WHAT'S NEW IN DIABETES CARE?

AN UPDATE FOR 2022

DISCLOSURES

- None

OBJECTIVES

- Name at least three reasons not to target hemoglobin A1c less than 7%.
- Name at least two non-glycemic indications for GLP-1 receptor agonists.
- Name at least two non-glycemic indications for SGLT2 inhibitors.
- Name at least two co-morbidities of diabetes that are neither microvascular nor macrovascular.

PRE-TEST

Which patient is LEAST appropriate for Hemoglobin A1c target less than 7%?

- 46yo female with rheumatoid arthritis and newly diagnosed Type 1 diabetes; A1c 9.6%
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At least one GLP-1 receptor agonist in the US is FDA-approved for which indication(s)?

- Secondary risk reduction for cardiovascular events in patients with Type 2 diabetes
- Secondary risk reduction for progression of diabetic kidney disease in patients with Type 2 diabetes
- Weight loss in non-diabetes
- A and C
- All of the above

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Which indication is NOT FDA-approved for any SGLT2 inhibitor in the US?

- Non-diabetic chronic kidney disease at risk for progression (excluding polycystic kidney disease)
- Chronic kidney disease due to diabetes in patients with Type 1 diabetes
- Primary cardiovascular risk reduction in patients with Type 2 diabetes and multiple CV risk factors
- Risk reduction for hospitalization due to HFrEF in patients with Type 2 diabetes

Which condition(s) is/are associated with Type 2 diabetes?

- Obesity
- Non-alcoholic fatty liver disease (NAFLD)
- Obstructive sleep apnea (OSA)
- Hypertension
- All of the above

STANDARDS OF CARE FOR DIABETES

- American Diabetes Association, updates annually, published in ADA journals every January
- American Association of Clinical Endocrinology, updates periodically, available at aace.com

DIAGNOSIS OF PREDIABETES AND DIABETES

PREDIABETES

- Hgb A1c 5.7-6.4%
- Fasting (8hr) serum glucose 100-125 mg/dL
- OGTT (75g) 2-hour serum glucose 140-199 mg/dL
- OGTT is validated for patients who are not carbohydrate-restricted

DIABETES

- Hgb A1c 6.5% or higher
- Fasting (8hr) serum glucose 126 mg/dL or higher
- OGTT (75g) 2-hour serum glucose 200 mg/dL or higher
- OGTT is contra-indicated in patients with symptomatic hyperglycemia

FYI: OGTT is useless in diagnosing hypoglycemia

DIAGNOSIS OF PREDIABETES AND DIABETES

- Two abnormal results are required for diagnosis.
- **Prediabetes**: now requires abnormal glucose result (fasting or OGTT). Abnormal A1c x2 is no longer sufficient for diagnosis.
- **Diabetes**: abnormal A1c x2, fasting glucose x2, or one of each; or OGTT.

SCREENING RECOMMENDATIONS

- All adults age 35 or older with risk factors (obesity, hypertension, PCOS, etc.)
- All adults undergoing investigation due to infertility
- Antibody testing recommended for all for newly diagnosed children and young adults
- Consider monogenic diabetes in children with onset prior to age 6 months, and any non-autoimmune child or young adult

TREATMENT TARGETS

- A1c 6.5% or lower (non-pregnant adults) <u>if safe</u>
- Not safe = history of severe hypoglycemia; hypoglycemia unawareness; limited life expectancy; advanced renal disease; long-standing diabetes unable to achieve target; *most patients with Type 1*
- "No RCTs have yet established optimal glycemic targets in persons with T2D."
- <u>Inpatient</u>: blood glucose140-180 mg/dL; consider IV insulin in critical care if glucose uncontrolled (persistently > 200 mg/dL)

HYPOGLYCEMIA

- Beware of hypoglycemia unawareness
- Beware of nocturnal hypoglycemia
- Ask spouse or other household member about "spells" and unwarranted anger
- Consider undetected hypoglycemia as a possible explanation for erratic blood glucose control
- Medical identification for insulin-treated patients; best if ID is worn, not carried
- Prescribe glucagon for insulin-treated patients who do not live alone, and educate household member in administration
- For inpatient: adjust insulin regimen before hypoglycemia occurs

