Managing the Risk of Hypoglycemia in the Patient with Type 2 DM

SPEAKERS
Frank Lavernia, MD
Dace Trence, MD, FACE

Lunch Symposium
12–1:30pm

Learning Objectives
• Assess the results and explain the clinical implications of ACCORD, ADVANCE, and VADT studies
• Identify risk factors that are associated with hypoglycemia in patients with type 2 diabetes and the importance of individualized glycemic targets
• Describe special patient groups who are at an increased risk of adverse outcomes due to hypoglycemia
• Outline currently available antihyperglycemic agents that do not promote hypoglycemia
• Devise regimens that employ complementary antihyperglycemic agents to optimize glycemic control while minimizing hypoglycemia risk in patients with type 2 diabetes

Lessons From Intensive Control Trials

Natural History of Type 2 Diabetes

Long-term Complications of Diabetes

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Dr. Lavernia is on the advisory board for Janssen, Eisai, and Eli Lilly.
► Dr. Trence is a grant recipient of Eli Lilly and stock owner of Sanofi.

Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
### Intensive Glucose Control Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT¹</td>
<td>1,441</td>
<td>Comparison of the effects of standard control of blood glucose versus intensive control on the complications of diabetes in T1DM</td>
</tr>
<tr>
<td>UKPDS²</td>
<td>3,867</td>
<td>Long-term prospective RCT of intensive vs conventional glycemic control in newly diagnosed patients with T2DM</td>
</tr>
<tr>
<td>ACCORD³</td>
<td>10,251</td>
<td>Multicenter randomized study of intensive vs less-intensive glycemic control using any treatment regimen</td>
</tr>
<tr>
<td>ADVANCE⁴</td>
<td>11,140</td>
<td>Multicenter study comparing intensive blood pressure and glycemic control vs less intensive blood pressure and glycemic control</td>
</tr>
</tbody>
</table>


### Glycemic Control & Vascular Complications in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Gender (% males)</th>
<th>Age (yrs)</th>
<th>Diabetes duration (yrs)</th>
<th>Baseline A1C (%)</th>
<th>CV events (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD¹</td>
<td>10,251</td>
<td>62</td>
<td>62</td>
<td>10</td>
<td>8.1</td>
<td>54</td>
</tr>
<tr>
<td>ADVANCE²</td>
<td>11,140</td>
<td>58</td>
<td>66</td>
<td>8</td>
<td>7.5</td>
<td>45</td>
</tr>
<tr>
<td>UKPDS³</td>
<td>1,791</td>
<td>97</td>
<td>60</td>
<td>11.5</td>
<td>7.1</td>
<td>45</td>
</tr>
<tr>
<td>VADT⁴</td>
<td>4,209</td>
<td>61</td>
<td>60</td>
<td>10</td>
<td>7.1</td>
<td>45</td>
</tr>
</tbody>
</table>

CV = cardiovascular; CI = confidence interval

### Baseline Characteristics of the Landmark Trials in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Gender (% males)</th>
<th>Age (yrs)</th>
<th>Diabetes duration (yrs)</th>
<th>Baseline A1C (%)</th>
<th>CV events (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS²</td>
<td>3,867</td>
<td>58</td>
<td>66</td>
<td>8</td>
<td>7.5</td>
<td>45</td>
</tr>
<tr>
<td>ACCORD³</td>
<td>10,251</td>
<td>97</td>
<td>60</td>
<td>11.5</td>
<td>7.1</td>
<td>45</td>
</tr>
<tr>
<td>ADVANCE⁴</td>
<td>11,140</td>
<td>61</td>
<td>60</td>
<td>10</td>
<td>7.1</td>
<td>45</td>
</tr>
<tr>
<td>VADT⁵</td>
<td>1,791</td>
<td>61</td>
<td>60</td>
<td>11.5</td>
<td>7.1</td>
<td>45</td>
</tr>
</tbody>
</table>

CV = cardiovascular; CI = confidence interval

### Risk of CV Events and Death in Patients with Versus without Severe Hypoglycemia (ADVANCE)

<table>
<thead>
<tr>
<th>Study Inclusion Criteria: T2DM + Major Vascular Disease or ≥1 CV Risk Factor</th>
<th>Macrovascular Events: Relative Risk Reduction (95% CI)</th>
<th>Mortality: Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.45 (2.34, 5.08); p&lt;0.001</td>
<td>3.30 (2.31, 4.72); p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>3.78 (2.34, 6.11); p&lt;0.001</td>
<td>2.86 (1.67, 4.90); p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

