Off-label use of adjunctive therapies with HCL

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Is this really off-label?

2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2026

A diagnosis of type 1 diabetes does not preclude also having features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities), and until more precise subsets are used in clinical practice, it may be appropriate to categorize such an individual as having features of both type 1 and type 2 diabetes to facilitate access to glucose monitoring systems and appropriate treatment (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] or sodium–glucose cotransporter 2 [SGLT2] inhibitor therapies for potential weight and other cardiometabolic benefits).

Disclosures

Research Grants (Indiana University School of Medicine): Alexion, NovoNordisk, Dexcom, Cystic Fibrosis Research Foundation, Lilly, Enable Bioscience, Medtronic, Zucara Therapeutics, DEKA research, Breakthrough T1D, and NIH

Consulting, Speaking or Ad Board: Dexcom, Insulet, Tandem Diabetes Care, Ascensia Diabetes Care, Embecta, Lilly, Sanofi, NovoNordisk, Sequel Med Tech, Biomea Fusion, Roche, and T1D Scout.

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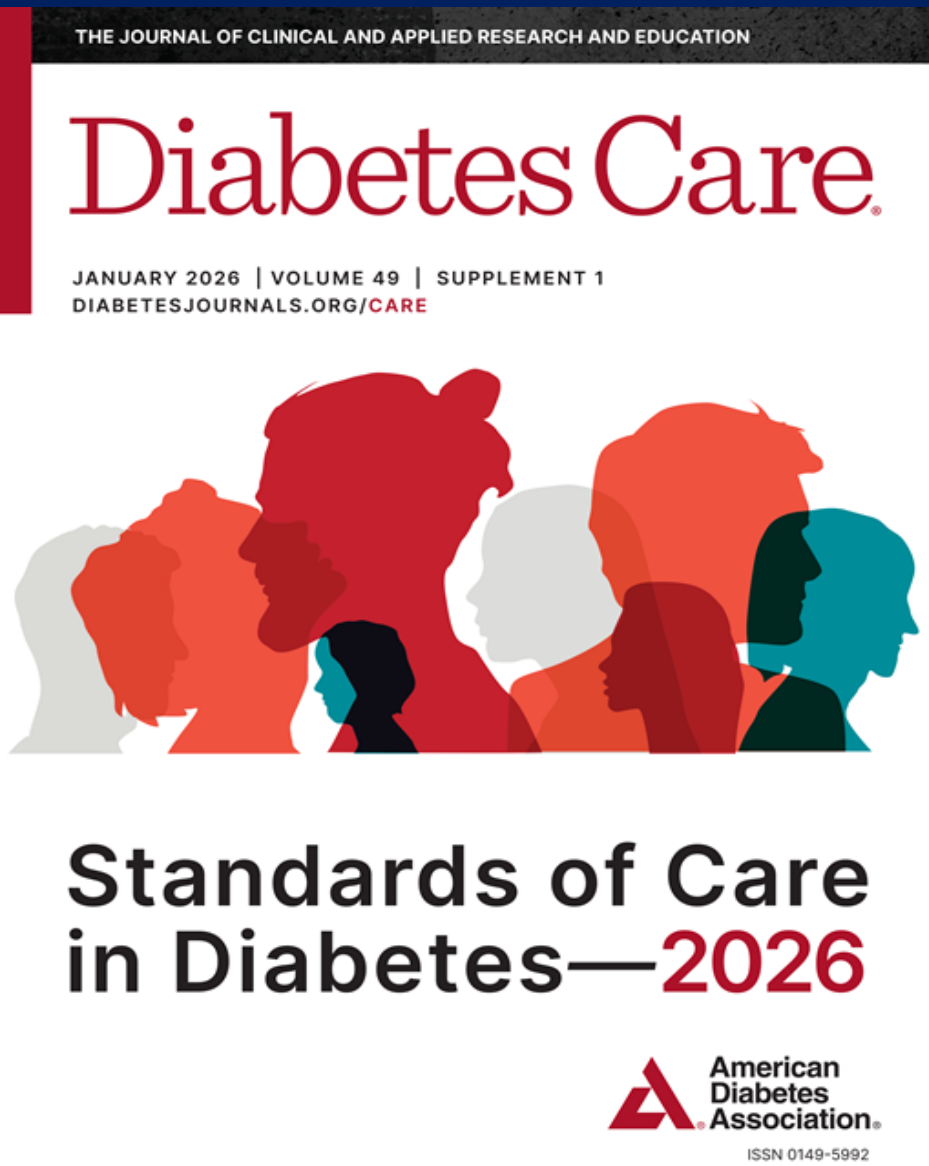
1. Why do we need adjunctive therapies in T1D ?

