Post-ADA meeting
31.08.2023
Diabetic Kidney Disease

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post - ADA
post - ENDO

Plan

> Introduction

1/ Are we following the guidelines ?

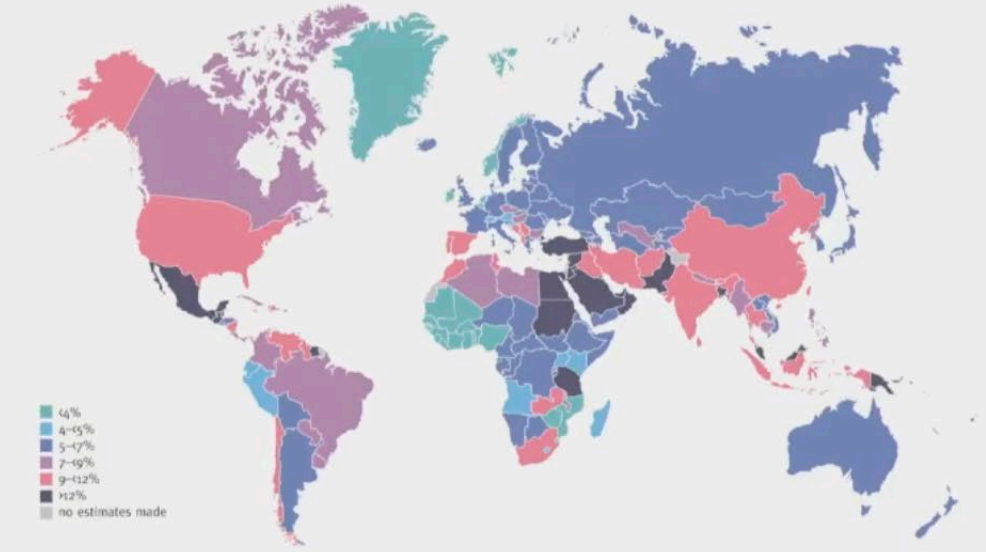
2/ CGM accuracy in DKD stage 4-5

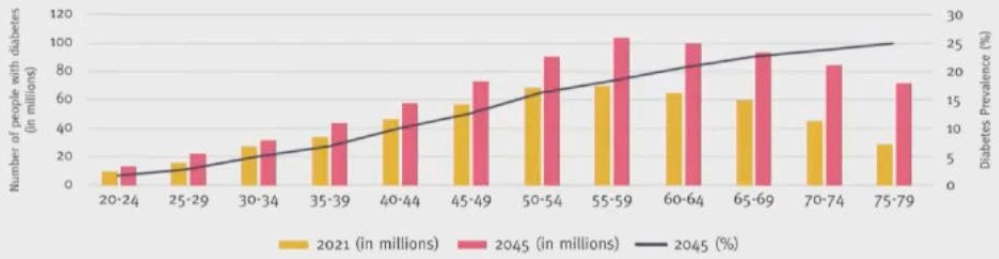
3/ Tirzepatide reduces albuminuria in T2D

4/ Effectiveness of the association GLP-1 agonists and SGLT-2 inhibitors on renal events

Increasing prevalence of DKD

Diabetic Kidney Disease is Highly Prevalent



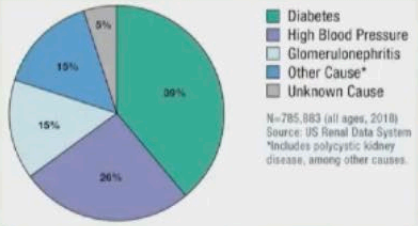


Worldwide diabetes prevalence, adults:

- 2021: **537 million (10.5%)** estimated
- 2030: **643 million (11.3%)** expected
- 2045: **783 million (12.2%)** expected

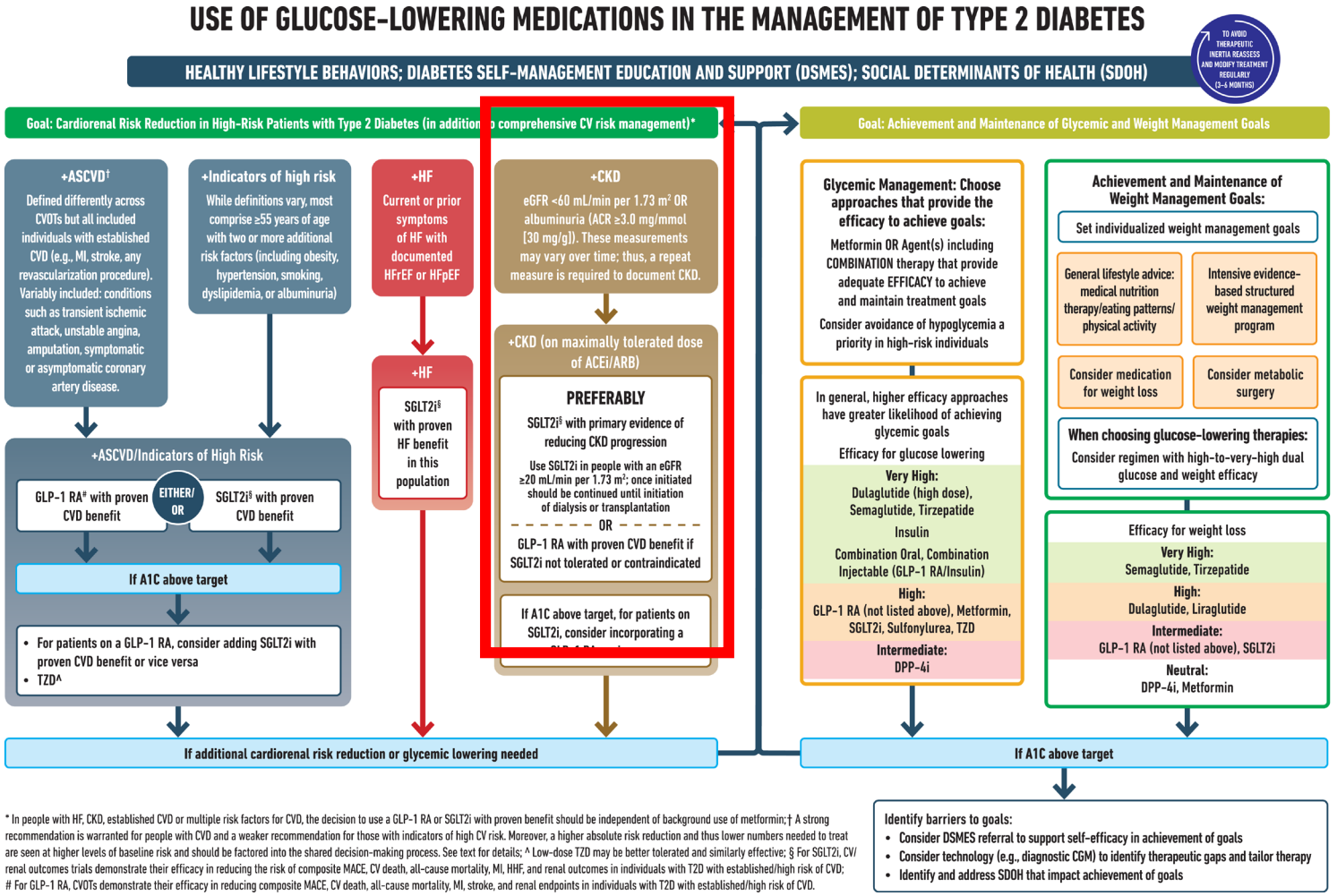
Diabetic kidney disease **affects 30-40%** of people with diabetes…

…and is the **leading cause of kidney failure** in the US



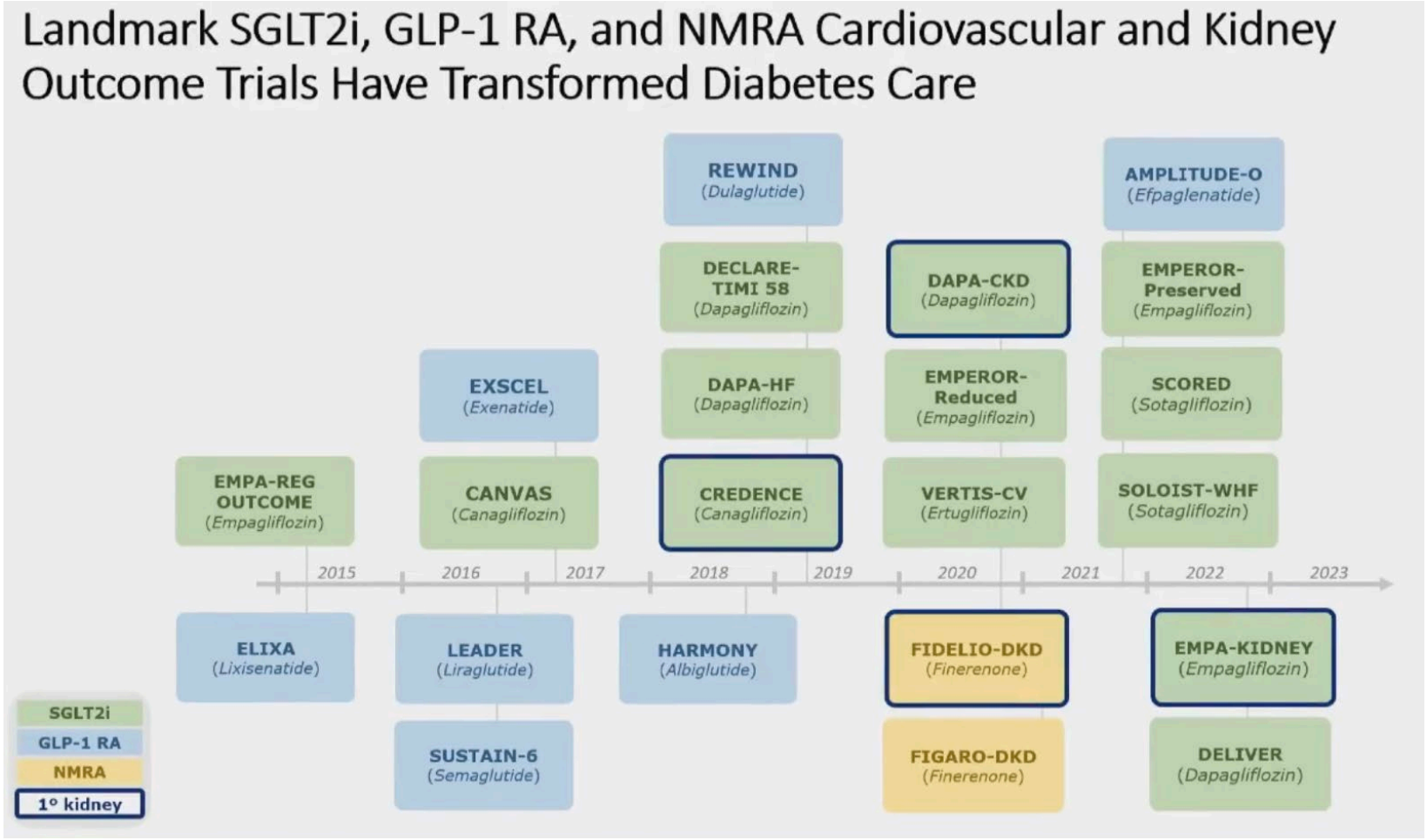
International Diabetes Foundation, *Diabetes Atlas*, 10th edition (2021)

Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023



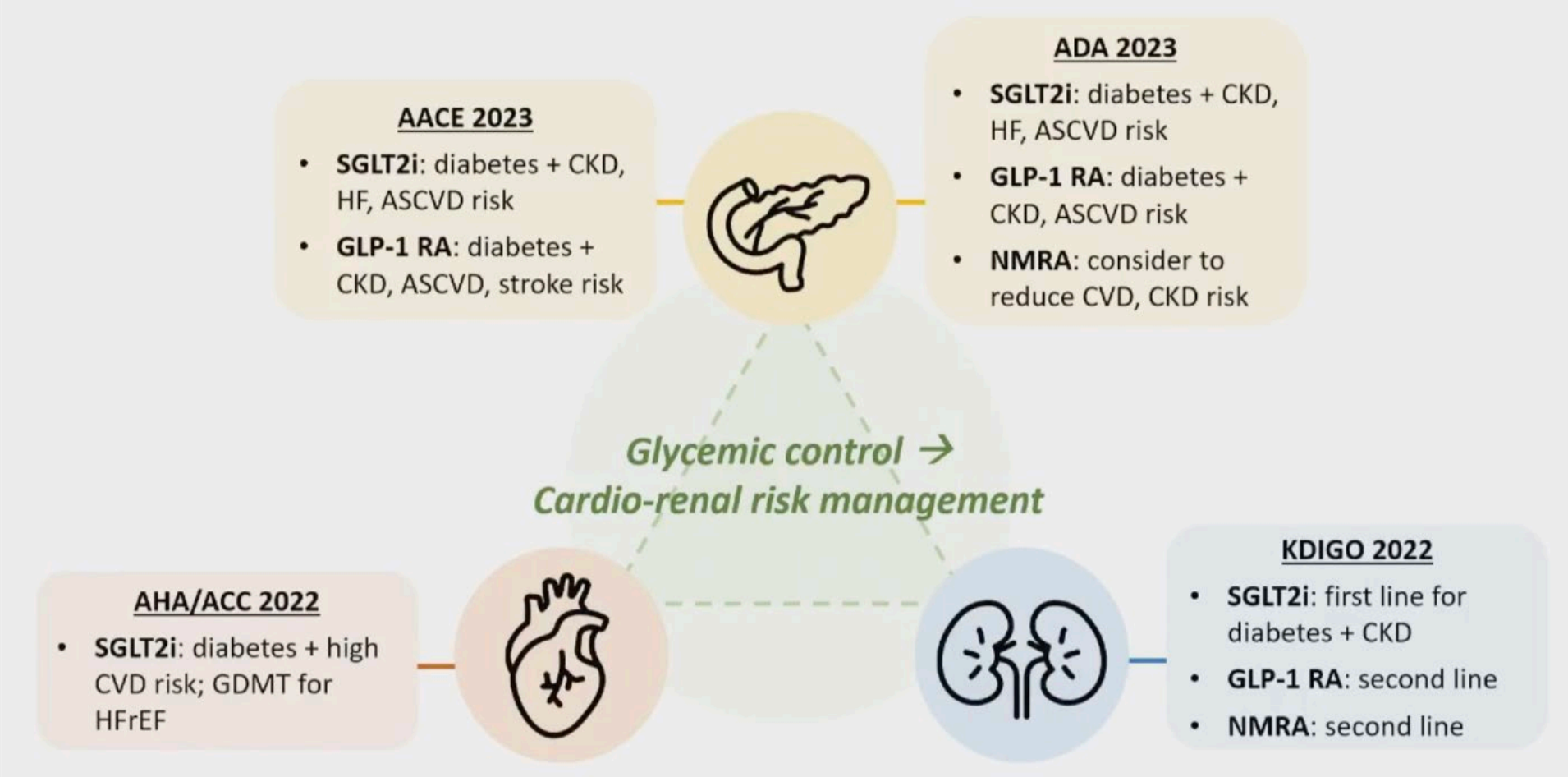
Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

4 trials with CKD as primary outcome



C. Limonte, University of Washington, ADA June 2023

Guidelines now center Diabetes Complications



C. Limonte, University of Washington, ADA June 2023

1/ Are we following the guidelines and using the newer therapies to protect against DKD?