CV = cardiovascular; CI = confidence interval

### ADGCE Outcomes: A Closer Look Shows Glycemic Control Benefit

<table>
<thead>
<tr>
<th>Combined Primary Outcomes: Major Macro or Microvascular Event</th>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk Reduction</td>
<td>10%</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Relative Risk Reduction
14%
p=0.015

ADVANCE: Impact on Microvascular Events

Major Microvascular Events

Cumulative Incidence (%)
5 15 20 25 66 10
Follow-up (months)
48 36 60 30 54 18 42 12 6 24

Standard Intensive


Intensive glycemic control generally reduces microvascular risks, but its role in reducing macrovascular risks has been more controversial.
A1C targets of 6.5%-7.0% per se do not increase mortality
A1C alone may be a misleading indicator of glycemic control in some patients because rates of protein glycation vary
Severe hypoglycemia can occur even in patients with elevated A1C
Severe hypoglycemia rates may increase with increasing A1C
Severe hypoglycemia can be difficult, serious, and life-threatening

Lessons Learned from DCCT, UKPDS, ACCORD, ADVANCE

Severe hypoglycemia can occur even in patients with elevated A1C
Severe hypoglycemia rates may increase with increasing A1C
Severe hypoglycemia can be difficult, serious, and life-threatening

Intensive glycemic control generally reduces microvascular risks, but its role in reducing macrovascular risks has been more controversial.
A1C targets of 6.5%-7.0% per se do not increase mortality
A1C alone may be a misleading indicator of glycemic control in some patients because rates of protein glycation vary
Severe hypoglycemia can occur even in patients with elevated A1C
Severe hypoglycemia rates may increase with increasing A1C
Severe hypoglycemia can be difficult, serious, and life-threatening

Setting the Appropriate Glycemic Target

Normoglycemia and Recommended Glycemic Targets in T2DM

<table>
<thead>
<tr>
<th>Glucose Control</th>
<th>Healthy Individuals1-3</th>
<th>ADA 20101</th>
<th>ADA &amp; AACE 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial PG, mg/dL</td>
<td>&lt;110</td>
<td>70-130</td>
<td>70-130</td>
</tr>
</tbody>
</table>

Setting the Appropriate Glycemic Target

Individualizing A1C Targets for Patients with T2DM

<table>
<thead>
<tr>
<th>Most Intensive</th>
<th>Less Intensive</th>
<th>Least Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, Comprehensive Support Systems</td>
<td>Less motivated, Non-adherent, Limited Insight, Poor Self-Care Capacities, Weak Support Systems</td>
<td>Highly motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, Comprehensive Support Systems</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
</tbody>
</table>

Psychosocial/Economic Considerations

Glycemic Targets

- Individualization is key
  - Tighter targets (6.0 – 6.5%) in young, healthier patients
  - Looser targets (7.5 - 8.0%+) in patients who are older, multiple comorbidities, cardiovascular disease, hypoglycemia prone, etc...
- Avoidance of hypoglycemia


Hypoglycemia

What is the blood glucose value to define hypoglycemia?

Whipple’s Triad
1. Symptoms and signs suggestive of hypoglycemia
2. Low plasma glucose which corresponds to symptoms
3. Resolution of symptoms on correction of plasma glucose


Symptoms of Hypoglycemia

- **Sympathoadrenal**
  - Diaphoresis, warmth, anxiety, tremor, nausea, hunger, palpitations/tachycardia
- **Neuroglycopenic**
  - Fatigue, dizziness, H/A, visual disturbance, drowsiness, difficulty speaking, inability to concentrate, amnesia, abnormal behavior, mood changes, loss of consciousness, seizure, focal neurological deficit

H/A = headache

Hypoglycemia in Type 2 Diabetes

- Hypoglycemia symptoms are common in type 2 diabetes [e.g., 38% of patients] \(^1\)
- Associated with: \(^1\)–\(^3\)
  - Increased morbidity and mortality
  - Reduced quality of life
  - Reduced treatment satisfaction
  - Increased barriers to adherence
  - More common at A1C < 7%


Asymptomatic Hypoglycemia May Go Unreported

- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring\(^4\)
- Other researchers have reported similar findings\(^5\)

Hypoglycaemia Increases Healthcare Costs

- Retrospective analysis of 536,381 patients with type 2 diabetes from 2004 to 2008 showed hypoglycaemia cost over $52 million.
- 3.5% (N=18,657) of the study sample had at least 1 inpatient, ED, or outpatient visit for hypoglycaemia. Rate higher in women than men (p<0.001).


