RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

Annual Internal Medicine Review

ENDOCRINOLOGY PART 3

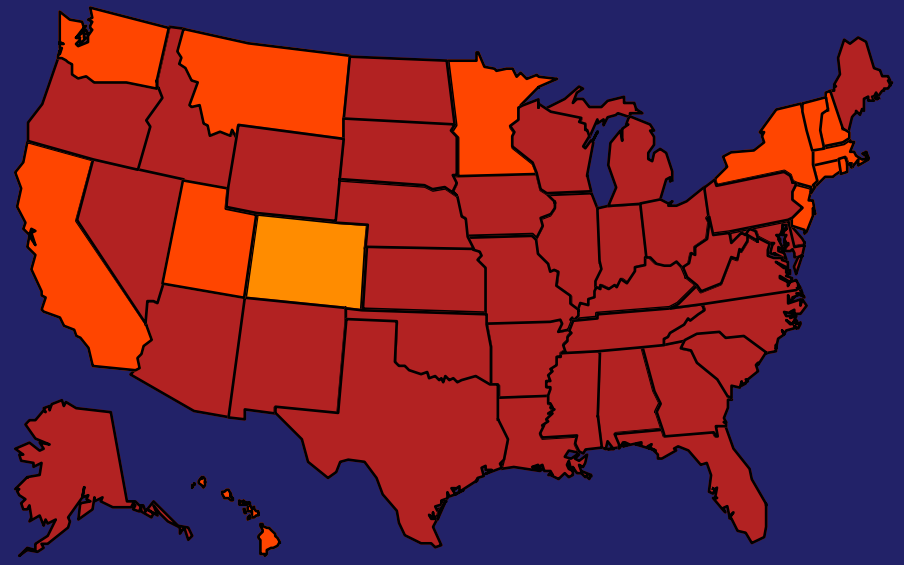
Sara Lubitz, MD

Associate Professor of Medicine
Medical Director of the Pituitary Center
Program Director, Endocrinology Fellowship
Rutgers Robert Wood Johnson Medical School
lubitzsa@rutgers.edu

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

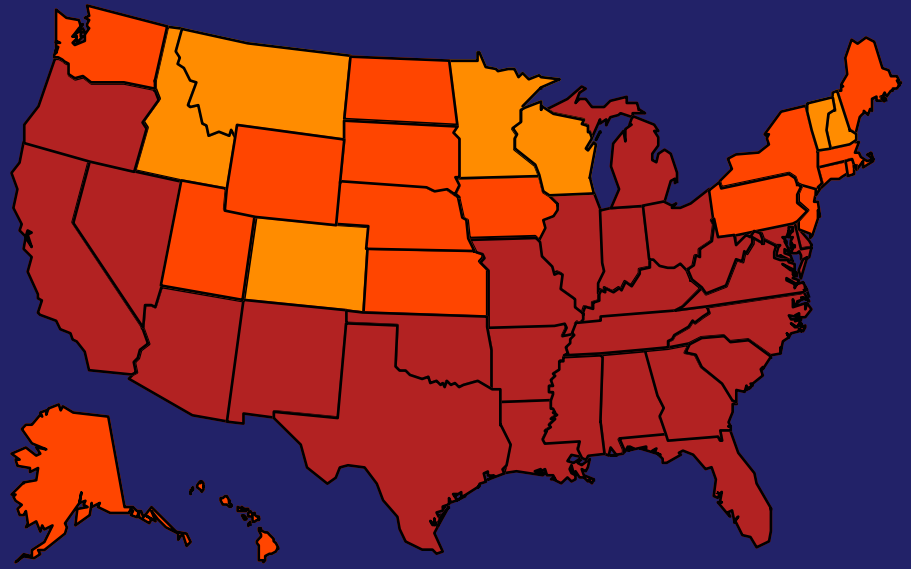
2015

Obesity (BMI≥30 kg/m^2)



Missing Data
14.0%–17.9%
22.0%–25.9%
<14.0%
18.0%–21.9%
≥26.0%

Diabetes



Missing data
4.5%–5.9%
7.5%–8.9%
<4.5%
6.0%–7.4%
≥9.0%

CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at http://www.cdc.gov/diabetes/data

Question 1

Who Has Diabetes Mellitus?

A. 30 year old obese African American male with a fasting blood sugar of 105 mg/dL and HbA1c 6.0%

B. 57 year old Caucasian male with renal disease on Epoetin Alpha injections for anemia with a fasting blood sugar of 130 mg/dL, 134mg/dL on repeat and HbA1c of 4.7%

C. 67 year old thin Southeast Asian female with fasting blood sugar of 120mg/dL, 124 mg/dL on repeat. She checks her sugar with her husband's glucometer 2 hours after meals when she feels dizzy and gets readings in the 80s

D. 18 year old obese Hispanic female with acanthosis, polyuria and polydipsia and a random plasma glucose of 188mg/dL

Diagnostic Criteria for the Diagnosis of Diabetes in Nonpregnant Adults

Table 2.2—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 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.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S13-S27

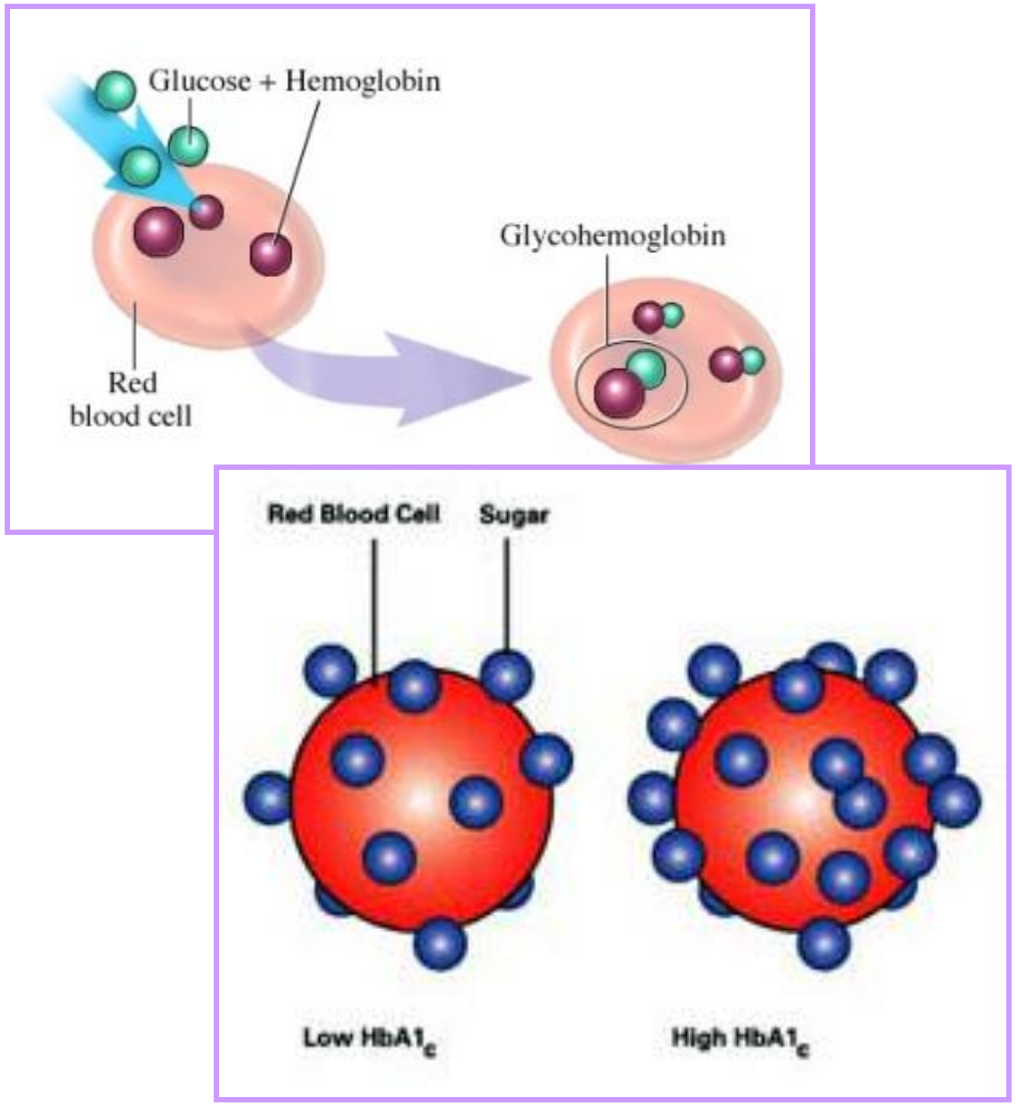
Diagnostic Criteria for the Diagnosis of Diabetes in Nonpregnant Adults

Table 2.4—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Hemoglobin A1c (Glycosylated Hemoglobin)



May not be accurate in any condition which affects red blood cell turnover or hemoglobinopathies

Question 2

A 68-year-old woman with diabetes for 20 years has begun to have labile glucose measurements. Originally well controlled on oral drugs, she now requires basal-bolus insulin therapy. She also has a history of Hashimoto's hypothyroidism. On physical examination, she is thin. An anti–glutamic acid decarboxylase antibody titer is positive.

Question 2

Which is the most likely diagnosis?

A. Type 1 Diabetes Mellitus
B. Type 2 Diabetes Mellitus
C. Latent Autoimmune Diabetes of Adulthood
D. Maturity Onset Diabetes of the Young

Type 1 Diabetes Mellitus

- Immune attack on the Beta Cells
  - Will have antibodies on blood tests
    - Anti-Insulin antibodies
    - Glutamic acid decarboxylase antibodies (GAD)- *most specific*
    - Islet cell-associated antigen antibodies
- Absolute insulin deficiency
- High risk for diabetic ketoacidosis (DKA)
- 20% will have other autoimmune disease
- Age of onset usually childhood and adolescence

Type 2 Diabetes Mellitus

- Metabolic disorder that is characterized by insulin resistance, relative insulin deficiency & hyperglycemia

Organ System	Defect
Major Role	
Pancreatic beta cells	Decreased insulin secretion
Muscle	Inefficient glucose uptake
Liver	Increased endogenous glucose secretion
Contributing Role	
Adipose tissue	Increased FFA production
Digestive tract	Decreased incretin effect
Pancreatic alpha cells	Increased glucagon secretion
Kidney	Increased glucose reabsorption
Nervous system	Neurotransmitter dysfunction

Other Diabetes Syndromes

- Latent Autoimmune Diabetes of Adulthood (LADA)
  - Older, usually lean patients
  - Autoimmune markers present
  - Gradual destruction of beta-cells results in absolute insulin deficiency
  - Additional autoimmune endocrine disorders are common (ex. Hypothyroidism)
- Maturity Onset Diabetes of the Young (MODY)
  - Hereditary autosomal dominant form of diabetes caused by mutations in a single gene; may respond well to sulfonylureas
- Defects in insulin action: lipodystrophy
- Diseases of the exocrine pancreas
  - Cystic Fibrosis
  - Hemochromatosis
  - Pancreatitis

Other Diabetes Syndromes

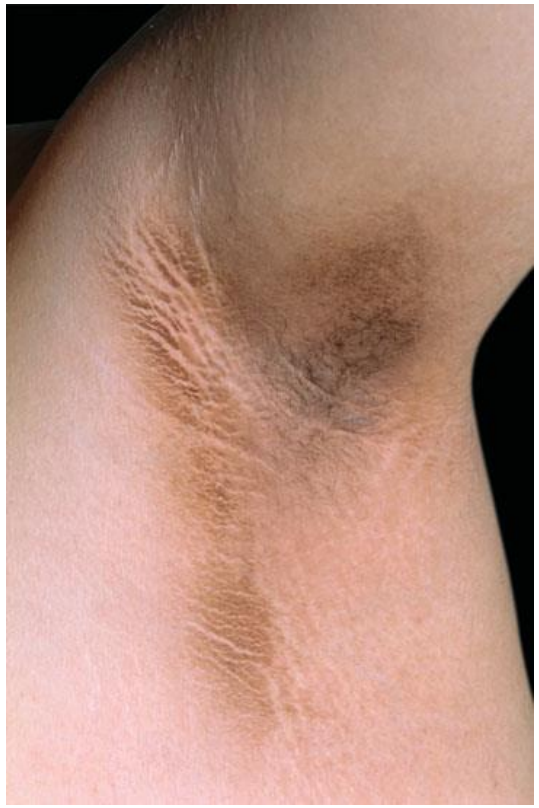
- Gestational
  - Diabetes that develops during pregnancy (usually not until 2nd trimester)
  - Increased risk of fetal macrosomia, neonatal hypoglycemia, jaundice
  - Typically resolves after birth but frequently recurs with subsequent pregnancies
- Endocrinopathies: Acromegaly, Cushing's, Pheochromocytoma
- Stress Hyperglycemia
- Drug induced:
  - Steroids
  - HCTZ, Beta-blockers, Niacin, Statins, Immune Checkpoint Inhibitors

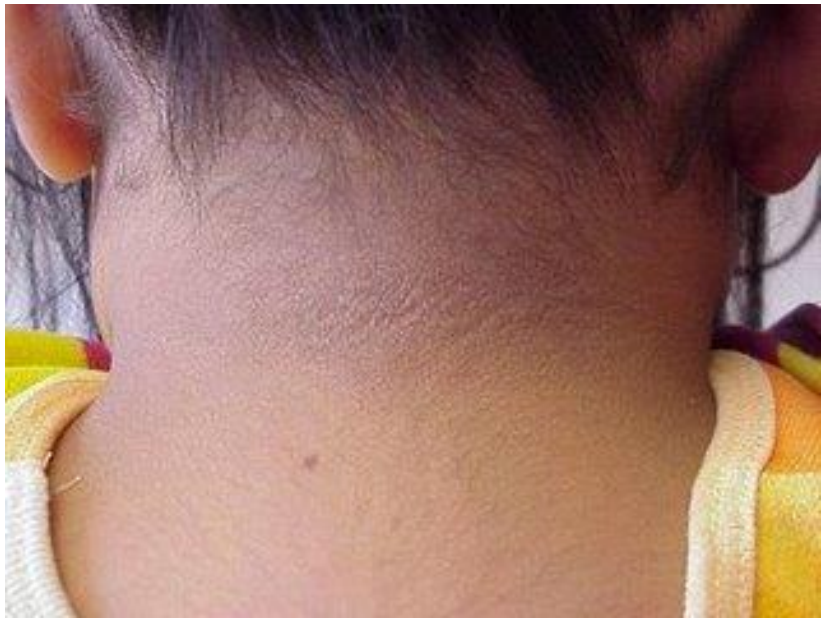
High Risk for the Development of DM2 = Who to Screen