Chistine Limonte
University of Washington
ADA June 2023

How many people are eligible for these drugs ?

A large proportion of T2D are eligible for SGLT-1i and GLP-1 RA in the USA

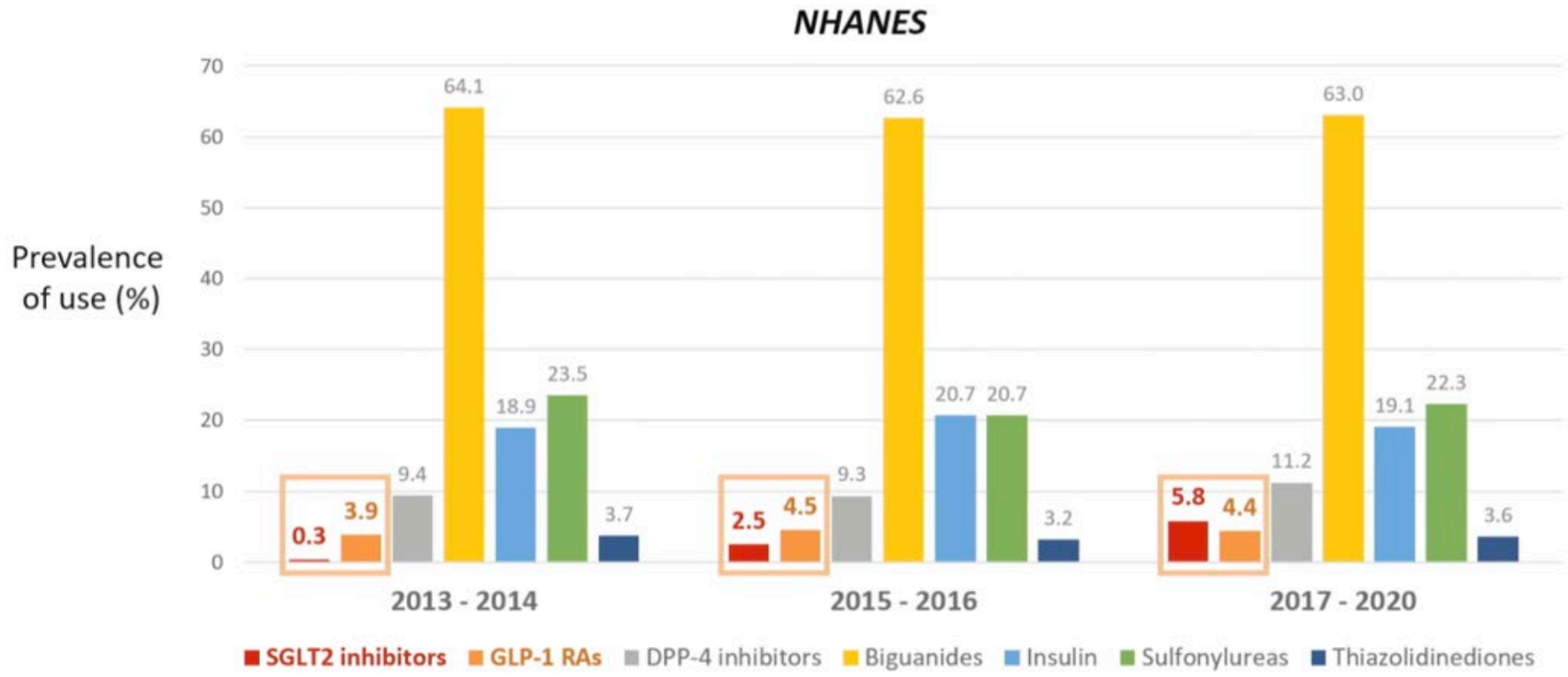
Distribution of eligibility in T2D – *NHANES 2017-2018*

	SGLT2i, weighted % (95% CI)	GLP-1 RA, weighted % (95% CI)	SGLT2i + GLP-1 RA, weighted % (95% CI)
Overall	52.6 (47.7, 57.5)	32.8 (28.8, 37.2)	26.6 (22.2, 31.7)
Age, years			
<65	44.0 (35.3, 53.1)	27.2 (21.8, 33.2)	20.9 (15.7, 27.3)
≥65	64.4 (56.9, 71.2)	40.6 (34.2, 47.2)	34.4 (27.6, 41.9)
Comorbidities			
Central obesity	50.7 (44.8, 56.7)	30.0 (25.7, 34.6)	24.1 (18.7, 30.5)
Hypertension	61.5 (56.0, 66.8)	32.3 (26.8, 38.4)	31.2 (25.7, 37.2)
Dyslipidemia	55.1 (49.3, 60.7)	28.5 (22.7, 35.2)	27.2 (21.7, 33.6)

*Based on **ADA and ACC 2020 guidelines** where **SGLT2i** are indicated for people with diabetes and CKD, HF, or established ASCVD with eGFR 30-60ml/min/1.73m^2 or UACR > 30 mg/g and **GLP-1 RA** are indicated for people with established or high risk ASCVD.*

Nargesi et al., *J Am Heart Assoc* (2021)

SGLT-1i and GLP-1 RA use is low among adults with T2D in the USA



Limonte et al., *J Diab Complications* (2022); Eberly et al., *JAMA Health Forum* (2021); Eberly et al., *JAMA Network Open* (2021)

SGLT-1i and GLP-1 RA use is not higher in DKD

SGLT2i and GLP-1 RA use is **not higher** among adults with **CKD** and is only **marginally higher** among adults with **heart failure** or **atherosclerotic cardiovascular disease**

Prevalence of SGLT2i and GLP-1 RA use in adults with T2D by comorbidity – *NHANES 2017-2020*

	SGLT2i		GLP-1 RA	
	Weighted prevalence (95% CI)	p-value	Weighted prevalence (95% CI)	p-value
CKD	-	0.98	-	0.61
No	5.9 (3.7, 9.1)	-	4.8 (2.7, 8.5)	-
Yes	5.8 (2.7, 12.2)	-	3.8 (2.2, 6.5)	-
CHF	-	0.40	-	0.20
No	5.4 (3.5, 8.2)	-	4.3 (2.9, 6.2)	-
Yes	11.2 (3.1, 32.8)	-	6.1 (3.4, 10.8)	-
ASCVD	-	0.09	-	0.31
No	4.8 (2.8, 8.1)	-	4.7 (3.3, 6.7)	-
Yes	9.4 (5.5, 15.5)	-	3.5 (1.7, 7.2)	-
CKD, CHF, or ASCVD	-	0.09	-	0.25
No	4.0 (2.3, 6.8)	-	5.4 (3.1, 9.0)	-
Yes	7.7 (4.5, 12.9)	-	3.5 (2.2, 5.4)	-

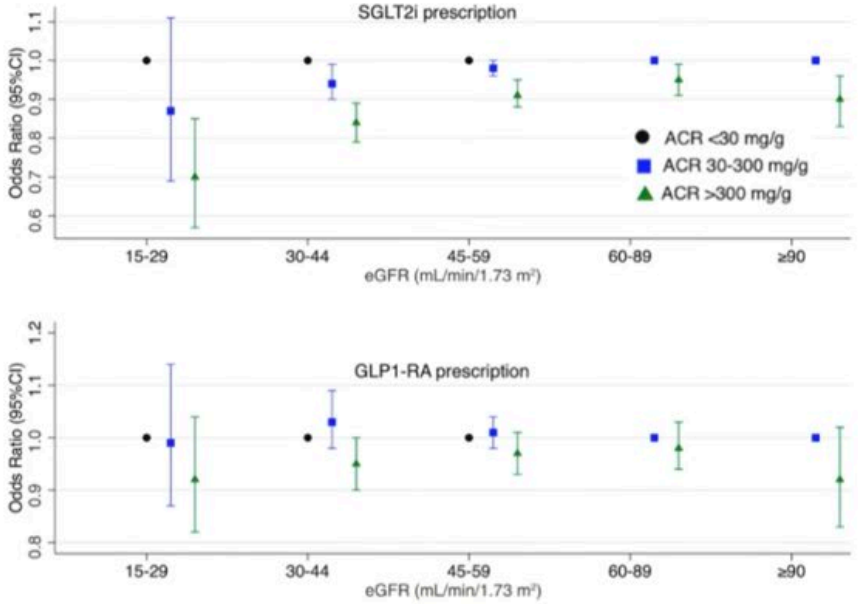
Limonte et al., *J Diab Complications* (2022)

SGLT-1i and GLP-1 RA less likely prescribed with more severe DKD and higher CV risk

- Prevalence of SGLT2i and GLP-1 RA prescriptions in the **Veterans Health Administration System (2019-2020; 1.2 million adults with T2D)**
- **Overall, 11% and 8%** prescribed **SGLT2i and GLP-1 RA**, respectively
- Among those with **CKD, 12% and 10%** prescribed **SGLT2i and GLP-1 RA**, respectively

Those with ***more severe kidney disease and higher cardiovascular and kidney risk*** were ***less likely*** to be prescribed ***SGLT2i and GLP-1 RA***

Association of albuminuria with SGLT2i and GLP-1 RA prescription

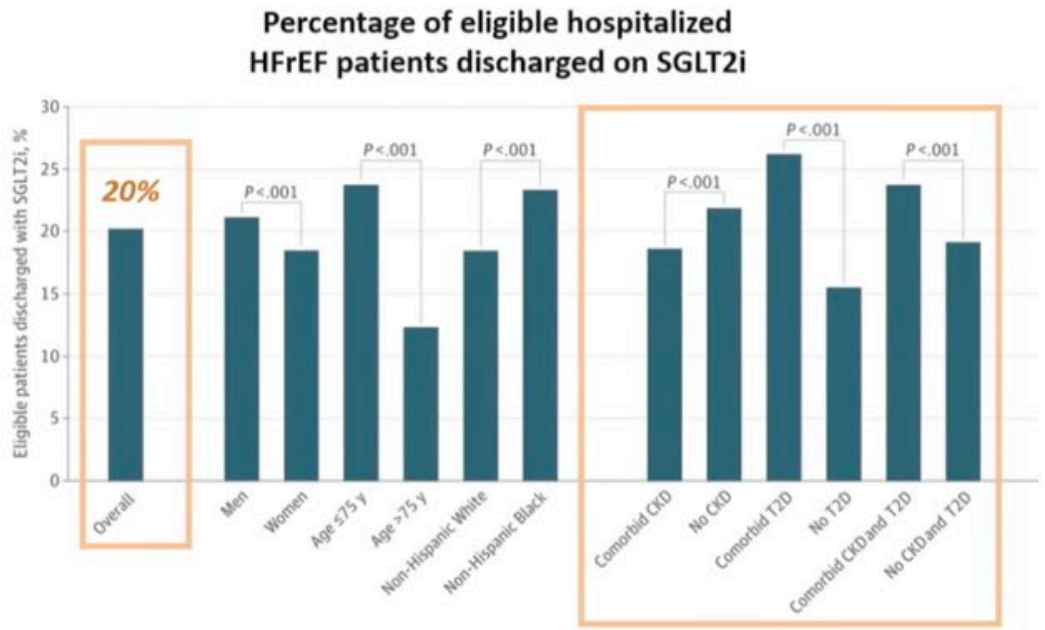


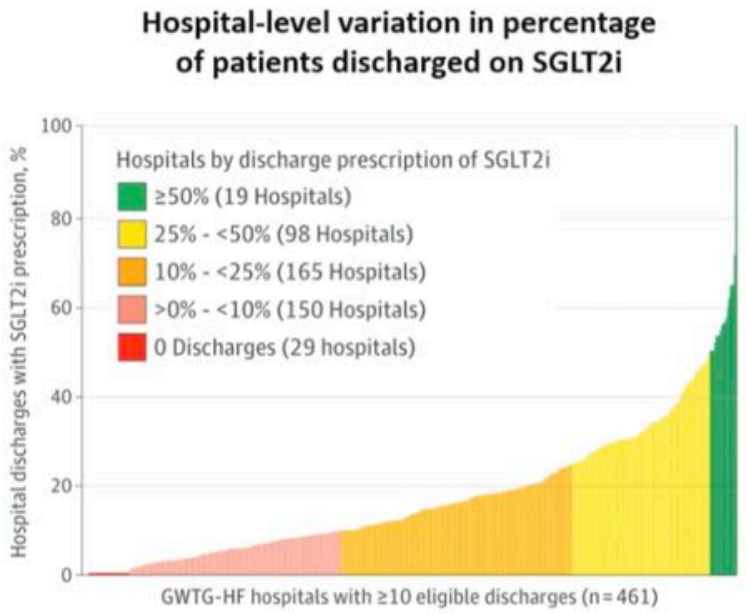
Models adjusted for age, sex, race, ethnicity, ZIP code median income, ZIP code area social deprivation index, VA diabetes and service connection, rurality, smoking status, alcohol use, HTN, BMI, mental health diagnosis, HbA1c, antidiabetes medications, specialty visits, frailty, COVID-19

Lamprea-Montealegre et al., *Diabetes Care* (2022)

SGLT2i use is low in HFrEF

Get with the Guidelines Heart Failure Registry, 2021-2022
(n = 49,399 hospitalized for HFrEF)

