ACP Board Review: Diabetes

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Disclosures

- Research: Dexcom
- Consulting: Abbott Diabetes Care, Hagar, embecta

Question 1

- A 47-year-old Caucasian woman presents with polyurea, polydipsia, and a 10-pound weight loss over the past 6 weeks. She has no family history of diabetes, but her sister was treated for Graves disease. She works out on a regular basis and has always had ideal body weight. Her menses are normal
- PE-unremarkable, no acanthosis or vitiligo, BMI = 22
- Lab-A1C = 12%, random glucose 333 mg/dL, no urinary ketones, normal HCO_3 and K

Question 1

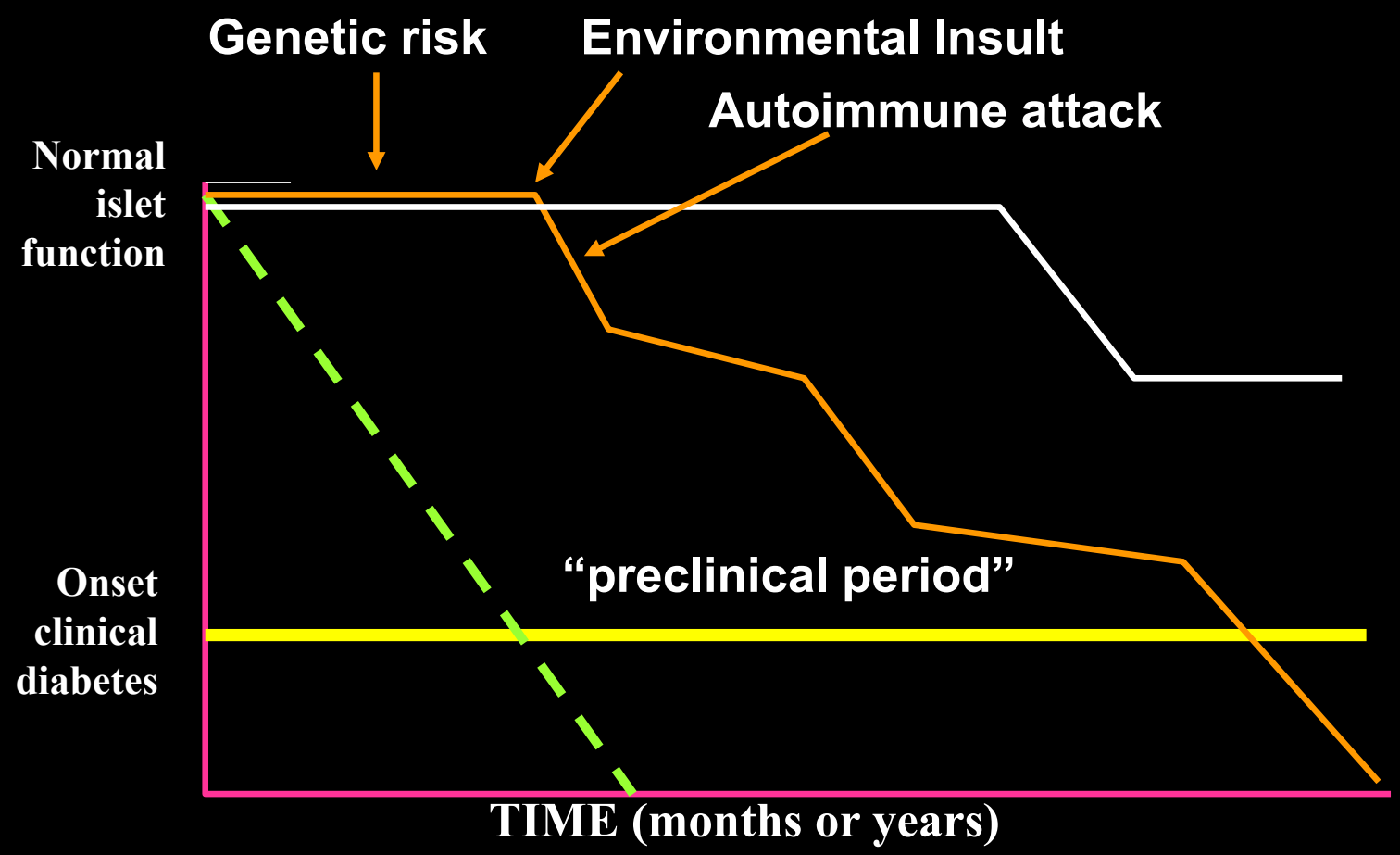
What is the best therapy for this woman?