BLOOD GLUCOSE MONITORING

- Insulin-treated patients with Type 2 diabetes should monitor BG at least twice daily, and preferably before each insulin injection
- Insufficient data for recommendation in patients not taking insulin
- Continuous glucose monitoring (CGM) recommended for all patients with Type 1 diabetes
- CGM recommended for insulin-treated Type 2 diabetes with hypoglycemia unawareness or at high risk for hypoglycemia regardless of insulin regimen (i.e., even if taking basal insulin only)

MEDICATION SELECTION FOR TYPE 2 DIABETES

- Known or high risk ASCVD: GLP-1 RA and/or SGLT2 inhibitor regardless of A1c
- Established heart failure (HFrEF and HFpEF): SGLT2 inhibitor regardless of A1c
- Known TIA/CVA: GLP-1 RA and/or pioglitazone
- Known CKD: SGLT2 inhibitor
- Obesity: GLP-1 RA and/or SGLT2 inhibitor

NON-INSULIN MEDICATIONS IN TYPE 1 DIABETES

- Sulfonylurea medications not approved and not useful (except short-term in LADA?)
- Metformin not approved, may have utility in "double" diabetes or PCOS
- Pioglitazone not approved, may have utility in NAFLD, PCOS, secondary stroke prevention
- Acarbose (Precose) and miglitol (Glyset) not approved, may improve A1c
- DPP-4 inhibitors not approved, may improve A1c
- **Pramlintide (Symlin, an amylin (incretin) analog) is the <u>only</u> non-insulin medication approved for Type 1 diabetes**
- GLP-1 RA medications not approved, may improve A1c and weight control
- SGLT-2 medications neither approved nor recommended
- Bromocriptine (Cycloset) neither approved nor recommended
- Colesevelam (Welchol) not approved, may improve A1c; approved to lower LDL-C

FDA-APPROVED NON-GLYCEMIC INDICATIONS

Secondary CV risk reduction

- **GLP-1 RA:** dulaglutide (Trulicity, CV and stroke); liraglutide (Victoza); semaglutide (Ozempic; Rybelsus; CV and stroke)
- **SGLT2 inhibitor:** canagliflozin (Invokana); dapagliflozin (Farxiga), empagliflozin (Jardiance)

Secondary renal risk reduction

- **GLP-1 RA:** none approved; secondary outcomes data to support exenatide (Bydureon), liraglutide, semaglutide, +/- dulaglutide, +/- lixisenatide (Lysumia)
- **SGLT2 inhibitor:** canagliflozin, dapagliflozin, empagliflozin

COMPLICATIONS: KIDNEY

- "Diabetic kidney disease" (DKD) replaces "diabetic nephropathy"
- ACE inhibitor or ARB for albuminuria (non-pregnant)
  - Not helpful for primary prevention; avoid in pregnancy
- SGLT2 inhibitor for CKD (eGFR 20 mL/min/1.73 m2 & up)
- GLP-1 RA for CKD (eGFR 15 & up)
- Non-steroidal MRA (finerenone) if albuminuria persists AND K+ is not high (eGFR 25 & up)

FINERENONE (KERENDIA)

- Non-steroidal mineralocorticoid receptor antagonist
- Approved 2021 to "reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with Type 2 diabetes (T2D)."
- Recommended dose 20mg once daily, with or without food

FINERENONE PRESCIBING INFORMATION

- eGFR 25 to less than 60: initial dose 10mg daily, titrate to 20mg after 4 weeks if able
- eGFR 60 and higher: initial dose 20mg daily
- Test serum potassium 4 weeks after medication initiated; consider dose titration
- CONTRAINDICATIONS
  - Serum potassium > 5 mEq/L
  - Primary adrenal insufficiency
  - Severe hepatic impairment (Child Pugh C)
  - Strong CYP3A4 inhibitor (grapefruit, itraconazole); leads to excess med
  - Strong CYP3A4 inducer (efavirenz (Sustiva for HIV), rifampicin (TB)); inactivates med