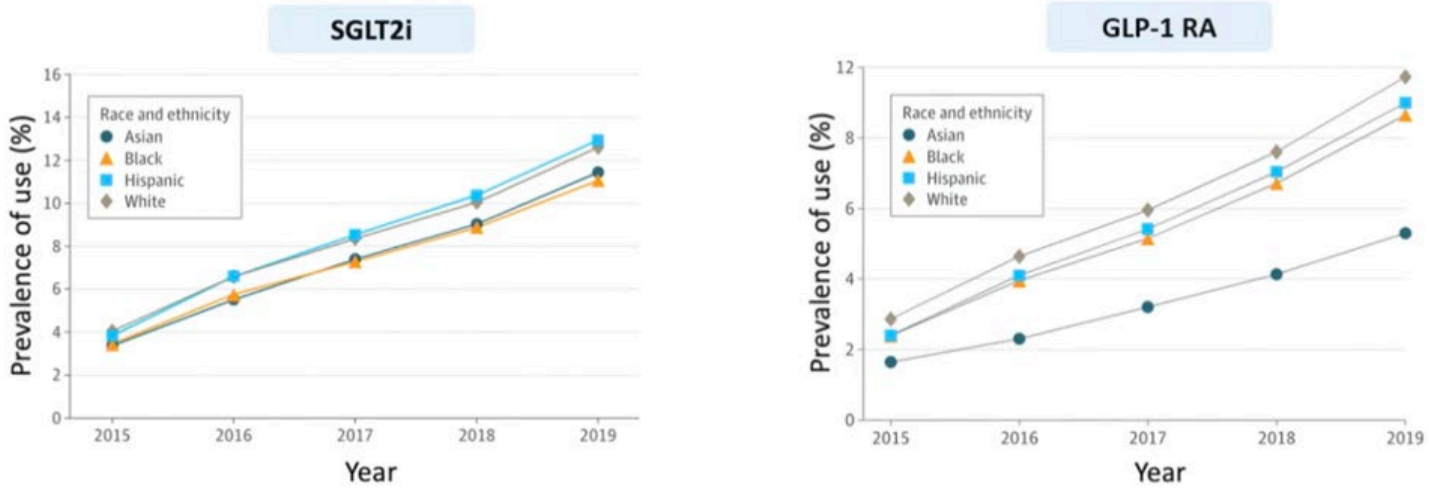




Pierce et al., *JAMA Cardiology* (2023)

Racial and ethnic disparities in SGLT2i and GLP-1 RA use

Prevalence of use in insured adults with T2D (n > 900,000)
– OptumInsight Clinformatics Data Mart

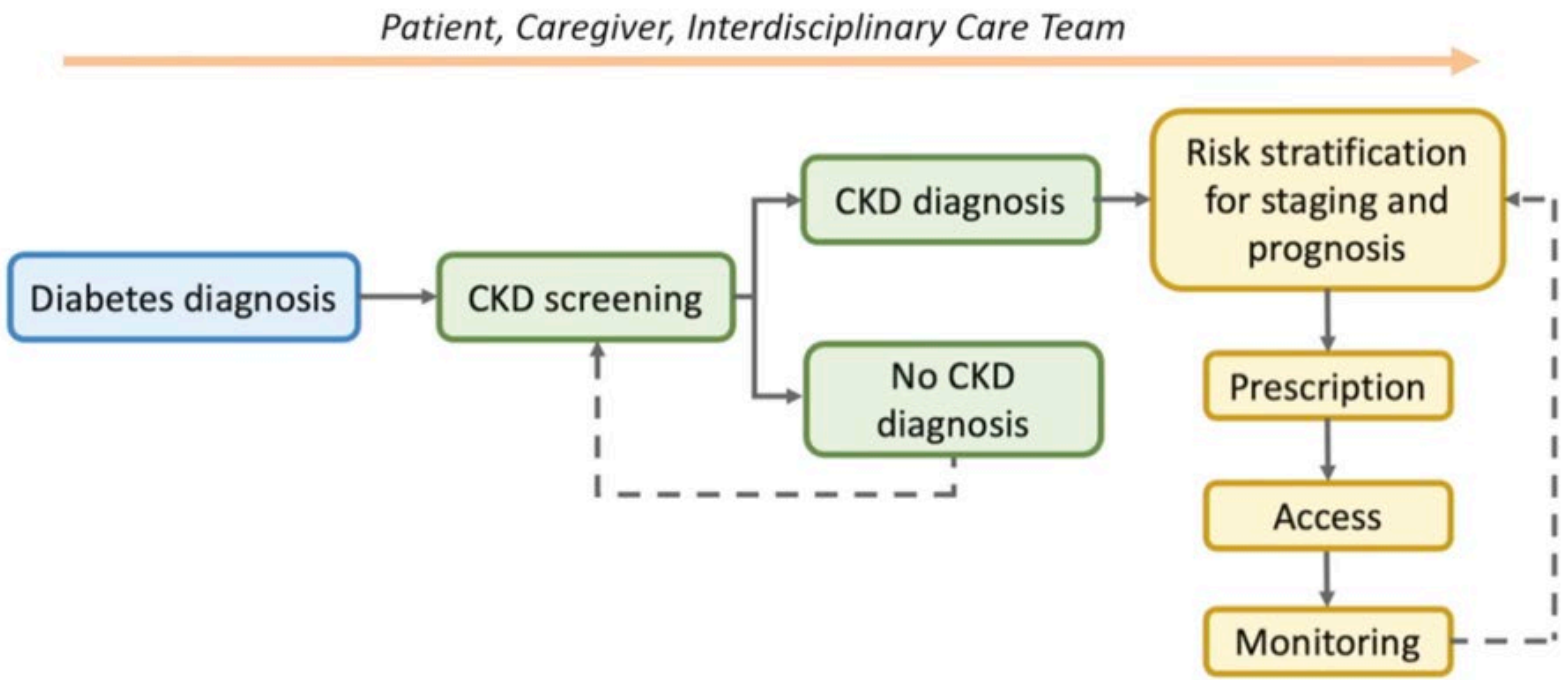


*In **NHANES 2017-2020 data**, similar lower prevalence of use of:*

- ***SGLT2i** in Non-Hispanic Black, Mexican American vs Non-Hispanic White adults (~3% vs 7%)*
- ***GLP-1 RA** in Mexican American vs Non-Hispanic White adults (2% vs 5%)*

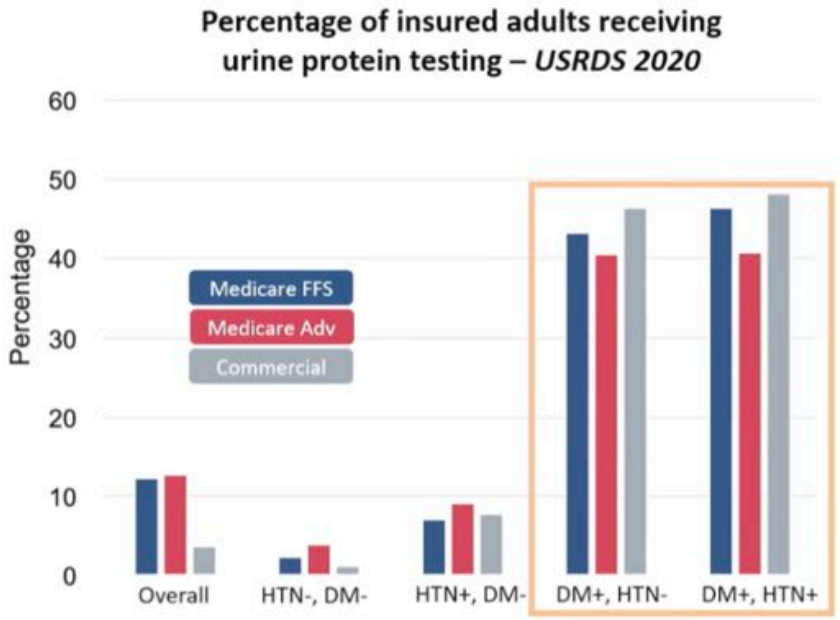
Eberly et al., *JAMA Health Forum* (2021); Eberly et al., *JAMA Network Open* (2021); Limonte et al., *J Diab Complications* (2022)

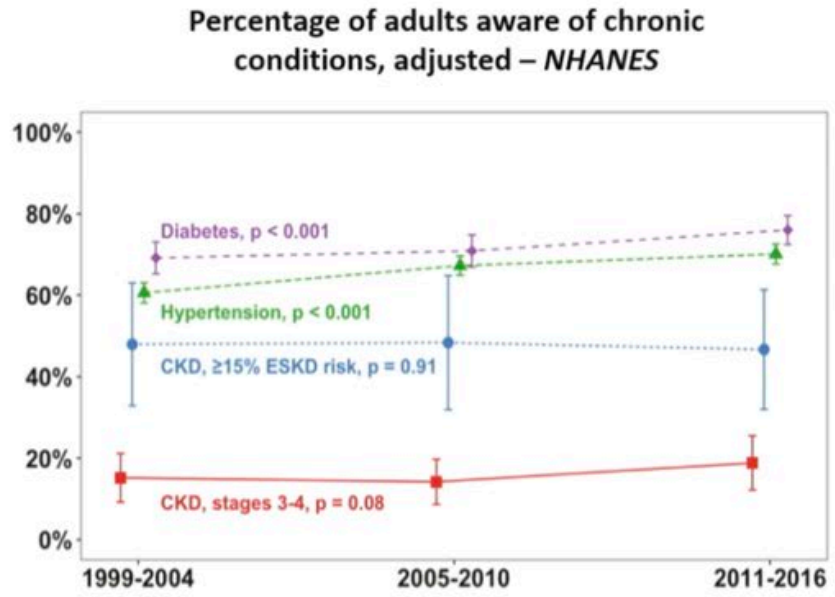
Barriers to implementation of novel kidney-protective agents



Adapted from Vassalotti et al., *KI Reports* (2022)

Low rates of CKD screening



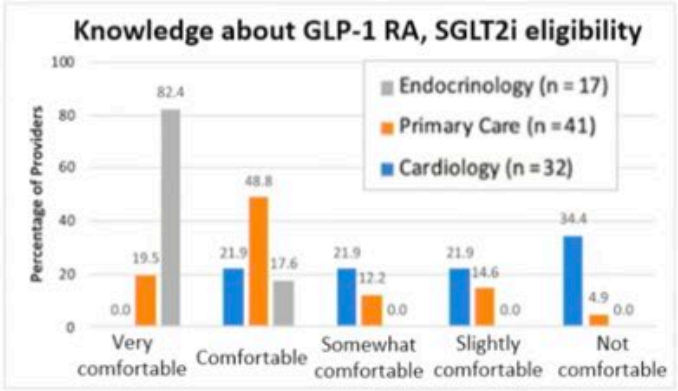


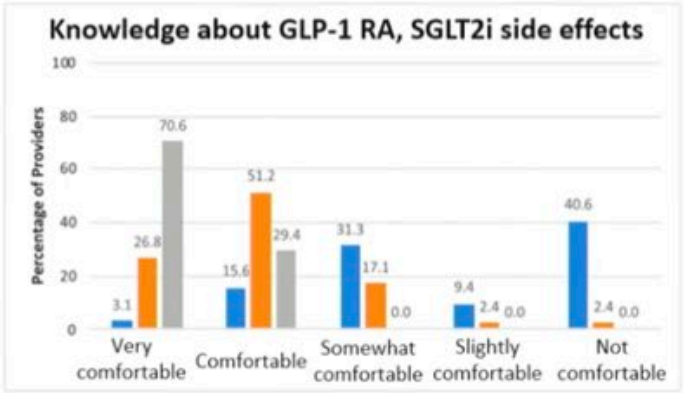
Diabetes diagnosis → CKD diagnosis → Risk stratification → Prescription → Access

https://usrds-adr.niddk.nih.gov/2022; Alfego et al., *Diabetes* Care (2021); Chu et al., *Am J Kidney Dis* (2020)

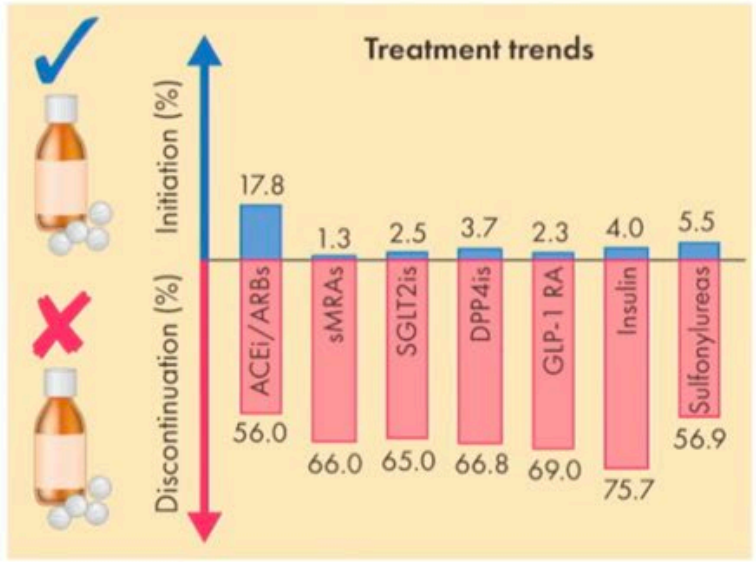
Provider uncertainty, inappropriate drug discontinuation

Questionnaire on provider comfort with SGLT2i and GLP-1 RA – *academic health system (2018)*





