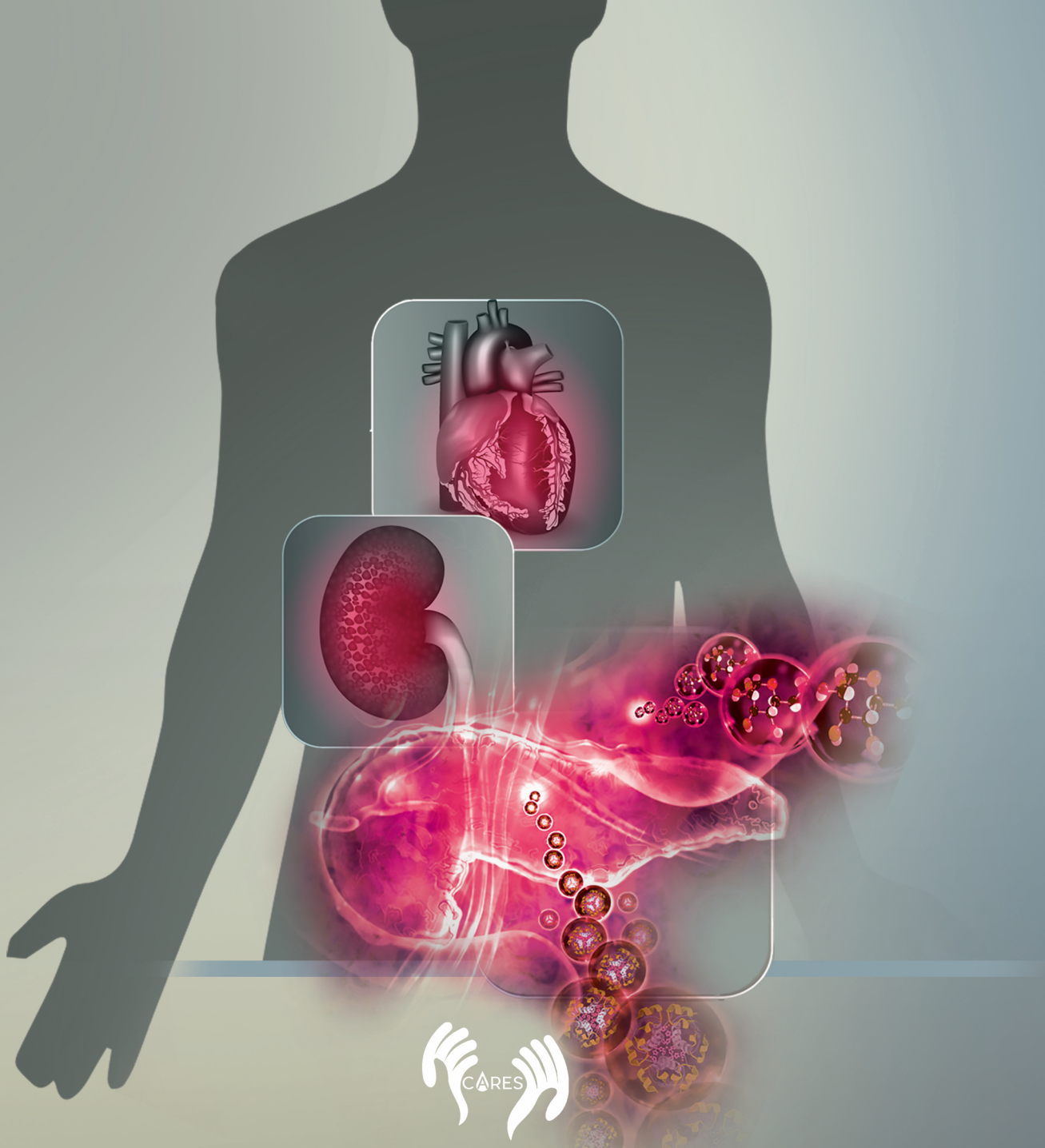

THE CARES APPROACH:

Improving Glycemic, Cardiovascular and Renal Outcomes

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.

The CARES Approach: Improving Glycemic, Cardiovascular, and Renal Outcomes

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PROGRAM OVERVIEW

This activity will cover the treatment and management of patients with type 2 diabetes mellitus (T2DM).

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 T2DM.

LEARNING OBJECTIVES

On completing the program, attendees should be able to:

- 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

ACCREDITATION STATEMENT

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

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Med Learning Group designates this live activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

NURSING CREDIT INFORMATION

Purpose:

This program would be beneficial for nurses involved and/or interested in the therapeutic management of patients with T2DM.

CNE Credits:

1.0 ANCC Contact Hour

CNE Accreditation Statement:

Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

AMERICAN OSTEOPATHIC ASSOCIATION CREDIT INFORMATION

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Faculty Member	Disclosure
Silvio Inzucchi, MD	Dr. Inzucchi reports that he serves as a 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.
Intekhab Ahmed, MD	Dr. Ahmed reports that he has no relevant relationships with a commercial entity or manufacturer.
Jonathan Anolik, MD	Dr. Anolik reports that he has no relevant relationships with a commercial entity or manufacturer.
Amy Fountain-Freeth, MD	Dr. Fountain-Freeth reports that she has no relevant relationships with a commercial entity or manufacturer.
Mark Molitch, MD	Dr. Molitch reports that he serves as a consultant for Merck, Pfizer and Chiasma. He also participates in research grants with Novartis, Chiasma, Bayer, Cortendo, Crinetics, Ionis, and NovoNordisk.

Dhiren Patel, PharmD, CDE	Dr. Patel reports that he serves as a consultant for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Insulet, Merck, Novo Nordisk, and Sanofi. He is also on the speakers bureau for Amarin, Astra Zeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Merck, Novo Nordisk, Valeritas, and Xeris.
Anne Peters, MD	Dr. Peters reports that she is on the speakers bureau for Novo Nordisk. She also serves as a consultant for Abbott Diabetes Care, Boehringer Ingelheim, Eli Lilly and Company, Livongo, MannKind, Merck, Novo Nordisk, Sanofi, and Pendulum Therapeutics. Dr. Peters has received research support from Dexcom, vTv Therapeutics, and donated devices from Abbott Diabetes Care. She also has stock options from Mellitus Health, Omada Health, Stability Health, Pendulum Therapeutics, and Livongo.
Richard E. Pratley, MD	Dr. Pratley reports that he has received speaker fees from Novo Nordisk. He serves as a consultant for Merck, Novo Nordisk, Pfizer, Sanofi, Scohia Pharma Inc., and Sun Pharmaceutical Industries. Dr. Pratley has also received grant support from Lexicon Pharmaceuticals, Hanmi Pharmaceuticals Co., Novo Nordisk, Poxel SA and Sanofi. All payments for all of his services were made directly to AdventHealth, a nonprofit organization.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was independently peer reviewed.

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The staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

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2. Participate in the live activity
3. Complete posttest and evaluation form online.

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Provided by Med Learning Group

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This activity is supported by educational grants from Lilly, Boehringer Ingelheim Pharmaceuticals and Lilly, and Merck & Co., Inc.

