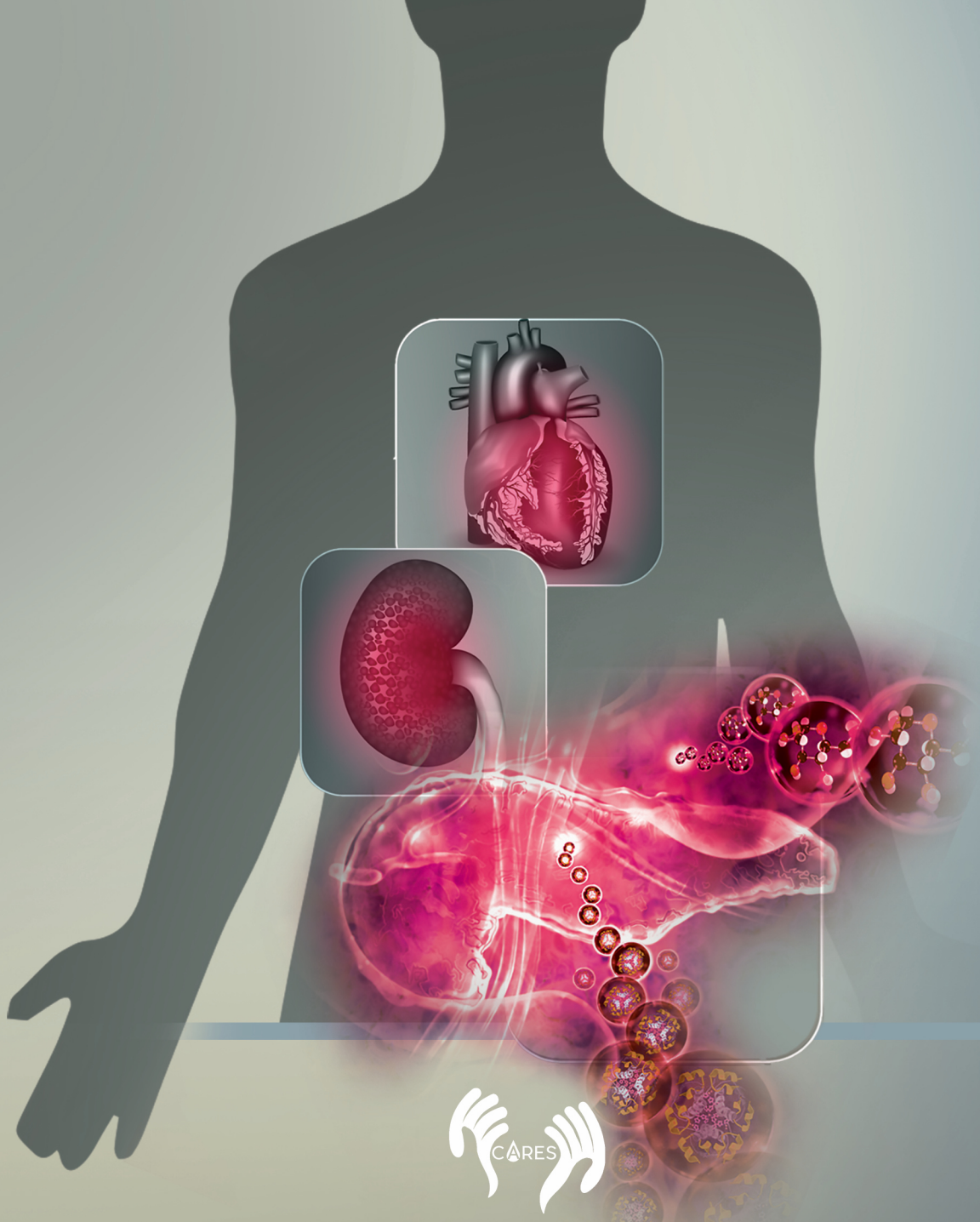

THE CARES APPROACH:

Improving Glycemic, Cardiovascular and Renal Outcomes

MEETING INFO

Wednesday, October 14, 2020
6:00 PM – 8:00 PM Eastern
5:00 PM – 7:00 PM Central

FACULTY

Silvio E. Inzucchi, MD
Director, Yale Medicine Diabetes Center
Professor of Medicine, Endocrinology
Yale University School of Medicine
New Haven, CT

Anne L. Peters, MD
Professor of Medicine
Keck School of Medicine
University of Southern California
Westside Center for Diabetes
Los Angeles, CA

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by educational grants from Lilly, Boehringer Ingelheim Pharmaceuticals and Lilly, and Merck & Co., Inc.

AGENDA

All times are in Eastern Standard Time

	Slide Numbers and Times	Section Time
Faculty Introductions, Pretest, Agenda (Inzucchi)	1-10 (6:00-6:15pm)	15 mins
Part 1 – What we treat: definitions, diagnosis, and pathogenesis (Inzucchi)	11-20 (6:15-6:25pm)	10 mins
Part 2 – Why we treat: reducing long-term complications (Peters)	21-32 (6:25-6:35pm)	10 mins
Part 3 – How we treat: major glucose-lowering drug classes (Peters)	33-36 (6:35-6:40pm)	5 mins
Part 4a– When to use newer therapies: SGLT2 inhibitors (Inzucchi)	37-56 (6:40-7:00pm)	20 mins
Part 4b– When to use newer therapies: GLP-1 receptor agonists (Peters)	57-70 (7:00-7:20pm)	20 mins
Part 5 – Where are we going? New T2DM treatment guidelines (Inzucchi)	71-80 (7:20-7:30pm)	10 mins
Conclusions (Inzucchi)	81 (7:30-7:33pm)	3 mins
Infographics Case Demonstrations (Peters)	82-98 (7:33-7:40pm)	7 mins
Posttest (Inzucchi)	99-104 (7:40-7:50pm)	10 mins
Questions & Answers (Inzucchi and Peters)	105 (7:50-8:00pm)	10 mins

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The CARES Approach:

Improving Glycemic, Cardiovascular, and Renal Outcomes

Co-Chairs

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- Personalize the selection of therapies for the management of cardiovascular and renal risk in patients with T2DM based on up-to-date standards of care
- Determine the clinical implications of results from cardiovascular outcomes trials of SGLT2 inhibitors and GLP-1 receptor agonists
- Utilize guidelines-based strategies for treatment intensification in patients with T2DM not meeting their glycemic goals

Target Audience

This educational activity is intended for cardiologists, endocrinologists, primary care physicians, NPs, PAs, nurses, and other clinicians involved in the treatment of patients with type 2 diabetes mellitus (T2DM).

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 2.00 *AMA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the virtual live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with type 2 diabetes mellitus. Credits: 2.00 ANCC Contact Hour(s)

ACCREDITATION STATEMENT

Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 2.00 contact hour(s) of continuing nursing education of RNs and APNs.

AAFP CREDIT INFORMATION This Virtual Live activity, The CARES Approach: Improving Glycemic, Cardiovascular, and Renal Outcomes, from 10/01/2020 - 10/01/2021, has been reviewed and is acceptable for up to 1.75 Elective credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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ACCREDITATION STATEMENT In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Med Learning Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

PHARMACISTS AND PHARMACY TECHNICIANS Amedco LLC designates this activity for a maximum of 2.0 knowledge-based CPE contact hours. NOTE: The only official Statement of Credit is the one you pull from CPE Monitor. You must request your certificate within 30 days of your participation in the activity to meet the deadline for submission to CPE Monitor.

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Dr. Peters discloses that she is on the speakers' bureau for Novo Nordisk. She is a consultant for Abbott Diabetes Care, Becton Dickinson, Boehringer Ingelheim, Eli Lilly and Company, Lexicon, Livongo, MannKind, Medscape, Merck, Novo Nordisk, Omada Health, OptumHealth, Sanofi, and Zafgen. Dr. Peters has also received research support from AstraZeneca, Dexcom, and MannKind and donated devices from Abbott Diabetes Care.

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The reviewer of this activity has nothing to disclose.

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Lauren Welch, MA, VP, Outcomes and Accreditation for Med Learning Group has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the web-based live activity.
3. Complete and submit the evaluation form to Med Learning Group.

You will receive your certificate after the web-based live activity.

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For CME questions, please contact Med Learning Group at info@medlearninggroup.com

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Provided by Med Learning Group

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The CARES Approach: Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

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Los Angeles, CA

Disclosures

- **Dr. Inzucchi** discloses that he is consultant for Boehringer Ingelheim, AstraZeneca, Sanofi/Lexicon, Novo Nordisk, Merck, vTv Therapeutics, Zafgen, Abbott/Alere, Eisai (TIMI). He has also received royalties from McGraw-Hill and Uptodate and has received salary from Elsevier.
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- Personalize the selection of therapies for the management of cardiovascular and renal risk in patients with T2DM based on up-to-date standards of care
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Pretest Questions

Dr. Inzucchi

Question 1

Meta-analyses for the SGLT2 inhibitor trials EMPA-REG, CANVAS, and DECLARE-TIMI demonstrated which of the following?

a. Reduced hazard ratios for the progression of chronic kidney disease with SGLT2 inhibitors vs placebo
b. Reduced hazard ratios for the development of bone fractures with SGLT2 inhibitors vs placebo
c. Increased hazard ratios for MACE with SGLT2 inhibitors vs placebo
d. Increased hazard ratios for heart failure hospitalizations with SGLT2 inhibitors vs placebo

Question 2

Meta-analyses for the GLP-1 receptor agonist trials LEADER, SUSTAIN 6, REWIND, and HARMONY demonstrated which of the following?

a. Increased hazard ratios for heart failure hospitalizations with GLP-1 receptor agonists vs placebo
b. Increased hazard ratios for MACE with GLP-1 receptor agonists vs placebo
c. Reduced hazard ratios for bone fractures with GLP-1 receptor agonists vs placebo
d. Reduced hazard ratios for stroke with GLP-1 receptor agonists vs placebo

Question 3

A 60-year-old man with T2DM and obesity has a HbA1c of 7.8 on metformin and a SGLT2 inhibitor. He has had trouble losing weight. What would be the most appropriate for treatment intensification in this patient based on current consensus guidelines?

a. A DPP-4 inhibitor
b. A GLP-1 receptor agonist
c. A sulfonylurea
d. Basal insulin

Question 4

When intensifying T2DM therapy for a patient with cardiovascular disease, which of the following agents has had positive results regarding reduction of major adverse cardiovascular events (MACE) based on cardiovascular outcomes trials (CVOTs)?

a. Saxagliptin
b. Lixisenatide
c. Ertugliflozin
d. Dulaglutide

Question 5

A 45-year-old woman with obesity has uncontrolled T2DM on metformin and a DPP-4 inhibitor. What would be the most appropriate intervention to add to her current treatment regimen for treatment intensification based on current consensus guidelines when cost is not a factor?

a. A GLP-1 receptor agonist
b. A SGLT2 inhibitor
c. A sulfonylurea
d. Pioglitazone

AGENDA: Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

1. ***What*** we treat: definitions, diagnosis, and pathogenesis (Dr. Inzucchi)
2. ***Why*** we treat: reducing long-term complications (Dr. Peters)
3. ***How*** we treat: major glucose-lowering drug classes (Dr. Peters)
4. ***When*** to use newer therapies
   - SGLT2 inhibitors (Dr. Inzucchi)
   - GLP-1 receptor agonists (Dr. Peters)
5. ***Where*** are we going? New T2DM treatment guidelines (Dr. Inzucchi)

SGLT2 = sodium-glucose cotransporter 2; GLP-1 = glucagon-like peptide 1; T2DM = type 2 diabetes mellitus.

Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

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Diabetes Mellitus: *Definition*

- Diabetes mellitus is a chronic disease manifested by high blood glucose (sugar) levels that is caused by a lack of or insufficient action of the hormone **insulin**
- Over time, diabetes leads to long-term complications, mainly involving blood vessels and the organs they feed, negatively impacting the quality and, in some circumstances, duration of life

Diagnosis of Diabetes

	ADA Pre-1997	ADA 1997–2009	ADA 2010
Fasting plasma glucose (FPG)	≥140 mg/dL (7.8 mmol/L)	≥126 mg/dL (7.0 mmol/L)	≥126 mg/dL* (7.0 mmol/L)
2-hour PG during OGTT	≥200 mg/dL (11.1 mmol/L)	≥200 mg/dL (11.1 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Random ("casual") PG*		≥200 mg/dL (11.1 mmol/L)	≥200 mg/dL (11.1 mmol/L)
HbA1c	—	—	≥6.5%†

*If accompanied by classic hyperglycemic symptoms; †If FPG and HbA1c results are discordant, default to most abnormal test.

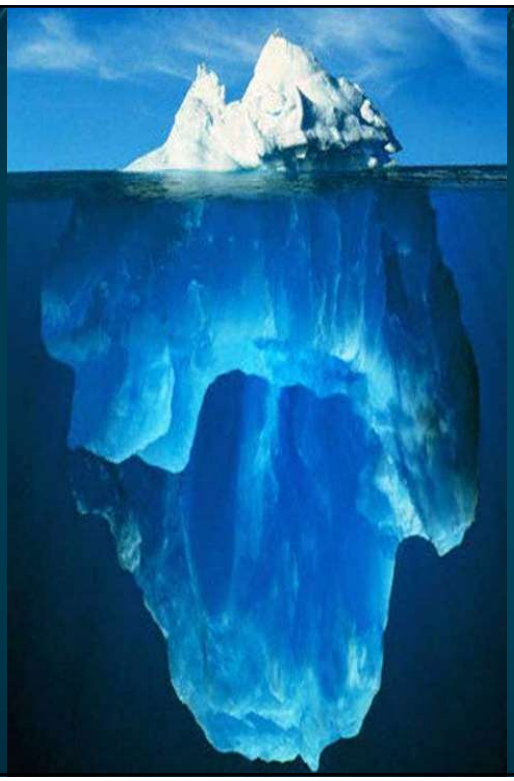
ADA = American Diabetes Association; PG = plasma glucose; OGTT = oral glucose tolerance test; HbA1c = glycosylated hemoglobin.

Mayfield J. *Am Fam Physician*. 1998;58:1355-1362, 1369-1370. ADA. *Diabetes Care*. 2010;33(suppl 1): S62-S69.

At-Risk States ("Pre-Diabetes")

	ADA 1997–2003	ADA 2003–2010	ADA 2010
FPG "Impaired fasting glucose (IFG)"	110–125 mg/dL (6.1–6.9 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L)
2-h PG (OGTT) "Impaired glucose tolerance (IGT)"	140–199 mg/dL (7.8–11.1 mmol/L)	140–199 mg/dL (7.8–11.1 mmol/L)	140–199 mg/dL (7.8–11.1 mmol/L)
HbA1C "High risk"	—	—	5.7 to <6.5%

Mayfield J. *Am Fam Physician*. 1998;58:1355-1362, 1369-1370. ADA. *Diabetes Care*. 2010;33(suppl 1): S62-S69.



34.2 million with diabetes

88 million with prediabetes

Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report—2020 (www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Accessed September 18, 2020.

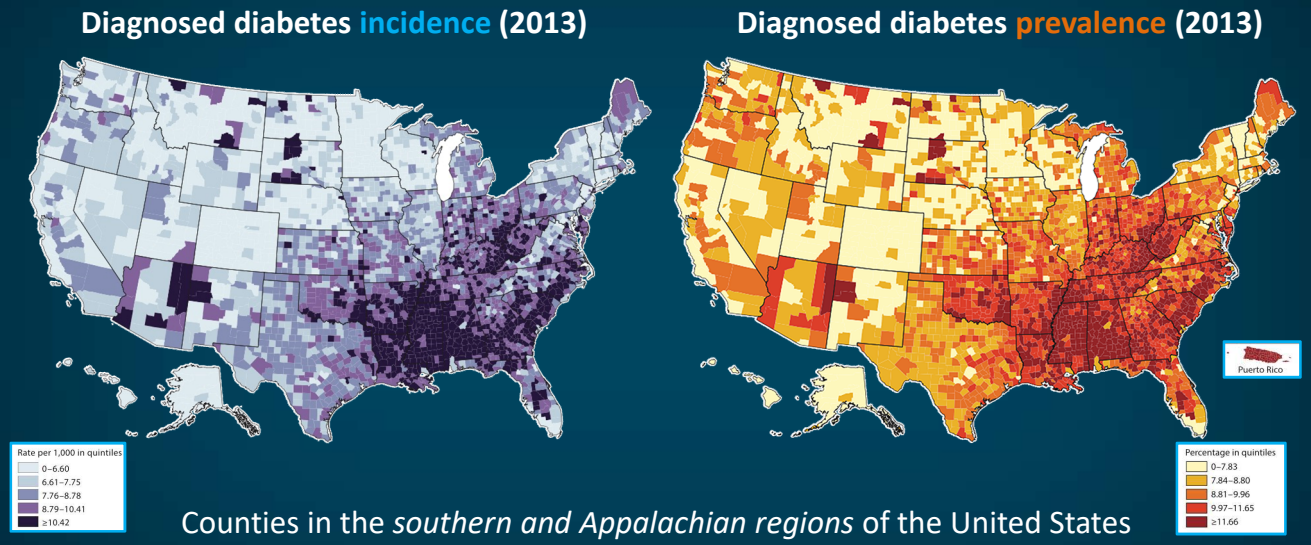
Criteria for Screening for Diabetes

1. Testing should be considered in all adults who are overweight and have additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (eg, Black, Latino, Native American, Asian American, Pacific Islander)
   - Women diagnosed with GDM
   - Hypertension (>140/90 mmHg or on therapy for hypertension)
   - History of CVD
   - HDL cholesterol <35 mg/dL and/or triglycerides >250 mg/dL
   - Women with polycystic ovary syndrome
   - HbA1C >5.7%, IGT, or IFG on previous testing
   - Other conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
2. For all patients, testing should begin at age 45 years
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (eg, people with prediabetes should be tested yearly) and risk status

GDM = gestational diabetes mellitus; CVD = cardiovascular disease.

ADA. *Diabetes Care*. 2020;43(suppl 1): S14-S31.

Incidence and Prevalence of Diabetes in United States by Region

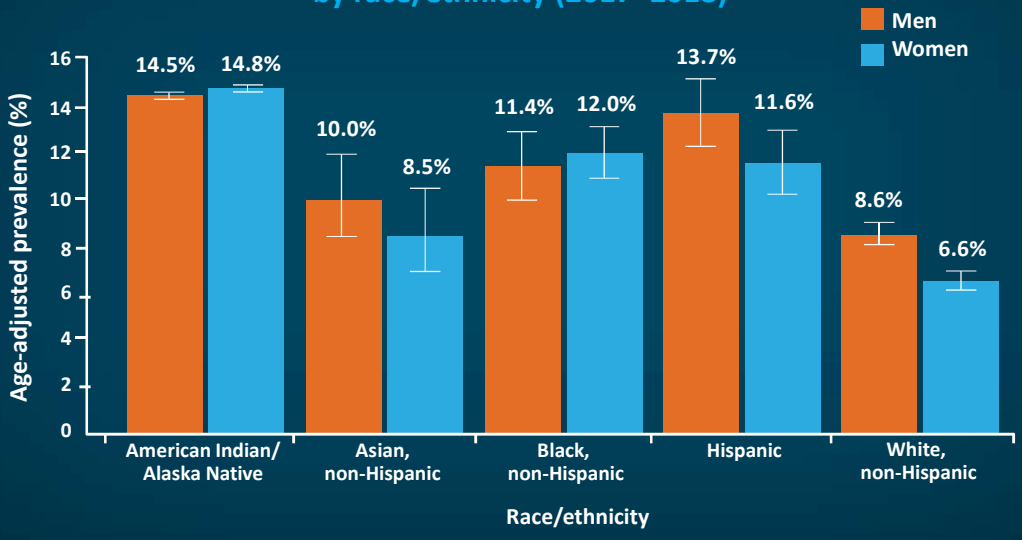


Counties in the *southern and Appalachian regions* of the United States tend to have the highest rates of **incidence** and **prevalence**

CDC. National Diabetes Statistics Report—2017 (https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf). Accessed September 18, 2020.

