ENDOCRINOLOGY & THE OLDER ADULT

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DISCLOSURES

• Spouse employed by Biogen, Inc.
• No relevance to the content of this presentation.
LEARNING OBJECTIVES

AT THE CONCLUSION OF THIS APPLICATION-BASED ACTIVITY, PARTICIPANTS SHOULD BE ABLE TO:

1. Discuss recent guideline changes regarding the management of diabetes in older adults.
2. Compare and contrast newly approved and established treatment options for type 2 diabetes.
3. Design an appropriate treatment plan to achieve patient specific goals of therapy.
4. Discuss recent evidence regarding the cardiovascular safety of therapies used to manage diabetes.

MEET JOHN...

- 72-year-old African-American male
- PMH of Type 2 DM (2008), CABG (2012), HTN, dyslipidemia, Stage 3 CKD, and COPD.
- He lives alone and receives assistance with cooking and maintaining his home from his daughter.
- Denies alcohol use; quit smoking 2 years ago
- He has mild cognitive impairment (MMSE 21/30)
- Recently received Medicaid (Dual-eligible)
**ADDITIONAL INFORMATION**

- **Medications:**
  - Aspirin EC 81mg daily
  - Metformin 1000mg twice daily
  - Lisinopril 20mg daily
  - HCTZ 25mg daily
  - Amlodipine 5mg daily
  - Atorvastatin 10mg daily
  - Tiotropium 18mcg daily
  - Fluticasone/Salmeterol 250/50 twice daily

- **Recent labs and vitals**
  - BP 154/80 mmHg
  - HR 76 (RRR)
  - Wt. 175 pounds (~80kg)
  - Ht. 66 in (168 cm)
  - A1C 8.5%
  - Scr 1.3 (eGFR 57 mL/min) (115 μmol/L)
  - LDL-C 102 mg/dL (2.64 mmol/L)

- **Average SMBG**
  - 7AM = 188 mg/dL (10.4 mmol/L)
  - 6PM = 196 mg/dL (10.9 mmol/L)
  - Bedtime = 204 mg/dL (11.3 mmol/L)

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**POLLING QUESTION #1**

According to the 2017 ADA Guidelines, which of the following is the most appropriate A1C goal for John?

A. < 7%
B. < 7.5%
C. < 8%
D. < 8.5%
DIABETES GUIDANCE

• ADA position statement
  – Updated every January
  – Diabetes care recommendations
  – Divided into 14 sections

• AACE/ACE guidance
  – 2015 clinical practice guidelines—comprehensive care plan
  – 2017 consensus statement—algorithm

S.3: FOUNDATIONS AND EVALUATION

• Diabetes Self management education and support (DSME, DSMS)
• Nutrition
• Counseling
• Physical activity
• Psychosocial care – Older adults (aged >65 years) should be considered for evaluation of cognitive function, depression screening and treatment.
• Smoking Cessation – Advise all patients not to use cigarettes, other tobacco products, or e-cigarettes.
• Medications
S.3: FOUNDATIONS AND EVALUATION

- Immunizations
  - Pneumococcal Vaccine
    - All patients with diabetes 2 years-64 years of age: pneumococcal polysaccharide vaccine 23 (PPSV23). Re-vaccinate after 65 or 5 years
    - At 65 years of age vaccinate pneumococcal conjugate vaccine (PCV) 13 once
  - Hep B vaccine
    - Unvaccinated adults with diabetes who are aged 19–59 years of age
    - Consider Hep B vaccine in adults > 60 years of age
    - Schedule 0,1, and 6 months
  - Annual influenza vaccine

S.4: PREVENTION/DELAY OF TYPE 2 DIABETES

- Patients with prediabetes
  - Intensive diet (7% body weight loss)
  - Physical activity (moderate-intensity for at least 150min/week)
- Metformin therapy
- Technology-assisted tools can be useful for effective lifestyle modification to prevent diabetes
  - Internet-based social networks
  - Distance learning
  - DVD-based content
  - Mobile applications
**S.2: DIAGNOSIS OF DIABETES**

