Endocrine and Metabolism PRN Focus Session—Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
Activity No. 0217-0000-11-081-L01-P (Knowledge-Based Activity)

Monday, October 17
3:45 p.m.–5:45 p.m.
Convention Center: Rooms 315 & 316

Moderator: Daniel M. Riche, Pharm.D., BCPS, CDE
Assistant Professor of Pharmacy Practice and Medicine, University of Mississippi School of Pharmacy, University of Mississippi Medical Center, Jackson, Mississippi

Agenda

3:45 p.m.  Emerging Therapies in Diabetes  
Nicole R. Pinelli, Pharm.D.  
Assistant Professor of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, Michigan

4:00 p.m.  GLP-1 Agents in Metabolic Syndrome/Obesity  
Rick Hess, Pharm.D., CDE, BC-ADM  
Assistant Professor, Department of Pharmacy Practice, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, Tennessee

4:15 p.m.  Metformin Use for Chronic Kidney Disease Patients  
Marissa Escobar Quinones, Pharm.D.  
Clinical Pharmacy Specialist, Parkland Southeast Dallas Health Center, Grand Prairie, Texas

4:30 p.m.  Glucose Variability Impact  
Kim L. Kelly, Pharm.D., FCCP, BCPS  
President, Kelly Diabetes Associates, LLC, Cupertino, California

4:45 p.m.  U-500: Appropriate Use and Common Pitfalls  
Jessica Trompeter, Pharm.D.  
Assistant Professor, Bernard J. Dunn School of Pharmacy, Winchester, Virginia
ADA Algorithm Versus AACE Algorithm for Diabetes—A Debate

Craig D. Logemann, Pharm.D., BCPS, CDE
Clinic Pharmacist, Partners in Health Clinics, Des Moines, Iowa

and

Tricia M. Russell, Pharm.D., BCPS, CDE
Assistant Professor, Department of Pharmacy Practice, Wilkes University, Nesbitt School of Pharmacy & Nursing, Wilkes Barre, Pennsylvania

Faculty Conflict of Interest Disclosures

Marissa Escobar Quinones: no conflicts to disclose
Rick Hess: no conflicts to disclose
Kim L. Kelly: member of advisory board for LifeScan; owns stock in Johnson & Johnson.
Craig D. Logemann: no conflicts to disclose
Nicole R. Pinelli: no conflicts to disclose
Tricia M. Russell: no conflicts to disclose
Jessica Trompeter: no conflicts to disclose

Learning Objectives

1. Explain at least 3 pharmacological mechanisms of emerging therapies for diabetes mellitus.
2. Summarize the preliminary clinical trial data examining the efficacy and safety of new medications for the management of diabetes mellitus.
3. Target individuals with diabetes mellitus who may benefit from emerging therapies.
4. Review the prevalence of metabolic syndrome/obesity.
5. Review current pharmacotherapy used in the treatment of metabolic syndrome/obesity.
6. Examine the clinical evidence for the utilization of GLP-1 agonists as pharmacotherapy options in the treatment of metabolic syndrome/obesity.
7. Review the history and contraindications of metformin in patients with chronic kidney disease.
8. Evaluate the current literature regarding the use of metformin in patients with chronic kidney disease.
10. Write a brief description of the evidence that glycemic variability is an independent risk factor for cardiovascular disease.
11. Write a brief description of the mechanism by which glycemic variability can result in oxidative stress.
12. Discuss at least three variables which may affect the pathophysiology of oxidative stress.
13. Discuss the studies that do not support glycemic variability and pathology, including at least one methodologic flaw in each study.
15. Evaluate the safety and educational barriers associated with initiating U-500 insulin and discuss potential solutions.
16. Summarize a dosing scheme for initiation and titration of U-500 insulin.
17. Review the advantages of recommending an A1c goal of <7% for the management of type 2 diabetes according to the ADA treatment algorithm.
18. Identify any concerns with the AACE treatment algorithm glycemic goal of A1c of <6.5%.
19. Discuss the benefits of initiating metformin as a preferred treatment early in the management of type 2 diabetes.
20. Review the advantages of recommending an A1c goal of <6.5% for the management of type 2 diabetes according to the AACE treatment algorithm.
21. Identify any concerns with the ADA treatment algorithm glycemic goal of A1c of <7%.
22. Discuss the benefits of initiating other medications besides metformin as monotherapy options, such as thiazolidinediones, DPP-4 inhibitors, incretin mimetics or alpha-glucosidase inhibitors.

**Self-Assessment Questions**

Self-assessment questions are available online at [www.accp.com/am](http://www.accp.com/am)
Emerging Therapies in Diabetes

Nicole R. Pinelli, Pharm.D., M.S., CDE
Assistant Professor of Pharmacy Practice
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Detroit, Michigan

Disclosure
No relevant financial relationship with any commercial interests to disclose

Learning Objectives
At the end of this presentation, participants should be able to:
- Explain at least 3 pharmacological mechanisms of emerging therapies for diabetes mellitus
- Summarize the preliminary clinical trial data examining the efficacy and safety of new medications for the management of diabetes mellitus
- Target individuals with diabetes mellitus who may benefit from emerging therapies

Emerging Therapies in Diabetes

Today’s Menu
Appetizer
“Triumvirate” to the “Ominous Octet” Sampler

Type 2 Courses
The Many Flavors of “GLP-1”
Recipe for Disaster with “SGLT2”?

Something for Everyone
“Ultra-Long-Acting” … Better in the Fasting State?

Dessert
“Pipeline” Sweet Table

“Triumvirate” to the “Ominous Octet” Sampler

DeFronzo RA. Diabetes 2009;58:773

2011 ACCP Annual Meeting
Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
Islet \( \beta \)-cell

Impaired Insulin Secretion

Increased Lipolysis

Incretin Effect

Decreased Glucose Uptake

Increased HGP

DeFronzo RA. Diabetes 2009;58:773

Islet \( \alpha \)-cell

Decreased Incretin Effect

Impaired Glucose Reabsorption

Increased Glucagon Secretion

Islet \( \beta \)-cell

Impaired Insulin Secretion

Decreased Lipolysis

Incretin Effect

Decreased Glucose Uptake

Increased HGP

DeFronzo RA. Diabetes 2009;58:773

Current Treatment of Type 2 Diabetes

TZDs

GLP-1 analogues

DPP-4 Inhibitors

Sulfonylureas/Meglitinides

Metformin

TZDs

Impaired Glucose Reabsorption

Islet \( \beta \)-cell

Decreased Incretin Effect

Increased Glucagon Secretion

Islet \( \alpha \)-cell

Impaired Glucose Reabsorption

Increased HGP

Neurotransmitter Dysfunction

DeFronzo RA. Diabetes 2009;58:773

Unmet Needs in Type 2 Diabetes

Multiple Defects in Type 2 Diabetes

Adverse Effects of Therapy

Weight Management → Type 2 Diabetes → Hyperglycemia

↓ CVD Risk (Lipid and Hypertension Control)

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Emerging Therapies in Diabetes

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The Many Flavors of “GLP-1”
Incretins Modulate Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food
Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Liver:
↓ Glucagon reduces hepatic glucose output

Limitations of the Endogenous Incretin Hormone

His Ala Glu Gly Thr Phe Thr Ser Asp Val
DPP-IV
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly

Mentlein R. Eur J Biochem. 1993;214:829-836

GLP-1 Receptor Agonists

Long Acting GLP-1 Receptor Agonists

Exendin-4 backbone
Human GLP-1 backbone

Weekly BID or QD
Exenatide Liraglutide
Lixisenatide
Exenatide QW
Taspoglutide
CJC-1134-PC
Albiglutide
Dulaglutide
Semaglutide


Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies


Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
Body Weight
Greater mean body weight reduction vs. sitagliptin (WMD -1.99 kg), but not vs. exenatide twice daily.