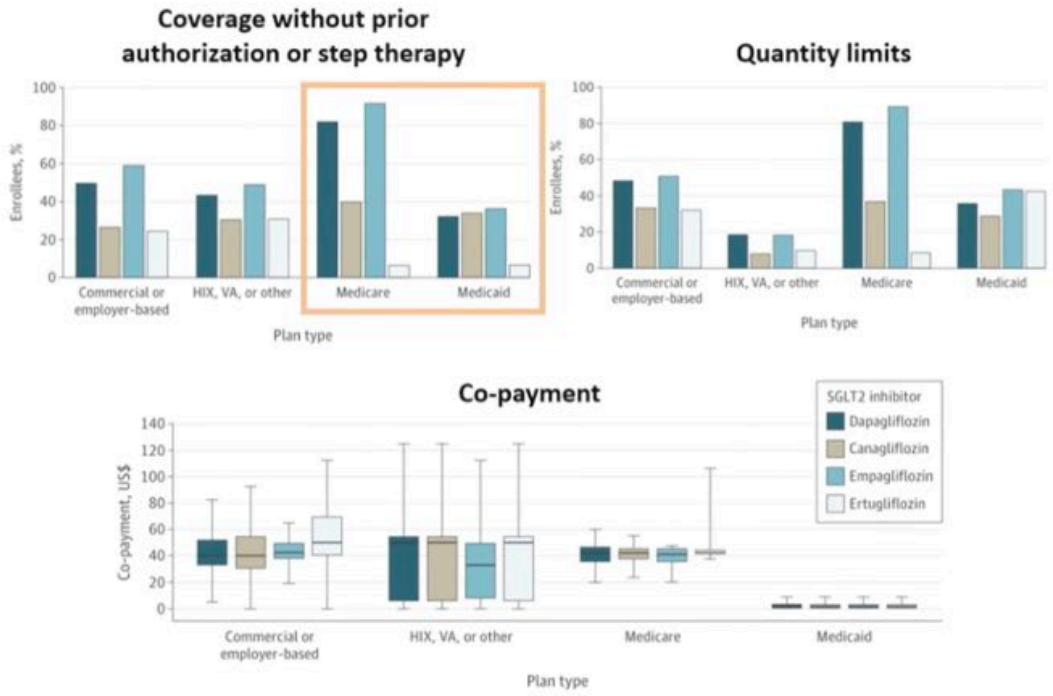
Drug discontinuation in T2D and incident CKD (n=63,271) or prevalent CKD (n=326,762) – *US claims data (2007-2019)*

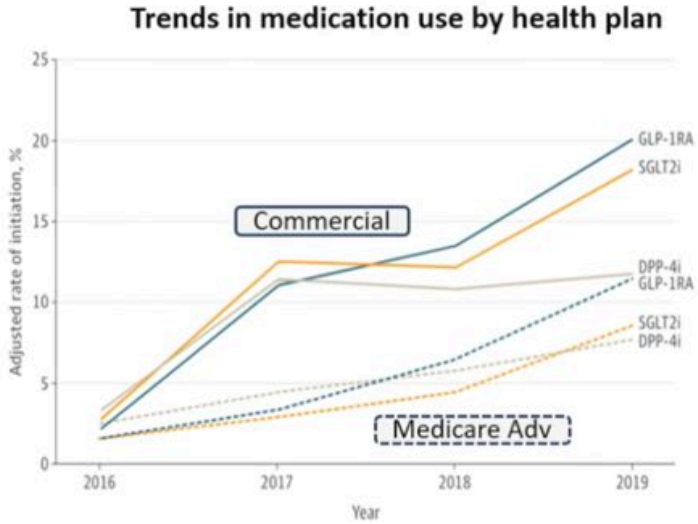


Diabetes diagnosis → CKD diagnosis → Risk stratification → Prescription → Access

Gao et al., *Am Heart J* (2020); Fried et al., *Nephrol Dial Transplant* (2023)

Prescription barriers and prohibitive costs



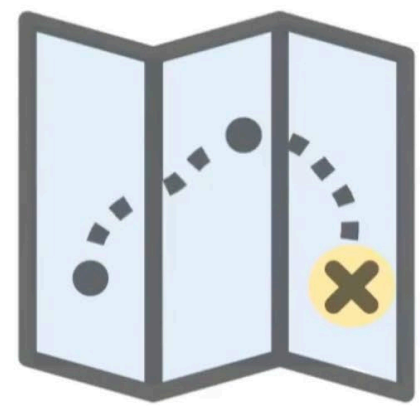


Diabetes diagnosis → CKD diagnosis → Risk stratification → Prescription → Access

Tummalapalli et al., *JAMA Health Forum* (2021); McCoy et al., *JAMA Network Open* (2021)

Conclusions

- Guidelines recommend use of SGLT2 inhibitors and GLP-1 RA to **reduce kidney and cardiovascular disease risk in T2D and CKD**
- **SGLT2 inhibitor and GLP-1 RA use is low,** especially among those who would experience the most benefit
- **Barriers to guideline implementation** include low rates of CKD screening, provider uncertainty and fragmented care, challenges accessing prescriptions, and inappropriate drug discontinuation
- Addressing barriers to guideline implementation requires **interdisciplinary collaboration and integration across the DKD care pathway**



2/ CGM accuracy in DKD

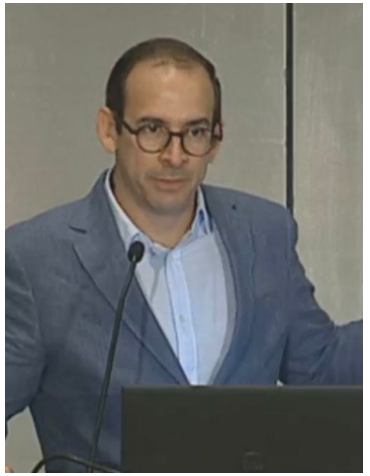
Symposium:
CGM: Are you using them correctly?

CGM in Special Populations: Accuracy and Efficacy Considerations

Rodolfo J. Galindo, MD, FACE
Associate Professor of Medicine
Miller School of Medicine at University of Miami

Director, Comprehensive Diabetes Center
Lennar Medical Foundation, UHealth

UNIVERSITY OF MIAMI



Accuracy of Glucose Meters

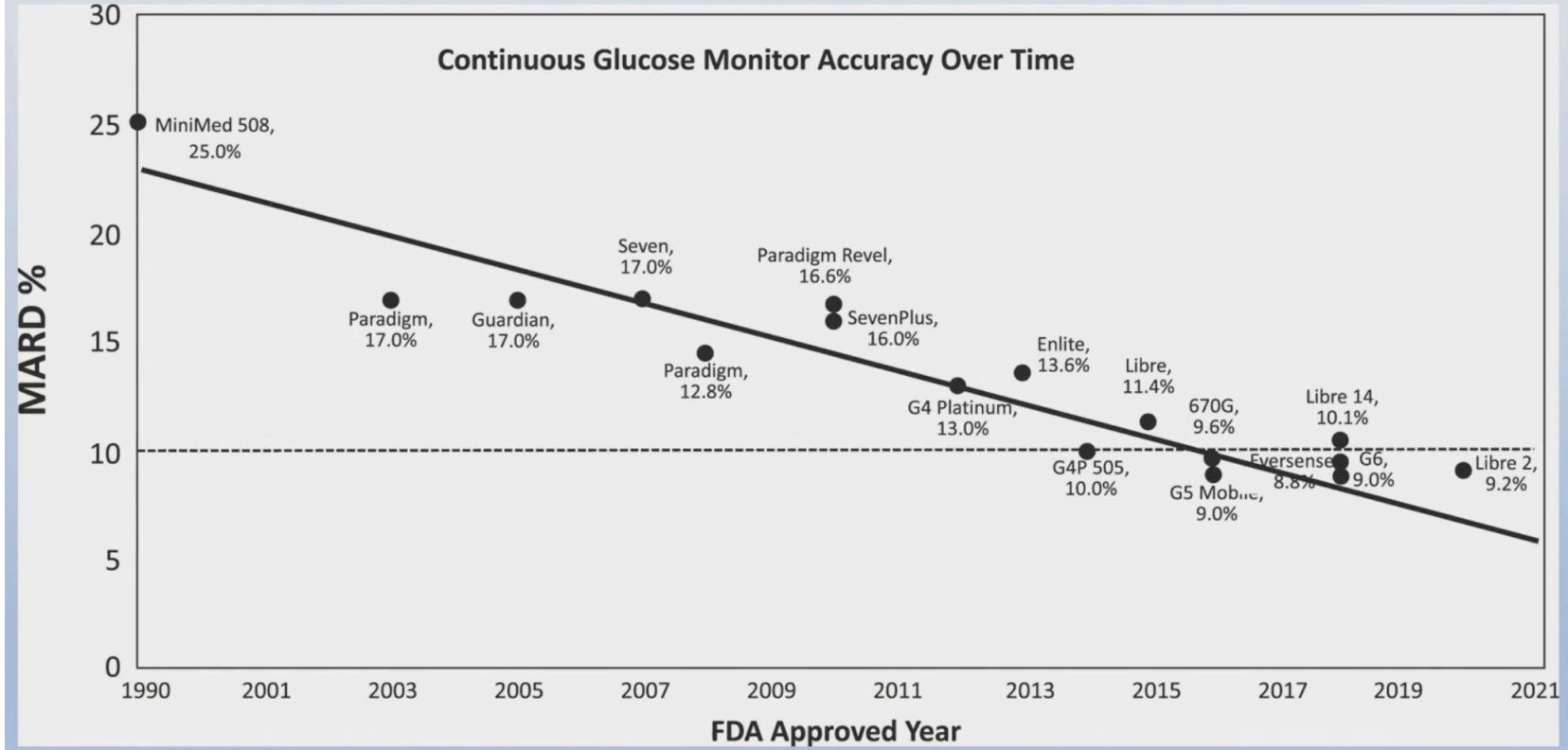
Table 2. Accuracy of Glucose Meters in Different Reference Glucose Ranges.

	MARD (%)	SD	MARD (%)	SD	MARD (%)	SD	MARD (%)	SD
Glucose meter	Overall		BS < 70 mg/dL		BS 70-179 mg/dL		BS ≥180 mg/dL	
Contour Next	5.6	6.4	8.9	13.2	4.8	3.5	5.4	5.2
StatStrip Xpress	6.3	6.1	11.1	9.6	4.9	3.9	6.0	5.5
OneTouch VeriolQ	7.1	6.9	9.9	13.0	6.3	4.7	6.8	5.9
Accu-Chek Nano	7.3	7.1	11.6	12.8	6.7	5.8	6.8	5.8
FreeStyle Freedom Lite	7.5	6.4	15.4	7.1	7.3	6.8	6.2	4.8
Accu-Chek Aviva Plus	7.6	7.9	12.1	15.2	7.3	5.8	6.9	6.4
FreeStyle Lite	8.2	8.1	16.6	6.5	7.9	5.7	6.8	8.3
Nova Max	9.7	12.6	27.0	24.6	8.9	10.5	6.9	6.0
TRUEresult	13.0	8.4	13.2	10.8	12.8	7.3	13.1	8.4
HemoCue Glucose 201	13.2	9.9	19.9	19.4	11.6	7.9	12.6	7.3
OneTouch Ultra2	13.6	11.5	30.3	14.9	15.7	10.8	9.7	7.4
ReliOn Prime	14.3	10.2	16.2	8.8	11.4	7.9	15.1	11.1
BREEZE ®2	15.8	12.4	25.7	19.1	13.3	9.7	14.9	11.0
ReliOn Micro	16.0	12.2	29.9	11.8	14.2	11.2	14.1	10.9
AgaMatrix PRESTO	16.2	13.7	39.2	14.4	21.2	11.3	9.8	7.8
AgaMatrix JAZZ	16.7	13.9	38.0	16.3	22.3	11.6	10.5	8.3
SideKick	20.8	16.6	31.7	16.1	16.7	12.9	20.4	17.2

Meters are listed in order of overall increasing MARD.

Ekhlaspaur L et al, Journal Diabetes Science Tech, 2016

CGM Accuracy: 30 years of advancement

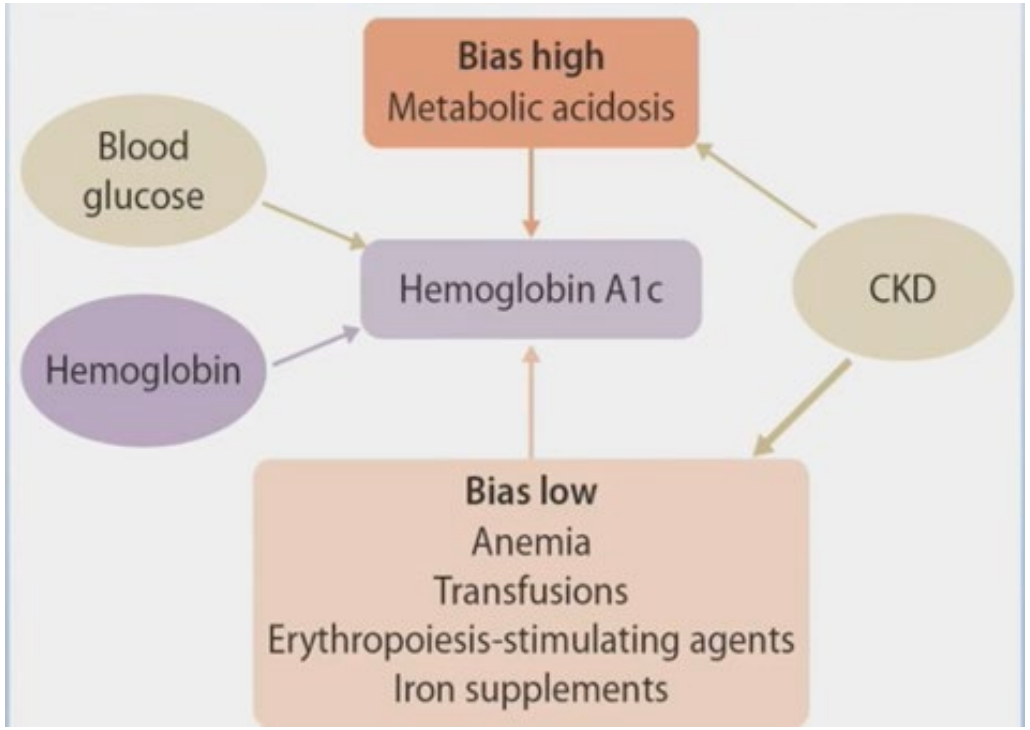


Libre 3
Dexcom One
Dexcom G7
Dexcom G6
Guardian 4

2023

Timothy S. Bailey, Diab Tech Therap, 2021
Pemberton, DOM, October 2022

Accuracy and precision of HbA1c measurement declines with advanced CKD (G4-5)



Targeting hypoglycemia with CGM in DKD patients

Glycemic Monitoring and Targets in Patients with Diabetes and CKD: KDIGO 2022

Practice Point 2.1.3: A **glucose management indicator (GMI) derived from continuous glucose monitoring (CGM)** data can be used to index glycemia for individuals in **whom HbA1c is not concordant** with directly measured blood glucose levels or clinical symptoms.

