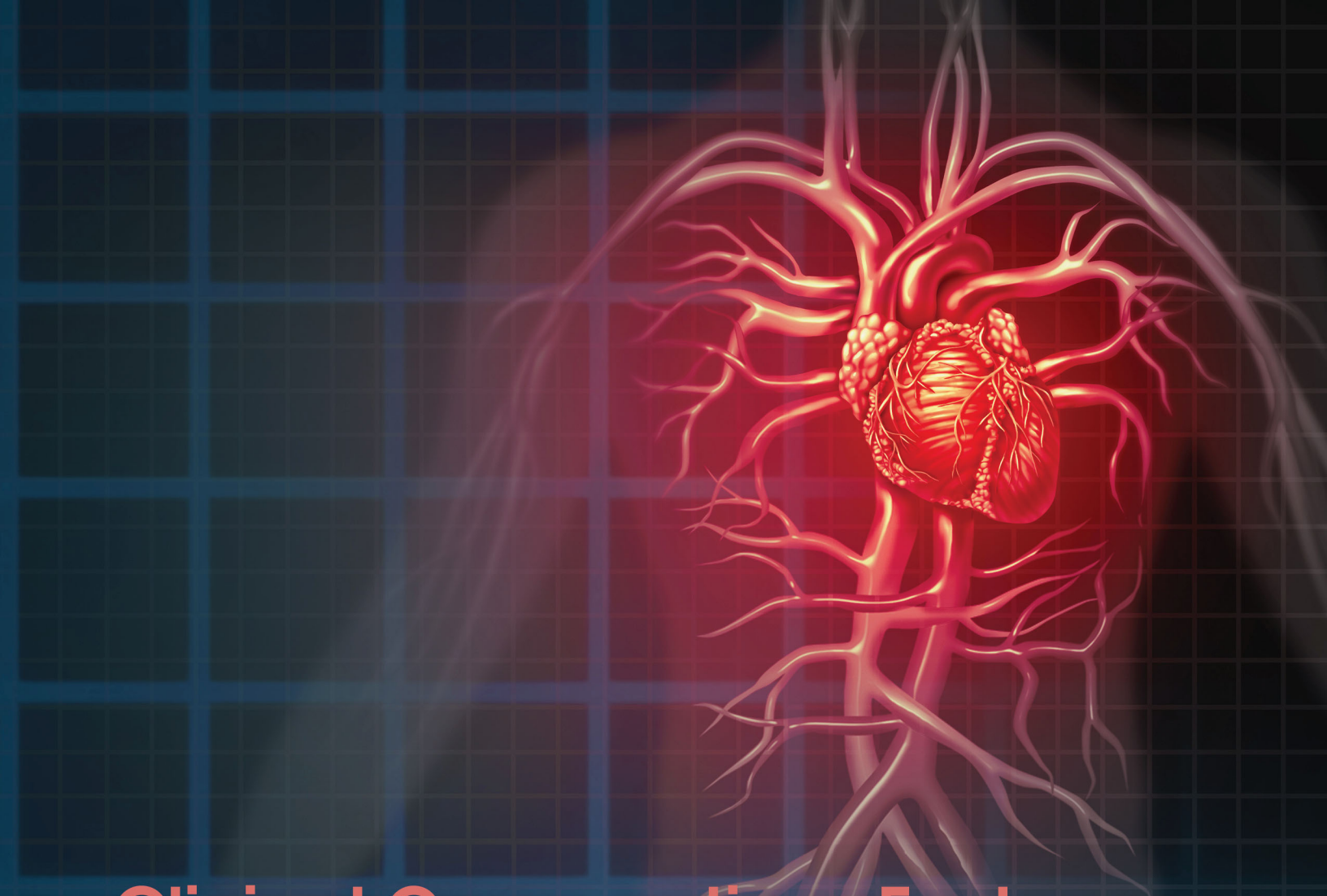

Clinical Conversations Exchange:

A Cardiologist-PCP Collaboration Discussing GLP-1 Receptor Agonists for Reducing Cardiovascular Risk in Patients with Diabetes

Co-Chairs

Michael J. Blaha, MD, MPH
(CARDIOLOGIST)
Professor of Medicine and Epidemiology
Director of Clinical Research,
Ciccarone Center for the Prevention of Cardiovascular Disease
Johns Hopkins University School of Medicine
Baltimore, MD

Jay Shubrook, DO, FACOFP, FAAFP
(PRIMARY CARE)
Professor and Diabetologist
Director for Clinical Research
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Touro University California
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Learning Objectives

- Determine the clinical implications of results from Cardiovascular Outcomes Trials of GLP-1 receptor agonists
- Identify patients with type 2 diabetes who are most likely to benefit from the use of GLP-1 receptor agonists
- Personalize the selection of GLP-1 receptor agonists based on indications, guidelines recommendations and clinical data
- Develop strategies for increasing collaboration between cardiologists and PCPs in managing cardiovascular risk in patients with T2DM

Target Audience

This educational activity is intended for cardiologists and primary care providers who manage and treat patients with type 2 diabetes.

ACCREDITATION AND DESIGNATION STATEMENTS

Accreditation Statement

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

Credit Designation Statement

Med Learning Group designates this web-based 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 web-based live activity.

Nursing Credit Information

Purpose: This program would be beneficial for nurses involved in the care of patients with type 2 diabetes mellitus.

Credits: 1.0 ANCC Contact Hour(s)

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(s) of continuing nursing education of RNs and APNs.

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- **Dr. Shubrook** is a consultant for Bayer and Novo Nordisk.

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.

Staff, Planners and Managers

Matthew Frese, General Manager of Med Learning Group has nothing to disclose.

Christina Gallo, SVP, Educational Development for Med Learning Group has nothing to disclose.

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

Russie Allen, Outcomes Coordinator for Med Learning Group has nothing to disclose.

Cindy Lampner, MSLIS, Medical Director, Scientific and Medical Services for Med Learning Group has nothing to disclose.

Melissa A Johnson, Senior Program Manager for Med Learning Group has nothing to disclose.

Amanda Jenkins, Associate Program Manager for Med Learning Group has nothing to disclose.

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During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

METHOD OF PARTICIPATION

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

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

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

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Provided by Med Learning Group

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This activity is supported by an educational grant from Lilly.

AGENDA

I.CV comorbidities in T2DM
- a. Epidemiology
- b. Traditional risk factors
- c. Pathophysiology

II. GLP-1 Receptor Agonists
- a. Mechanism of action
  - i. The incretin pathway
  - ii. Anti-hyperglycemic mechanisms
  - iii. Mechanisms of CV benefit
- b. Clinical trial results
  - i. Results from CVOT
    1. Primary prevention
    2. Secondary prevention
  - ii. Anti-hyperglycemic results
  - iii. Weight loss results
- c. Guidelines and algorithms
  - i. ADA
  - ii. ACC
- d. Practical strategies for use of preferred agents based on CVOT trials (dulaglutide, liraglutide, and injectable semaglutide) utilizing cast studies including:
  - i. Patient selection
  - ii. Indications
  - iii. Dosing
  - iv. Adverse effects
  - v. Adjusting other medications
  - vi. Follow-up care
- e. New incretin-based therapies in development

III. Cardiologist/PCP collaboration strategies
IV. Case studies
V. Conclusions/Question-and answer session

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Clinical Conversations Exchange: A Cardiologist-PCP Collaboration Discussing GLP-1 Receptor Agonists for Reducing Cardiovascular Risk in Patients with Diabetes

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1

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- Dr. Shubrook is a consultant for Astra Zeneca, Bayer and Novo Nordisk.
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2

CV Comorbidities in Patients with T2DM

3

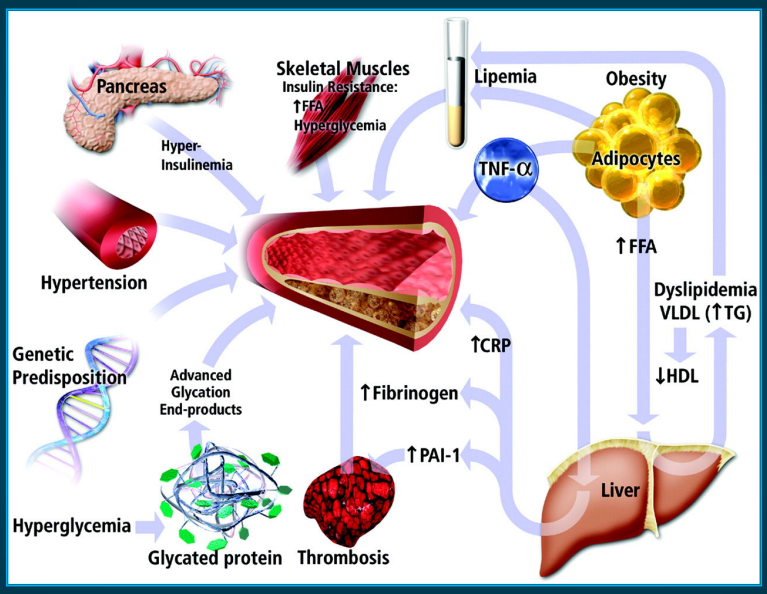
Audience Poll

What do you see as the primary purpose of GLP-1 receptor agonists?

