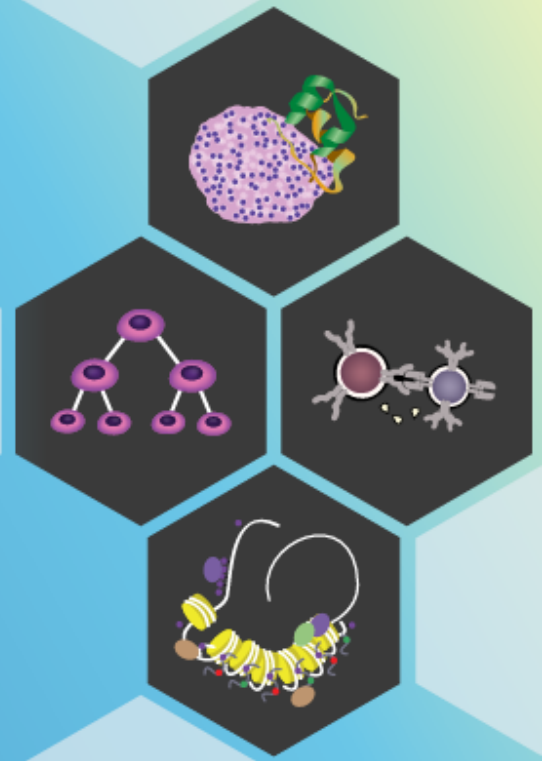
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Treatment of Type 2 Diabetes in Youth: Need for Aggressive Use of Glucose Lowering Medications



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Disclosures

- Grant/Research Support from Rhythm Pharmaceuticals.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Pioglitazone, Semaglutide, Tirzepatide, and Canagliflozin will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discuss the culture of adult diabetes that is often present in youth with type 2 diabetes and the barrier to care that this can create and the extreme psychosocial stressors that youth-onset type 2 diabetes is associated with and how this affects our approach to treatment.*
- *Discuss the notion that many patients have that type 2 diabetes is their fault, often due to messaging from the medical community.*

PART 1: Why non-approved?

Medications with FDA-approval for T2D in youth:

- Metformin
- Insulin (only degludac and brand Toujeo approved for T2D in youth)
- SGLT2 inhibitors: empagliflozin, dapagliflozin
- GLP-1 agonists: once-weekly exenatide, liraglutide, dulaglutide

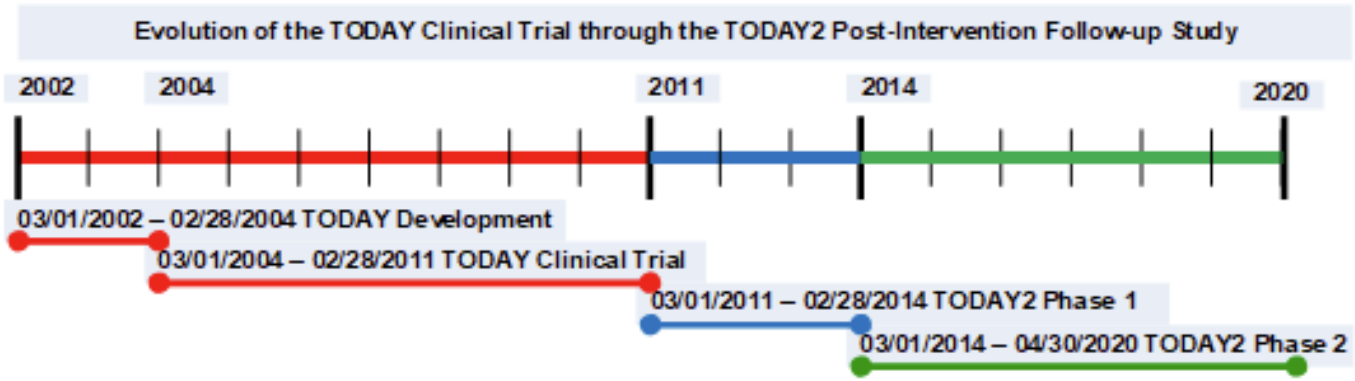
Food for thought…

- AAP published statement: Off-Label Use of Drugs in Children (Frattarelli *et al*, Pediatrics, 2014)
- “Use of drug, whether off or on label, should be based on sound scientific evidence, expert medical judgement or published literature whenever possible”
- Pediatric labeling available on <50% of products used and more likely to rely on expert opinion in less common diseases

Treatment Options for Type 2 Diabetes in Adolescents and Youth

- Clinical trial of:
  1. Metformin alone
  2. Metformin + intensive lifestyle intervention
  3. Metformin + rosiglitazone

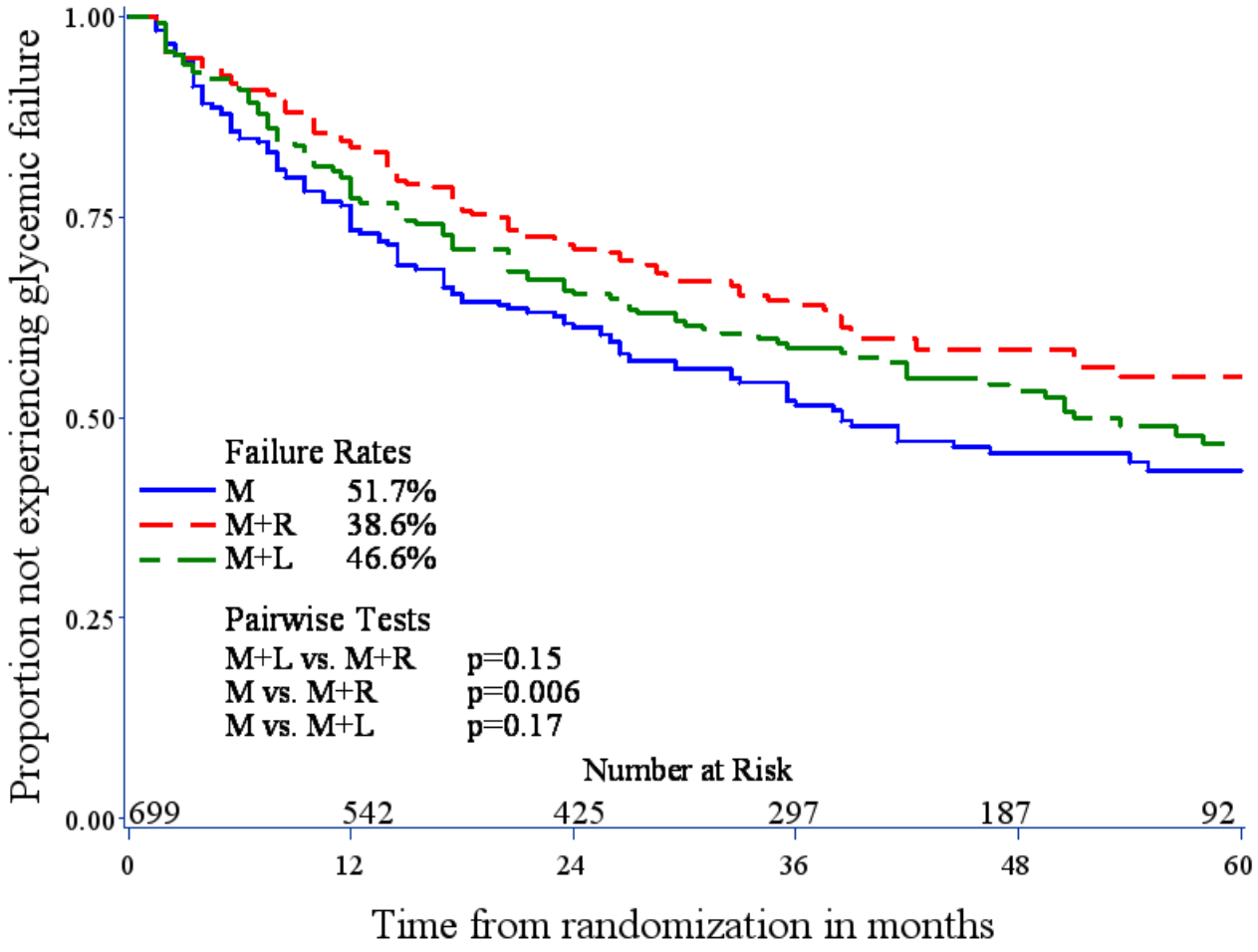
Primary outcome: loss of glycemic control



Run-in phase of TODAY: metformin monotherapy allowed 90% of those who entered to be eligible, even if on insulin therapy at screening (Kelsey, *et al*, Pediatr Diabetes, 2016)