### 2017 ADA Criteria

- A1C >6.5%
- OR
- FPG ≥126 mg/dL (7 mmol/L)
- OR
- 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT
- OR
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing*

Diabetes Care 2017;40:S11–S24

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### A1C CORRELATION TO AVERAGE GLUCOSE

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean plasma glucose (mg/dL)</th>
<th>Mean plasma glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
<td>14.9</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
<td>16.5</td>
</tr>
</tbody>
</table>

*These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG.*

ADA. V. Diabetes Care. Diabetes Care 2013;36(suppl 1):S19; Table 8.
**INTENSIVE CONTROL: LONG TERM CV OUTCOMES**

- The VADT extended follow-up
  - Previously found no difference in CV events at 5.6 years
  - Median A1C at study end (8.4% vs. 6.9%)
  - Time to first major CV event (composite) improved (HR 0.83, 0.7-0.99 p = 0.04 over 9.8 years)
  - No difference in CV or total mortality

- The ACCORD extended follow-up
  - Previously found increased CV mortality at 3.5 years
  - Median A1C at study end (7.5% vs. 6.4%)
  - Composite CV outcome not different
  - CV death remained significant (HR 1.20, 1.03-1.40 p = 0.02 over 9 years)

**Bottom Line:**
A1C <7 vs. <6.5
**ADA A1C Goals**

- < 7% is reasonable for most nonpregnant adults
- < 6.5% is reasonable if:
  - Short duration of DM
  - Treated with lifestyle or metformin only
  - Long life expectancy
  - No history of CVD
- < 8% is reasonable if:
  - H/o severe hypoglycemia
  - Limited life expectancy
  - Advanced vascular disease
  - Long-standing DM
  - Poor self-management skills

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**S.10: OLDER ADULTS – TREATMENT GOALS**

<table>
<thead>
<tr>
<th>Patient Characteristics/Health Status</th>
<th>Reasonable A1c goal (AGS 2013)</th>
<th>Pre-meal glucose mg/dL (mmol/L)</th>
<th>Bedtime glucose mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few chronic illnesses, intact cognitive/functional status)</td>
<td>&lt; 7.5% (7-7.5%)</td>
<td>90-130 (5-7.2)</td>
<td>90-150 (5-8.3)</td>
</tr>
<tr>
<td>Complex/intermediate (multiple chronic illnesses or 2+ instrumental ADL impairments or mild-moderate cognitive impairment)</td>
<td>&lt; 8.0% (7.5-8%)</td>
<td>90-150 (5-8.3)</td>
<td>100-180 (5.6-10)</td>
</tr>
<tr>
<td>Very complex/poor health (long-term care or end-stage chronic illness or mod-severe cognitive impairment or 2+ ADL dependencies)</td>
<td>&lt; 8.5% (8-8.5%)</td>
<td>100-180 (5.6-10)</td>
<td>110-220 (6.1-12.2)</td>
</tr>
</tbody>
</table>
RE-POLLING QUESTION #1

According to the 2017 ADA Guidelines, which of the following is the most appropriate A1c goal for John?

- A. < 7%
- B. < 7.5%
- C. < 8%
- D. < 8.5%

MEDICATION THERAPY
ADA ALGORITHM 2017

A1C < 9%

A1C > 9%

A1C > 10%

GLYCEMIC CONTROL ALGORITHM 2017

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

MONOTHERAPY*

Metformin

GLP-1 RA

SGLT-2i

DPP-4i

TZD

AGI

SULGLIN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY*

GLP-1 RA

SGLT-2i

DPP-4i

TZD

Basal Insulin

AGI

SULGLIN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

GLP-1 RA

SGLT-2i

DPP-4i

Basal Insulin

AGI

SULGLIN

If not at goal in 3 months refer to Intensify Insulin Therapy

SYMPTOMS

NO

YES

DUAL THERAPY OR

TRIPLE Therapy

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

PROGRESSION OF DISEASE

* Choice of medications represents a suggested hierarchy of options. Length of use & effectiveness of individual medications vary. Use with caution.
DM: Treatment Burden