FINERENONE

- FIDELIO-DKD
- 5000+ patients with CKD (eGFR 25-74 mL/min/1.73m2) associated with Type 2 diabetes
- Mean age 66 years; 70% male; 63% white (5% black); 46% with established ASCVD (CHF excluded); 54% with eGFR < 45 mL/min/1.73m2)
- All patients taking ACEi or ARB at maximum tolerated dose (per FDA labeling); diabetes and blood pressure controlled (only 4.5% taking SGLT2 inhibitor)
- Median follow-up 2.6 years
- Relative risk reduction 18% for CKD progression to ESRD, eGFR decline > 40%, or renal death
- Relative risk reduction 14% for CV death, nonfatal MI, nonfatal stroke, hospitalization for CHF

- N Engl J Med 2020; 383:2219-2229; doi: 10.1056/NEJMoa2025845

COMPLICATIONS: EYE

- Comprehensive eye examination by eye doctor (not IRIS) at diagnosis for adults
- First screening exam 5 years after diagnosis for younger patients
- Every trimester during pregnancy and once post-partum
- IRIS or similar screening acceptable after initial exam

COMPLICATIONS: NEUROPATHY

- Screen at diagnosis for T2D, 5yr after diagnosis for T1D, then annually
  - Any two of: vibration, pinprick, temp, monofilament, ankle DTR
- Foot exam every visit
- Consider screening for CV autonomic neuropathy

COMORBIDITIES: HYPERTENSION

- Hypertension target < 130/80 mmHg (consider 120/70 if CKD, ASCVD, retinopathy)
  - ACEI or ARB preferred if medication needed
  - Second line: diuretic, calcium channel blocker, labetalol, newer beta blocker (like carvedilol)
  - Consider mineralocorticoid receptor antagonist (steroidal or nonsteroidal) if resistant (BP140/90 or higher on 3 or more meds including diuretic)

COMORBIDITIES: HYPERTENSION

- Consider secondary causes of hypertension, especially if hypertension is resistant or unusual in any way
  - Primary hyperaldosteronism – common
    - Screen with serum aldosterone/plasma renin activity ratio
  - Pheochromocytoma
  - Cushing's syndrome
  - Renal artery stenosis

COMORBIDITIES: CHOLESTEROL

- LDL-C target < 100 mg/dL for high risk; < 70 mg/dL for very high risk; < 55 mg/dL for extreme risk
  - Applicable to Type 1 diabetes when above the age of 40
  - Consider monitoring Apo B if ASCVD risk unclear
  - Statin first
  - Ezetimibe second
  - PCSK9 inhibitor (evolocumab, alirocumab, inclisiran) third

COMORBIDITIES: TRIGLYCERIDES

- Optimize diabetes control
- Consider insulin therapy
- Low carbohydrate, low fat, low alcohol diet
- Statins first line, to achieve LDL-C goal
- Fibrates second line
- High-grade omega-3 fatty acid third line for trigs persistently 500 mg/dL or higher (EPA (Vascepa))
- Niacin fourth line only if trigs > 1000 mg/dL, to reduce risk for pancreatitis

OBESITY AND ABCD (ADIPOSITY-BASED CHRONIC DISEASE)

- Mediterranean diet associated with reduced CV risk
- Other dietary approaches are safe and effective but lack evidence for long-term benefit
- GLP-1 RA and SGLT2 inhibitor preferred for diabetes control
- Consider weight loss medications if needed
  - N.B., liraglutide and semaglutide approved for weight loss, **with or without diabetes**
- Consider bariatric surgery for BMI 35 kg/m2 and ABCD
- Caution if 65 years old and older: loss of muscle and bone mass

COMORBIDITIES: NAFLD

- Primary defect is ectopic fat deposition, including liver, leading to inflammation and fibrosis
- Liver fibrosis progresses 1 stage every 7 years on average (3 stages before cirrhosis), leads to cirrhosis, hepatocellular carcinoma and liver death
- Associated with obesity, but can occur with normal weight patients (particularly Asian ethnicity)
- 50-74% of patients with Type 2 diabetes have NAFLD, increases to 90% if BMI 35 or higher
- AST and ALT usually normal
- Usually diagnosed incidentally (liver biopsy during surgery, etc.)
- UNDER-DIAGNOSED

