

Update on the Standards of Diabetes Care

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Disclosure

Advisory Board: AbbVie; Boehringer Ingelheim; Corcept; Eli Lilly; Fractyl Health; Gan & Lee; Genentech/Roche; Graviton Bioscience; i2o Therapeutics; Keros Therapeutics; Madrigal; MetSera; Neurocrine; Novo Nordisk; Pfizer; Regeneron; Terns Pharmaceuticals; Zealand

Data Monitoring Committee: Boehringer Ingelheim; Eli Lilly

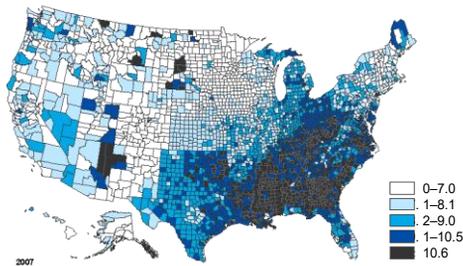
Research Grant: Eli Lilly; Genentech/Roche; Kaleira; Novo Nordisk; Terns Pharmaceuticals; Viking Therapeutics; Zealand



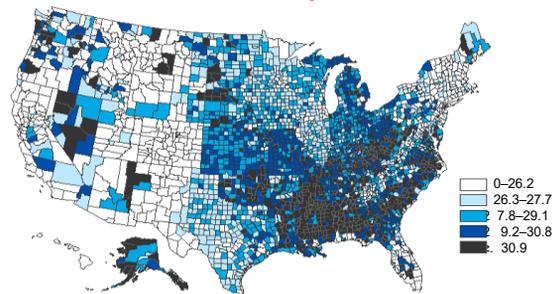
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Co-Localization of Diabetes, Obesity, Heart Disease, and Stroke

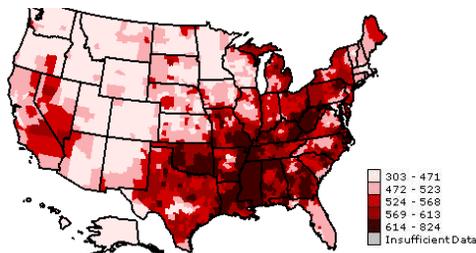
Prevalence Rates for **Diabetes**, 2007: MMWR 58:1259, 2009



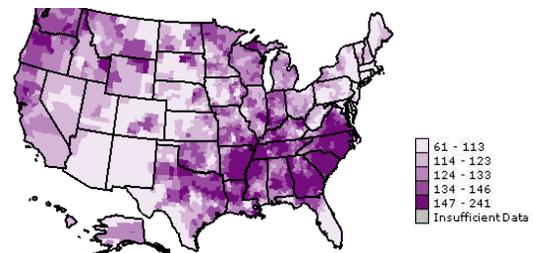
Prevalence Rates for **Obesity**, 2007: MMWR 58:1259, 2009



Prevalence Rates for **Heart Disease** 1997-2003: CDC NCHS



Prevalence rates for **Stroke** 1997-2003: CDC NCHS



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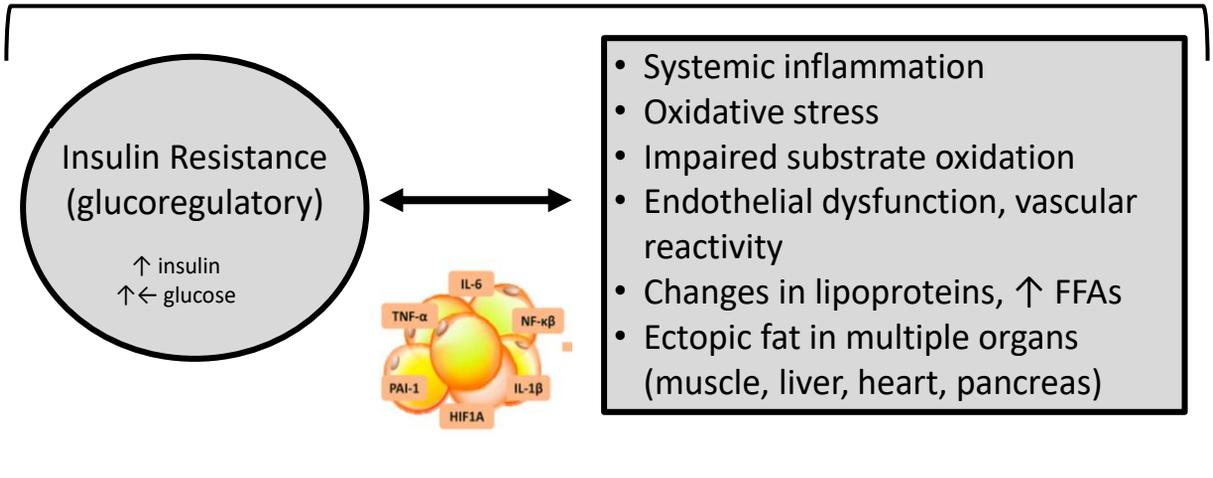
T2D and Cardiometabolic Disease

- T2D exists within the broader pathophysiological context of cardiometabolic disease
- One disease process that gives rise to metabolic and vascular disease outcomes
- Core lesion is insulin resistance
- Current Guidelines for Type 2 Diabetes address:
 - **(i)** glycemic control
 - **(ii)** metabolic and cardiovascular disease risk reduction in the context of cardiometabolic disease
 - **(iii)** Emphasize treatment of obesity in diabetes using new pharmacological tools

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The Insulin Resistant State: Insulin Resistance as a Systemic Metabolic, Vascular, and Inflammatory Process

The Insulin Resistant State



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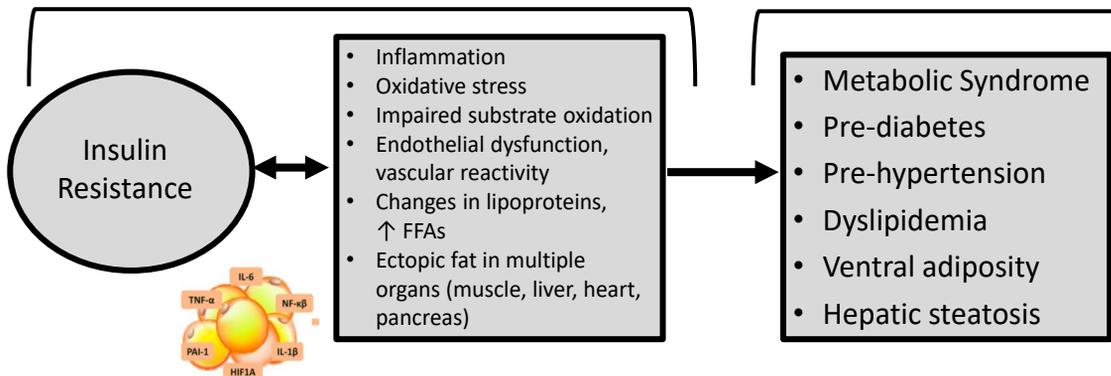
The Insulin Resistance State Gives Rise to Clinical Manifestations