- Lifetime DM treatment, \(\downarrow\) A1C 1% QALY gained:
  - 45 year-old: \(~1\) QALY
  - 65 year-old: \(~0.3\) QALY
  - 75 year-old: \(~0.1\) QALY

- \(\uparrow\) burden negates benefit
  - Common reported burden of insulin eliminates benefit
**HYPOGLYCEMIA: WHY THE FUSS?**

### Healthcare Utilization

- **Adults 75+:**
  - 2x ↑ Emergency department (ED) visits
  - 2x ↑ hospitalizations
- **Adults 85+**
  - 2.5x ↑ ED visits
  - 5x ↑ hospitalizations
- **Implicated medications**
  - Warfarin (33%)
  - Oral antiplatelet (13%)
  - Insulin (14%)
  - Oral hypoglycemics (11%)

### Unique Considerations

- **↓ Symptom recognition**
  - Less intense symptoms
  - Start at lower levels
  - Fast psychomotor deterioration
  - Only 8% older patients correctly reported hypoglycemia vs 50% middle-aged
- **Medication management**
  - Too much short acting with meals
  - Wrong dose/product
  - Wrong time of day
  - Self over-correcting

### New(er) Agents

- **Newer agents:**
  - GLP-1 agonists
  - SGLT2 inhibitors
  - DPP4 inhibitors
- **Insulins**
  - Insulin glargine 300 U/mL (Toujeo®) – US: 2015
  - Insulin glargine 100 U/mL (Basalglar®) – US 2015
  - Insulin lispro 200 U/mL (Humalog KwikPen®) – US: 2015
  - Insulin regular 500 U/mL (Humalog KwikPen®) – US:2016
  - Insulin degludec (Tresiba) 100 U/mL and 200 U/mL (concentrated) – US: 2015
  - Insulin glargine 100 U/mL PLUS lixisenatide 33 mcg/mL (Soliqua®) – US 2016

*FDA requires CV testing. Thanks, rosiglitazone!*
COMPARISON OF GLP-1 AGONISTS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Schedule</th>
<th>Mixing Required</th>
<th>Pre-injection waiting time</th>
<th>Dosing</th>
<th>Weight Loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta)</td>
<td>BID</td>
<td>-</td>
<td>-</td>
<td>5mcg, 10mcg</td>
<td>2.9 at 30 weeks</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon)</td>
<td>Weekly</td>
<td>Yes</td>
<td>-</td>
<td>2mg</td>
<td>2.3 at 24 weeks</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>QD</td>
<td>-</td>
<td>-</td>
<td>0.6, 1.2, 1.8mg</td>
<td>2.5 at 30 weeks</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum)</td>
<td>Weekly</td>
<td>Yes</td>
<td>15-30 min</td>
<td>30mg, 50mg</td>
<td>0.6 at 32 weeks</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>Weekly</td>
<td>-</td>
<td>-</td>
<td>0.75mg, 1.5mg</td>
<td>2.5 at 26 weeks</td>
</tr>
<tr>
<td>Lisixenatide (Adlyxin; Soliqua)</td>
<td>QD</td>
<td>-</td>
<td>-</td>
<td>10mcg, 20 mcg</td>
<td>1.94 at 12 weeks</td>
</tr>
</tbody>
</table>


LIRAGLUTIDE (LEADER): CV OUTCOMES

- Liraglutide 1.8mg daily versus placebo
- 50+ with CVD or 60+ with CV risk
- N= 9,340 over 3.8 years, average age 64


All-cause mortality
NNT = 71 over 3.5 years
($2.08 million)

