Disclosures

- None
Objectives

- Be able to diagnose diabetes and assess control
- Be able to identify appropriate classes of medications for diabetes treatment and basics of mechanisms of action
- Begin to manage diabetes and co-morbidities
Epidemiology of Diabetes in the US

- Prevalence: 30.3 million
  - Approx 1.25 million DM1
- 9.4% of the U.S. population
  - Diagnosed: 23.1 million
  - Undiagnosed: 7.2 million
- Leading cause of kidney failure, nontraumatic lower-limb amputation, new cases of blindness among adults
- Major cause of heart disease and stroke
- **Seventh** leading cause of death

Epidemiology of Diabetes in the US

- **New Cases:**
  - Approx 1.5 million new diagnoses/yr
- **Prediabetes in 84.1 million Americans above age 18 in 2015**
- **Cost:** in 2017 total cost of $327 billion

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

### Obesity (BMI ≥30 kg/m²)

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;14.0%</th>
<th>14.0%–17.9%</th>
<th>18.0%–21.9%</th>
<th>22.0%–25.9%</th>
<th>≥26.0%</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
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<td>&lt;14.0%</td>
<td>14.0%–17.9%</td>
<td>18.0%–21.9%</td>
<td>22.0%–25.9%</td>
<td>≥26.0%</td>
</tr>
<tr>
<td>2000</td>
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</table>

### Diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;4.5%</th>
<th>4.5%–5.9%</th>
<th>6.0%–7.4%</th>
<th>7.5%–8.9%</th>
<th>≥9.0%</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
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<td>2015</td>
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</tr>
</tbody>
</table>

CDC’s Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015

Care in Populations

- 33-49% of patients do not meet recommended targets for glycemic, blood pressure or cholesterol control
- Only 14% meet all 3 targets and also avoid smoking
- Mean A1c:
  - 1999-2002: 7.6%
  - 2007-2010: 7.2%

ADA. Diabetes Care 2018;41(suppl 1):S1-159
Standards of Medical Care in Diabetes - 2018
## ADA Evidence Grading System for Clinical Practice Recommendations

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Clear evidence from adequately powered well-conducted, generalizable, randomized controlled trials</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Supportive evidence from well-conducted cohort studies</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Supportive evidence from poorly controlled or uncontrolled studies</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>Expert consensus or clinical experience</td>
</tr>
</tbody>
</table>

ADA. Diabetes Care 2018;41(suppl 1):S1-159
Recommendations: Strategies for Improving Diabetes Care

- Care should be aligned with components of the Chronic Care Model to ensure productive interactions between a prepared proactive practice team and an informed activated patient A

- When feasible, care systems should support team-based care, community involvement, patient registries, and embedded decision support tools to meet patient needs B

ADA. Diabetes Care 2018;41(suppl 1):S1-159
CLASSIFICATION AND DIAGNOSIS OF DIABETES
Classification of Diabetes

- **Type 1 diabetes**
  - autoimmune β-cell destruction with absolute insulin deficiency

- **Type 2 diabetes**
  - Progressive insulin secretory defect in the background of insulin resistance

ADA. Diabetes Care 2018;41(suppl 1):S1-159
Classification of Diabetes

- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action (MODY)
  - Diseases of the exocrine pancreas (CFRD)
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)
Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A random plasma glucose ≥200 mg/dL (11.1 mmol/L)
Categories of Increased Risk for Diabetes (Prediabetes)*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose in the 75-g OGTT
140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

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

ADA. Diabetes Care 2018;41(suppl 1):S1-159
• Screening for prediabetes and risk for future diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. B

• Testing for prediabetes and risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI $\geq 25$ kg/m$^2$ or $\geq 23$ kg/m$^2$ in Asian Americans) and who have one or more risk factors for diabetes (Table 2.3). B

• For all people, testing should begin at age 45 years. B
Testing for Diabetes or Prediabetes in Asymptomatic Adults

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.

3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.