1. **Glucose control**
2. **Cardiovascular risk protection**
3. **Other**

4

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.

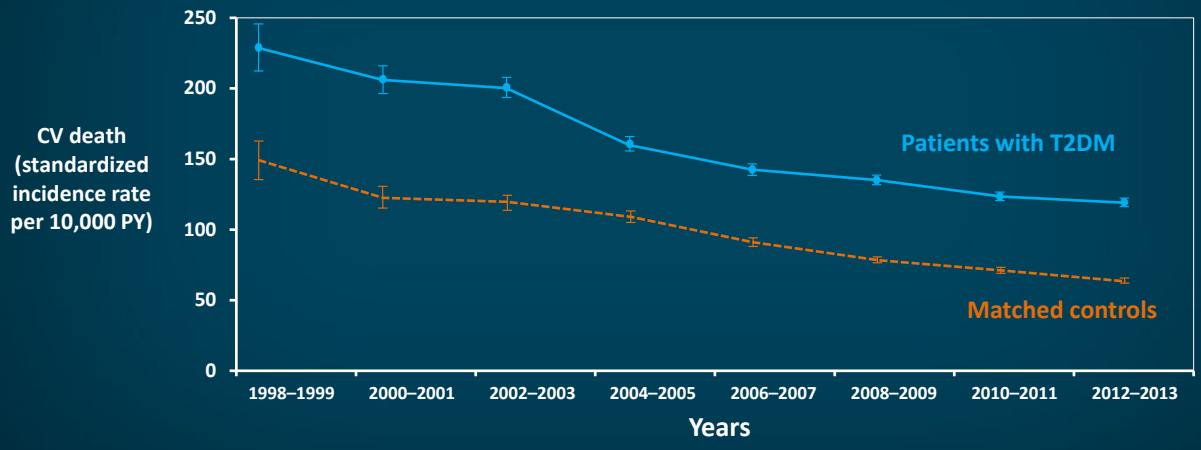
Libby P, Plutzky J. *Circulation*. 2002;106:2760-2763.

5

T2DM Associated with Excess Risk of CVD Death

Data from Swedish National Diabetes Register

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



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

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

6

Prevalence of Modifiable Risk Factors in Young Adults During First Acute MI

	During a first myocardial infarction in young adults (18–59 years) in the US		
25%	Diabetes mellitus	>1 in 4	34%
6%	Drug Abuse	>1 in 20	5%
57%	Hypertension	>1 in 2	61%
58%	Dyslipidemia	>1 in 2	52%
16%	Obesity	>1 in 6	23%
54%	Smoking	>1 in 2	50%
92%	Any of the modifiable risk factors	>9 in 10	50%

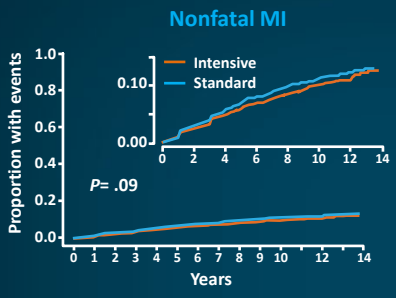
MI = myocardial infarction.

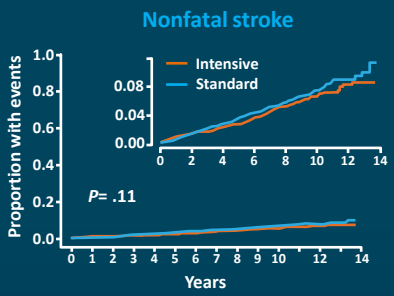
Yandrapalli S, et al. *J Am Coll Cardiol.* 2019;73:573-584.

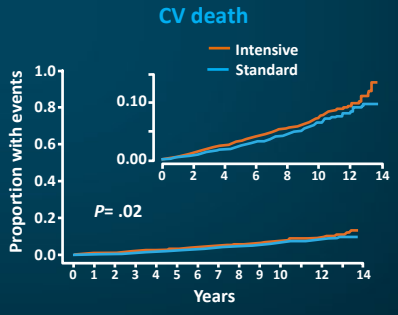
7

Does Intensive Glycemic Control Translate Into Better CV Outcomes ?

ACCORDION trial included 8601 participants with T2DM who did not suffer a primary outcome or death during ACCORD trial and were monitored for a median of 8.8 years and a mean of 7.7 years from randomization







Conclusion: mean of 3.7 years of intensive glycemic control had a **neutral effect** on death and nonfatal CV events but increased CV-related death during active phase

ACCORD Study Group. *Diabetes Care.* 2016;39:701-708.

8

GLP-1 Receptor Agonists

9

US Regulatory History

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Announces New Recommendations for Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

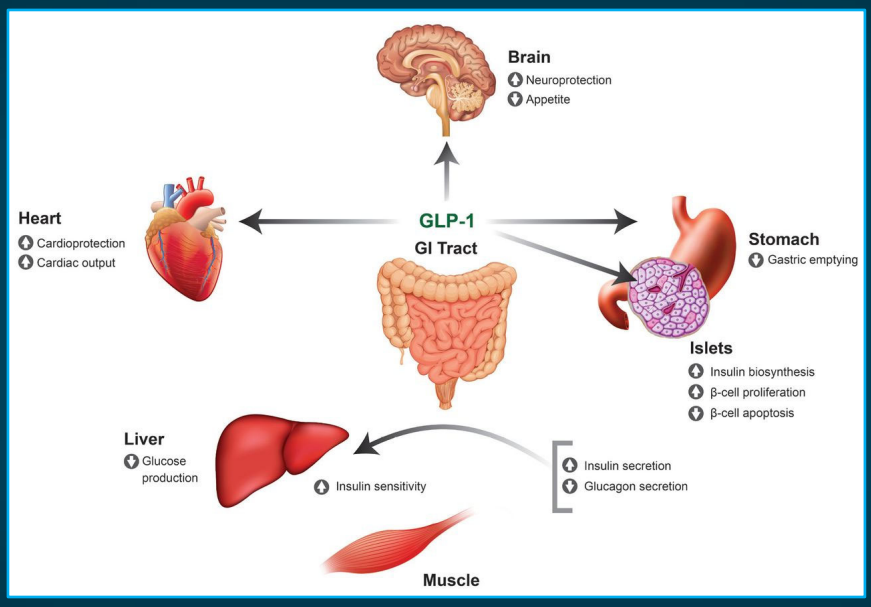
"Sponsors should demonstrate that therapy will not result in an unacceptable increase in cardiovascular risk"

*FDA 2008 guideline: requires ~**15,000** patients-years of exposure, exclusion of a 30% hazard for MACE events in a risk population*

US = United States: FDA = US Food and Drug Administration; MACE = major adverse cardiovascular events.

10

GLP-1 RA Mechanism of Action



GLP-1 = glucagon-like peptide 1; RA receptor agonist; GI = gastrointestinal.

Hinnen D. *Diabetes Spectr.* 2017;30:202-210.