Logo and drawing courtesy of the TODAY study coordinating center

Time-to-event analysis

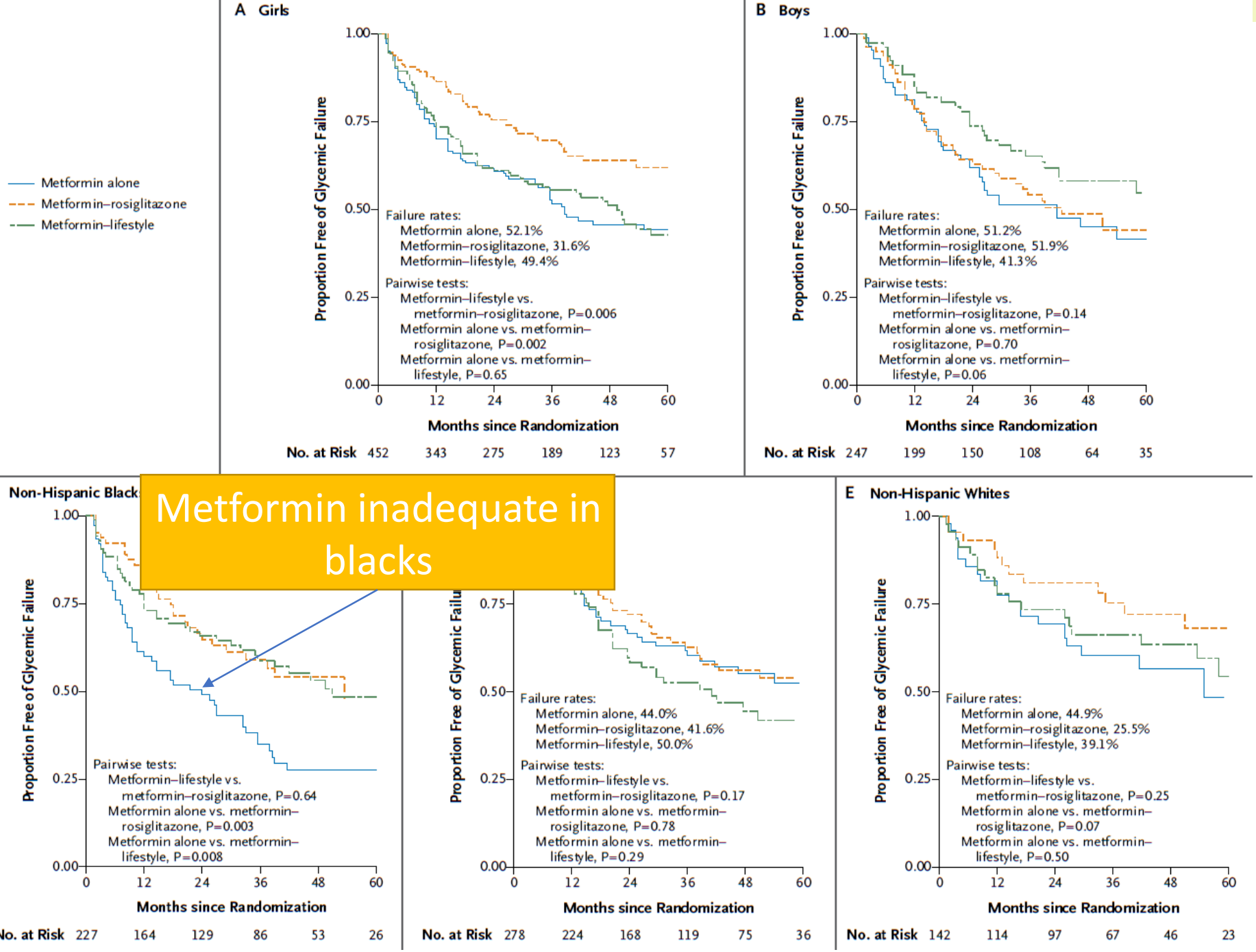


T2D in youth associated with:

- Rapid β-cell failure, early need for insulin in 50% of participants
- Metformin + rosiglitazone associated with lower failure rates

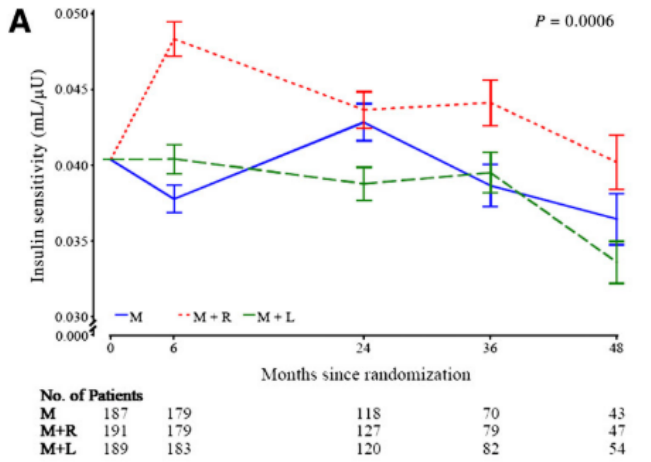
N Engl J Med. 366:2247-56, 2012

Sex and Race/ Ethnicity Effects

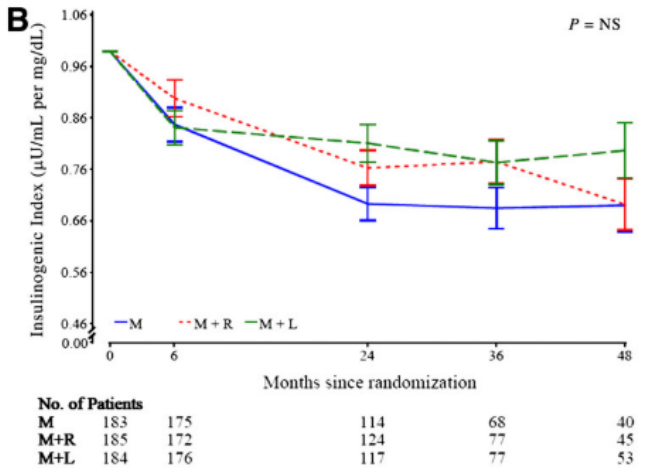


Thiazolidinediones:

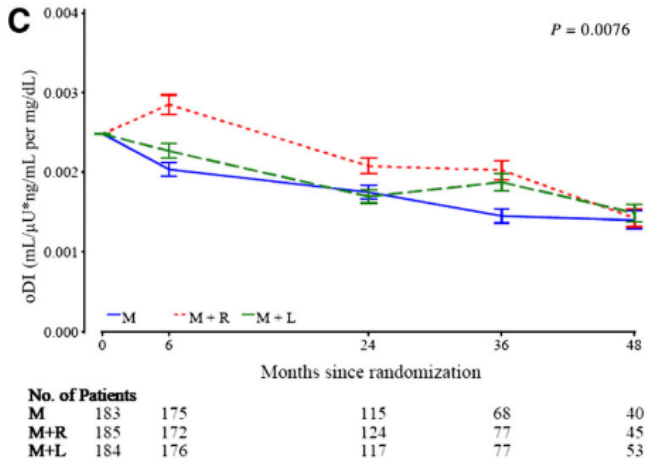
- Not approved in pediatrics
- Rosiglitazone in TODAY associated with:
  - Greater reduction in A1c, fewer with glycemic failure
  - Greater gains in BMI, body fat, no difference in fat distribution
  - Fewer participants needed to stop due to hepatotoxicity (ALT change not reported)
  - No difference in cardiovascular outcomes, including echo outcomes



