A Review of Diabetes Management Options

NAME: Yolanda Smith MSN, RN, ANP-BC

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Objectives

At the conclusion of this presentation, the participant should be able to:

1. Discuss the Epidemiology of Diabetes and Mississippi Rates
2. Discuss the ADA Standards of Medical Care
3. Discuss the AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm
4. Discuss recent Cardiovascular Outcomes Trials (CVOT's) in the Management of Type 2 Diabetes.

Diabetes by the Numbers

30.3 million
Americans have DM

Diagnosed – 23.1 million
Undiagnosed – 7.2 million

86 million
Americans have pre-diabetes

7th
leading cause of death in the U.S.

CDC: National Diabetes Statistics Report 2017
https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
(Accessed 8/14/2017)

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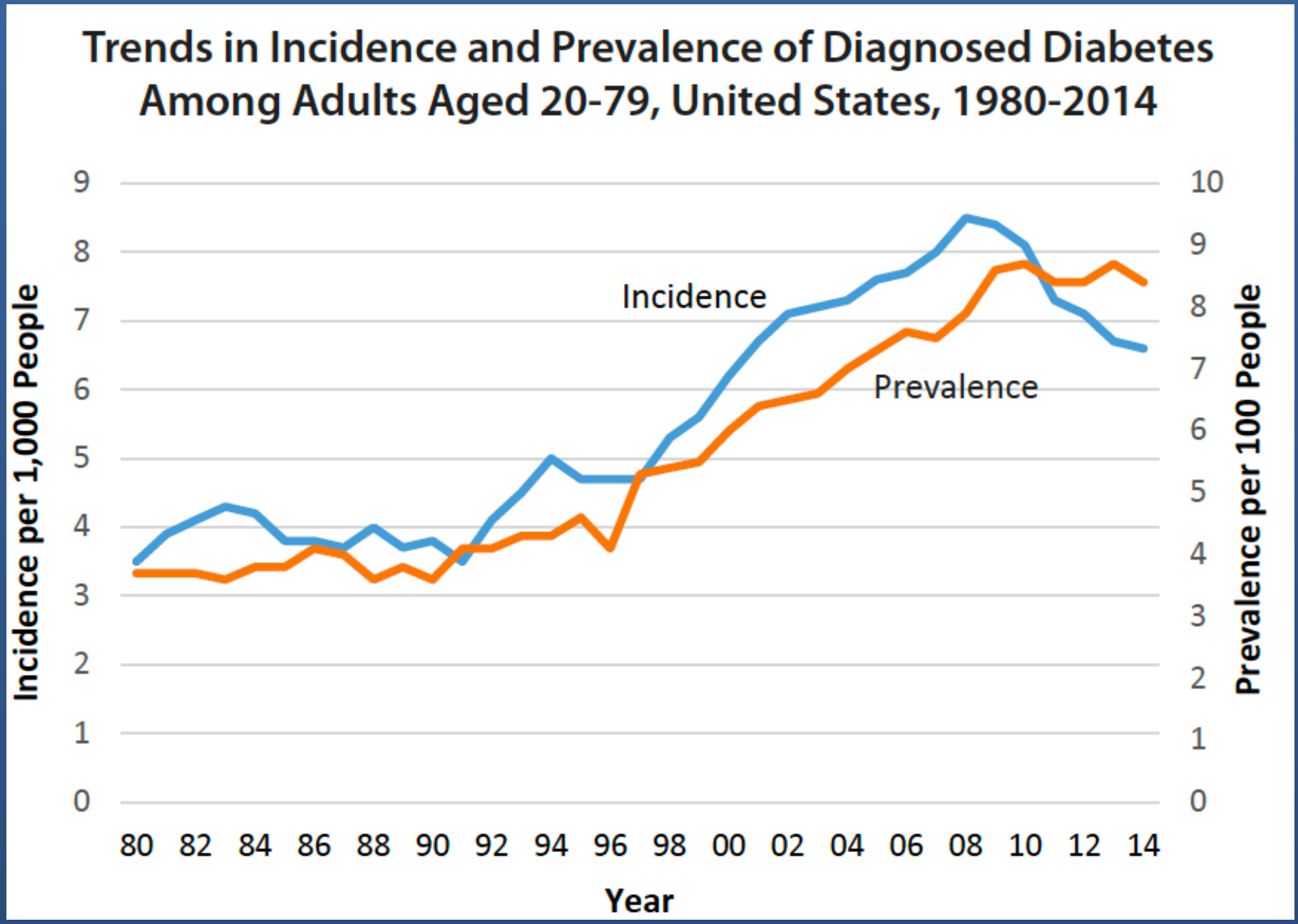
Diabetes in the United States (U.S.)

- Leading cause of:
  - Kidney failure
  - Lower-limb amputations
  - Adult-onset blindness
- Diagnosed diabetes accounts for **>20%** of health-care spending!

https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/diabetes-aag.pdf (Accessed 2/14/2017)



https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/diabetes-aag.pdf (Accessed 2/14/2017)

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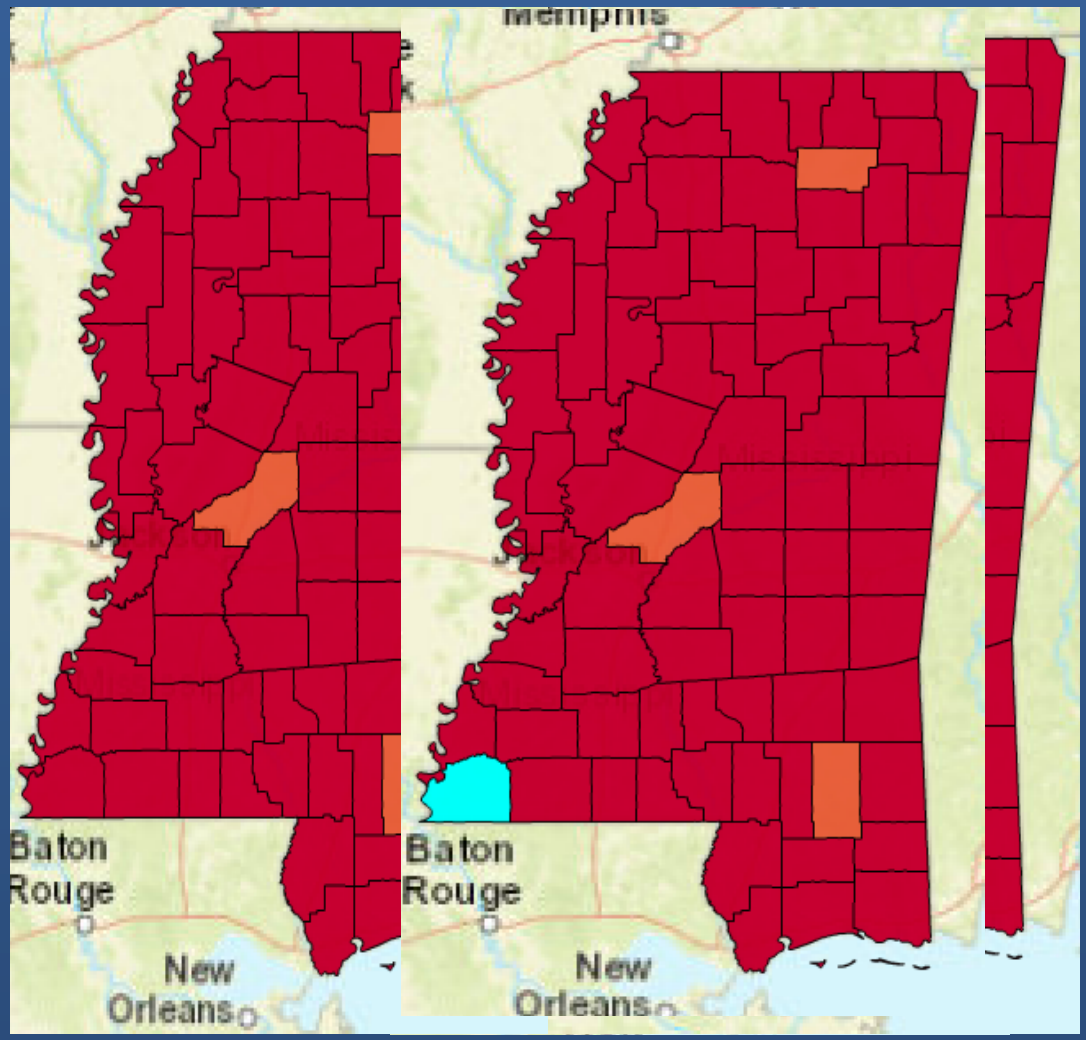
Diagnosed Diabetes Among Adults: 2015

- MS is #1 – 13.6% diagnosed with DM
  - The county data is 2014
- Trail
  - Puerto Rico – 14.7%
  - Guam – 14.2%
- Highest Rate in MS Counties (2014)
  - Wilkinson – 16.7%
  - Holmes – 16.3%
  - Tunica – 16.2%
  - Noxubee/Claiborne – 15.9%



https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html (Accessed 8/14/2017)