Grand Rounds Agenda

I. CVD and Renal Implications in T2DM
- a. Epidemiology
- b. Traditional risk factors
- c. Pathophysiology

(**Whiteboard animation:** Effects of T2DM and role of HbA1c)

II. Guidelines and Standards for T2DM Treatment
- a. ADA standards of care/AACE glycemic control algorithm
  - i. Lifestyle interventions
    - 1. Healthy eating, weight control, physical activity, diabetes education
  - ii. Therapeutic management
    - 1. Algorithms for treatment intensification
    - 2. Selection of medications for patients with renal or cardiovascular risks or comorbidities
    - 3. Avoiding clinical inertia
    - 4. Encouraging adherence

(**Whiteboard animation:** Incretins and SGLT2 inhibitors in the management of T2DM)

III. GLP-1 Receptor Agonists
- a. Mechanism of action
- b. Distinctions between agents in the class
- c. Glycemic outcomes
- d. Results from CVOTs

IV. SGLT2 Inhibitors
- a. Mechanism of action
- b. Distinctions between agents in the class
- c. Glycemic outcomes
- d. Results from CVOTs

V. Conclusions

VI. Q&A

The CARES Approach: Improving Glycemic, Cardiovascular, and Renal Outcomes

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1

Disclosures

- Dr. Silvio Inzucchi is a consultant for Boehringer Ingelheim, AstraZeneca, Sanofi/Lexicon, Novo Nordisk, Merck, vTv Therapeutics, Zafgen, Abbott/Alere, and Eisai (TIMI). He has also received salary from Elsevier, McGraw-Hill, and UpToDate.
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Educational Objectives

- 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

3

A Case Example

Patient with T2DM and CAD

4

Patient with T2DM and CAD

- 67-year-old woman with a 8-year history of T2DM on metformin monotherapy
  - Metformin initially started and titrated to a dose of 1500 mg/day; her A1c fell to 6.8%
- Has suboptimal glycemic control in the setting of known coronary artery disease (CAD)
  - Current HbA1c = 7.9%

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Patient with T2DM and CAD (continued)

Past Medical History:
hypertension, hyperlipidemia, breast cancer, colonic polyps, primary hypothyroidism (Hashimoto disease), NAFLD, OA knees

Other 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, anastrozole 1 mg QD

Physical exam
Vitals: weight = 181 lbs, BMI = 29.3 kg/m^2, BP = 128/82, HR = 66, RR = 16
No evidence of HF, no retinopathy, no neuropathy

Labs
- FPG = 116, HbA1c = 7.9%
- Cr = 0.79, eGFR = 87, UACR = 54 mcg/mg Cr
- AST = 49, ALT = 62
- LDL-C = 98 mg/dL, HDL-C = 44 mg/dL, TGs = 161 mg/dL

Studies
- EKG: normal
- Cardiac echo: normal

What would you do for this patient?

NAFLD = nonalcoholic fatty liver disease; OA = osteoarthritis; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

6

34.2 million with diabetes

88 million with prediabetes*

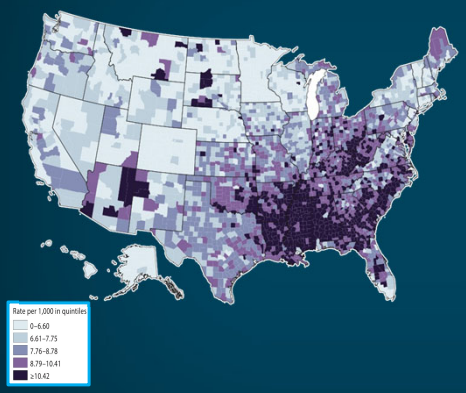
*Hemoglobin A1c between 5.7% and 6.4%.

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 July 30, 2020.

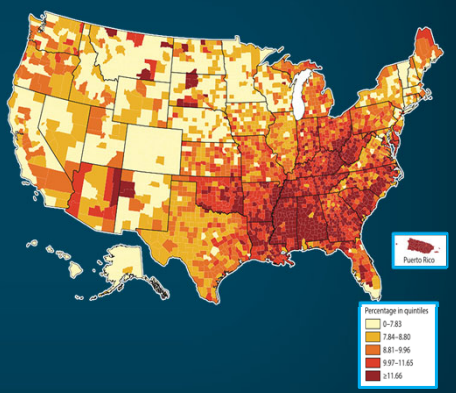
7

Incidence and Prevalence of Diabetes in United States by Region

Diagnosed diabetes incidence (2013)



Diagnosed diabetes prevalence (2013)



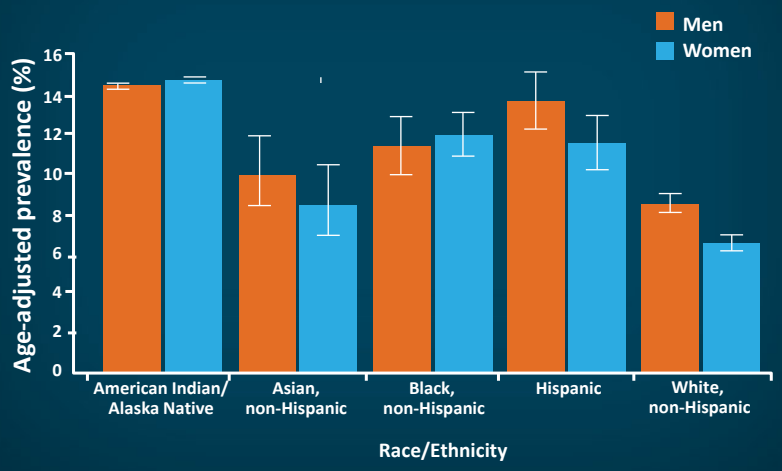
Counties in the *southern and Appalachian regions* of the United States tend to have the highest rates of incidence and prevalence

CDC. National Diabetes Statistics Report—2017 (https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf). Accessed July 30, 2020.

8

Prevalence of Diabetes by Ethnicity

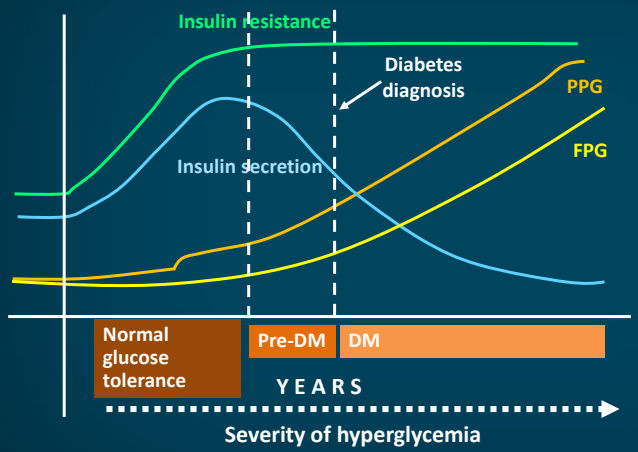
Estimated age-adjusted adult prevalence of diagnosed diabetes by race/ethnicity (2017–2018)



CDC. National Diabetes Statistics Report—2020 (www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Accessed July 30, 2020.

9

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.

T2DM = type 2 diabetes mellitus; DM = diabetes mellitus; PPG = postprandial plasma glucose; FPG = fasting 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.