11

GLP1-RA Cardiovascular Outcome Trials

	ELIXA Lixisenatide (n = 6068)	LEADER Liraglutide (n = 9340)	SUSTAIN-6 Semaglutide (n = 3297)	EXSCEL Exenatide QW (n = 14,752)	HARMONY Albiglutide QW (n = 9463)	REWIND Dulaglutide QW (n = 9901)	PIONEER-6 Semaglutide PO (n = 3182)
Median follow-up, years	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Mean age, years	60	64	54	62	64	66	66
Female, %	30	36	39	38	31	46	32
Mean BMI, kg/m^2	30.2	NR	NR	NR	32.3	32.3	32.3
HbA1c, %	7.7	8.7	8.7	8.1	8.8	7.3	8.2
BL metformin, %	76	73	76	74	81	57	51
Baseline eGFR	76	75	75	76	79	75	74
eGFRt <60, %	23	23	28.5	18	23	22	27
Prior CVD, %	100	81	83	73	100	32	85
Prior HF, %	22	18	24	16	20	9	NR
3P-MACE	1.02 (0.89–1.17)	**0.87 (0.78–0.97)**	**0.74 (0.58–0.95)**	0.91 (0.83–1.00)	**0.78 (0.68–0.90)**	**0.88 (0.79–0.99)**	0.79 (0.57–1.11)
CV death	0.98 (0.78–1.22)	**0.78 (0.66–0.93)**	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	**0.75 (0.61–0.90)**	0.96 (0.79–1.16)	1.18 (0.73–1.90)
Stroke	1.12 (0.79–1.58)	0.86 (0.71–1.06)	**0.61 (0.38–0.99)**	0.85 (0.70–1.03)	0.86 (0.66–1.14)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
All-cause mortality	0.94 (0.78–1.13)	**0.85 (0.74–0.97)**	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.95 (0.79–1.16)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
HHF	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	NR	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Renal events	0.81 (0.66–0.99)	**0.78 (0.67–0.92)**	**0.64 (0.46–0.88)**	0.85 (0.73–0.98)	NR	**0.85 (0.77–0.93)**	NR
Weight loss	0.7 (0.9–0.5)	2.3 (2.5–2.0)	2.9 (2.3–3.5)/ 4.3 (3.8–4.9)	1.3 (1.1–1.4)	0.83 (0.6–1.1) at 16 months	1.5 (1.3–1.7)	3.6

QW = every week; PO = oral/by mouth; BMI = body mass index; HbA1c = glycosylated hemoglobin; BL = baseline; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; HHF = hospitalization for HF; NR = not reported.

Wilcox T, et al. *J Am Coll Cardiol*. 2020;75:1956-1974.

12

ELIXA: Lixisenatide vs Placebo

Primary endpoint: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

First Confirmed Primary Endpoint		
Study arms	Events/Total	Percent
Lixisenatide	406/3034	13.4
Placebo	399/3034	13.2

HR = 1.02 (95% CI, 0.89–1.17)

Number at risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

CV = cardiovascular; ELIXA = Evaluation of LIXisenatide in Acute Coronary Syndrome; UA = unstable angina; HR = hazard ratio; CI = confidence interval.

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

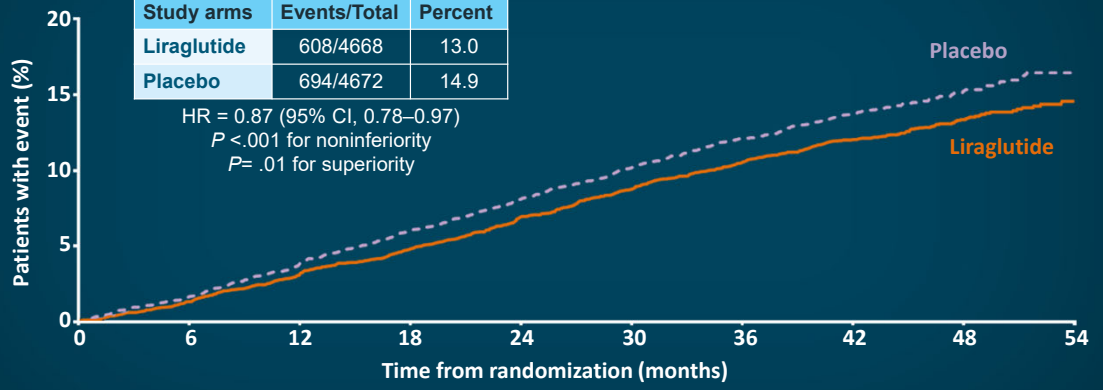
13

LEADER: Liraglutide vs Placebo

Primary outcome: CV death, nonfatal MI, or nonfatal stroke

Primary Outcome		
Study arms	Events/Total	Percent
Liraglutide	608/4668	13.0
Placebo	694/4672	14.9

HR = 0.87 (95% CI, 0.78–0.97)
P <.001 for noninferiority
P= .01 for superiority

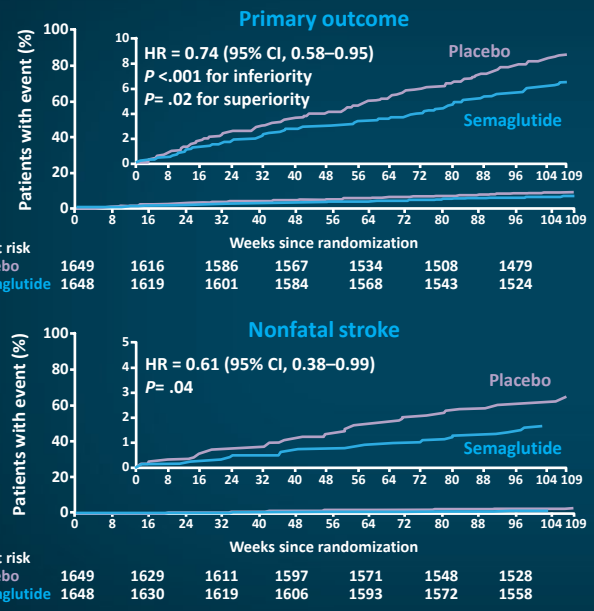


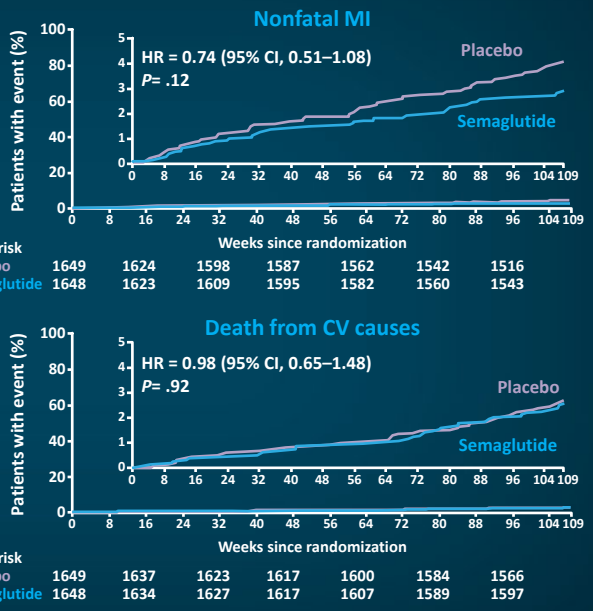
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

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

14

SUSTAIN-6: Semaglutide vs Placebo



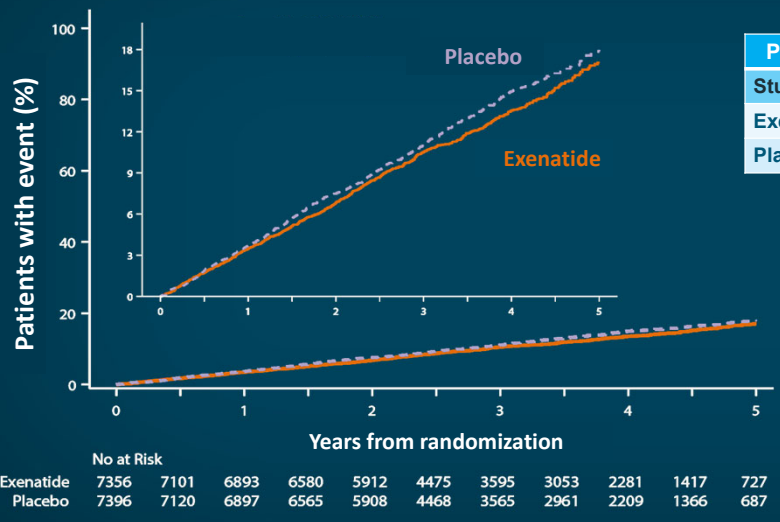


Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

15

EXSCEL: Exenatide vs Placebo

Intention-to-treat analysis for noninferiority and superiority



Primary CV Composite Outcome		
Study arms	Events/Total	Percent
Exenatide	839/7356	11.4
Placebo	905/7396	12.2