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C <35 mg/dL and/or triglycerides >250 mg/dL)
- History of gestational diabetes
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Antiretroviral therapy for HIV
- Chronic glucocorticoid exposure
- Sleep disorders
  - Obstructive sleep apnea
  - Chronic sleep deprivation
  - Night shift work

Acanthosis Nigricans

- Acanthosis nigricans is characterized by velvety hyperpigmented patches most prominent in intertriginous areas





- Cutaneous marker of insulin resistance
- Present in ~90% of patients with Type 2 DM

ATP III: The Metabolic Syndrome*

Risk Factor	Defining Level
Abdominal obesity (Waist circumference)	
Men	**>102 cm (>40 in)**
Women	**>88 cm (>35 in)**
TG	**≥150 mg/dL**
HDL-C	
Men	**<40 mg/dL**
Women	**<50 mg/dL**
Blood pressure	**≥130/≥85 mm Hg**
Fasting glucose	**≥110 mg/dL**

*Diagnosis is established when at least 3 of the criteria are present

Metabolic Syndrome

- Also called the “insulin resistance syndrome” or “Syndrome X”
- 35% of the US adult population
  - Higher risk in Mexican and African Americans
- 2-3.5 fold increase in risk of Type 2 DM
- 2 fold increase risk of Cardiovascular Disease
- Associated with:
  - PCOS
  - Sleep Apnea
  - Hyperuricemia and Gout
  - Chronic Kidney Disease
  - NAFLD / NASH
- Treat each individual component to prevent development of Type 2 DM and CVD

Diabetic Ketoacidosis

A collection of severe and potentially life-threatening metabolic disturbances:

- Hyperglycemia → Osmotic diuresis
  - Urinary loss of fluids & electrolytes
  - ECFv contraction
  - Depletion of total body K^+ stores
    (even though may be hyperkalemic 2° to cell shift)
- Ketone production → Metabolic acidosis
  - Compensatory Respiratory alkalosis
- Uncontrolled lipolysis → severe ↑ TG

DKA: Treatment

1. Intensive Monitoring (Consider ICU)
2. IV Fluid Resuscitation (3-9L deficit)
3. IV insulin
4. Potassium
    - K^+ deficit 3-5 mEq/Kg
5. Calcium, Phosphate, and Magnesium replacement
6. Identify & Rx underlying cause
    - Noncompliance, infection, MI, etc.

Pitfalls of DKA Treatment

1. Potassium supplementation should start once K is < 4.5-5 mg/dL if normal renal function

2. Goal glucose decline is no more than 75- 100mg/dL/hr; once glucose <200-250 add dextrose to fluids

3. Don’t forget calcium, phosphate, and magnesium replacement

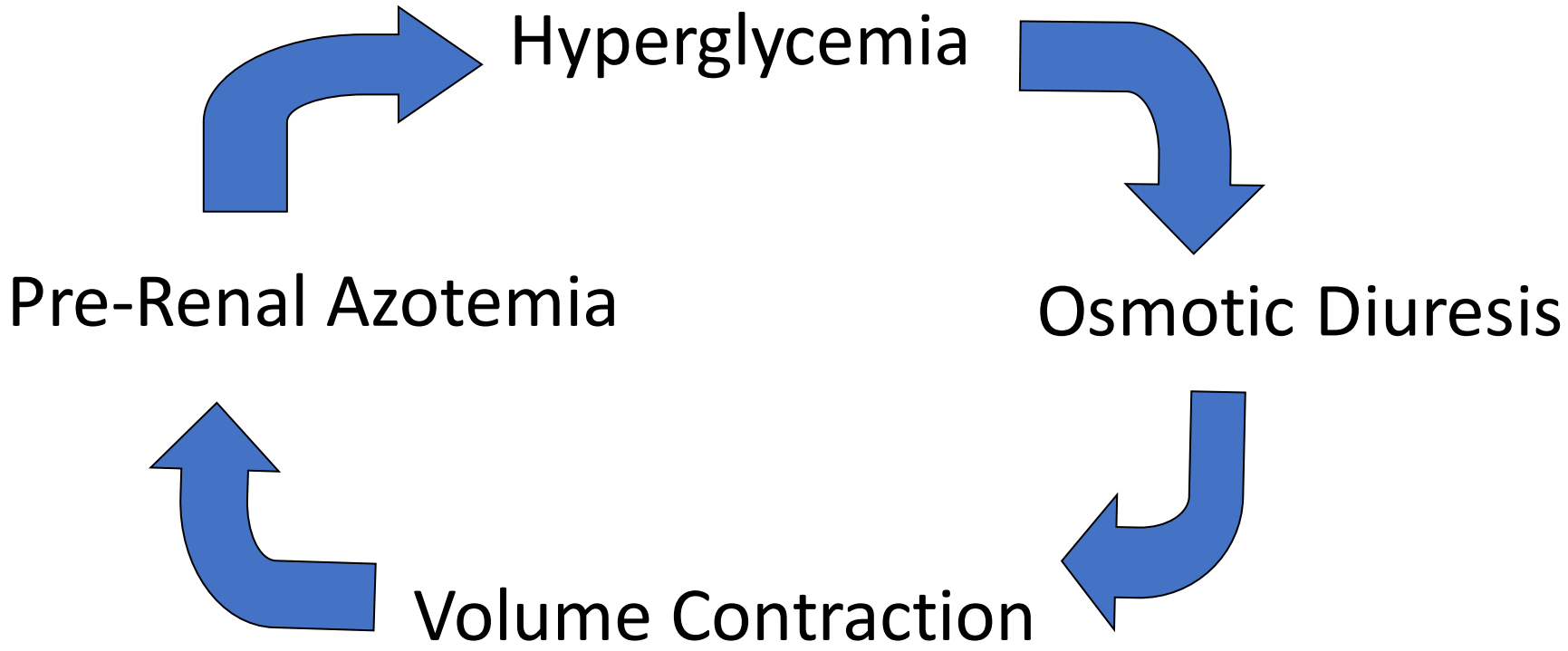
4. Remember to overlap insulin gtt with SubQ insulin

HONK or HHS

Hyperosmolar Non-Ketotic State | Hyperosmolar Hyperglycemic State

- T2DM, elderly (mean age 60-73)
- Pathogenesis poorly understood
- Mild ECFv↓ instigating factor
- Insulin/Glucagon ratio sufficient to limit DKA
- Diminished thirst or access to water
- Vicious cycle develops…

HONK or HHS


Hyperglycemia
Osmotic Diuresis
Volume Contraction
Pre-Renal Azotemia

Monitoring for Diabetes Complications

- Every visit
  - BP measurement
  - Foot inspection
- Every 3-6 months
  - Hemoglobin A_{1c} measurement
- Annually
  - Spot urine for albumin to creatinine ratio
  - Dilated ophthalmologic examination
  - Comprehensive foot examination (monofilament)
  - Lipid profile

Diabetic Neuropathy

- Any part of the peripheral or autonomic nervous system may be affected
- Peripheral Symptoms: pain, numbness, hyperesthesia, paresthesia
  - Stocking/Glove distribution
  - High risk for diabetic foot
- Autonomic symptoms: tachycardia, orthostatic hypotension, gastroparesis, diarrhea, erectile dysfunction

Diabetic Neuropathy Treatment

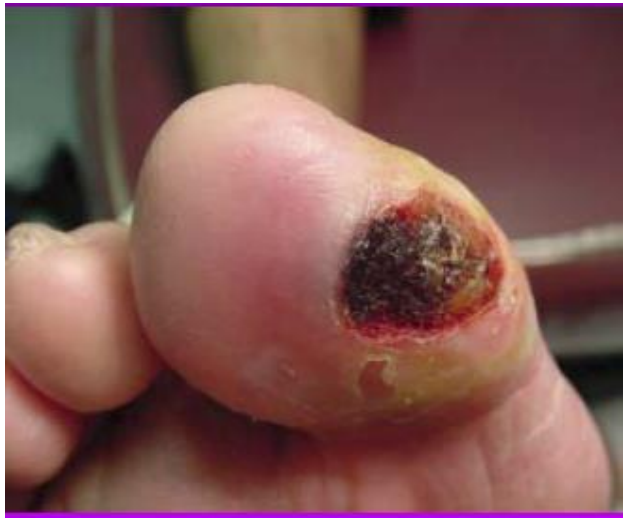
New Recommendation for 2017:

- Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes

American Diabetes Association Standards of Medical Care in Diabetes.
Microvascular complications and foot care. Diabetes Care 2019;42(Suppl. 1):S124–S138

Diabetic Foot

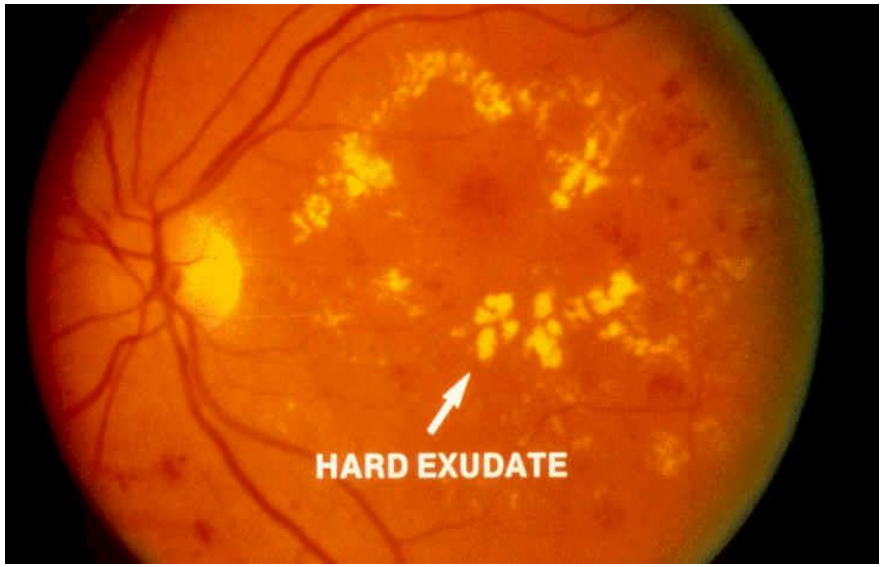
- Sensory loss and loss of proprioception leads to abnormal gait and repeated trauma to the tarsal bones and soft tissue
- Risk Factors
  - Polyneuropathy
  - Peripheral Arterial Insufficiency
  - Obesity
  - Poor diabetes control

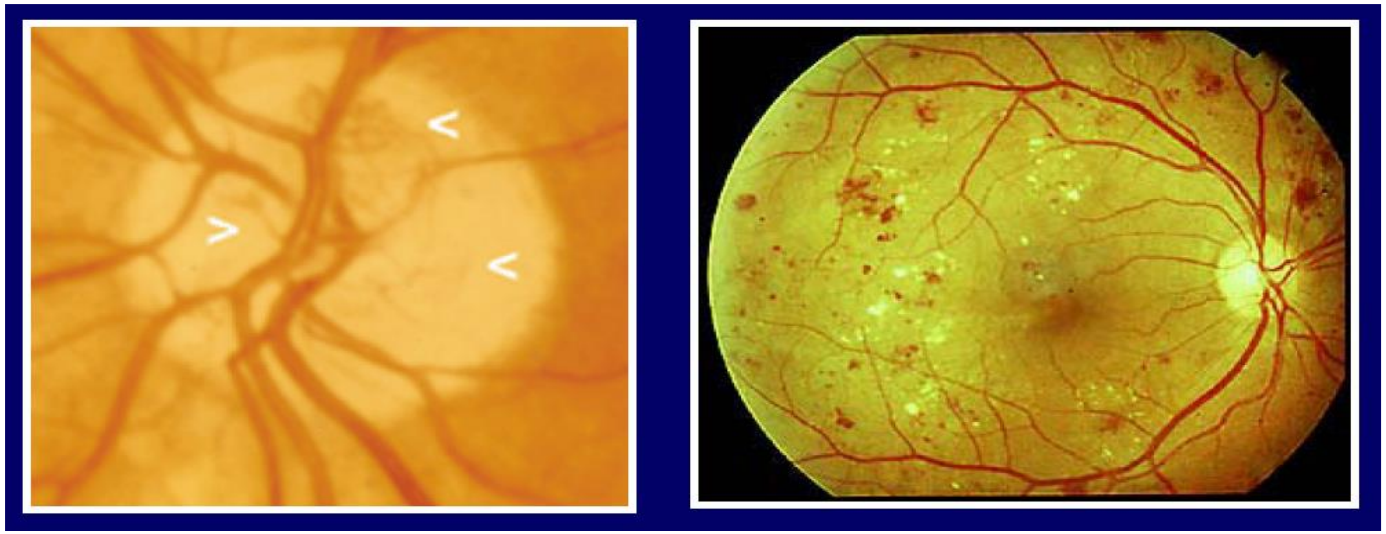


- Foot ulcers → osteomyelitis → gangrene → amputation
- Screening for early loss of vibratory sensation, reflexes, and light touch (monofilament)
- Patient education about foot care

Diabetic Retinopathy

- Related to long history or poor control
  - Microaneurysms
  - Hemorrhages and exudates
  - Proliferative changes
  - Retinal retraction due to vitreous clot
  - Retinal artery thrombosis