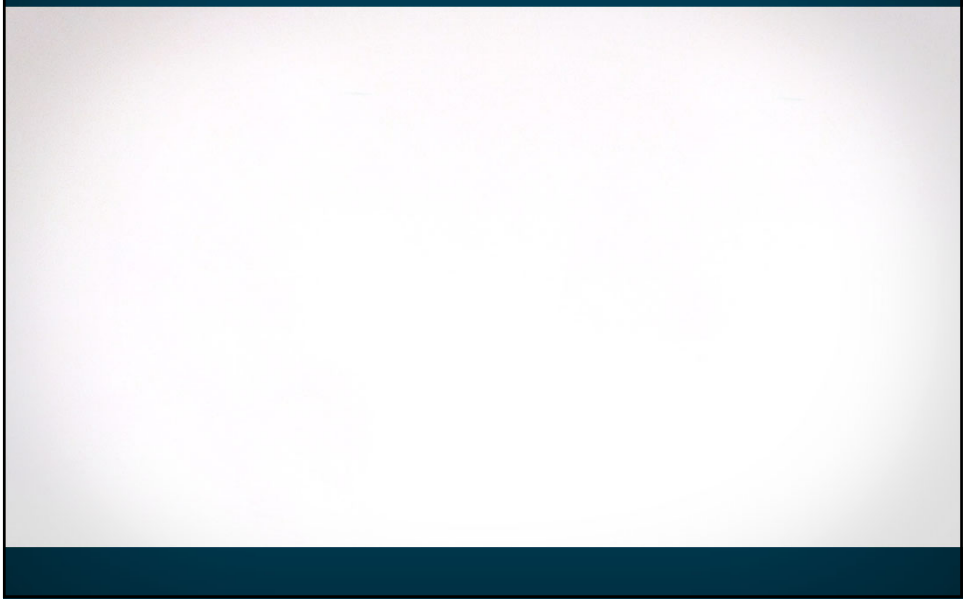
10

Whiteboard Animation 1

Relationship between HbA1c and T2DM

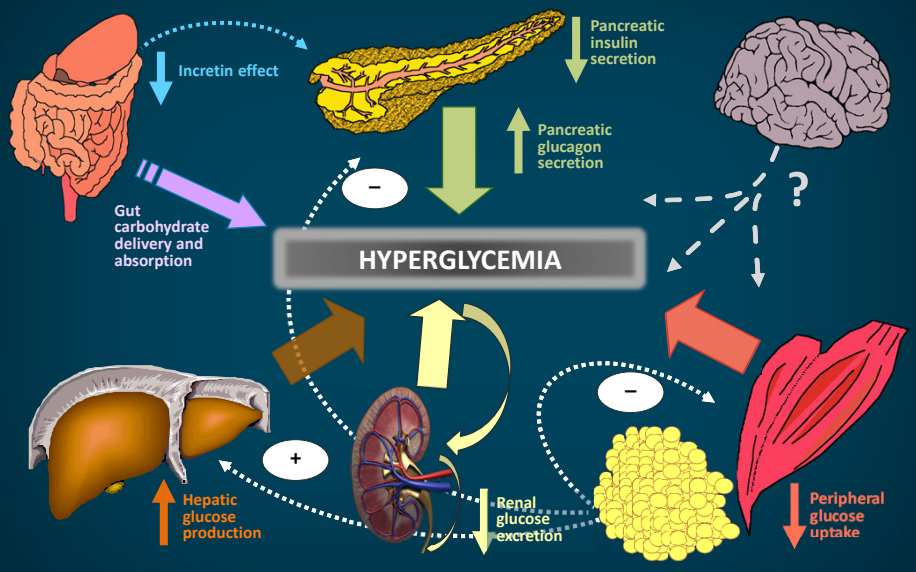
11

Relationship between HbA1c and T2DM
https://youtu.be/US_gtvNuDEA



12

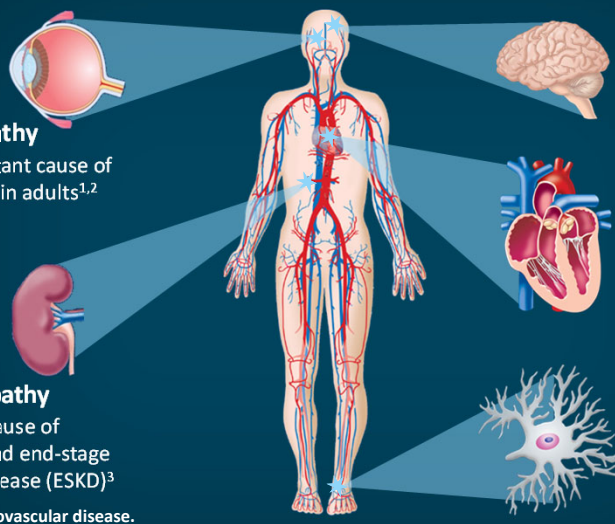
Major Pathophysiological Abnormalities in T2DM



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

13

Complications of Diabetes



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

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

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

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

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

CVD = cardiovascular disease.

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.

14

Disease Burden of Diabetes

Hospitalizations with diabetes-associated conditions

Condition	Age-Adjusted Rate (per 1000)
Congestive heart failure (CHF)	9.4
Stroke	6.0
Myocardial infarction (MI)	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 and older with diabetes demonstrated overall prevalence of multiple cardiovascular diseases

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 July 30, 2020.

15

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 ($)
Overall	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 July 30, 2020.

16

Aspects of Diabetes Care in Relationship to COVID-19 Pandemic

- Diabetes is common in patients with COVID-19 (as high as 58% in a small US study), often in patients in very poor glycemic control
- 40–50% of COVID patients are obese; may develop "new hyperglycemia" when sick
- **All the more reason to get patients with diabetes to control their blood glucose levels optimally and to encourage obese patients to lose weight; eating healthy and staying active may be more challenging during a pandemic**
- Strong inflammatory response → more hyperglycemia
- Frequent use of steroids (dexamethasone) in critically ill patients → more hyperglycemia
- For hospitalized patients, need to minimize staff room entries and conserve PPE

US = United States; PPE = personal protective equipment.

Singh AK, et al. *Diabetes Metab Syndr.* 2020;14:303-310. Bhatraju PK, et al. *N Engl J Med.* 2020;382:2012-2022. Brufsky A. *J Med Virol.* 2020;92:770-775. Garg S, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69:458-464. Tamez-Pérez HE, et al. *World J Diabetes.* 2015;6:1073-1081. Al-Jaghbeer MJ, Lansang MC. *Cleve Clin J Med.* 2020;Epub ahead of print. Zhou K, et al. *Cleve Clin J Med.* 2020:Epub ahead of print.

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Aspects of Diabetes Care and COVID-19

- Should ***more conservative*** BG targets (ie, <180–200 mg/dL) be considered?
- Should ***less frequent*** BG monitoring be considered?
- What is the role of continuous glucose monitoring in hospitalized patients?
- Should simplified basal insulin strategies be considered?
- Consider use of selected oral agents in selected hospitalized patients (if stable/eating)?

- **DPP-4 inhibitors—safe, modestly effective, can be used in CKD (watch dosing, however)**
- **Metformin—avoid if CKD, AKI, dye studies, tenuous hemodynamic status**
- **Sulfonylureas—can be used if renal function is normal and patient is eating normally**
- **SGLT2 inhibitors—probably avoid because of increased risk of DKA**

BG = blood glucose; DPP = dipeptidyl peptidase; SGLT = sodium-glucose transporter; AKI = acute kidney injury; DKA = diabetic ketoacidosis; CKD = chronic kidney disease.

Al-Jaghbeer MJ, Lansang MC. *Cleve Clin J Med.* 2020: Epub ahead of print. Mardones PS, et al. *J Diabetes Metab Disord Control.* 2020;7:6-7. Dicker D. *Diabetes Care.*2011;34(suppl 2):S276-S278. Metformin (Glucophage®) prescribing information (PI). 2018 (https://packageinserts.bms.com/pi/pi_glucophage.pdf). Hahr AJ, Molitch ME. *Clin Diabetes Endocrinol.* 2015;1:2. Tabangcora ID. Sulfonylureas. 2019 (https://nurseslabs.com/sulfonylureas/). National Inpatient Diabetes COVID-19 Response Group.2020 (https://abcd.care/sites/abcd.care/files/site_uploads/COvID_Front_Door_v2.0.pdf). URLs accessed July 30, 2020.

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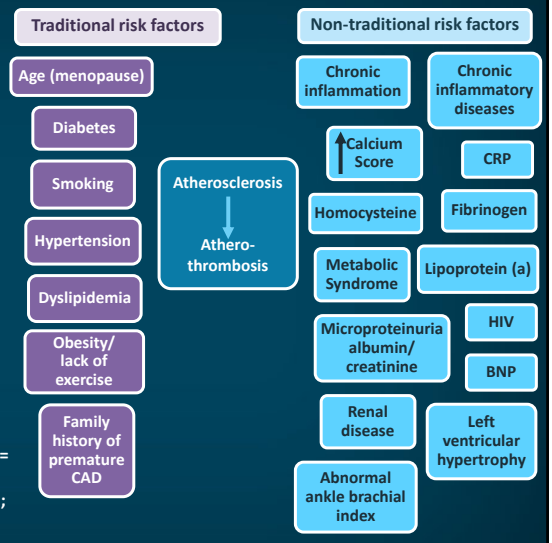
Risk Factors for CVD in Diabetes

- Age: men ≥45 years; women ≥55 years
- Family history of premature CAD
  - CAD in male 1st-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



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.

