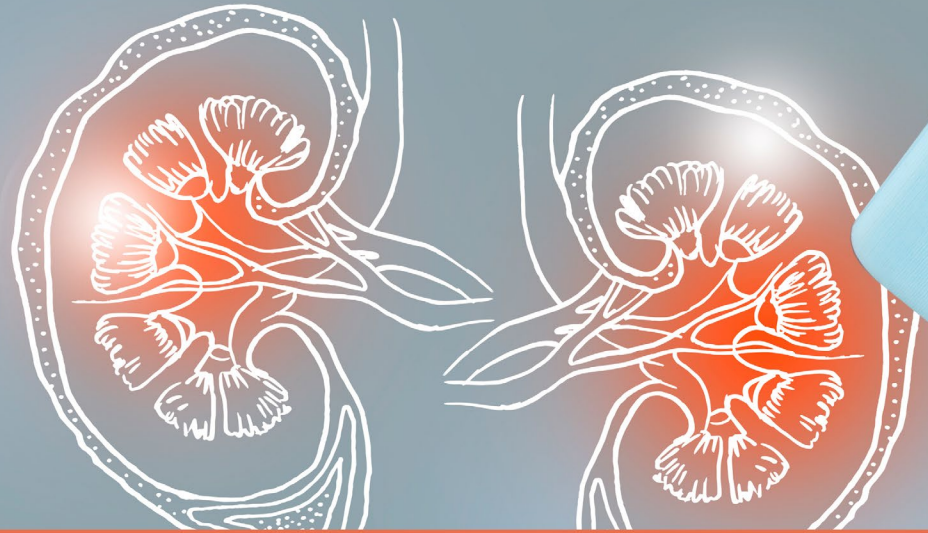
CLINICAL COMPENDIUM

Advancing the Care of Patients With Type 2 Diabetes and Chronic Kidney Disease: Role of the Glucagon-Like Peptide-1 Receptor Agonists



ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

Supported by an independent educational grant from Novo Nordisk Inc.

Learning Objectives

- Describe the impact of diabetes on the progression of chronic kidney disease and cardiovascular disease.
- Differentiate glycemic and nonglycemic effects among glucagon-like peptide-1 receptor agonists (GLP-1 RAs).
- Describe the efficacy, safety, and role of GLP-1 RAs in the treatment of adults with type 2 diabetes, chronic kidney disease, and established atherosclerotic cardiovascular disease.
- Initiate evidence-based GLP-1 RA therapy in patients with T2D and CKD.

Faculty Presenters

John E. Anderson, MD
Internal Medicine and Diabetes
The Frist Clinic
Nashville, Tennessee

George Bakris, MD
Professor of Medicine
Director, American Heart Association Comprehensive Hypertension Center
University of Chicago Medicine
Chicago, Illinois

John B. Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Director, Diabetes Center
Director, NC Translational and Clinical Sciences Institute
Senior Associate Dean, Clinical Research
University of North Carolina School of Medicine
Chapel Hill, North Carolina

It is the policy of the Annenberg Center to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty participating in accredited programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others whose products or services are discussed.

Module Outline

1	Background
2	Standard of Care
3	Glucagon-Like Peptide-1 Receptor Agonists
4	Case #1 – Robyn | Part A
5	Guidance & Guidelines for Type 2 Diabetes
6	Case #1 Continued – Robyn | Part B
7	Cardiorenal Effects of GLP-1 RAs
8	Multidisciplinary Management
9	Case #1 Conclusion – Robyn | Part C
10	Case #2 – Jerry
11	Summary and Conclusions

Background

- Epidemiology, pathophysiology, and burden of diabetic kidney disease
- Chronic kidney disease, cardiovascular disease, and recommendations for screening

Type 2 Diabetes and Kidney Disease

- In the next 20 years, the number of patients with diabetes mellitus is estimated to rise by 51%, reaching 700 million or 10.9% of the global population by 2045
- Diabetic kidney disease (DKD) is one of the most common complications arising from diabetes, affecting approximately 40% of patients with diabetes
- DKD may be present at the time of diagnosis in type 2 diabetes (T2D)
- DKD is defined as kidney structure or function abnormalities, present for >3 months, and requires 1 of 2 criteria:
  - Estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2
  - Persistent albuminuria

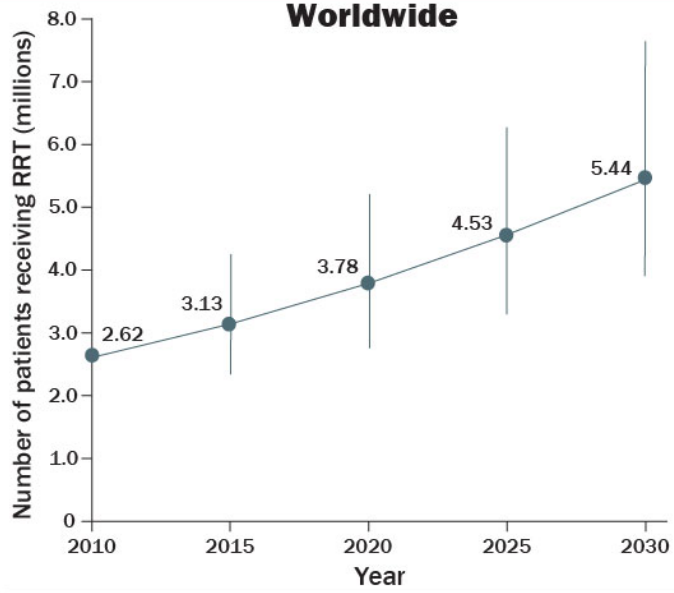
DeFronzo RA, et al. *Nat Rev Nephrol.* 2021;17(5): 319-334. International Expert Committee. *Diabetes Care.* 2009;32(7):1327-1334. Thomas MC, et.al. *Nat Rev Dis Primers.* 2015;1:15018. Thomson SC, et al. *J Clin Invest.* 2001;107(2):217-224. Ruggenenti P, C, et al. *Nat Rev Nephrol.* 2010;6(6): 319-330.
DeFronzo R, Bakris G. *Diabetes Obes Metab.* 2022;24:1197–1205.

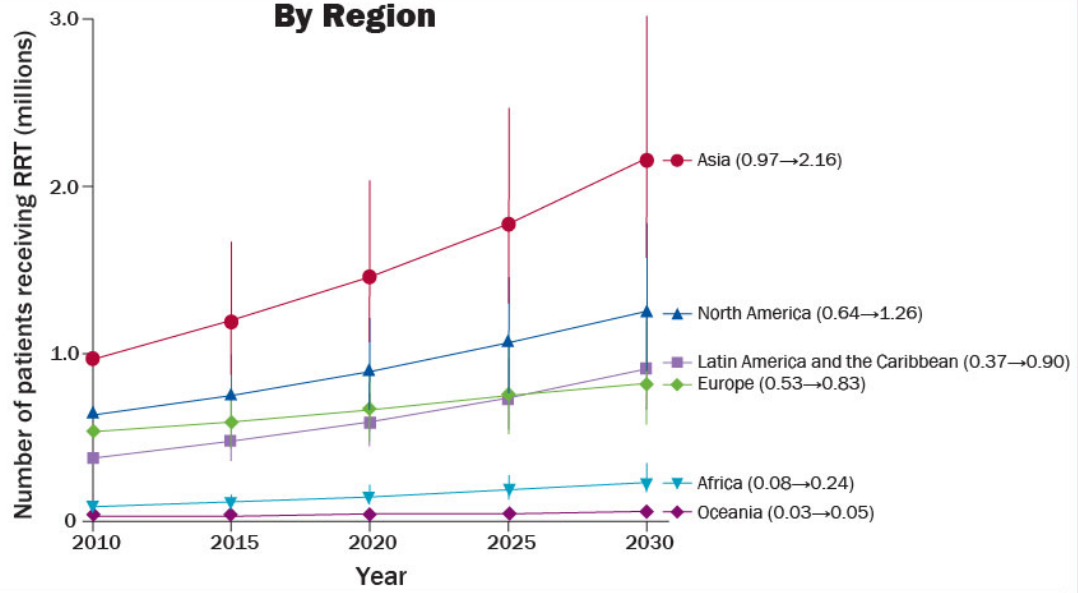
Pathophysiology of Diabetic Nephropathy

- Chronic hyperglycemia is the key risk factor for development and progression of DKD
- Various renal cells and tubules are susceptible to glucose-induced toxicity
- High intracellular glucose concentrations activate multiple metabolic and inflammatory pathways in these cells that lead to:
  - Generation of toxic intermediates
  - Advanced glycation end products
  - Reactive oxygen species
  - Inflammatory cytokines
  - Growth and fibrotic factors
- Prolonged exposure to such a toxic environment exerts deleterious effects on kidney function and morphology

DeFronzo RA, et al. *Nat Rev Nephrol.* 2021;17(5): 319-334. International Expert Committee. *Diabetes Care.* 2009;32(7):1327-1334. Thomas MC, et.al. *Nat Rev Dis Primers.* 2015;1:15018. Thomson SC, et al. *J Clin Invest.* 2001;107(2):217-224. Ruggenenti P, C, et al. *Nat Rev Nephrol.* 2010;6(6): 319-330.
DeFronzo R, Bakris G. *Diabetes Obes Metab.* 2022;24:1197–1205.

Number of People Receiving Renal Replacement Therapy Is Projected to Double

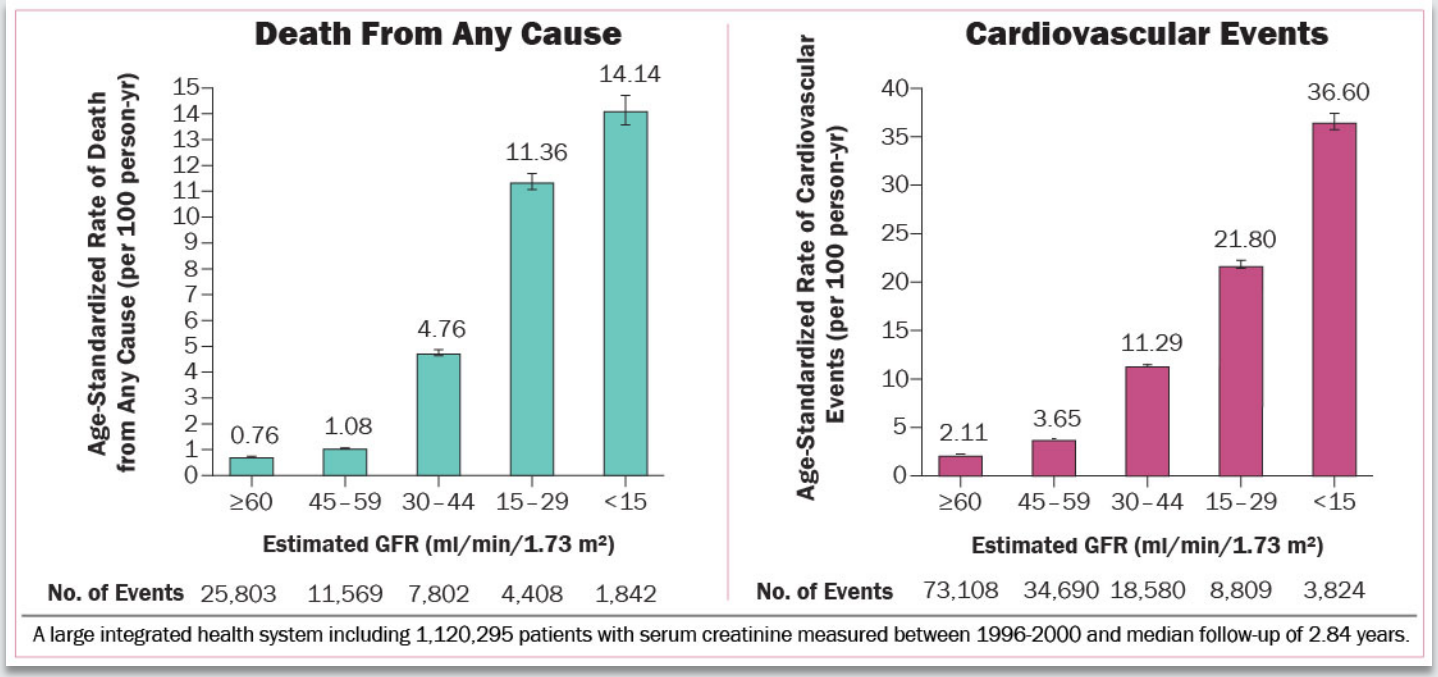




95% CIs shown as error bars.
RRT, renal replacement therapy.