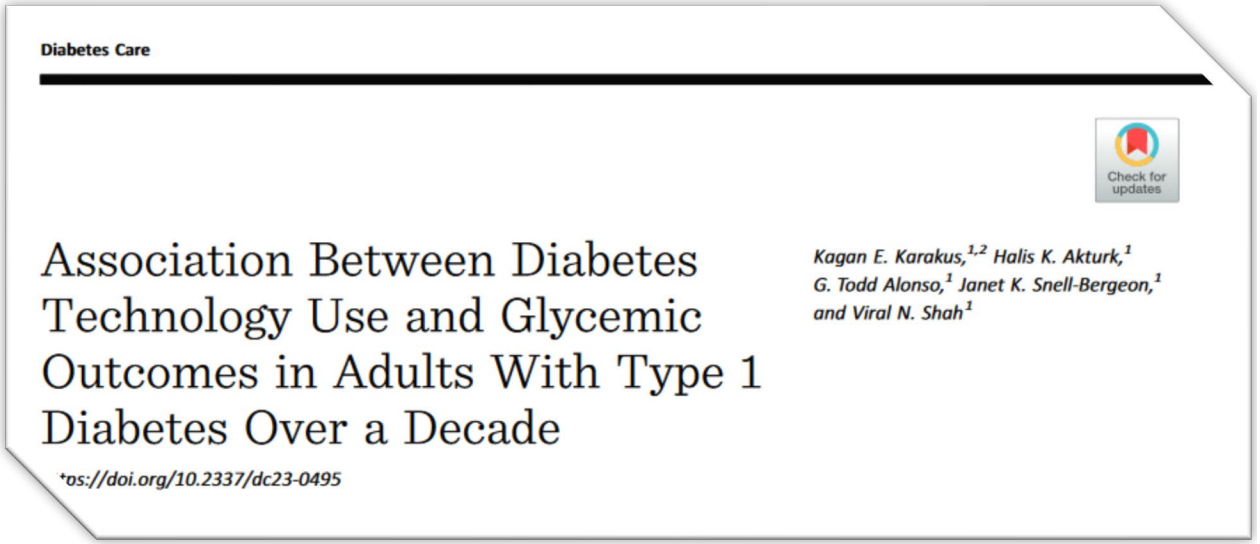
AID is standards of care in T1D

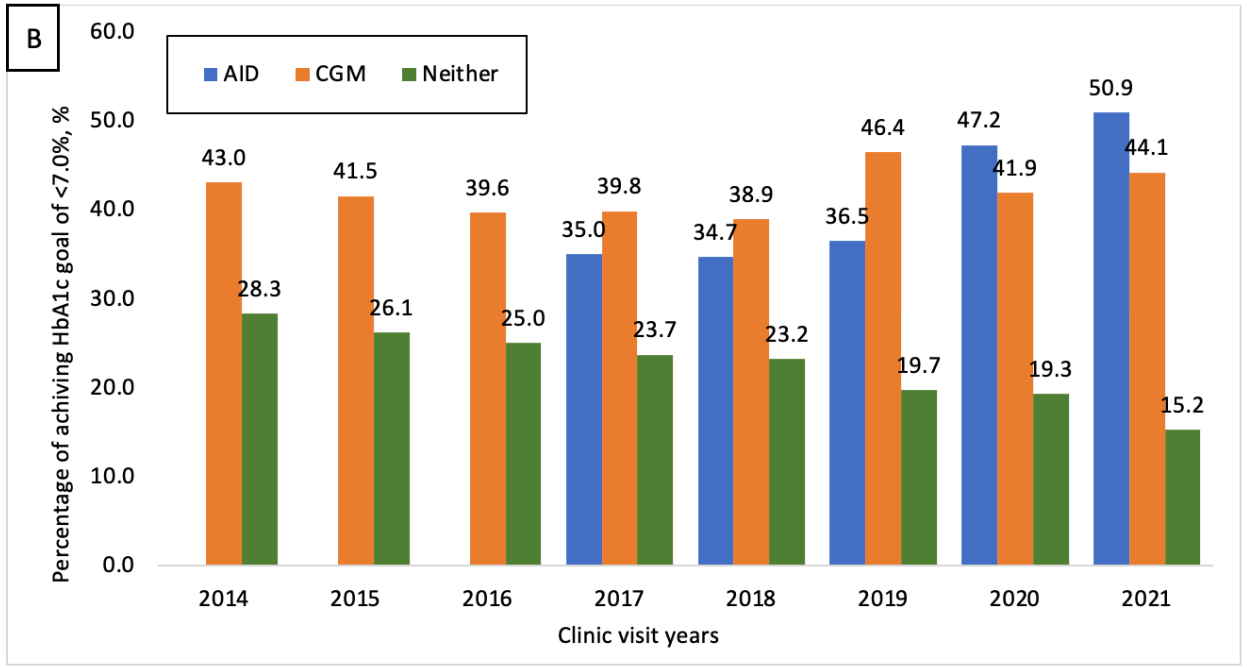


7.25a AID systems are the preferred insulin delivery method over MDI, CSII, and sensor-augmented pumps in people with type 1 diabetes, **A** adults with type 2 diabetes, **A**

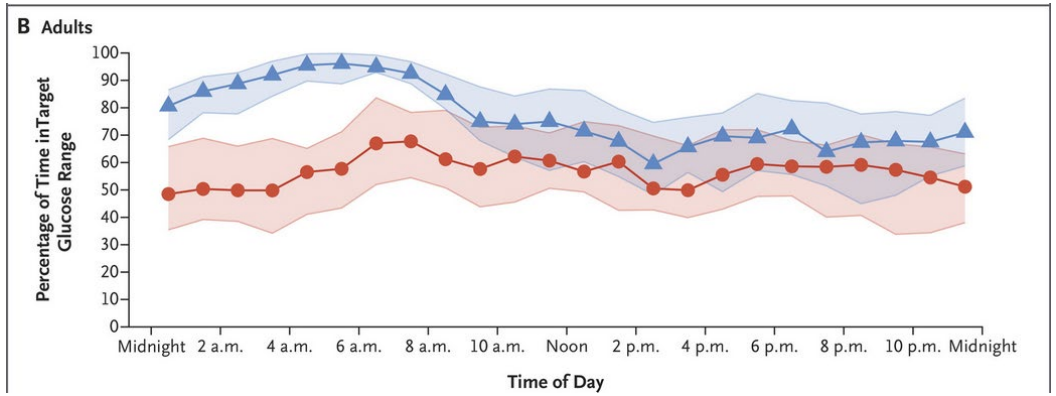
AID alone is not sufficient

Despite AID use, only 50% of adults are able to achieve A1c <7%

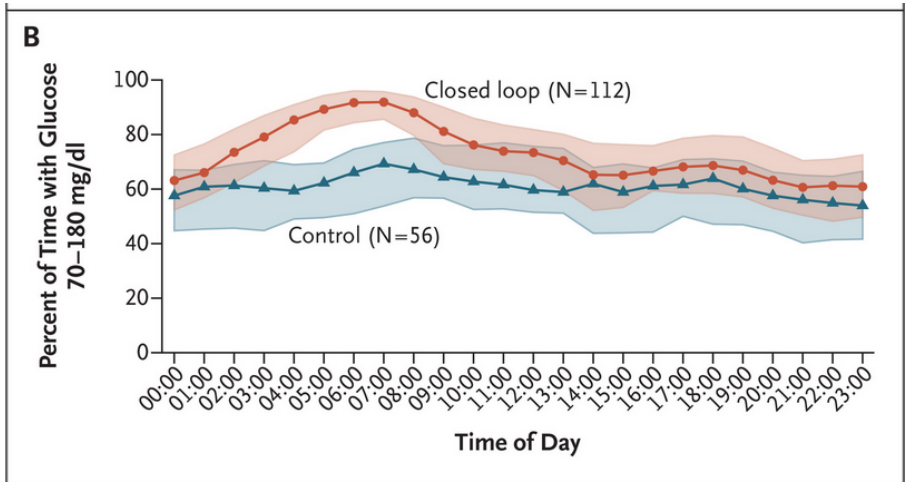




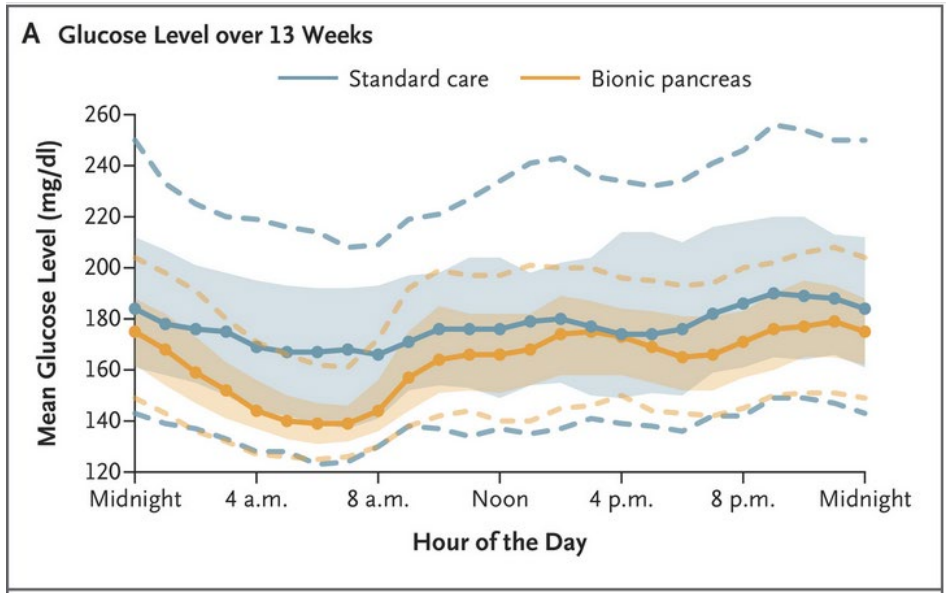
1. Daytime control with AID is not optimal



Open-source Automated Insulin Delivery in T1D. NEJM 2022;387:869-881



Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. NEJM 2019;381:1707-1717



Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. N Engl J Med 2022; 387:1161-1172

2. Prevalence of Obesity is increasing

▸ Ann Intern Med. Author manuscript; available in PMC: 2023 Sep 1.

