Session 1: Managing Cardiometabolic Disease in Patients With, or at Risk for, Type 2 Diabetes

Learning Objectives

1. Assess CVD risk factors in patients with T2DM and establish individualized treatment goals for comprehensive patient management.
2. Evaluate the therapeutic profiles of incretin-based therapies and the safe use of these agents, alone or in combination with other antihyperglycemic agents.
3. Identify patients that would benefit from insulin therapy and select insulin regimens that would best provide postprandial insulin replacement.

Faculty

Scott V. Joy, MD, FACP
Associate Clinical Professor of Medicine
Clinical Chief of the Division of General Internal Medicine
Duke University Medical Center
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Scott Joy, MD, FACP, is an associate professor of medicine and medical director of Duke Primary Care Pickett Road. He is also the associate medical director of managed care for the Duke Private Diagnostic Clinics, and is a member of the Duke Institute for Genome Sciences and Policy and the Duke Hospital Pharmacy and Therapeutics Committee.

Dr. Joy’s research interests include process improvement in diabetes management and education, including the evaluation of postprandial hyperglycemia and self-blood glucose monitoring strategies, the role of genetic testing for prediabetes and cholesterol management, the application of pharmacogenomic principles in clinical decision making, and applications of technology and quality improvement processes into clinical practice. He has published articles and abstracts in such publications as *Diabetes, The Journal of Clinical Outcomes Management, Annals of Pharmacotherapy,* and *The Journal of General Internal Medicine.*

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Sandy, Utah

Adjunct Faculty, University of Utah School of Medicine
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Michael E. Cobble, MD, is director of Canyons Medical Center in Sandy, Utah, where he has been in private practice for 13 years. He is an adjunct faculty member of the University of Utah School of Medicine, where he is a preceptor for family practice physician assistants. He also serves as clinical trainer at University of Utah College of Nursing in Salt Lake City and accepts medical students and nurse practitioners in clinical rotations. Dr. Cobble also serves as chief medical officer at Atherotech Diagnostic Laboratories.

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Jeffrey S. Freeman, DO, FACOI, is professor and chairman of the division of endocrinology and metabolism in the department of internal medicine, at the Philadelphia College of Osteopathic Medicine.

Dr. Freeman earned his medical degree at the College of Osteopathic Medicine and Surgery in Des Moines, Iowa. He served an internship at the Pontiac Osteopathic Hospital and a residency at the University of Medicine and Dentistry of New Jersey (UMDNJ) Stratford Division; he completed a fellowship in endocrinology and metabolism at the UMDNJ/Veterans Hospital in East Orange.

Dr Freeman is a member of the Philadelphia Endocrinology Society and the American Diabetes Association, and a founding board member of the Northeast Lipid Association. For the past 17 years, he has been chairman of the division of metabolic diseases for the Pennsylvania Osteopathic Medical Association. As chairman, he has developed high-level educational programs relating to diabetes and other endocrine disorders for primary care providers.
Faculty Financial Disclosure Statements
The presenting faculty report the following:
Dr. Joy reports that he receives consulting honoraria from Lilly.

Dr. Cobble reports that he is an advisory board member or a speakers’ bureau member for Abbott, AstraZeneca, BMS, Eli Lilly & Company, Forest Laboratories, and Kowa.

Dr. Freeman reports that he is a speakers’ bureau member for Amylin, Boehringer Ingelheim, Lilly, Merck, and Novo Nordisk Inc.

Education Partner Financial Disclosure Statement
The content collaborators at Global Directions in Medicine report the following:
Anne Sendaydiego, PharmD, has no financial relationships to disclose.
Deanna Schuly has no financial relationships to disclose.

Suggested Reading List
Managing Cardiometabolic Disease in Patients With, or at Risk for, Type 2 Diabetes

Therapeutic Challenges for Patients With Type 2 Diabetes
Scott V. Joy, MD, FACP

T2D is Associated With Significant Morbidity and Mortality

Diabetes disproportionately affects senior care sector

- Diabetes is highly prevalent and costly among seniors
  - 23.1% of Americans ≥60 years old and older have diabetes
  - Approximately 1 in 5 nursing home residents has diabetes
  - Diabetes accounts for an estimated 32% of Medicare expenses
- Residents with diabetes require more care in LTC
  - 6.4 major diagnoses in residents with diabetes vs. 2.4 without
  - 90% of nursing home residents have CAD, stroke, and/or PVD
  - More likely to have lengths of stay >90 days, more cardiovascular morbidities, depression, and pain
T2D is a Multiethnic, Multicultural, Disease

<table>
<thead>
<tr>
<th>Racial/Ethnic Group</th>
<th>US-Diabetes Related Death Rate (2006)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black/African American</td>
<td>127</td>
</tr>
<tr>
<td>Hispanic</td>
<td>52</td>
</tr>
<tr>
<td>- Cuban</td>
<td></td>
</tr>
<tr>
<td>- Mexican American</td>
<td>104</td>
</tr>
<tr>
<td>- Puerto Rican</td>
<td>108</td>
</tr>
<tr>
<td>American Indian</td>
<td>98</td>
</tr>
<tr>
<td>White</td>
<td>69</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>55</td>
</tr>
</tbody>
</table>

*Deaths per 100,000 (only 30% of diabetes-related deaths were documented on death certificates).
Source: CDC Wonder (the Healthy People 2010 Database).

T2D is a Progressive Disease

Clinical Consequences
- Glycemic control is difficult to achieve and maintain
- Treatment must be intensified to maintain glycemic control:
  - More intensive treatment may increase risk for hypoglycemia
  - Some antidiabetic treatments are associated with weight gain that may blunt the CV benefit of decreasing blood glucose
  - Safe treatments with complementary mechanisms of action that address diabetes pathophysiology should be used

UKPDS 49: Multiple Antihyperglycemic Agents Are Needed Over Time

More Clinical Items and Less Time During Primary Care Visits

Clinical Inertia: Common in T2D Treatment

Studies reveal that therapy is intensified for <50% of patients with A1C above target

Impact of Medication Adherence on T2D Disease-Related Health Care Costs and Hospitalization Risk

Estimated diabetes-related healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80–100% adherence group (P<0.05). Sokol MC et al. Med Care. 2004;42:521-530.
Type 2 Diabetes and Comorbid Cardiometabolic Disease