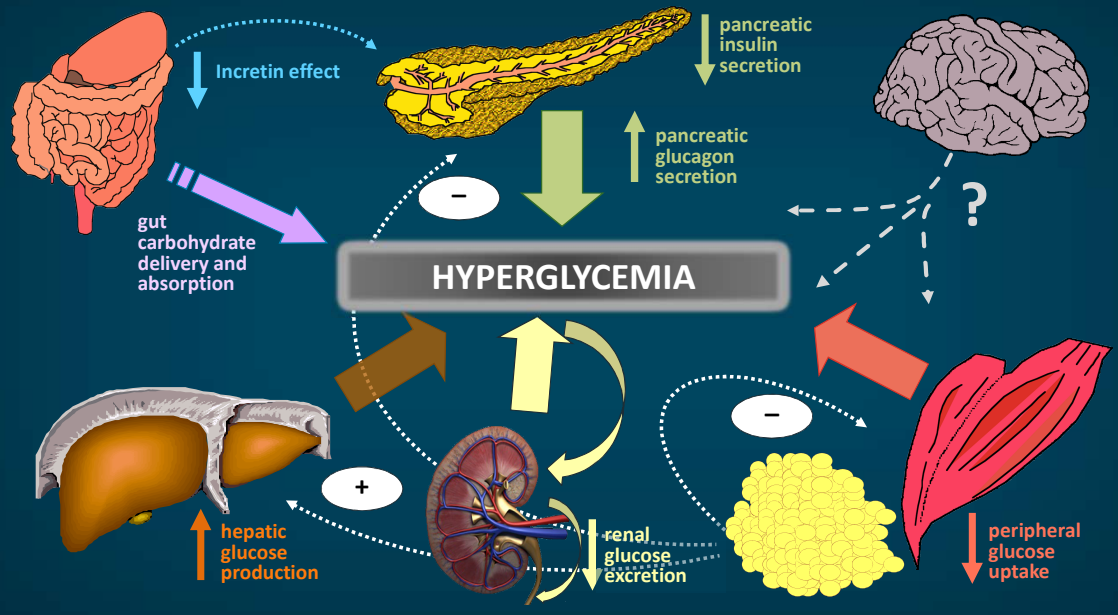
Prevalence of Diabetes by Ethnicity

Estimated age-adjusted adult prevalence of diagnosed diabetes by race/ethnicity (2017–2018)



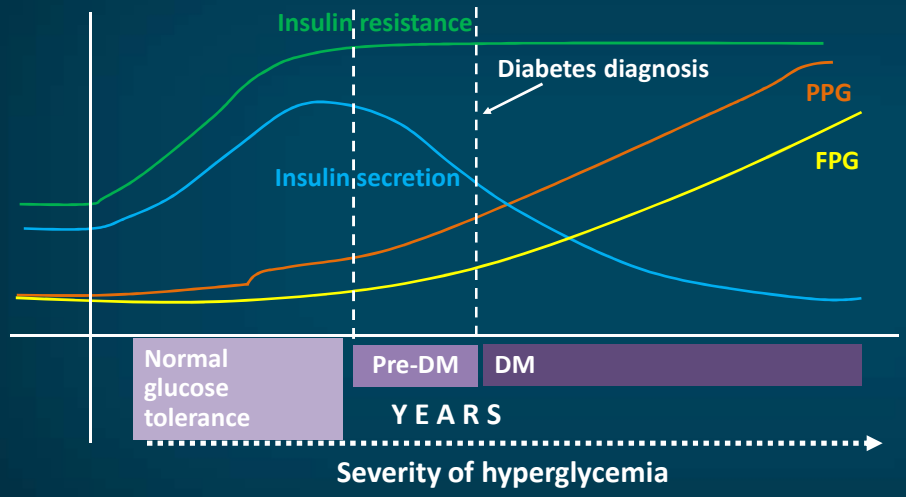
CDC. National Diabetes Statistics Report—2020 (www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Accessed September 18, 2020.

Major Pathophysiological Abnormalities in T2DM



Adapted from Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI (eds). *Goldman's Cecil Medicine,* 24th edition. Saunders Elsevier, 2011:e95-e108.

Progressive β-Cell Dysfunction Is Key Driver of Progressive Dysglycemia in T2DM



By time diabetes is diagnosed, up to 80% of β-cell function may be lost

DM = diabetes mellitus; PPG = postprandial plasma glucose.

Defronzo RA. *Diabetes*. 2009;58:773-795. Fehse F, et al. *J Clin Endocrinol Metab*. 2005;90:5991-5997. Figure adapted from Kendall DM, et al. *Am J Med*. 2009;122(6 suppl):S37-S50.

Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

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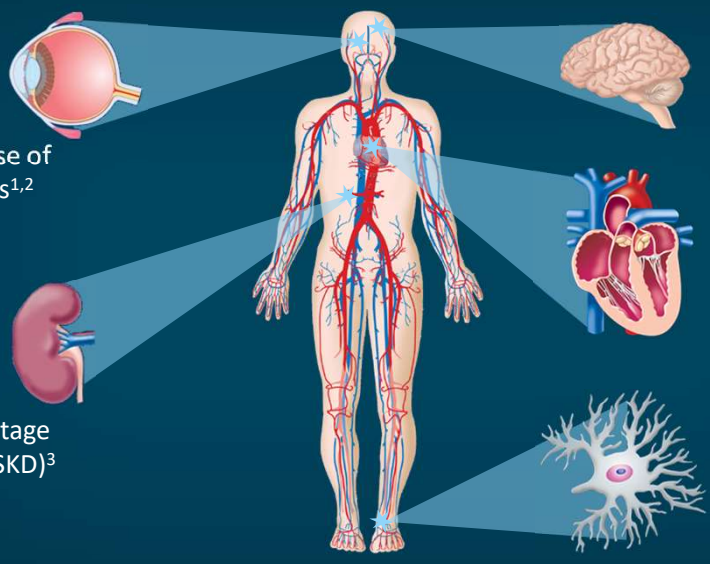
Complications of Diabetes

Diabetic retinopathy
An important cause of blindness in adults[1,2]

Diabetic nephropathy
Leading cause of chronic and end-stage kidney disease (ESKD)[3]



Stroke
Hypertension in ~20–60%, increasing risk of stroke[4]

Cardiovascular disease
CVD is major cause of morbidity and mortality in T2DM[5]

Diabetic neuropathy
Leading cause of non-traumatic lower extremity amputations[6,7]

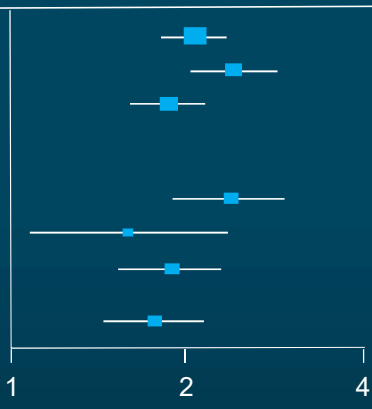
1. Klein R, Klein BE. Chapter 21. *Diabetes in America, 3rd edition*. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2016. 2. Fong DS, et al. *Diabetes Care.* 2003;26(suppl 1):S99-S102. 3. Afkarian M, et al. *JAMA.* 2016;316:602-610. 4. Arauz-Pacheco, C et al. *Diabetes Care.* 2003;26(suppl 1):S80-S82. 5. Barrett-Connor E, et al. Chapter 18. *Diabetes in America, 3rd edition*. NIDDK, 2016. 6. Mayfield JA, et al. *Diabetes Care.* 2003;26(suppl 1):S78-S79. 7. ADA. *Diabetes Care.* 2020;43(suppl 1):S135-S151.

T2DM Doubles Risk for Macrovascular Outcomes

Meta-analysis of 102 Prospective Studies, with Data for 698,782 People

Vascular outcomes in patients with vs without DM

	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26,505	2.00 (1.83–2.19)	64 (54–71)
Coronary death	11,556	2.31 (2.05–2.60)	41 (24–54)
Nonfatal MI	14,741	1.82 (1.64–2.03)	37 (19–51)
Stroke subtypes*			
Ischemic stroke	3799	2.27 (1.95–2.56)	1 (0–20)
Hemorrhagic stroke	1183	1.56 (1.19–2.05)	0 (0–26)
Unclassified stroke	4973	1.84 (1.59–2.13)	33 (12–48)
Other vascular deaths	3826	1.73 (1.51–1.98)	0 (0–26)



*Includes both fatal and nonfatal events.

MI = myocardial infarction; HR = hazard ratio; CI = confidence interval.

Sarwar N, et al; Emerging Risk Factors Collaboration. *Lancet*. 2010;375:2215-2222.

Disease Burden of Diabetes

Hospitalizations with diabetes-associated conditions can include:

Condition	Age-Adjusted Rate (per 1000)
Congestive heart failure (CHF)	9.4
Stroke	6.0
Myocardial infarction	5.6
Lower extremity amputations	3.4
Hyperosmolar hyperglycemic nonketotic syndrome (HHNK)	1.3
Diabetic ketoacidosis (DKA)	17.1
Hypoglycemia	3.0

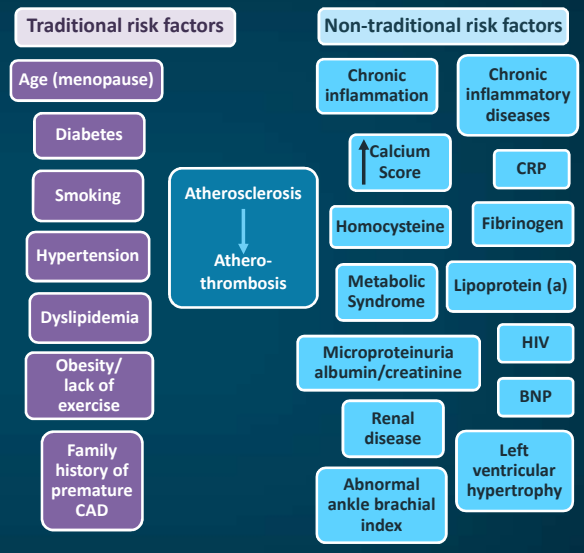
Medicare data for beneficiaries aged ≥65 years with diabetes demonstrated overall prevalence of multiple cardiovascular diseases, including:

Condition	Age-Adjusted Rate (per 100)
Coronary heart disease	46.8
CHF	26.2
Chronic kidney disease (CKD)	31.0
Peripheral vascular disease	20.7

CDC. Diabetes Health Burden Toolkit (https://nccd.cdc.gov/Toolkit/DiabetesBurden/Home/Health). (Hospitalizations data from 2016 and Medicare data from 2013). Accessed September 18, 2020.

Risk Factors for CVD in Diabetes

- Age: men ≥45 years; women ≥55 years
- Family history of premature CAD
  - CAD in male first-degree relative at <65 years
- Hypertension
  - BP >140/90 mmHg or on anti-HTN medication
- Cigarette smoking
- Diabetes
- Hypercholesterolemia
- Low HDL-C (<40 mg/dL)
- Hypertriglyceridemia (>200 mg/dL)
- Obesity

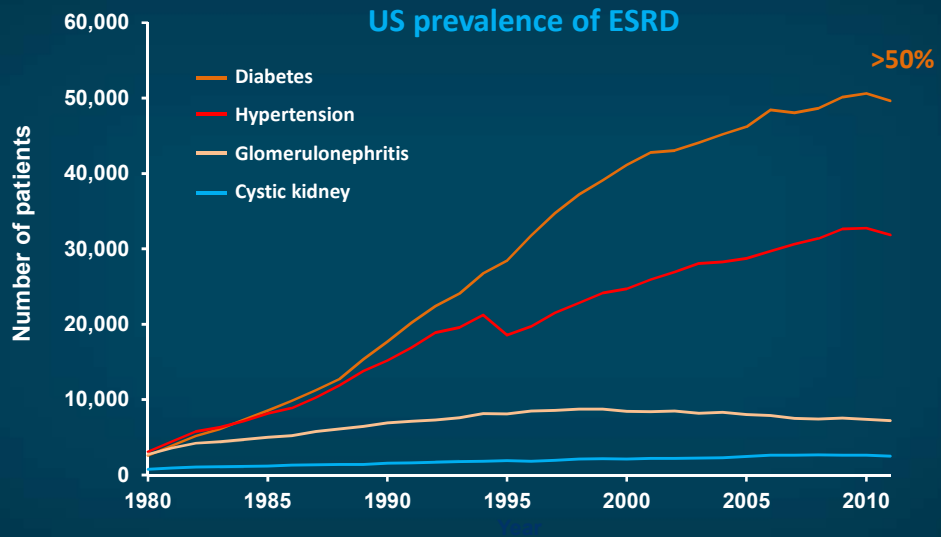


Major risk factors for CAD

BP = blood pressure; HTN = hypertension; HDL-C = high-density lipoprotein-cholesterol; CAD = coronary artery disease; CRP = C-reactive protein; HIV = human Immunodeficiency virus; BNP = B-type natriuretic peptide.

NIDDK. 2017 (www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke). Accessed September 18, 2020. Barrett-Connor E, et al. Chapter 18. *Diabetes in America, 3rd edition*. NIDDK, 2016.

Diabetes Is the Leading Cause of End-Stage Renal Disease

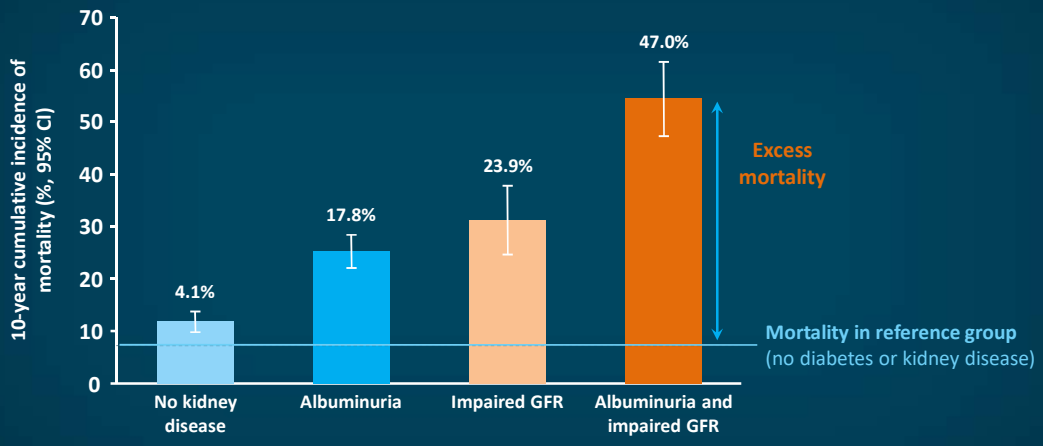


ESRD = end-stage renal disease.

United States Renal Data System. Annual data report. *Am J Kidney Dis*. 2014;63(1 suppl):e215-e228 (www.ajkd.org/article/S0272-6386(13)01411-X/pdf). Accessed September 18, 2020.

Mortality Is Increased In Patients With T2D and Kidney Disease

Standardized 10-year cumulative incidence of mortality



Percentages above bars indicate excess mortality **above** the reference group

GFR = glomerular filtration rate.

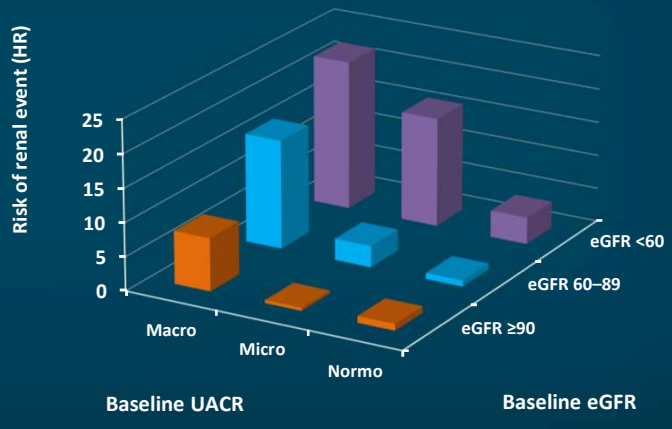
Afkarian M, et al. *J Am Soc Nephrol*. 2013;24:302-308.

Albuminuria and Reduced GFR Are Associated With Increased Risk of Renal Events

ADVANCE: Observational analyses examining the association between albuminuria and GFR at baseline or during follow-up and risk for CV events and renal events in T2D

10,640 patients with available data

Average follow-up of 4.3 years



UACR = urinary albumin-to-creatinine ratio; eGFR = estimated GFR; Macro = macroalbuminuria; Micro = microalbuminuria; Normo = normoalbuminuria.

Ninomiya T, et al. *J Am Soc Nephrol*. 2009;20:1813-1821.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

Green = low risk (if no other markers of KD, no CKD)
Yellow = moderately increased risk
Orange = high risk
Red = very high risk

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

KDIGO = Kidney Disease: Improving Global Outcomes; KD = kidney disease; CKD = chronic kidney disease.

International Society of Nephrology. Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Supplements 2013; 3(1). (https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf). Accessed September 18, 2020.

