Diabetes Update – 2025

Gary Ferenchick MD
Professor of Medicine
Michigan State University

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Objectives: Understand …

- Decoupling A1c from Outcomes (Targeting Risk, Not Just Glucose)
- Obesity & T2D
- Diabetes and the pivotal role of GLP-1 receptor agonists.
  - This data is rapidly evolving

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Disease oriented outcomes

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Patient oriented outcomes

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Beyond the A1c

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Patient Oriented Outcomes

What we are aiming to avoid with treatment

Patient Outcomes of Disease (the 5 D's)	
Death	A bad outcome if untimely
Disease	A set of symptoms, physical signs, and laboratory abnormalities
Discomfort	Symptoms such as pain, nausea, dyspnea, itching, and tinnitus
Disability	Impaired ability to go about usual activities at home, work, or recreation
Dissatisfaction	Emotional reaction to disease and its care, such as sadness or anger

What's not on this list is "lower glycohemoglobin" or "fasting blood glucose control" or "less glycosylation of glomerular proteins" or other surrogate outcomes.

Sometimes these surrogate outcomes (i.e., "disease-oriented outcomes") correlate with one or more of the 5 D's (i.e., "patient-oriented outcomes"), and sometimes they don't

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Fletcher, R. H., Fletcher, S. W., & Fletcher, G. S. (2020). Clinical epidemiology: The essentials (6th ed.). Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

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Example 1 | Rosiglitazone

Surrogate marker – disease oriented

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Good "glycemic control" associated with worse macrovascular clinical outcomes

↑

Clinical outcome – patient oriented

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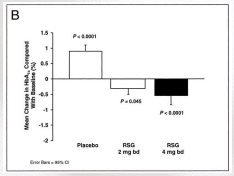
Rosiglitazone & Improved Glycemic Control

To study efficacy and safety of rosiglitazone monotherapy in patients with type 2 diabetes

Design: RCT of 533 patients randomized to rosiglitazone 2 or 4 mg daily (N=335; mean age 61; Average A1c 8.9%) or placebo (N=158; mean age 59; Average A1c 9.0%)
Primary outcome: Change in glycohemoglobin (A1c) & fasting blood sugar



Rosiglitazone ↓ A1c 1.2 and 1.5% compared to placebo (P=0.0001)

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Rosiglitazone monotherapy is effective in patients with type 2 diabetes.

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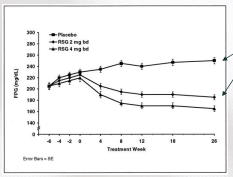

Rosiglitazone ↓ fasting glucose levels 58 & 76 mg/dL compared to placebo (P=0.0001)

Rosiglitazone use associated with A1c goals ~20- 40% vs 2% for placebo

- Insulin resistance reduced 16.0% and 24.6%,
- Improved β-cell function over baseline by 49.5% and 60.0%
- Urinary albumin excretion decreased significantly in the rosiglitazone (4 mg bd) group.
- There was no increase in adverse events with rosiglitazone in the short-term.

None of these outcomes directly reflect a 5D

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Rosiglitazone monotherapy is effective in patients with type 2 diabetes.

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Rosiglitazone & ↑ CV Risk

To determine the effect of rosiglitazone on cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus.

Design: Meta-analysis of 42 randomized trials of patients (mean age 56; Average A1c 8.2%) receiving rosiglitazone vs control group
Primary outcome: Myocardial infarction, death from cardiovascular diseases

Patient-oriented evidence (POE) or one of the 5D's

Odds Ratio for MI = 1.43 (CI 1.03-1.98; P=0.03)
Odds Ratio for CV death = 1.64 (CI 0.98-2.74; P=0.06)

43 – 64% relative *increase* in MI or CV death

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

"…the use of blood glucose measurements as a surrogate end point in regulatory approval must be carefully reexamined."

i.e., Disease-oriented evidence or DOE

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes.

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In 2008, the FDA required industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes.

Previously approved diabetes medications were not subject to the guidance.