Risk Factors and Consequences of Hypoglycaemia

Risk Factors for Hypoglycaemia

- Long duration of diabetes
- CAD or micro- & macro-VAD
- Extensive comorbidities
- Peripheral neuropathy
- Impaired awareness
- Missed/irregular meals/physical activity
- Renal dysfunction
- Cognitive dysfunction
- Advanced age

CAD = coronary artery disease; VD = vascular disease.

Clinical Consequences of Hypoglycaemia

- Hospital admissions: 25% of hospital admissions for diabetes were for severe hypoglycaemia
- Increased mortality: 9% in a study of severe SU-associated hypoglycaemia
- Road accidents caused by hypoglycaemia: 45 serious events per month

SU = sulfonylureas
Special Populations at Greater Risk of Morbidity and Mortality with Hypoglycemia

- Elderly
- Cardiovascular (macrovascular) disease
- Microvascular disease (nephropathy, retinopathy, and neuropathy)
- Extensive comorbid conditions
- Autonomic neuropathy

Summary: Hypoglycemia in T2DM

- Hypoglycemia is a major factor limiting intensive control in T2DM – ACCORD, ADVANCE, and VADT
- The risk of hypoglycemia is increased in older patients, those with longer diabetes duration, renal dysfunction, lesser insulin reserve, and with strict glycemic control
- Hypoglycemia has substantial economic and clinical impact, in terms of cost, morbidity, mortality, and quality of life.
- Special populations such as the elderly, those with macrovascular and microvascular disease, and extensive comorbid conditions are at increased risk of morbidity and mortality when exposed to hypoglycemia
- Individualization of glycemic targets is key to optimizing care and minimizing the risk of hypoglycemia

Current Strategies for Achieving Glycemic Goals: Consideration for Hypoglycemic Risk

Frequency and Management of Hypoglycemia

How Often Does Hypoglycemia Occur in Diabetes?

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily to about 1/wk</td>
<td>12</td>
<td>40.2</td>
</tr>
<tr>
<td>1/mo to several times/mo</td>
<td>23.5</td>
<td>34.9</td>
</tr>
<tr>
<td>Only a few times/y or very rarely</td>
<td>64.5</td>
<td>24.9</td>
</tr>
</tbody>
</table>

Survey 409 US patients with T1DM (n = 200) and with T2DM (n = 209).

When Does Hypoglycemia Occur with Diabetes?

- Awake and at Work
- Awake but Not at Work
- During Sleep at Night

1/5 of all nonsevere hypoglycemia occurs nocturnally

NSHE = non-severe hypoglycemic events.
Survey 409 US patients with T1DM (N=200) and with T2DM (N=209).
Guidelines for Preventing Hypoglycemia

**AACE**
- Address in each patient contact
- If problematic, adjust regimen by:
  - Reviewing/applying diabetes self-management
  - Frequent SMBG
  - Flexible, appropriate insulin regimens
  - Individualized glycemic goals
  - Ongoing professional guidance and support
  - Consider each of the known risk factors for hypoglycemia

**ADA**
- Reevaluate SMBG skills periodically
- Avoid aggressive targets in advanced disease
- Limit alcohol intake
  - ≤ 3 drinks/day in adult women
  - ≤ 2 drinks/day in adult men
- Add carbohydrate before exercising if BG < 100 mg/dL
- Strict avoidance of hypoglycemia for several weeks partly resolves repeated severe hypoglycemia, hypoglycemia unawareness