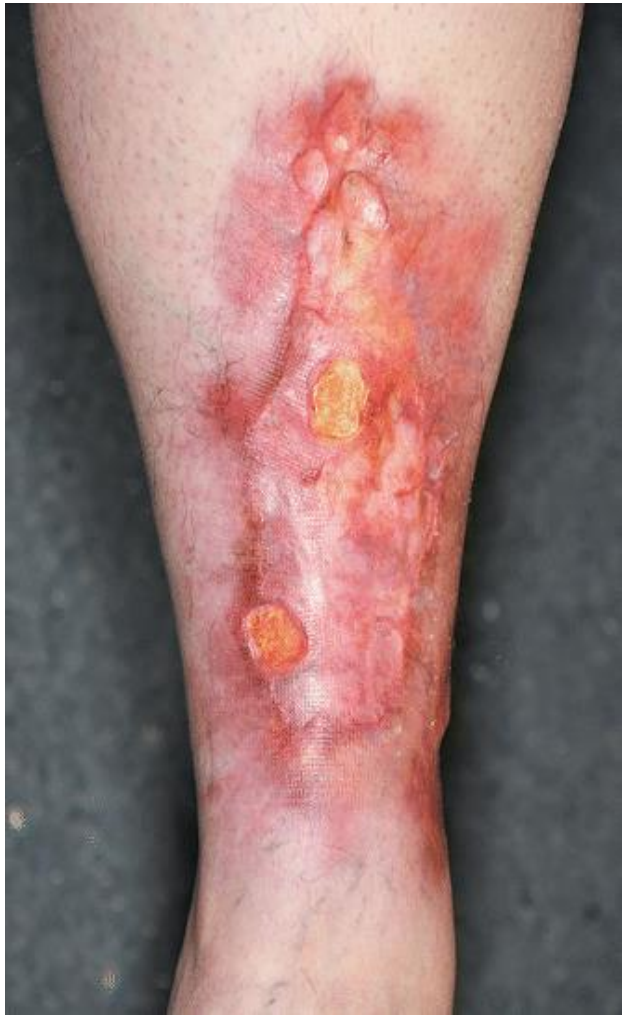


Diabetic Retinopathy

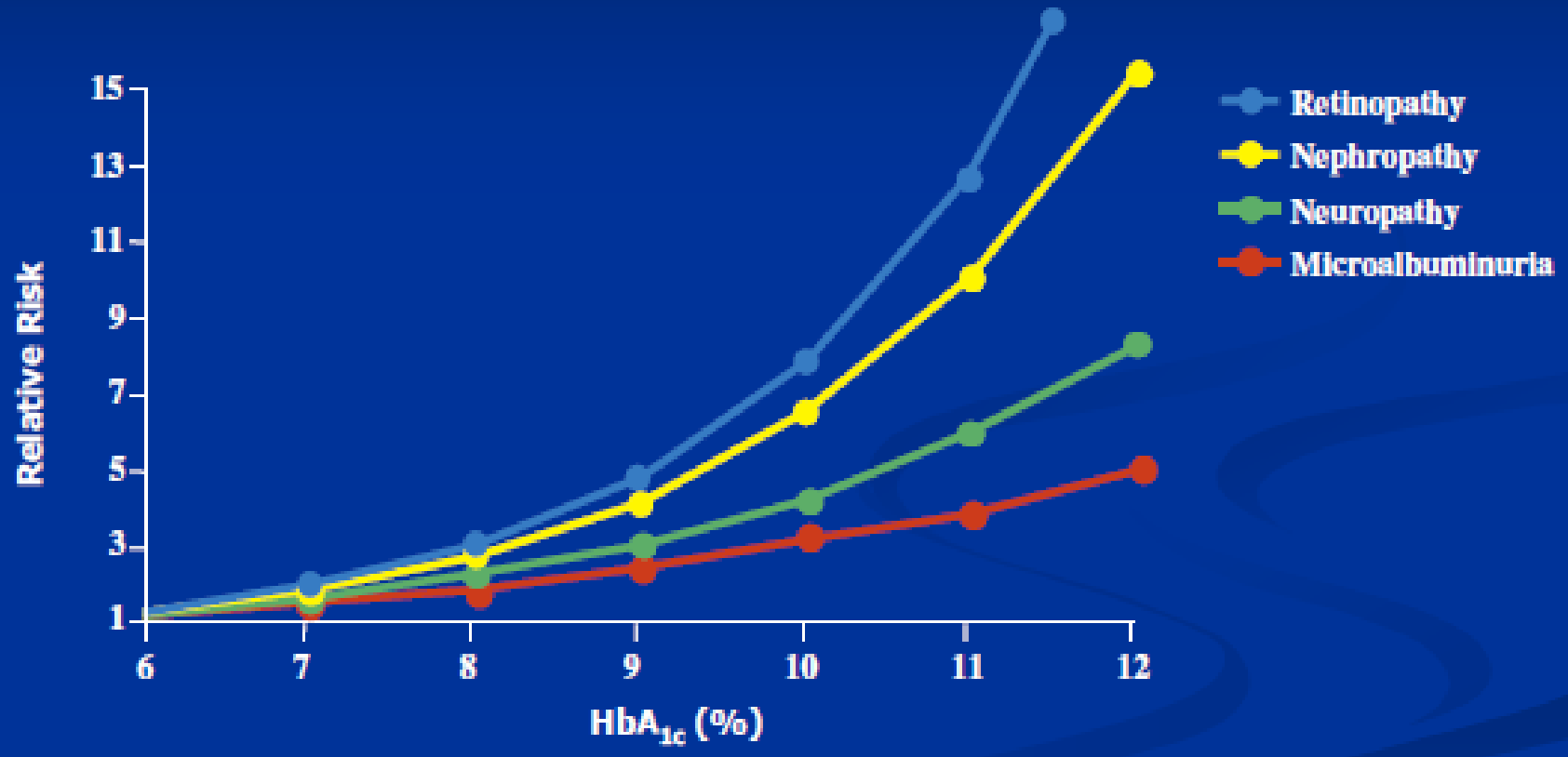
- 35% of diabetics will develop ESRD
- Diabetes is the most common cause of renal failure needing dialysis in the US
- The first sign is albumin in the urine
  - albumin-to-creatinine ratio >30mg/g creatinine
- Screening: yearly urine albumin and eGFR
- Treat with ACE/ARB and BP control
- Optimize glucose control

Necrobiosis Lipoidica Diabeticorum

- Chronic granulomatous rash on the lower legs
  - Slightly raised shiny red-brown patches
  - The centers are often yellowish and may develop open sores that are slow to heal
- More common in women
- Strong association with diabetes
  - ~25% of patients lesions develop before the onset of diabetes



DCCT: Relationship of HbA_{1c} to Risk of Microvascular Complications



Skyler. *Endocrinol Metab Clin.* 1996;25:243-254, with permission.

Question 3

How to prevent a cardiac event?

A 65 year old male comes to you because he is about to become a grandparent and is worried about dying of a heart attack like his father and brother did before they ever got to meet their grandchildren.

He is obese with a BMI of 32.3 and does not exercise regularly

He has had Type 2 DM for 12 years and is on Insulin Glargine 30 units QHS, Glimepiride 4mg daily, Metformin 1000mg BID and Sitagliptin 100mg daily. He has mild neuropathy, no retinopathy and a urine microalbumin/creatinine ratio of 30. HbA1c is 8% and fasting blood sugars are 120-160

He takes Enalapril 20mg daily with a blood pressure of 154/84 mmHg

He takes simvastatin 40 mg daily and the most recent lipid panel showed total cholesterol 210 triglycerides 205 LDL 90 HDL 40

He also takes a baby aspirin daily

Question 3

If you could make one change at this visit which would be the most effective to prevent a cardiac event?

A. Stop his oral diabetic medications and switch him to basal/bolus insulin using insulin glargine and insulin aspart titrated to a HbA1c goal of <7%

B. Increase his simvastatin to 80 mg daily

C. Increase his enalapril to 40 mg daily

D. Add fenofibrate

CV Disease and Risk Management

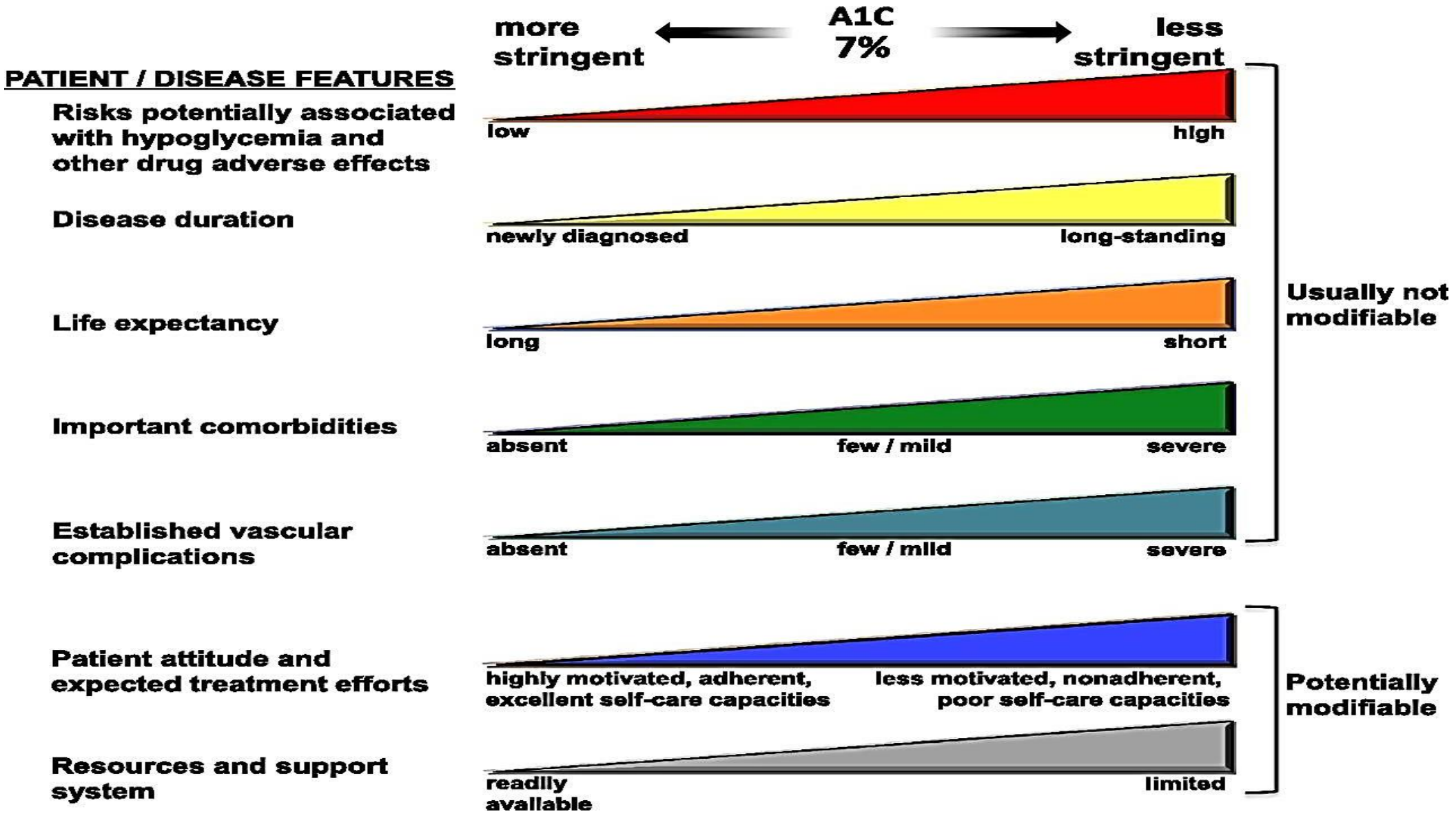
- CVD is the major cause of morbidity & mortality for those with diabetes
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for CVD
- Diabetes diagnosis confers independent risk
- Strong evidence for managing individual cardiovascular risk factors in primary and secondary prevention

- ****BP goal <140/90 (some say 130/80)*
- ****moderate- high intensity statin*

Risks of Hypoglycemia

- Intensive insulin or oral hypoglycemic agents pushing A1c to <6.5% can lead to hypoglycemia
- Repeated hypoglycemic episodes attenuate the counter-regulatory response to hypoglycemia
- Hypoglycemia with or without diabetic dysautonomia prolongs the QT interval
- Increased cardiac death rates have precluded the benefits of tight control in treating Type 2 diabetes

Therapeutic Targets for DM



Adapted from *Standards of Medical Care in Diabetes - 2018. Diabetes Care* 2018; 41 (Suppl. 1): S55-S64