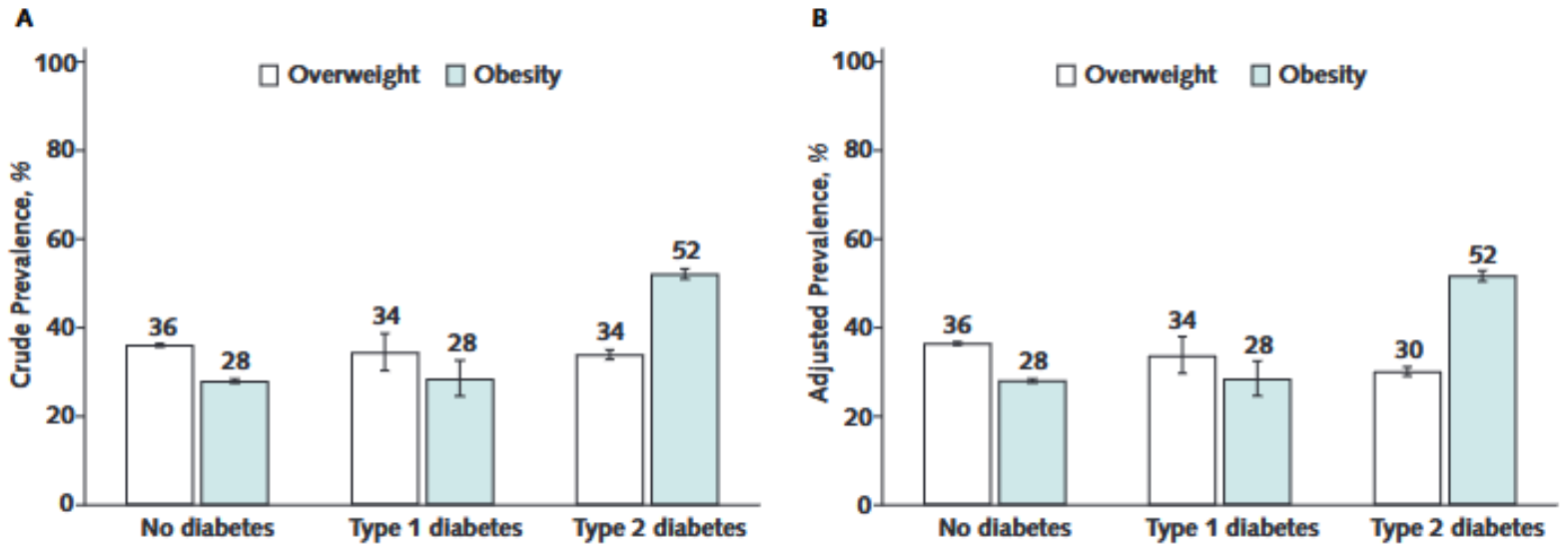
Published in final edited form as: Ann Intern Med. 2023 Feb 14;176(3):427–429. doi: 10.7326/M22-3078

Prevalence and Management of Obesity in U.S. Adults With Type 1 Diabetes

Michael Fang [1], Yein Jeon [2], Justin B Echouffo-Tcheugui [3], Elizabeth Selvin [4]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC10033389 NIHMSID: NIHMS1879393 PMID: 36780652



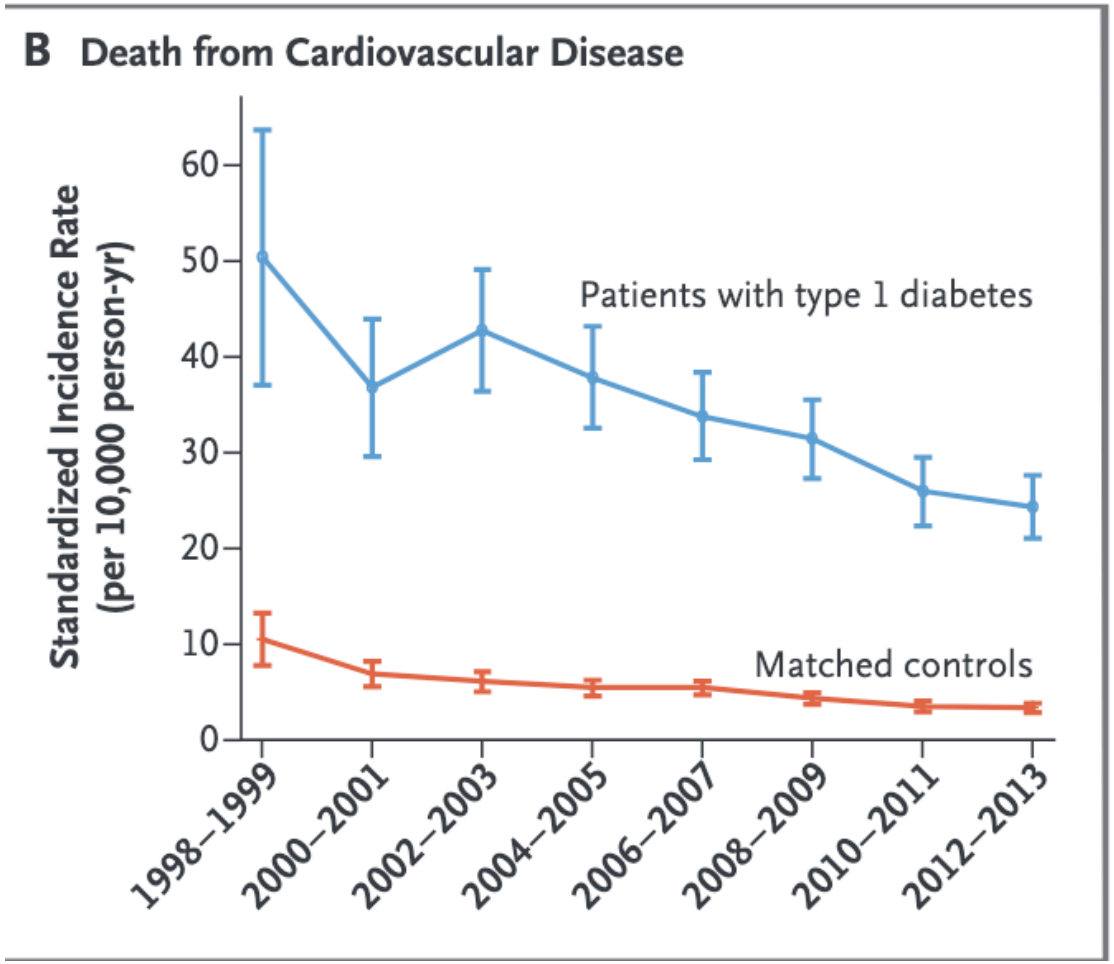
CVD Mortality is higher in T1D

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2017 VOL. 376 NO. 15

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D., Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

