Diabetic Kidney Disease

Post ADA 2022
01.09.22

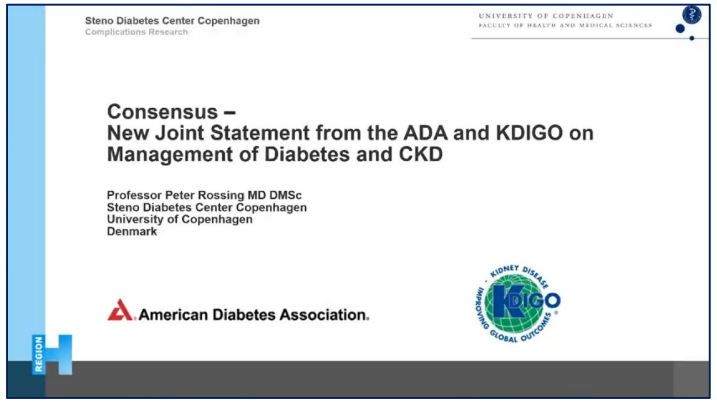
Dr Christophe Kosinski
PD MER Dr Anne Zanchi

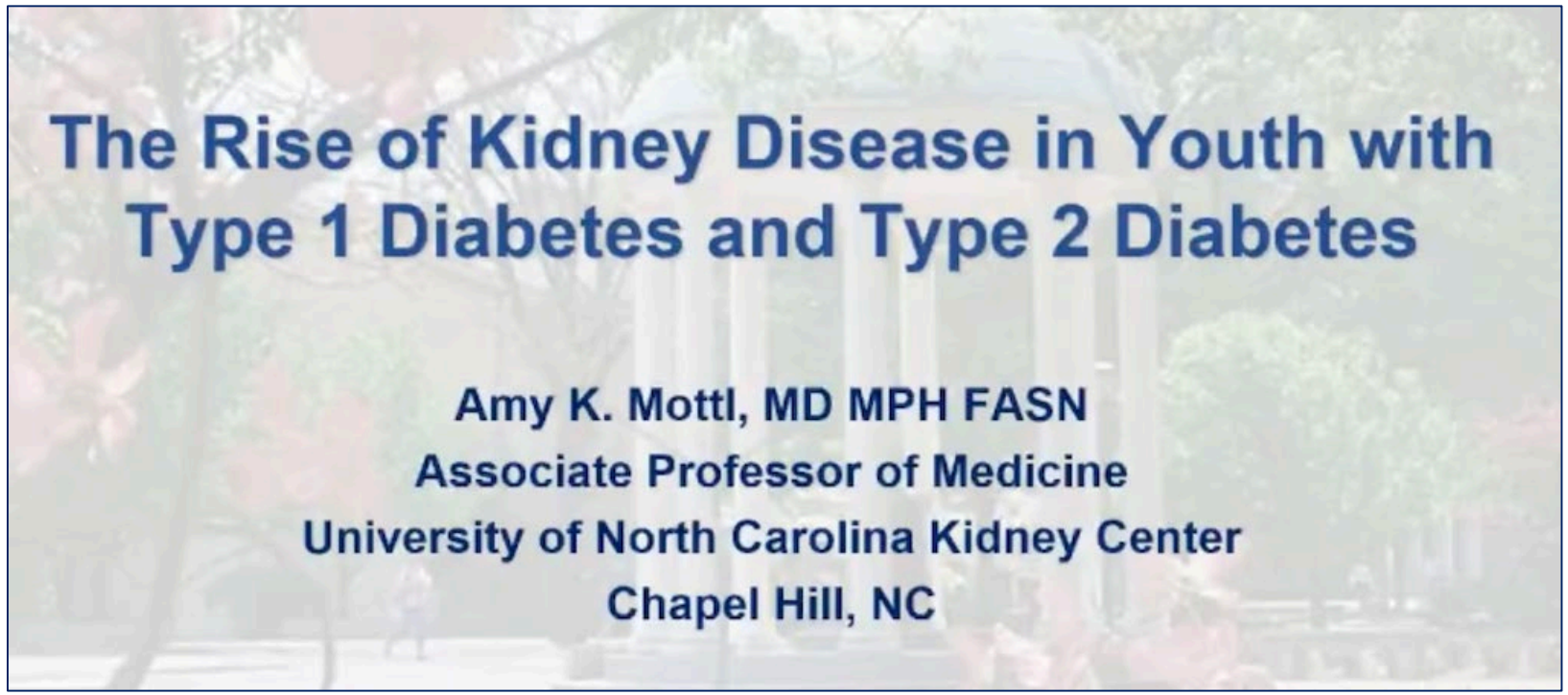
Service d'Endocrinologie, Diabétologie & Métabolisme
CHUV

DKD Post ADA

- Epidemiology
- DKD trials
  - SGLT2i
  - Finerenone
- Twincretin
- Future perspectives

including




The Rise of Kidney Disease in Youth with Type 1 Diabetes and Type 2 Diabetes
Amy K. Mottl, MD MPH FASN
Associate Professor of Medicine
University of North Carolina Kidney Center
Chapel Hill, NC

Morton et al. Diabetes Care 2020; 43: 1788-1795

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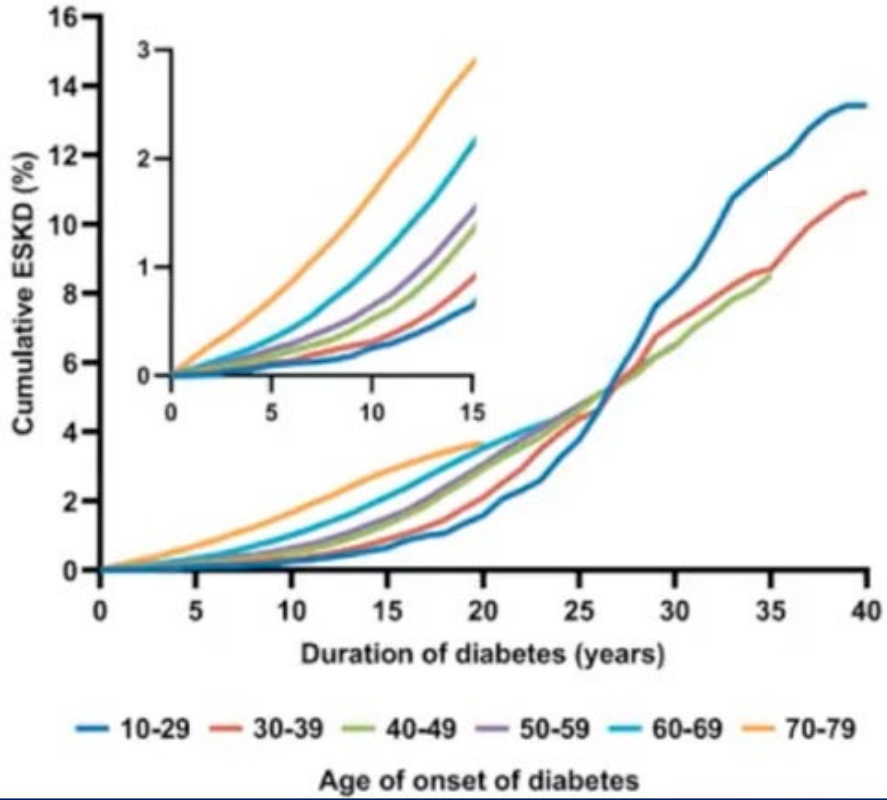
Rates of stage 5 CKD in T2D by age of onset in Australia



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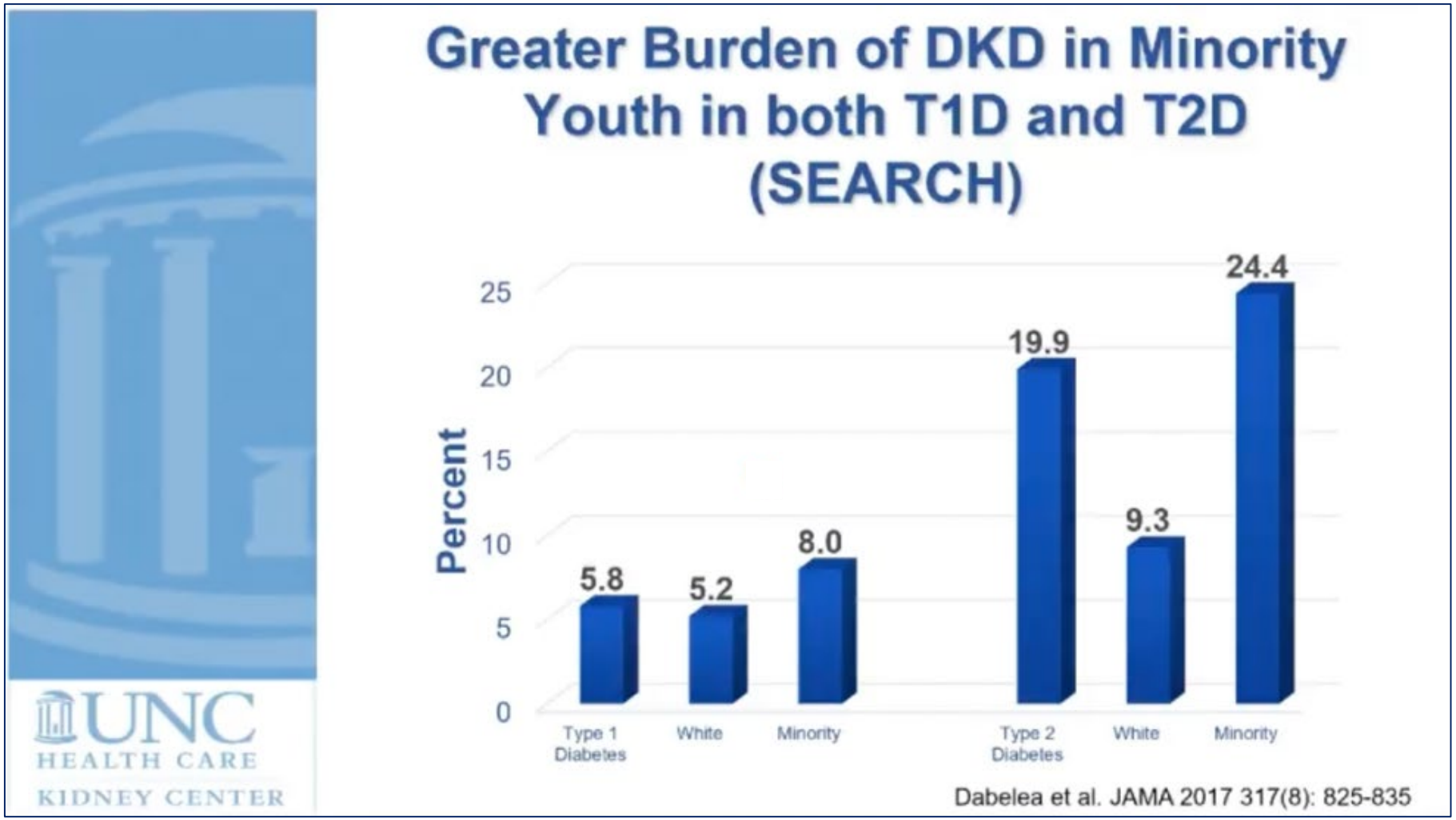
Cohorts for Discussion