Impact of Intensive Glucose-Lowering Therapy in T2DM

Summary of Major Randomized Controlled Trials

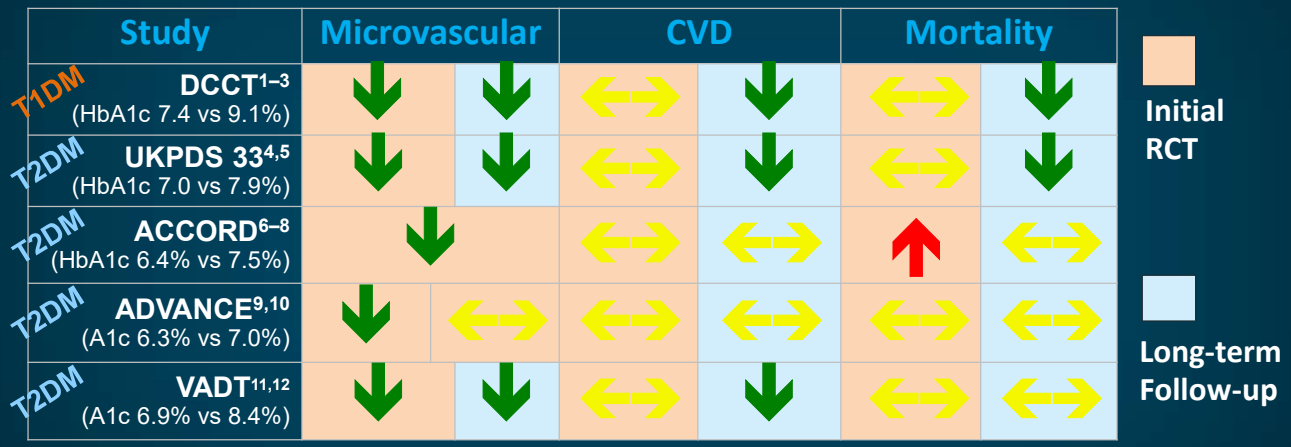
Study	Microvascular	CVD	Mortality
T1DM DCCT[1] (HbA1c 7.2 vs 9.1%)	↓	↔	↔
T2DM UKPDS 33[2] (HbA1c 7.0 vs 7.9%)	↓	↔	↔
T2DM ACCORD[3,4] (HbA1c 6.4% vs 7.5%)	↓	↔	↑
T2DM ADVANCE[5] (HbA1c 6.3% vs 7.0%)	↓	↔	↔
T2DM VADT[6] (HbA1c 6.9% vs 8.4%)	↓	↔	↔

Initial RCT

RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus.

1. DCCT Group. *N Engl J Med*. 1993;329: 977-986. 2. UKPDS Group. *Lancet*. 1998;352:837-853. 3. Gerstein HC, et al. *N Engl J Med*. 2008;358:2545-2559. 4. Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430. 5. Patel A, et al. *N Engl J Med*. 2008;358:2560-2572. 6. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139 .

Impact of Intensive Glucose-Lowering Therapy in T2DM
Summary of Major RCTs



1. DCCT Group. *N Engl J Med.* 1993;329: 977-986. 2. Nathan DM, et al. *N Engl J Med.* 2005;353:2643-2653. 3. DCCT Group. *JAMA* 2015;313:45-53. 4. UKPDS Group. *Lancet.* 1998;352:837-853. 5. Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589. 6. Gerstein HC, et al. *N Engl J Med.* 2008;358:2545-2559. 7. Ismail-Beigi F, et al. *Lancet.* 2010;376:419-430. 8. ACCORD study group. Diabetes Care. 2016;39:701-708. 9. Patel A, et al. *N Engl J Med.* 2008;358:2560-2572. 10. Zoungas S, et al. *N Engl J Med.* 2014;371:1392-1406. 11. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139.

Healthcare Cost of Diabetes

Annual Total Costs Attributable to Diabetes, United States (2013)				
Age Group (in years)	Direct Cost ($ in Millions)	Indirect Cost ($ in Millions)	Total Cost ($ in Millions)	Total Cost per Person with Diabetes ($)
19–64	107,250.8	193,148.5	300,399.3	20,181
65+	84,228.9	36,969.9	121,198.8	11,647
Total	191,479.7	230,118.4	421,598.0	16,670

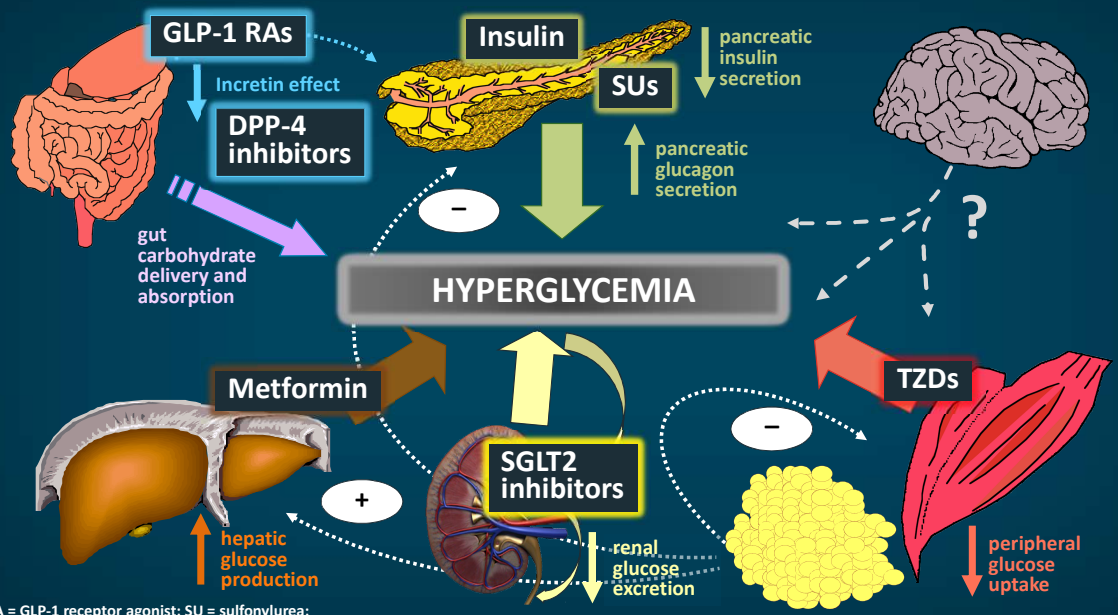
Indirect costs include **inability to work** (1.2 million persons, with annual cost of $74.5 million) and **premature mortality** (240,250 persons, resulting in mortality cost of $68.7 million in work productivity and $33.5 million in household productivity)

CDC. Diabetes Health Burden Toolkit (https://nccd.cdc.gov/Toolkit/DiabetesBurden/Home/Economic). (Healthcare cost data from 2013). Accessed September 18, 2020.

Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

1. *What* we treat: definitions, diagnosis, and pathogenesis
2. *Why* we treat: reducing long-term complications
3. ***How* we treat: major glucose-lowering drug classes (Dr. Peters)**
4. *When* to use newer therapies
   - SGLT2 inhibitors
   - GLP-1 receptor agonists
5. *Where* are we going? New T2DM treatment guidelines

Major Pathophysiologically Based T2DM Therapies



GLP-1RA = GLP-1 receptor agonist; SU = sulfonylurea; TZD = thiazolidinedione; DPP-4 = dipeptidyl peptidase 4.

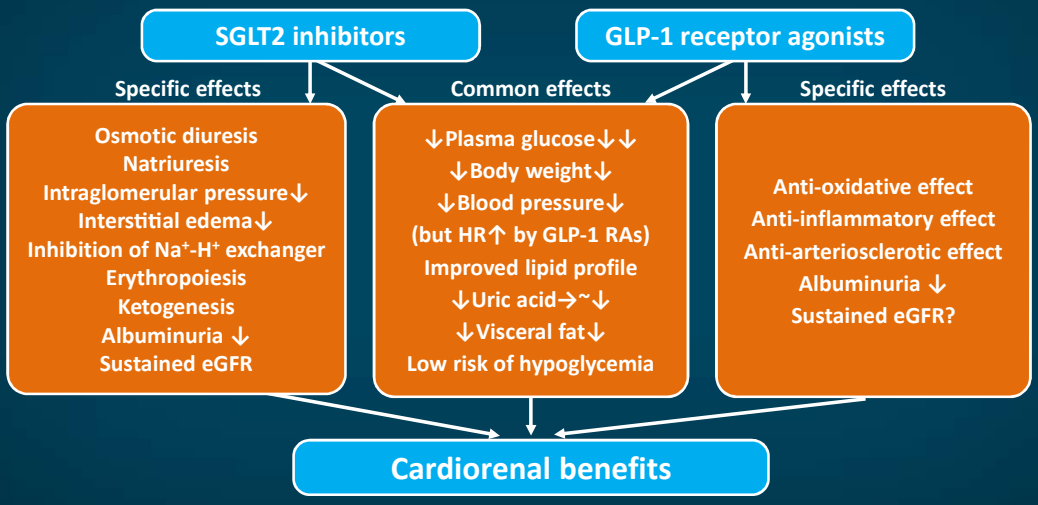
Adapted from Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI (eds). *Goldman's Cecil Medicine, 24th edition*. Saunders Elsevier, 2011.

Major Glucose-Lowering Drugs Classes

Class	Generic Names	↓HbA1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, glargine, detemir, NPH, regular, lispro, aspart, glulisine	No limit	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypo, weight gain	highly variable
SU	Glyburide, glipizide, glimepiride	1–1.5%	↑ endogenous insulin production	Extensive experience	Hypo, weight gain	$
Metformin	Metformin	1–1.5%	↓ hepatic glucose production (? others)	±Wt loss, no hypo, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZD	Rosiglitazone, pioglitazone	1–1.5%	Enhances peripheral insulin sensitivity	Durability, no hypo, ↓ CV events*, ↓ NASH	Weight gain, edema, HF, bone fxs, ? bladder ca*	$–$$$
DPP-4 i	Sitagliptin, saxagliptin, alogliptin, linagliptin	0.5–1%	↓ DPP-4 activity and ↑ incretins (GLP1, GIP)	Well-tolerated; no hypo	Urticaria, ? pancreatitis, ? CHF	$$$$
GLP-1 RA	Exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide	1–1.5%	↑ insulin & ↓ glucagon, ↓ gastromotility, hunger	Wt loss, no hypo, ↓ BP, ↓ MACE*	GI, ? pancreatic disease,? thyroid, medullary ca	$$$$
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1%	↑ urinary glucose excretion	Wt loss, no hypo, ↓s BP, ↓ MACE*, ↓ HF†, ↓ CKD#	Polyuria, GU, DKA; bone fxs*, amputations*	$$$$

Potential Mechanisms for Cardiorenal Protection

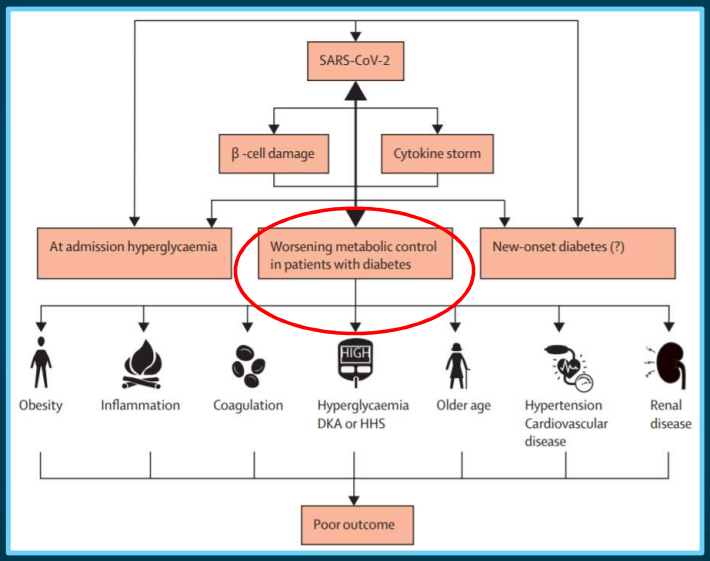
GLP-1 Receptor Agonists and SGLT2 Inhibitors



Na^+ = sodium (ion) H^+ = hydrogen (ion); HR = heartrate.

Nagahisa T, Saisho Y. *Diabetes Ther*. 2019;10:1733-1752.

Reciprocal Effects of Diabetes and COVID-19: Considerations for Management



Apicella M, et al. *Lancet Diabetes Endocrinol.* 2020 Sep;8(9):782-792. doi: 10.1016/S2213-8587(20)30238-2. Epub 2020 Jul 17. Erratum in: *Lancet Diabetes Endocrinol.* 2020 Oct;8(10):e5.2.

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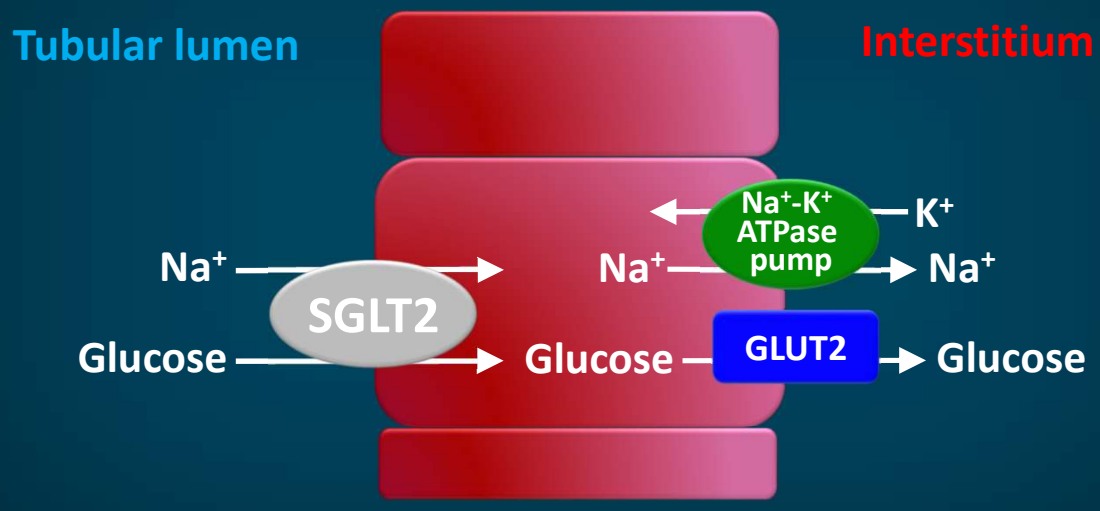
3. ***How* we treat: major glucose-lowering drug classes**
4. ***When* to use newer therapies**
   - **SGLT2 inhibitors (Dr. Inzucchi)**
   - GLP-1 receptor agonists
5. *Where* are we going? New T2DM treatment guidelines

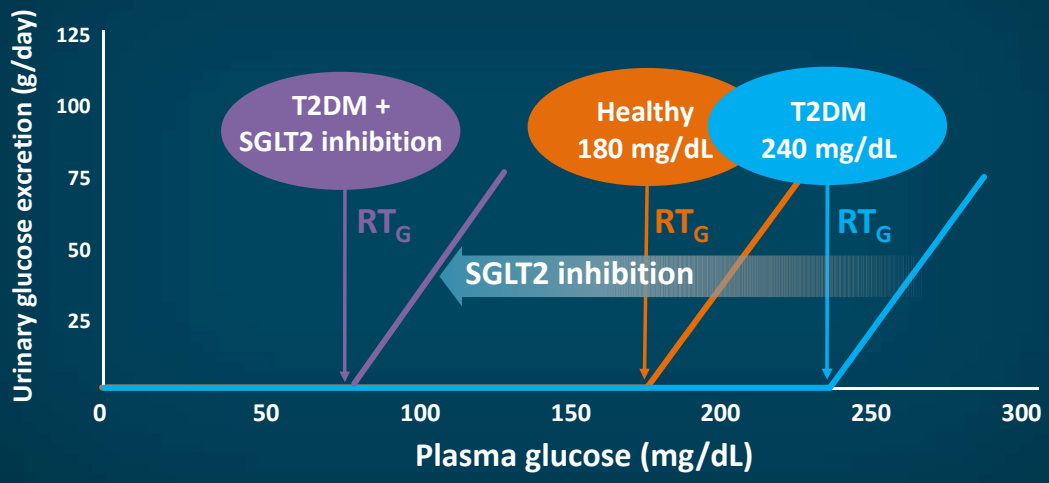
Active (SGLT2) and Passive (GLUT2) Glucose Transport in Renal Proximal Tubular Cell



GLUT2 = glucose transporter 2; K^+ = potassium (ion); ATPase = adenosine triphosphatase.

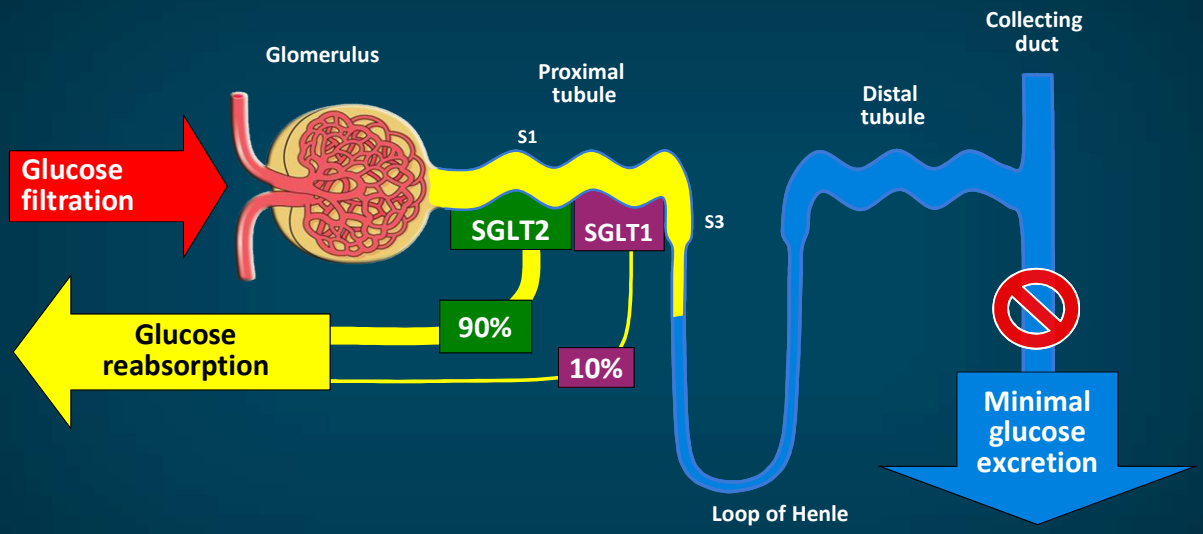
Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42.

SGLT2 Inhibitors Lower the Renal Threshold for Glucose Excretion (RT_G)



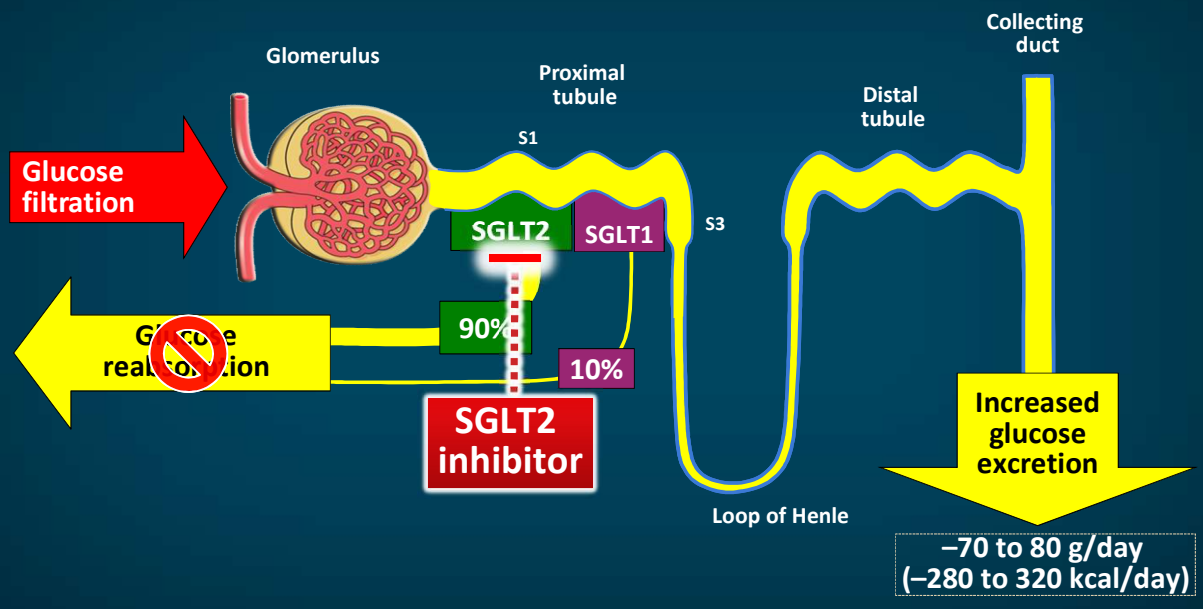
Adapted from Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790. Adapted from Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42.

