PRACTITIONER'S EDGE

Medical Education for Practical Application

Advances in Treatment Options for Children and Adolescents with T2DM

INTEGRITY CONTINUING EDUCATION

Provided by Integrity Continuing Education, Inc.
Supported by an educational grant from Novo Nordisk, Inc.

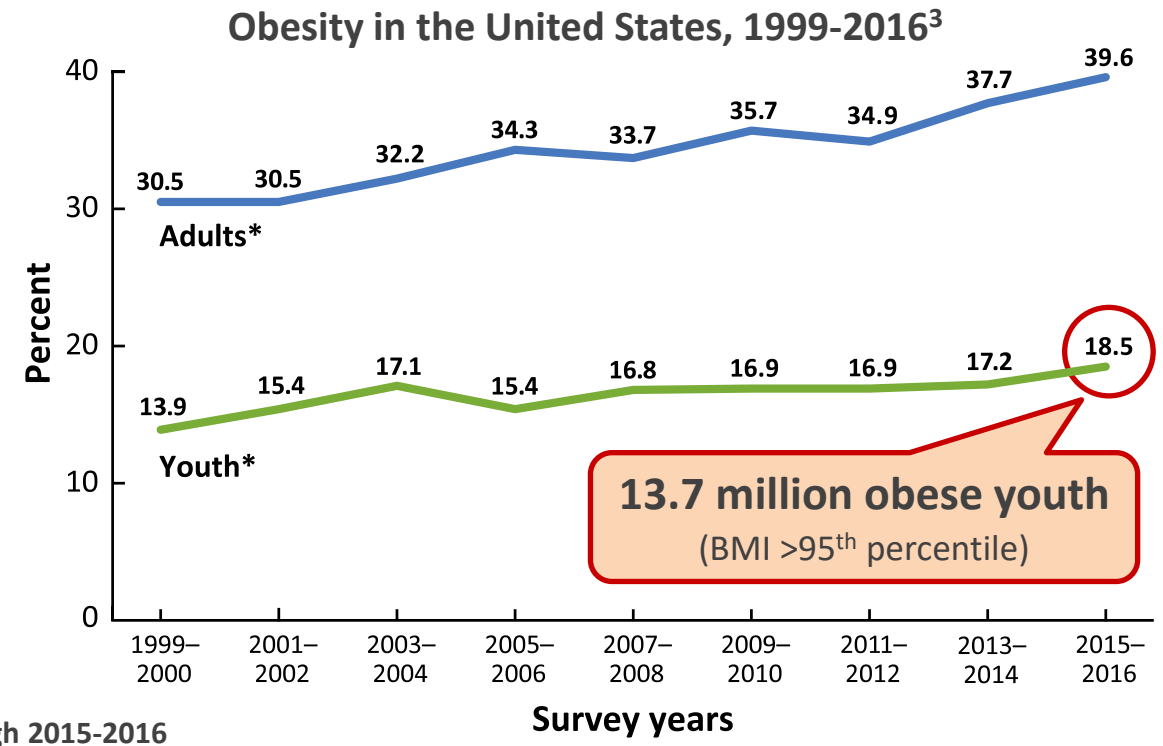
Learning Objectives

- Describe the increasing prevalence of T2DM among children and adolescents, along with evidence-based screening and diagnostic recommendations to identify at-risk youth
- Integrate guideline-directed strategies into routine management of children and adolescents with T2DM
- Review efficacy and safety outcomes, mechanisms of action, and prescribing information on newly approved and emerging therapies for pediatric patients with T2DM
- Apply effective communication strategies involving shared decision-making (SDM) with the pediatric patient and family to achieve lifestyle changes and foster medication adherence

Recognizing T2DM in Children and Adolescents

Sedentary Lifestyle + Obesity = T2DM

- Children ages 2-5 are sedentary 7-7.5 hours daily[1]
- Overweight 5-year-olds are **4x more likely** than normal weight children **to become obese** over the next 9 years[2]

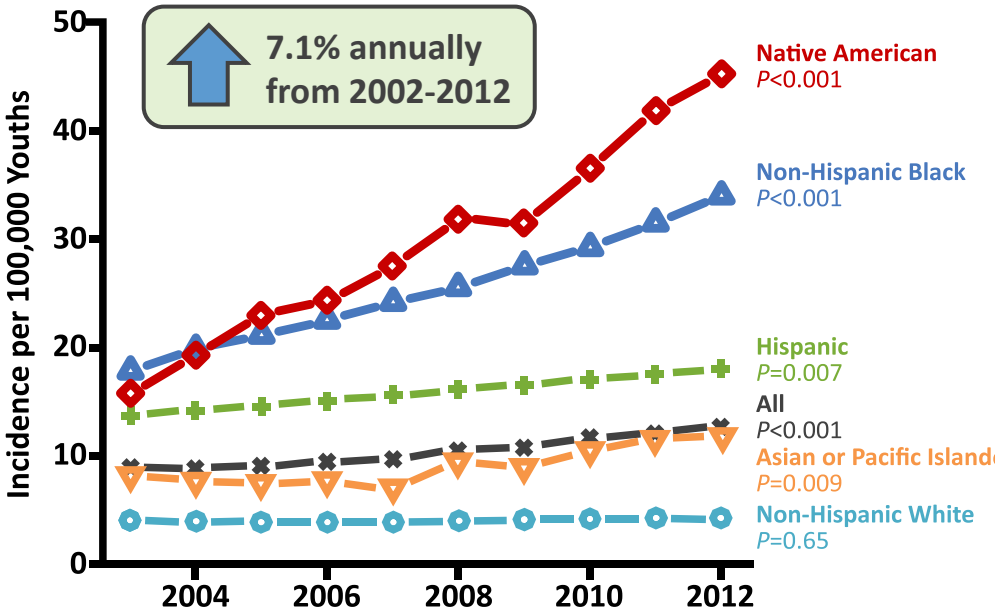


***Significant increasing trend from 1999-2000 through 2015-2016**

1. Garriguet D, et al. *Heal Reports*. 2016;27(9):14-23. 2. Cunningham SA, et al. *N Engl J Med*. 2014;370(5):403-411.
3. Hales CM, et al. *NCHS Data Brief*. 2017;(288):1-8.