Scott V. Joy, MD, FACP

Case Presentation: Olivia

- 44-year-old African-American woman with HTN
  - Height: 5’ 7”; Weight: 205 lb; BMI: 32.1 kg/m² (obese)
  - Office manager
- Medical history
  - HTN for ~20 yrs
  - Chronic head aches
- Family history
  - Mother and father both have HTN, dyslipidemia, and T2D
  - Father with ESRD
  - 2 sisters, also obese, with HTN and dyslipidemia

Case Presentation: Olivia

- Current medications
  - Enalapril 20 mg daily; HCTZ 25 mg daily
- Labs and office measurements
  - BP = 135/88 mm Hg
  - A1C = 6.0%
  - FPG = 110 mg/dL
  - LDL-C = 108 mg/dL, TG = 210 mg/dL, HDL-C = 41 mg/dL
  - SCR = 1.3 mg/dL
- Olivia met with a diabetes educator and discussed lifestyle changes, including diet and exercise recommendations and potential adherence challenges

Pre-test Question #1

Which of the following is not a NCEP criterion for the diagnosis of metabolic syndrome?

1. BP ≥ 130/85 mmHg
2. BMI ≥ 30 kg/m²
3. Triglycerides ≥ 150 mg/dL
4. FPG ≥ 100 mg/dL

Metabolic Syndrome: NCEP (ATPIII) Criteria*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm (40 in.)</td>
</tr>
<tr>
<td>Woman</td>
<td>&gt; 88 cm (35 in.)</td>
</tr>
<tr>
<td>II. Triglycerides</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>III. HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Woman</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>IV. Blood pressure</td>
<td>≥ 130/85 mm Hg</td>
</tr>
<tr>
<td>V. Fasting glucose</td>
<td>≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

*Must have 3 or more risk factors

NCEP = National Cholesterol Education Program; ATPIII = Adult Treatment Panel III.

National Institutes of Health. NCEP ATPIII. NIH Publication No. 02-5215. September 2002

Does the Metabolic Syndrome Increase Risk of Vascular Events?

YES!
Literature to Support


Does Treating the Dysmetabolic Syndrome Reduce Cardiac Events?

UNKNOWN AT THIS TIME

Pre-test Question #2

At what glucose level does a patient have prediabetes?
1. 90 mg/dL
2. 95 mg/dL
3. 99 mg/dL
4. 100 mg/dL

Categories of Increased Risk for T2D*

- FPG 100–125 mg/dL (5.6–6.9 mmoL/L)
- 2-hr plasma glucose in the 75g OGTT 140–199 mg/dL (7.8–11.0 mmoL/L); IGT
- A1C 5.7%–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range. American Diabetes Association. Diabetes Care. 2012;35(suppl 1):S11-S63.

Which Patients Will Progress to T2D?

<table>
<thead>
<tr>
<th>Metabolic Abnormality</th>
<th>Cumulative incidence of T2D over 5-6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal IFG and IGT</td>
<td>4-5%</td>
</tr>
<tr>
<td>IFG and normal 2hr OGTT</td>
<td>20-34%</td>
</tr>
<tr>
<td>IGT and normal fasting glucose</td>
<td>20-34%</td>
</tr>
<tr>
<td>Both IFG and IGT</td>
<td>38-65%</td>
</tr>
</tbody>
</table>


DPP: Study Interventions

- Eligible participants
- Randomized
- Standard lifestyle recommendations
  - Intensive Lifestyle Intervention (n=1079)
  - Metformin (n=1073)
  - Placebo (n=1082)

DPP=Diabetes Prevention Program
**DPP: Intensive Lifestyle Intervention**

An intensive program with the following specific goals:

- ≥7% loss of body weight and maintenance of weight loss
  - Dietary fat goal: <25% of calories from fat
  - Calorie intake goal: 1200–1800 kcal/day
- ≥150 minutes per week of physical activity

**DPP: Incidence of Diabetes**

Risk reduction

- 31% by metformin
- 58% by lifestyle

**Higher Conversion for TCF7L2 Positive Individuals**

Prediabetics who are positive for TCF7L2 test have ~55% chance of converting to T2D over the next 3 years versus ~30% (US DPP)

**DPP: Diabetes Incidence Rates by Age**

**Major Published Studies: Reducing Risk of Developing Diabetes**

- TRIPOD- Troglitazone in women with history of gestational diabetes; reduced risk of progression to T2D
- STOP-NIDDM-Acarbose in reducing progression of IGT to T2D
- HOPE-(Ramipril) Reduction in new cases of T2D
- LIFE-(Losartan) Reduction in new cases of DM
- WOSCOPS-(Pravastatin) Reduction in new cases of T2D

**Should I Write an Exercise Prescription?**

- Start date:
- Type of exercise:
- Start with: (step count, duration, frequency)
- Goal:
- Return for recheck:

<table>
<thead>
<tr>
<th>Pedometers (daily step count)</th>
<th>Sedentary</th>
<th>Low active</th>
<th>Somewhat active</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5,000 steps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,000 - 7,499 steps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,500 to &lt;9,999 steps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10,000 steps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**References**

Chiasson JL et al. Lancet. 2002;359:2072-2077
### Financial Incentive for Weight Loss

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control (n = 19)</th>
<th>Deposit Contract (n = 19)</th>
<th>Lottery (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total weight loss, lb</td>
<td>3.9 (8.1)</td>
<td>14.0 (10.2)*</td>
<td>13.1 (12.6)*</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.20–13.2</td>
<td>9.4–18.6</td>
<td>7.4–18.8</td>
</tr>
<tr>
<td>Met 16-lb weight loss goal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (total %)</td>
<td>2/19 (10.5)</td>
<td>9/19 (47.4)*</td>
<td>10/19 (52.6)*</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.3–33.1</td>
<td>24.4–71.1</td>
<td>28.9–75.5</td>
</tr>
<tr>
<td>&gt;20-lb loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (total %)</td>
<td>1/19 (5.3)</td>
<td>7/19 (36.8*)</td>
<td>5/19 (26.3*)</td>
</tr>
<tr>
<td>95% CI, %</td>
<td>0.1–26.0</td>
<td>16.3–61.6</td>
<td>9.2–51.2</td>
</tr>
</tbody>
</table>

*CI = confidence interval.
Conversion factor: To convert pounds to kilograms, multiply by 0.45.
*Difference between incentive and control conditions significant at \( P \leq 0.05 \).