2. Therapeutic options besides insulin

Adjunct Therapies in T1D

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 15, Number 11, 2013

DOI: 10.1089/dia.2013.0281

DTT
Diabetes Technology & Therapeutics

EDITORIAL

Use of Non-Insulin Therapies for Type 1 Diabetes

Satish K. Garg, MD,[1–3] Aaron W. Michels, MD,[1,2] and Viral N. Shah, MD[1]

Metformin- Neutral

DPP4i- Neutral

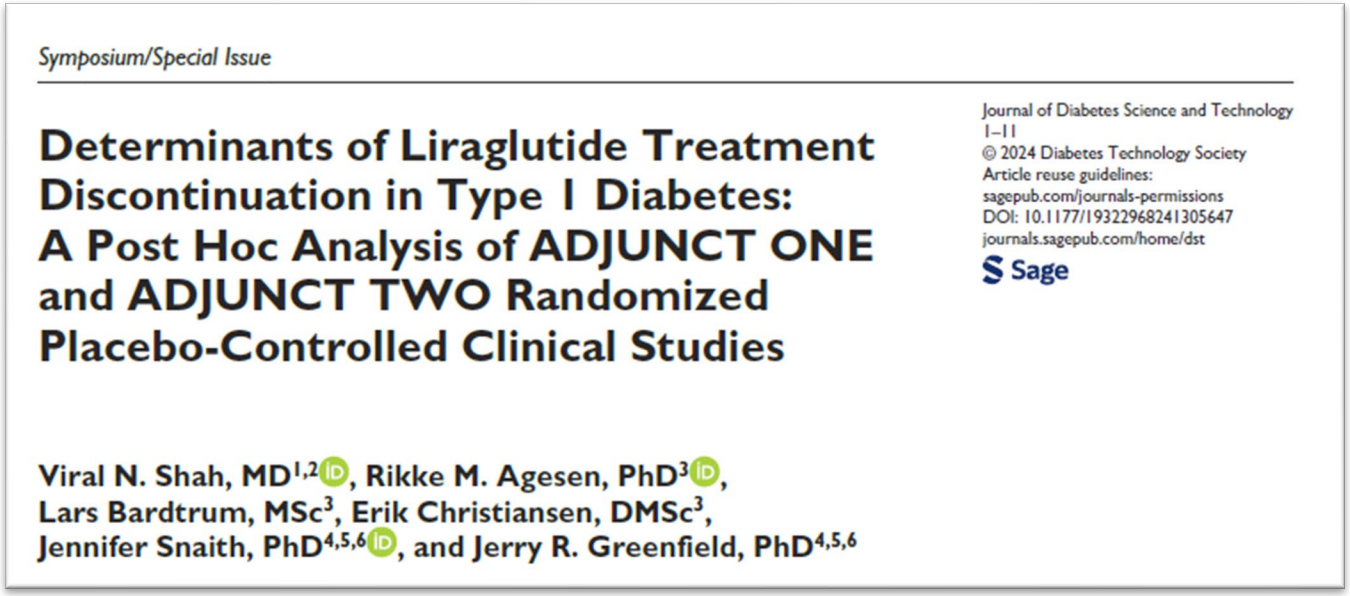
SGLT2- Increased risk for DKA

3. Evidence with GLP-1RA in T1D

Daily GLP-1RA in T1D

Drug (Liraglutide)		Benefits	Risks
ADJUNCT ONE n=1398 52 Wk Randomization: 3:1, Lira 0.6, 1.2 and 1.8 vs placebo. Treat-to-target **Ref:** Diabetes Care 2016 Oct;39(10):1702-10	No dose reduction permitted. TDD was reduce to 25% at randomization and 10% at dose escalation every 2 weeks. BMI ≥20. Mean A1c of 8.1%. Pump use ~30%	A1c: -0.2% for 1.8, -0.15% for 1.2 and -0.09% for 0.6 mg Weight: -4.9 kg for 1.8, -3.6 for 1.2 and -2.2 for 0.6. (baseline weight ~86 kg)	The rate of symptomatic hypoglycemia increased. ERR ~1.3 Hyperglycemia with ketosis increased for liraglutide 1.8 mg only (event rate ratio 2.22 [95% CI 1.13; 4.34]).
ADJUNCT TWO n=835 26 Wk Randomization: 3:1	Dose increment every 2 week. Insulin titration based on SMBG. Pump ~25%	A1c: -0.33% for 1.8, -0.22% for 1.2 and -0.23% for 0.6 Weight: -5.1, -4.0, -2.5 Kg	The rate of symptomatic hypoglycemia increased. ERR 1.33 Hyperglycemia ketosis rate was 0.5 vs 0.1 events.

What did we learn from ADJUNCT studies?



Symposium/Special Issue

Determinants of Liraglutide Treatment Discontinuation in Type 1 Diabetes: A Post Hoc Analysis of ADJUNCT ONE and ADJUNCT TWO Randomized Placebo-Controlled Clinical Studies

Viral N. Shah, MD[1,2], Rikke M. Agesen, PhD[3], Lars Bardtrum, MSc[3], Erik Christiansen, DMSc[3], Jennifer Snaith, PhD[4,5,6], and Jerry R. Greenfield, PhD[4,5,6]

Journal of Diabetes Science and Technology
1–11

DOI: 10.1177/19322968241305647
journals.sagepub.com/home/dst
Sage

- ✓ CGM is essential for insulin titration
- ✓ AID is even better
- ✓ GLP-1 dose adjustment should be flexible
- ✓ Insulin dose titration should be based on A1c and CGM data
- ✓ Frequent insulin dose adjustment may be necessary

- ✓ Lower BMI (<27), longer duration of diabetes (>25), lower daily insulin dose, and undetectable c-peptide were associated with higher AE related discontinuation.

- ✓ Above factors for discontinuation remained same regardless of dose of Liraglutide.