A) Low carbohydrate diet, increase in exercise
B) Metformin
C) Pioglitazone
D) Dapagliflozin
E) Insulin

Type 1 Diabetes

- Past eras: presents only in children
  - Now: ~50% present in adulthood and the reason for this change is not known (lots of speculation); usually misdiagnosed
  - Classic teaching of low BMI not true any longer (in US 1/3 obese)
  - Genetic risk scores with HLA, chronic autoimmunity
  - Environmental factors important. 30-50% twin concordance
  - In adult onset T1D, 20-25% still making insulin 40 years later

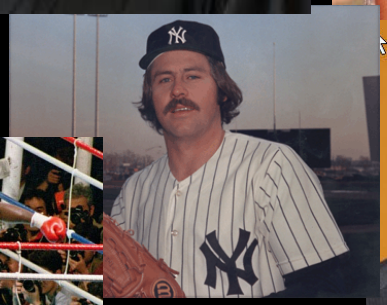
The Natural History of T1D

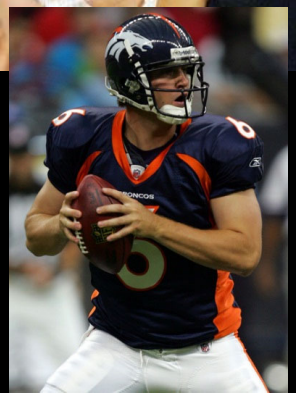


Diabetes Autoantibodies (all commercially available)

- **ICA-positive in 60-90% of newly diagnosed patients**
  - **Only of importance for historical reasons**
- **IAA-positive in about 60% newly diagnosed patients but best for children < 12 years old**
  - **assay can't distinguish Ab's from insulin Rx**
- **GAD->80% newly diagnosed patients**
  - **Often persist over time, similar rates in adults**
- **IA-2-Ab to a transmembrane tyrosine phosphatase**
  - **often more common in prepubertal patients**
- **ZnT8-found in 60-80% @ Dx; found in 25% of T1DM negative for other Abs**

Question 2: Can you name all of these with T1D?





Question 3

- A 55 year-old woman comes in concerned about her weight gain and risk for diabetes. Her two brothers both have diabetes, and all 3 sibs are obese. She has no symptoms to suggest diabetes. You have her return the next day for blood work and determine her fasting glucose is 120 mg/dL and her A1C is 6.3%

Question 3

Her diagnosis is

A)Prediabetes

B)Type 2 diabetes

C) Impaired glucose tolerance

D) Dysglycemia

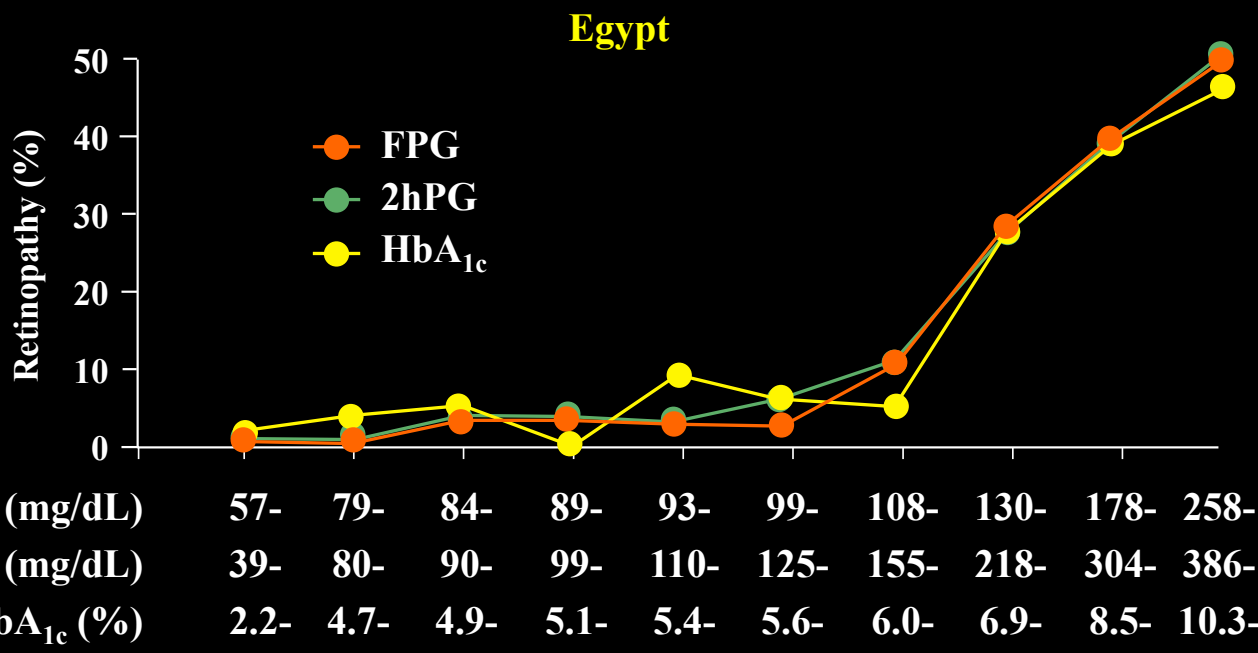
E) Normal Glucose Tolerance

Question 3a

The diagnosis of diabetes is based on where a population is found to have:

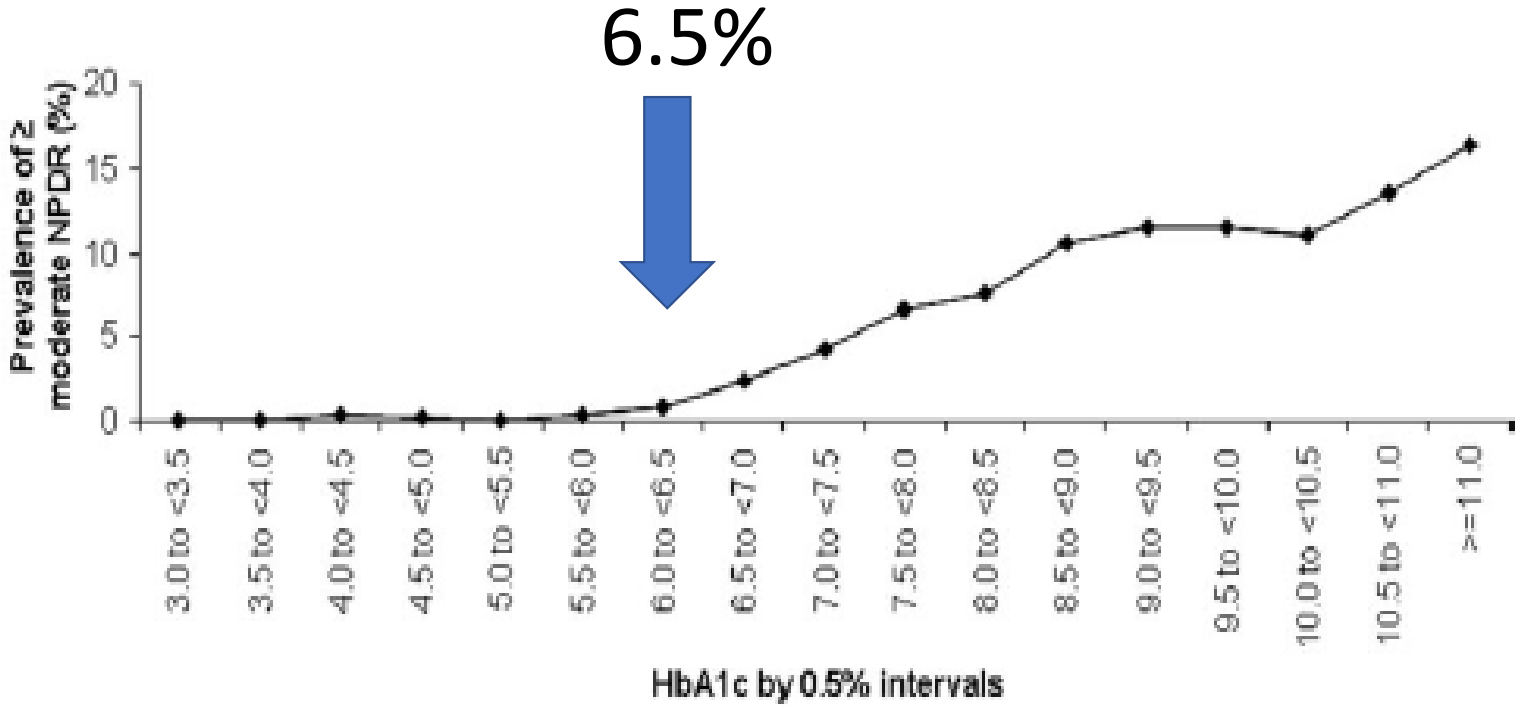
A. Diabetic neuropathy
B. Diabetic kidney disease
C. Diabetic retinopathy
D. Coronary artery disease
E. Peripheral vascular disease

Retinopathy in Adults not Known to Have Diabetes



Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1999;22(Supp 1):S5-S19.

International Expert Committee Report on the Role of A1C in the Diagnosis of Diabetes



THE INTERNATIONAL EXPERT COMMITTEE. Diabetes Care 2009;32:1327

Criteria for the Diagnosis of Diabetes

- A1C ≥ 6.5% (must be a standardized assay)*
- OR fasting plasma glucose ≥ 126 mg/dL*
- OR 2-h plasma glucose ≥ 200 mg/dL during an OGTT*
- OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL

* “In the absence of unequivocal hyperglycemia, results should be confirmed on repeat testing”

Diabetes Care 2022;45(Suppl. 1):S17–S38

Categories for Increased Risk of Diabetes

Normal	Impaired fasting glucose or Impaired glucose tolerance	**Diabetes**
Fasting plasma glucose (FPG) < 100 mg/dL	IFG: FPG ≥ 100-125 mg/dL	FPG ≥ 126 mg/dL
2 hr PG < 140 mg/dL	IGT : 2 h PG ≥ 140 – 199 mg/dL	2 h PG ≥ 200 mg/dL; random PG ≥ 200 mg/dL + symptoms
A1C ≤ 5.6%	**5.7-6.4%**	**≥ 6.5%**

Risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher ends

Question 4

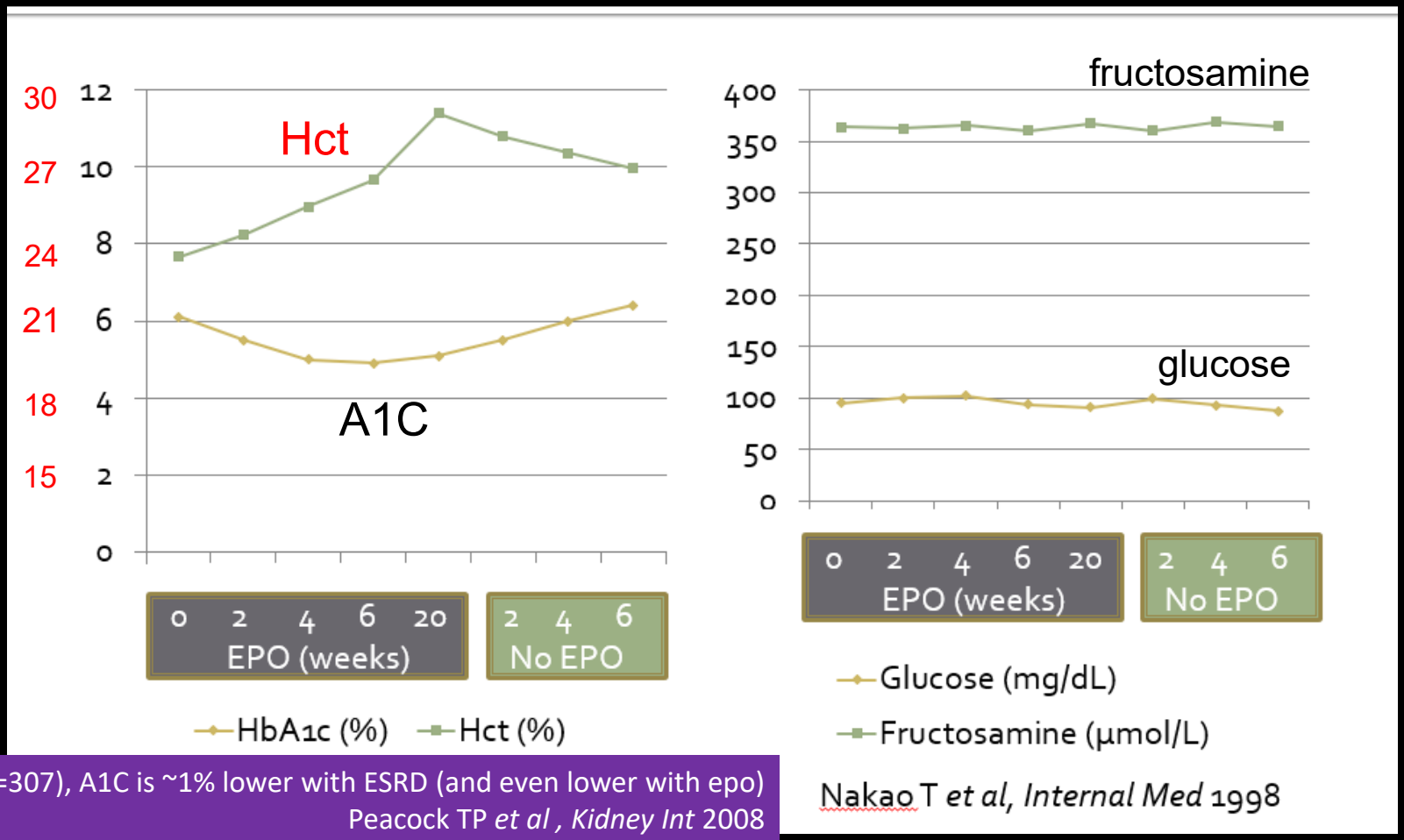
You are asked to see a 60 year-old man with a 15-year history of type 2 diabetes complicated by proliferative retinopathy, polyneuropathy, and ESRD on dialysis. For his diabetes he takes insulin glargine and aspart, and his other meds include calcitriol, amlodipine, atenolol, a phosphate binder, and epoetin alpha. His HbA1c is 6.2% (normal 4-6%)

Question 4

For his diabetes, you are able to conclude from this information that

A) His glucose control is too tight and he needs to reduce his insulin
B) He should be able to be managed with a sulfonylurea and a GLP-1 agonist
C) He would benefit from pioglitazone
D) No conclusions about his diabetes can be made

Epo Administration in ESRD (N = 15 no diabetes)



Nakao T *et al*, *Internal Med* 1998

On average (N=307), A1C is ~1% lower with ESRD (and even lower with epo)
Peacock TP *et al* , *Kidney Int* 2008