Volpp KG et al. JAMA. 2008; 300:2631-2637.

### Olivia: 6 months later

Current labs and office measurements:
- BP = 139/90 mm Hg
- A1C = 7.1%
- FPG = 135 mg/dL
- Lipids WNL
- SCr = 1.2 mg/dL
- Thyroid and liver function WNL
- Weight 208 lbs (increase of 3 lbs since last visit)

### ARS Question #3

Which of the following would be Olivia’s current diagnosis?
1. No diabetes
2. Pre-diabetes
3. Type 2 diabetes
4. Inconclusive; more information required

### Criteria for the Diagnosis of T2D

- A1C ≥6.5%*
- FPG ≥126 mg/dL (7.0 mmoL/L)*
- 2-hr plasma glucose ≥200 mg/dL (11.1 mmoL/L) during an OGTT*

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.


### Current Glycemic Treatment Goals

<table>
<thead>
<tr>
<th>Organization</th>
<th>A1C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>AACE</td>
<td>≤8.5%</td>
</tr>
<tr>
<td>AMDA</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>AGS</td>
<td>≤7% (8% if life expectancy &lt;5 yrs)</td>
</tr>
<tr>
<td>NCQA</td>
<td>(HEDIS®) &lt;7%</td>
</tr>
</tbody>
</table>

*AGS recommendations for A1C goals are based on life expectancy, frailty, presence of comorbidities, cognitive impairment, and functional disability.

NCQA = National Committee for Quality Assurance; HEDIS = Health Plan Employer Data and Information Set

### Less Stringent A1C Goal May Be Appropriate for Some Patients: ADA/AHA/ACC Consensus Recommendations

- History of severe hypoglycemia
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive co-morbid conditions
- Long-standing diabetes where goals have not been achieved despite optimal Rx

Improving glycemic control has the greatest impact on which of the following?

1. Heart failure
2. Myocardial infarction
3. Stroke
4. Microvascular complications (neuropathy, nephropathy, retinopathy)

Impact of Intensive Antihyperglycemic Therapy in Major Diabetes Clinical Trials

- DCCT/EDIC,1,2 UKPDS,3,4 ADVANCE,5 and VADT6 improved microvascular disease with improved A1C
  - None showed decrease in macrovascular disease during initial trial; benefit seen in long-term follow-up of DCCT/EDIC and UKPDS
- ACCORD7: increased mortality did not occur in those whose A1C became too low (hypoglycemia), but rather in those whose A1C was not reduced despite intensive efforts

Target Treatment Goal

- Blood pressure <130/80 mm Hg
- Cholesterol (lipids)
  - LDL-C <100 mg/dL (<70 mg/dL for patients with diabetes and CAD)
  - HDL-C >40 mg/dL, in men; >50 mg/dL, in women;
  - Triglycerides <150 mg/dL
- Thrombosis
  - Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy for T2D at increased CV risk (10-year risk >10%)
  - Use aspirin therapy as a secondary prevention strategy in those with T2D and history of CVD
  - Use clopidogrel (75 mg/day) in patients with CVD and aspirin allergy
- Smoking cessation
  - Advise patients not to smoke; cessation counseling
- Weight loss
  - Initial goal of therapy should be to reduce BMI by ~10% from baseline

Intentional loss resulted in a relative risk reduction† of:

- 22% ↓ all-cause death
- 24% ↓ death from CVD + diabetes

Extra Calories Cause Weight Gain

- A pound of fat tissue has about 3500 kcal
- A daily 60 kcal cookie would be expected to:
  - 0.5 lb weight gain in 1 month
  - 6 lbs in 1 year
  - 27 lbs in 10 years
- 25% of men and 43% of women attempt to lose weight in 1 year
  - ? success rate


Intensive Lifestyle Intervention: Look AHEAD

- Diet modification / Exercise / Behavioral training
- Group support with in-person and telephone follow-ups


Parameter | Intensive Lifestyle Intervention (n=2570) | T2D Support and Education (Control, n=2575)
--- | --- | ---
Weight loss, % | -6.5% | -0.88*
Treadmill fitness, % METS | 12.74 | 1.96*
A1C, % | -0.36 | -0.09*
Systolic pressure, mm Hg | -5.33 | -2.97**
Diastolic pressure, mm Hg | -2.92 | -2.48**
HDL, mg/dL | 3.87 | 1.97*
Triglycerides, mg/dL | -25.56 | -19.75*

*P<0.001, **P=0.01

Look AHEAD: Effect of Lifestyle Intervention in T2DM

- Weight loss, % - 6.5% - 0.88*
- Treadmill fitness, % METS 12.74 1.96*
- A1C, % - 0.36 - 0.09*
- Systolic pressure, mm Hg - 5.33 - 2.97**
- Diastolic pressure, mm Hg - 2.92 - 2.48**
- HDL, mg/dL 3.87 1.97*
- Triglycerides, mg/dL - 25.56 - 19.75*

Effect of Lowering Blood Pressure in Diabetes

BP-lowering (mm Hg)

- Intervention group
  - HOPE Study
  - LIFE Study
  - CARE Study
  - CARDS Study
  - AHEAD Study

Control group

- MDRD Study
- UKPDS

Change in Weight, %

- HOPE Study: 0%
- LIFE Study: -5.27 (%)

Change in HbA1c Level, %

- HOPE Study: 0%
- LIFE Study: -0.27 (%)

Lipid Treatment in Diabetes and CV Risk Reduction

CV=cardiovascular

- AFCAPS/TexCAPS Study (n=130)
- CARE Study (n=586)
- VAHIT Study (n=518)

Change in CV risk reduction (%)

- 60%
- 43%
- 35%
- 30%
- 22%
- 10%
- 6%
- 2%
- 0%

Metformin Use Among Patients With T2DM and Atherothrombosis

Prospective evaluation of 19,691 patients with T2D and established atherothrombosis participating in the REACH Registry, treated with or without metformin as part of a secondary CVD prevention strategy

Metformin Use, CVD Risk, and CKD

Metformin Use, Yes No

Adjusted HR (95% CI) # Value

Propensity-matched (99 mg) 0.65 (0.47–0.89) 0.03
Lipid lowering (80 mg) 0.87 (0.62–1.23) 0.41
Fish oil (500 mg) 0.70 (0.47–1.07) 0.09

Hazard Ratio

-13
Benefit of Multifactorial Interventions in T2D Patients

Benefit of Multifactorial Interventions in T2D Patients

Steno-2 Trial Update: Reduction in CV Events with Intensive Therapy*

N = 160 with type 2 diabetes and microalbuminuria

*Intensified multifactorial intervention included tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents.

