Liraglutide in Children and Adolescents with Type 2 Diabetes

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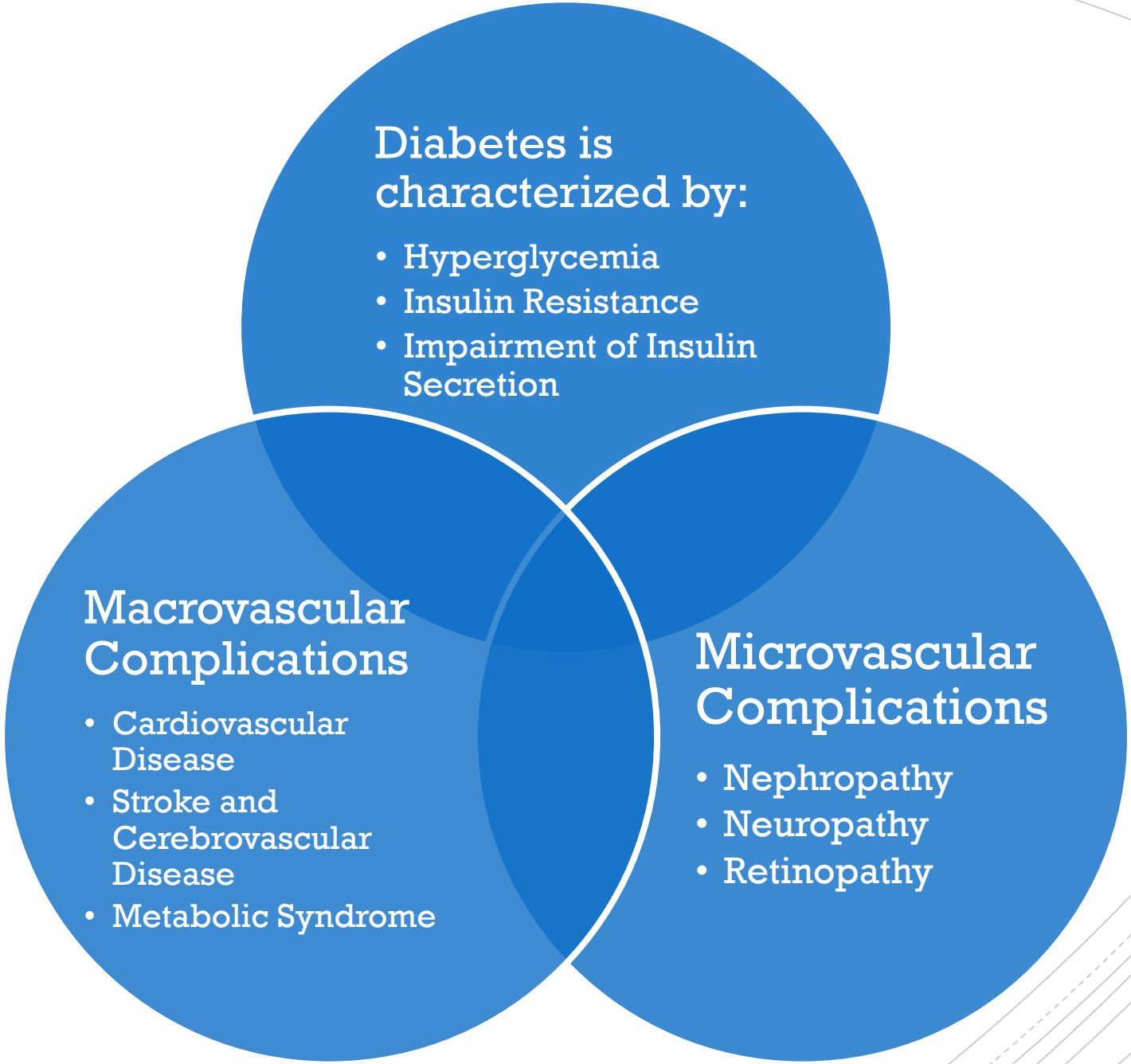
Objectives

1. Define the increased incidence of type 2 diabetes mellitus in children and adolescents
2. Explain the limitations of current treatment options for type 2 diabetes in children and adolescents
3. Discuss the results of the Ellipse Trial
4. Apply the results of the Ellipse Trial to clinical practice and future research

Diabetes Mellitus (DM)



Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes.* 2008;26(2):77.