Insulin sensitivity

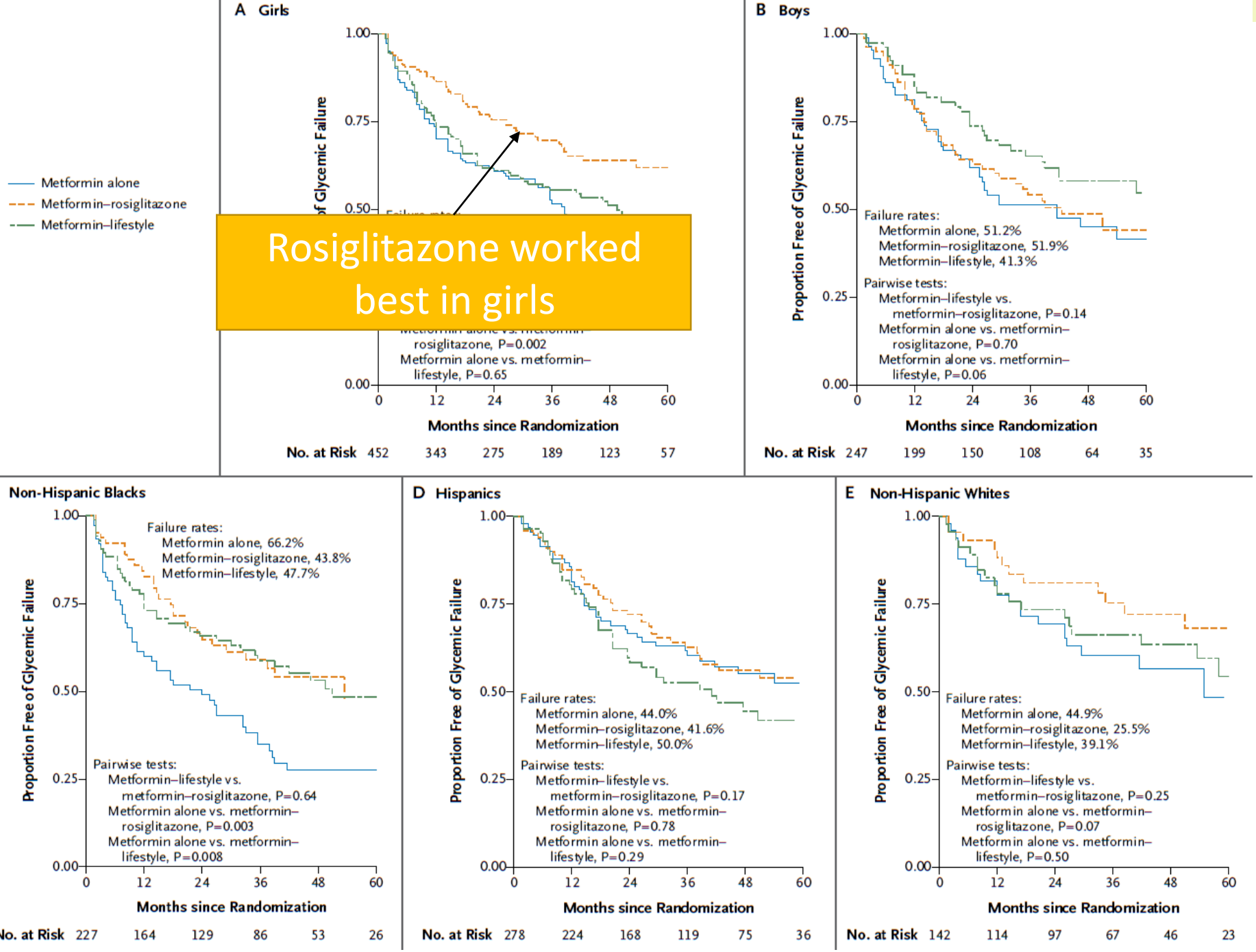


Insulinogenic index



oDI

Sex and Race/ Ethnicity Effects

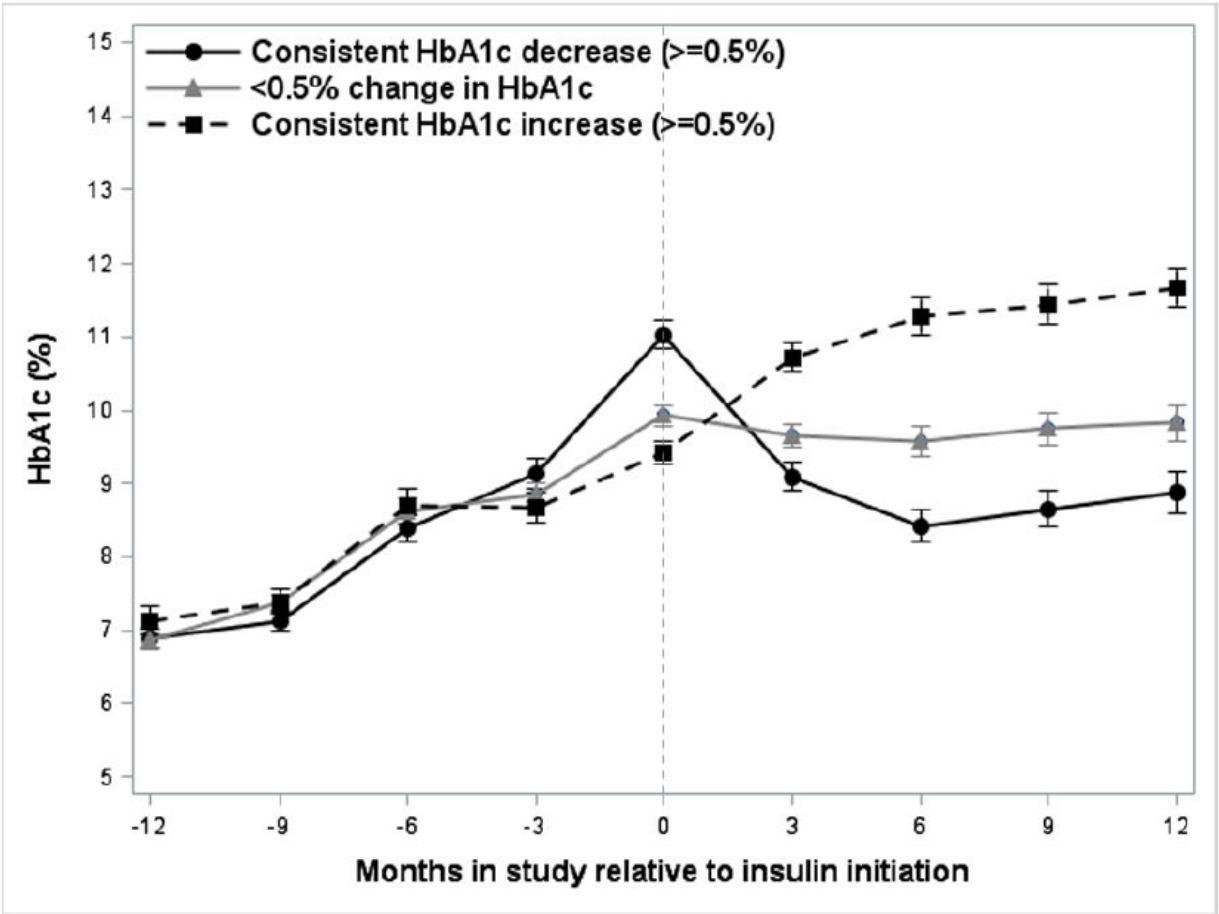


Rosiglitazone worked best in girls

10.1056/NEJMoa1109333 NEJM.ORG

Glycemic Control Post-Insulin Initiation in TODAY

- No difference in mean HbA1c 1 year after glycemic failure:
  - At failure: 9.7 ± 1.7%
  - 1 year later: 9.5 ± 2.0%



20.6%

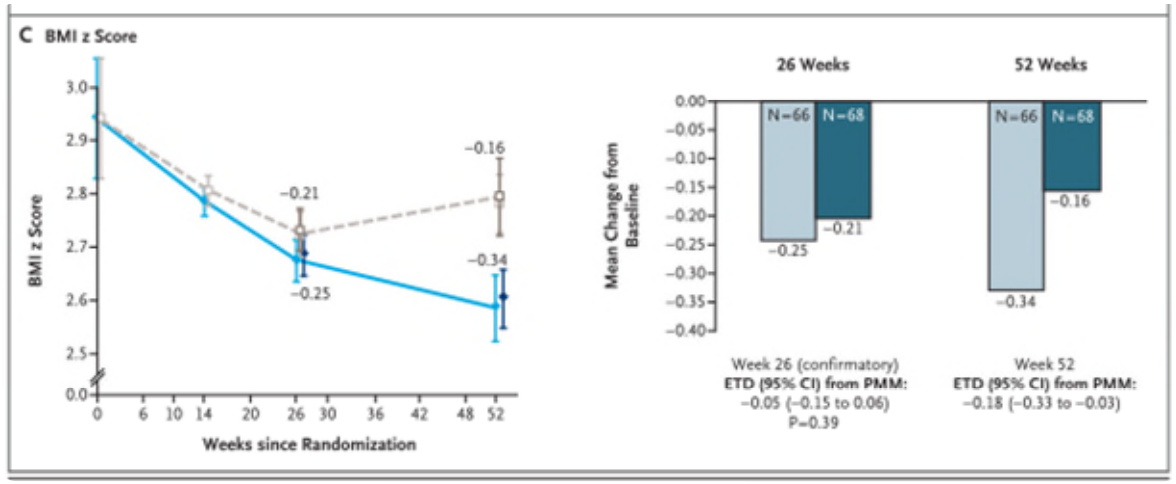
46.2%

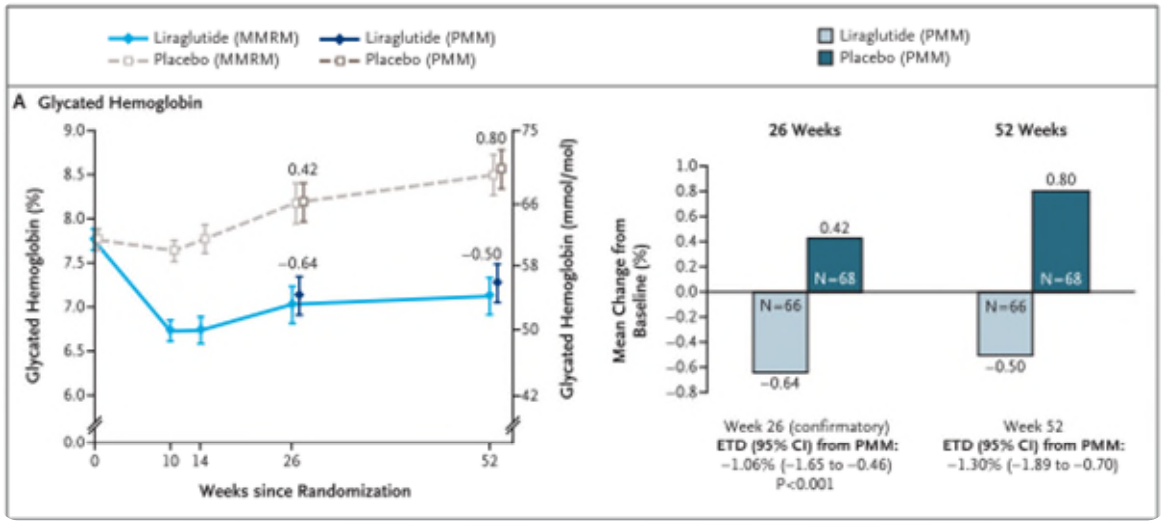
33.2%

Bacha *et al*, Pediatr Diabetes 2019; 20 (7)

