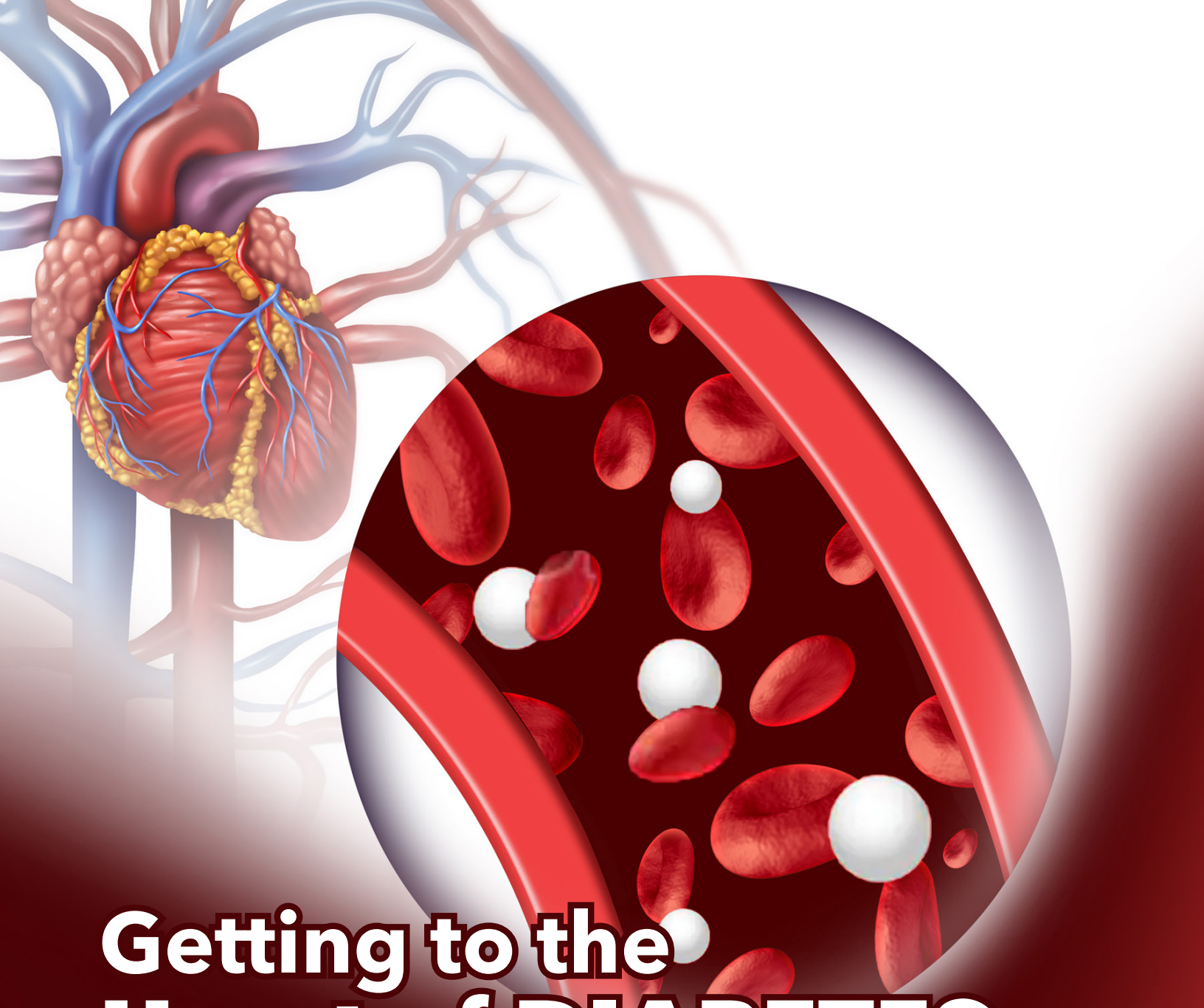

Getting to the Heart of DIABETES:

The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk

FRIDAY, NOVEMBER 13, 2020

This event is not part of the official Scientific Sessions as planned by theAHA Committee on Scientific Sessions Programming.

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 an educational grant from Lilly.

Getting to the Heart of Diabetes: The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk

FACULTY

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Dallas Heart Ball Chair for Research on Heart Disease in Women
University of Texas Southwestern Medical Center
Lead Physician
Parkland Hospital and Health System Cardiology Clinics

PROGRAM OVERVIEW
This case-based live activity will cover the long-term treatment, management, and improvement of cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM).

TARGET AUDIENCE
This educational activity is intended for cardiology healthcare professionals.

Learning Objectives
- Select patients with T2DM who would benefit from the CV effects of GLP-1 RAs
- Apply guidelines and recent clinical data to the choice of GLP-1 receptor agonists for reducing CV risk in patients with T2DM
- Analyze the clinical implications of results from Cardiovascular Outcomes Trials of GLP-1 receptor agonists and emerging incretin-based therapies
- Implement practical strategies for initiating and administering GLP-1 receptor agonists (including device training, dosing and escalation, follow-up care and adjustment of other medications)

ACCREDITATION STATEMENT
Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT
Med Learning Group designates this live activity for a maximum of 1.5 *AMA Category 1 Credits*™. 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 in the long-term treatment, management, and improvement of CV outcomes in patients with T2DM. **CNE Credits:** 1.5 ANCC Contact Hour(s).

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 1.5 contact hours of continuing nursing education of RNs and APNs.

COMMISION ON DIETETIC REGISTRATION
This program has received prior approval with the Commission on Dietetic Registration for dietitians and RDs.

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Richard Pratley, MD reports research grants and consulting and/or speakers fees from Hanmi Pharmaceutical Co, Janssen, MSD, Novo Nordisk, Pfizer Inc, Poxel SA, Sanofi, Scohia Pharma Inc, and Sun Pharmaceutical Industries. All honoraria are directed toward a non-profit organization supporting education and research.

He has contracted research for Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Lilly, Merck, Novo Nordisk and Sanofi. All grant fund payments were made directly to AdventHealth, a nonprofit organization.

Darren K. McGuire, MD, MHSc reports clinical trials leadership for Merck & Co, Pfizer, AstraZeneca, Janssen, Lilly USA, Boehringer Ingelheim, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Sanofi, and CSL Behring. He consults for Novo Nordisk, Sanofi, Boehringer Ingelheim, Lilly USA, Merck & Company; AstraZeneca, Metavant Sciences, Applied Therapeutics, and Afimmune.

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 peer-reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

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Christina Gallo, SVP, Educational Development of Med Learning Group has nothing to disclose.
Ashley Whitehurst, Program Manager of Med Learning Group has nothing to disclose.
Cindy Lampner, Medical Director of Med Learning Group has nothing to disclose.
Lauren Welch, MA, VP of Accreditation and Outcomes of Med Learning Group has nothing to disclose.
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1. Read the CME/CNE information and faculty disclosures;
2. Participate in the live streamed activity; and
3. Complete pre-and-post surveys and evaluation.

You will receive your certificate as a downloadable file.

DISCLAIMER

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Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at www.medlearninggroup.com/privacy-policy/

AMERICANS WITH DISABILITIES ACT

Staff will be glad to assist you with any special needs. Please contact Med Learning Group prior to the live event at info@medlearninggroup.com

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Co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by an educational grant from Lilly.

AGENDA

I. Introduce case studies

a. New diagnosis of T2DM in a 65-year old male patient with clinical ASCVD (primary prevention).
b. New diagnosis of ASCVD in a 57-year old female patient with T2DM currently receiving metformin and a dipeptidyl peptidase-4 inhibitor. Has CKD and multiple CV risk factors.

II. CV comorbidities in T2DM (CVD/CKD/HF))

a. Epidemiology
b. Traditional risk factors
c. Pathophysiology

III. GLP-1 Receptor Agonists

a. Compare/contrast with SGLT2 inhibitors
b. Mechanism of action
    i. The incretin pathway
    ii. Anti-hyperglycemic mechanisms
    iii. Mechanisms of CV benefit
c. Results from CVOT
    i. Primary prevention
    ii. Secondary prevention
    iii. Outcomes in CKD and heart failure

IV. First Q&A Session

V. Practical strategies

a. Indications
b. Dosing
c. Adverse effects
d. Adjusting other medications
e. Devices and injection techniques
f. Follow-up care
g. Agents in development
h. Algorithms from ACC Expert Consensus Decision Pathway
i. Endocrinologist/cardiologist collaboration

VI. Case studies

VII. 2nd Q&A Session

VIII. Conclusion

November 13, 2020

Getting to the Heart of Diabetes: The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk

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Disclosures

- Richard Pratley, MD reports research grants and consulting and/or speakers fees from Hanmi Pharmaceutical Co, Janssen, MSD, Novo Nordisk, Pfizer Inc, Poxel SA, Sanofi, Scohia Pharma Inc, and Sun Pharmaceutical Industries. **All honoraria are directed toward a non-profit organization supporting education and research.**
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Educational Objectives

- Select patients with T2DM who would benefit from the CV effects of GLP-1RAs
- Apply guidelines and recent clinical data to the choice of GLP-1RAs for reducing CV risk in patients with T2DM
- Analyze the clinical implications of results from cardiovascular outcomes trials of GLP-1 receptor agonists and emerging incretin-based therapies
- Implement practical strategies for initiating and administering GLP-1 receptor agonists (including device training, dosing and escalation, follow-up care, and adjustment of other medications)

Case 1: ND

- 65-year-old male with new-onset T2DM
- PMH
  - NSTEMI ~1 y ago – DES x 2, Circ and LAD
  - Hypertension
  - Hypercholesterolemia
  - Prior smoker (quit 1 year ago)
- Meds
  - Atorvastatin 40 mg/d
  - Losartan 100 mg/d
  - Metoprolol XR 100 BID
  - Aspirin 81 mg/d
  - Ticagrelor 60 mg BID

Case 1: ND
(continued)

- PE
  - BMI: 33.2 kg/m^2
  - BP: 136/88
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses intact, no edema
- Labs
  - Fasting plasma glucose: 137 mg/dL
  - HbA1c: 7.4%
  - CMP, CBC normal
  - LDL-C: 101; HDL-C: 40; TG: 198
  - eGFR: 80 mL/min/1.73m^2 ; UACR: 5 mg/g

Case 1: ND—Questions to Consider

- What is an optimal HbA1c for this patient?
- What would be your preferred first-line treatment for his diabetes?
- Should you initiate metformin prior to an SGLT2 inhibitor or GLP-1RA?
- What clinical considerations would lead you to select an SGLT2 inhibitor vs a GLP-1RA?

Case 2: CK

- 57-year-old female with T2DM and multiple CVD risk factors
- PMH
  - T2DM x 6 y
  - Hypertension x 12 y
  - Hypercholesterolemia
- Meds
  - Rosuvastatin 20 mg/d
  - Lisinopril 40 mg/d
  - HCTZ 25 mg/d
  - Metformin XR 1000 mg QD
  - Sitagliptin 100 mg/d

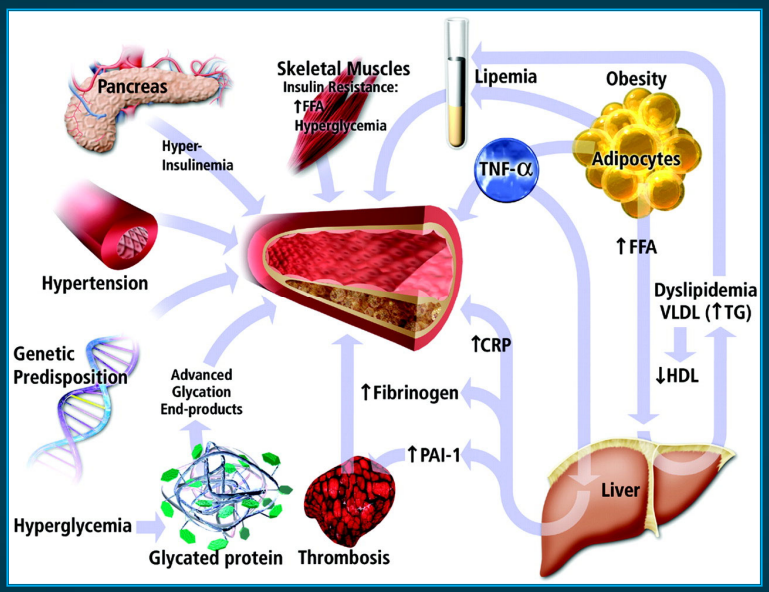
Case 2: CK
(Continued)

- PE
  - BMI 31.4 kg/m^2
  - BP 148/92
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses intact, trace pedal edema
- Labs
  - Fasting plasma glucose 154
  - HbA1c 7.8%
  - LDL-C 121 HDL-C 36 TG 254
  - eGFR 42 mL/min/1.73m^2

Case 2: CK—Questions to Consider

- What is an optimal HbA1c for this patient?
- Should you continue metformin given her CKD?
- What clinical considerations would lead you to select an SGLT2 inhibitor vs a GLP-1RA?