Normal Physiology of Renal Glucose Homeostasis



Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18. Lee YJ, et al. *Kidney Int Suppl.* 2007;106:S27-S35. Han S, et al. *Diabetes.* 2008;57:1723-1729.

SGLT2 Inhibition Reduces Renal Glucose Reabsorption



Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18. Lee YJ, et al. *Kidney Int Suppl.* 2007;106:S27-S35. Han S, et al. *Diabetes.* 2008;57:1723-1729. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149.

SGLT2 Inhibitors

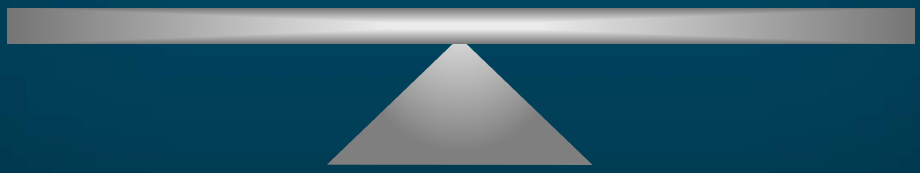
Risk-to-Benefit Ratio Prior to CV Outcome Trials

BENEFITS

- ↓HbA1c ~0.6–0.9%
- Low hypoglycemia risk
- Modest ↓ weight
- Modest ↓ BP
- ↓ Albuminuria
- Small ↓ TGs
- Small ↑ HDL-C

RISKS

- Polyuria/dehydration
- Genital mycotic infections
- ? UTIs
- Small ↓ GFR (reversible)
- Diabetic ketoacidosis (DKA)
- Small ↑ LDL-C
- ? ↑ Fracture risk



TG = triglyceride(s); UTI = urinary tract infection; LDL-C = low-density lipoprotein-cholesterol.

Kim Y, Babu AR. *Diabetes Metab Syndr Obes.* 2012;5:313-327. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149. Burke KR, et al. *Pharmacotherapy.* 2017;37:187-194.

Overview of FDA-Approved SGLT2 Inhibitors

Drug Name	Dosage* mg	Reduction in HbA1c†	Usage and Indications
Canagliflozin (Invokana®)	100, 300	–0.77 to –1.03	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease • To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria
Empagliflozin (Jardiance®)	10, 25	–0.66 to –0.78	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease
Dapagliflozin (Farxiga®)	5, 10	–0.82 to –0.89	• As an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus • To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors
Ertugliflozin (Steglatro™)	5, 15	–0.99 to –1.16	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

*All dosages are once per day (QD). †Percentage reduction from baseline 24–26 weeks.

Prescribing information for these agents. Adapted from Simes BC, MacGregor GG. *Diabetes Metab Syndr Obes.* 2019;12:2125-2136.

FDA-Mandated CV Outcomes Non-insulin Trials in T2DM: SGLT2 Inhibitors

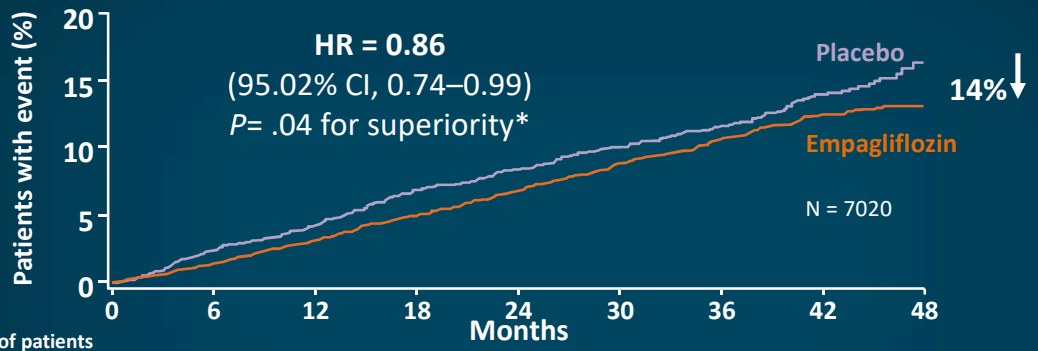
Study	EMPA-REG[1,2]	CANVAS[2,3]	(CREDENCE[2,4])	DECLARE[2,5]	VERTIS CV[2,6]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7020	4330	4401	17160	8246
Results	2015	2017	2018	2018	2020

NEUTRAL

1. NCT01131676 (EMPA-REG). 2. Tehrani D, et al. *Latest Cardiol.* 2020 (www.acc.org/latest-in-cardiology/articles/2020/08/31/09/40/vertis-cv-trial). Accessed September 21, 2020. 3. NCT01032629 (CANVAS). 4. NCT02065791 (CREDENCE). 5. NCT01730534 (DECLARE). 6. NCT01986881 (VERTIS CV).

EMPA-REG OUTCOME: Primary Outcome

Cumulative Incidence of 3-Point MACE (CV death, nonfatal MI, or nonfatal stroke)



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Primary outcome (composite of death from CV causes, nonfatal MI, or nonfatal stroke) occurred in a significantly lower percentage of patients in empagliflozin group (10.5%) vs placebo (12.1%).

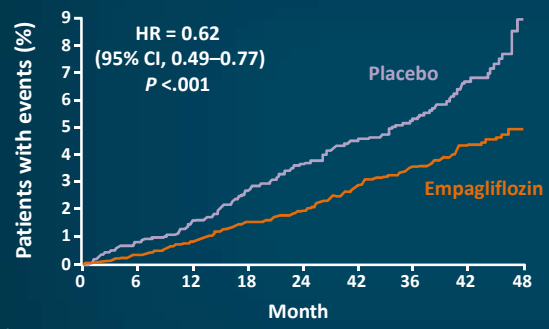
*Two-sided tests for superiority were conducted (statistical significance was indicated if $P \leq .0498$).

MACE = major adverse cardiovascular events.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

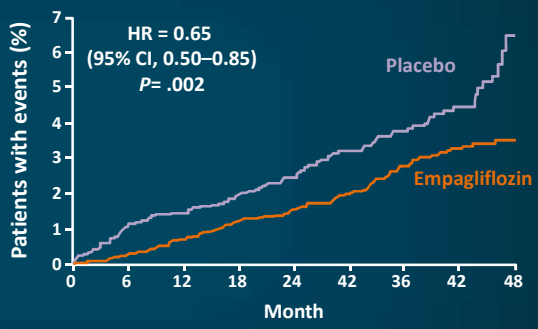
EMPA-REG OUTCOME: CV Death and Heart-Failure Hospitalization

Death from CV causes



No. at risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1772	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

HF Hospitalization



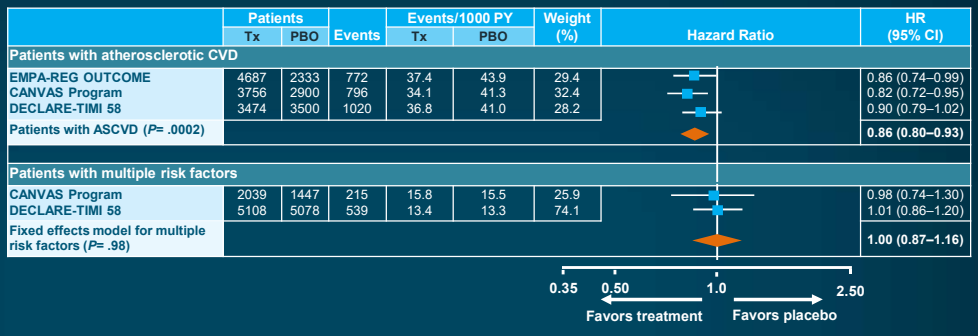
No. at risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

HF = heart failure.

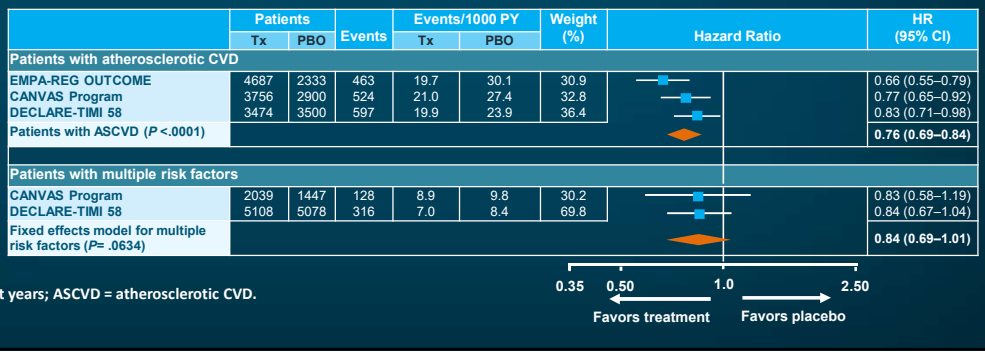
Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

SGLT2i Trial Meta-analysis of Cardiovascular Outcomes

Meta-analysis on MI, stroke, and CV death (MACE)*



Meta-analysis on HF hospitalizations and CV death*



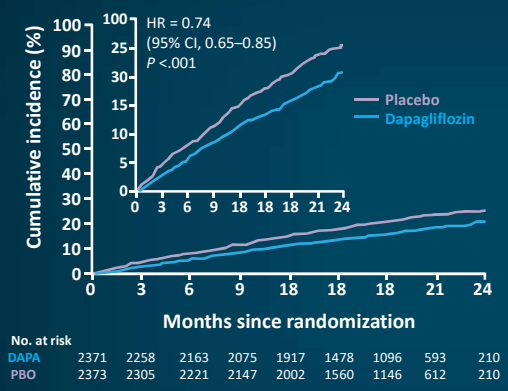
**Stratified by presence of established atherosclerotic disease*

Tx = treatment; PBO = placebo; PY = patient years; ASCVD = atherosclerotic CVD.

Zelniker TA, et al. *Lancet*. 2019;393:31-39.

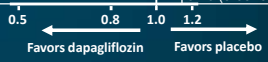
DAPA HF Primary Outcomes: DM vs Non-DM Subgroups

Primary outcome



Primary outcome subgroup analysis

Subgroup	DAPA n = 2373 Patients/total, no.	PBO n = 2371 Patients/total, no.	Hazard Ratio (95% CI)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63–0.90)
No	171/1298	231/1307	0.73 (0.60–0.88)
Afib or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Non-ischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)



Primary outcome was composite of worsening HF (*hospitalization for HF or urgent visit resulting in IV treatment for HF*) or CV death, which occurred in a significantly lower (*P* <.001) percentage of patients in dapagliflozin group (16.3%) vs placebo (21.2%).

DAPA = dapagliflozin; AFib = atrial fibrillation; ECG = electrocardiogram; IV = intravenous.

McMurray JJV, et al. *N Engl J Med.* 2019;381:1995-2008.

Randomized Controlled Trials of SGLT2 inhibitors in HF

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2,3]	Dapa-HF[4,5]	DELIVER[6]
Intervention	Empagliflozin	Empagliflozin	Dapagliflozin	Dapagliflozin
Sample size	4126*	2850*	4744*	Estimated 6100 (recruiting)
HF criteria	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)	HFpEF (LVEF >40%), structural heart disease), and NYHA II–IV
Primary endpoint	Time to first event of adjudicated CV death or adjudicated HHF		Time to first occurrence of CV death, HHF, or urgent HF visit	Time to first occurrence of CV death, HHF, or urgent HF visit
Key secondary endpoints	• Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence of sustained reduction of eGFR • Change from baseline in KCCQ		• Total number of CV deaths or HHF • All-cause mortality • Composite of ≥50% sustained eGFR decline, ESRD, or renal death • Change from baseline in KCCQ	• Total number of CV death or HHF • All-cause mortality • Proportion of patients with worsened NYHA class • Change from baseline in KCCQ
Start date Expected completion	March 2017 April 2021	March 2017 COMPLETED	February 2017 COMPLETED	August 2018 June 2021

*NT-proBNP-based enrichment of population with patients at higher severity of HF; †NYHA class II–IV.

NT-proBNP = N-terminal of prohormone brain natriuretic peptide; NYHA = New York Heart Association; HFpEF = HF with preserved ejection fraction; LVEF = left ventricular ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; ESRD = end-stage renal disease; HFrEF = HF with reduced ejection fraction.

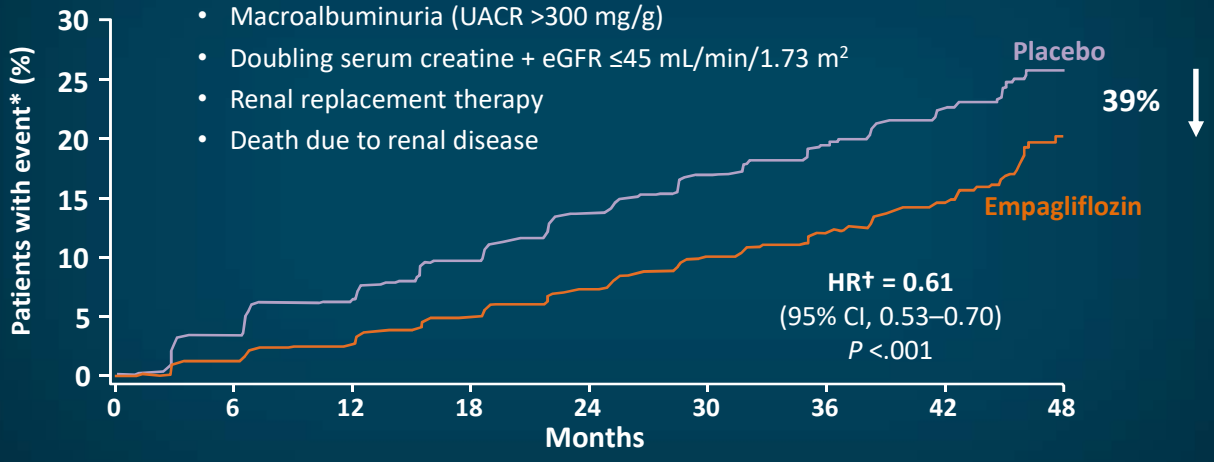
1. NCT03057951 (EMPEROR-Preserved). 2. NCT03057977 (EMPEROR-Reduced). 3. Packer M, et al. *N Engl J Med*. 2020 Aug 29. doi: 10.1056/NEJMoa2022190. 4. NCT03036124 (DAPA-HF). 5. McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008. 6. NCT03619213 (DELIVER).

EMPA-REG OUTCOME: Secondary Outcome

Cumulative Incidence of Incident or Worsening Nephropathy

Incident or worsening nephropathy includes:

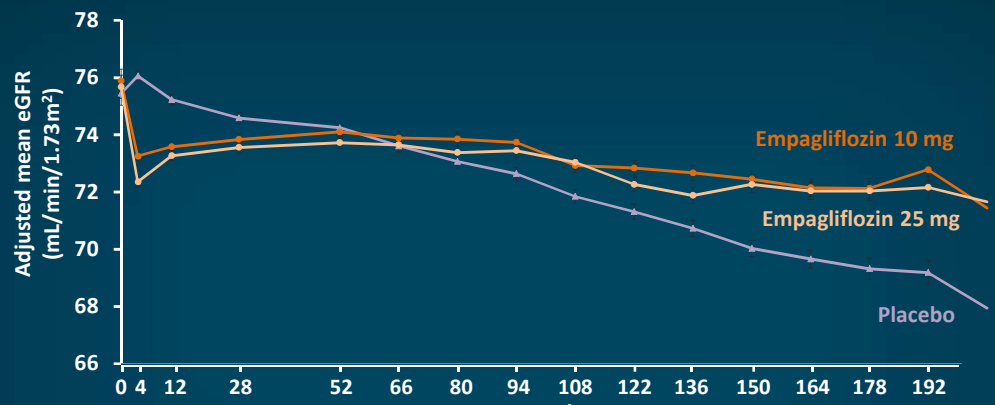
- Macroalbuminuria (UACR >300 mg/g)
- Doubling serum creatine + eGFR ≤45 mL/min/1.73 m^2
- Renal replacement therapy
- Death due to renal disease



*Kaplan-Meier estimate; †Hazard ratio based on Cox regression analyses.

Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

EMPA-REG: eGFR (CKD-EPI formula) Over 192 Weeks



No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in total follow-up for adverse/outcome events	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Mixed model repeated measures analysis.

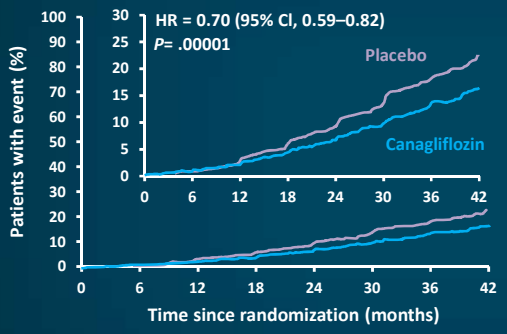
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

Wanner C, et al. *N Engl J Med*. 2016;375:323-334

Progression of Nephropathy—CREDENCE

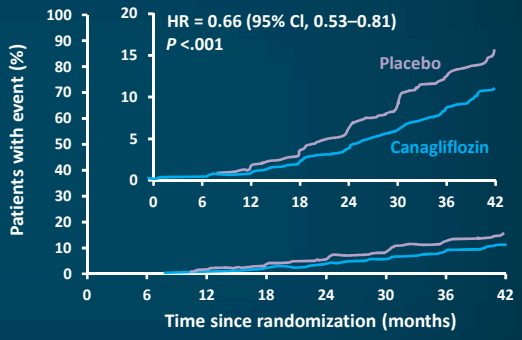
Primary and Secondary Endpoints

Primary composite outcome*



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Renal-specific composite outcome*



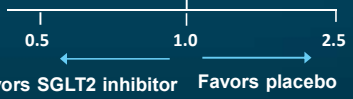
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

*Indicated to reduce risk of ESKD, doubling of serum creatinine, CV death, and HHF in adults with T2DM and diabetic nephropathy with albuminuria.

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306. Canagliflozin (Invokana®) prescribing information (PI) 2020. (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf). Accessed September 18, 2020.