NIH. NIDDK. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke. Accessed September 4, 2020.

19

AHA: Top 10 Take-Home Messages for the 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 edify 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

AHA = American Heart Association; GLP-1 RA = glucagon-like peptide-1 receptor agonist; ASCVD = atherosclerotic cardiovascular disease; ASA = aspirin; LDL-C = low-density lipoprotein-cholesterol.

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

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AHA Life's Simple 7®

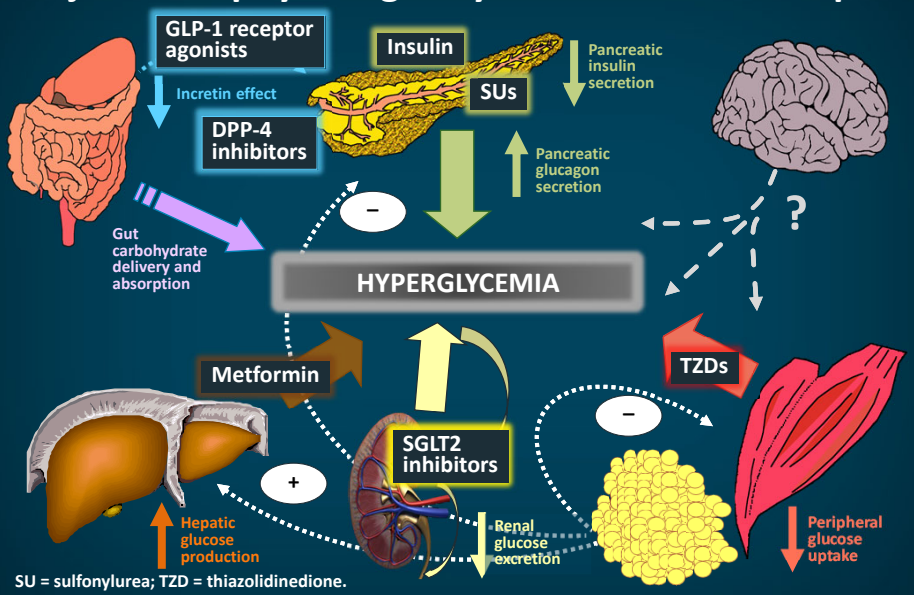
- Ideal cardiovascular health based on 7 of the 10 most costly risk factors—Life's Simple 7—that can be improved through lifestyle changes
- Studies have shown:
  - Annual employer healthcare cost were $2021 less with at least 6 risk factors in optimal ranges
  - 78% risk reduction for heart-related death with at least 5 risk factors in optimal ranges

Stop smoking | Eat better | Get active | Manage weight | Manage BP | Lipid control | Reduce BG

AHA. Life's simple 7, 2020 (www.heart.org/en/professional/workplace-health/lifes-simple-7). Accessed July 31, 2020.

21

Major Pathophysiologically Based T2DM Therapies



SU = sulfonylurea; TZD = thiazolidinedione.

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

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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*	$–$$$
DPP-4 i	Sitagliptin, saxagliptin, alogliptin, linagliptin	0.5–1%	↓ DPP-4 activity and ↑ incretins (GLP1, GIP)	Well-tolerated; no hypo	Urticaria, ? pancreatitis, ? CHF	$$$$
GLP-1 RA	Exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide	1–1.5%	↑ insulin & ↓ glucagon, ↓ gastromotility, hunger	Wt loss, no hypo, ↓ BP, ↓ MACE*	GI, ? pancreatic disease,? thyroid, medullary ca	$$$$
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1%	↑ urinary glucose excretion	Wt loss, no hypo, ↓s BP, ↓ MACE*, ↓ HF†, ↓ CKD#	Polyuria, GU, DKA; bone fxs*, amputations*	$$$$

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Whiteboard Animation 2

Incretin Therapies and SGLT2 Inhibitors

24

Incretin Therapies and SGLT2 Inhibitors
https://youtu.be/Tzm_0SnAYCo

25

Reducing CV Risk

Role of GLP-1 Receptor Agonists and SGLT2 Inhibitors

26

Summary of 25 Years of Diabetes Clinical Trials Linking Glucose Control to Vascular Complications

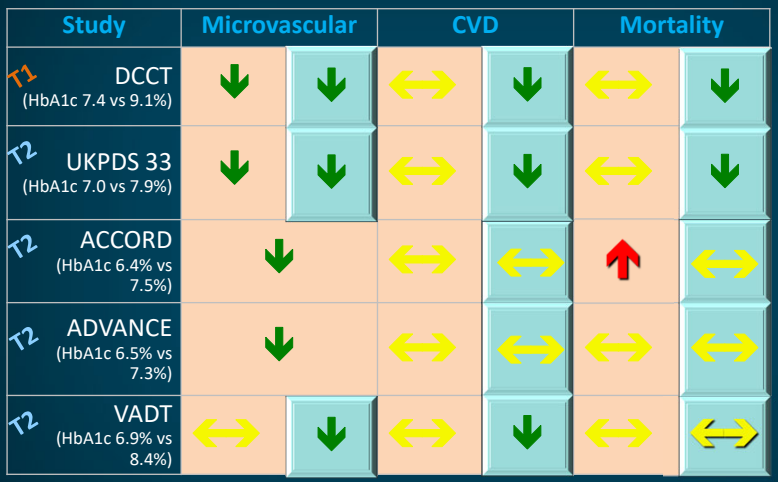
1. **Glycemic control** (**HbA1c ~7%, perhaps even lower**) reduces ***micro***vascular complications in both T1DM and T2DM, with relative risk reduction (RRR) in the 25%–60% range.
2. However, the **impact** of glycemic control itself on ***macro***vascular complications in T2DM is **small to nonexistent**. Any benefit is on the order of a RRR of ~15%. This is mainly for non-fatal MI (not CV death) and seems to require long-term efforts before it can be appreciated. Benefit may be larger in T1DM.

HbA1c = glycosylated hemoglobin; T1DM = type 1 diabetes mellitus; CV = cardiovascular.

Inzucchi S. Update on Diabetes Drugs and CVD Risk. ADA 2017 (https://professional.diabetes.org/sites/professional.diabetes.org/files/media/inzucchi_update_on_diabetes_drugs_and_cvd_risk_final.pdf). Accessed July 31, 2020.

27

Impact of Intensive Glucose-Lowering Therapy in DM
Summary of Major Randomized Controlled Trials



Diabetes Control and Complications Trial (DCCT) Group. *N Engl J Med.* 1993;329: 977-986. Nathan DM, et al. *N Engl J Med.* 2005;353:2643-2653. DCCT Group. *JAMA.* 2015;313:45-53. United Kingdom Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-853. Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589. Gerstein HC, et al. *N Engl J Med.* 2008;358:2545-2559. Patel A, et al. *N Engl J Med.* 2008;358:2560-2572. Duckworth W, et al; Veterans Affairs Diabetes Trial (VADT) investigators. *N Engl J Med.* 2009;360:129-139. Kendall DM, et al. *Am J Med.* 2009;122(6 suppl):S37-S50.