4. For all other patients, testing should begin at age 45 years.

5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

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

American Diabetes Association.
PREVENTION/DELAY OF TYPE 2 DIABETES
Recommendations: Prevention/Delay of Type 2 Diabetes

- Annual monitoring/testing in patients with prediabetes E

- Diabetes Prevention Program A
  - Targeting weight loss of 7% of body weight
  - Increasing physical activity to at least 150 min/week of moderate activity (e.g. brisk walking)

- Pharmacologic Therapy
  - Metformin should be considered in prediabetes, especially if BMI ≥35, age <60 or prior GDM. A
GLYCEMIC TARGETS
Diabetes Care: Glycemic Control

3 primary techniques available for health providers and patients to assess effectiveness of management plan on glycemic control

- Patient self-monitoring of blood glucose (SMBG)
- A1C
- Continuous Glucose Monitoring (CGM)
SMBG meter download example:
CGM report example:
Diabetes Care: Glycemic Control

- Perform the A1C test at least two times a year in patients meeting treatment goals (and have stable glycemic control) **E**
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals **E**
A1C Goals in Adults: Recommendations

- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). A
- Providers might reasonably suggest more stringent A1C goals (such as <6.5%) for select individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C

Glycemic Targets: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64
A1C Goals in Adults: Recommendations (2)

• Less stringent goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B
A1C and CVD Outcomes

- DCCT: Trend toward lower risk of CVD events with intensive control (T1DM)
- EDIC: 57% reduction in risk of nonfatal MI, stroke, or CVD death (T1DM)
- UKPDS: Nonsignificant reduction in CVD events (T2DM)
- ACCORD, ADVANCE, VADT suggested no significant reduction in CVD outcomes with intensive glycemic control. (T2DM)
## Approach to the Management of Hyperglycemia

### Patient/Disease Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>More Stringent</th>
<th>A1C 7%</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of hypoglycemia/drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude &amp; expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
<td></td>
</tr>
<tr>
<td>Resources &amp; support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

### Glycemic Targets:

*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64*
APPROACHES TO GLYCEMIC TREATMENT
Recommendations: Pharmacological Therapy For Type 1 Diabetes

Most people with type 1 diabetes should:

• Be treated with MDI injections of basal and prandial insulin or continuous subcutaneous insulin infusion (CSII) A

• Be **educated in how to match prandial insulin dose to carbohydrate intake**, premeal blood glucose, and anticipated activity E

• Use insulin analogs to reduce hypoglycemia risk A
Pharmacologic Therapy For T2DM: Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM. A

- 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. B
Recommendations: Therapy for Type 2 Diabetes (2)

- A patient-centered approach should be used to guide choice of pharmacological agents
  - Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes
- Overall each class of noninsulin agent decreases A1c by 0.9-1.1%
Recommendations: Therapy for Type 2 Diabetes (3)

- In patients with T2DM and established ASCVD, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse CV events and CV mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors A

- Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. A
For patients with T2DM who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. B

Avoid Inertia
Antihyperglycemic Therapy in Adults with T2DM

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85
At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- **A1C is less than 9%**, consider Monotherapy.
- **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 (See Figure 8.2).

### Monotherapy

**Lifestyle Management + Metformin**

Initiate metformin therapy if no contraindications* (See Table 8.1)

- **A1C at target after 3 months of monotherapy?**
  - **Yes:** - Monitor A1C every 3–6 months
  - **No:** - Assess medication-taking behavior
    - Consider Dual Therapy

### Dual Therapy

**Lifestyle Management + Metformin + Additional Agent**
Antihyperglycemic Therapy in Adults with T2DM

Pharmacologic Approaches to Glycemic Treatment:
*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85*
Case

- 58 yo M has had DM2 for 16 yrs, poorly controlled. Current regimen below. [+]
MI and CHF. [+ ] retinopathy and gastroparesis. No hypoglycemia.
Nonsmoker. [+ ] family history. BP 138/90, BMI 34. Lungs clear. [+ ] BLE
edema.
  - Metformin 1000mg BID
  - Glipizide 10mg BID
  - Atorvastatin 40 mg daily
Case - continued

- Hemoglobin $A_{1c} = 8.4\%$
- Creatinine $= 0.67 \text{ mg/dL}$
- TSH $= 2.83 \text{ mIU/L}$
- LDL cholesterol $= 92 \text{ mg/dL}$
Case - continued

Addition of which medication below will improve glucose control and minimize side effects?