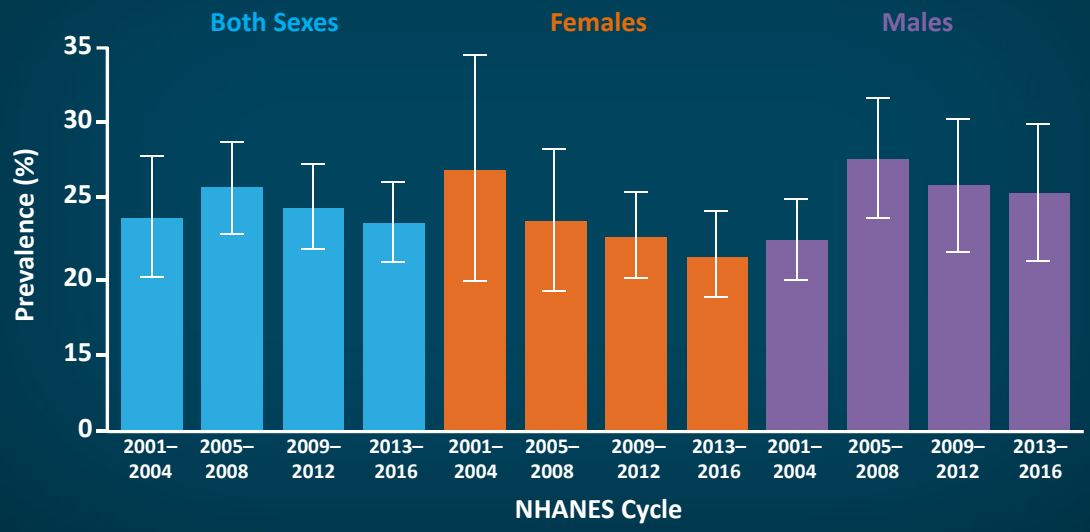
Macrovascular Disease in Patients with Diabetes



FFA = free fatty acids; TNF = tumor-necrosis factor; VLDL = very low-density lipoprotein; TG = triglyceride; CRP = C-reactive protein; HDL = high-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1.

Libby P, Plutzky J. *Circulation*. 2002;106:2760-2763.

Age-Adjusted Prevalence of Cardiovascular Diseases Among Adults (20+ Years) with Diabetes Mellitus in US: NHANES



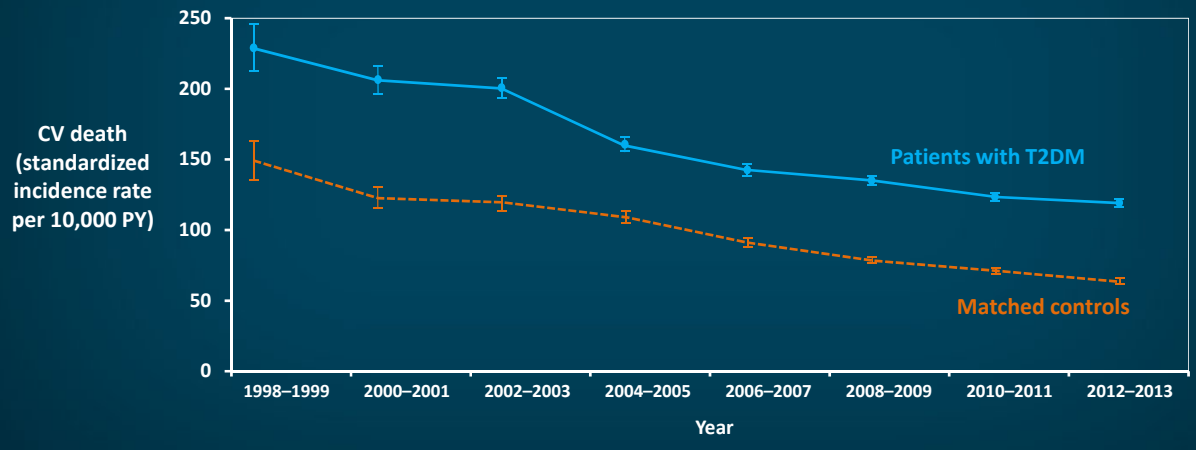
NHANES = National Health and Nutrition Examination Survey.

American Heart Association (AHA). (https://healthmetrics.heart.org/prevalence-of-cardiovascular-disease-among-us-adults-20-years-in-the-united-states-1999-2016/). Accessed 11/11/2020.

T2DM Still Associated with Excess Risk of CVD Death

Data from Swedish National Diabetes Register

36,869 patients with T1DM and 457,473 patients with T2DM included, along with matched controls for each diabetes cohort



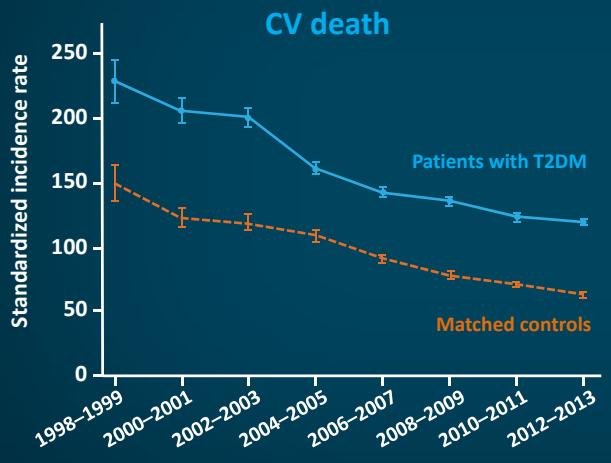
T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; T1DM = type 1 diabetes mellitus; CV = cardiovascular.

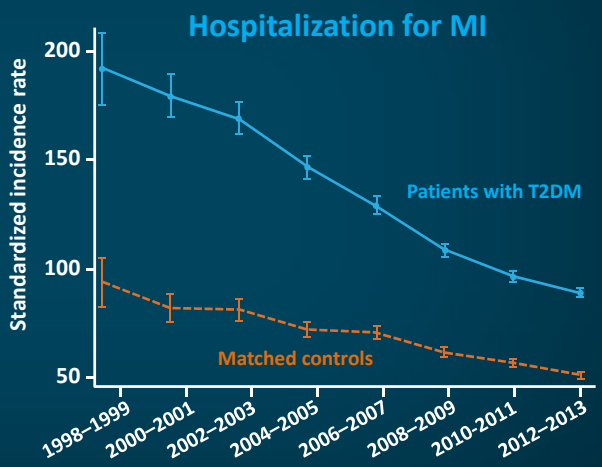
Rawshani A, et al. *N Engl J Med*. 2017;376:1407-1418.

ASCVD Risk Associated with T2DM

Swedish National Registry Data 1998–2013

Standardized incidence rate is per 10,000 PY

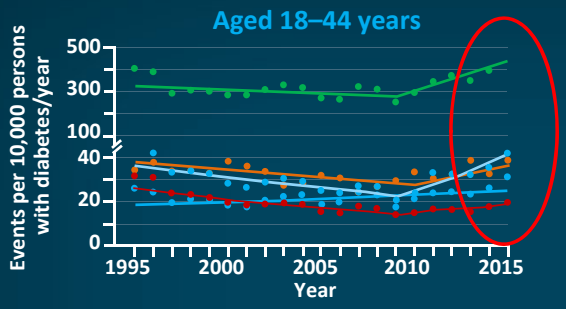


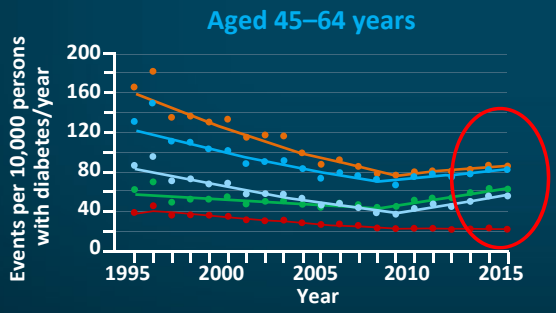


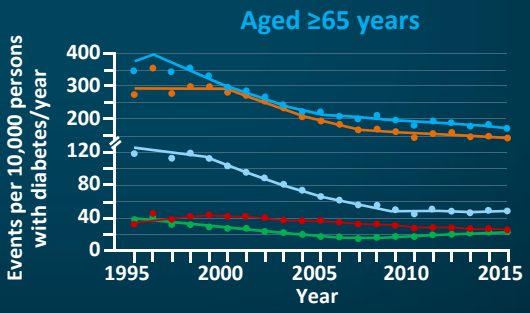
ASCVD = atherosclerotic CVD; PY = person years; MI = myocardial infarction.

Rawshani A, et al. *N Engl J Med.* 2017;376:1407-1418.

Hospitalization for CV Events in People With T2DM



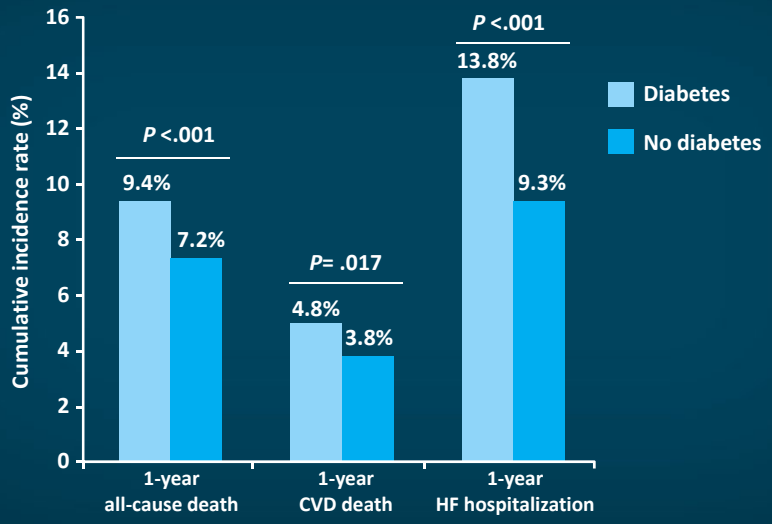




- Acute MI
- Stroke
- Lower-extremity amputation
- Hyperglycemia
- End-stage kidney disease

Gregg EW, et al. *JAMA*. 2019;321:1867-1868.