Blood Pressure
Although trial results are inconsistent, the blood pressure lowering (SBP and DBP) ability of long-acting agents and other incretin-based therapies appears to be similar.

Lipids
Current evidence cannot confirm a difference in lipid lowering between incretin-based therapies.

Severe Hypoglycemia
• Did not occur in the majority of trials

Nonsevere Hypoglycemia
• Occurred infrequently and at similar rates in the majority of trials
• More frequently associated with SU

Antibodies
• Mean anti-exenatide antibody levels were higher with exenatide once weekly compared with twice daily

Injection site reactions
• More frequent injection site pruritis with exenatide once weekly in the majority of trials

Calcitonin levels
• No differences between therapies

Pancreatitis
• No acute pancreatitis reported
• One case reported after 88 days of therapy with long acting GLP-1RA

DURATION 4:
• 26-week, randomized, double-blind, double-dummy superiority trial
• Exenatide once weekly (2 mg) vs. metformin (1000 mg/day), pioglitazone (30 mg/day), and sitagliptin (100 mg/day) as monotherapy in patients with T2DM
• Primary endpoint, reduction in A1c
• 1.5% with both exenatide once weekly and metformin, 1.6% with pioglitazone, 1.2% with sitagliptin
• No major hypoglycemia
• Expected AEs

DURATION 6:
• 26-week, randomized, open-label superiority study
• Exenatide once weekly (2 mg) vs. lixisenatide (1.8 mg) added to oral agent(s) in T2DM
• Primary endpoint, reduction in A1c
• 1.3% exenatide once weekly (n=461), 1.5% lixisenatide (n=451)
• Safety
• No major hypoglycemia reported
• No less GI adverse events with exenatide once weekly

Presented at ADA, 71st Sessions; 2011; San Diego, CA (280-OR)

Comparison of DPP-IV Inhibitors

<table>
<thead>
<tr>
<th>Structure</th>
<th>Sitagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
<th>Saxagliptin</th>
<th>Vildagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>dimer</td>
<td>Non-covalent</td>
<td>Non-covalent</td>
<td>Non-covalent</td>
<td>Non-covalent</td>
<td>Non-covalent</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg QD</td>
<td>5 mg QD</td>
<td>25 mg QD</td>
<td>5 mg QD</td>
<td>50 mg BID</td>
</tr>
<tr>
<td>Half-Life</td>
<td>12.4 hrs</td>
<td>12 hours</td>
<td>12.5-21.1 hrs</td>
<td>2.2-3.8 hrs</td>
<td>1.3-2.4 hrs</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Renal/Renal</td>
<td>Renal/Renal</td>
</tr>
<tr>
<td>Renal Adjustment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for DDI</td>
<td>Low</td>
<td>Strong</td>
<td>Non-covalent</td>
<td>Low</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Diabetes Metab Res Rev 2010;26:540-549
• 18-week, randomized, double-blind, non-inferiority trial
• Sitagliptin vs. Saxagliptin both added to metformin
• Similar efficacy
• Both well-tolerated
**The Many Flavors of “GLP-1”**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LA GLP-3RA</th>
<th>Exenatide BID</th>
<th>DPP-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c reduction</td>
<td>~1.5%</td>
<td>~1.0%</td>
<td>~0.5-0.8%</td>
</tr>
<tr>
<td>FPG reduction</td>
<td>Good</td>
<td>Modest</td>
<td>Modest</td>
</tr>
<tr>
<td>PPG reduction</td>
<td>Modest</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Little or None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Body weight</td>
<td>Weight loss</td>
<td>Weight loss</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Effect CVD risk factors</td>
<td>Improve</td>
<td>Improve</td>
<td>Improve</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>? Less Nausea</td>
<td>Nausea</td>
<td>Well-Tolerated</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>Most</td>
<td>Less</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypoglycemia with SU</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Injection</td>
<td>Injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Administration</td>
<td>QD or Weekly</td>
<td>BID with Meals</td>
<td>QD</td>
</tr>
</tbody>
</table>

**Rationale for SGLT2 Inhibitors**

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes will likely respond

**Emerging Therapies in Diabetes**

**Today’s Menu**

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**Type 2 Courses**
The Many Flavors of “GLP-1”
Recipe for Disaster with “SGLT2”?

**Something for Everyone**
“Ultra-Long-Acting” … Better in the Fasting State?

**Dessert**
“Pipeline” Sweet Table

**Renal Handling of Glucose**

(180 L/day) (900 mg/L)=162 g/day

**SGLT2 Mediates Glucose Reabsorption in the Kidney**

- Major transporter of glucose in the kidney
  - Low affinity, high capacity for glucose
  - Nearly exclusively expressed in the kidney
  - Responsible for ~90% of renal glucose reabsorption in the proximal tubule

**Sodium-Glucose Cotransporters**

<table>
<thead>
<tr>
<th>Site</th>
<th>SGLT1</th>
<th>SGLT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar specificity</td>
<td>Glucose or galactose</td>
<td>Glucose</td>
</tr>
<tr>
<td>Glucose affinity</td>
<td>K_m=0.4 mM</td>
<td>K_m=2 mM</td>
</tr>
<tr>
<td>Glucose transport capacity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Role</td>
<td>Dietary absorption of glucose and galactose</td>
<td>Renal glucose reabsorption</td>
</tr>
</tbody>
</table>

Dapagliflozin: Clinical Efficacy

Dapagliflozin: Glucosuric & Metabolic Effects

Dapagliflozin Glucosuric & Metabolic Effects

Glucosuria ↑ 52–85 g/day
FPG ↓ 16–30 mg/dL
PPG ↓ 23–29 mg/dL
Body weight ↓ 2.2–3.2 kg (2.5%–3.4%)
Urine volume ↑ 107–470 mL/day


A Recipe for Disaster with “SGLT2”? Unanswered Questions About SGLT2 Inhibition

Durability
Data submitted to FDA to provide evidence of dapagliflozin durability is not convincing. Only 21–43% of individuals receiving dapagliflozin completed long-term extension studies because of the need for ‘rescue’ therapy or due to subject attrition.

Safety and Tolerability
Risk of genitourinary infections recognized in phase III trials. Possible safety concerns include bladder and breast CA and hepatic injury. Long-term CV safety needs to be established.

Renal Impairment
SGLT2 inhibition does not appear to be effective in patients with renal impairment (<60 mL/min/1.73m²).