ACP American College of Physicians℠
Leading Internal Medicine, Improving Lives

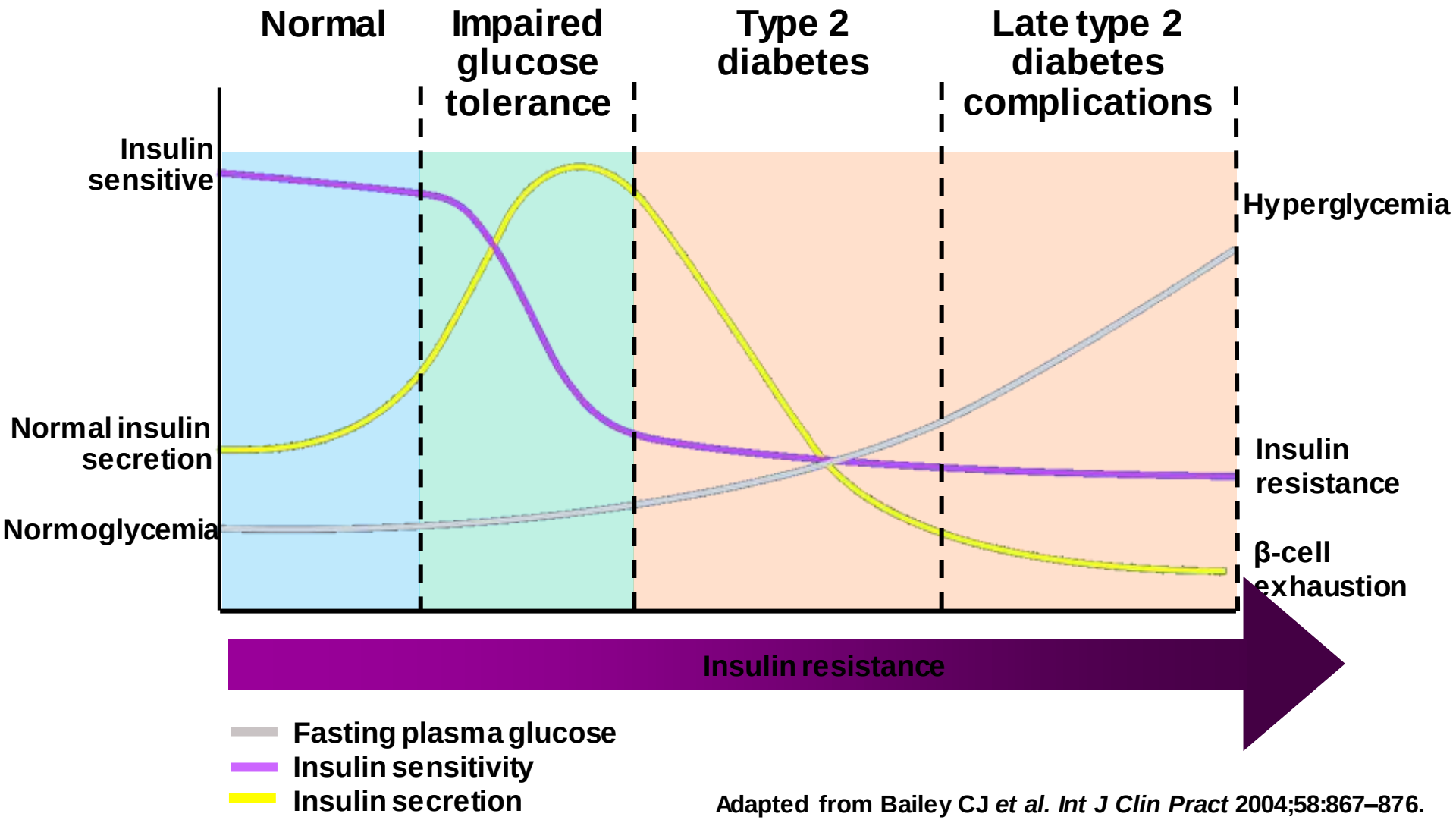
CLINICAL GUIDELINE

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

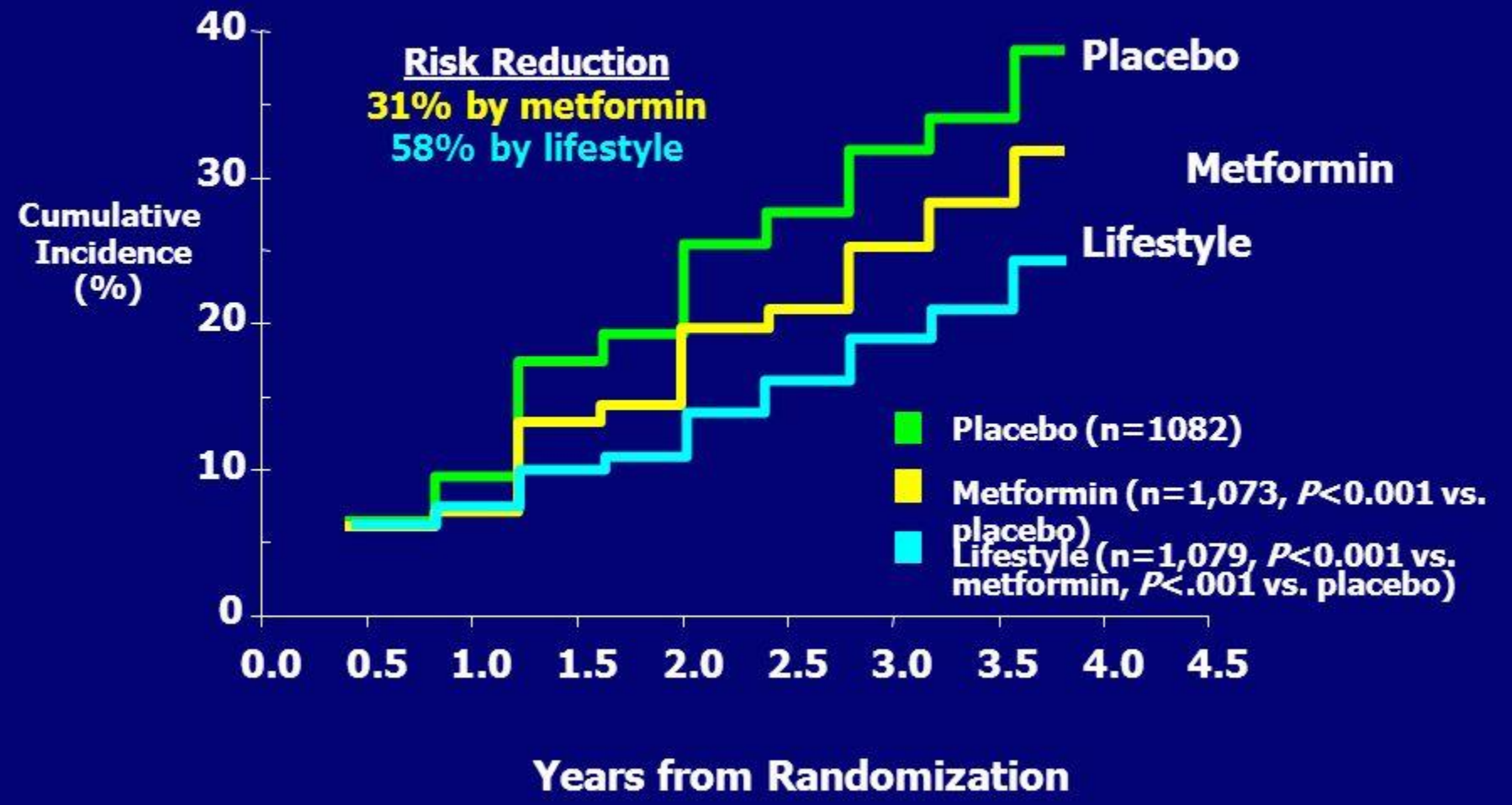
Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

The Progressive Nature of Type 2 Diabetes



Adapted from Bailey CJ *et al. Int J Clin Pract* 2004;58:867–876.
Groop LC. *Diabetes Obes Metab* 1999;1 (Suppl. 1):S1–S7.

Preventing Diabetes: Results from the Diabetes Prevention Program



Diabetes Prevention Program Research Group. N Engl J Med. 2002;346:393-403.

Pharmacologic Therapy for T2DM

- Biguanides: Metformin

  The first oral agent used should be metformin

  - Mechanism: decrease hepatic glucose output and enhance hepatic & muscle insulin sensitivity without a direct effect on beta-cell function
  - Side Effects: GI upset, metallic taste, B12 deficiency
  - Because of concerns about lactic acidosis, Metformin is contraindicated in patients with:
    - impaired renal function
    - administration of radiocontrast material
    - known hepatic disease, hypoxemic conditions, severe infections, or alcohol abuse

- Alpha Glucosidase Inhibitors: Acarbose, Miglitol

  - Mechanism: Slow the hydrolysis of complex carbohydrates and carbohydrate absorption
  - Side Effects: Flatulence, bloating, diarrhea

Pharmacologic Therapy for T2DM

- Sulfonylureas/Meglitinides: glimepiride, glyburide, glipizide, repaglinide, nateglinide
  - Mechanism: promote insulin secretion from beta cells
  - Side Effects: Weight gain and hypoglycemia
  - Caution in renal disease

- Thiazolidinediones: rosiglitazone, pioglitazone
  - Mechanism: improves peripheral insulin sensitivity (PPARγ)
  - May take 10-12 weeks for full effect
  - Side Effects: weight gain, fluid retention, osteoporosis
  - Black box warning: may cause or exacerbate CHF

Pharmacologic Therapy for T2DM

- DPP4 Inhibitors: sitagliptin, saxagliptin, linagliptin, alogliptin
  - Mechanism: Block DDP4 the enzyme responsible for cleavage inactivation of GLP-1 and GIP
    - Stimulates insulin in response to elevated glucose levels
    - Inhibits release of glucagon following a meal
  - Side Effect: rare
  - Safe in renal disease (may require decreased doses)
  - Weight neutral
  - Pancreatitis risk, Heart failure risk

- Bile Acid Sequestrants: colesevelam
  - Mechanism unclear
  - Lowers LDL
  - Side Effects: gastric upset, increased triglycerides

- Dopamine D2 Receptor Agonists: quick release bromocriptine
  - Mechanism: Modulates hypothalamic regulation of metabolism

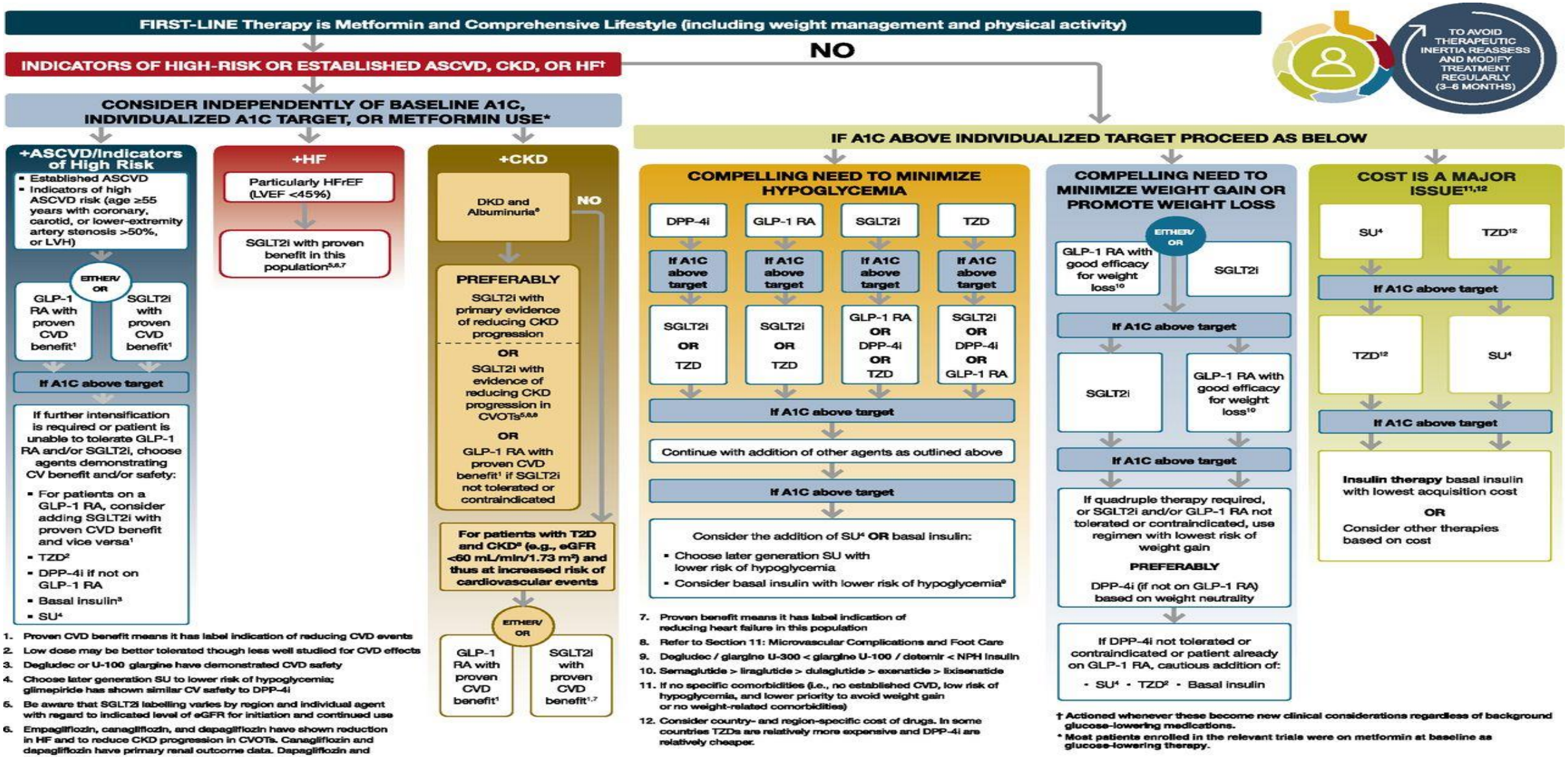
Pharmacologic Therapy for T2DM

- GLP-1 agonists: exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, semaglutide
  - Mechanism:
    - Stimulates insulin in response to elevated glucose levels
    - Inhibits release of glucagon following a meal
    - Slows gastric emptying
    - Increases satiety
  - Side Effect: GI upset
  - Benefits: Weight loss, ASCVD reduction
  - ?Pancreatitis risk
  - Contraindicated in patients with personal/family history of medullary thyroid cancer or MEN2

Pharmacologic Therapy for T2DM

- Sodium Glucose Transporter 2 Inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
  - Mechanism: Blocks reabsorption of glucose from the proximal tubule
  - Benefits: ASCVD and Heart Failure reduction, decreased CKD progression, weight loss
  - Side Effects: UTIs and genital candida infections and Fournier's gangrene, volume depletion, DKA, fractures, amputation, increased LDL
  - Should be discontinued with illness or prior to surgery to avoid risk of DKA
  - Decreased A1c lowering efficacy as GFR decreases

Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.