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ACCORD Trial

To determine the effect of intensive therapy targeting the A1c to "normal" on cardiovascular events

Design: RCT of 10,251 patients (mean age 62, mean A1c 8.1%) of intensive glycemic control (N=5128; target < 6%) vs standard therapy (N=5123; target 7 – 7.9%)

Primary outcome: MACE

Mean duration of DM = 10 years
Preexisting CV Dz = 35%

How the patients got to the target A1c was at the discretion of the investigators and patients
No single class of medications was prespecified

Dose adjustments occurred 4.4 times yearly vs 2.0 times yearly

MACE = Major Adverse Cardiovascular Events (commonly MI, Stroke, CV Death)

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Effects of Intensive Glucose Lowering in Type 2 Diabetes.

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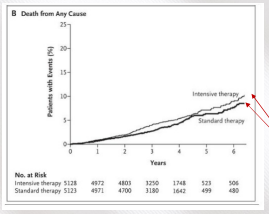
ACCORD Trial

To determine the effect of intensive therapy to target the A1c to "normal" on cardiovascular events

Design: RCT of 10,251 patients (mean age 62, mean A1c 8.1%) of intensive glycemic control (N=5128; target < 6%) vs standard therapy (N=5123; target 7 – 7.9%)
Primary outcome: MACE*



"Good glycemic control" achieved"
6.4% vs 7.5%

Excellent effect on decreasing the A1c (surrogate or disease-oriented outcome)

Effect not so good with the patient-oriented outcome: 22% increase in mortality with intensive glycemic control
NNH = 100

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*MACE = Major Adverse Cardiovascular Events (commonly MI, Stroke, CV Death)

Effects of Intensive Glucose Lowering in Type 2 Diabetes.

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Primary outcome: MACE

Rate of hypoglycemia requiring any assistance 16.2% vs 5.1%

"As compared with standard therapy, the use of intensive therapy to *target normal glycated hemoglobin levels* for 3.5 years increased mortality and did not significantly reduce major cardiovascular events."

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Effects of Intensive Glucose Lowering in Type 2 Diabetes.

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American Diabetes Association

- A reasonable A1C goal for many nonpregnant adults is <7%***
- More stringent for selected patients***
- Less stringent if hx of hypoglycemia, advanced complications, extensive co-morbid conditions

How you and your patients achieve glycemic control is key

***If hypoglycemia can be avoided

Glycemic Goals and Hypoglycemia. Standards of Medical Care in Diabetes—2024

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Obesity & Diabetes: Diabesity?*

- Prevalence of DM worldwide is 10.5% (537 million adults aged 20 – 79; 96% T2D)
- DM is a major cause of death & disability, driven by microvascular complications (kidney disease, retinopathy, neuropathy) & macrovascular complications (heart disease, stroke).
- Over 85% of adults with type 2 diabetes are overweight or have obesity.

* MSU Dept of Endocrinology

The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306

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#1: Diabesity*

- Systematic review & meta-regression of RCTs of adults with T2D & overweight/obesity.
- Analyzed 62 remission outcomes from 22 RCTs to assess how weight loss affects type 2 diabetes remission at 1 year.
- Remission
  - Complete = A1c < 6.0% off meds
  - Partial = A1c < 6.5% off meds

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The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306

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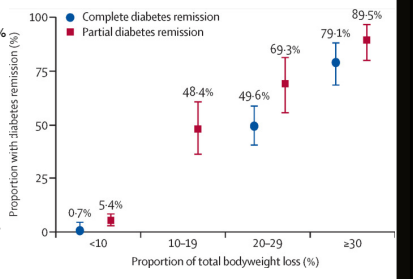
#1: Diabesity*

Complete remission
- <10% weight loss → only **0.7%** reached complete remission
- 20–29% weight loss → ~**50%** achieved remission
- ≥30% weight loss → ~**80%** in remission

Partial remission
- <10% → **5.4%**
- 10–19% → **48.4%**
- 20–29% → **69.3%**
- ≥30% → **89.5%**

Each 1% drop in weight -> 2.2 - 2.8% chance of remission



(Note: No data reported for 10–19% weight loss group for complete remission)

The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306

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#1: Diabesity*

- **Weight loss is the primary driver** of remission—not age, race, baseline A1c, diabetes duration, insulin use, or intervention type.
- Therefore, prioritizing meaningful weight loss as a therapeutic goal