Meeting Unmet Needs in Diabetes Care

Corrects a Novel Pathophysiologic Defect
No Hypoglycemia

Improves Glycemic Control

Implements in Glucose and Weight Support Other CVD Interventions

Complements Action of Other Antidiabetic Agents

Meeting Unmet Needs in Diabetes Care

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“Ultra-Long-Acting” … Better in the Fasting State?

Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism 9
At 16 weeks, IDeg70/30 is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to liraglutide at similar doses with reduced rates (20%) of confirmed nocturnal hypoglycemia (>56 mg/dL). At 26 weeks, IDeg70/30 is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to Detemir with reduced rates (17%) of confirmed nocturnal hypoglycemia (>56 mg/dL); increased weight (1.04 kg) and less injections.

### Comparison of Basal Insulin Analogs

**“Ultra-Long-Acting” ... Better in the Fasting State?**

**Author**
- Mrozdzinska K et al.
- Hirsch B et al.

**Population**
- 1064 T1D patients
- 918 T2D patients

**Intervention**
- Basal insulin analogs
- Basal insulin analogs

**Results**
- Basal insulin analogs:
  - IDeg 900
  - IDetemir per labeling

- Basal insulin analogs:
  - IDeg 600
  - IGlargine

**Comparison**
- IDeg70/30 had more confirmed hypoglycemia (<56 mg/dL).
- IDeg70/30 had significantly lower FPG and lower glycemic control to BIAsp30.
- IDeg70/30 is safe and well tolerated, provides comparable glycemic control to BIAsp30. IDeg70/30 was associated with a significantly lower FPG and lower rate of confirmed overall (96%) and nocturnal hypoglycemia (>56 mg/dL) than BIAsp30.

### Emerging Therapies in Diabetes

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  - Recipe for Disaster with “SGLT2”?

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### Emerging Therapies in Diabetes

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**Dessert**
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GLP-1 Agents in Obesity/Metabolic Syndrome

October 17th 2011
Rick Hess, Pharm.D., CDE, BC-ADM
Assistant Professor, Department of Pharmacy Practice, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, Tennessee

Conflicts of Interest
I have no conflicts of interest to disclose

Objectives
- Review the prevalence of obesity/metabolic syndrome
- Summarize current pharmacotherapy used in the treatment of obesity
- Examine the clinical evidence for the utilization of GLP-1 agonists as pharmacotherapy options in the treatment of obesity/metabolic syndrome

Prevalence

Obesity

- Definition
  - BMI ≥ 30 kg/m²
  - Adults
    - 32.2% men
    - 35.6% women

Metabolic Syndrome

- Definition
  - At least 3 out of 5 risk factors present
  - Waist circumference
  - HTN
  - Hypertriglyceridemia
  - Low HDL
  - Fasting hyperglycemia
  - Adults
    - 35.1% men
    - 32.6% women

Criteria for Clinical Diagnosis of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical cut points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>&gt; 40 inches (102 cm) for males &gt; 35 inches (88 cm) for females</td>
</tr>
<tr>
<td>Elevated triglycerides (Rx for elevated triglycerides is an alternate indicator)</td>
<td>≥150 mg/dL.</td>
</tr>
<tr>
<td>Reduced HDL cholesterol (Rx for reduced HDL cholesterol is an alternate indicator)</td>
<td>&lt;40 mg/dL, for males and &lt;50 mg/dL, for females</td>
</tr>
<tr>
<td>Elevated blood pressure (Rx for elevated blood pressure is an alternate indicator)</td>
<td>Systolic ≥130 mm Hg and/or Diastolic ≥85 mm Hg</td>
</tr>
<tr>
<td>Elevated fasting glucose (Rx for elevated glucose is an alternate indicator)</td>
<td>≥100 mg/dL.</td>
</tr>
</tbody>
</table>

Treatment Overview

Obesity

- Lifestyle changes
- Pharmacotherapy
  - BMI > 30 kg/m²
  - BMI of 27 – 30 kg/m² with comorbid conditions

Metabolic Syndrome

- Lifestyle changes
- Treat individual risk factors
**FDA Approved Anti-Obesity Pharmacotherapy Options**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily Dose (mg)</th>
<th>Average Baseline Characteristics</th>
<th>Mean Weight Loss (months)</th>
<th>Clinical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>60 – 120</td>
<td>Age 55 – 79 men 75 – 300 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>15 – 30</td>
<td>Age 55 – 65 men 80 – 300 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Phentermine</td>
<td>15 – 37.5</td>
<td>Age 25 – 65 men 60 – 250 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>150 – 450</td>
<td>Age 25 – 65 men 70 – 250 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
</tbody>
</table>

**“Off-Label” Anti-Obesity Pharmacotherapy Options**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily Dose (mg)</th>
<th>Average Baseline Characteristics</th>
<th>Mean Weight Loss (months)</th>
<th>Clinical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>60 – 180</td>
<td>Age 55 – 79 men 60 – 300 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100 – 200</td>
<td>Age 55 – 65 men 120 – 300 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Topiramate</td>
<td>175 – 250</td>
<td>Age 25 – 65 men 150 – 250 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
<tr>
<td>Buproprion</td>
<td>300 – 400</td>
<td>Age 25 – 65 men 300 – 400 lb</td>
<td>2.7 kg</td>
<td>Limited</td>
</tr>
</tbody>
</table>

**Obesity**

- Options
  - Limited
    - Safety issues
    - Orlistat withdrawn Oct. 2010
    - Recent investigational agents
      - Orlistat/topiramate withdrawn Oct. 2010
      - Locaterin withdrawn Oct. 2010
      - Naltrexone/bupropion withdrawn Feb. 2011

- GLP – 1 Agonist Therapy in Obesity

  **Effects of Exenatide and Lifestyle**
  **Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Prediabetes**

  Diabetes Care 2010;33:1173 – 1175

- Weight Change in Patients With Diabetes Using GLP – 1 Agonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>GLP – 1 Agonist</th>
<th>Background Therapy</th>
<th>Mean Weight Change from Baseline (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG1</td>
<td>Exenatide 10mcg</td>
<td>Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>ABG2</td>
<td>Exenatide 25mcg</td>
<td>Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 1</td>
<td>Liraglutide 1mg</td>
<td>Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 2</td>
<td>Liraglutide 1mg</td>
<td>Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 3</td>
<td>Liraglutide 1mg</td>
<td>Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 4</td>
<td>Liraglutide 1mg</td>
<td>Metformin + Rosiglitazone</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 5</td>
<td>Liraglutide 1mg</td>
<td>Metformin + Metformin</td>
<td>2.6</td>
</tr>
<tr>
<td>LEAD – 6</td>
<td>Liraglutide 1mg</td>
<td>Metformin + Metformin</td>
<td>2.6</td>
</tr>
</tbody>
</table>

- Rosenstock J, et al.

  - Design
    - 24 week RCT
    - Obese (BMI > 30 kg/m²) subjects
    - Exclusion
      - Diagnosis of T2DM
      - Previous use of glucose-lowering agents > 3 months or
      - Unstable body weight
    - Stratified into subgroups based on OGTT results

  Diabetes Care 2010;33:1173 – 1175
Rosenstock J, et al.