How we know that the patient has Cardiometabolic Disease



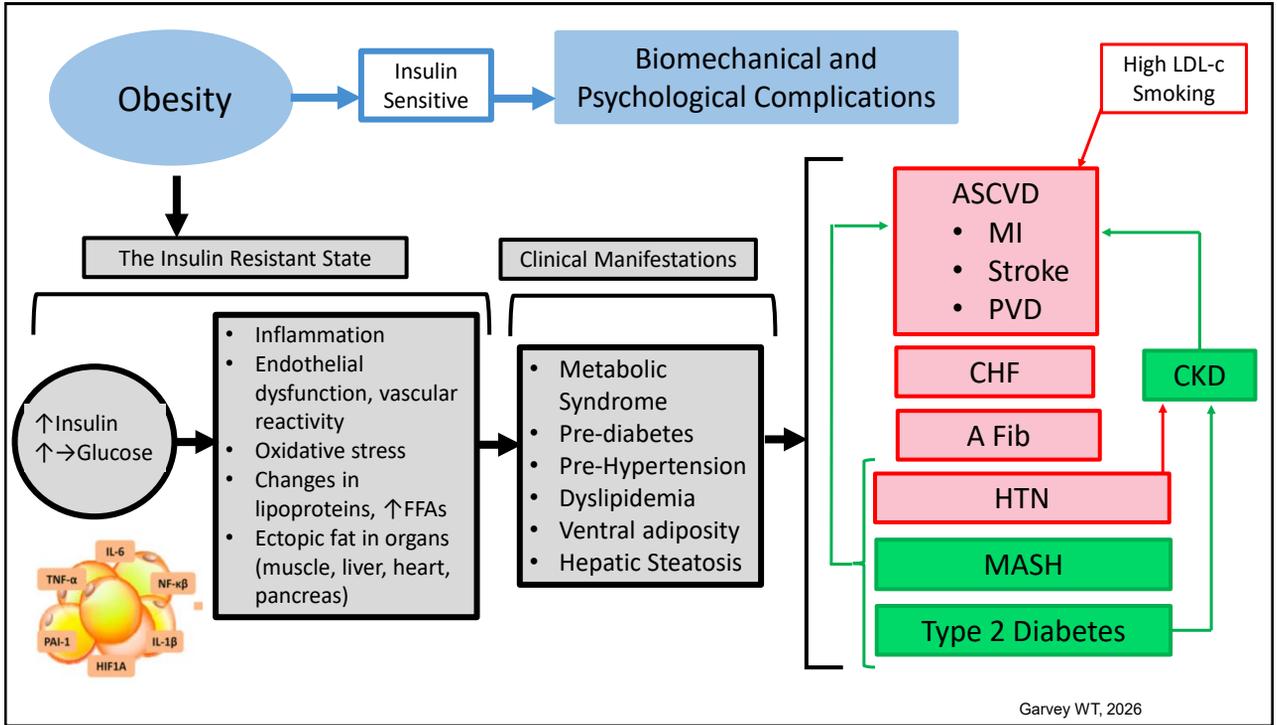
The Insulin Resistant State

Clinical Manifestations

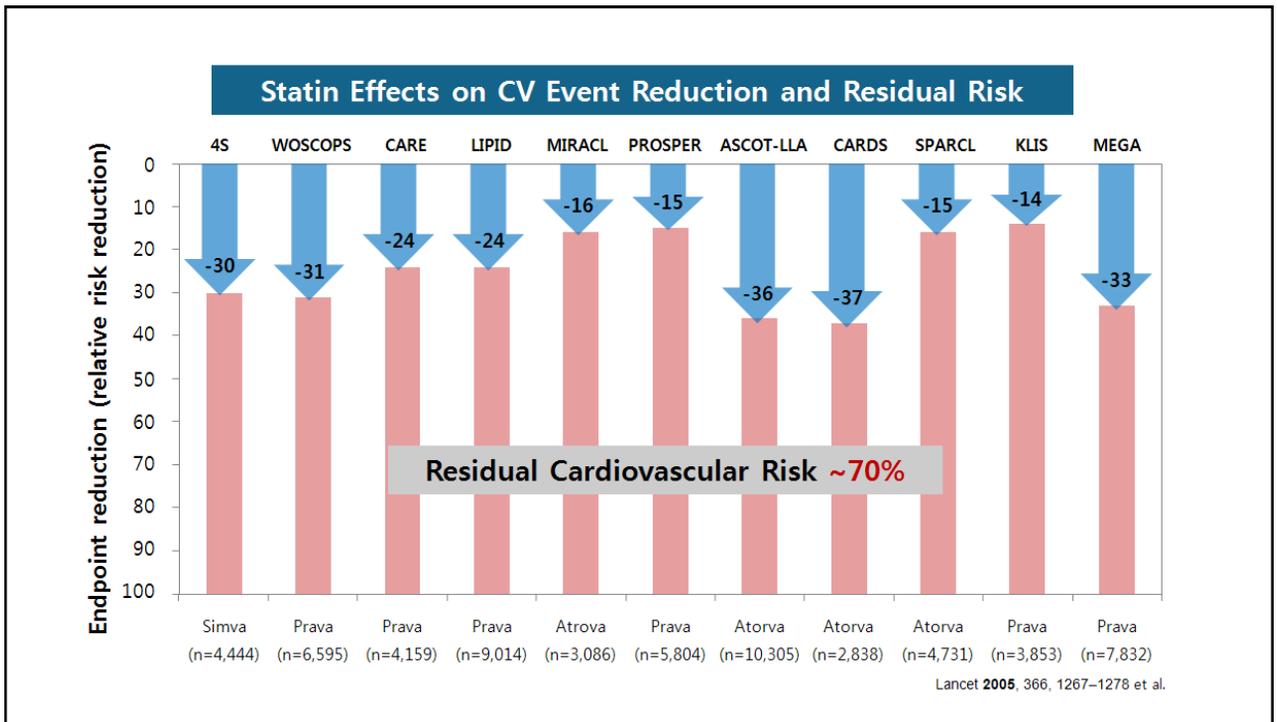


■ core pathophysiology of cardiometabolic disease

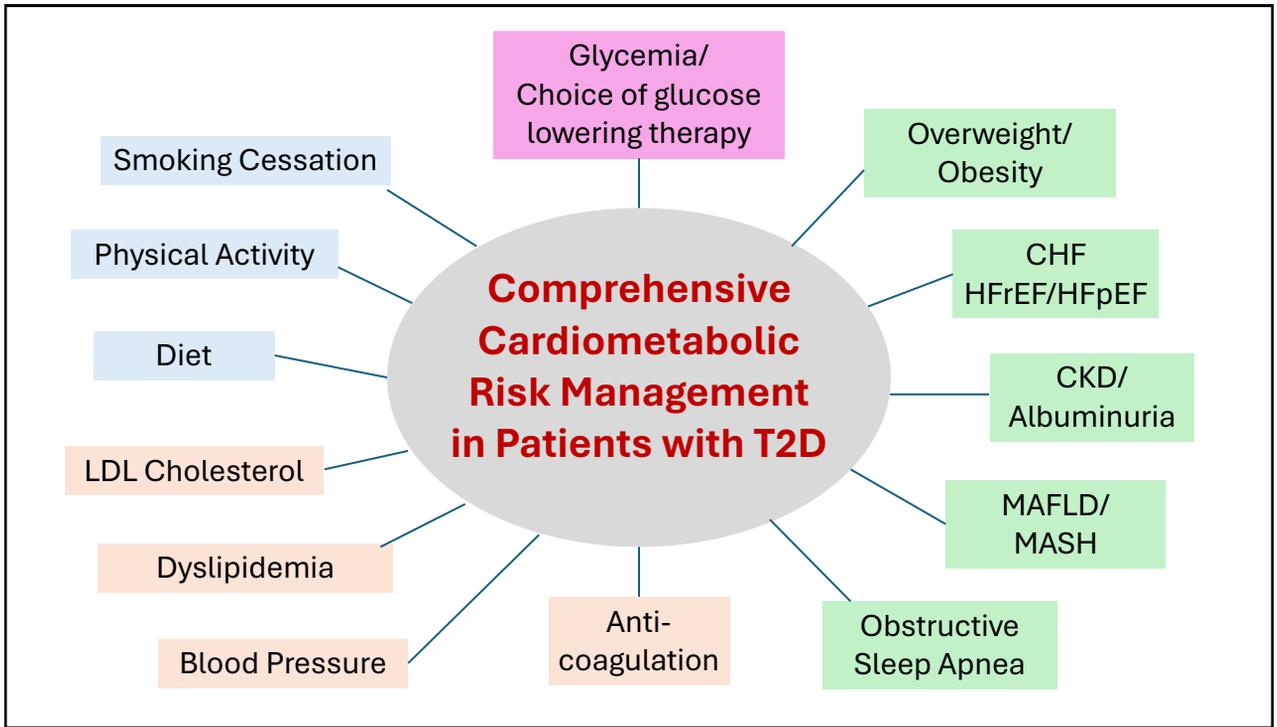
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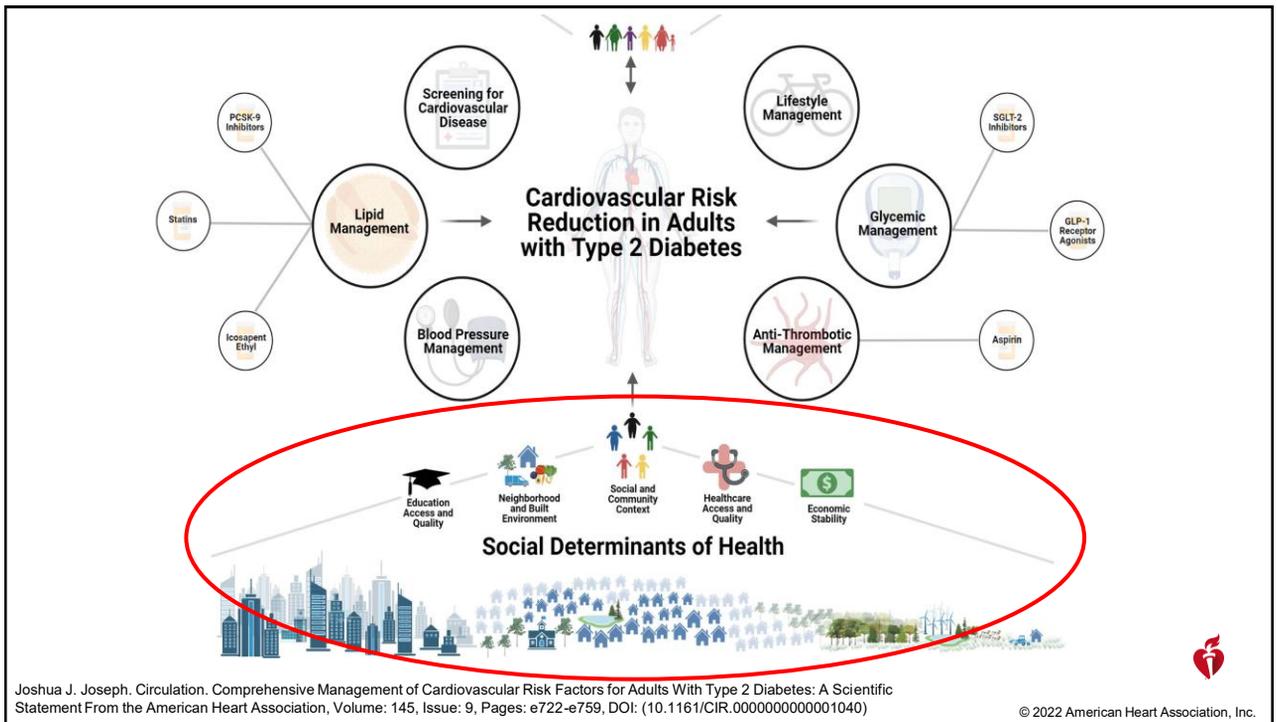
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Joshua J. Joseph. Circulation. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association, Volume: 145, Issue: 9, Pages: e722-e759, DOI: (10.1161/CIR.0000000000001040)

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Recommended Lifestyle Therapy for Risk Management in Diabetes

	ESC	AACE	ADA	AHA
Diet	Med Diet	Med Diet, DASH	Med Diet, DASH “healthy meal plan”, reduce fat, emphasize fiber	Med Diet, DASH “healthy meal plan”, replace PUFAs with MUFAs
Physical Activity	increase in activity at any level; optimal ≥ 150 min/week moderate; aerobic + resistance	≥ 150 min/week aerobic exercise in 3 to 5 sessions; with 2 to 3 sessions of resistance exercise; sleep hygiene	Any physical activity better than none; ≥ 150 min/week moderate exercise; accommodate disabilities	≥ 150 min/week moderate exercise; aerobic plus resistance; limit sedentary activity
Smoking	Stop	Stop	Stop	Stop

Marx N et al. Eur Heart J. 2023 Oct 14;44(39):4043-4140. Samson SL et al. Endocr Pract. 2023 May;29(5):305-340. ADA, chapter 10 *Standards of Care in Diabetes—2024*. *Diabetes Care* 2024; 47 (Supplement_1): S179–S218. Arnett DK et al. J Am Coll Cardiol. 2019;74(10):e177-e232.

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Principle 1

A Changing Role for Metformin

Ghosted? Unrequited love!

“I have been thinking about you a lot. We were good together. Tender memories of happier times. I haven’t heard from you. We should get together more often”

Sing to tune, “I’ve been loving you too long” Otis Redding

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Metformin Is an Old Friend

- After approval by the FDA in 1995, metformin rapidly became the first line drug for type 2 diabetes
- Long-term experience, inexpensive, and available
- Weight neutral
- Impairs absorption of vitamin B12
- Well-tolerated
- 25-30% of people develop GI side effects and 5-10% of people cannot tolerate medication
 - Can reduce dose from 1,000 mg bid to 500 mg bid and still retain efficacy
 - Extended-release preparations better tolerated
- Cannot take if eGFR is below 30 ml/min/1.73 m²

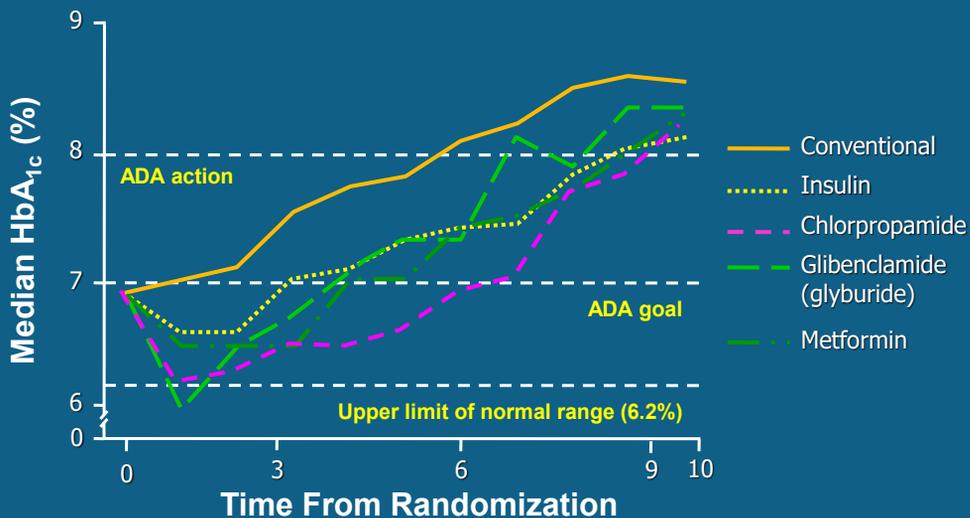
Question: Is metformin the best starting medication for patients with T2D

Silverii GA. Optimizing metformin therapy in practice: Tailoring therapy in specific patient groups to improve tolerability, efficacy and outcomes. Diabetes Obes Metab. 2024 Aug;26 Suppl 3:42-54

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Intensive Treatments and Increase in HbA_{1c} Over Time

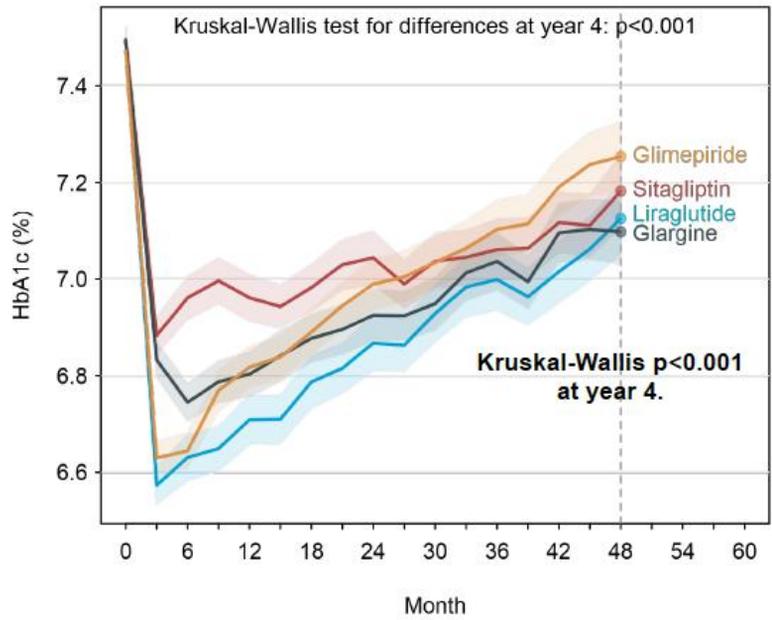
United Kingdom Prospective Diabetes Study (UKPDS)



UK Prospective Diabetes Study (UKPDS 34) Group. *Lancet*. 1998;352:854-65.

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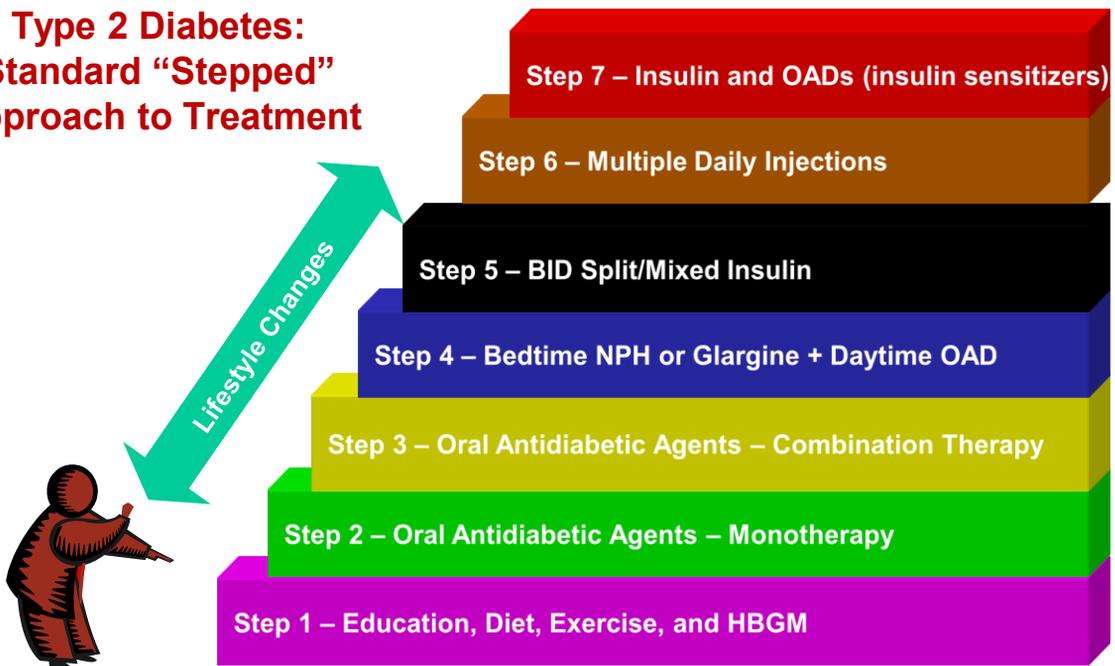
GRADE Study: Rise in HbA1c Over Time:
 Patients on Metformin and Randomized to Addition of Glargine, Sitagliptin, Liraglutide, or Glargine



81st meeting of the American Diabetes Association (virtual), June 26-29, 2021

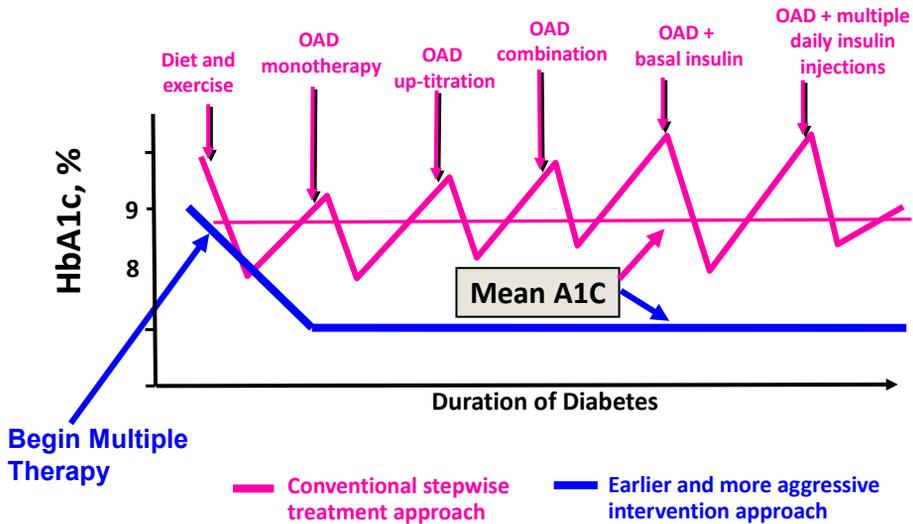
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Type 2 Diabetes: Standard “Stepped” Approach to Treatment