---

**Practical Tips for Treating Hypoglycemia**
- Have a plan to manage hypoglycemia (eg, Rule of 15)
- Patient, family, and friends should be aware of hypoglycemia signs and symptoms
- Note timing of physical activity (exercise), eg, before meal
- Test BG, if possible
- Treat hypoglycemia with 15 to 20 grams of sugar (4-5 glucose tablets) or test BG, if possible
- If experiencing hypoglycemia, rest
- If BG ≤ 50 mg/dL, wait 15 minutes and test BG again
- Follow treatment of hypoglycemia with protein and carbohydrates if needed (eg, ½ cup juice)
- Overcorrect for elevated postprandial glucose after dinner
- Strenuous daytime exercise
- Skipping dinner, but taking prandial insulin dose anyway
- Exercise near bedtime
- Shrunken daytime exercise with inadequate energy intake

**Addressing Nocturnal Hypoglycemia**

**Self-Management Factors**
- Accidental or intentional medication overdose, especially with insulin
- Overcorrecting for elevated postprandial glucose after dinner
- Skipping dinner, but taking prandial insulin dose anyway
- Exercise near bedtime
- Shrunken daytime exercise without adequate energy intake

- Impaired counterregulatory hormone response
- Hypoglycemia unawareness, especially while sleeping
- Physical activity
- Severe underlying illness
- Malabsorption syndromes
- Insulinomas

---

**Efficacy of Glucose-Lowering Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction</th>
<th>Fasting vs PPG</th>
<th>Dosing (times/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>Fasting</td>
<td>1, injected</td>
</tr>
<tr>
<td>Insulin, long-acting</td>
<td>1.5 - 2.5</td>
<td>Fasting</td>
<td>1, injected</td>
</tr>
<tr>
<td>Insulin, rapid-acting</td>
<td>1.5 - 2.5</td>
<td>PPG</td>
<td>1-4, injected</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Fasting</td>
<td>1</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5 - 1.4</td>
<td>Fasting</td>
<td>1</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>0.5 - 1.0</td>
<td>PPG</td>
<td>2, injected*</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5</td>
<td>Fasting*</td>
<td>1, injected*, Qw*</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5 - 0.8</td>
<td>Fasting</td>
<td>3</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>0.5 - 0.8</td>
<td>PPG</td>
<td>3</td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>0.5 - 1.0</td>
<td>PPG</td>
<td>3, injected</td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>0.5 - 1.0</td>
<td>Fasting</td>
<td>1-2</td>
</tr>
</tbody>
</table>

---

**Troubleshooting Hypoglycemia: Event Checklist**

- When did the event(s) occur? (Daytime / Overnight)
- How was the hypoglycemia treated? (Carbohydrate ingested / Glucagon administered / Follow-up BG monitoring)
- Did the patient test before driving? (Yes / No / Not applicable)
- What were the circumstances? (Missed meal / Excess medication / Alcohol use)
- What were the symptoms? ________________
- What was the BG reading? ________mg/dL

---

**Overall Benefits and Risks of Current Antidiabetic Therapies**

- Benefits:
  - Ongoing professional guidance and care
  - Individualized glycemic goals
  - Flexible, appropriate insulin regimens
  - Frequent SMBG
  - Reviewing/applying diabetes self-management

- Risks:
  - Hypoglycemia unawareness, especially while sleeping
  - Physical activity
  - Severe underlying illness
  - Malabsorption syndromes
  - Insulinomas

---

**BG = blood glucose**
**Weight and Hypoglycemia Effects of Antidiabetic Agents**

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Mild</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>Neutral</td>
</tr>
<tr>
<td>Glinides</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>Neutral</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>Neutral</td>
</tr>
<tr>
<td>Pankrease</td>
<td>Neutral</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

**There Are Many Problems Associated with Routine Therapies**

- Secretagogues lack durability of glucose-lowering effects and pose risk for hypoglycemia
- Most therapies, esp. SFUs, associated with weight gain
- Most therapies fail to adequately control PPG
- Wide BG fluctuations occur despite most drug treatments
- Most recent therapies have failed to maintain long-term glycemic control because of progressive beta cell loss
- Decreased CVD events an important but unmet need!
- Simplicity of treatment plan and enhanced adherence are essential components of durable, successful treatment!

SU = Sulfonylurea; PPG = post-prandial glucose; BG = blood glucose; CVD = cardiovascular disease.