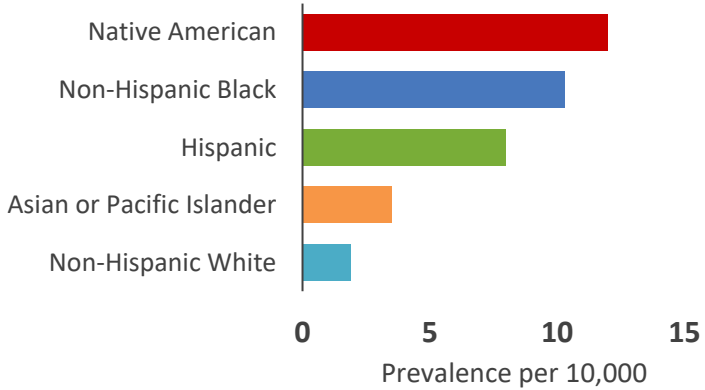
Increasing Prevalence of T2DM Among Youth

Incidence of T2DM, 10-19 Years of Age[1]



- Racial and ethnic trends likely due to several factors
  - Genetics
  - Metabolic characteristics
  - Culture/environment
  - Quality of and access to healthcare

Prevalence of Youth-Onset T2DM by Race/Ethnicity, 2009[2]



1. Mayer-Davis EJ, et al. *N Engl J Med*. 2017;376(15):1419-1429. 2. Nadeau KJ, et al. *Diabetes Care.* 2016;39:1635–1642

Youth-Onset T2DM

- High therapeutic failure rates + rapid β-cell loss = **insulin treatment earlier in disease course**
- Accelerated development of DM comorbidities
  - Hypertension
  - Microalbuminuria
  - Low HDL cholesterol
  - High triglycerides

Rapidly progressive β-cell decline

3-4x **faster than adult-onset T2DM[1]**

Renal/neurological complications within **5 years** of diagnosis[1]

Major complications (dialysis, blindness, or amputation) within **10 years** of diagnosis[2]

1. Hannon TS, et al. *Ann N Y Acad Sci*. 2015;1353(1):113-137. 2. Dart AB, et al. *Diabetes Care*. 2014 Feb;37(2):436-43.

Risk-Based Screening Criteria

Consider testing in youth* who are overweight (≥85%) or obese (≥95%)

Plus 1 or More of the Following Risk Factors

- **Maternal history** of diabetes or GDM during the child's gestation
- **Family history** of T2DM in first- or second-degree relative
- **Race/ethnicity**: Native American, African American, Latino, Asian American, Pacific Islander
- **Signs of insulin resistance** or conditions associated with insulin resistance
  - Acanthosis nigricans
  - Hypertension
  - Dyslipidemia
  - Polycystic ovary syndrome
  - Small-for-gestational age birth weight

**After the onset of puberty or after 10 years of age, whichever occurs earlier.*

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Diagnostic Criteria: Prediabetes

- **A1C 5.7% to <6.5%** (39 to <48 mmol/mol).
- **Impaired Fasting Glucose** (IFG): fasting glucose ≥100 but <126 mg/dL (≥5.6 but <7.0 mmol/L).
- **Impaired Glucose Tolerance** (IGT): 2-h plasma glucose ≥140 but <200 mg/dL (≥7.8 but <11.1 mmol/L) during an oral glucose tolerance test (OGTT).

Fasting plasma glucose, 2-h plasma glucose after 75-g OGTT, or A1C can be used to test for prediabetes/diabetes.

If tests are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI is increasing.

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Diagnostic Criteria: Diabetes

- **A1C ≥6.5%** (≥48 mmol/mol). ***OR***
- **FPG ≥126 mg/dL** (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.* ***OR***
- **2-h plasma glucose ≥200 mg/dL** (11.1 mmol/L) during an OGTT. ***OR***
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, **a random plasma glucose >200 mg/dL** (11.1 mmol/L).

****In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.***

Fasting plasma glucose, 2-h plasma glucose after 75-g OGTT, or A1C can be used to test for prediabetes/diabetes.

If tests are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI is increasing.

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Pediatric Clinical Practice Guidelines Focused on Improving T2DM Outcomes

Lifestyle and Dietary Recommendations
Children and Adolescents with T2DM

Obese/ Overweight

Goal of **7% to 10%** weight loss

Exercise

Moderate to vigorous physical activity

30-60 minutes 5 days per week

Strength training

3 days per week

Nutrition

Nutrient-dense, high-quality foods

Calorie-dense, nutrient-poor foods

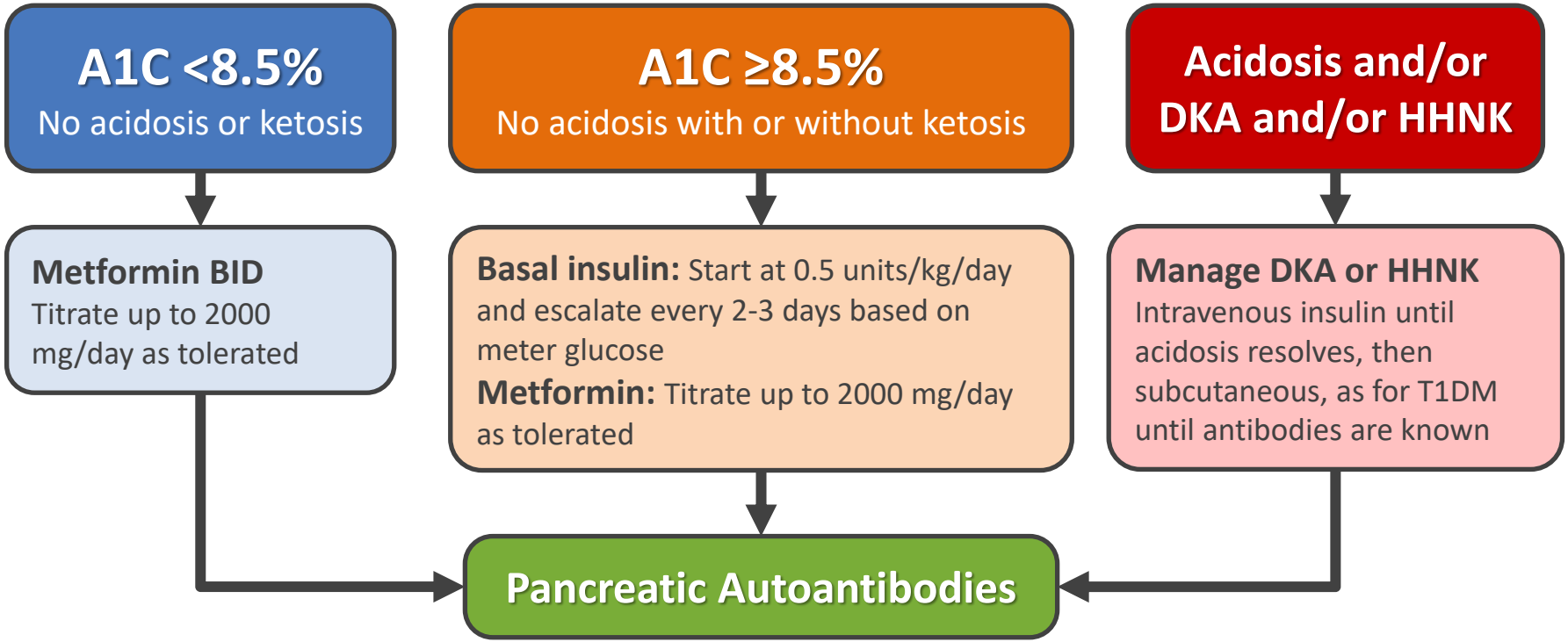
Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