HR = 0.91 (95% CI, 0.83–1.00)
P <.001 for noninferiority
P= .06 for superiority

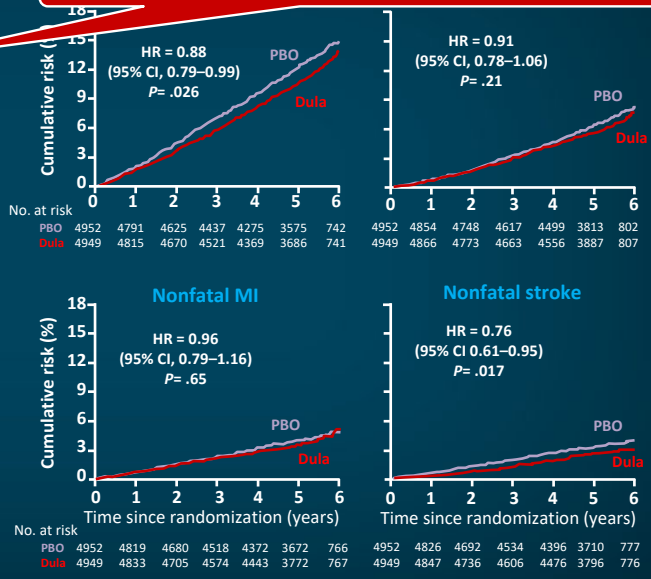
Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239.

16

REWIND Trial: Dulaglutide vs Placebo

REWIND Trial	N = 9901
Follow-up, median	5.4 years
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*



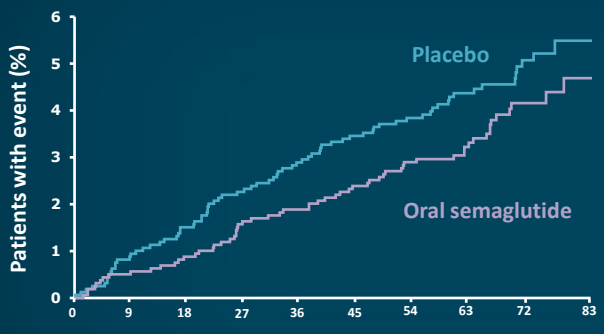
Dula = Dulaglutide; PBO = placebo.

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

17

PIONEER 6: Oral Semaglutide vs Placebo

First occurrence of MACE (CV death nonfatal MI, or nonfatal stroke)



No. at risk										
Oral Sema	1591	1583	1575	1564	1557	1547	1512	1062	735	16
Placebo	1592	1577	1565	1551	1538	1528	1489	1032	713	11

Primary Outcome—MACE			
Study arms	Events/ Total	Percent	Rate (100 PY)
Semaglutide PO	61/1591	3.8	2.9
Placebo	76/1592	4.8	3.7

HR = 0.79 (95% CI, 0.57–1.11)
P <.001 for noninferiority; *P*= .17 for superiority

Sema = semaglutide; PY = person years.

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

18

Comparing GLP-1RAs

GLP-1RA	Dose range	Weight Change	HbA1c change	Renally excreted?	ASCVD benefit?
Lixisenatide	10–20 mcg	–0.7 kg	–0.55%	yes	no
Exenatide BID	5–10 mcg	1.67 kg	–0.70%	yes	no
Exenatide weekly	2 mg	–1.27 kg	–1.08%	yes	no
Liraglutide	0.6–1.8	–2.3 kg	–1.15%	no	yes
Dulaglutide	0.75–1.5	–1.46 kg	–1.21%	no	yes
Semaglutide weekly	0.25–1.0	–4.3 kg	–1.90%	no	yes
Semaglutide oral, daily	3–14	–3.4 kg	–0.70%	no	no

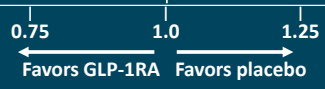
BID = twice daily.

Htike ZZ, et al. *Diabetes Obes Metab*. 2017;19:524-536. Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257. Chiquette E, et al. Vasc Health Risk Manag. 2012;8:621-629. Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239. Marso SP, et al. *N Engl J Med*. 2016;375:311-322. Gerstein HC, et al. *Lancet*. 2019;394:121-130. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844. Husain M, et al. *N Engl J Med*. 2019;381:841-851 and supplement. Davies M, et al. *JAMA*. 2017;318:1460-1470.

19

Meta-analysis of GLP-1RA Effects on MACE in T2DM

	GLP-1RA (n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value interaction
ASCVD	2431/21,253 (11%)	2755/21,202 (13%)		0.86 (0.80–0.93)	0.24
NO ASCVD	480/6428 (7.5%)	518/6555 (7.9%)		0.94 (0.83–1.07)	



7.5 vs 7.9%
ARR = 0.4%
NNT = 250

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

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

20

What Do the Guidelines Say?

AMERICAN COLLEGE of CARDIOLOGY

ESC European Society of Cardiology

American Diabetes Association®

ENDOCRINE SOCIETY

NATIONAL LIPID ASSOCIATION

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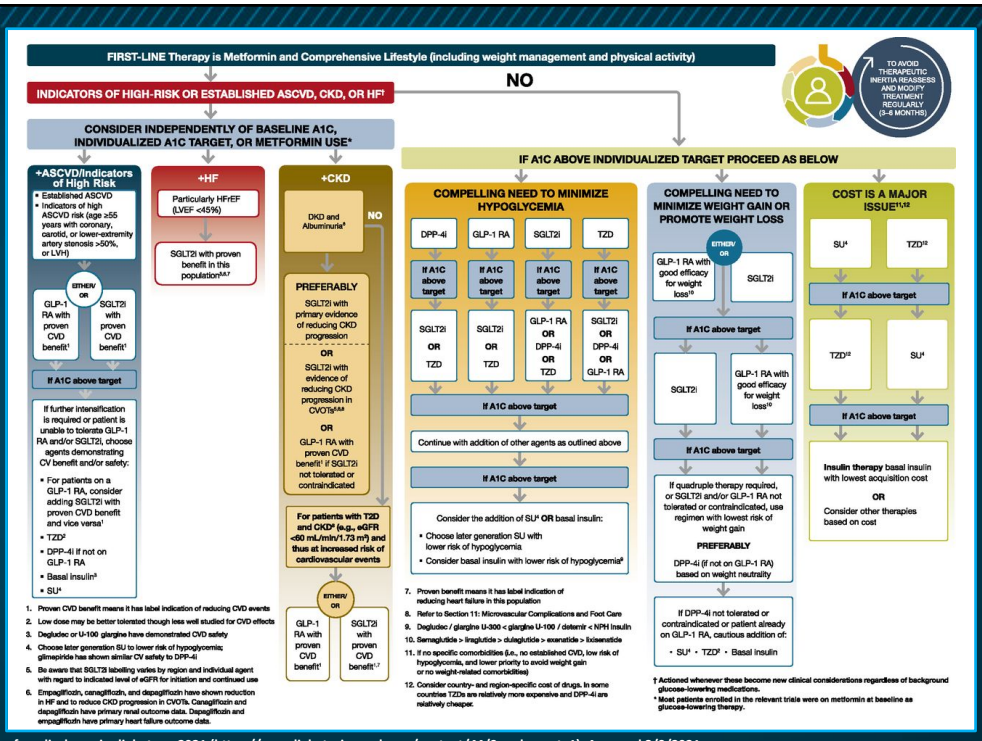
Glucose-Lowering Medications in T2DM



A1c (also HbA1c) = glycosylated hemoglobin; CKD = chronic kidney disease; CVOTs = CV outcomes trials; DPP-4i = dipeptidyl peptidase 4 inhibitor; HFrEF = HF with reduced ejection fraction; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; SU = sulfonylurea; TZD = thiazolidinedione.

American Diabetes Association (ADA). Standards of medical care in diabetes—2021 (https://care.diabetesjournals.org/content/44/Supplement_1). Accessed 8/9/2021.