- Design (continued)
  - 1 week single-blind placebo lead in period
  - Randomization
    - Exenatide 5mcg SQ BID x 4 weeks dose initiation period followed by
    - 10mcg SQ BID x 20 weeks or Placebo
  - All participants received structured program of diet
  - and physical activity x 24 weeks
  - Follow-up visit 4 weeks following completion
- Primary end-point
  - Change in body weight

Diabetes Care 2010;33:1173-1175

- Results at week 24
  - Baseline characteristics comparable

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (n = 73)</th>
<th>Placebo (n = 79)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Body Weight (kg)</td>
<td>109.5 ± 2.7</td>
<td>107.6 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Weight loss (kg) @ week 24</td>
<td>5.1 ± 0.5</td>
<td>1.6 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difference in weight reduction (%)</td>
<td>- 3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants experiencing &gt; 5% weight reduction (%)</td>
<td>32</td>
<td>17</td>
<td>0.039</td>
</tr>
<tr>
<td>Daily caloric reduction</td>
<td>- 449 ± 64</td>
<td>- 387 ± 63</td>
<td></td>
</tr>
<tr>
<td>Converted to NGT (%)</td>
<td>77</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Care 2010;33:1173-1175

- Safety
  - No deaths, serious AEs or hypoglycemia reported

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (n = 73)</th>
<th>Placebo (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (%)</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

Diabetes Care 2010;33:1173-1175

- Conclusion
  - Exenatide plus lifestyle changes in obese patients without diabetes was associated with significantly greater reduction in body weight vs. lifestyle changes alone (P < 0.001)
  - Normalization of glucose tolerance and reduced caloric intake favored exenatide therapy

Diabetes Care 2010;33:1173-1175

- GLP – 1 Agonist Therapy in Obesity

Effects of Liraglutide in the Treatment of Obesity: A Randomized, Double-Blind, Placebo-Controlled Study
Lancet 2009;374:1606 – 16

Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism 13
Astrup A, et al.

**Design**
- 20 week multicenter RCT with open label orlistat comparator
- Obese adults (BMI 30 – 40 kg/m²)
  - Stable body weight (<5% change during previous 3 months)
  - Fasting glucose < 126mg/dl
- Exclusion
  - Diagnosis of T1DM or T2DM
  - Use of approved weight-lowering pharmacotherapy within previous 3 months
  - Previous bariatric surgery

**Primary end point**
- Change in body weight
- Proportion of people losing > 5% or >10% of baseline weight

**Results of primary end points at week 20**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Liraglutide Dose (Day)</th>
<th>Mean weight loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2mg</td>
<td>-2.8</td>
</tr>
<tr>
<td></td>
<td>1.8mg</td>
<td>-4.8</td>
</tr>
<tr>
<td></td>
<td>2.4mg</td>
<td>-5.5</td>
</tr>
<tr>
<td></td>
<td>3.0mg</td>
<td>-6.3</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>-7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Liraglutide Dose (Day)</th>
<th>Mean difference (kg) vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2mg</td>
<td>-2.1</td>
</tr>
<tr>
<td></td>
<td>1.8mg</td>
<td>-2.8</td>
</tr>
<tr>
<td></td>
<td>2.4mg</td>
<td>-3.5</td>
</tr>
<tr>
<td></td>
<td>3.0mg</td>
<td>-4.4</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Liraglutide Dose (Day)</th>
<th>% participants who lost &gt; 5% of baseline weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2mg</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td>1.8mg</td>
<td>52.1</td>
</tr>
<tr>
<td></td>
<td>2.4mg</td>
<td>53.3</td>
</tr>
<tr>
<td></td>
<td>3.0mg</td>
<td>60.8</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>76.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Liraglutide Dose (Day)</th>
<th>% participants who lost &gt; 10% of baseline weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2mg</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>1.8mg</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>2.4mg</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>3.0mg</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>28.3</td>
</tr>
</tbody>
</table>

**Safety at week 20**
- No significant effects on serum calcitonin concentrations
- No events of acute pancreatitis reported

**Metabolic Syndrome**

**Prediabetes**

---
Astrup A, et al.

**Conclusion**
- Liraglutide therapy along with a caloric-restricted, low-fat diet and exercise program leads to clinically relevant and dose-dependent weight loss
  - Significantly greater (at all doses) vs. placebo
  - Significantly greater at daily dose of 2.4mg and 3.0mg vs. orlistat
- More than 50% of participants treated with liraglutide achieved 5 – 10% weight reduction
- Positive effects on other cardiovascular disease risk factors

Lancet 2009;374:1606-16

---

Should GLP-1 Agonists Be Used to Treat Obesity?

**Pros**
- GLP – 1 agonists appear effective for weight loss in obese patients without diabetes
- Positive effects on
  - Cardiovascular disease risk factors
  - Prediabetes/metabolic syndrome

**Cons**
- Gastrointestinal effects & safety concerns
- Costs
- Injectable dosage form
- Long-term risk/benefit unknown

---

**Questions?**
The use of metformin in diabetic patients with chronic kidney disease.
Marissa Quinones, Pharm.D.
Clinical Pharmacy Specialist
Parkland Health and Hospital Southeast Dallas Health Center

Objectives
• Review the history and contraindications of metformin in patients with chronic kidney disease.
• Evaluate the current literature regarding the use of metformin in patients with chronic kidney disease.
• Provide recommendations for the use of metformin in chronic kidney disease.

History of Metformin
• In the 1970’s, phenformin removed due to cases of lactic acidosis
• Metformin released for use in the U.S. in 1995
• Metformin – used widely as a 1st line agent in treatment of Type 2 diabetes

Advantages and Disadvantages of Metformin
• Advantages
  – Great & Old Drug
  – No hypoglycemia
  – Weight loss
  – Reduces mortality and morbidity in Type 2
  – Decreases microvascular and macrovascular risk
  – Other benefits
    – ALc lowering 1.5-2%
    – Used in PCOS/Prevention of DM
• Disadvantages
  – Adverse events
    • GI upset (N/V/D)
  – Elimination unchanged in the kidney
  – Contraindications
    • SCr ≥ 1.4 mg/dL (males);
    ≥ 1.5 mg/dL (males)
  – Cases of lactic acidosis (rare)
    • Risk is minimal

Metformin and Renal Impairment

Comparison of Tmax and Cmax for Metformin in Type 2 DM and Renal Impairment

Table taken from: Glucophage® package insert.

Metformin and Kidney Disease

The Problem
decreased renal impairment / CrCl decreases =
  decreased renal clearance
  = metformin accumulation
  = concerns for lactic acidosis

What do we do?
What do the guidelines say?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA Guidelines</td>
<td>Contraindicated in renal dysfunction. Safe unless GFR falls to &lt;30ml/min</td>
</tr>
<tr>
<td>GluconPage® Package insert</td>
<td>Renal disease or renal dysfunction - GFR ≥ 1.4 (female), ≥ 1.5 (male) – or abnormal CrCl. Need to monitor closely in those with renal disease and elderly. No real guide regarding CrCl cut off.</td>
</tr>
<tr>
<td>FDA</td>
<td>Serum creatinine ≥ 1.4mg/dl in women and 1.5mg/dl in men or decreased clearance in people over 80.</td>
</tr>
<tr>
<td>KDOQI Guidelines</td>
<td>Serum creatinine of 15mg/dl or greater in men and 15mg/dl or greater in women. “...it is cleared by the kidney and may build up with even modest impairment of kidney function, putting patients at risk of lactic acidosis.”</td>
</tr>
</tbody>
</table>

Review by Herrington and Levy 2008

“Metformin: effective and safe in renal disease?”