Steno-2 Trial Update: Reduction in CV Events with Intensive Therapy*

Implement a Systematic Approach to CV Risk-Reduction

- Focused treatment guidelines and algorithms
- Preprinted order sheets
- Focused lectures by opinion leader
- Rx checklist and outpatient flow process
- Patient education materials
- Measurement and utilization reports

Olivia: Revisited

- Olivia’s clinician recommends that she begin treatment with an oral glucose-lowering medication.

ARS Question #4

Which of the following strategies can help increase Olivia’s success with her management plan?

1. Discuss medication costs with Olivia
2. Determine how Olivia feels about being diagnosed with T2D
3. Provide heart-health recipes for African American foods in your office
4. Include patient literature centered around the treatment of African American in your office
5. All of the above

Culturally-Sensitive Approaches in Clinical Practice

- Establish trust
- Improve communication
- Be sensitive to financial concerns
- Consider family dynamics
- Modify office environment
- Provide nutrition education, including that specific to ethnic food preparation

Readiness to Change Affects Outcomes in a Diabetes Educational Program

Changes in Outcome Measures From Baseline to 6 Months

<table>
<thead>
<tr>
<th>Measure</th>
<th>Reciprocal Peer-Support Group</th>
<th>Nurse Care Management Group</th>
<th>P-Value for Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Baseline 8.0 (12.0)</td>
<td>7.73 (1.50)</td>
<td>-0.28</td>
</tr>
<tr>
<td></td>
<td>3 Months 8.1 (10.0)</td>
<td>7.95 (1.10)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>12 Months 8.4 (10.0)</td>
<td>7.90 (1.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Precontemplator contemplation</td>
<td>Baseline 5.0 (1.5)</td>
<td>4.72 (1.3)</td>
<td>-0.28</td>
</tr>
<tr>
<td></td>
<td>3 Months 5.0 (1.5)</td>
<td>4.72 (1.3)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>12 Months 5.0 (1.5)</td>
<td>4.72 (1.3)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Peer Support vs Nurse Care Management

*P<0.05 for within-group difference.

Conclusions

• T2D is both a metabolic and vascular disease
  - Multiple factors contribute to the cardiometabolic risk
• Simultaneous treatment of all CV risk factors can reduce the impact of CVD in patients with T2D
  - Hyperglycemic is a risk factor for CVD in diabetes
• Treatment goal is to near-normalize the level of each risk factor
  - Consider age-related and ethnic factors
  - Utilize culturally competent treatment approaches

Post-test Question #1

Which of the following is not a NCEP criterion for the diagnosis of metabolic syndrome?
1. BP ≥130/85 mm Hg
2. BMI ≥30 kg/m²
3. Triglycerides ≥150 mg/dL
4. FPG ≥100 mg/dL

Post-test Question #2

At what glucose level does a patient have prediabetes?
1. 90 mg/dL
2. 95 mg/dL
3. 99 mg/dL
4. 100 mg/dL

Post-test Question #3

Improving glycemic control has the greatest impact on which of the following?
1. Heart failure
2. Myocardial infarction
3. Stroke
4. Microvascular complications (neuropathy, nephropathy, retinopathy)

Pre-test Question #4

GLP-1 enhances endogenous insulin secretion in a glucose-dependent manner.
1. True
2. False

The Incretin System and Regulation of Glycemic Control

Jeffrey S. Freeman, DO, FACOI
Multiple Metabolic Defects Contribute to Hyperglycemia in T2D

- Decreased insulin secretion
- Increased lipolysis
- Increased glucose resorption
- Decreased glucagon secretion
- Neurotransmitter dysfunction
- Increased hepatic glucose production
- Increased glucagon secretion
- Decreased incretin effect

Hyperglycemia

- Decreased insulin secretion
- Increased lipolysis
- Increased glucose resorption
- Decreased glucagon secretion
- Neurotransmitter dysfunction
- Increased hepatic glucose production
- Increased glucagon secretion
- Decreased incretin effect

What is the Incretin Effect and Why Are Incretins Important?

The Incretin Effect Is Reduced in T2DM Compared With NGT

<table>
<thead>
<tr>
<th>p-Cell Secretory Response</th>
<th>Oral glucose load</th>
<th>IV glucose infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>36.9, 34.7</td>
<td>23.6</td>
</tr>
<tr>
<td>T2DM</td>
<td>10.9</td>
<td></td>
</tr>
</tbody>
</table>

Decreased incretin effect in T2DM

Incretins Are Important Because They Modulate Numerous Effects in Humans

- Major incretins in humans
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic polypeptide (GIP)
- GLP-1 effects following food intake:
  - Promotes satiety and reduces appetite
  - ↓ Postprandial glucagon secretion
  - Helps regulate gastric emptying
  - Enhances glucose-dependent insulin secretion

Strategies for Enhancing GLP-1 Action: 2 Different Approaches

- GLP-1 secretion is impaired in type 2 diabetes.
  - Natural GLP-1 has an extremely short half-life.
  - DPP-4 enzyme rapidly inactivates GLP-1.
- Injectable GLP-1 receptor agonists with longer half-life, providing supraphysiologic GLP-1:
  - Exenatide
  - Liraglutide
  - Exenatide LAR
- Oral DPP-4 inhibitors inhibit the actions of DPP-4, reducing degradation of existing GLP-1:
  - Linagliptin
  - Sitagliptin
  - Saxagliptin
  - Vildagliptin*
  - Alogliptin*

Actions of DPP-4 Inhibitors and GLP-1 Receptor Agonists in Regulating Glucose Homeostasis

- Physiologic
  - GLP-1R Agonists
  - Satiety & Weight Loss
  - ↓ Gastric Emptying
- Pharmacologic
  - DPP-4 Inhibition
  - ↑ Insulin Secretion
  - ↓ Glucagon Secretion