NEJM Evidence

Published June 23, 2025

DOI: 10.1056/EVIDoa2500173

ORIGINAL ARTICLE

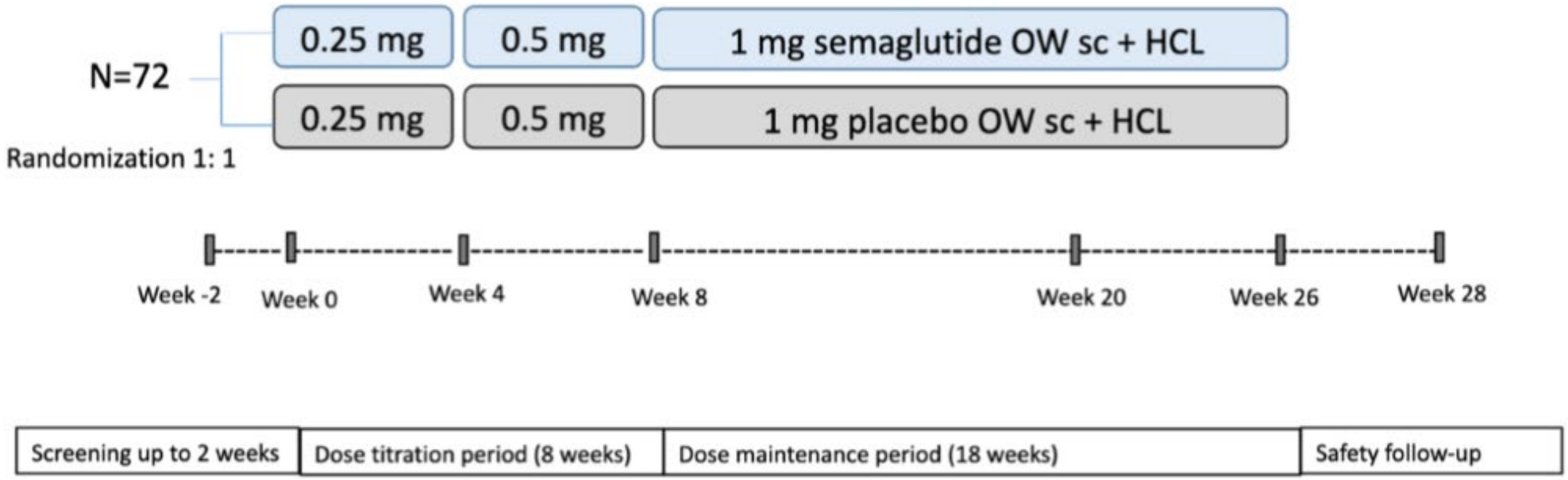
Semaglutide in Adults with Type 1 Diabetes and Obesity

Viral N. Shah, M.D.,[1] Halis K. Akturk, M.D.,[2] Davida Kruger, N.P.,[3] Andrew Ahmann, M.D.,[4] Anuj Bhargava, M.D.,[5] Giorgos Bakoyannis, Ph.D.,[6] Laura Pyle, Ph.D.,[7] and Janet K. Snell-Bergeon, Ph.D.[2]

Study Design

Key Inclusion

- Adults with T1D > 1 year
- AID use > 3 months
- HbA1c 7-10%
- BMI ≥ 30 kg/m^2



Insulin titration guidance

PRACTICAL POINTERS | SEPTEMBER 20 2024

Insulin Titration Recommendations When Using Glucagon-Like Peptide 1 Receptor Agonist Therapy in Adults With Type 1 Diabetes

Zeb I. Saeed; Halis K. Akturk; Grazia Aleppo; Davida Kruger; Carol J. Levy; Julia K. Mader; Jennifer L. Sherr; Viral N. Shah

Check for updates

Z.I.S. and V.N.S. contributed equally to this work.

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Clin Diabetes cd240067

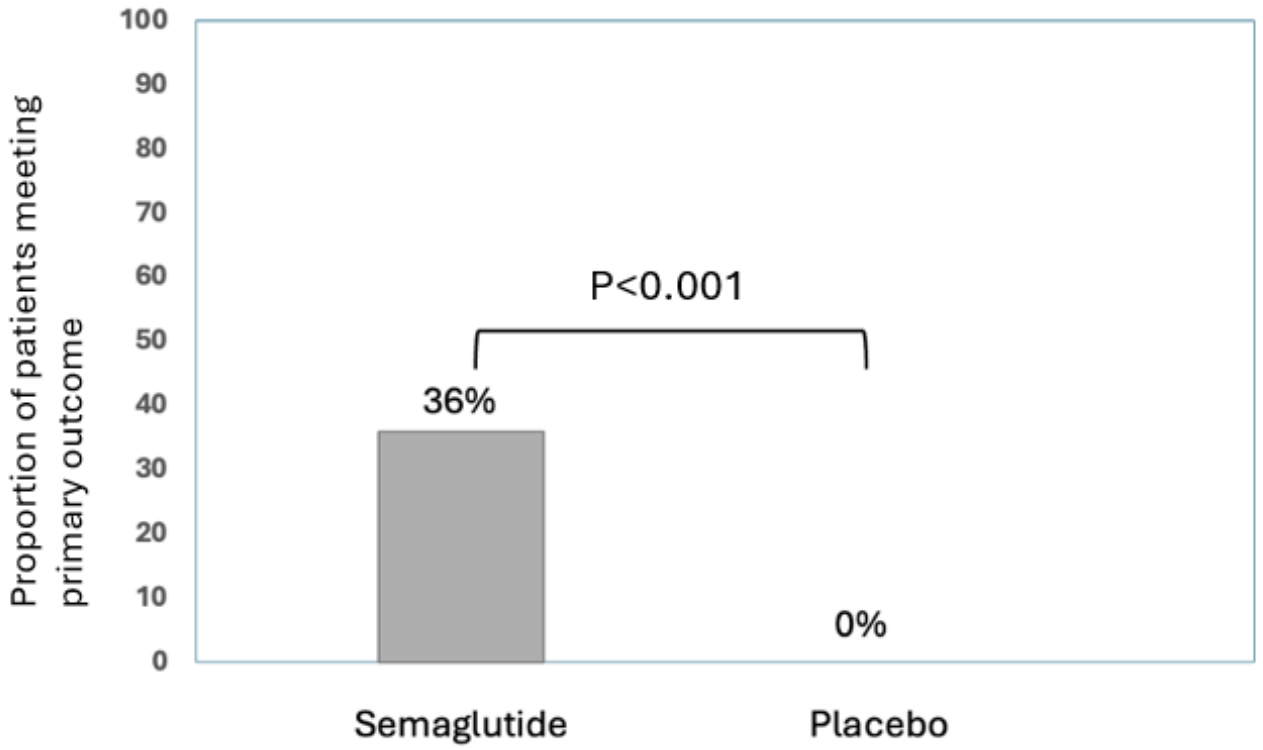
https://doi.org/10.2337/cd24-0067 **Article history**

Baseline Characteristics

	Semaglutide (n=36)	Placebo (n=36)
Age, mean (Years)	41.4 ±11.6	38.9± 13.1
Female, n (%)	22 (61.1)	20 (55.6)
Diabetes Duration, years		
Mean/SD	23.4±11.2	21.9±11.6
Range (years)	(4-51)	(4-51)
Weight (Kg) g	99.5± 14.6	104.5 ± 16.3
Body mass index (kg/m2)	34.7± 3.9	36.0±5.2
Obesity Class 1 (BMI 30-34.9)	22 (61.1%)	21 (58.3%)
Obesity Class 2 (BMI 35-39.9)	10 (27.8%)	8 (22.2%)
Obesity Class 3 (BMI 40+)	4 (11.1%)	7 (19.4%)
Glycated hemoglobin level (%)	7.8± 0.6	7.7±0.6
Type of AID, N (%)		
Medtronic	6 (16.7%)	5 (13.9%)
Tandem	25 (69.4%)	23 (63.9%)
Omnipod 5	5 (13.9%)	8 (22.2%)
Total daily insulin dose		
Units/day	73.4±29.9	72.4±23.6
Units/kg/day	0.7±0.2	0.7±0.3

Most participants were White and had private insurance.