28

FDA-Mandated CV Outcomes Trials* in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pla	pla	pla	placebo	glimepiride
N	16,492	5380	14,671	6979	6033
Results	2013	2013	2015	2018	2018

NEUTRAL

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LR	dulaglutide	albiglutide
Comparator	pl	placebo	placebo	placebo	placebo	placebo
N	6068	9340	3297	14,752	9901	9463
Results	2015	2015	2016	2017	2018	2018

NEUTRAL

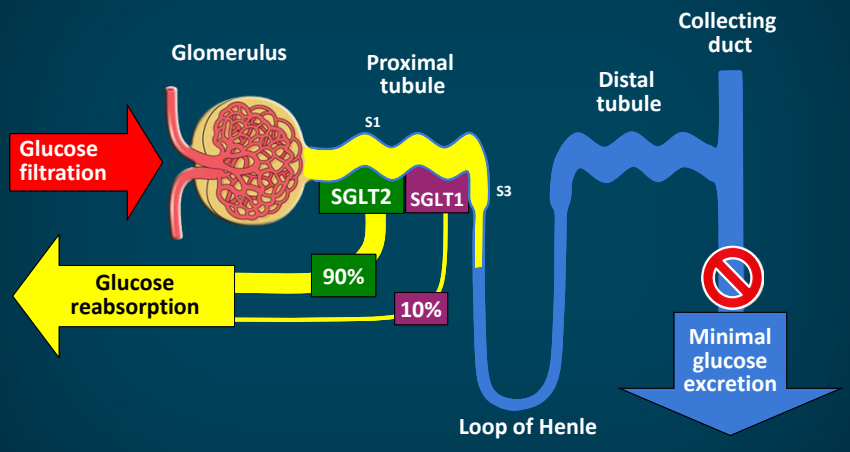
Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7020	4330	4401	17,160	8246
Results	2015	2017	2018	2018	2020

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13. NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

* non-insulin

29

Normal Physiology of Renal Glucose Homeostasis

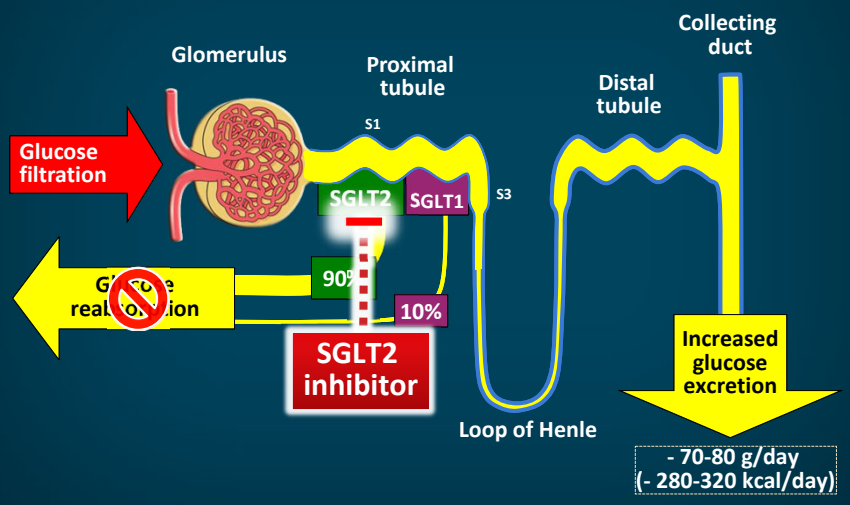


SGLT = sodium-glucose cotransporter.

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.

30

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.

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SGLT2 Inhibitors
Risk-to-Benefit Ratio Prior to CV Outcome Trials

BENEFITS

- ↓HbA1c ~0.6–0.9% (insulin-independent, irrespective of disease duration)
- Low hypoglycemia risk
- Modest ↓ weight
- Modest ↓ BP
- ↓ Albuminuria
- Small ↓ TGs
- Small ↑ HDL-C

RISKS

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

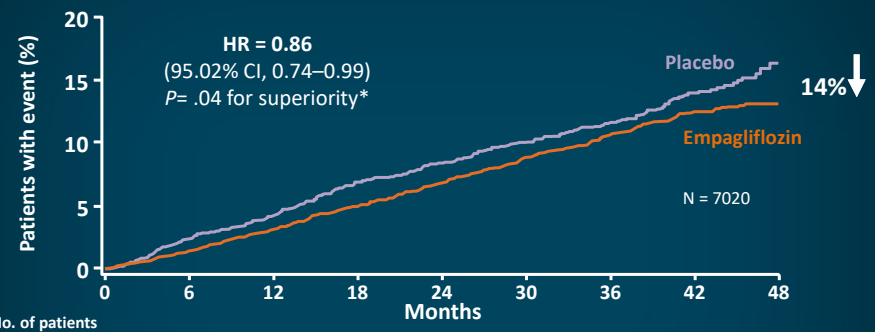
UTI = urinary tract infection; LDL-C = low-density lipoprotein-cholesterol.

Kim Y, Babu AR. *Diabetes Metab Syndr Obes.* 2012;5:313-327. Inzucchi SE et al. *Diabetes Care.* 2015;38:140-159

32

EMPA-REG: 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 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; HR = hazard ratio; CI = confidence interval.
Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

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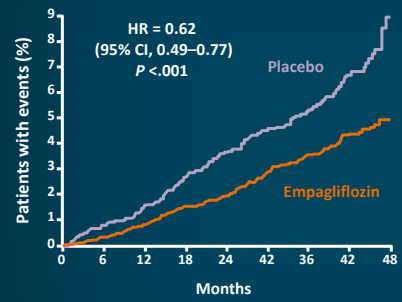
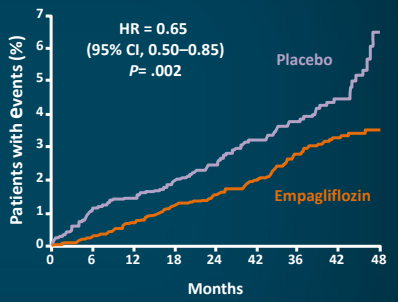
EMPA-REG: CV Death and Hospitalization for Heart Failure

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

Hospitalization for HF



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.

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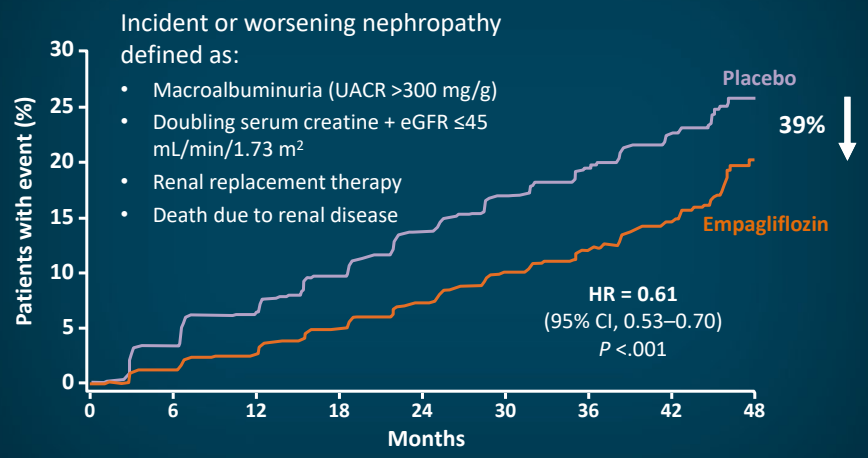
EMPA-REG OUTCOME *Secondary* Outcome

Cumulative Incidence of Incident or Worsening Nephropathy



Kaplan-Meier estimate. Hazard ratio based on Cox regression analyses.
UACR = urinary albumin-to-creatinine ratio; eGFR = estimated GFR.

