SGLT-2i als neue Therapieoption bei CKD

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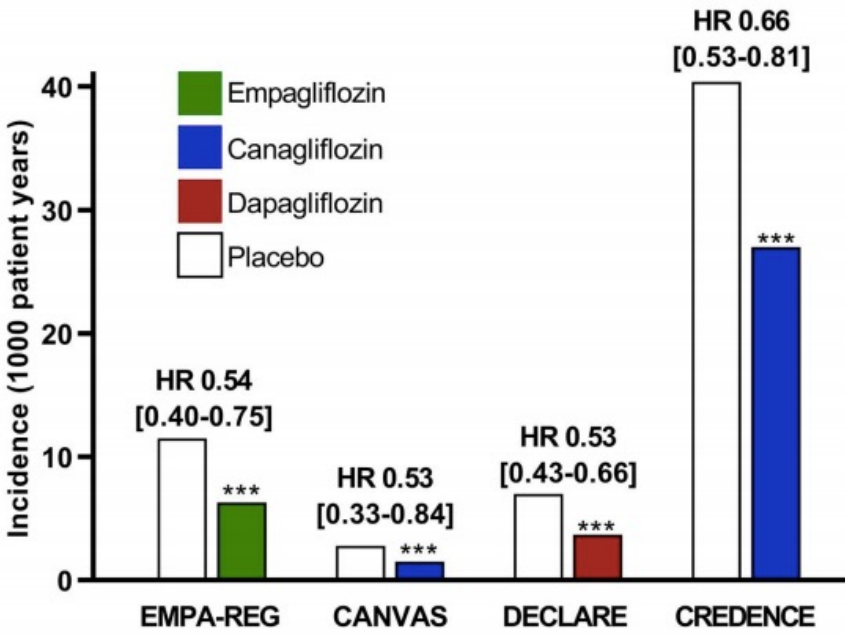
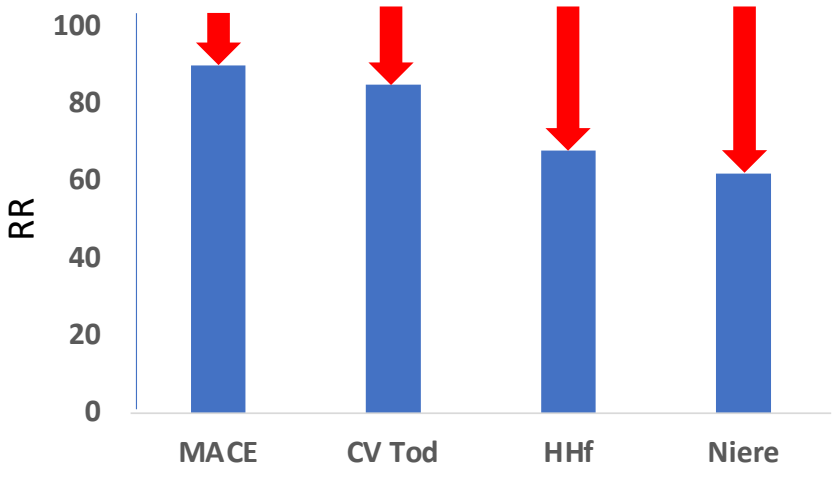
Conflict of Interest