The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306

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Weight Loss & GLP1 GIP/GLP1

	Weight | ~ 1yr	A1c < 6.%	Other Metabolic parameters
Semaglutide | STEP 2	2.4 mg = -9.6% 1.0 mg = -7.0% Placebo = -3.4%	A1c <6.5% 2.4 mg = 67.5% 1.0 mg = 60.1% Placebo = 15.5%	SBP Lipids Urine albumin Liver enzymes Physical function
Tirzepatide | SURMOUNT -2	15 mg = - 14.7% 10 mg = - 12.8 % Placebo = - 3.2%	A1c <6.5% 15 mg = 79% 10 mg = 80% Placebo = 20%	SBP/DBP Lipids Physical function

STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971–984

SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023 Aug 19;402(10402):613-626

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2. Tirzepatide vs semaglutide

Purpose: To evaluate the effects of tirzepatide & semaglutide on weight loss

Methods: 751 patients mean BMI 39 & age 45; 60% with prediabetes; | open-label controlled trial Tirzepatide (10 or 15 mg/wk) vs semaglutide 1.7 or 2.4 mg/wk) for 72 weeks

Outcomes: Primary: Δ body weight; **Secondary**: Waist circumference and weight reductions of 10, 15, 20 & 25%

	Tirzepatide	Semaglutide
Δ Body Weight (%)	-20.2	- 13.7
Waist circumference (cm)	-18.4	-13.0
Tirzepatide patients more likely to have weight reductions of 10 (82 v 61%), 15 (65 v 40%). 20 48 vs 27%) and 25% (32 v 16%)		

Conclusions: Tirzepatide superior to treatment with semaglutide for weight reduction and waist circumference

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Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med. 2023;390(22):2045-2056

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3. Tirzepatide & Pre-Diabetes

Purpose: To evaluate the effects of GIP/GLP-1 on pre-Diabetes outcomes

Methods: 1032 patients mean BMI 38; mean A1c 5.8% | DBRCT of Tirzepatide 5, 10 or 15 mg/wk vs placebo for 172 weeks followed by 17 week off treatment

Outcomes: Primary: Δ body weight & onset of T2D;

	Tirzepatide 5	Tirzepatide 10	Tirzepatide 15	Placebo
Δ Body Weight (%)	12.3	18.7	19.7	1.3
New onset DM (%)	1.3	2.0	0.4	13.3
Δ Body Weight (%) After 17 weeks off med	12.3	15.6	17.9	2.8
Tirzepatide led to lasting improvements in: Waist size, blood pressure, and cholesterol; Physical functioning; Mental and emotional well-being; Overall physical and psychosocial quality of life				

Conclusions: 3 years of tirzepatide treatment led to major, lasting weight loss and significantly reduced the risk of developing type 2 diabetes compared to placebo.

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SURMOUNT-1 Investigators. Tirzepatide for obesity treatment and diabetes prevention. N Engl J Med. 2025;392(10):958-971

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#4 GLP1 RA & ASCVD Outcomes

GLP1 Agonists & ASCVD Outcomes

Drug	Duration	Δ MACE	Δ CHF endpoints	Δ Mortality	Δ Hypoglycemia	Δ A1c
Lixisenatide | T2D + ASCVD (AGLM 2015)	2.1	NS	NS	NS	1.4%	0.27%
Liraglutide | T2D + ↑ ASCVD Risk (ELIXA 2015)	3.8	1.9%	NS	NS	1.4%	0.9%	0.4%
Semaglutide | T2D + ASCVD or CKD (SUSTAIN 6)	2.1	3.2%	NS	NS	2.2%	1.1%	~1.4%
Exenatide | T2D (EXSCEL 2017)	3.2	NS	NS	NS	0.4%	0.53%
Albiglutide | T2D (Aleglut 2018)	1.5	2.0%	NS	NS	0	1.0%
Dulaglitide | T2D + ASCVD or + ↑ ASCVD Risk (Lancet 2019)	5.4	1.4%	NS	NS	0.2%	0.61%
Oral semaglutide | T2D + ASCVD or + ↑ ASCVD Risk (NEJM 2019)	1.3	NS	NS	1.4%	0.6%	0.7%

Semaglutide (Ozempic®)
Liraglutide (Victoza®)
Dulaglitide (Trulicity®)

Tirzepatide is approved for T2DM and weight management but not yet approved for reducing cardiovascular events. Its impact on ASCVD outcomes is being studied in the ongoing SURPASS-CVOT trial.