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

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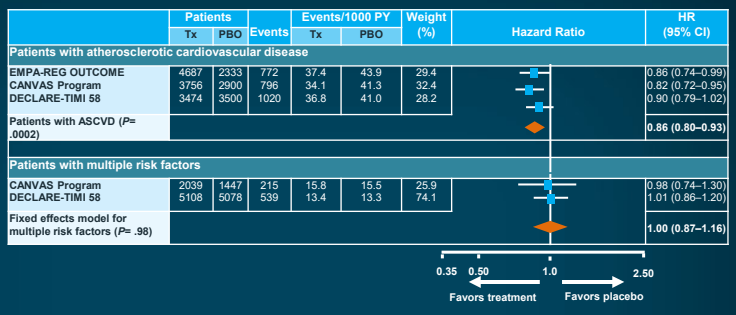
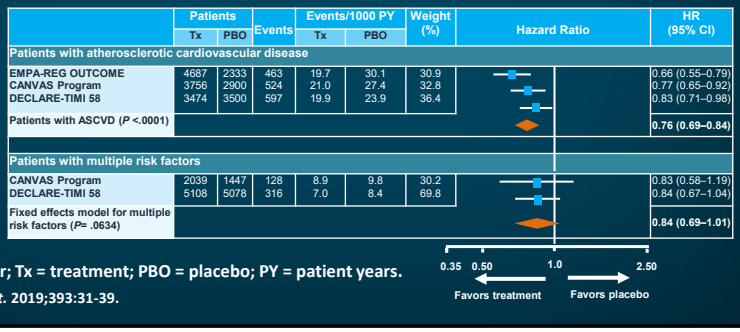
SGLT2i Trial Meta-analysis of CV Outcomes

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



Meta-analysis on HF hospitalizations and CV death*



*Stratified by presence of established atherosclerotic disease

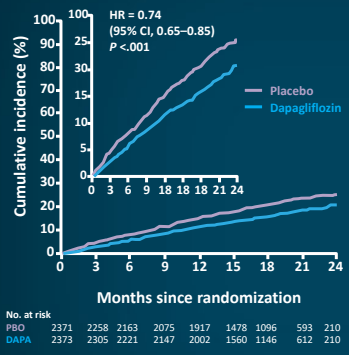
SGLTi = SGLT inhibitor; Tx = treatment; PBO = placebo; PY = patient years.

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

36

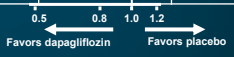
HF Primary Outcomes for Dapagliflozin: DM vs Non-DM Subgroups

Primary outcome



Primary outcome subgroup analysis

Subgroup	DAPA n = 2373	PBO n = 2371	Hazard Ratio (95% CI)
	Patients/total, no.		
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 percentage of patients in dapagliflozin group (16.3%) vs placebo (21.2%), *P* <.001.

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

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

37

FDA-Mandated CV Outcomes Trials* in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pla	pla	pla	placebo	glimepiride
N	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Results	2013	2013	2015	2018	2018

NEUTRAL

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LR	dulaglutide	albiglutide
Comparator	pla	placebo	placebo	placebo	placebo	placebo
N	[illegible]	9340	3297	14,752	9901	9463
Results	2015	2015	2016	2017	2018	2018

NEUTRAL

Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Results	2015	2017	2018	2018	2020

NEUTRAL

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13. NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

* non-insulin

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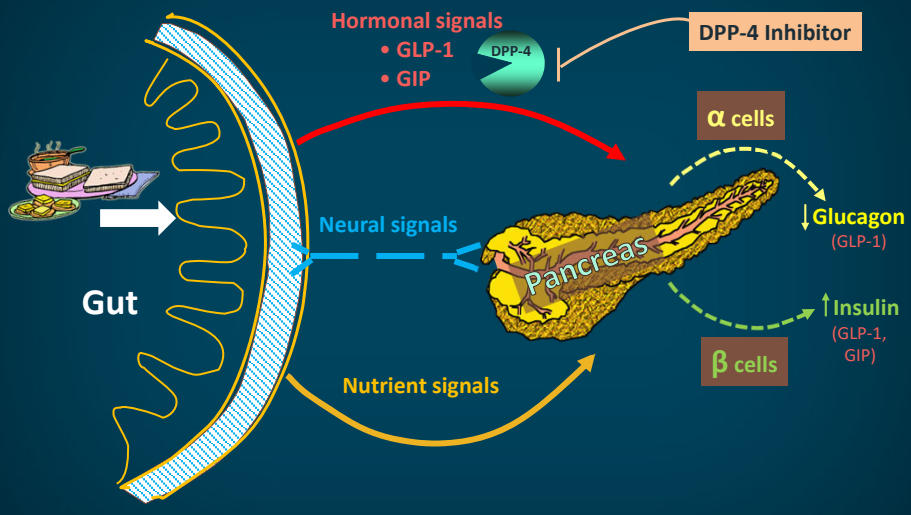
The Enteroinsular Axis



GIP = glucose-dependent insulinotropic peptide.

Adapted with permission from Creutzfeldt W. *Diabetologia*. 1979;16:75-85. Copyright © 1979 Springer-Verlag. 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.

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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.

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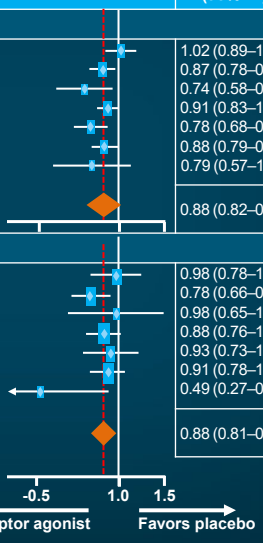
GLP-1 RA Trial Meta-analysis of Cardiovascular Outcomes

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)	1277/27,977 (4.6%)	1471/28,027 (5.2%)	0.88 (0.81–0.96)



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

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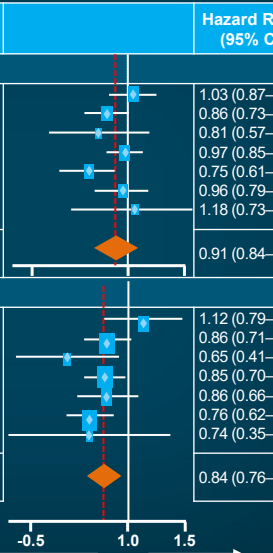
GLP-1 RA Trial Meta-analysis of Cardiovascular Outcomes

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

	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%)	31/1592 (2%)	1.18 (0.73–1.90)
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*	12/1591 (1%)	16/1592 (1%)	0.74 (0.35–1.57)
Overall (I^2=0.0%, *P*= .557)	721/27,977 (2.6%)	852/28,027 (3.0%)	0.84 (0.76–0.93)



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

42

FDA-Mandated CV Outcomes Trials* in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pla	pla	pla	plac	glimepiride
N	16,492	5,380	14,671	6,979	6,033
Results	2013	2013	2015	2018	2018

NEUTRAL

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide	dulaglutide	albiglutide
Comparator	pl	placebo	placebo	pl	placebo	placebo
N	6,068	9340	3,297	14,752	9,901	9463
Results	2015	2015	2016	2017	2018	2018

NEUTRAL

Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7,020	4,330	4401	17,160	8246
Results	2015	2017	2018	2018	2020

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13. NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

* non-insulin

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GLP-1 Receptor Agonists Notes and Updates

- Dulaglutide approved for the reduction of major adverse cardiovascular events (MACE) in adults with T2DM in both primary ***and*** secondary prevention populations
  - Dulaglutide indication update (Feb 2020) based on the REWIND study
- Additional GLP-1 agents with CV indications and approved for risk reduction of MACE in T2DM adults with ***established*** CVD (secondary prevention) include:
  - Liraglutide
  - Semaglutide

AJMC. Press Release: Dulaglutide (www.ajmc.com/newsroom/fda-approves-dulaglutide-for-adults-with-t2d-regardless-of-cvd). Dulaglutide (Trulicity®) PI 2020 (http://pi.lilly.com/us/trulicity-uspi.pdf). Liraglutide (Victoza®) PI 2019 (www.novo-pi.com/victoza.pdf). Semaglutide (Ozempic®) PI 2020 (www.novo-pi.com/ozempic.pdf). URLs accessed July 31, 2020.