HbA1c

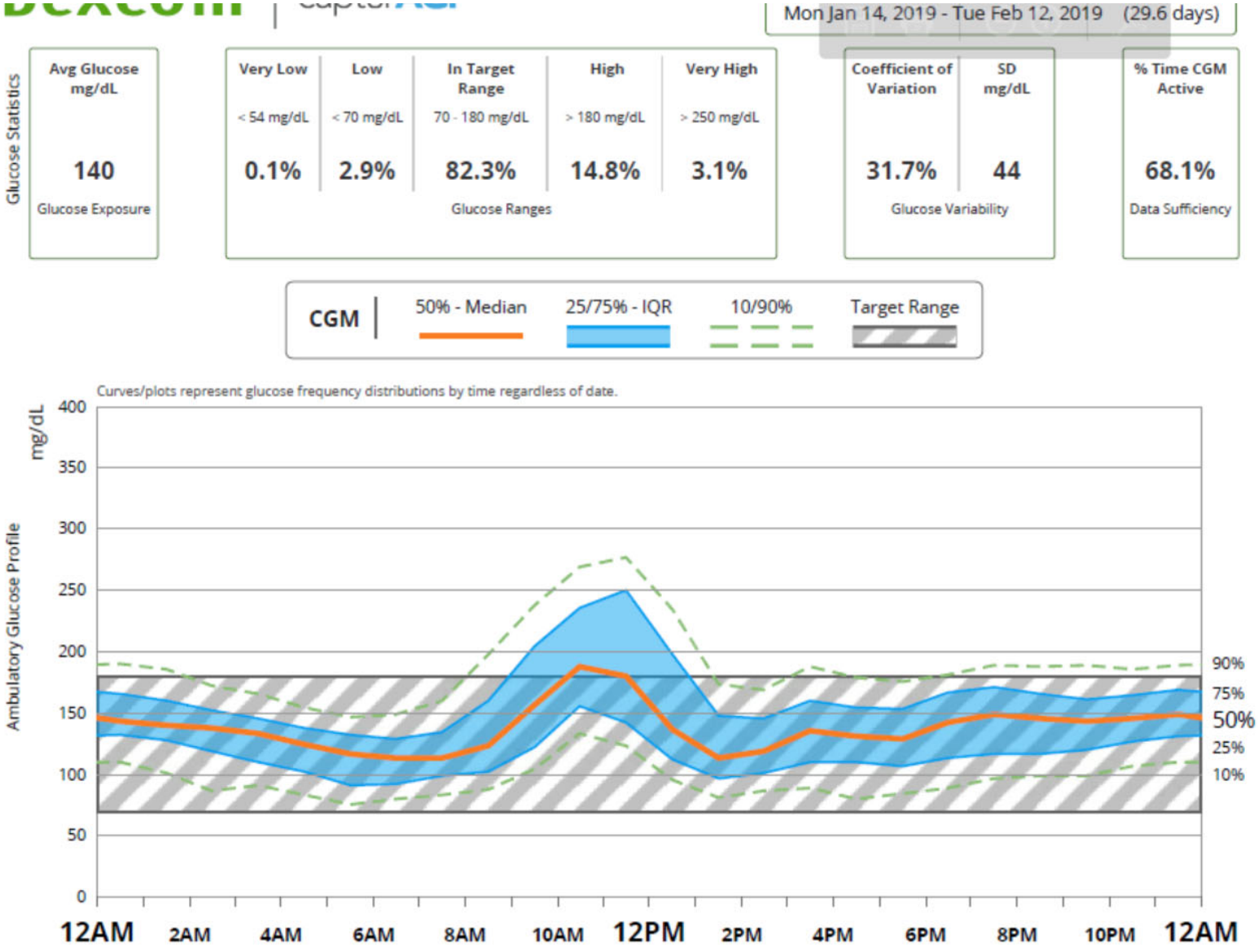
- Non-enzymatic glycation of hemoglobin which lives about 90 days in most people
- 50% of the HbA1c is based on the last 30 days
- Anything that changes hemoglobin molecule (binding), the rate of glycation or RBC survival time will change the A1C
  - Hemoglobinopathies, hemolysis, drugs

What Alters A1C

- Hematologic conditions
  - Anemia
  - Accelerated erythrocyte turnover
  - Thalassemia
  - Sickle cell disease
  - Reticulocytosis
  - Hemolysis
- Physiologic States
  - Aging
  - Pregnancy
- Drugs/Medications
  - Alcohol
  - Opioids
  - Vitamin C
  - Vitamin E
  - Aspirin
  - Erythropoetin
  - Dapsone
  - Ribavirin
- Disease States
  - HIV infection, COVID-19
  - Uremia
  - Hyperbilirubinemia
  - Dyslipidemia
  - Cirrhosis
  - Hypothyroidism
- Medical Therapies
  - Blood transfusion
  - Hemodialysis
- Miscellaneous
  - Glycation rate
  - Protein turnover
  - Race and ethnicity*
  - Laboratory assay
  - Glycemic Variability
  - Smoking
  - Mechanical heart valves
  - Exogenous testosterone?

Question 5

- An 82 y/o woman with 15 years of type 2 diabetes, a history of CAD with stent placement to 2 arteries 5 years ago is now receiving metformin, semaglutide, and 25 units of bedtime glargine. She wears a continuous glucose monitor. Her HbA1c is 6.6%. What changes do you suggest?



A. Add breakfast lispro
B. Increase bedtime glargine
C. Reduce bedtime glargine
D. Add empagliflozin
E. Do nothing

What You Should Know About CGM Downloads

- For most, “time in range” (70-180) target is > 70% but for “elderly and frail” it is >50%
- “Time below range” (< 70) target is < 4% but for “frail and elderly” is < 1%

Question 6

- A 45-year-old man with a 2-year history of type 2 diabetes and no complications has a HbA1c of 7.6% on metformin and most recently, dapagliflozin. He works out 3 times each week with a personal trainer but after losing 10 pounds over the past 6 months his weight has been stable. His BMI is 35.0 kg/m^2

The best strategy for this patient now would be:

- A. Add bedtime insulin degludec to bring HbA1c below 7%
- B. Add mealtime fast-acting aspart to bring HbA1c below 7%
- C. Add glimepiride
- D. Add sitagliptin
- E. Add semaglutide

Glucose Control: What You Need to Know (10-20-Year-Old Data)

- UKPDS (and DCCT): early after the diagnosis of diabetes
  - Both studies showed meticulous glucose control reduced the burden of microvascular complications short-term and macrovascular disease long-term ("metabolic memory")
- ACCORD-older population, 10 year T2DM history, + CVD or high-risk

The ACCORD Trial in addition to ADVANCE/VADT created a LOT of confusion!