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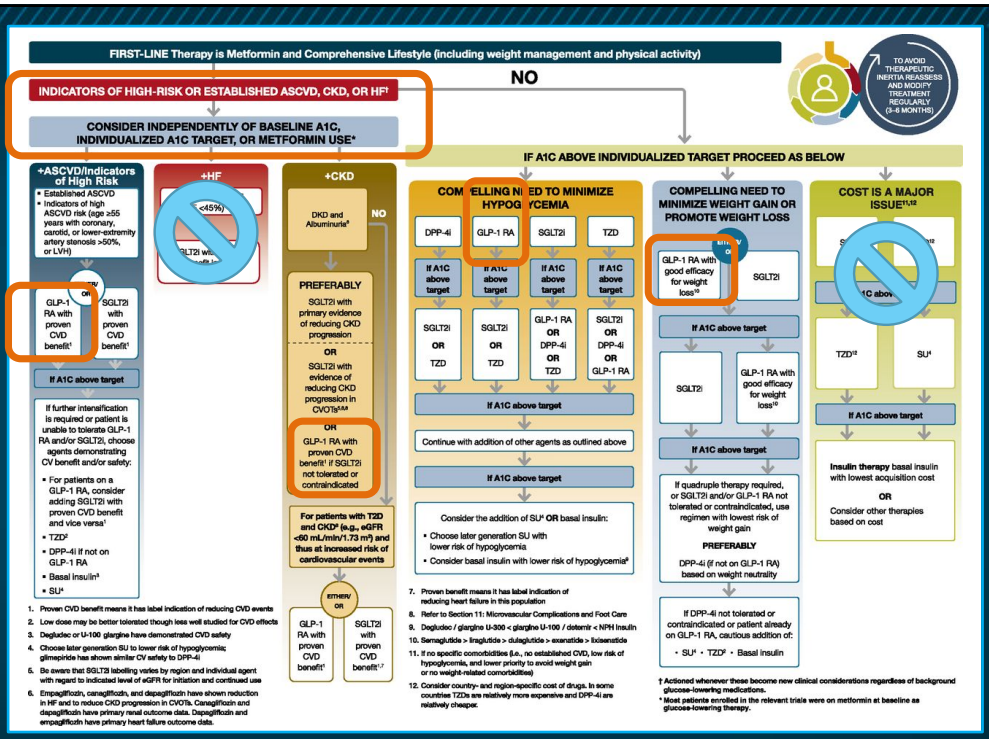
Glucose-Lowering Medications in T2DM (continued)



American Diabetes Association (ADA). Standards of medical care in diabetes—2021 (https://care.diabetesjournals.org/content/44/Supplement_1). Accessed 8/9/2021.

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European Society of Cardiology (ESC) Guidelines

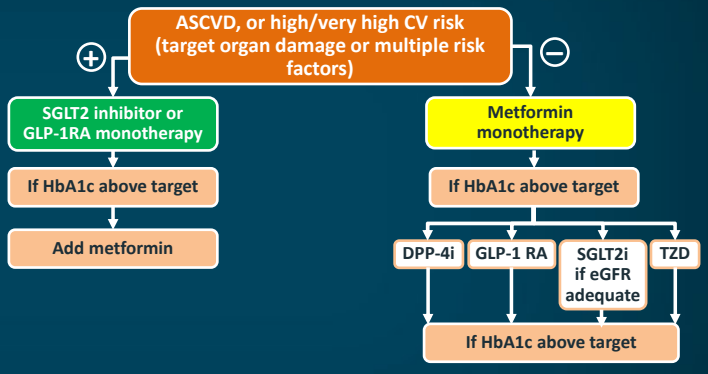
CV risk categories in DM

Very high-risk	Patients with DM and established CVD OR other target organ damage OR ≥3 major risk factors† or early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage + any other additional risk factor
Moderate-risk	Young patients (T1DM <35 years or T2DM <50 years) with DM duration <10 years, without other risk factors

*Proteinurea, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy; †Age, hypertension, dyslipidemia, smoking, obesity

Recommendations	Class	Level
CAC score with CT may be considered a risk modifier in CV risk assessment of moderate-risk asymptomatic patients with DM	IIb	B

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk—drug naïve



Recommendations	Class	Level
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.	IIa	C

DM = diabetes mellitus; CAC = coronary artery calcium; CT = computed tomography.

Modified from Cosentino F, et al. *Eur Heart J.* 2019;41:255-323.

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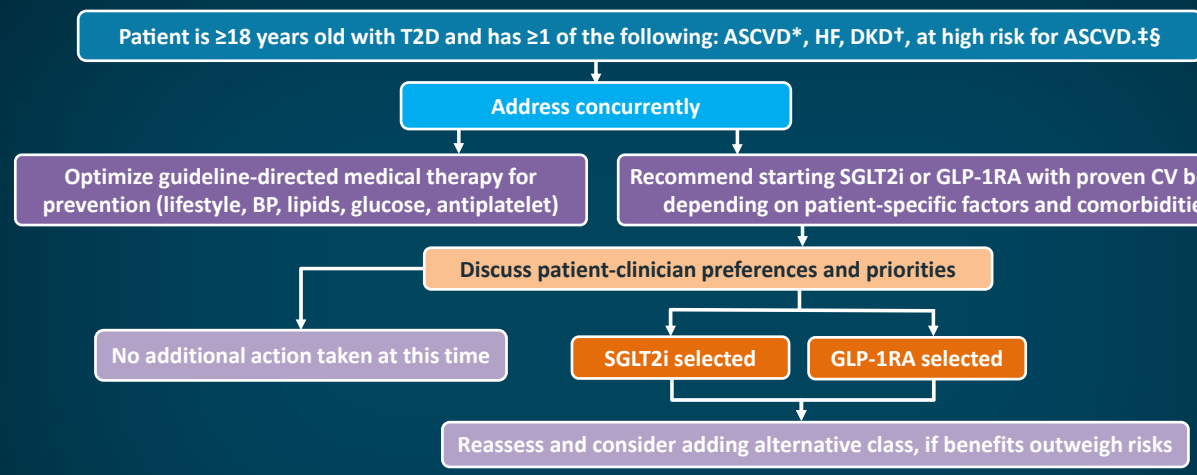
ACC Diabetes Decision Pathway



*ASCVD defined as history of acute coronary syndrome or MI, stable or unstable angina, CHD ± revascularization, other arterial revascularization, stroke, or PAD assumed to be atherosclerotic in origin; †DKD is clinical diagnosis marked by reduced eGFR, presence of albuminuria, or both; ‡Consider SGLT2i when patient has established ‡ASCVD, HF, DKD or is at high risk for ASCVD, and consider GLP-1RA when patient has established ASCVD or is at high risk for ASCVD; §Patients at high risk for ASCVD include those with end-organ damage, such as left ventricular hypertrophy or retinopathy or with multiple CV risk factor (eg, age, hypertension, smoking, dyslipidemia, obesity); ‖Most patients enrolled in relevant trials were on metformin at baseline as glucose-lowering therapy.

ACC = American College of Cardiology; CHD = coronary heart disease; PAD = peripheral artery disease; BP = blood pressure.

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

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GLP-1 RAs: CV Indications*

- **Liraglutide** (subcutaneous injection)[1]: to reduce the risk of major adverse CV events in adults with T2DM and established CVD
- **Semaglutide** (subcutaneous injection)[2]: to reduce the risk of adverse CV events in adults with T2DM and established CV disease
- **Dulaglutide** (subcutaneous injection)[3]: to reduce the risk of major adverse CV events in adults with T2DM who have established CVD or multiple CV risk factors

***All listed agents are also indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM**

1. Liraglutide subcutaneous injection (Victoza®) prescribing information (PI), 2020 (www.novo-pi.com/victoza.pdf). 2. Semaglutide subcutaneous injection (Ozempic®) PI, 2021 www.novo-pi.com/ozempic.pdf).
3. Dulaglutide subcutaneous injection (Trulicity®) PI, 2021 (http://pi.lilly.com/us/trulicity-uspi.pdf). All URLs accessed 8/9/2021.

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Audience Poll

In your estimation, what percentage of patients who could benefit from the cardiovascular effects of GLP-1 receptor agonists are receiving them?

1. **0%-25%**
2. **25%-50%**
3. **50%-75%**
4. **75%-100%**

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GLP-1 Receptor Agonists: Side Effects

- Nausea
- Vomiting
- Diarrhea
- Dyspepsia
- Constipation
- Injection-site reactions

- Warnings
  - History of pancreatitis
  - Risk factors for pancreatitis
  - Gastroparesis
  - Personal or family history of:
    - Medullary thyroid cancer
    - MEN2

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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.