Progressive GLP-1R Activation

Case Presentation: Javier

- 56-year-old overweight Hispanic man who presents for evaluation of his T2D, which was diagnosed ~3 yrs ago
- PMH
  - HTN x 30+ yrs and dyslipidemia x 15 yrs; generally uncontrolled until ~1 yr ago
  - Stable angina
  - Renal insufficiency diagnosed ~2 yrs ago
  - Past heavy alcohol use; quit drinking alcohol ~2 yrs ago

Javier: Physical Exam and Labs

Physical Exam:
- BP = 136/88 mm Hg; HR = 86, regular
- Height = 5’10”; Weight = 221 lbs; BMI = 31.7 kg/m²
- 1+ ankle edema; foot exam normal

Recent Labs:
- A1C = 8.3%; FPG = 170 mg/dL; 2-hr PPG = 270 mg/dL
- SCr = 2.0 mg/dL; BUN = 49 mg/dL (eGFR = 37 mL/min/m²)
- Microalbumin 310 µg/mg creatinine
- LDL = 92 mg/dL; HDL = 43 mg/dL; TG = 160 mg/dL; non-HDL = 124 mg/dL

Javier: Current Medications

- Metformin: 500 mg PO BID
- Ramipril: 5 mg PO QAM
- Chlorthalidone: 25 mg PO QAM
- Pravastatin: 40 mg PO QAM
- Aspirin: 81 mg PO QAM

ARS Question #5

Javier’s current FPG is 170 mg/dL, 2-hr PPG is 270 mg/dL, and A1C is 8.3%. What contribution to his A1C is from postprandial glucose?
1. 30%
2. 50%
3. 70%
4. 90%

FPG and PPG: Contribution to A1C

<table>
<thead>
<tr>
<th>Contribution to A1C (%)</th>
<th>FPG</th>
<th>PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% 30%</td>
<td>&lt;7.3</td>
<td></td>
</tr>
<tr>
<td>50% 50%</td>
<td>7.3-8.4</td>
<td></td>
</tr>
<tr>
<td>45% 55%</td>
<td>8.5-9.2</td>
<td></td>
</tr>
<tr>
<td>40% 60%</td>
<td>9.3-10.2</td>
<td></td>
</tr>
<tr>
<td>30% 70%</td>
<td>&gt;10.2</td>
<td></td>
</tr>
</tbody>
</table>

Antihyperglycemic Agents: Many Choices Exist

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic (Brand) Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Regular Insulin; NPH Insulin; Insulin Analogs</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Gliniuride; Glipizide; Glyburide</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone; Rosiglitazone</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>Dapagliflozin; Canagliflozin</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>Acarbose; Miglitol</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Exenatide; Liraglutide</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Sitagliptin; Saxagliptin; Linagliptin</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>Exenatide; Liraglutide; Exenatide Extended Release</td>
</tr>
<tr>
<td>bile acid sequestrant</td>
<td>Colesevelam</td>
</tr>
<tr>
<td>Dopamine receptor agonist</td>
<td>Bromocriptine</td>
</tr>
</tbody>
</table>
Pharmacotherapy Selection for T2D: Key Considerations

Drug Selection

- Degree of HbA1c lowering needed
- Which glucose level is not at target
- Coexisting medical conditions
- Duration of disease
- Patient preference for route of medication
- Side effect profile


Which of the following statements about incretin-based therapy is true?

1. According to the AACE treatment algorithm, GLP-1 agonists should not be used in patients with A1C <7.5%.
2. Linagliptin can be used safely in patients with renal impairment.
3. Saxagliptin is associated with high rates of hypoglycemia when used as monotherapy.
4. Clinical trial evidence has demonstrated increases in systolic BP with use of exenatide.

Pre-test Question #5

AACE/ACE Diabetes Algorithm

- Asymptomatic
  - 6.5%
  - 7.5%
  - 9.0%
- HbA1c continuum—If not at goal, advance Rx to 12%

Therapeutic choice should match the drug with patient characteristics.

- Monotherapy
  - Metformin
  - Pioglitazone
  - GLP-1 agonist
  - DPP-4 inhibitor (or AGI)
- Dual Combination
  - Metformin
  - Pioglitazone
  - GLP-1 agonist
  - DPP-4 inhibitor (or AGI)/secretagogue/colesevelam
- Triple Combination
  - Metformin
  - Pioglitazone
  - GLP-1 agonist
  - DPP-4 Inhibitor (or AGI/secretagogue/colesevelam)

Insulin
- Asymptomatic
  - +/- other agents
  - Not NPH/regular
  - If >3.5% and symptomatic
  - If triple combo fails

Diet and Exercise

Javier: Revisited

Javier’s clinician would like to start him on an incretin-based therapy. Javier would prefer an oral medication. He is started on a DPP-4 inhibitor.

Based on published studies, what reduction in A1C can you expect to see over the next 3 months?

1. ~0–0.5%
2. ~0.5–1.0%
3. 1.0–2.0%
4. >2.0%

ARS Question #6
Glucose Control With Sitagliptin: Mono- and Combination Therapy

Baseline A1C (%) 8.0 8.0 8.6 8.6 8.0 8.1 8.1 8.2

Summary of Clinical Trial Data

Use of Exenatide in T2D: Summary of Clinical Trial Data

A1C Reductions with Use of Liraglutide in T2D

Javier: Revisited

What A1C reductions would you expect to see if Javier was prescribed a GLP-1 agonist?
Efficacy and Safety of Exenatide Once Weekly across Background Therapies: A Pooled Analysis of DURATION Studies

<table>
<thead>
<tr>
<th>Diet/Exercise</th>
<th>MET</th>
<th>MET+TZD</th>
<th>MET+SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>43</td>
<td>427</td>
<td>28</td>
</tr>
<tr>
<td>HbA1C Baseline (%)</td>
<td>8.4±1.1</td>
<td>8.4±1.1</td>
<td>8.1±1.0</td>
</tr>
<tr>
<td>ΔHbA1C (%)</td>
<td>-1.6 (-2.0, -1.2)</td>
<td>-1.4 (-1.6, -1.3)</td>
<td>-1.5 (-1.8, -1.2)</td>
</tr>
<tr>
<td>MET+TZD at endpoint (%)</td>
<td>72%</td>
<td>68%</td>
<td>76%</td>
</tr>
<tr>
<td>ΔPPG (mg/dL)</td>
<td>-34 (-48, -20)</td>
<td>-35 (-40, -30)</td>
<td>-37 (-55, -18)</td>
</tr>
<tr>
<td>ΔBaseline weight (kg)</td>
<td>0.7±2.6</td>
<td>0.7±1.4</td>
<td>0.5±2.1</td>
</tr>
<tr>
<td>ΔWeight (kg)</td>
<td>0.3 (0.5, -1.1)</td>
<td>0.0 (0.3, -2.6)</td>
<td>2.3 (4.6, 0.1)</td>
</tr>
</tbody>
</table>