Table 1. Primary and Secondary Outcomes.®

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Liraglutide (N=4668)</th>
<th>Incidence Rate</th>
<th>Placebo (N=4672)</th>
<th>Incidence Rate</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. of events/ 100 patient-yr</td>
<td>no. of patients (%)</td>
<td>no. of events/ 100 patient-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary composite outcome:</td>
<td>608 (13.0)</td>
<td>3.4</td>
<td>654 (14.9)</td>
<td>3.9</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite outcome:</td>
<td>948 (20.3)</td>
<td>5.3</td>
<td>1062 (22.7)</td>
<td>6.0</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>381 (8.2)</td>
<td>2.1</td>
<td>447 (9.6)</td>
<td>2.5</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>219 (4.7)</td>
<td>1.2</td>
<td>278 (6.0)</td>
<td>1.6</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
<td>162 (3.5)</td>
<td>0.9</td>
<td>169 (3.6)</td>
<td>1.0</td>
<td>0.95 (0.77-1.18)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
**Semaglutide (Sustain-6): CV Outcomes**

- Semaglutide 0.5 mg or 1 mg once weekly versus placebo
- 50+ with CVD/CKD/CHF or 60+ with CV risk
- N = 2735 over 2.1 years, mean age 65

**Class Effect?**

EXSCEL (exenatide) & ELIXA (lixisenatide) found no reduction

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**Advancing Injectable Therapy (4B Study)**

**Type 2 DM**
- Insulin glargine & metformin ± SU
- A1C: 7 – 10%
- BMI: 25 – 45 kg/m²

12-weeks glargine titration to FPG ≤ 100 (5.4 mmol/L)

**A1C > 7.0%**

- Exenatide 2x daily before largest meals
- Insulin lispro 3x daily with meals

30 weeks
4B STUDY: RESULTS

- Mean A1C decreased ~1.1% in each group
  - Exenatide group had better QOL scores

- 85% of patients in each group completed the study
  - Adverse event rate was 5% in the exenatide group vs. 2% in the placebo group
  - Lower incidence of hypoglycemia with exenatide
  - Weight increased 2.1kg with lispro compared to a 2.5kg weight loss in the exenatide group

SODIUM-GLUCOSE COTRANSporter 2 INHIBITORS
SGLT2 INHIBITOR BASICS

Advantages

- ↓ A1C 0.5-1.0%
- ↓ Weight 1-2 kg
- ↓ BP 4/2 mmHg

Disadvantages

- Genital/urinary tract infections
- Hypovolemia/hypotension
- Limited use in those with moderate renal impairment
- Cardiovascular benefit???

<table>
<thead>
<tr>
<th>Dosage (Initial/Max)</th>
<th>Canagliflozin (Invokana®)</th>
<th>Dapagliflozin (Farxiga®)</th>
<th>Empagliflozin (Jardiance®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Adjustments: (GFR, ml/min)</td>
<td>100 mg/300 mg once daily</td>
<td>5 mg/10 mg once daily</td>
<td>10 mg/25 mg once daily</td>
</tr>
<tr>
<td>45-60: max 100mg/d</td>
<td>&lt;45: Not recommended</td>
<td>&lt;60 ml/min: Not recommended</td>
<td>&lt;45: Not recommended</td>
</tr>
</tbody>
</table>

Canagliflozin (Invokana®). [Package Insert].
Dapagliflozin (Farxiga®). [Package Insert].
Empagliflozin (Jardiance®). [Package Insert].

EMPA-REG: CV OUTCOMES

- Randomized double-blind placebo-controlled non-inferiority study in high risk patients with type 2 diabetes on background standard of care
- Randomized 1:1:1: to placebo, empagliflozin 10 mg, or empagliflozin 25 mg daily
- Inclusion criteria
  - A1C 7-10%
  - Established cardiovascular disease
  - GFR > 45 mL/min/1.73m
  Average Age: 63 years

N Engl J Med 2015; 373:2117-2128
EMPREG: RESULTS

All-cause mortality
NNT: 38 over 3.3 years

Renal replacement
NNT in high-risk patients: 333

Morbidity and Mortality benefit compared to placebo

Early separation of events between groups

No difference in outcomes between empagliflozin doses

Class effect?