- **SEARCH for Diabetes in Youth Cohort Study**
  - Longitudinal, observational study from 2002-2020
  - Youth onset type 1 and type 2 diabetes
  - Recruited from multicenter SEARCH registry – low bias
  - Study visits every 5 years (2-3 visits per participant)
- **TODAY 2 Study**
  - Ongoing, longitudinal, observational study of clinical trial participants (2004-2009)
  - Youth onset type 2 diabetes
  - Study visits every year


Greater Burden of DKD in Minority Youth in both T1D and T2D (SEARCH)
Percent
25
20
15
10
5
0
5.8
5.2
8.0
19.9
9.3
24.4
Type 1 Diabetes
White
Minority
Type 2 Diabetes
White
Minority
Dabelea et al. JAMA 2017 317(8): 825-835
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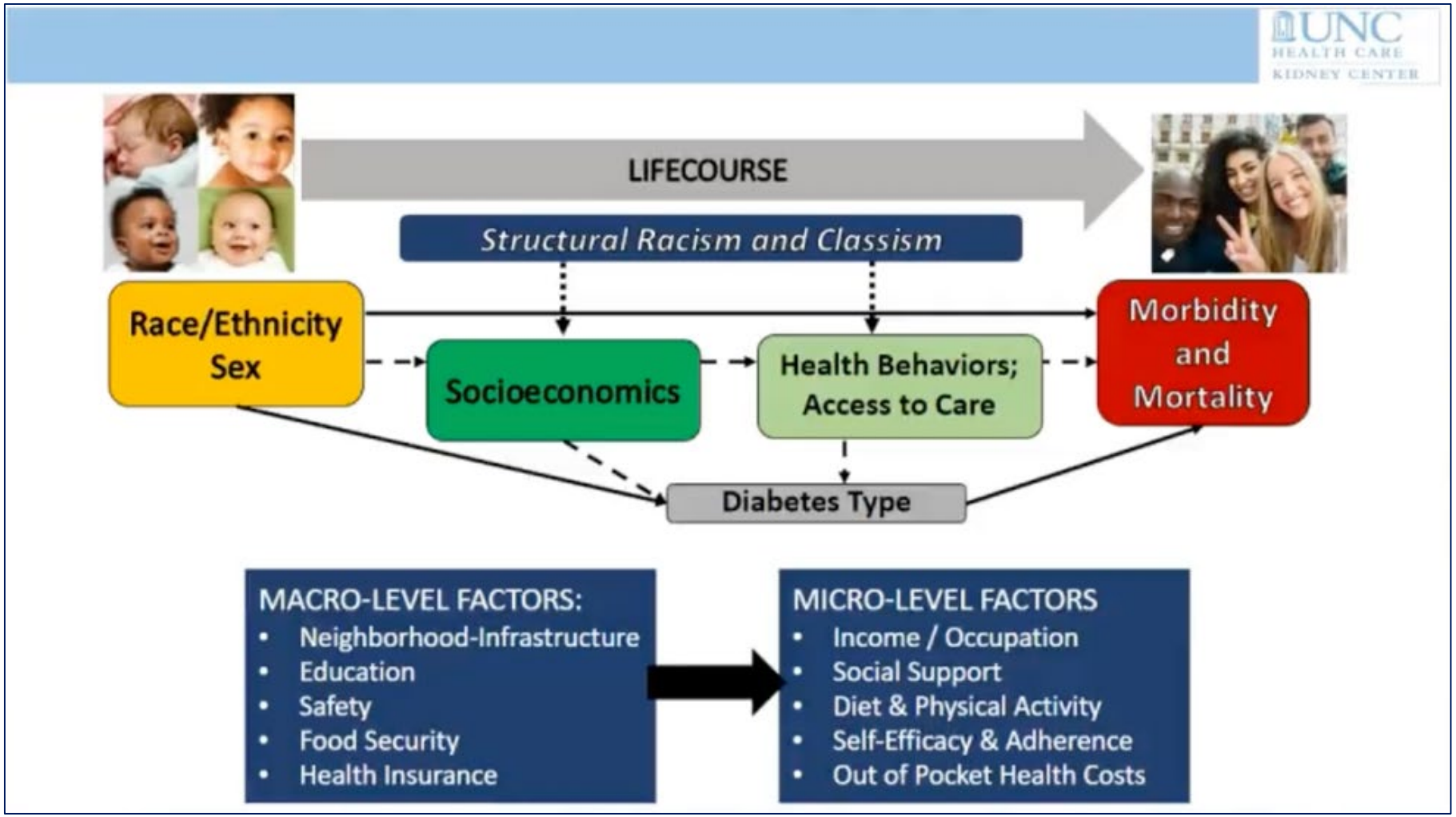
T2D vs T1D

- More hypertensive (11.5-21.6% vs 10.1%)
- More albuminuric (28-55% vs 11%)
- More progression of albuminuria (15.4% vs 6.0%)
- Incident cases of ESRD: 5/10’000 person-years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LIFECOURSE
Structural Racism and Classism
Race/Ethnicity Sex
Socioeconomics
Health Behaviors; Access to Care
Morbidity and Mortality
Diabetes Type
MACRO-LEVEL FACTORS:
Neighborhood-Infrastructure
Education
Safety
Food Security
Health Insurance
MICRO-LEVEL FACTORS
Income / Occupation
Social Support
Diet & Physical Activity
Self-Efficacy & Adherence
Out of Pocket Health Costs

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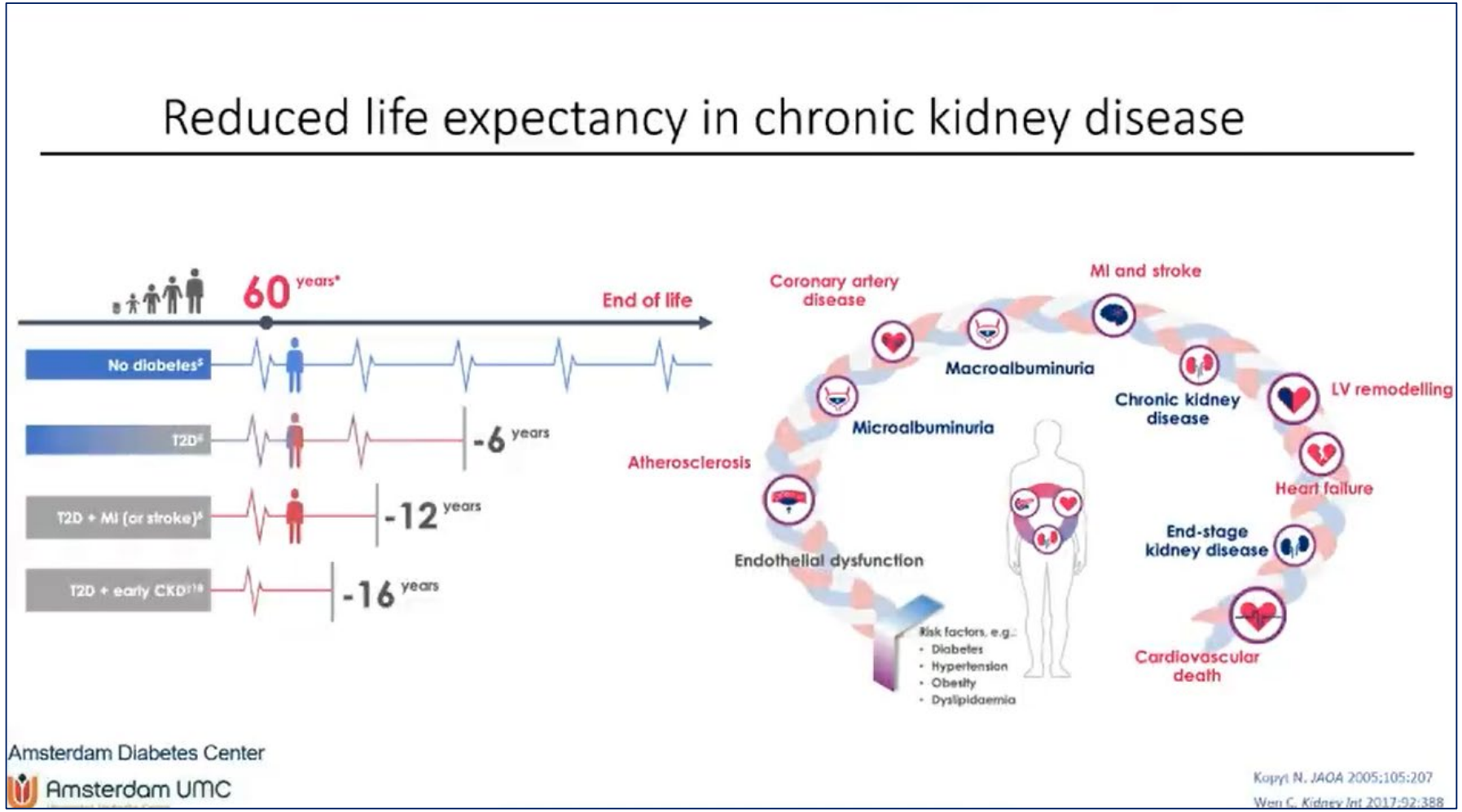
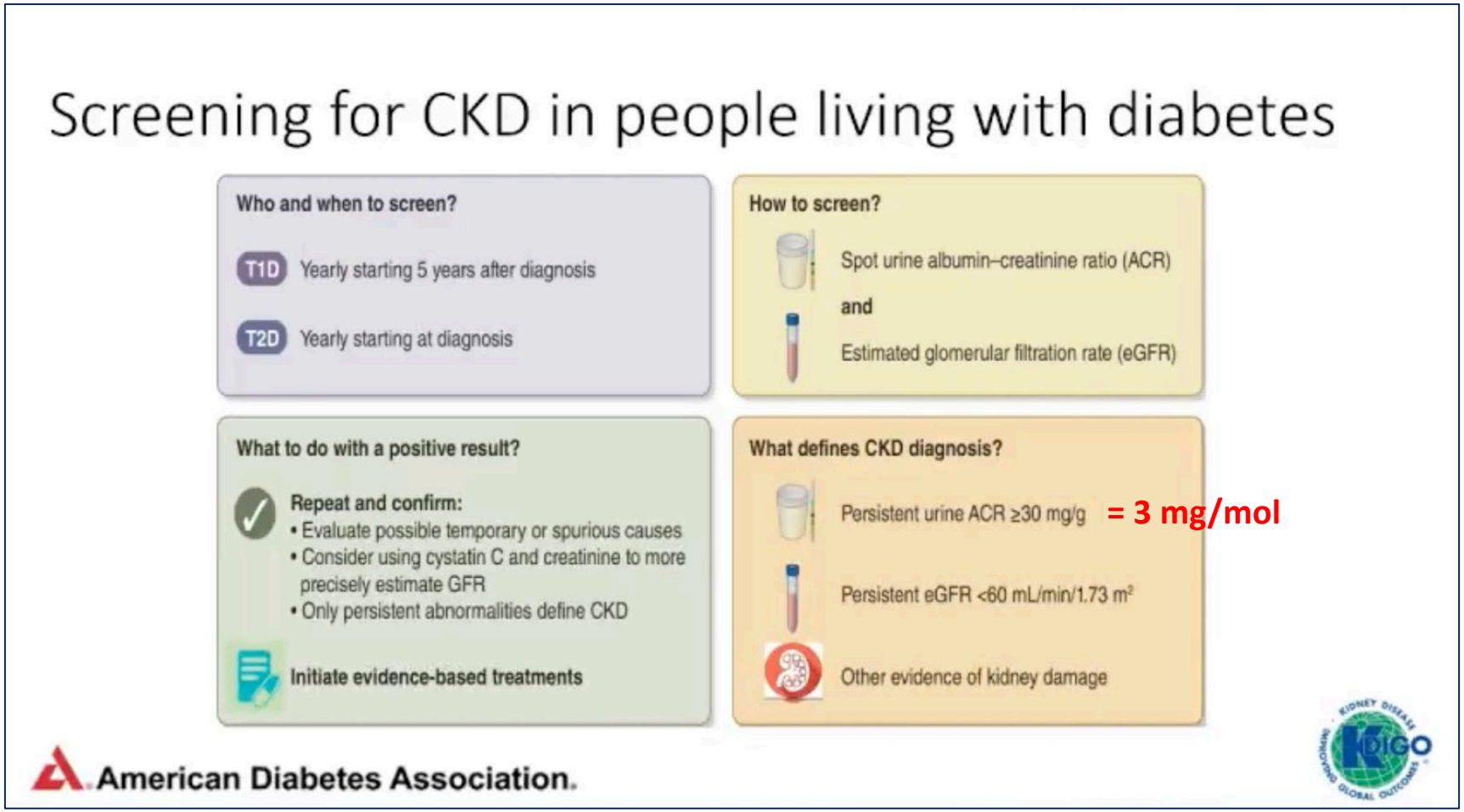
Conclusions