<table>
<thead>
<tr>
<th>Guideline/Paper</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>British National Formulary (BNF)</td>
<td>Warning not to use metformin in mild renal impairment (GFR 20-59ml/min)</td>
</tr>
<tr>
<td>Jones, et. al.</td>
<td>SCR absolute cut off point of 1.7mg/dl; use caution in elderly</td>
</tr>
<tr>
<td>Canadian Pharmacists Association</td>
<td>GFR ≥ 1.5 in males and ≥ 1.4 females; caution in advanced age (&gt;80) unless CrCl not reduced.</td>
</tr>
<tr>
<td>McCormack, et. al.</td>
<td>Acknowledged problem with use of Scr alone; use CrCl based on PK principles reduce the max dose of metformin by 50% when CrCl decreases &lt;60ml/min</td>
</tr>
<tr>
<td>Nisbet, et.al.</td>
<td>Use Cockcroft Gault; absolute cut off GFR of 30ml/min (discontinue metformin); GFR 30-50ml/min extreme caution</td>
</tr>
</tbody>
</table>

Herrington and Levy 2008

- Recommend
  - Stage 1 - 2 (GFR 60 – 90 ml/min): continue but may reduce starting dose of metformin by 50%
  - Stage 3 (GFR 30 – 60 ml/min): then further reduce metformin dose by another 50%
  - Stage 4 (GFR < 30 ml/min): do not use
- Once pt reaches Stage 3 we must consider the risk versus the benefit
- AND NEED TO CAREFULLY MONITOR

Lipska, et. al.

<table>
<thead>
<tr>
<th>Proposed recommendations for use of Metformin based on eGFR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR level</td>
<td>Action</td>
</tr>
<tr>
<td>&lt;60</td>
<td>No renal contraindication to metformin</td>
</tr>
<tr>
<td></td>
<td>Monitor renal function annually</td>
</tr>
<tr>
<td>≥60 and &lt; 45</td>
<td>Increase monitoring of renal function (every 3-6 months)</td>
</tr>
<tr>
<td></td>
<td>Prescribe metformin with caution</td>
</tr>
<tr>
<td>≥45 and &lt; 30</td>
<td>Use lower doses (e.g., 50% or half-maximal dose)</td>
</tr>
<tr>
<td></td>
<td>Closely monitor renal function (every 3 months)</td>
</tr>
<tr>
<td></td>
<td>Do not start new patients on metformin</td>
</tr>
<tr>
<td>≥30</td>
<td>Stop Metformin</td>
</tr>
</tbody>
</table>

Conclusion

- The data is lacking
- Lack of studies using metformin with renal impairment
- No good evidence base
- Use of SCr versus CrCl?
  - Cockcroft Gault versus MDRD
- Must consider risk versus benefit

Questions

Marissa E. Quinones, Pharm.D.
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Community Oriented Primary Care Clinic
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E-mail: marissa.quinones@phhs.org
Office: 214-266-1738
Pager: 214-786-4875
Objectives

At the conclusion of this presentation, the participant will be able to:

- write a brief description of the evidence that glycemic variability is an independent risk factor for cardiovascular disease
- write a brief description of the mechanism by which glycemic variability can result in oxidative stress
- discuss at least three variables which may affect the pathophysiology of oxidative stress
- discuss the studies that do not support glycemic variability and pathology including at least one methodologic flaw in each study.

Disclosures:

- Education Program consultant; LifeScan, Animas and J&J Diabetes Institute
- Stockholder; Johnson & Johnson

Relationship Between Increasing A1C and Retinopathy

… it all started with an article in Diabetes in 1995
Numerous Studies on PPG/PCG and CV Risk

Standl E, Schnell O, Ceriello A. Diabetes Care 2011;34 (Suppl 2):S120

Other observations...

Esposito K, et al J Clin Endocrinol Metab 2008;93:1345
Incremental glucose peaks are frequent… occur for most (95%) within 1 h after meal, timing of IGPs is not influenced by treatment (diet or drugs), and IGPs correlate with CIMT

Egi M, et al Anesthesiology 2006;105:244
The SD of glucose concentration is a significant independent predictor of ICU and hospital mortality

Glycemic variability in NGT, IGR and T2DM

Variability of Blood Glucose Results in Type 1 and Type 2 Diabetes

• N=277 T1DM, and 323 T2DM
• Avg of 230 SMBG and 3 A1c readings over 3 months
• Calculated indices of of hypo- and hyperglycemic episodes

Glucose excursions in ‘stable’ patients with type 2 diabetes on oral agents

“So many measures, I just can’t count them all…”


2011 ACCP Annual Meeting

Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
So how might variability affect processes we know are involved in complications?

• Glycolysis (Embden-Meyerhoff)
  - Takes the 6 carbon sugar and breaks it into three carbon chunks

• Krebs (Citric Acid) Cycle
  - Takes 3 carbon chunks breaks them down for energy, storing excess as fatty acids through lipogenesis

The Point of all this... Making H’s

Superoxides occur in other ways...

The excess O\textsubscript{2}\textsuperscript{-} combines with NO resulting in production of other oxidative intermediates
Superoxides and Insulin Release

- Insulin release requires energy in the form of ATP
- ATP comes from glucose metabolism.
- Increased superoxide from excess glucose results in less energy (ATP) from glucose and decreases insulin release


The pancreas is a target of glucotoxicity

Damage to the pancreas from “glucotoxicity” results in deposition of amyloid replacing viable insulin producing cells with amyloid deposits. This is the basis of the progressive nature of type 2 diabetes.


Glucose fluctuations and cell damage in experimental cell cultures

- Human umbilical vein endothelial cells were incubated in 5 mmol or 20 mmol or alternating 5 and 20 mmol/L solutions of glucose and then tested for markers of cell damage.
- At 7 days and 14 days, there were significantly more damaged cells with the higher glucose concentration and even more damaged cells when the glucose was alternated between 5 and 20 mmol/L each day.


Variability in glucose is associated with oxidative stress...

- Nitrotyrosine (NT) and 8-OH deoxyguanosine (8OHDG) are markers of oxidative stress.
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days.
- NT and 8OHDG levels are higher when glucose fluctuates between 5mmol/L and 20mmol/L than when held at 20mmol/L at 7 and 14 days.


...and with increased cytokines and adhesion molecules

- Cytokines are a group of proteins that regulate the immune system, many are pro-inflammatory.
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days.
- All the cytokines measured were higher when the glucose was varied between 5mmol and 20mmol than when the solution was held at a constant 20 mmol.

Piconi L. et al, J Thrombosis and Haemostasis 2004;2:1453

...and with increased levels of Protein Kinase-C

- Protein Kinase C (PKC) is a molecule that appears to be central to activation of a number of processes of cell damage.
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days.
- PKC levels were increased more when glucose was varied from 5mmol to 20mmol than when held at 20mmol.