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Management of Stable Coronary Artery Disease (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 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 mg/dL) to reduce 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

LV = left ventricular; 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.

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GLP-1/GIP Dual Receptor Agonists

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GLP-1/GIP Dual Receptor Agonists

Organ	GLP-1 RA action	GIP action
Pancreas		
Beta cell	Increase insulin synthesis and secretion Increased glucose sensing	Increase insulin synthesis and secretion Increased glucose sensing
Alpha cell	Decrease glucagon secretion	Increase glucagon secretion
Brain	Increased satiety, decreased appetite	
GI system	Decreased GI motility and decreased gastric emptying	
Adipose tissue		Increase lipolysis and fatty acid synthesis

GIP = glucose-depended insulinotropic polypeptide.

Modified from Min T, Bain SC. *Diabetes Ther.* 2021;12:143-157.

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Tirzepatide: a "Twincretin"

Tirzepatide (GLP-1/GIP RA) Lilly–SURPASS clinical trial program

- SURPASS 1—versus placebo
- SURPASS 2—versus semaglutide (both + metformin)
- SURPASS 3—versus degludec (both metformin ± SGLT2i)
- SURPASS 4—versus glargine (+ 1–3 oral meds)
- SURPASS 5—versus placebo (+ glargine ± metformin)
- SURPASS J—versus dulaglutide (oral naïve or oral monotherapy)
- SURPASS-AP-Combo—versus glargine (+ metformin ± SU)
- SURPASS CVOT—versus dulaglutide (+ established oral/injectable treatment)

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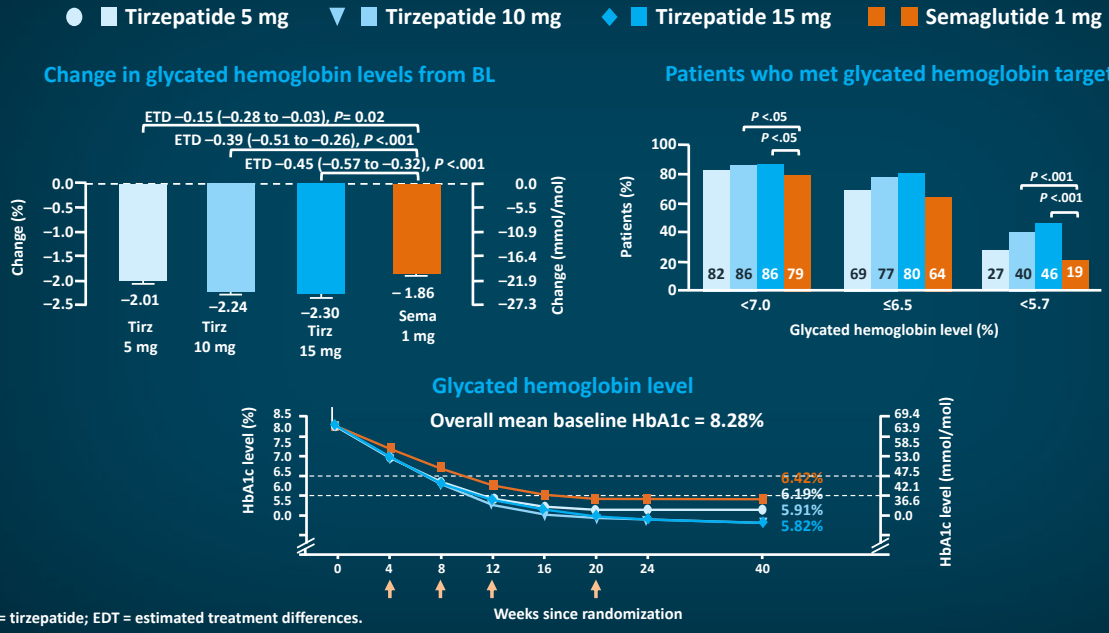
Tirzepatide vs Semaglutide (SURPASS 2): HbA1c



Tirz = tirzepatide; EDT = estimated treatment differences.

Frias JP, et al. *N Engl J Med.* 2021;385:503-515.

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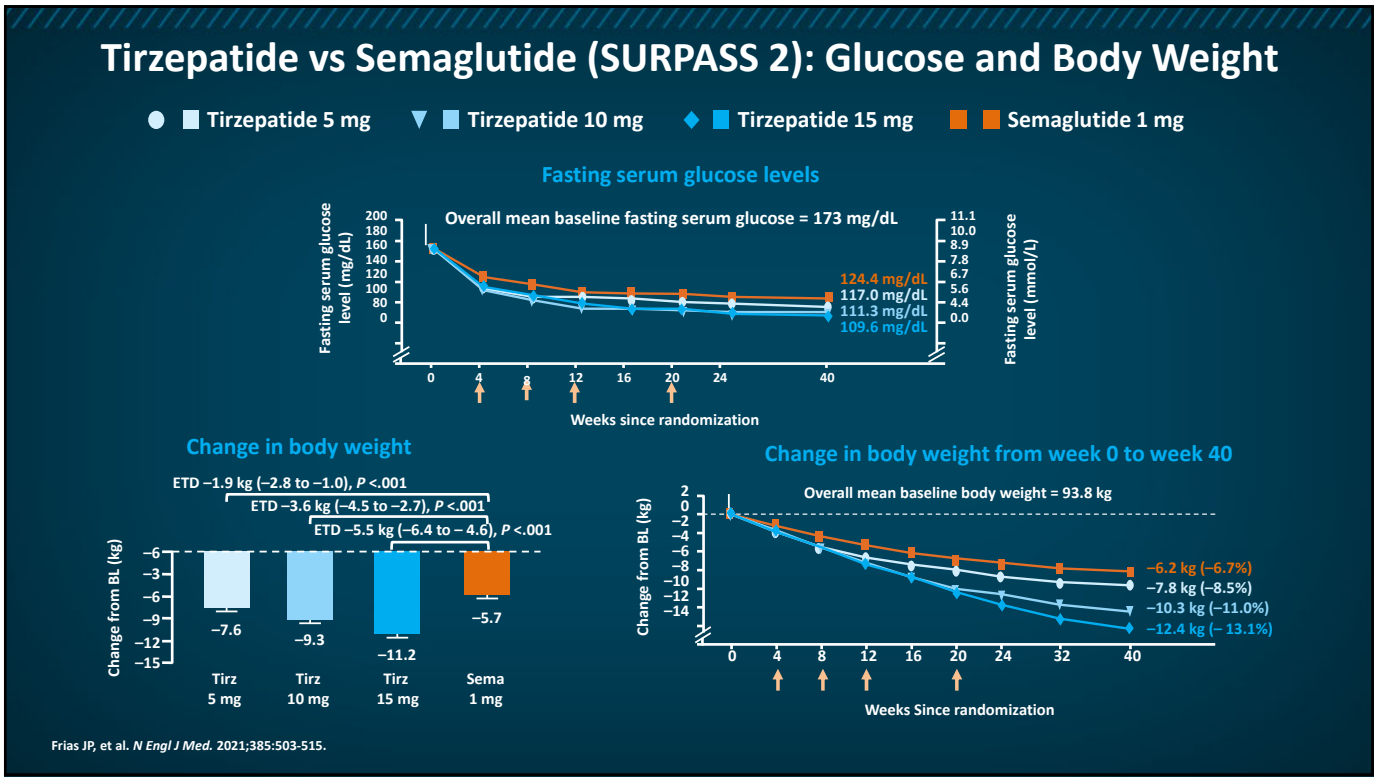
Tirzepatide vs Semaglutide (SURPASS 2): Glucose and Body Weight



Frias JP, et al. *N Engl J Med.* 2021;385:503-515.

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Questions?

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Cardiologist/PCP Collaboration

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Audience Poll

What specialty should take responsibility for prescribing GPL-1 receptor agonists and monitoring their effects?