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Reducing Renal Risk

Role of GLP-1 Receptor Agonists and SGLT2 Inhibitors

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Meta-analysis: Effects of SGLT2 Inhibitors on 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 CVD or kidney disease	2323	38,676	0.71 (0.63–0.82)
Acute kidney injury	943	38,684	0.75 (0.66–0.85)

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

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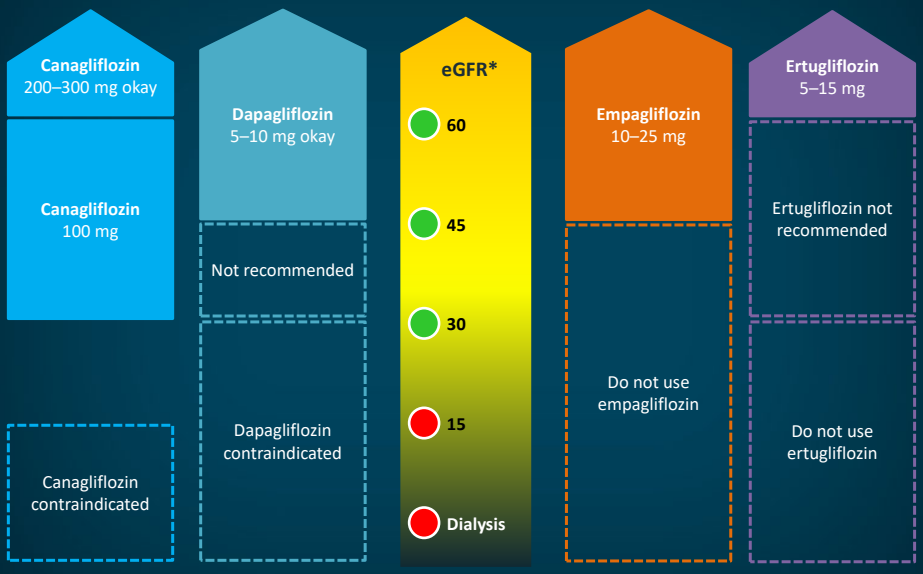
Current Renal Restrictions: SGLT2 Inhibitors

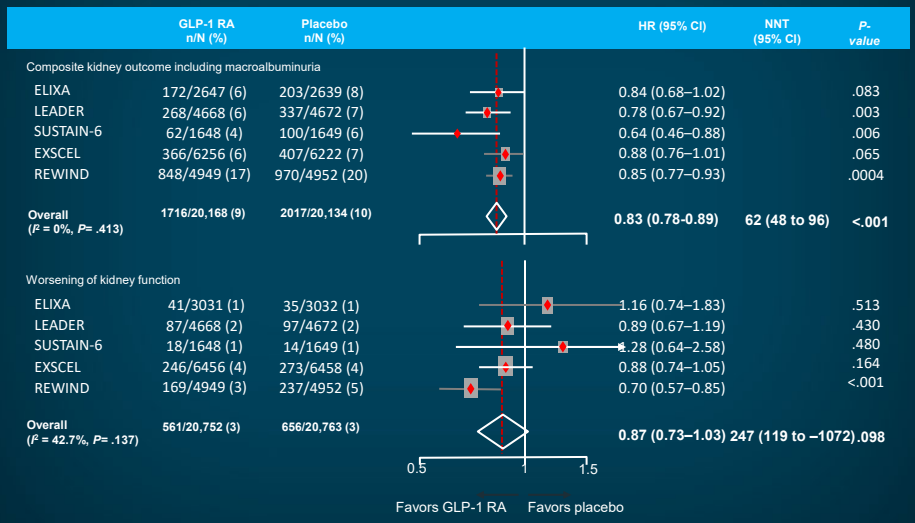


*eGFR in mL/min/1.73m².

Prescribing information for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

47

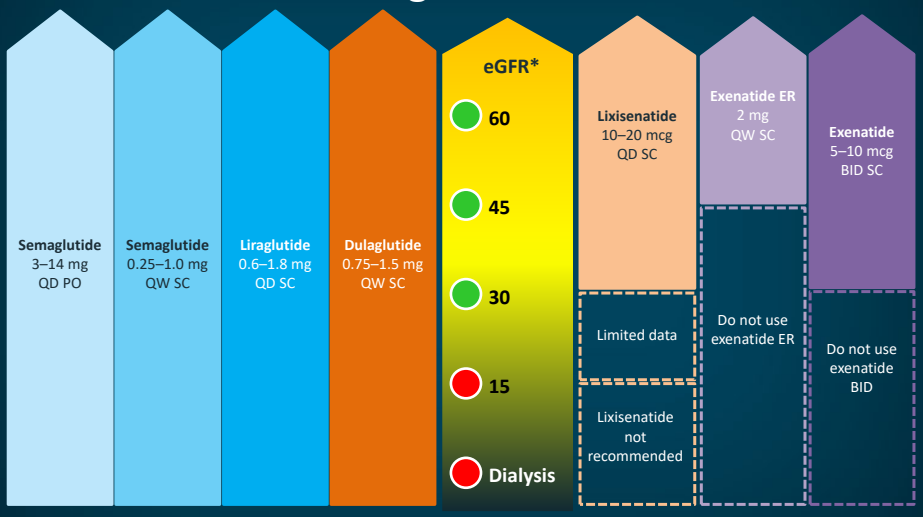
CV Outcomes Trials for GLP-1 Receptor Agonists: Renal Endpoints



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

48

Current Renal Restrictions: GLP-1 Receptor Agonists



*eGFR in mL/min/1.73m^2.

QD = each day; PO = by mouth; QW = each week; SC =subcutaneous; ER = extended release; BID = twice daily.

Prescribing information for semaglutide (SC and oral), liraglutide, dulaglutide, lixisenatide, and exenatide (ER and BID).

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Treatment Guidelines for Primary and Secondary Prevention of CVD in Diabetes

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2019 ACC/AHA Guidelines on Primary Prevention of CVD

Hypertension	Lipids	Antiplatelet therapy	CVD	Glycemic control to reduce CVD risk
Log-linear association of *increasing* systolic BP (SBP) and diastolic BP (DBP) levels and risk of ASCVD	**Primary ASCVD prevention** *requires risk- factor assessment* in childhood *Statin therapy indicated in those <19 y with familial dyslipidemia history (hx)*	Low-dose aspirin • *Secondary ASCVD* prevention • **Lack of net benefit** in primary ASCVD prevention (select patient consideration)	Dietary counseling for heart-healthy diet *Lowers CVD events and CVD mortality*	**1st line—metformin** ***Reductions:*** • ***39%*** *MI* • ***36%*** *all-cause mortality* • ***32%*** *DM-related micro- and macrovascular outcomes*
BP increase (20 mm/Hg *SBP or* 10 mm/Hg *DBP*) **doubled death risk** from: • Stroke • Heart disease • Other vascular disease	**Lifetime risk** assessment for young adults (20–39 y) *Consider statins with family hx of premature ASCVD and LDL-C ≥160*		**≥150 minutes/week** moderate-to-vigorous physical activity (aerobic and resistance) *Lowers HbA1c ~ 0.7%*	**SGLT2 inhibitors** *Significant reduction in ASCVD events and heart failure*
BP-lowering meds advised *even at stage 1 HTN* with estimated 10-year ASCVD risk ≥10%			**Quit smoking** • Increases ***all-cause mortality*** risk • Causal for ASCVD	**GLP-1 receptor agonists** *Significant ASCVD reduction in T2DM and high ASCVD risk*

It may be reasonable to initiate **SGLT2-i** or **GLP-1 RA** therapy for **primary CVD prevention** in T2DM patients with additional risk factors for CVD

ACC = American College of Cardiology.

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

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Strategies for Reducing CV Risk Factors 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; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; EPA = eicosapentaenoic acid.

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

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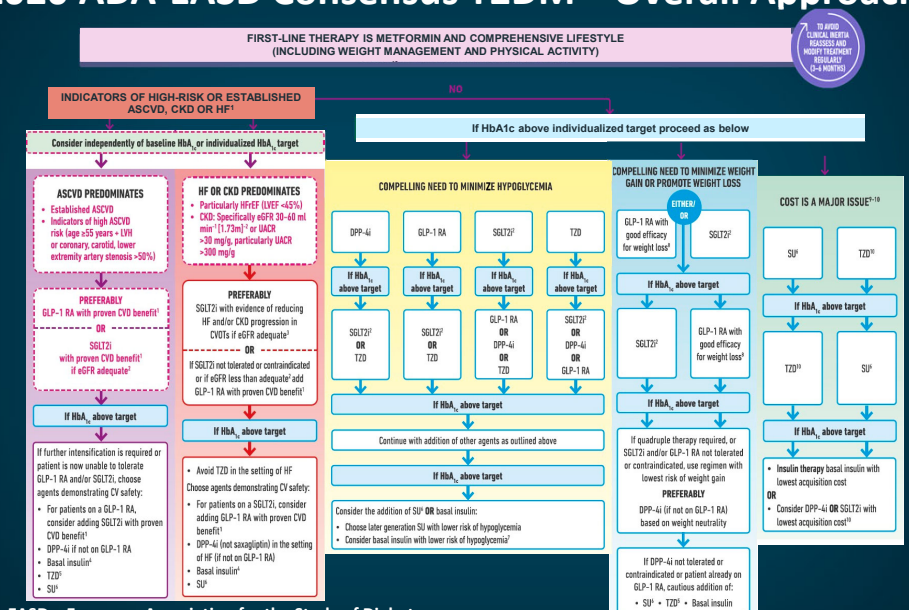
2020 ADA-EASD Consensus T2DM—Overall Approach



EASD = European Association for the Study of Diabetes.