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Earlier and More Aggressive Intervention May Reduce Lifetime HbA1c

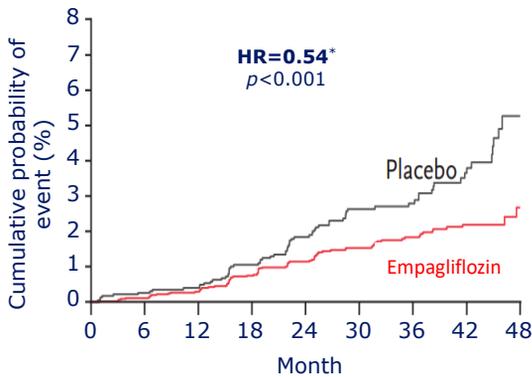


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SGLT2i's Are Cardioprotective, Renoprotective, and Reduce CHF Outcomes in T2D

Empagliflozin – EMPA-REG: Renoprotective

Time to double creatinine, renal replacement, death

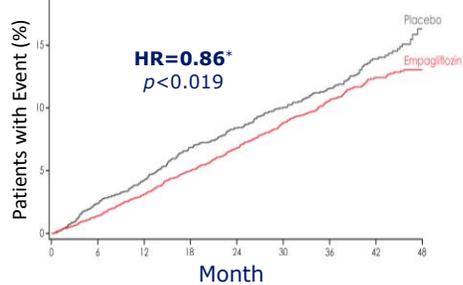


Wanner et al. *N Engl J Med* 2016;375:323-34

Zinman et al. *N Engl J Med* 2015;373:2117-28

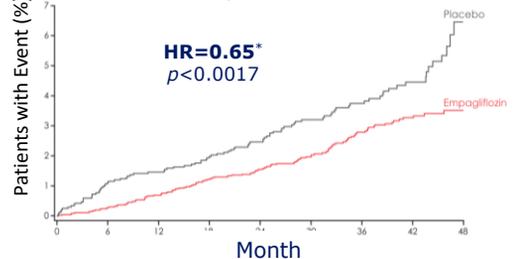
Empagliflozin - EMPA-REG: Cardioprotective

MACE: CV death, non-lethal MI, stroke



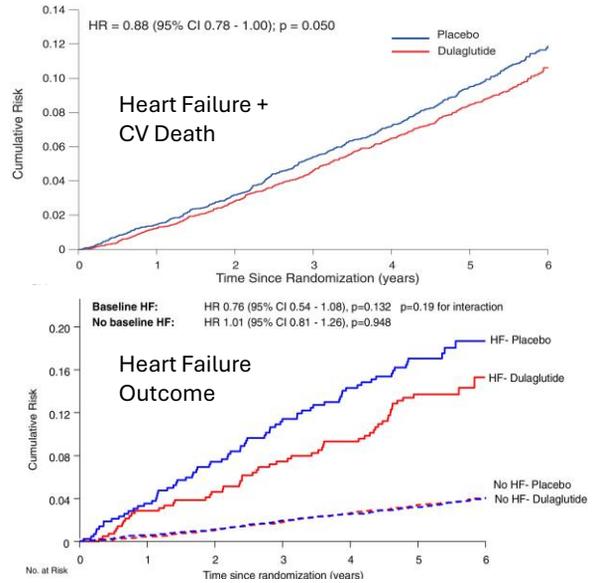
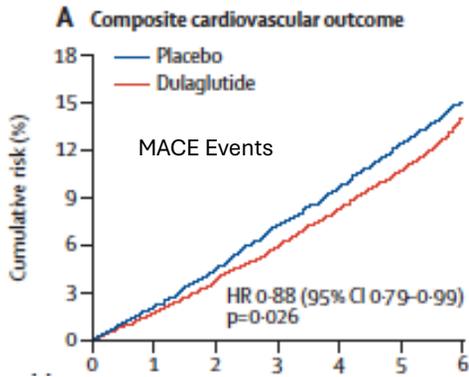
Empagliflozin – EMPA-REG: CHF Outcomes

Hospitalization



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Dulaglutide Reduces Hazard Ratios for MACE Events and Heart Failure Outcomes



Gerstein HC et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130

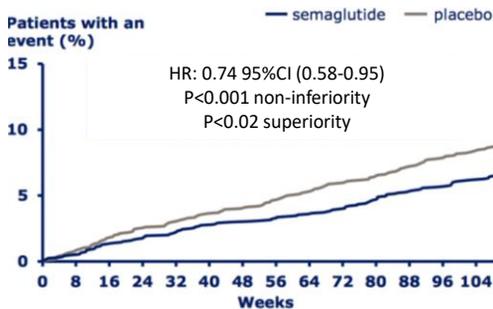
Branch KRH et al. Dulaglutide and cardiovascular and heart failure outcomes in patients with and without heart failure: a post-hoc analysis from the REWIND randomized trial. *Eur J Heart Fail*. 2022;24(10):1805-1812

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GLP-1 RAs Are Cardioprotective and Renoprotective in T2D

Semaglutide – SUSTAIN 6: Cardioprotective

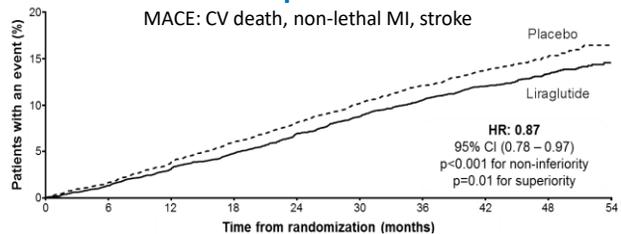
MACE: CV death, non-lethal MI, stroke



Marso SP et al. *N Engl J Med*. 2016;375(19):1834-1844
Marso SP et al. *N Engl J Med*. 2016;375(4):311-22
Mann JFE et al. *N Engl J Med*. 2017;377(9):839-848

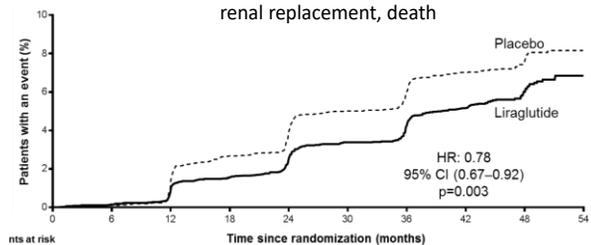
Liraglutide – LEADER Trial: Cardioprotective

MACE: CV death, non-lethal MI, stroke



Liraglutide. - LEADER TRIAL: Renoprotective

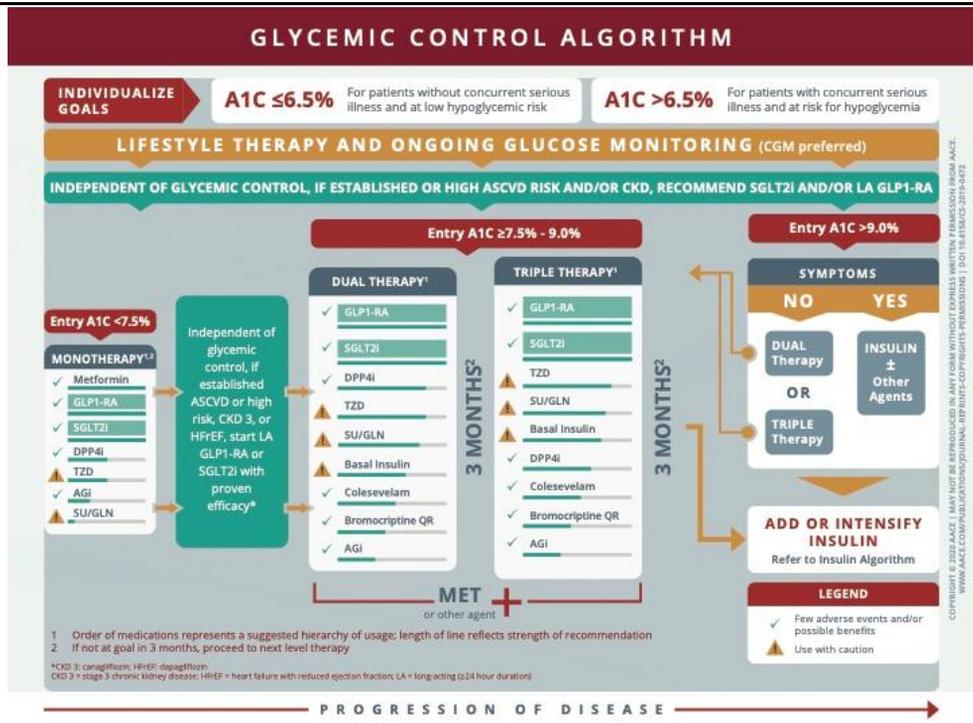
Time to macroalbuminuria, double creatinine, renal replacement, death



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**AACE
Diabetes
Algorithm
2020**

Garber A et al. *Endocr Pract* 2020; 26(1):107-139

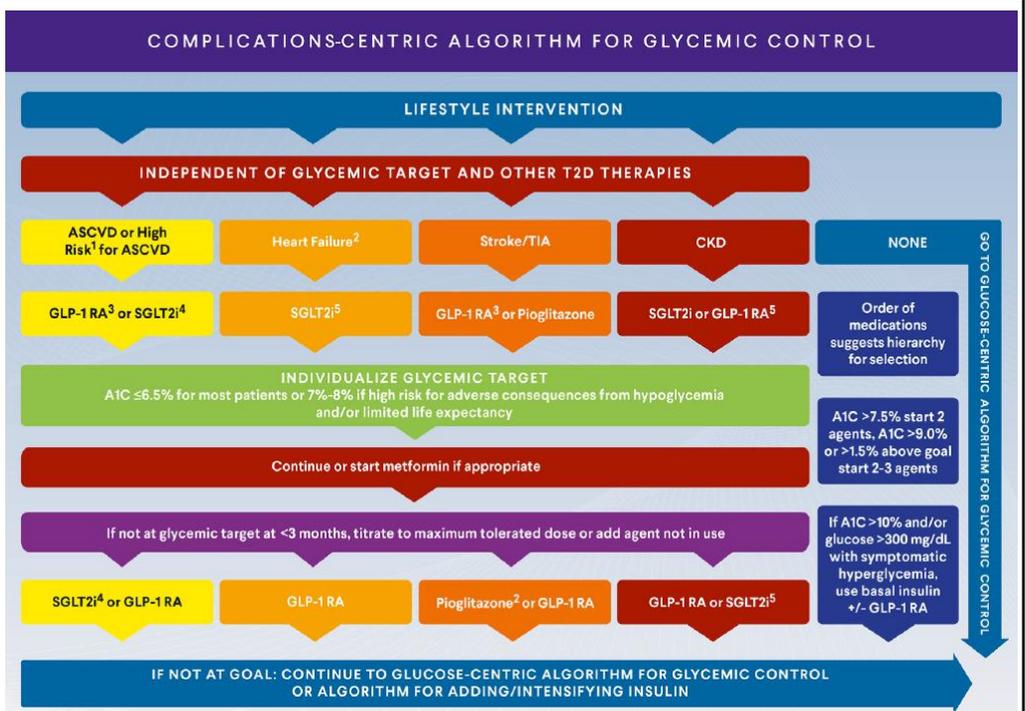


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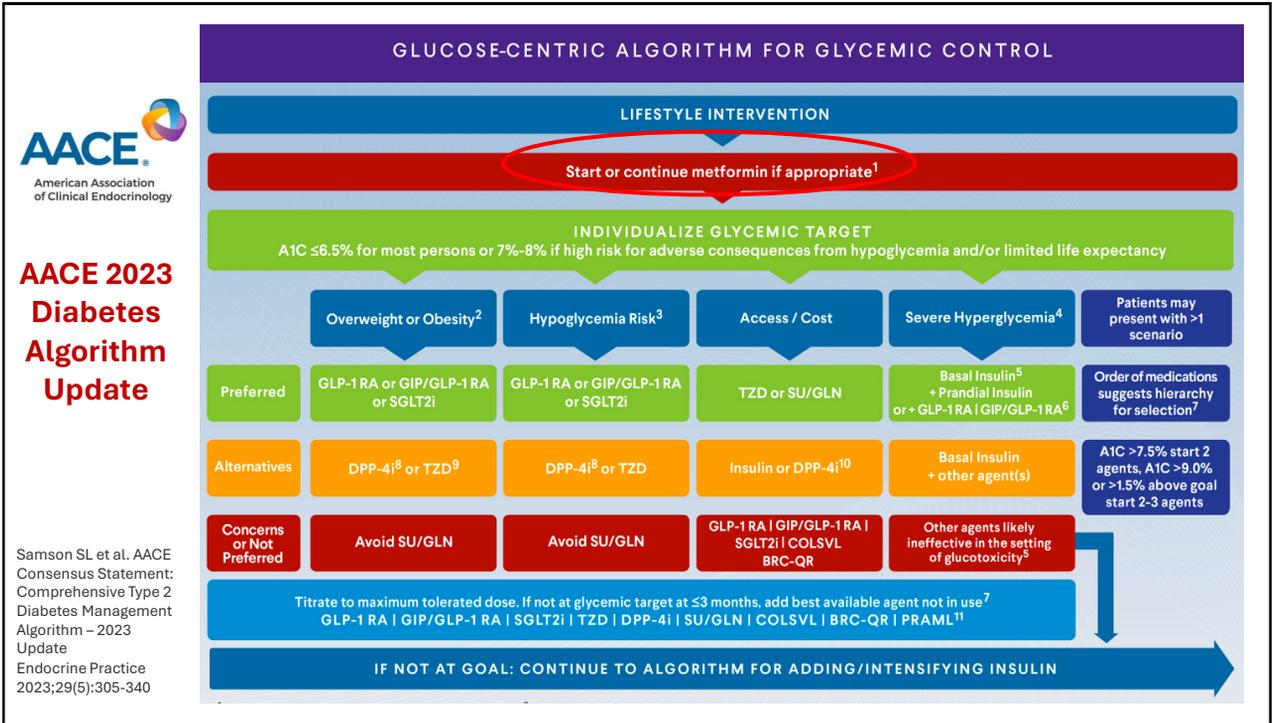