Meta-analysis of Effects of SGLT2 Inhibitors on Major Kidney Outcomes

Major kidney outcomes	Events	Patients	RR (95% CI)
Dialysis, transplantation, or death due to kidney disease	252	38,723	0.67 (0.52–0.86)
ESKD	335	38,723	0.65 (0.53–0.81)
Substantial loss of kidney function, ESKD, or death due to kidney disease	967	38,671	0.58 (0.51–0.66)
Substantial loss of kidney function, ESKD, or death due to CV or kidney disease	2323	38,676	0.71 (0.63–0.82)
Acute kidney injury	943	38,684	0.75 (0.66–0.85)



RR = relative risk.

Neuen BL, et al. *Lancet Diabetes Endocrinol*. 2019;7:845-854.

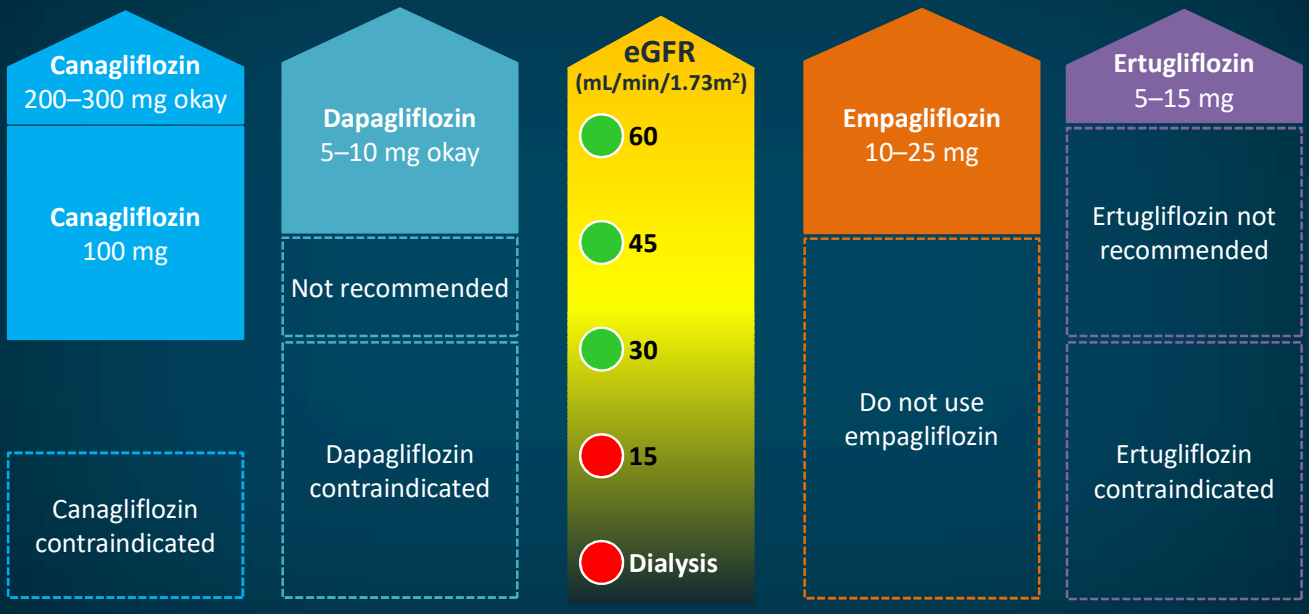
Randomized Controlled Trials of SGLT2 Inhibitors in CKD

	CREDENCE[1,2]	Dapa-CKD[3,4]	EMPA-KIDNEY[5,6]
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin
Population	DKD	CKD	CKD
No. of patients	4401	4304	~5000
Key inclusion criteria	eGFR ≥30 to <90 ml/min/1.73 m^2 and UACR >300 to ≤5000 mg/g	eGFR ≥25 to ≤75 ml/min/1.73 m^2 and UACR ≥200 to ≤5000 mg/g	eGFR ≥20 to <45 ml/min/1.73 m^2 OR eGFR ≥45 to <90 ml/min/1.73 m^2 AND UACR ≥200 mg/g
Primary outcome	Doubling of serum creatinine, ESKD, or renal or CV death	eGFR decline of ≥50%, ESKD, or renal or CV death	eGFR decline of ≥40%, ESKD, or renal or CV death
Key secondary outcomes	Composite of CV death and HHF All-cause mortality	Composite of CV death or HHF All-cause mortality	Composite of CV death or HHF All-cause hospitalization All-cause mortality
Start date Est. completion	2014 COMPLETED	2017 COMPLETED	2019 2022

DKD = diabetic kidney disease; Est = estimated.

1. Jardine MJ, et al. *Am J Nephrol.* 2017;46:462-472. 2. NCT02065791 (CREDENCE). 3. NCT03036150 (Dapa-CKD). 4. Heerspink HJL, et al; DAPA-CKD Trial Committees and Investigators. *N Engl J Med.* 2020 Sep 24. doi: 10.1056/NEJMoa2024816. Epub ahead of print. 5. NCT03594110 (EMPA-KIDNEY). 6. Boehringer Ingelheim. Press release. 2018 (www.boehringer-ingelheim.com/EMPA-KIDNEY. URLs accessed September 21, 2020.

Current Renal Restrictions: SGLT2 Inhibitors

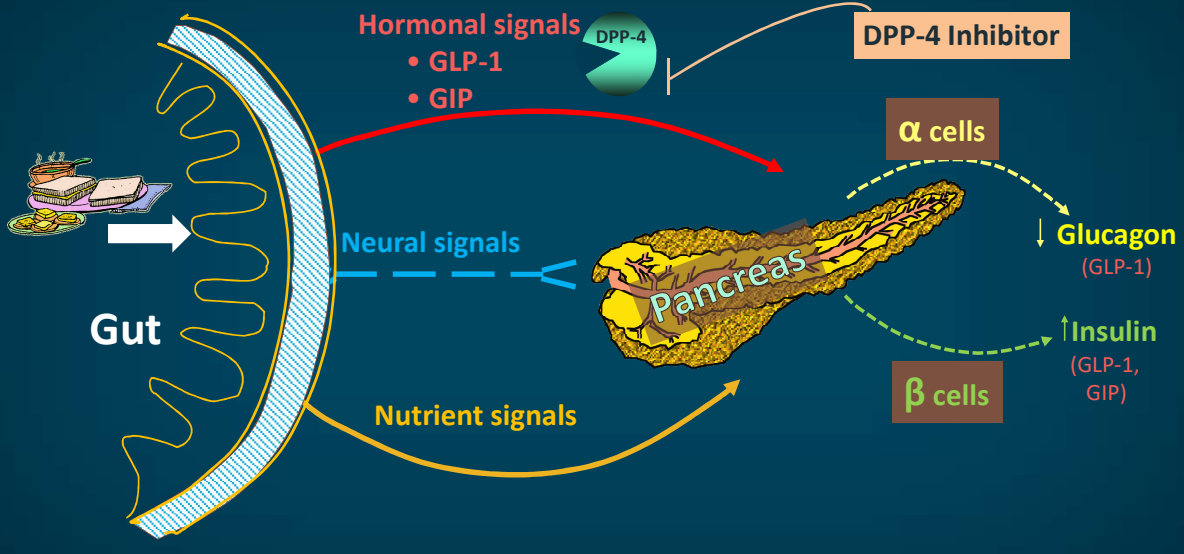


Prescribing information for these agents.

Improving Glycemic, Cardiovascular, and Renal Outcomes in Type 2 Diabetes

1. *What* we treat: definitions, diagnosis, and pathogenesis
2. *Why* we treat: reducing long-term complications
3. ***How* we treat: major glucose-lowering drug classes**
4. ***When* to use newer therapies**
   - SGLT2 inhibitors
   - **GLP-1 receptor agonists (Dr. Peters)**
5. *Where* are we going? New T2DM treatment guidelines

The Enteroinsular Axis

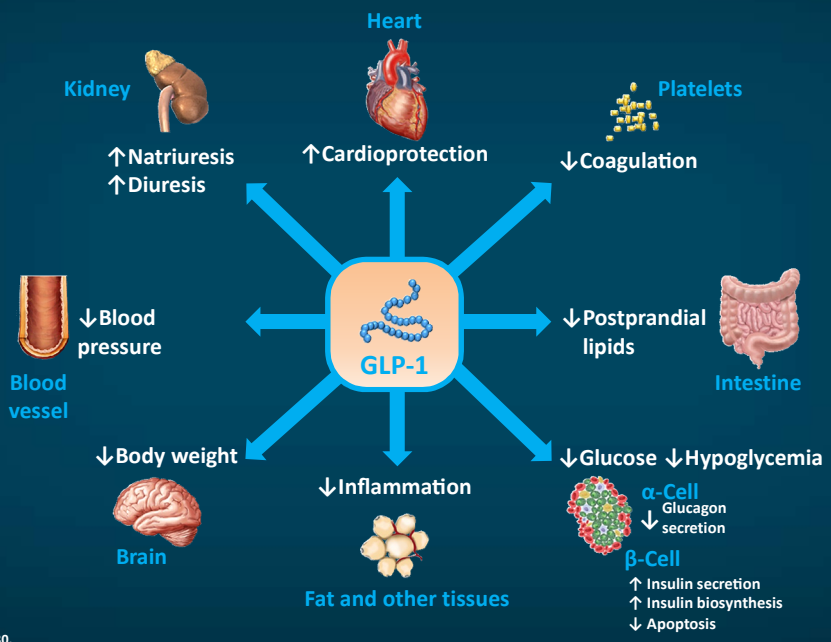


GIP = glucose-dependent insulinotropic peptide.

Adapted with permission from Creutzfeldt W. *Diabetologia*. 1979;16:75-85. Drucker DJ. *Diabetes Care*. 2003;26:2929-2940. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876-913. Nauck MA, et al. *Diabetologia*. 1993;36:741-744.

3

GLP-1 Has Myriad Effects In Multiple Organ Systems



Drucker DJ. *Cell Metab*. 2016;24:15-30.

GLP-1 Receptor Agonists

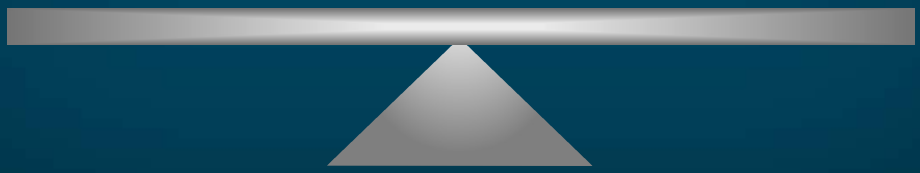
Risk-to-Benefit Ratio Prior to CV Outcome Trials

BENEFITS

- ↓HbA1c ~1.0–1.5%
- Low hypoglycemia risk
- Significant ↓ weight
- Modest ↓ BP
- ↓ Albuminuria
- Modest ↓ LDL-C, TGs
- ↓ Inflammatory markers
- ? Direct cardiac effects

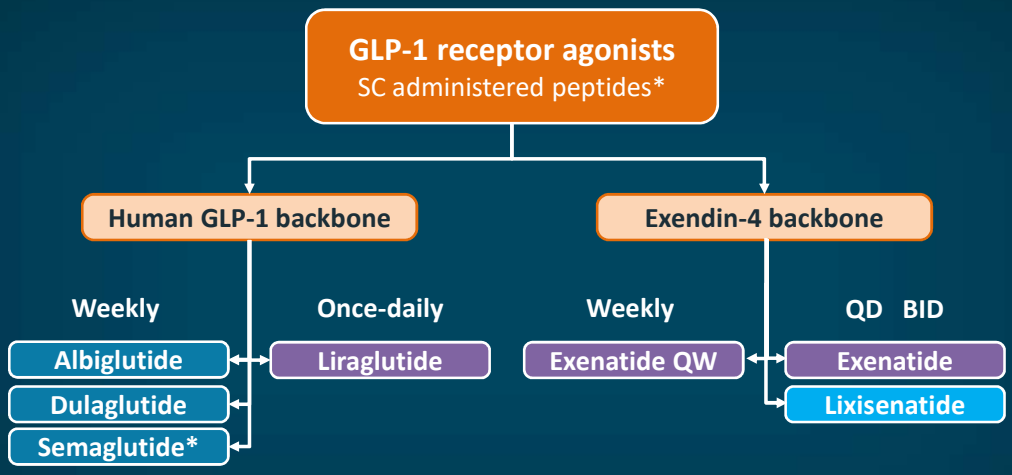
RISKS

- Injectables
- Nausea/vomiting
- ? Pancreatitis risk
- Medullary thyroid cancer (mice)



Kim Y, Babu AR. *Diabetes Metab Syndr Obes*. 2012;5:313-327. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149. Abdul-Ghani M, DeFronzo RA. *Diabetes Care*. 2017;40:1121-1127. Lee YS, Jun HS. *Mediators Inflamm*. 2016;2016:3094642. Dalsgaard NB, et al. *Diabetes Obes Metab*. 2018;20:508-519. Greco EV, et al. *Medicina (Kaunas)*. 2019;55:233.

Overview of GLP-1 Receptor Agonists



*Semaglutide also has an oral formulation.

SC = subcutaneous; QD = daily; QW = once weekly; BID = twice daily.

Adapted from Madsbad S, Holst JJ. Treatment with GLP-1 receptor agonists. In: Bonora E., DeFronzo R. (eds) *Diabetes: Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention, and Treatment*. Springer, 2018 (https://doi.org/10.1007/978-3-319-27317-4_20-1). Accessed September 18, 2020.

Overview of Currently Available FDA-Approved GLP-1 Receptor Agonists

Key characteristics of currently available injectable GLP-1 receptor agonists

	Exenatide (Byetta®)	Liraglutide (Victoza®)	Exenatide ER (Bydureon®)	Dulaglutide (Trulicity®)	Semaglutide (Ozempic®)	Lixisenatide (Adlyxin®)
Recommended Dosing	Initiate at 5 mcg BID; increase to 10 mcg twice BID after 1 month based on clinical response	Initiate at 0.6 mg QD for 1 wk,; increase to 1.2 mg; may increase to 1.8 mg for additional glycemic control	Administer 2 mg QW	Initiate at 0.75 mg QW; may increase to 1.5 mg for additional glycemic control	Initiate at 0.25 mg QW; after 4 wk increase to 0.5 mg QW; may increase to 1 mg for additional glycemic control	Initiate at 10 mcg QD for 2 wk; increase to 20 mcg QD
Indication(s)	Adjunct to diet and exercise to improve glycemic control in T2DM	• Adjunct to diet and exercise to improve glycemic control in T2DM • To reduce risk of major adverse CV events in adults with T2DM and eCVD	Adjunct to diet and exercise to improve glycemic control in T2DM	• Adjunct to diet and exercise to improve glycemic control in T2DM • To reduce risk of major adverse CV events in adults with T2DM with or without eCVD*	• Adjunct to diet and exercise to improve glycemic control in T2DM • To reduce risk of major adverse CV events in adults with T2DM and eCVD	Adjunct to diet and exercise to improve glycemic control in T2DM
Administration Frequency	Twice Daily	Once daily	Once weekly	Once weekly	Once weekly	Once daily
GLP-1 RA Type	Short-acting	Long-acting	Long-acting	Long-acting	Long-acting	Long-acting
Hypoglycemia risk**	Low	Low	Low	Low	Low	Low
Weight Effects	Loss	Loss	Loss	Loss	Loss	Loss

*AJMC. Press Release. Dulaglutide (www.ajmc.com/newsroom/fda-approves-dulaglutide-for-adults-with-t2d-regardless-of-cvd); **monotherapy.

GLP=1 RA = GLP-1 receptor agonist; eCVD = established CVD.

Prescribing information for agents listed.

FDA-Mandated CV Outcomes Non-insulin Trials in T2DM: GLP-1 Receptor Agonists

Study	ELIXA[1,2]	LEADER[2,3]	SUSTAIN 6[2,4]	EXSCEL[2,5]	REWIND[2,6]	HARMONY[2,7]	PIONEER 6[2,8,9]
GLP-1 RA	lixisenatide	liraglutide	semaglutide	exenatide ER	dulaglutide	~~albiglutide*~~	semaglu
Comparator	pla	pla	pla	p	pla	pla	
N	68	93	3	,752	9	9	
Results	2015	2015	2016	2017	2018	2018	2019

NEUTRAL

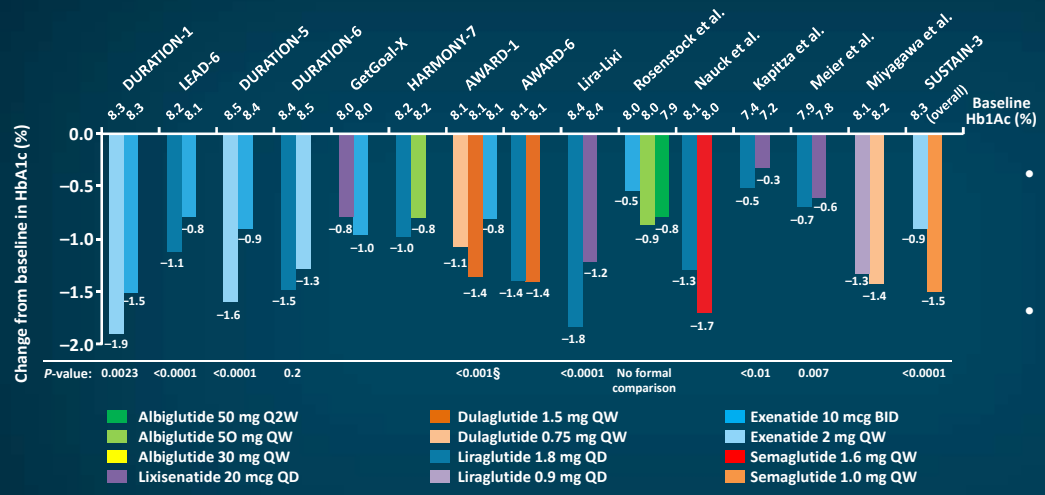
NEUTRAL

Noninferior to placebo**

*In July 2017, the manufacturer of albiglutide announced the discontinuation of its sale due to limited prescribing.
**Cardiovascular safety profile similar to SUSTAIN 6.

1. NCT01147250 (ELIXA). 2. Kristensen SL, et al. *Lancet Diabetes Endocrinol*. 2019;7:776-785. 3. NCT01179048 (LEADER). 4. NCT01720446 (SUSTAIN 6). 5. NCT01144338 (EXSCEL). 6. NCT01394952 (REWIND). 7. NCT02465515 (HARMONY). 8. NCT02692716 (PIONEER 6). 9. Husain M, et al. *N Engl J Med*. 2019; 381:841-851.