GLP-1 Agonists

Liraglutide in youth-onset T2D





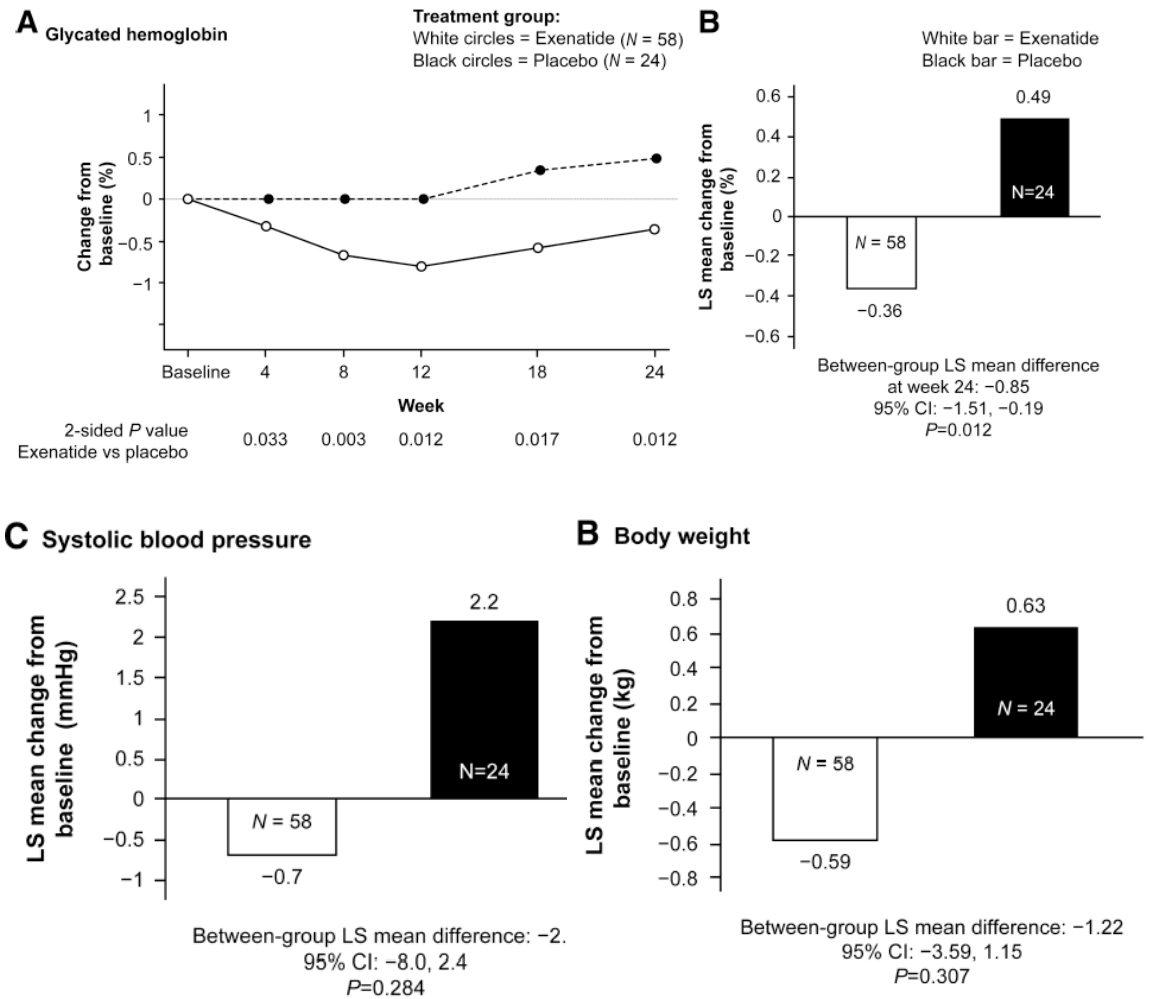
- Dose adjustment to max of 1.8 mg weekly based on efficacy (FBG) and S/Es
- Placebo-subtracted change in HbA1c -1.06% ($p<0.001$)
- Placebo subtracted change in BMIz -0.05

BUT…just over half (55%) of participants were titrated up to the maximum dose

Tamborlane *et al*, NEJM, 2019

Exenatide in youth-onset T2D

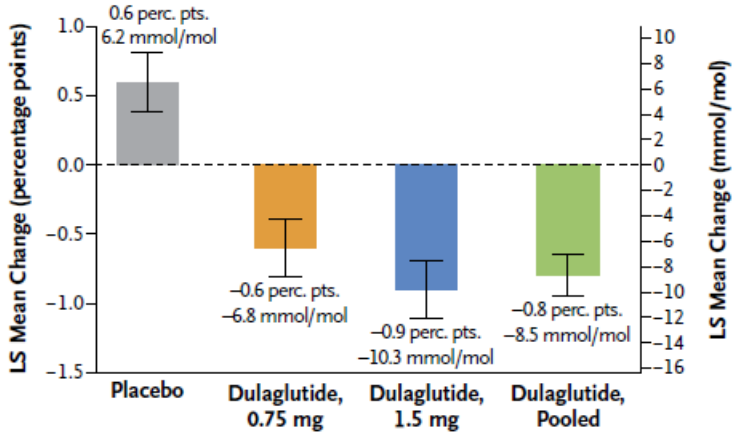
- Age 10-17, n=89
- Double-blind, placebo controlled
- 24-week treatment
- Dose 2 mg weekly
- Placebo-subtracted change in HbA1c -0.85% (p=0.012)
- Placebo subtracted change in BMIz -0.05



Tamborlane *et al*, Diabetes Care 2022

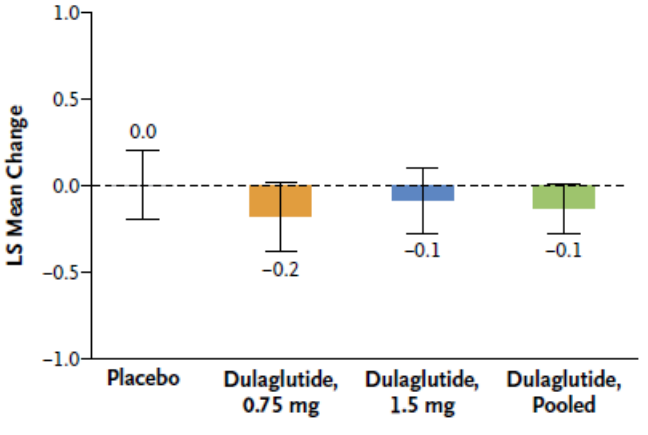
Dulaglutide in youth-onset T2D

A Change from Baseline in Glycated Hemoglobin Level at Wk 26



ETD (95% CI) — perc. pts.	−1.2 (−1.8 to −0.6)	−1.5 (−2.1 to −0.9)	−1.4 (−1.9 to −0.8)
ETD (95% CI) — mmol/mol	−13.0 (−19.5 to −6.5)	−16.5 (−23.0 to −10.0)	−14.8 (−20.4 to −9.1)
P Value	<0.001	<0.001	<0.001

D Change from Baseline in BMI at Wk 26



ETD (95% CI)	−0.2 (−0.7 to 0.4)	−0.1 (−0.6 to 0.5)	−0.1 (−0.6 to 0.5)
P Value			0.55

Arslanian, S. A. *et al*. (2022). Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. *New England Journal of Medicine, 387(5), 433-443.*