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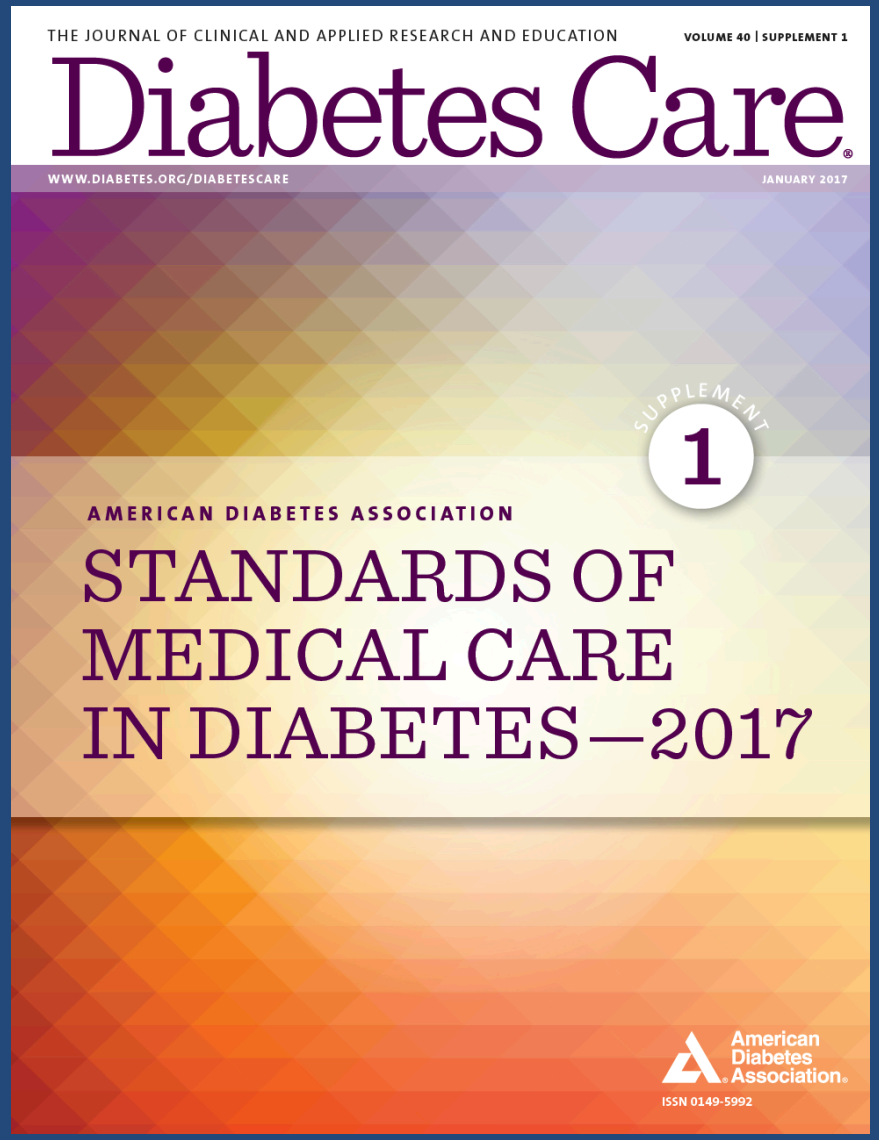
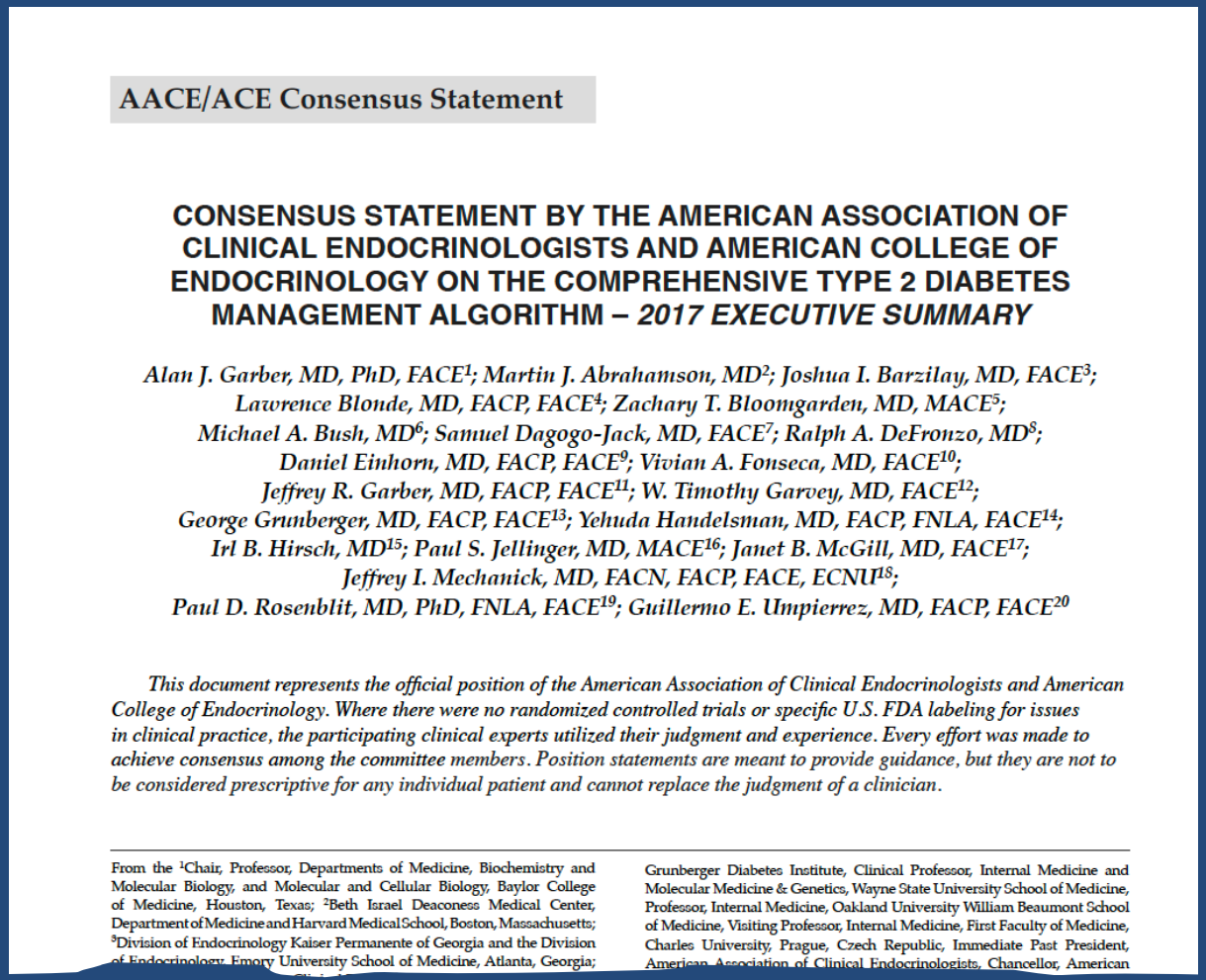
Diabetes Treatment Guidelines





AACE/ACE Consensus Statement

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2017 EXECUTIVE SUMMARY*

Alan J. Garber, MD, PhD, FACE[1]; Martin J. Abrahamson, MD[2]; Joshua I. Barzilay, MD, FACE[3]; Lawrence Blonde, MD, FACP, FACE[4]; Zachary T. Bloomgarden, MD, MACE[5]; Michael A. Bush, MD[6]; Samuel Dagogo-Jack, MD, FACE[7]; Ralph A. DeFronzo, MD[8]; Daniel Einhorn, MD, FACP, FACE[9]; Vivian A. Fonseca, MD, FACE[10]; Jeffrey R. Garber, MD, FACP, FACE[11]; W. Timothy Garvey, MD, FACE[12]; George Grunberger, MD, FACP, FACE[13]; Yehuda Handelsman, MD, FACP, FNLA, FACE[14]; Irl B. Hirsch, MD[15]; Paul S. Jellinger, MD, MACE[16]; Janet B. McGill, MD, FACE[17]; Jeffrey I. Mechanick, MD, FACN, FACP, FACE, ECNU[18]; Paul D. Rosenblit, MD, PhD, FNLA, FACE[19]; Guillermo E. Umpierrez, MD, FACP, FACE[20]

This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

From the [1]Chair, Professor, Departments of Medicine, Biochemistry and Molecular Biology, and Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas; [2]Beth Israel Deaconess Medical Center, Department of Medicine and Harvard Medical School, Boston, Massachusetts; [3]Division of Endocrinology Kaiser Permanente of Georgia and the Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia; Grunberger Diabetes Institute, Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine, Professor, Internal Medicine, Oakland University William Beaumont School of Medicine, Visiting Professor, Internal Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic, Immediate Past President, American Association of Clinical Endocrinologists, Chancellor, American

Endocrine Practice. 2017; 23(2):207 - 238

ADA Standards of Medical Care: 2017

1. Promoting Health and Reducing Disparities in Populations
2. Classification and Diagnosis of Diabetes
3. Comprehensive Medical Evaluation and Assessment of Comorbidities
4. Lifestyle Management
5. Prevention or Delay of T2DM
6. Glycemic Targets
7. Obesity Management for the Treatment of T2DM
8. Pharmacologic Approaches to Glycemic Treatment
9. Cardiovascular Disease and Risk Management
10. Microvascular Complications and Foot Care
11. Children and Adolescents
12. Management of Diabetes in Pregnancy
13. Diabetes Care in the Hospital

Diabetes Care. 2017;40(1): S4-S5

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Classification and Diagnosis

- Type 1 diabetes (T1DM)
  - Autoimmune β-cell destruction leading to absolute insulin deficiency
- Type 2 diabetes (T2DM)
  - Due to progressive loss of β-cell insulin secretion after insulin resistance
- Gestational diabetes mellitus (GDM)
  - Diabetes diagnosed in the 2nd or 3rd trimester of pregnancy that was not clearly overt diabetes prior to gestation
- Specific types due to other causes (monogenic diabetes syndromes)
  - Neonatal diabetes
  - Maturity-onset diabetes of the young (MODY)
  - Diseases of the exocrine pancreas (i.e. cystic fibrosis)
  - Other: drug/chemical induced (i.e. glucocorticoid use, HIV/AIDS treatment, organ transplantation)

Diabetes Care. 2017;40(1): S11-S24

Criteria for the Diagnosis of Diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
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, results should be confirmed by repeat testing.

