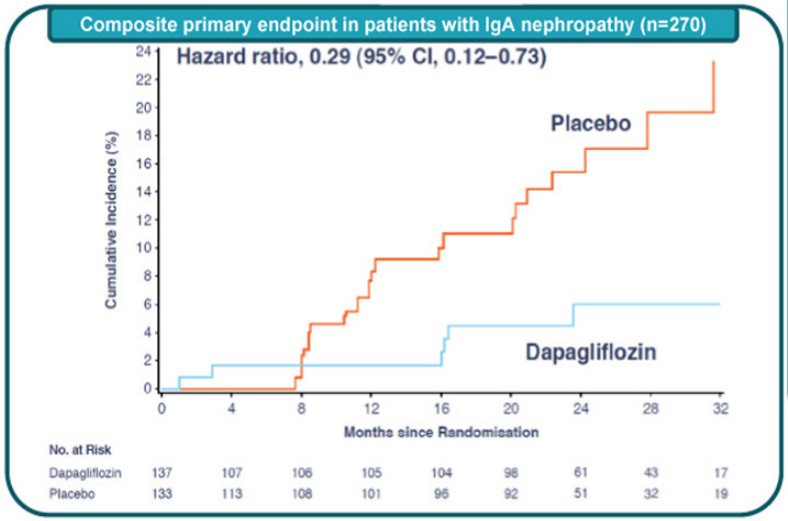
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

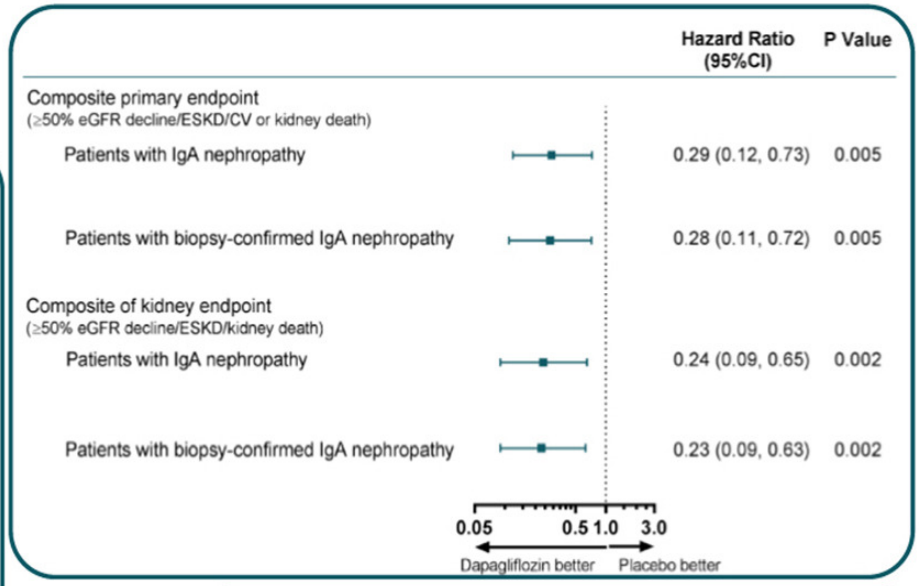
DAPA-CKD population:

- 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)