DM Is Associated with Increased Heart Failure Hospitalization and Mortality

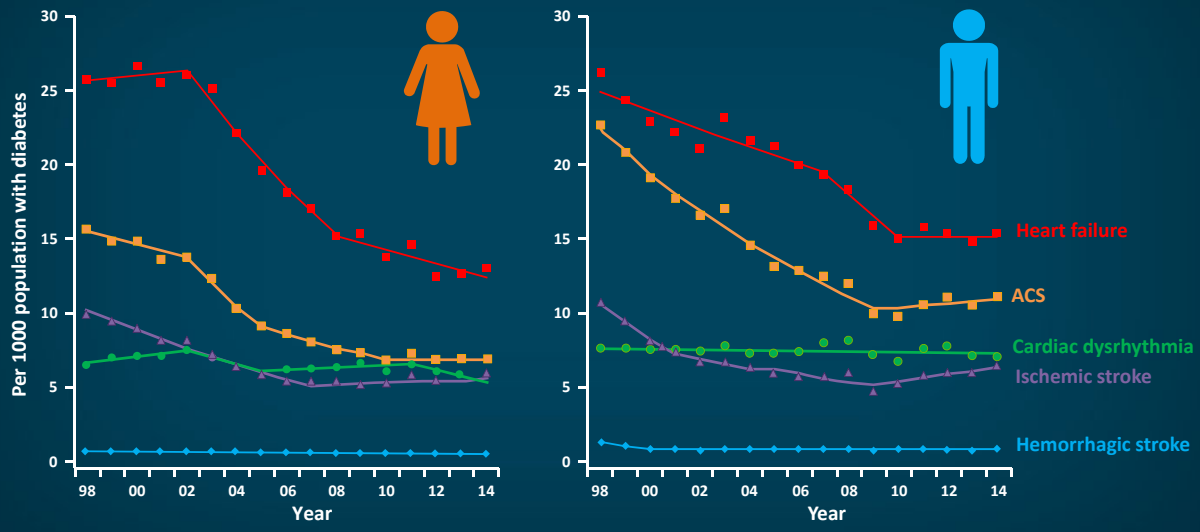


DM = diabetes mellitus; HF = heart failure; ESC = European Society of Cardiology; HFA = ESC-Heart Failure Association.

Dauriz M, et al; ESC-HFA Registry. *Diabetes Care.* 2017;40:671-678.

US National Inpatient Sample (1998–2014)

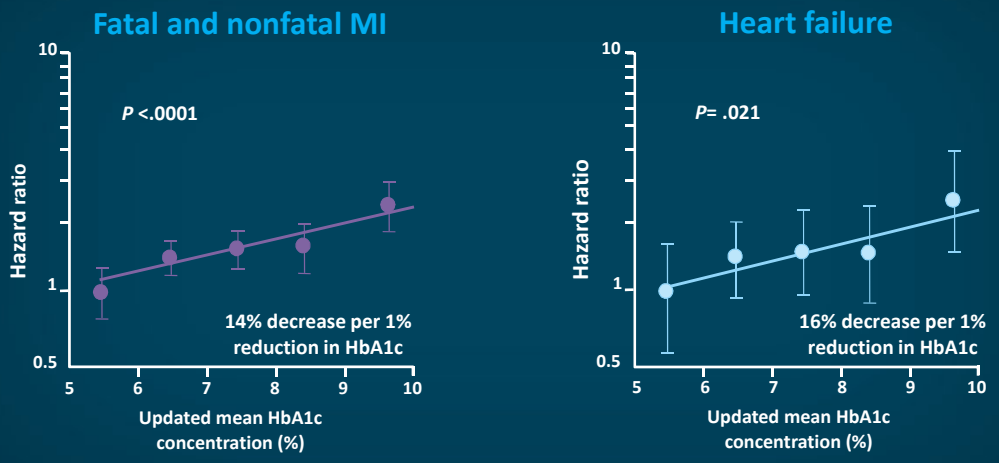
HHF Predominates Among Diabetes-Related Hospital Admissions



HHF = hospitalization for heart failure; ACS = acute coronary syndrome.

Burrows NR, et al. *Diabetes Care*. 2018;41:293-302.

UKPDS 35: Macrovascular Complications Increase as Glycemic Control Worsens



14–16% reduction in cardiovascular events per 1% HbA1c reduction

Stratton IM, et al. *BMJ*. 2000:321;405-412.

Impact of Intensive Therapy for Diabetes

Summary of Major Clinical Trials

Study	Microvascular	CVD	Mortality
UKPDS[1,2]	↓	↔	↔
DCCT/EDIC*[3,4]	↓	↔	↔
ACCORD[5]	↓	↔	↑
ADVANCE[6]	↓	↔	↔
VADT[7]	↓	↔	↔

Initial trial | Long-term follow-up

*in T1DM

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865. 2. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589. 3. Nathan DM, et al; Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med*. 1993;329;977-986. 4. Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. 5. Gerstein HC, et al. *N Engl J Med*. 2008;358:2545-2559. 6. Patel A, et al. *N Engl J Med*. 2008;358:2560-2572. 7. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

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

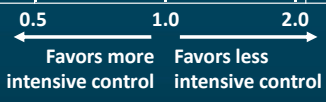
- Glycemic control (HbA1c ~7%, perhaps even lower) reduces ***micro***vascular complications in both T1DM and T2DM with relative RR ~25–60%.
- Impact of glycemic control itself on ***macro***vascular complications in T2DM is small to nonexistent.
  - For the most part, any benefit is on the order of a RRR of ~15%.
  - This is mainly for nonfatal MI and also requires long-term efforts before it can be observed; RRRs may be larger in T1DM

HbA1c = glycosylated hemoglobin; RR = risk reduction; RRR = relative RR.

Intensive Glucose Control Does Not Reduce Heart Failure Incidence

Admission to hospital/fatal heart failure

	Number of events (yearly event rate, %)		ΔHbA1c (%)	HR (95% CI)
	More intensive	Less intensive		
ACCORD	152 (0.90)	124 (0.75)	–1.01	1.18 (0.93–1.49)
ADVANCE	220 (0.83)	231 (0.88)	–0.72	0.95 (0.79–1.14)
UKPDS	8 (0.06)	6 (0.11)	–0.66	0.55 (0.19–1.60)
VADT	79 (1.80)	85 (1.94)	–1.16	0.92 (0.68–1.25)
Overall	**459**	**446**	**–0.88**	**1.00 (0.86–1.16)** (Q=3.59, p=0.31, I2=16.4%)

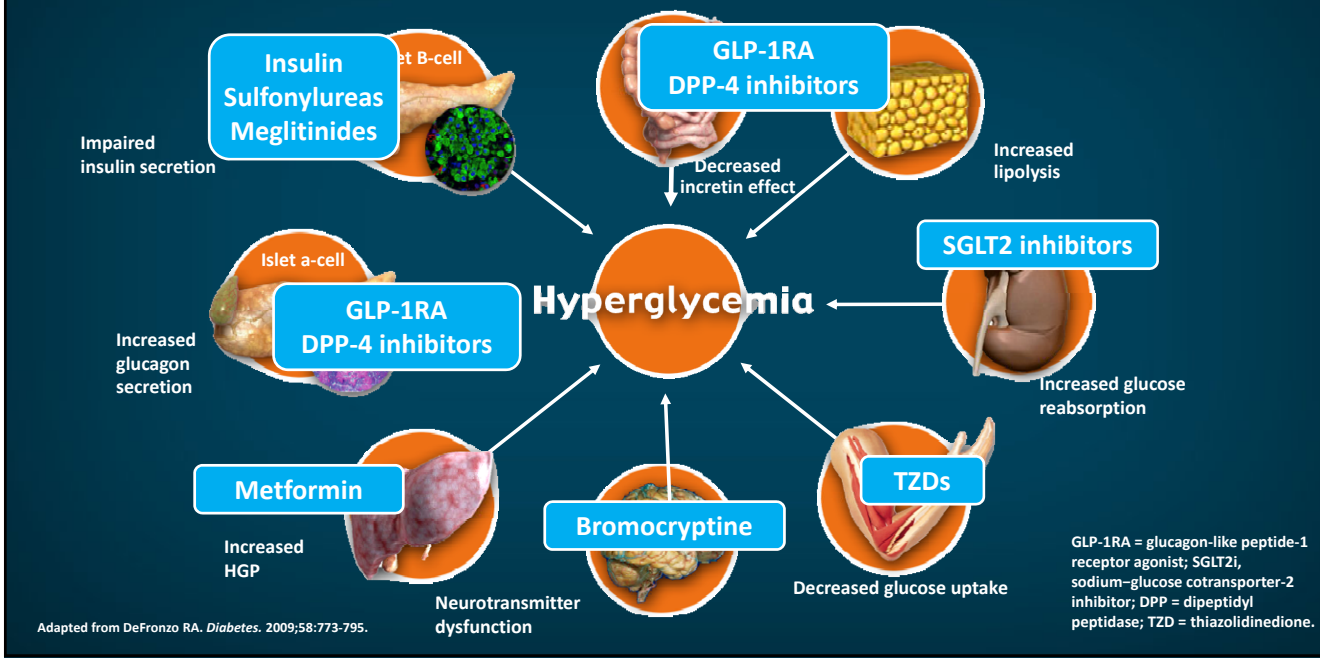


HR = hazard ratio; CI = confidence interval.

Turnbull FM, et al. *Diabetologia*. 2009;52:2288-2298.

Multiple Metabolic Abnormalities in T2DM

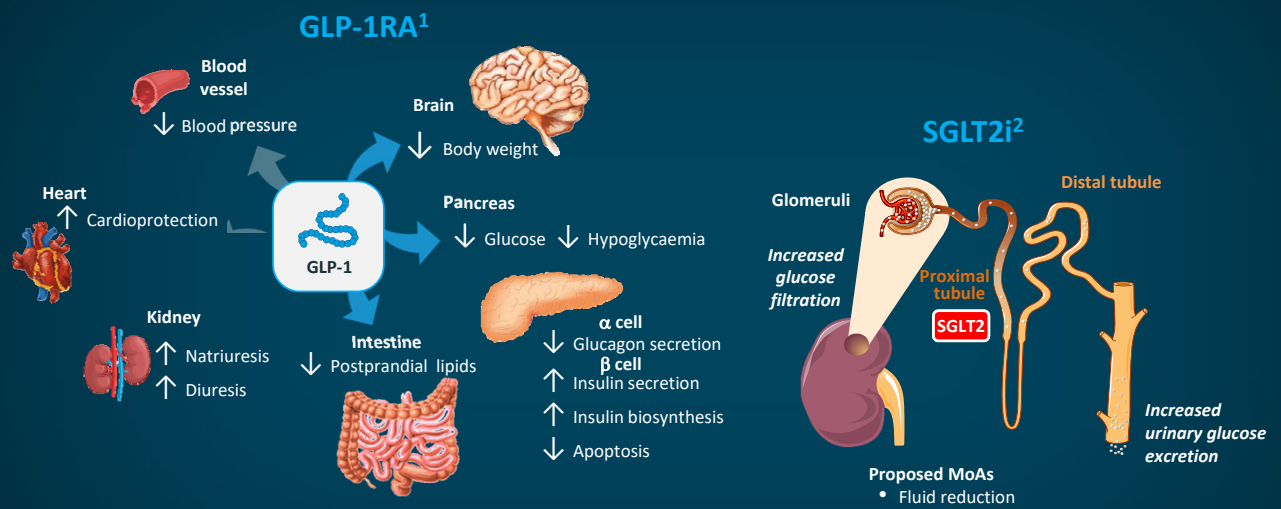
Matching Pharmacology to Pathophysiology



Adapted from DeFronzo RA. *Diabetes.* 2009;58:773-795.

GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; DPP = dipeptidyl peptidase; TZD = thiazolidinedione.

Mode of Action of GLP-1RA and SGLT2i Agents



Dark blue arrows indicate main MoA of GLP-1 analogues.
MoA = mode of action.

