Update on Agents for Type 2 Diabetes

This presentation will:

• Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering achieved, patient-specific concerns, adverse drug reactions, and contraindications.

• Discuss the role and timing of combination therapy in achieving A1C goals.

• Explain the implications of recent, large randomized clinical trials on clinical decision-making.
## Goals for Glycemic Control

### Individuate Goals

<table>
<thead>
<tr>
<th>A1C ≤ 6.5%</th>
<th>A1C &gt; 6.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients without concurrent serious illness and at low hypoglycemic risk</td>
<td>For patients with concurrent serious illness and at risk for hypoglycemia</td>
</tr>
</tbody>
</table>
Approach to Management of Hyperglycemia

Figure 1.

Glycemic Management of Type 2 Diabetes: Treatment Goals

- Lowering A1C
- Preventing Hypoglycemia

Individualized Algorithm
Main Pathophysiological Defects in T2DM

“The Ominous Octet”

- Islet β-cell: Impaired insulin secretion
- Islet α-cell: Increased glucagon secretion
- Neurotransmitter dysfunction
- Increased hepatic glucose production
- Decreased glucose uptake
- Increased glucose reabsorption
- Increased lipolysis
- Decreased incretin effect

Insulin Resistance: Receptor And Post-receptor Defects

Increased Glucose Production

Insufficient Glucose Disposal

Liver

↑ Glucose

Pancreas

Peripheral Tissues (skeletal muscle)

Impaired Insulin Secretion

Hepatic Insulin Resistance: Increased Hepatic Glucose Output


FPG=Fasting Plasma Glucose
Current Antihyperglycemic Medications

12 groups with different mechanisms of action

- **Insulin replacement therapy**
- **Sulfonylureas**
  - Generalized insulin secretagogue
  - 12 groups with different mechanisms of action
  - **α-Glucosidase inhibitors**
    - Delay CHO absorption
  - **Glinides**
    - Restore postprandial insulin patterns
  - **TZDs**
    - Reduce peripheral insulin resistance
  - **Biguanide**
    - Reduces hepatic insulin resistance
  - **Amylin analog**
    - Suppresses glucagon
  - **GLP-1 analogs**
    - Stimulate beta-cells
    - Suppress glucagon
  - **DPP-4 inhibitors**
    - Restore GLP-1 Levels
  - **SGLT-2 inhibitors**
    - Block renal glucose reabsorption
  - **Colesevelam**
    - Bile acid sequestrant
  - **Bromocriptine**
    - Hypothalamic pituitary reset

CHO = carbohydrate; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-dependent glucose cotransporters-2; TZD = thiazolidinedione.
Algorithm to Achieve Glycemic Goals

Baseline A1C 6.5% - 7.5%

- Monotherapy may be effective in this range
  - Metformin first choice for monotherapy if no contraindications
  - Consider DPP-4 if ↑PP and FPG, GLP-1 if ↑↑PP, TZD if metabolic syndrome or NAFLD, AGI if ↑PP
  - Do not recommend secretagogue (SU or glinide) in this range due to risk of hypoglycemia; short-lived effect

- If monotherapy is unsuccessful, move on to dual oral rx; often need to augment reduction in PP BG to get to goal in this A1C range

DPP-4 = dipeptidyl peptidase-4; PP = post-prandial; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione; NAFLD = non-alcoholic fatty liver disease; AGI = alpha-glucosidase inhibitor; SU = sulfonylurea; A1C = glycated hemoglobin; SGLT-2 = sodium glucose transport-2
Algorithm to Achieve Glycemic Goals
Baseline A1C 7.6%-9.0%

- Dual therapy with metformin provides superior glycemic control over metformin alone.
- If dual oral rx is unsuccessful, consider triple therapy.
- If triple oral rx fails to achieve A1C goal, initiate insulin.

GLP-1 RA = glucagon-like peptide-1 receptor agonist
DPP4-I = dipeptidyl peptidase 4 inhibitor
TZD = thiazolidinedione
SGLT-2 = sodium glucose cotransporter 2 inhibitor
QR = quick-release
AG-I = alpha-glucosidase inhibitor
SU = sulfonylurea
GLN = glinide

Algorithm to Achieve Glycemic Goals

Baseline A1C > 9.0%

If patient is asymptomatic with recent onset of disease and drug naïve, may consider starting with dual or triple oral regimens

Once A1C has improved to <7.5%, consider initiation of dual oral therapy with tapering and possible discontinuation of insulin rx

If symptomatic, start insulin
Targeted Sites of Action of Oral Anti-Hyperglycemic Drug Classes

<table>
<thead>
<tr>
<th>Liver</th>
<th>Skeletal Muscle</th>
<th>Pancreas</th>
<th>Gut</th>
<th>Fat</th>
<th>Kidney</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biguanides</td>
<td>• Sulfonylureas</td>
<td>• DPP-IV Inhibitors</td>
<td>• α-Glucosidase inhibitors</td>
<td>• TZDs</td>
<td>• SGLT-2 inhibitors</td>
<td>• Bromocriptine</td>
</tr>
<tr>
<td>• TZDs</td>
<td>• TZDs</td>
<td>• Sulfonylureas</td>
<td>• Biguanides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DPP-IV inhibitors</td>
<td>• Glinides</td>
<td>• Insulin</td>
<td>• Colesevelam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin</td>
<td>• TZDs</td>
<td>• Amylin</td>
<td>• GLP-1 RA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↓ Glucose production  ↑ Glucose uptake  ↑ Insulin release  ↓ Glucose absorption  ↑ Insulin sensitivity  ↓ Glucose reabsorption  ↓ Glucose production

DPP = dipeptidyl peptidase; SGLT-2 = Sodium-glucose co-transporter 2; TZD = thiazolidinediones

Clinical Considerations

- Combining therapeutic agents with different modes of action may be advantageous.
- In many if not most patients (unless contraindicated or intolerance has been demonstrated), use metformin, which increases insulin sensitivity, and/or insulin sensitizers such as TZDs, as part of the therapeutic regimen.
- Dosage of secretagogues or insulin should be adjusted as blood glucose levels decline when used in combination with metformin, TZD, DPP-4 inhibitors, and/or incretin mimetics (GLP-1 agonists).