- Incident/prevalent rates of youth onset type 1 and type 2 diabetes is rising between 2-5% per year
- Albuminuria is common in youth onset diabetes during adolescence and young adulthood
- Major risk factors for DKD include minority race/ethnicity, youth onset type 2 diabetes and poor access to care
- Hope for a better future necessitates rectifying the inequities in basic human needs, particularly access to primary & subspecialty care and technologic and pharmacologic interventions

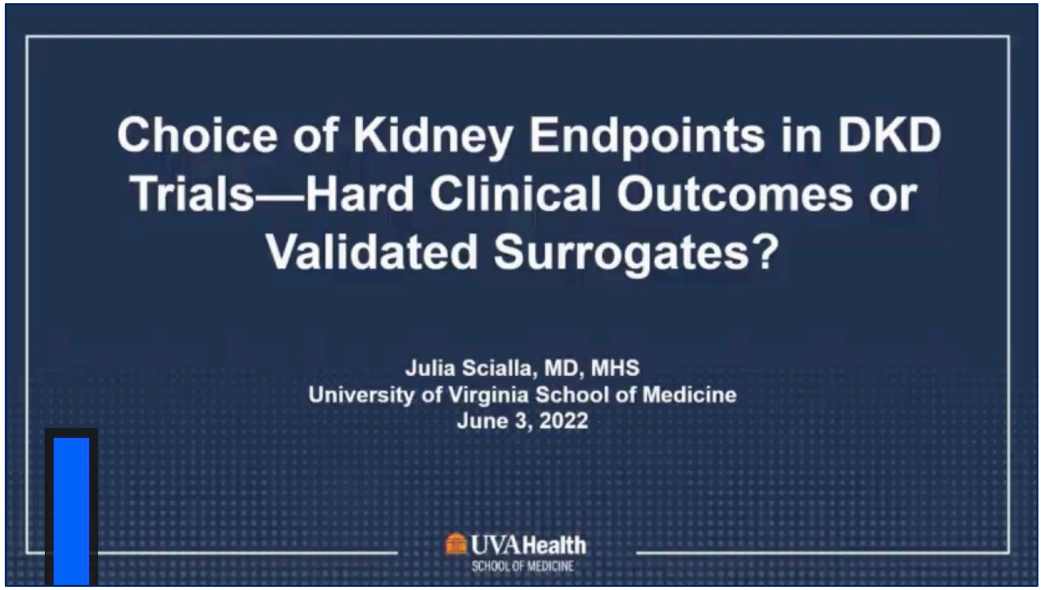


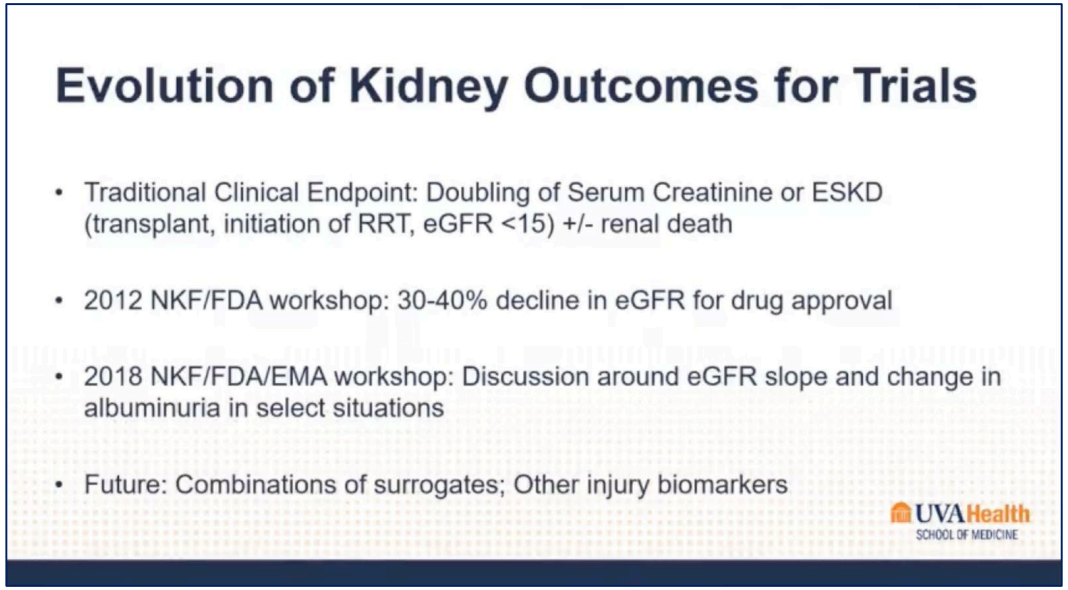
Daniël van Raalte. Symposium 1-AC-SY08. June 6th 2022.



➔ **Only 50% are tested within 1 year for UACR and eGFR** *Stempniewicz N et al., Diabetes Care, 2021*