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#5: Oral semaglutide & ASCVD

Purpose: To evaluate the effects of oral semaglutide in T2D + ASCVD

Methods: 9650 patients (mean age ~ 55; BMI 31; A1c 8.0%) DBRCT of semaglutide 2.4 mg/wk or placebo 47-month fu.

Outcome: MACE (CV death, nonfatal MI or CVA)

	Semaglutide	Placebo	
Weight Loss	-4.22 kg	-1.3 kg	
Primary Outcome	12.0%	13.8%	P<0.006

Conclusion: In people with type 2 diabetes and ASCVD, CKD, or both, oral semaglutide significantly reduced the risk of major cardiovascular events without increasing serious adverse events.

ΔA1c = 0.6%

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SOUL Study Group. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. N Engl J Med. 2025 May 29;392(20):2001-2012

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#6. Semaglutide CKD + T2D

Purpose: To evaluate the effects of GLP-1 on renal outcomes

Methods: 3533 patients with T2D & CKD | RCT of semaglutide 1.0 mg/wk or placebo 3.4 years of follow up (mean age ~ 66; A1c 7.8%; BMI 31; eGFR 46, UA ~ 560)

Outcome: Multiple renal outcomes (↓ eGFR > 50%; persistent eGFR < 15, renal replacement, CV death)

	Semaglutide	Placebo	
Primary outcome (%)	18.7	23.2	P<0.0003
Active treatment slowed kidney function decline (eGFR decline reduced by 1.16 mL/min/1.73 m² per year); 18% lower risk of major cardiovascular events; 20% lower risk of death from any			

Conclusion: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

ΔA1c = 0.81% | Δ % weight loss 4%

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FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024 Jul 11;391(2):109-121.

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7. Semaglutide & MASH

Purpose: To evaluate the effects of GLP-1 on MASH outcomes

Methods: 800 patients with biopsy-defined MASH (Fibrosis stage 2 or3) DBRCT of semaglutide 2.4 mg/wk or placebo 72 wks. (mean age ~ 55; BMI 34; 55% with T2D)

Outcome: Resolution of steatohepatitis reduction in fibrosis

	Semaglutide	Placebo	
Weight Loss	–10.5%	-2.0%	P<0.001
Resolution (%)	62.9	34.3	P<0.001
Reduced fibrosis (%)	36.8	22.4	P<0.001
Noninvasive liver markers (AST, ALT, liver stiffness, FAST, ELF, PRO-C3) improved vs placebo. Also led to improvements in glycemic control, insulin resistance, and other cardiometabolic risk factors			

Conclusion: In patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histologic results.

ΔA1c = 1.1%

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ESSENCE Study Group. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025 Jul 5;393(1):2595-2606

Metabolic dysfunction–associated steatohepatitis (MASH).

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GLP-1 and OA

Purpose: To evaluate the effects of GLP-1 on OA outcomes

Methods: 407 adults (BMI ~40) + radiological and clinical moderate knee OA | DBPCT diet & activity counselling and semaglutide 2.4 mg/wk or placebo 68 wks.

Outcome: Δ body weight and WOMAC scores and SF-36 physical functioning score

	Semaglutide	Placebo	
Weight Loss	--13.7%	-3.2%	P<0.001
WOMAC	-41.7 points	-27.5%	P<0.001
SF-36	+12 points	+6.5 points	P<0.001

Conclusion: In adults with obesity and moderate-to-severe knee osteoarthritis, semaglutide 2.4 mg weekly led to significant weight loss, reduced knee pain, and improved physical function compared to placebo.