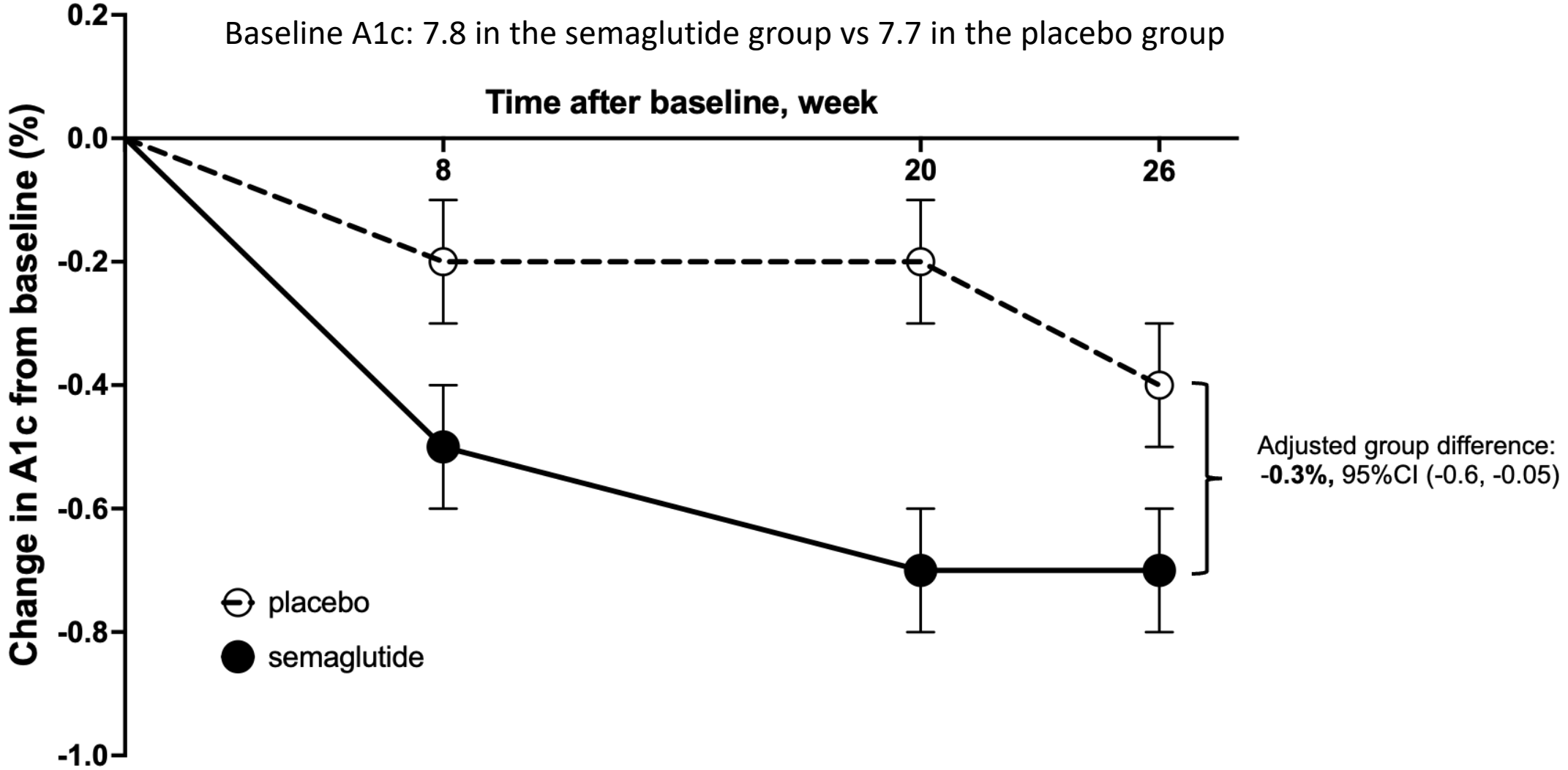
Primary Outcome



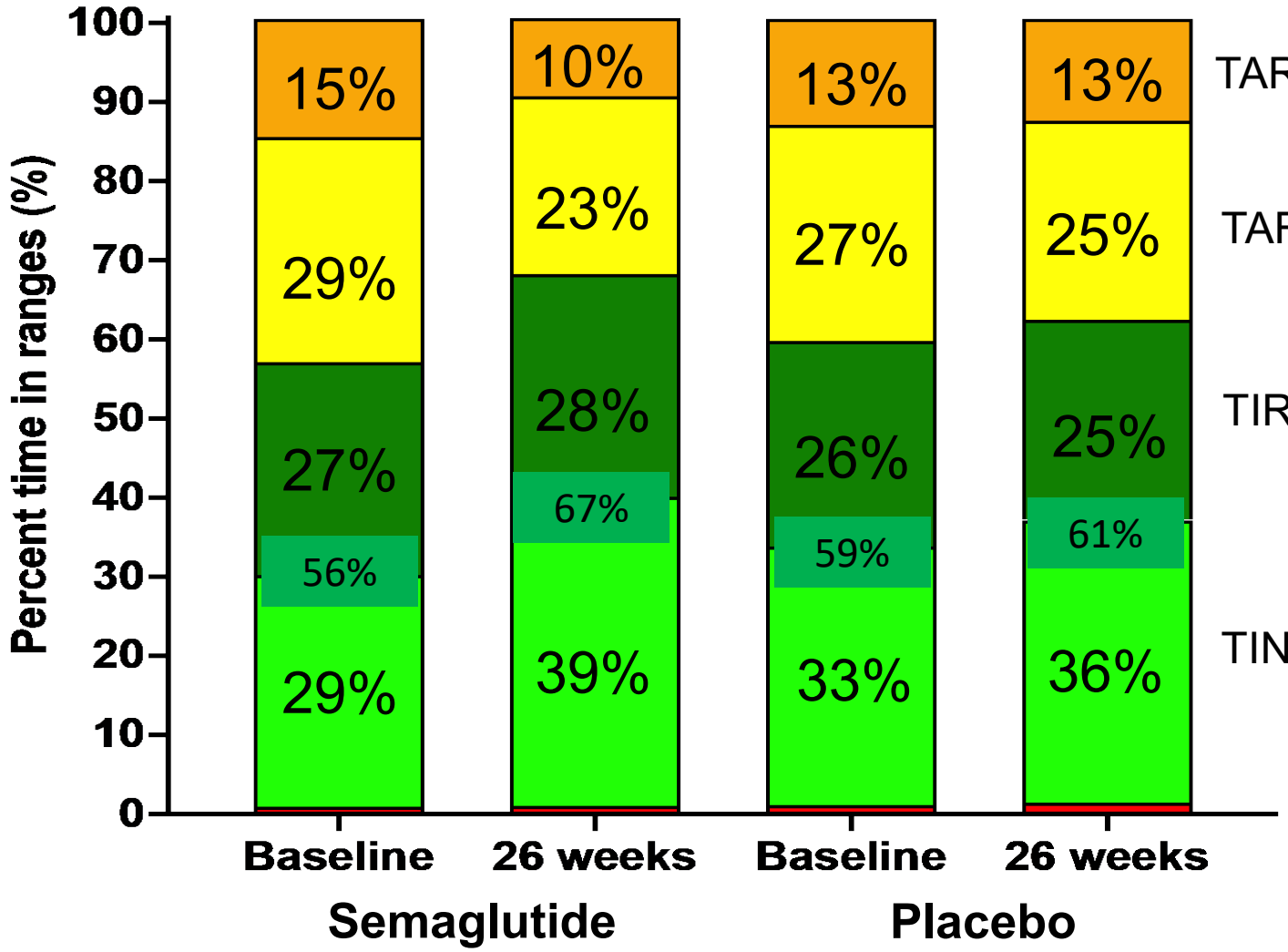
Composite primary outcome was patients meeting all three criteria: a) percentage of time spent in sensor glucose between 70-180 mg/dL of more than 70%, b) percentage time spent in sensor glucose below 70 mg/dL of less than 4% and c) reduction in bodyweight by 5%.