Head-to-Head Comparison Trials of GLP-1 RAs: Change in HbA1c



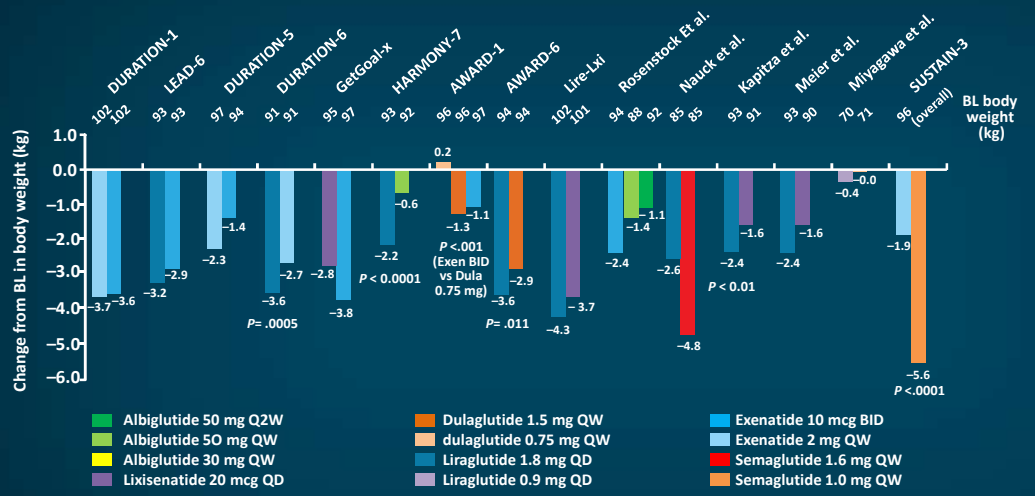
All legend colors depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose)

- Most GLP-1 RAs reduce HbA1c by about 1%–1.5%
- This relates in part to starting level and in part to formulation and dose

To aid comparisons, only the highest doses of the GLP-1RA in any given dosing schedule in these trials were included.
BL = baseline; Q2W = every 2 weeks.

Dalsgaard NB, et al. *Diabetes Obes Metab*. 2018;20:508-519. Full references for the studies cited are available in Dalsgaard et al.

3 Head-to-Head Comparison Trials of GLP-1 RAs: Change in Body Weight



Albiglutide 50 mg Q2W
Albiglutide 5O mg QW
Albiglutide 30 mg QW
Lixisenatide 20 mcg QD
Dulaglutide 1.5 mg QW
dulaglutide 0.75 mg QW
Liraglutide 1.8 mg QD
Liraglutide 0.9 mg QD
Exenatide 10 mcg BID
Exenatide 2 mg QW
Semaglutide 1.6 mg QW
Semaglutide 1.0 mg QW

All legend colors depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose)

Most GLP-1 RAs reduce weight about 3–5 kg

This relates in part to starting weight and in part to formulation and dose

Exen = exenatide; Dula = dulaglutide.

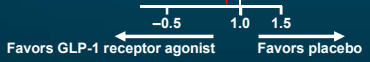
Dalsgaard NB, et al. *Diabetes Obes Metab*. 2018;20:508-519.

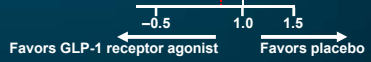
GLP-1 RA Trial Meta-analysis of Cardiovascular Outcomes

Meta-analysis on risk of MACE (MI, stroke, and CV death)

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Three-component MACE			
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89–1.17)
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78–0.97)
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58–0.95)
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83–1.00)
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68–0.90)
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79–0.99)
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57–1.11)
Overall (I^2=40.9%, *P*= .118)	2948/27,977 (10.5%)	3304/28,027 (11.8%)	0.88 (0.82–0.94)
Cardiovascular death			
ELIXA	156/3034 (5%)	158/3034 (5%)	0.98 (0.78–1.22)
LEADER	219/4668 (5%)	278/4672 (6%)	0.78 (0.66–0.93)
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0.98 (0.65–1.48)
EXSCEL	340/7356 (5%)	383/7396 (5%)	0.88 (0.76–1.02)
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0.93 (0.73–1.19)
REWIND	317/4949 (6%)	346/4952 (7%)	0.91 (0.78–1.06)
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0.49 (0.27–0.92)
Overall (I^2=13.5%, *P*= .327)	1213/27,977 (4.3%)	1371/28,027 (4.9%)	0.88 (0.81–0.96)

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Fatal or non-fatal myocardial infarction			
ELIXA	270/3034 (9%)	261/3034 (9%)	1.03 (0.87–1.22)
LEADER	292/4668 (6%)	339/4672 (7%)	0.86 (0.73–1.00)
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0.81 (0.57–1.16)
EXSCEL	483/7356 (7%)	493/7396 (7%)	0.97 (0.85–1.10)
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0.75 (0.61–0.90)
REWIND	223/4949 (5%)	231/4952 (5%)	0.96 (0.79–1.15)
PIONEER 6*	37/1591 (2%)	35/1592 (2%)	1.04 (0.66–1.66)
Overall (I^2=27.4%, *P*= .219)	1540/27,977 (5.5%)	1662/28,027 (5.9%)	0.91 (0.84–1.00)
Fatal or non-fatal stroke			
ELIXA	67/3034 (2%)	60/3034 (2%)	1.12 (0.79–1.58)
LEADER	173/4668 (4%)	199/4672 (4%)	0.86 (0.71–1.06)
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0.65 (0.41–1.03)
EXSCEL	187/7356 (3%)	218/7396 (3%)	0.85 (0.70–1.03)
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0.86 (0.66–1.14)
REWIND	158/4949 (3%)	205/4952 (4%)	0.76 (0.62–0.94)
PIONEER 6*	13/1591 (1%)	17/1592 (1%)	0.76 (0.37–1.56)
Overall (I^2=0.0%, *P*= .557)	722/27,977 (2.6%)	853/28,027 (3.0%)	0.84 (0.76–0.93)

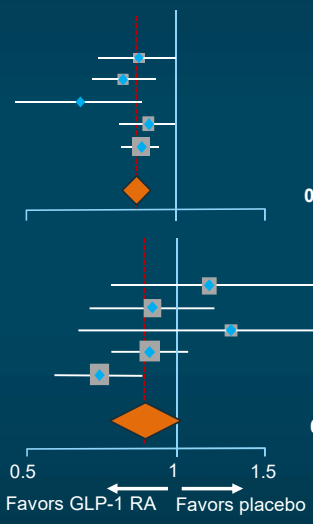




Kristensen SL, et al. *Lancet Diabetes Endocrinol*. 2019;7:776-785.

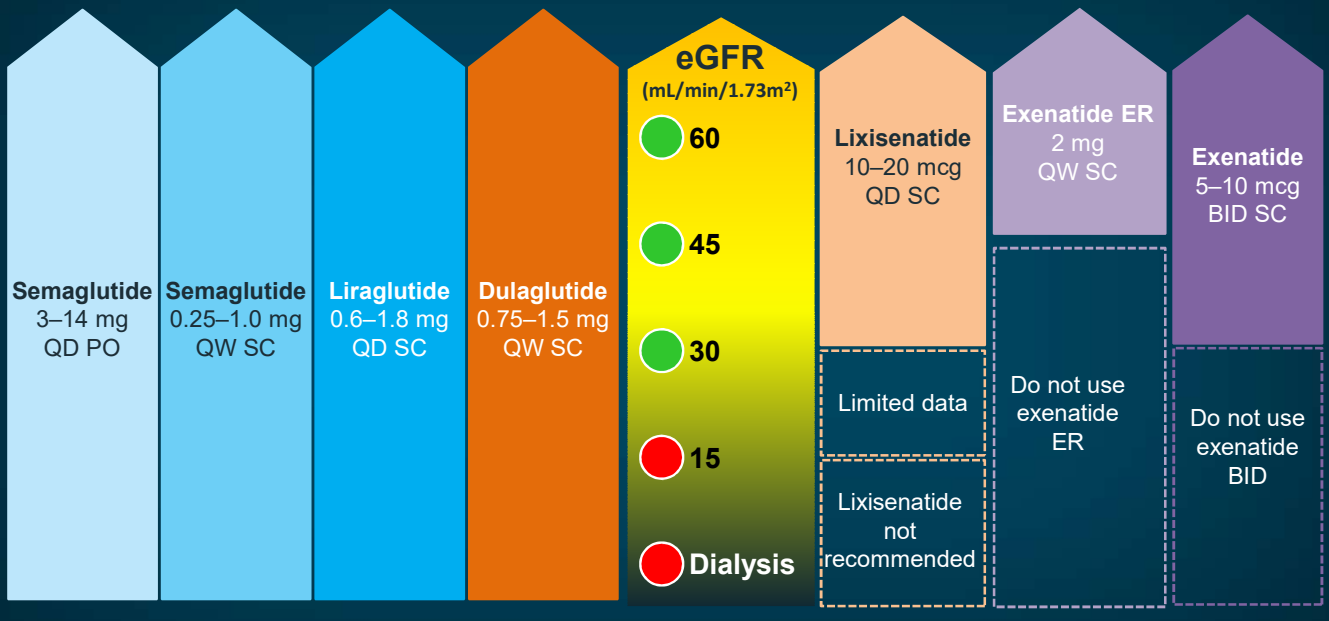
CV Outcomes Trials for GLP-1 Receptor Agonists: Renal Endpoints

	GLP-1 RA n/N (%)	Placebo n/N (%)	HR (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)		.083
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67–0.92)		.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46–0.88)		.006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76–1.01)		.065
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77–0.93)		<.001
Overall (I^2 = 0%, *P*= .413)	**1716/20,168 (9%)**	**2017/20,142 (10%)**	**0.83 (0.78–0.89)**	**62 (48 to 96)**	**<.0001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1.16 (0.74–1.83)		.513
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67–1.19)		.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64–2.58)		.48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74–1.05)		.164
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57–0.85)		<.001
Overall (I^2 = 42.7%, *P*= .137)	**561/20,752 (3%)**	**656/20,763 (3)**	**0.87 (0.73–1.03)**	**245 (118 to –1072)**	**.098**



Kristensen SL, et al. *Lancet Diabetes Endocrinol*. 2019;7:776-785.

Current Renal Restrictions: GLP-1 Receptor Agonists



PO = by mouth (oral).

Prescribing information for these agents.

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1. *What* we treat: definitions, diagnosis, and pathogenesis
2. *Why* we treat: reducing long-term complications
3. ***How* we treat: major glucose-lowering drug classes**
4. *When* to use newer therapies
   - SGLT2 inhibitors
   - GLP-1 receptor agonists
5. ***Where* are we going? New T2DM treatment guidelines (Dr. Inzucchi)**

Diabetes in the COVID-19 Era

- People with diabetes and COVID-19 are at a greater risk of worse prognosis and mortality[1]
- Many patients with diabetes have overweight/obesity
- Having obesity increases risk of severe illness from COVID-19[2]
  - An elevated BMI is associated with increased risk of hospitalizations from COVID-19[3]
- Reasons contributing to worse prognosis and outcomes are multifactorial and include[1]:
  - Age, sex, ethnicity
  - Comorbidities: hypertension, cardiovascular disease, obesity
  - Pro-inflammatory and pro-coagulative state

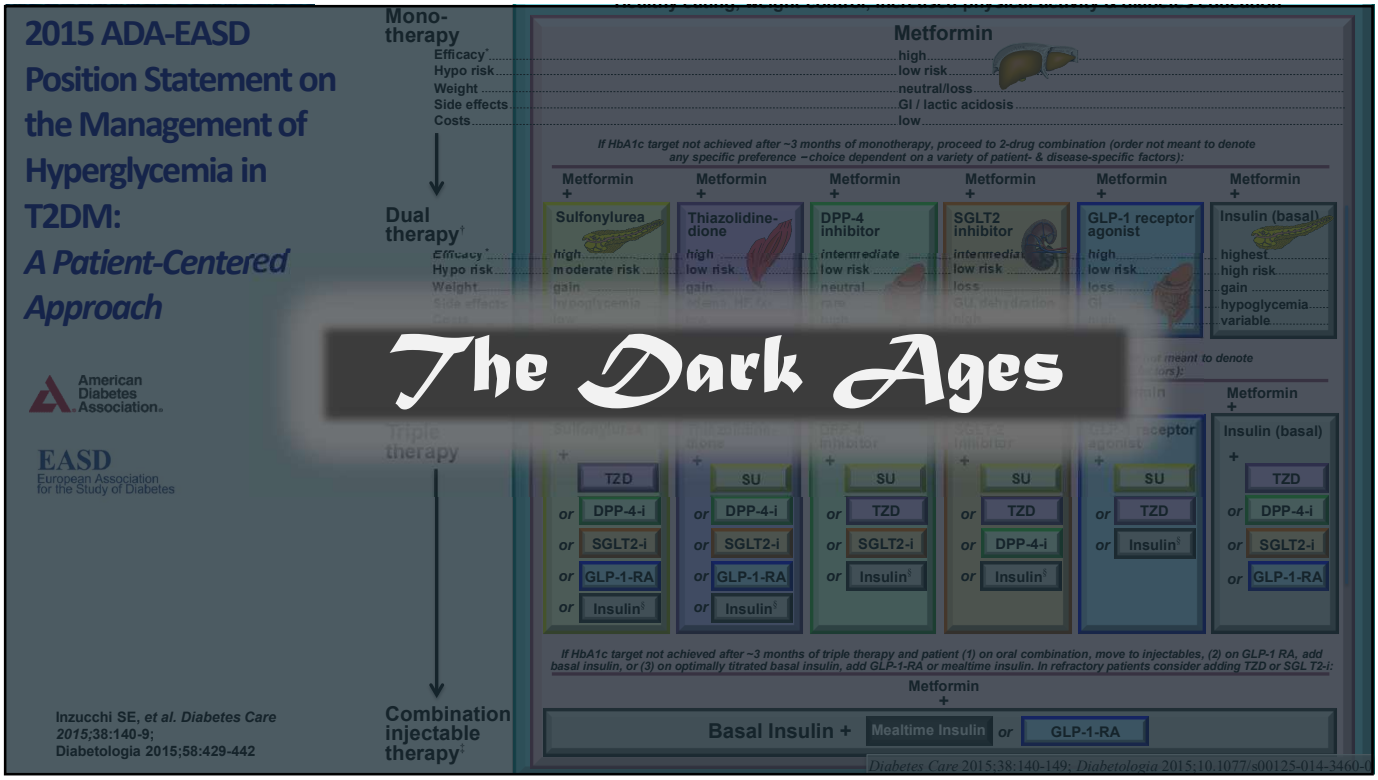
1. Apicella M, et al. *Lancet Diabetes Endocrinol.* 2020 Sep;8(9):782-792. doi: 10.1016/S2213-8587(20)30238-2. Epub 2020 Jul 17. Erratum in: *Lancet Diabetes Endocrinol.* 2020 Oct;8(10):e5.2. CDC. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html#obesity. 3. Petrilli CM, et al. *BMJ.* 2020;360:m1966.

Avoiding Clinical Inertia and Encouraging Adherence

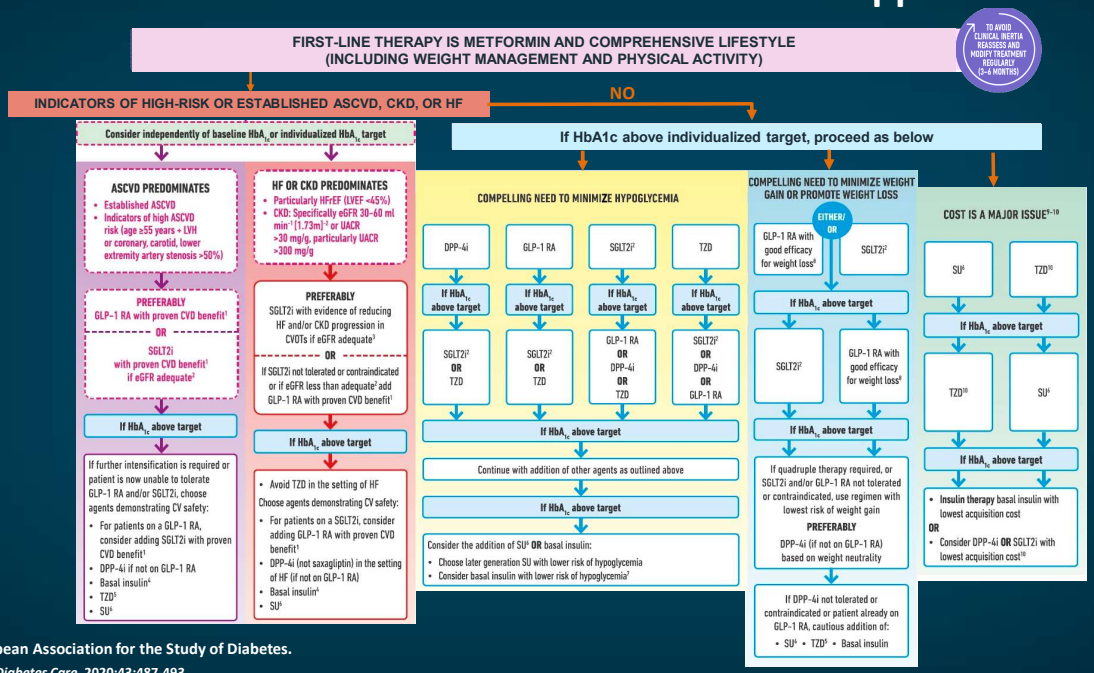
6 *Ps* of *Personalizing* Diabetes Care

1. ***P*athophysiology**	Insulin resistance vs deficiency? Stage of disease?
2. ***P*otency**	Distance from HbA1c target?
3. ***P*recautions**	Side effects, contraindications?
4. "***P*erks"**	Added benefits beyond glucose control? (weight, BP, CV, renal)
5. ***P*racticalities**	Tablets vs injections? Administration frequency? Need for blood glucose monitoring?
6. ***P*rice**	Branded vs generic? Insurance coverage?

Adapted from Inzucchi SE. *Endocrinol Metab Clin North Am.* 2018;47:137-152.



2020 ADA-EASD Consensus T2DM—Overall Approach



EASD = European Association for the Study of Diabetes.

Buse JB, et al. *Diabetes Care*. 2020;43:487-493.

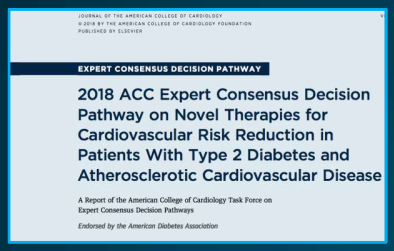
AHA: Top 10 Take-Home Messages for *Primary* Prevention of CVD

1. **Most important preventative modality is *promotion of a healthy lifestyle***
2. Team-based care approaches; social determinants of health (SDOH) assessment to inform treatment decisions
3. 10-year ASCVD risk estimation/discussion prior to pharmacological therapy (adults 40–75 years)
4. Healthy diet (vegetables, fruits, nuts, whole grains, lean protein, and fish), and weight loss for overweight/obese
5. Physical activity (150 min/week moderate-intensity, 75 min/week vigorous)
6. **Lifestyle changes in T2DM are *crucial*; if pharmacotherapy is indicated,** metformin is 1st line, followed by consideration of **SGLT2-i or GLP-1 RA**
7. Tobacco cessation
8. Use ASA **infrequently**—lack of net benefit
9. Statins are 1st-line therapy for ASCVD prevention in people with elevated LDL-C (≥190 mg/dL), DM patients 40–75 years, and those identified at sufficient ASCVD risk
10. Nonpharmacologic interventions for all adults with elevated BP or hypertension; target BP <130/80 with pharmacotherapy

ASA = aspirin.