Practice Point 2.1.4: Daily glycemic **monitoring with CGM or self-monitoring of blood glucose (SMBG) may help to prevent hypoglycemia** and improve glycemic control when antihyperglycemic therapies associated with risk of hypoglycemia are used.

Practice Point 2.1.5: For patients with type 2 diabetes (T2D) and CKD who **choose not to do daily glycemic monitoring by CGM or SMBG, antihyperglycemic agents that pose a lower risk of hypoglycemia are preferred** and should be administered in doses that are appropriate for the level of eGFR.

Practice Point 2.2.2: **CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA1c** for defining glycemic targets in some patients.

Is CGM accurate in hemodialysis?

CGM in Hemodialysis – recent sensors

Author & Year	Population	CGM duration	Results
Olafsdottir, 2017	DM1, n: 50 (at least 10 pairs of glucose)	Dexcom G5 Libre 14 days (vs HemoCue)	Libre MARD 19.3.0% (vs 22.5% for non HD patients) Dexcom G5 MARD 15.5% (vs 15% for non HD pts)
Yajima, 2019	DM2, HD, n: 13	14 days (FreeStyle Libre Pro) Ipro2	Overall, MARD 19.5% (vs OneTouch Ultra Verio) MARD 31.9% for glucose <70 mg/dl Only 49% and 51% of glucoses fell into Zone A and B of EGA CGM glucose -24.4 mg/dL (166.9 ± 57.4 mg/dL vs 142.5 ± 63.9 mg/dL, *P* < .0001)
Matoba, 2020	DM2, n: 13	Freestyle Libre Pro Ipro 2	DuringHD: MARD 18.2%, Ipro 15% CEG Zone A/B: 86.9% for Flash vs 95% for Ipro
Nasser Hissa, 2021	DM2, HD, n: 12	14 days (FreeStyle Libre)	Overall, MARD 21.4% (± 17.8) Similar values in pre-dialysis between capillary and CGM
Mambelli, 2021	DM2, non-DM, n: 31	14 days (FreeStyle Libre)	Good correlation between SMBG and Flash Glucose Monitoring, CEG analyses revealed 97.6% of the readings fell within the A+B regions
Villard, Diab Care, 2022	DM1 (4), DM2. (12), PTDM (1)	Dexcom G6 Pro 10 days	Overall, MARD 13.8-14.3 TIR 38%
Hissa, 2021	DM2, n: 12	Libre 14 days AccuCheck	Overall MARD 21.4%
Toyoda, 2021	DM, n: 41	Freestyl Libre	MARD 23.4%, PreHD MARD 21.7%, PostHD MARD 25.8%. Sensor glucose lower than capillary

Rodolfo J. Galindo, Roy Beck, F. Scioscia, G. Umpierrez, Katherine Tuttle. Endocrine Reviews, 2020
Rodolfo J. Galindo, Ian DeBoer, Joshua Neumiller, Katherine Tuttle, Clinical Journal of American Societ of Nephrology, 2022

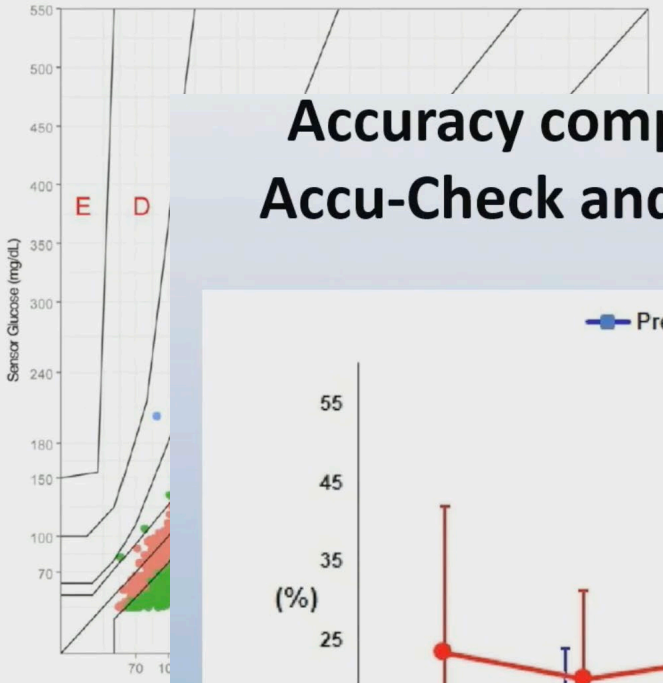
MARD is higher after hemodialysis

- FreeStyle Libre
- n=41 patients
- MARD day 5 > day 1
- Before HD MARD lower than after HD
- Sensor glucose levels were significantly lower than the capillary glucose levels

MARD, %

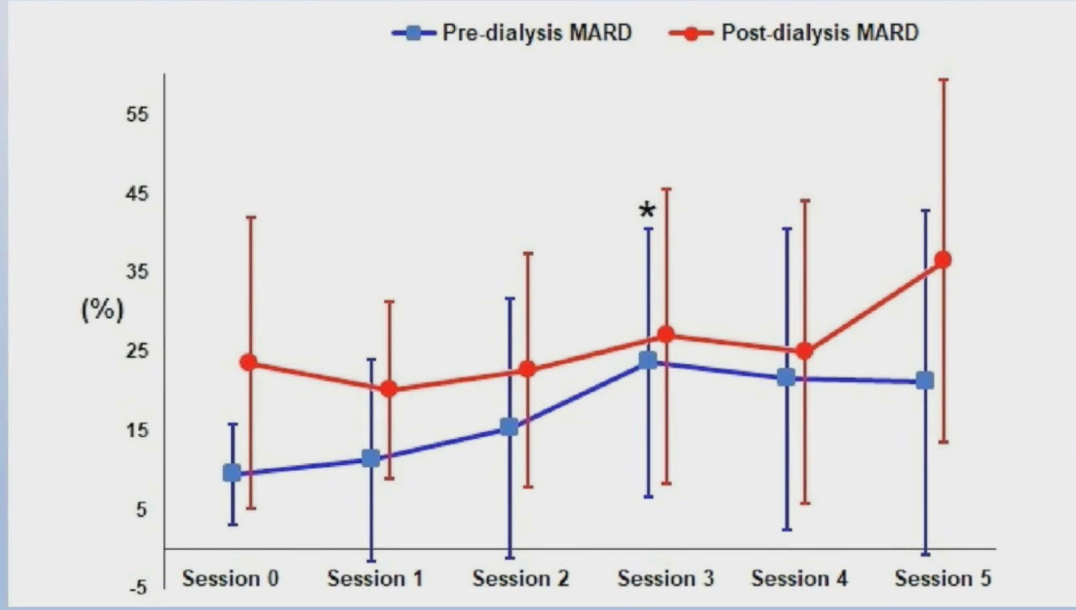
14 days	23.4 (12.9)
Before HD	21.7 (12.2)
After HD	25.8 (11.9)*

*P<0.05 (vs. before dialysis)



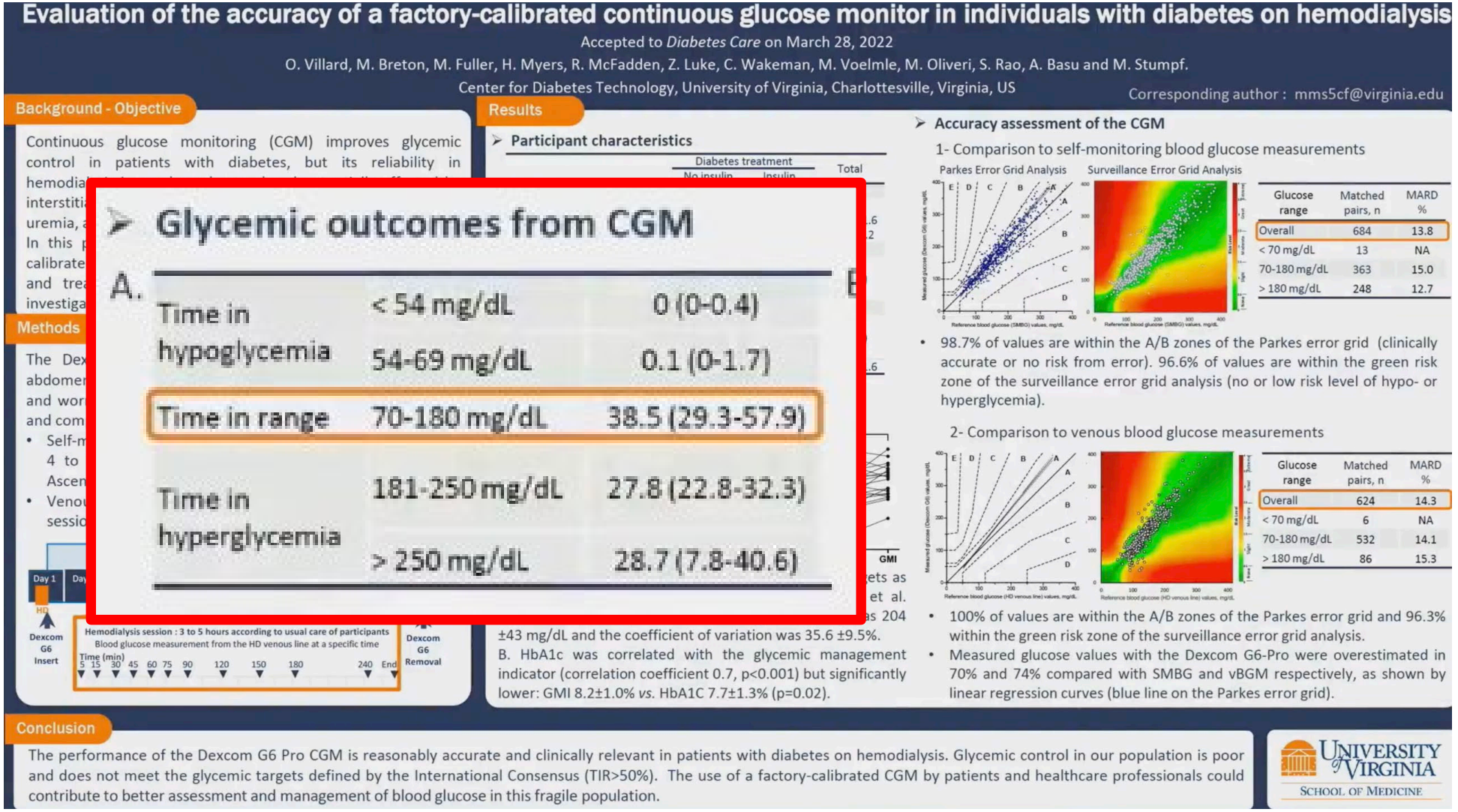
Toyoda

Accuracy comparison between Accu-Check and Freestyle Libre 1



Hissa MRN, Hissa PNG, Guimarães SB, Hissa MN. Use of continuous glucose monitoring system in patients with type 2 mellitus diabetic during hemodialysis treatment. Diabetol Metab Syndr. 2021 Oct.

Hyperglycemia in hemodialysed people



Evaluation of the accuracy of a factory-calibrated continuous glucose monitor in individuals with diabetes on hemodialysis

Accepted to *Diabetes Care* on March 28, 2022

O. Villard, M. Breton, M. Fuller, H. Myers, R. McFadden, Z. Luke, C. Wakeman, M. Voelmle, M. Oliveri, S. Rao, A. Basu and M. Stumpf.
Center for Diabetes Technology, University of Virginia, Charlottesville, Virginia, US
Corresponding author : mms5cf@virginia.edu

Background - Objective

Continuous glucose monitoring (CGM) improves glycemic control in patients with diabetes, but its reliability in hemodia… interstiti… uremia, a… In this p… calibrate… and trea… investiga…

Methods

The Dex… abdomen… and wor… and com…
- Self-m… 4 to … Ascen…
- Venou… sessio…

Day 1 | Day …
HD
Dexcom G6 Insert
Hemodialysis session : 3 to 5 hours according to usual care of participants
Blood glucose measurement from the HD venous line at a specific time
Time (min) 5 15 30 45 60 75 90 120 150 180 240 End
Dexcom G6 Removal

Results

➢ **Participant characteristics**

	Diabetes treatment: No insulin	Diabetes treatment: Insulin	Total
…	…	…	…

➢ **Glycemic outcomes from CGM**

A. Time in hypoglycemia	< 54 mg/dL	0 (0-0.4)
	54-69 mg/dL	0.1 (0-1.7)
Time in range	70-180 mg/dL	38.5 (29.3-57.9)
Time in hyperglycemia	181-250 mg/dL	27.8 (22.8-32.3)
	> 250 mg/dL	28.7 (7.8-40.6)

GMI … ets as … et al. … as 204 ±43 mg/dL and the coefficient of variation was 35.6 ±9.5%.

B. HbA1c was correlated with the glycemic management indicator (correlation coefficient 0.7, p<0.001) but significantly lower: GMI 8.2±1.0% *vs.* HbA1C 7.7±1.3% (p=0.02).

➢ **Accuracy assessment of the CGM**

1- Comparison to self-monitoring blood glucose measurements

Parkes Error Grid Analysis

Surveillance Error Grid Analysis

Glucose range	Matched pairs, n	MARD %
Overall	684	13.8
< 70 mg/dL	13	NA
70-180 mg/dL	363	15.0
> 180 mg/dL	248	12.7

- 98.7% of values are within the A/B zones of the Parkes error grid (clinically accurate or no risk from error). 96.6% of values are within the green risk zone of the surveillance error grid analysis (no or low risk level of hypo- or hyperglycemia).

2- Comparison to venous blood glucose measurements

Glucose range	Matched pairs, n	MARD %
Overall	624	14.3
< 70 mg/dL	6	NA
70-180 mg/dL	532	14.1
> 180 mg/dL	86	15.3

- 100% of values are within the A/B zones of the Parkes error grid and 96.3% within the green risk zone of the surveillance error grid analysis.
- Measured glucose values with the Dexcom G6-Pro were overestimated in 70% and 74% compared with SMBG and vBGM respectively, as shown by linear regression curves (blue line on the Parkes error grid).