N Engl J Med 2015; 373:2117-2128

CANCAS: CV OUTCOMES

• Combination of 2 randomized double-blind placebo-controlled non-inferiority study in high risk patients with type 2 diabetes
• Randomized 1:1: to placebo or canagliflozin
• Inclusion criteria
  – A1C 7-10.5%
  – Symptomatic cardiovascular disease OR at least 2 risk factors
  – GFR > 30 mL/min/1.73m

Average Age: 63 years

**CANVAS: Results**

- All-cause mortality: Not significant
- Composite endpoint NNT: 200 over 3.6 years
- NNH range for ADR: 20-330

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**DECLARE: CV Outcomes**

- Randomized double-blind placebo-controlled non-inferiority study in high risk patients with type 2 diabetes
- Randomized to placebo or dapagliflozin
- Primary endpoints include:
  - Composite endpoint of CV death, MI or ischemic stroke
  - Composite endpoint of CV death or hospitalization due to heart failure
- Estimated completion 2019

[Link to clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT01730534)
• 20 cases of DKA identified
• Each patient required an ED visit or hospitalization
• Blood sugars not as high as those normally seen with DKA in T1 DM
• Contributing factors
  • Off-label use in Type 1 patients
  • Reduced food/fluid intake
  • Reduced insulin dose
  • Recent major illness


SGLT2-INHIBITORS AND ACIDOSIS

↑Glycosuria  
↑Volume depletion

↑Glucagon

↑Gluconeogenesis  
↑Free-fatty-acid release  
↑Ketones

Acidosis

Diabetes Care. June 15, 2015; DOI: 10.2337/dc15-0843
## COMPARISON OF DPP-IV INHIBITORS

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (Januvia®)</th>
<th>Saxagliptin (Onglyza®)</th>
<th>Linagliptin (Tradjenta®, Trajenta®)</th>
<th>Alogliptin (Nesina®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>100 mg once daily</td>
<td>5 mg once daily</td>
<td>5 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td><strong>Dose Adjustments: Renal Impairment</strong></td>
<td>30-50 ml/min 50 mg daily</td>
<td>≤ 50 ml/min 2.5 mg daily</td>
<td>No dose adjustment</td>
<td>30-60 ml/min 12.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt;30 ml/min 25 mg daily</td>
<td></td>
<td></td>
<td>15-29 ml/min 6.25 mg daily</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: 25 mg daily</td>
<td>Hemodialysis: 2.5 mg daily</td>
<td></td>
<td>Hemodialysis: 6.25 mg daily</td>
</tr>
<tr>
<td><strong>Dose Adjustments: Hepatic Impairment</strong></td>
<td>No dose adjustments.</td>
<td>Mild impairment: no dose adjustment</td>
<td>Moderate to severe impairment: not recommended.</td>
<td>No dose adjustments.</td>
</tr>
</tbody>
</table>

### DPP-IV INHIBITORS: PANCREATITIS

- **2006**
  - 88 post-marketing reports of acute pancreatitis
- **2009**
  - FDA revises labeling information
- **2013**
  - Reports reveal possible association with pancreatic cancer
  - FDA issues safety communication regarding potential for increased risk or pre-cancerous findings
- **2014**
  - FDA and EMA Assessment: Data for casual association between incretin based drugs and pancreatitis or pancreatic cancer is inconsistent
**DPP-IV INHIBITORS: CV OUTCOMES**

**Saxagliptin**
- **SAVOR-TIMI 53 Trial** (n=16,492)
- Saxagliptin vs. placebo in patients at high risk for CV events
- No difference in ischemic events
- ↑ hospitalizations for HF in saxagliptin arm vs. placebo

**Alogliptin**
- **EXAMINE Trial** (n=5380)
- Alogliptin vs. placebo in patients with recent acute coronary syndrome
- No difference; no outcomes for HF

**Sitagliptan**
- **TECOS Trial** (n=14,671)
- Sitagliptan vs. placebo in ≥50 y/o, established CVD
- No difference in CVD outcomes
- 30% less likely to start insulin

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**POLLING QUESTION #2**

According to the 2017 ADA Guidelines, which of the following would be the best addition to John’s diabetes regimen?