The problem of various renal endpoints

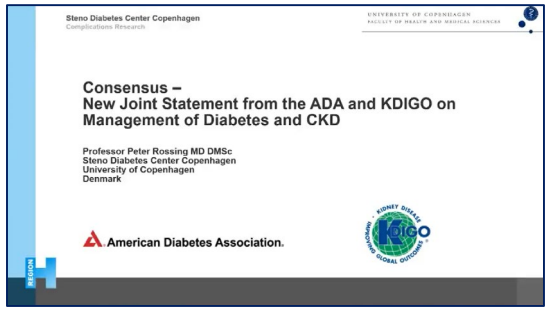


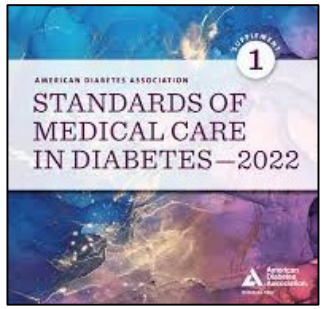


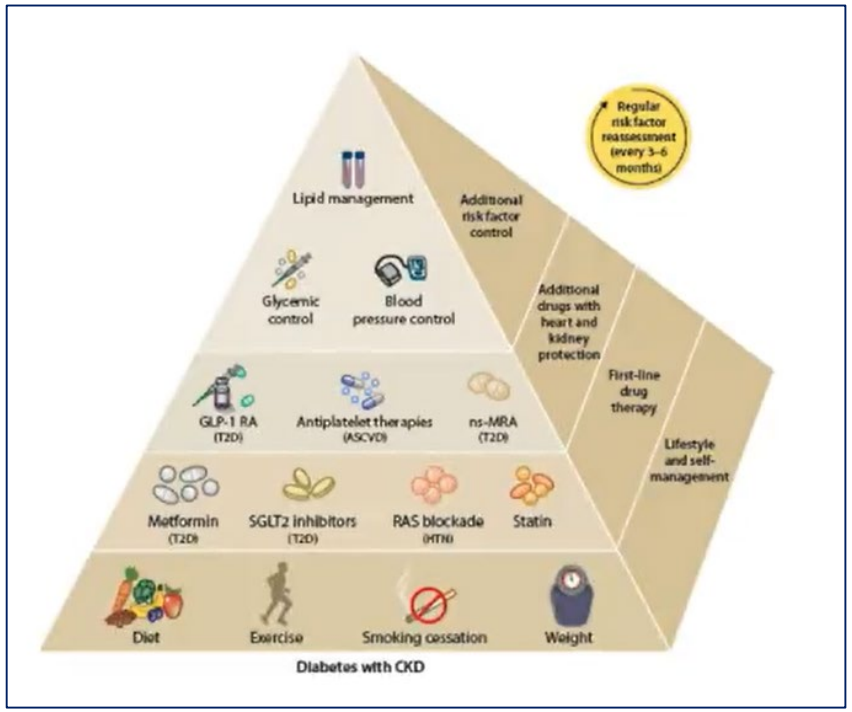
Recent renal outcome trials

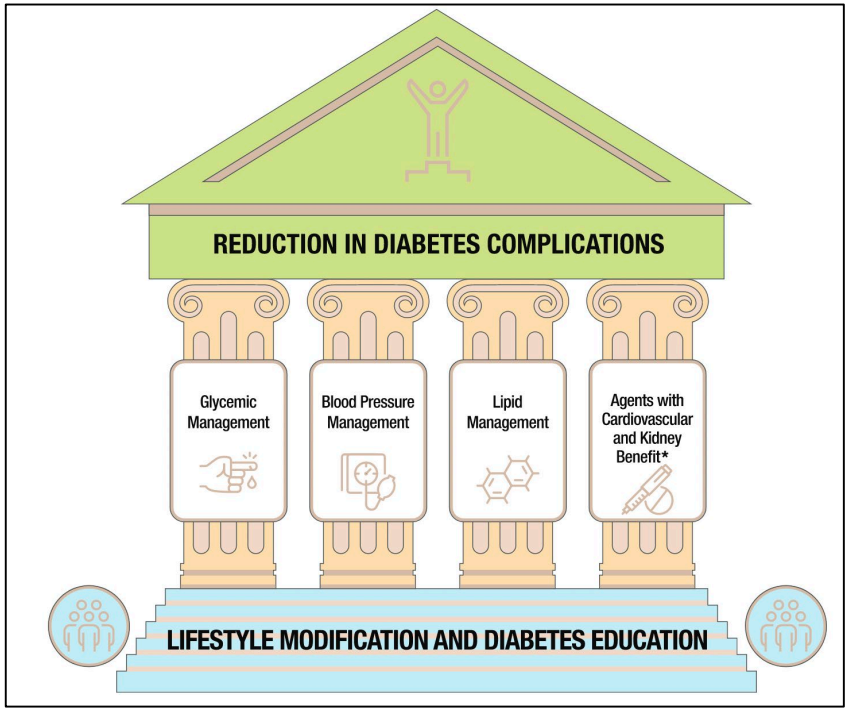
CREDENCE canagliflozin *NEJM 2019*	• Doubling of serum creatinine • ESRD, transplantation, sustained eGFR<15ml/min • Death from renal or CV causes
DAPA-CKD dapagliflozin *NEJM 2020*	• Sustained > 50% eGFR decline • ESKD • Renal or CV death
FIDELIO finerenone *NEJM 2020*	• Sustained > 40% eGFR decline for at least 4w. • ESKD • Renal death
FLOW semaglutide	• Persistent eGFR decline of ≥50% • ESKD • Death from renal or CV causes

DKD Post ADA Consensus ADA KDIGO

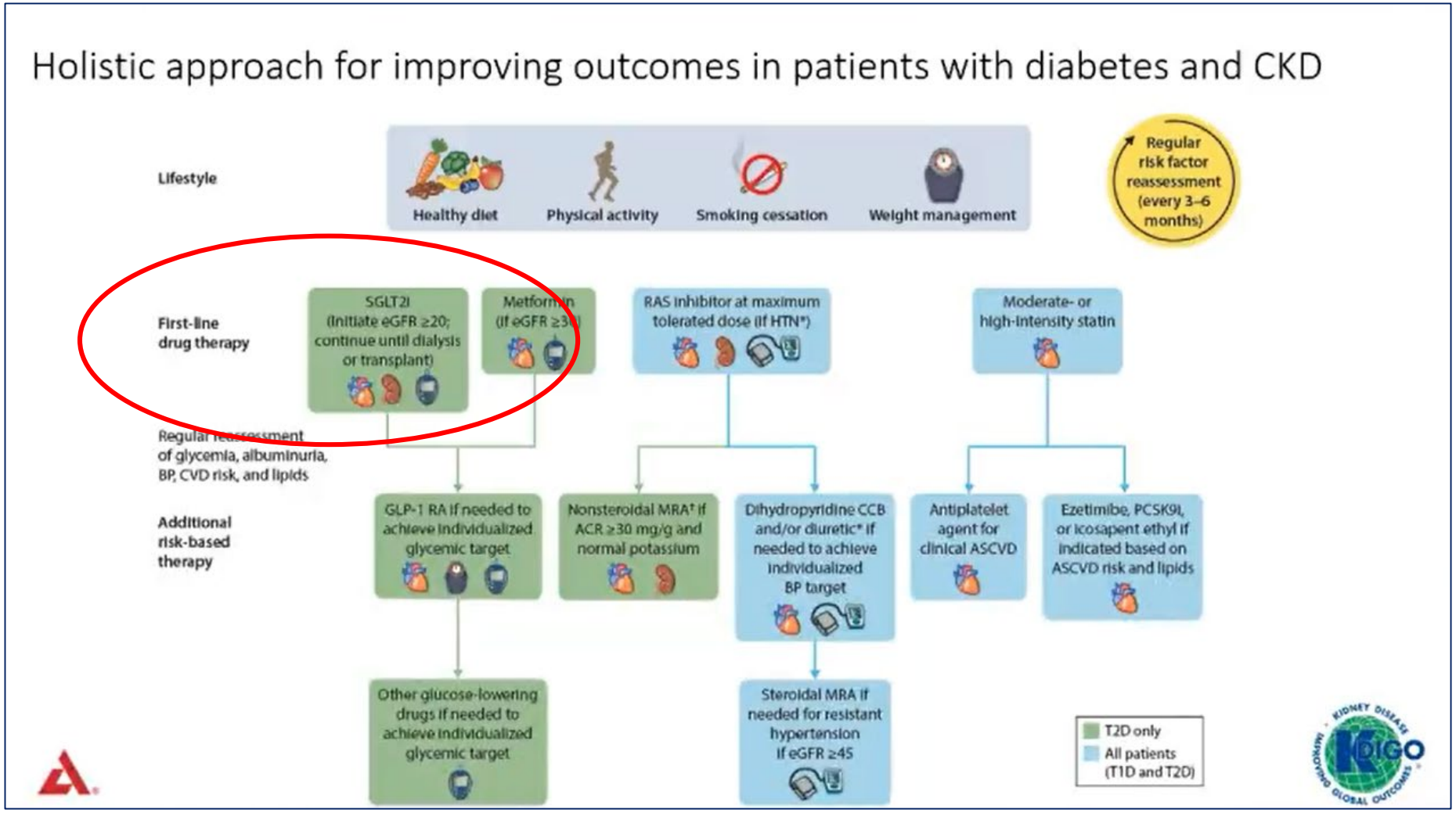








Post ADA 2022


Holistic approach for improving outcomes in patients with diabetes and CKD
Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)
Metformin (If eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
Additional risk-based therapy
GLP-1 RA if needed to achieve individualized glycemic target
Nonsteroidal MRA* if ACR ≥30 mg/g and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
T2D only
All patients (T1D and T2D)
KDIGO

Rationale for new SGLT2i eGFR initiation threshold of ≥20 mL/min/1.73 m^2

- Benefits & risks of SGLT2i generally similar across all included eGFR groups (other than HbA1c lowering)
- EMPEROR trials included participants with eGFR ≥20 mL/min/1.73 m^2 (and HF)
- DAPA-CKD included participants with eGFR ≥25 mL/min/1.73 m^2 (and albuminuria ≥200 mg/g)
- Subgroup analyses of CREDENCE & DAPA-CKD participants with eGFR <30 mL/min/1.73 m^2
- CREDENCE, DAPA-CKD, and other trial protocols included on-trial continuation of drug below initiation threshold

Diabetes Ther (2021) 12:499–508
https://doi.org/10.1007/s13300-020-00953-4

ORIGINAL RESEARCH

Linear Projection of Estimated Glomerular Filtration Rate Decline with Canagliflozin and Implications for Dialysis Utilization and Cost in Diabetic Nephropathy

Michael Durkin · Jaime Blais

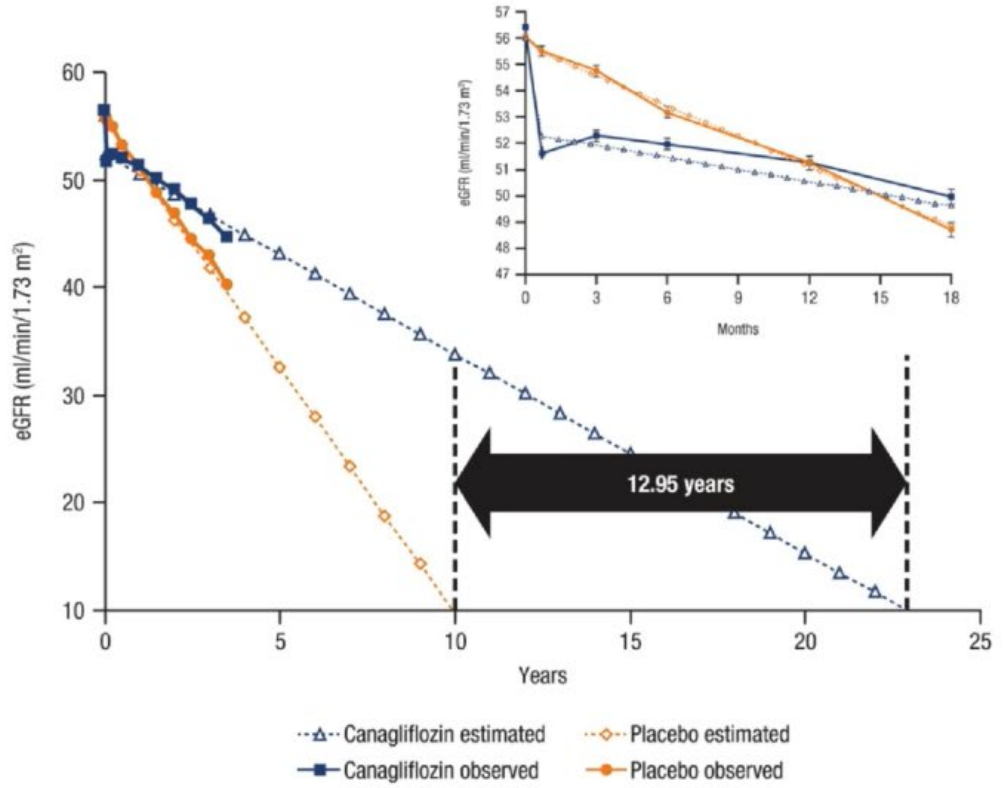


Fig. 1 Estimated eGFR values used to project the delay in time to dialysis (eGFR of 10 ml/min/1.73 m^2) by treatment in the CREDENCE trial (overlaid with observed data). *eGFR* estimated glomerular filtration rate

- Future:
  - ➢ Safety in renal transplant patients?
  - ➢ Effect in advanced CKD?