Conclusion

The performance of the Dexcom G6 Pro CGM is reasonably accurate and clinically relevant in patients with diabetes on hemodialysis. Glycemic control in our population is poor and does not meet the glycemic targets defined by the International Consensus (TIR>50%). The use of a factory-calibrated CGM by patients and healthcare professionals could contribute to better assessment and management of blood glucose in this fragile population.

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Discordance Between Glycated Hemoglobin A1c and GMI in DKD

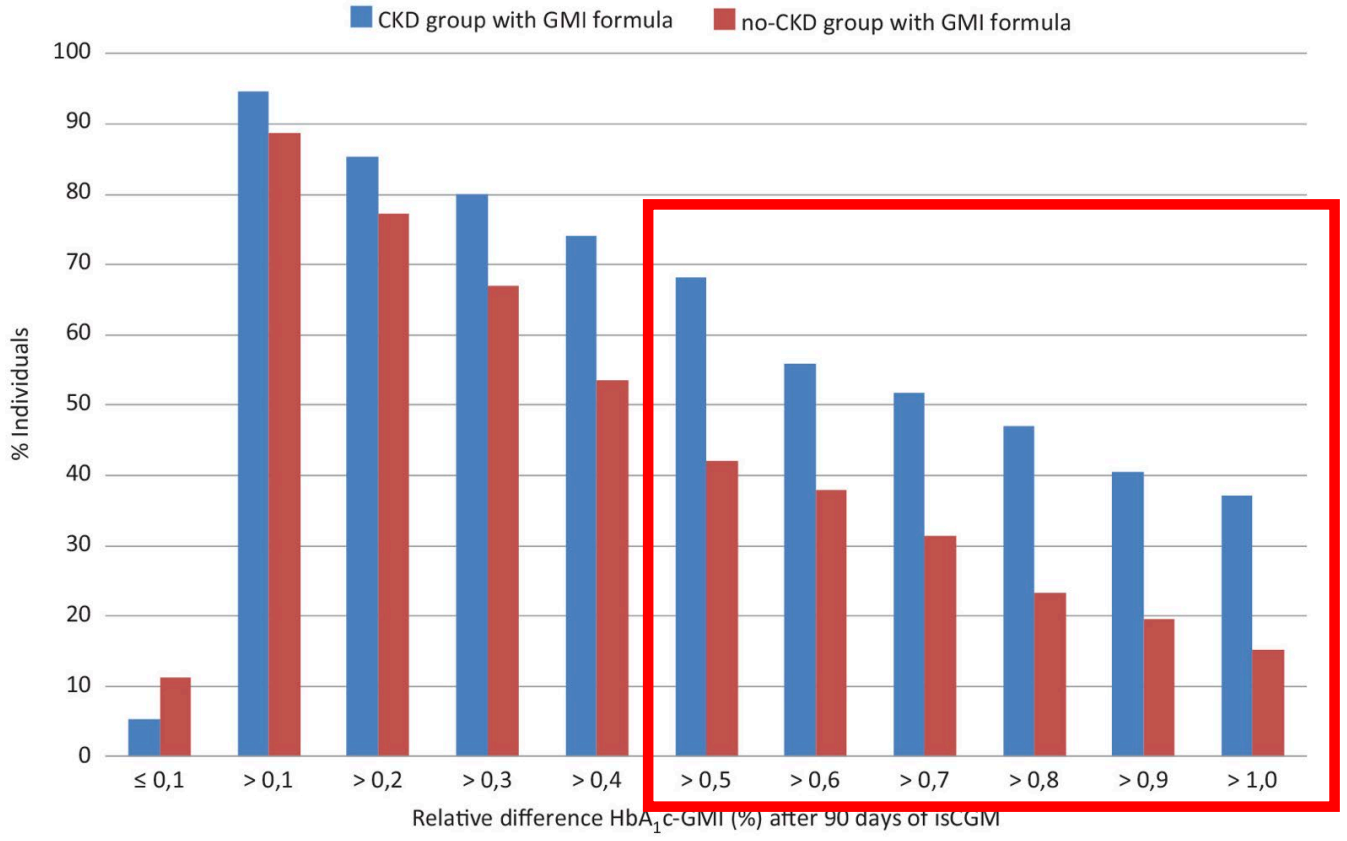


Figure 1. Individuals were subdivided as a percentage ratio based on the relative difference HbA_1c-GMI threshold between CKD and no-CKD groups. Abbreviations: GMI, glucose management indicator; CKD, chronic kidney disease.

Oriot P et al. *Journal of Diabetes Science and Technology*. 2022

...with use of a specific formula CKD-GMI

based on the linear regression between HbA_1c and CGM mean glucose at 90 days = 3.558 + 0.026 × [CGM mean glucose (mg/dL)]

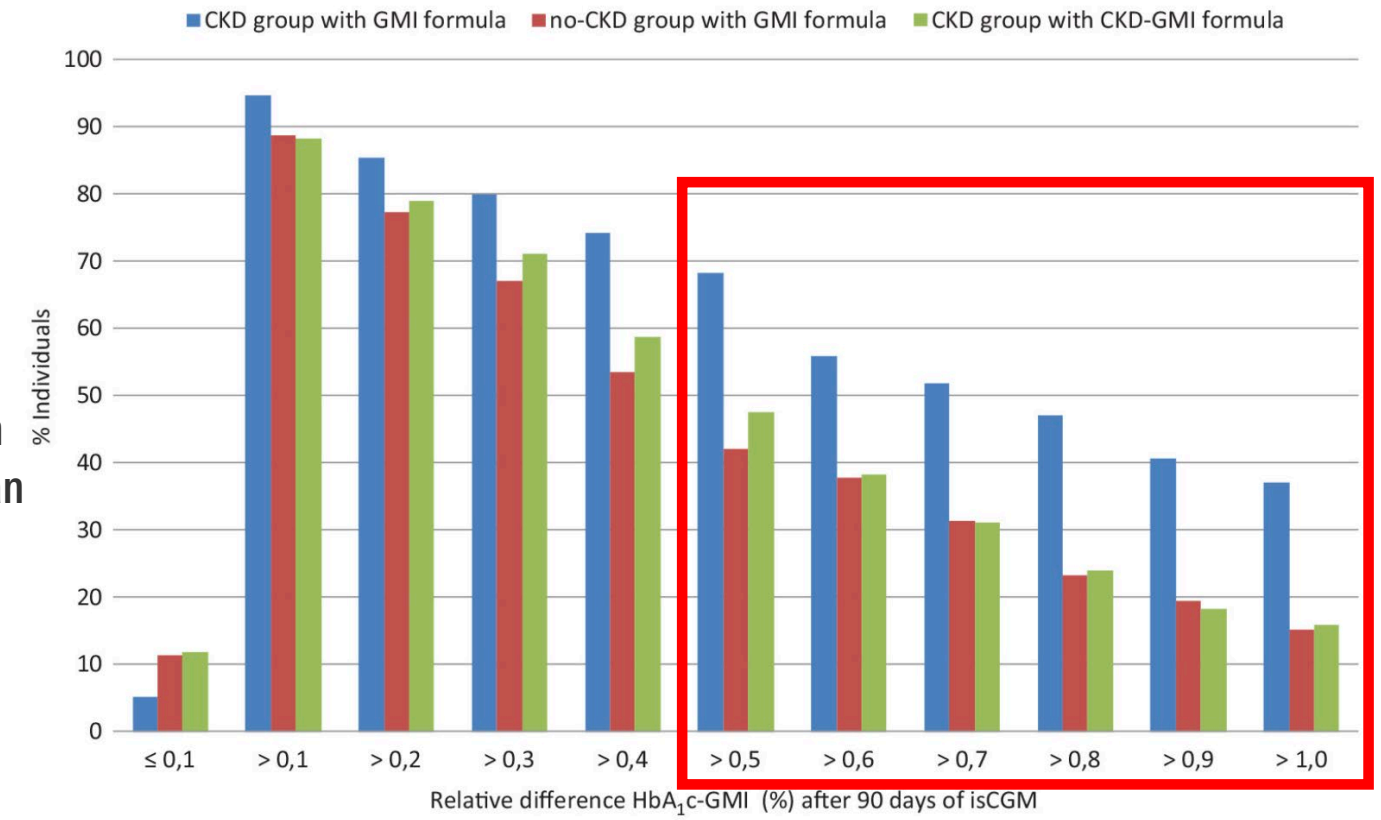


Figure 4. Individuals were subdivided as a percentage ratio based on the relative difference HbA_1c-GMI threshold between CKD and no-CKD groups. Abbreviations: GMI, glucose management indicator; CKD, chronic kidney disease.

Oriot P et al. *Journal of Diabetes Science and Technology*. 2022

Potential chemical interferences

CGM system	Glucose sensing methods	Known interferences from chemical substances
Abbott Diabetes Care FreeStyle Libre 14 day system[28]	GO + Redox Sensing Membrane	Ascorbic acid Salicylic acid
Abbott Diabetes Care FreeStyle Libre 2[29,30]	GO + Redox Sensing Membrane	Ascorbic acid
Dexcom G6[31,32]	GO + Perm-selective membrane coating	Hydroxyurea
Medtronic MiniMed Guardian Sensor 3[34,35]	GO	Acetaminophen
Senseonics Eversense[36,37]	Nonenzymatic electrochemical fluorescent-based polymer	Mannitol Tetracycline

Galindo et al, JDST, 2020

In conclusion, CGMS is of clinical use in hemodialysis

79F DM2 x 34 years, ESKD due to DM2

Hemodialysis for 5 years, starting mid-mornings.

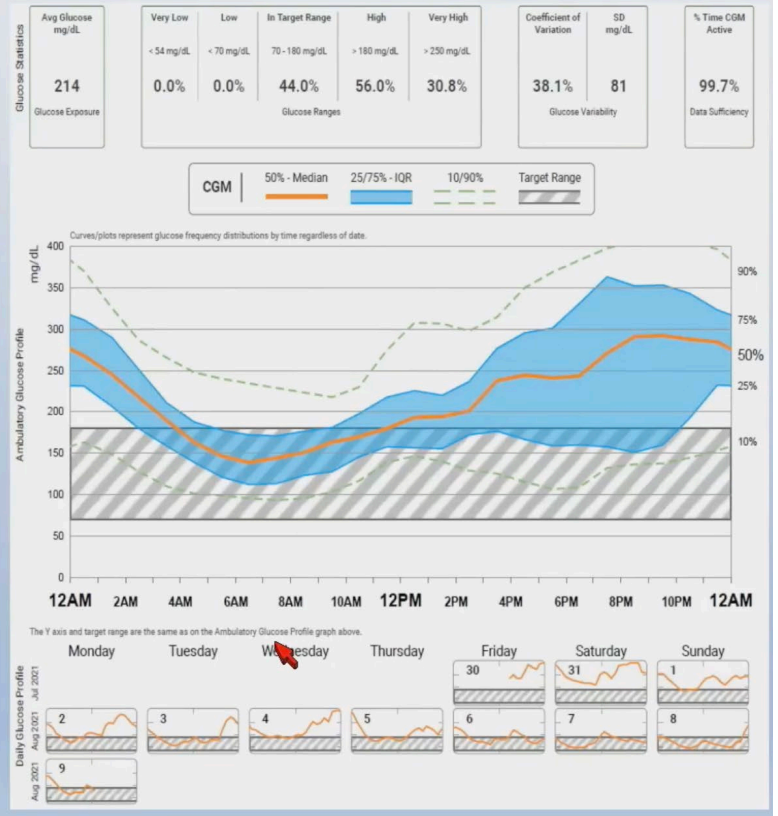
Insulin glargine, 10 u each evening

Hemoglobin A1c was 4.8%

Most recent monthly laboratory glucose concentrations were 128 and 147 mg/dL.

Overall pattern is consistent with excess basal insulin administration relative to insufficient prandial blood glucose control,

Initiate prandial insulin



Galindo, DeBoer, Neumiller, Tuttle, CJASN, 2022

3/ Tirzepatide reduces albuminuria in T2D

318-OR

Tirzepatide Reduces Albuminuria in Patients With T2D: Post-Hoc Pooled Analysis of SURPASS 1-5

Hiddo J.L. Heerspink[1], Katherine Tuttle[2], Imre Pavo[3], Axel Haupt[3], Zhengyu Yang[3], Russell Wiese[3], Andrea Hemmingway[3], David Cherney[4], Naveed Sattar[5]

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Background and Objective

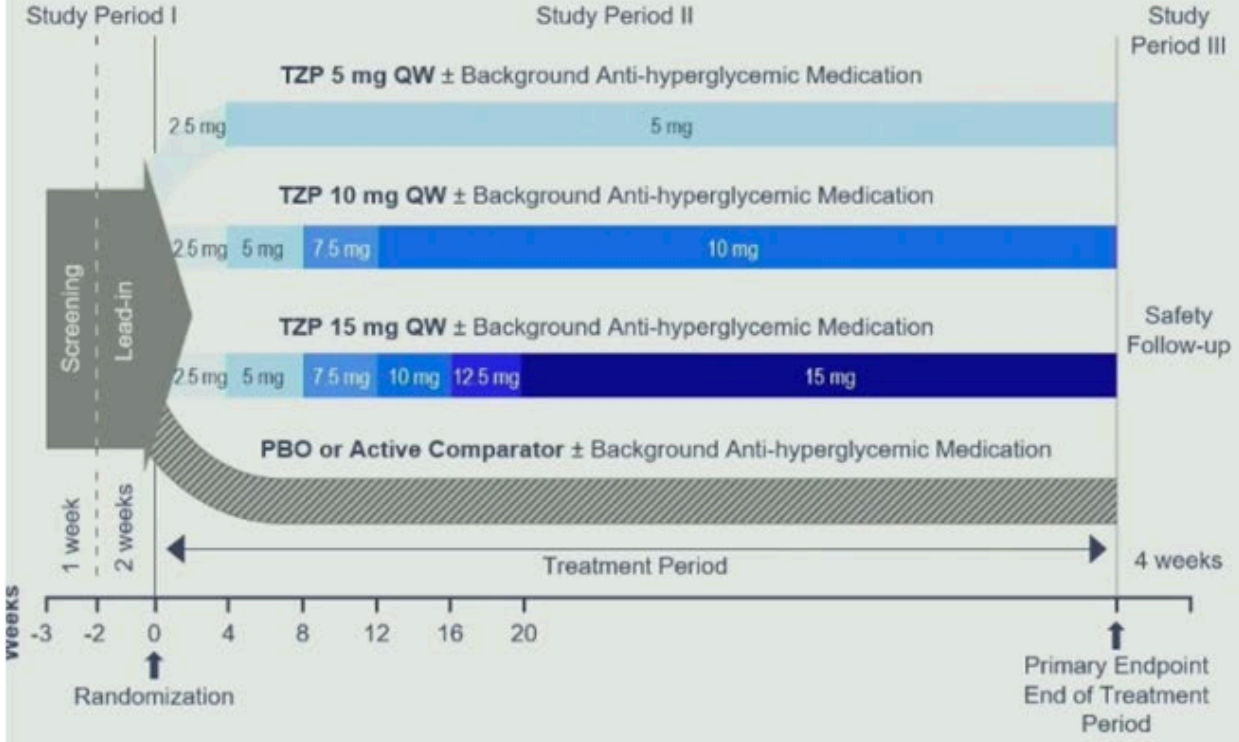
Background

- Chronic kidney disease (CKD), defined by decreased estimated glomerular filtration rate (eGFR)[a] and increased albuminuria,[b] is common in people with type 2 diabetes (T2D)[1]
- In SURPASS-4, the glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide showed a potential kidney protective effect in people with T2D and high cardiovascular risk[2]
- Tirzepatide slowed the rate of eGFR decline and reduced urine albumin-creatinine ratio (UACR) vs. insulin glargine over 2 years[2]