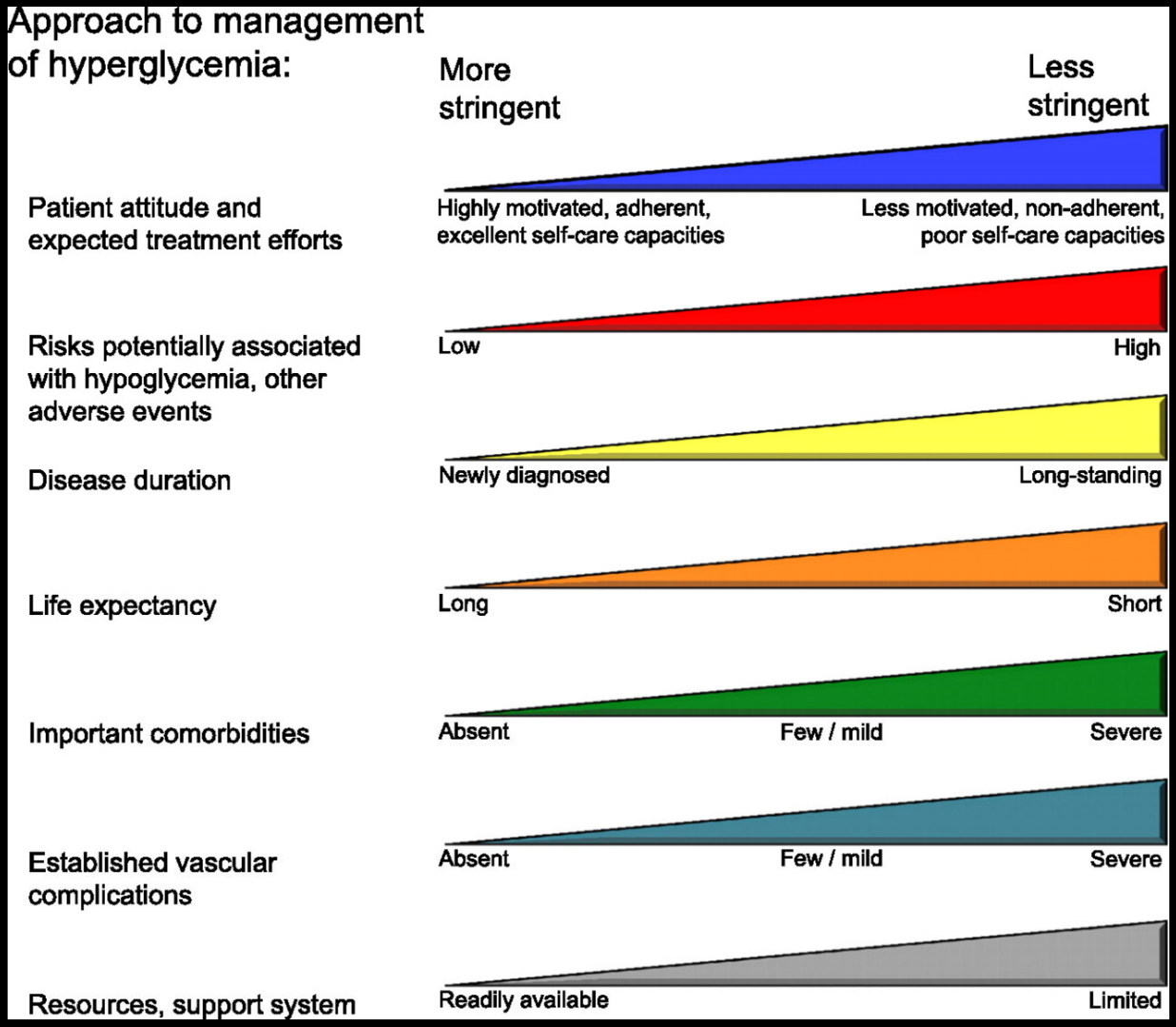
Impact of Intensive Therapy in Diabetes Summary of Major Clinical Trials

Study	Microvascular		CVD		Mortality	
DCCT/EDIC	↓	↓	↔	↓	↔	↓
UKPDS	↓	↓	↔	↓	↔	↓
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

*More recent data has confirmed the critical importance of glucose control in the first decade after diagnosis of type 2 diabetes