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

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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?

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

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Characteristics to Consider When Individualizing Therapy in Older Patients With T2DM

- Comorbid conditions (CHF, cancer, etc)
- Diabetes duration
- Presence of macrovascular disease
- Presence of CKD
  - Decreased drug clearance
  - Associated CVD
- Presence of advanced retinopathy, with impaired vision
- History of severe hypoglycemia
- Psychologic, social, and economic characteristics
  - Safety concerns and support systems
  - Adverse effects of medications (polypharmacy)
  - Psychological/cognitive status
  - Economic considerations
  - Quality of life

Moghissi E. *Diabetes Ther*. 2013;4:239-256. ADA. *Diabetes Care*. 2020;43(suppl 1):S152-S162.

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ADA Standards of Medical Care in Diabetes – 2019/2020
Glycemic Treatment Goals for Older Adults

Health Status	Rationale	HbA1c Goal	Glucose (mg/dL)		BP (mmHg)
			Fasting/ preprandial	Bedtime	
Healthy (few coexisting illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/90
Complex/intermediate health (multiple coexisting chronic illnesses, 2+ ADL impairments, or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150	100–180	<140/90
Very complex/poor health (LTC or end-stage chronic illness, or moderate-to-severe cognitive impairment, or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain.	<8.5%	100–180	110–200	<150/90

ADL = activities of daily living; LTC = long-term care.

ADA. *Diabetes Care*. 2020;43(suppl 1):S152-S162.

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Revisiting the Case

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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: SGLT2 inhibitor or GLP-1 receptor agonist
- HbA1c target <7.5%

- Weight loss
- Increase aerobic activity
- Intensify lipid therapy

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Conclusions

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Reducing Atherosclerotic Cardiovascular Disease in T2DM Summary

1. T2DM has a complex pathogenesis
2. Glucose-lowering options have expanded markedly over the past 10–15 years
3. "Foundation therapy" remains **lifestyle** and **metformin**
   - Several options are available beyond metformin
4. 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**
5. 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
6. Also, ***don't forget to address CV and CKD risk factors***!

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Thank you!

Questions and Answers

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The CARES Approach:
Improving Glycemic, Cardiovascular, and Renal Outcomes
TOOLKIT

Overview of Diabetes and Diabetic Care

Resource	Address
Centers for Disease Control and Prevention (CDC). Diabetes State Burden Toolkit: Health Burden.	https://nccd.cdc.gov/Toolkit/DiabetesBurden/Home/Health
Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report—2020.	https://www.cdc.gov/diabetes/data/statistics/statistics-report.html
Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report—2017.	https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf
Afkarian M, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016;316:602-610.	https://jamanetwork.com/journals/jama/fullarticle/2542635
American Diabetes Association (ADA). 10. Cardiovascular disease and risk management: Standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(suppl 1):S111-S134.	https://care.diabetesjournals.org/content/43/Supplement_1/S111
American Diabetes Association (ADA). 11. Microvascular complications and foot care: Standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(suppl 1):S124-S138.	https://care.diabetesjournals.org/content/42/Supplement_1/S124
American Diabetes Association (ADA). 12. Older adults: Standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(suppl 1):S139-S147.	https://care.diabetesjournals.org/content/42/Supplement_1/S139
Davies MJ, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018;41:2669-2701.	https://care.diabetesjournals.org/content/41/12/2669

DeFronzo RA. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773-795.	https://diabetes.diabetesjournals.org/content/58/4/773
Moghissi E. Management of type 2 diabetes mellitus in older patients: Current and emerging treatment options. *Diabetes Ther*. 2013;4:239-256.	https://link.springer.com/article/10.1007%2Fs13300-013-0039-6
NIH. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diabetes in America, 3rd edition. 2018.	https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/diabetes-in-america-3rd-edition

Diabetes and Cardiovascular and Renal Risks

Resource	Address
Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74:e177-e232.	https://www.ahajournals.org/doi/10.1161/CIR.0000000000000677
Buse JB, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2020;43:487-493.	https://care.diabetesjournals.org/content/43/2/487
Inzucchi SE. Update on diabetes drugs and CVD risk. American Diabetes Association (ADA). Presented at 64th Advanced Postgraduate Course, February 19, 2017.	https://professional.diabetes.org/sites/professional.diabetes.org/files/media/inzucchi_update_on_diabetes_drugs_and_cvd_risk_final.pdf
Inzucchi SE. Personalizing glucose-lowering therapy in patients with type 2 diabetes and cardiovascular disease. *Endocrinol Metab Clin North Am.* 2018;47:137-152.	https://www.sciencedirect.com/science/article/abs/pii/S0889852917301160
Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-	https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30249-9/fulltext

analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776-785.	
Zelniker TA, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393:31-39.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32590-X/fulltext

Cardiovascular (CVOT) Clinical Trials in Diabetes

Resource	Address
CANVAS NCT01032629	https://clinicaltrials.gov/ct2/show/NCT01032629
CARMELINA NCT01897532	https://clinicaltrials.gov/ct2/show/NCT01897532
CAROLINA NCT01243424	https://clinicaltrials.gov/ct2/show/NCT01243424
CREDENCE NCT02065791	https://clinicaltrials.gov/ct2/show/NCT02065791
DECLARE NCT01730534	https://clinicaltrials.gov/ct2/show/NCT01730534
ELIXA NCT01147250	https://clinicaltrials.gov/ct2/show/NCT01147250
EMPA-REG NCT01131676	https://clinicaltrials.gov/ct2/show/NCT01131676
EXAMINE NCT00968708	https://clinicaltrials.gov/ct2/show/NCT00968708
EXSCEL NCT01144338	https://clinicaltrials.gov/ct2/show/NCT01144338
HARMONY NCT02465515	https://clinicaltrials.gov/ct2/show/NCT02465515
LEADER NCT01179048	https://clinicaltrials.gov/ct2/show/NCT01179048
REWIND NCT01394952	https://clinicaltrials.gov/ct2/show/NCT01394952

SAVOR NCT01107886	https://clinicaltrials.gov/ct2/show/NCT01107886
SUSTAIN 6 NCT01720446	https://clinicaltrials.gov/ct2/show/NCT01720446
TECOS NCT00790205	https://clinicaltrials.gov/ct2/show/NCT00790205
VERTIS CV NCT01986881	https://clinicaltrials.gov/ct2/show/NCT01986881

Patient Resources

Resource	Address
American Diabetes Association (ADA). Resources.	https://www.diabetes.org/resources
American Heart Association (AHA). Diabetes Tools and Resources.	https://www.heart.org/en/health-topics/diabetes/diabetes-tools--resources
American Heart Association (AHA). Prediabetes Tools and Resources.	https://www.heart.org/en/health-topics/diabetes/diabetes-tools--resources/prediabetes-tools-and-resources
Association of Diabetes Care and Education Specialists (ADCES). Resources for People Living with Diabetes.	https://www.diabeteseducator.org/living-with-diabetes
Centers for Disease Control and Prevention (CDC). National Diabetes Education Program.	https://www.cdc.gov/diabetes/ndep/index.html