Diabetes Care. 2017;40(1): S13

Glycemic Targets

- Patient self-monitoring of blood glucose (SMBG)
  - Utilized by major clinical trials as part of interventions to demonstrate benefit
- Hemoglobin A1c (A1C)
  - An indirect measure of average glycemia and does NOT provide a measure of glycemic variability or hypoglycemia
- Continuous glucose monitoring (CGM)
  - Measures interstitial glucose and includes alarms for hypo/hyperglycemia

Diabetes Care. 2017;40(1): S48-56

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Glycemic Targets
Nonpregnant Adults with Diabetes

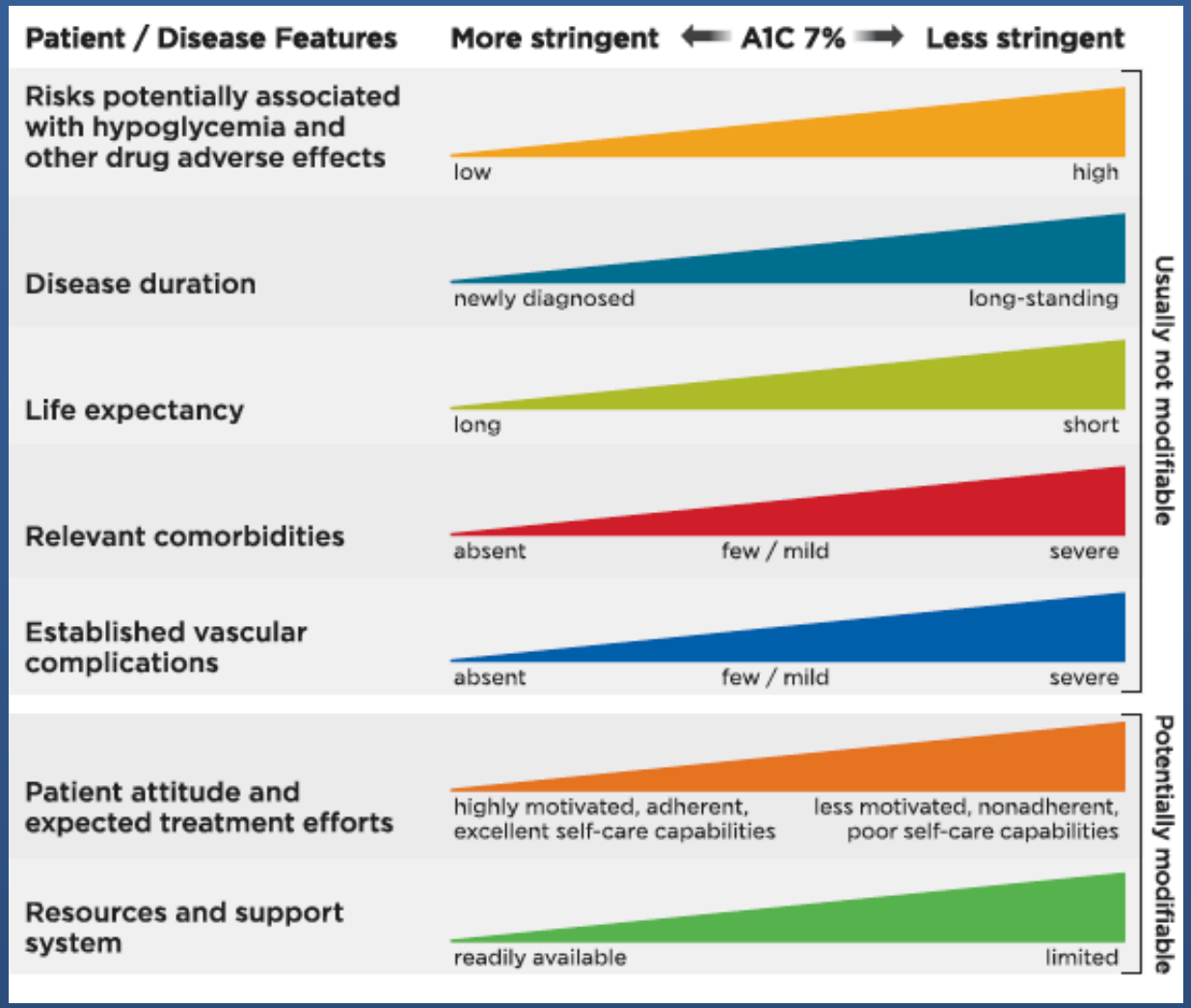
A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Diabetes Care. 2017;40(1): S48-56

Balancing Act of Glycemic Control

- Evaluate patient and disease factors to determine optimal A1C goal
- Hypoglycemia risk should also be assessed prior to determining goal



Diabetes Care. 2017;40(1): S53

Classification of Hypoglycemia

Level	Glycemic Criteria	Description
Glucose alert value (level 1)	≤ 70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose lowering therapy
Clinically significant hypoglycemia (level 2)	< 54 mg/dL	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with **severe cognitive impairment requiring external assistance** for recovery

- Hypoglycemia prevention is a critical component of diabetes management

Diabetes Care. 2017;40(1): S53

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Pharmacologic Therapy for T1DM

- Most people with T1DM should be treated with multiple daily injections of prandial insulin and basal insulin (basal/bolus) or continuous subcutaneous insulin infusion (CSII).
- Most individuals with T1DM should use rapid-acting insulin analogs to reduce hypoglycemia risk.
- Consider educating individuals with T1DM on matching prandial insulin doses to carbohydrate intake, pre-meal blood glucose levels, and anticipate physical activity.
- Individuals with T1DM who have been successfully using CSII should have continued access to this therapy after they turn 65 years of age.

Diabetes Care. 2017;40(1): S64

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Pharmacologic Therapy for T2DM

- **Metformin**, if not contraindicated and if tolerated, is **the preferred initial pharmacologic agent** for the treatment of T2DM.
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed T2DM who are symptomatic and/or have A1C ≥ 10% and/or blood glucose levels ≥ 300 mg/dL.
- If noninsulin monotherapy at maxi tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin.

Diabetes Care. 2017;40(1): S65

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Pharmacologic Therapy for T2DM, cont'd

- A patient-centered approach should be used to guide the choice of pharmacologic agents. Consideration: efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences.
- For patients with T2DM who are not achieving glycemic goals, **insulin therapy should not be delayed.**
- In patients with long-standing suboptimally controlled T2DM and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as **they have been shown to reduce cardiovascular and all-cause mortality** when added to standard care.
  Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.
  (Canagliflozin has now shown benefit)

Diabetes Care. 2017;40(1): S65

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Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy**

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy

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Therapy Additions

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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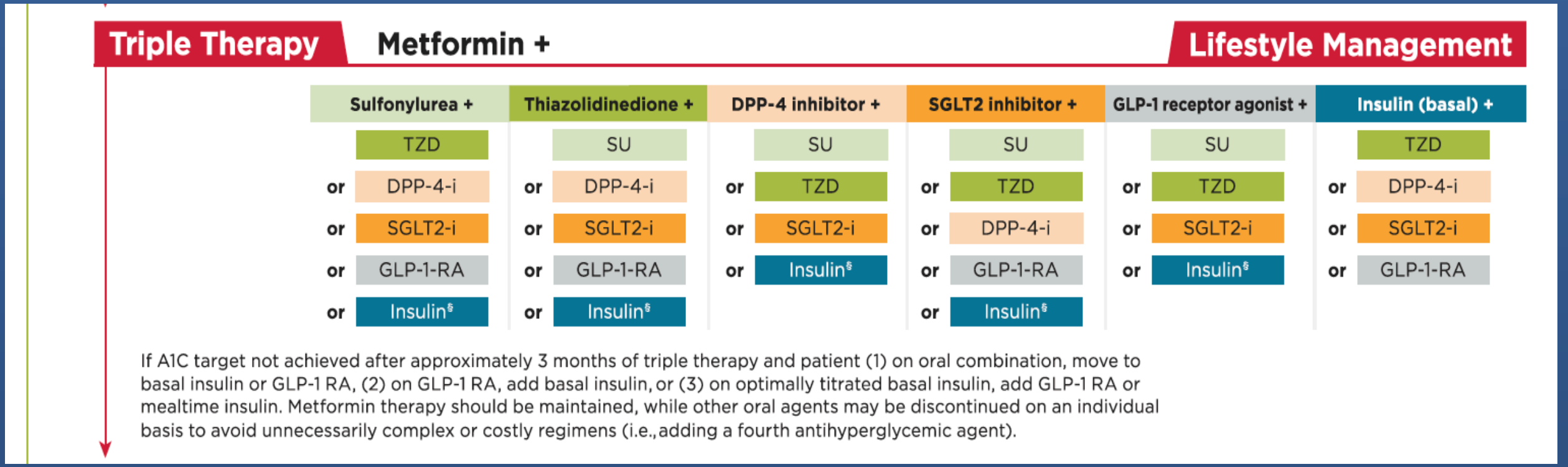
Therapy Additions



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A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy**