- The RENAL LIFECYCLE Trial: **RCT dapagliflozin in severe CKD**

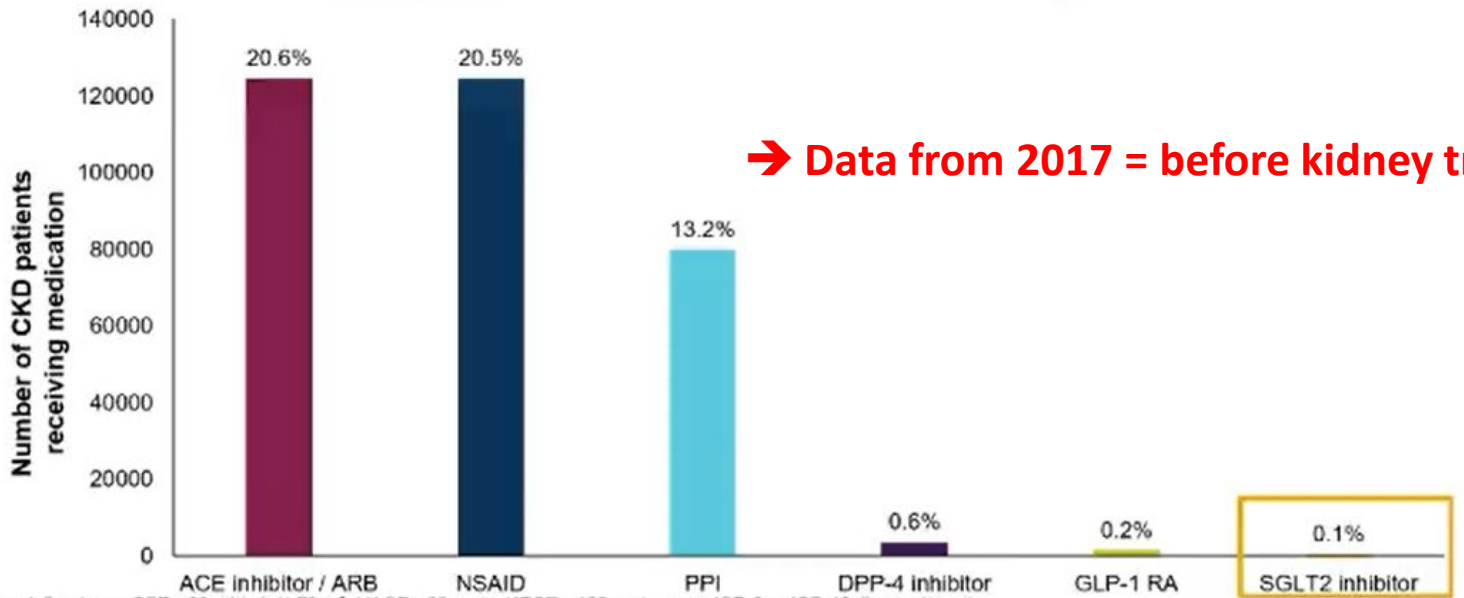
Inclusion Criteria:

- Patients with advanced CKD i.e. an eGFR <25 mL/min/1.73m2
- Dialysis patients with a residual diuresis >500 mL/24h (at least 3 months after start of dialysis)
- Transplant patients with an eGFR ≤45 mL/min/1.73m2 (at least 6 months after transplantation)

The uptake of SGLT2 inhibitors in CKD is lower compared with other glycemic and nonglycemic agents

- The CURE-CKD registry investigated prescription patterns of 606,064 adult US CKD patients

Prevalence of prescription medication use in CKD patients[1,a]



➔ **Data from 2017 = before kidney trials !**

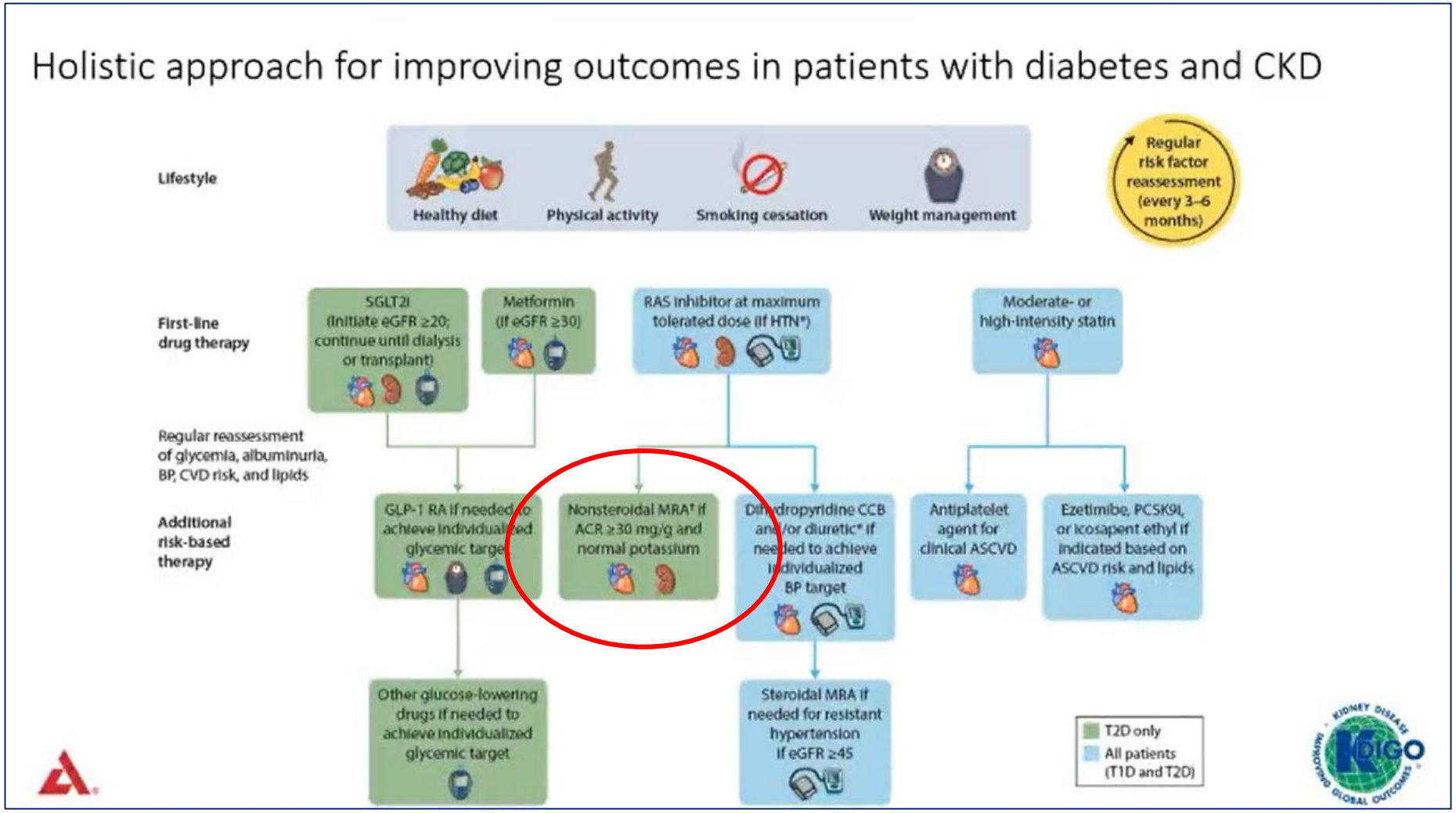
[a]CKD was defined as: eGFR <60 mL/min/1.73 m², UACR >30 mg/g, UPCR >150 mg/g, or an ICD-9 or ICD-10 diagnosis code
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ICD, International Classification of Diseases; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio; UPCR, urine protein:creatinine ratio
1. Tuttle KR, et al. *JAMA Netw Open* 2019;2:e1918169.

CHUV: Diabetic patients with CKD (eGFR<60 or ACR>30mg/mmol)

Outpatient diabetes clinic

n=596
Age: 62.5
eGFR: 60.2ml/min
ACR: 41.5mg/mmol
BMI: 29.4kg/m^2
HbA1C: 7.8%

SGLT2i: 28% (30% if eGFR<30 excluded)
GLP1Ra: 43%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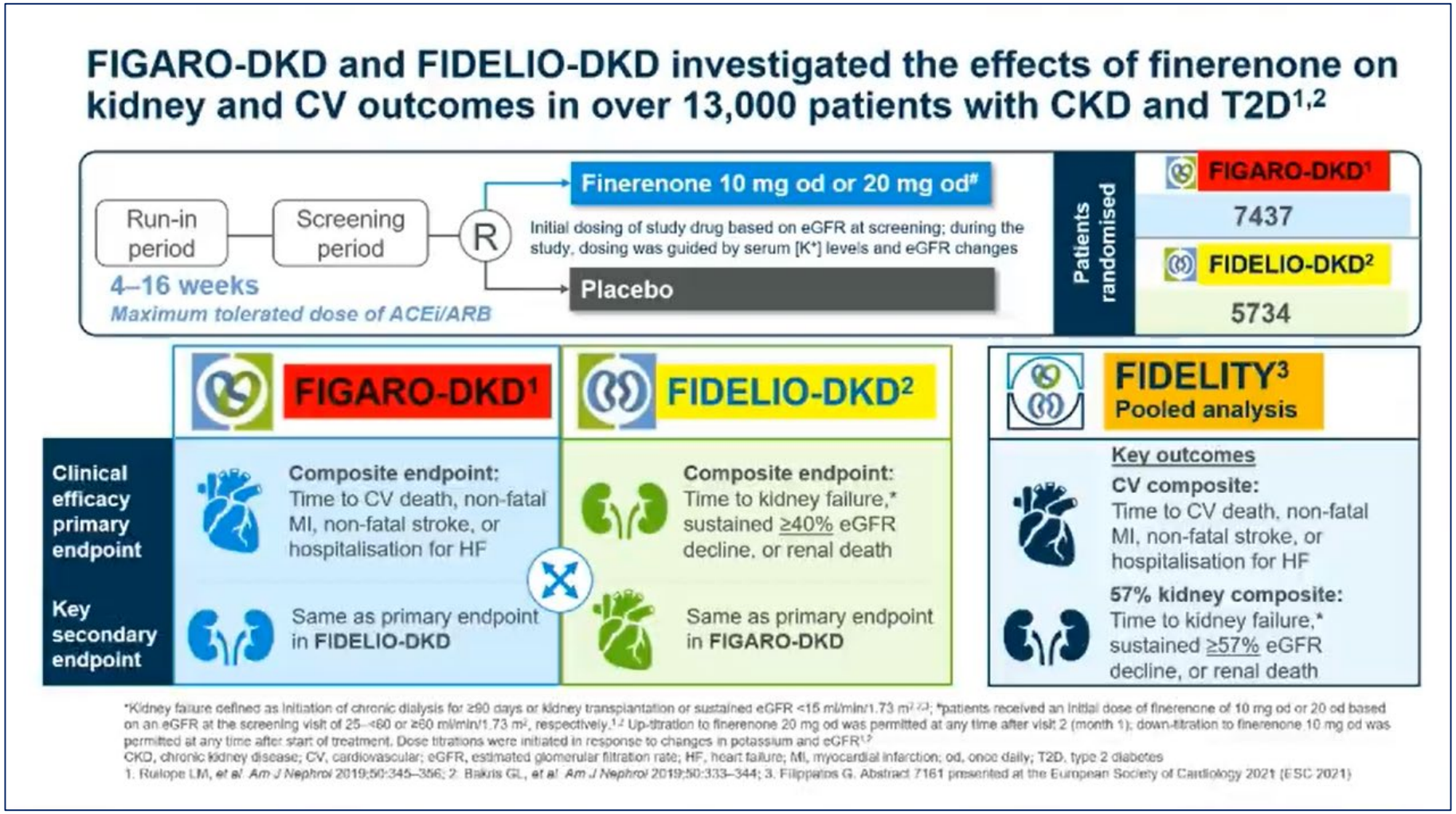
All patients (T1D and T2D)
KDIGO