Javier: 12 months Later

- Javier’s A1C has steadily reduced over the last 12 months
  - Current A1C is 7.2%
- Unfortunately, however, Javier’s renal function continues to decline
  - Current eGFR is 28 mL/min/m²

Javier: Revisited

What antihyperglycemic agents can we safely prescribe to Javier given his renal dysfunction?

Metabolism/Clearance and Dosing Adjustments of Incretin-Based Therapies in the Presence of Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism/Clearance</th>
<th>Dose Adjustment in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Renal</td>
<td>50 mg/d if GFR 30-60 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg/d if GFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Hepatic/renal</td>
<td>2.5 mg/d if GFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Hepatic</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Renal</td>
<td>Do not use with CrCl &lt;30 mL/min or ESRD; use with caution in patients with renal transplantation. Use with caution when starting or increasing dose with CrCl 30–50 mL/min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use with caution when starting or increasing dose in patients with renal impairment</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>In vivo</td>
<td>No dose adjustment necessary; use with caution when starting or increasing dose in patients with renal impairment</td>
</tr>
</tbody>
</table>

DPP-4 Inhibitors: Safety Summary

- In regulatory trials:
  - Small percentage of patients experienced URI, nasopharyngitis, and headache
  - GI: abdominal pain, nausea, diarrhea (rare)
- Reports of association with pancreatitis for incretin-related agents but no conclusive data
- Discontinue medication if signs/symptoms of pancreatitis; do not use if pancreatitis is confirmed
- Consider lowering the dose of concomitantly used SUs or insulin to reduce the risk of hypoglycemia when initiating DPP-4 inhibitors

GLP-1 Agonists: Safety Summary

- Commonly reported side effects: nausea, vomiting, diarrhea, indigestion and upper abdominal discomfort
  - More common with shorter-acting agents
- Low risk for hypoglycemia except when combined with SU or insulin
- Reports of association with pancreatitis for incretin-related agents but no conclusive data
- Discontinue medication is S/S of pancreatitis; do not use if pancreatitis is confirmed
- Liraglutide use is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
Incretin Agents and CV Safety

- To date, no adverse CV safety signals have been retrospectively reported from phase III clinical trials.
- Several large-scale, prospective CV outcome trials are currently ongoing.

Saxagliptin Clinical Trials: CV Safety

Data from 8 randomized, double-blind, phase 2b/3 trials:

- Event type
  - Saxagliptin (n = 2279)
  - Comparator (n = 1920)
- CV events:
  - Saxagliptin: 23 (1.8)
  - Comparator: 38 (1.1)
- MACE:
  - Saxagliptin: 18 (1.4)
  - Comparator: 23 (0.7)
- All deaths:
  - Saxagliptin: 12 (1.0)
  - Comparator: 10 (0.3)
- CV deaths:
  - Saxagliptin: 10 (0.5)
  - Comparator: 7 (0.3)

Linagliptin Clinical Trials*:

- CV Safety

<table>
<thead>
<tr>
<th>MACE†</th>
<th>Linagliptin (n=3319) Rate/1000 pt-yr</th>
<th>Comparator (n=1920) Rate/1000 pt-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint</td>
<td>16.8</td>
<td>5.3</td>
</tr>
<tr>
<td>CV death</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>5.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>8.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hosp. for UA</td>
<td>202</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Exenatide*: Effect on CV Risk Factors

- Mean CRP concentration: 4.7 ± 0.8 vs. 3.2 ± 0.4 mg/dL.
- Mean systolic blood pressure (SBP): 132 ± 6 mmHg vs. 125 ± 4 mmHg.
- Mean A1C: 7.8 ± 0.6% vs. 7.2 ± 0.2%.

Liraglutide*: Effect on CV Risk Factors When Used as a Glucose-Lowering Agent

- Retrospective analysis of 110 patients treated with liraglutide in clinical practice.
- Parameters:
  - A1C: 7.2 ± 0.2%
  - Weight: 115 ± 3 kg
  - Triglycerides: 151 ± 15 mg/dL
  - Mean systolic blood pressure (SBP): 125 ± 4 mmHg
  - Mean CRP concentration: 3.2 ± 0.4 mg/dL

CV Outcomes Trials in Patients with T2D
DPP-4 Inhibitors and GLP-1 Agonists: A Comparison

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-dependent insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FPG reduction</td>
<td>18–25 mg/dL</td>
<td>25–61 mg/dL</td>
</tr>
<tr>
<td>Effect on PPG</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight effects</td>
<td>Weight neutral</td>
<td>Weight loss</td>
</tr>
<tr>
<td>A1C reduction</td>
<td>0.5%–1.1%</td>
<td>0.8%–1.5%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Low risk if not used in combination with SU or insulin*</td>
<td>Low risk if not used in combination with SU or insulin†</td>
</tr>
<tr>
<td>Improved beta-cell function (during treatment)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral</td>
<td>Injectable</td>
</tr>
</tbody>
</table>

*Sitagliptin combination with insulin FDA approved
†Liraglutide combination with insulin is investigational.