Combination Injectable Therapy

Initiate Basal Insulin

Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day

Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target

For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

If A1C not controlled, **consider combination injectable therapy**

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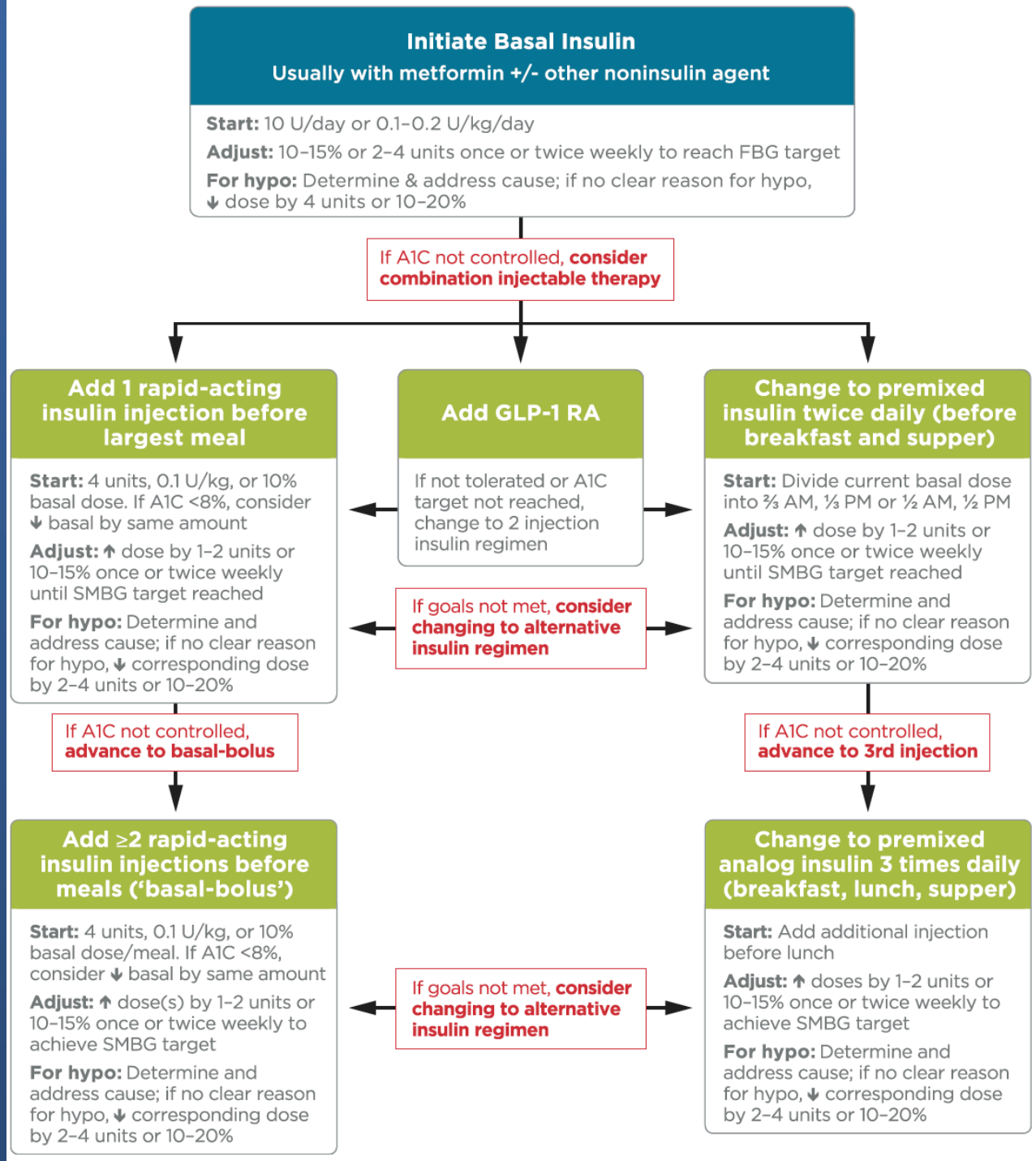
Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent
Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%
If A1C not controlled, consider combination injectable therapy
Add 1 rapid-acting insulin injection before largest meal
Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to basal-bolus
Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
Add GLP-1 RA
If not tolerated or A1C target not reached, change to 2 injection insulin regimen
If goals not met, consider changing to alternative insulin regimen
If goals not met, consider changing to alternative insulin regimen
Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to 3rd injection
Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Initiate Basal Insulin

Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day

Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target

For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

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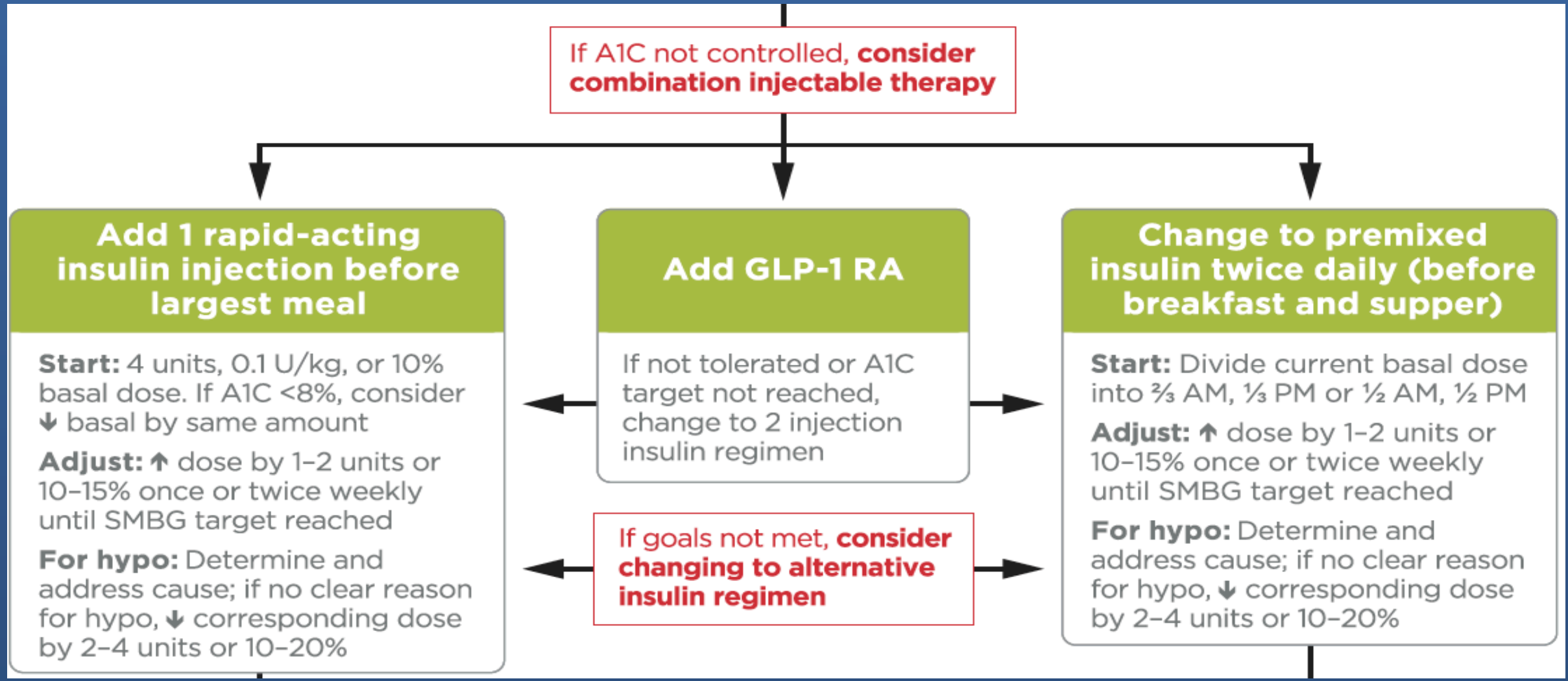

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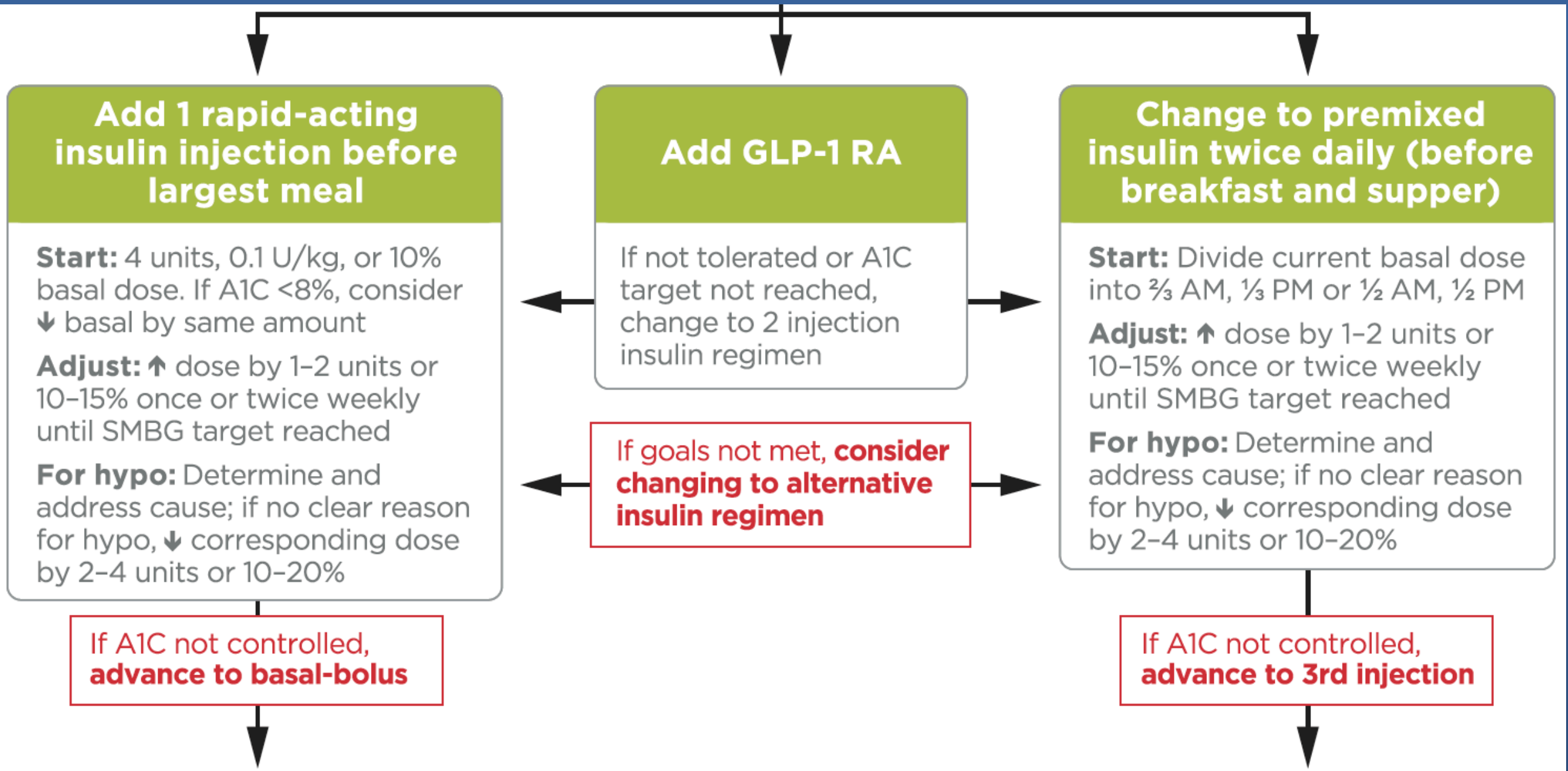