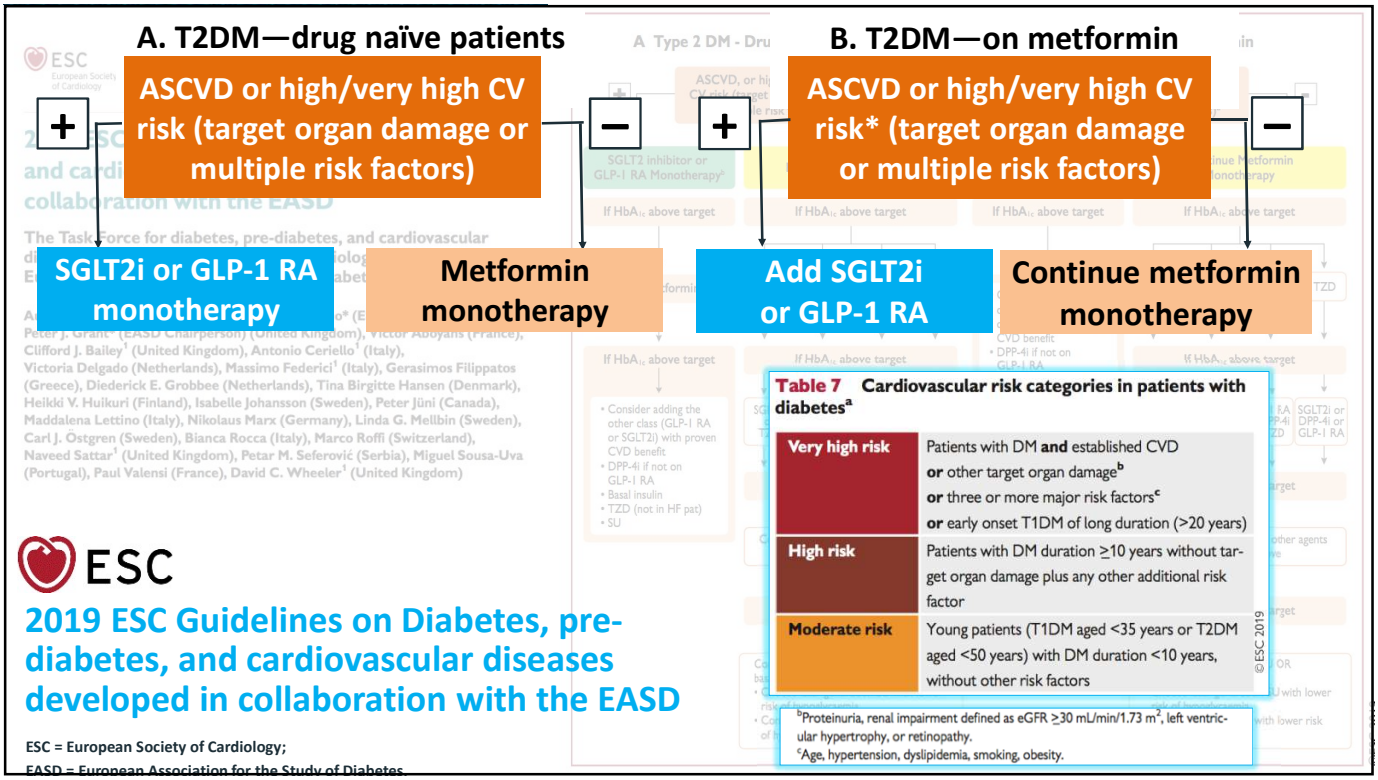
Arnett DK, et al. *J Am Coll Cardiol*. 2019;74:e177-e232.

2018 ACC Expert Consensus Decision Pathway



ADD = American College of Cardiology.

Das SR, et al. *J Am Coll Cardiol.* 2018;72:3200-3223.



ESC

2019 ESC Guidelines on Diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

ESC = European Society of Cardiology;
EASD = European Association for the Study of Diabetes.

CV Risk Factor Reduction Strategies in DM

American Diabetes Association (ADA)			
BP (mm/Hg)	• Lifestyle for >120/80; drug therapy for ≥140/90 • Use ACEI*/ARB*, dihydropyridine CCB, or thiazide-like diuretics; target BP <140/90 • Start with 2 drugs if BP ≥160/100 • Multiple drug therapy usually necessary		
Lipids (mg/dL)	**20–39 years + CVD RFs**	**40–75 years + CVD RFs**	**>75 years**
	Moderate-intensity statin	**Moderate-intensity statin**	**Moderate-intensity statin**
	• **In adults with diabetes at higher risk**: High-intensity statin if 10-yr ASCVD risk is ≥20%. If overt ASCVD, high-intensity statin and add ezetimibe or PCSK-9i if LDL >70.		
	TGs ≥500	**TGs 135–499 +ASCVD/other CV risk on statin**	**TGs 175–499**
	Treat pharmacologically (fibrates, EPA)	**Consider adding icosapent ethyl**	**Address lifestyle, glycemic control, other factors (eg, TG-raising meds)**
Aspirin	• **+ ASCVD**: ASA 75–162 mg/d for *secondary prevention* • 'High-risk': Consider ASA 75–162 mg/d for *primary prevention* after weighing risks/benefits		

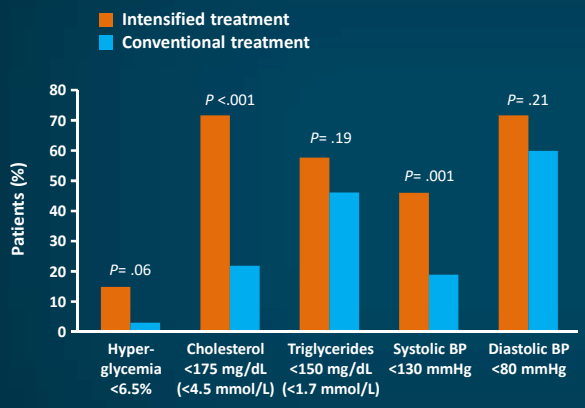
*favored if albuminuria.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; RF = risk factor; EPA = eicosapentaenoic acid.

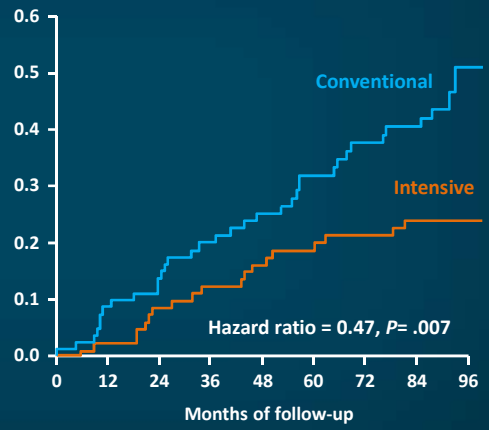
ADA. *Diabetes Care.* 2020;43(suppl 1):S111-S134.

Steno-2: Intensified Multifactorial Intervention Reduces CV Risk

Reached treatment goal at 8 years (%)



Risk for composite CV endpoint*



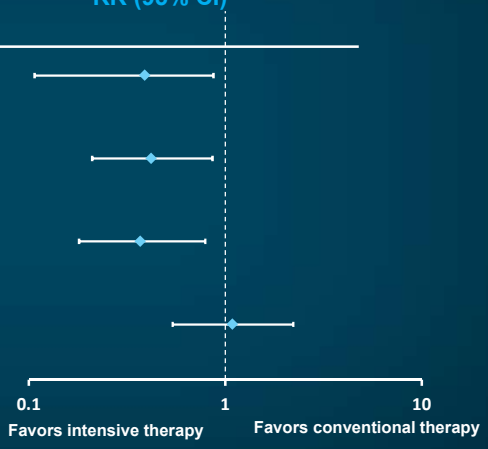
All patients in this study had microalbuminuria at baseline.

*Composite CV endpoint = death from CV causes, nonfatal MI, nonfatal stroke, revascularization, and amputation.

Gaede P, et al. *N Engl J Med*. 2003;348:383-393.

Steno-2: Intensified Multifactorial Intervention Reduces Risk of Microvascular Events

Variable	Relative risk (95% CI)	*P*-value
Nephropathy	0.39 (0.17–0.87)	.003
Retinopathy	0.42 (0.21–0.86)	.02
Autonomic neuropathy	0.37 (0.18–0.79)	.002
Peripheral neuropathy	1.09 (0.54–2.22)	.66



All patients in this study had microalbuminuria at baseline.

Gaede P, *et al. N Engl J Med.* 2003;348:383-393.

Improving Glycemic, Cardiovascular, and Renal Outcomes in T2DM Summary

- T2DM has a complex pathogenesis
- Glucose-lowering options have expanded markedly over the past 10–15 years
- "Foundation therapy" remains **lifestyle** and **metformin**; several options are available beyond metformin
- Recent clinical trials demonstrate that CV (and CKD) risk are reduced with certain classes of glucose-lowering agents, including **SGLT2 inhibitors** and **GLP-1 receptor agonists**
- With any treatment decision, it is important to weigh both the risks and benefits of each agent and design a treatment regimen ***individualized*** to the patient
- Also, ***don't forget to address CV risk factors*** in a comprehensive fashion

Infographic Cases

A Virtual Tutorial (Dr. Peters)

CASE STUDY 1 EXAMPLE

Newly Diagnosed T2DM Patient Status Post (s/p) CABG

Newly Diagnosed T2DM Patient s/p CABG

- CC: 54-year-old man with newly diagnosed T2DM, which was discovered during recent cardiovascular admission. He is referred to address his diabetes management.
- HPI:
  - He developed fatigue and chest pain with radiation to left shoulder while rushing to catch a commuter train. He was brought to a local hospital and found to have a STEMI.
  - Cardiac catheterization demonstrated triple-vessel CAD; he was referred for a CABG, which proceeded uneventfully.
  - During the admission, his blood glucose was found to be >180; an HbA1c was obtained and was found to be elevated at 8.3%. There is no known prior h/o diabetes, but he recalls being told that he had "borderline sugars" in the past.

CC = chief complaint; HPI = history of present illness; STEMI = ST-elevation MI; CABG = coronary artery bypass graft; h/o = history of.

Newly Diagnosed T2DM Patient s/p CABG: History

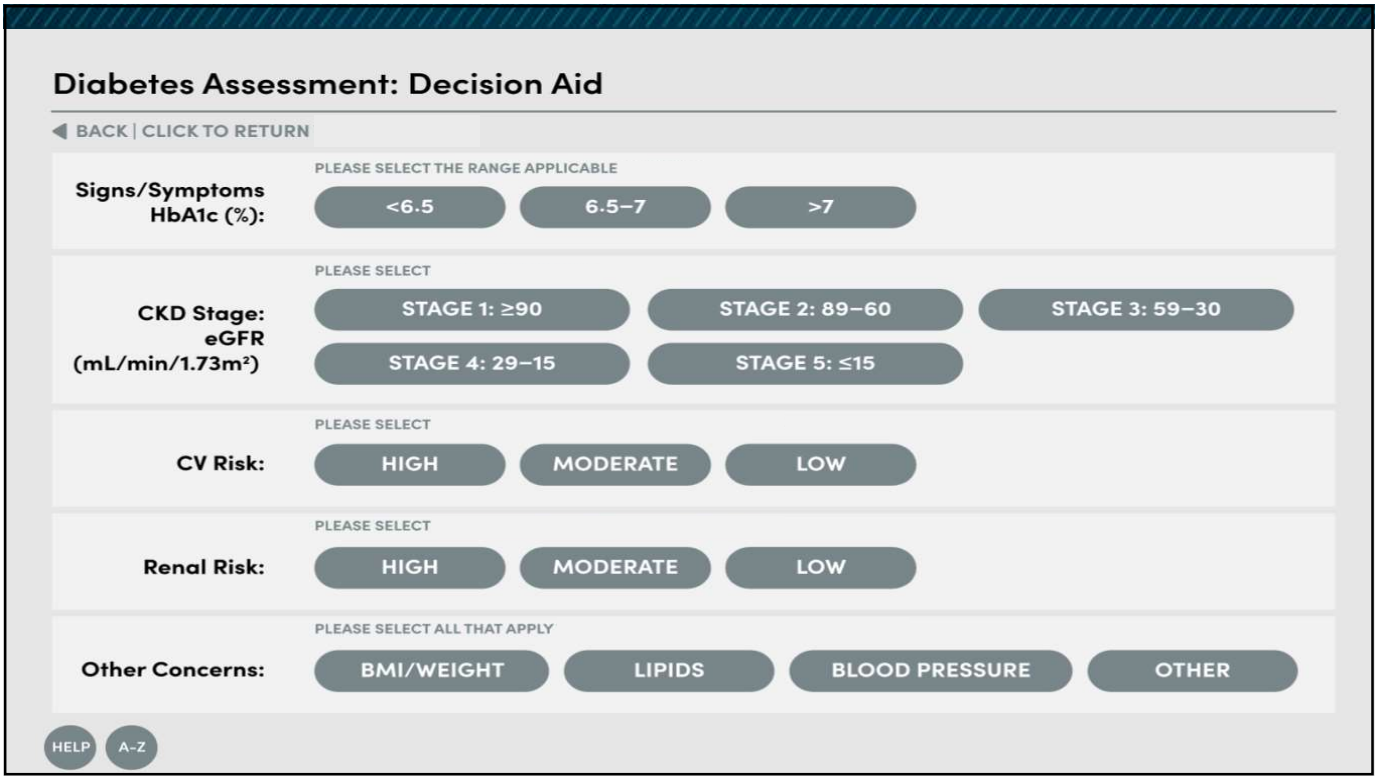
- **Past medical history:** hypertension, gout, obesity, OSA
- **Past surgical history:** R rotator cuff repair, laparoscopic cholecystectomy, LASIK
- **Social history:** commodities trader; married, with 3 teenage children; smokes 1 ppd; social drinker; inactive; eats out a lot, including fast foods; high-salt and high-fat diet
- **Family history:** + T2DM on father's side (multiple members), + CAD father (MI at age 49)
- **Allergies:** shellfish
- **Medications**
  - Prior to admission: lisinopril/HCTZ 10/25 mg QD, allopurinol 300 mg QD
  - Upon discharge: lisinopril 20 mg QD, metoprolol 100 mg QD, atorvastatin 40 mg QD, aspirin 81 mg QD, allopurinol 300 mg QD

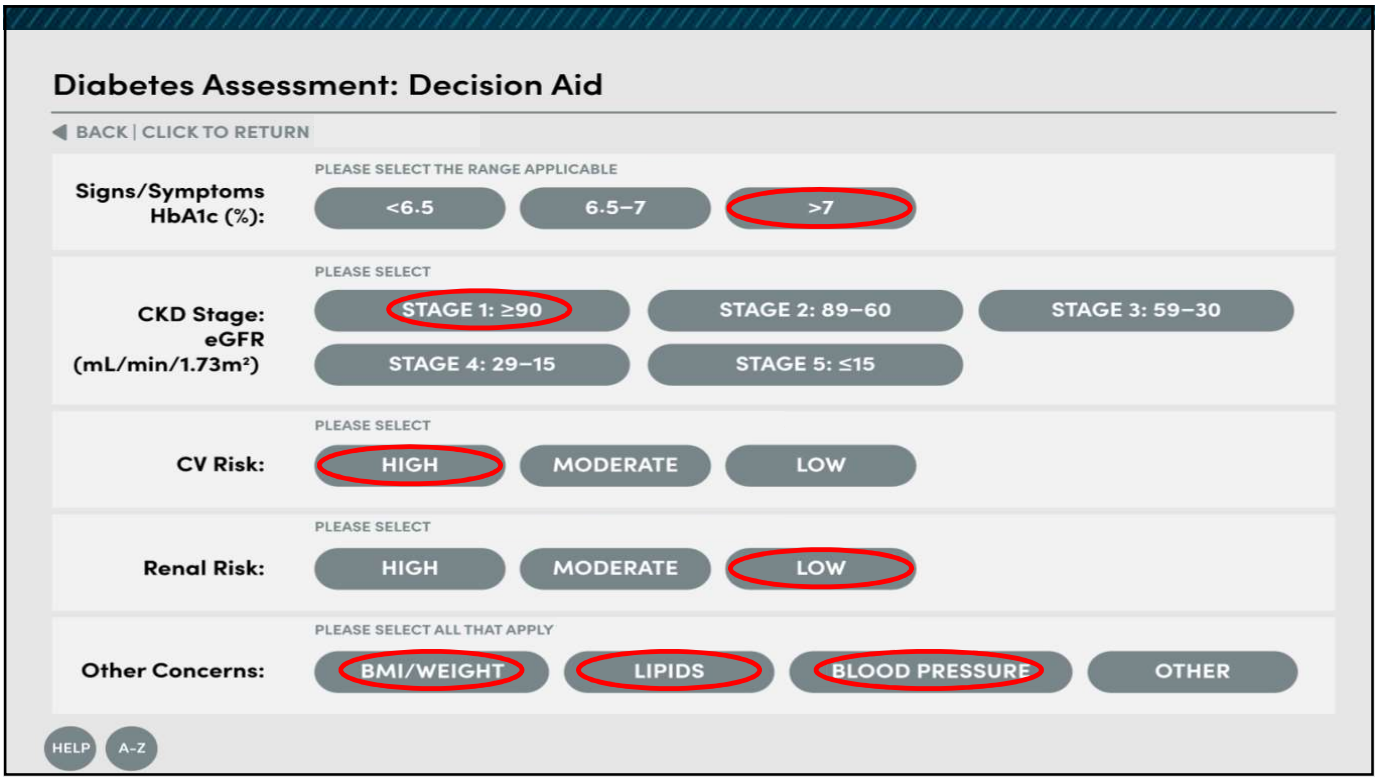
OSA = obstructive sleep apnea; R = right; LASIK = laser-assisted in situ keratomileusis; ppd = pack per day; HCTZ = hydrochlorothiazide.

Newly Diagnosed T2DM Patient s/p CABG: Exams, Labs, and Studies

- Physical exam
  - Vitals: weight = 235 lbs, BMI = 33.2 kg/m^2, BP = 143/92 mmHg, HR = 78 bpm, RR = 14 breaths/minute
  - Acanthosis nigricans, no retinopathy, no signs of HF, no edema, distal pulses reduced but feet warm and well perfused, no ulcerations of bony deformities, intact sensation distally
- Laboratories
  - FPG = 154 mg/dL, HbA1c = 8.6%
  - Cr = 0.84 mg/dL, eGFR = 95 mL/min/1.73m^2, UACR = 15 mcg/mg Cr
  - LDL-C = 83 mg/dL, HDL-C = 39 mg/dL, TGs = 184 mg/dL
- Studies
  - EKG: LVH, inferior Q-waves
  - Cardiac echo: LVH, mild inferior hypokinesis, trace MR, LVEF = 50–55%

BMI = body mass index; HR = heart rate; bpm = beats per minute; RR = respiratory rate (in this context); Cr = creatinine; EKG = electrocardiogram; LVH = left ventricular hypertrophy; MR = mitral regurgitation; LVEF = left ventricular ejection fraction.