Sugar, Sugar, how'd you get so fly?

The Rise of Type 2 DM in Children and Adolescents

- Historically, DM in children and adolescents was type 1 DM
  - 1990s: Only 3% of DM cases were Type 2
  - 2003: 20% of pediatric and 50% of adolescent cases were type 2
- The SEARCH for Diabetes in Youth Study (2014)
  - Prevalence has increased by 30.5% (95% CI 17.3-45.1)
- Driven by a rise in childhood obesity and sedentary lifestyle

Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr.* 2005;146(5):693-700.
Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr.* 1996;128(5 Pt 1):608-615.
Dabelea D, Bell RA, D'Agostino RB, Jr., et al. Incidence of diabetes in youth in the United States. *Jama.* 2007;297(24):2716-2724.

Question 1

What are the implications of the increased prevalence of type 2 DM in our young patients?

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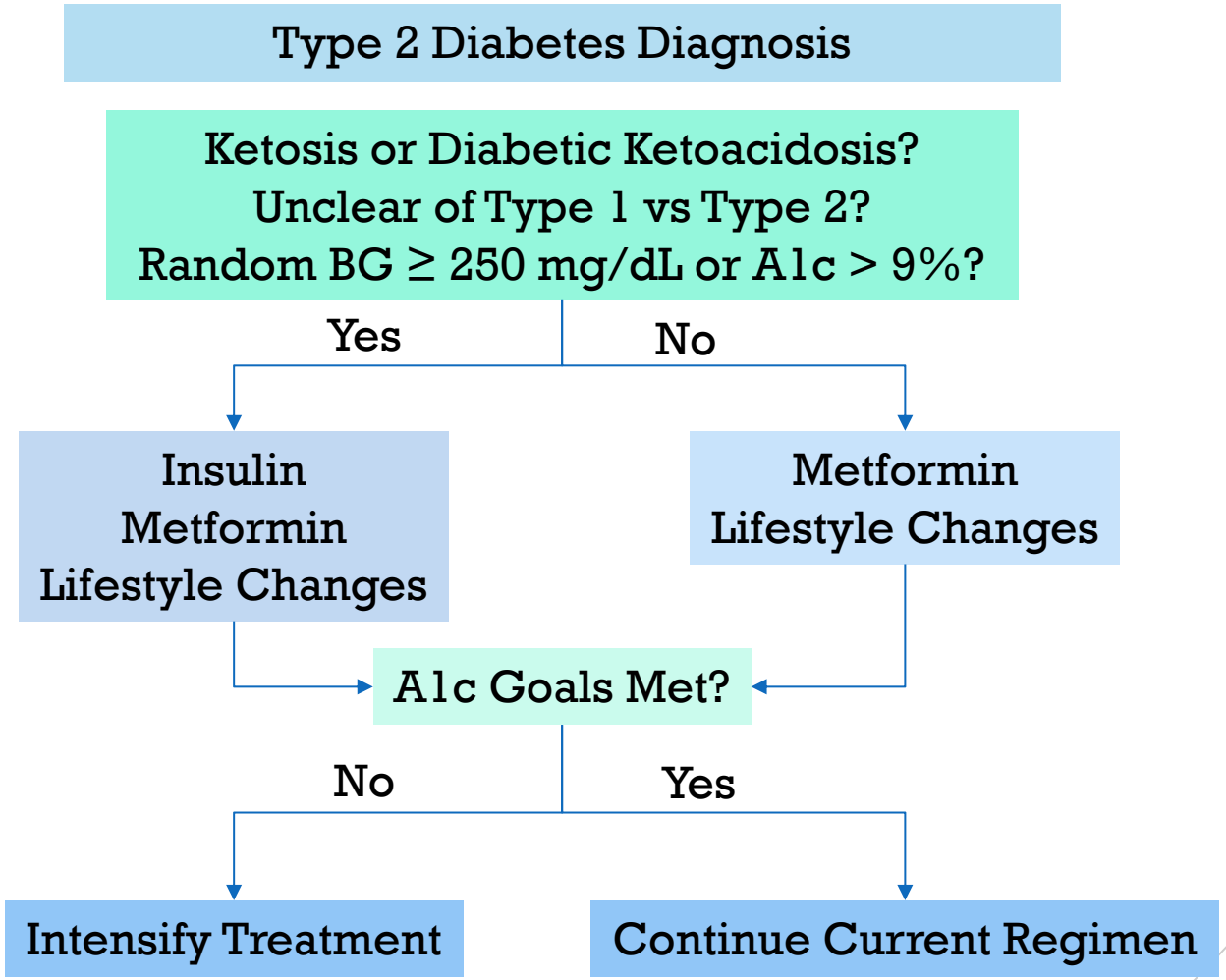
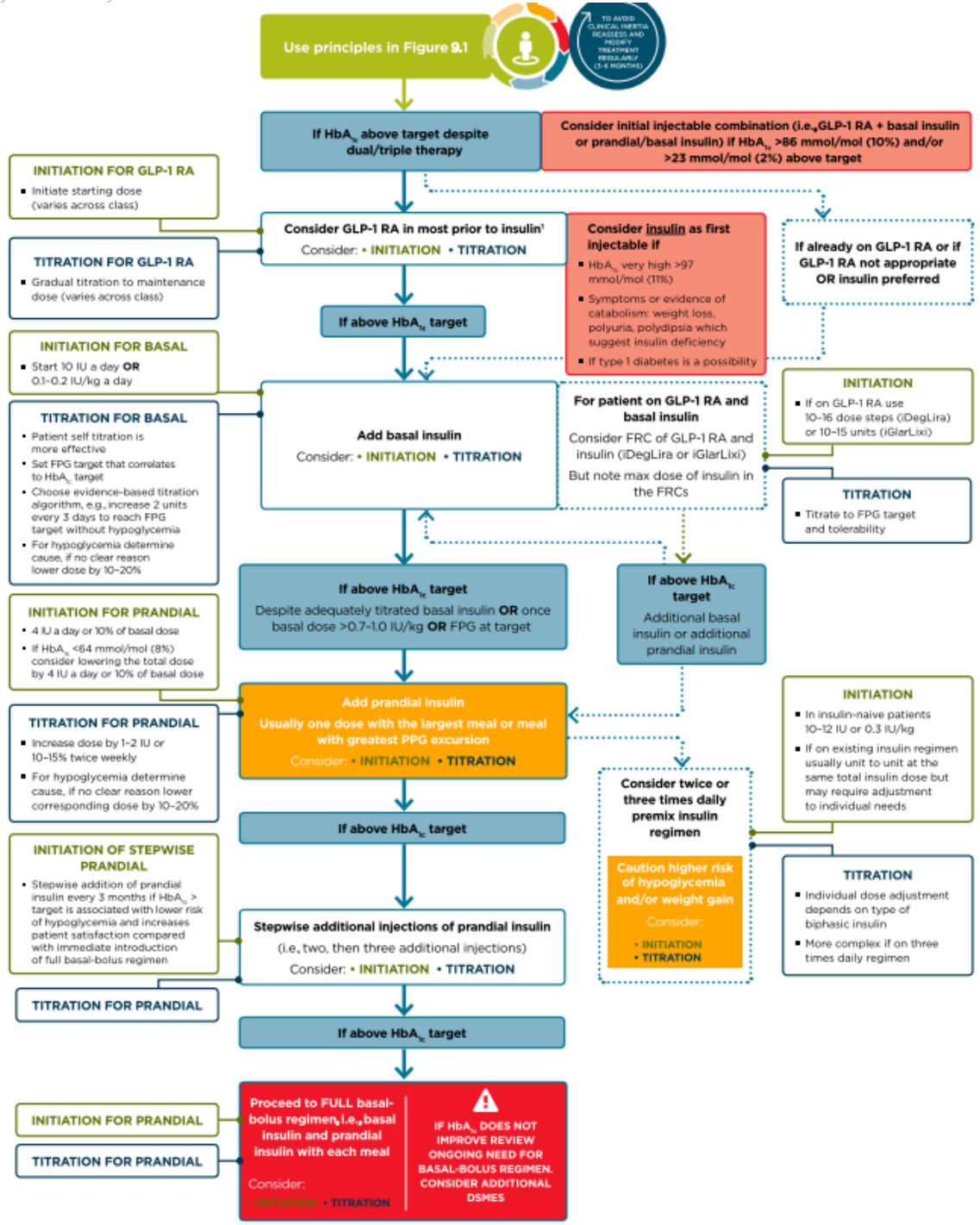
Management of Type 2 Diabetes Mellitus in Children and Adolescents