**AACE 2023
Diabetes
Algorithm
Update**

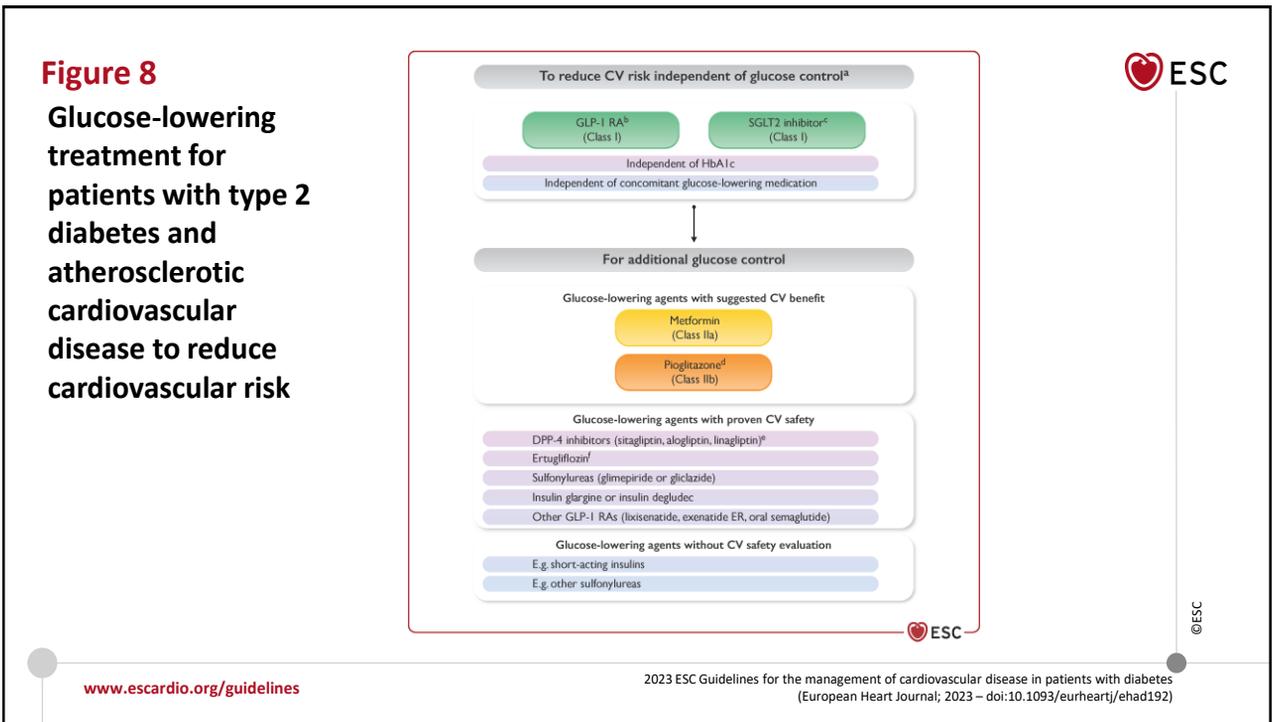
Samson SL et al. *American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update* *Endocrine Practice* 2023;29(5):305-340



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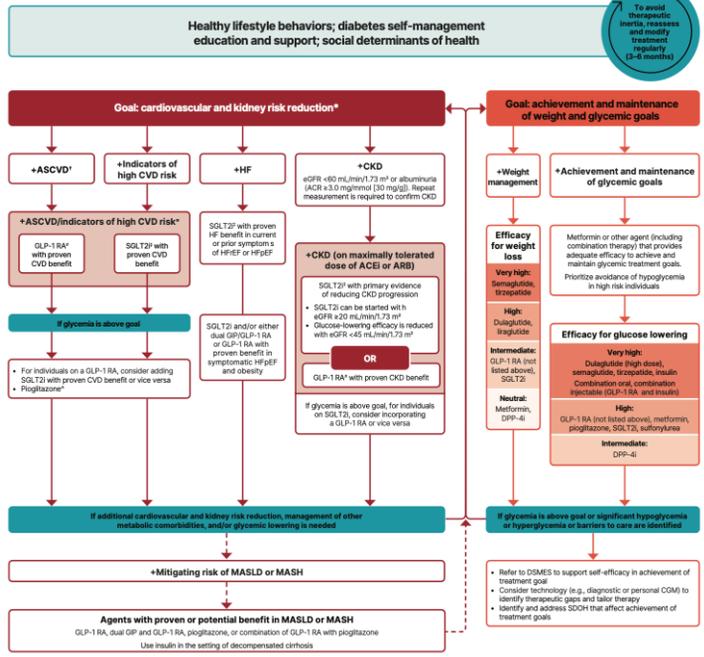


9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026

“For individuals with type 2 diabetes..... who do not have additional considerations informing choice of therapy beyond need for glucose lowering, metformin is a commonly used medication that historically has been the first-line treatment for type 2 diabetes.”

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. Diabetes Care 2026;49(Suppl. 1):S183–S215

Use of glucose-lowering medications in the management of type 2 diabetes
(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)



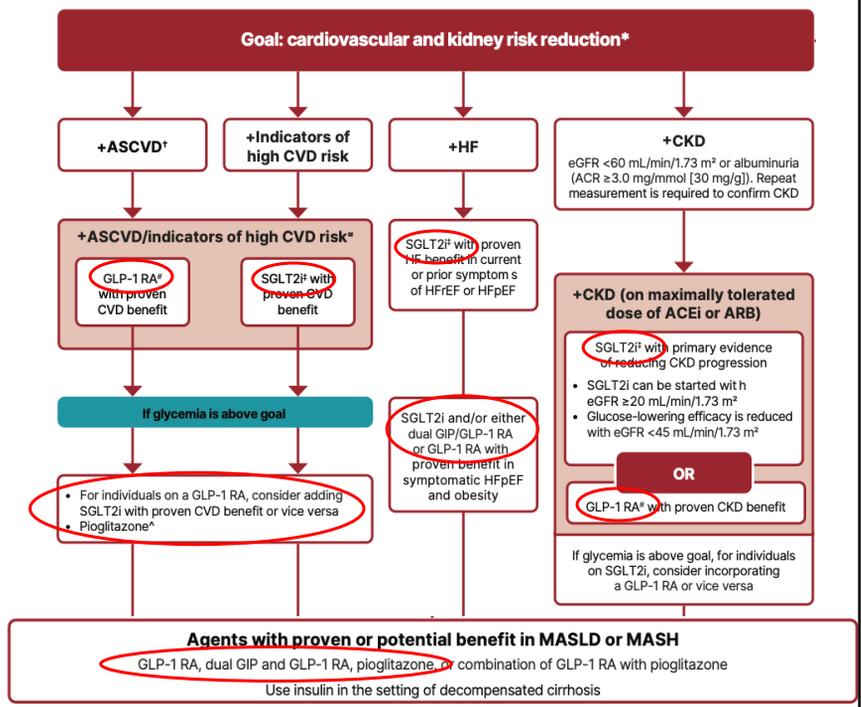
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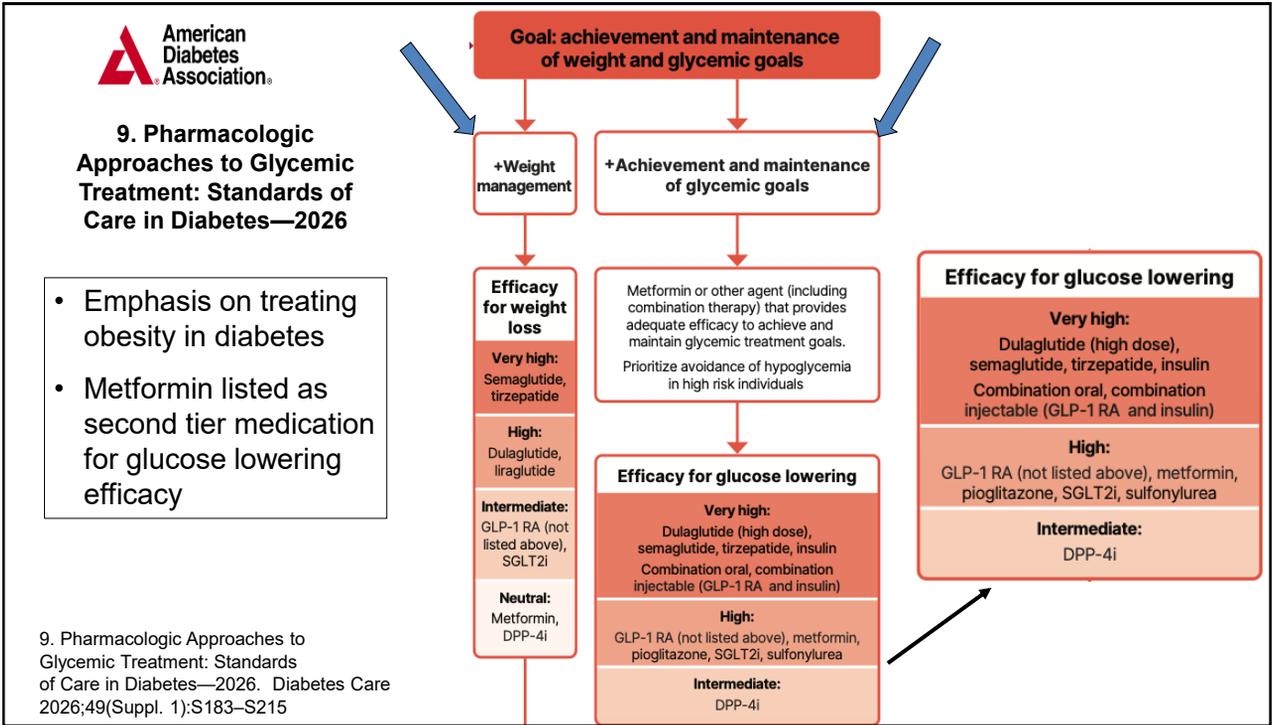
9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026

Emphasis on GLP-1 agonists and SGLT2i

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. Diabetes Care 2026;49(Suppl. 1):S183–S215



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Principle 2

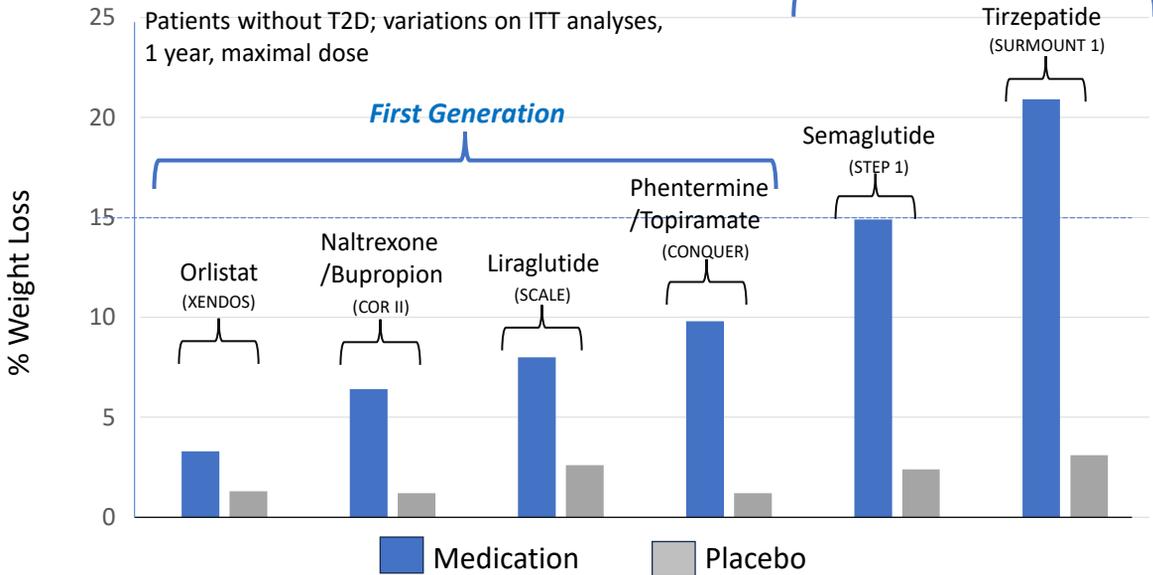
The Best Medications for Obesity Are the Best Medications for T2D

“I know. I miss you too. But now I have new friends and new interests. You left me no choice. I wasn’t fulfilled. I had to move on.”