- Finerenone a non steroidal MRA in DKD
  - FIDELIO *Bakris et al. NEJM 2020*
  - FIGARO *Pitt et al. NEJM 2021*
  - FIDELITY (FIDELIO + FIGARO) *Agarwal et al. European Heart Journal 2022*

- SGLT2i vs MRA in DKD ?



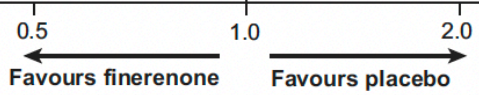
*Kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 ml/min/1.73 m²[1,2]; #patients received an initial dose of finerenone of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m², respectively.[1,2] Up-titration to finerenone 20 mg od was permitted at any time after visit 2 (month 1); down-titration to finerenone 10 mg od was permitted at any time after start of treatment. Dose titrations were initiated in response to changes in potassium and eGFR[1,2]

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; od, once daily; T2D, type 2 diabetes

1. Ruilope LM, *et al*. *Am J Nephrol* 2019;50:345–356; 2. Bakris GL, *et al*. *Am J Nephrol* 2019;50:333–344; 3. Filippatos G. Abstract 7161 presented at the European Society of Cardiology 2021 (ESC 2021)

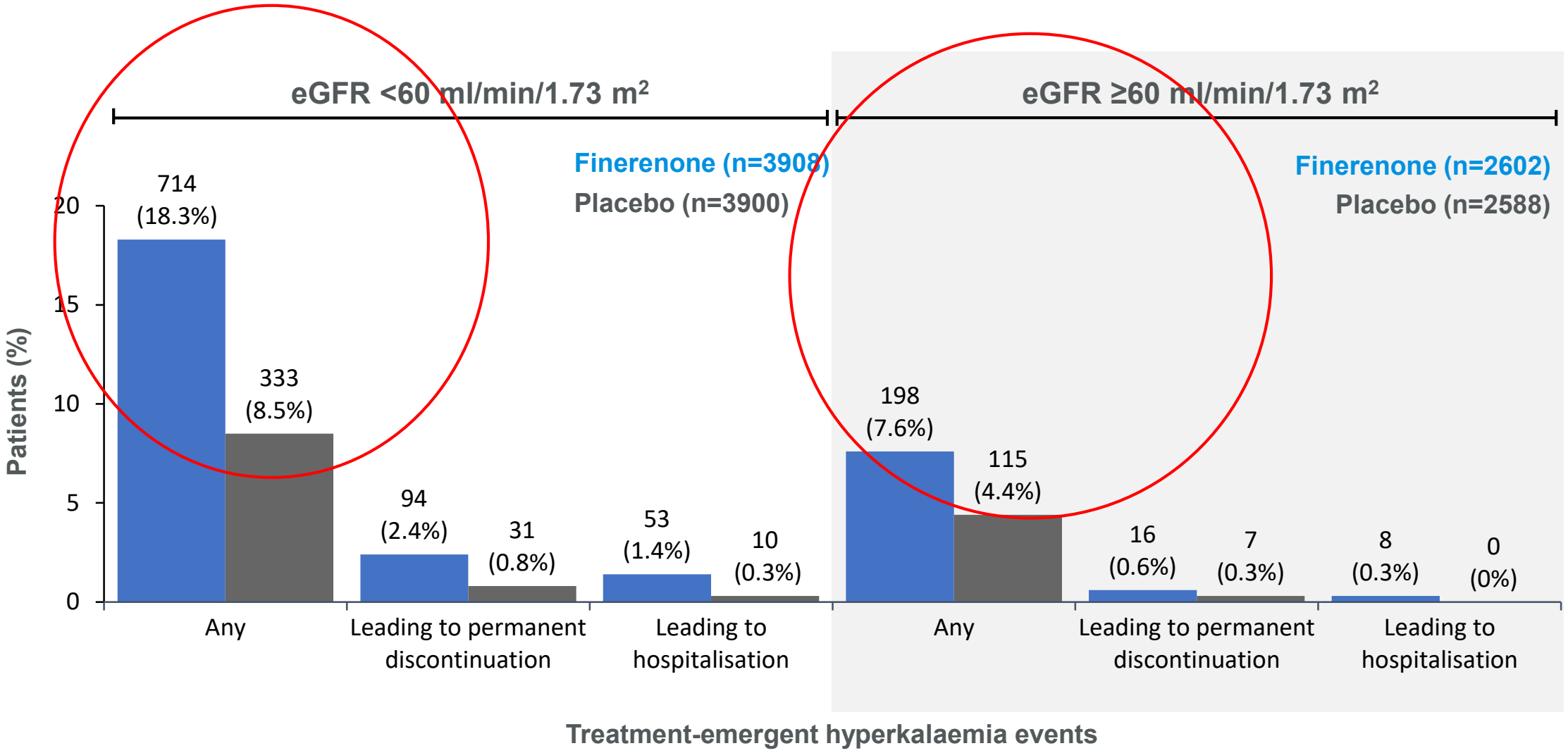
DKD Post ADA Finerenone

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]



Agarwal et al. European Heart Journal 2022

Finerenone - Risk of hyperkalemia



Bakris G, *et al. ASN* 2021; Poster PO2531

Finerenone - Risk of hyperkalemia

Baseline variable	Category	HR (95% CI)	*P*-value
Age, years	18–44	1.03 (0.67–1.59)	0.0465
	45–64	1.09 (0.94–1.25)	
	65–74	Ref	
	≥75	0.81 (0.65–0.99)	
Sex	Male vs female	0.85 (0.74–0.97)	0.0200
Serum potassium, mmol/L	≤4.1	0.44 (0.35–0.55)	<0.0001
	>4.1–≤4.5	Ref	
	>4.5–≤4.8	1.53 (1.29–1.82)	
	>4.8–≤5.0	2.78 (2.25–3.44)	
	>5.0	4.18 (3.45–5.05)	
eGFR, mL/min/1.73 m^2	<25	2.04 (1.35–3.07)	<0.0001
	25–<45	1.51 (1.19–1.91)	
	45–<60	1.02 (0.80–1.32)	
	≥60	Ref	
Log2 of UACR	Per 1 unit increase[a]	1.12 (1.06–1.17)	<0.0001
Diuretic use	Yes vs no	0.76 (0.66–0.87)	<0.0001
SGLT-2i use	Yes vs no	0.45 (0.27–0.75)	0.0023
Label-recommended dose of ACEi or ARB	≤min	0.96 (0.82–1.12)	0.8508
	>min but <max	0.97 (0.83–1.15)	
	≥max	Ref	
Beta-blocker use	Yes vs no	1.18 (1.04–1.35)	0.0133
Treatment assignment	Finerenone vs placebo	2.13 (1.86–2.45)	<0.0001

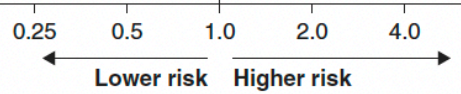


Figure 3. Multivariate analysis of time to any serum [K^+] >5.5 mmol/L. [a]UACR is modeled as a continuous variable; 1 unit change in $\log_2$ UACR denotes doubling of UACR. 95% CI, 95% confidence interval; Ref, reference category.