**Risks of T2DM Medications AACE/ACE Algorithm**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Risk in renal insufficiency</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lactic acidosis/ risk in liver failure</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure/ edema</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Intake</strong></td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Meeting the Clinical Challenges and Future Therapeutic Approaches — Where are we and where do we go?**

- **Inadequate Postprandial Glucose Control**
- **Weight Gain**
- **Increased Risk of Hypoglycemia**
- **Specific Contraindications**
- **Progressive Loss of β-Cell Function**

**Future Therapies for Type 2 Diabetes**

- Reduce
  - Macrovascular/CV Disease
  - Microvascular Risk
- Improve
  - Insulin Secretion & Resistance
  - Safety Profile
  - Low Risk of Hypoglycemia
  - No Weight Gain
  - No Other Clinically Relevant Side Effects
- Address Hyperglycemia
  - Fasting & Postprandial Effects
  - Sustained Glycemic Control Over Time

**Incretin-Based Therapies: MOA**

- GLP-1 Agonists
  - Release of active incretin GLP-1 and GIP
  - Pancreas
  - Insulin from beta cells (GLP-1 and GIP)
  - Glucagon from alpha cells (GIP-1)
  - Hepatic glucose production
  - Peripheral glucose uptake
  - Blood glucose in fasting and postprandial states

By increasing and prolonging active incretin levels, DPP-4 inhibition increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

**Clinical Benefits Associated With Emerging Antidiabetic Therapies**

**Newer Antidiabetic Therapies: DPP-4 Inhibitors**

- Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin
  - Inhibits the degradation of endogenous incretin hormones
    - ↑ insulin secretion
    - ↓ glucagon release
    - ↓ food intake
  - Reduces FPG and PPG
  - Dosed once daily orally
  - Dosage modification needed in renal impairment except for Linagliptin
  - Adverse events
    - Most common – headache, respiratory infection
    - Reports of pancreatitis

**Newer Antidiabetic Therapies: GLP-1 Receptor Agonists**

- Exenatide, Exenatide XR, and Liraglutide
  - Stimulates GLP-1 receptors
  - ↑ insulin secretion
  - ↓ glucagon release
  - ↓ food intake
  - Slows gastric emptying
  - Injected therapy
  - Reduces FPG and PPG
  - Adverse events
    - Most common – transient IV
    - Reports of pancreatitis
    - Improved CV risk factors – lipids, blood pressure, hs CRP, others

**Pancreatic Safety of Incretin-Based Therapies**

- FDA and EMA conducted an extensive review of the safety of incretin-based drugs
  - Toxicology and histology
  - Clinical data
    - FDA reviewed >200 trials involving 41,000 participants
    - EMA conducted similar review
  - Both agencies concluded that based on current data, there is no causal relationship between incretin-based drugs and pancreatitis or pancreatic cancer

**Novel Antidiabetic Therapies SGLT-2 Inhibitors**

- Canagliflozin and Dapagliflozin
  - SGLT2 inhibition leads to glucosuria in kidneys
  - Works independent of insulin
  - A1C reduction 0.5-0.8%
  - Based once daily
  - Contraindicated in patients with severe renal impairment
  - Causes a small dose-dependent diuretic effect
  - Weight loss from glucosuria
  - Adverse effects include:
    - Urinary frequency, Candida infections, and UTIs

**SGLT-2 Inhibitors: MOA**

- Glucose
  - Normally all filtered glucose is reabsorbed
  - ~180 g/day
  - SGLT2 inhibitors increase renal glucose elimination
  - Normally no glucosuria

**Effects of SGLT2 Inhibitors**

- Inhibition of SGLT2
  - Reversal of Glucotoxicity
  - Insulin sensitivity in muscle
    - ↑ GLUT4 translocation
    - ↑ Insulin signaling
    - Other
  - Insulin sensitivity in liver
    - ↓ Glucose-6-phosphatase
  - Gluconeogenesis
    - Decreased Cori cycle
    - ↓ PEP carboxykinase
  - β-Cell function

---


Current Guideline Recommendations for the Management of Hyperglycemia

**More complex insulin strategies**

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- Metformin + Sulfonylurea + TZD
- DPP-4-i
- GLP-1-RA
- Insulin

**Two drug combinations**

- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote specific preference):

- Metformin + Sulfonylurea
- high risk
- moderate risk
- gain
- hypoglycemia
- low risk

- Metformin + Thiazolidinedione
- high risk
- low risk
- gain
- edema, HF, fx's
- high risk