HbA1c Targets

- Measured every 3 months
- Goal in most: <7%
- More stringent goals (e.g. <6.5%) may be appropriate for select patients
  - Short duration of diabetes
  - Lesser degrees of B-cell dysfunction
  - Significant weight loss with lifestyle and dietary interventions
- HbA1c targets for youth on insulin must be individualized
- Home self-monitoring of blood glucose (SMBG) should be individualized

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Management of T2DM



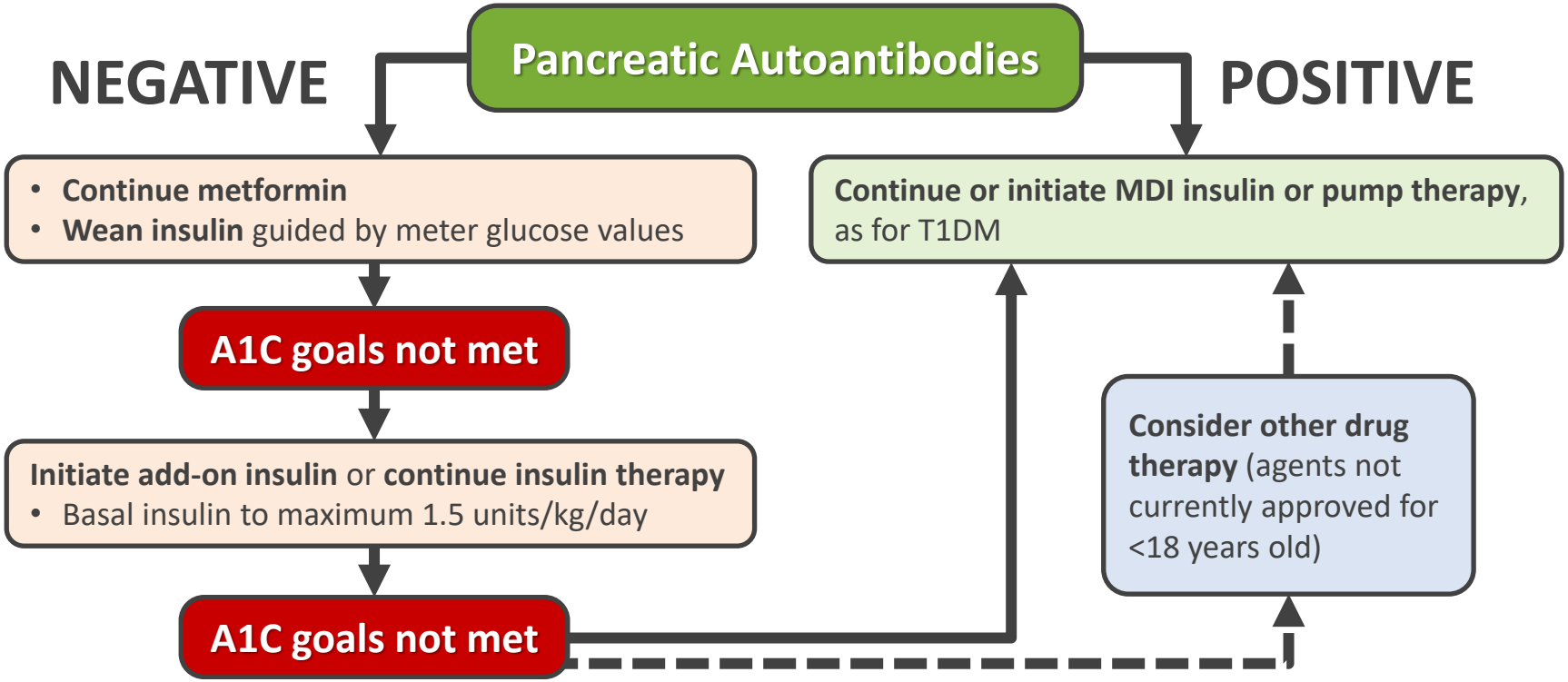
Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Pancreatic Autoantibodies

- Important to exclude the possibility of autoimmune T1DM
- Ab+ youth present more like individuals with T1DM
  - Progress to insulin more rapidly
  - At risk for other autoimmune disorders
- Testing should include
  - GAD65 antibodies
  - IA2 antibodies
  - Insulin autoantibody (individuals who have not yet been exposed to exogenous insulin)
- Benefit of ZnT8 antibody testing remains unclear

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Management of T2DM



Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

New and Emerging Therapeutic Options for Pediatric Patients with T2DM

Liraglutide FDA-Approved for Pediatric T2DM

- June 2019: expanded approval for patients **ages 10 and older**
- GLP-1 receptor agonist
- Administered subcutaneously once-daily
  - Initiate at 0.6 mg daily for at least a week
  - Increase to 1.2-1.8 mg as necessary
    - Must be on 1.2 mg dose for at least a week before increasing to 1.8 mg
- Dispensed in a pre-filled, multi-dose pen capable of delivering doses of 0.6, 1.2, or 1.8

Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

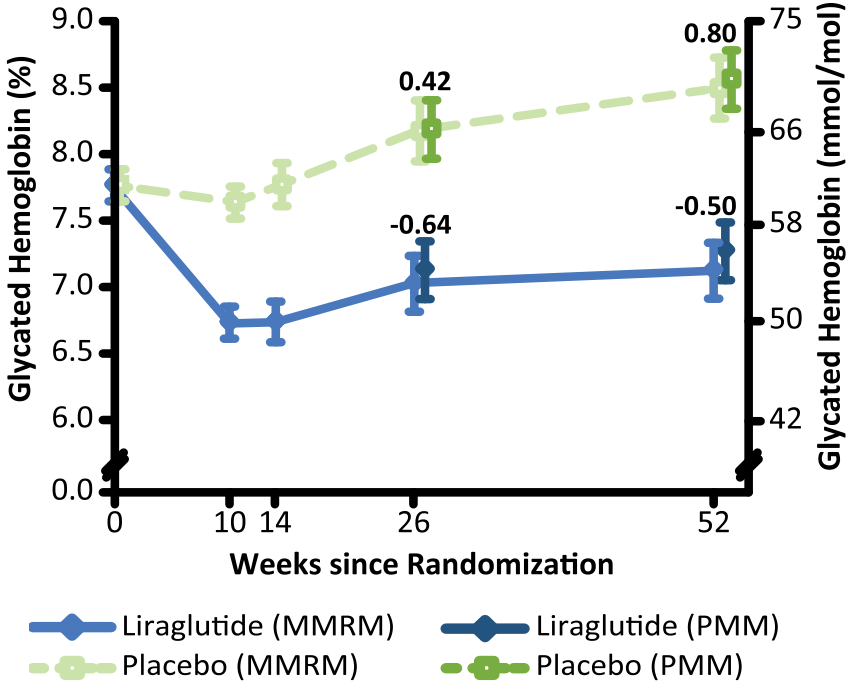
Ellipse Trial

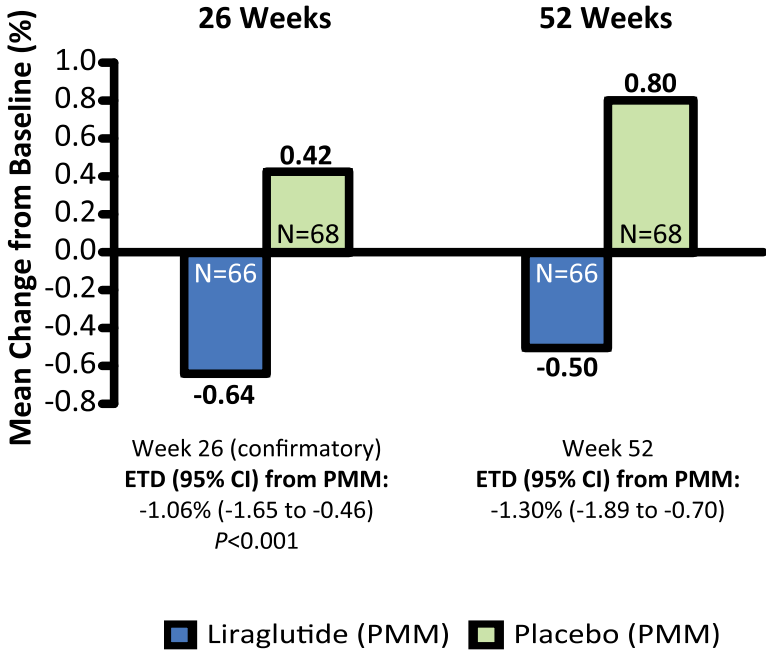
- 135 patients ages 10 to 17 years with T2DM
  - Mean age 14.6 years
- Inclusion criteria
  - BMI >85th percentile
  - HbA1c 7% to 11% if treated with diet and exercise alone
  - HbA1c 6.5% to 11% if treated with metformin
- Primary end point: change from baseline in HbA1c by 26 weeks
- Secondary end points included change in FPG and BMI

Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

Ellipse Trial: Primary End Point
Glycated Hemoglobin

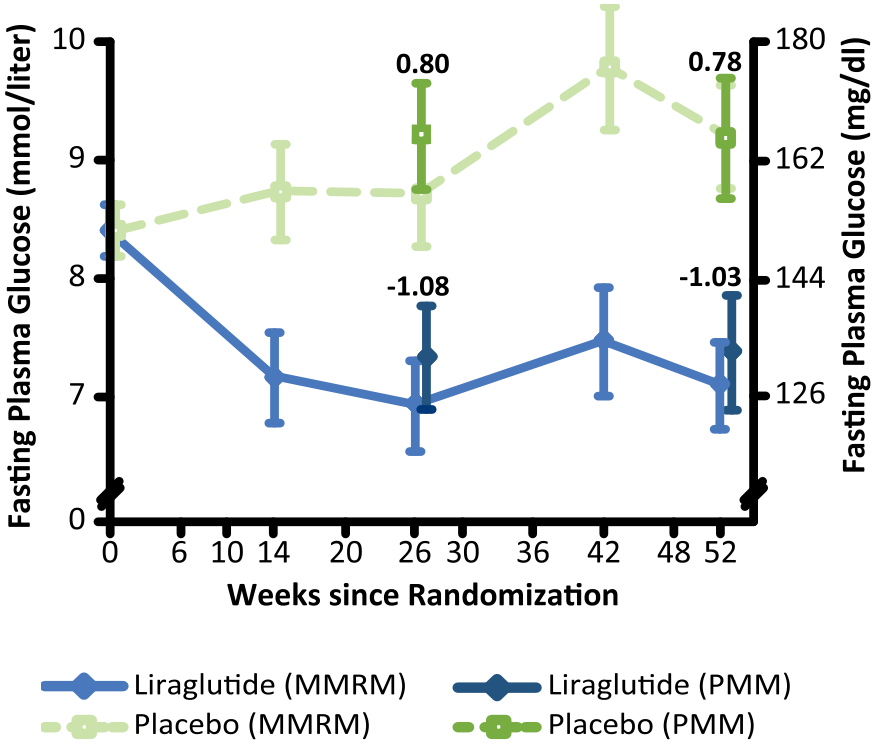
63.7% and 36.5% of liraglutide and placebo groups achieved HbA1c <7%