Astra Zeneca, Bayer, Boehringer-Ingelheim, Merck, Novartis, Otsuka, Vifor Pharma

Kardiovaskuläre und nephroprotektive Effekte der SGLT-2i

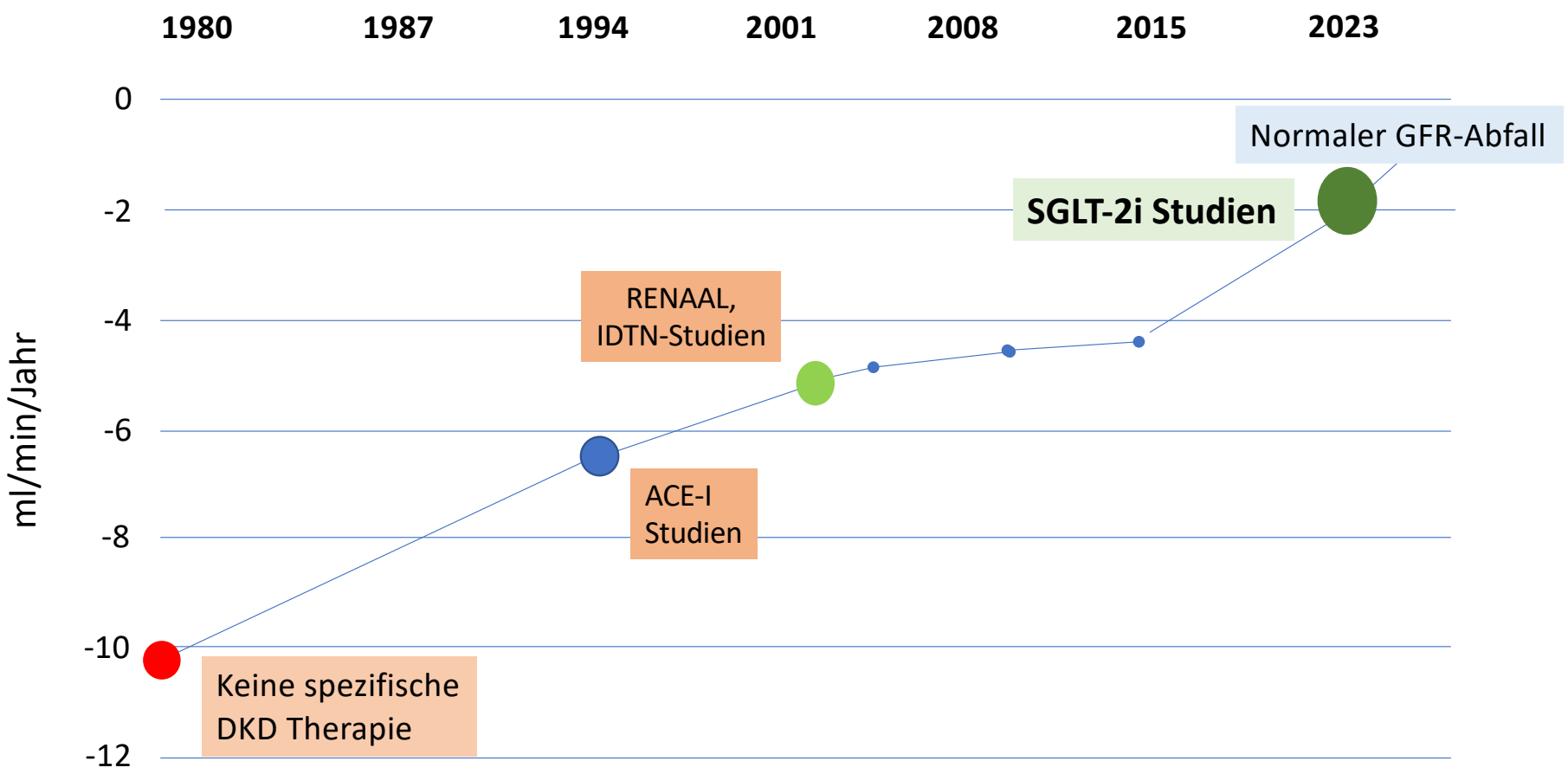


Lytvyn J et al., Endocrine Rev 2020

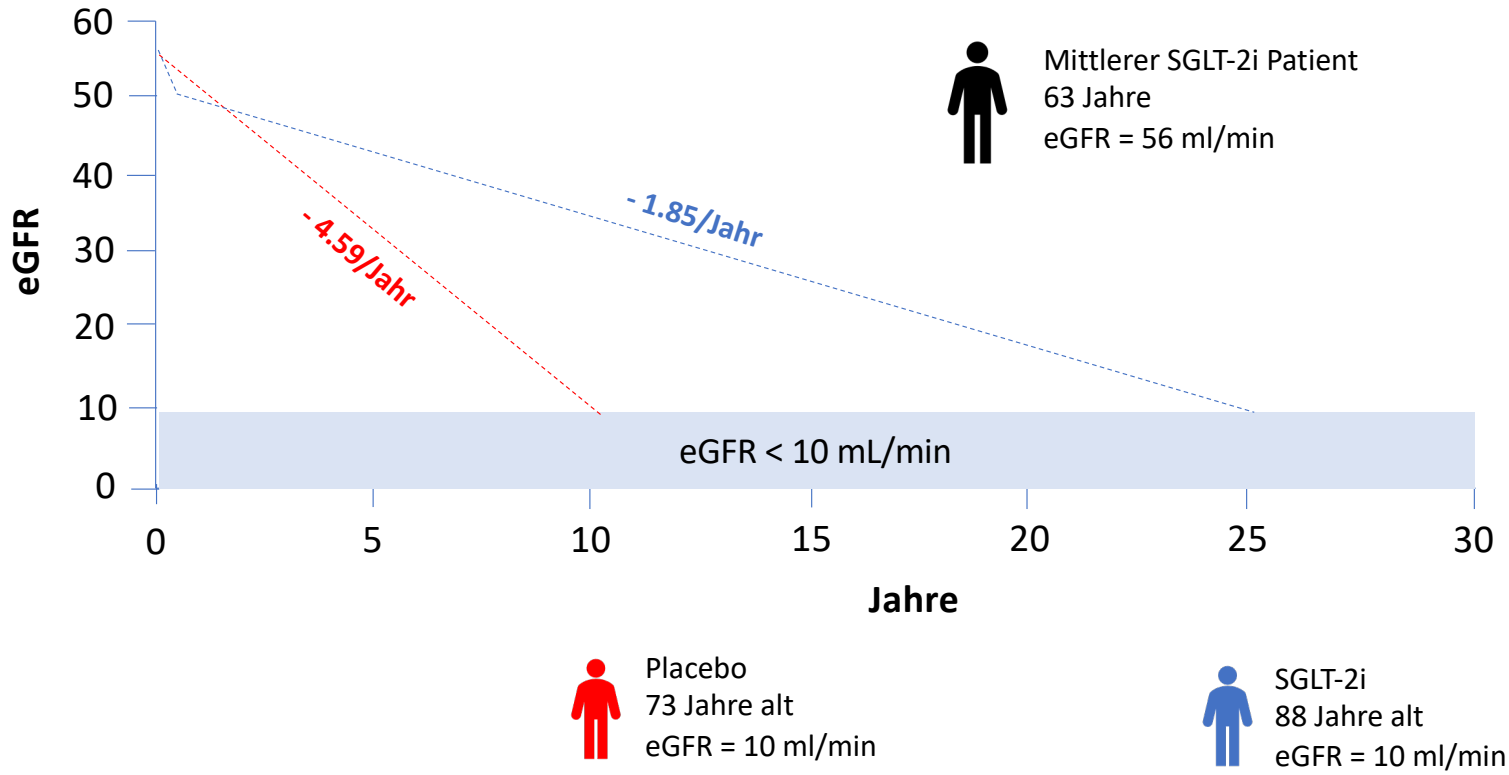


McGuire et al., 2021

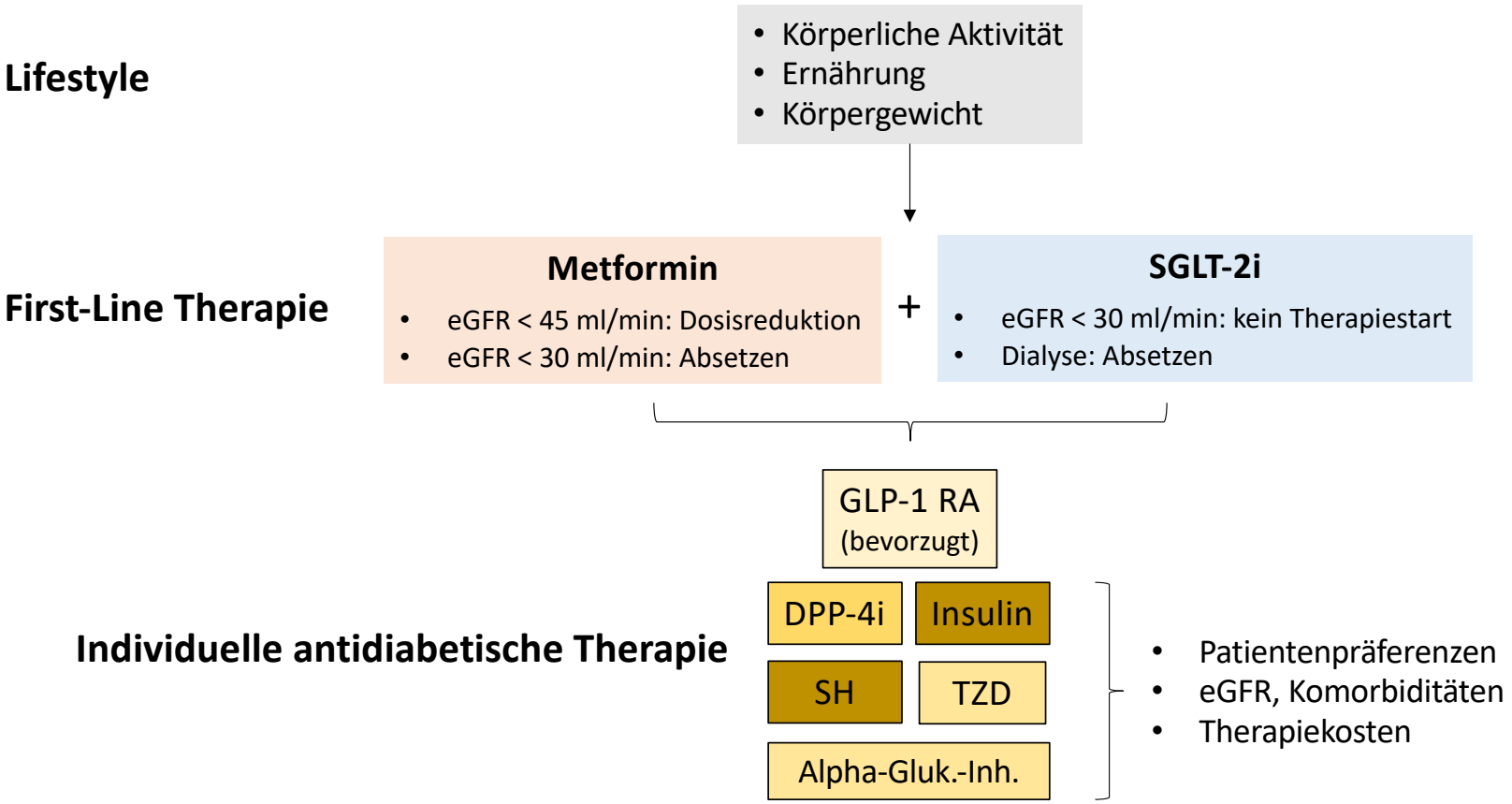
Zeitliche Perspektive zur pharmakologischen Nephroprotektion bei DKD



Behandlungserfolg durch SGLT-2i bei Typ 2 Diabetes und CKD Stadium G3



KDIGO 2020: Diabetes & Niere



DAPA-CKD

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

Objective

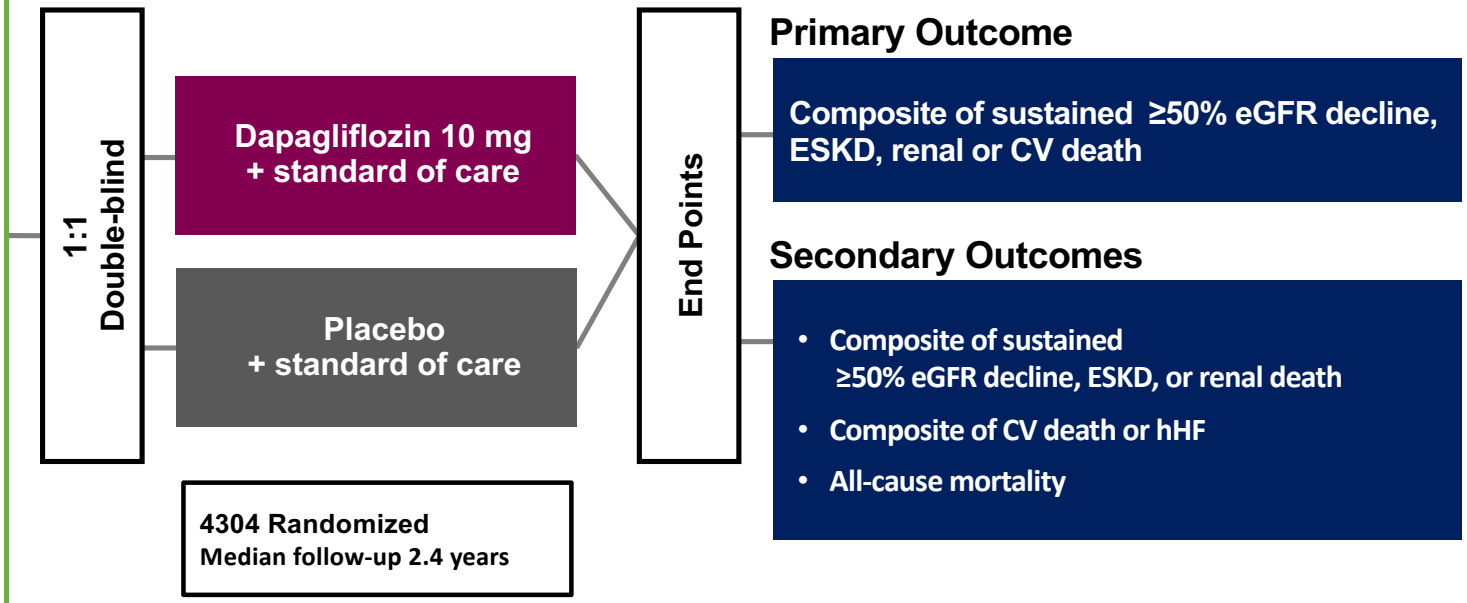
To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