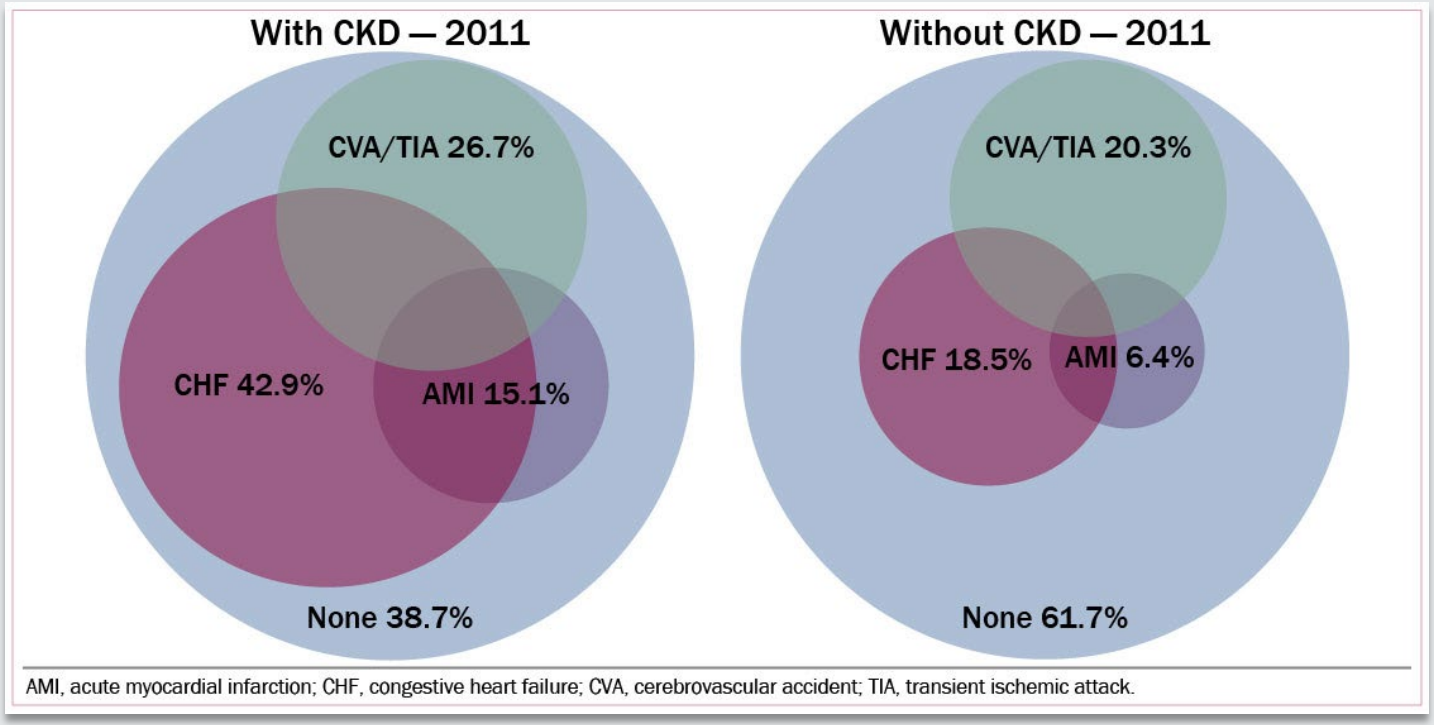
Liyanage T, et al. *Lancet*. 2015;385(9981):1975-1982. Illustration adapted from Figure 5.

Lower eGFR Is Associated With Cardiovascular Events and Death



Go AS, et al. *N Engl J Med.* 2004;351:1296-1305. Illustration adapted from Figure 1 A & B.

Cardiovascular Disease in Patients With or Without Chronic Kidney Disease



House AA. *Am J Kidney Dis.* 2018;72(2):284–295. Illustration adapted from Figure 2 (Reproduced from Figure 4.1.i of the US Renal Data System 2013 Annual Data Report).

ADA/KDIGO: Screening for CKD

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m²

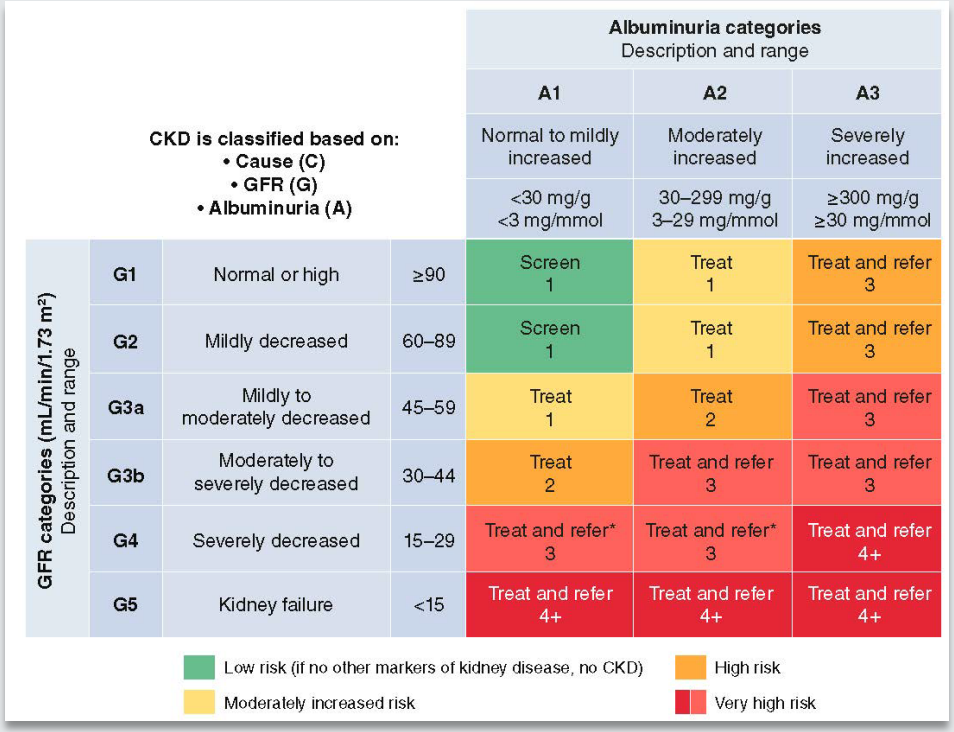
and/or

Other evidence of kidney damage

ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes.

ADA/KDIGO

Risk of CKD progression, frequency of visits, and referral to nephrology



CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

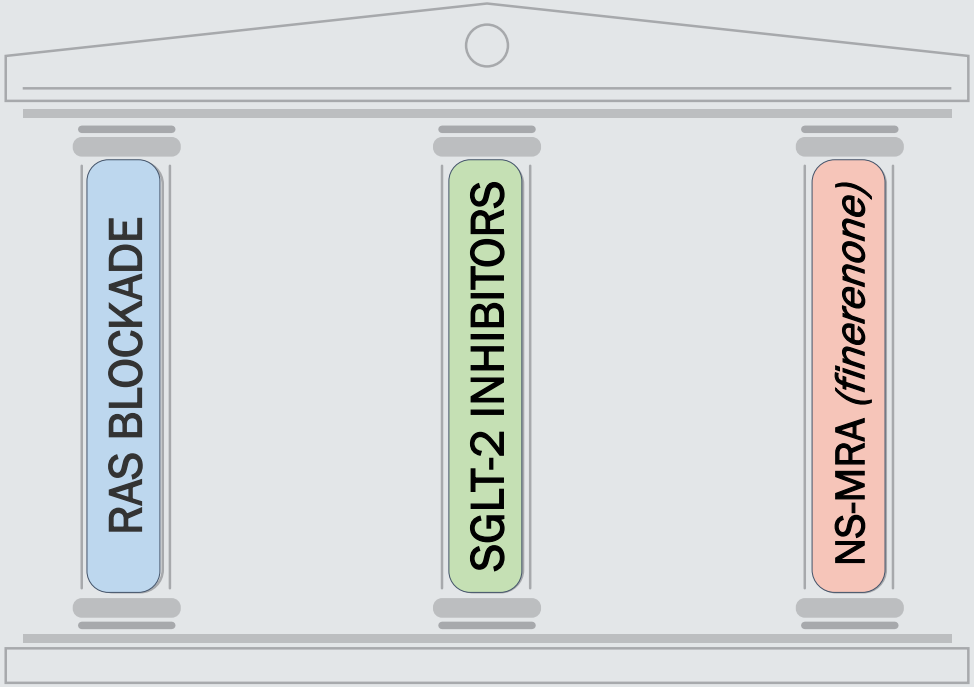
Standard of Care

- Evolving pillars of pharmacotherapy for diabetic kidney disease
- Cardiorenal clinical trials and the 2022 ADA/KDIGO Consensus Report

Pillars of Therapy to Reduce Cardiorenal Risk in 2001

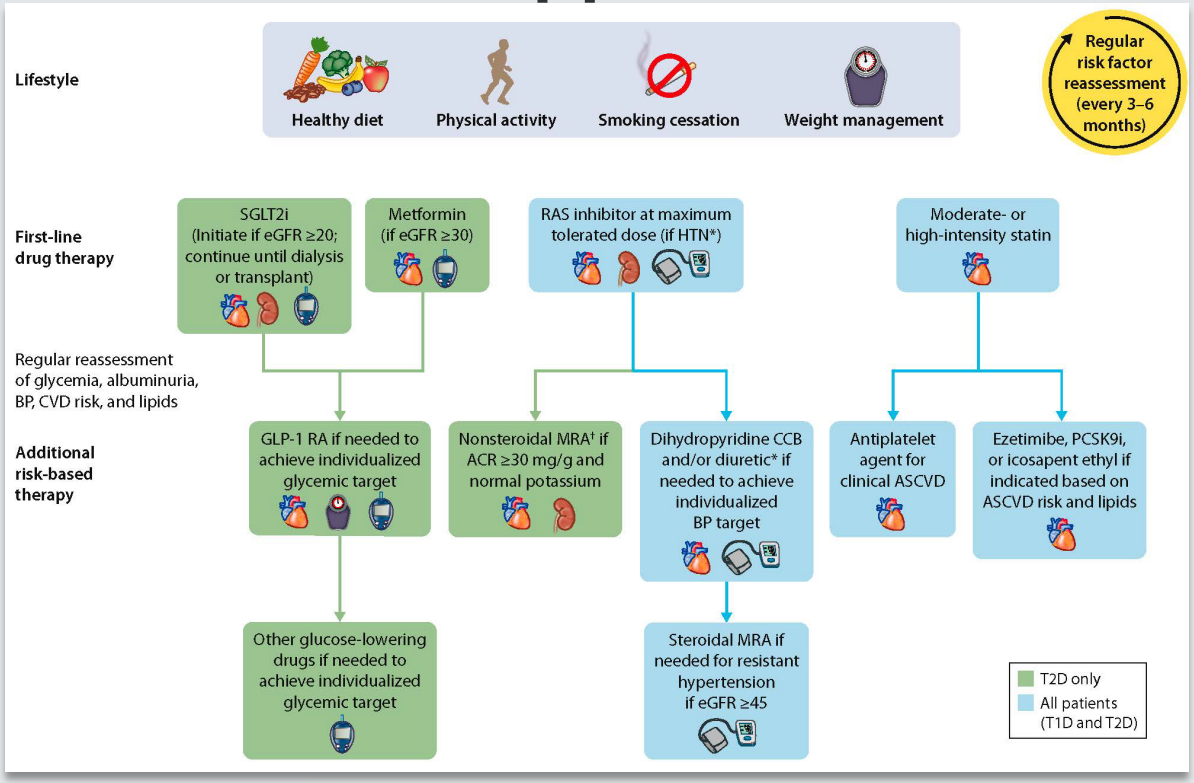
Slowing DKD Progression and Reduce CV Risk

Pillars of Therapy to Reduce Cardiorenal Risk in 2022



Slowing DKD Progression and Reduce CV Risk

ADA/KDIGO Holistic Approach



SGLT2i in Adults With Diabetic Kidney Disease: Meta-analysis

Table 1 Effect of SGLT2 inhibitors on clinical outcomes in adults with diabetic kidney disease

Outcome	No. studies	No. events	Sample size	HR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
MACE	6	2271	21,913	0.83 (0.75–0.93)	33.8	0.183	0.287
Kidney composite	5	1197	21,195	0.66 (0.58–0.75)	0.0	0.949	0.513
HHF	6	1219	22,346	0.62 (0.55–0.71)	0.0	0.844	0.267
Cardiovascular death	5	953	20,539	0.84 (0.74–0.96)	0.0	0.639	0.996
Fatal and nonfatal MI	5	498*	20,108	0.78 (0.67–0.92)	7.7	0.363	0.671
Fatal and nonfatal stroke	5	332*	20,108	0.76 (0.59–0.97)	41.3	0.146	0.564
All-cause mortality	5	1451	21,406	0.86 (0.77–0.96)	14.5	0.322	0.268

*The number of MI events and stroke cases from the SCORED trial were not reported in the primary trials and are not included in the table. CI indicates confidence interval; *HHF* hospitalization for heart failure, *HR* hazard ratio, I^2, I-squared, *MACE* Major Adverse Cardiovascular Events, *MI* myocardial infarction, *SCORED* Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk, *SGLT2* sodium-glucose cotransporter 2; SGLT2, sodium-glucose cotransporter 2, *SOLOIST-WHF* Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure, *VERTIS CV* Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial

SGLT2i in Adults With Diabetic Kidney Disease: Meta-analysis

Table 4 Effect of SGLT2 Inhibitors on safety events among patients with diabetic kidney disease

Outcome	No studies	No events	Sample size	RR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
Male genital mycotic infections	2	98	4091	**3.89 (1.42–10.62)**	62.1	0.072	0.392
Female genital mycotic infections	2	53	2100	**2.50 (1.32–4.72)**	0.0	0.384	NA
Diabetic ketoacidosis	2	56	14,974	3.54 (0.82–15.39)	54.3	0.139	NA
Volume depletion	4	1016*	18,832	**1.29 (1.13–1.48)**	0.0	0.713	0.936
Amputations	4	248*	18,832	1.21 (0.85–1.72)	25.4	0.244	0.767
Bone fractures	4	475*	18,832	1.00 (0.84–1.20)	0.0	0.953	0.447
Urinary tract infections	4	1739*	18,832	1.04 (0.95–1.14)	0.0	0.781	0.339
Acute kidney injury	3	197*	8255	0.85 (0.66–1.11)	0.0	0.975	0.535
Hyperkalemia	3	359*	8255	0.82 (0.67–1.01)	0.0	0.692	0.601

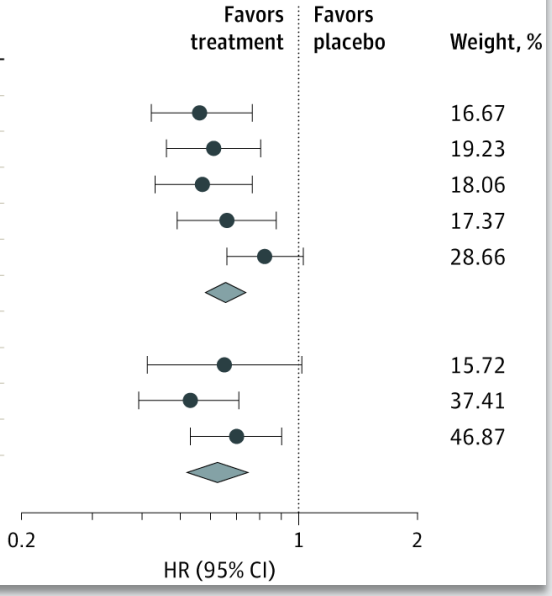
Bold values indicate statistically significant estimates

*The number of events from the EMPA-REG OUTCOME trial were not reported and therefore not included in the table for the following outcomes: volume depletion, amputations, fractures, urinary tract infection, acute kidney injury, and hyperkalemia. CI indicates confidence interval, *EMPA-REG OUTCOME* Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients; I^2, I-squared, *RR* relative risk, *SGLT2* sodium-glucose cotransporter 2

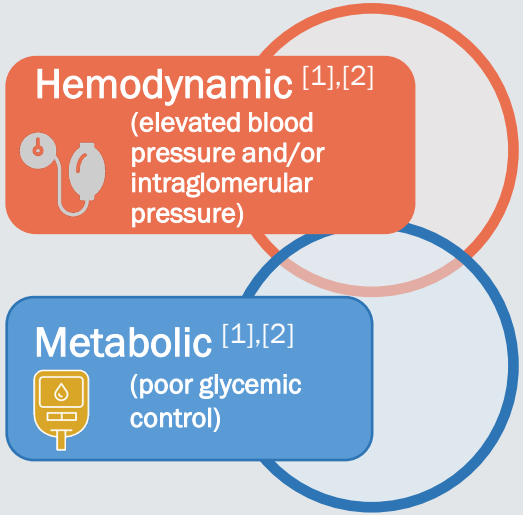
Meta-analysis of SGLT2i trials on the composite of worsening of renal function, end-stage renal disease, or renal death

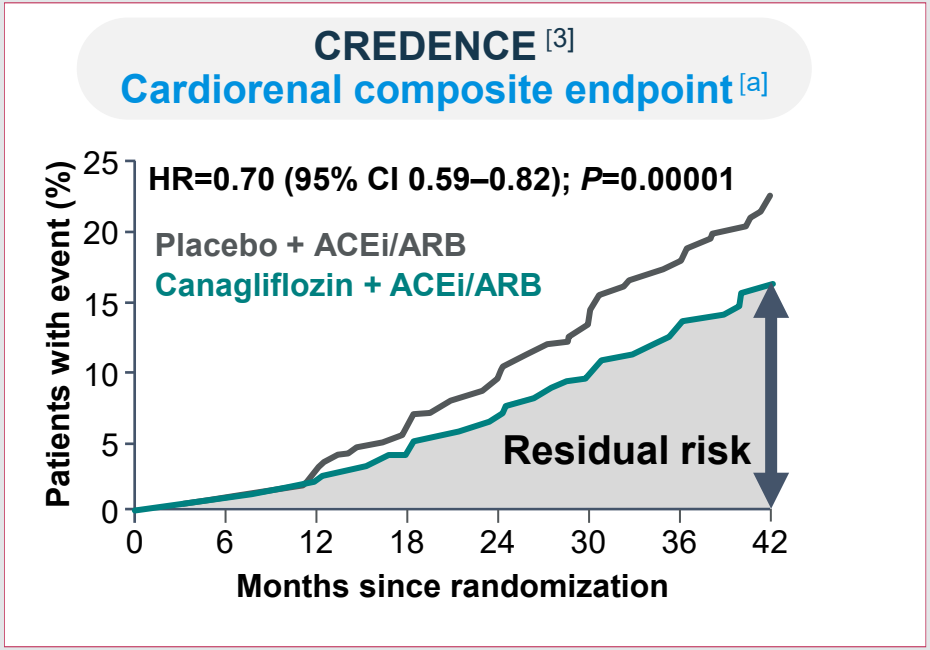
B Kidney outcomes by ASCVD status

	Treatment		Placebo			
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Weight, %
Patients with ASCVD						
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)	16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)	19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)	18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)	17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)	28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)	
Patients without ASCVD						
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)	15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)	37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)	46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)	



Nonsteroidal MRA rationale high residual risk of CKD progression with current therapies





a. End-stage kidney disease, doubling of serum creatinine level from baseline sustained for at least 30 days, or death from renal or cardiovascular disease.

1. Alicic RZ, et al. *Clin J Am Soc Nephrol.* 2017;12(12):2032–2045.
2. Mora-Fernández C, et al. *J Physiol.* 2014;18:3997–4012.
3. Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295–2306.

FIDELITY is a large individual patient data pooled analysis of FIDELIO-DKD [1] and FIGARO-DKD [2]

48 countries

13,171 patients randomized

3 years' median follow-up

R

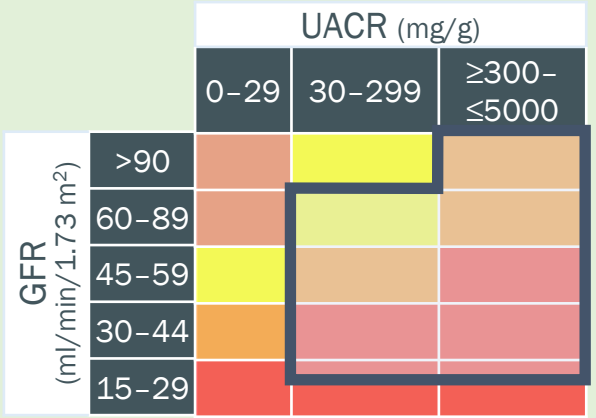
Finerenone 10 or 20 mg od [a]

Placebo

Max. tolerated RAS blockade

Key eligibility criteria

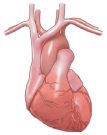
- T2D
- CKD
- On single RASi
- Serum [K^+] ≤4.8 mmol
- Symptomatic HFrEF



Key outcomes

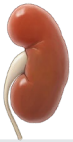
CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



57% eGFR kidney composite

Time to kidney failure,[b] sustained ≥57% decrease in eGFR from baseline, or renal death



ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; [K+], potassium concentration; MI, myocardial infarction; RASi, renin–angiotensin system inhibitor; od, once daily.

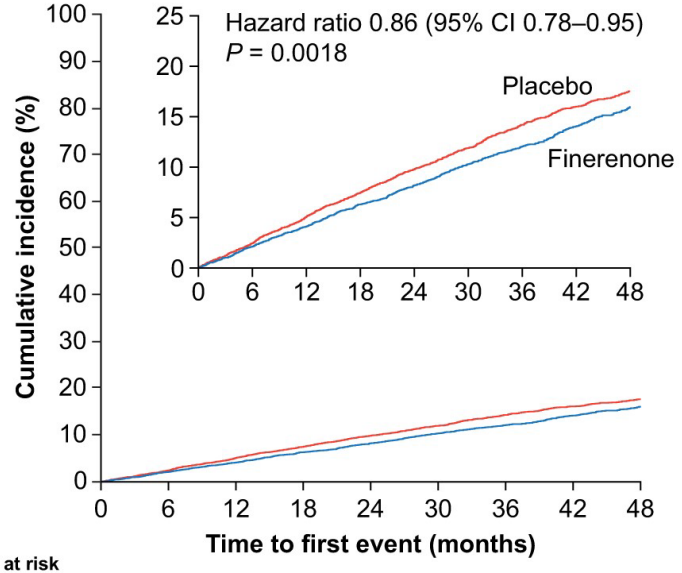
ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

a. 10 mg if screening eGFR 25–<60 ml/min/1.73 m²; 20 mg if ≥60 ml/min/1.73 m², up-titration encouraged from month 1 if serum [K+] ≤4.8 mEq/l and eGFR stable.
b. Kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 ml/min/1.73 m².

1. Bakris GB, et al. *N Engl J Med*. 2020;383:2219–2229; 2. Pitt B, presented at ESC congress 2021.

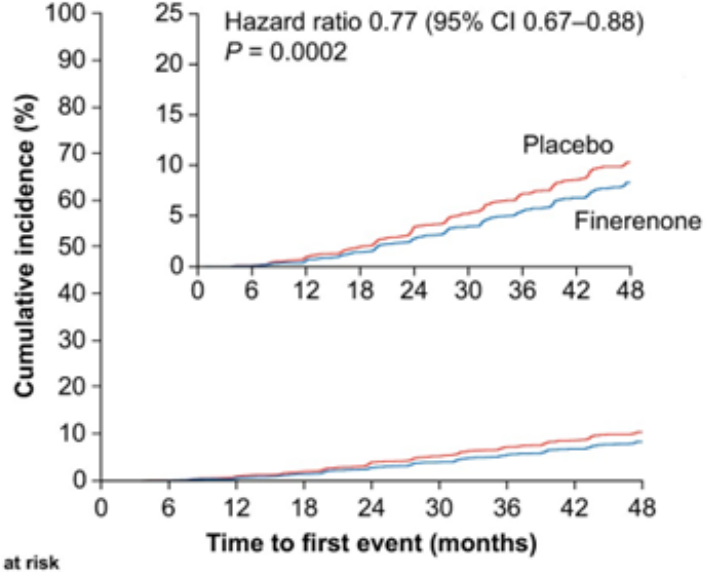
Time to Efficacy Outcomes

Composite Cardiovascular Outcome



No. at risk									
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087

eGFR ≥57% Composite Kidney Outcome



No. at risk									
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959

(Left) The composite cardiovascular outcome defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (Aalen–Johansen curve). (Right) The composite kidney outcome defined as kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death (Aalen–Johansen curve).

Placebo
Finerenone

Agarwal R, et al. *Eur Heart J.* 2022; 43(6):474–484. [Bakris GL coauthor] Figure 1 A & B used under terms of the Creative Commons Attribution-NonCommercial License.

ADA/ KDIGO Consensus Report

GLP-1 receptor agonists

10.42 Among patients with T2D who **HAVE** established ASCVD or established kidney disease, an SGLT2i or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens (1A).