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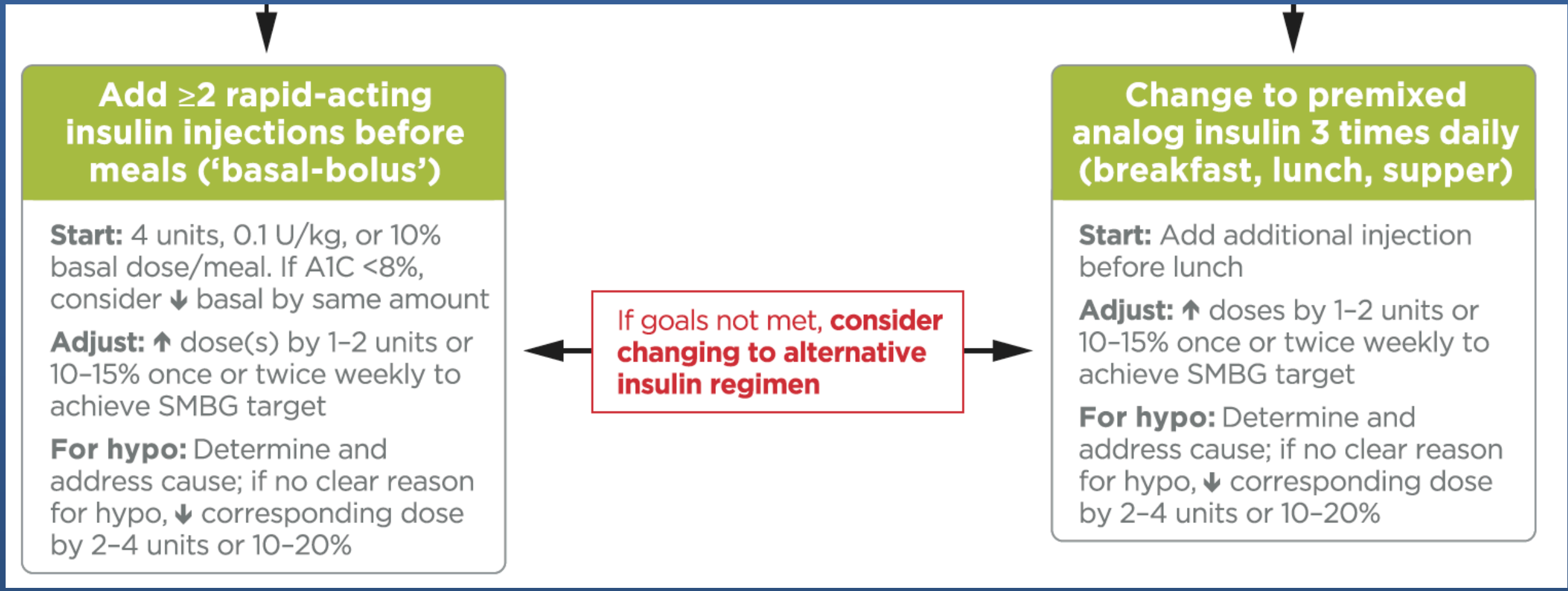

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Chart of Medication for Diabetes

Class	Compound(s)	Cellular mechanism(s)	action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR <30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• Rare hypoglycemia • Relatively higher A1C efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA (IRIS study [42], pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Rare hypoglycemia • ↓ LDL-C	• Modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH • Basal insulin analogs - Glargine - Detemir - Degludec • Premixed insulin products - NPH/Regular 70/30 —70/30 aspart mix —75/25 lispro mix —50/50 lispro mix	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	High#

AACE/ACE Consensus Statement

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2017 EXECUTIVE SUMMARY*

Alan J. Garber, MD, PhD, FACE[1]; Martin J. Abrahamson, MD[2]; Joshua I. Barzilay, MD, FACE[3]; Lawrence Blonde, MD, FACP, FACE[4]; Zachary T. Bloomgarden, MD, MACE[5]; Michael A. Bush, MD[6]; Samuel Dagogo-Jack, MD, FACE[7]; Ralph A. DeFronzo, MD[8]; Daniel Einhorn, MD, FACP, FACE[9]; Vivian A. Fonseca, MD, FACE[10]; Jeffrey R. Garber, MD, FACP, FACE[11]; W. Timothy Garvey, MD, FACE[12]; George Grunberger, MD, FACP, FACE[13]; Yehuda Handelsman, MD, FACP, FNLA, FACE[14]; Irl B. Hirsch, MD[15]; Paul S. Jellinger, MD, MACE[16]; Janet B. McGill, MD, FACE[17]; Jeffrey I. Mechanick, MD, FACN, FACP, FACE, ECNU[18]; Paul D. Rosenblit, MD, PhD, FNLA, FACE[19]; Guillermo E. Umpierrez, MD, FACP, FACE[20]

This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

From the [1]Chair, Professor, Departments of Medicine, Biochemistry and Molecular Biology, and Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas; [2]Beth Israel Deaconess Medical Center, Department of Medicine and Harvard Medical School, Boston, Massachusetts; [3]Division of Endocrinology Kaiser Permanente of Georgia and the Division [illegible] University School of Medicine, Atlanta, Georgia; Grunberger Diabetes Institute, Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine, Professor, Internal Medicine, Oakland University William Beaumont School of Medicine, Visiting Professor, Internal Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic, Immediate Past President, [illegible]

Endocrine Practice. 2017; 23(2):207 - 238

Diabetes Coalition of MISSISSIPPI

AACE/ACE Comprehensive T2DM Management Algorithm

1. Principles for treatment of T2DM
2. Lifestyle therapy
3. Complications-centric Model for care of the overweight/ obese patient
4. Prediabetes algorithm
5. ASCVD risk factor modifications algorithm
6. Goals for glycemic control
7. Glycemic control algorithm
8. Algorithm for adding/ intensifying insulin
9. Profiles of antidiabetic medications.

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AACE/ACE: Principles of the Algorithm

1. Lifestyle therapy
2. Complications-centric Model for care of the overweight/obese pt
3. Individualize A1C target
4. Glycemic targets include fasting and post-prandial
5. Individualize therapy choices
   - Pt characteristics, impact of net cost, formulary restrictions, personal preferences, etc.
6. Minimize hypoglycemia
7. Minimize weight gain
8. Initial cost is only part of total cost
9. Initial A1C stratifies therapy choice
10. Combination therapy usually required – complimentary agents
11. Comprehensive management includes lipids, BP, & related comorbidities
12. Evaluate tx until stable (eg – every 3 mo's)
13. Therapy as simple as possible
14. Algorithm includes every FDA approved agent for DM (12/2016)

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AACE/ACE T2DM A1C Targets

- Individualize target based on:
  - Age
  - Comorbidities
  - Hypoglycemia risk
- A1C ≤ 6.5% - acceptable for most patients
- A1C > 6.5% to < 8%
  - Acceptable if lower target cannot be achieved without adverse outcomes

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AACE Lipid Targets for Patients with Type 2 Diabetes (188,189,197,200,240-251)				
Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme Risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3,4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High Risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease – Diabetes or CKD 3, 4 with 1 or more risk factor(s) – Heterozygous familial hypercholesterolemia	<70	<100	<80
High Risk	≥2 risk factors and 10-year risk >10% **or** CHD risk equivalent[c], including diabetes or CKD 3, 4 with no other risk factors	<100	<130	<90
Moderate Risk	≥2 risk factors and 10-year risk <10%	<100	<130	<90
Low Risk	≤1 risk factor	<130	<160	NR

How many patients with T2DM will fall into Moderate/Low Risk Categories??

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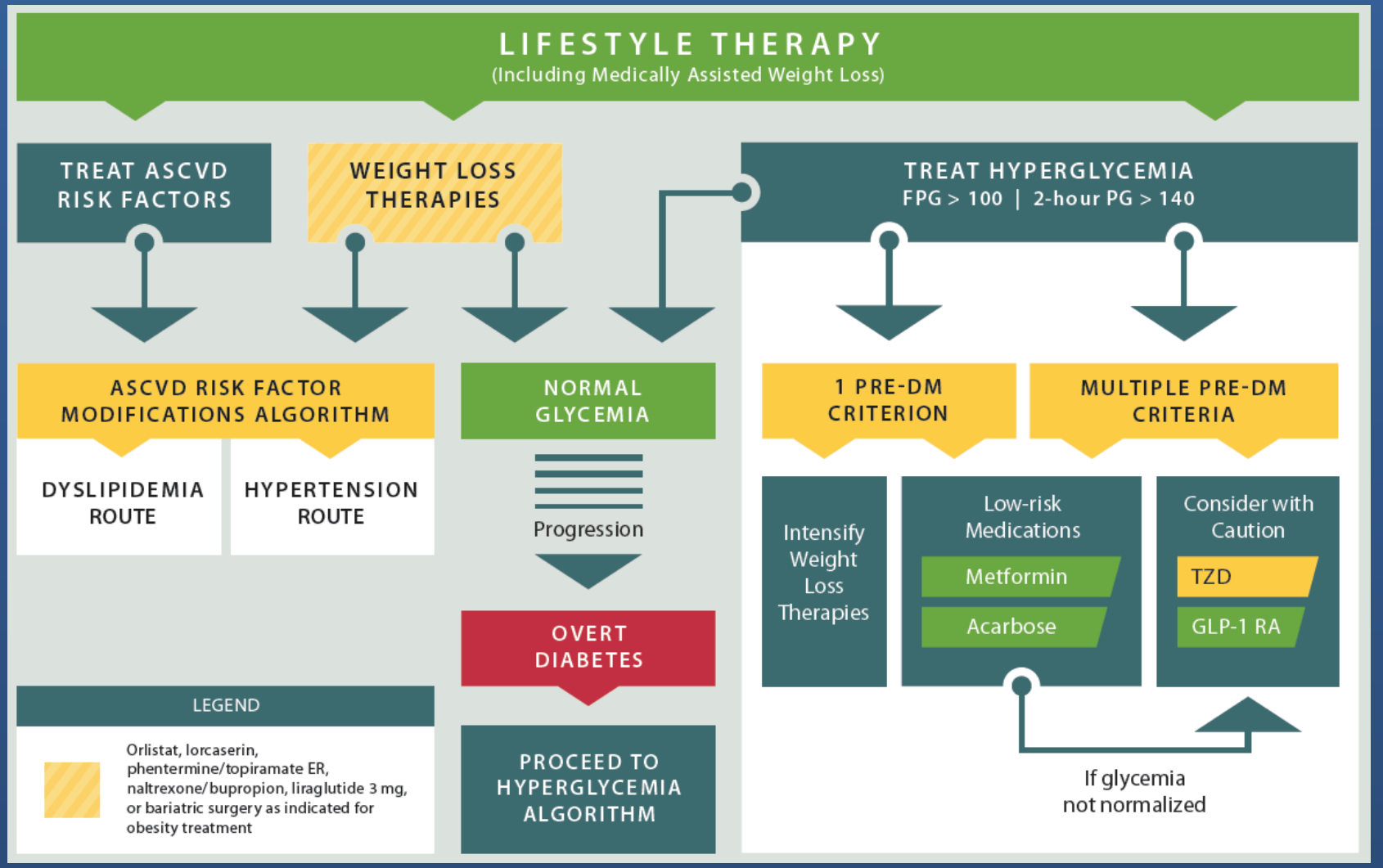
Prediabetes Algorithm