Sing to the tune, “You Gotta Move On” The Rolling Stones

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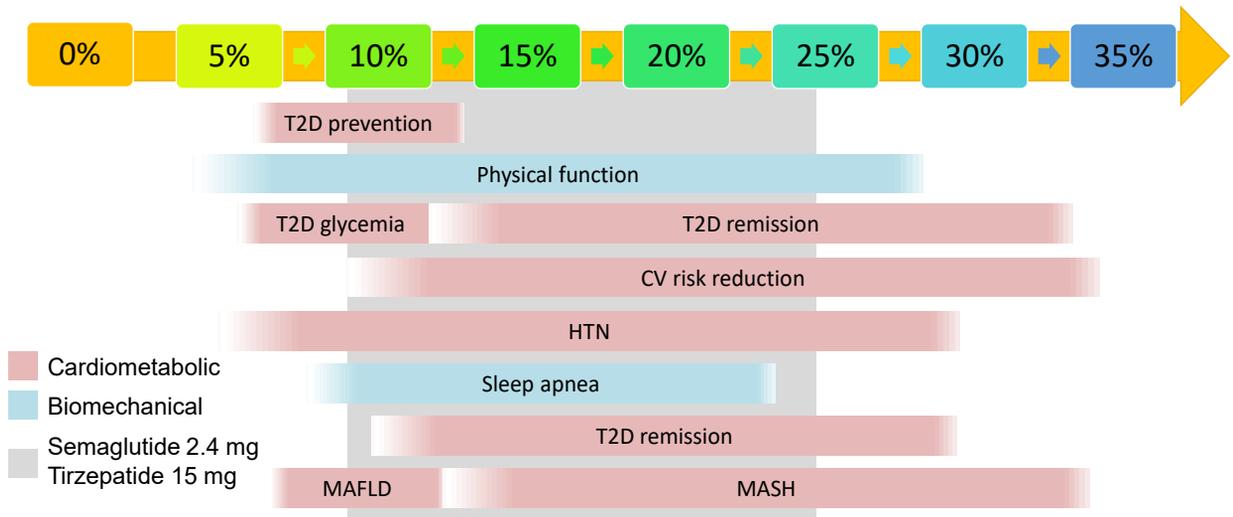
Relative Efficacy of Obesity Meds



Torgerson Diabetes Care 2004;27:155 - Apovian Obesity 2013;21:935 - Pi-Sunyer NEJM 2015;373:11 - Gadde Lancet 2011;377:1341 - Wilding NEJM 2021;384:989 - Jastreboff NEJM 2022;387:205

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Second-Generation Medications: Treating ABCD/Obesity



Garvey WT. New Horizons: A New Paradigm for Treating to Target with Second Generation Obesity Medications. JCEM. 2022 Mar 24;107(4):e1339-e1347

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Principles of Complications-Centric Care

We treat obesity to improve the health of the patient

The complications of obesity impair health

- Cardiometabolic
- Biomechanical
- Quality of Life

The prevention and treatment of complications is the goal and end-point of therapy, not the loss of a given amount of kilograms per se

Adiposity-Based Chronic Disease (ABCD)

Adiposity-Based

Abnormalities in Adipose Tissue Mass, Distribution, Function

Chronic Disease

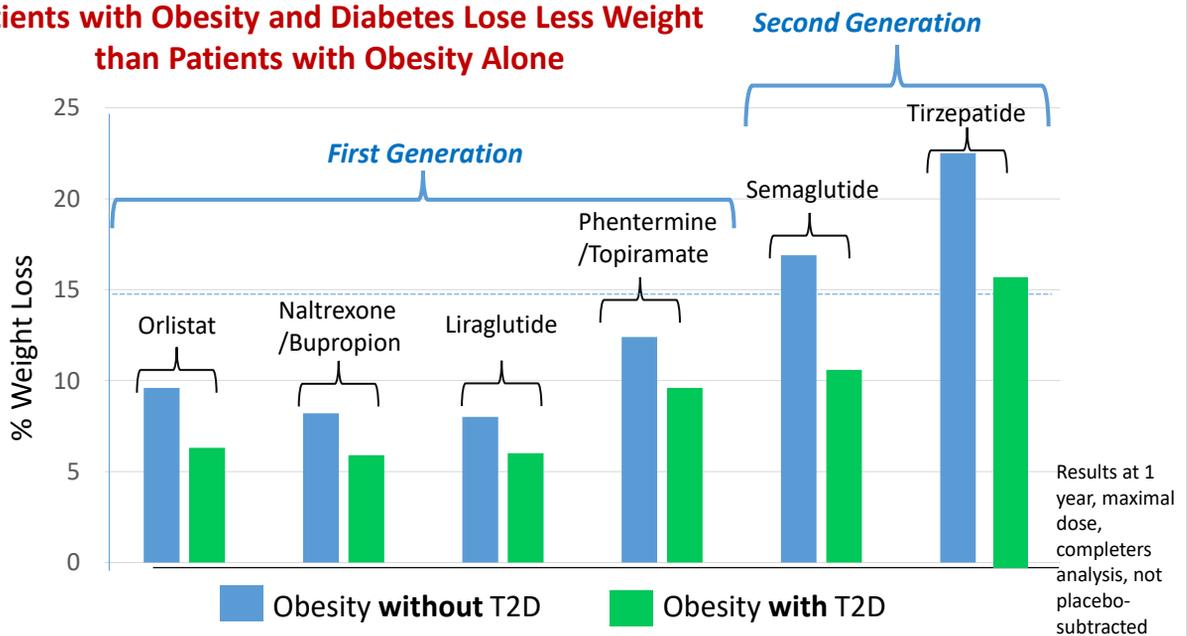
Lifelong disease with complications that impair health and confer morbidity & mortality

Garvey WT et al. Endocrine Practice 22(Suppl 3):1-203, 2016

Mechanick JI, Hurley DL, Garvey WT. Adiposity Based Chronic Disease as a new diagnostic term: AACE/ACE Position Statement. Endocr Pract. 2017 Mar;23(3):372-378

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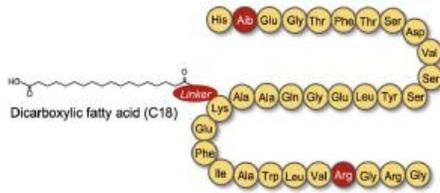
Patients with Obesity and Diabetes Lose Less Weight than Patients with Obesity Alone



Torgerson Diabetes Care 2004;27:155 - Hollander Diabetes Care 1998;21:1288 - Apovian Obesity 2013;21:935 - Hollander Diabetes Care 2013;36:4022 - Pi-Sunyer NEJM 2015;373:11 - Davies JAMA 2015;314:687 - Gadde Lancet 2011;377:1341 - Garvey Diabetes Care 2014;37:3309 - Wilding NEJM 2021;384:989 - Davies Lancet 2021;397:971 - Jastreboff NEJM 2022;387:205 - Garvey WT Lancet 2023 Jun 26 Epub

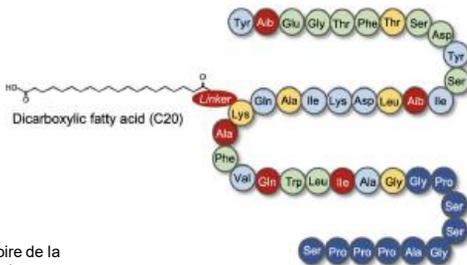
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Structures



SEMAGLUTIDE (½ life 165 hr)

yellow = GLP1

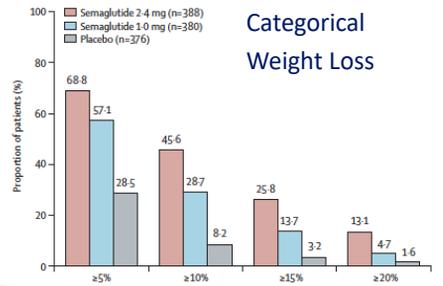
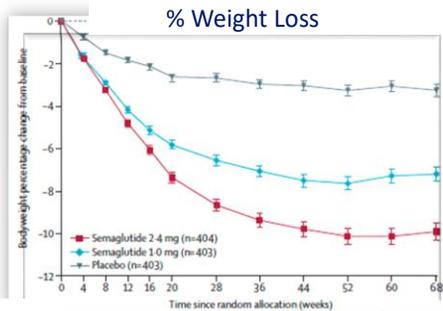


TIRZEPATIDE (1/2 life 120 hr)

yellow = GLP1
blue = GIP
green = both GLP1 and GIP

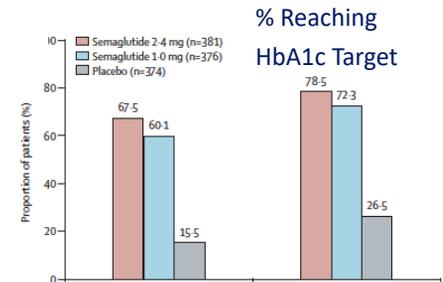
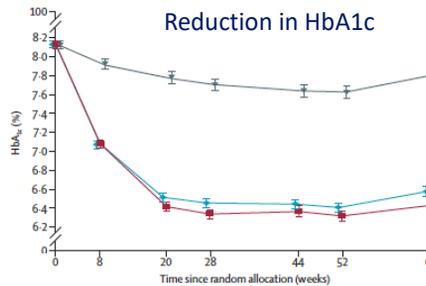
Juneau M. l'Observatoire de la prévention de l'Institut de Cardiologie de Montréal. 2023

STEP 2 Trial: Once Weekly Semaglutide Reduces Weight and HbA1c in T2D



■ Semaglutide 2.4 mg (n=388)
■ Semaglutide 1.0 mg (n=380)
■ Placebo (n=376)

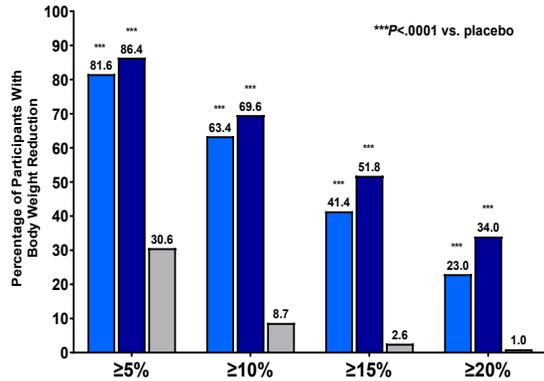
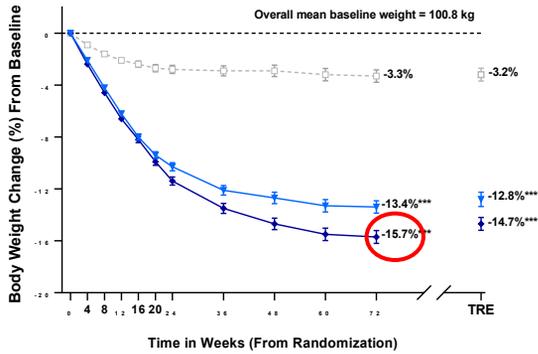
Symptomatic hypoglycemia
5.7% Sema 2.4 mg
5.5% Sema 1.0 mg
3.0% placebo



Davies M et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity and Type 2 Diabetes. Lancet 397:971, 2021

SURMOUNT 2: Tirzepatide in Patients with Obesity and T2D Change in Body Weight from Baseline to Week 72

Percentage Change in Body Weight From Baseline (Efficacy Estimand)



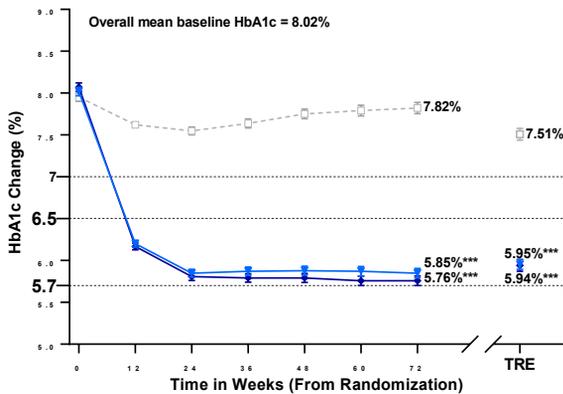
▼ Tirzepatide 10 mg
 ◆ Tirzepatide 15 mg
 ◻ Placebo

***P<.0001 vs. ANCOVA=Analysis of Covariance; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; mITT=Modified Intention-to-Treat; MMRM=Mixed Model for Repeated Measures; SE=Standard Error; TRE=Treatment-Regimen Estimand.
 Garvey WT, et al. *Lancet*. 2023 Jun 26:S0140-6736(23)01200-X. Epub ahead of print

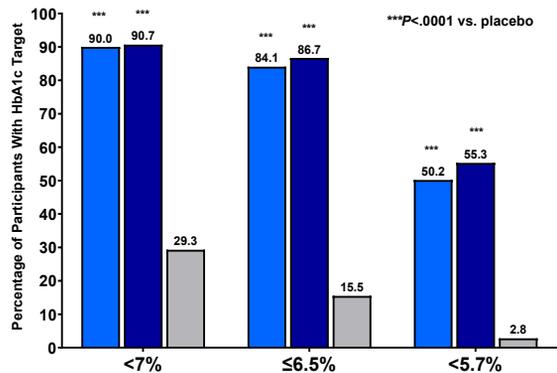
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SURMOUNT 2: Tirzepatide in Patients with Obesity and T2D Change in HbA1c from Baseline to Week 72

Percentage Change in HbA1c From Baseline (Efficacy Estimand)



Participants Who Achieved HbA1c Targets at Week 72 (Efficacy Estimand)



▼ Tirzepatide 10 mg
 ◆ Tirzepatide 15 mg
 ◻ Placebo

***P<.0001 vs. placebo.
 Garvey WT, et al. *Lancet*. 2023 Jun 26:S0140-6736(23)01200-X. Epub ahead of print

No level 3 hypoglycemia
 4-5% level 2 hypoglycemia

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Percent of Participants Experiencing Hypoglycemia in SURMOUNT 2

LEVEL 2 Hypoglycemia (Blood glucose <54 mg/dL <3.0 mmol/L)

- Placebo 1%
- Tirzepatide 10 mg 4%
- Tirzepatide 15 mg 5%

LEVEL 3 Hypoglycemia (Severe hypoglycemia requiring assistance)

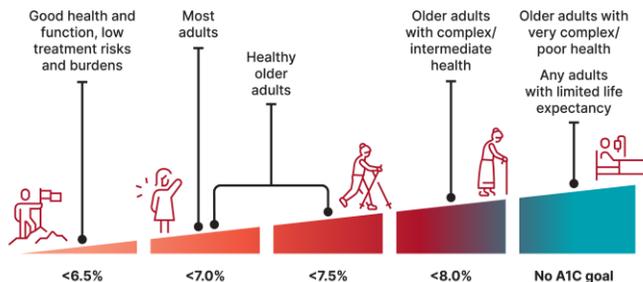
- None observed

Garvey WT, et al. *Lancet*. 2023 Jun 26;S0140-6736(23)01200-X. Epub ahead of print

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From: 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025



Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

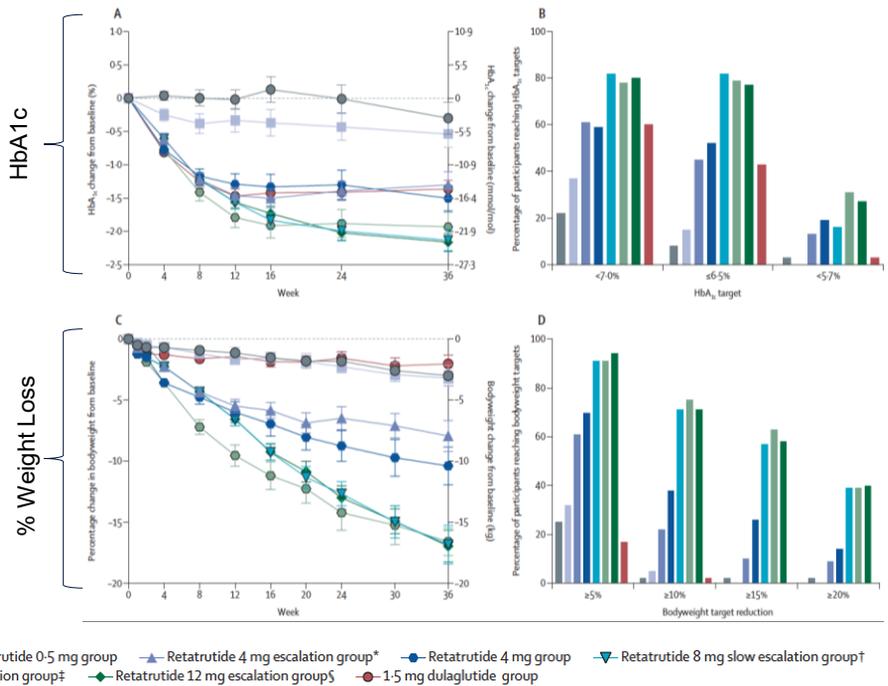
Diabetes Care. 2024;48(Supplement_1):S128-S145. doi:10.2337/dc25-S006

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Retatrutide (GLP1-GIP-GCGR) Triple Agonist and Treatment of Patients with T2D and Obesity: A Phase 2 Trial

Level 2-3 hypoglycemia 2-4%

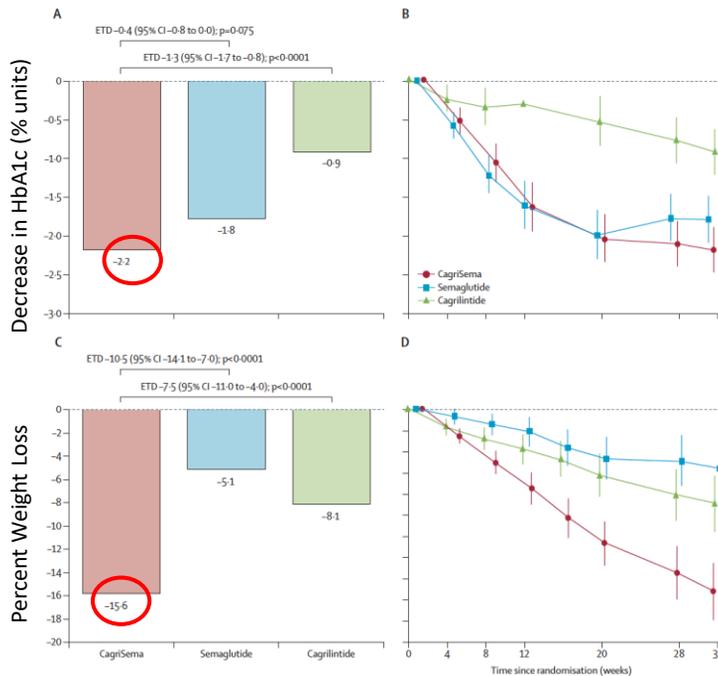
Rosenstock J et al. Lancet. 2023 Aug 12;402(10401):529-544



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Effectiveness of Cagrilintide + Semaglutide in Patients with T2D and Obesity: A Phase 2 Trial

Frias JP et al. Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. Lancet. 2023 Jun 23. Epub ahead of print.



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Principle 3

Treating T2D in the Broader Pathophysiological Context of Cardiometabolic Disease

“I have had to move on as well and have new friends. I needed room to grow, new directions. We both have future lives to live and there is a whole big world out there. We can still be friends.”

Take your choice:

“Landslide” Fleetwood Mac

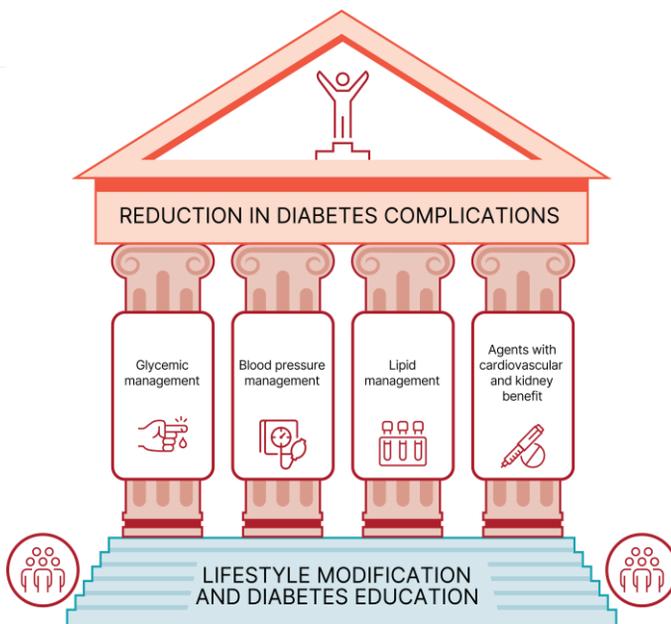
“It’s Too Late” Carole King

“Someone Like You” Adele



Multifactorial Approach to Reduction in Risk of Diabetes Complications

From: 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2026 Diabetes Care. 2025;49 (Supplement_1):S216-S245



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Recommended Management of Hypertension in Diabetes

	ESC	AACE	ADA	AHA
BP Target (mmHg)	<ul style="list-style-type: none"> SBP 120-130, DBP 70-80; for >65 years SBP 130-140; 	<ul style="list-style-type: none"> <130 / <80 <120 / <70 if albuminuria, mod/high CVD risk, established ASCVD, PVD, or retinopathy 	<ul style="list-style-type: none"> <130 / <80 	Individualize based on 10-yr risk of ASCVD: <ul style="list-style-type: none"> <130 / <80 if risk ≥ 10% or if eGFR is <60; <140 / <90 if risk <10%
Medications	<ul style="list-style-type: none"> Begin combination treatment with ACEi/ARB + CCB or HCTZ 	<ul style="list-style-type: none"> First-line ACEi or ARB; then add thiazide, CCB; then consider beta-1 selective blocker, combined alpha/beta blocker, MRA Dual therapy if >150/100 	<ul style="list-style-type: none"> First line agents: ACEi or ARB, thiazides, CCB; 2 drugs if BP >150/90; beta blocker if prior MI, angina, or HFrEF; add MRA as 4th drug if needed 	<ul style="list-style-type: none"> First-line agents: thiazides, CCB, ACEi or ARB; two first-line agents for stage 2 hypertension or BP > 20/10 mm Hg above target

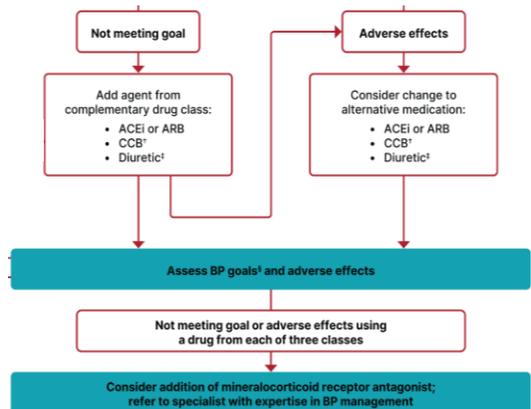
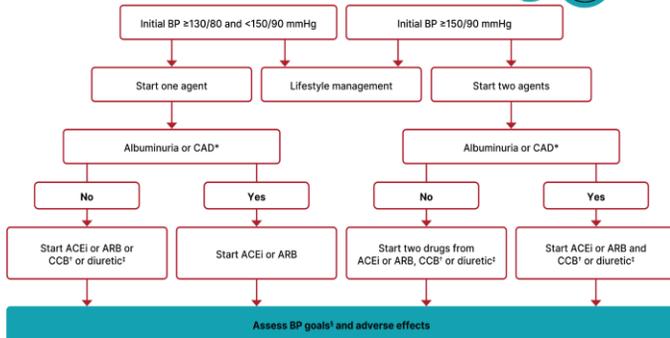
Marx N et al. Eur Heart J. 2023 Oct 14;44(39):4043-4140. Samson SL et al. Endocr Pract. 2023 May;29(5):305-340. ADA, chapter 10 *Standards of Care in Diabetes—2024. Diabetes Care* 2024; 47 (Supplement_1): S179–S218. Arnett DK et al. J Am Coll Cardiol. 2019;74(10):e177-e232.

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Management of Hypertension

Recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes

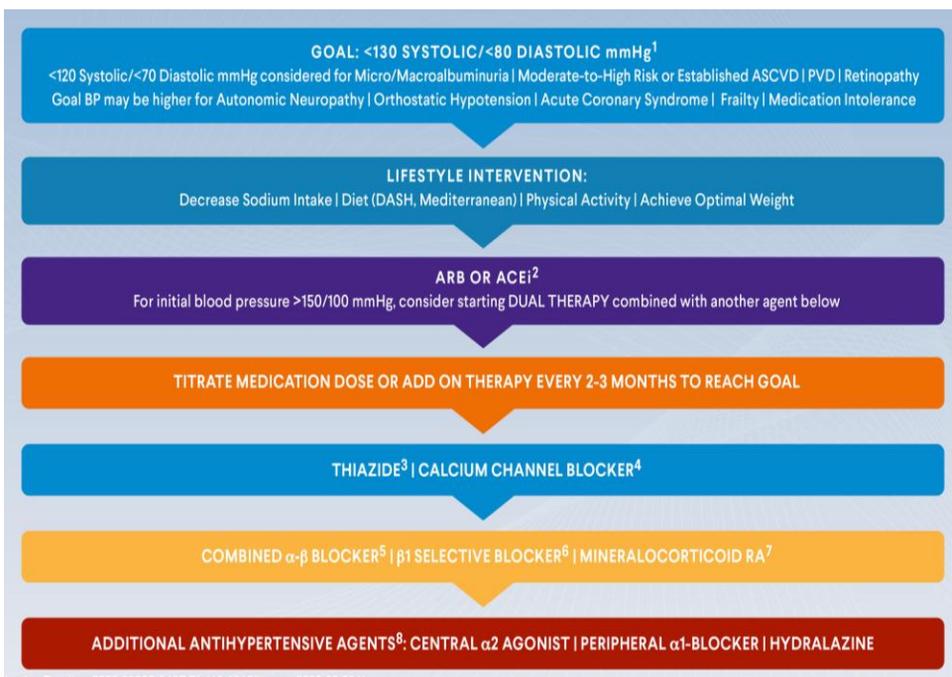


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ASCVD Risk Reduction Algorithm: Hypertension



Samson SL et al.
 Endocr Pract. 2023
 May;29(5):305-340.

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Recommended Management of LDL-Cholesterol in Diabetes

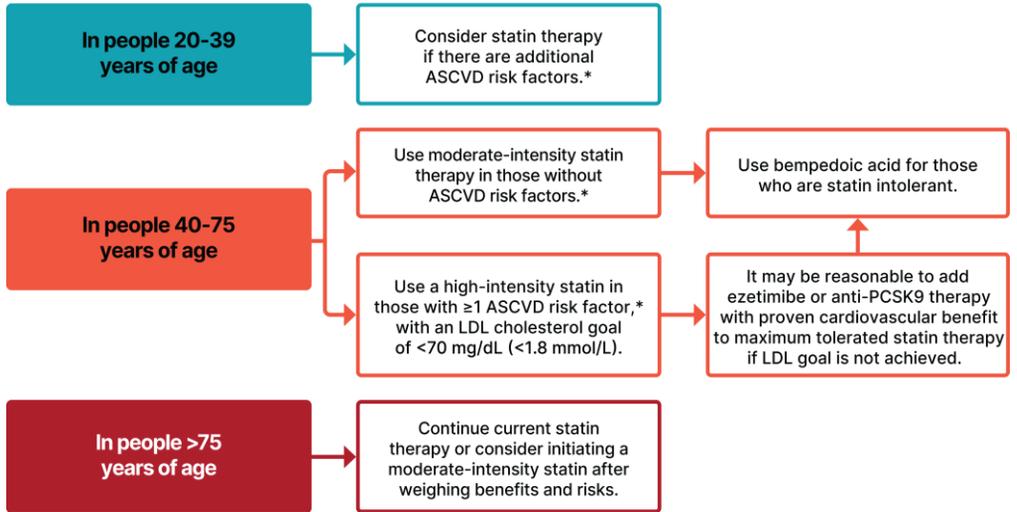
	ESC	AACE	ADA	AHA
LDL-c Target (mg/dL)	<ul style="list-style-type: none"> Moderate Risk LDL <100 High Risk LDL <70 non-HDL <100 Very High Risk LDL <55 non-HDL <85 	<ul style="list-style-type: none"> High risk LDL <100 Non-HDL < 130 Apo B < 90 Very high risk LDL <70 Non-HDL < 100 Apo B < 80 Extreme risk LDL <55 Non-HDL < 80 Apo B < 70 	<ul style="list-style-type: none"> DM wo/ASCVD, mod intensity statin; DM w/ high ASCVD risk, high intensity statin to reduce LDL by 50% and to <70; DM with ASCVD, use high intensity statin to reduce by 50% and to <55 DM age 20-39 with risk factors, use statin. 	<ul style="list-style-type: none"> Intermediate risk 7.5-20%, reduce LDL by 30% depending on CAC score (no statin if 0, begin statin for age >55 yrs if 1-99, begin statin if >100) High risk >20%, lower LDL by 50%
Medications	<ul style="list-style-type: none"> Max statin, then ezetimibe, then add PCSK9i; PCSK9i if statin intolerant; For high TG use icosapent ethyl 	<ul style="list-style-type: none"> Statin and glycemic control, then ezetimibe, then PCSK9i, or consider bempedoic acid, inclisiran, bile acid sequestrant. For high TG: glycemic control, icosapent ethyl, fibrate, niacin 	<ul style="list-style-type: none"> Statin, then ezetimibe, then PCSK9i, or consider bempedoic acid and inclisiran For high TG use Icosapent ethyl Dim view of fibrates and niacin but need to get TG below 500 	<ul style="list-style-type: none"> All DM get mod intensity statin without need for 10-yr risk score. At higher risk (multiple risk factors or those 50- 75 years), use high-intensity statin to reduce the LDL-C level by ≥50%.