Initial Trial

Long Term Follow-up

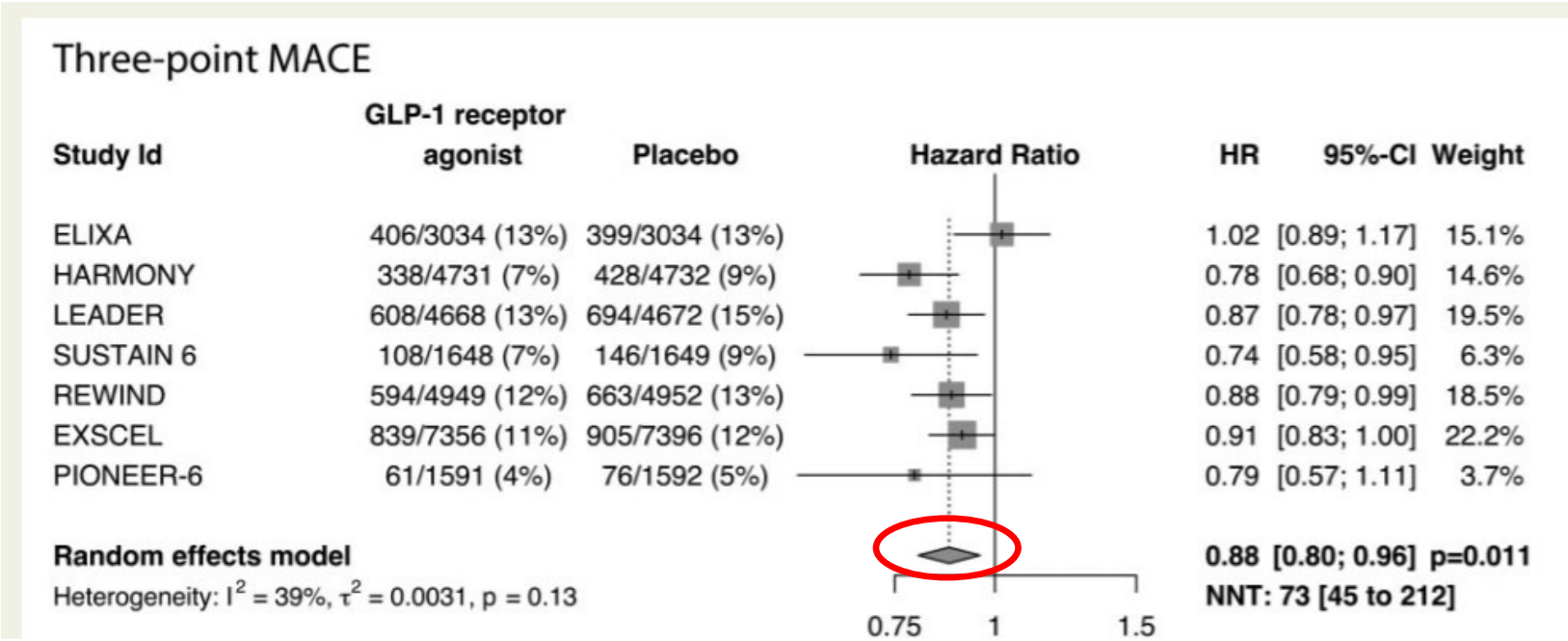


Inzucchi S E et al. Diabetes Care 2012;35:1364-1379

What You Need To Know About GLP-1 RAs in 2023 For Your Boards (no tirzepatide this year)

- In the US: exenatide, liraglutide, dulaglutide, semaglutide, tirzepatide
- Expect 0.8-1.0% A1C reduction, on average
- Dose-dependent weight loss
- All except exenatide and lixixenatide, have had positive CVOTs with improvement of 3-point MACE and CV mortality mostly *in those with pre-existing CVD*.
- Positive renal benefits but all secondary outcome (as of now)
- *By ADA recommended first injectable therapy for type 2 diabetes before insulin for most patients

The Effect of GLP-1 RAs on 3-Point MACE



European Heart Journal 2020; 41:3346–3358

Question 7

- A 67 y/o woman with 15 years of type 2 diabetes was recently diagnosed with idiopathic cardiomyopathy and an EF of 38%. For her diabetes she receives metformin, insulin glargine, and insulin lispro. She has never had severe hypoglycemia and her HbA1c now is 6.5%.
- For her diabetes, what would you suggest now?
  - A. add dulaglutide while reducing insulin
  - B. add dapagliflozin while reducing insulin
  - C. add pioglitazone while reducing insulin
  - D. Do nothing

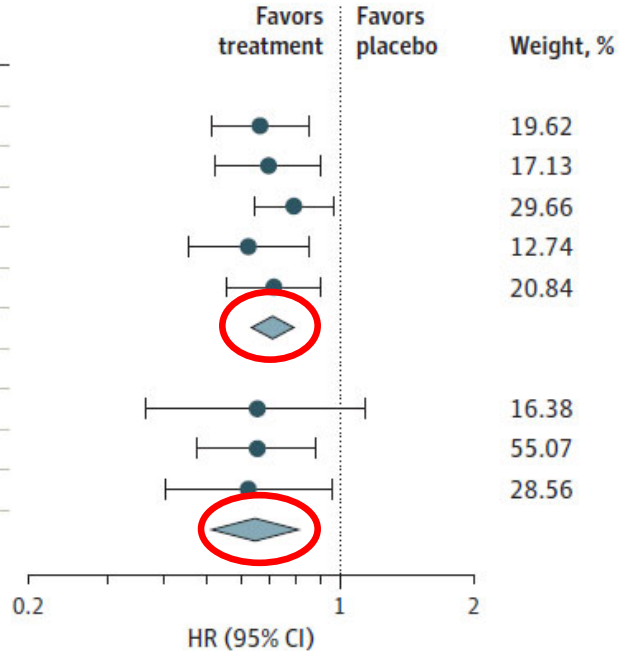
What You Need to Know About SGLT2 Inhibitors in 2023

- Induces glycosuria-no risk of hypoglycemia when used alone
- Modest HbA1c lowering: usually 0.5-0.8%
- Modest weight loss (less than GLP1 RAs)
- Main side effect: genital yeast infections
- Most concerning side effect: euglycemic DKA (can be seen in both type 2 and type 1 diabetes)
- Now used for heart failure with and *without* diabetes
- Beneficial to diabetic kidney disease (and non-diabetic CKD)