IFG (100 – 125 mg/dL) | IGT (140 – 199 mg/dL) | Metabolic Syndrome (NCEP 2001)



Endocrine Practice. 2017; 23(2):233

Goals for Glycemic Control

Individualize Goals

A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

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PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

TREAT HYPERGLYCEMIA
FPG > 100 | 2-hour PG > 140

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

Intensify Weight Loss Therapies

Low-risk Medications
- Metformin
- Acarbose

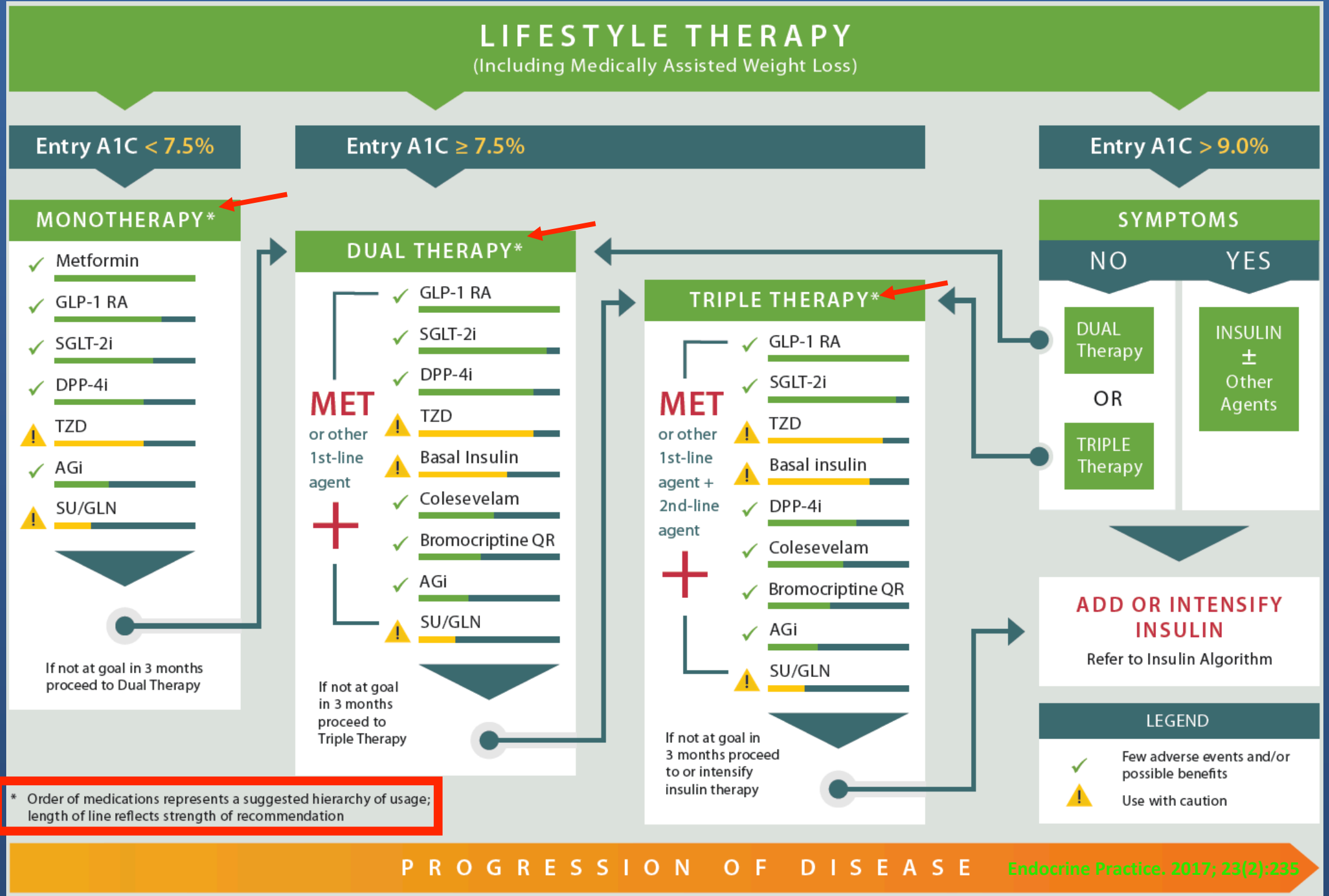
Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

 DOI 10.4158/EP161682.CS


LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)
Entry A1C < 7.5%
Entry A1C ≥ 7.5%
Entry A1C > 9.0%
MONOTHERAPY*
Metformin
GLP-1 RA
SGLT-2i
DPP-4i
TZD
AGi
SU/GLN
If not at goal in 3 months proceed to Dual Therapy
DUAL THERAPY*
MET
or other 1st-line agent
+
GLP-1 RA
SGLT-2i
DPP-4i
TZD
Basal Insulin
Colesevelam
Bromocriptine QR
AGi
SU/GLN
If not at goal in 3 months proceed to Triple Therapy
TRIPLE THERAPY*
MET
or other 1st-line agent + 2nd-line agent
+
GLP-1 RA
SGLT-2i
TZD
Basal insulin
DPP-4i
Colesevelam
Bromocriptine QR
AGi
SU/GLN
If not at goal in 3 months proceed to or intensify insulin therapy
SYMPTOMS
NO
YES
DUAL Therapy
OR
TRIPLE Therapy
INSULIN ± Other Agents
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm
LEGEND
Few adverse events and/or possible benefits
Use with caution
* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
PROGRESSION OF DISEASE
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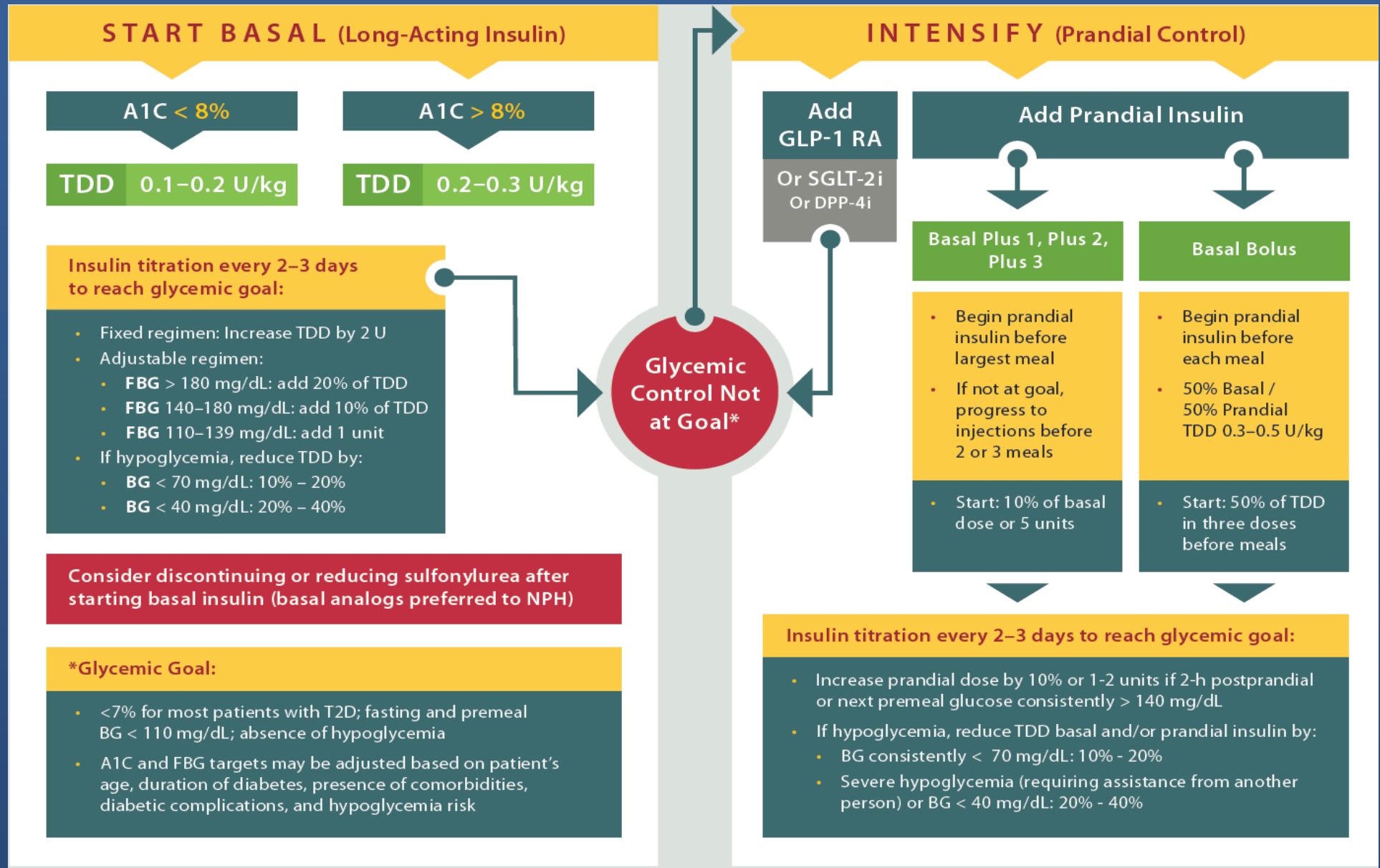
Algorithm for Adding/Intensifying Insulin



PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain-dicated if eGFR < 30 mL/min/1.73 m^2	Exenatide Not Indicated CrCl < 30 / Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m^2 / Genital Mycotic Infections / Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA Indication to prevent CVD death in diabetes plus prior CVD events

Cardiovascular Outcomes Trials (CVOT's)

FDA Guidance for CVOT's

Upper bound of a 2-sided 95% confidence interval for estimated CV risk	
> 1.8	The data are inadequate to support approval. A large safety trial should be conducted
1.3 – 1.8	The potential for CV harm may still exist. An adequately powered and designed post-marketing trial is necessary to show an upper bound < 1.3 *
< 1.3	A post-marketing trial is generally not needed *
* With a reasuring point estimate for overall CV risk	

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf (Accessed 3/30/2017)

Cardiovascular Outcomes Trials

Name of Trial	Drug	Estimated enrollment	
SAVOR *TIMI-53*	Saxagliptin	18,206	Neutral
CAROLINA	Linagliptin	6,000	
CARMELINA	Linagliptin	8,300	
TECOS	Sitagliptin	14,000	Neutral
EXAMINE	Alogliptin	5,380	Neutral
EXSCEL	Exenatide-QW	14,000	Neutral
REWIND	Dulaglutide	9,622	
LEADER	Liraglutide	9,340	Positive benefits
SUSTAIN-6	Semaglutide	3,297	Positive benefits
ELIXA	Lixisenatide	6,000	
DEVOTE	Insulin Degludec	7,500	Neutral
DECLARE TIMI-58	Dapagliflozin	17,150	
CANVAS	Canagliflozin	4,330	Positive benefits (increased amputations)
CANVAS-R	Canagliflozin	5,700	
CREDENCE	Canagliflozin	3,627	
EMPA-REG OUTCOME	Empagliflozin	7,042	Positive benefits

Complete CVOT's

Positive CV Results

- EMPA-REG – Empagliflozin
- LEADER – Liraglutide
- SUSTAIN-6 – Semaglutide
- CANVAS - Canagliflozin

Neutral CV Results

- SAVOR-TIMI – Saxagliptin
- EXAMINE – Alogliptin
- TECOS – Sitagliptin
- ELIXA – Lixisenatide
- EXSCEL – Bydureon LAR

Insulin

- ORIGIN – Insulin glargine (vs placebo)
- DEVOTE – Insulin degludec (vs glargine)

Characteristics in Positive Trials

	#	Mean Age (years)	DM Duration (years)	Baseline A1C	Δ A1C	Years follow-up
EMPA -REG	7020	63	57% > 10	8.07	-0.24 (10mg) -0.36 (25mg)	3.1
LEADER	9340	64	12.8	8.7	-0.4	3.8
SUSTAIN-6	3297	65	13.9	8.7	-0.7 -1	2.1
CANVAS & CANVAS-R	10,142	63	13.5	8.2	-0.58	3.6

Outcomes in Positive Trials

	MACE RRR	MACE ARR	CV Death RRR	NF MI RRR	NF Stroke RRR	All Death RRR
EMPA -REG	14%*	1.6%	38%*	13%	+24%	32%*
LEADER	13%*	1.9%	22%*	12%	11%	15%*
SUSTAIN-6	26%*	2.3%	2%	26%	39%*	5%
CANVAS & CANVAS-R	14%	4.6%	13%	15%	10%	13%

DM CVOT Outcomes: Summary

- DPP-4 trials have been neutral
- Two trials showing benefit with SGLT-2 inhibitors
  - Empagliflozin showed CV improvement when added to standard care.
  - Canagliflozin showed lower risk of CV events compared to placebo, but a greater risk of amputation, primarily at the level of the toe or metatarsal.
  - Additional studies ongoing
- Two trials showing benefit with GLP-1 RA's
  - Liraglutide showed CV improvement when added to standard care.
  - Semaglutide (NOT currently marketed) showed CV improvement when added to standard care.
  - Numerically fewer CV events were observed with exenatide LAR, but the primary objective of superior reduction in MACE did not reach statistical significance.

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DM CVOT Outcomes: Summary

- When choosing therapy for a patient with T2DM, keep in mind the recommendation for the ADA:

  "In patients with long-standing suboptimally controlled T2DM and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care."

- Canagliflozin has now shown CV benefit: NEJM Authors – "patients treated with canagliflozin had a lower risk of cv events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal."

Diabetes Care. 2017;40(1): S65
NEJM. 2017 e-pub online June 12, 2017.

DSME/T

Diabetes Self-Management Education

- DSME
- Diabetes Self-Management Training (DSMT)
- DSME/T
- Diabetes Self-Management Services (DSMS)

62% of Rural U.S. Counties Don't have DSME Program

- People diagnosed with DM who live in rural communities face barriers and challenges to DSMA.
- Rural population have higher prevalence of DM and lower rates of participation in preventive care practices
- The number of people with DM, & the percentage that are insured, have a high school education or less, & those unemployed, was significantly associated with whether a rural county had a DSME program

Morbidity and Mortality Weekly Report (*MMWR*)

Diabetes Self-Management Education Programs in Nonmetropolitan Counties — United States, 2016

Surveillance Summaries / April 28, 2017 / 66(10);1–6

Stephanie A. Rutledge, PhD[1]; Svetlana Masalovich, MS[2]; Rachel J. Blacher, MPH[1]; Magon M. Saunders, PhD[1] (View author affiliations)

Abstract

Problem/Condition: Diabetes self-management education (DSME) is a clinical practice intended to improve preventive practices and behaviors with a focus on decision-making, problem-solving, and self-care. The distribution and correlates of established DSME programs in nonmetropolitan counties across the United States have not been previously described, nor have the characteristics of the nonmetropolitan counties with DSME programs.

Reporting Period: July 2016.

Description of Systems: DSME programs recognized by the American Diabetes Association or accredited by the American Association of Diabetes Educators (i.e., active programs) as of July 2016 were shared with CDC by both organizations. The U.S. Census Bureau's census geocoder was used to identify the county of each DSME program site using documented addresses. County characteristic data originated from the U.S. Census Bureau, compiled by the U.S. Department of Agriculture's Economic Research Service into the *2013 Atlas of Rural and Small-Town America* data set. County levels of diagnosed diabetes prevalence and incidence, as well as the number of persons with diagnosed diabetes, were previously estimated by CDC. This report defined nonmetropolitan counties using the rural-urban continuum code from the *2013 Atlas of Rural and Small-Town America* data set. This code included six nonmetropolitan categories of 1,976 urban and rural counties (62% of counties) adjacent to and nonadjacent to metropolitan counties.

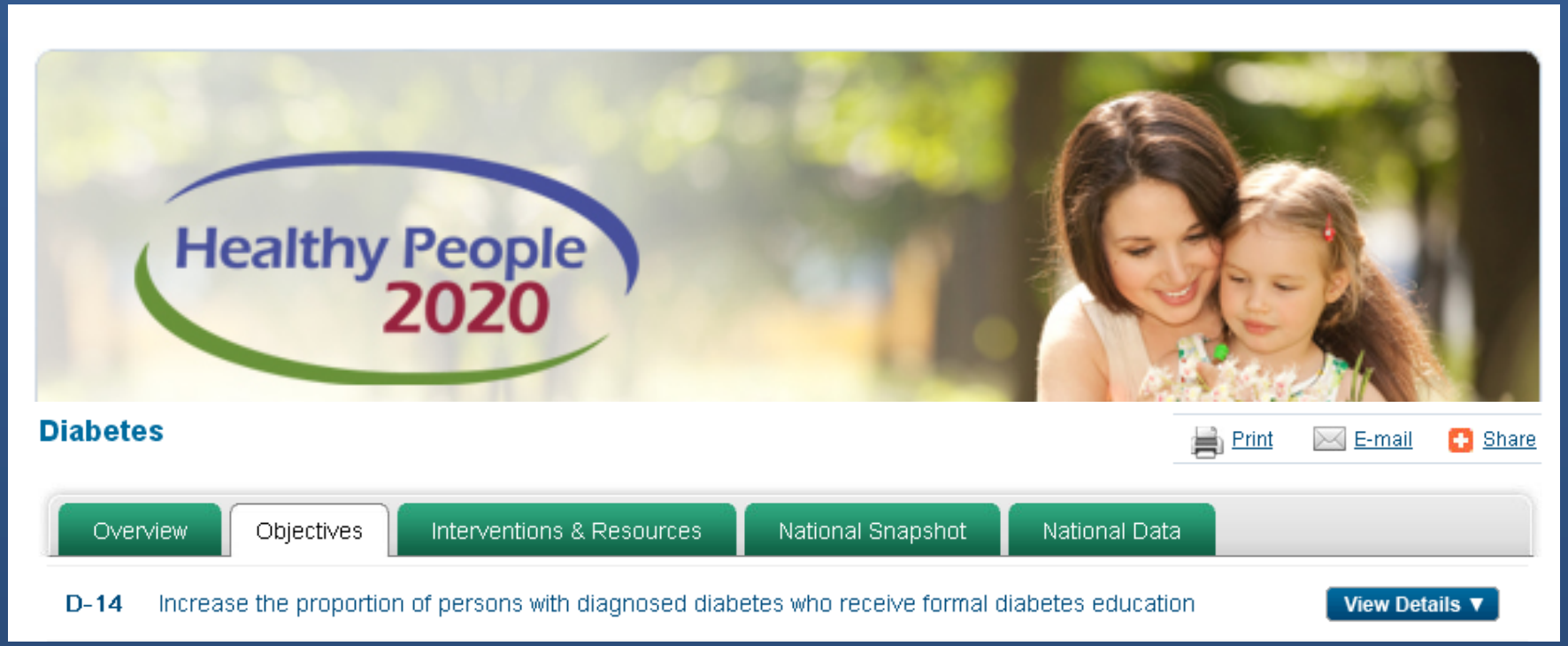
Results: In 2016, a total of 1,065 DSME programs were located in 38% of the 1,976 nonmetropolitan counties; 62% of nonmetropolitan counties did not have a DSME program. The total number of DSME programs for nonmetropolitan counties with at least one DSME program ranged from 1 to 8, with an average of 1.4 programs. After adjusting for county-level characteristics, the odds of a nonmetropolitan county having at least one DSME program increased as the percentage insured increased (adjusted odds ratio [AOR] = 1.10, 95% confidence interval [CI] = 1.08–1.13), the percentage with a high school education or less decreased (AOR = 1.06, 95% CI = 1.04–1.07), the unemployment rate decreased (AOR = 1.19, 95% CI = 1.11–1.23), and the natural logarithm of the number of persons with diabetes increased (AOR = 3.63, 95% CI = 3.15–4.19).