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~ 46% of pts with T2D have knee OA

Glucagon-like peptide-1 receptor agonists and osteoarthritis. N Engl J Med. 2024;391(17):1643–1644

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9. Tirzepatide and OSA

Purpose: To evaluate the effects of GIP/GLP-1 on OSAS outcomes

Methods: DBRCT of Tirzepatide 10 or 15 mg/wk vs placebo for 52 weeks
- Trial 1 | 234 patients (BMI ~39; AHI 51.5) | No baseline PAP use
- Trial 2 | 235 patients (BMI ~38; AHI 49.5) | Baseline PAP use

< 5 normal
5 - 15 mild
15 - 30 moderate
> 30 severe

Outcomes: Primary: Δ AHI & body weight

	Tirzepatide (pooled)	Placebo
Trial 1 Δ AHI	-25.3	-5.3
Trial 2 Δ AHI	`29.3	-5.5
Trial 1 Δ Weight	--17.7%	-1.6%
Trial 2 Δ Weight	-19.6%	-2.3%
Sig changes also noted in SBP; and hsCRP		

Conclusion: In adults moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes

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~ 56% of pts with T2D have OSAS

SURMOUNT-OSA Investigators. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391(14):1116–1124

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10. Semaglutide & ASCVD (no T2D)

Purpose: To evaluate the effects of GLP-1 on ASCVD outcomes (no T2D)

Methods: 17,604 patients (mean age 61) with ASCVD and BMI 33 | DBRCT of 2.4 mg semaglutide weekly vs placebo for 34 months

Outcomes: Primary: MACE (ASCVD death, nonfatal MI or CVA)

	Semaglutide	Placebo
Primary (%)	6.5	8.0
Discontinuation	16.6%	8.2%
Δ Weight %	-9.4%	-0.9%

Conclusion: In people with cardiovascular disease and overweight or obesity but without diabetes, semaglutide 2.4 mg weekly significantly reduced the risk of major cardiovascular events (CV death, heart attack, or stroke) over ~40 months compared to placebo.

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SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221–2232.

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SGLT2 inhibitors

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11. SGLT2 Inhibitors & MACEs

Drug Yr	T2D	Duration (yrs)	% Δ MACE	% Δ CHF endpoints	% Δ Mortality	% Δ Hypoglycemia	% Δ A1c
Empagliflozin | ASCVD (NEJM 2015)	100%	3.1	1.6	1.4	2.6	0.1	0.24%
Canagliflozin | ASCVD (NEJM 2017)	100%	3.6	4.6	3.2	NS	3.6	0.58%
Dapagliflozin | ASCVD (NEJM 2018)	100%	4.2	NS	0.9	NS	0.3	0.42%
Dapagliflozin | HFrEF (NEJM 2019)	42%	1.5	1.9	4.9	2.3		0.24%
Empagliflozin | HFrEF (NEJM 2020)	50%	1.3	NS	5.1	NS	0.1	0.16%
Dapagliflozin | CKD (NEJM 2020)	67%	2.4	1.8	1.8	2.1	0.6	-
Empagliflozin | HFpEF (NEJM 2021)	49%	2.2	0.9	3.2	NS	0.2	0.19%

1.3 to 4.2 yrs of follow-up

Absolute differences (NNT)
- MACEs = 27 - 111
- CHF = 19 – 111
- Mortality = 38 - 47

Change in outcomes vs placebo

ACC AHA 1A recommend SGLT2i for HFrEF irrespective of T2D

The disease-oriented changes *were less impressive* than the patient-oriented outcomes

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MACEs = major adverse cardiovascular | Cardiovascular death | Nonfatal myocardial infarction | Nonfatal stroke | Hospitalization for unstable angina. Hospitalization for heart failure events

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12. SGLT2i & Renal Outcomes

SGLT2i & Renal Outcomes

Drug Yr	T2D	RAS Inhibitor	Duration	Δ GFR endpoints (HR)	Δ Mortality	Baseline eGFR
Empagliflozin | T2D + CKD (NEJM 2016)	100%	80%	3.1	0.61		48 - 83
Canagliflozin | T2D (NEJM 2017)	100%	80%	3.6	0.60	2.2%	76
Dapagliflozin | T2D (NEJM 2019)	100%	81%	4.2	0.76	0.4%	85
Canagliflozin | T2D + CKD (NEJM 2019)	100%	80%	2.6	0.68	1.5%	56
Empagliflozin | HFrEF (NEJM 2020)	49%	80%	1.3	0.50	0.8%	61
Dapagliflozin | CKD (NEJM 2020)	67%	98%	2.4	0.61	2.1%	43 (13% eGFR 20-29)
Empagliflozin | CKD (NEJM 2023)	46%	85%	2.0	0.71	0.6%	37 (30% eGFR 20-29)

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Decoupling A1c from Outcomes
The evolution of recent ADA guidance on pharmacotherapy