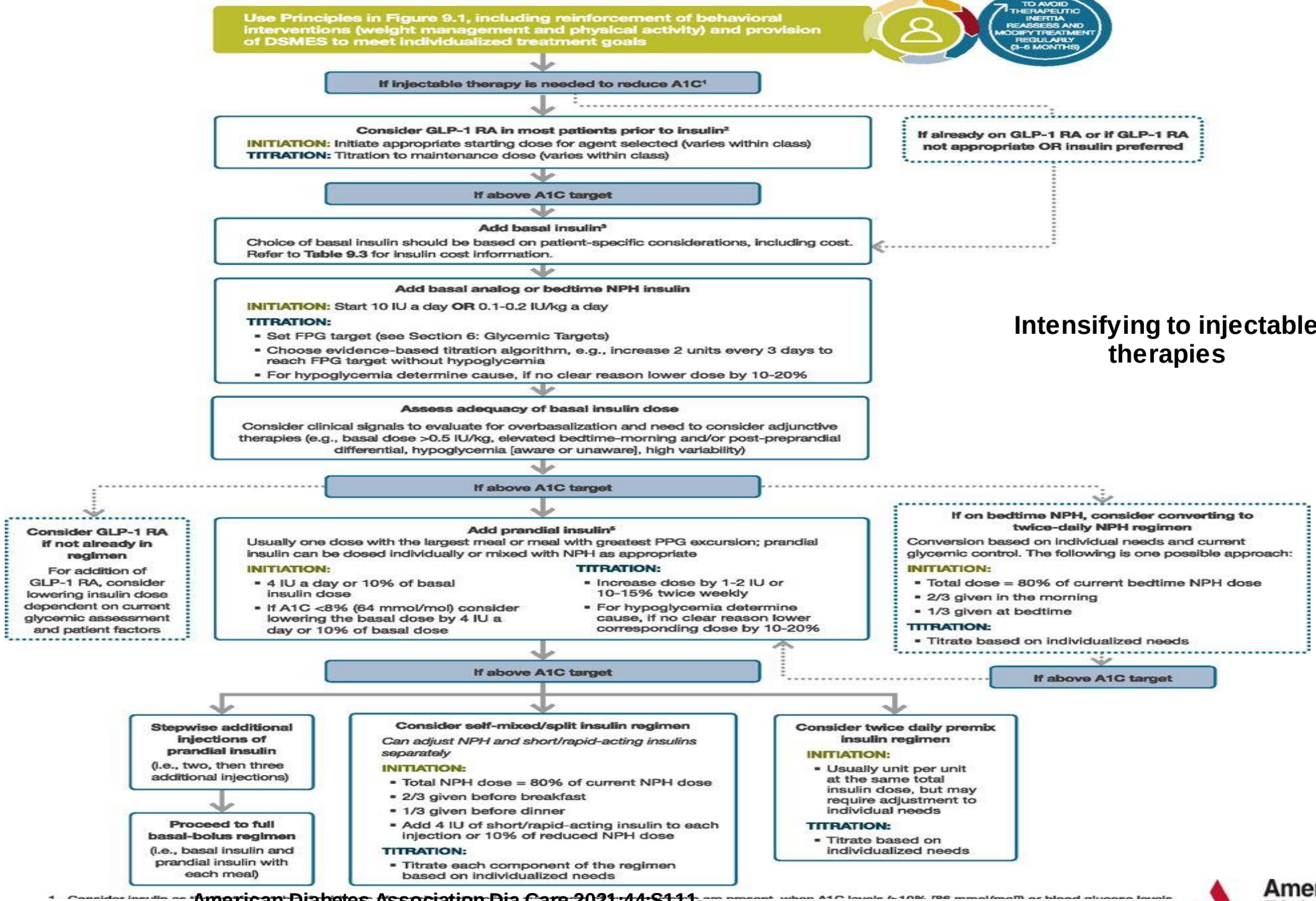


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.



Intensifying to injectable therapies

American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

Treatment of DM - Insulin

- Essential treatment for Type 1 Diabetes
- ~58% of patients with Type 2 Diabetes will eventually require exogenous insulin
- Risk of Hypoglycemia
- Weight Gain

Question 4

- 32 yo woman who has had T1DM for 16 years reports 3 weeks of fatigue, excessive sweating and occasional headache on awakening.
- She is using 32 units of premixed insulin BID (75/25 neutral protamine lispro/lispro mix)
- She exercises each evening after work and occasionally experiences hypoglycemic symptoms around lunchtime if she doesn't eat enough.
- She monitors sugar BID. BG log shows fasting glucose readings 125-146 mg/dL and pre-dinner readings average 176. Recent HbA1c 7.0%
- She is engaged and will be planning pregnancy in the next year and hopes to get her A1c lower pre-conception
- Examination reveals normal weight and blood pressure, and no evidence of diabetic complications

Adapted from MKSAP 16

Question 4

Which of the following is the most likely cause of her symptoms?

- A Nocturnal Hypoglycemia
- B Dawn Phenomenon
- C Sleep Apnea
- D Pheochromocytoma

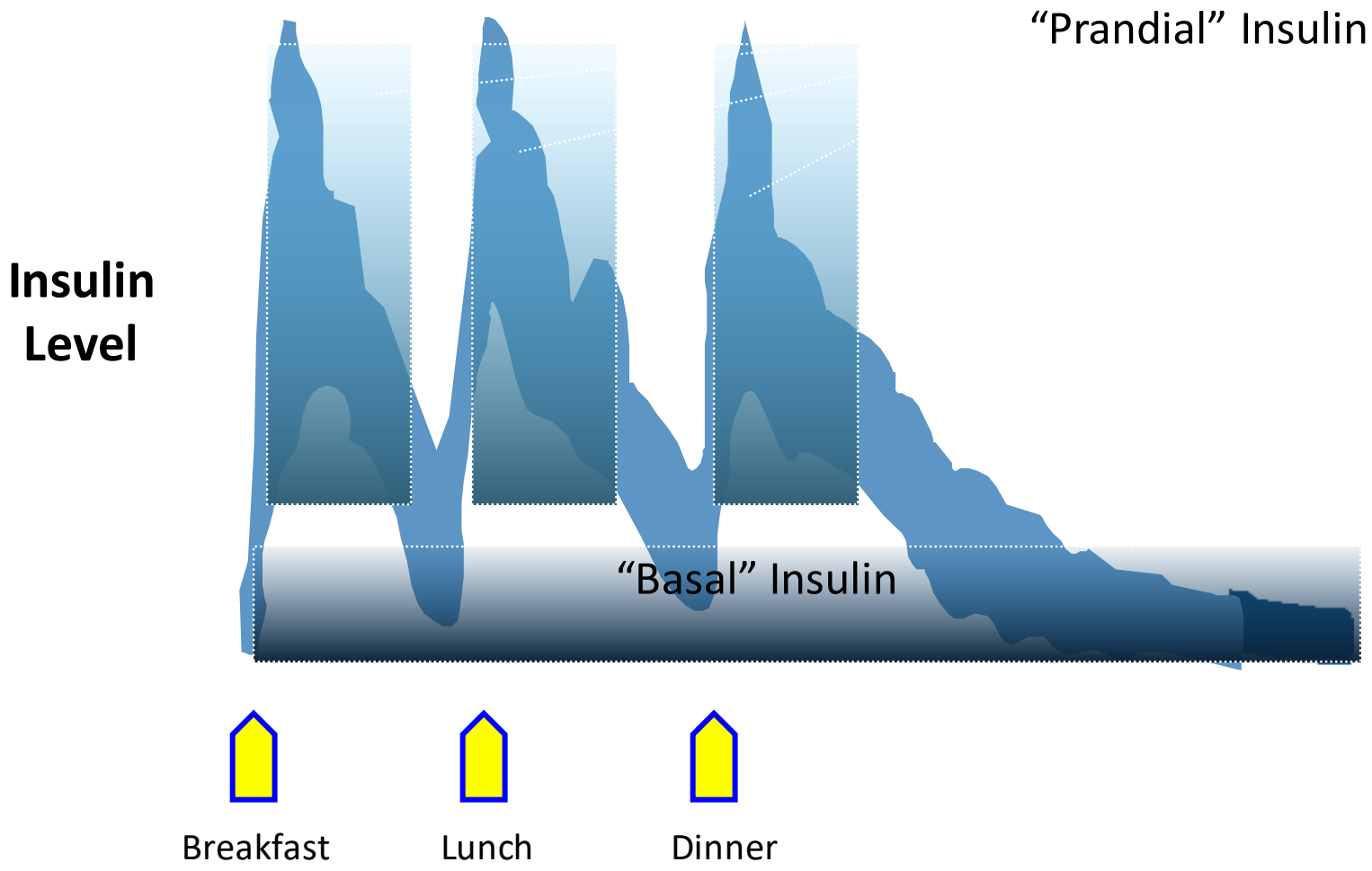
Adapted from MKSAP 16

Question 5

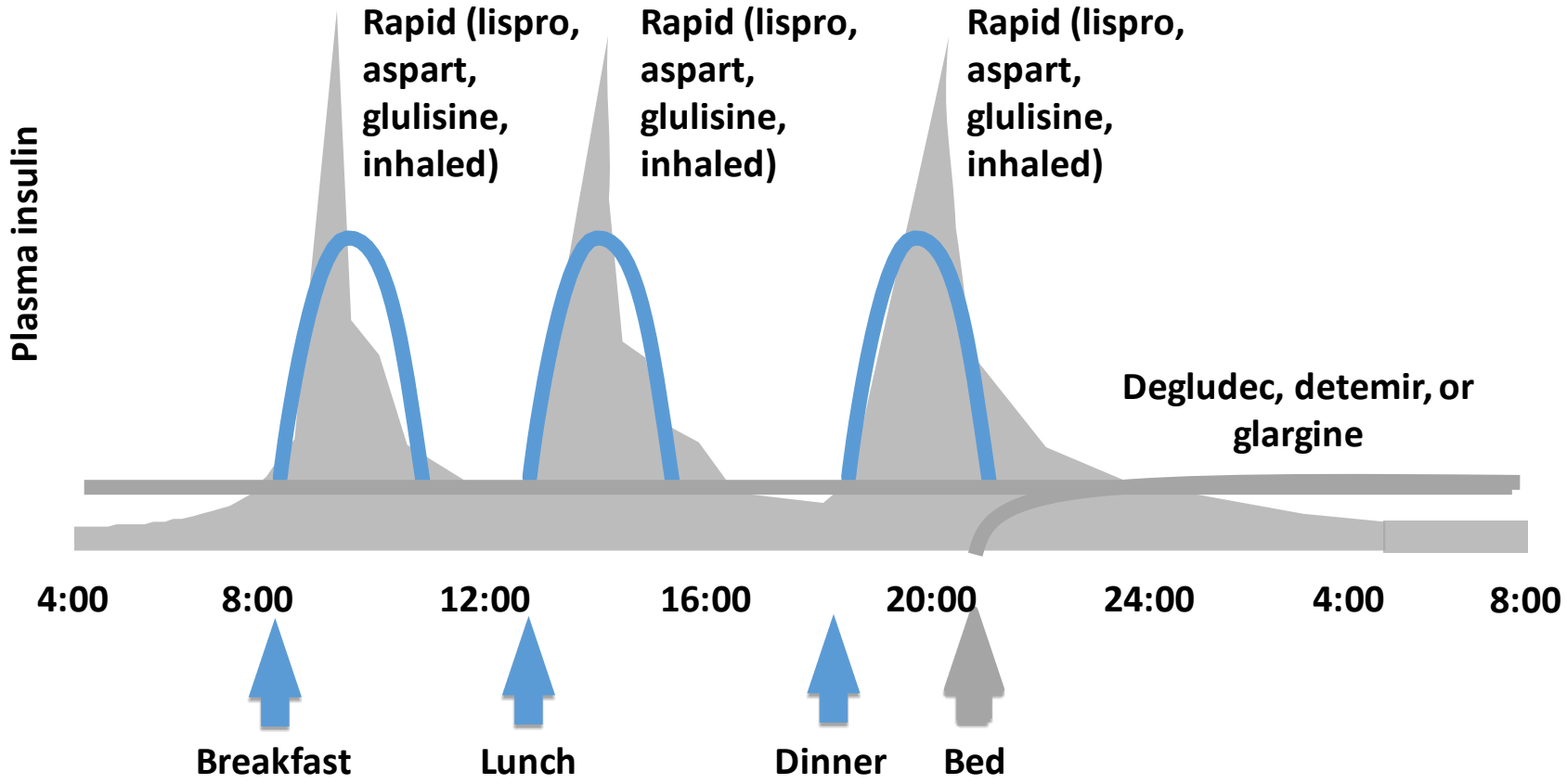
Which of the following options is the most appropriate management to improve her glucose control?

A. Increase the dose of the morning premixed insulin and decrease the dose in the evening
B. Increase the dose of both the morning and the evening premixed insulin
C. Switch to self-mixed NPH and lispro before breakfast and supper
D. Change insulin to glargine at bedtime with three premeal injections of lispro a day
E. Reduce caloric consumption

Normal Secretory Pattern of Insulin



Physiologic Multiple Insulin Injections "Basal/Bolus"



Question 6

A type 2 diabetic patient is admitted to trauma service ICU after a MVA. On his home meds he is taking Insulin glargine (Lantus) 50 units BID and Humalog 40 units with meals. He weighs 80kg. He is intubated and sedated and requiring pressors. He will require surgery in the AM. You are writing his admission orders. Blood glucose on SMA7 is 362.

Question 6

What is the most appropriate treatment regimen at this time?