Interpretation: In 2016, there were few DMSE programs in nonmetropolitan, socially disadvantaged counties in the United States. The number of persons with diabetes, percentage insured, percentage with a high school education or less, and the percentage unemployed were significantly associated with whether a DSME program was located in a nonmetropolitan county.

Public Health Action: Monitoring the distribution of DSME programs at the county level provides insight needed to strategically address rural disparities in diabetes care and outcomes. These findings provide information needed to assess lack of availability of DSME programs and to explore evidence-based strategies and innovative technologies to deliver DSME programs in underserved rural communities.

The Need for Diabetes Education

- Diabetes Self-Management Training (DSMT)
  - Covered by Medicare and most health plans
- Healthy People 2020 priority



Diabetes Education Patient Benefits

- Studies have shown people who receive diabetes education:

Use primary care / prevention services

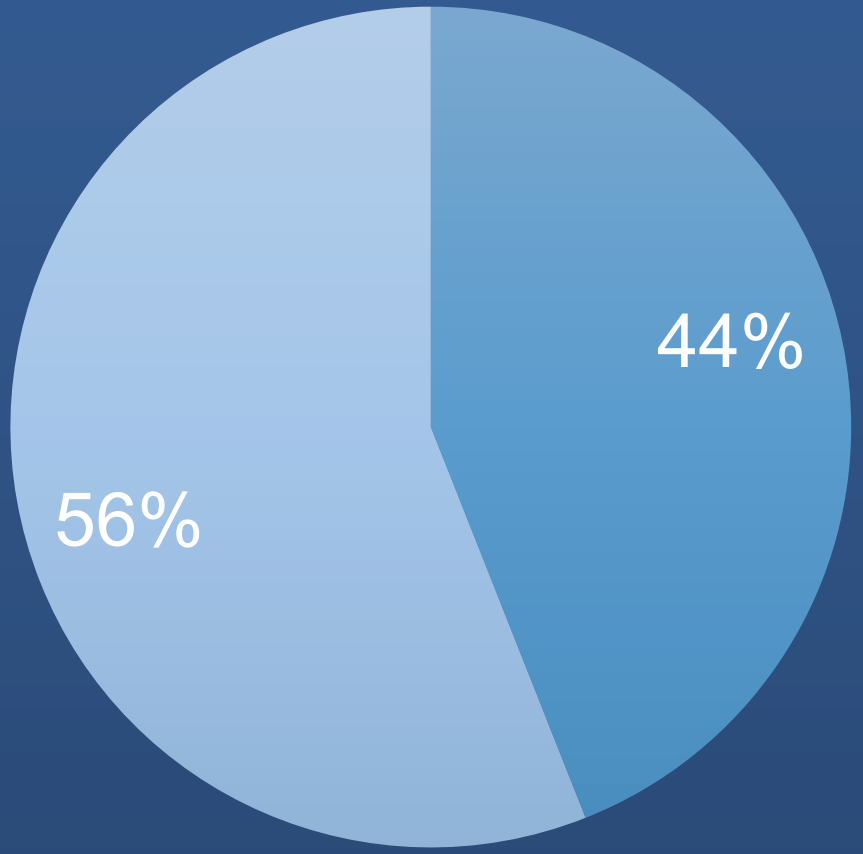
Take medications as prescribed

Control glucose, blood pressure, LDL cholesterol

Have lower health costs

Diabetes Education Underutilized

- Few people with diabetes receive diabetes education…



The research shows:

People with Diabetes

- Don't follow through on referral
- Are emotional / shocked at diagnosis
- End up relying on family / friends
- Believe they know enough / can handle it on their own

Providers

- Know importance of DE, but don't necessarily prescribe – or don't prescribe definitively enough
- Sometimes forget to follow up with patients to encourage attendance

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Treating People With Diabetes

Demands on your practice are escalating

- Enabling patients to help themselves
- Balancing priorities and goals

Partner With a Diabetes Educator

We help your patients:

- Develop self-management skills
- Achieve better metabolic control
- Improve lipid levels
- Reduce blood pressure

How Do Diabetes Educators Help?

- We help people with diabetes:

Learn basic information	**Understand** how to use devices	**Adopt** healthy eating and physical activity habits
• Seven tenets of self-care behavior • Incorporating diabetes management into life	• Blood glucose meters • Insulin pens • Insulin pumps • Continuous glucose monitors	• Nutrition education • Meal planning • Weight loss strategies

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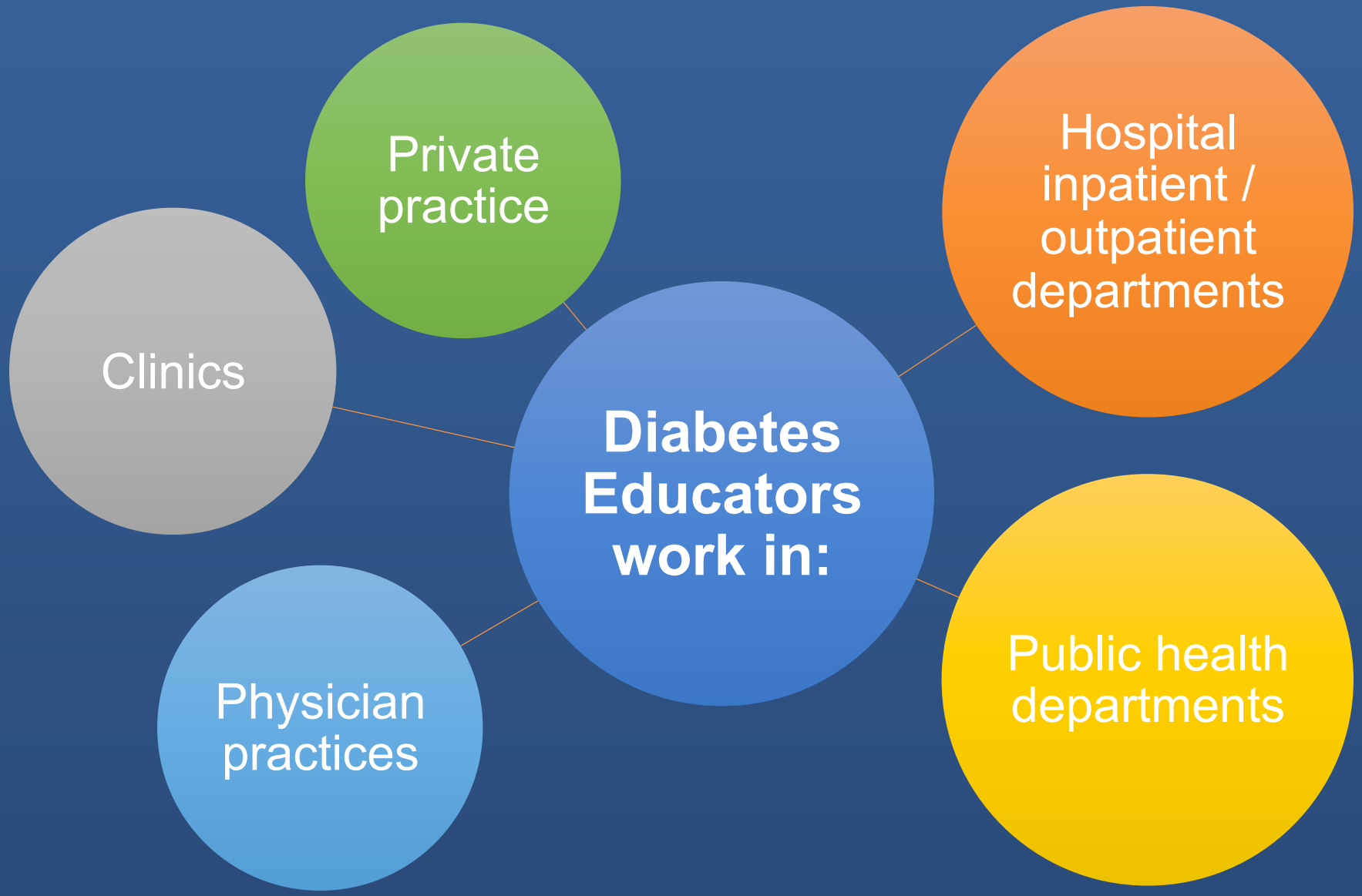
How Do Diabetes Educators Help?

- Develop problem-solving and stress management strategies / skills
- Monitor blood glucose – interpret and respond
- Understand how medications work

Find a Diabetes Educator



Questions