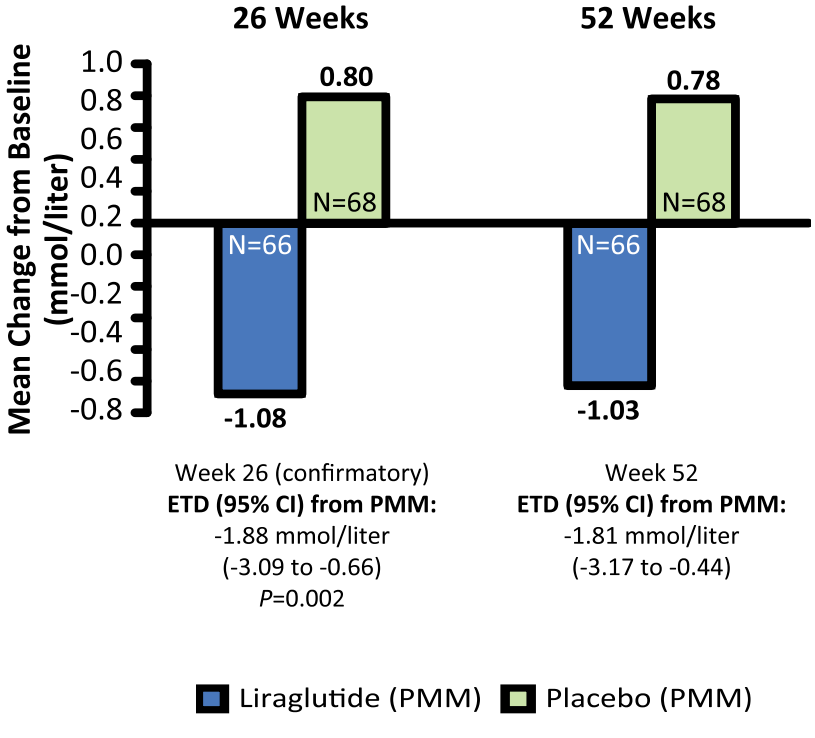




Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

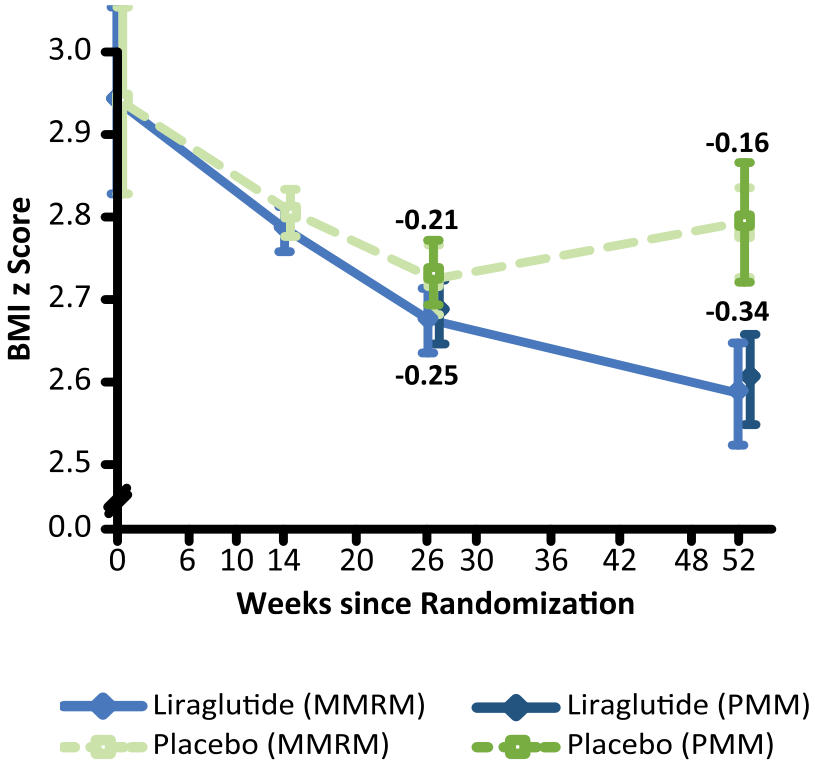
Ellipse Trial: Secondary End Points
Fasting Plasma Glucose

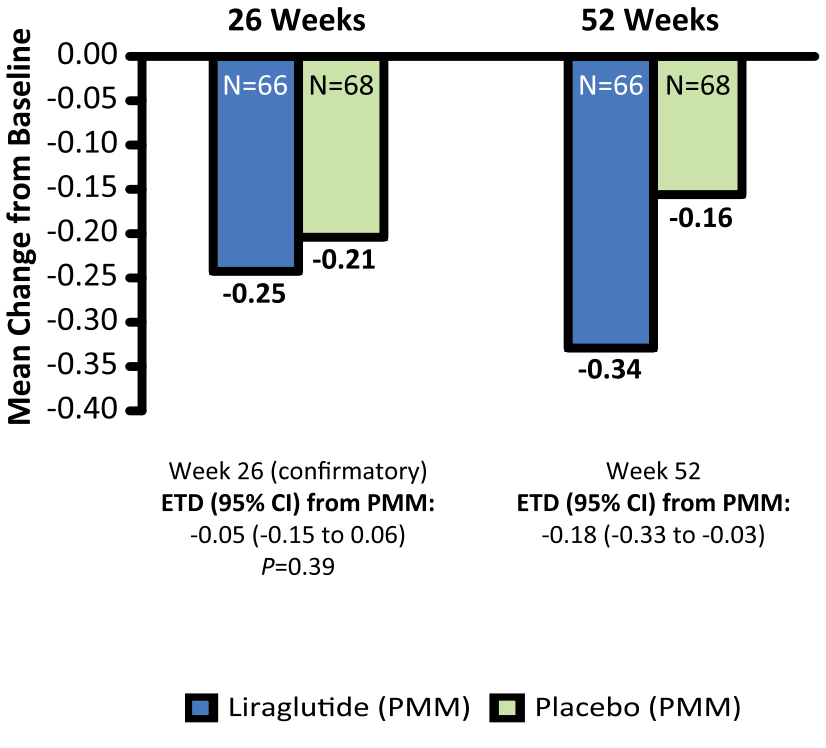




Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

Ellipse Trial: Secondary End Points
BMI z Score





Week 26 (confirmatory)
ETD (95% CI) from PMM:
-0.05 (-0.15 to 0.06)
P=0.39

Week 52
ETD (95% CI) from PMM:
-0.18 (-0.33 to -0.03)

Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

Ellipse Trial: Safety and Tolerability

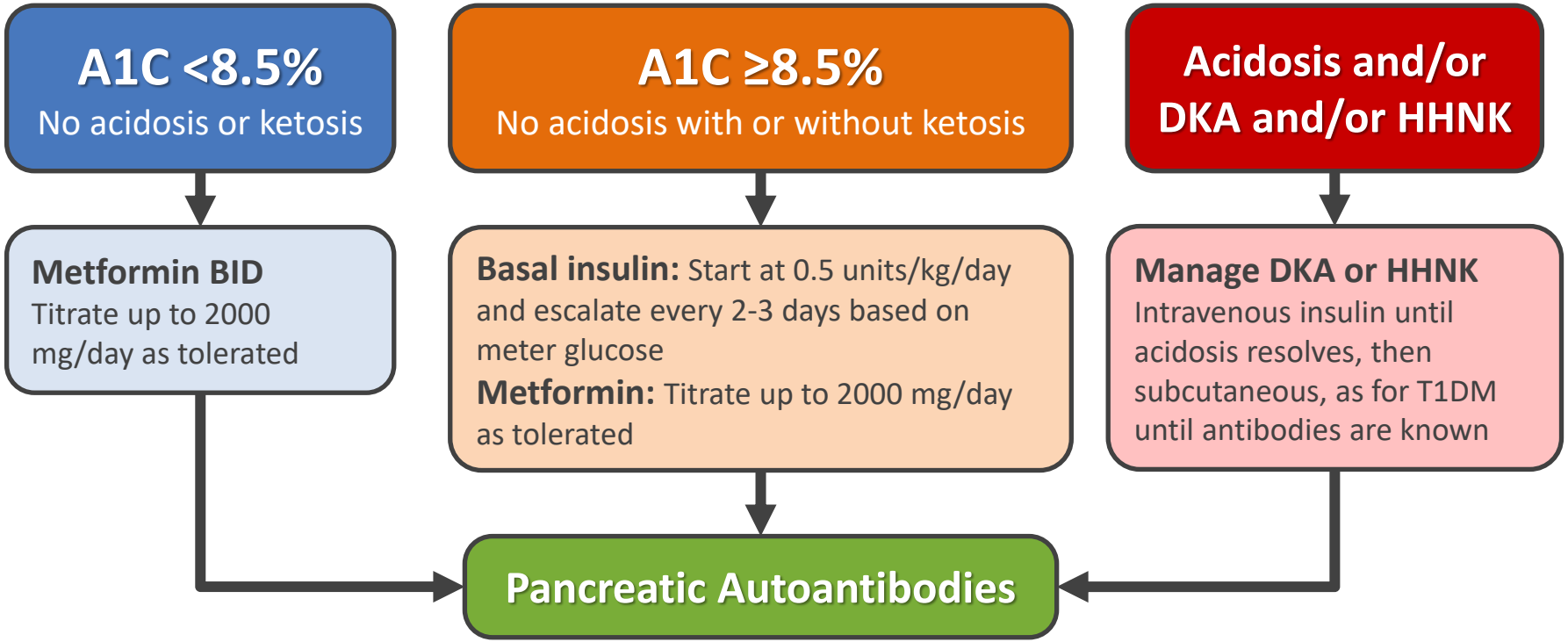
Tolerability	26 Weeks		52 Weeks Extension	
	Liraglutide	Placebo	Liraglutide	Placebo
Completed Treatment, %	90.9	84.1	84.8	76.8
No Rescue Medication, %	86.4	66.7	71.2	50.7