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Management of LDL Cholesterol: Primary Prevention

Lipid management for primary prevention of atherosclerotic cardiovascular disease events in people with diabetes in addition to healthy behavior modification



*ASCVD risk factors include older age, hypertension, dyslipidemia, smoking, chronic kidney disease, or obesity.

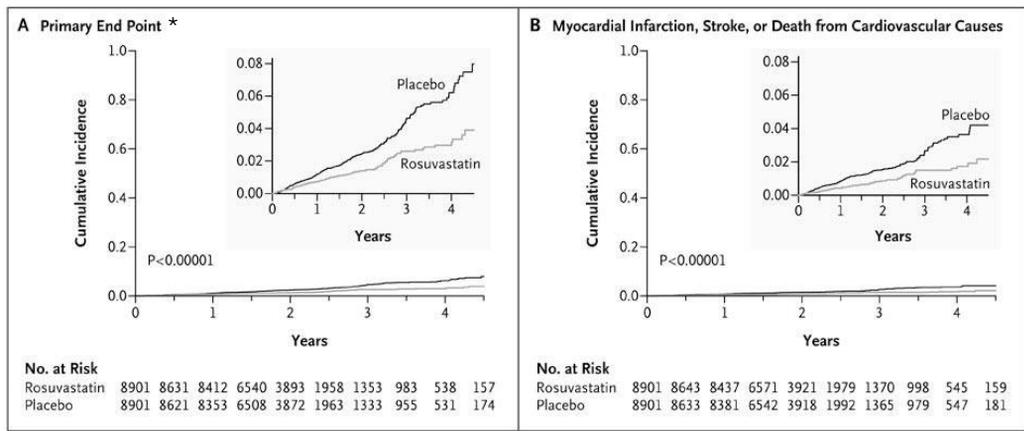
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Lowering LDL-C to < 70 mg/dl Lowers CVD Events in Patients with Metabolic Syndrome: The Jupiter Study

- Primary prevention in patients with elevated CRP (most with Metabolic Syndrome)
- 17,802 patients randomized to placebo vs 20 mg/d rosuvastatin
- LDL-c decreased from 108 at baseline to 55 mg/dl at 4 years

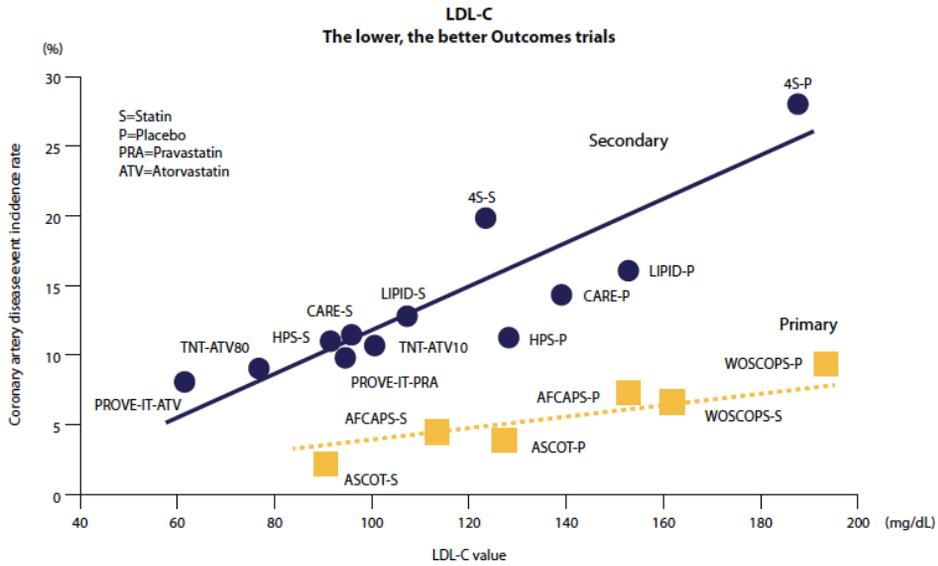


* First major cardiovascular event, defined as nonfatal MI, nonfatal stroke, hospital for unstable angina, revascularization on procedure, or CV death.

Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. NEJM 359:2195-2207, 2008

48

Statin Trials, LDL Cholesterol Lowering, and CAD Risk



Tokgozoglu L, Zamorano JL. Drugs in Context. 2020; 9:2020-4-4.DOI:10.7573/dic.2020-4-4

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Management of LDL Cholesterol: Secondary Prevention

Lipid management for secondary prevention of atherosclerotic cardiovascular disease events in people with diabetes

Use lifestyle and high-intensity statin therapy to reduce LDL cholesterol by $\geq 50\%$ from baseline to a goal of **<55 mg/dL** (<1.4 mmol/L).

Add ezetimibe or anti-PCSK9 therapy with proven cardiovascular benefit if LDL cholesterol goals are not met on maximum tolerated statin therapy.

Use an alternative lipid-lowering treatment for those who are statin intolerant:

- PCSK9 monoclonal antibody with proven cardiovascular benefit
- Bempedoic acid
- PCSK9 inhibition with siRNA inclisiran

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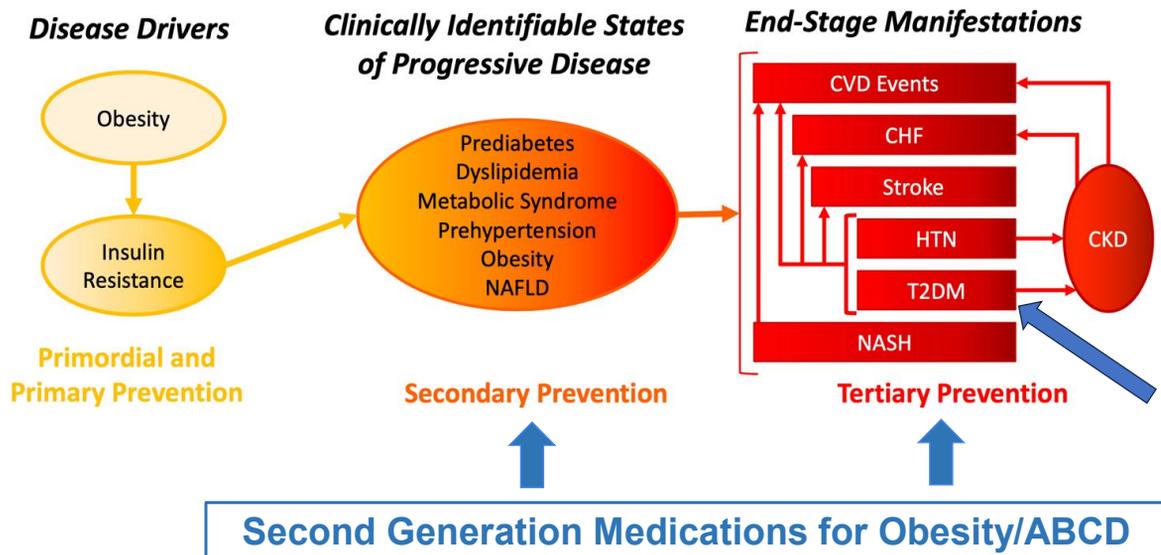
ASCVD Risk Stratification in Diabetes: 2022 AACE Diabetes Guidelines Update

HIGH RISK <10% T2D <10 years <2 other risk factors No target organ damage		VERY HIGH RISK 10%-20% T2D >10 years Age >40 years No ASCVD No target organ damage ≥2 additional risk factors	EXTREME RISK >20% T2D & ASCVD Severe target organ damage: eGFR <45 mL/min/1.73 m ² , UACR >300, ABI <0.9, LV systolic/diastolic dysfunction	
Moderate-intensity statin		High-intensity statin		
G O A L	LDL-C (mg/dL)	<100	<70	<55
	Non-HDL-C (mg/dL)	<130	<100	<80
	TG (mg/dL)	<150	<150	<150
	Apo B (mg/dL)	<90	<80	<70

Blonde L et al. Endocrine Practice 2022;(28):923-1049
Samson SL et al. Endocr Pract. 2023 May;29(5):305-340

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Second Generation Obesity Medications Treat Cardiometabolic Disease

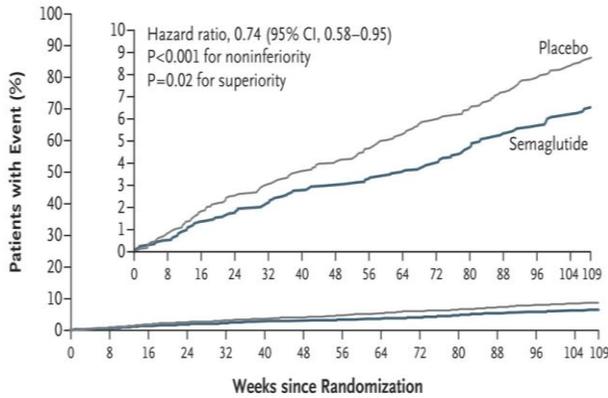


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Semaglutide Is Cardioprotective in Patients With and Without T2D

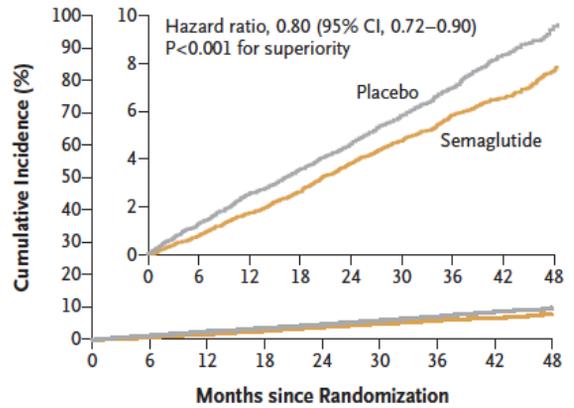
MACE Primary Composite Outcome (CVD death, non-fatal MI, non-fatal stroke)

SUSTAIN 6: Semaglutide 0.5-1.0 mg in T2D



Marso SP et al. NEJM 2016;375:1834-1844

SELECT: Semaglutide 2.4 mg in Obesity Without T2D



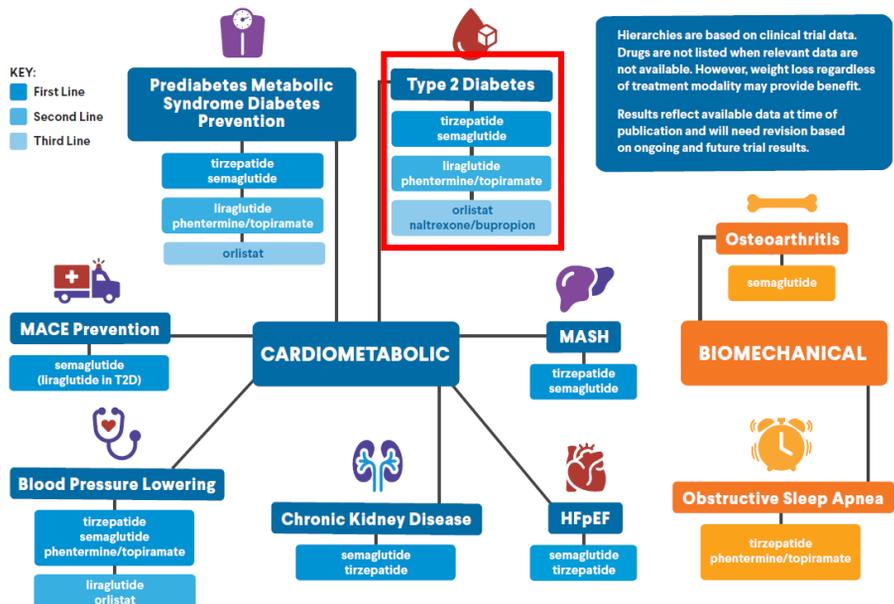
Lincoff AM et al. NEJM 2023;389(24):2221-2232

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HIERARCHIES OF PREFERRED MEDICATION FOR COMPLICATION-CENTRIC CARE OF PERSONS WITH ABCD



Nadolsky K, Garvey WT, Agarwal M et al. AAACE Consensus Statement: Algorithm for the Evaluation and Treatment of Adults with Obesity/Adiposity-Based Chronic Disease - 2025 Update. Endocr Pract. 2025 Nov; 31(11):1351-1394



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ADA Standards of Care for Obesity: Pharmacotherapy

American Diabetes Association Professional Practice Committee for Obesity*; Pharmacologic Treatment of Obesity in Adults: Standards of Care in Overweight and Obesity. *DOCN CARE2026; doc1250008.*

Goal: improvement in obesity-related diseases and complications* and accounting for achievement and maintenance of weight reduction

+PreDM	+T2D	+HTN	+ASCVD	+HFpEF	+MASH	+OSA	+OA
Preventing progression to T2D Demonstrated benefit Tirzepatide (A) Semaglutide (A) Potential benefit Phentermine-topiramate (B) Liraglutide (B) Orlistat (B)	BP lowering Demonstrated benefit Tirzepatide (A) Semaglutide (A) Orlistat (A) Potential benefit Phentermine-topiramate (B) Liraglutide (B)	Reducing HF events Demonstrated benefit Semaglutide (A) Potential benefit Tirzepatide (B)	Reducing AHI Demonstrated benefit Tirzepatide (A) Potential benefit Liraglutide (B) Phentermine-topiramate (C)	Glucose lowering Demonstrated benefit Tirzepatide (A) Semaglutide (A) Liraglutide (A) Potential benefit Phentermine-topiramate (B) Naltrexone-bupropion (B) Orlistat (B)	Reducing MACE Demonstrated benefit Semaglutide (A) Potential benefit Liraglutide (B) Tirzepatide (B)	MASH benefits Demonstrated benefit Semaglutide (A) Potential benefit Tirzepatide (B) Liraglutide (C)	Reducing pain Potential benefit Semaglutide (B) Tirzepatide (C) Liraglutide (C)