1. Drucker DJ. *Cell Metab*. 2016;24:15-30. 2. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

Comparing GLP-1RA and SGLT2i Agents

↓↑ Positive effect ↓↑ Negative effect ↔ Neutral effect

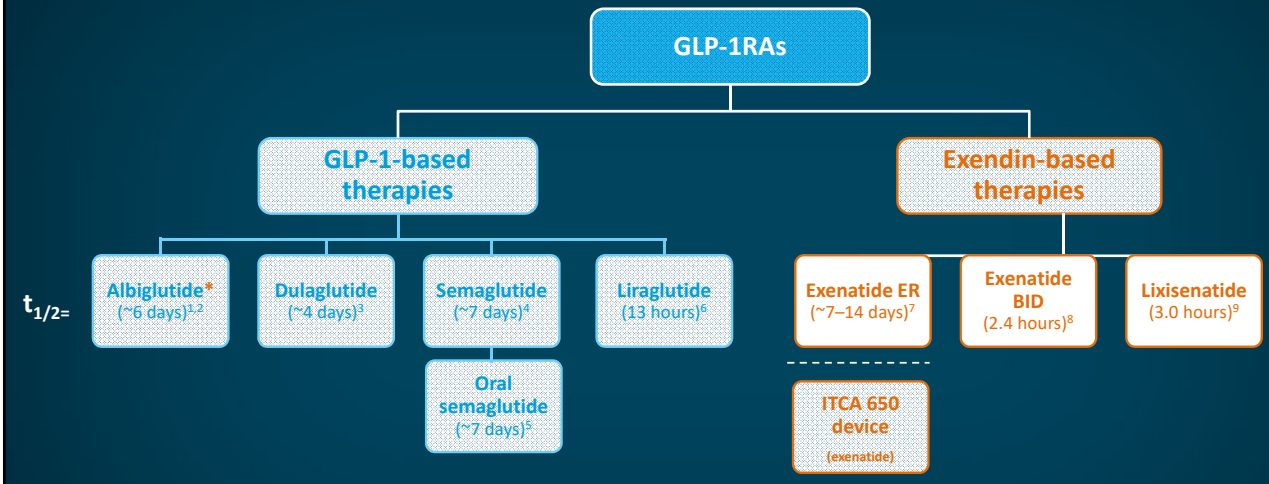
	GLP-1RA	SGLT2i	Combination therapy*
Appetite	↓	↑ (?)	↓
Body weight	↓	↓	↓↓
Ischaemic CV events	↓	↓	↓
Heart failure events	↔	↓	↓
Insulin secretion	↑	↓	↑
Glucagon secretion	↓	↑	↔
Hepatic glucose output	↓	↑	↔
Ketone body production	↓ (?)	↑	↔
Muscle glucose uptake	↑ (?)	↑	↑↑
Diuresis, natriuresis	↑ (acutely)	↑	↑
Urinary glucose secretion	↔	↑	↑
Renoprotection	↔	↑	↑

*Effects of combination therapy are based on findings from Frías et al (DURATION-8), Fulcher et al (CANVAS), Lundkvist et al, or inference from mechanistic studies.

Adapted from Nauck MA, Meier JJ. *Lancet Diabetes Endocrinol.* 2016;4:963-964. Frías JP, et al. *Lancet Diabetes Endocrinol.* 2016;4:1004-1016. Fulcher G, et al. *Diabetes Obes Metab.* 2016;18:82-91. Lundkvist P, et al. *Diabetes Obes Metab.* 2017;19:49-60.

Whiteboard animation: GLP-1 CV MOA

GLP-1RA Landscape

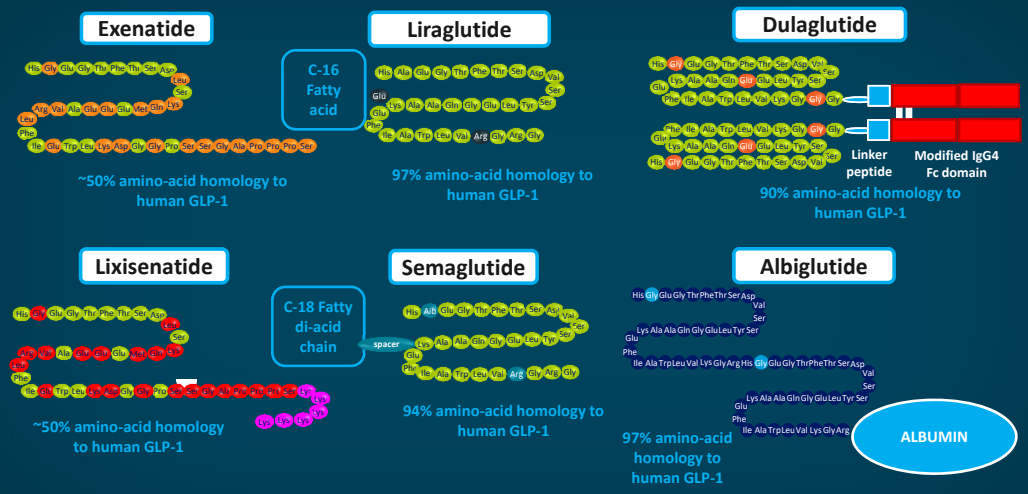


$t_{1/2}$ depicts agent elimination half live. *Albiglutide was withdrawn from market July 2018.

BID = twice daily; ER = extended release.

1. Bush MA, et al. *Diabetes Obes Metab.* 2009;11:498-505. 2. Matthews JE, et al. *J Clin Endocrinol Metab.* 2008;93:4810-4817. 3. Barrington P, et al. *Diabetes Obes Metab.* 2011;13:434-438. 4. Semaglutide [Rybelsus®] prescribing information (PI) 2020. 5. Semaglutide oral [Rybelsus®] PI 2020. 6. Liraglutide [Victoza®] summary of product characteristics (SPC) (www.ema.europa.eu/en/documents/product-information/victoza-epar-product-information_en.pdf). 7. Fineman E, et al. *Clin Pharmacokinet.* 2011;50:65-74. 8. Exenatide [Byetta®] SPC (www.ema.europa.eu/en/documents/product-information/byetta-epar-product-information_en.pdf). 8. Lixisenatide [Lyxumia®] SPC (www.ema.europa.eu/en/documents/product-information/lyxumia-epar-product-information_en.pdf). URLs accessed 11/10/2020.

Structure of GLP-1 Receptor Agonists



Fc = fragment crystallisable; IgG4 = immunoglobulin G4.

FREEDOM-CVO. Intarcia Therapeutics 2016 press release (www.prn.to/1SVcaXg). Accessed 11/9/2020. Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-2257. Marso SP, et al. *N Engl J Med.* 2016;375:311-322. Marso SP, et al. *N Engl J Med.* 2016;375:1834-1844. Holman RR, et al. *N Engl J Med.* 2017;377:1228-1239. Gerstein HC, et al. *Diabetes Obes Metab.* 2017;20:42-49. Green J, et al. Presented at 54th annual meeting of the European Association for the Study of Diabetes, 4 October 2018. Berlin, Germany.

GLP-1 RA Pharmacokinetic Profiles

Increasing half-life

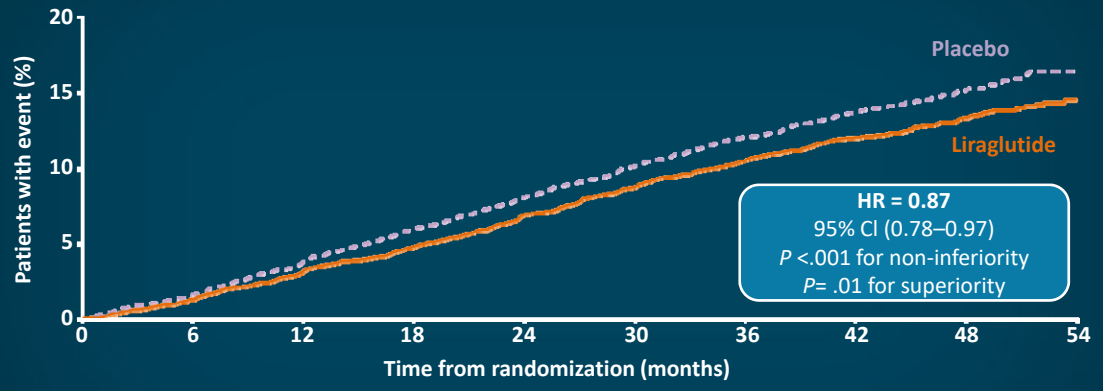
GLP-1 RAs	Half-life	T_{max}
Exenatide BID[1]	2.4 hours	2 hours
Lixisenatide OD[2]	3 hours	1.0–3.5 hours
Liraglutide OD[3]	13 hours	8–12 hours
Semaglutide OW[4,5]	165–184 hours (6.5–7.5 days)	24–36 hours (1–1.5 days)
Dulaglutide OW[6]	90 hours (3.75 days)	24–48 hours (1–2 days)
Albiglutide OW[7]	~5 days	3–5 days
Exenatide OW[8]	7–14 days	6–7 weeks

BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor; OD, once daily; OW, once weekly; T_{max}, time to reach maximum concentration

1. Byetta. Summary of Product Characteristics; 2. Lyxumia. Summary of Product Characteristics; 3. Victoza. Summary of Product Characteristics; 4. Marbury T et al. Diabetes 2014;63(Suppl.1):A260(1010-P); 5. Kapitza C et al. *J Clin Pharm* 2015;55:497–504; 6. Barrington et al. *Diabetes Obes Metab* 2011;13:434–438; 7. Tanzeum. Prescribing information; 8. Fineman M et al. *Clin Pharmacokinet* 2011;50:65–74.

LEADER: Liraglutide vs Placebo

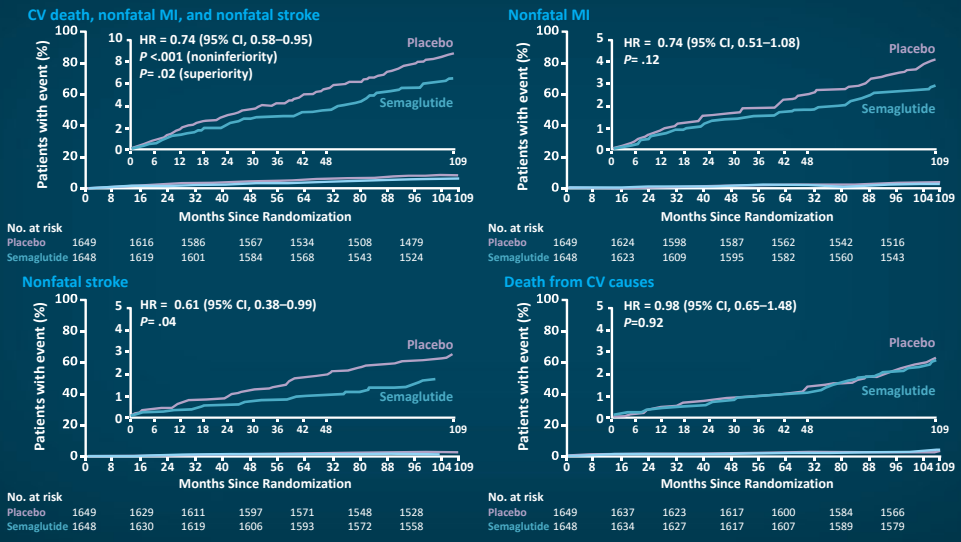
CV death, nonfatal MI, or nonfatal stroke



Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4362	4237	4123	4010	3914	1543	407

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

SUSTAIN 6: Semaglutide and CV Outcomes in Patients with T2DM at High CV Risk

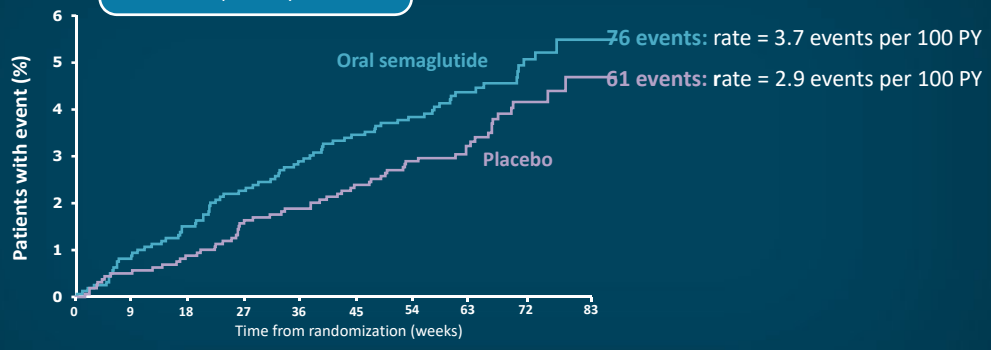


HHF: HR = 1.11 (95% CI, 0.77–1.61) **Nephropathy: HR = 0.64** (95% CI, 0.46–0.88)

Marso SP, *et al. N Engl J Med.* 2016;375:1834-1844.