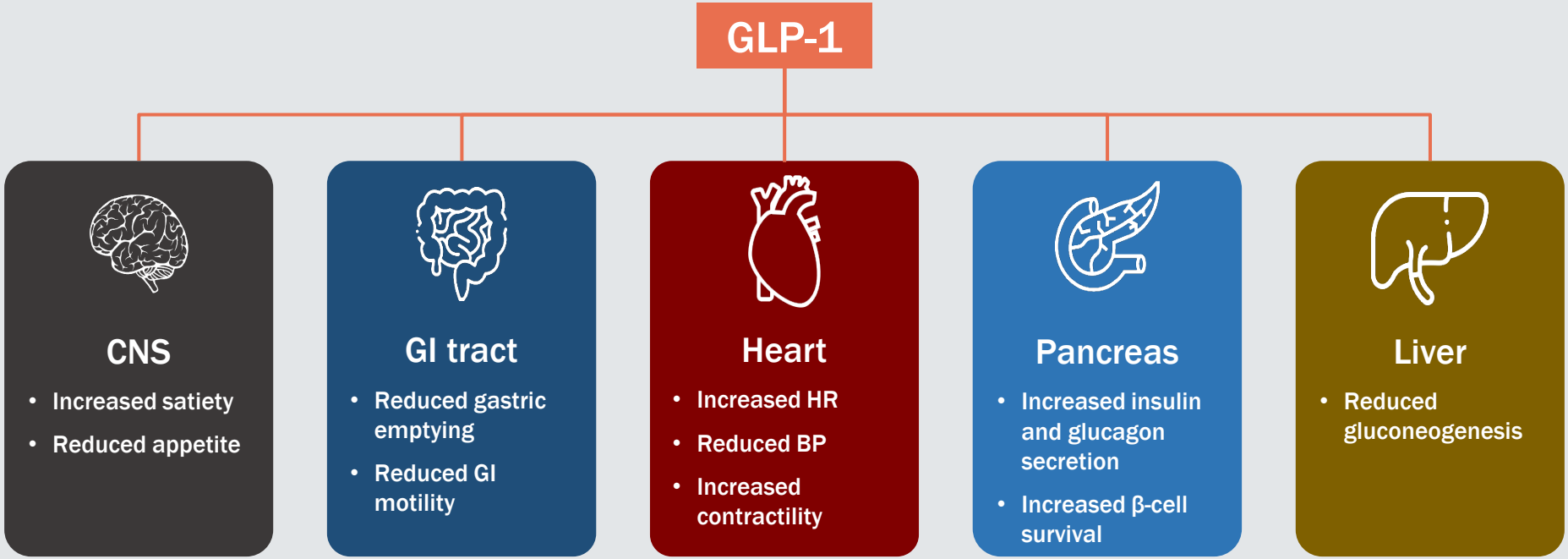
For patients with T2D and CKD who **HAVE NOT** achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 receptor agonist is recommended (1B).

de Boer IH, et al. *Diabetes Care.* 2022. dci220027:45.

Glucagon-Like Peptide-1 Receptor Agonists

- Comparison of structure, pharmacodynamics, and pharmacokinetics of GLP-1 RAs
- Prescribing considerations and expert opinions with the utilization of GLP-1 RAs

Pleotropic Physiological Effects of GLP-1



BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HR, heart rate.

Saraiva FK, Sposito AC. *Cardiovasc Diabetol.* 2014;13:142.

GLP-1 RAs are not exactly alike…

Pharmacokinetics		Structure		Size	
Short-acting	Long-acting	Exendin-4-based	GLP-1-based	Small	Large
Exenatide BID	Exenatide QW	Exenatide BID	Liraglutide	Exenatide BID	Albiglutide
Lixisenatide	Liraglutide	Exenatide QW	Albiglutide	Exenatide QW	Dulaglutide
	Albiglutide	Lixisenatide	Semaglutide	Liraglutide	
	Semaglutide		Dulaglutide	Lixisenatide	
	Dulaglutide			Semaglutide	
Short-acting GLP-1 RAs retain their effect on gastric emptying (and PPG), while long-acting GLP-1 RAs seem to have more pronounced effects on FPG and HbA_{1c}		Exendin-based GLP-1 RAs seem to give rise to the formation of antibodies to a higher degree than the GLP-1-based ones; clinical implication uncertain		The large GLP-1 RAs may not be able to penetrate into the brain to the same extent as the smaller ones, possibly affecting appetite signalling differently	

Oral formulation		
Product	Molecule	Route
Oral semaglutide	Semaglutide	Oral with carrier molecule

BID, twice daily; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; PPG, postprandial glucose; QW, once weekly

ADA/KDIGO: Prescribing Considerations

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

ADA/KDIGO: Prescribing Considerations

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

ADA/KDIGO: Key risk mitigation strategies

Medication	Consideration	Monitoring and/or risk mitigation strategies
Metformin	Metformin-associated lactic acidosis	• Monitor eGFR with increasing frequency as eGFR falls to <60 mL/min/1.73 m^2 • Adjust metformin dose as appropriate per eGFR (see Table 4) • Consider dose reduction in the presence of conditions that predispose patients to hypoperfusion and hypoxemia for eGFR 45–59 mL/min/1.73 m^2 • Discontinue for eGFR <30 mL/min/1.73 m^2 • Institute a sick day protocol
	B_{12} malabsorption	• Monitor patients for vitamin B_{12} deficiency when treated with metformin for >4 years
SGLT2i	Genital mycotic infections	• Counsel on genital hygiene
	Volume depletion	• Monitor for hypovolemia and consider proactive dose reduction of diuretics in patients at high risk • Hold SGLT2i during illness
	Diabetic ketoacidosis	• Educate about signs/symptoms to facilitate early recognition • Monitor blood or urine ketones in the case of very high risk • Institute a sick day protocol • Maintain at least low-dose insulin in insulin-requiring individuals
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

ADA/KDIGO: Key risk mitigation strategies

Medication	Consideration	Monitoring and/or risk mitigation strategies
Metformin	Metformin-associated lactic acidosis	• Monitor eGFR with increasing frequency as eGFR falls to <60 mL/min/1.73 m^2 • Adjust metformin dose as appropriate per eGFR (see Table 4) • Consider dose reduction in the presence of conditions that predispose patients to hypoperfusion and hypoxemia for eGFR 45–59 mL/min/1.73 m^2 • Discontinue for eGFR <30 mL/min/1.73 m^2 • Institute a sick day protocol
	B_{12} malabsorption	• Monitor patients for vitamin B_{12} deficiency when treated with metformin for
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
		• Maintain at least low-dose insulin in insulin-requiring individuals
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

ADA/KDIGO: Dosing for eGFR <45

	Stage 3b (eGFR 30–44 mL/min/1.73 m^2)	Stage 4 (eGFR 15–29 mL/min/1.73 m^2)	Stage 5 (eGFR <15 mL/min/1.73 m^2)
GLP-1 receptor agonists			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		

de Boer IH, et al. *Diabetes Care.* 2022; dci220027. [Bakris GL coauthor] Adapted from Table 4; American Diabetes Association *Diabetes Care*, American Diabetes Association, 2022.

GLP-1 RA Summary

Drug	Within class comparability of A1C lowering efficacy	Within class comparability of effect on weight	Within class comparability of GI adverse effects
Exenatide (twice daily)	Low	Low	Highest
Lixisenatide	Low	Low	Intermediate
Liraglutide	High	High	Intermediate
Exenatide XR	Intermediate	Low	Low
Dulaglutide	High	Intermediate	Intermediate/high
Semaglutide	Highest	Highest	High
Semaglutide (oral)	High/highest	Highest	Intermediate/high

A1C, hemoglobin A1C; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonists.

Trujillo JM, et al. *Ther Adv Endocrinol Metab.* 2021;12:2042018821997320. Table 4.

Successful prescribing for GLP-1 RA inhibitors

- **Advantages:** great efficacy, weight loss, blood pressure reduction
- **Compelling indications:** prevalent atherosclerotic cardiovascular disease and high risk for CVD
- **Adverse events:** nausea, other GI adverse events; generally resolves over time; consider in the context of satiety
- **Important safety issues:**
  - Gall bladder events
  - Acute kidney injury
  - Pancreatitis (not increased vs placebo in CVOTs)
  - In the setting of persistent nausea and vomiting, hold the drug and seek medical attention if it does not resolve over hours or if other worrisome symptoms are present
- **Contraindications:** medullary thyroid cancer, multiple endocrine neoplasia, or family history
- **Initiation:** Start with lowest dose, titrate slowly, back off for GI adverse events
- **Consider specific attributes of specific products:** exenatide twice daily (best postprandial efficacy), exenatide once weekly (lowest GI AE rate), liraglutide (most titratable), dulaglutide (easiest injection), semaglutide SQ (highest efficacy, particularly for weight), oral semaglutide (oral)

Adapted from Romera I, et al. *Diabetes Ther.* 2019;10:5-19.

Case #1 – Robyn | Part A

Question 1 of 5: PREVIEW

Robyn A., a 58-year-old woman with a 10-year history of type 2 diabetes and an 8-year history of hypertension, is evaluated by her primary care provider for a routine follow-up. Robyn is currently prescribed metformin 500 mg twice daily, glipizide 10 mg twice daily, pioglitazone 30 mg once daily, and amlodipine 10 mg once daily.

Today's vitals reveal a blood pressure of 134/78 mmHg and heart rate of 86 beats/minute. Laboratory results reveal hemoglobin A1C increased to 7.7% from 7.2% and estimated glomerular filtration rate (eGFR) at 70 mL/min/1.73 m^2.

Robyn reports frustrations that her blood glucose levels are highly variable and that she is not losing weight (body mass index [BMI] = 34 kg/m^2) despite exercising 30 minutes per day and reducing carbohydrates. Per patient report and blood glucose log, patient has experienced 3–4 episodes of symptomatic hypoglycemia in the last 3 months:

- Prebreakfast blood glucose readings average: 73 mg/dL (range: 58 mg/dL–99 mg/dL)
- Postprandial blood glucose readings average: 192 mg/dL (range: 136 mg/dL–248 mg/dL)

Question 1 of 5

Which one of the following is the most appropriate next step in the management of this patient?

A. Decrease metformin to 500 mg once daily

B. Initiate insulin aspart 5 units SQ with each meal

C. Decrease glipizide to 5 mg twice daily with meals

D. Decrease pioglitazone to 15 mg once daily

Question 1 of 5: DISCUSSION

The correct answer is C: *Decrease glipizide to 5 mg twice daily with meals*

- In managing patients with diabetes, it is important to reduce present discomfort (eg, hypoglycemia) to increase patient's motivation to prevent long-term microvascular and macrovascular complications.[1]
- Episodes of frequent symptomatic hypoglycemia are a concern requiring reduction of the sulfonylurea.
- The addition of rapid-acting insulin would likely increase the risk of hypoglycemia. This patient is not appropriate for insulin therapy according to current guidelines. Insulin is initiated as basal first.[1]
- Decreasing the doses of metformin and pioglitazone would not reduce the risk of hypoglycemia, but would negatively impact glycemic control.

1. Davies MJ, et al. Management of hyperglycemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.

Guidance and Guidelines

- Timeline of international diabetes and kidney disease guidelines in the last 5 years
- 2022 ADA/EASD Consensus Report person-centered approach and treatment algorithm

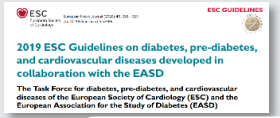
International Guidelines 2018–2022

January 2018
ADA Standards of Care 2018

September 2018
EASD/ADA Consensus Report 2018

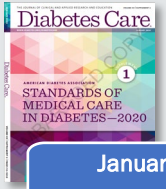
January 2019
ADA Standards of Care 2019

March 2019
AHA/ACC Guidelines 2019



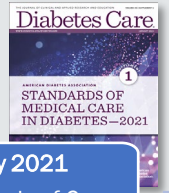
September 2019
ESC Guidelines 2019

December 2019
EASD/ADA Consensus Report 2019



January 2020
ADA Standards of Care 2020

October 2020
KDIGO Guidelines 2020



January 2021
ADA Standards of Care 2021

January 2022
ADA Standards of Care 2022

ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; KDIGO, Kidney Disease Improving Global Outcomes.

ADA/EASD Consensus Report

September 24, 2022

Diabetologia (2022) 65:1925–1966
https://doi.org/10.1007/s00125-022-05787-2

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · Vanita R. Aroda[3] · Billy S. Collins[4] · Robert A. Gabbay[5] · Jennifer Green[6] · Nisa M. Maruthur[7] · Sylvia E. Rosas[8] · Stefano Del Prato[9] · Chantal Mathieu[10] · Geltrude Mingrone[11,12,13] · Peter Rossing[14,15] · Tsvetalina Tankova[16] · Apostolos Tsapas[17,18] · John B. Buse[19]

Received: 2 August 2022 / Accepted: 18 August 2022 / Published online: 24 September 2022

Abstract

The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the previous consensus statements on the management of hyperglycaemia in type 2 diabetes in adults, published since 2006 and last updated in 2019. The target audience is the full spectrum of the professional healthcare team providing diabetes care in the USA and Europe. A systematic examination of publications since 2018 informed new recommendations. These include additional focus on social determinants of health, the healthcare system and physical activity behaviours including sleep. There is a greater emphasis on weight management as part of the holistic approach to diabetes management. The results of cardiovascular and kidney outcomes trials involving sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, including assessment of subgroups, inform broader recommendations for cardiorenal protection in people with diabetes at high risk of cardiorenal disease. After a summary listing of consensus recommendations, practical tips for implementation are provided.

Keywords Cardiovascular disease · Chronic kidney disease · Glucose-lowering therapy · Guidelines · Heart failure · Holistic care · Person-centred care · Social determinants of health · Type 2 diabetes mellitus · Weight management

This article is being simultaneously published in *Diabetologia* (https://doi.org/10.1007/s00125-022-05787-2) and *Diabetes Care* (https://doi.org/10.2337/dci22-0034) by the European Association for the Study of Diabetes and American Diabetes Association.