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

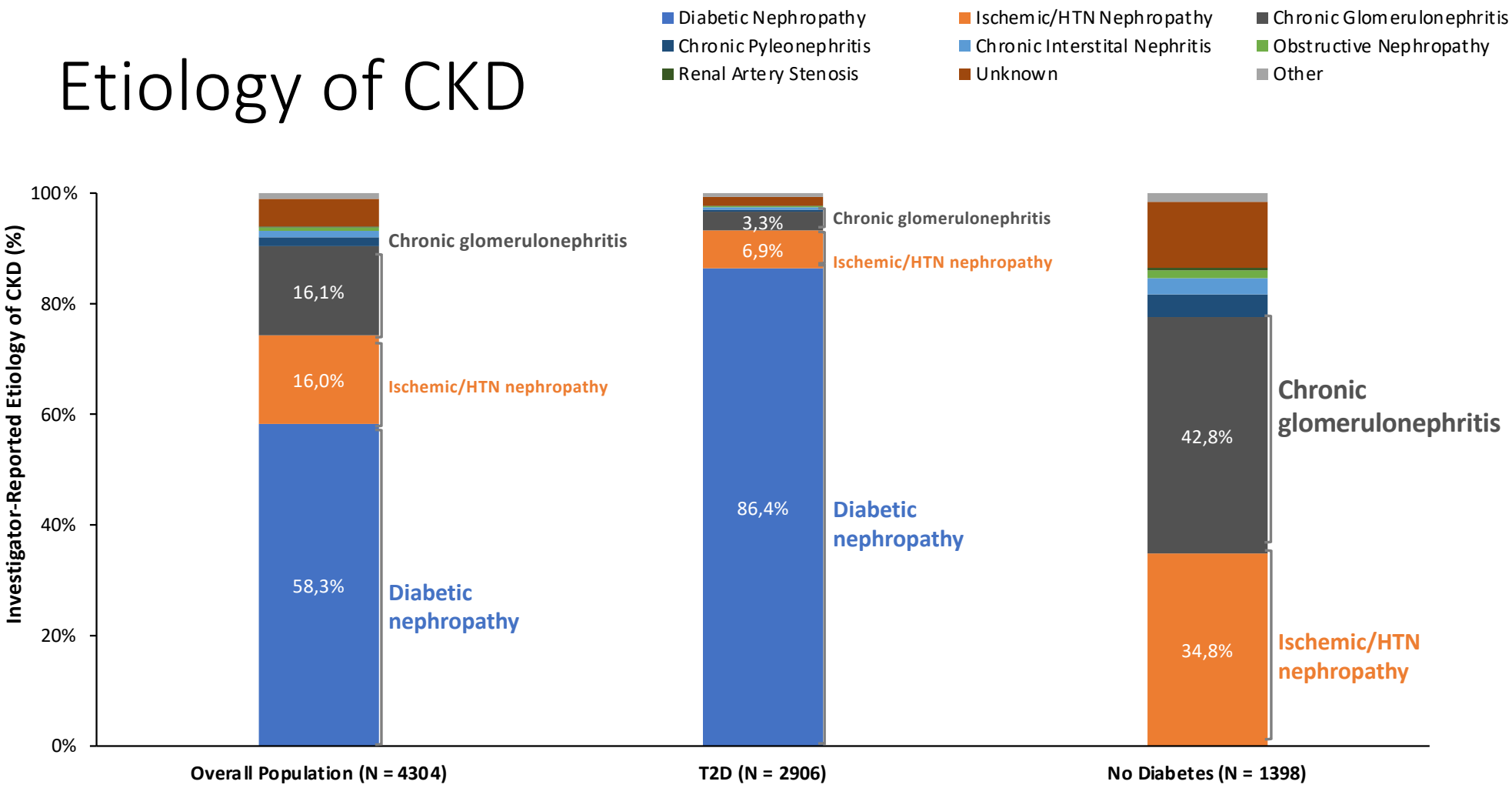
Key Exclusion Criteria

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



1. Heerspink HJL et al. N Engl J Med. 2020

Etiology of CKD



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

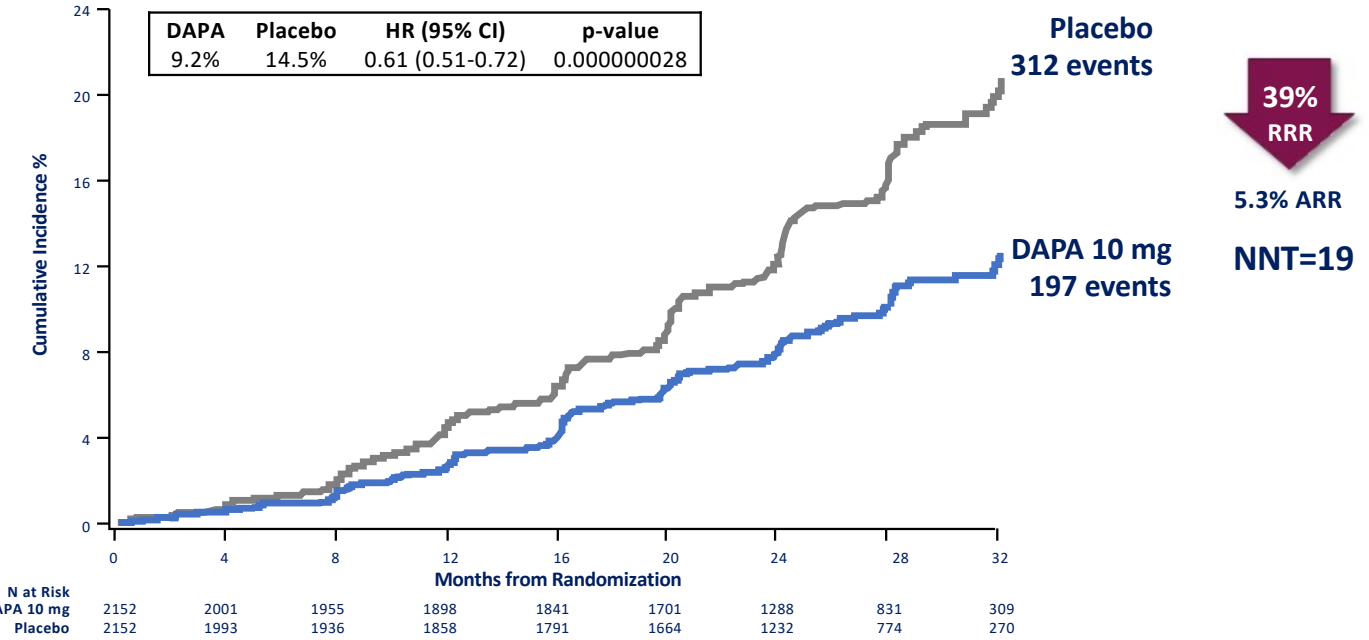
Heerspink HJL et al., N Engl J Med. 2020

Renal Characteristics

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

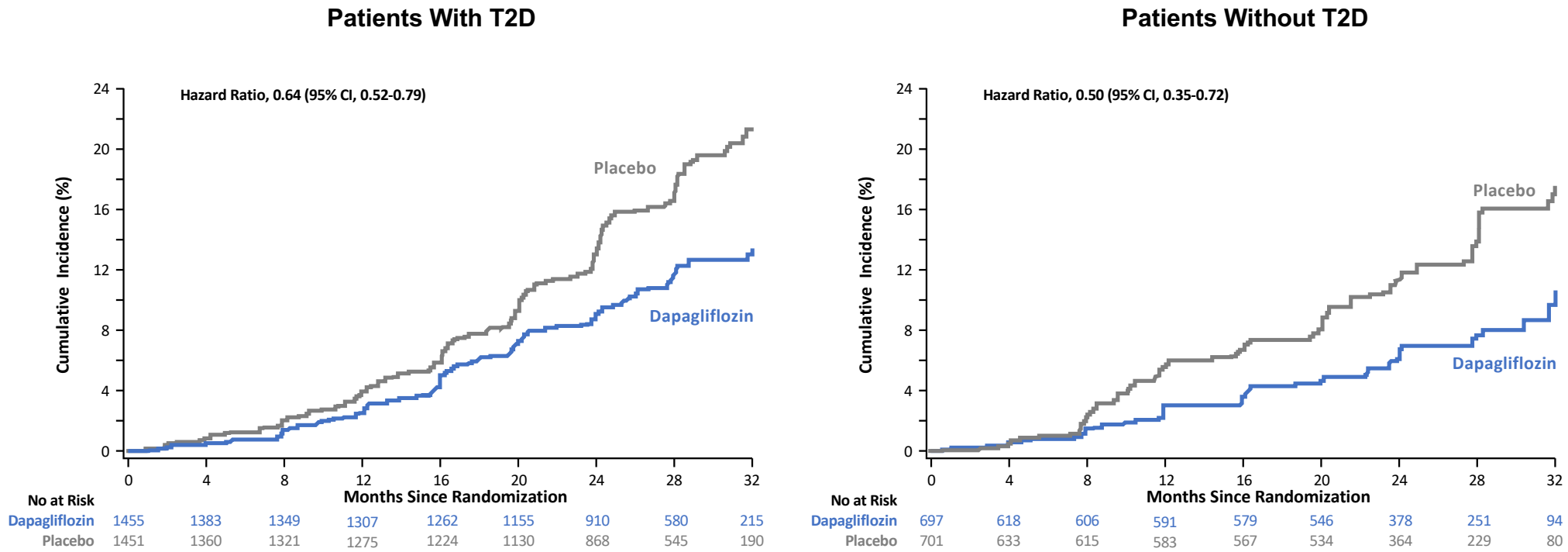
Heerspink HJL et al., N Engl J Med. 2020

DAPA-CKD: Primary Composite Outcome



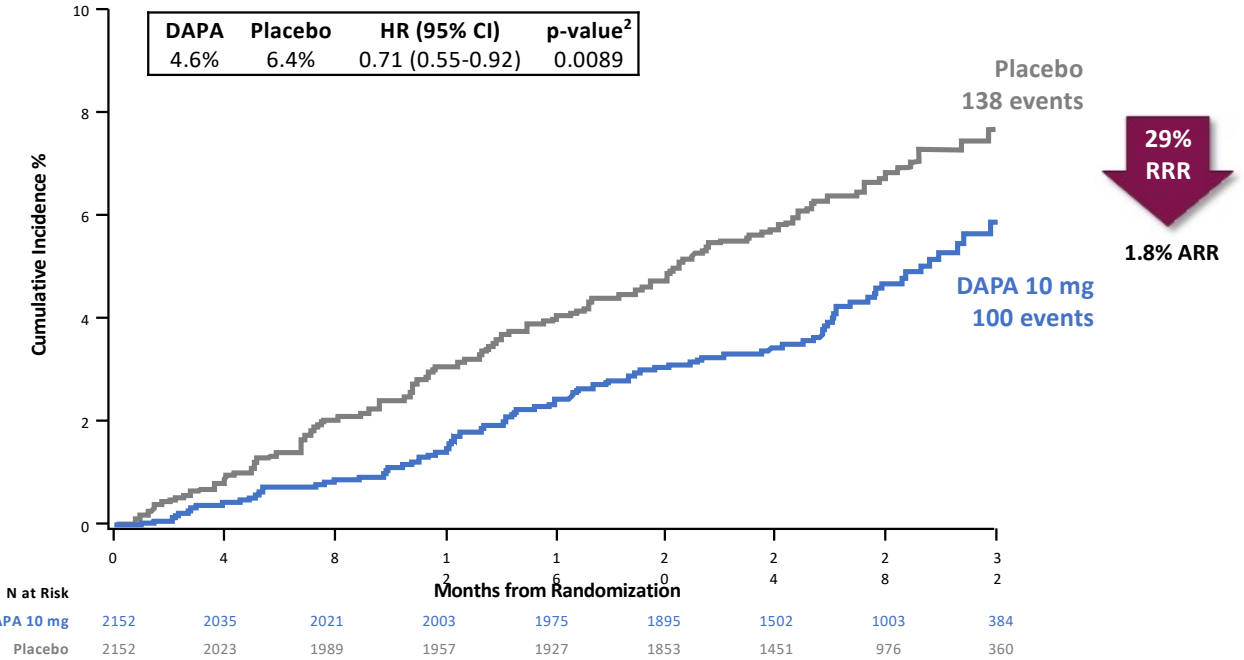
Heerspink HJL et al., N Engl J Med. 2020