A. Insulin glargine (Lantus) 50 units BID (home dose)
B. Start Humalog sliding scale insulin Q6h for BG 0-150= 0 units 150-200=1u, 151-200=2u, 201-250=3u, 251-300=4u, 301-350=5u, 351-400=6u, 400-450=8u, >450=10u and call MD
C. Regular insulin IV drip
D. Insulin glargine (Lantus) 20 units daily (weight-based dose)

Diabetes Care in the Hospital

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL

- A basal bolus correction insulin regimen, with the addition of nutritional insulin in patients who have good nutritional intake, is the preferred treatment for noncritically ill patients

- Sole use of sliding scale insulin the inpatient hospital setting is strongly discouraged

- Target glucose range of 140-180 mg/dL is recommended for the majority of critically ill patients and noncritically ill patients

Insulin Infusions in the Critically Ill

ICU setting

- BG targets on insulin 140-180mg/dL
- More stringent goals of 110-140 mg/dL, may be appropriate for selected patients, if this can be achieved without significant hypoglycemia
- IV insulin is the preferred method for achieving and maintaining glucose control in the critically ill

- Initial results in surgical patients after trauma or open heart surgery have shown benefit with intensive control of sugar with IV insulin protocols
- MICU/CCU results have been counterproductive

Gestational Diabetes

- Definition: Diabetes diagnosed during pregnancy
- May be undiagnosed Type 2 diabetes OR

  hyperglycemia due to pregnancy induced insulin resistance that goes away once baby is delivered
- Complications:
  - Fetus Malformations (Hyperglycemia 1st Trimester)
  - Pre-eclampsia
  - Macrosomia and delivery complications
  - Fetal Death
  - Increased risk of Type 2 Diabetes in mother and infant

Gestational Diabetes

- Screening
  - High risk women in the first trimester
  - Most women at 24-28 weeks
- Treatment
  - Diet
  - Insulin **preferred*
  - Newer trials show safety with oral agents
    - Metformin
    - Sulfonylureas
- Post-pregnancy screening for persistent DM
  - 2hr OGTT 6 weeks post-partum

Diabetic Patient Pre-conception Counseling

- Preconception A1c target
  - Lower is better (< 6 or 6.5%)
- Risk of development and/or progression of diabetic retinopathy
- Medications to be avoided
  - Statins: Category X
  - ACE/ARB: Category D
  - ASA: Category D

Pregnancy and Diabetes

Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 60–150mg/day (usual dose 81 mg/day) from the end of the first trimester until the baby is born in order to lower the risk of preeclampsia.

American Diabetes Association Standards of Medical Care in Diabetes. Management of Diabetes in Pregnancy Diabetes Care Volume 42, Supplement 1, January 2019

Highly Recommended Immunizations for Adult Patients with Diabetes (Condensed)

Hepatitis B
Age: <60 years of age; ≥60 years of age discuss with doctor | Frequency: 2- or 3-dose Series |*Ref 1: CDC*

HPV
Age: ≤26 years of age; 27–45 yrs may be vaccinated after discussion with doctor| Frequency: 3 doses over 6 months |*Ref 2: MMWR 2019;68:698–702*.

Influenza
Age: All patients;| Frequency: Annually |*Ref 3: Demicheli, 2018;2:CD004876*

Pneumonia (PPSV23)
Age: 19–64 years of age | Frequency: 1 dose |Ref 4: *MMWR 2010;59:1102–1106*

≥ 65 years – see *Ref 5. Falkenhorst et al. PLoS ONE 2017; 12:e0169368*

Pneumonia (PCV13)
Age: 19-64 years, no recommendation; ≥65 years w/o immuno-compromising condition discuss with doctor | Frequency:1 dose|*Ref 6: MMWR 2019;68:1069–1075*

Tetanus, diphtheria, pertussis (TDAP)
Age: All adults; pregnant women - an extra dose| Frequency: Booster every 10 years |*Ref 7: MMWR 2020;69: 77–83*

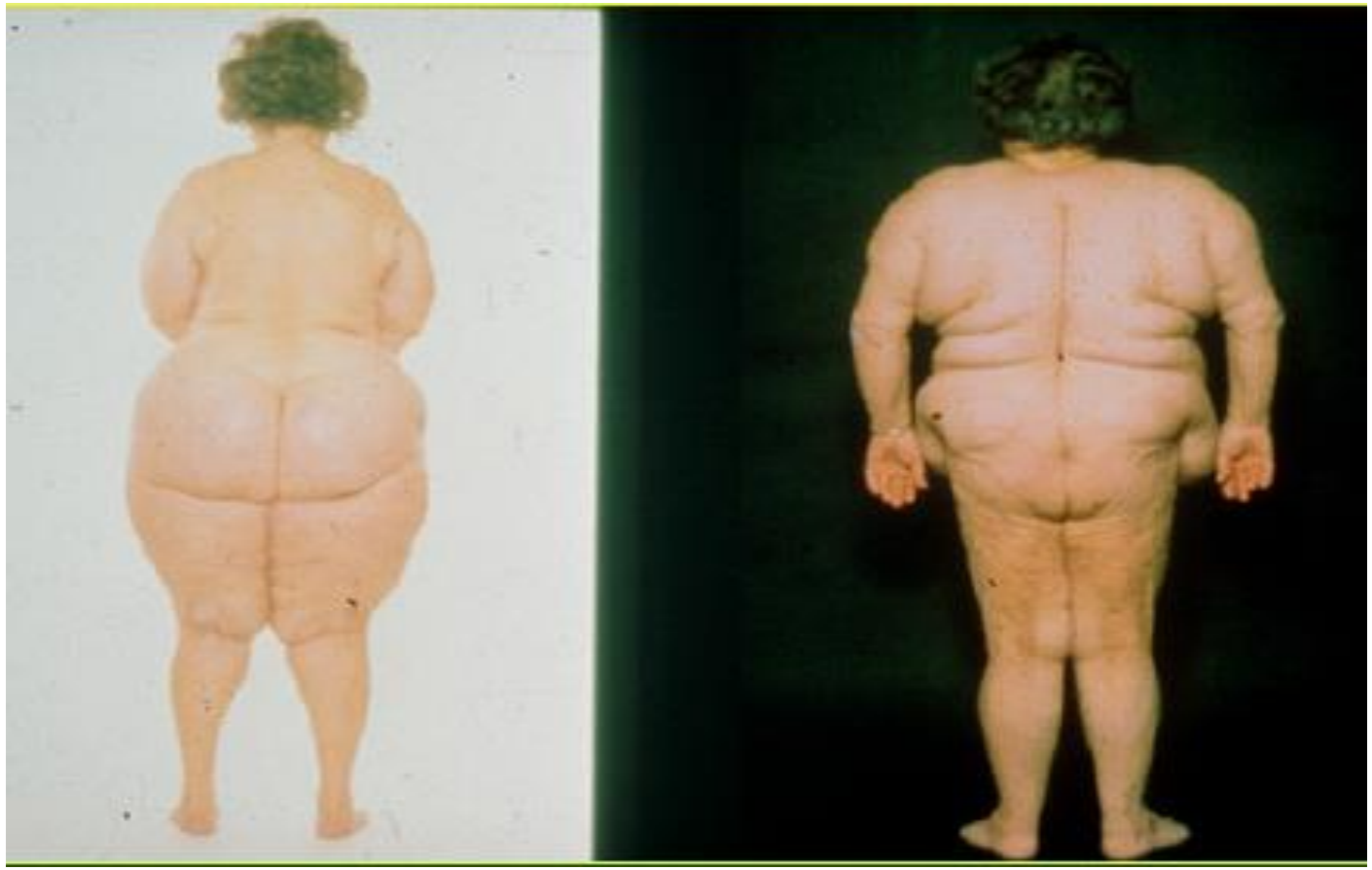
Zoster
Age: ≥50 years of age| Frequency: Two-dose Shingrix, even if previously vaccinated |*Ref 8: MMWR 2018;67:103–108*

Adapted from:
American Diabetes Association, Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetesd-2021, Diabetes Care 2021;44(Suppl. 1):S40–S52 | https://doi.org/10.2337/dc21-S004

Highly Recommended Immunizations for Adult Patients with Diabetes (Condensed)

1. CDC. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60: 1709–1711
2. Meites E, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR 2019;68:698–702
3. Demicheli V, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2018;2:CD004876
4. CDC. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccaride vaccine (PPSV23). MMWR 2010;59:1102–1106
5. Falkenhorst G, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS ONE 2017;12:e01693
6. Matanock A, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged $65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR 2019;68:1069–1075
7. Havers FP, et al. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practicesd United States, 2019. MMWR 2020;69: 77–83
8. Dooling KL, et al. The Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR 2018;67:103–108

Which patient is at higher risk for Type 2 DM and Heart Attack?



Question 7

A 54-year-old man with prediabetes and hyperlipdemia is concerned about his risk of developing type 2 diabetes mellitus and cardiovascular disease. He understands that he needs to lose weight. He has incorporated exercise into his routine by adding brisk walking for 25 minutes 3 to 4 times per week and has begun weight training under the guidance of a trainer but has not seen a significant change in his weight.

Question 7

Which of the following diets is most likely to lead to long-term weight loss for this patient?

A. Low-fat diet

B. Low-carbohydrate diet

C. Vegetarian diet

D. Mediterranean diet

E. Dietary Approaches to Stop Hypertension (DASH diet)

Question 8

Which of the following diets is most likely to reduce the risk of major cardiovascular events?

A. Low-fat diet

B. Low-carbohydrate diet

C. Vegetarian diet

D. Mediterranean diet

Obesity

- Etiology
  - Genetic and epigenetic influences- 70%
  - Acquired: 30%
  - Increased caloric in take
  - Biological influences of hormones (leptin, adiponectin etc.)
  - Gut microbes
  - Imbalance of signals related to energy regulation
  - Hypothalamic lesion (RARE)
- Weight loss of as little as 5-15% of initial weight improves many obesity-related co-morbidities

Overweight / Obesity Treatment

	Body Mass Index (BMI) Category (kg/m^2)				
Treatment	**25.0-26.9 (or 23.0-26.9*)**	**27.0-29.9**	**30.0-34.9 (or 27.5-32.4*)**	**35.0-39.9 (or 32.5-37.4*)**	**≥40 (or ≥37.5*)**
Diet, physical activity & behavioral therapy	┼	┼	┼	┼	┼
Pharmacotherapy		┼	┼	┼	┼
Metabolic surgery			┼	┼	┼

* Asian-American individuals

┼ Treatment may be indicated for selected, motivated patients.

Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S65-S72

Obesity Treatment: Lifestyle

- Diets: Only total calories matter- NOT macronutrient composition
- Popular diets (Weight Watchers, Ornish, Atkins, South Beach) all result in 7-10% weight loss (JAMA 2006)
- Mediterranean diet may be best for CAD prevention
- Key is adherence!

CURRENT PHARMACOLOGICAL THERAPY FOR OBESITY

Drug	Mechanism of action	Contraindications	Side effects
Phentermine	Appetite- suppressant drug Causes NE release+ minor DA release	Cardiovascular disease, hyperthyroidism, glaucoma, agitated states, pregnancy	Insomnia, dry mouth, constipation, agitation, HTN
Orlistat	Modulates dietary absorption of fats by reducing fat hydrolysis & absorption by inhibiting gastric & pancreatic lipases	Chronic malabsorption syndrome, cholestasis, pregnancy	Oily spotting, flatus with discharge, diarrhoea, faecal urgency
Phentermine/ Topiramate	Topiramate: neurostabilizer, enhance thermogenesis Phentermine: appetite suppressant	Glaucoma, hyperthyroidism pregnancy	Parasthesia, dizziness, dysguesia, insomnia, constipation, dry mouth
Naltrexone/ Bupropion SR	Bupropion: stimulates POMC Naltrexone: blocks orexigenic effects of β endorphin activity	Uncontrolled HTN, seizures, chronic opioid use, pregnancy	Nausea, constipation, headache, insomnia, dry mouth, diarrhoea
Liraglutide	GLP-1 receptor agonist Directly stimulates POMC and other anorexigenic neurons Activates reward system: ventral trigeminal area, nucleus accumbens	Personal/family history of medullary thyroid Ca, MEN type 2, pregnancy	Nausea, hypoglycemia, diarrhoea, constipation, decreased appetite, dyspepsia, abdominal pain

Bariatric (Metabolic) Surgeries

Restrictive

- Adjustable gastric banding
- Sleeve gastrectomy

Malabsorptive

- Roux-en-Y gastric bypass
- Biliopancreatic diversion +/- duodenal switch

Mechanisms of Weight Loss

Intestinal Malabsorption:

- Reducing the intestinal surface of nutrient absorption (J-I bypass)
- Distal diversion of pancreatic and biliary secretions (maldigestion)

Gastric Restriction:

- Limits the capacity of the stomach- early satiety and smaller meals
- Dumping syndrome: Anticipation fear

Acute Complications

- Mortality (0-1.1%)
- Anastomotic Leaks
- Pulmonary Embolism
- Bleeding
- Obstruction
- Infections
- Stomach Prolapse (banding)

Long-Term Complications

- Vomiting and Dumping Syndrome
- Protein Malnutrition
- Hair Loss
- Gallstones
- Ulcers (marginal, difficult endoscopy)
- B12 deficiency
- Iron Deficiency
- Vitamin D deficiency
- Thiamine Deficiency

Long-Term Complications

- Rapid Weight Loss Neuropathy
- Intestinal obstruction/strictures
- Incisional Hernia
- Fertility- Unwanted Pregnancy
- Redundant Skin (cosmetic surgery)
- Weight Regain
- Hyperinsulinemia / Nisedeoblastosis

Improvements of DM2 with different Bariatric Surgeries

	Roux-en-Y	Bilio-pancreatic diversion	Gastric Banding
Remission of DM2	84%	>95%	48%
Recurrence after 10 yrs	Rare	Rare	More Frequent
Evolution	Days to weeks	Days to weeks	> 6 months
Weight loss	Marked	Most marked	Less
Incretins	Increased	Increased	Unchanged

Question 9

- A 19-year-old woman is referred for evaluation of hypoglycemia. For 10 months, she has had episodes of somnolence, extreme fatigue, and difficulty being aroused from sleep.
- Symptoms usually appear overnight or 3 to 4 hours after a meal- they are always relieved by drinking orange juice
- Findings from her physical examination are unremarkable except for being overweight (BMI = 27.1 kg/m2)
- Her family history is significant for her twin brother having Type 1 DM on insulin since age 11. Past medical history is significant for depression.

Question 9

- During a spontaneous episode of hypoglycemia in your office occurring 2 and a half hours after a meal, the following laboratory values are obtained:
- Serum glucose 38 mg/dL
- Plasma insulin 25.2 µIU/mL (nl 2-17)
- C-peptide 0.3 ng/mL (nl 0.78-1.89)
- Pro-insulin 1 pmol/L (nl 6.4-8.9)
- Sulfonylurea level is undetectable

Question 9

What is the most likely cause of the patient's hypoglycemia?