Copeland KC, Silverstein J, Moore KR, et al. Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents. *Pediatrics.* 2013;131(2):364-382.
Springer SC, Silverstein J, Copeland K, et al. Management of type 2 diabetes mellitus in children and adolescents. *Pediatrics.* 2013;131(2):e648-664.

Question 2

Who can tell me how to manage type 2 diabetes in adults…?


Use principles in Figure 9.1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If HbA1c above target despite dual/triple therapy
Consider initial injectable combination (i.e. GLP-1 RA + basal insulin or prandial/basal insulin) if HbA1c >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target
INITIATION FOR GLP-1 RA
Initiate starting dose (varies across class)
TITRATION FOR GLP-1 RA
Gradual titration to maintenance dose (varies across class)
Consider GLP-1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
HbA1c very high >97 mmol/mol (11%)
Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
If type 1 diabetes is a possibility
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above HbA1c target
INITIATION FOR BASAL
Start 10 IU a day OR 0.1–0.2 IU/kg a day
TITRATION FOR BASAL
Patient self titration is more effective
Set FPG target that correlates to HbA1c target
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Add basal insulin
Consider: • INITIATION • TITRATION
For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs
INITIATION
If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)
TITRATION
Titrate to FPG target and tolerability
If above HbA1c target
Despite adequately titrated basal insulin OR once basal dose >0.7–1.0 IU/kg OR FPG at target
If above HbA1c target
Additional basal insulin or additional prandial insulin
INITIATION FOR PRANDIAL
4 IU a day or 10% of basal dose
If HbA1c <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose
TITRATION FOR PRANDIAL
Increase dose by 1–2 IU or 10–15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION
INITIATION
In insulin-naive patients 10–12 IU or 0.3 IU/kg
If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs
Consider twice or three times daily premix insulin regimen
Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION
TITRATION
Individual dose adjustment depends on type of biphasic insulin
More complex if on three times daily regimen
If above HbA1c target
INITIATION OF STEPWISE PRANDIAL
Stepwise addition of prandial insulin every 3 months if HbA1c > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION
TITRATION FOR PRANDIAL
If above HbA1c target
INITIATION FOR PRANDIAL
TITRATION FOR PRANDIAL
Proceed to FULL basal-bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION
IF HbA1c DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES

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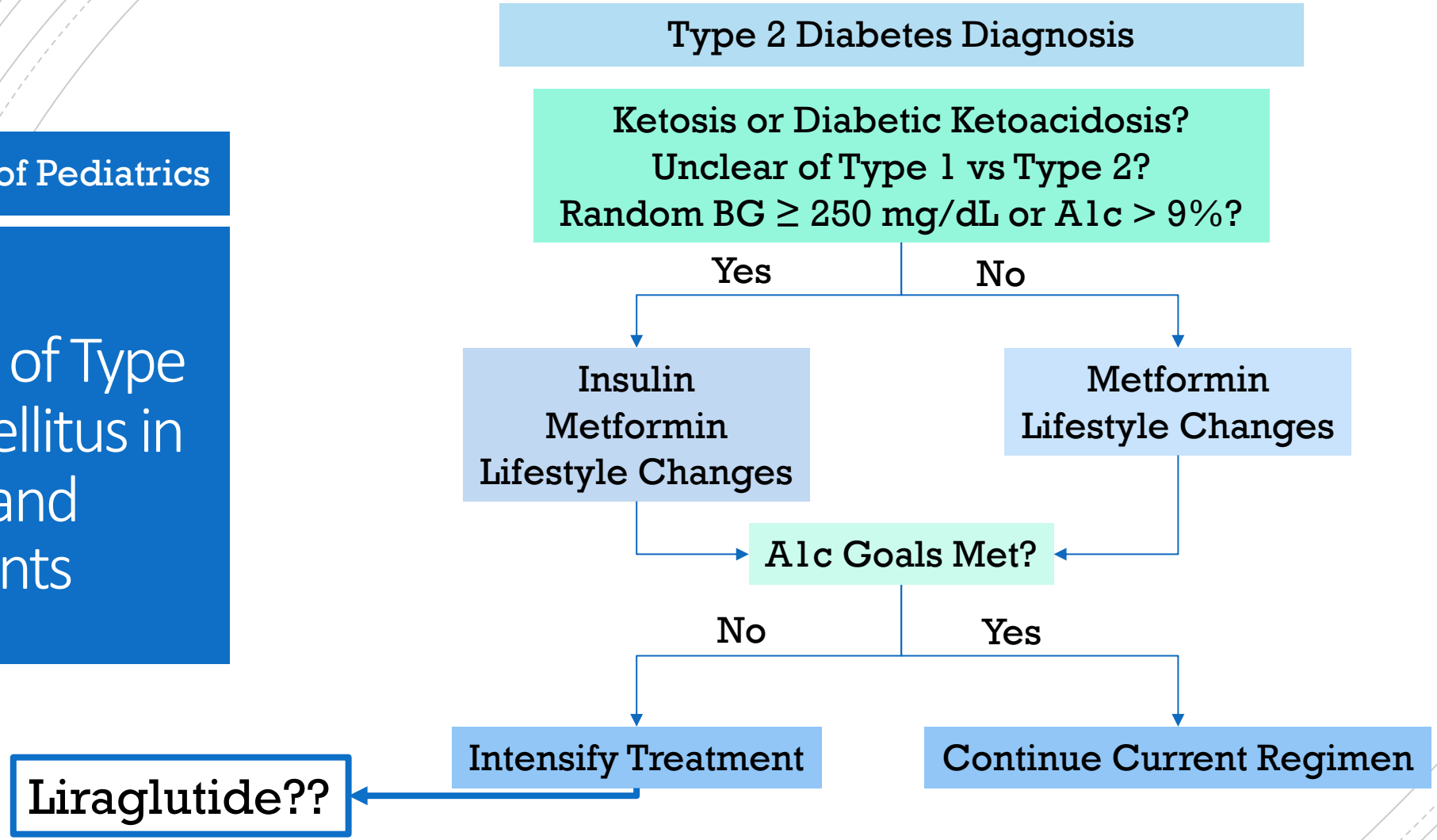
Management of Type 2 Diabetes Mellitus in Children and Adolescents