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American Diabetes Asso (ADA) Standards of Care
2021 → 2025

Focus on pharmacotherapy

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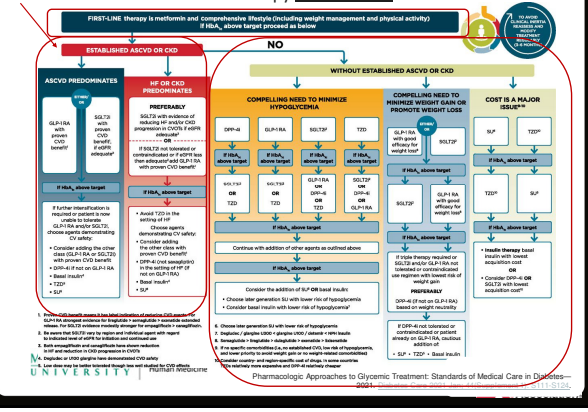
ADA 2021

Established disease

First-line therapy *is* metformin .....



Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021 Jan; 44(Supplement_1):S111-S124.

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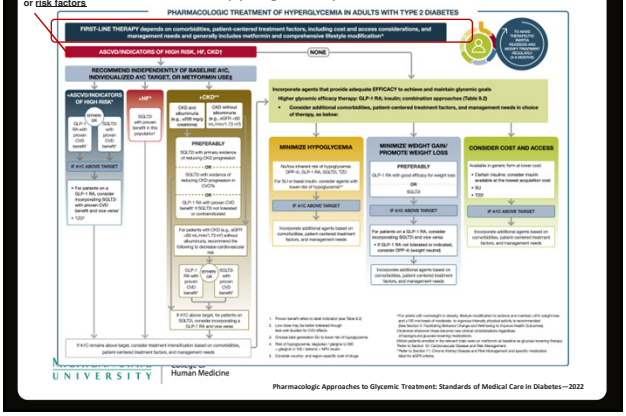
ADA 2022

Established disease or risk factors

First-line therapy "...*generally includes* metformin.."



Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022

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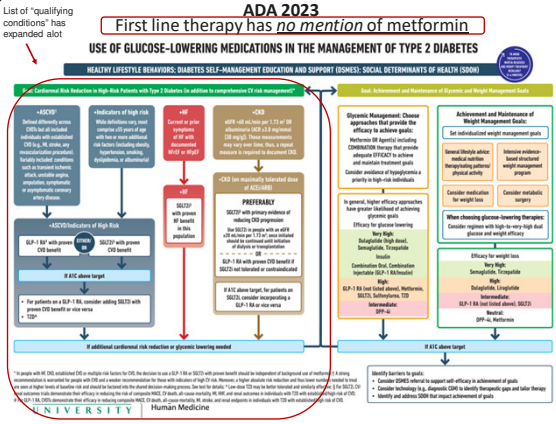
ADA 2023

List of "qualifying conditions" has expanded alot

First line therapy has *no mention* of metformin



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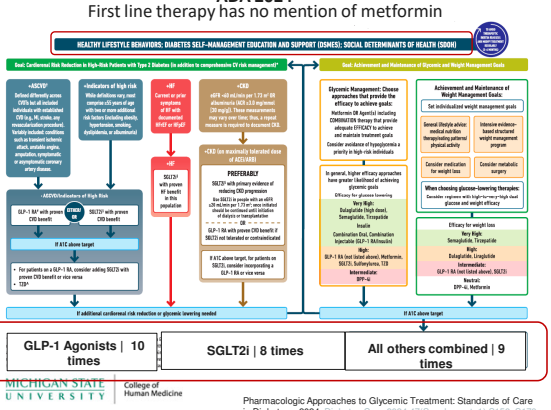
ADA 2024

First line therapy has no mention of metformin



Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Supplement_1):S158–S178

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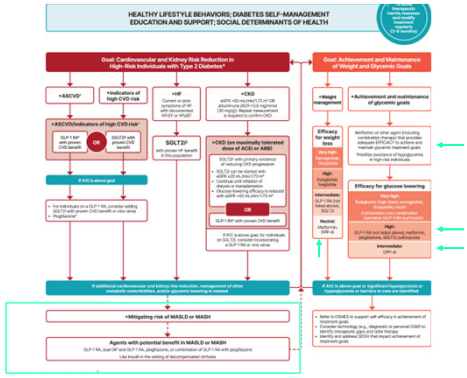
ADA 2025