Key Secondary Outcome: HbA1c

Baseline A1c: 7.8 in the semaglutide group vs 7.7 in the placebo group



Key Secondary outcome: CGM metrics



TAR 2: -4.6 (-7.7, -1.5)

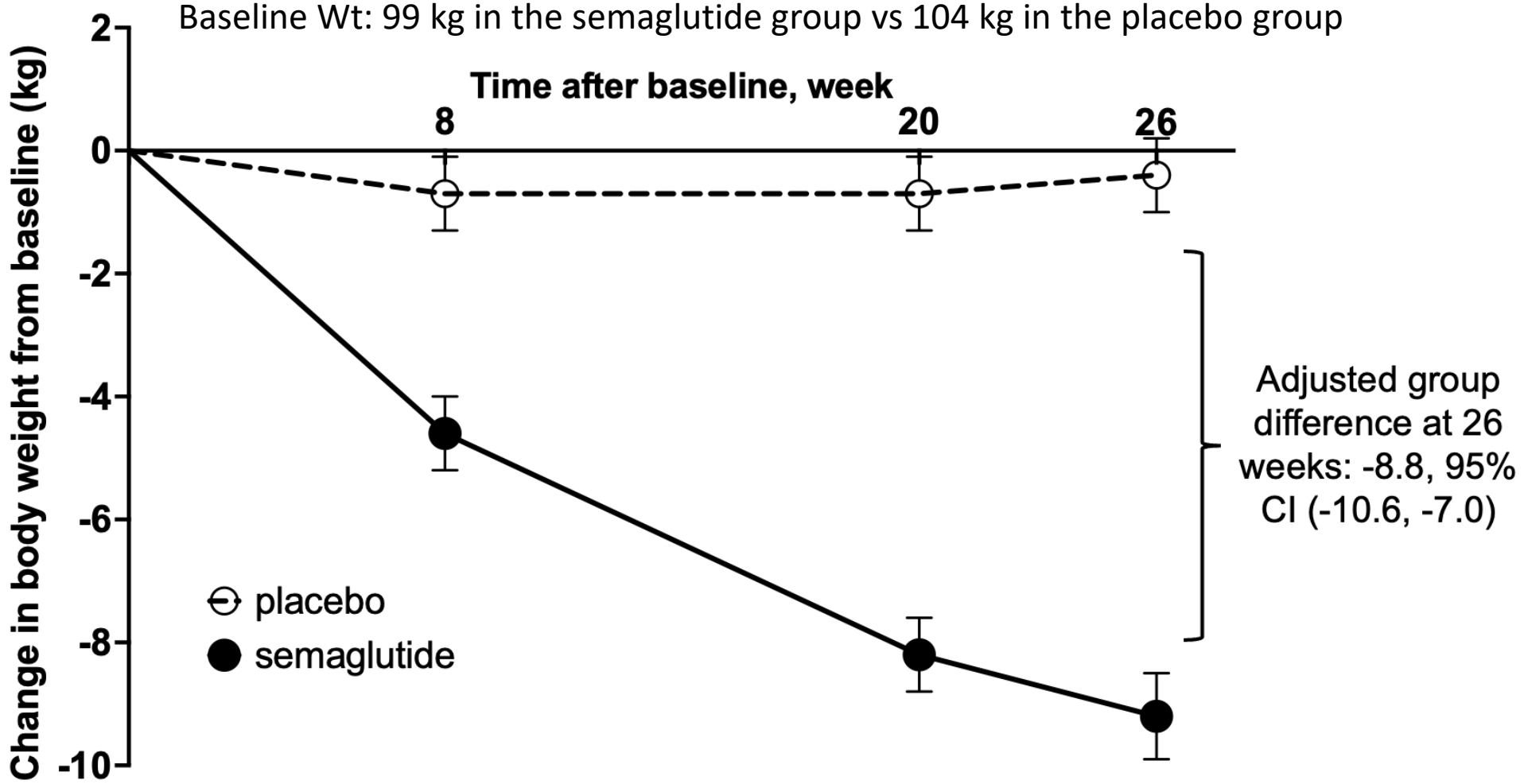
TAR 1: -8.4 (-13.3, -3.4)

TIR: 8.8% (3.9, 13.7)

TING: 6.9%(2.1, 11.8)