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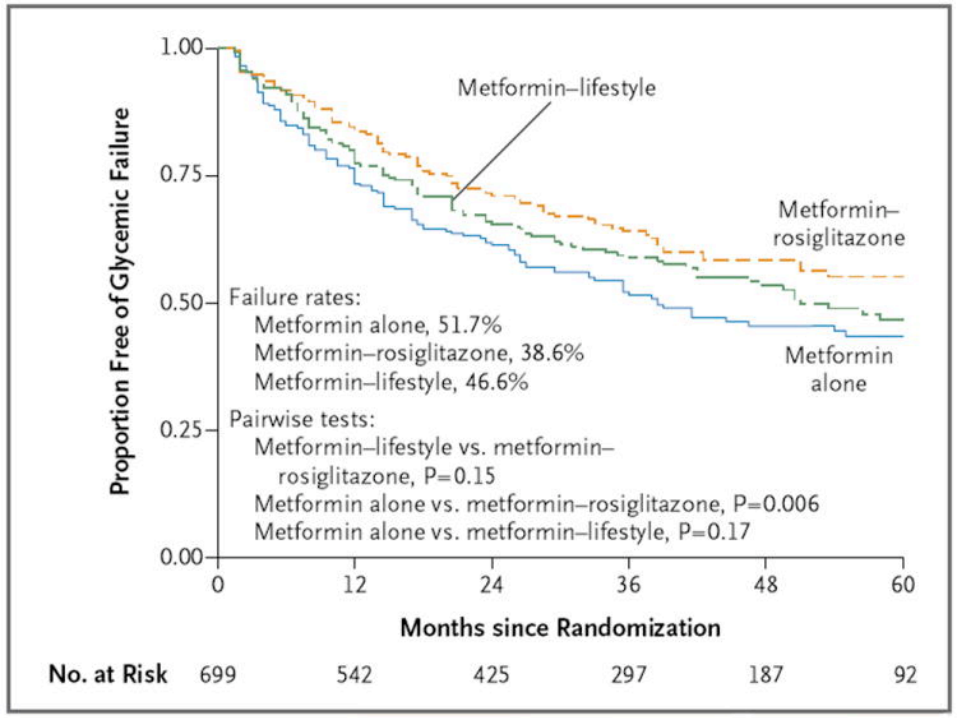
Springer SC, Silverstein J, Copeland K, et al. Management of type 2 diabetes mellitus in children and adolescents. *Pediatrics.* 2013;131(2):e648-664.
9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S90-S102.
13. Children and Adolescents: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S148-S164.

The TODAY Study

A clinical trial to maintain glycemic control in youth with type 2 diabetes.



Results:

- 45.6% of patients experienced treatment failure
- Median time to treatment failure of 11.5 months
- Rates of treatment failure were higher than in comparable studies in adults

Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med.* 2012;366(24):2247-2256.

Bottom Line

1. Prevalence of type II DM continues to increase in young patients
2. Treatment options are limited
3. High failure rates

Pharmacology Review

GLUCAGON-LIKE PEPTIDE 1 (GLP-1)

- GLP-1 is an incretin hormone secreted the lower gut
- Stimulates endogenous insulin secretion in a glucose-dependent manner
- Decreases glucagon levels, reduces gastric emptying, and reduces food intake

LIRAGLUTIDE (*VICTOZA®*)

- GLP-1 analog to mimic endogenous GLP-1
- Approved for type 2 DM in children and adolescents June 2019
- U.S. BOXED WARNING: Thyroid Tumors
- Dose: 0.6 mg SC daily x 7 days, then 1.2 mg SC daily
  - May titrate up to a maximum of 1.8 mg SC daily, if tolerated

Lind M, et al. Glucagon-like peptide 1 (GLP-1) analogue combined with insulin reduces HbA1c and weight with low risk of hypoglycemia and high treatment satisfaction. Prim Care Diabetes. 2012;6(1):41-6.
DeVries JH, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care. 2012;35(7):1446-54.

NEMJ, April 2019.

The ELLIPSE TRIAL

- Primary Investigator:
  - Dr. William V. Tamborlane from Yale Pediatrics Department
- Trial Design:
  - Double-blind, randomized, placebo-controlled study
- Primary Objective:
  - Confirm the superiority of liraglutide versus placebo when added to metformin ± basal insulin in controlling type 2 DM in children and adolescents
- Primary Endpoint:
  - Change in HbA1c from baseline to week 26
- Safety Endpoints:
  - Adverse events (AE) and Serious Adverse Events (SAE)

Tamborlane WV, Barrientos-Perez M, Fainberg U, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. *N Engl J Med.* 2019;381(7):637-646.