New 2025

Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. Diabetes Care 2024;48(Supplement_1):S181–S206

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ADA 2025 Definitions

- Indicators of HR
  - > 55 with ≥ 2 additional risk factors (including obesity, HTN, smoking, dyslipidemia, albuminuria)
- ASCVD
  - MI, CVA, any revascularization procedure
  - TIA, unstable angina, amputation, sx or asx CAD
- HF | HFpEF or HFrEF
- CKD = eGFR < 60 &/or albuminuria (>30 mg / d)

The ACC/AHA has an expanded list of "Risk Enhancing Factors"

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Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. Diabetes Care 2024;48(Supplement_1):S181–S206

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ADA Snippets – 2025

In people with heart failure, chronic kidney disease, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 receptor agonist or a SGLT-2 inhibitor with proven benefits should be made irrespective of background use of metformin or A1C.

"irrespective of the need for additional glucose lowering and irrespective of metformin use."

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Preferred Agents
"Demonstrated benefit"

	CV Effects		Kidney Effects	MASH Effects
	MACE	HF	Progression of CKD	
SGLT2 inhibitors	canagliflozin empagliflozin	canagliflozin empagliflozin dapagliflozin ertugliflozin	canagliflozin empagliflozin dapagliflozin	Unknown
GLP-1 RAs	dulaglutide liraglutide semaglutide	Neutral	Albuminuria dulaglutide liraglutide semaglutide	Potential benefit
			CKD progression semaglutide	
Dual GIP & GLP-1 RA	Under investigation	Under investigation	Under investigation	Potential benefit

Canagliflozin (Invokana®)
Empagliflozin (Jardiance®)
Dapagliflozin (Farxiga®)
Ertugliflozin (Steglatro®)

Dulaglutide (Trulicity®)
Liraglutide (Victoza®)
semaglutide (Ozempic® – SC; Rybelsus® - oral)

Modified from: Table 9.2 2025 Standards of Care

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- **Class effect SGLT2i's in Patients with DM + HF**
  - "… with T2D & established HFpEF or HFrEF, an SGLT2 inhibitor … is recommended to reduce the risk of worsening HF, CV death, … improves symptoms, physical limitations, & QOL. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering
- **In T2D SGLT2 = GLP1 in ↓ MACE**
  - "… GLP-1 RAs & SGLT2i's reduce risk of atherosclerotic MACEs *to a comparable degree in people with type 2 diabetes and established ASCVD*"

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GLP-1 RA and SGLT2i | Outcomes

	GLP-1 RA	SGLT2i
MACE	X	X
CV Death	X	X
All-cause mortality	X	X
MI	X	X
Kidney endpoints	X	X
CVA	X	
Heart failure hospitalizations		X

Demonstrated outcomes in individuals with T2D & established or high risk of cardiovascular disease.

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American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Suppl 1):S181–S206.

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ADA Snippets – 2025

Combined Therapy Option:

- Consider combining a GLP-1 RA + SGLT2 inhibitor (both with demonstrated CV benefit) in patients with:
  - Established ASCVD or
  - Multiple ASCVD risk factors
- → For additive reduction in CV and kidney events

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Rapidly Evolving Landscape

The 2024 ADA Standards of Care recommendations (published January 2024) did not include recommendations on the use of GLP-1 agonists for treatment of CKD*

*This was added to the ADA January of 2025 Standards of Care

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Rapidly Evolving Landscape

ORIGINAL RESEARCH — Annals of Internal Medicine

Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes

Target Trial Emulation Using Real-World Data

William Wang; Nora D. Volkow, MD; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; and Rong Xu, PhD

Semaglutide was associated with lower risks for TUD-related health care measures in patients with comorbid T2DM and TUD compared with other antidiabetes medications including other GLP-1Ras,primarily within 30 days of prescription. These findings suggest the need for clinical trials to evaluate semaglutide's potential for TUD treatment.