Key Secondary Outcome: Weight

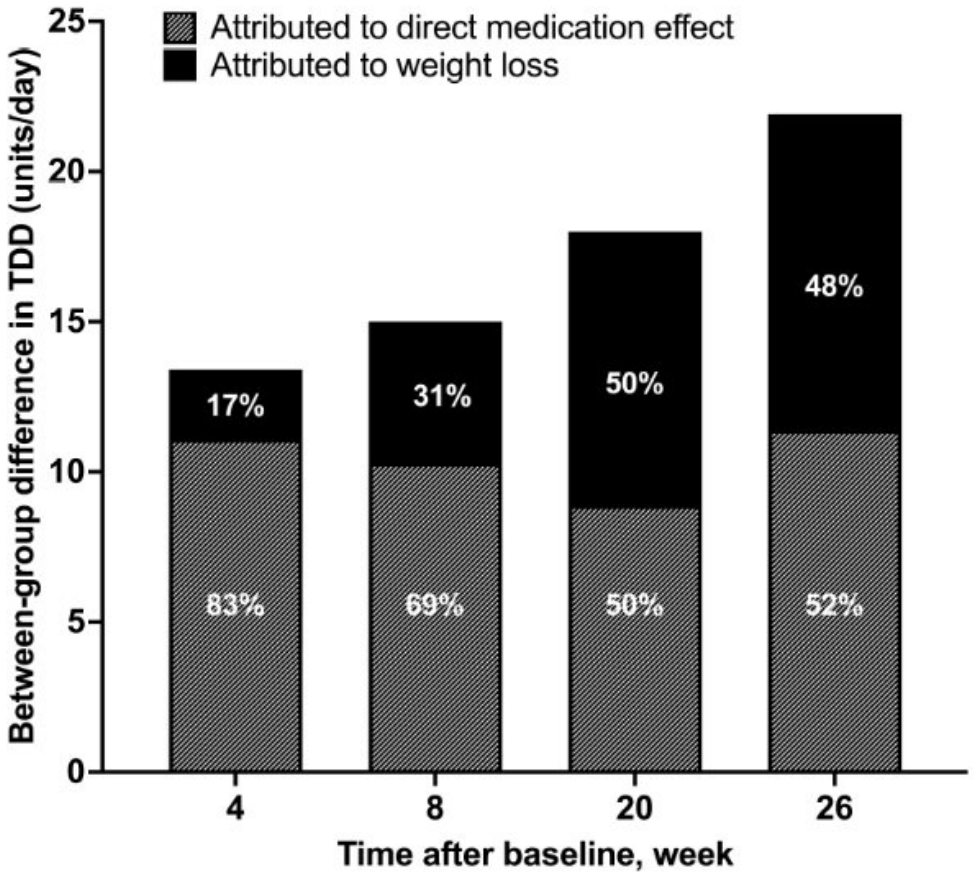
Baseline Wt: 99 kg in the semaglutide group vs 104 kg in the placebo group



Safety Outcomes

	Semaglutide (n=36)		Placebo (n=36)	
	No of events	No of patients (%)	No of events	No of patients (%)
Any SAE	1	1 (2.8%)	0	0
Any AE	85	26 (72.2%)	23	17 (47.2%)
AE reported by >5% of patients				
Gastrointestinal events	57	19 (52.8%)	13	9 (25%)
Upper respiratory infection	4	3 (8.3%)	1	1 (2.8%)
Coronavirus disease (COVID-19)	4	4 (11.1%)	1	1 (2.8%)
Adverse event of special Interest				
Severe hypoglycemia	2	2 (5.5%)	2	2 (5.5%)
Diabetic ketoacidosis (DKA)	0	0	0	0

Effects of Semaglutide on Insulin dose in T1D



- ~25% reduction in TDD from baseline
  - Bolus >basal
  - ?AID effect
- Insulin dose reduction starts within first week with 0.25 mg dose
- Insulin reduction is not explained by weight change in first 4 weeks
- Reduction in carbs is ~30 grams per day. Reduction in carbs does not fully explain reduction in TDD
- GLP-1RA may have secretory effects on pancreatic beta cells in T1D despite 20+ years of diabetes. Long-term effects of such action is unknown.

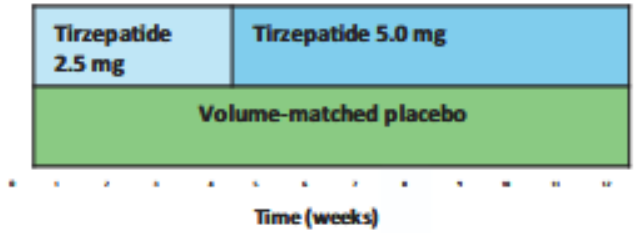
Jennifer R. Snaith, Ruth Frampton, Dorit Samocha-Bonet, and Jerry R. Greenfield

Diabetes Care 2026;49(1):1–10 | https://doi.org/10.2337/dc25-2379

Tirzepatide in Adults With Type 1 Diabetes: A Phase 2 Randomized Placebo-Controlled Clinical Trial

Background

- Overweight and obesity are prevalent in type 1 diabetes and contribute to cardiovascular risk.
- Tirzepatide has not been studied in type 1 diabetes.



Study design (*n* = 24)

- TIRTLE1 trial: phase 2, 12-week, double-blinded, placebo-controlled trial
- Participants: adults with type 1 diabetes and BMI greater than 30 kg/m^2.
- Randomized 1:1 to once-weekly subcutaneous tirzepatide (2.5 mg for 4 weeks, 5.0 mg for 8 weeks) or placebo injection.
- Primary end point: change in body weight at 12 weeks.

Results

After 12 weeks, adjunctive tirzepatide vs. placebo:

Weight ↓ 8.7 kg (8.8% weight loss)

HbA_{1c} ↓ 0.4%
Total insulin use ↓ 35.1%
Bolus insulin ↓ 49%
Basal insulin ↓ 25%

No significant adverse events

Conclusion: Among adults with type 1 diabetes and obesity, tirzepatide was superior to placebo for weight loss over 12 weeks.

TIRTLE1, Tirzepatide in Type 1 Diabetes: Cardiometabolic Effects.

Questions and future research

- What is the long-term effects of GLP-1RA in T1D?
- Can we use GLP-1RA in lower dose for glycemic management in those with BMI <25?
- What is ideal de-escalation strategy for glycemia and weight loss maintenance?
- Effects of GLP-1RA on CVD/Renal/Hepatic outcomes

ATTD
Advanced Technologies & Treatments for Diabetes

11-14 MARCH 2026
BARCELONA, SPAIN

SCIENTIFIC PARALLEL SESSION 19: ADJUNCT THERAPIES WITH AUTOMATED INSULIN DELIVERY

Session Type PARALLEL SESSION
Date Fri, 13.03.2026
Session Time 17:15 - 18:45
Room Hall 116

ADJUST T1D STUDY – DESIGN AND GLYCEMIC OUTCOME

Lecture Time 17:15 - 17:35
Author(s) Viral N. Shah (United States of America)

ADJUST T1D STUDY - CARDIOVASCULAR OUTCOMES

Lecture Time 17:35 - 17:55
Author(s) Janet K. Snell-Bergeon (United States of America)

Ongoing studies

- **Type 1 Diabetes Impacts of Semaglutide on Cardiovascular Outcomes (T1-DISCO):** NCT05819138
  - Randomized trial (18-49 years) in young individuals with BMI 20-45. outcomes: change in Aortic PWV and cPWV and insulin sensitivity
- **Trial of Semaglutide for Diabetic Kidney Disease in Type 1 Diabetes (RT1D):** NCT05822609
  - Semaglutide vs placebo for renal outcomes
- **Obesity Complicating Type 1 Diabetes: GLP-1 Analogue Anti-obesity Treatment:** ID NCT06411210
  - Randomized trial: change in body composition, MRI abdominal fat, insulin sensitivity-clamp

- **SURPASS T1D 1 and 2** (Eli- Lilly), Phase 3 FDA approval studies

Summary

- AID is standards of care for people with T1D. However, nearly 50% of people may not be able to achieve optimal glycemic goal
- Overweight and obesity is increasing in T1D
- Insulin therapy alone does not address obesity and CVD risk management
- GLP-1RA is promising adjunctive therapy for adults with T1D

Breakthrough T1D™
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Thank you!