Resulted in FDA and EMA approval for youth 10 years and older

Semaglutide

Approved for youth ≥ 12 years, BMI ≥ 95th percentile or ≥85%ile + comorbidity

Weekly subcutaneous injection

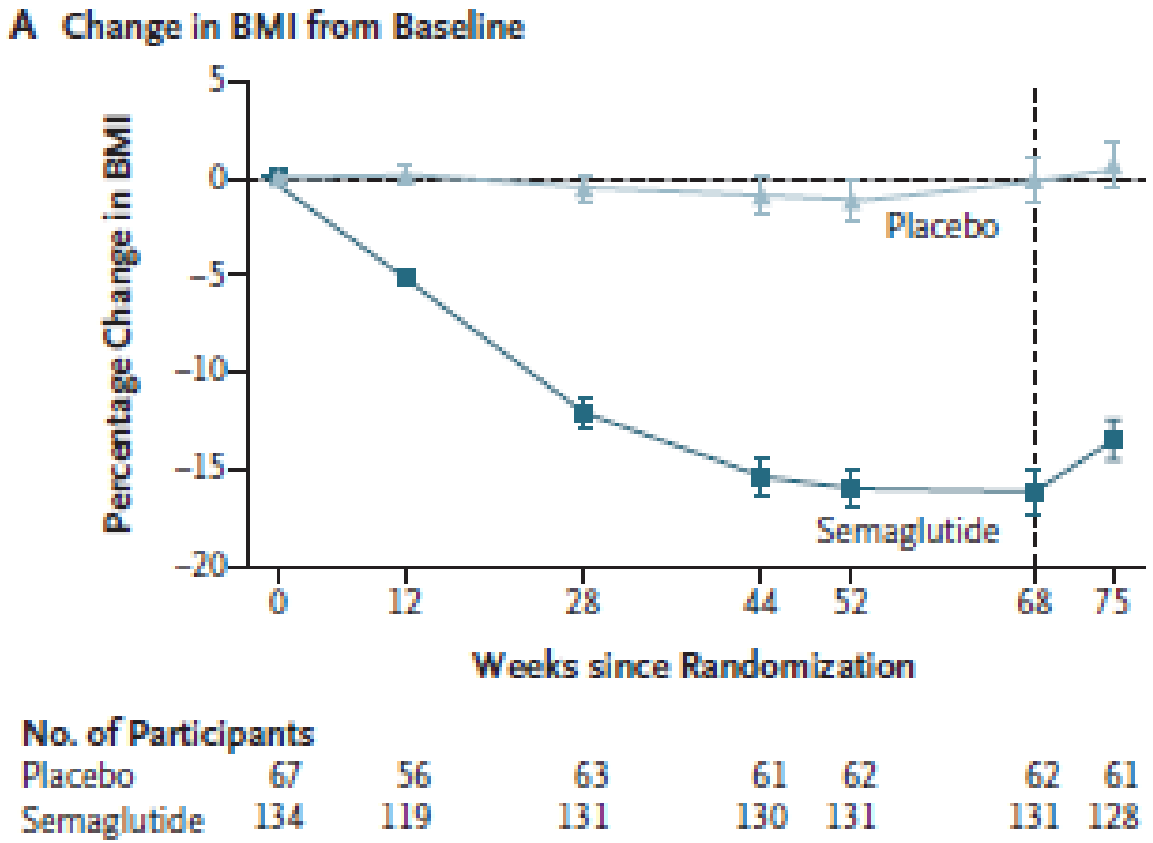
68-week median BMI loss of 16.7%

Improved WC, HbA1c, lipids,ALT

No serious adverse effects (GI side effects common)

Not currently approved by most insurance, monthly cost ≈$1000

Mechanism: glucagon-like peptide-1 (GLP-1) agonist: Central suppression of appetite, slows gastric emptying



Kelly et al, NEJM 2020

SGLT2 inhibitors

Treatment Studies: Empagliflozin and Linagliptin

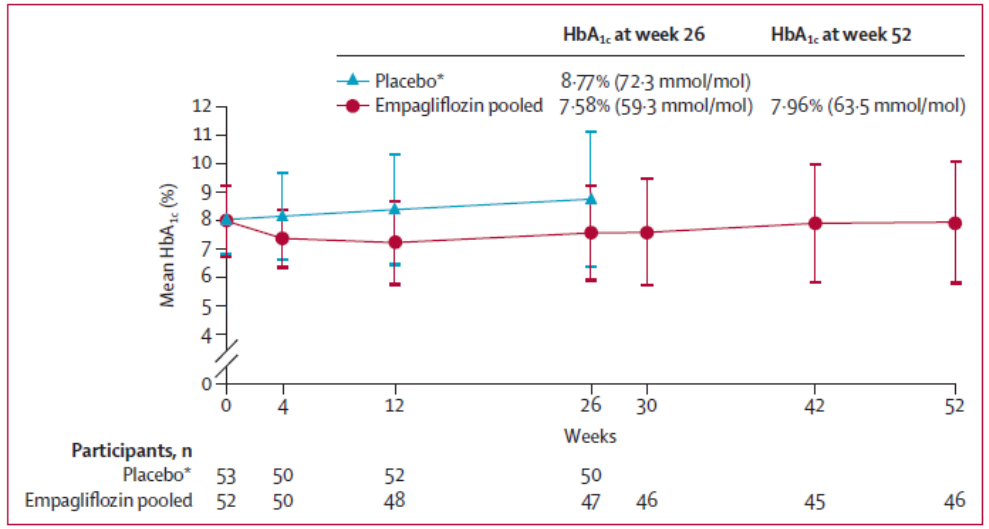


Figure 2: **Change in HbA_{1c} from baseline to week 26**
Descriptive data reflecting mean HbA_{1c} over time from baseline to week 52 for empagliflozin versus placebo in the modified intention-to-treat population. Error bars denote SDs. *Placebo treatment stopped at week 26.

- Placebo-subtracted treatment effect on HbA1c:
  - Empagliflozin -0.84% (-9.2 mmol/mol), p=0.012
  - Linagliptin -0.34% (-3.8 mmol/mol), p=0.29)
- Placebo subtracted change in weight not significant: -0.75 kg (-2.68 to 1.19 kg)
- Adverse events similar between 2 groups, slightly more hypoglycemia in empa group, but no severe hypoglycemia, no DKA

Laffel, L. M. *et al*. (2023),*Lancet Diabetes Endocrinol, 11(3), 169-181.*

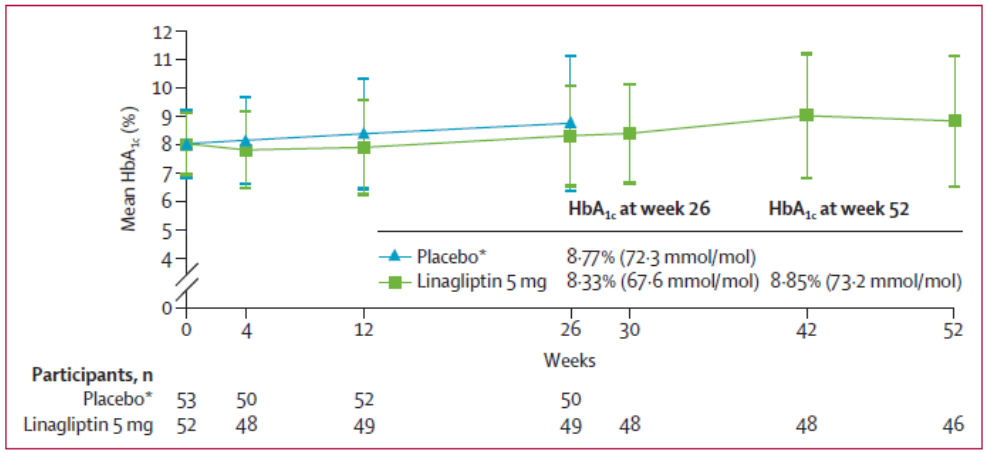
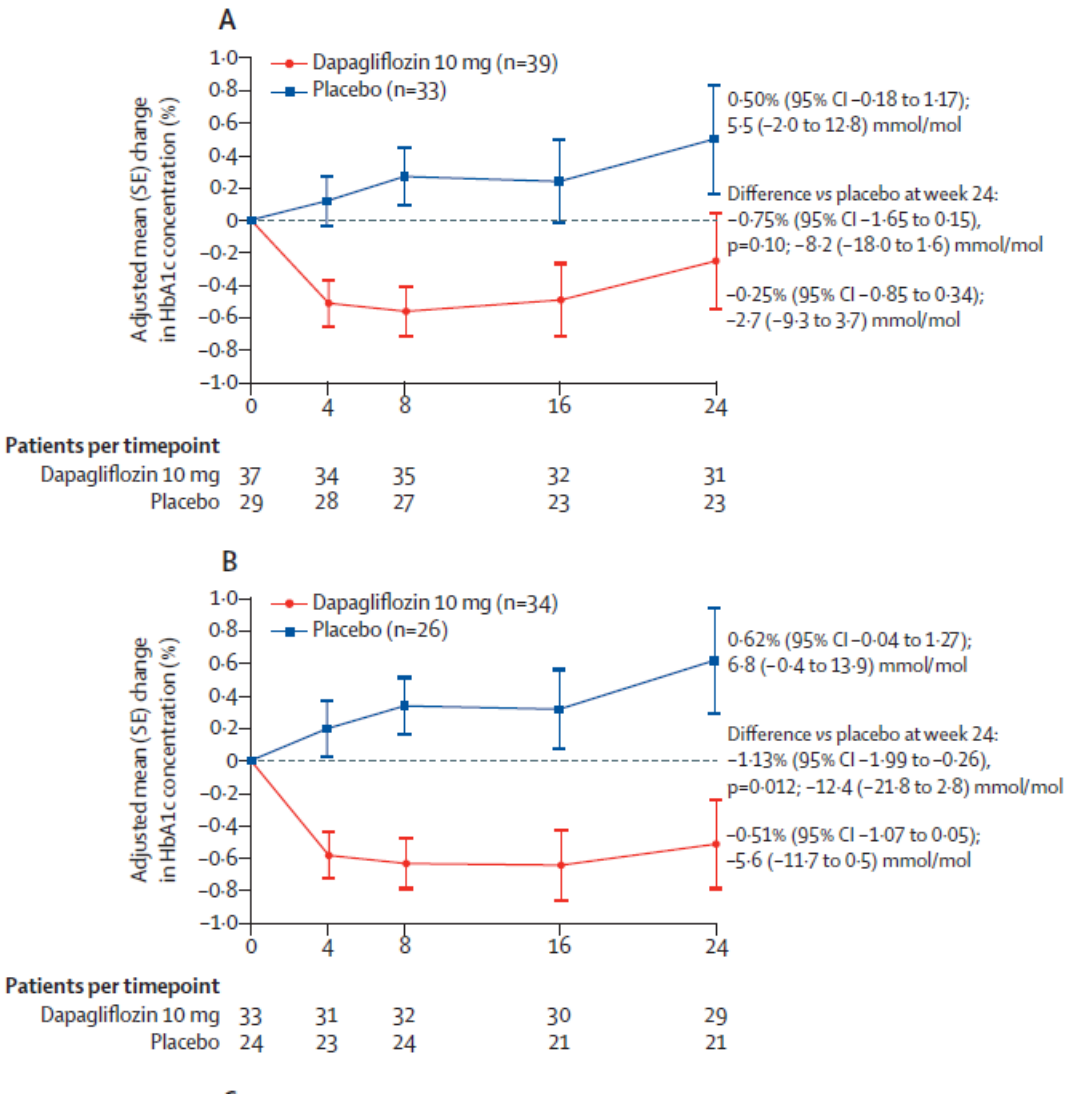