Summary: When to Start Therapy With Incretin Agents
- If lifestyle modifications and metformin have failed, add another medication within 2 to 3 months of initiating therapy or at any time when target A1C is not being achieved.
- ADA/EASD and AACE/ACE algorithms include multiple treatment options.
  - GLP-1 receptor agonists recommended as Tier 2, Step 2 therapy, after metformin (ADA/EASD)
  - DPP-4 inhibitors and GLP-1 receptor agonists listed as options for monotherapy (tho metformin preferred and liraglutide not recommended for first-line therapy) and combination therapy (AACE/ACE)
- DPP-4 inhibitors may be considered when:
  - Oral therapy preferred
  - Hypoglycemia is particularly undesirable
  - Minimizing weight gain is an important consideration and A1C is close to target
  - Some degree of renal impairment is present
  - Renal dosing not required with linagliptin

Post-test Question #4
GLP-1 enhances endogenous insulin secretion in a glucose-dependent manner.
1. True
2. False

Post-test Question #5
Which of the following statements about incretin-based therapy is true?
1. According the AACE treatment algorithm, GLP-1 agonists should not be used in patients with A1C <7.5%.
2. Linagliptin can be used safely in patients with renal impairment
3. Saxagliptin is associated with high rates of hypoglycemia when used as monotherapy
4. Clinical trial evidence has demonstrated increases in systolic BP with use of exenatide

Post-test Question #6
Potential benefits of incretin-based therapy include all of the following, except:
1. Low risk for edema
2. Neutral-to-beneficial effects on weight loss
3. Reduction of postprandial hyperglycemia
4. Low risk for hypoglycemia
5. None of the above; all are benefits

Disease Progression and Treatment Intensification: Role of Insulin
Michael E. Cobble, MD
A1C Level Increases With Time, Irrespective of Treatment Choice

T2DM is a Progressive Disease
Advancement of Therapies Is Required

Case Presentation: James

- James is a 76-year-old man complaining of several episodes of dizziness over the last 2 wks
- He was recently discharged from the hospital 2 wks ago following debridement of a foot ulcer
  – This is the first time following up with a physician
- James lives alone, but his daughter has been staying with him since his d/c
- PMH
  – T2D x 20 yrs
  – CAD; s/p CABG in 1999
  – Renal insufficiency

James: Current Medications

- Current medications upon discharge from hospital:
  - Metformin 1000 mg BID
  - Glimepiride 4 mg QD
  - NPH insulin 20 U BID
  - Aspirin 81 mg QD
  - Lisinopril 20 mg QD
  - Pantoprazole 40 mg QD

ARS Question

What is the most likely source of James’ dizziness?
1. Depression
2. Hypoglycemia
3. Anemia
4. Hypotension
5. Unknown; more information required
Recognizing Hypoglycemia in Older Adults

- Dizziness, confusion, tremors/falls
- Symptoms of hypoglycemia in the elderly are often atypical
- Unrecognized symptoms of hypoglycemia are often attributed to:
  - Dementia
  - Psychosis
  - Behavior changes
  - Cardiovascular events
  - Seizures

Minimizing the Risk of Hypoglycemia in Older Adults

- Be knowledgeable about the oral medications that may cause hypoglycemia
- Discourage the use of sliding-scale insulin
- Use physiologic insulin regimens (basal/bolus)
- Develop protocols for glycemic management
- Provide staff education
- Develop a hypoglycemia protocol

James: 2 Weeks Later

- James’ clinician determined the most likely source of his dizziness was due to an inappropriate dose of NPH insulin that James had been taking since his discharge from the hospital
- Although James’ clinician reduced his NPH dose at his last visit, James hasn’t been taking it
  - James is now reluctant to take any kind of insulin therapy and is adamantly against using NPH

ARS Question

In your practice, what is the most common patient barrier to insulin initiation?
1. Sense of failure
2. Worsening disease severity
3. Loss of control
4. Perception of insulin ineffectiveness
5. Fear of injections
6. Fear of hypoglycemia
7. Burden of care and complexity
8. Cost of care
The Insulin Paradox

Many patients have high blood glucose levels, which put them at risk for complications

AND

Insulin is the most powerful medication for lowering blood glucose

BUT

Many patients with poor glycemic control do not receive insulin treatment

Pre-test Question #7

According the AACE/ACE treatment algorithm, at what A1C level is insulin recommended in a drug-naïve patient with T2DM?

1. 6.5% – 7.5%
2. 7.5% – 9.0%
3. >9.0%
4. None of the above

Insulin Therapy Selection

Starting Strategy

Basal-Bolus Insulin + Oral Agent(s)

Basal Bolus Insulin
+ metformin unless contraindication or intolerance

Gold standard but more complicated

More flexible

Long-acting:

Detemir

Glargine

Intermediate-acting:

NPH

Rapid-acting:

Aspart

Lispro

Glulisine

Human regular

Premixed Insulin
+ metformin unless contraindication or intolerance

Elevated PPQ

May be used 1, 2, 3 times a day

Premixed:

Human premix 70/30

Analogas:

Insulin lispro mix 75/25, 50/50

Biphasic insulin aspart 70/30

Self-ex:

Rapid-acting analog or regular + NPH

Initiation and Adjustment of Insulin Regimens

Start once-a-day long-acting insulin analog or NPH bedtime or morning

Starting dose 10 units or 0.2 units/kg

Titrate against FPG until in target range (70–130 mg/dL)

Increase dose typically by 2 units q 3 days

Premixed:

If hypoglycemia occurs or if BG <70 mg/dL, reduce dose by 24 units q 3 days

If BG >180 mg/dL, can increase dose by 4 units q 3 days

If hypoglycemia occurs or if BG <70 mg/dL

Check A1C every 3 months

If A1C level >7% after 2–3 months

No

Yes

Premixed

Continue regimen, recheck A1C level q 3 months


Insulin Therapy Selection

T2DM = type 2 diabetes mellitus; FPG = fasting plasma glucose; BG = blood glucose; PPQ = postprandial glucose.


Insulins Used in Clinical Practice:
Time-Action Profiles

Rapid-acting analogs:
- Aspart
- Glulisine
- Lispro

Intermediate-acting insulin:
- NPH

Short-acting insulin:
- Regular (soluble)

Premixed Analogs
- Insulin lispro mix 75/25, 50/50
- Biphasic insulin aspart 70/30

Long-acting insulin:
- Glargine
- Detemir

Human insulin (HI) 70/30 premix

James: 2 Weeks Later (con’t)

- James discusses the risks and benefits of insulin therapy with a diabetes educator in his clinician’s office
- He agrees to “try it out”
- James is started on a long-acting basal insulin analog and instructed in how to up-titrate his dose to reach FBG <110 mg/dL

Pre-test Question #8

All of the following statements regarding insulin replacement therapy is false, except:

1. Patients using insulin analogs generally experience higher nocturnal hypoglycemia rates compared to those using human basal insulin
2. Rapid-acting human insulin generally achieves greater PPG control compared with rapid-acting insulin analogs
3. Long-acting insulin analogs demonstrate less activity variability day-to-day compared with long-acting human insulin
4. All of the above

Why Insulin Analogs?
Advantages of Insulin Analogs Over Human Insulin

Rapid-acting
- More rapid onset
- Higher peaks
- More rapid return to basal levels
- Convenient mealtime administration
- Better PPG control
- Greater predictability
- Less hypoglycemia

Basal
- Less variability from day to day
- Longer-acting (up to 24 hours), once-a-day administration
- Lower risk of nocturnal and overall hypoglycemia
- Less weight gain

Treat-to-Target Study:
Insulin Glargine vs NPH Insulin Added to Oral Therapy

- 70% of patients achieved A1C <7%

A1C & Weight Changes

Risk of Hypoglycemia

James: Follow-Up in 3 months

- 3 months later
  - FBG: ~115–130 mg/dL
  - A1C level = 8.2%
- His current basal dose is 20 units at bedtime
- He has not experienced any hypoglycemic episodes

What would your next step be with James’ treatment?
1. Increase his basal insulin dose further
2. Add a second dose of basal insulin in the morning
3. Add a rapid acting insulin analog to his largest meal
4. Discontinue basal insulin and start a premixed insulin
5. Add incretin agent

The BeAM Factor: An Objective, Clinical Indicator for When To Add Prandial Insulin vs Continued Basal Insulin Titration

“BeAM” factor = differences between bedtime and AM blood glucose levels
- A larger BeAM factors was associated with
  - Reduced likelihood of attaining A1C≤7.0% (P<0.0001)
  - Increased risk of nocturnal (P<0.0001), but not overall, hypoglycemia.
- Patients on basal insulin (BI) with a BeAM >55 mg/dL were less likely to approach A1C ≤7.0%.
  - These patients may not benefit from continued BI titration and addition of prandial insulin should be considered to correct glucose excursions and achieve glycemic goals

Options When Patient Is Not at Goal With One Injection of Basal Insulin

- Add rapid-acting analog before at least one meal
  OR
- Switch to a premixed insulin analog
  - Divide dose in half and give twice daily (before breakfast and dinner)
  OR
- Switch to basal-bolus regimen

The PRESENT Substudy: Reductions in Daytime Hypoglycemia

The rate (events/patient/year) of overall hypoglycemia remained relatively constant for patients who switched from analog basal insulin, but it was significantly lower for those who switched from human basal insulin (change from baseline: 3.8; P< 0.001).
Monitoring Glycemic Control

**A1C**
- Risk assessment
  - Overall glycemic exposure for previous 2-3 months
  - Best assessment of vascular (especially microvascular) risk
- SMBG
  - Treatment adjustment
  - Identify glycemic burden, patterns, and variability
  - Fasting, postprandial, or both
  - Allows for targeting of therapy
  - Education
  - Real-time feedback on glycemic response to diet, activity, and medications
- Detect hypoglycemia
- Use for real-time medication (insulin) adjustments

SMBG = self-monitoring of blood glucose

Twice-daily Exenatide in Basal Insulin-treated Patients With T2DM*

**Hypoglycemia**

<table>
<thead>
<tr>
<th></th>
<th>Minor</th>
<th>Minor Nocturnal</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (n=137), n, %</td>
<td>34 (25%)</td>
<td>23 (17%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insulin Glargine (n=122), n, %</td>
<td>35 (29%)</td>
<td>32 (26%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Adults with T2DM and an A1C level of 7.1% to 10.5% who were receiving insulin glargine alone or in combination with metformin or pioglitazone (or both agents); study duration = 30 weeks

*Recently approved FDA indication.


Saxagliptin Add-on Therapy Improves Glycemic Control in Patients Poorly Controlled on Insulin Alone or Insulin + Metformin

<table>
<thead>
<tr>
<th>Endpoint</th>
<th><strong>SAXA 5 mg + INS</strong> (n = 304)</th>
<th><strong>PBO + INS</strong> (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c, % (SE)</td>
<td>-6.73 (0.054)*</td>
<td>-6.32 (0.074)</td>
</tr>
<tr>
<td>PPG AUC, mg* min/dL (SE)</td>
<td>-4949 (687.7)*</td>
<td>-719 (981.6)</td>
</tr>
<tr>
<td>120-min PPG, mg/dL (SE)</td>
<td>-27.2 (4.35)**</td>
<td>-4.2 (8.08)</td>
</tr>
<tr>
<td>FPG, mg/dL (SE)</td>
<td>-10.1 (2.87)</td>
<td>-6.1 (3.98)</td>
</tr>
</tbody>
</table>

*∆ = 0.41%, P < 0.0001
†∆ = -3830 mg* min/dL, P = 0.0011
‡∆ = -23.0 mg/dL, P = 0.0016

LOCF = last observation carried forward
Use with insulin is not an FDA-approved indication.
**Adjunctive Therapy of Exenatide or Sitagliptin: Affect on Blood Glucose**

Mean (SEM) meal BG profiles.

**Summary and Conclusions**

- Be aware of the recognizable, as well as atypical, signs and symptoms of hypoglycemia in elderly patients
- Set reasonable targets for glucose and A1C
- Match the insulin to the glucose pattern
- Insulin analogs can offer advantages over human insulin
- Incorporate SMBG into daily care

**Post-test Question #7**

According the AACE/ACE treatment algorithm, at what A1C level is insulin recommended in a drug-naïve patient with T2DM?

1. 6.5% – 7.5%
2. 7.5% – 9.0%
3. >9.0%
4. None of the above

**Post-test Question #8**

All of the following statements regarding insulin replacement therapy is false, except?

1. Patients using insulin analogs generally experience higher nocturnal hypoglycemia rates compared to those using human basal insulin
2. Rapid-acting human insulin generally achieves greater PPG control compared with rapid-acting insulin analogs
3. Long-acting insulin analogs demonstrate less activity variability day-to-day compared with long-acting human insulin
4. All of the above
Post-test Question #9

Which of the following statements self-monitoring of blood glucose (SMBG) is true?

1. SMBG is complex and difficult for patients to implement
2. SMBG can help detect hypoglycemia
3. SMBG is important to help adjust insulin dose
4. Only 1 and 3
5. Only 2 and 3