This increased oxidative stress has now been demonstrated in people with diabetes

- Twenty one patients were studied with urinary excretion rates of 8-iso-prostaglandin F2α (a marker of oxidative stress)
- Glucose fluctuations were monitored with CGMS, and calculations of Mean Amplitude of Glycemic Excursions (MAGE)
- “Glucose fluctuations during postprandial periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia”

Monnier, et al. JAMA 2006;295:1681

All this from transient glucose spikes after meals?

Nitrosative stress, oxidative stress and superoxide dismutase

Differential effects of components of oxidative stress

When is a spike not a spike?

Is there controversy about the importance of glycemic variability?

“In summary, the observations reported here show that transient hyperglycemia causes persistent atherogenic effects during subsequent normoglycemia by inducing long-lasting changes in chromatin remodeling, recruitment of the histone methyltransferase Set7, and increased H3K4 monomethylation in the proximal NF-κB promoter, leading to increased expression of p65, MCP-1, and VCAM-1.”


“Kilpatrick and others used DCCT 7-point profiles to assess glycemic variability.
- With that data, they have been unable to connect glycemic variability with outcomes
- They HAVE connected A1C variability with complications
- Other authors have connected glucose variability with A1C variability
- SOOoooo...what about the DCCT dataset?”
Variability and oxidative stress in T1DM

• Patients with type 1 diabetes have higher levels of urinary 15(S)-8-iso-PGF2α than healthy controls, suggesting that in addition to glucose variability, other factors favouring oxidative stress may exist.
• There is no relationship between glucose variability and urinary 15(S)-8-iso-PGF2α.

Wentholt IME, et al. Diabetologia 2008;51:183

What affects oxidative stress from glycemic variability?

“We did not find a relevant relationship between glucose variability and 15(S)-8-iso-PGF2α excretions in T2DM patients well-regulated with oral medication that would support an interaction between hyperglycemia and glucose variability with respect to the formation of reactive oxygen species.”

A re su l t oxides the onl y py problem?

Relationship between glucose variability and hypoglycemia

Take Home Messages

• Chronic elevations of glucose produce toxicity to major end organs; oxidative stress and superoxides are major components of glucoxicity.
• Glucose excursions may be significant in glucose toxicity as their effects last longer than the excursion.
• Lowering variability should be a therapeutic goal.
• What we still don’t know:
  - Is the degree or the frequency of elevations that makes a difference?
  - What is the best variability index?
  - How much weight should variability be given vs. A1C (or in combination)?
  - If we are trying to control variability, what does success look like?
U-500: Appropriate Use and Common Pitfalls
Jessica Tompeter, Pharm.D.

Objectives

- Recognize the role of U-500 insulin in the treatment of severe insulin resistance.
- Summarize a dosing scheme for initiation and titration of U-500 insulin.
- Evaluate the safety and educational barriers associated with initiating U-500 insulin and discuss potential solutions.

Conflicts of Interest

No conflict of interest to declare

Use of U-500 insulin

- Reserved for:
  - Insulin receptor defects
  - Insulin receptor autoantibodies
  - Endocrine disorders associated with insulin resistance
  - Severe insulin resistance
    - >200 units of insulin daily

Efficacy of U-500 insulin

- Based on case series
  - A1C reduction ~1.6%
    - Some case reports reduction >2%

- Benefits:
  - Decreased volume
  - Cost effective

U-500 insulin

- "Concentrated"

<table>
<thead>
<tr>
<th>PK profile</th>
<th>Nonobese subjects</th>
<th>Obese subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>30 minutes</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Peak PD action</td>
<td>3.5-4.5 hours</td>
<td>7-8.5 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>6-10+ hours</td>
<td>11.5 hours</td>
</tr>
</tbody>
</table>

Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
Dosing: Initiation U-500 insulin

Total Daily Dose 150-300 units
- Before breakfast and dinner: 50/50 or 60/40
- Before meals: 33/33/33

Total Daily Dose 300-600 units
- Before breakfast and dinner: 50/50 or 60/40
- Before meals: 33/33/33
- Before meals and bedtime: 30/30/30/10

Total Daily Dose > 600 units
- Four times daily: 30/30/30/10

References

CLINICAL DEBATE:
ADA ALGORITHM VERSUS AACE ALGORITHM FOR TYPE 2 DIABETES MELLITUS

TRICIA M. RUSSELL, PHARM.D., BCPS, CDE
CRAIG LOGEMANN, PHARM.D., BCPS, CDE

MONDAY, OCTOBER 17, 2011
CONVENTION CENTER, ROOMS 315 & 316

Conflict of Interest Disclosure

Dr. Russell has no conflicts of interest to disclose.

Objectives

- Review the advantages of recommending an A1c goal of <7% for the management of type 2 diabetes according to the ADA treatment algorithm.
- Identify any concerns with the AACE treatment algorithm glycemic goal of A1c of ≤6.5%.
- Discuss the benefits of initiating metformin as a preferred treatment early in the management of type 2 diabetes.

Background

- American Diabetes Association (ADA) Diabetes Guidelines
  - Clinical Practice Recommendations – Jan 2011 (annually)
  - Consensus Algorithm on Medical Management of Type 2 DM: (ADA/European Association for the Study of Diabetes [EASD]) – Jan 2009
    - 7 authors (clinicians and clinical investigators)

Treatment Goals

<table>
<thead>
<tr>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c (%)</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>70-130</td>
</tr>
<tr>
<td>Postprandial plasma glucose* (PPG in mg/dL)</td>
<td>&lt;180</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>&lt;100 (&lt;70 if CHD)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>&gt;40 for men &gt;≥50 for women</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>&lt;150</td>
</tr>
</tbody>
</table>

*PPG glucose measurements should be made 1-2 h after beginning meal.
*Highest risk = DM plus CVD and high risk = DM without CVD.
ADA: Current Glycemic Recommendations

Table 10—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C: ≤6.5% is treatment goal
- Individualize on basis of age, comorbidities, duration of diabetes; in general ≤6.5 for most; closer to normal for healthy; less stringent for "less healthy"

AACE/ACE Current Glycemic Recommendations

- A1c ≤6.5% is treatment goal

Glycemic Control: Reviewing Known Evidence

DCCT (Type 1 DM)
Kumamoto Study (Type 2 DM)
UK Prospective Diabetes Study (UKPDS) (Type 2 DM)

"Improved glycemic control...decreases microvascular complications."

ADA DM Treatment Algorithm

Intensive Glucose Lowering/Cardiovascular Outcomes ACCORD: Long-Term Follow-up

- Randomized, Open-Label, Controlled, Intention to Treat Study
- 10,251 patients with diabetes (mean A1c: 8.1%) received:
  - Intensive Therapy: Target A1c: <6.0% (N=5128)
  - Standard Therapy: Target A1c: 7.0-7.9%(N=5123)

- Outcomes Measured – Five Years
  - Primary: Composite of Nonfatal MI, Nonfatal Stroke, or Death from CV Causes
  - Secondary: All-Cause Mortality

ACCORD Study Update

- Outcomes: Intensive vs Standard Therapy

Intensive Glucose Lowering-Cardiovascular Outcomes ACCORD Study Update


A rapid clinical pearls and a clinical debate in endocrinology and metabolism.
Concerns with AACE Treatment Algorithm A1c goal ≤6.5%

- Insufficient evidence of CV and mortality benefit with intensive glycemic control compared to standard glycemic control.
- Increased risk of hypoglycemia with intensive glycemic lowering compared to standard glycemic lowering.