Primary Outcome by Diabetes Status



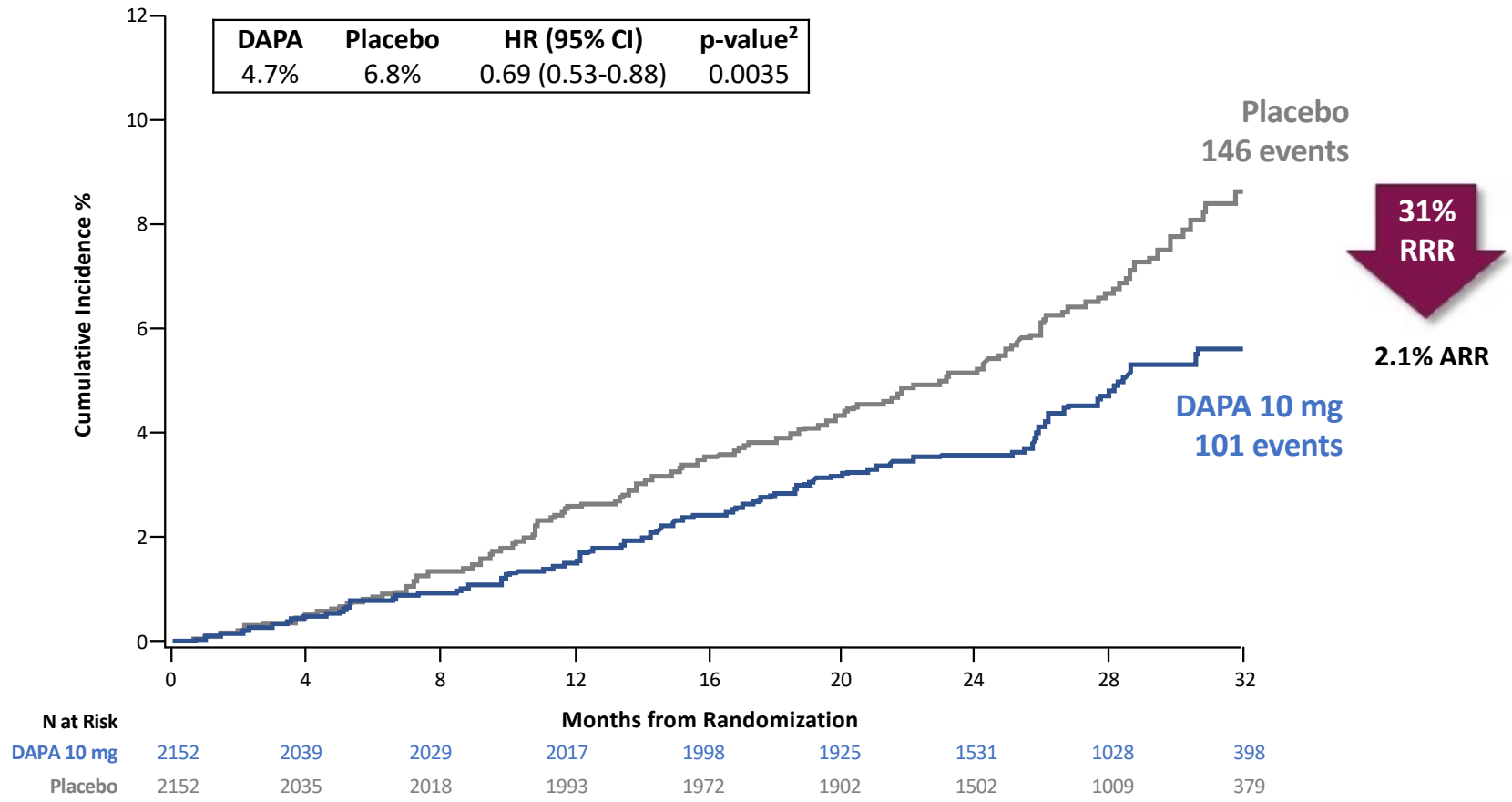
p-interaction=0.24

Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure



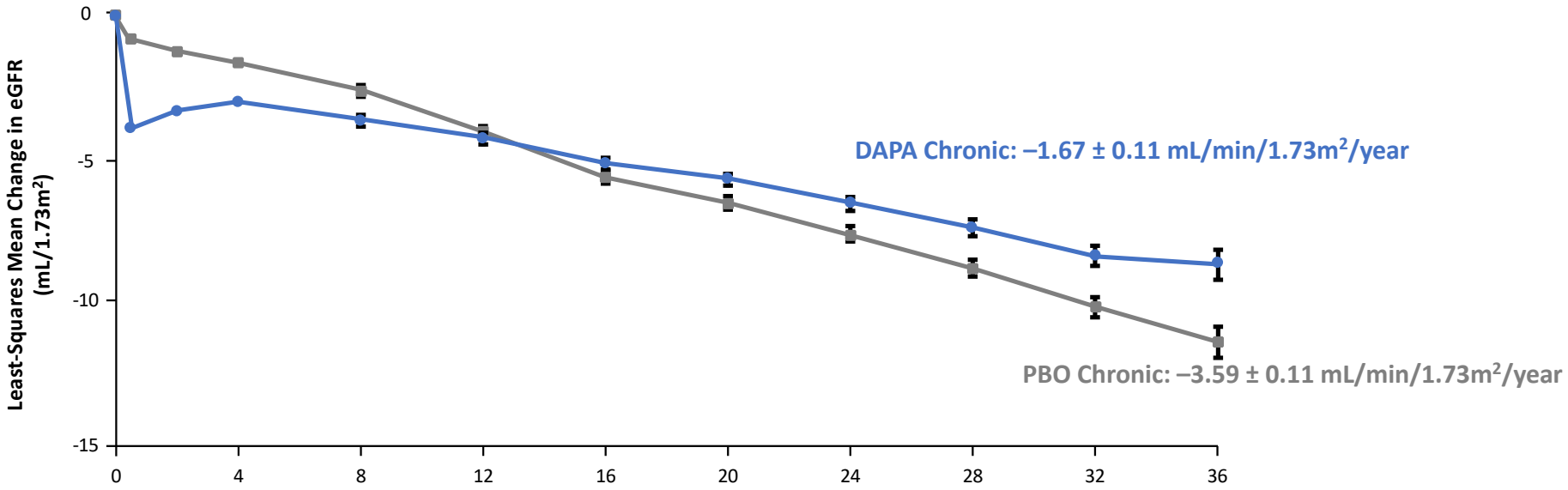
Heerspink HJL et al., N Engl J Med. 2020

Secondary Outcome: All-cause Mortality



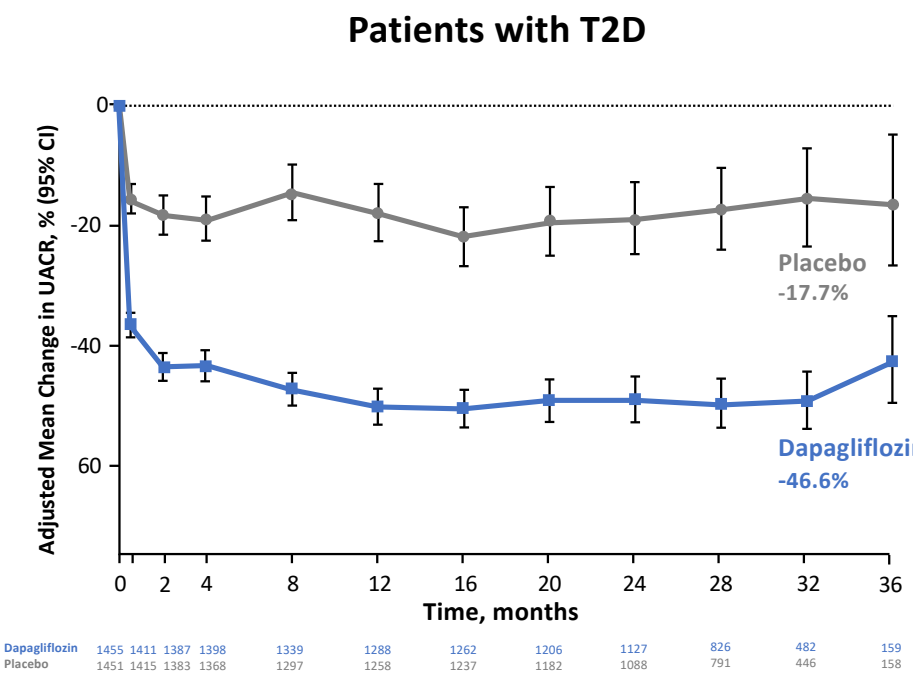
Heerspink HJL et al., N Engl J Med. 2020