Study Population

INCLUSION CRITERIA

- Children and adolescents between the ages of 10–16 years
- Diagnosis of type 2 diabetes mellitus and treated for at least 30 days
- HbA1c
  - ≥ 7.0% and ≤ 11% if diet and exercise treated
  - ≥ 6.5% and ≤ 11% if treated pharmacologically
- Body mass index (BMI) >85% percentile

EXCLUSION CRITERIA

- Type 1 diabetes or Maturity onset diabetes of the young (MODY)
- Use of agents other than metformin and/or basal insulin
- Recurrent severe hypoglycemia or hypoglycemic unawareness
- History of chronic pancreatitis or idiopathic acute pancreatitis
- Uncontrolled hypertension

Question 3

Who was the 'average' patient in this trial?

Baseline Demographics

Study Participants	
Age	14.6 years old
Time from Diagnosis	1.9 years
Weight	91.5 kg
Body Mass Index	33.9 kg/m^2
Diabetes Management at Baseline	
A1c	7.78%
Fasting Blood Glucose	151.8 mg/dL
Average Metformin Dose	1894 mg/day
Patients on Insulin	18.7%

Trial Design

Screening (n=307) → 12 Week Run In Period → Randomization (n=135)

26 Weeks

Liraglutide or Placebo Titration
- Initial Dose: 0.6 mg/day
- Increased by 0.6 mg/day each week over 2-3 weeks based on efficacy and ADR

Liraglutide Group (n=66)
- Liraglutide 0.6 mg – 1.8 mg SC daily
- Metformin 1000 mg – 2000 mg PO daily
- +/- Insulin (↓ x 20%)
- Diet and Exercise Regimen

VS

Placebo Group (n=69)
- Placebo 0.6 mg – 1.8 mg SC
- Metformin 1000 mg – 2000 mg PO daily
- +/- Insulin (↓ x 20%)
- Diet and Exercise Regimen

Rescue Treatment PRN
- Either basal insulin alone, or in combination with rapid-acting insulin

Statistical Methodology

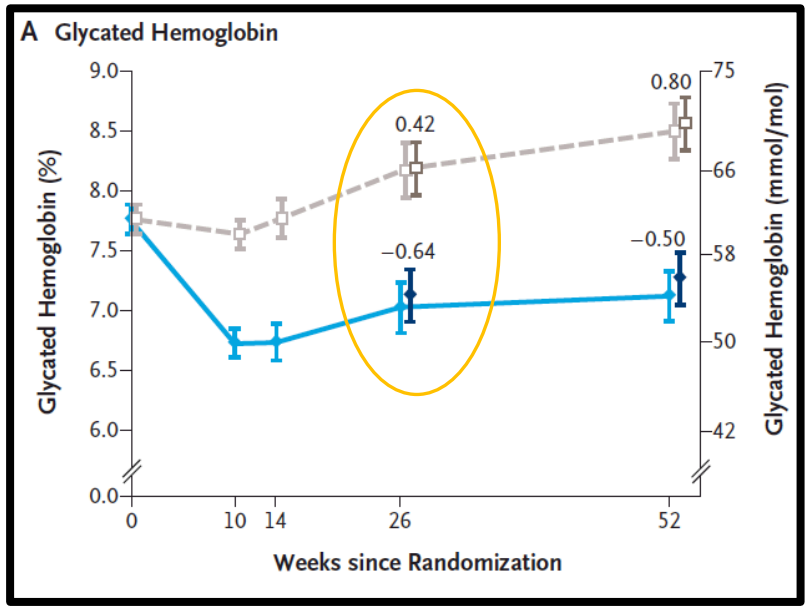
N = 47 per group	Required for **80% power,** assuming mean difference in A1c change of 0.9%
Pattern-Mixture Model	To help determine the **true treatment difference** regardless of rescue treatment
Statistical Analyses	**Appropriately used** for all endpoints