- A. Exenatide
- B. Pioglitazone
- C. Saxagliptin
- D. Canagliflozin
- E. Insulin glargine
Thiazolidinediones

- Pioglitazone, Rosiglitazone
- Activates nuclear transcription factor PPAR-γ, increasing insulin sensitivity

Pros:
- No hypoglycemia, ? Decreased CVD (pio), generic

Cons:
- Wt increase, edema, CHF, ? MI (rosi)
Glucagon-like-peptide-1 agonists

- Exenetide, exenetide extended release, liraglutide, semaglutide, dulaglutide
- Increases glucose dependent insulin secretion, increases satiety, slows gastric emptying

Pros:
- Low hypoglycemia, Dec wt, Dec postprandial gluc
- Dec CV event (lira)

Cons:
- GI side effects, ?pancreatitis, medullary thyroid cancer, cost
Dipeptidyl peptidase-4 inhibitors

- Sitagliptin, saxagliptin, linagliptin, alogliptin
- DPP-4 breaks down GLP-1
- Results in increased glucose dependent insulin secretion

Pros:
- Low hypoglycemia, oral

Cons:
- Increased CHF, acute pancreatitis, angioedema, arthralgia, cost
Sodium-glucose Cotransporter 2 inhibitors

- Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
- Inhibits SGLT-2 in the proximal nephron, leading to glucosuria

Pros:
- No hypoglycemia, wt loss, decreased BP
- Dec CV events, CHF (empa, cana)

Cons:
- GU infections, polyuria, hypotension, dehydration, increased LDL, cost
Insulins (onset / duration)

- **Rapid acting** *(15’ / 3-5h)*
  - Lispro
  - Aspart
  - Glulisine
  - Inhaled insulin *(15’ / 2h)*

- **Short acting** *(30-60’ / 4-8h)*
  - Human regular

- **Intermediate**
  - Human NPH *(2-4h / 10-18h)*
  - U-500 regular *(30-60’ / 10-18h)*
Insulins (onset / duration)

- **Basal insulin analogs**
  - Lantus® (Glargine U-100) (4-6h / 24h)
  - Detemir (2-3h / 6-24h)
  - Toujeo® (Glargine U-300) (6h / 24h)
  - Degludec (can last 30-42hrs)

- **Pre-mixed insulins**
  - 70/30
  - 75/25
  - 50/50
CARDIOVASCULAR DISEASE AND RISK MANAGEMENT
Cardiovascular Disease

- CVD is the major cause of morbidity, mortality for those with diabetes
  - Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for CVD
- **Diabetes itself confers independent risk**
- Benefits observed when individual cardiovascular risk factors are controlled to prevent/slow CVD in people with diabetes
Goals

- Most people with diabetes and hypertension should be treated to a systolic blood pressure goal of $<140 \text{ mmHg}$ and diastolic blood pressure $<90 \text{ mmHg}$.

- Lower systolic and diastolic BP targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of CVD, if they can be achieved without undue treatment burden.
Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

1. Initial BP between 140/90 mmHg and 160/100 mmHg
   - Start one agent
     - Start one drug: ACEi, ARB, CCB*, Diuretic**
   - Assess BP Control and Adverse Effects
     - Treatment tolerated and target achieved: Continue therapy
     - Not meeting target on two agents: Add agent from complementary drug class: ACEi or ARB, CCB*, Diuretic**
     - Adverse effects: Consider change to alternative medication: ACEi or ARB, CCB*, Diuretic**

2. Initial BP ≥ 160/100 mmHg
   - Lifestyle management
   - Start two agents
     - Start drug from 2 of 3 options: ACEi or ARB, CCB*, Diuretic**
   - Assess BP Control and Adverse Effects
     - Treatment tolerated and target achieved: Continue therapy
     - Not meeting target or adverse effects using a drug from each of three classes: Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management
Recommendations: Dyslipidemia/Lipid Management

Screening

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. E
Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD</th>
<th>Recommended statin intensity and combination treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>No</td>
<td>None†</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If LDL cholesterol $\geq 70$ mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#</td>
</tr>
<tr>
<td>≥40 years</td>
<td>No</td>
<td>Moderate‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If LDL cholesterol $\geq 70$ mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)</td>
</tr>
</tbody>
</table>

*In addition to lifestyle therapy. †For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. ‡Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol $\geq 100$ mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. #High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.
## Table 9.3—High-intensity and moderate-intensity statin therapy*

<table>
<thead>
<tr>
<th>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</th>
<th>Moderate-intensity statin therapy <em>(lowers LDL cholesterol by 30% to 50%)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
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<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40–80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
</tr>
</tbody>
</table>

*Once-daily dosing. XL, extended release.
Lipid Management: Recommendations (6)

Treatment of Other Lipoprotein Fractions or Targets

• For patients with fasting triglyceride levels $\geq 500$ mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C
Other Combination Therapy

• Combination therapy (statin/fibrate) has not been shown to improve ASCVD outcomes and is generally not recommended. A

• Combination therapy (statin/niacin) has not been shown to provide additional CV benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A
Questions?