Adverse Events	Liraglutide N = 68	Placebo N = 66	Relative Risk (95% CI)
All Adverse Events, %	84.8	80.9	1.05 (0.90-1.22)
Serious Adverse Events, %	13.6	5.9	2.32 (0.75-7.16)
AEs leading to discontinuation, %	1.5	1.5	1.03 (0.07-16.13)
Nausea, %	28.8	13.2	2.18 (1.06-4.46)
Vomiting, %	25.8	8.8	2.92 (1.23-6.95)
Hypoglycemia (minor*), %	24.2	10.3	2.35 (1.04-5.35)

**Plasma glucose of less than 55.8 mg per deciliter (3.1 mmol per liter)*

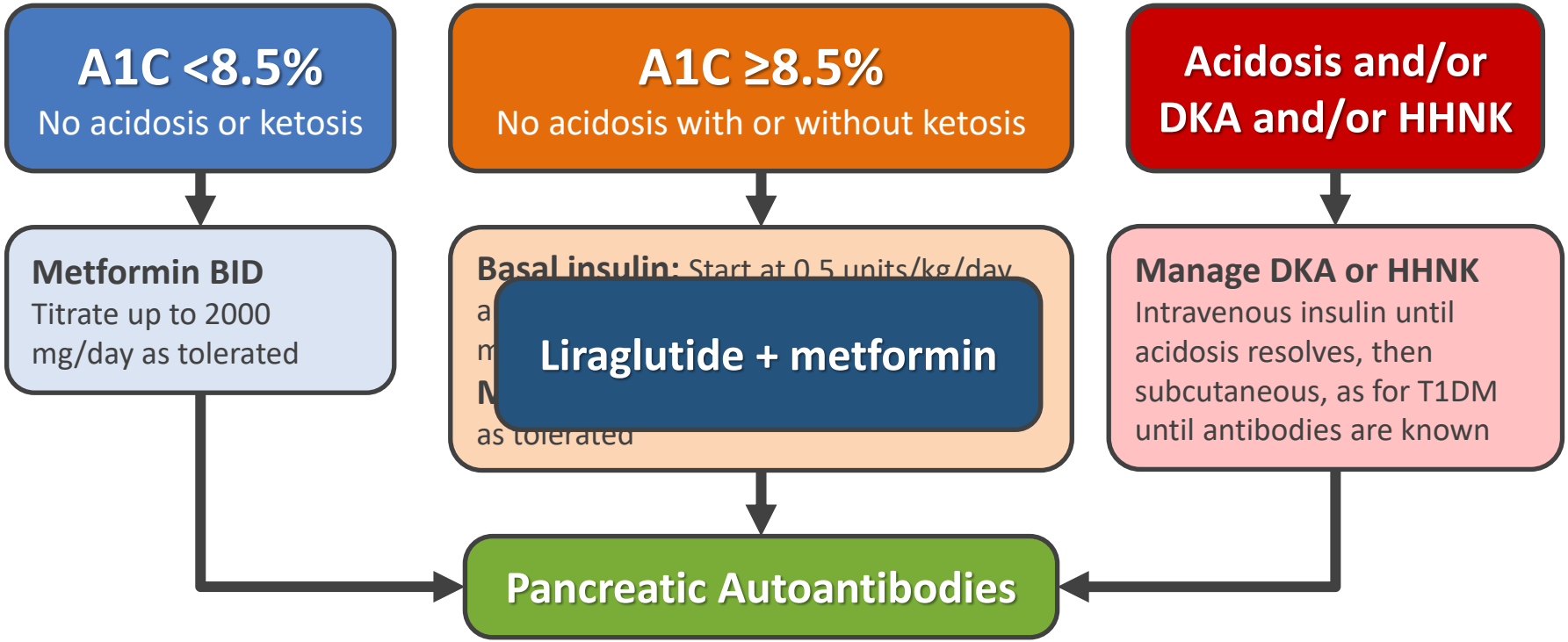
Tamborlane W V, et al. *N Engl J Med*. April 2019:NEJMoa1903822.