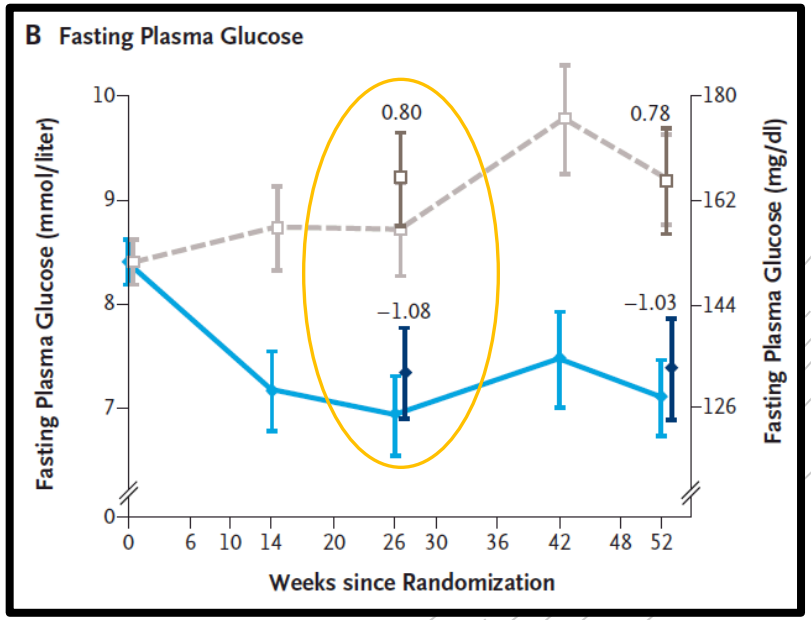
Results

Efficacy Endpoints

- ★ Change in A1c: **-0.64%** vs. +0.42%
  - Treatment Difference: -1.06% (90% CI: -1.89 to -0.70)
- ★ Treatment Goal (A1c < 7.0%): **63.7%** vs. 36.5%
- ★ Change in Fasting BG: **-19.44 mg/dL** vs. 14.4 mg/dL
  - Treatment Difference: -33.84 mg/dL (90% CI: -3.09 to -0.66)
- Rescue Therapy Required: **13.6%** vs. 33.3%

"LIRAGLUTIDE IS SUPERIOR TO PLACEBO IN IMPROVING GLYCEMIC CONTROL…"





Safety Endpoints

- Adverse Events: **84.8%** vs. 80.9%
  - Relative Risk: 1.05 (90% CI: 0.90 to 1.22)
- Serious Adverse Events: **13.6%** vs. 5.9%
  - Relative Risk: 2.32 (90% CI: 0.75 to 7.16)
- ★ 'Minor' Hypoglycemia: **24.2%** vs. 10.3%
  - Relative Risk: 2.35 (90% CI: 1.04 to 5.35)
- ★ Symptomatic Hypoglycemia: **28.8%** vs. 8.8%
  - Relative Risk: 3.26 (90% CI: 1.39 to 7.66)

Adverse Events Definition	
Serious	Death, life-threatening, hospitalization, or required intervention
Hypoglycemia Definitions	
'Minor'	Symptoms of hypoglycemia or BG < 55.8 mg/dL (trial defined)
Documented Symptomatic	Symptoms of hypoglycemia + BG ≤ 70 mg/dL (ADA defined)

"… AT THE COST OF MORE ADVERSE EVENTS"

Assessment

STRENGTHS

- Studied in a population with limited treatment options
- Used pattern-mixture model to estimate treatment effect
- Addressed missing data conservatively

LIMITATIONS

- Did not discuss diet and exercise regimen
- Liraglutide Group at baseline:
  - +4 kg, +0.18% A1c, +10 mg/dL BG, +% on insulin
- Definition of 'Minor Hypoglycemia'
- Trial Duration

So, Now What?

- Liraglutide is **not on formulary** at Beaumont
  - Not used for acute glucose management, but may show up in transitions of care
- Liraglutide **reduces A1c** in children/adolescents with DM
  - Treatment option for patients who are unable to control their diabetes on metformin ± insulin
  - Clinical outcomes are still lacking
- Liraglutide increases risk of **hypoglycemia**
  - Particularly concerning in young patients
- Future Direction
  - Long-term, clinical outcome trials
  - Response Durability