- Metformin + DPP-4 Inhibitor
- intermediate risk
- low risk
- neutral
- rare
- high risk

- Metformin + GLP-1 receptor agonist
- high risk
- low risk
- loss
- GI
- high risk

- Metformin + Insulin (usually basal)
- highest risk
- high risk
- gain
- hypoglycemia
- variable

**Healthy eating, weight control, increased physical activity**

**Initial drug monotherapy**

- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

- Metformin
- high risk
- low risk
- neutral/loss
- GI / lactic acidosis

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote specific preference):

**Lifestyle Modification** (Including Medically Assisted Weight Loss)

**Considerations for Therapy Selection**

- Age
- Weight
- Racial and ethnic differences
- Coronary artery disease
- Heart failure
- Renal dysfunction
- Hypoglycemia risk
- Patient preferences

**Patient-Centered Approach to Treatment**

**Patient-Centered Care**

- “…providing care that is respectful of and responsive to individual patient preferences, needs, and values…”
- Patient preferences for diabetes medications
  - Oral
  - Once daily
  - Low hypoglycemia risk
  - No weight gain or weight loss
  - Effective
  - Low side-effects

Therapeutic Strategies for Minimizing Risk of Hypoglycemia

Oral Agents & Non-insulin Injectables with Low Risk of Hypoglycemia

**Oral agents**
- Metformin
- Thiazolidinediones
- alpha-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- DPP-4 inhibitors
- SGLT-2 inhibitors

**Injectables**
- Amylin mimetics
- GLP-1 receptor agonists

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter 2.


New Developments for Reduction of Hypoglycemia Risk in T2DM

- Newer agents available that do not augment insulin secretion or do so in a glucose-dependent manner (e.g., bile acid sequestrants, bromocriptine, incretins, SGLT-2 inhibitors)
- It is clear that earlier use of combination therapy is often required
- Caution must be used when some of the newer agents are used in combination with secretagogues or insulin (e.g., incretins, SGLT-2 inhibitors)
- Reduction of secretagogue or insulin dose may be required

Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

Addition of Sitagliptin or Glimepiride in Patients Inadequately Controlled on Metformin: Clinical Assessment of Hypoglycemia over 30 Weeks

APaT Population

Hypoglycemic Events over 2.1 Years with Saxagliptin Add-on Therapy in Patients with T2DM and CVD or Risk Factors – SAVOR-TIMI 43

Hospitalization for heart failure was higher with SAXA (3.5%) than with Placebo (2.8%); hazard ratio, 1.27; \( p = .007 \).
Hypoglycemic Events over 1.5 Years with Alogliptin Add-On Therapy in Patients with T2DM and Recent Acute Coronary Syndrome – EXAMINE

Hypoglycemia was reported by site investigators; no definitions were given. Between-group differences were not significant (P = .86 for serious hypoglycemia and P = .74 for any hypoglycemia).


Hospitalization for heart failure was nonsignificantly higher with ALO than with Placebo (hazard ratio, 1.19; p=0.220) using the “standard” heart failure composite definition.

Severe Hypoglycemia and GLP-1 RAs – Meta-Analysis of 25 Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Any Hypoglycemia (% of Participants)</th>
<th>Major Hypoglycemia (episodes, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGLT2 Inhibitor</td>
<td>Comparator</td>
</tr>
<tr>
<td>DAPA (4 yr)</td>
<td>5.4</td>
<td>51.5</td>
</tr>
<tr>
<td>DAPA (102 wk)</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>DAPA (52 wk)</td>
<td>3.4</td>
<td>39.7</td>
</tr>
<tr>
<td>CANA (104 wk)</td>
<td>7.8</td>
<td>41</td>
</tr>
<tr>
<td>CANA (52 wk)</td>
<td>3.4</td>
<td>39.7</td>
</tr>
<tr>
<td>EMPA (24 wk)</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Avoiding Hypoglycemia With Noninsulin Therapy in T2DM: Pearls for Practice