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

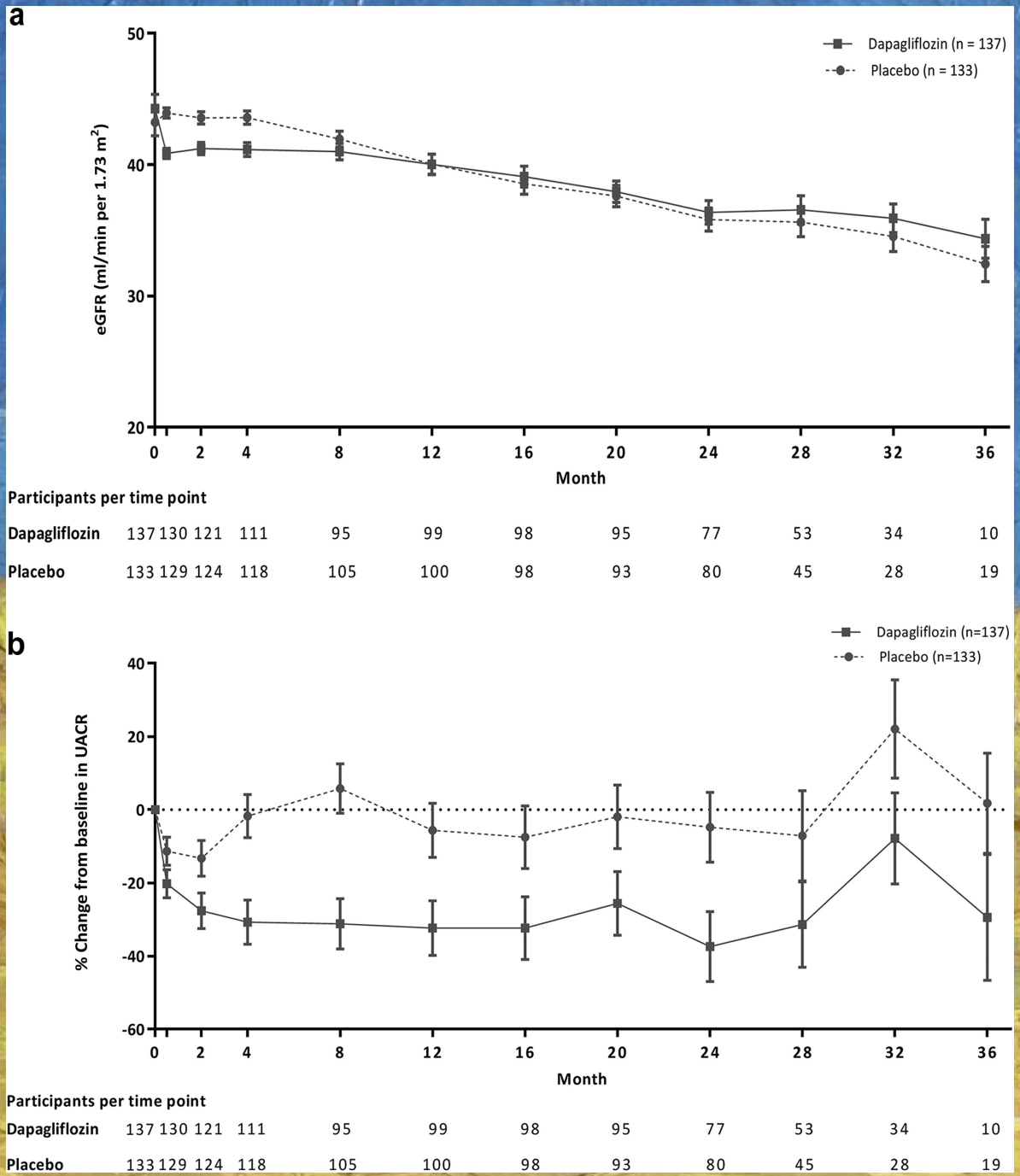
kidney INTERNATIONAL ISN

Wheeler et al, 2021

CONCLUSION:

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

DAPA CKD IgA


a
Dapagliflozin (n = 137)
Placebo (n = 133)
eGFR (ml/min per 1.73 m²)
50
40
30
20
0 2 4 8 12 16 20 24 28 32 36
Month
Participants per time point
Dapagliflozin 137 130 121 111 95 99 98 95 77 53 34 10
Placebo 133 129 124 118 105 100 98 93 80 45 28 19
b
Dapagliflozin (n=137)
Placebo (n=133)
% Change from baseline in UACR
40
20
0
-20
-40
-60
0 2 4 8 12 16 20 24 28 32 36
Month
Participants per time point
Dapagliflozin 137 130 121 111 95 99 98 95 77 53 34 10
Placebo 133 129 124 118 105 100 98 93 80 45 28 19

Message

Depiste

- Urine
- Sang

Diagno

- Imagerie
- Spé.

Traite

- Etio
- RAASi
- SGLT2
- Bicar.

Surveille

- Etio.
- eGFR slpoe
- UACR-PCR