Agarwal et al JASN 33: 225-237, 2022

Finerenone - Risk of hyperkalemia

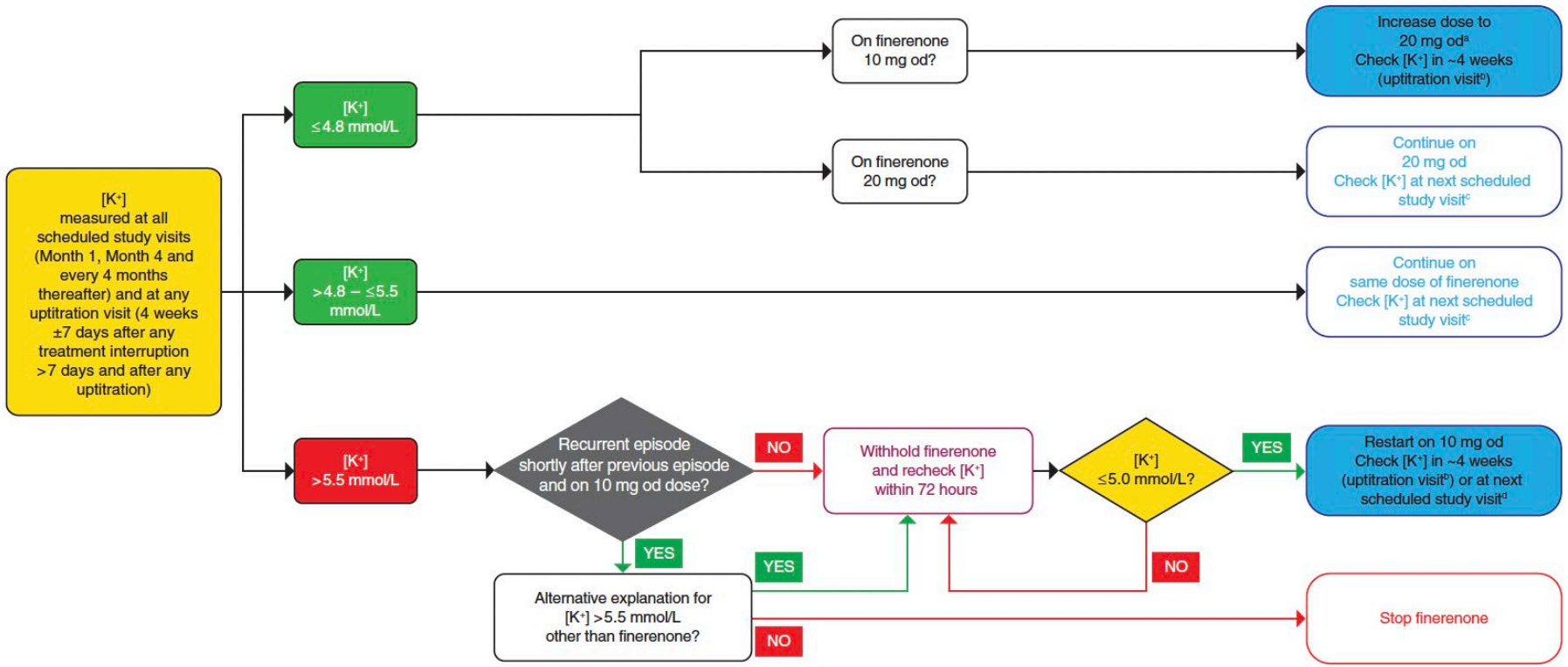


Figure 1. Potassium management algorithm in FIDELIO-DKD. [a]If eGFR is stable (*i.e.*, ≤30% decrease since last available measurement). [b]Uptitration visits were performed at 4 weeks ±7 days after any treatment interruption >7 days and after any uptitration. [c]Regular study visits were scheduled at month 1, month 4, and every 4 months thereafter. [d]If treatment interruption ≤7 days.

Agarwal et al JASN 33: 225-237, 2022

- **Finerenone** is **a potent highly selective non steroidal MRA**
  - Finerenone reduces significantly kidney and CV outcomes in patients with stage A2-A3 DKD
  - <1% sexual adverse events

  - Possible increase in potassium levels needs careful monitoring
  - Do not introduce if serum potassium >5mmol/l or eGFR < 25ml/min/1.73m^2

- **2022 ADA recommendations:**
  - Finerenone is recommended to reduce CKD progression and CV events (evidence A)

- **2022 KDIGO recommendations (under review)**
  - Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies.

Effects of Tirzepatide versus Insulin Glargine 100 U/mL on Kidney Outcomes in Participants with Type 2 Diabetes in SURPASS-4

Hiddo J L Heerspink, Naveed Sattar, Imre Pavo, Axel Haupt, Kevin L Duffin, Zhengyu Yang, Russell J Wiese, Katherine R Tuttle, David Z I Cherney

Department of Clinical Pharmacy and Pharmacology
University Medical Center Groningen
Netherlands

American Diabetes Association - 82nd Annual Scientific Sessions; New Orleans, LA, USA; 3 – 7 June 2022

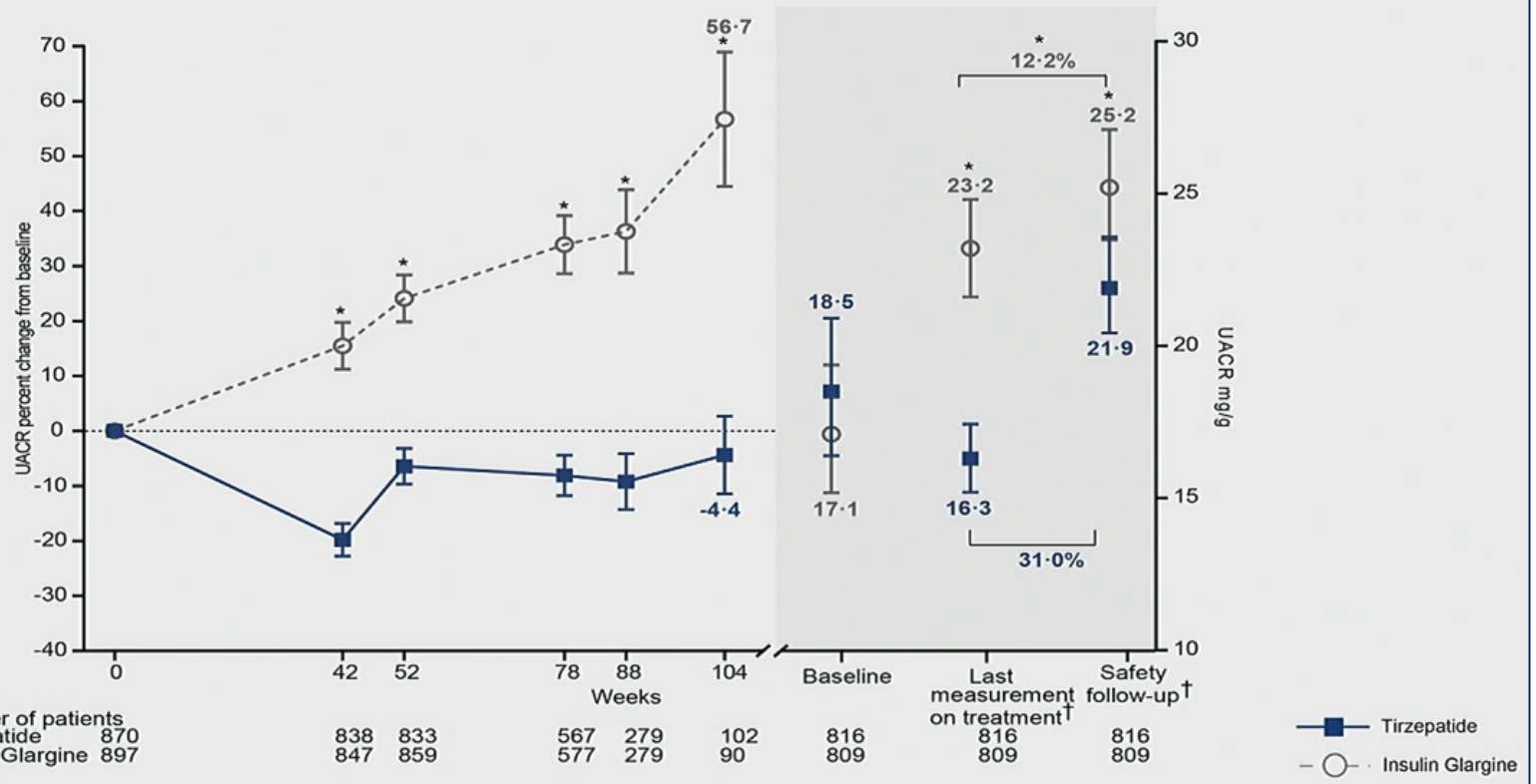
umcg

Baseline Characteristics

	Tirzepatide (N=995)	Insulin glargine (N=1000)
Age, years	63.4 (8.6)	63.8 (8.5)
Sex – male	610 (61%)	636 (64%)
Race – White	804 (81%)	825 (83%)
Duration of diabetes, years	11.5 (7.4)	12.0 (7.7)
HbA1c, %	8.54 (0.9)	8.50 (0.9)
Weight, kg	90.3 (18.3)	90.2 (19.0)
BMI, kg/m^2	32.6 (5.5)	32.5 (5.6)
eGFR, mL/min/1.73 m^2	81.1 (21)	81.5 (21)
eGFR <60 mL/min/1.73 m^2	176 (18%)	166 (17%)
UACR, mg/g	16.8 (5.3, 62.0)	13.0 (5.0, 54.0)
No albuminuria (UACR <30 mg/g)	621 (63%)	630 (64%)
Microalbuminuria (UACR 30-300 mg/g)	276 (28%)	270 (28%)
Macroalbuminuria (UACR >300 mg/g)	82 (8%)	79 (8%)
SGLT-2i use, yes	245 (25%)	256 (26%)
ACE inhibitor or ARB use, yes	804 (81%)	811 (81%)

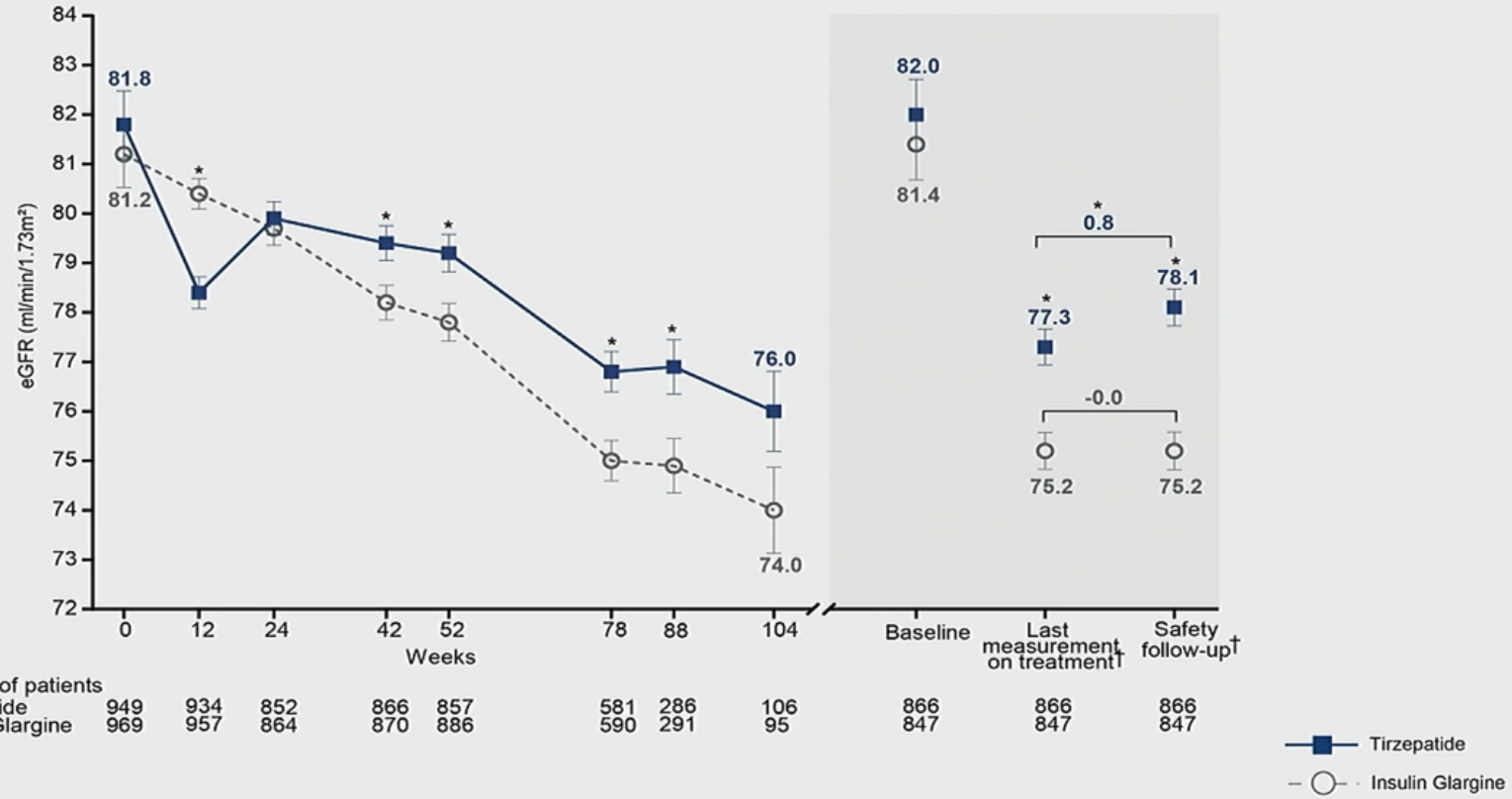
Data are presented as mean (SD) or N (%). UACR is presented as median (25th to 75th percentile)