A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel and represents the panel's collective analysis, evaluation and opinion. MJD and JBB were co-chairs for the Consensus Report Writing Group. VRA, BSC, RAG, JG, NMM and SER were the writing group members for ADA. SDP, CM, GM, PR, TT and AT were the writing group members for EASD. The article was reviewed for EASD by its Committee on Clinical Affairs and approved by its Executive Board. The article was reviewed for ADA by its Professional Practice Committee.

✉ Melanie J. Davies (for *Diabetologia*)
melanie.davies@uhl-tr.nhs.uk
✉ John B. Buse (for *Diabetes Care*)
jbuse@med.unc.edu

Extended author information available on the last page of the article

Abbreviations

BGM	Blood glucose monitoring
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
CVOT	Cardiovascular outcomes trial
DKA	Diabetic ketoacidosis
DPP-4i	Dipeptidyl peptidase-4 inhibitors
DSMES	Diabetes self-management education and support
ETD	Estimated treatment difference
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1 RA	Glucagon-like peptide-1 receptor agonist(s)
HF	Heart failure
HHF	Hospitalisation for heart failure
MACE	Major adverse cardiovascular events
MNT	Medical nutrition therapy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
SGLT1i	Sodium–glucose cotransporter-1 inhibitor

Springer

Davies MJ, et al. *Diabetologia.* 2022;65:1925–1966. [Buse JB coauthor]
Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786. [Buse JB coauthor]

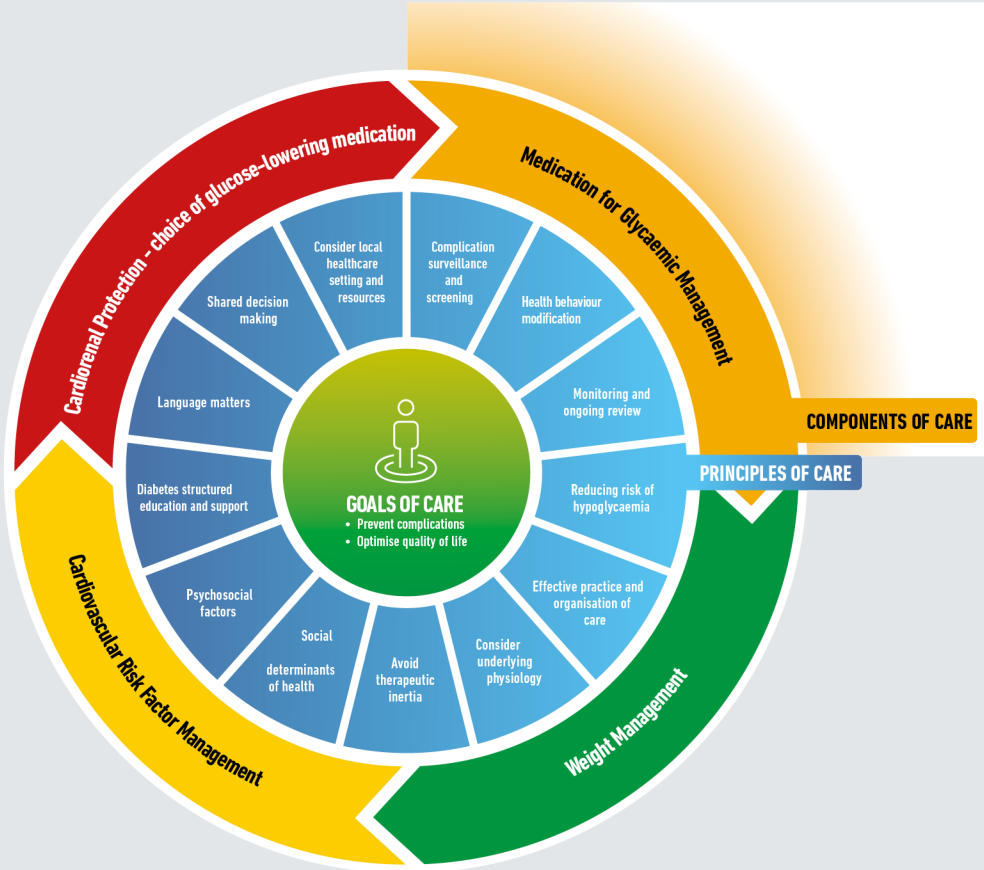
FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

Davies MJ, et al. *Diabetologia*. 2022;65:1925–1966. [Buse JB coauthor] Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786. [Buse JB coauthor] Graphical Abstract—Figure 4 American Diabetes Association *Diabetes Care*, American Diabetes Association, 2022.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

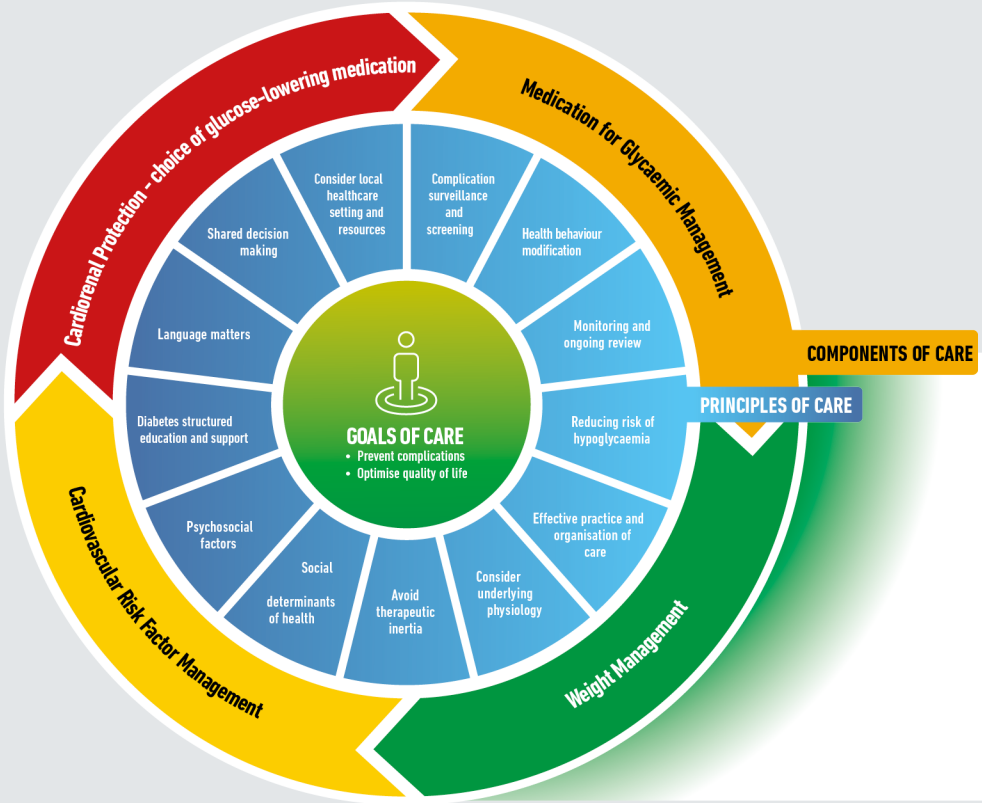
Consider avoidance of hypoglycaemia a priority in high-risk individuals

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity	Intensive evidence-based structured weight management programme
Consider medication for weight loss	Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

COMPONENTS OF CARE

PRINCIPLES OF CARE

Ensure strategies are in place to detect and optimise management of CV risk factors[1] including

- CV risk factor screening and surveillance
- BP lowering
- Lipid lowering
- Antithrombotic agents
- Smoking cessation

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

Davies MJ, et al. *Diabetologia*. 2022;65:1925–1966. [Buse JB coauthor] Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786. [Buse JB coauthor] Graphical Abstract—Figure 4 American Diabetes Association *Diabetes Care*, American Diabetes Association, 2022.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

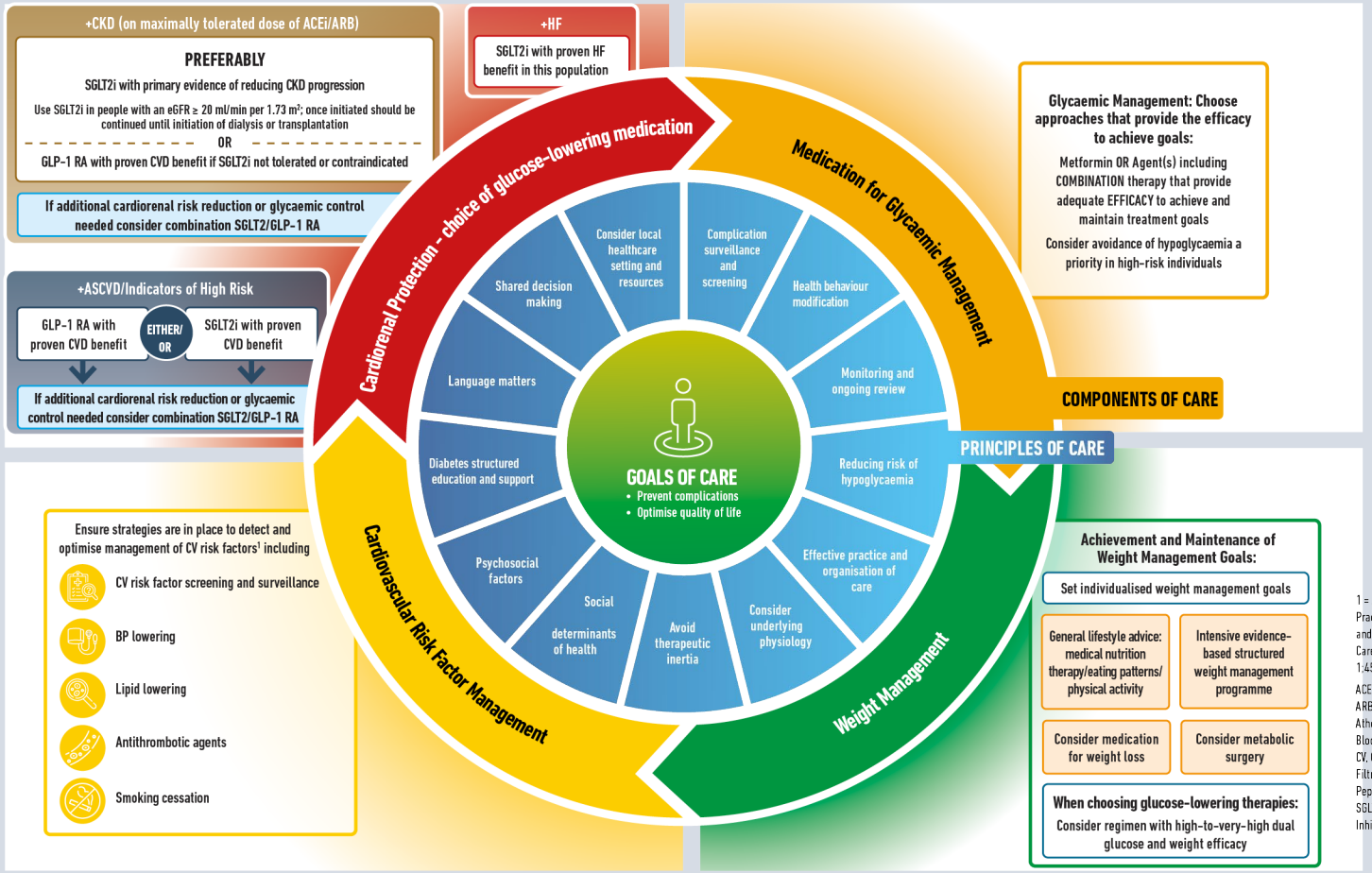
SGLT2i with proven HF benefit in this population