Information from a presentation by Dr. Scott Isaacs, Emory University

COMORBIDITIES: NAFLD

FIB-4 INDEX – SCREENING TEST

- Age (years) x AST (U/L) / platelet count x square root of ALT (U/L)
- FIB-4 < 1.3, low risk, manage risk factors
- FIB-4 1.3 – 2.67, intermediate risk, further testing
- FIB-4 > 2.67, high risk, refer to hepatology
- FIB-4 predicts fibrosis risk and CV risk; nearly 40% CV events at 5 years in high risk patients

SECONDARY TESTING

- Enhanced Liver Fibrosis (ELF) biomarker (blood) – 3 markers of liver fibrosis: hyaluronic acid (HA), Type III procollagen peptide (PIIINP), tissue inhibitor of matrix metalloproteinase a (TIMP-1)
- ELF < 9.8, low risk, repeat in 2-3 years
- ELF 9.8 – 11.3, intermediate risk, further testing
- ELF > 11.3, high risk, refer to hepatology
- ELF predicts liver-related events
- Good imaging techniques not widely available; ask at your institution. Ultrasound is not sensitive.

NAFLD MANAGEMENT: LIFESTYLE

- Weight loss 3% needed to improve steatosis; 5% to improve inflammation; 7% needed for NASH resolution; 10% needed for fibrosis.
- Mediterranean diet with caloric deficit to reduce CV risk
- Exercise
- 7-9 hours of nighttime sleep; treatment of OSA if present
- Very limited alcohol intake (< 2 servings per day for men, < 1 serving per day for women)
- Coffee is good: 2 cups per day or more

NAFLD MANAGEMENT: MEDICATIONS

- Consider pioglitazone: 30-40% resolution of NASH
- Consider semaglutide, tirzepatide, SGLT2 inhibitor
- Consider bariatric surgery for intermediate and high risk patients per FIB-4 and ELF
- Vaccinations: Heptitis A and B; pneumonia

COMORBIDITIES: SLEEP APNEA (OSA)

- 30% of patients with OSA have Type 2 diabetes
- 70% of patients with Type 2 diabetes have OSA, most undiagnosed
- "Health care professionals should assess persons with T2D for symptoms and signs of OSA, especially in the presence of obesity or suggestive clinical features of OSA."

COMORBIDITIES: DEPRESSION

- ~25% of people with diabetes experience significant depressive symptoms; most are undiagnosed and untreated
- "Routine screening of adults with DM for depression and DM distress is recommended during each clinic encounter, if appropriate."

AN OLD PLAYER: GLP-1

- GLP-1 = glucagon-like peptide-1
- Secreted throughout the gut, distal > proximal but increases promptly with feeding
- Slows gastric emptying; reduces small bowel motility
- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon, gluconeogenesis, and appetite
- Inhibits beta cell apoptosis, may increase beta cell mass

A NEW PLAYER: GIP

- GIP = gastric inhibitory polypeptide = glucose-dependent insulinotropic polypeptide
- Secreted from duodenum and proximal jejunum
- Stimulates glucose-dependent insulin secretion
- Decreases GI motility

TIRZEPATIDE (MOUNJARO)

- Dual agonist for GLP1 and GIP, approved in May 2022
- Weekly subcutaneous injection, 2.5mg to start, 15mg max
- A1c reduction of 1.6% compared to placebo
- Outperformed semaglutide and basal insulin (degludec and glargine) for A1c reduction and weight loss

TIRZEPATIDE: OBESITY

- 72 week RCT re obesity (not diabetes-specific)
  - 20 week dose escalation period
- 2539 adults with average BMI 38

N Engl J Med 2022; 387:205-216

DOI: 10.1056/NEJMoa2206038

TIRZEPATIDE: OBESITY

- 5mg dose: -15%
- 10mg dose: -19.5%
- 15mg dose: -20.9%
- Placebo: -3.1%
- 85% to 91% of subjects lost at least 5% from baseline (compared to 35% with placebo)
- 50% to 57% of subjects reduced weight at least 20% with10-15mg doses (compared to 3% with placebo)

Not approved by FDA for obesity management as of October 23, 2022

TIRZEPATIDE: CAVEATS

- C-cell tumors in rats
- Unknown risk for pancreatitis
- Not indicated for Type 1 diabetes
- Best tolerated with careful dose titration

POST-TEST

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