Objective

- To examine the effects of tirzepatide vs. comparator treatments on UACR across the SURPASS-1 through -5 trials

Surpass studies designs



Trial	(Sample Size); Randomization Ratio; Background GLT	Comparator	Primary Endpoint
SURPASS-1	(N=478); 1:1:1:1; None	PBO QW	Wk 40
SURPASS-2	(N=1878); 1:1:1:1; Add-on to metformin	Semaglutide 1 mg QW	Wk 40
SURPASS-3	(N=1437); 1:1:1:1; Add-on to metformin ± SGLT-2i	Titrated iDeg QD	Wk 52
SURPASS-4	(N=1995); 1:1:1:3; Add-on to 1-3 OAMs (metformin, SGLT-2i, and/or SU)	Titrated iGlar QD	Wk 52
SURPASS-5	(N=475); 1:1:1:1; Add-on to titrated iGlar ± metformin	PBO QW	Wk 40

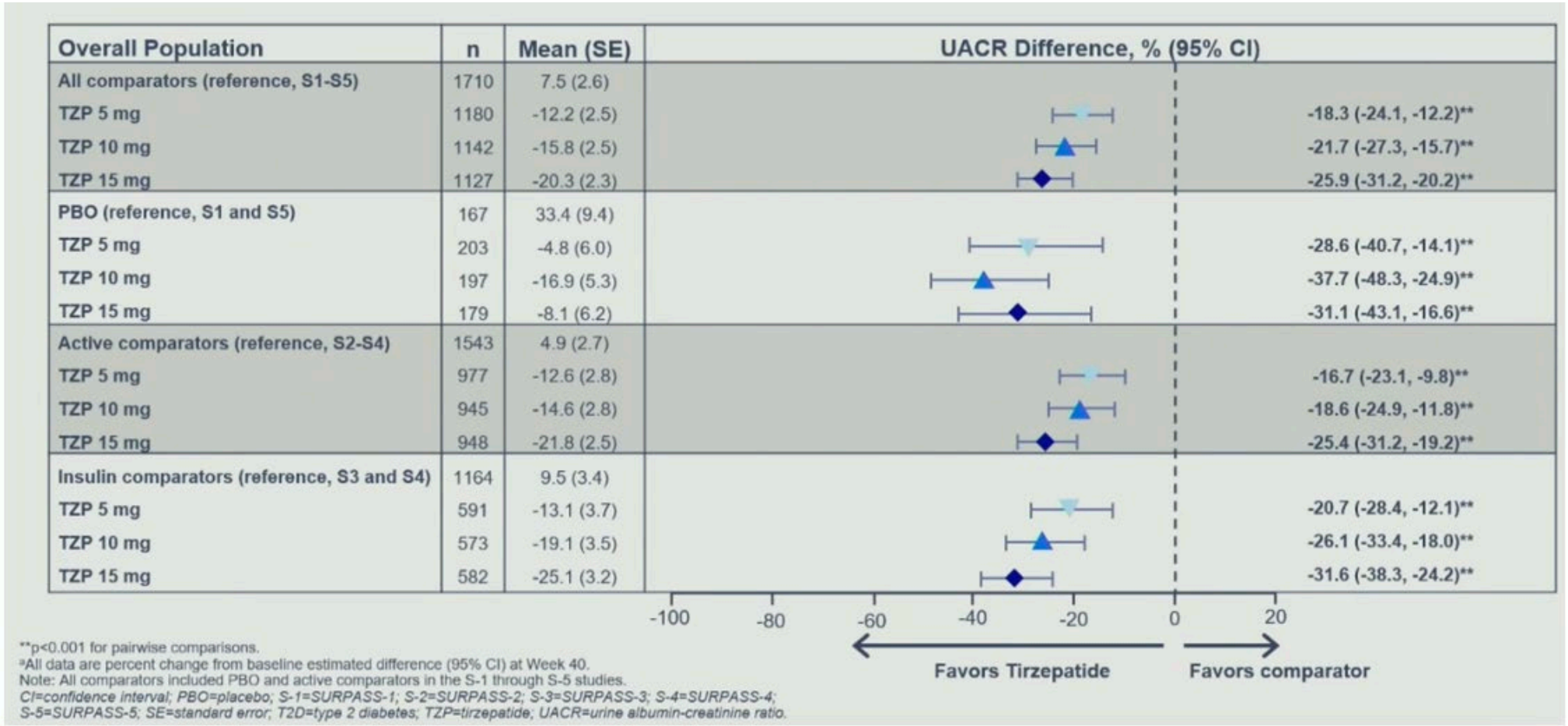
iDeg=insulin degludec; iGlar=insulin glargine; N=number of randomized participants who took ≥1 dose of study drug (modified intent-to-treat); GLT=glucose lowering therapy; OAM=oral anti-hyperglycemic medication; PBO=placebo; QD=once daily; QW=once weekly; SGLT-2i=sodium-glucose co-transporter-2 inhibitor; SU=sulfonylurea; TZP=tirzepatide; Wk=Week.

Demographics and baseline characteristics

	TZP 5 mg (N=1394)	TZP 10 mg (N=1397)	TZP 15 mg (N=1408)	Pooled Comparator (N=2064)	Total (N=6263)
Age, years, mean (SD)	58.3 (10.3)	58.9 (10.3)	58.3 (10.6)	60.3 (10.3)	59.1 (10.4)
Male, %	51.6	56.3	52.5	57.9	54.9
eGFR					
mL/min/1.73 m^2, mean (SD)	91.3 (20.2)	90.7 (18.8)	90.9 (19.4)	87.8 (20.3)	89.9 (19.8)
<60 mL/min/1.73 m^2, n (%)	117 (8.4)	100 (7.2)	98 (7.0)	222 (10.8)	537 (8.6)
UACR					
mg/g, median (IQR)	11.0 (5.0-38.0)	10.6 (4.4-37.0)	12.0 (5.0-40.0)	12.0 (5.0-43.0)	11.0 (5.0-39.8)
Macroalbuminuria, n (%)	73 (5.3)	96 (6.9)	69 (4.9)	115 (5.6)	353 (5.7)
Microalbuminuria, n (%)	336 (24.2)	308 (22.2)	347 (24.7)	502 (24.6)	1493 (24.0)
Duration of T2D, years, mean (SD)	9.5 (7.1)	9.3 (6.8)	9.4 (7.2)	10.1 (7.3)	9.6 (7.1)
BMI, kg/m^2, mean (SD)	33.3 (6.4)	33.4 (6.4)	33.5 (6.2)	33.0 (6.1)	33.3 (6.3)
HbA1c, %, mean (SD)	8.3 (1.0)	8.3 (1.0)	8.3 (1.0)	8.3 (0.9)	8.3 (1.0)

BMI=body mass index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin; IQR=interquartile range; N=number of randomized participants who took ≥1 dose of study drug (modified intent-to-treat); SD=standard deviation; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

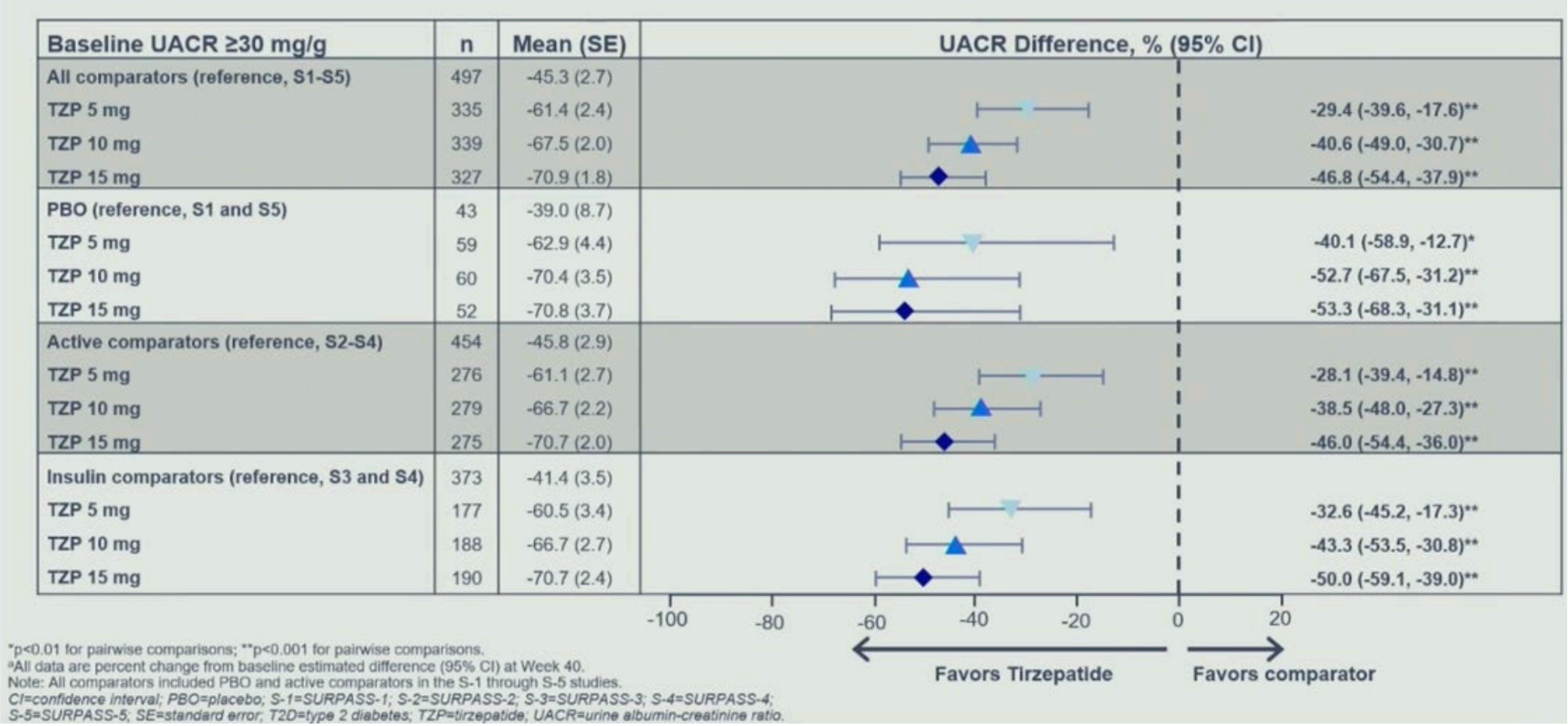
Tirzepatide reduces albuminuria (whole population)



Overall Population	n	Mean (SE)	UACR Difference, % (95% CI)
All comparators (reference, S1-S5)	1710	7.5 (2.6)	
TZP 5 mg	1180	-12.2 (2.5)	-18.3 (-24.1, -12.2)**
TZP 10 mg	1142	-15.8 (2.5)	-21.7 (-27.3, -15.7)**
TZP 15 mg	1127	-20.3 (2.3)	-25.9 (-31.2, -20.2)**
PBO (reference, S1 and S5)	167	33.4 (9.4)	
TZP 5 mg	203	-4.8 (6.0)	-28.6 (-40.7, -14.1)**
TZP 10 mg	197	-16.9 (5.3)	-37.7 (-48.3, -24.9)**
TZP 15 mg	179	-8.1 (6.2)	-31.1 (-43.1, -16.6)**
Active comparators (reference, S2-S4)	1543	4.9 (2.7)	
TZP 5 mg	977	-12.6 (2.8)	-16.7 (-23.1, -9.8)**
TZP 10 mg	945	-14.6 (2.8)	-18.6 (-24.9, -11.8)**
TZP 15 mg	948	-21.8 (2.5)	-25.4 (-31.2, -19.2)**
Insulin comparators (reference, S3 and S4)	1164	9.5 (3.4)	
TZP 5 mg	591	-13.1 (3.7)	-20.7 (-28.4, -12.1)**
TZP 10 mg	573	-19.1 (3.5)	-26.1 (-33.4, -18.0)**
TZP 15 mg	582	-25.1 (3.2)	-31.6 (-38.3, -24.2)**

**p<0.001 for pairwise comparisons.
[a]All data are percent change from baseline estimated difference (95% CI) at Week 40.
Note: All comparators included PBO and active comparators in the S-1 through S-5 studies.
CI=confidence interval; PBO=placebo; S-1=SURPASS-1; S-2=SURPASS-2; S-3=SURPASS-3; S-4=SURPASS-4; S-5=SURPASS-5; SE=standard error; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