PIONEER 6: Oral Semaglutide—First MACE

HR = 0.79 (95% CI, 0.57–1.11)
P <.001 for non-inferiority
P= .17 for superiority



Oral Sema	1591	1583	1575	1564	1557	1547	1512	1062	735	16
Placebo	1592	1577	1565	1551	1538	1528	1489	1032	713	11

MACE = major adverse cardiovascular events; Sema = semaglutide.

Hussain M, et al. *N Engl J Med.* 2019;381:841-851.

Cardiovascular Indications: Liraglutide and Injectable Semaglutide

To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

SGLT2i and GLP-1RA Meta-analysis in Patients with T2DM and Multiple ASCVD Risk Factors

Meta-analysis of GLP-1RA and SGLT2i on composite of MI, stroke, and CVD death (multiple risk factors)

	Patients	Events	Weight	HR (95% CI)
GLP-1RA	7097	506	40.4	1.03 (0.87–1.23)
SGLT2i	12672	754	59.6	1.00 (0.87–1.16)
Random effects for MRF (*P*= .81)				1.01 (0.87–1.19)

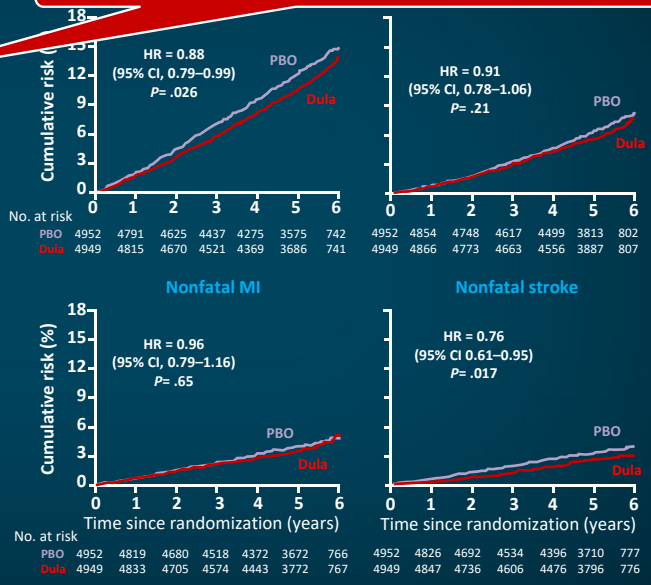
SGLT2i = sodium-glucose cotransporter 2 inhibitor; GLP-1RA = glucagon-like peptide 1 receptor agonist; MRF = multiple risk factors.

Zelniker TA, et al. *Circulation* 2019;139:2022-2031.

REWIND Trial: Dulaglutide vs Placebo

REWIND Trial	N = 9901
Follow-up, median	5.4 yrs
Primary composite outcome	0.88 (0.79–0.99) *P*= .026
CV Death	0.91 (0.78–1.06) *P*= .21
Nonfatal MI	0.96 (0.79–1.16) *P*= .65
Nonfatal stroke	0.76 (0.61–0.95) *P*= .017
All-cause mortality	0.90 (0.80–1.01) *P*= .067

*68.5% did **NOT** have overt CVD at baseline*



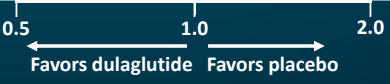
Dula = Dulaglutide; PBO = placebo.

Gerstein HC, et al. *Lancet*. 2019;394:121-130.

REWIND: CV Composite by Prior CVD/CV Event

Dulaglutide Versus Placebo

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide /100py	Placebo Events/Total (%)	Placebo /100py	Hazard ratio	HR (95% CI)	P-value interaction
Overall	594/4949 (12.0)	2.4	663/4952 (13.4)	2.7		0.88 (0.79–0.99)	
Prior CVD	280/1560 (17.9)	3.7	315/1554 (20.3)	4.2		0.87 (0.74–1.02)	
No prior CVD	277/3093 (8.9)	1.7	317/3128 (10.1)	2.0		0.87 (0.74–1.02)	0.97
Prior CV event	196/1028 (19.1)	4.0	236/1007 (23.4)	5.0		0.79 (0.66–0.96)	
No prior CV event	396/3896 (10.2)	2.0	423/3920 (10.8)	2.1		0.93 (0.81–1.07)	0.18



Courtesy of Hertzel C Gerstein, MD, MSc, FRCPC

Dulaglutide Is First Antihyperglycemic with CV Indication That Includes Primary Prevention

---------- INDICATIONS AND USAGE ----------

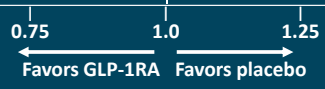
Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:

- 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 who have established cardiovascular disease **or multiple cardiovascular risk factors**

Dulaglutide (Trulicity®) PI 9/2020 (http://pi.lilly.com/us/trulicity-uspi.pdf). Accessed 11/7/2020.

Meta-analysis of GLP-1RA Effects on MACE

	GLP-1RA (n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value interaction
ASCVD	2431/21253 (11%)	2755/21202 (13%)		0.86 (0.80–0.93	0.24
NO ASCVD	480/6428 (7%)	518/6555 (8%)		0.94 (0.83–1.07)	



7.5 vs 7.9%
ARR = 0.4%
NNT = 250

ARR = absolute risk reduction; NNT = number needed to treat.

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

GLP-1RAs Reduce CV Risk

Change in Relative Risk (Based on Hazard Ratio)						
	Lixisenatide (ELIXA)[1]	Exenatide QW (EXSCEL)[2]	Liraglutide (LEADER)[3]	SC Semaglutide (SUSTAIN 6)[4]	Dulaglutide (REWIND)[5]	Oral Semaglutide (PIONEER)[6]
MACE*	NS	NS	↓13%	↓26%	↓12%	↓21%†
CV Death		NS	↓22%	NS	NS	↓51%
HF hospitalization		NS	NS	NS	NS	
All-cause death		NS	↓15%		NS	↓49%
Nonfatal stroke			NS	↓39%	↓24%	

*MACE = death From CV Causes, nonfatal MI, or nonfatal Stroke (± hospitalization for unstable angina or heart failure); †significant for noninferiority but not superiority.
QW = every week; SC = subcutaneous (injection); NS = non-statistically significant change

1. Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257. 2. Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239. 3. Marso SP, et al. *N Engl J Med*. 2016;375:311-322. 4. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844. 5. Gerstein HC, et al. *Lancet*. 2019;394:121-130. 6. Husain M, et al. *N Engl J Med*. 2019;381:841-851.

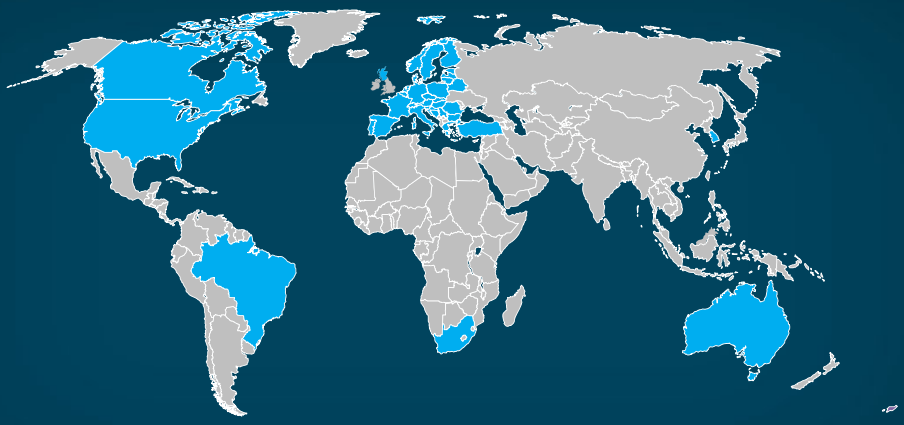
Conclusions from CVOTs

- Diabetes is associated with substantial cardiovascular risk
  - Demonstrating CV safety and efficacy of antihyperglycemic medications is imperative
  - CVOT results have dramatically altered the care of patients with T2DM
- Completed trials demonstrating CV safety of 3 GLP-1RAs
  - lixisenatide, exenatide ER, oral semaglutide
- Completed trials have reported CV benefit of 4 GLP-1RAs
  - liraglutide, injectable semaglutide, albiglutide*, dulaglutide
- Trial results have directly impacted contemporary T2DM guideline recommendations for mitigation of CV risk

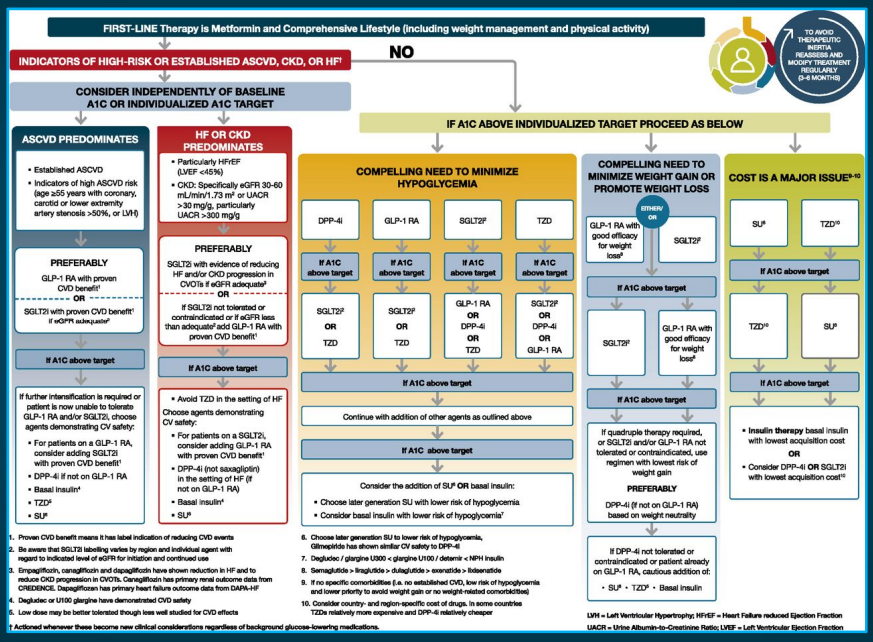
*albiglutide is no longer available.

CVOTs = cardiovascular outcome trials; ER = extended release.

International and Local Guidelines Have Changed In Response To New CVOTs



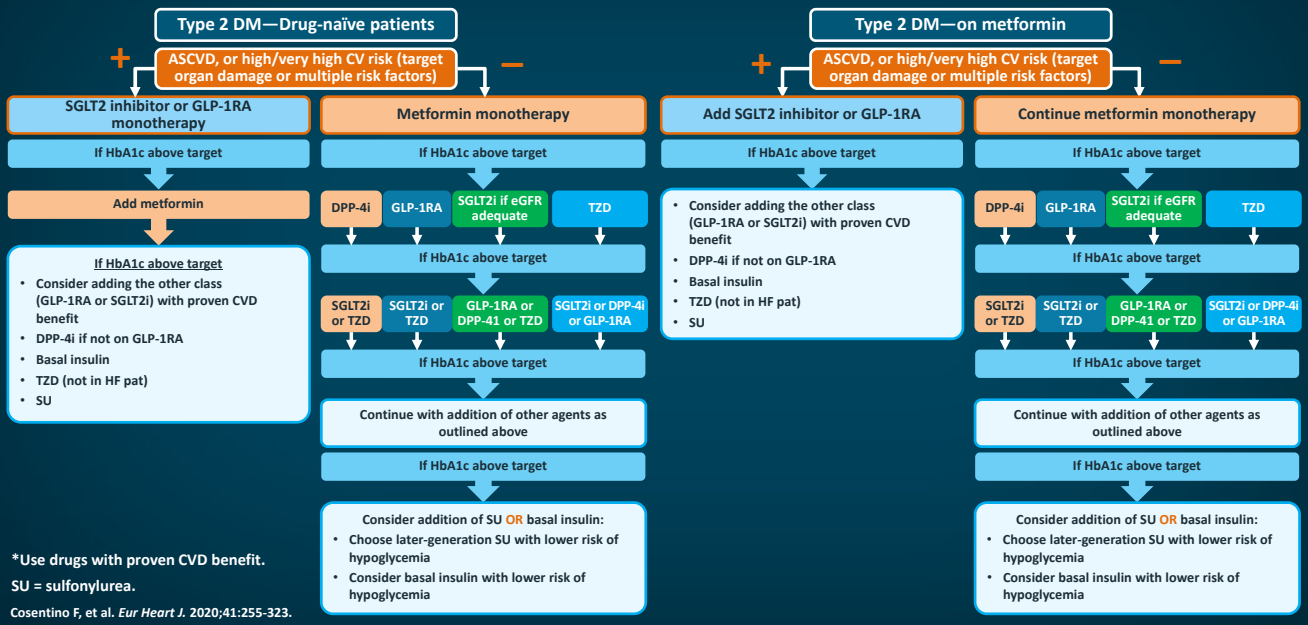
ADA 2020 Standards of Care: Overall Approach



ADA. *Diabetes Care*. 2020;43(suppl 1):S98-S110

ESC Guidelines 2019

Recommended Treatment Pathway In Patients With T2DM



*Use drugs with proven CVD benefit.