Severe Hypoglycemia Rates in Recent Trials

ACCORD: annual incidence of hypoglycemia:

<table>
<thead>
<tr>
<th></th>
<th>ACCORD (%)</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive glycemic control arm</td>
<td>16.2%</td>
<td>2.7%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Standard glycemic control arm</td>
<td>5.1%</td>
<td>1.5%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

Benefits of Initiating Metformin Early

- Treats insulin resistance
- Evidence
  - UKPDS 43
  - 10-year follow-up study (UKPDS 80)
    - Significant risk reduction continued for diabetes-related endpoint (21%), MI (33%), and mortality (27%)
  - REACH
    - Mortality rates: 6.3% metformin vs. 9.3% without metformin
- Tolerable
- Inexpensive

UKPDS 10-yr Follow-up Any Diabetes-Related End Point

UKPDS 10-yr Follow-up Myocardial Infarction

UKPDS 10-yr follow-up Death from Any Cause
ADA Treatment Algorithm Pros - Conclusions

- ADA treatment algorithm is evidence-based and practical.
- A1c goal <7% appropriate in majority of patients based on current evidence.
- Metformin preferred starting therapy for patients – effective, safe and inexpensive compared to other therapies.
- ADA algorithm provides rapid titration and addition of other therapies if needed.

Conflict of Interest Disclosure

- Dr. Logemann has no conflicts of interest to disclose.

Objectives

- Review the advantages of recommending an A1c goal of ≤6.5% for the management of type 2 diabetes according to the AACE treatment algorithm.
- Identify any concerns with the ADA treatment algorithm glycemic goal of A1c of <7%.
- Discuss the benefits of initiating other medications besides metformin as monotherapy options, such as thiazolidinediones, DPP-4 inhibitors, incretin mimetics or alpha-glucosidase inhibitors.

Background

Statement by an American Association of Clinical Endocrinologists / American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control

- Published in Endocrine Practice 2009; Vol 15(6):541-9.
- 12 Authors (clinicians and clinical investigators, both academicians and practitioners)
Things that are in common with the ADA Guidelines

- Lifestyle modification important
- A1c target should be customizable based on other patient factors
- Metformin considered cornerstone of therapy
- Choose agents with different mechanism of action when adding therapy

Things that are different from the ADA Guidelines

- **A1c goal (for most patients):**
  - AACE: < 6.5
  - ADA: < 7.0
- **Initial therapy:**
  - AACE: More choices listed (Metformin, TZD, DPP-4 inhibitors, incretin mimetics & alpha-glucosidase inhibitors)
  - ADA: Metformin listed as primary choice
- **A1c stratification:**
  - AACE: Categorizes treatment choices based on initial A1c (6.5-7.5%, 7.6-9.0%, >9.0%)
  - ADA: No specific breakdown for treatment choices, unless initial A1c >10% (severe hyperglycemia)
- **Sulfonylurea use:**
  - AACE: Lower priority given to this class when dual or triple therapy warranted
  - ADA: Considered a "well-validated" core therapy as an add-on medication

**AACE/ACE Algorithm (Simplified)**

<table>
<thead>
<tr>
<th>A1c 6.5 – 7.5%</th>
<th>A1c 7.6 – 9.0%</th>
<th>A1c &gt; 9.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>Dual Therapy</td>
<td>Insulin ± other agents</td>
</tr>
<tr>
<td>Metformin (primary choice) or DPP-4 or GLP-1 or TZD or AGI</td>
<td>Metformin + 1 other agent</td>
<td>Insulin ± other agents</td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td>Or Metformin + 1-2 other agents</td>
</tr>
</tbody>
</table>

**AACE: Why more initial choices for monotherapy?**

- Metformin is considered the preferred initial agent by AACE
- Other options listed in the guidelines:
  - DPP-4: if 1PPG and ↑ FPG
  - GLP-1: if ↑ 1 PPG
  - TZD: if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
  - AGI: if 1PPG

**AACE: Why more initial choices for monotherapy?**

- **DPP-4 Inhibitors:** Good safety profile; low risk of hypoglycemia; no weight gain
- **GLP-1 Analogs:** Added benefit of wt loss to assist with other metabolic disorders; sustained glycemic control
- **TZD’s:** Low risk of hypoglycemia; sustained glycemic control; efficacy with prediabetes
- **α-Glucosidase inhibitors (Acarbose & Miglitol):** Decrease post-prandial hyperglycemia

**Impaired Insulin Secretion**

<table>
<thead>
<tr>
<th>Increased Lipolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D’s</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
</tr>
<tr>
<td>Sulfonylureas</td>
</tr>
</tbody>
</table>

**Increased Hepatic Glucose Production**

<table>
<thead>
<tr>
<th>Decreased Glucose Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D’s</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
</tbody>
</table>

**Adapted from Am J of Med 2010;123:S38-48.**

Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
AACE: Why A1c goal < 6.5 for majority of patients?

- Meta-Analysis of 5 trials (n=33,040)
  - UKPDS, PROactive, ADVANCE, VADT, ACCORD
    - Intensive Treatment vs. Standard Treatment
      - Mean A1c at follow-up (6.6% vs. 7.5%)
      - 17% reduction in non-fatal MI
        - (odds ratio 0.83, 95% CI 0.75-0.93)
      - 15% reduction in CAD events
        - (odds ratio 0.85, 95% CI 0.77-0.93)
      - No difference in overall mortality
        - (odds ratio 1.02, 95% CI 0.87-1.19)


AACE: Why A1c goal ≤ 6.5% for majority of patients?

- ADVANCE Study (NEJM 2008;358:2560-72)
  - n=11,140; Median duration of 5 yrs. Baseline A1c=7.5%. f/u A1c=6.5% (intensive) and 7.3% (standard)
  - Benefits of intensive treatment
    - Delayed onset of microalbuminuria
      [HR=0.91; 95% CI=0.85-0.98; p=0.02]
    - Decreased incidence of nephropathy
      [HR=0.79; 95% CI=0.66-0.93; p=0.01]

AACE: Why Sulfonylureas less favored?

- ADOPT Study (NEJM 2006;355:2427-43)
  - Rosiglitazone vs. Metformin vs. Glyburide Monotherapy.
  - N=4360 Newly Diagnosed Type 2 Diabetics
  - Median Duration of treatment = 4 yrs
  - Failure rate at 5 yrs
    - 15% ROSI vs. 21% METF vs. 34% GLYB
  - Concern: Progressive loss of β cell function with SU’s compared to insulin sensitizers


"...many of the agents (especially the sulfonylureas and insulin) currently used are associated with hypoglycemia and weight gain. Given our increased knowledge regarding the pathophysiology of type 2 diabetes and the role of β-cell dysfunction, a more targeted approach is warranted."
ADA vs. AACE/ACE DM Treatment Algorithm

- ADA recommends A1c <7% vs. A1c ≤ 6.5% (AACE/ACE).
- Clinical trials did not find improved CV mortality and all-cause mortality.
- Increase in hypoglycemia.
- Recent meta-analysis results show minimal benefits of intensive glucose lowering compared to standard glucose lowering on all-cause and CV mortality.