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

FIGURE 4: HOLISTIC PERSON–CENTRED APPROACH TO T2DM MANAGEMENT

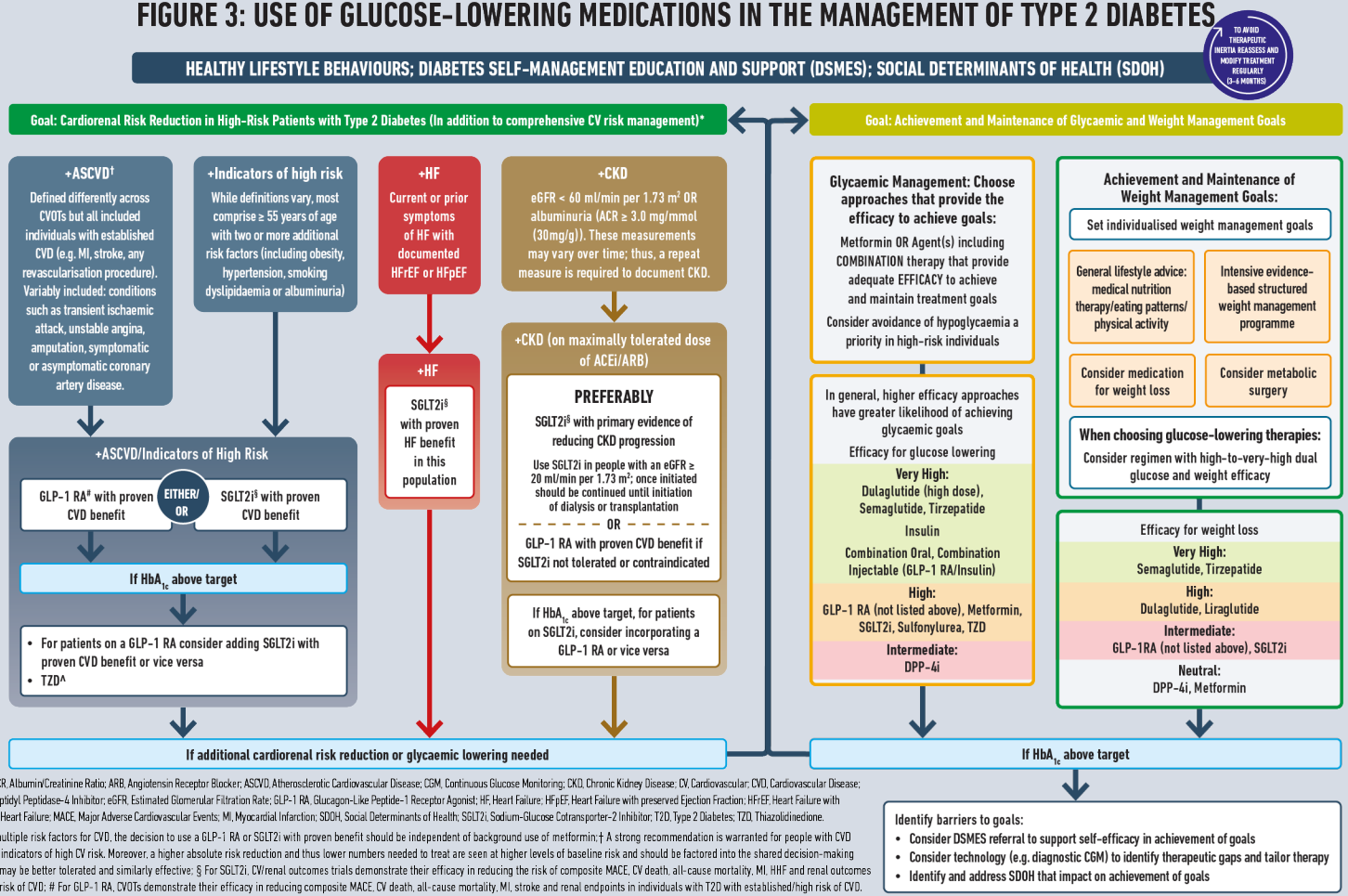


1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

Davies MJ, et al. *Diabetologia*. 2022;65:1925–1966. [Buse JB coauthor] Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786. [Buse JB coauthor] Graphical Abstract—Figure 4 American Diabetes Association *Diabetes Care*, American Diabetes Association, 2022.

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Davies MJ, et al. *Diabetologia*. 2022;65:1925–1966. [Buse JB coauthor] Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786. [Buse JB coauthor] Figure 3 American Diabetes Association *Diabetes Care*, American Diabetes Association, 2022.

Case #1 – Robyn | Part B

Question 2 of 5: PREVIEW

Robyn A., a 58-year-old woman with a 10-year history of type 2 diabetes, an 8-year history of hypertension and obesity (BMI=34 kg/m^2), is referred by her primary care provider to an endocrinologist for evaluation and management. One month ago, Robyn's primary care provider decreased glipizide from 10 mg twice daily to 5 mg twice daily, increased metformin 500 mg twice daily to 1000 mg twice daily, and continued pioglitazone 30 mg once daily and amlodipine 10 mg once daily. Despite these changes, Robyn continues to report episodes of hypoglycemia. The endocrinologist:

- Discontinued glipizide
- Initiated linagliptin 5 mg daily as patient is resistant to injectable therapy
- Initiated losartan 100 mg daily for blood pressure management in setting of diabetes
- Referred to dietitian for medical nutrition therapy

Over the next year, Robyn's hemoglobin A1C decreased to 7.1% and she had no further episodes of hypoglycemia. She is now being seen by her primary care provider for a routine follow-up.

Today's vitals reveal a blood pressure of 126/72 mmHg and heart rate of 84 beats/minute. Laboratory results reveal eGFR decreased from 70 to 52 mL/min/1.73 m^2 over the past 12 months and urine albumin-creatinine ratio (uACR) is increased at 80 mg/g.

Question 2 of 5

At what stage is her kidney disease?

A. CKD stage I
B. CKD stage II
C. CKD stage IIIa
D. CKD stage IIIb
E. CKD stage IV
F. CKD stage V

Question 2 of 5: DISCUSSION

The correct answer is C: *CKD stage IIIa*

- According to a study conducted in 2019 by Vistisen et al, the mean annual decline of eGFR after diagnosis of CKD stage III for patients with type 2 diabetes was 1.9 to 3.0 mL/min/1.73 m^2. A dramatic decrease of eGFR experienced by this patient (18 mL/min/1.73 m^2) may indicate rapidly progressive decline and warrants additional investigation and monitoring. [1]
- According to KDIGO's CKD staging (heatmap): the patient's eGFR of 52 mL/min/1.73 m^2 and albuminuria of 80 mg/g indicate the patient has stage IIIa kidney disease with mild to moderately decreased eGFR (G3a) and moderately increased albuminuria (A2). [2],[3]
- It is pertinent for healthcare providers to discuss the KDIGO staging heatmap with patients to improve awareness, risk mitigation, and treatment adherence. [2]

1. Vistisen D, et al. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function—even without albuminuria. *Diabetes Care.* 2019;42(10):1886-1894.
2. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022. *Kidney Int.* 102(5), 974–989.
3. de Boer IH, et al. *Diabetes Care.* 2022; dci220027.

CKD Staging Chart – ADA/KDIGO guidelines

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

CKD Staging Chart – ADA/KDIGO guidelines

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
High risk
Moderately increased risk
Very high risk

Question 3 of 5: PREVIEW

The primary care provider refers Robyn A. to a local nephrologist for further evaluation and treatment for her declining kidney function. Current medications:

- Metformin 1000 mg twice daily with meals
- Pioglitazone 30 mg once daily
- Linagliptin 5 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Question 3 of 5

Based on her stage IIIa CKD, which of the following changes should be made to the patient's medications at this time?

A. Discontinue metformin

B. Discontinue linagliptin

C. Initiate SGLT-2 inhibitor with cardiorenal benefit

D. Initiate GLP-1 receptor agonist with atherosclerotic cardiovascular benefit

Question 3 of 5: DISCUSSION

The correct answer is C: *Initiate SGLT-2 inhibitor with cardiorenal benefit*

- SGLT-2 inhibitor with primary evidence of reducing CKD progression is recommended. [1]
- A GLP-1 receptor agonist with atherosclerotic cardiovascular benefit is recommended for patients who do not tolerate or have a contraindication to an SGLT-2 inhibitor with primary evidence of reducing CKD progression. A GLP-1 receptor agonist can be added if the A1C is above target despite SGLT-2 inhibitor therapy. [1],[2]
- Although the patient's renal function has declined, the current metformin dose should be continued at an eGFR of 52 mL/min/1.73 m^2. At an eGFR of 30 to 44 mL/min/1.73 m^2, caution is recommended in initiating metformin, and for patients currently on metformin it is recommended to reduce to a maximum dose of 500 mg twice daily. Metformin is contraindicated for eGFR <30 mL/minute/1.73 m^2. [3]
- Linagliptin does not require renal dose adjustments and should be continued. [4]

Question 3 of 5: DISCUSSION

1. Davies MJ, et al. Management of hyperglycemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.
2. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022. *Kidney Int.* 102(5), 974–989.
3. Glucophage (metformin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2018.
4. Tradjenta (linagliptin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; April 2022.

Cardiorenal Effects of GLP-1 RAs

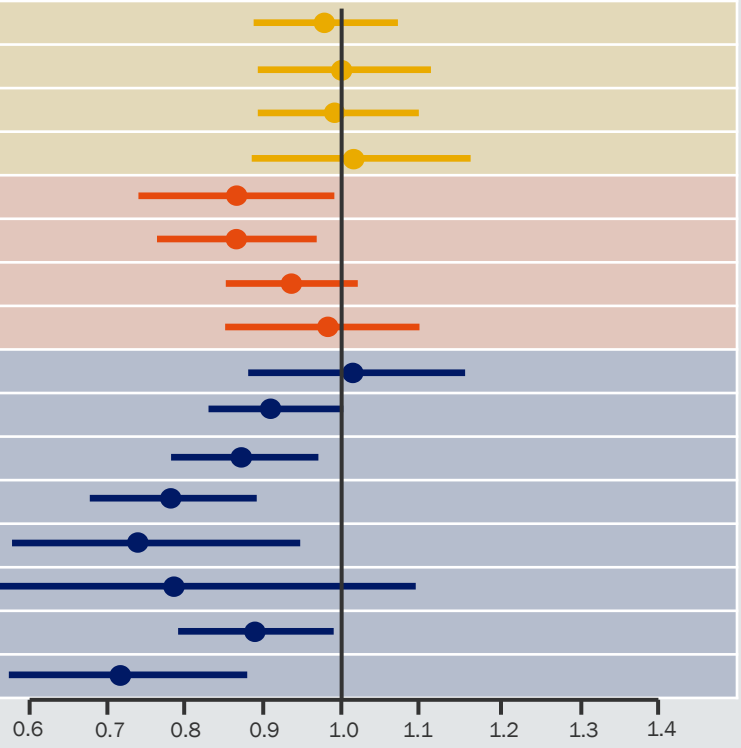
- Cardiovascular outcomes trials for GLP-1 RAs
- Meta-analysis of GLP-1 RA trials with emphasis on secondary kidney outcomes

Definition of Major Adverse Cardiac Events (MACE) & Secondary Kidney Outcomes

- 3-point MACE:
  - CV death, nonfatal myocardial infarction (MI), or nonfatal stroke
- 4-point MACE:
  - 3-point MACE + hospitalization for unstable angina/revascularization
- Composite kidney outcome:
  - Development of macroalbuminuria, doubling of serum creatinine or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease
- Worsening kidney function:
  - Doubling of serum creatinine or at least 40% decline in eGFR

CVOTs in Type 2 Diabetes (3P-MACE)

	Study	Compound	Primary endpoint	Hazard ratio (95% CI)
DPP-4 inhibitors	EXAMINE[1]	Alogliptin	3P-MACE	
	SAVOR[2]	Saxagliptin	3P-MACE	
	TECOS[3]	Sitagliptin	4P-MACE	
	CARMELINA[4]	Linagliptin	3P-MACE	
SGLT2 inhibitors	EMPA-REG[5]	Empagliflozin	3P-MACE	
	CANVAS[6]	Canagliflozin	3P-MACE	
	DECLARE[7]	Dapagliflozin	3P-MACE	
	VERTIS[8]	Ertugliflozin	3P-MACE	
GLP-1 receptor agonists	ELIXA[9]	Lixisenatide	4P-MACE	
	EXSCEL[10]	Exenatide	3P-MACE	
	LEADER[11]	Liraglutide	3P-MACE	
	HARMONY[12]	Albiglutide	3P-MACE	
	SUSTAIN-6[13]	Semaglutide	3P-MACE	
	PIONEER 6[14]	Oral semaglutide	3P-MACE	
	REWIND[15]	Dulaglutide	3P-MACE	
	AMPLITUDE[16]	Efpeglenatide	3P-MACE	

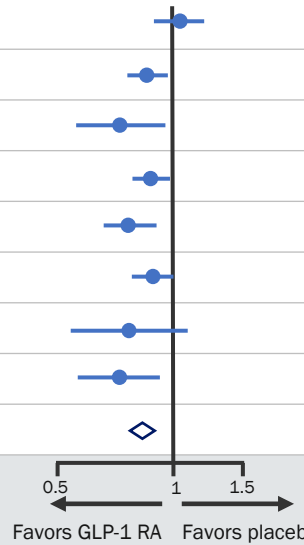


No direct comparisons of outcomes should be made between clinical trials.
3P, three-point; 4P, four-point; CI, confidence interval; CVOT, cardiovascular outcome trial; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose co-transporter-2.

1. White WB et al. *N Engl J Med.* 2013;369:1327–1335; 2. Scirica BM et al. *N Engl J Med.* 2013;369:1317–1326; 3. Green JB et al. *N Engl J Med.* 2015;373:232–424; 4. Rosenstock J et al. *JAMA.* 2019;321:69–79; 5. Zinman B et al. *N Engl J Med.* 2015;373:2117–2128; 6. Neal B et al. *N Engl J Med.* 2017;377:644–657; 7. Wiviott SD et al. *N Engl J Med.* 2018;380:347–357; 8. Cannon CP et al. *N Engl J Med.* 2020;383:1425–1435; 9. Pfeffer MA et al. *N Engl J Med.* 2015;373:2247–2257; 10. Holman RR et al. *N Engl J Med.* 2017;377:1228–1239; 11. Marso SP et al. *N Engl J Med.* 2016;375:311–322; 12. Hernandez AF et al. *Lancet.* 2018;392:1519–1529; 13. Marso SP et al. *N Engl J Med.* 2016;375:1834–1844; 14. Husain M et al. *N Engl J Med.* 2019;381:841–851; 15. Gerstein HC et al. *Lancet.* 2019;394:121–130; 16. Gerstein HC et al. *N Engl J Med.* 2021;385:896–907.