SU = sulfonylurea.

Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

ESC guidelines 2019

Recommendations for Glucose-Lowering Treatment for Patients with DM

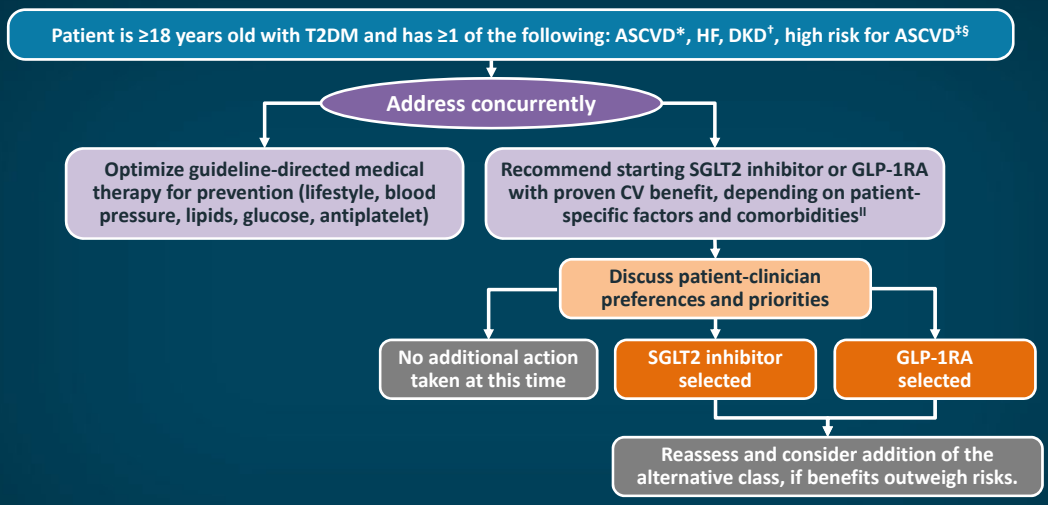
Recommendations	COR	LOE
SGLT2i agents		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce CV events	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce risk of death	I	B
GLP-1RA agents		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce CV events	I	A
Liraglutide is recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce the risk of death	I	B
Biguanides		
Consider metformin in overweight T2DM patients without CVD and at moderate CV risk	IIa	C
Insulin		
Insulin-based glycemic control should be considered in patients with ACS with significant hyperglycemia (>180 mg/dL [(>10 mmol/L]), adapting target according to comorbidities	IIa	C
TZDs		
TZDs are not recommended in patients with HF	III	A
DPP-4is		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF	III	B

Class of Recommendation (COR)	
I	Recommended or is indicated
IIa	Should be considered
IIb	May be considered
III	Is not recommended

Level of Evidence (LOE)	
A	Multiple RCTs and meta-analyses
B	Single RCT or large non-randomized studies
C	Expert opinion and/or small and/or retrospective studies, registries

Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

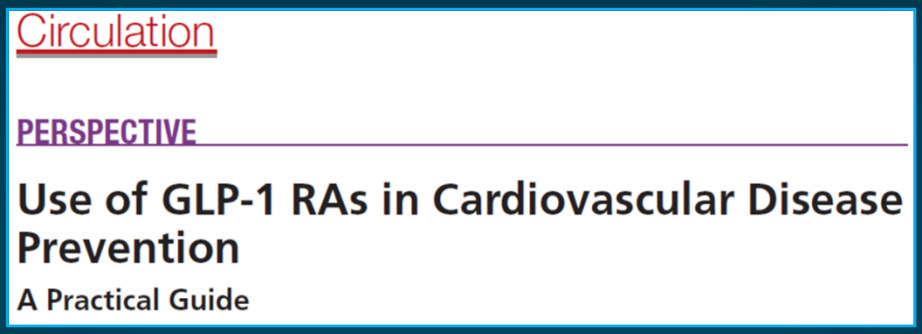
American College of Cardiology Clinical Decision Pathway



*ASCVD is defined as a history of ACS or MI, stable or unstable angina, coronary heart disease ± revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin; †DKD is clinical diagnosis marked by reduced eGFR, presence of albuminuria, or both; ‡Consider an SGLT2 inhibitor when patient has established ASCVD, HF, DKD or is at high risk for ASCVD, and consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD; §Patients at high risk for ASCVD include those with end-organ damage, eg, left ventricular hypertrophy or retinopathy or with multiple CV risk factors (eg, age, hypertension, smoking, dyslipidemia, obesity); ‖Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Das SR, et al. *J Am Coll Cardiol.* 2020;76:1117-1145.

GLP-1RAs in Prevention of CVD



- Start at lowest dose and increase at 1–2-week intervals
- Counsel patients to expect some nausea initially that almost always resolves in a week or 2 and uncommonly prohibitive
- Encourage eating small portions and to stop eating when satisfied instead of when full

Lingvay I, Leiter LA. *Circulation.* 2018;137:2200-2202.

Whiteboard animation: Overcoming Objections to Injectable Therapies

Adjusting Other Antihyperglycemic Therapies at Initiation of GLP-1RAs

- Sulfonylureas
  - If HbA1c is ≤7.5% or hypoglycemic episodes, stop sulfonylurea medication
  - If HbA1c is 7.6–8.5%, decrease sulfonylurea medication by 50%
  - If HbA1c is >8.5%, continue sulfonylurea medication with possibility of future weaning
- Insulin
  - If HbA1c is at or below individualized target or hypoglycemic episodes, decrease basal insulin by 20–30%
  - Coordination with primary care physician and/or endocrinologist strongly encouraged
- Dipeptidyl peptidase-4 inhibitors
  - Discontinue after starting GLP-1RA
- Other agents do not require adjustment

Honigberg MC, et al. *JAMA Cardiol.* 2020;5:1182-1190.

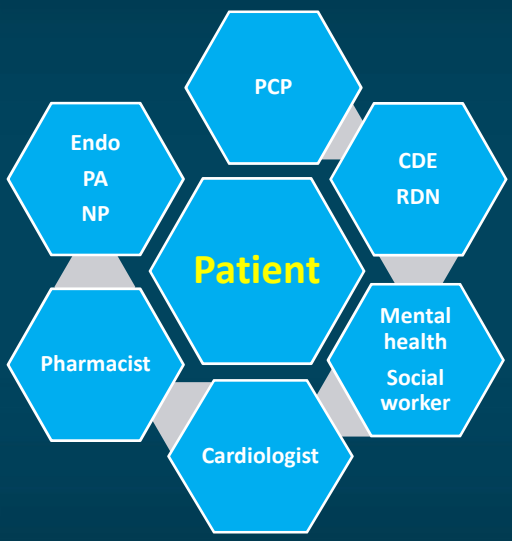
Considerations for Selecting Between GLP-1RAs and SGLT2 Inhibitors

Considerations	GLP-1RAs may be a better choice…	SGLT2 Inhibitors may be a better choice…
Cardiorenal	Established atherosclerotic cardiovascular and/or cerebrovascular disease; eGFR <30 mL/min/1.73 m^2	HF or CKD dominates
Glycemic control and DKA	More HbA1c reduction needed; history of DKA	
Comorbidities	Obesity; frequent genital mycotic infections; osteoporosis or history of fractures; lower-limb ulcers or amputations	Active gallbladder disease; pancreatitis; gastroparesis or delayed gastric emptying; personal or family history of MTC or MEN-2; history of proliferative retinopathy
Other	Patient preference	Patient preference

DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; MTC = medullary thyroid cancer; MEN-2 = multiple endocrine neoplasia type 2.

Honigberg MC, et al. *JAMA Cardiol.* 2020;June 17; Epub ahead of print.

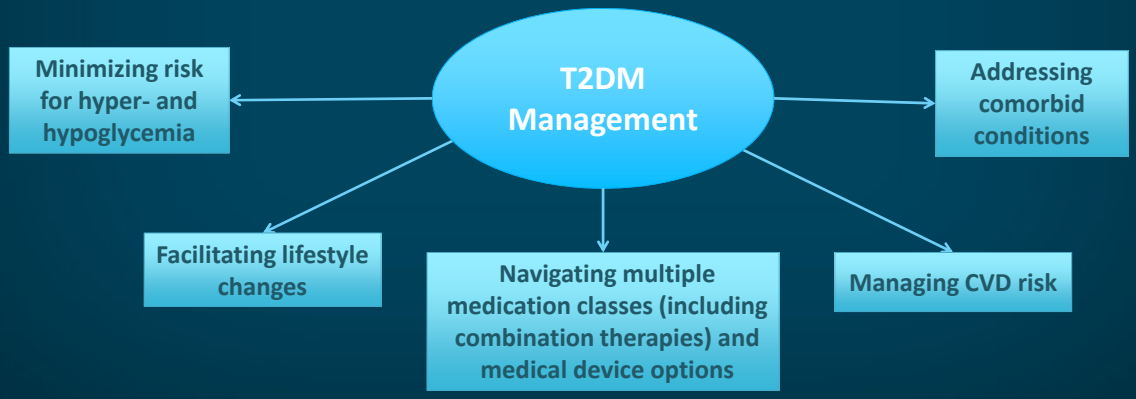
Team Approach—Collaborative Care



PCP = primary care provider; Endo = endocrinologist; PA = physician assistant; NP = nurse practitioner; CDE = certified diabetes educator; RDN = registered dietitian nutritionist.

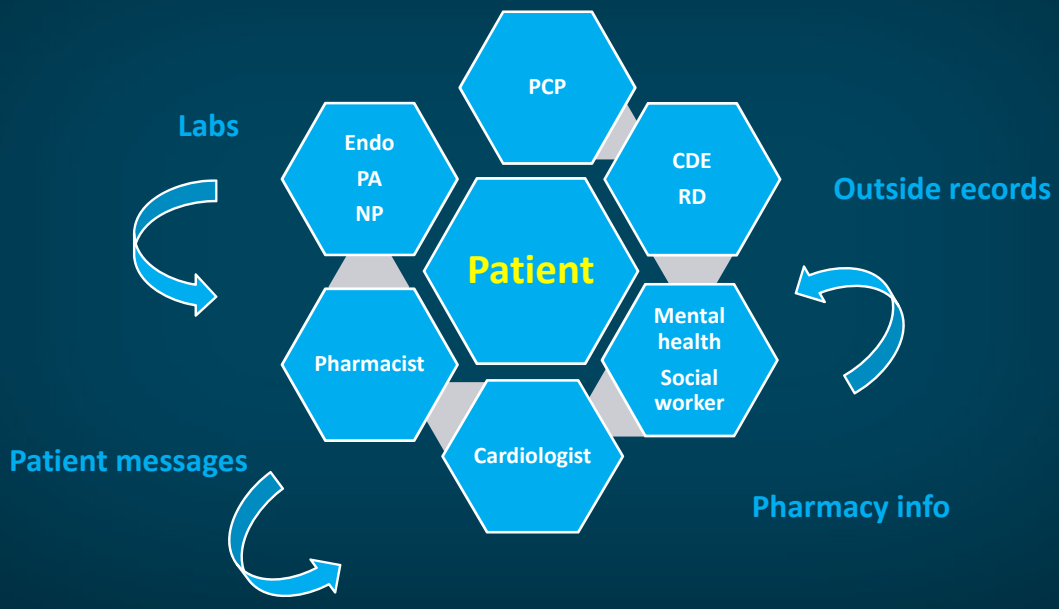
Evolving Role of PCPs in T2DM Management

- PCPs deliver clinical care to ~90% of individuals with T2DM
- This will likely increase over time with the growth of the aging population
- T2DM management has become increasingly complex:



Shrivastav M, et al. *Diabetes Spectr.* 2018;31:279-287.