A. Insulinoma
B. Factitious use of insulin
C. Reactive hypoglycemia
D. Adrenal Insufficiency
E. Growth hormone deficiency

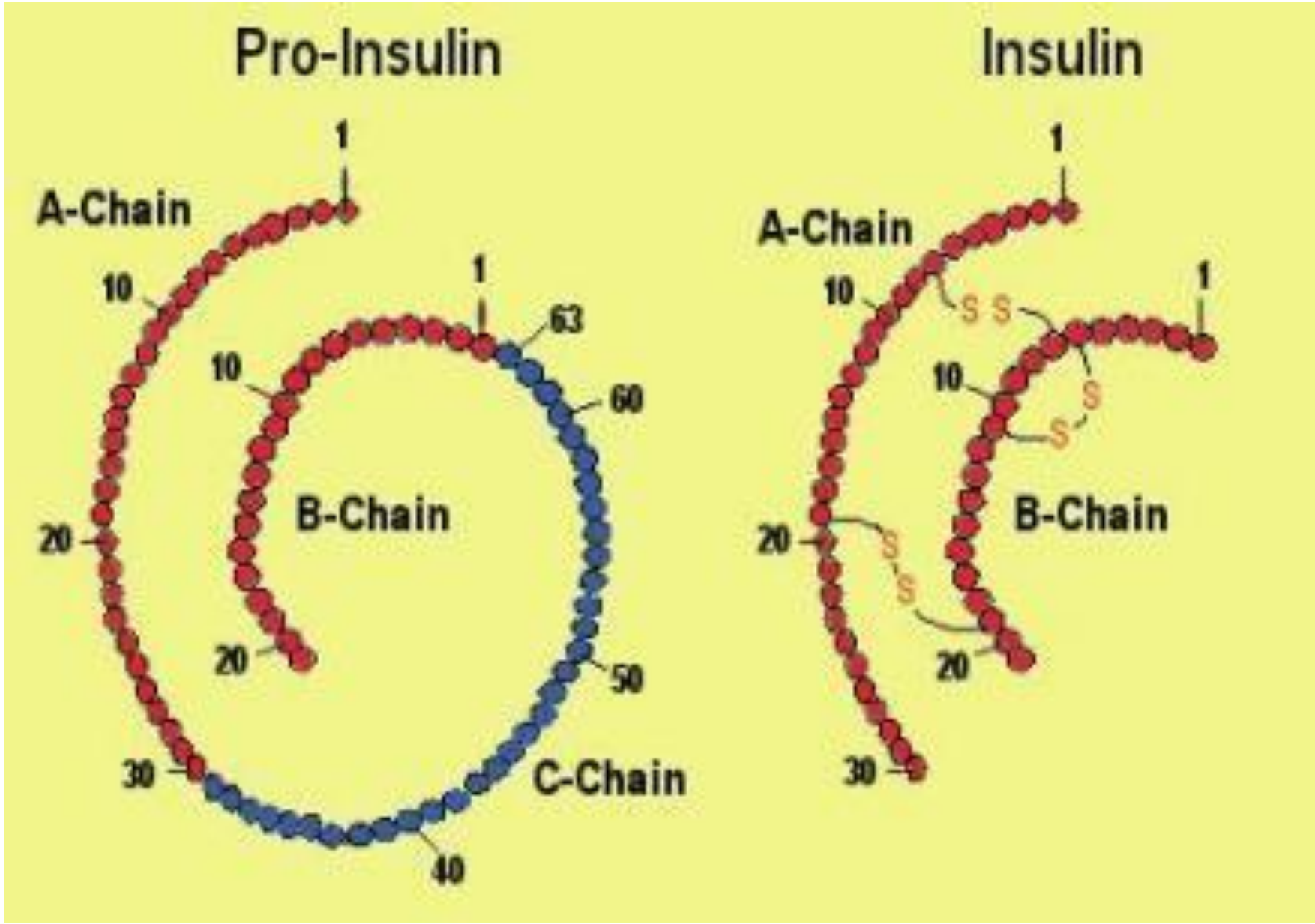
Hypoglycemia

- Definition as a disease: Whipple's Triad
  - Documented hypoglycemia
  - Neuroglycopenic symptoms during time of hypoglycemia
  - Resolution of symptoms with administration of glucose
- Hypoglycemia
  - Lower limit of normal glucose 70 mg/dL
  - Release of counter-regulatory hormones (65-70 mg/dL)
  - Symptoms of hypoglycemia (50-55 mg/dL)
- Neuroglycopenic Symptoms
  - Caused by sympathetic nervous activation
  - Tremor, Palpitations, Anxiety, Sweating, Hunger, Paresthesias, Cognitive impairment, Seizure, Coma

Hypoglycemia Etiologies

- Drugs
- Alcohol
- Critical Illness
- Tumors that make IGF-1 or IGF-2
- Hormone Deficiency (cortisol, glucagon, epinephrine)
- Exogenous Hyperinsulinism
  - Very common in diabetics on insulin
  - Surreptitious or Malicious use of insulin
- Endogenous Hyperinsulinism
  - Insulinoma
  - Functional beta-cell disorders
  - Autoimmune
  - Sulfonylurea

Check insulin, pro-insulin, sulfonylurea and c-peptide levels during an episode of hypoglycemia


Pro-Insulin
A-Chain
1
10
20
30
B-Chain
1
10
20
63
60
50
40
C-Chain
Insulin
A-Chain
1
10
20
30
S S
S
S
S S
B-Chain
1
10
20

Hypoglycemia Etiologies

Diagnosis	Insulin	C-peptide	Proinsulin	Sulphonylurea in plasma or urine
Exogenous insulin	↑↑	↓	↓	–
Insulinoma	↑	↑	↑	–
Sulphonylurea use	↑	↑	↑	+

↑ = increased; ↓ = decreased

Insulinoma

- Rare, incidence 1:250,000
- Associated with MEN1 Syndrome
- Fasting Hypoglycemia (diagnose with 72hr fast)
- Weight gain in 20% of patients
- Treatment
  - Surgical Resection
  - Medications that inhibit secretion of insulin
    - Diazoxide
    - Octreotide

Question 10

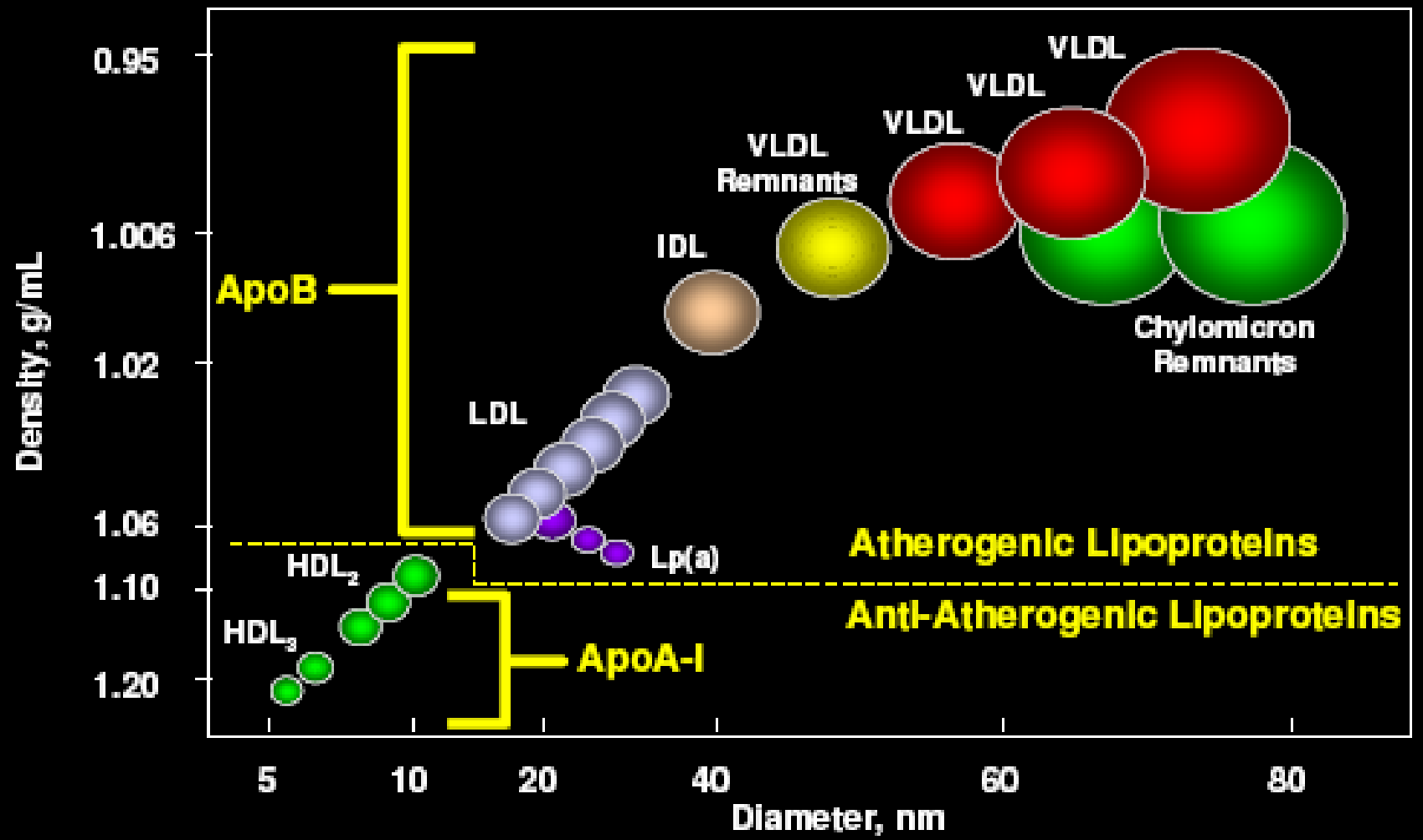
- A 38 year old healthy female is admitted to the hospital with acute onset abdominal pain
- Her only medication is birth control pills
- No family history of CVD or hyperlipidemia
- Selected Laboratory Data:
  - Total Cholesterol: 458
  - LDL: 120
  - HDL: 38
  - Triglycerides: 3000
  - Glucose: 89
  - Amylase: 5 x ULN
  - Thyroid, Liver and Renal Function normal

Question 10

The most likely diagnosis is?

A. Dysbetalipoproteinemia Type III- Hyperlipoproteinemia
B. LCAT deficiency
C. Familial Hypercholesterolemia
D. Drug induced hypertriglyceridemia
E. CETP deficiency

Atherogenic and Anti-atherogenic Plasma Lipoproteins



Adapted from Segrest JP et al. *Adv Protein Chem.* 1994;45:303–369.

Chylomicronemia Syndrome
Type I Hyperlipoproteinemia

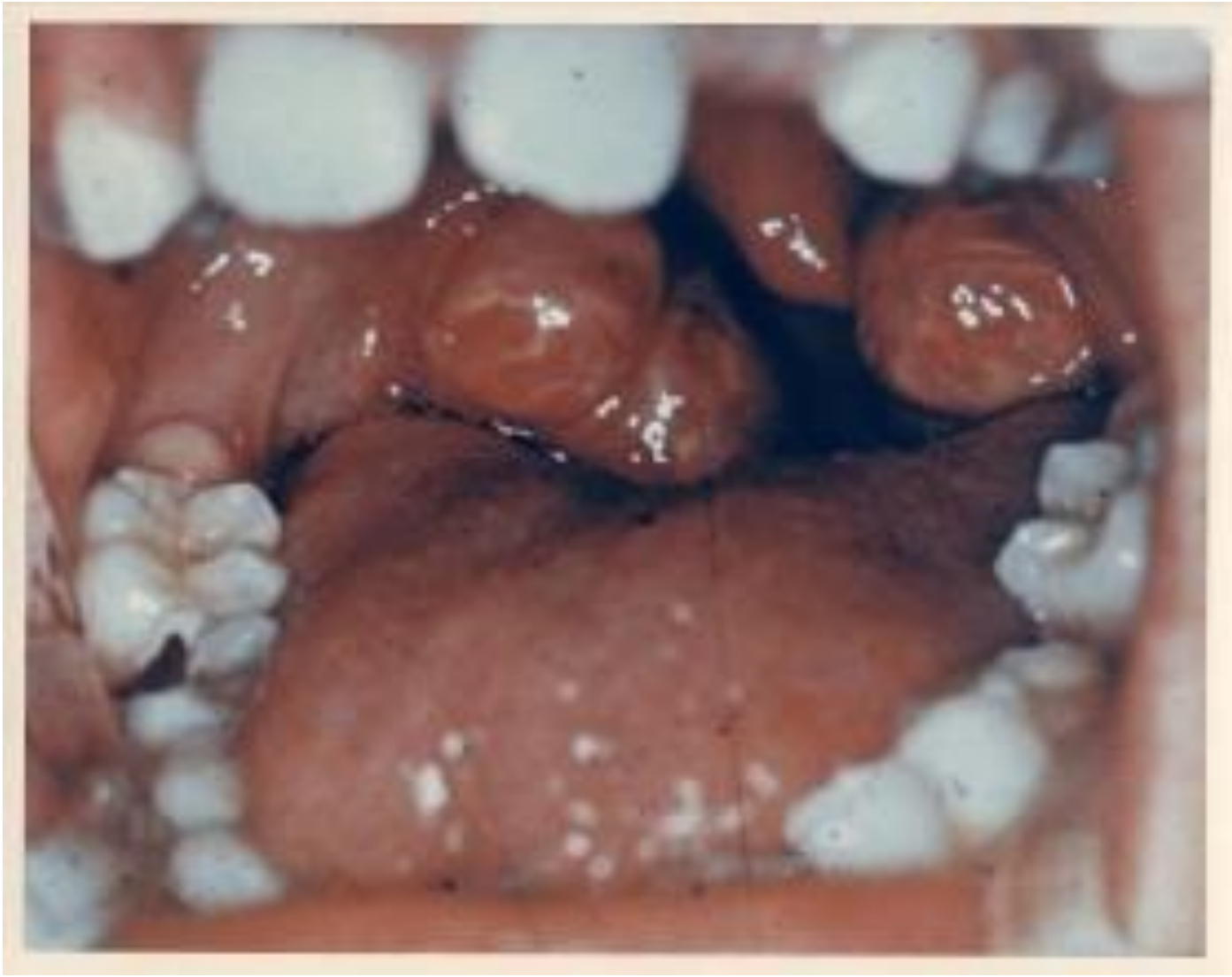
- Clinical Features: lipemic plasma, lipemia retinalis, eruptive xanthomas, recurrent pancreatitis
- Plasma lipids and lipoproteins: Elevated plasma triglycerides, chylomicrons, and VLDL
- Molecular defects: Deficiency in lipoprotein lipase or ApoC-II