- Diet and exercise can precipitate hypoglycemia
- Hypoglycemia can occur with any antihyperglycemic agent (even metformin), but more likely to occur with insulin, SUs, and glinides
- Glyburide is associated with higher rates of hypoglycemia, CV events, and mortality than other SUs
- Potential cardiovascular risks of SUs need to be confirmed in long-term cardiovascular outcomes trials
- Hypoglycemia generally increases with an increasing number of antihyperglycemic agents used in combination
- Of the major classes of antihyperglycemic agents, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs, and TZDs are associated with the lowest rates of hypoglycemia
Summary

- Hypoglycemia is common and under recognized
- Hypoglycemia negatively impacts patient outcomes; accordingly, treatment recommendations highlight the importance of hypoglycemia avoidance when treating hyperglycemia in patients with diabetes
- In patients at increased risk of hypoglycemia, use drugs and drug combinations that minimize the risk of hypoglycemia
- Novel combinations such as SGLT-2 inhibitors plus a DPP-4 inhibitors or GLP-1 RAs need to be investigated

Patient Cases

Case Study 1: Charlie

- Charlie is brought to the ER due to acute onset chest pain requiring hospitalization.
- He does not visit with doctors even though his wife is concerned due to family history of heart disease and recent complaints of feeling tired.
- He is diagnosed of having an acute MI and has a random blood glucose of 168 mg/dL. An A1C of 8.1% confirms that he has T2DM with diabetes dyslipidemia and hypertension.
- He has an uncomplicated MI and was prescribed a statin, a beta-blocker, and encouraged to exercise.
- His blood glucose levels are routinely elevated throughout his 5 day hospitalization. A decision regarding the treatment of his diabetes has to be made prior to discharge.

Case Study 1: Charlie Cont’d

- History
  - Male, aged 62 years
  - Newly diagnosed T2DM
  - Newly diagnosed hypertension
  - Newly diagnosed dyslipidemia
  - Height 6 ft
  - Weight 250 lbs
  - BMI 34 kg/m2
- Lab results
  - In-hospital glucose ≈ 168 mg/dL
  - A1C = 8.1%
  - eGFR = 32 mL/min
  - LFT: normal
  - Blood Pressure: elevated
  - Lipids: elevated total cholesterol
- Medications
  - None

Case Study 1: Charlie Follow-up

- Charlie was started on a DPP-4 inhibitor and discharged.
- He saw a primary care physician 2 weeks after discharge and is doing well. He is taking all his medications regularly with no complaints.
- At his 3 month checkup, his A1C was 7.4%.

Case Study 2: Bernard

- He recently had an embarrassing episode at a church conference during which his friends said “he was sweating, acting strange and saying weird things” and brought him to the ED
- ED diagnosed him with hypoglycemia (admission BG = 43 mg/dL)
- He travels a lot, has a somewhat chaotic lifestyle and does not perform SMBG regularly
- You recommend Bernard switch from glyburide to a GLP-1 RA, but he is distrustful of new medicines and especially does not want an injection
- He also insists on minimizing his out-of-pocket medication costs
Case Study 2: Bernard Cont’d

- **History**
  - Male, aged 48 years
  - T2DM, 4 years
  - Hypertension, 12 years
  - Dyslipidemia, 12 years
  - Height 5’7”
  - Weight 186 lb
  - BMI 29.3 kg/m²

- **Lab results**
  - In-office glucose ≈ 70 mg/dL
  - A1C = 8.3%
  - eGFR = 62 mL/min
  - LFTs: normal
  - BP: borderline elevated
  - Lipids: borderline elevated total cholesterol

- **Medications**
  - Metformin recently discontinued by primary care because of declining eGFR
  - Glyburide 5 mg (was 2.5 mg before metformin d/c)
  - ACE inhibitor/HCTZ and a statin

**T2DM = type 2 diabetes; BMI = body mass index; eGFR = estimated glomerular filtration rate; LFT = liver function test; BP = blood pressure.**

Case Study 2: Bernard Cont’d

- Glyburide was discontinued and he was started on metformin plus a DPP-4 inhibitor.
- With an eGFR of 62 mL/min, Bernard can be safely and effectively treated with metformin based on current guidelines.
- At 6 month checkup his A1C was 7.5%.

Case Study 2: Bernard Follow-up

- Since Bernard is at an increased risk for hypoglycemia, his glycemic target should be an A1c 7.5% to 8.0%
- He is maintained on metformin and a DPP-4 inhibitor.
- At 1 year checkup his A1C was 7.6%.

Question & Answer