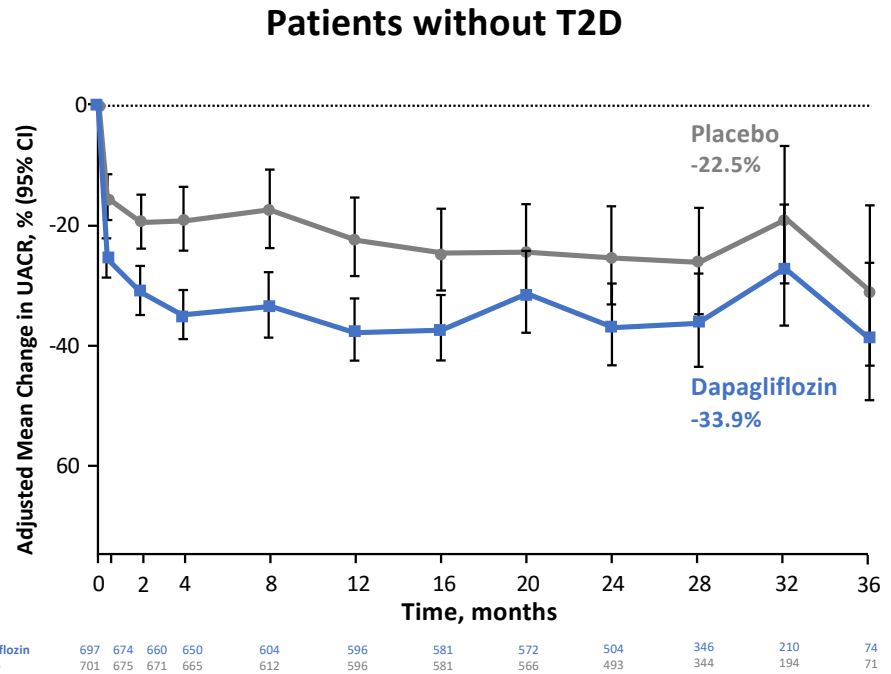
Change from Baseline in eGFR



Heerspink HJL et al., N Engl J Med. 2020

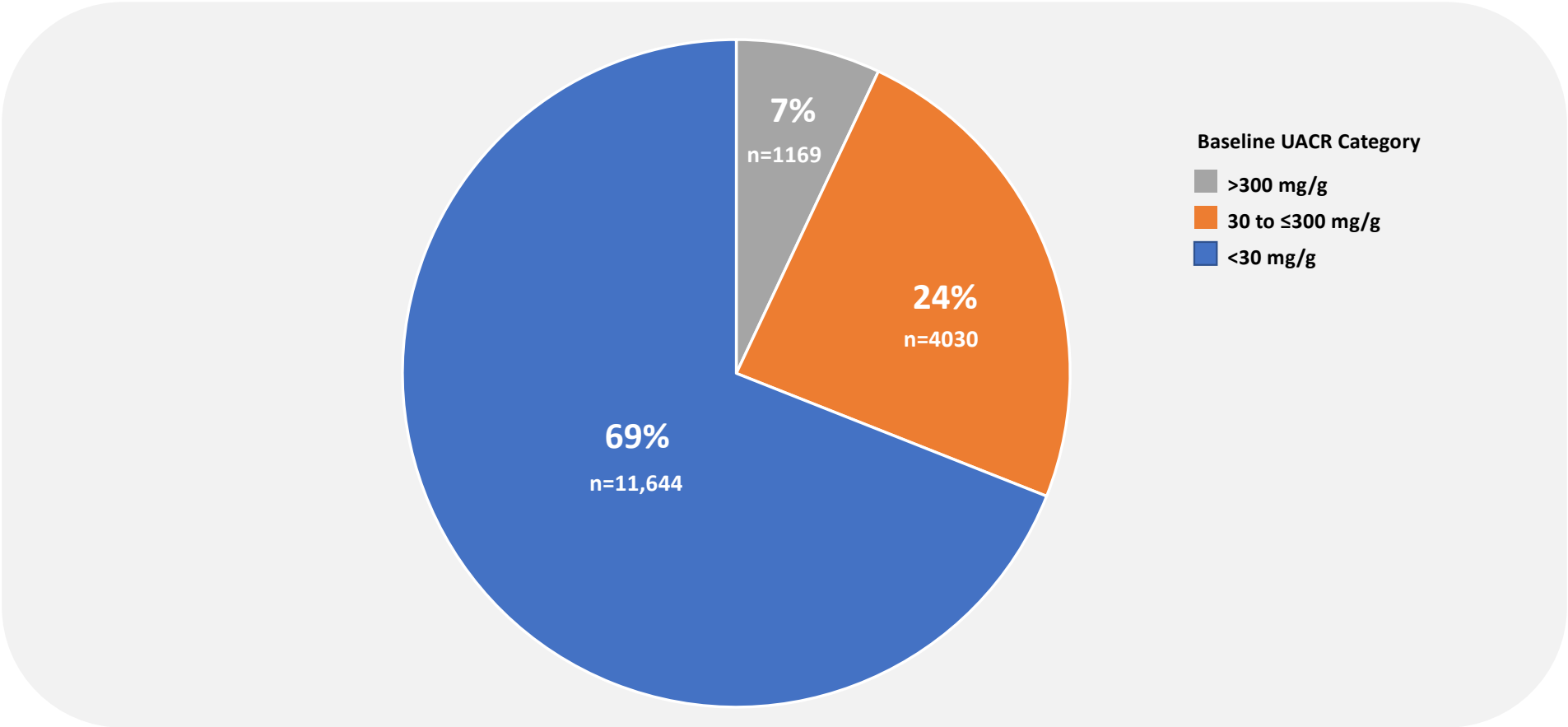
Change in Albuminuria by T2D Status





Jongs N et al. Presented at: ERA-EDTA Congress; 2021

Distribution of UACR Categories Among the Overall DECLARE-TIMI 58 Population

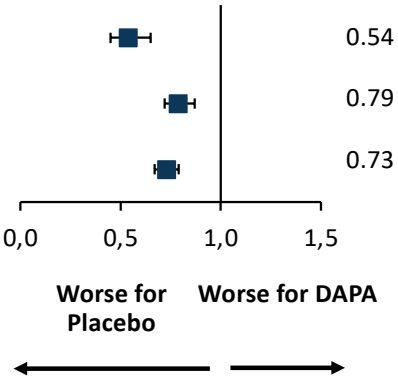


UACR = urine albumin-to-creatinine ratio

Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA.

Deterioration of Albuminuria Category from Baseline

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Deterioration from baseline						
Normo/Micro to Macro	181/7836 (2..3)	2.30%	330/7838 (4.2)	4.2%	0.54 (0.45, 0.65)	<0.0001
Normo to Micro/Macro	772/5819 (13.3)	13.30%	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)	11.90%	1243/7838 (15.9)	15.8%	0.73 (0.67, 0.79)	<0.0001

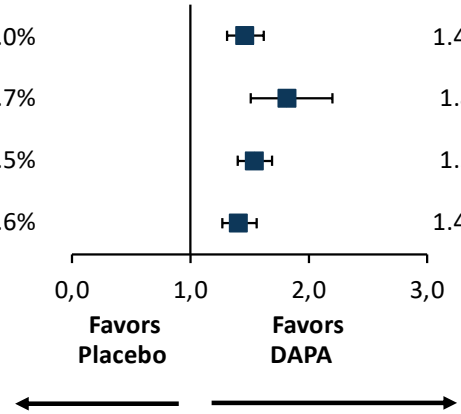


Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

Mosenzon et al., Diabetes Care 2021

Improvement of Albuminuria Category from Baseline

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	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)	41.00%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<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 = urine albumin-to-creatinine ratio.

Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA.

IgA - Nephropathie

- Häufigste glomeruläre Erkrankung
- 30% aller Patienten über 6 Jahre CKD Progression ⟶ CKD5
- Keine Therapieforstschritte in den letzten drei Jahrzehnten: RAS Blockade
- Immunosuppression ? (Budesonid ?)

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

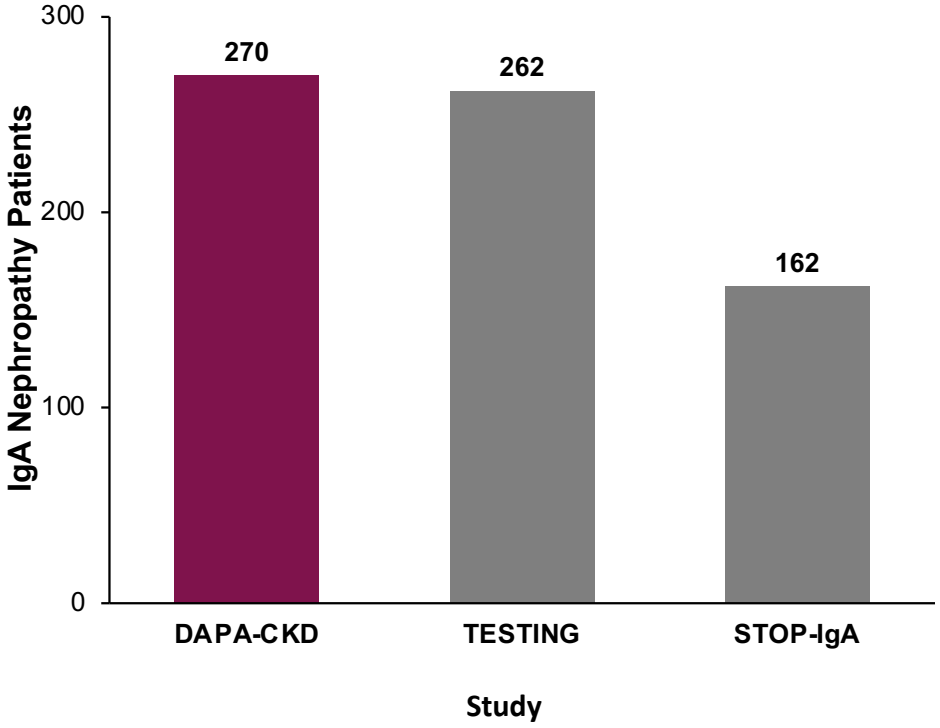
OPEN

David C. Wheeler[1,2], Robert D. Toto[3], Bergur V. Stefansson[4], Niels Jongs[5], Glenn M. Chertow[6,7], Tom Greene[8], Fan Fan Hou[9], John J.V. McMurray[10], Roberto Pecoits-Filho[11,12], Ricardo Correa-Rotter[13], Peter Rossing[14,15], C. David Sjöström[4], Kausik Umanath[16,17], Anna Maria Langkilde[4] and Hiddo J.L. Heerspink[5]; for the DAPA-CKD Trial Committees and Investigators

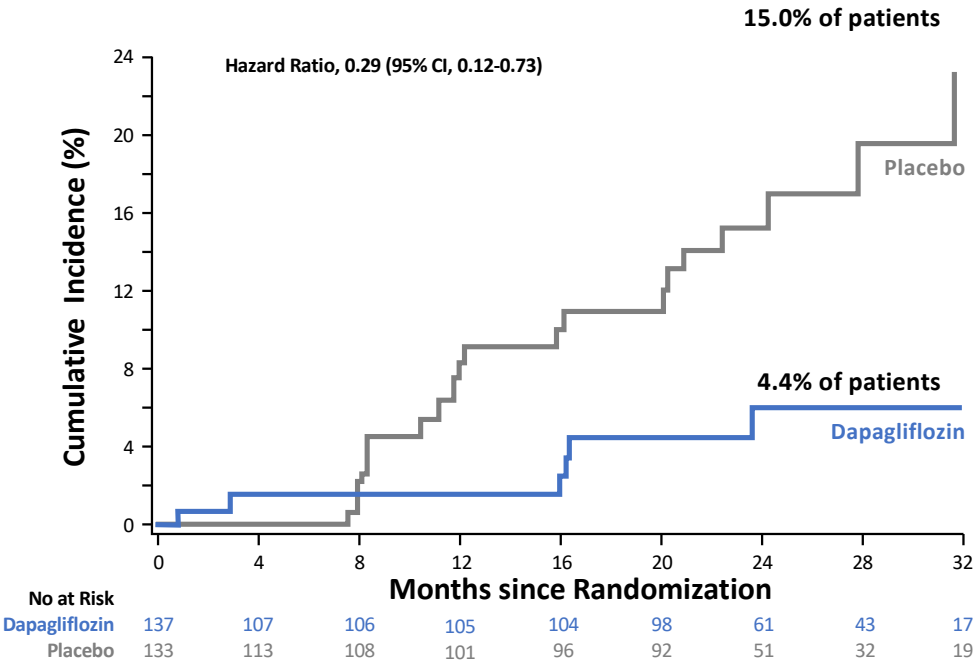
[1]Department of Renal Medicine, University College London, London, UK; [2]The George Institute for Global Health, Sydney, Australia; [3]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, Texas, USA; [4]Late-Stage Development, Cardiovascular, Renal and Metabolism, Biopharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [5]Department Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [6]Department of Medicine, Stanford University School of Medicine, Stanford, California, USA; [7]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, USA; [8]Study Design and Biostatistics Center, University of Utah Health Sciences, Salt Lake City, Utah, USA; [9]Division of Nephrology, Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China; [10]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [11]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [12]School of Medicine, Pontifical Catholic University of Paraná, Curitiba, Paraná, Brazil; [13]National Medical Science and Nutrition Institute Salvador Zubirán, Mexico City, Mexico; [14]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [15]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [16]Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan, USA; and [17]Division of Nephrology and Hypertension, Wayne State University, Detroit, Michigan, USA