Change in Albuminuria in All Patients



LSMean (SE) percent change from baseline in log-transformed UACR over time and adjusted geometric mean (95% CI) UACR at baseline, last measurement during treatment and safety follow-up. Adjusted geometric mean UACR calculated from analysis of covariance model. †The time from baseline to last measurement on treatment was median (IQR) 79 (69-88) weeks. The safety follow-up visit occurred 30 days after last measurement during treatment. *p<0.05 versus insulin glargine for between-group differences and between-group change from last measurement during treatment to safety follow-up.

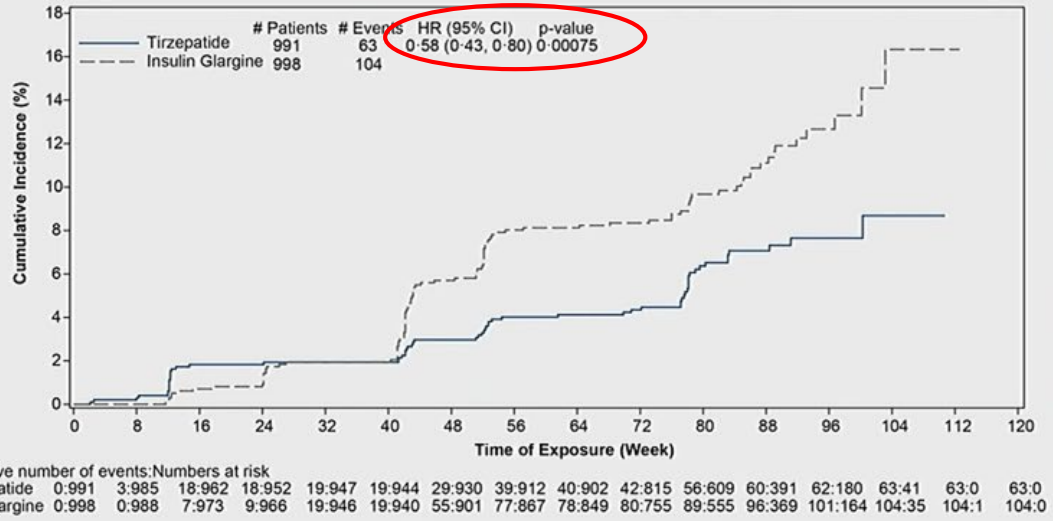
Change in eGFR in all Patients



LSMean (SE) eGFR (creatinine CKD-EPI) over time and adjusted LSMean (SE) at baseline, last measurement during treatment and safety follow-up.
Adjusted mean eGFR calculated from analysis of covariance model. †The time from baseline to last measurement on treatment was median (IQR) 79 (69-88) weeks. The safety follow-up visit occurred 30 days after last measurement during treatment. *p<0.05 versus insulin glargine for between-group differences and between-group change from last measurement during treatment to safety follow-up.

Tirzepatide Reduces the Risk of the Composite Kidney Endpoint (Macroalbuminuria, 40% eGFR Decline, ESKD, Renal Death)

Incidence composite kidney endpoint



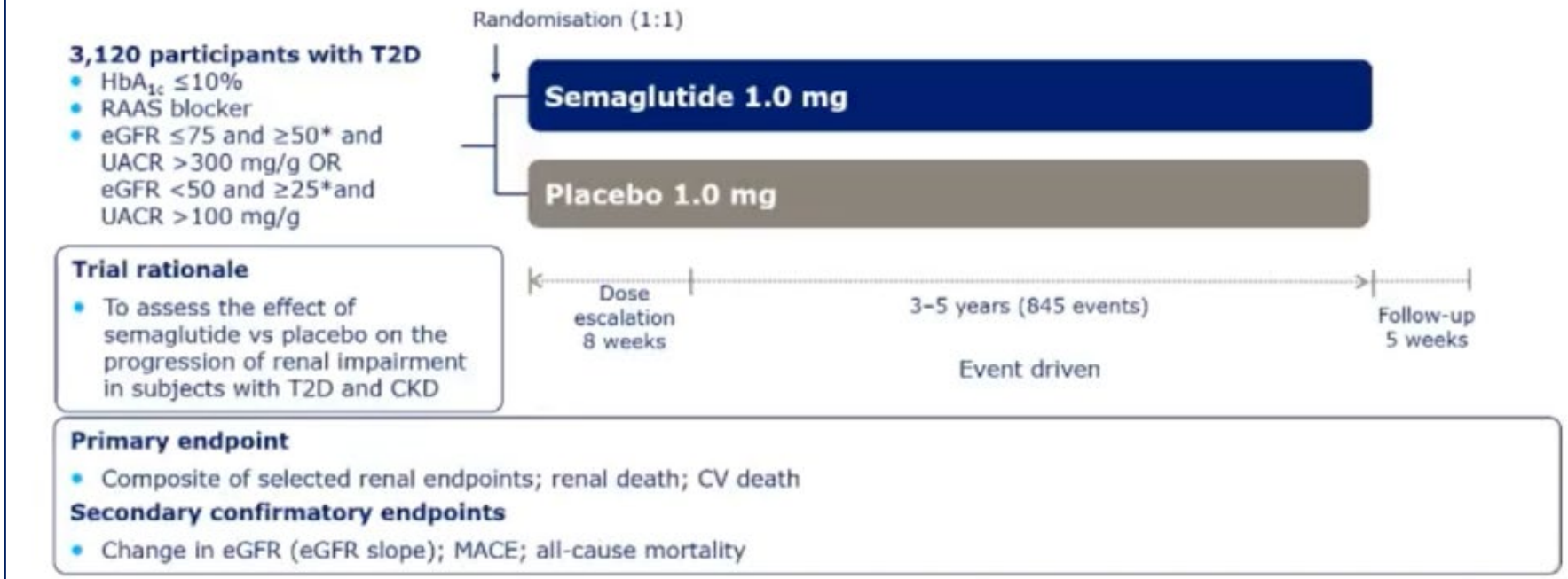
Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	0.87 (0.56,1.33)
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria[a]	TZP	25 (2.5%)	**0.41 (0.26,0.66) ***
	iGLAR	61 (6.1%)	

Cumulative incidence of time to renal composite endpoint 1. HR, CI, and p-value are derived from a Cox proportional-hazards model with treatment (tirzepatide vs. insulin glargine) as a fixed effect.

HR estimate with CI is not calculated when either the TZP or iGLAR arm has no event. [a]UACR ≥30 mg/g. *P<.05 versus iGLAR.

FLOW: renal outcomes trial with semaglutide

- TRIAL DESIGN



Amsterdam Diabetes Center

Amsterdam UMC

- Screening at least once per year
- Lifestyle = always mandatory
- SGLT2i = first line therapy, new cut-off eGFR > 20 ml/min
- Finerenone to consider
- Combination therapies

CKD stage	1-2	3a	3b	4	5
	eGFR>60ml/min/1.73m2	eGFR 45-60ml/min/1.73m2	eGFR 30-45ml/min/1.73m2	eGFR: 15-30ml/min/1.73m2	Hemodialysis
Insulins		decrease dose			
Glinides					
Novonorm® Repaglinide	0.5-12mg/d				
Starlix® Nateglinide	60-360mg/d		60mg/dose		
DPP-IV inhibitors					
Januvia® Sitagliptin	50-100mg/d	50mg/d		25mg/d	
Trajenta® Linagliptin	5mg/d				
Galvus® Vildagliptin	2 x 50mg/d	1 x 50mg/d			
Vipidia® Alogliptin	25mg/d	12.5mg/d		6.25mg/d	
Onglyza® Saxagliptin	5mg/d		2.5mg/d		
GLP1R agonists					
Byetta® Exenatide	10 µg 2x/j		5 µg 2x/j		
Bydureon® Exenatide	2mg/w				
Victoza® Liraglutide	0.6-1.8mg/d				
Lyxumia® Lixisenatide	10-20ug/d				
Trulicity® Dulaglutide	0.75-1.5mg/w				
Rybelsus® Semaglutide	3-14mg/j				
Ozempic® Semaglutide	0.25-1mg/w				
Thiazolidinediones					
Actos® Pioglitazone	15-45mg/d				
Metformin					
Glucophage® Metformin	500-2550mg/j	500-1500mg	500-1000mg/j do not initiate		
SGLT2 inhibitors					
Invokana® Canagliflozin	100-300mg	100mg	initiation only if ACR>30mg/mmol	OK until dialysis if ACR>30mg/mmol. Do not initiate	
Jardiance® Empagliflozin	10mg/j		if HFrEF	if HFrEF->20ml/min/1.73m2	
Forxiga® Dapagliflozin	5-10mg/j		if HFrEF or CKD	if CKD initiation->25ml/min/1.73m2 OK until dialysis	
Ertugliflozin® Steglatro	5mg/j				
Sulfonylureas					
Diamicron® Gliclazide	30-120mg/j				
Daonil® Glibenclamide	2.5-10mg/j				
Amaryl® Glimepiride	1-6mg/j				

Thank you for your attention

christophe.kosinski@chuv.ch