How Do We Manage Information and Communication?

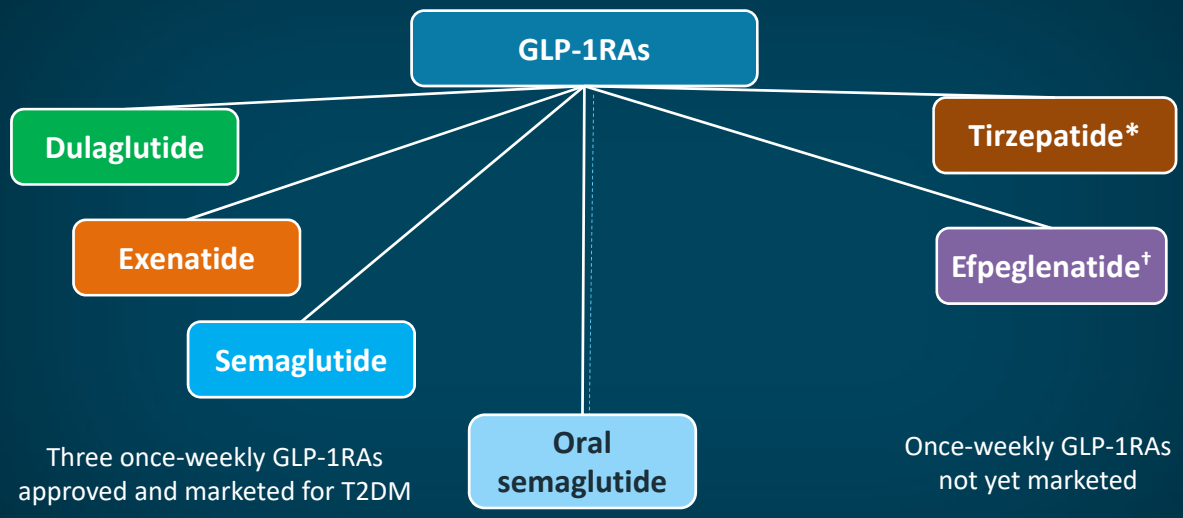


Endocrinologist and Cardiologist Coordination

- Shared, coordinated care
- Direct EMR messaging
- Delineate who is doing what
- Multispecialty clinics for cardiometabolic care
- Training pathway for cardiometabolic specialists

EMR = electronic medical record.

GLP-1RAs…2020 and Beyond

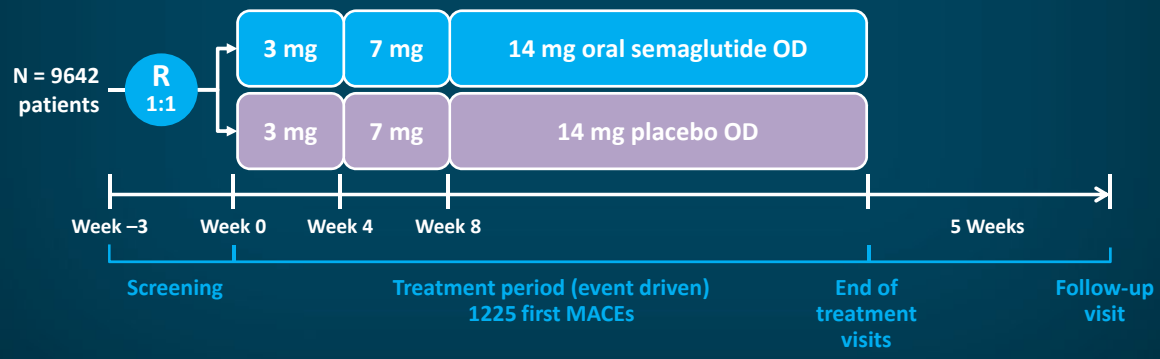


*Dual GIP/GLP-1RA action; †a once-monthly formulation is also being investigated

SOUL Trial: Oral Semaglutide

Overall Trial Design

Primary objective is to demonstrate that oral semaglutide **lowers the risk of MACE** compared with placebo, when both are added to standard of care in patients with type 2 diabetes and at high risk of CV events



NCT03914326 (https://clinicaltrials.gov/ct2/show/NCT03914326). Accessed 11/11/2020.

AMPLITUDE-OP: CVOT of Efpeglenatide

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

CLINICAL TRIAL DESIGN | Free Access

Design and baseline characteristics of the AMPLITUDE-O cardiovascular outcomes trial of efpeglenatide, a weekly glucagon-like peptide-1 receptor agonist

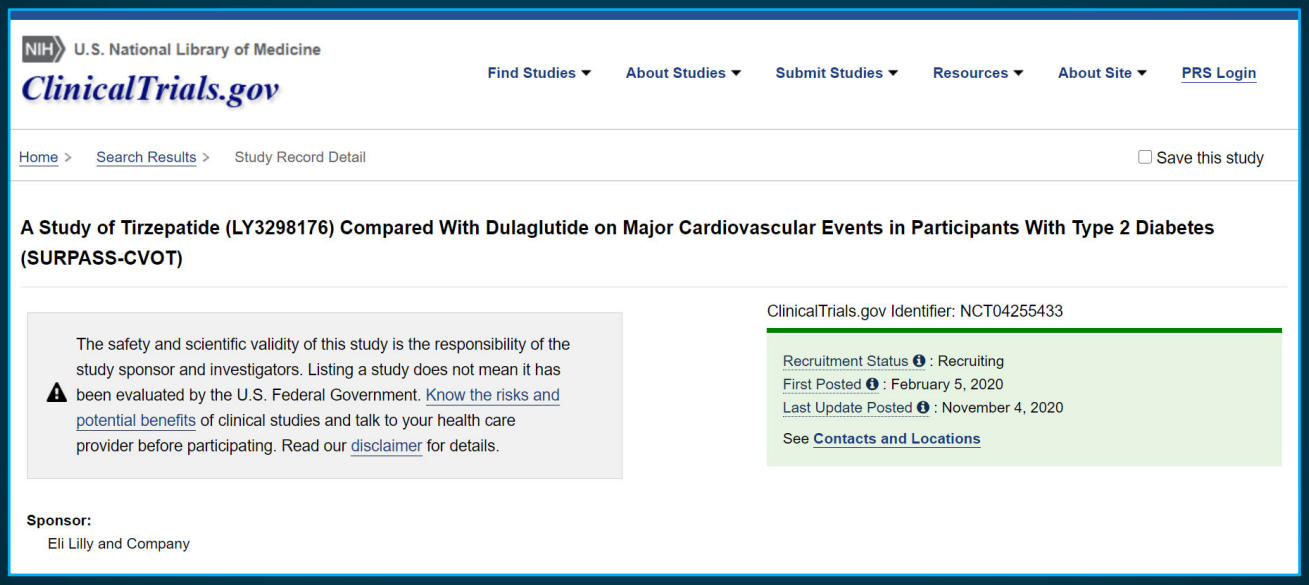
Hertzel C. Gerstein MD, Kelley Branch MD, Laura Heenan MSc, Stefano Del Prato MD, Nardev S. Khurmi MD, Carolyn S. P. Lam MBBS, Richard Pratley MD, Julio Rosenstock MD, Naveed Sattar MD

First published: 07 October 2020 | https://doi.org/10.1111/dom.14223

ClinicalTrials.gov Identifier: NCT03496298.

Gerstein HC, et al. *Diabetes Obes Metab.* 2020;Oct 7: Epub ahead of print.

SURPASS-CVOT: CVD Outcomes With Tirzepatide vs Dulaglutide



NCT04255433 (SURPASS-CVOT) (https://clinicaltrials.gov/ct2/show/NCT04255433?term=NCT04255433&draw=2&rank=1). Accessed 11/9/2020.

Case Study Recap—Case 1: ND

- 65-year-old male with new-onset T2DM
- PMH
  - NSTEMI ~1 y ago – DES x 2, R Circ and LAD
  - Hypertension
  - Hypercholesterolemia
  - Prior smoker (quit 1 year ago)
- Meds
  - Atorvastatin 40 mg/d
  - Losartan 100 mg/d
  - Metoprolol XR 100 BID
  - Aspirin 81 mg/d
  - Ticagrelor 60 mg BID

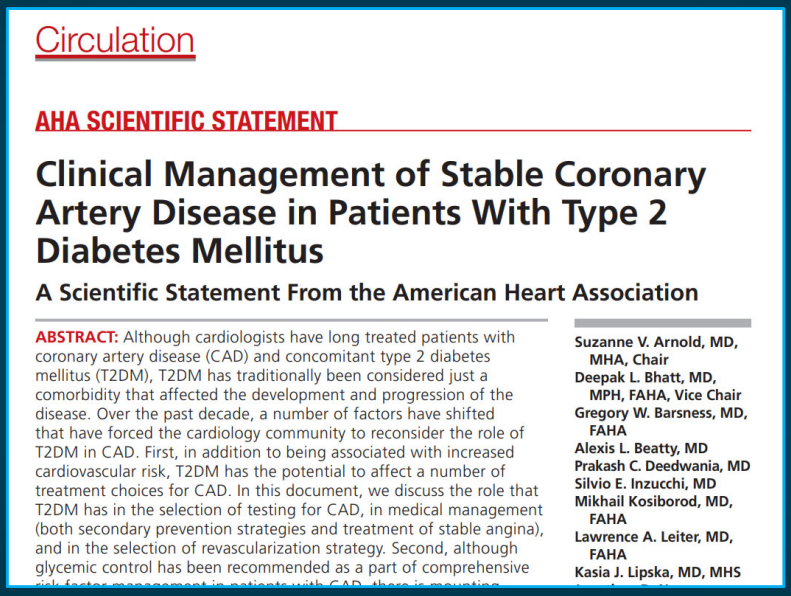
Case 1: ND
(continued)

- PE
  - BMI 33.2 kg/m2
  - BP 136/88
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses intact, no edema
- Labs
  - Fasting plasma glucose 137
  - HbA1c 7.4%
  - CMP, CBC normal
  - LDL-C ; 101; HDL-C: 40; TG: 198
  - eGFR: 80 mL/min/1.73m^2; UACR: 5 mg/g

Case 1: ND—Questions to Consider

- What is an optimal HbA1c for this patient?
- What would be your preferred first-line treatment for his diabetes?
- Should you initiate metformin prior to an SGLT2 inhibitor or GLP-1RA?
- What clinical considerations would lead you to select an SGLT2 inhibitor vs a GLP-1RA?

AHA: Management of CAD in Patients with T2DM



Circulation

AHA SCIENTIFIC STATEMENT

Clinical Management of Stable Coronary Artery Disease in Patients With Type 2 Diabetes Mellitus

A Scientific Statement From the American Heart Association

ABSTRACT: Although cardiologists have long treated patients with coronary artery disease (CAD) and concomitant type 2 diabetes mellitus (T2DM), T2DM has traditionally been considered just a comorbidity that affected the development and progression of the disease. Over the past decade, a number of factors have shifted that have forced the cardiology community to reconsider the role of T2DM in CAD. First, in addition to being associated with increased cardiovascular risk, T2DM has the potential to affect a number of treatment choices for CAD. In this document, we discuss the role that T2DM has in the selection of testing for CAD, in medical management (both secondary prevention strategies and treatment of stable angina), and in the selection of revascularization strategy. Second, although glycemic control has been recommended as a part of comprehensive

Suzanne V. Arnold, MD, MHA, Chair
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Mikhail Kosiborod, MD, FAHA
Lawrence A. Leiter, MD, FAHA
Kasia J. Lipska, MD, MHS

CAD = coronary artery disease.