Effect of Dapagliflozin in IgA Nephropathy

Number of participants with IgA nephropathy in clinical trials



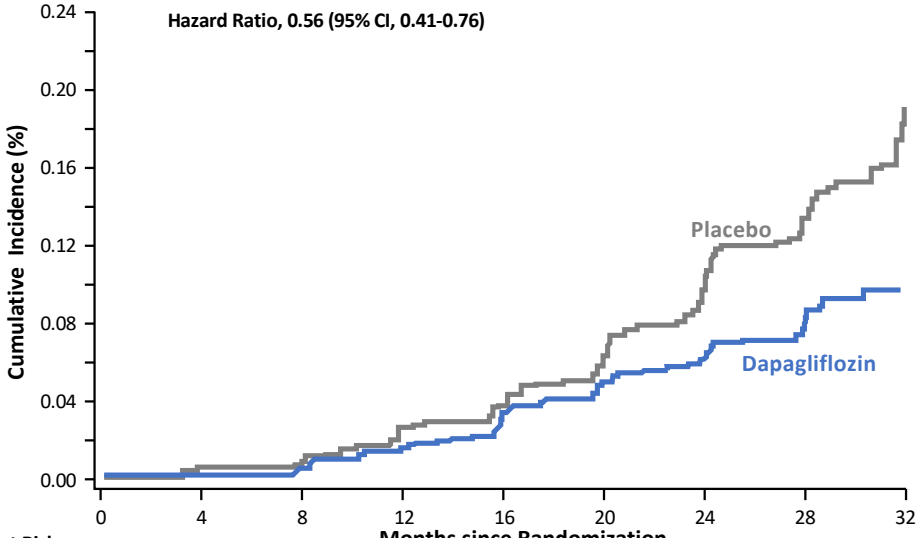
Primary outcome in participants with IgA nephropathy



Wheeler DC et al. Kidney Int 2021

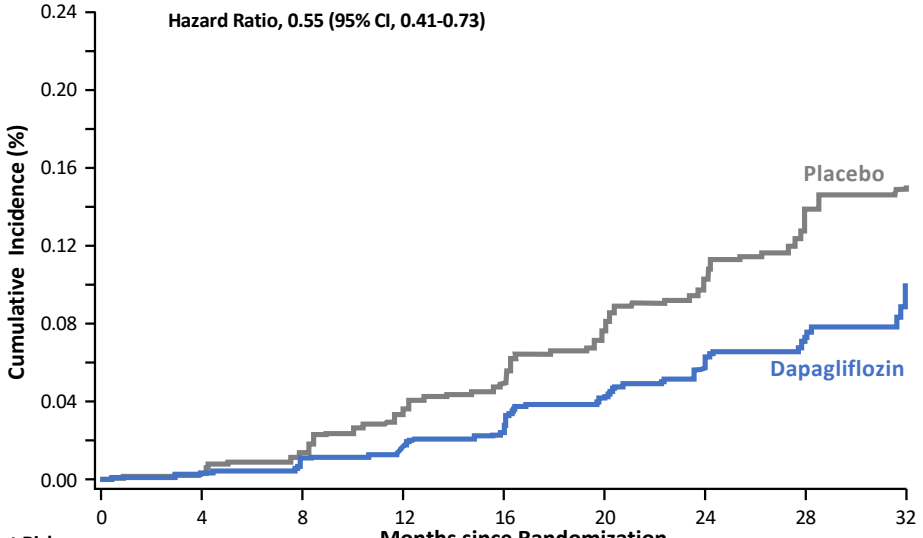
Renal Composite Outcome in Patients With/Without Diuretics

With Diuretic Use



No at Risk									
Dapagliflozin	928	897	876	854	826	765	593	375	150
Placebo	954	906	880	847	818	757	587	358	125

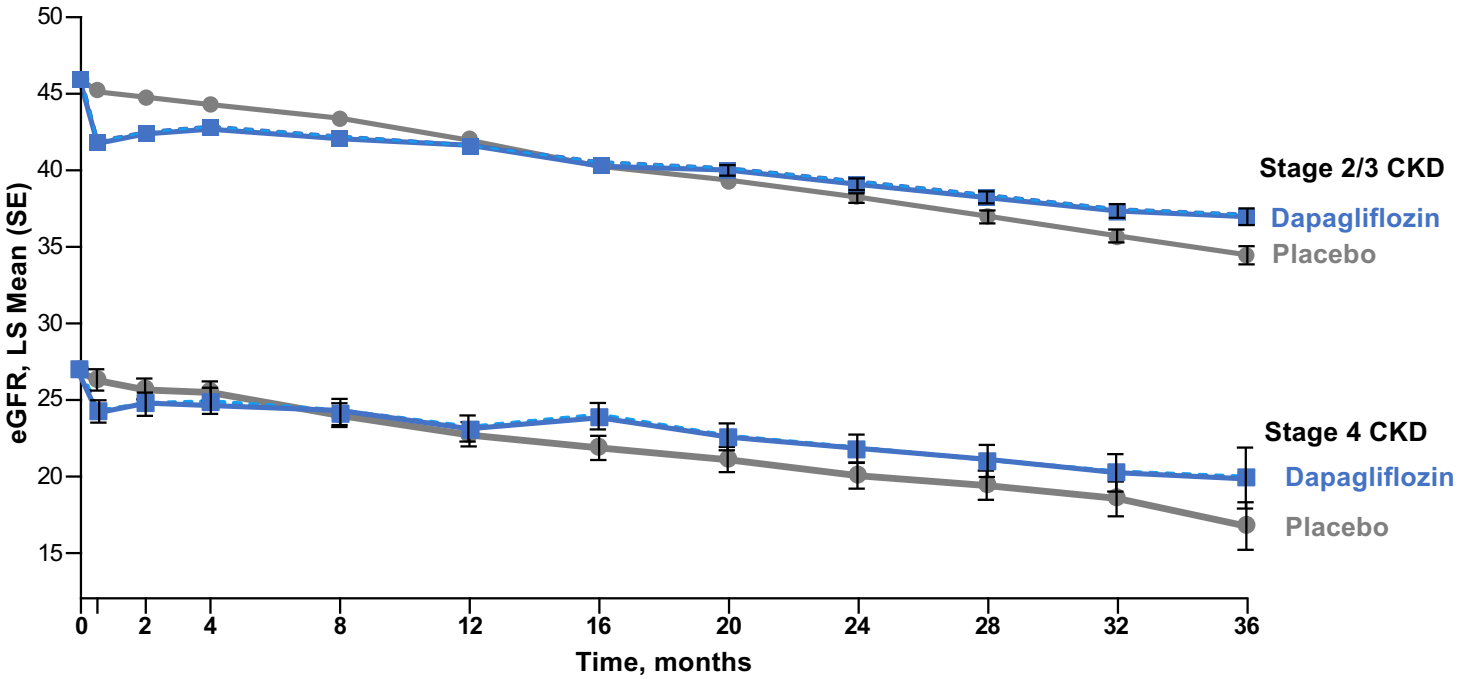
Without Diuretic Use



No at Risk									
Dapagliflozin	1224	1104	1079	1044	1015	936	695	456	159
Placebo	1198	1087	1056	1011	973	907	645	416	145

Heerspink HL. ASN – Kidney Week 2020

eGFR Decline Over the Study by Baseline CKD Stage



Chertow GM et al. Presented at: WCN; April 16-19, 2021

Safety Outcomes According to CKD Stage

Safety outcomes, %	Stage 4 CKD		Stage 2/3 CKD	
	Dapagliflozin (n=293)	Placebo (n=331)	Dapagliflozin (n=1859)	Placebo (n=1821)
Discontinuation due to adverse event	9.6	10.9	4.8	4.8
Any serious adverse event	34.5	41.7	28.7	32.5
Adverse event of interest				
Amputation	1.0	1.2	1.7	1.9
Definite or probable DKA	0	0.3	0	0.1
Fracture	3.8	4.5	4.0	3.0
Renal-related adverse event	14.7	13.3	6.0	7.9
Major hypoglycemia	0.7	2.4	0.6	1.1
Volume depletion	4.8	4.5	6.1	4.1

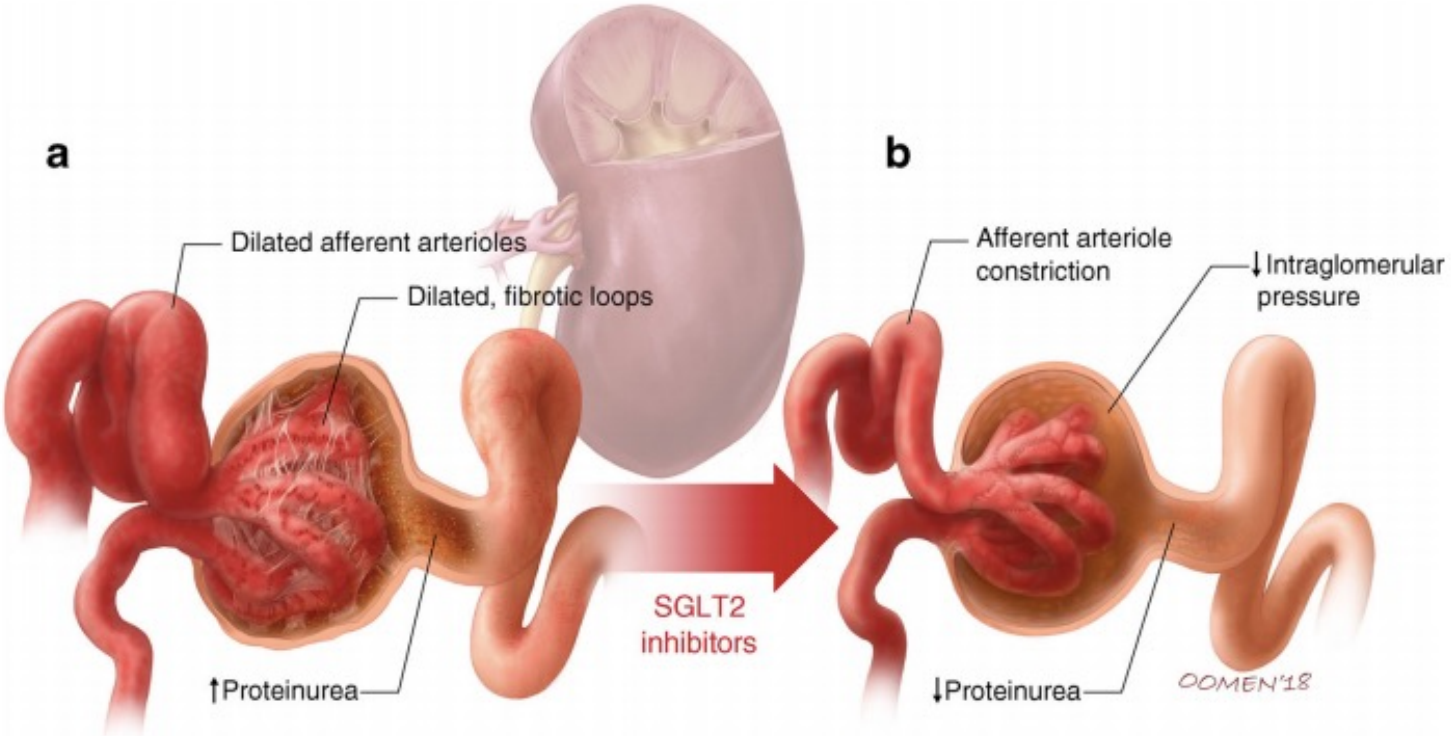
Chertow GM et al. Presented at: WCN; April 16-19, 2021