Figure 3: **Change in HbA_{1c} from baseline to week 52**
Descriptive data reflecting mean HbA_{1c} over time from baseline to week 52 for linagliptin versus placebo in the modified intention-to-treat population. Error bars denote SDs. *Placebo treatment stopped at week 26.

2 studies of sitagliptin (DPP-4 inhibitor)
- As monotherapy
- As add-on to metformin

No significant treatment effect

Treatment Studies: Dapagliflozin



- Placebo-subtracted treatment effect on HbA1c:
  - Intent to treat: -0.75% (95%CI -0.18 to 1.6), p=0.10
  - Study completers: -1.13% (95%CI -21.8 to -0.26), p=0.012
- No notable effects of dapagliflozin on BMI, BMIz, BP
- Adverse events similar between dapa and placebo groups (including UTI and hypoglycemia), no DKA

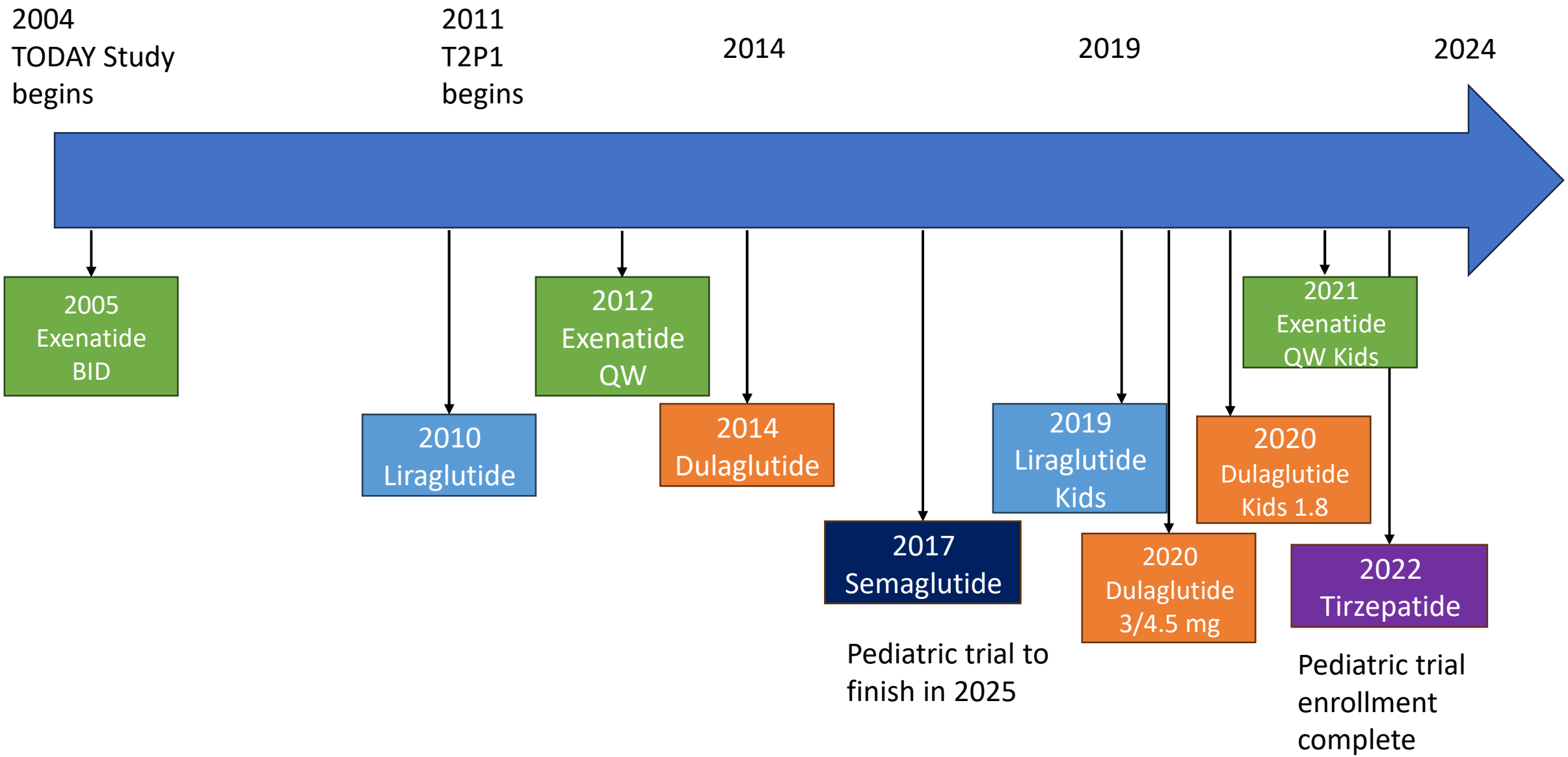
Tamborlane, WV *et al*. (2022),*Lancet Diabetes Endocrinol,* 10(5), 169-181.

Adult vs. Pediatric Outcome comparison

Medication	HbA1c difference	BMIz/weight difference	HbA1c difference	BMI/weight difference
Liraglutide	-1.06%**	-0.05 (NS)	-1.30%	-2.8 kg**
Weekly exenatide*	-0.85%**	-0.05 (NS)	-1.8% (BID-subtracted)**	-4.1 kg (QW), -4.5 (BID)
Dulaglutide				
1.5 mg#	-0.9%**	-0.1 (NS)	-1.54%	-3.0 kg
4.5 mg#	?	?	-1.77%	-4.6 kg**
Semaglutide# (1.0mg)	?	?	-1.6%**	-6.1 kg**
Tirzepatide	?	?	-2.07%**	-9.5 kg**
Dapagliflozin	-0.75% (NS)	? (NS)	-1.3%**	-2.9 kg**
Empagliflozin	-0.84%**	-0.75kg (NS)	-0.64%**	-2.0 kg**
Canagliflozin	?	?	-0.76%**	-3.7 kg**

*Adult trial compared to BID, #no placebo

Timeline: GLP-1 agonist FDA approval



Part 1 summary:

- Pediatric diabetes is associated with rapid β-cell failure on “standard of care” pediatric treatments
- The most efficacious treatments in adults in terms of glycemic improvement and weight loss still unapproved in youth
- Sample sizes in pediatric trials small, so evidence base lacks ability to dive deep in terms of prevention of complications and safety assessment
- Trials in youth particularly cautious despite the fact that they are adult-sized, have more aggressive disease, and are generally more health than adults with T2D
- Pediatric evidence base significantly lags behind that in adults

PART 2: Why is this urgent?