Question 11

- A 44 year old man is admitted to the hospital with chest pain for rule out MI
- He reports a history of high triglycerides for which he takes fenofibrate
- Family history is significant for his father d. at age 54 from a MI and his brother had CABG at age 50
- Selected Laboratory Data:
  - Total Cholesterol: 174
  - LDL: 100
  - HDL: 4
  - Triglycerides: 280
  - Fasting Glucose: 88
  - Thyroid, Liver and Renal Function normal

Question 11

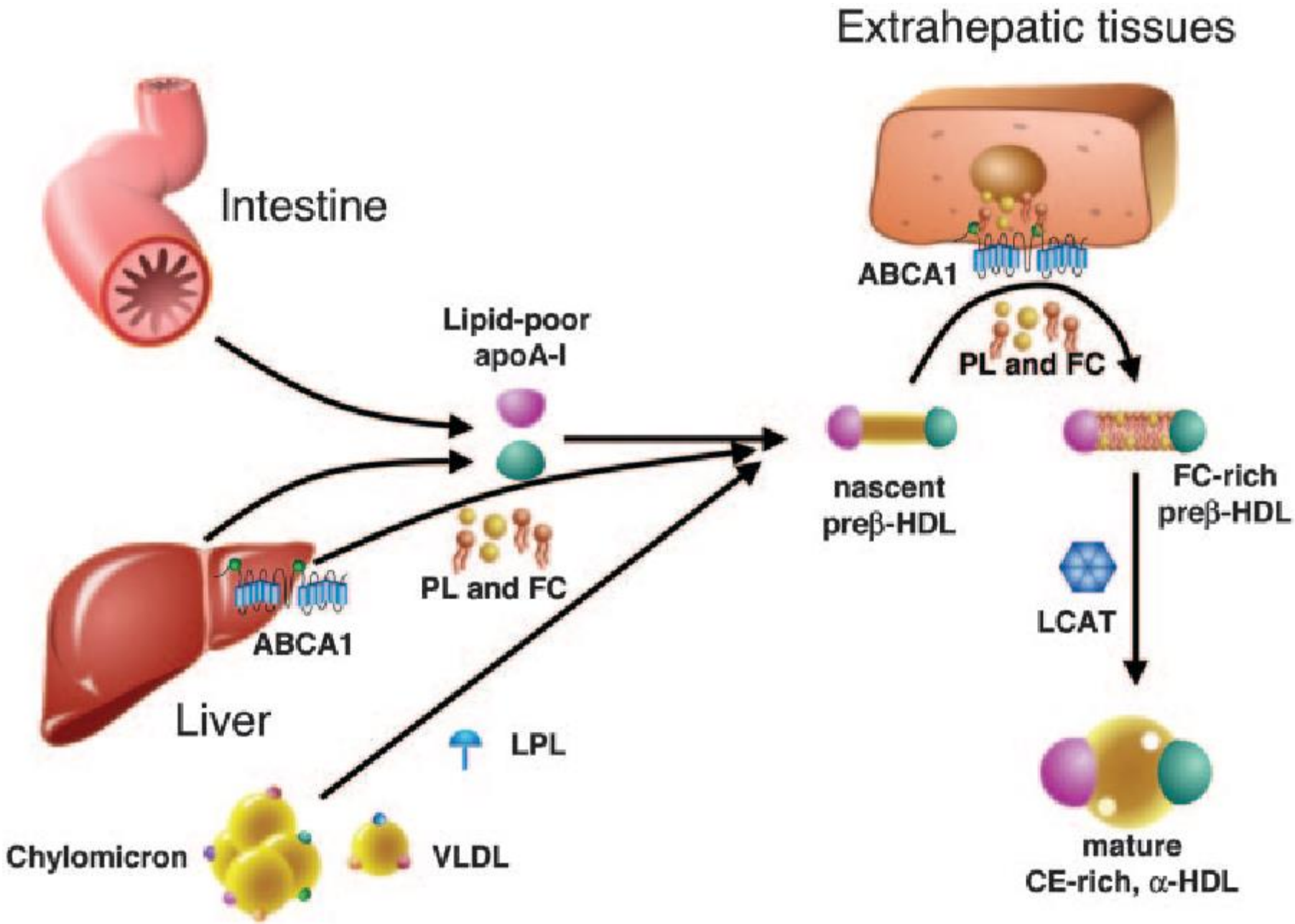
Physical Exam



Question 11

The most likely diagnosis is?

A. Tangier Disease
B. Lipoprotein Lipase Deficiency
C. Beta Sitosterolemia
D. Abetalipoproteinemia
E. CETP deficiency


Extrahepatic tissues
Intestine
ABCA1
Lipid-poor
apoA-I
PL and FC
nascent
preβ-HDL
FC-rich
preβ-HDL
LCAT
PL and FC
ABCA1
Liver
LPL
Chylomicron
VLDL
mature
CE-rich, α-HDL

Tangier Disease – Defect in the ABCA1 Transporter

- Clinical Features: Orange tonsils, premature CVD, cloudy cornea, peripheral neuropathy, hepatosplenomegaly, pancytopenia

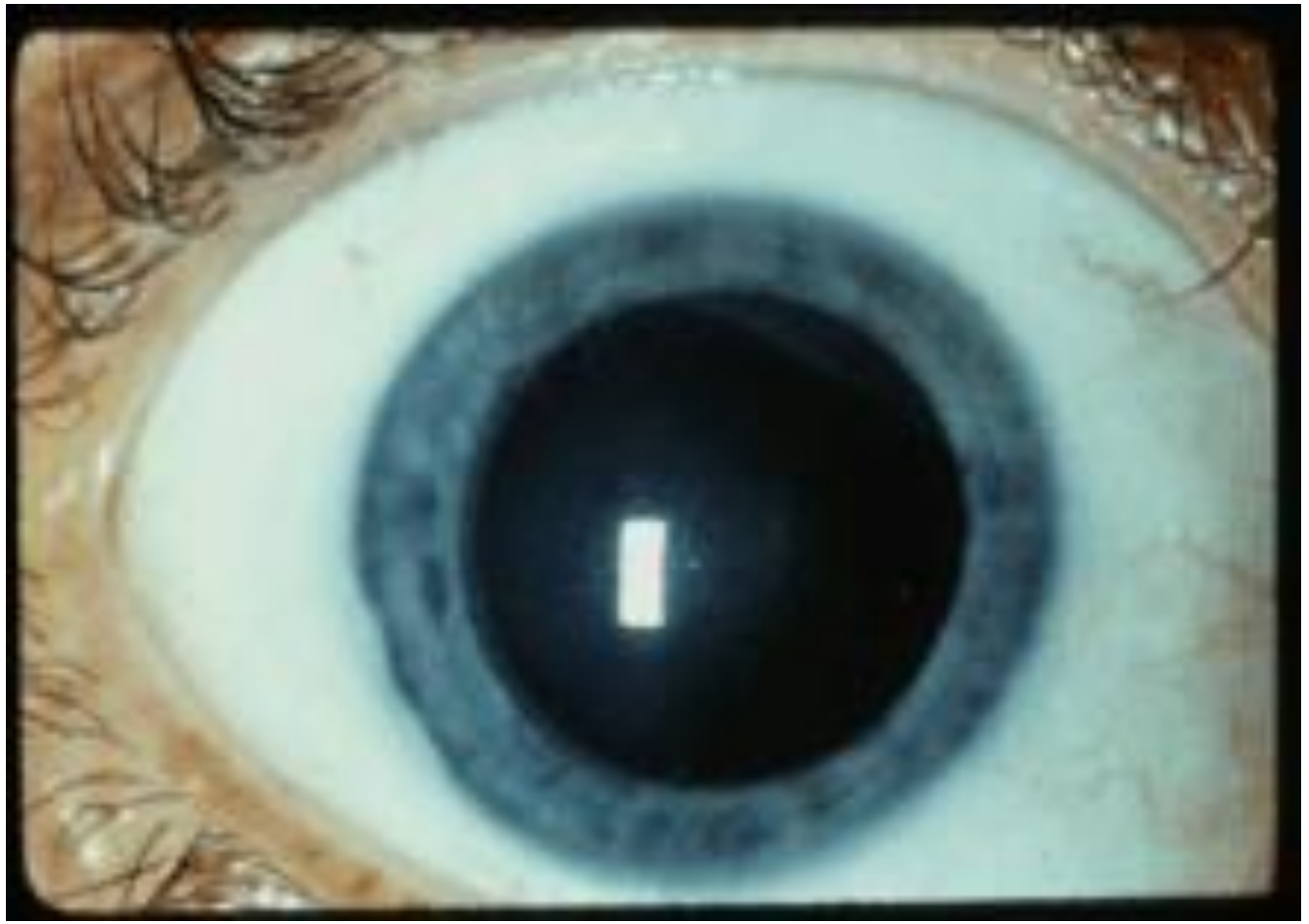
- Plasma lipids and lipoproteins: Low plasma HDL, elevated triglycerides with low LDL. Heterozygotes will have 50% normal levels of HDL. Very low plasma ApoA-I and ApoA-II

- Molecular defect: Defect in the ABCA1 Transporter

LCAT Deficiency

- Clinical Features: severe cloudy cornea (fish eye disease), chronic renal disease. NO CVD
- Plasma lipids and lipoproteins: Very low plasma HDL, elevated triglycerides with low LDL. Very low plasma ApoA-I and ApoA-II
- Molecular defect: Defect in LCAT enzyme

LCAT Deficiency – Fish Eye Disease



Choosing Wisely®

An initiative of the ABIM Foundation

American Association of Clinical Endocrinologists
and The Endocrine Society

Five Things Physicians and Patients Should Question

1 Avoid routine multiple daily self-glucose monitoring in adults with stable type 2 diabetes on agents that do not cause hypoglycemia.

Once target control is achieved and the results of self-monitoring become quite predictable, there is little gained in most individuals from repeatedly confirming. There are many exceptions, such as for acute illness, when new medications are added, when weight fluctuates significantly, when A1c targets drift off course and in individuals who need monitoring to maintain targets. Self-monitoring is beneficial as long as one is learning and adjusting therapy based on the result of the monitoring.

2 Don't routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function.

Many practitioners become confused when ordering a vitamin D test. Because 1,25-dihydroxyvitamin D is the active form of vitamin D, many practitioners think that measuring 1,25-dihydroxyvitamin D is an accurate means to estimate vitamin D stores and test for vitamin D deficiency, which is incorrect. Current Endocrine Society guidelines recommend screening for vitamin D deficiency in individuals at risk for deficiency.

Serum levels of 1,25-dihyroxyvitamin D have little or no relationship to vitamin D stores but rather are regulated primarily by parathyroid hormone levels, which in turn are regulated by calcium and/or vitamin D. In vitamin D deficiency, 1,25-dihydroxyvitamin D levels go up, not down.

Unregulated production of 1,25-dihydroxyvitamin D (i.e., sarcoidosis, granulomatous diseases) is an uncommon cause of hypercalcemia; this should be suspected if blood calcium levels are high and parathyroid hormone levels are low and confirmed by measurement of 1,25-dihydroxyvitamin D. The enzyme that activates vitamin D is produced in the kidney, so blood levels of 1,25-dihydroxyvitamin D are sometimes of interest in patients on dialysis or with end-stage kidney disease. There are few other circumstances, if any, where 1,25-dihydroxyvitamin D testing would be helpful.

Serum 25-hydroxyvitamin D levels may be overused, but when trying to assess vitamin D stores or diagnose vitamin D deficiency (or toxicity), 25-hydroxyvitamin D is the correct test.

Choosing Wisely®

An initiative of the ABIM Foundation

3

Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.

Thyroid ultrasound is used to identify and characterize thyroid nodules, and is not part of the routine evaluation of abnormal thyroid function tests (over- or underactive thyroid function) unless the patient also has a large goiter or a lumpy thyroid. Incidentally discovered thyroid nodules are common. Overzealous use of ultrasound will frequently identify nodules, which are unrelated to the abnormal thyroid function, and may divert the clinical evaluation to assess the nodules, rather than the thyroid dysfunction. Imaging may be needed in thyrotoxic patients; when needed, a thyroid scan, not an ultrasound, is used to assess the etiology of the thyrotoxicosis and the possibility of focal autonomy in a thyroid nodule.

4

Don't order a total or free T3 level when assessing levothyroxine (T4) dose in hypothyroid patients.

T4 is converted into T3 at the cellular level in virtually all organs. Intracellular T3 levels regulate pituitary secretion and blood levels of TSH, as well as the effects of thyroid hormone in multiple organs; a normal TSH indicates an adequate T4 dose. Conversion of T4 to T3 at the cellular level may not be reflected in the T3 level in the blood. Compared to patients with intact thyroid glands, patients taking T4 may have higher blood T4 and lower blood T3 levels. Thus the blood level of total or free T3 may be misleading (low normal or slightly low); in most patients a normal TSH indicates a correct dose of T4.

5

Don't prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.

Many of the symptoms attributed to male hypogonadism are commonly seen in normal male aging or in the presence of comorbid conditions. Testosterone therapy has the potential for serious side effects and represents a significant expense. It is therefore important to confirm the clinical suspicion of hypogonadism with biochemical testing. Current guidelines recommend the use of a total testosterone level obtained in the morning. A low level should be confirmed on a different day, again measuring the total testosterone. In some situations, a free or bioavailable testosterone may be of additional value.