Safety Outcomes

Safety Outcomes[a], n (%)	Dapagliflozin 10 mg (N=2149)	Placebo (N=2149)	p-value
Discontinuation of study drug	274 (12.7)	309 (14.4)	NA
Discontinuation due to adverse event	118 (5.5)	123 (5.7)	0.79
Any serious adverse event	633 (29.5)	729 (33.9)	0.002
Adverse events of interest			
Amputation	35 (1.6)	39 (1.8)	0.73
Any definite or probable diabetic ketoacidosis	0	2 (0.1)	0.50
Fracture	85 (4.0)	69 (3.2)	0.22
Renal-related adverse event	155 (7.2)	188 (8.7)	0.07
Major hypoglycemia	14 (0.7)	28 (1.3)	0.04
Volume depletion	127 (5.9)	90 (4.2)	0.01
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)	NA
Fournier's Gangrene	0	1(<0.1)	NA

Heerspink HJL et al., *N Engl J Med*. 2020

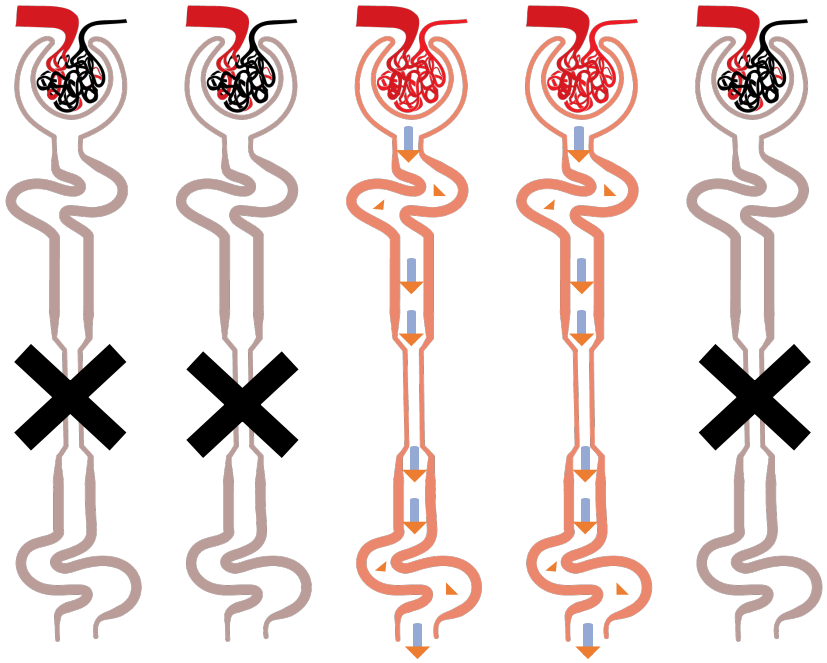
CKD and SGLT-2i



Verma S & McMurray JJ et al., Diabetologia 2018

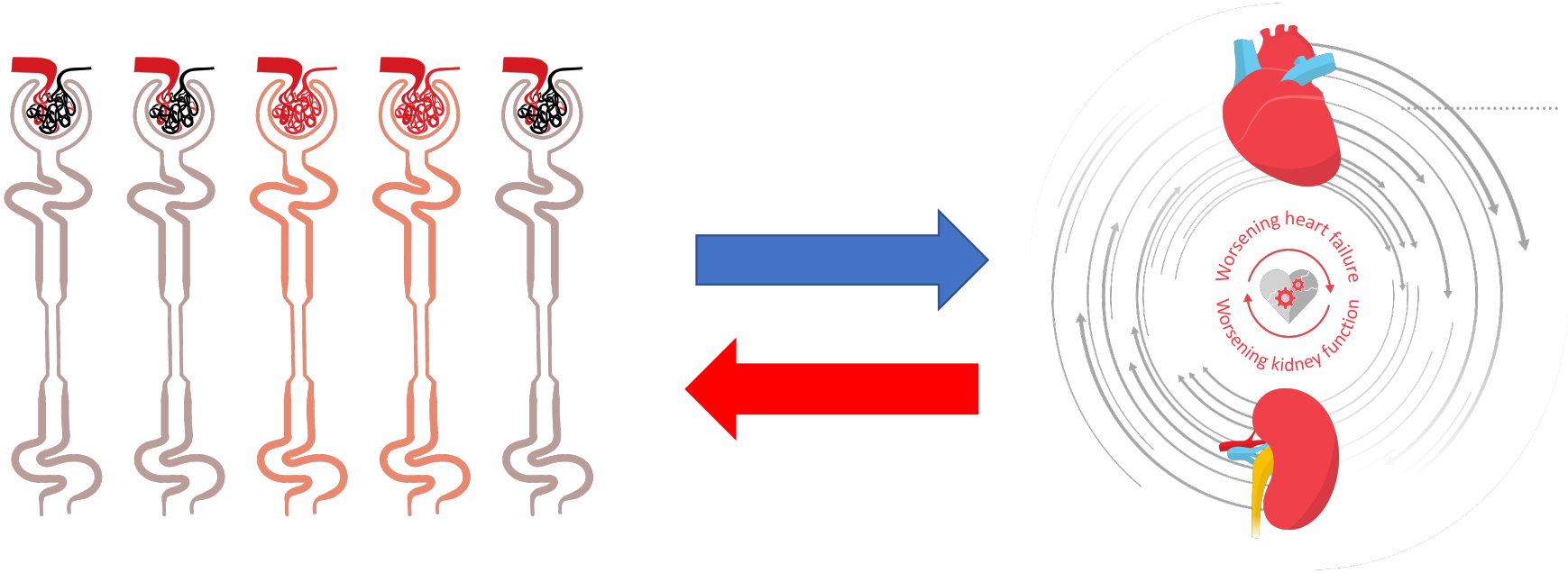
Glomerular hypertension causes glomerular damage & progressive nephron loss

- Eventually single nephrons are lost
- Remaining nephrons adapt, increasing filtration by glomerular hypertension
- Vicious cycle of progressive CKD



CKD

- Progressive loss of functioning nephrons despite hyperfiltration.
- When the total amount of functioning nephrons decreases, hyperfiltration **accelerates nephron loss**.



SGLT-2-Hemmung und Nephroprotektion: Mechanismen

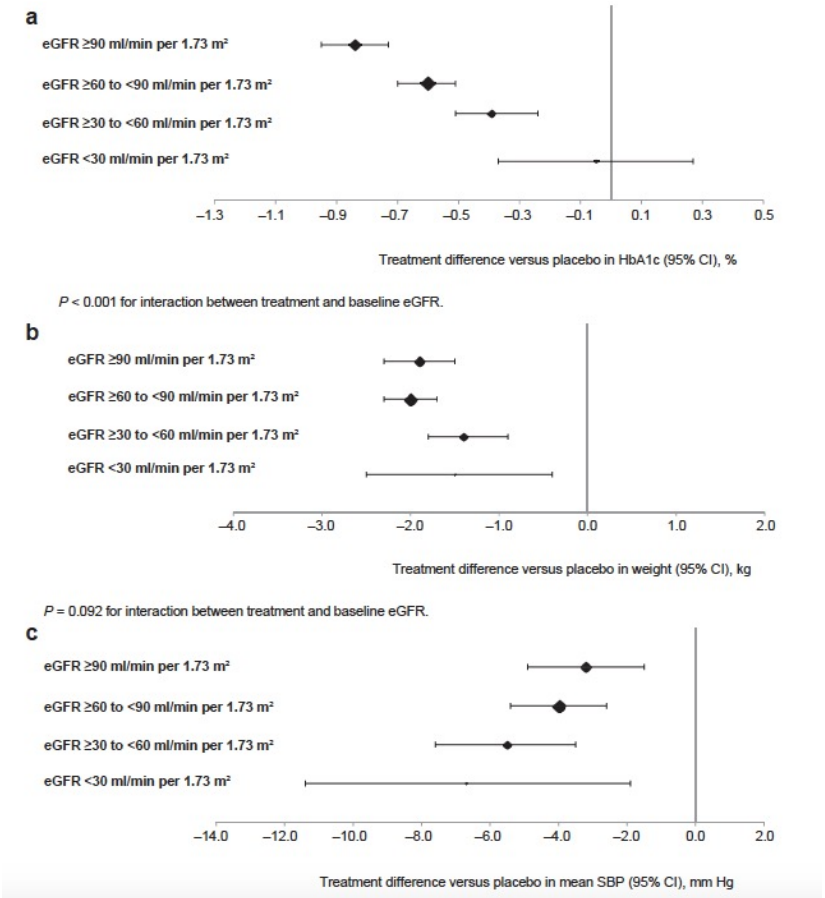
1. **CKD-Progression: GFR-Abfall**
2. **Albuminurie: Primär- & Sekundärprävention**
3. **Nierenersatz-Therapie**
4. **AKI-Inzidenz**

- Glomeruläre Hämodynamik
- Tubulärer Workload und Hypoxie

1. Hospitalisierung wegen Herzinsuffizienz
2. Kardiovaskuläre Morbidität
3. Gesamt-Mortalität

- Diurese/Natriurese
- Blutdruck
- Körpergewicht
- Interstitielles Plasmavolumen
- Endotheliale Dysfunktion
- Erythropoietin-Aktivität - Erythrozytenmasse
- Insulinresistenz
- Ketonkörper-Bildung
- Anti-inflammatorische & antifibrotische Effekte
- Sympathikusaktivität