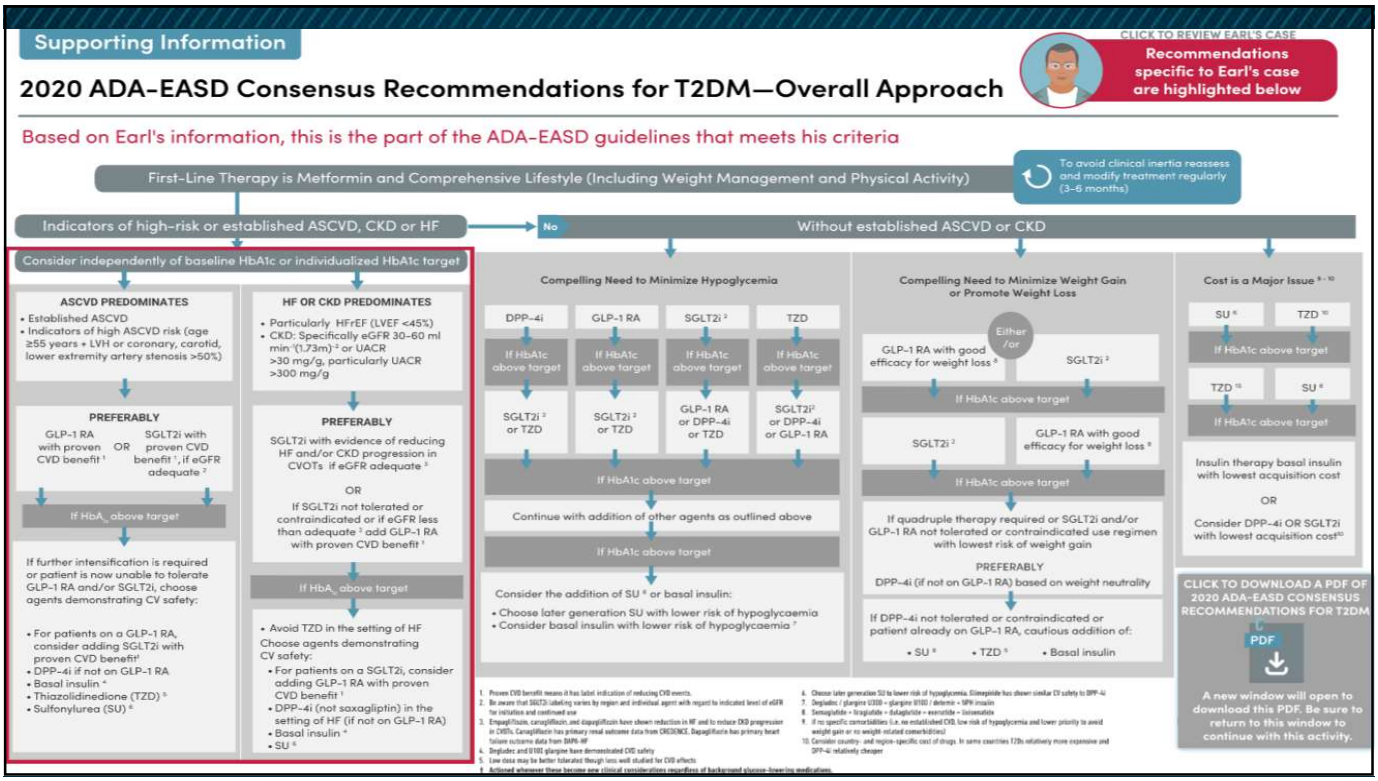


Newly Diagnosed T2DM Patient s/p CABG: Considerations

- **Additional interventions to consider:**
- **Studies**
  - None
- **Therapeutic management**
  - How would you address this patient's T2DM?
  - How would you address this patient's other CV risk factors

- HbA1c target <7%
- Nutrition referral
- Start with metformin
- May need 2 drugs
- If so, SGLT2i or GLP-1RA

- Stop smoking
- Weight loss
- Increase aerobic activity
- Intensify lipid therapy
- Intensify HTN therapy



CASE STUDY 2 EXAMPLE

Add-On Therapy in a T2DM Patient with CAD

Add-On Therapy in T2DM Patient with CAD

- CC: 63-year-old man with a 6-year history of T2DM on metformin monotherapy, who is referred for suboptimal glycemic control in the setting of known CAD.

- HPI:
  - –He presented 6 years ago with a HbA1c of 7.5% after 2–3 years of prediabetes. Metformin was started and titrated to a dose of 1500 mg/day, and his HbA1c fell to 6.8%. Over the intervening years, his HbA1c has slowly climbed to his most recent result of 7.9%.
  - –During these years, he developed exertional angina with a positive nuclear stress test. Cardiac catherization showed single-vessel disease, for which he received a drug-eluting stent, with resolution of his symptoms. He has known normal left-ventricular function.

Add-On Therapy in a T2DM Patient with CAD: History

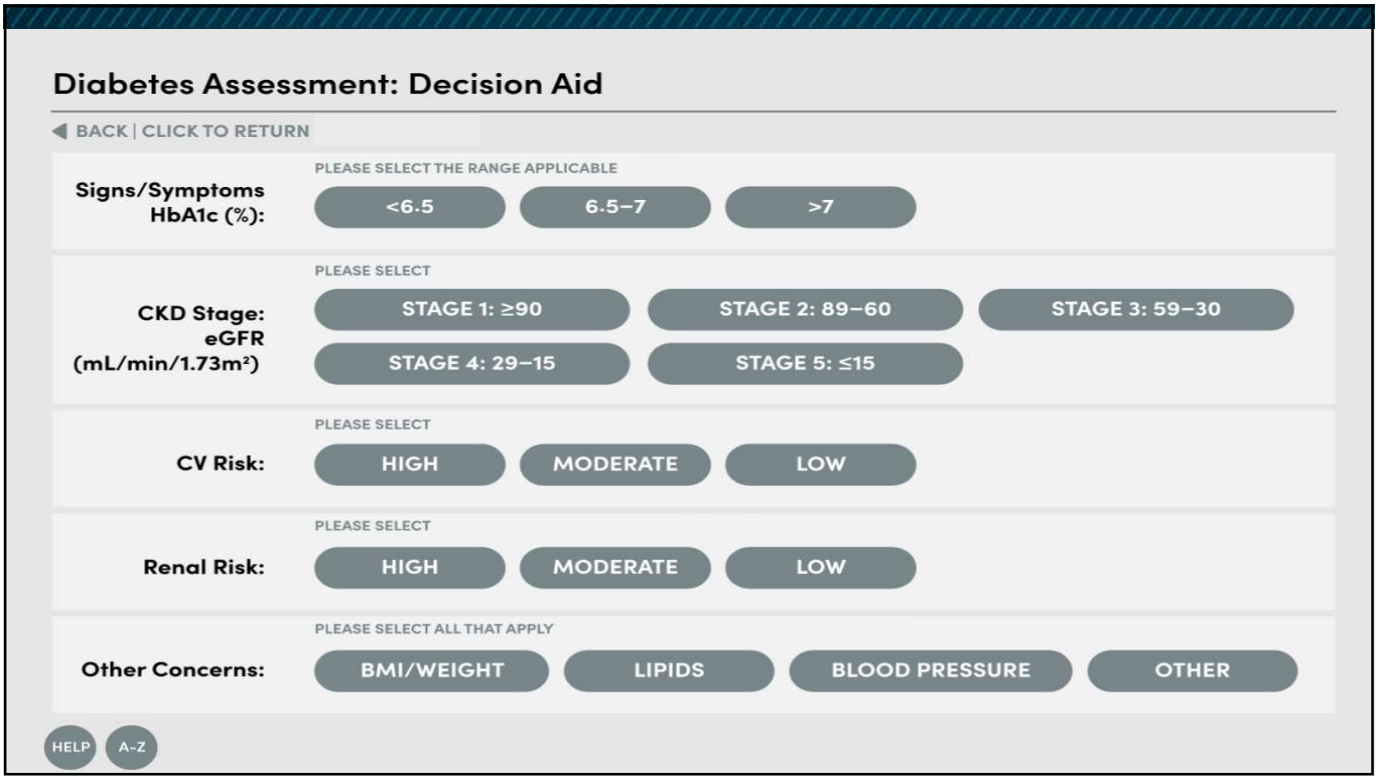
- **Past medical history:** hypertension, hyperlipidemia, colonic polyps, primary hypothyroidism (Hashimoto disease), NAFLD, OA knees
- **Past surgical history:** polypectomy, arthroscopic meniscal surgery L knee
- **Social history:** high school math teacher; divorced, with one adult child; former smoker; 2 glasses wine most days; inactive; diet high in carbs (sweets)
- **Family history:** + T2DM both parents; mother had stroke, and father had heart failure
- **Allergies:** PCN, sulfa drugs
- **Medications:** losartan 50 mg QD, amlodipine 5 mg QD, chlorthalidone 25 mg QD, lovastatin 20 mg QD, aspirin 81 mg QD, ticagrelor 60 mg BID

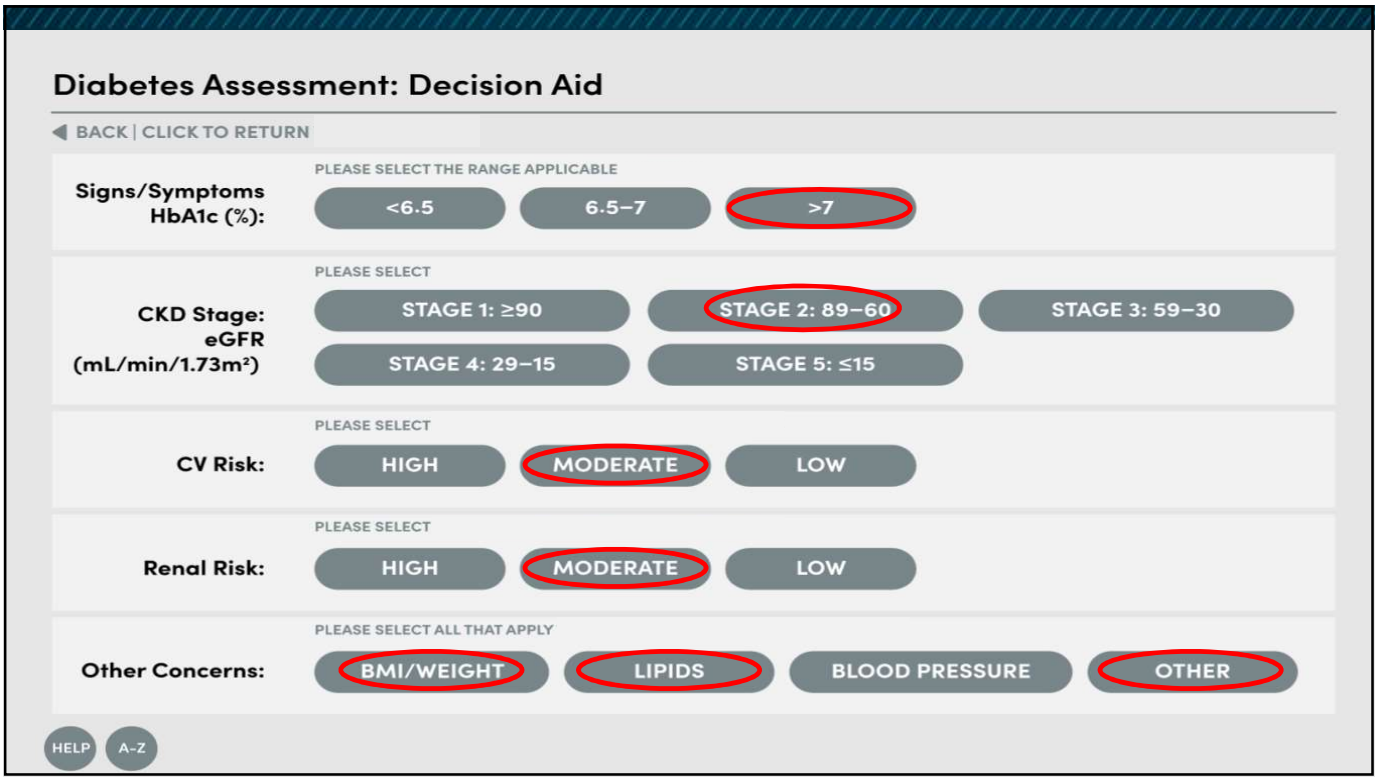
OA = osteoarthritis; L = left; PCN = penicillin.

Add-On Therapy in a T2DM Patient with CAD: Exams, Labs, and Studies

- **Physical exam**
  - –Vitals: weight = 181 lbs, BMI = 29.3 kg/m^2, BP = 128/82 mmHg, HR = 66 bpm, RR = 16 breaths per minute
  - –No evidence of HF, no retinopathy, no neuropathy
- **Laboratories**
  - –FPG = 116 mg/dL, HbA1c = 7.9%
  - –Cr = 0.79 mg/dL, eGFR = 87 mL/min/1.73m^2, UACR = 54 mcg/mg Cr
  - –AST = 49 U/L, ALT = 62 U/L
  - –LDL-C = 98 mg/dL, HDL-C = 44 mg/dL, TGs = 161 mg/dL
- **Studies**
  - –EKG: normal
  - –Cardiac echo: normal

AST = aspartate aminotransferase; U/L = units/liter; ALT = alanine aminotransferase.



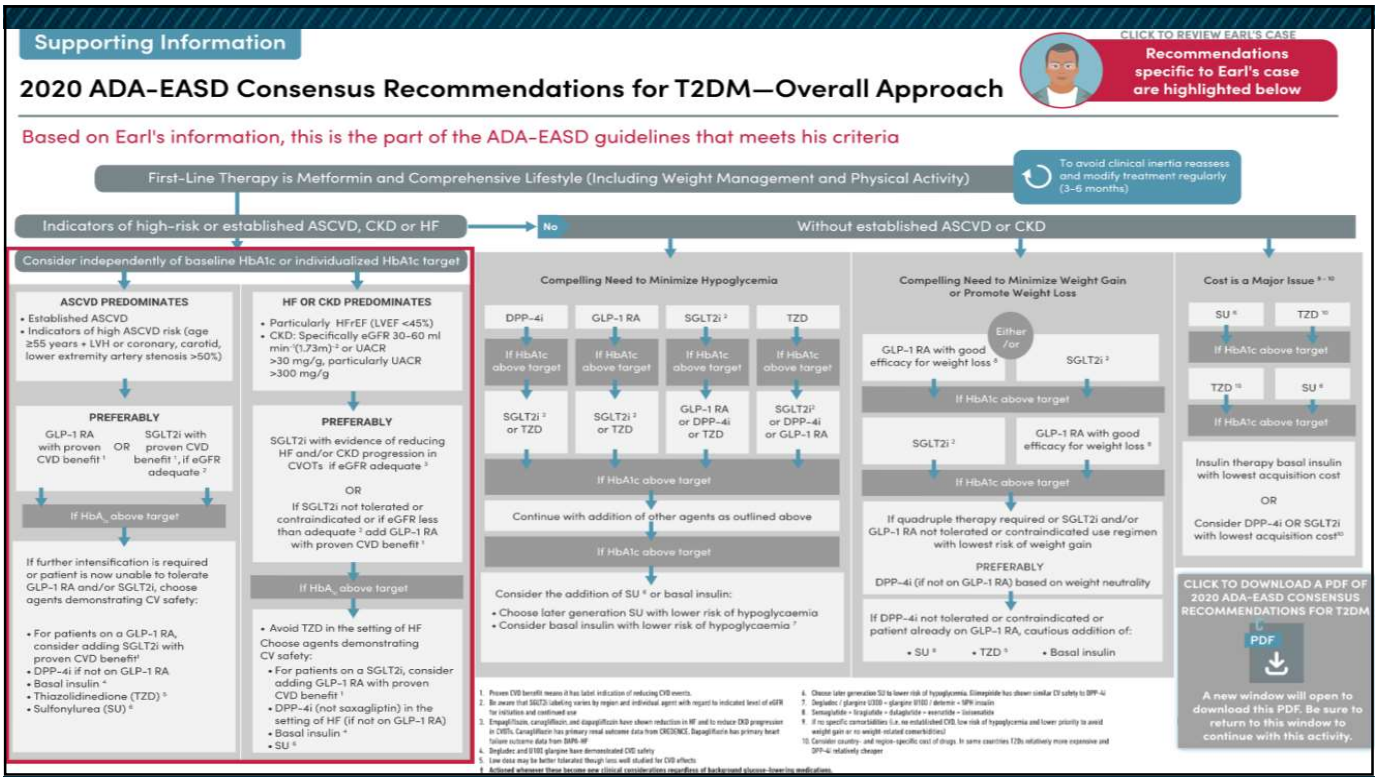


Add-On Therapy in a T2DM Patient with CAD: Considerations

- **Additional interventions to consider:**
- **Studies**
  - None
- **Therapeutic management**
  - How would you address this patient's T2DM?
  - How would you address this patient's other CV risk factors

- Consider maximizing metformin dose
- Add 2nd agent: SGLT2i or GLP-1 RA
- A1c target <7.5%

- Weight loss
- Increase aerobic activity
- Intensify lipid therapy



Posttest Questions

Dr. Inzucchi

Question 1

Meta-analyses for the SGLT2 inhibitor trials EMPA-REG, CANVAS, and DECLARE-TIMI demonstrated which of the following?

a. Reduced hazard ratios for the progression of chronic kidney disease with SGLT2 inhibitors vs placebo
b. Reduced hazard ratios for the development of bone fractures with SGLT2 inhibitors vs placebo
c. Increased hazard ratios for MACE with SGLT2 inhibitors vs placebo
d. Increased hazard ratios for heart failure hospitalizations with SGLT2 inhibitors vs placebo

Question 2

Meta-analyses for the GLP-1 receptor agonist trials LEADER, SUSTAIN 6, REWIND, and HARMONY demonstrated which of the following?

a. Increased hazard ratios for heart failure hospitalizations with GLP-1 receptor agonists vs placebo
b. Increased hazard ratios for MACE with GLP-1 receptor agonists vs placebo
c. Reduced hazard ratios for bone fractures with GLP-1 receptor agonists vs placebo
d. Reduced hazard ratios for stroke with GLP-1 receptor agonists vs placebo

Question 3

A 60-year-old man with T2DM and obesity has a HbA1c of 7.8 on metformin and a SGLT2 inhibitor. He has had trouble losing weight. What would be the most appropriate for treatment intensification in this patient based on current consensus guidelines?

a. A DPP-4 inhibitor
b. A GLP-1 receptor agonist
c. A sulfonylurea
d. Basal insulin

Question 4

When intensifying T2DM therapy for a patient with cardiovascular disease, which of the following agents has had positive results regarding reduction of major adverse cardiovascular events (MACE) based on cardiovascular outcomes trials (CVOTs)?

1. Saxagliptin
2. Lixisenatide
3. Ertugliflozin
4. Dulaglutide

Question 5

A 45-year-old woman with obesity has uncontrolled T2DM on metformin and a DPP-4 inhibitor. What would be the most appropriate intervention to add to her current regimen for treatment intensification based on current consensus guidelines when cost is not a factor?

1. A GLP-1 receptor agonist
2. A SGLT2 inhibitor
3. A sulfonylurea
4. Pioglitazone

Thank You!

Questions and Answers

Please visit our two interactive Infographic patient decision trees to aid you in better managing your patients with T2DM.

After the live meeting, visit http://www.mlgdecisiontree.com/ to use these interactive patient decision trees!

Please build your own complimentary poster for the office!