Effect of SGLT-2s on Hospitalization for HF (most published before 2019)

B HHF by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model ($Q = 1.97$; $df = 4$; $P = .74$; $I^2 = 0.0\%$)					0.70 (0.62-0.78)
Patients without ASCVD					
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)
Fixed-effects model ($Q = 0.03$; $df = 2$; $P = .99$; $I^2 = 0.0\%$)					0.63 (0.50-0.80)



JAMA Cardiol. 2021;6(2):148-158

What You Need to Know for IM Boards, 2023

- We've known since 2015-2016 SGLT2 I's and GLP1 RAs have independent effects for CV and renal outcomes
- Since 2019 recommendations are to use these agents *independent of HbA1c* for patients for those with ASCVD, HF, and CKD

Question 8

- A 52 y/o woman with known gestational diabetes 15 years ago presents to your clinic with polyuria, polydipsia, and a HbA1c of 13%. Exam is unremarkable except for acanthosis nigricans and a BMI of 31 kg/m^2 (she has lost 5 pounds in the past 2 months without trying).
- Her random glucose is 355 mg/dL and all of her other lab is unremarkable except for 4+ glycosuria

Question 8

- How do you want to treat this patient?
  - A. Metformin alone
  - B. Metformin and semaglutide
  - C. Bedtime glargine
  - D. Combination product insulin degludec with liraglutide
  - E. Bedtime glargine with premeal lispro

General Principles

- The higher the HbA1c, the greater the insulin deficiency
- Hyperglycemic symptoms suggests severe insulin deficiency and physiologic insulin replacement (“basal bolus”)will be required, at least initially
- With severe hyperglycemia, one has to always consider type 1 diabetes while awaiting workup
- The higher the HbA1c, the less likely basal insulin alone will reach target yet insulin shown not to be started until quite late in the US (N = 1251, HbA1c = 10.1%, Diab Therap 2018;9:1169-1184)

Question 9

- A 40 year-old woman with a known history of gestational diabetes is admitted to the neurosurgery service after head trauma. You are called when a random glucose after dexamethasone was found to be 310 mg/dL. Her A1C is 5.6% and she is eating a regular diet
- How would you treat her hyperglycemia?
  - A) Exenatide
  - B) Insulin glargine
  - C) AM NPH with premeal correction dose lispro
  - D) Sliding scale regular insulin q 6 hours
  - E) pre-meal insulin lispro

Steroid-Induced Hyperglycemia

- Major effect from insulin resistance with usual doses of steroids we use is muscle > liver; thus, post-prandial glucose levels will be most impacted.
- Kinetics of morning steroids, especially prednisone, matches well with kinetics of morning NPH insulin

Question 10

- You receive a report from the ophthalmologist that your 62-year-old woman with type 2 diabetes has pre-proliferative retinopathy in her right eye, but no retinopathy in her left eye. At this point you should
- A) Order a head CT
- B) Order a carotid duplex
- C) Order a CRP
- D) Order a VEGF (vascular endothelial growth factor) level

Question 11

- On a routine foot exam, you find your 63-year-old patient with a 25-year history of type 2 diabetes to have absent ankle jerk, absent vibratory sensation, and no ability to appreciate the 10 g monofilament on his right foot, but his left foot has a normal exam. His A1C is 9%
  - At this point you suggest
    - A) Intensify therapy to improve A1C to < 7%
    - B) Lumbar/sacral MRI
    - C) Urine N-telopeptide
    - D) Anti-transglutaminas Ab

Question 12

- A 68-year-old man with > 60 years of type 1 DM, no retinopathy and no previous history of albuminuria is found to have 1.2 grams of proteinuria on routine check. His creatinine is 1.0 mg/dL. He is already on enalapril and HCTZ and his BP levels average 110/70. His A1C is 7%
- At this point you should
  - A) add valsartin
  - B) order IVP
  - C) order UPEP, SPEP, ANA, CRP
  - D) order hemoglobin electrophoresis

Question 13

- An 18-year-old college freshman is referred because during her school exam, she was found to have a random glucose of 214 mg/dL followed by a fasting glucose of 134 mg/dL and HbA1c of 7.3%. She has no symptoms of concern, she takes no medications, and her BMI is 21 kg/m^2. Her family history is significant in that her mother and a brother both are treated for type 1 diabetes. At this time, all of her diabetes auto-antibodies and her urine pregnancy test are negative. What is the best answer?
  - A. Order a serum hCG test
  - B. Order MODY testing
  - C. Test for fasting c-peptide
  - D. Order CT of pancreas

Have Things Changed?

"The vast majority of diabetes in the US is not controlled in any real sense. The ignorance and carelessness of patients can often rightly be blamed. Nevertheless, the majority are largely influenced the the attitude and personality of the physician. Inadequately trained physicians are apt to treat diabetes in the easiest way…"

Allan FM: NEJM 248:133, 1953

Thank You and Good Luck!

Multiple Choice Answers: Diabetes

1. E
2. --
3. A, 3a C
4. D
5. C
6. E
7. B
8. E
9. C
10. B
11. B
12. C
13. B