Arnold SV, et al. *Circulation.* 2020;141:e779-e806.

Management of Stable CAD

Antithrombotics—Underlying issue: T2DM is a generalized prothrombotic state caused by both altered coagulation and altered platelet function.		
Aspirin alone	Lowest risk of bleeding but high residual platelet reactivity increases CV risk	
Clopidogrel alone	Decreased CV risk without meaningfully increased risk of bleeding vs aspirin alone	
Aspirin + clopidogrel/ticagrelor	Decreased CV risk with increased risk of bleeding; targets patients with additional risk factor and low risk of bleeding (use risk scores)	
Aspirin + low-dose rivaroxaban	Decreased CV risk with increased risk of bleeding: targets aberrant coagulation with T2DM	
Blood pressure—Underlying issue: Coexisting hypertension increases the risk of MI, stroke, and all-cause mortality.		
Target blood pressure	<140/90 mm Hg in most patients; consider <130/80 mm Hg if additional risk factors for stroke or microvascular complications	
ACE inhibitor/ARB	First-line therapy because of decreased CV risk with CAD	
Long-acting thiazide diuretic	Good CV risk reduction but slight increase in glucose	
Calcium channel blockers	Good CV risk reduction and effective antianginal	
Aldosterone antagonists	Particularly effective in patients with prior MI or LV dysfunction	
β-Blockers	Do not reduce mortality in uncomplicated patients with stable CAD; choose vasodilating β-blocker for less adverse metabolic impact	
Lipids—Underlying issue: Atherogenic lipid anomalies include hypertriglyceridemia, low HDL-C, and small, dense LDL particles.		
High-intensity statins	Cornerstone of lipid therapy and secondary prevention	
Ezetimibe and PCSK9 inhibitors	Additional CV risk reduction when LDL is >70 mg/dL despite maximally tolerated statins	
Niacin	Not recommended	
Fibrates	Recommended when triglycerides are very high (eg, >500 ma/dL) to reduce the risk of pancreatitis	
Icosapent ethyl	Consider for further CV risk reduction when triglycerides remain elevated (>135 mg/dL) despite maximally tolerated statin	
Glycemic control—Underlying issue: Hyperglycemia increases CV risk, but impact of glucose-towering therapies on outcomes is complex, and therapy needs to be individualized.		
Glycemic target	<7.0% if young and healthy (life expectancy >10-20 years); depends on preferences and capacity	
	<8.0% or 8.5% for older patients with comorbidities or at high risk for hypoglycemia; depends on preferences, capacity, and types of treatment used	
Glucose-lowering medications	CV effects	Noncardiovascular effects
Metformin (usually first line)	CV benefit possible (low-quality evidence)	No associated weight gain or hypoglycemia
SGLT2 inhibitors	CV benefit (largely consistent among individual drugs); reduction in MACEs and HF hospitalizations	Associated with weight loss, no hypoglycemia, lower blood pressure, and less progression of CKD
GLP-1 receptor agonists	CV benefit: reduction in MACEs (some inconsistency among individual drugs)	Associated with weight loss and no hypoglycemia
Thiazolidinediones	Likely CV benefit (but not heart failure)	No hypoglycemia; associated with weight gain, edema, risk of HF, and bone fractures
DPP4 inhibitors	Neutral effect on CV outcomes	No associated weight gain or hypoglycemia
Insulin and sulfonylureas	Likely neutral effect on CV outcomes	Associated with weight gain and hypoglycemia

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HDL-C = high-density lipoprotein-cholesterol: LDL = low-density lipoprotein; LV = left ventricular; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Arnold SV, et al. *Circulation.* 2020;141:e779-e806.

Case Study Recap—Case 2: CK

- 57-year-old female with established T2D
- PMH
  - T2DM x 6 y
  - Hypertension x 12 y
  - Hypercholesterolemia
- Meds
  - Rosuvastatin 20 mg/d
  - Lisinopril 40 mg/d
  - HCTZ 25 mg/d
  - Metformin XR 1000 mg QD
  - Sitagliptin 100 mg / d

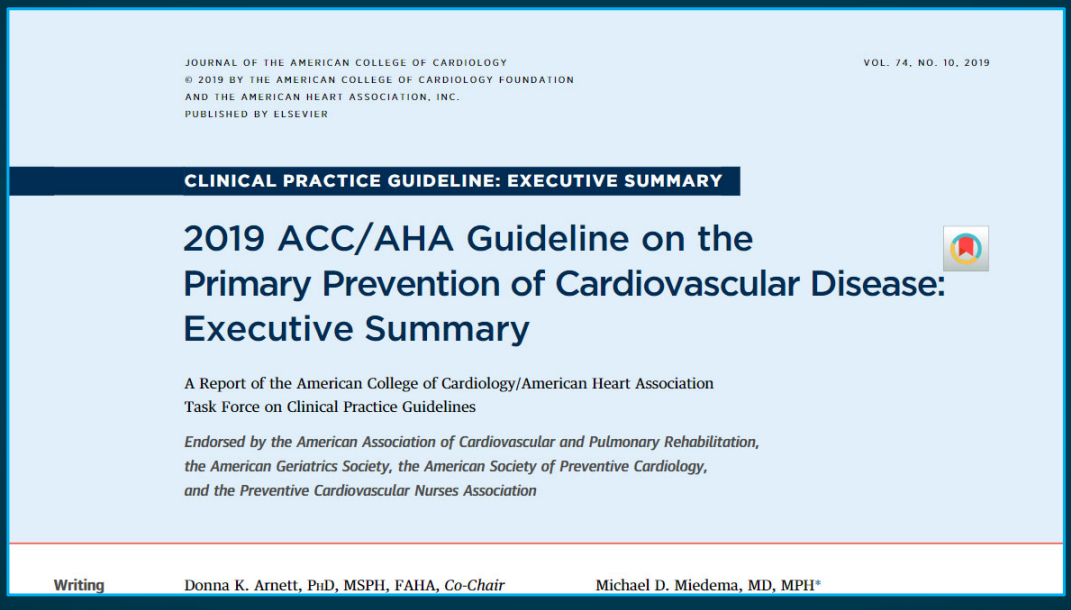
Case 2: CK
(continued)

- PE
  - BMI 31.4 kg/m2
  - BP 148/92
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses intact, trace pedal edema
- Labs
  - Fasting plasma glucose 154
  - HbA1c 7.8%
  - LDL-C 121 HDL-C 36 TG 254
  - eGFR 42 mL/min/1.73m2

Case 2: CK—Questions to Consider

- What is an optimal HbA1c for this patient?
- Should you continue metformin given her CKD?
- What clinical considerations would lead you to select an SGLT2 inhibitor vs a GLP-1RA?

ACC/AHA: Guideline on Primary Prevention of CVD



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CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

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

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatrics Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association

Writing Donna K. Arnett, PhD, MSPH, FAHA, *Co-Chair* Michael D. Miedema, MD, MPH*

ACC = American College of Cardiology.

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

Adults with Type 2 Diabetes Mellitus

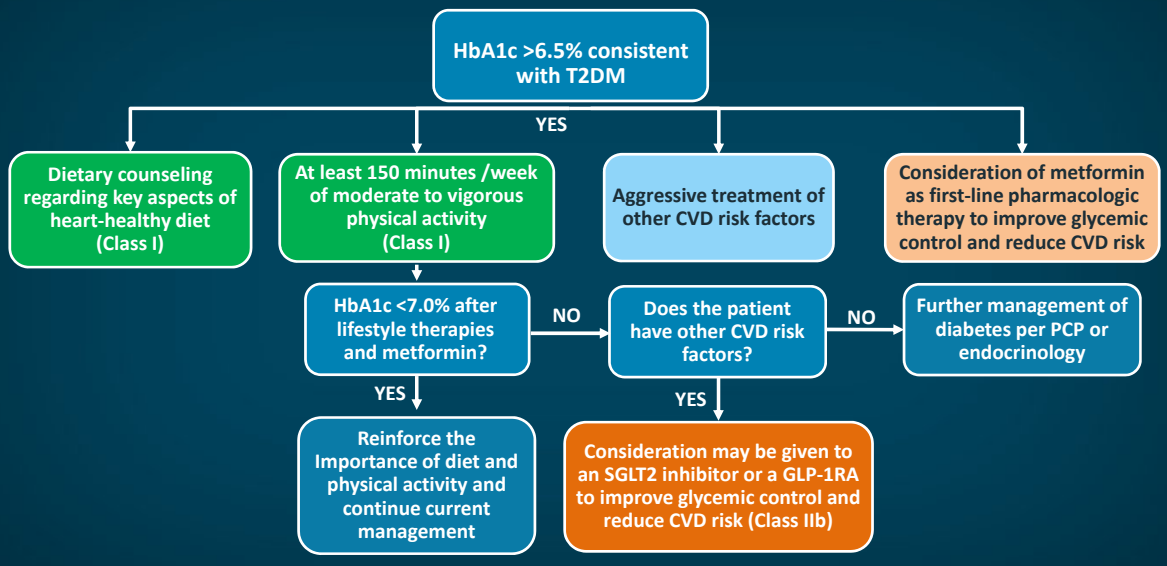
Recommendations for Adults With T2DM		
COR	**LOE**	**Recommendations**
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1RA) to improve glycemic control and reduce CVD risk.

Class of Recommendation (COR)	
I (strong)	Recommended or is indicated
IIa (moderate	Is reasonable and can be useful
IIb (weak)	May be reasonable and may be considered

Level of Evidence (LOE)	
A	Multiple RCTs and meta-analyses
B-R	≥1 RCT or meta-analyses of moderate-quality RCTs

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

Treatment of T2DM for Primary Prevention of Cardiovascular Disease

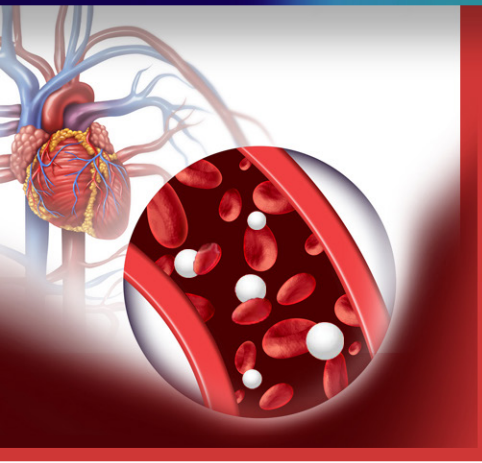


Arnett DK, et al. *J Am Coll Cardiol*. 2019;74:e177-e232.

Getting to the Heart of DIABETES:

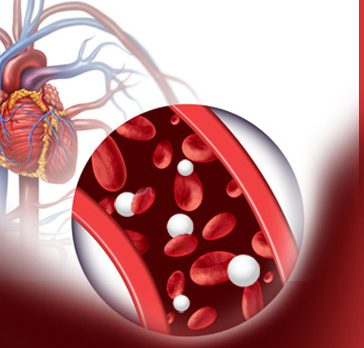
The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk

More resources about diagnosing and managing diabetes and its comorbidities, including new and emerging treatment options, American Diabetes Association standards, and recommendations for patient-centered care are available through the CARES Initiative at www.caresdiabetes.com. This website has web links, statistical information, reference literature, and pertinent, practical guidance for patients with diabetes and the clinicians who treat them.



Getting to the Heart of DIABETES:

The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk



Getting to the Heart of DIABETES:

The Role of GLP-1 Receptor Agonists in Reducing Cardiovascular Risk

WHITEBOARD ANIMATIONS

Overcoming Obstacles to Injectable Therapies:
https://youtu.be/-FJx7FParJQ

GLP-1 RA Cardiovascular Mechanisms of Action:
https://youtu.be/YMavSjI3GAY

This activity is provided by Med Learning Group. *This activity is supported by an educational grant from Lilly.*
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