1. Cardiology
2. Endocrinology
3. Primary care
4. Other
5. Any of the above

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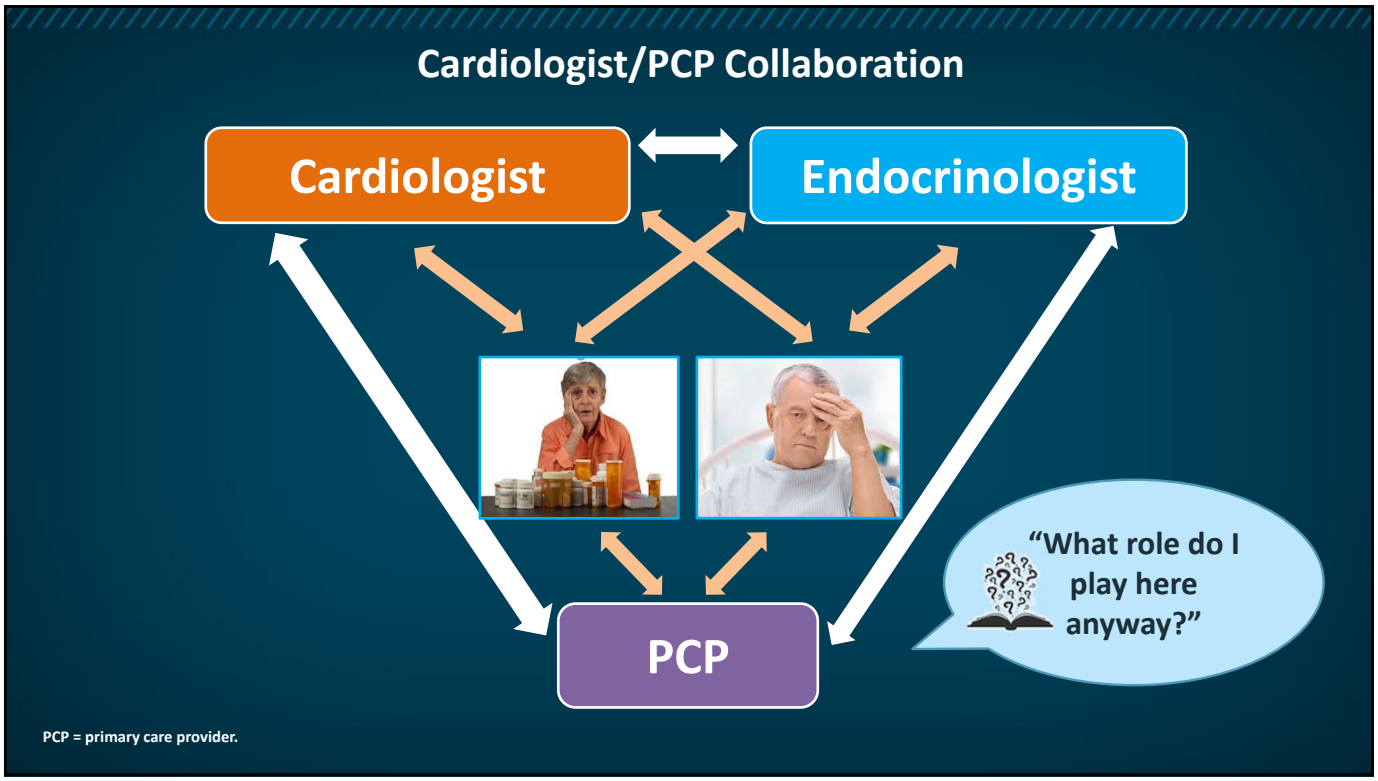
Cardiologist/PCP Collaboration



PCP = primary care provider.

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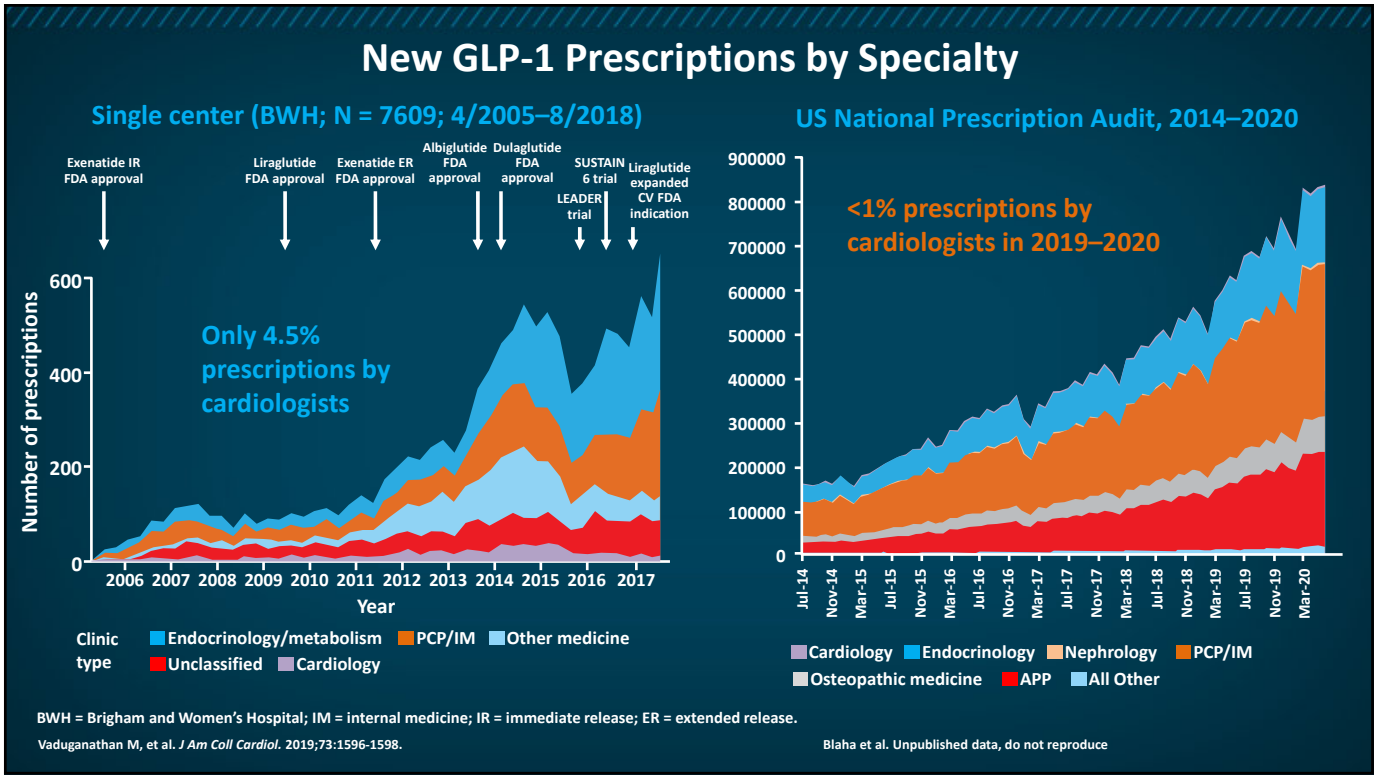
New GLP-1 Prescriptions by Specialty



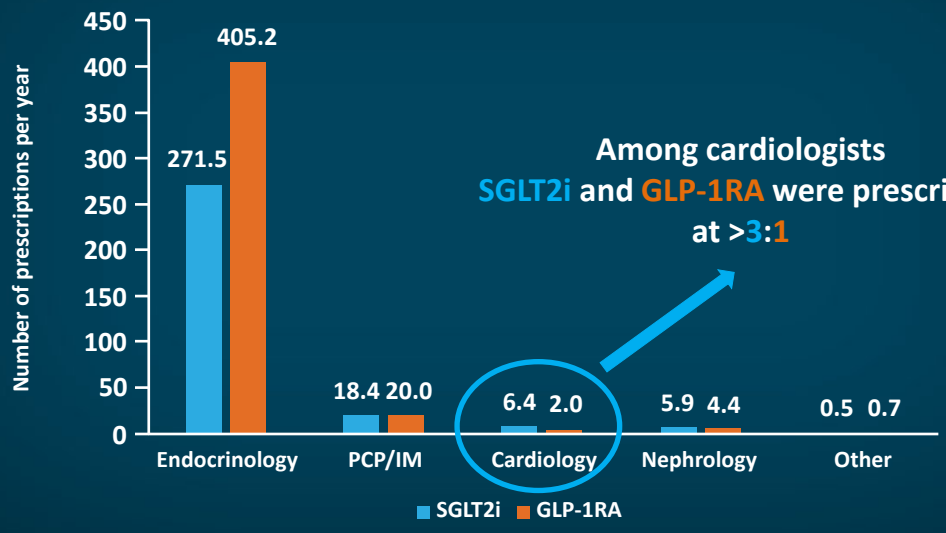
BWH = Brigham and Women's Hospital; IM = internal medicine; IR = immediate release; ER = extended release.