Meta-analysis of GLP-1 RA CVOTs in Type 2 Diabetes at high risk for CVD

	GLP-1 Receptor Agonist, n/N (%)	Placebo n/N (%)		Hazard Ratio (95% CI)	NNT (95% CI)	*P* Value
3-point MACE						
ELIXA (lixisenatide)	400/3034 (13%)	392/3034 (13%)		1.02 (0.89, 1.17)		.78
LEADER (liraglutide)	608/4668 (13%)	694/4672 (15%)		0.87 (0.78, 0.97)		.01
SUSTAIN-6 (semaglutide SQ)	108/1648 (7%)	146/1649 (9%)		0.74 (0.58, 0.95)		.016
EXSCEL (exenatide OW)	839/7356 (11%)	905/7396 (12%)		0.91 (0.83, 1.00)		.061
Harmony Outcomes (albi – NA)	338/4731 (7%)	428/4732 (9%)		0.78 (0.68, 0.90)		.0006
REWIND (dulaglutide)	594/4949 (12%)	663/4952 (13%)		0.88 (0.79, 0.99)		.026
PIONEER 6 (oral semaglutide)	61/1591 (4%)	76/1592 (5%)		0.79 (0.57, 1.11)		.17
AMPLITUDE-O (investigational)	189/2717 (7%)	125/1359 (9%)		0.73 (0.58, 0.92)		.0069
Subtotal (I^2 = 44.5%, P = .082)				**0.86 (0.80, 0.93)**	**65 (45, 130)**	**< .0001**



Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs were calculated over a weighted average median follow-up of 3.0 years. P values are for superiority. Efpeglenatide not FDA-approved. Not all agents and formulations are indicated for cardiovascular risk reduction. CVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular event; NNT, number needed to treat.

Sattar N, et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662. Adapted from Figure 2.

Meta-analysis of GLP-1 RA CVOTs in Type 2 Diabetes at high risk for CVD

Outcome	HR (95% CI)	NNT	*P* value	Heterogeneity
MACE-3	0.86 (0.80, 0.93)	65 (45, 130)	< .0001	Marginal
CV death	0.87 (0.80, 0.94)	163 (103, 353)	0.001	No
Fatal and nonfatal MI	0.90 (0.83, 0.98)	175 (103, 878)	0.02	No
Fatal and nonfatal stroke	0.83 (0.76, 0.92)	198 (140, 421)	0.0002	No
All-cause mortality	0.88 (0.82, 0.94)	114 (76, 228)	0.0001	No
Hospital admission for HF	0.89 (0.82, 0.98)	258 (158, 1422)	0.013	No
Composite kidney outcome including macroalbuminuria	0.79 (0.73, 0.87)	47 (37, 77)	< .0001	Marginal
Worsening of kidney function	0.86 (0.72, 1.02)	241 (120 to 1694)	0.089	No

Efpeglenatide not FDA-approved. Not all agents and formulations are indicated for cardiovascular risk reduction.
CVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular event; NNT, number needed to treat.

Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;9:653-662. Table not in print.

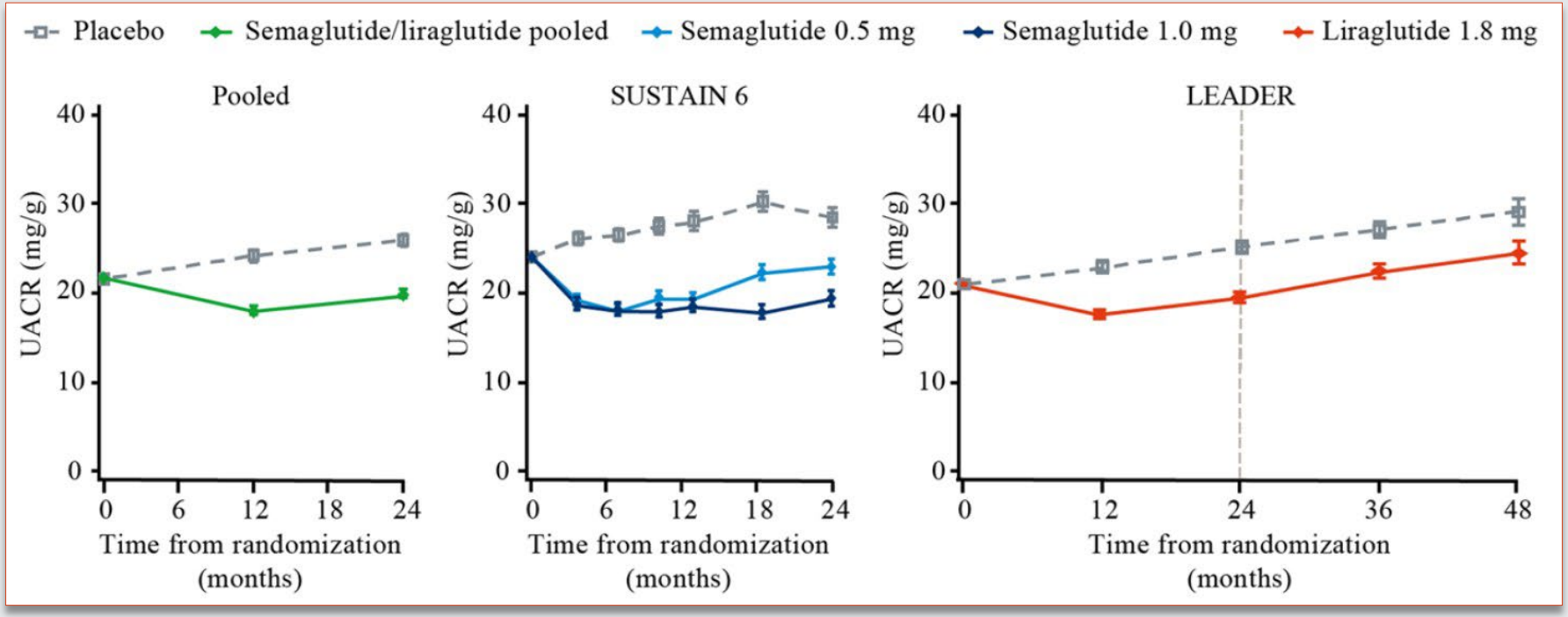
Meta-analysis of GLP-1 RA CVOTs in Type 2 Diabetes at high risk for CVD

Adverse event	Odds ratio (95% CI)	*P* value	Heterogeneity
Severe hypoglycemia	0.90 (0.74, 1.10)	0.32	Yes
Retinopathy	1.07 (0.92, 1.25)	0.39	Marginal
Pancreatitis	1.02 (0.77, 1.36)	0.88	No
Pancreatic cancer	0.98 (0.56, 1.70)	0.93	No

Efpeglenatide not FDA-approved. Not all agents and formulations are indicated for cardiovascular risk reduction.
CVOT, cardiovascular outcomes trial.

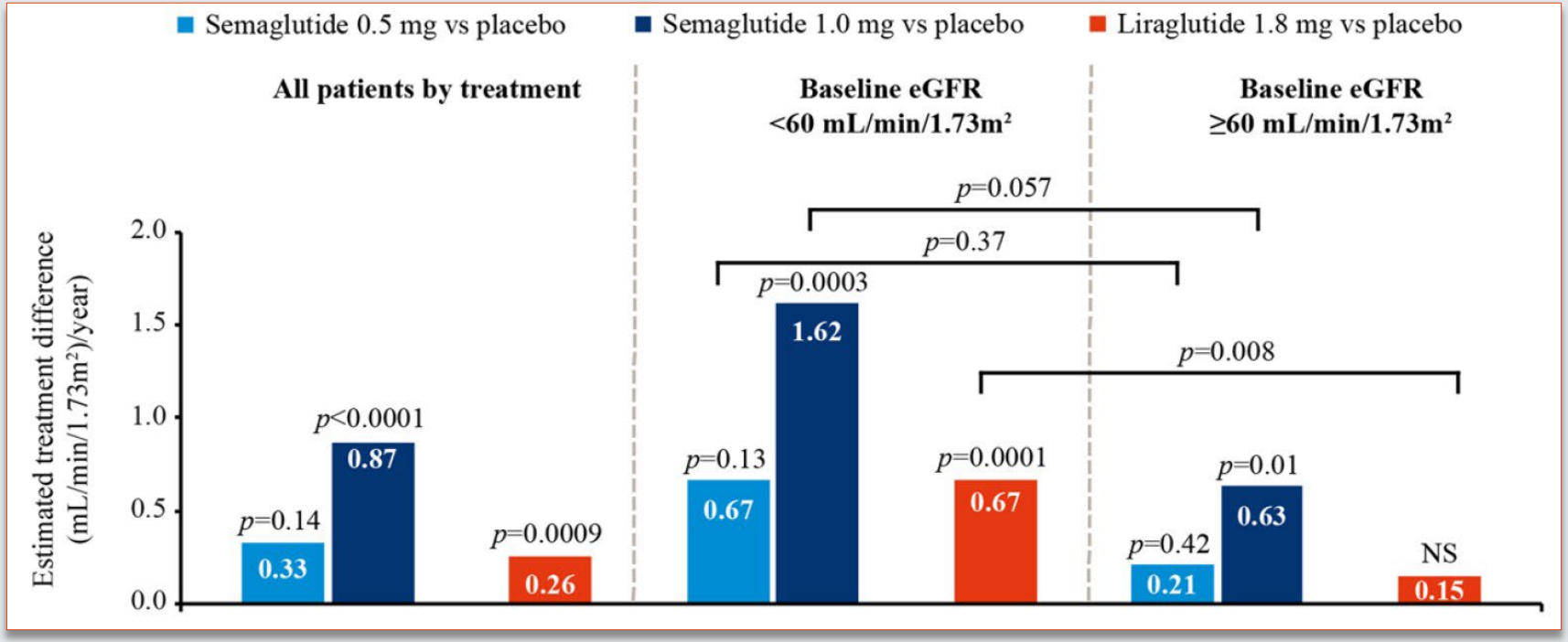
Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;9:653-662. Table not in print.

Effects of once-weekly semaglutide and once-daily liraglutide vs placebo on albuminuria over time



UACR urinary albumin-to-creatinine ratio.

Effects of once-weekly semaglutide and once-daily liraglutide vs placebo on albuminuria over time



Shaman AM, et al. *Circulation*. 2022;145:575–585. [Bakris GL, Buse JB coauthors] Figure 1 used under terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) License.

Meta-analysis of GLP-1 RA CVOTs

Composite kidney outcome including macroalbuminuria

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0.84 (0.68-1.02)		0.083
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67-0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46-0.88)		0.005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76-1.01)		0.065
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77-0.93)		0.0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0.68 (0.57-0.79)		<0.0001
Subtotal (I^2=47.5%, p=0.090)			**0.79 (0.73-0.87)**	**47 (37-77)**	**<0.0001**

Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Data on kidney outcomes were not available in Harmony outcomes and PIONEER 6. The composite kidney outcome consisted of development of macroalbuminuria, doubling of serum creatinine or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease; for ELIXA, data are for new-onset macroalbuminuria alone NNTs were calculated over a weighted average median follow-up of 3.4 years.

CVOTs. cardiovascular outcome trials; GLP-1, glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; NNT, number needed-to-treat.

Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662. Adapted from Figure 3.

Meta-analysis of GLP-1 RA CVOTs

Worsening of kidney function

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1.16 (0.74-1.83)		0.513
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67-1.19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64-2.58)		0.48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74-1.05)		0.16
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57-0.85)		0.0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0.35 (0.10-1.27)		0.11
Subtotal (I^2=43.0%, p=0.12)			**0.86 (0.72-1.02)**	**241 (120 to -1694)***	**0.089**

Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Data on kidney outcomes were not available in Harmony outcomes and PIONEER 6. The worsening of kidney function outcome was defined as either doubling of serum creatinine or at least 40% decline in eGFR; for EXSCEL, the worsening of kidney function outcome included kidney replacement therapy, or death due to kidney disease. NNTs were calculated over a weighted average median follow-up of 3.4 years; *negative value indicates a number needed to harm

CVOTs. cardiovascular outcome trials; GLP-1, glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; NNT, number needed-to-treat.

Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662. Adapted from Figure 3.