A. Glyburide  
B. Linagliptin  
C. Empagliflozin  
D. Liraglutide
INHALED INSULIN (AFREZZA®)

- FDA approved for type 1 and 2 diabetes
- Ultra rapid-acting insulin
  - Peaks in 12-15 minutes
- Storage
  - If cartridges not refrigerated, use within 10 days
  - Opened cartridge strips must be used within 3 days
  - Inhaler can be stored anywhere, but inhaler and cartridge should be at room temperature for 10 minutes before use
**INHALED INSULIN: SAFETY**

- Cough (27% vs. only 5% in placebo group)
- Pulmonary function decline
  - Occurs in first 3 months and shown to persist over 2 years
  - Recommended to monitor FEV1 at baseline, after 6 months, then annually (even in the absence of symptoms)
- Diabetic ketoacidosis (type 1 patients)
- Weight gain
- Lung cancer

**WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE**
- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA.
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD.
- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients.

**RAPID ACTING INSULIN LISPRO 200 U/mL**

- Humalog KwikPen®
- 600 units per pen vs. 300 units (U-100)
- Provides same dose of insulin in half the volume as U-100 pen
- Same storage/handling requirements
LONG-ACTING INSULINS – 100 U/mL

Basalglar® KwikPen® (insulin glargine)
- NOT biosimilar/interchangeable
- 24 hour duration
- 28 day shelf-life (opened)

Tresiba® Flextouch® (insulin degludec)
- NEW reference listed drug
- 36 hour duration
- 56 day shelf-life (opened)

<table>
<thead>
<tr>
<th>Agent</th>
<th>New Start</th>
<th>Once-daily basal insulin</th>
<th>Twice-daily NPH insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glargine</td>
<td>0.2 U/kg initial dose (T2DM); 0.2-0.4 U/kg initial dose (T1DM)</td>
<td>1:1 conversion *</td>
<td>80% of total daily NPH dose</td>
</tr>
<tr>
<td>Insulin Degludec</td>
<td>10 Unit QD (T2DM); 0.2-0.4 U/kg initial dose (T1DM)</td>
<td>1:1 conversion</td>
<td>1:1 conversion</td>
</tr>
</tbody>
</table>

LONG-ACTING INSULINS – 200 U/mL

- Insulin Degludec (Tresiba® Flextouch®) 200 U/mL
  - NEW reference listed drug
  - 36 hour duration (8 hrs between doses)
  - 160 units per injection
  - Box of #3, 3 mL pens (9 mL)
  - Two unit increments
  - 56 day shelf-life (opened)
LONG-ACTING INSULINS – 300 U/mL

- Insulin Glargine 300 U/mL (Toujeo® SOLOSTAR®)
  - Reduces insulin volume by two-thirds
  - Lower rates of nocturnal hypoglycemia
    - The FDA did not include this in the labeling
  - Similar A1C levels regardless of the insulin type used
    - 300 U/mL users required 10% more insulin
      - More susceptible to tissue peptidases?

Inhaled glargine 300 U/mL (Toujeo®). [Package Insert]. 7/29/15.

LONG-ACTING INSULINS – 300 U/mL

- Insulin Glargine 300 U/mL (Toujeo® SOLOSTAR®)
  - 80 units per injection
  - Box of #3 or #5, 3ml pens (9-15 mL)
  - Single unit increments
  - 42 day shelf-life (opened) [vs. 28 for 100 U/mL version]
  - Note: “less injection force” and 5-second hold time [vs. 10-seconds for 100 U/mL version]
U-500 U/mL INSULIN: PHARMACOKINETICS

Pharmacokinetics of U-500 regular insulin become similar to NPH at doses greater than 0.12mL.