Vaduganathan M, et al. *J Am Coll Cardiol.* 2019;73:1596-1598.

Blaha et al. Unpublished data, do not reproduce

40

In 2020, Endocrinologists Exceeded All Other Physician Specialties in Per-physician Prescribing of SGLT2i and GLP-1RA



Adhikari R, et al. Unpublished data, do not reproduce.

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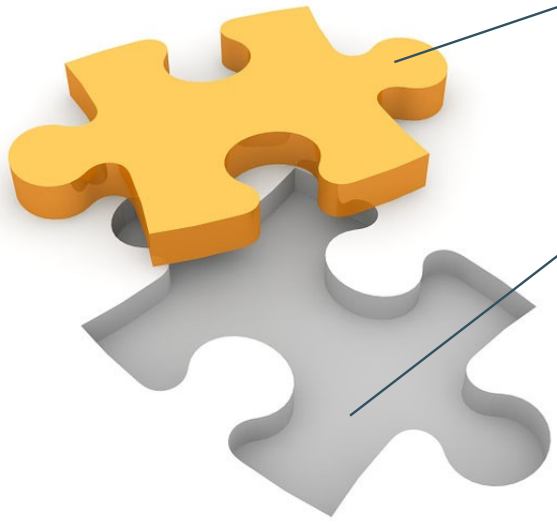
Cardiometabolic Clinic Model



SOLUTION:

Cardiometabolic clinic model

OPPORTUNITY:

Treat several cardiometabolic patients, improve their clinical outcome, increase efficiency of health care and reduce cost

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Cardiometabolic clinic model

- Harmonious unification of cardiometabolic management under one specialist
- Emphasis on multiple interrelated conditions, increased patient convenience, reduced polypharmacy, decreased clinical inertia, and mitigation of miscommunications
- Decrease in referrals, increase in patient-centered outcomes, and reduced cost

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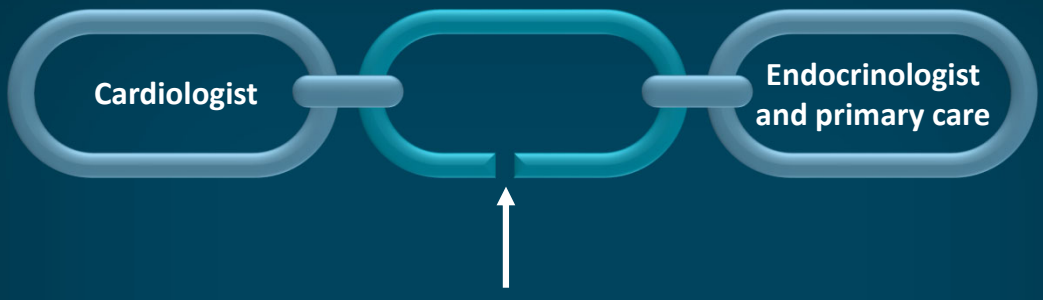
The Broken Link



The broken link

1. Current fractured care model presents barriers to a cardiometabolic clinic, ie, “turf wars”
2. Viewpoint differences of cardiology vs endocrinology vs primary care

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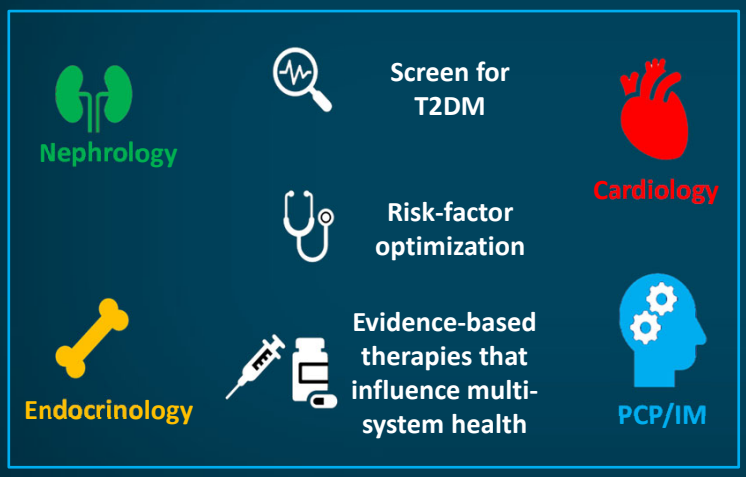
Promoting Healthcare Collaboration

Why multidisciplinary care pathways are needed



- Improve therapeutic inertia
- Decrease polypharmacy
- Medication compliance
- Better clinical outcomes
- Resource utilization
- Decrease healthcare cost

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Case Studies

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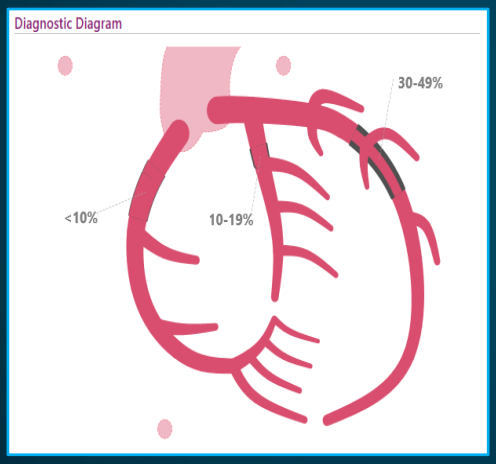
Case 1: 55 Y/F, Active Smoking, Stage II Obesity, and Subclinical CAD. Previously Diagnosed with Prediabetes. Presents for Evaluation of Recent CTA Result.



- Family history of premature CAD (father CABG 50yrs), works as bank accountant (sedentary)
- Meds: Lisinopril 10mg, Atorvastatin 10mg
- Exam: BMI: 36, BP: 140/80mmHg, no signs of fluid overload
- Current Labs: HbA1c: 6.5%, Cr: 0.8 (eGFR >60)

Questions to consider:

- ***What changes should we make to her current medical regimen?***
- ***What considerations would lead us to select GLP-1RA vs SGLT2i?***

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Case 1: Assessment and Treatment

55 years of age, obesity, sedentary lifestyle	Family history of CAD, subclinical CAD, HTN, active smoker, prediabetes
Red flags	**PMHx**
Alarming lab	**Treatment**
Elevated HbA1c, CTA showed 50% stenosis	1.GLP-1 ± metformin 2.Encourage follow-up

HTN = hypertension; PMHx = prior/past medical history.

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Case 2: 60 Y/M STEMI (s/p DES x1 RCA 1 year ago), T2DM, CKD stage III, & HTN was Referred by PCP for CV Risk Optimization

- Exam: CVD exam normal, Lung clear, Weight: 15lbs weight gain (last 12 months)
- Labs: Cr: 2.3 (eGFR 29.5), AST: ALT:: 50:70, HbA1c: 7.0%, LDL: 60 mg/dL
- Meds: Metformin 1gm BID, Losartan 100mg, Atorvastatin 80mg, Aspirin 81mg and Clopidogrel 75mg

Questions to consider:

- ***What changes should we make to his current medical regimen?***
- ***What considerations would lead us to select GLP-1RA vs SGLT2i?***

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Case 2: Assessment and Treatment

60 years of age, significant weight gain	CAD, T2DM, HTN, suspected NAFLD
Red flags	**PMHx**
Alarming lab	**Treatment**
Elevated HbA1c, eGFR <35	GLP1RA >>> metformin or SGLT2i

NAFLD = nonalcoholic fatty liver disease.

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Questions?

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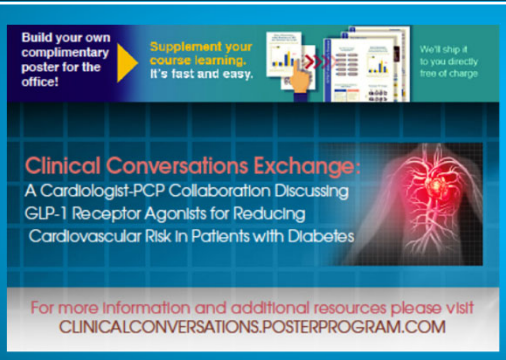
Additional Resources



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Thank you!

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