TODAY Long-term glycemic control

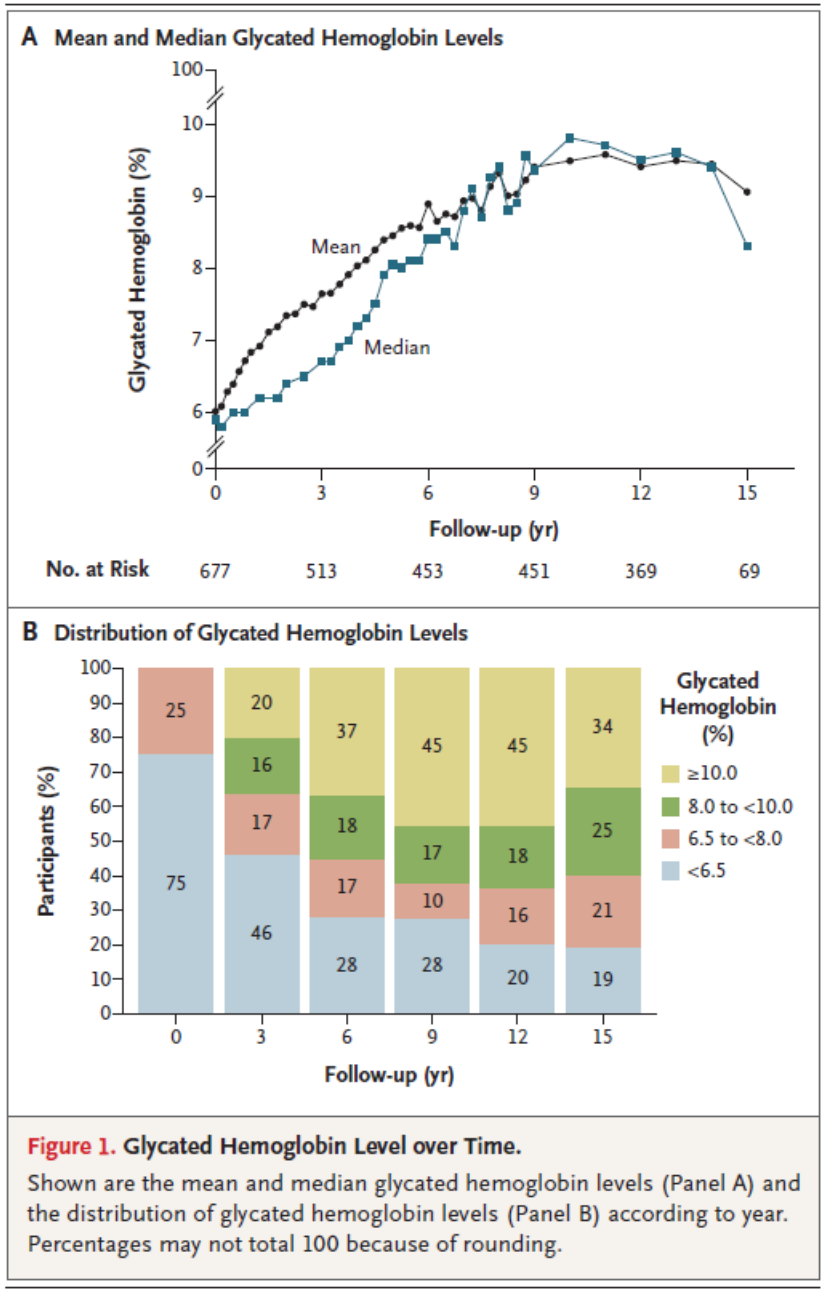
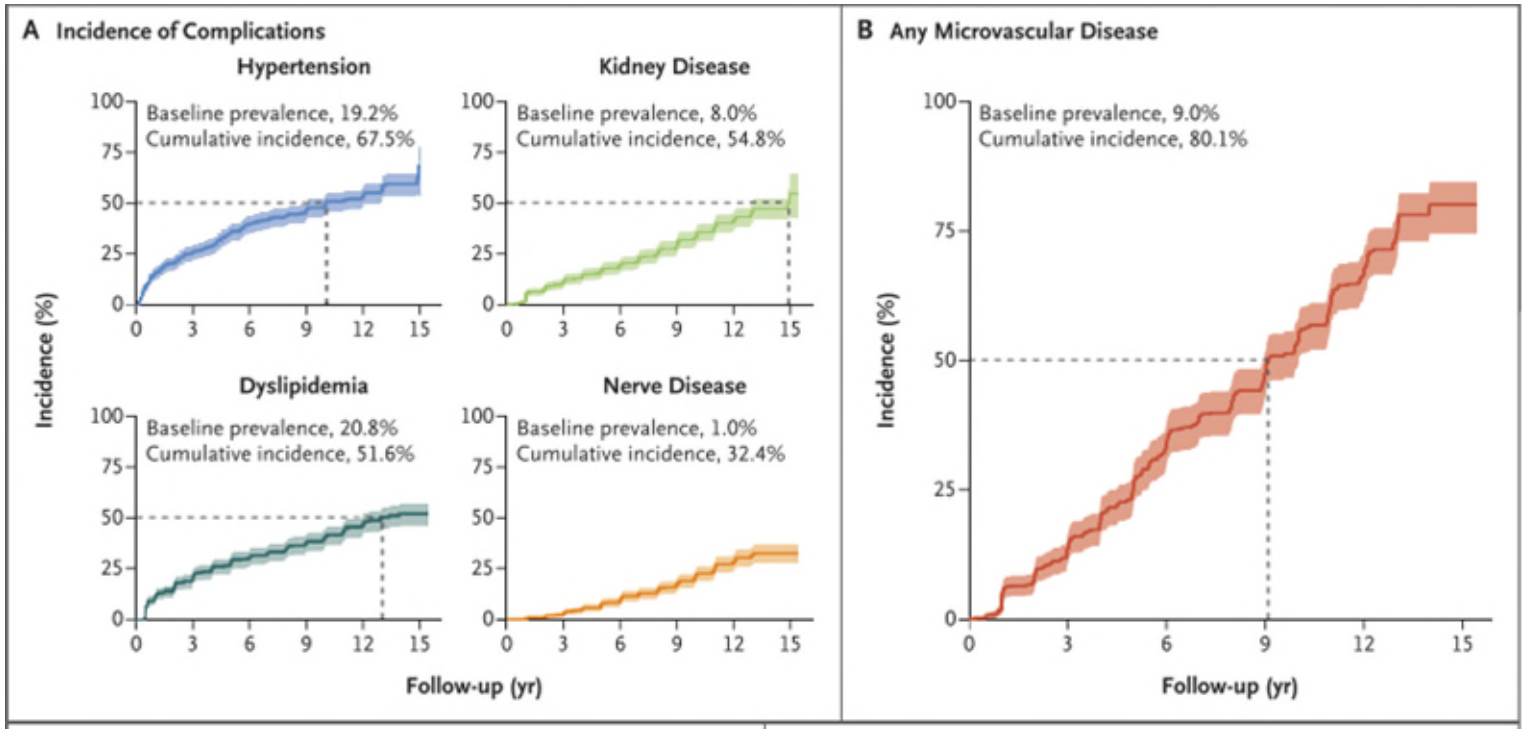


Figure 1. Glycated Hemoglobin Level over Time.

Shown are the mean and median glycated hemoglobin levels (Panel A) and the distribution of glycated hemoglobin levels (Panel B) according to year. Percentages may not total 100 because of rounding.

TODAY Study Group, NEJM, 2021 Jul 29;385(5):416-426.

TODAY Complications—long-term outcomes



- Prevalence of retinal disease 13.7% in 2010-2011; 51% in 2017-2018
- 17 serious cardiovascular events (4 MI, 6 CHF, 3 CAD events and 4 strokes) and 6 deaths

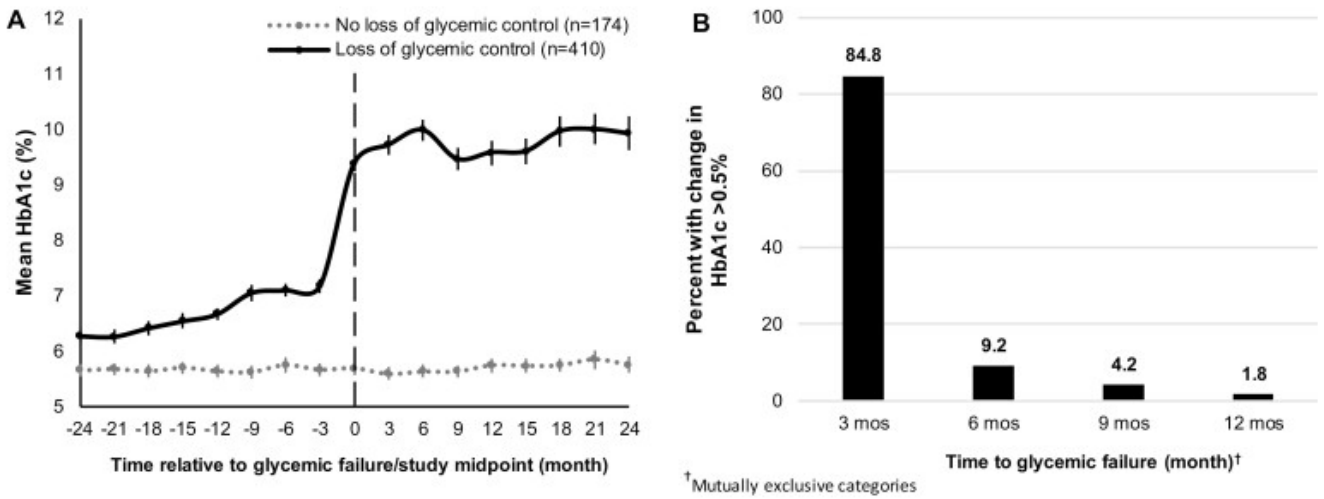
Multigenerational Consequences of Pregnancy