- After 0.2 units/kg
- Onset: 30 minutes
- Peak: 1.75-4 hours
- Duration: 6 to >10 hours

Not available in Canada

U-500 U/mL INSULIN PEARLS

- U-500 insulin is five (5) times as concentrated as U-100 insulin
- Indicated for patients taking greater than 200 units per day
- Dosing depends on administration

U-500 KwikPen: UNITS

- To calculate mL to units: multiply volume by 500
  - Example: 0.1mL x 500 units per 1mL = 50 units
  - Pen dials in 5-unit increments

Vial and syringe: MILLILITERS

- Tuberculin or allergy syringe (mLs) with a fixed needle, or use a U-100 1mL syringe
- To calculate units to mL: divide by 500
  - Example: Order = 100 of U-500 insulin
  - 100/500 = 0.2mL of U-500 insulin
  - 0.2mL = 20 units on a U-100 insulin syringe
  - 20 units (on a U-100 syringe) x 5 = 100 units delivered

**INSULIN GLARGINE + LIXISENATIDE INJECTION**

- **Soliqua® SoloStar®** (Insulin Glargine 100 U/mL + Lixisenatide 33mcg/mL)
  - FDA approved for inadequate control on basal insulin (less than 60 units daily) or lixisenatide
- **Similar SoloStar® technology with key differences:**
  - Dose window allows for 2 unit test dose, or 15-60 units per dose
  - Box of #5, 3 mL pens (15 mL)
  - 14 day shelf-life (opened)

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**INSULIN GLARGINE + LIXISENATIDE INJECTION**

- **Dosing of Soliqua®** (Insulin Glargine 100 U/mL + Lixisenatide 33mcg/mL) depends on basal insulin dose

<table>
<thead>
<tr>
<th>Basal Insulin Dose</th>
<th>Soliqua® Dose</th>
<th>Insulin Glargine Content</th>
<th>Lixisenatide Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>15 units</td>
<td>15 units</td>
<td>5 mcg</td>
</tr>
<tr>
<td>&lt;30 units/day</td>
<td>15 units</td>
<td>15 units</td>
<td>5 mcg</td>
</tr>
<tr>
<td>30-60 units/day</td>
<td>30 units</td>
<td>30 units</td>
<td>10 mcg</td>
</tr>
<tr>
<td>60 units/day</td>
<td>60 units</td>
<td>60 units</td>
<td>20 mcg</td>
</tr>
</tbody>
</table>

*Titrates: 2-4 units/week to effect (15-60 unit max)*
Polling Question #3

- One year later... John is now on insulin glargine (U-100) 66 units QHS. Metformin was dc’d because his eGFR is now 40 mL/min/1.73m². His A1c today is 8.7% (SMBG averages: FBG 140 mg/dL (7.8 mmol/L); PPG 268 mg/dL (14.9 mmol/L)).
- SH: still living alone, cognitive function relatively unchanged, eating only 2 meals/day (breakfast at 7am; dinner at 6pm), John is concerned about further weight gain and risk of hypoglycemia
- Today’s vitals: Wt 186 lbs (↑11 lbs from last year), BP 138/80 mmHg

Which of the following would be the most appropriate addition to John’s diabetes regimen?

A. Add U-500 insulin with meals  
B. Add liraglutide once daily  
C. Add inhaled insulin with meals  
D. Add lispro U-200 6 units with meals

S.8: CVD and CVD Risk Management

- Blood pressure control
- Lipid management
- Antiplatelet therapy
Hypertension: JNC 8 vs. ADA

<table>
<thead>
<tr>
<th></th>
<th>JNC 8</th>
<th>ADA 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP goal</td>
<td>&lt; 140 mm Hg</td>
<td>&lt; 130*</td>
</tr>
<tr>
<td>DBP goal</td>
<td>&lt; 90 mm Hg</td>
<td>&lt; 80*</td>
</tr>
</tbody>
</table>

Initial treatment:
- ACE-I; ARB; CCB; or Thiazide
- CKD: ACE-I or ARB
- Albuminuria: ACE-I or ARB

*ADA goal of <130/80 mmHg with any of the following:
1. Albuminuria or CKD
2. Smoking
3. Dyslipidemia
4. Family history of premature ASCVD