SGLT-2i and eGFR



$HbA1_c$

Weight

RR

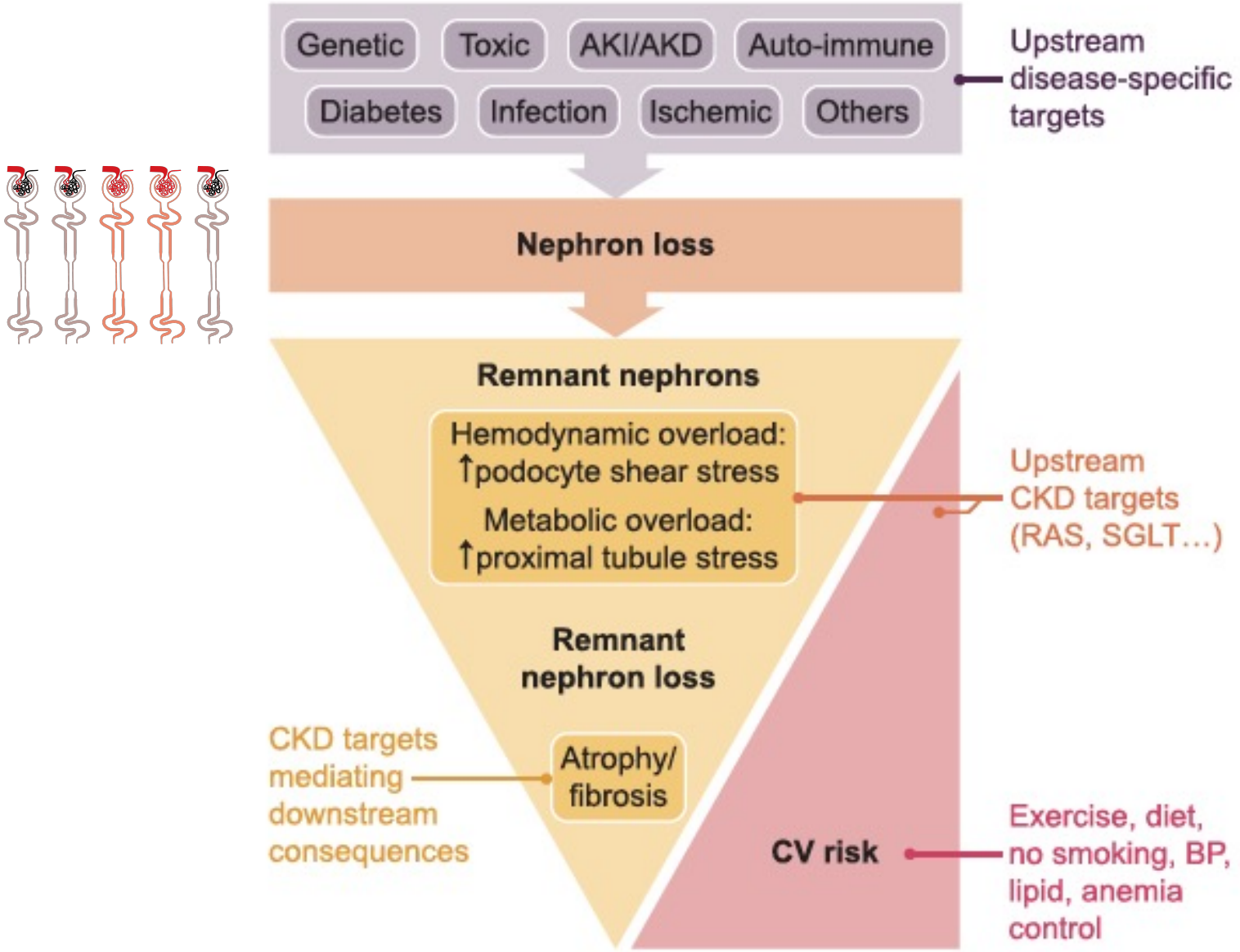
Cherney D et al., Kidney Int 2017

SGLT-2 inhibitors are *"cardiorenal risk reducing agents with glucose lowering as a side effect."*

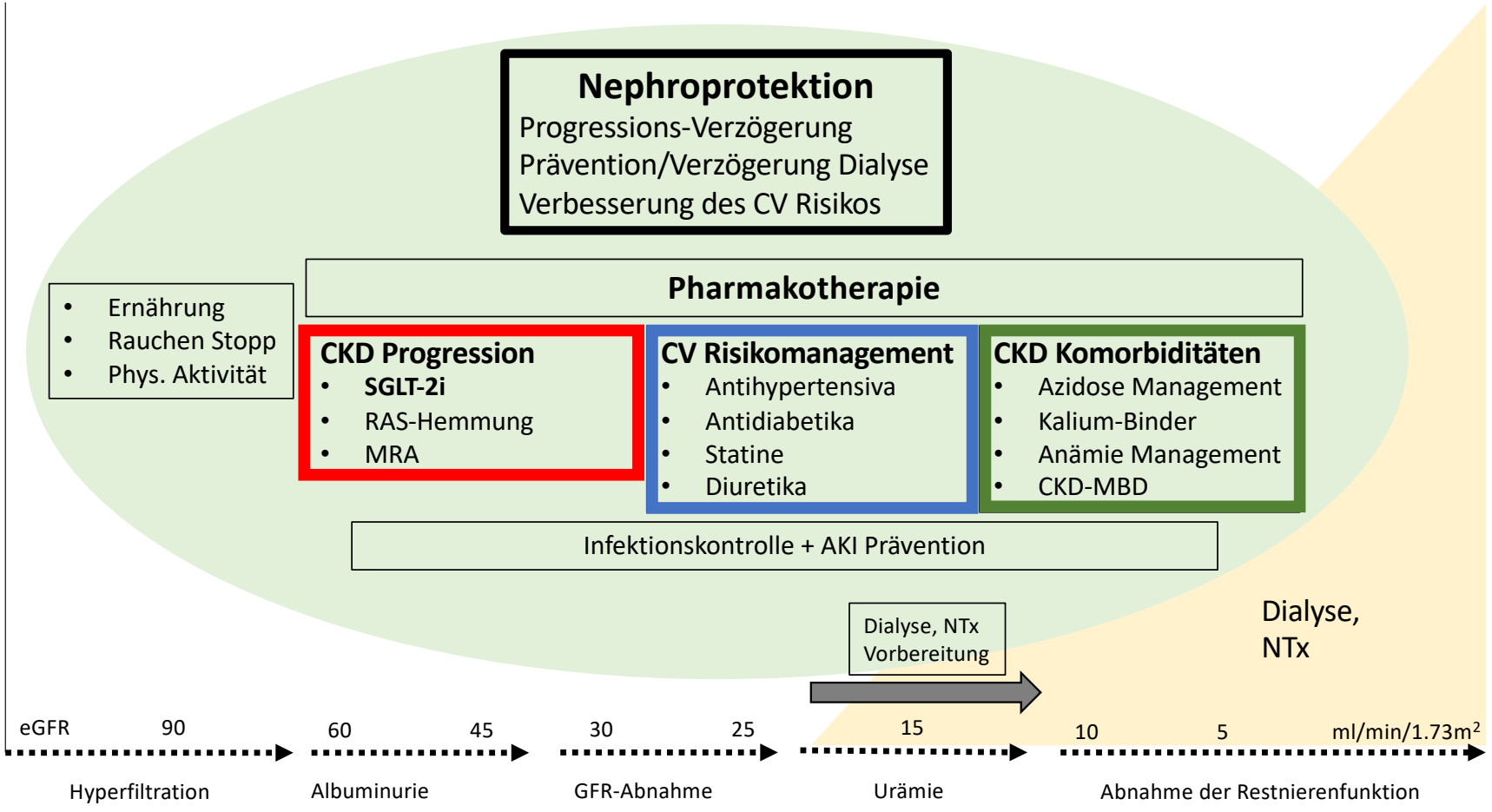
Bakris G, AJKD 2019

These agents are "*disease-modifying therapies*".

Ofri Mosenzon, EASD 2019


Genetic
Toxic
AKI/AKD
Auto-immune
Diabetes
Infection
Ischemic
Others
Upstream disease-specific targets
Nephron loss
Remnant nephrons
Hemodynamic overload: ↑podocyte shear stress
Metabolic overload: ↑proximal tubule stress
Upstream CKD targets (RAS, SGLT…)
Remnant nephron loss
CKD targets mediating downstream consequences
Atrophy/ fibrosis
CV risk
Exercise, diet, no smoking, BP, lipid, anemia control

Konservatives CKD Management



SGLT-2i und CKD in der Praxis

CKD Patient
Kardiorenaler Patient
eGFR ≥ 25 ml/min

SGLT-2i Ausschlussgründe ?

- ADPKD, Lupus Nephrits, Vaskulitis → Nephrologisches Zentrum
- Hypovolämie: Reduktion Diuretika, Flüssigkeits-Management

Nephroprotektive Basis-Therapie Erweiterung

ACE-Hemmer/Sartan/ARNi → **Dapagliflozin 10 mg/Tag** → Vereinbarte CKD Kontrollen

Dapagliflozin 10 mg/Tag → ACE-Hemmer/Sartan/ARNi → Hochtitration Kontrolle eGFR, Elektrolyte

Erwäge Diuretika ↓

Vor SGLT-2i-Therapie beachten:

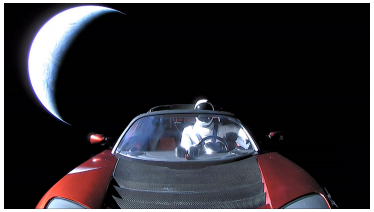
- Anamnese einer diabetischen Ketoazidose
- Rekurrente signifikante urogenitale Infektion
- Rezidivierende akute Nierenversagen
- Hypovolämie - arterielle Hypotension
- Einnierigkeit
- ADPKD, SLE, bestehende Immunsuppression

Erwäge vor Therapiebeginn:

- Transfer an nephrologisches Zentrum
- Optimiertes Flüssigkeitsmanagement:
  - *Trinkmenge*
  - *Adaptieren von Antihypertensiva bzw. Diuretika, insbesondere Schleifendiuretika*
- Hygiene-Vorschriften

SGLT-2i Pause („*sick day drug*“):

a) im Rahmen akuter Erkrankungen (z.B. Fieber, Infektionen, Diarrhöe, etc.)
b) bei prolongierten Fastenperioden
c) perioperativ



CKD Therapie neu: SGLT-2i als CKD Basistherapie

- Progressionsverzögerung - GFR Stabilisierung: DKD und CKD
- Antialbuminurisch (Primär-, Sekundärprävention)
- Wirksam und sicher bis *zumindest* eGFR 25 ml/min
- Weniger AKI - nierensicher: Sicher kombinierbar mit RAASi & Diuretika
- Kardioprotektion
- Überlebensvorteil - Dialyse-Delay: 15 Jahre !
- Einsatz bei glomerulären Erkrankungen: Guidelines !

Vielen Dank für Ihre Aufmerksamkeit !