Select obesity medication that aligns with individual goals and does not present barriers to its long-term use†

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Pharmacology Treatment Algorithm from the EASO for Individuals with Obesity

McGowan B, Ciudin A, Baker JL et al. Framework for the pharmacological treatment of obesity and its complications from the EASO. *Nat Med.* 2025 Oct;31(10):3229-3232

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CASE 1: GS Is a 59-year-old Man

- Referred to you as a new patient after previous PCP retired (became tired of all the documentation, pre-auths, insurance company fights, etc).
- Known History of T2D, Hypertension, and CAD with NSTEMI tx medically 2 years ago

Meds

- Metformin 2,000 mg/day, Empagliflozin 10 mg, Rosuvastatin 40mg, ASA 81 mg daily, Lisinopril 40mg, Metoprolol 25mg bid

Physical Exam

- 5' 8", 243lbs, waist 112 cm, BMI 37 kg/m²; BP 140/90 mmHg
- Acanthosis, heart & lungs normal, no edema

Labs

- HbA1c 8.2%, FBG 164 mg/dl
- LDL 95, HDL 38, TG 172, non-HDL 129
- eGFR 55, uAlb/Cr 50 mg/g
- ECG unremarkable



Assessment

1. Adiposity Based Chronic Disease
 - Anthropometric: class II Obesity
 - Clinical: multiple weight related complications, stage 3
2. T2D, HbA1c 8.2% not at target
3. CAD, NSTEMI 2 years ago
4. Hypertension - two medications with BP not at target
5. eGFR 55, microalbuminuria
6. Dyslipidemia – LDL-c 95, TG 172, non-HDL-c 129

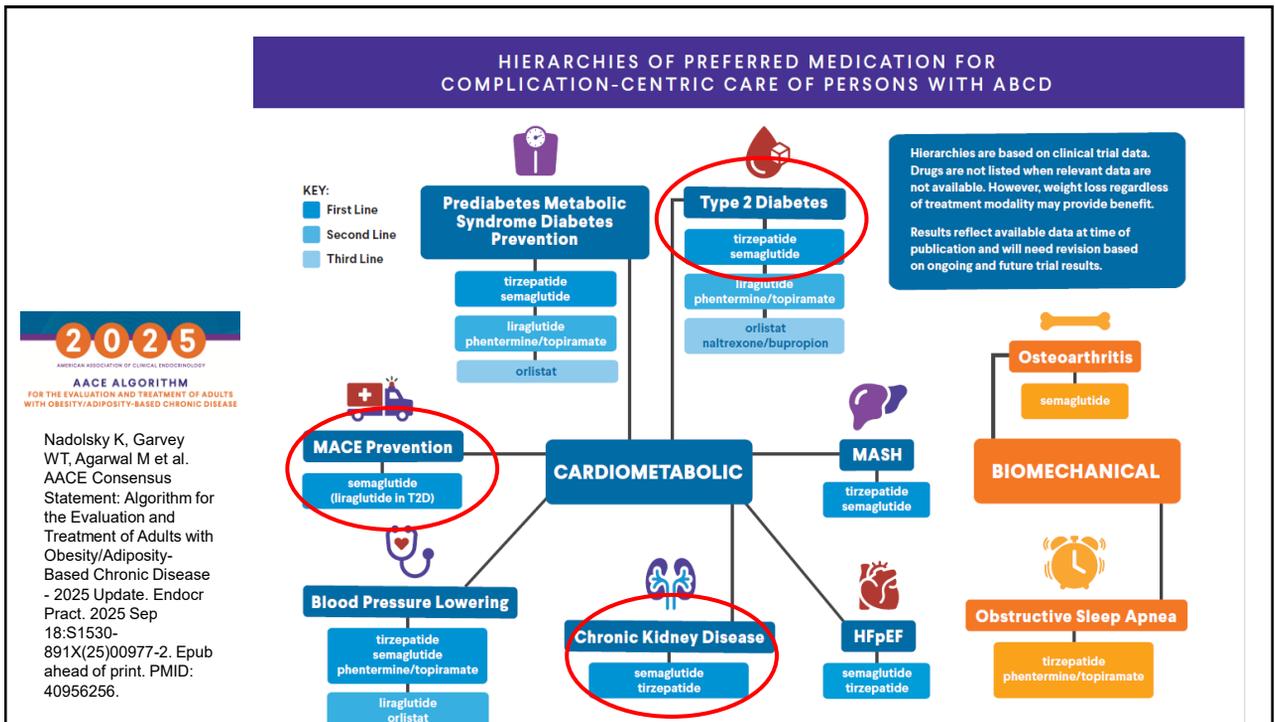
What is best single medication to treat this patient with metabolic and cardiovascular complications of Cardiometabolic Disease?

Best Single Medication to Treat GS with ABCD and Metabolic & Cardiovascular Complications of Cardiometabolic Disease?

- A. SGLT2i, empagliflozin
- B. GLP-1/GIP dual agonist, tirzepatide
- C. GIP-1 agonist, dulaglutide
- D. GLP-1 agonist, semaglutide
- E. Non-steroidal MRA, finerenone



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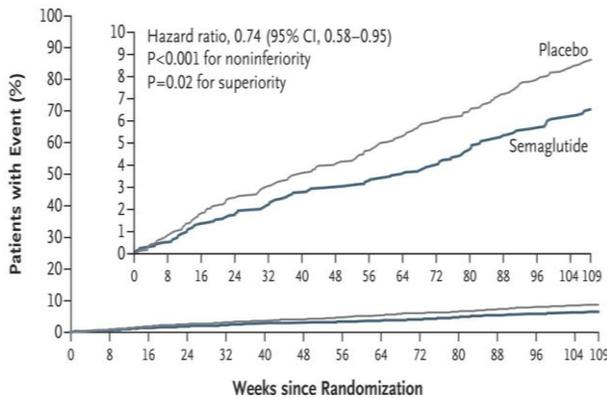


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Semaglutide Is Cardioprotective in Patients With and Without T2D

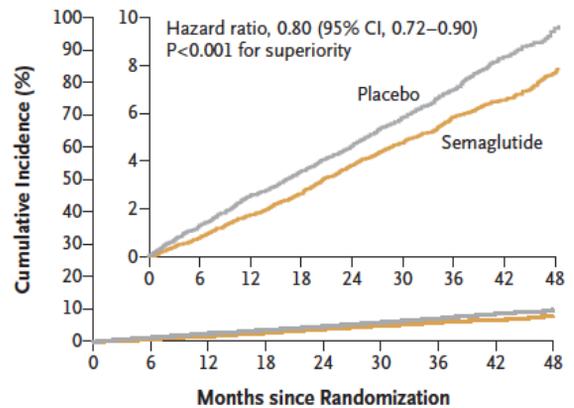
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Marso SP et al. NEJM 2016;375:1834-1844

SELECT: Semaglutide 2.4 mg in Obesity Without T2D



Lincoff AM et al. NEJM 2023;389(24):2221-2232

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What Are the Appropriate Lipid Goals for GS?

- A. LDL <55, non-HDL <100
- B. LDL <70, non-HDL <100
- C. LDL <55, non-HDL < 80
- D. LDL <100, non-HDL <130
- E. LDL <130, non-HDL <160

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AACE Lipid Guidelines for ASCVD Risk Reduction

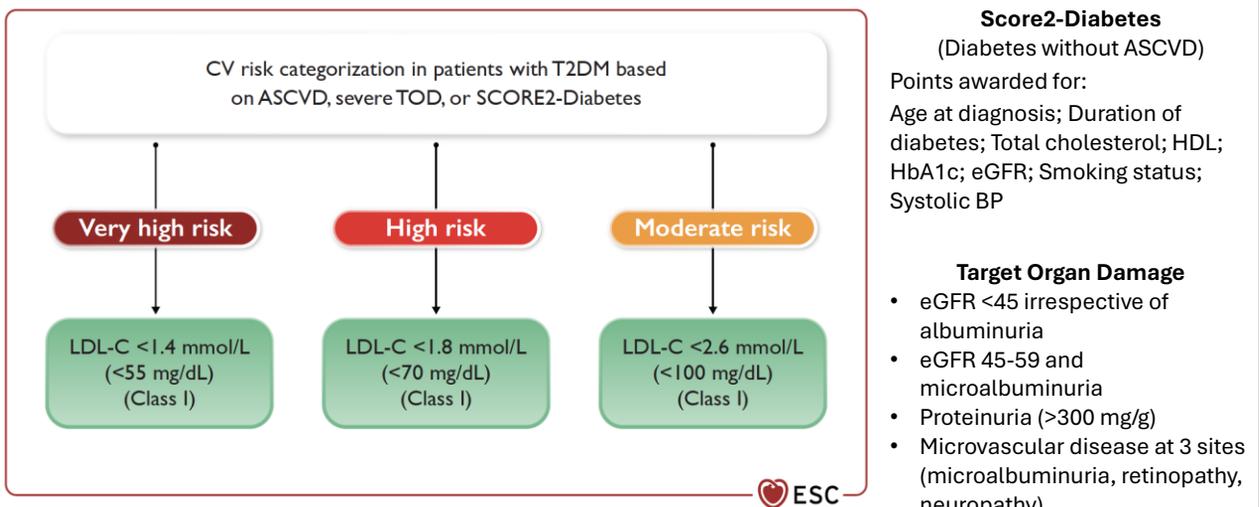
RISK LEVELS	HIGH	VERY HIGH	EXTREME	RISK LEVELS: ■ HIGH*: DM but no other major risk and/or age <40 ■ VERY HIGH*: DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4) ■ EXTREME*: DM plus established clinical CVD
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS	
LDL-C (mg/dL)	<100	<70	<55	
Non-HDL-C (mg/dL)	<130	<100	<80	
TG (mg/dL)	<150	<150	<150	
Apo B (mg/dL)	<90	<80	<70	

*Individuals with prediabetes (impaired fasting glucose and/or impaired glucose tolerance), especially those with MetS, are considered to be at increased risk for ASCVD. Lipid treatment goals for these individuals should be the same as those with diabetes [EL 4; NE]).

*Handelsman Y, Jellinger PS, Guerin CK, Bloomgarden ZT, Brinton EA, Budoff MJ, Davidson MH, Einhorn D, Fazio S, Fonseca VA, Garber AJ, Grunberger G, Krauss RM, Mechanick JL, Rosenblit PD, Smith DA, Wyne KL. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. *Endocr Pract.* 2020 Oct;26(10):1196-1224.

ESC Recommendations for Assessing ASCVD Risk in Diabetes:

The need to consider multiple historical, clinical, laboratory, and other diagnostics as well as target organ damage



Marx N,.... ESC Scientific Document Group et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J.* 2023 Oct 14;44(39):4043-4140.

What Is the Next Change You Would Make in GS's Lipid-lowering Medications?

- A. Add bempedoic acid 180 mg plus ezetimibe 10 mg/day
- B. Switch to Atorvastatin 80 mg/day
- C. Add ezetimibe 10 mg/day
- D. Add ezetimibe 10 mg/day plus PCSK9 inhibitor
- E. Add icosapent ethyl 4 g/day
- F. Mediterranean diet plus ezetimibe 10 mg/day
- G. Add PCSK9 inhibitor



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Recommended Escalation of Pharmacotherapy to Reach LDL Cholesterol Target

ESC 2023

AACE 2022

Lipid-lowering treatment

Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.²⁴⁷⁻²⁴⁹

If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.^{259,260}

A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.^{267,286}

I	A
I	B
I	A

Monitor and titrate therapy every 3-6 months to achieve lipid targets according to risk²

Intensify statin and lifestyle & optimize glycemic control

Add ezetimibe

Consider additional therapy: bile acid sequestrant, bempedoic acid, PCSK9 inhibitor, inclisiran

Marx N et al. Eur Heart J. 2023 Oct 14;44(39):4043-4140.

Samson SL et al. Endocr Pract. 2023 May;29(5):305-340

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Semaglutide Is Renal Protective in T2D: The FLOW Trial

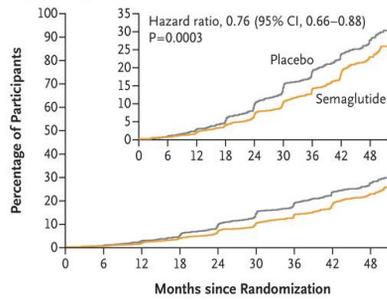
- 3,160 patients with T2D
- Reduced eGFR and micro- or macro-albuminuria
- On RAAS blockade
- Sema 1 mg vs placebo

Primary outcome

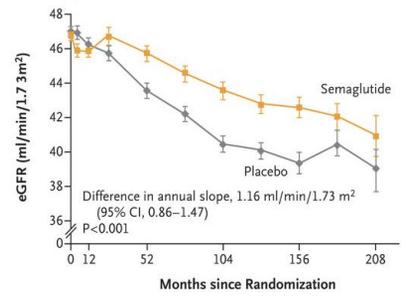
- Time to first occurrence
- $\geq 50\%$ reduction in eGFR
- eGFR < 15
- Dialysis or transplantation
- Kidney or CVD death

Perkovic V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. NEJM 2024 May 24, Epub ahead of print.

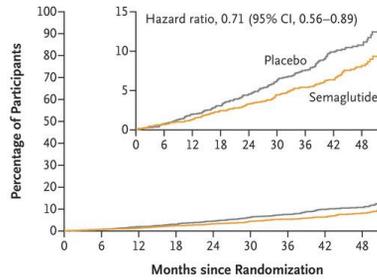
First Major Kidney Disease Event



Total eGFR Slope



Death from Cardiovascular Causes



Death from Any Cause