Multidisciplinary Management

- Benefits of utilizing the multidisciplinary team in patient care
- ADA/EASD and ADA/KDIGO recommendations

Benefits of the Multidisciplinary Care Team

- Improved health outcomes
- Enhanced patient satisfaction
- Efficient use of resources
- Enhanced job satisfaction for team members

- Utilization/role of the multidisciplinary care team
  - One organizational umbrella or range of organizations?
  - Primary care/community health nurses/allied professionals
  - Agreed upon systems for effective communication

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

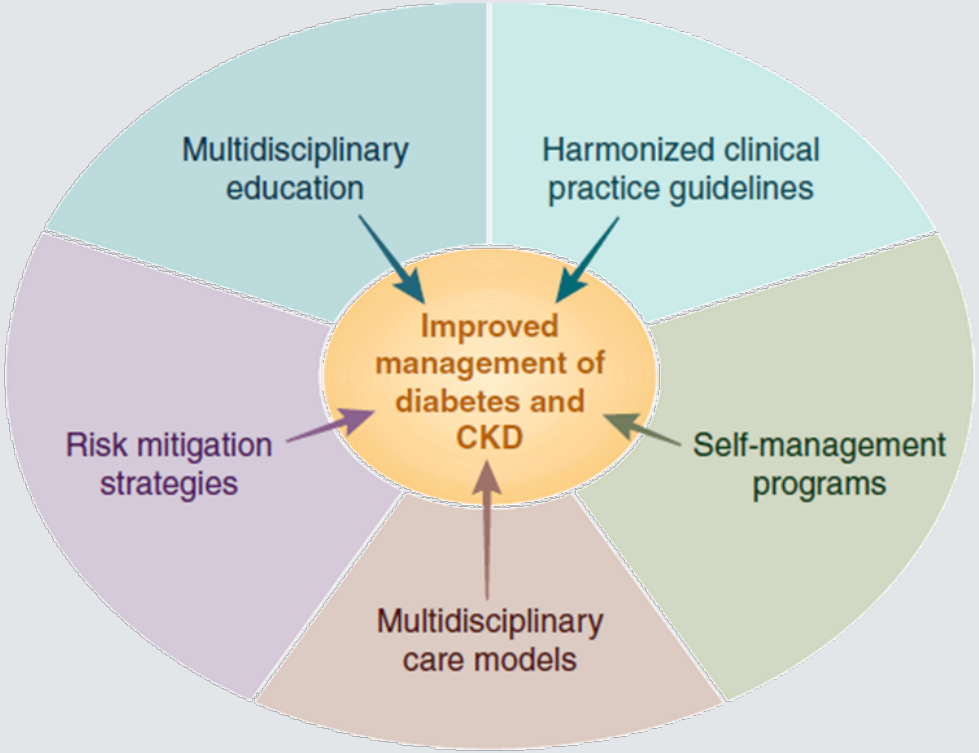
SGLT2i with proven HF benefit in this population

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

ADA/KDIGO: Overcoming barriers



Case #1 – Robyn | Part C

Question 4 of 5: PREVIEW

Robyn A., a 59-year-old woman with an 11-year history of type 2 diabetes (hemoglobin A1C 7.1%), is evaluated by a nephrologist in follow-up. The patient was diagnosed 7 months ago with stage IIIa chronic kidney disease with albuminuria. The patient was prescribed losartan and the SGLT-2 inhibitor empagliflozin for diabetic kidney disease standard of care, but she discontinued empagliflozin because of frequent genital mycotic infections. Current medications:

- Metformin 1000 mg twice daily with meals
- Linagliptin 5 mg once daily
- Pioglitazone 30 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Laboratory results reveal an eGFR 48 mL/min/1.73 m^2.

Question 4 of 5

Which one of the following classes of medication should replace empagliflozin in this patient?

A. Alpha-glucosidase inhibitor

B. Glucagon-like peptide-1 receptor agonist with atherosclerotic cardiovascular benefit

C. Sulfonylurea

D. Basal insulin

Question 4 of 5: DISCUSSION

The correct answer is B: *Glucagon-like peptide-1 receptor agonist with atherosclerotic cardiovascular benefit*

- Of these 4 classes of medications, only selected GLP-1 receptor agonists have demonstrated benefit in kidney outcomes. A GLP-1 receptor agonist with atherosclerotic cardiovascular benefit is recommended for patients who do not tolerate or have a contraindication to an SGLT-2 inhibitor.[1]

1. Davies MJ, et al. Management of hyperglycemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.

Question 5 of 5: PREVIEW

After receiving education from the patient's nephrologist, Robyn A. is now amenable to injectable therapy if warranted. Current medications:

- Metformin 1000 mg twice daily with meals
- Linagliptin 5 mg once daily
- Pioglitazone 30 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Question 5 of 5

Which GLP-1 receptor agonist would be the best choice for this patient with chronic kidney disease?

A. Exenatide IR 5 mcg SQ twice daily within 60 minutes prior to meals

B. Lixisenatide 10 mcg SQ once daily x 14 days and titrate per directions

C. Semaglutide 0.25 mg SQ once weekly x 4 weeks and titrate per directions

D. Semaglutide 3 mg PO once daily x 30 days and titrate per directions

Question 5 of 5: DISCUSSION

The correct answer is C: *Semaglutide 0.25 mg SQ once weekly x 4 weeks and titrate per directions*

- Injectable semaglutide has been shown to confer kidney benefits, whereas oral semaglutide, exenatide, and lixisenatide have not. [1],[2]
- Liraglutide and dulaglutide, also shown to confer kidney benefits, are alternatives to injectable semaglutide. [1],[2]
- The decision to select a once-weekly or once-daily GLP-1 RA (with atherosclerotic cardiovascular benefit) should be discussed with the patient, and factors such as ease of administration, adverse effects, medication costs, and formulary options should be considered.
- In a patient that is highly resistant to injectable therapy, oral semaglutide can be a consideration, however, it is important to note that oral semaglutide has not been proven to confer cardiorenal benefits. [1],[2]
- Linagliptin should be discontinued as DPP-IV inhibitors and GLP-1 receptor agonists should not be used together due to similar mechanisms of action causing lack of therapeutic benefit. [3]

Question 5 of 5: DISCUSSION

1. Davies MJ, et al. Management of hyperglycemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.
2. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022. *Kidney Int.* 102(5), 974–989.
3. Tradjenta (linagliptin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; April 2022.

Case #2 – Jerry

Question 1 of 3: PREVIEW

Jerry W. is a 73-year-old man who presented to his primary care provider 2 weeks ago after being lost to follow-up for several years. He is now being seen in follow-up. Diagnostic evaluation reveals type 2 diabetes (A1C 8.7%).

Patient has a history of NSTEMI s/P PCI (8 months ago), hyperlipidemia x 11 years (LDL-C 53 mg/dL), hypertension x 14 years (BP 138/82 mmHg), and CKD stage IV (eGFR 19 mL/min/1.73 m^2). Patient is prescribed: empagliflozin, losartan, atorvastatin, aspirin, clopidogrel, carvedilol, and furosemide.

Question 1 of 3

What additional information is pertinent to obtain from this patient?

A. Labs/Data, including uACR, potassium, BMI

B. Medication adherence history

C. Patient awareness of CKD significance

D. All of the above

Question 1 of 3: DISCUSSION

The correct answer is D: *All of the above*

- The patient has history of CKD, therefore, related information such as uACR as well as potassium and body mass index may provide pertinent information to guide treatment options. [1]
- According to a study conducted by Neuen et al, the combination of an increase in uACR and a decrease in eGFR was strongly associated with increased risk of advanced CKD than either parameter alone. [2]
- An increase in uACR can be viewed as an inflammatory maker to portray the magnitude of kidney damage, whereas a decrease in eGFR is evidence of functional impairment.
- The patient has been lost to follow-up for several years, therefore discussion on medication adherence is significant before decisions for medication therapy are made.
- It is of utmost importance that patients understand the natural history of their disease as this is often very motivating for treatment.

Question 1 of 3: DISCUSSION

- It is also important to not reprimand the patient for being lost to follow-up. Education is crucial to ensure the patient is empowered to work with the healthcare team to potentially alter the course of their disease.

1. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022. *Kidney Int.* 102(5), 974–989.
2. Neuen BL, et al. Changes in GFR and albuminuria in routine clinical practice and the risk of kidney disease progression. *Am J Kidney Dis.* 2021;78(3):350-360.e1.

Question 2 of 3: PREVIEW

Additional laboratory information reveals:

- uACR 160 mg/g
- K+ 4.8 mEq/L
- BMI 36.4 kg/m^2

Jerry W. indicates he is motivated to take better care of himself as he does not want to suffer another CV event. He is committed to following the treatment plan, with his family's support. Current medications:

- Empagliflozin 10 mg PO once daily
- Losartan 50 mg PO once daily
- Atorvastatin 80 mg PO once daily
- Aspirin 81 mg PO once daily
- Clopidogrel 75 mg PO once daily
- Carvedilol 25 mg PO twice daily
- Furosemide 40 mg PO once daily

Question 2 of 3

Which one of the following would be the most appropriate change to the patient's current medications?

A. Add liraglutide 0.6 mg SQ once daily

B. Add finerenone 20 mg PO once daily

C. Add metformin 500 mg PO twice daily

D. Replace losartan with hydrochlorothiazide 12.5 mg PO once daily

Question 2 of 3: DISCUSSION

The correct answer is A: *Add liraglutide 0.6 mg SQ once daily*

- Liraglutide, similar to injectable semaglutide and dulaglutide, is a GLP-1 RA that has exhibited atherosclerotic cardiovascular benefit in patients with/or at risk for ASCVD and CKD. Per ADA/KDIGO guidelines, selected GLP-1 RAs can be considered as an option in patients with DKD who require additional glucose-lowering. [1]
- Liraglutide is a viable option in patients that prefer once-daily administration and for those who experience nausea/vomiting since these adverse events resolve more quickly than once-weekly GLP-1 RAs.
- The decision to select a once-weekly or once-daily GLP-1 RA (with atherosclerotic cardiovascular benefit) should be discussed with the patient, and factors such as ease of administration, adverse effects, medication costs, and formulary options should be considered.
- The addition of a mineralocorticoid receptor antagonist (finerenone) to ACEI or ARB therapy provides additional benefit in kidney outcomes, however, finerenone is contraindicated in eGFR <25 mL/minute/1.73 m^2. [1],[2]

Question 2 of 3: DISCUSSION

- Metformin is contraindicated in eGFR <30 mL/minute/1.73 m^2. [3]
- ACEI or ARB therapy is standard of care for patients with diabetic kidney disease, therefore it is important to continue losartan in this patient. [1]

1. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022. *Kidney Int.* 102(5), 974–989.
2. Kerendia (finerenone) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; September 2022.
3. Glucophage (metformin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2018.

Question 3 of 3

What other healthcare clinicians should be involved in the care of this patient?

A. Cardiologist

B. Endocrinologist

C. Nephrologist

D. Pharmacist

E. All of the above

Question 3 of 3: DISCUSSION

The correct answer is E: *All of the above*

- Multidisciplinary and interprofessional care is important to address the variety of health issues experienced by patients with type 2 diabetes, chronic kidney disease, and cardiovascular disease.
- Due to the patient's history of recent NSTEMI, hypertension, and hyperlipidemia, it would be beneficial to involve a cardiologist in this patient's care.
- Due to the patient's history of uncontrolled diabetes (A1C 8.7%), an endocrinologist can assist with adjusting patient's antihyperglycemic regimen. However, not every patient may be able to see an endocrinologist due to availability; it is important that primary care providers are educated to be able to work with the patient to directly address their treatment regimen for diabetes.

Question 3 of 3: DISCUSSION

- Due to the patient's history of CKD Stage IV (eGFR 19 mL/minute/1.73 m^2 and uACR 160 mg/g), it is important to involve a nephrologist in this patient's care. It is recommended to refer a patient to a nephrologist when their eGFR is < 30 mL/minute/1.73 m^2. According to a study conducted by Kinchen et al, late referral (defined as less than 4 months from initiation of dialysis) was associated with greater burden of disease and reduced survival. [1]
- This patient is on multiple medications and involving a pharmacist would assist with addressing potential polypharmacy, medication compliance, pharmacotherapy monitoring, and drug-drug interactions.

1. Kinchen KS, et al. The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med.* 2002;137(6):479.

Summary & Conclusions

- Overview of content discussed from modules 1 to 10
- Important take-home points for clinicians to optimize patient care

Overview

- There is an urgent need for guideline directed screening and early treatment of patients with T2DM and CKD
- Pillars of therapy to reduce cardiorenal risk include RAAS blockade, SGLT2 inhibitors, and NS-MRA (finerenone)
- GLP1 RAs remain a potent option for glycemic lowering as well as CV risk reduction, with favorable data thus far on composite kidney outcomes including macroalbuminuria
- ADA/EASD guidelines focus on a holistic person-centered approach to T2DM management
- Effective person-centered care requires a multidisciplinary care team

Take-Home Points

- Make screening for CKD a priority in patients with T2D
- Current therapies allow a new opportunity to alter the course of both CKD progression and CV risk in patients with T2D
- Always keep the patient at the center of the conversation and involved in shared decision-making
- Communicate with colleagues and ensure the sharing of important information