New Drug Updates in Diabetes Mellitus

Objectives

• Recognize clinical indications of pharmacotherapy agents discussed
• Identify brand/generic and pertinent side effects of new pharmacotherapy agents utilized to treat hyperglycemia in diabetes mellitus

Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Guidelines for Diabetes Management

• Recommendations made by multiple groups
• All support individualizing therapy
  • “Patient centered approach”
• Revisions to Standards of Medical Care in Diabetes
  • Most recent update released January 2014
  • American Diabetes Association (ADA)

Standards in Diabetes Care

<table>
<thead>
<tr>
<th>Topic</th>
<th>2014 Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>• Added A1c as an available method to diagnose diabetes</td>
<td></td>
</tr>
<tr>
<td>• A1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>• Must use method certified by the NGSP and standardized or traceable to the DCCT reference assay</td>
<td></td>
</tr>
<tr>
<td>• POC testing not approved</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening for Type 1 Diabetes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study</td>
<td></td>
</tr>
</tbody>
</table>

NGSP = National Glycohemoglobin Standardization Program
DCCT = Diabetes Control and Complications Trial

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DCCT = Diabetes Control and Complications Trial
**Standards in Diabetes Care**

<table>
<thead>
<tr>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td><strong>Gestational Diabetes</strong></td>
<td>• Provides additional method for screening and diagnosing</td>
</tr>
<tr>
<td></td>
<td>&quot;One-step&quot; method (IADPSG Consensus)</td>
</tr>
<tr>
<td></td>
<td>One time fasting OGTT at weeks 24-28 gestation</td>
</tr>
<tr>
<td></td>
<td>&quot;2-step&quot; method (NIH Consensus) - NEW</td>
</tr>
<tr>
<td></td>
<td>Non-fasting GLT at weeks 24-28 gestation</td>
</tr>
<tr>
<td></td>
<td>If serum glucose ≥140 mg/dL measured 1 hour after load, then perform fasting OGTT</td>
</tr>
<tr>
<td><strong>Continuous Glucose Monitoring</strong></td>
<td>Can be used to supplement SMBG for patients with type 1 diabetes with frequent nocturnal hypo or hyperglycemic episodes</td>
</tr>
</tbody>
</table>

OGTT = Oral glucose tolerance test. GLT = Glucose load test. SMBG = Self-monitoring of blood glucose.

**Standards in Diabetes Care**

<table>
<thead>
<tr>
<th>Topic</th>
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<tbody>
<tr>
<td><strong>Pharmacotherapy in Type 2 Diabetes</strong></td>
<td>• Reduced duration of non-insulin monotherapy trial to 3 months</td>
</tr>
<tr>
<td></td>
<td>Previously 3-6 months</td>
</tr>
<tr>
<td><strong>Medical Nutrition Therapy</strong></td>
<td>• Reflects updated position statement on nutritional therapy for adults</td>
</tr>
<tr>
<td></td>
<td>Updated on October 2013</td>
</tr>
<tr>
<td><strong>Antithrombotic Therapy</strong></td>
<td>• Recommends more general therapy for patients with DM post ACS</td>
</tr>
<tr>
<td></td>
<td>&quot;Dual antithrombotic therapy&quot; per most recent AHA/ACC STEMI guidelines</td>
</tr>
<tr>
<td></td>
<td>Previously only aspirin + clopidogrel</td>
</tr>
</tbody>
</table>

ACS = Acute coronary syndrome.

**Managing Hyperglycemia**

- Type 1 diabetes - Insulin therapy
  - Multiple dose injections
  - 3–4 injections/day
  - Basal and prandial insulins
- Continuous subcutaneous insulin infusion
- Prefer insulin analogs to reduce hypoglycemia risk
- Type 2 diabetes – noninsulin +/- insulin therapy
- Patient centered approach
- Insulin therapy is eventually indicated for many

**Standards in Diabetes Care**

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<tr>
<td><strong>Nephropathy</strong></td>
<td>• Replaced &quot;macroalbuminuria&quot; with albuminuria ≥300 mg/24 hrs</td>
</tr>
<tr>
<td></td>
<td>Replaced &quot;microalbuminuria&quot; with albuminuria 30-299 mg/24 hrs</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
<td>• If no retinopathy present, re-examine every 2 years</td>
</tr>
<tr>
<td></td>
<td>Previously every 2-3 years</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>• Recommend more descriptive treatment options for neuropathic pain</td>
</tr>
<tr>
<td></td>
<td>No treatment available for underlying nerve damage or reverse neuronal loss</td>
</tr>
</tbody>
</table>

**Managing Hyperglycemia**

- Antihyperglycemic Therapy for T2DM
**Evaluating Treatment Options**

**Efficacy**
- Achieves improved glucose control
- Preserved pancreatic β-cell function
- Cardiovascular benefit

**Safety**
- Minimizes hypoglycemia
- Weight gain
- Adverse drug effects
- Drug interactions

**Cost**
- Limits financial burden
- Emotional burden
- Time

**Cost Limiting Factors**
- Minimizes hypoglycemia
- Weight gain
- Adverse drug effects
- Drug interactions

**Emerging Therapies for Glucose Management**

**Non Insulin**
- Oral
- Injectable

**Injectable**
- DPP-4 Inhibitors
- GLP-1 Agonists

**GLP-1 Agonists**
- Alogliptin + Metformin
- Pioglitazone

**DPP-4 Inhibitors**
- Omaglitipin
  - MK-3102
  - Phase III trials for once daily use in T2DM
- Trelaglitipin
  - SYR-472
  - Phase III trials for once daily use in T2DM