Intensive Glucose Lowering - Vascular Outcomes - ADVANCE

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=2,032)</th>
<th>Standard Control (N=2,032)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined major macrovascular and microvascular events</td>
<td>191 (9.4)</td>
<td>214 (10.5)</td>
<td>0.95 (0.78-1.14)</td>
<td>5% (0.04-10.68)</td>
</tr>
<tr>
<td>Major macrovascular events</td>
<td>137 (6.8)</td>
<td>138 (6.8)</td>
<td>1.02 (0.74-1.41)</td>
<td>2% (0.02-10.41)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>234 (1.2)</td>
<td>279 (1.3)</td>
<td>0.82 (0.72-0.93)</td>
<td>18% (0.11-0.29)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>135 (0.7)</td>
<td>179 (0.9)</td>
<td>0.76 (0.65-0.87)</td>
<td>23% (0.13-0.39)</td>
</tr>
<tr>
<td>Major microvascular events</td>
<td>289 (1.4)</td>
<td>283 (1.4)</td>
<td>1.04 (0.86-1.25)</td>
<td>6% (0.04-0.20)</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>792 (4.3)</td>
<td>782 (4.1)</td>
<td>1.02 (0.95-1.08)</td>
<td>2% (0.02-0.17)</td>
</tr>
<tr>
<td>New or worsening retinopathy</td>
<td>172 (8.5)</td>
<td>179 (8.7)</td>
<td>1.02 (0.91-1.14)</td>
<td>2% (0.02-0.17)</td>
</tr>
</tbody>
</table>

Meta-analysis of intensive glucose lowering vs. standard glucose lowering

- To determine all-cause mortality and CV mortality related to intensive glucose lowering in patients with Type 2 DM.
- 13 RCT studies (34,533 patients)
- Results:
  - Intensive glucose lowering did not significantly affect all-cause mortality (risk ratio 0.94, CI 0.91-1.19) or CV mortality (risk ratio 1.11, 0.86-1.43).
  - Reductions in non-fatal MI (0.85, 0.74-0.96, P<0.001) and microalbuminuria (0.90, 0.85-0.96, P<0.001)
  - 2-fold increase in severe hypoglycemia (2.33, 2.16-2.36, P<0.001)

Meta-analysis of intensive glucose lowering vs. standard glucose lowering - continued

- Over 5 years,
  - NNT to avoid 1 MI: 117-150
  - NNT to avoid 1 episode of microalbuminuria: 32-142
  - NNH: for every 15-52 patients treated, one severe episode of hypoglycemia would occur
  - Analysis of high-quality studies performed (Jadad score >3)
  - Intensive treatment not associated with significant risk reductions
  - 47% increased risk of CHF
AACE/ACE Algorithm (Simplified)

Lifestyle Modification

- **A1c 6.5 – 7.5%**
  - Monotherapy
    - Metformin (primary choice) or DPP-4 or GLP-1 or TZD or AGI
  - Dual Therapy
    - Metformin + 1 agent
    - Insulin + Lifestyle Modification

- **A1c 7.6 – 9.0%**
  - Monotherapy
    - Dual Therapy
      - Metformin + 2 other agents
  - Triple Therapy
    - Insulin + 2 other agents
    - Or
    - Metformin + 1-2 other agents

- **A1c > 9.0%**
  - Triple Therapy
    - Metformin + 2 other agents
    - Insulin + other agents
    - Or
    - Metformin + 1-2 other agents

Why metformin preferred initial agent compared to other therapies?
- Metformin preferred first-line treatment
  - Efficacy
  - Safety
  - Cost
- AACE Treatment Algorithm
  - Recommends metformin as preferred agent, but other therapies as well
  - Less evidence/clinical use
  - Branded name medications

ADA's Glycemic Control Recommendations

- **Goal A1C = < 7%**
  - Lower microvascular/neuropathic complications
  - Implement soon after diagnosis for macrovascular benefits
- **Stringent A1C Goal**
  - Benefits: Microvascular benefits
  - Who?:
    - Short duration of diabetes
    - Long life expectancy
    - No significant CVD
    - Low hypoglycemia risk

- **Less Stringent A1C Goal**
  - Who?:
    - Severe hypoglycemic episodes
    - Limited life expectancy
    - Advanced microvascular or macrovascular complications
    - Extensive comorbid conditions
    - Having longstanding DM

Cochrane Review:
Targeting Intensive Glycemic Control vs. Conventional Glycemic Control for Type 2 DM

"There is insufficient evidence to demonstrate whether targeting intensive glycemic control influences all-cause or CV mortality. Intensive glycemic control is likely to reduce microvascular disease as a composite outcome and may reduce occurrence of specific patient outcomes such as non-fatal MI and lower extremity amputation. It increases risk of severe adverse events (e.g., hypoglycemia). The A1c must be evaluated individually for different patients and should take both benefits and harms into account."


Glycemic Control Conclusions

- Guidelines are guidelines!
  - Guidelines vary
  - Overall goal is to ensure appropriate patient care
  - Treat the individual patient! 
Rebuttal

Why AACE algorithm preferred?

Concerns with setting the A1c goal < 7 for majority of patients
- Lack of aggressive treatment during early stages of Type 2 DM
  - Importance of maintaining β-cell function
- Clinical inertia: Delayed response to elevated A1c levels especially during early stages of T2DM
  - Less emphasis in ADA guidelines about dual therapy at time of diagnosis
- Applying findings in the ACCORD study to the universe of T2 DM patients

Clinical inertia

AACE: Why A1c stratification important?
- Secondary Failure of Metformin Monotherapy in Clinical Practice

<table>
<thead>
<tr>
<th>Baseline A1c</th>
<th>Failure rate per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7%</td>
<td>12.3% (10.5-14.4)</td>
</tr>
<tr>
<td>7 - 7.9%</td>
<td>17.6% (15.7-20.1)</td>
</tr>
<tr>
<td>8 - 8.9%</td>
<td>19.2% (16.2-22.8)</td>
</tr>
<tr>
<td>&gt;=9.0%</td>
<td>19.4% (16.8-22.4)</td>
</tr>
</tbody>
</table>

Clinical inertia may be simply defined as failure to intensify treatment of a patient who is not at their evidence-based HbA1c goal.

Improving Diabetes Care by Combating Clinical Inertia

AACE: Why A1c stratification important?
- Benefits: Emphasis placed on achieving improved glucose control rapidly to help preserve β-cell function.
  - The higher the baseline A1c, the greater the risk of secondary failure of Metformin monotherapy.

Kaiser Permanente Northwest (KPNW) database
- Observational study n=1799 Type 2 DM patients who lowered their A1c<7.0 using Metformin monotherapy.
- 42% of 1,799 patients who achieved A1c < 7% with the initiation of metformin monotherapy experienced secondary failure within a 2- to 5-year follow-up

Diabetes Care 2010;33:501-6.

Final Comments
- Cochrane Review
  - “Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings.”

Questions