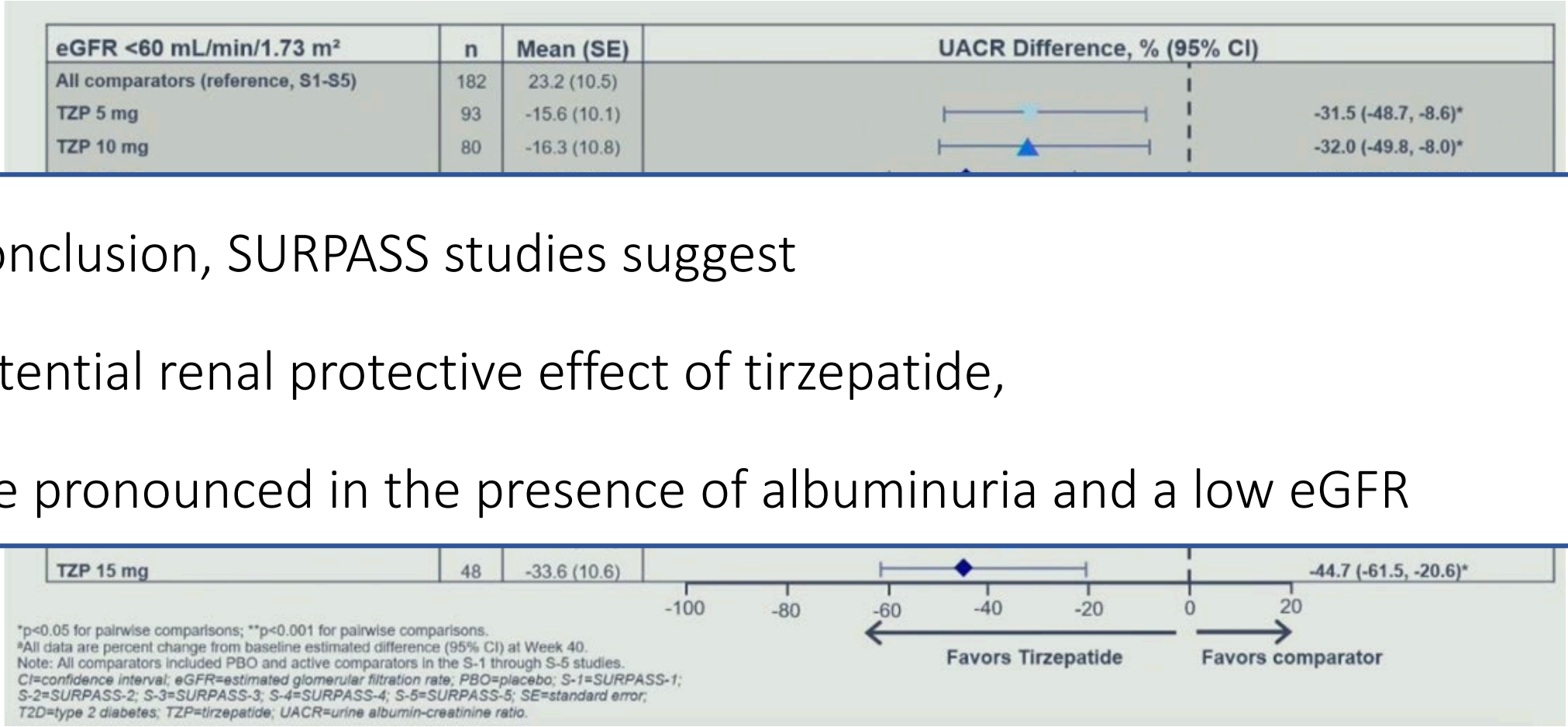
Tirzepatide reduces albuminuria in T2D with microalbuminuria



Baseline UACR ≥30 mg/g	n	Mean (SE)	UACR Difference, % (95% CI)
All comparators (reference, S1-S5)	497	-45.3 (2.7)	
TZP 5 mg	335	-61.4 (2.4)	-29.4 (-39.6, -17.6)**
TZP 10 mg	339	-67.5 (2.0)	-40.6 (-49.0, -30.7)**
TZP 15 mg	327	-70.9 (1.8)	-46.8 (-54.4, -37.9)**
PBO (reference, S1 and S5)	43	-39.0 (8.7)	
TZP 5 mg	59	-62.9 (4.4)	-40.1 (-58.9, -12.7)*
TZP 10 mg	60	-70.4 (3.5)	-52.7 (-67.5, -31.2)**
TZP 15 mg	52	-70.8 (3.7)	-53.3 (-68.3, -31.1)**
Active comparators (reference, S2-S4)	454	-45.8 (2.9)	
TZP 5 mg	276	-61.1 (2.7)	-28.1 (-39.4, -14.8)**
TZP 10 mg	279	-66.7 (2.2)	-38.5 (-48.0, -27.3)**
TZP 15 mg	275	-70.7 (2.0)	-46.0 (-54.4, -36.0)**
Insulin comparators (reference, S3 and S4)	373	-41.4 (3.5)	
TZP 5 mg	177	-60.5 (3.4)	-32.6 (-45.2, -17.3)**
TZP 10 mg	188	-66.7 (2.7)	-43.3 (-53.5, -30.8)**
TZP 15 mg	190	-70.7 (2.4)	-50.0 (-59.1, -39.0)**

*p<0.01 for pairwise comparisons; **p<0.001 for pairwise comparisons.
[a]All data are percent change from baseline estimated difference (95% CI) at Week 40.
Note: All comparators included PBO and active comparators in the S-1 through S-5 studies.
CI=confidence interval; PBO=placebo; S-1=SURPASS-1; S-2=SURPASS-2; S-3=SURPASS-3; S-4=SURPASS-4; S-5=SURPASS-5; SE=standard error; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

Tirzepatide reduces albuminuria in T2D with baseline eGFR < 60 ml/min



In conclusion, SURPASS studies suggest

a potential renal protective effect of tirzepatide,

more pronounced in the presence of albuminuria and a low eGFR

4/ Effectiveness of the association GLP-1a and SGLT-2i on renal events

Reknown cardiorenal benefits

	CV effects	Renal effects
	Effect on MACE	Progression of diabetic kidney disease
GLP-1 RAs	**Benefit:** dulaglutide, liraglutide, semaglutide (subcutaneous) Neutral: exenatide once weekly, lixisenatide	**Benefit** on renal end points in cardiovascular outcome trials (CVOTs), driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (subcutaneous)
SGLT-2 inhibitors	**Benefit:** canagliflozin, empagliflozin	**Benefit:** canagliflozin, dapagliflozin, empagliflozin

Adapted from American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009 (Table 9.2)

Objective and method

Objective: to determine wheter the combined use of SGLT2i and GLP-1 RA is associated with a decrease risk in 2 primary outcomes: MACE and serious renal events when compared to the use of either drug class along among T2D

Method: data sources (UK clinical practice research datalink CPRD)

- 60 million patients from GP practices
- Hospital Episode Statistics Admitted patient care
- Office for national statistics (registred deaths)

Methods – study design

- Population-based prevalent new-user design
- **Cohort 1:** compared the combined use of GLP-1 RAs and SGLT-2 inhibitors to the use of GLP-1 RAs alone
- **Cohort 2:** compared the combined use of GLP-1 RAs and SGLT-2 inhibitors to the use of SGLT-2 inhibitors alone

Two co-primary outcomes:

- Major adverse cardiovascular events (MACE)
  - Myocardial infarction, ischemic stroke, and cardiovascular mortality
- Serious renal events
  - Hospitalizations for kidney complications, chronic kidney disease, and kidney failure

Cohort 1: combination vs GLP-1 RA alone

Results – Cohort 1, combination vs. GLP-1 RAs alone

Characteristics of GLP-1 RA–SGLT-2 Inhibitor Combination Users and GLP-1 RA Users After Matching

Characteristics	GLP-1 RA–SGLT-2 Inhibitor Combination Users	GLP-1 RA Users	Absolute Standardized Difference
Total	6696	6696	
Age, years, mean (SD)	56.7 (10.4)	57.3 (10.4)	0.05
Male sex, n (%)	3,652 (54.5)	3,643 (54.4)	0.00
Body mass index, n (%)			
< 30 kg/m²	837 (12.5)	840 (12.5)	0.00
≥ 30.0 kg/m²	5,782 (86.4)	5,790 (86.5)	0.00
Unknown	77 (1.1)	66 (1.0)	0.02
Smoking status, n (%)			
Ever	5,384 (80.4)	5,434 (81.2)	0.02
Never	1,302 (19.4)	1,251 (18.7)	0.02
Unknown	10 (0.1)	11 (0.2)	0.00
Alcohol-related disorders, n (%)	566 (8.5)	567 (8.5)	0.00
Duration of GLP-1 RA use, years, mean (SD)	1.6 (1.4)	1.6 (1.4)	0.00
Duration of diabetes, years, mean (SD)	11.0 (6.1)	11.2 (6.3)	0.03
Hemoglobin A1c, n (%)			
≤7.0%	323 (4.8)	281 (4.2)	0.03
7.1%-8.0%	983 (14.7)	994 (14.8)	0.00
>8.0%	5,374 (80.3)	5,409 (80.8)	0.01
Unknown	16 (0.2)	12 (0.2)	0.01
Type of antihyperglycemic drugs, n (%)			
Metformin	6,048 (90.3)	6,035 (90.1)	0.01
Thiazolidinediones	469 (7.0)	467 (7.0)	0.00
Meglitinides	26 (0.4)	21 (0.3)	0.01
Alpha-glucosidase inhibitors	7 (0.1)	4 (0.1)	0.02
Sulfonylureas	3,411 (50.9)	3,386 (50.6)	0.01
DPP-4 inhibitors	1,705 (25.5)	1,695 (25.3)	0.00
Insulin	1,705 (25.5)	1,701 (25.4)	0.00

Less serious renal outcomes with the combination compared to GLP-1 RA alone

Hazard Ratios for MACE and Serious Renal Events Comparing Combination Use of GLP-1 RA/SGLT-2 Inhibitor with GLP-1 RA Use Alone

Exposure	No. of patients	Events	Person-years	HR (95% CI) †
Primary outcomes				
MACE				
GLP-1 RA alone	6696	113	10,971	1.00 [Reference]
GLP-1 RA/SGLT-2 inhibitor combination	6696	45	6417	0.70 (0.49-0.99)
Serious renal outcomes				
GLP-1 RA alone	6696	51	10,992	1.00 [Reference]
GLP-1 RA/SGLT-2 inhibitor combination	6696	13	6453	0.43 (0.23-0.80)

Abbreviations: HR, hazard ratio; CI, confidence interval; SGLT, sodium-glucose transport protein; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular events.

† Patients were matched on duration of GLP-1 RA use, GLP-1 RA molecule, and propensity score.

Cohort 2: combination vs SGLT-2i alone

Results – Cohort 2, combination vs. SGLT-2 inhibitors alone

Characteristics of SGLT-2 Inhibitor–GLP-1 RA Combination Users and SGLT-2 Inhibitor Users After Matching

Characteristics	SGLT-2 Inhibitor–GLP-1 RA Combination Users	SGLT-2 Inhibitor Users	Absolute Standardized Difference
Total	8942	8942	
Age, years, mean (SD)	57.6 (10.2)	57.5 (10.3)	0.00
Male sex, n (%)	4,676 (52.3)	4,752 (53.1)	0.02
Body mass index, n (%)			
< 30 kg/m²	1,567 (17.5)	1,628 (18.2)	0.02
≥ 30.0 kg/m²	7,296 (81.6)	7,235 (80.9)	0.02
Unknown	79 (0.9)	79 (0.9)	0.00
Smoking status, n (%)			
Ever	7,177 (80.3)	7,149 (79.9)	0.01
Never	1,758 (19.7)	1,787 (20.0)	0.01
Unknown	7 (0.1)	6 (0.1)	0.00
Alcohol-related disorders, n (%)	759 (8.5)	756 (8.5)	0.00
Duration of SGLT-2 inhibitor use, years, mean (SD)	1.5 (1.4)	1.5 (1.4)	0.01
Duration of diabetes, years, mean (SD)	10.8 (6.3)	10.8 (6.4)	0.00
Hemoglobin A1c, n (%)			
≤7.0%	344 (3.8)	319 (3.6)	0.01
7.1%-8.0%	1,661 (18.6)	1,652 (18.5)	0.00
>8.0%	6,924 (77.4)	6,959 (77.8)	0.01
Unknown	13 (0.1)	12 (0.1)	0.00
Type of antihyperglycemic drugs, n (%)			
Metformin	8,099 (90.6)	8,044 (90.0)	0.02
Thiazolidinediones	504 (5.6)	491 (5.5)	0.01
Meglitinides	32 (0.4)	40 (0.4)	0.01
Alpha-glucosidase inhibitors	13 (0.1)	11 (0.1)	0.01
Sulfonylureas	3,845 (43.0)	3,832 (42.9)	0.00
DPP-4 inhibitors	3,834 (42.9)	3,820 (42.7)	0.00
Insulin	1,550 (17.3)	1,571 (17.6)	0.01

Less serious renal outcomes with the combination compared to SGLT-2i alone

Hazard Ratios for MACE and Serious Renal Events Comparing Combination Use of GLP-1 RA/SGLT-2 Inhibitor with SGLT-2 Inhibitor Use Alone

Exposure	No. of patients	Events	Person-years	HR (95% CI) †
Primary outcomes				
MACE				
SGLT-2 inhibitor alone	8942	141	13,160	1.00 [Reference]
SGLT-2 inhibitor/GLP-1 RA combination	8942	55	7250	0.71 (0.52-0.98)
Serious renal outcomes				
SGLT-2 inhibitor alone	8942	26	13,243	1.00 [Reference]
SGLT-2 inhibitor/GLP-1 RA combination	8942	10	7278	0.67 (0.32-1.41)

Abbreviations: HR, hazard ratio; CI, confidence interval; SGLT, sodium-glucose transport protein; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular events.

† Patients were matched on duration of SGLT-2 inhibitor use, SGLT-2 inhibitor molecule, and propensity score.

Conclusion

- In this population-based cohort study using real-world data, the combined use of GLP-1 RAs and SGLT-2 inhibitors was associated with a decreased risk of MACE and serious renal events, when compared to the use of either drug class alone

- These findings highlight the potential of combining two effective anti-hyperglycemic drug classes for the prevention of macrovascular complications of type 2 diabetes

Take Home Message: Diabetic Kidney Disease

1/ Barriers to implementation of novel kidney-protective agents: multidiscipinary approach

2/ CGMS is of clinical use in hemodialysis

3/ Tirzepatide has a potential renal protective effect of tirzepatide

more pronounced in the presence of albuminuria and a low eGFR

4/ The association GLP-1a and SGLT-2i might decrease MACE and serious renal events compared to either drug alone. Need of radomized clinical trials

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