**DPP-4 Inhibitors**

**Small Intestine**

**Oral Intake**

**Glucose**

**GLP-1**

**Insulin**

**Pancreas**

**GLP-1**

**GIP**

**Insulin**

**Deactivation**

**Insulin Uptake**

**Glucose Production**

**Emerging Agent Status**

<table>
<thead>
<tr>
<th>Emerging Agent</th>
<th>Status</th>
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<tbody>
<tr>
<td>Alogliptin + Metformin</td>
<td>FDA approved for once daily use in T2DM (January 2013)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td></td>
</tr>
<tr>
<td>Omaglitipin</td>
<td>MK-3102</td>
</tr>
<tr>
<td>Trelaglitipin</td>
<td>SYR-472</td>
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</tbody>
</table>

**Abbreviations**
- DPP-4 = Dipeptidyl peptidase-4
- SGLT-2 = Sodium glucose co-transporter-2
- GLP-1 = Glucagon-like peptide-1

**Center for Drug Evaluation and Research Guidance for Industry Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.** 2008
**DPP-4 Inhibitors**

**Benefit**

- A1c reduction ~1-2%
- Low hypoglycemia risk
- Neutral effect on weight
- Possible β-cell protection
- Cardiovascular benefit

**Risks**

- Increased risk of pancreatitis
- Frequent adverse effects include headache, nasopharyngitis
- Cost to patient

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**SGLT-2 Inhibitors**

**Benefit**

- A1c reduction ~0.7-1%
- Low hypoglycemia risk
- Increases weight loss
- Cardiovascular benefit

**Risks**

- Frequent adverse effects include genital mycotic infections, urinary tract infection, increased urination
- Avoid in uncircumcized males or patients susceptible to frequent UTIs
- Cost to patient

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**SGLT-2 Inhibitors**

- **S1 Segment of Proximal Tubule**
- **Distal Segment of Proximal Tubule**
- **Collecting Duct**

- **SGLT-2 Inhibitor**
- **SGLT-1 Inhibitor**

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**GLP-1 Agonists**

**Emerging Agent**

- **Albiglutide**
  - **Syncria** (formerly)
  - Phase III trials for additional cardiovascular safety data for once weekly use in T2DM

- **Dulaglutide**
  - **LY2189265**
  - Awaiting FDA decision on marketing approval submissions for once weekly use in T2DM

- **Lisenatide**
  - **Lyxumia**
  - Phase III trials for additional cardiovascular safety data for once weekly use in T2DM

- **Semaglutide**
  - **NN9535**
  - Phase III trials for once weekly use in T2DM
**GLP-1 Agonists**

**Benefit**
- A1c reduction ~0.8-1.5%
- Low hypoglycemia risk
- Increases weight loss
- Cardiovascular benefit
- Possible β-cell protection

**Risks**
- Increased risk of pancreatitis and thyroid cancer
- Frequent adverse effects include nausea, vomiting, diarrhea, constipation, headache
- Cost to patient

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**Bolus Insulin Products**

<table>
<thead>
<tr>
<th>Emerging Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin human, inhaled</td>
<td>Awaiting FDA decision on NDA submission for use in T1DM or T2DM</td>
</tr>
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**Emerging Therapies for Glucose Management**

**Basal**
- Mechanism to prolong duration of action
  - Concentration of insulin > 1 unit/mL
  - Counseling on administration
  - All have durations of 24 hours or longer

**Bolus**
- Ultra rapid acting
  - t-peak = 12-15 minutes
  - May be associated with less weight gain and lower hypoglycemia risk
  - Barriers to inhalation administration

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**Basal Insulin Agents**

<table>
<thead>
<tr>
<th>Emerging Agent</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Insulin degludec</td>
<td>Tresiba, Ryzodeg, IDegLira Phase III trials for additional cardiovascular safety data for once daily use in T1DM and T2DM (NDA rejected Feb 2013)</td>
</tr>
<tr>
<td>Insulin glargine, U300</td>
<td>Phase III trials for once daily use in T2DM</td>
</tr>
<tr>
<td>Insulin peglispro</td>
<td>LY2605541 Recruiting for phase III trials for once daily use in T1DM and T2DM</td>
</tr>
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**Novel Insulin Considerations**

**Basal**
- Mechanism to prolong duration of action
  - Concentration of insulin > 1 unit/mL
  - Counseling on administration
  - All have durations of 24 hours or longer

**Bolus**
- Ultra rapid acting
  - t-peak = 12-15 minutes
  - May be associated with less weight gain and lower hypoglycemia risk
  - Barriers to inhalation administration

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**Conclusion**

- Multiple agents in the pipeline
  - Mostly “me-too” agents
- Novel agents include SGLT-2 inhibitors and agents with improved kinetics for decreased dosing frequency
- FDA required cardiovascular outcomes data has halted approval new agents
- Therapy should be individualized and agent use should be patient specific
  - Risks, benefits, costs
Questions?