Blood Pressure Control in Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison groups</th>
<th>DM pt %</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>SBP &lt;120 mmHg vs. SBP 130-140 mmHg</td>
<td>100%</td>
<td>No difference in rate of composite outcome of fatal and nonfatal CV event. &lt;120 was not better than &lt;140.</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Perindopril &amp; Indapamide combo vs. placebo, added CCB at baseline vs. placebo</td>
<td>100%</td>
<td>Perindopril &amp; Indapamide ADDED TO BASELINE CCB reduced mortality. BP differences of SBP 140 versus 135.</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP ≤ 90 mmHg vs. DBP ≤ 85 mmHg vs. DBP ≤ 80 mmHg</td>
<td>24%</td>
<td>Intensive lowering of diastolic BP (baseline ~105 DBP) associated with low rate of CV events (82.6mm Hg)</td>
</tr>
<tr>
<td>UK CPRD*</td>
<td>Increments of 5 mmHg SBP/5 mmHg DBP</td>
<td>100%</td>
<td>Lowest nadir for mortality with BP 150/90-155/95</td>
</tr>
</tbody>
</table>

*Adults 80+
# Lipid Management

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Recommended statin intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>Non ASCVD risk factors*</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>40-75 years</td>
<td>None ASCVD risk factors*</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ACS and LDL-C &gt;50 mg/dL (1.29)</strong> in patients who cannot tolerate high-intensity statin**</td>
<td>Moderate + ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None ASCVD risk factors</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td><strong>ACS and LDL-C &gt;50 mg/dL (1.29)</strong> in patients who cannot tolerate high-intensity statin**</td>
<td>Moderate + ezetimibe</td>
</tr>
</tbody>
</table>

*ASCVD risk factors: LDL-C >100 mg/dL (2.58 mmol/L), high blood pressure, smoking, and overweight and obesity, and family history of premature ASCVD.

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*Diabetes Care 2017;40:S75–S87*
**Polling Question #4**

Today’s fasting lipid panel shows John’s LDL-C is 112 mg/dL (2.98 mmol/L) on atorvastatin 10mg daily. *According to the 2017 ADA Guidelines*, which of the following would be most appropriate for John’s hyperlipidemia?

A. Continue atorvastatin 10mg daily  
B. Increase atorvastatin to 40mg daily  
C. Switch to simvastatin 40mg daily  
D. Switch to rosuvastatin 10mg daily

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**Aspirin (75–162 mg/day)**

- Secondary Prevention  
- All patients with history of ASCVD  
- Primary Prevention  
- Men or women age >50 plus one additional major risk factor  
  - Family history of premature ASCVD  
  - Hypertension  
  - Smoking  
  - Dyslipidemia  
  - Albuminuria
S.11: OLDER ADULTS SUMMARY

- Higher rates of premature death, functional disability, and coexisting illnesses than those without diabetes.
- Older adults with diabetes should be considered a “high-priority” population for depression screening and treatment.

<table>
<thead>
<tr>
<th>Patient Characteristics/Health Issues</th>
<th>A1C goal</th>
<th>BP goal (mmHg)</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few coexisting chronic illnesses, intact cognitive and functional status)</td>
<td>&lt;7.5% (7-7.5%)</td>
<td>&lt;140/90</td>
<td>Statin</td>
</tr>
<tr>
<td>Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-moderate cognitive impairment)</td>
<td>&lt;8% (7.5-8%)</td>
<td>&lt;140/90</td>
<td>Statin</td>
</tr>
<tr>
<td>Very complex/poor health (LTC or end-stage chronic illnesses or mod-sev cognitive impairment or 2+ ADL dependence)</td>
<td>&lt;8.5% (8-8.5%)</td>
<td>&lt;150/90</td>
<td>Consider statin benefit</td>
</tr>
</tbody>
</table>

Diabetes Care 2017;40:S99–S104

FINAL THOUGHTS

- 2017 ADA Guidelines continue to support more relaxed A1C goals for patients >65 years old.
- The EMPA-REG Outcome trial highlights the cardiovascular benefit of SGLT2-I class, but at this time there is insufficient evidence to suggest a class effect.
- GLP-1 agonists are reasonable alternatives to mealtime insulin for patients unable to achieve their A1c goal on standard oral therapy + basal insulin.
- Guidelines generally agree on how to reduce ASCVD risk in older adults with diabetes, but there are notable differences; highlighting the relative absence of conclusive evidence in older adults.
time for questions