Place of Liraglutide in Management



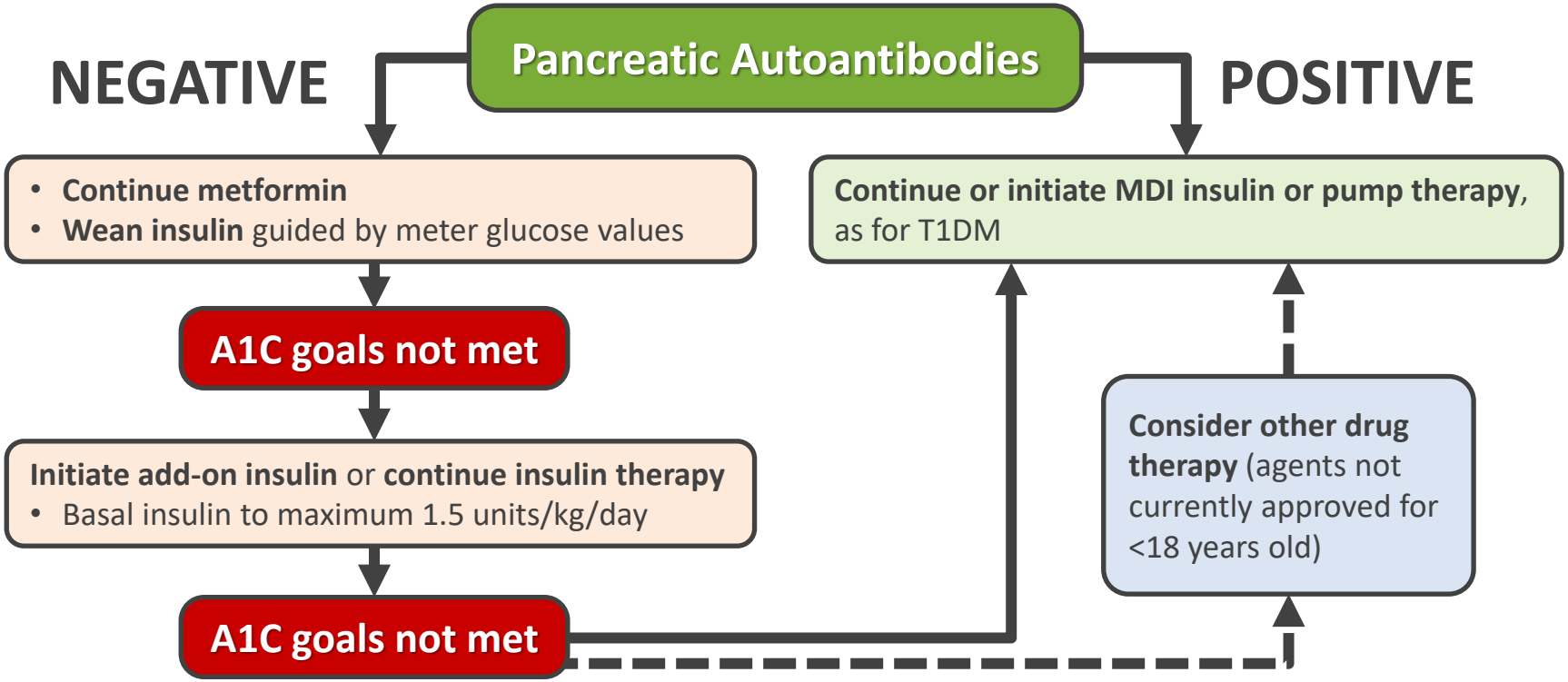
Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Place of Liraglutide in Management



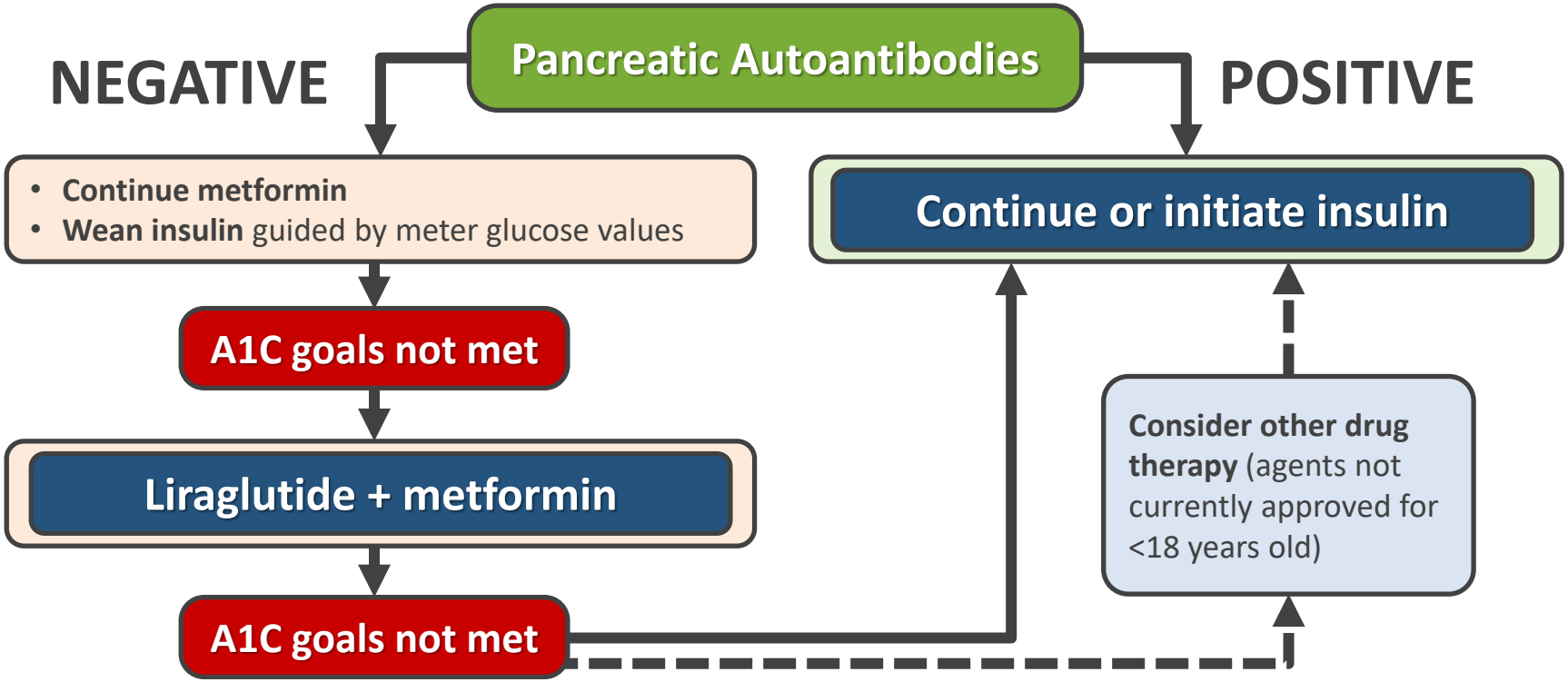
Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Place of Liraglutide in Management



Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Place of Liraglutide in Management



Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Ongoing Phase 3 Clinical Trials

Drug	Age	Completion	Status	NCT
DPP-4 Inhibitors				
Sitagliptin	10-17 years 10-17 years 10-17 years	September 2019 September 2019 October 2019	**Trials completed but no results available**	NCT01760447 NCT01472367 NCT01485614
Alogliptin	10-17 years	June 2021		NCT02856113
SGLT2 Inhibitors				
Dapagliflozin	10-24 years	April 2020		NCT02725593
Canagliflozin	10-17 years	June 2022		NCT03170518
GLP-1 Receptor Agonists				
Dulaglutide	10-17 years	Jan 2022		NCT02963766
Exenatide QW	10-17 years	June 2023		NCT01554618
Combinations				
Linagliptin + Empagliflozin	10-17 years	Jan 2022		NCT03429543
Dapagliflozin + Saxagliptin	10-18 years	Nov 2022		NCT03199053

Importance of Effective Communication with the Patient and Family

Guideline Recommendations

- Psychosocial issues and family stresses should be assessed at diagnosis and during routine follow-up care
  - Starting around 7-8 years old
- Mental health professionals should be integral to the pediatric multidisciplinary team
- Encourage family involvement
- Start offering one-on-one time with provider around age 12
- Starting at puberty, all girls should receive preconception counseling as part of routine care

Arslanian S, et al. *Diabetes Care*. 2018;41(12):2648-2668.