- Despite frequent contraception education and provision, 10% females experienced pregnancy, 30% of those had 1+ pregnancies
- LGA (22%), SGA (6%), pre-term (23%) similar to adults with T1D or T2D (4x general pop)
- 21% major congenital anomalies (50%)—4x reported rate in women with adult T2D

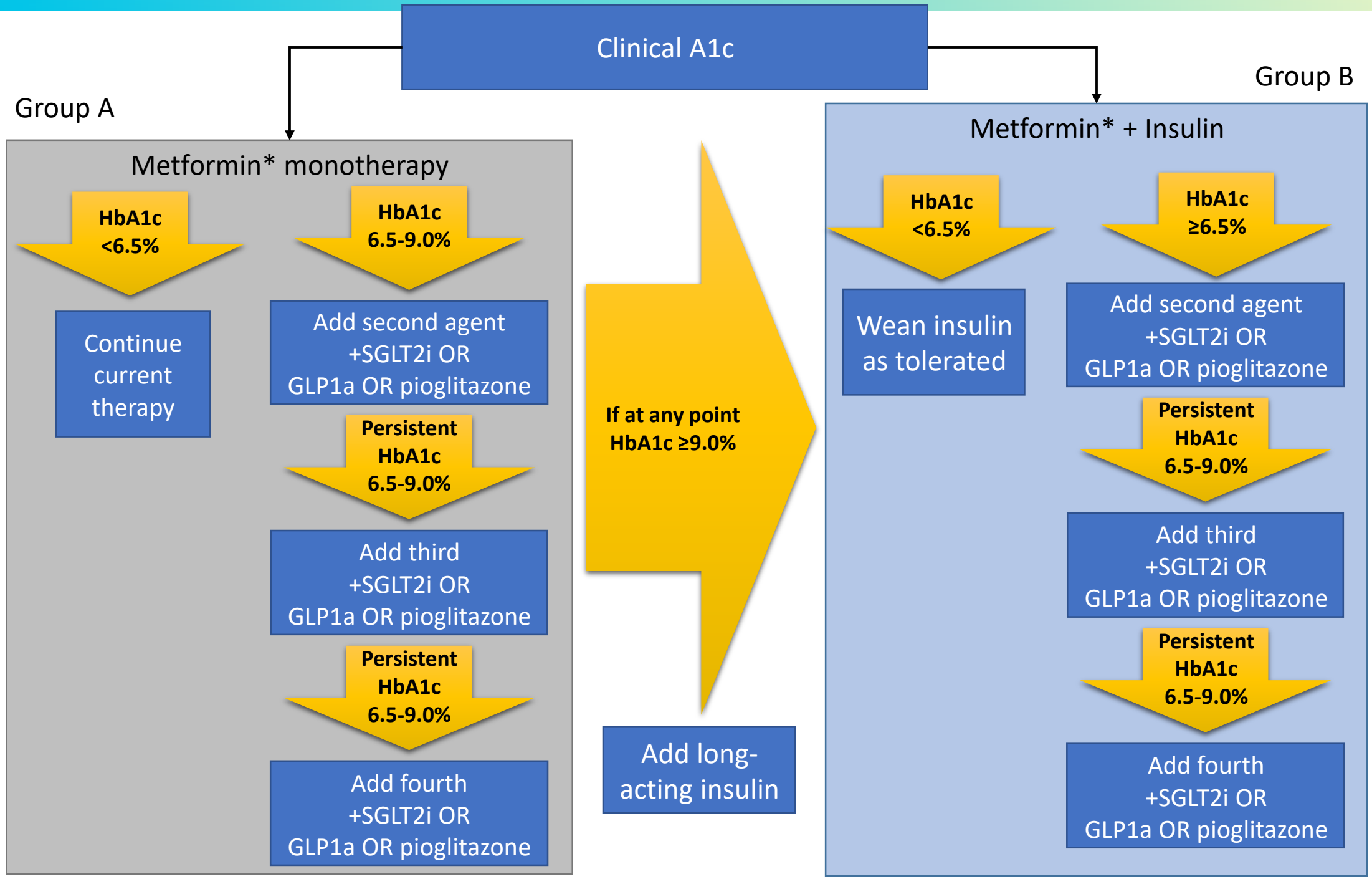
TODAY Study Group, NEJM, 2021 Jul 29;385(5):416-426.

Natural progression of YO-T2D

HbA1c of 6.3% or higher after 3-months of metformin predicts loss of glycemic control



Zeitler, P. *et al* (2022). *Journal of Clinical Endocrinology and Metabolism, 107(8), e3384-e3394.*

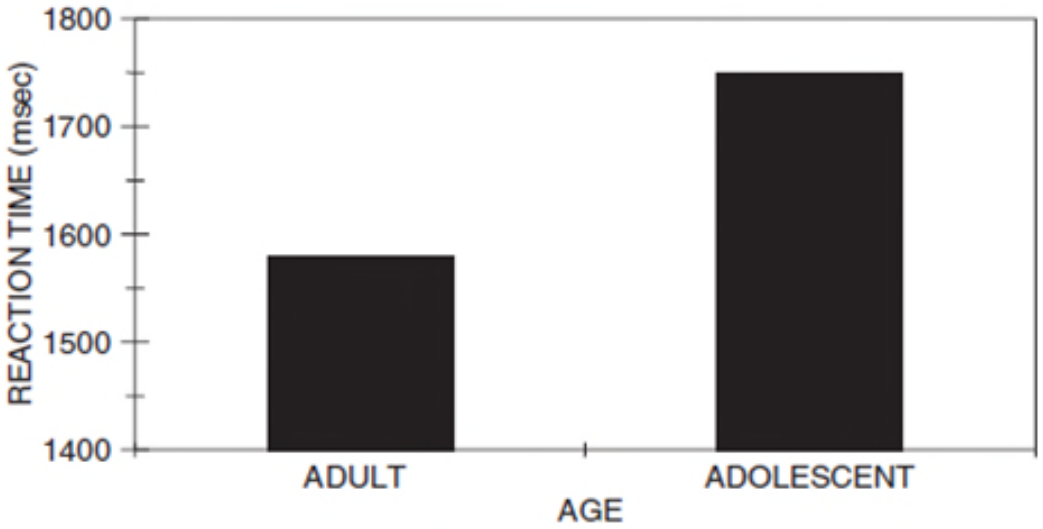

Clinical A1c
Group A
Metformin* monotherapy
HbA1c <6.5%
Continue current therapy
HbA1c 6.5-9.0%
Add second agent +SGLT2i OR GLP1a OR pioglitazone
Persistent HbA1c 6.5-9.0%
Add third +SGLT2i OR GLP1a OR pioglitazone
Persistent HbA1c 6.5-9.0%
Add fourth +SGLT2i OR GLP1a OR pioglitazone
If at any point HbA1c ≥9.0%
Add long-acting insulin
Group B
Metformin* + Insulin
HbA1c <6.5%
Wean insulin as tolerated
HbA1c ≥6.5%
Add second agent +SGLT2i OR GLP1a OR pioglitazone
Persistent HbA1c 6.5-9.0%
Add third +SGLT2i OR GLP1a OR pioglitazone
Persistent HbA1c 6.5-9.0%
Add fourth +SGLT2i OR GLP1a OR pioglitazone

Other considerations:

We're dealing with teenagers (need I say more?)

- Physical changes
- Cognitive changes
  - Rapidly developing and changing brain
  - Incomplete frontal lobe development
- Behavioral changes
  - Want to take on more independence but not able to do so consistently
  - High importance of social cues

- Is it wise to…
  - Swim with sharks?
  - Drink Drano?
  - Set your hair on fire?



Baird & Fugelsang. Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences, 2004, 359:1797–1804.

Psychosocial barriers to care are high

- Come from low-income families: 41.5% have household income <$25, 000/yr, 75% <$50 K
- Low educational attainment in parents: 16.8% of parents have a bachelor's degree or higher
- 52% live in single parent households, 9% live with neither parent

Copeland *et al* (2011) J Clin Endocrinol Metab 96(1):159-67

- High proportion with mental health challenges (depression, anxiety, disordered eating)
- Family culture of diabetes→difficulty accepting differences in their kids
- Youth suffer from weight-related stigma and bullying

While urgent treatment is needed…

- Medication is only as good as what gets in the body
- Need to establish trust
- Need to treat patients with grace
- Need to discuss expected need for additional treatments, including bariatric surgery, early in the process

Summary Part 2

- “Use of drug, whether off or on label, should be based on sound scientific evidence, expert medical judgement or published literature whenever possible” –AAP position statement on off-label use of treatments in pediatrics
- We have a pretty good idea of what **does not** work well
- Disease is still relatively uncommon, pool of potential trial participants is low
- The barriers to studying youth-onset T2D are high, particularly in light of FDA mandates
- Consequences of inadequately treated T2D are catastrophic


Thank
you!
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