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Ann Intern Med. 2024;177:1016-1027

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Rapidly Evolving Landscape

RESEARCH ARTICLE — Alzheimer's & Dementia — THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

Semaglutide was associated with significantly reduced risk for first-time AD diagnosis, most strongly compared with insulin (hazard ratio [HR], 0.33 [95% CI: 0.21to 0.51]) and most weakly compared with other GLP-1RAs (HR, 0.59 [95% CI: 0.37 to0.95]). Similar results were seen across obesity status, gender, and age groups.

Original Investigation

GLP-1RA and SGLT2i Medications for Type 2 Diabetes and Alzheimer Disease and Related Dementias

JAMA Neurol. Published Online: April 7, 2025. 2025;82(5):439-449. doi:10.1001/jamaneurol.2025.0353

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Alzheimer's Dement. 2024;1–12.

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Rapidly evolving landscape

Advertisement

Medscape Medical News > Conference News > AES 2024

GLP-1R agonists reduce migraine burden in obese patients

lepsy

Journal of Autoimmunity
Volume 155, July 2025, 103453

Association between autoimmune diseases and glucagon-like peptide-1 receptor agonists: A real-world evidence study

Yun-Jui Lee [a], Yu-Wei Fang [b c d], Mon-Ting Chen [d], Hung-Hsiang Liou [e], Tzu-Hao Li [f], Ming-Hsien Tsai [b c d]

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Rapidly evolving landscape

ORIGINAL ARTICLE

Semaglutide in Adults with Type 1 Diabetes and Obesity

Authors: Viral N. Shah, M.D., Halis K. Akturk, M.D., Davida Kruger, N.P., Andrew Ahmann, M.D., Anuj Bhargava, M.D., Giorgos Bakoyannis, Ph.D., Laura Pyle, Ph.D., and Janet K. Snell-Bergeon, Ph.D. Author Info & Affiliations

Published June 23, 2025 | DOI: 10.1056/EVIDoa2500173 | Copyright © 2025

In adults with type 1 diabetes and obesity, semaglutide treatment, compared with AID use alone, significantly improved achievement of a composite of time in range of greater than 70%, with time below range of less than 4%, and a 5% body weight reduction."

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AID = automated insulin delivery | 26 week study

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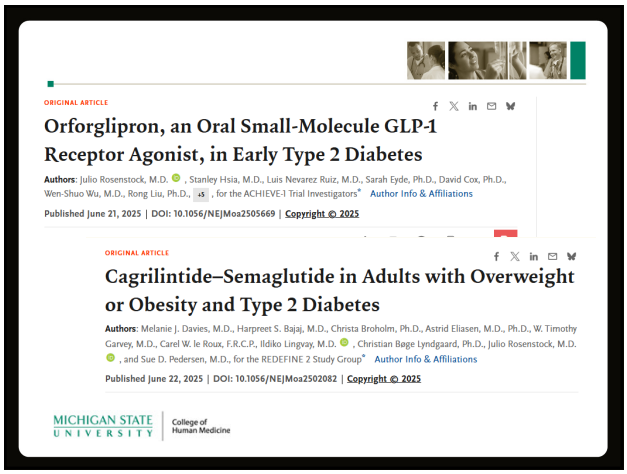

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

Authors: Julio Rosenstock, M.D., Stanley Hsia, M.D., Luis Nevarez Ruiz, M.D., Sarah Eyde, Ph.D., David Cox, Ph.D., Wen-Shuo Wu, M.D., Rong Liu, Ph.D., +5, for the ACHIEVE-1 Trial Investigators* Author Info & Affiliations

Published June 21, 2025 | DOI: 10.1056/NEJMoa2505669 | Copyright © 2025

ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

Authors: Melanie J. Davies, M.D., Harpreet S. Bajaj, M.D., Christa Broholm, Ph.D., Astrid Eliasen, M.D., Ph.D., W. Timothy Garvey, M.D., Carel W. le Roux, F.R.C.P., Ildiko Lingvay, M.D., Christian Bøge Lyndgaard, Ph.D., Julio Rosenstock, M.D., and Sue D. Pedersen, M.D., for the REDEFINE 2 Study Group* Author Info & Affiliations

Published June 22, 2025 | DOI: 10.1056/NEJMoa2502082 | Copyright © 2025

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Conclusion

- GLP-1 agonists (& SGLT2 inhibitors) have taken over center stage in the ADA standards of care (for good reason) but the landscape on these classes of medications is changing rapidly

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