Addressing Adherence

- Key predictors of HbA1c in the year following diagnosis[1]
  - Treatment adherence
  - BMI reduction
- Perceived **provider compassion** and **optimism** positively affect coping ability with T2DM[2]

Premature transfer of diabetes care to child can lead to **burn-out**, **nonadherence**, and **deterioration in glycemic control**

1. Candler, TP, et al. *Pediatr Diabetes*. 2018 Dec;19(8):1393-1399. 2. Freeman-Hildreth, Y, et al. *PLoS One*. 2019 Apr 2;14(4):e0214713.

Strategies for Motivational Interviewing

1. **Open-ended questions.** Avoid asking questions that can be answered with a “yes” or “no.”
2. **Affirmations.** Never underestimate the power of expressing empathy during tough spots or in celebrating patients’ accomplishments.
3. **Reflective listening.** Patients often have the answers; the physician’s role is to help guide them.
   - Acknowledge the patient’s mood about what he or she is telling you
   - Reflecting patients’ statements and feelings back to them reinforces self-efficacy

Stewart EE, Fox C. *Fam Pract Manag*. 2011 May-June;18(3):21-25.

Why Shared Decision-Making?

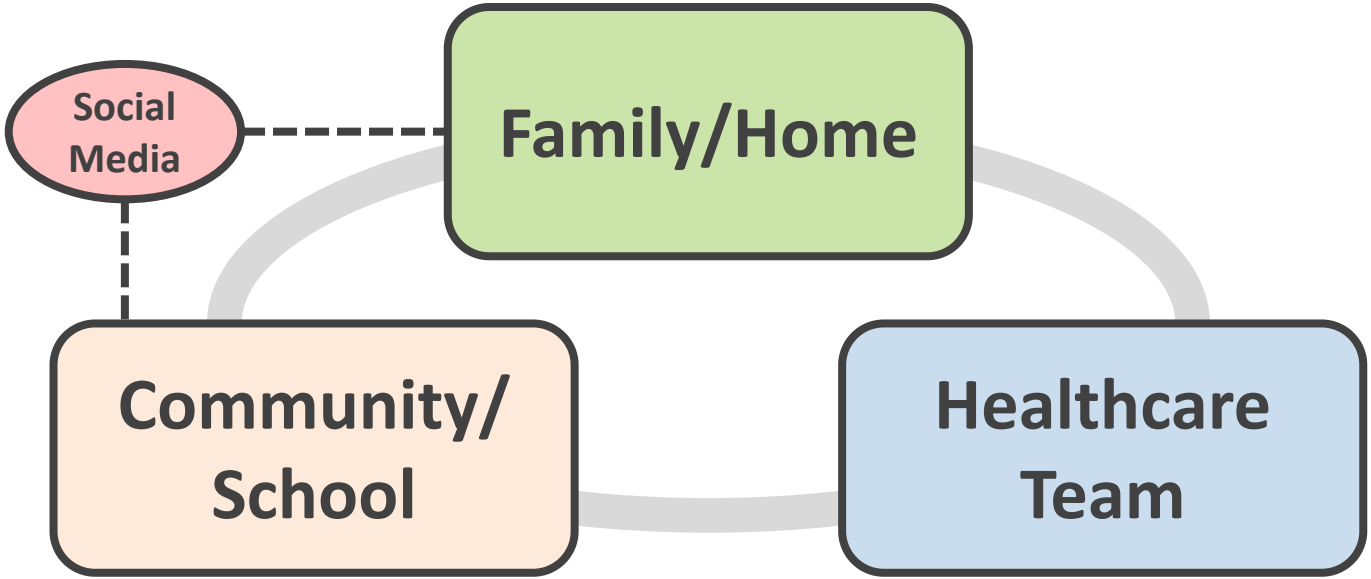
Patient-centered health care

When youth and their parents engage in shared decision-making, they…

- Learn about their health and understand their health conditions
- Recognize that a decision needs to be made and are informed about the options
- Understand the pros and cons of different options
- Have the information and tools needed to evaluate their options
- Are better prepared to talk with their healthcare provider
- Collaborate with their health care team to make a decision right for them
- Are more likely to follow through on their decision (improved adherence)

Available at: https://www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf.

It Takes a Village



EHR = BFF? A Qualitative Study of DM Support Based in an EHR

*"**I feel much safer now** than I did before... If I had to pick one thing out of how this [programme] has affected my life and my everyday living, [it's] the fact that **I'm not chronically worrying about everything**. If I didn't have any access to knowing what's going on with my health, I think I'd probably go back on ulcer medicine... **If I suddenly didn't have all this, I would probably be just a raving hypochondriac**."*

Ralston JD, et al. *BMJ* 2004; 328:1159.

EHR = BFF? A Qualitative Study of DM Support Based in an EHR

"Somebody should have been looking at them [the blood glucose levels], and if they were looking at them, I would have thought that they might have at least let me know that they were looking at them and that they understood what was going on. ***Maybe they looked at the record, I don't know, but they never let me know that they had done anything about it****. I mean it was like sending it off into a void, into a black hole, and* ***never hearing anything back****."*

Ralston JD, et al. *BMJ* 2004; 328:1159.

Summary

Summary

- Prevalence of T2DM among youth is increasing
  - Sedentary lifestyle + obesity
  - Native American, Non-Hispanic Black, and Hispanic patients are most affected
- Youth-Onset T2DM
  - High therapeutic failure rates + rapid β-cell loss = insulin treatment earlier in the disease course
- Risk-based screening criteria should be applied to overweight or obese youth
- Risk factor considerations include maternal history, family history, race/ethnicity, and signs of insulin resistance

Summary

- Diagnostic criteria
  - **Prediabetes**: A1C 5.7% to <6.5%, IFG, IGT
  - **Diabetes**: A1C ≥6.5% or FPG ≥126 mg/dL or 2-h plasma glucose ≥200 mg/dL or random plasma glucose >200 mg/dL (patient with hyperglycemia)
- Lifestyle and diet: weight loss, exercise, nutrition
- Pancreatic autoantibodies should be checked
- Guideline-directed management relies on use of metformin and insulin depending on current HbA1c and target

Summary

- Liraglutide now approved for patients age 10 and older
- Ellipse Trial
  - HbA1c (%): -0.64 by 26 weeks, -0.50 by 52 weeks
  - FPG (mmol/liter): -1.08 by 26 weeks, -1.03 by 52 weeks
  - BMI (kg): -2.3 by 26 weeks, -1.91 kg by 52 weeks
  - Well-tolerated with AEs consistent to liraglutide use
    - Nausea (28.8%), vomiting (25.8%), and hypoglycemia (24.2%)
- Provider compassion and optimism aid adherence
- Involve the youth and parent: effective communication involving shared decision-making

Thank You!