TZD = thiazolidinediones; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1
Clinical Considerations

• The weight gain associated with thiazolidinediones in some patients may be partly offset by combination therapy with metformin.

• If A1C is elevated and preprandial blood glucose measurements are at target levels, carefully assess postprandial glucose levels.

• **Individualize treatment regimens!**
## Effect of Glucose-lowering Drugs on Patient Weight

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Metformin&lt;sup&gt;7&lt;/sup&gt;</td>
<td>⇐⇒</td>
</tr>
<tr>
<td>DPP-4 inhibitor&lt;sup&gt;8&lt;/sup&gt;</td>
<td>⇐⇒</td>
</tr>
<tr>
<td>GLP-1 receptor agonist&lt;sup&gt;9&lt;/sup&gt;</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors&lt;sup&gt;10&lt;/sup&gt;</td>
<td>↓</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium glucose co-transporter-2; TZD = thiazolidinedione

Risk of Hypoglycemia

• Plays a significant role in choice of agents in AACE algorithm
• For patients at highest risk of hypoglycemia, may consider close evaluation of agents chosen as well as therapeutic goal
• Patients with type 2 diabetes at highest risk of low blood glucose include those with:
  – Diabetes duration >15 years
  – Advanced macrovascular disease
  – Hypoglycemia unawareness
  – Limited life expectancy
  – Severe comorbidities

# Biguanides

## Metformin

| Mechanism | Insulin sensitivity
|           | Hepatic glucose production
<table>
<thead>
<tr>
<th></th>
<th>FPG more than PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>A1C 1%-2%</td>
</tr>
<tr>
<td>Advantages</td>
<td>No weight gain or hypoglycemia, potential weight loss</td>
</tr>
</tbody>
</table>
| Disadvantages | GI side effects
|          | Lactic acidosis *(rare)* |
| Contraindications | Renal disease; CHF |

Combinations available with SU, TZD, repaglinide, and DPP-4 inhibitors

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A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; PPG = post-prandial glucose; SU = sulfonylurea; TZD = thiazolidinedione

Metformin [package insert]. Princeton NJ; Bristol Myers Squibb; 2009.
# Sulfonylureas and Glinides

**Glipizide, Glimepiride, Glyburide**  
**Repaglinide, Nateglinide**

| **Mechanism** | Insulin secretion  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPG</td>
</tr>
<tr>
<td></td>
<td>PPG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Strong short term efficacy</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Weight gain, hypoglycemia, tend to lose efficacy after several years</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Avoid in severe hepatic and renal impairment</td>
</tr>
</tbody>
</table>

Combinations available with metformin, TZD

FPG = fasting plasma glucose; PPG = post-prandial glucose; TZD = thiazolidinedione

# Thiazolidinediones

## Pioglitazone, Rosiglitazone

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↑ Insulin sensitivity, especially at muscle, lowers both FPG and PPG, but effect may be delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Moderate (↓ A1C 1.0%-1.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No hypoglycemia, no reliance on renal excretion</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Fluid retention, edema, heart failure, weight gain, slow onset of action, bone fractures, macular edema, osteoporosis, anemia, and bladder cancer</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Class III or IV CHF or hepatic impairment w/ALT &gt;2.5 times upper normal limits</td>
</tr>
</tbody>
</table>

Combinations available with metformin and sulfonylurea

A1C = glycated hemoglobin; ALT = alanine aminotransferase; CHF = congestive heart failure; FPG = fasting plasma glucose; PPG = postprandial plasma glucose.

### Bile Acid Sequestrants

#### Colesevelam

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Raises cholecystokinin, which slows gastric emptying and post-prandial glucose. Exact mechanism unknown, may be mediated via TGR5, and/or farnesoid X receptor (FXR/bile acid receptor) effects on intestinal glucose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>↓ LDL-C (also FDA approved for LDL-C reduction); weight neutral, no hypoglycemia, can complement statin treatment in lowering LDL and cardiac event risk.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Constipation, nausea, dyspepsia, myalgia, pharyngitis, ↑ triglycerides, drug interactions.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of bowel obstruction, TGs &gt;500 mg/dL; history of hypertriglyceridemia-induced pancreatitis</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride
Effects of Colesevelamam on A1C Levels in Add-On Therapy Trials: ≥0.5% Reductions

Mean Change in A1C (%)

-0.10
-0.20
-0.30
-0.40
-0.50
-0.60

GLOWS Week 12
Metformin Week 26
Sulfonylurea Week 26
Insulin Week 16

-0.50*
-0.54*
-0.54*
-0.50*

*P ≤ 0.007
n = >1,000

Strategies for Enhancing GLP-1 Action

• **GLP-1 receptor agonists** (injectable therapies)
  – Short acting: exenatide BID, liraglutide, lixisenatide
  – Long acting: exenatide QR, albiglutide, dulaglutide
  – Under investigation: semaglutide and ITCA 650

• **DPP-4 inhibitors** (oral therapies)
  – Inhibit actions of DPP-4
  – Sitagliptin, saxagliptin, linagliptin, alogliptin
Summary of Incretin Actions on Different Target Tissues

Drucker D. J. *Cell Metabolism* 2006
Inhibition of DPP-4 Increases Active Incretin Levels, Enhancing Downstream Incretin Actions

![Diagram showing the effect of DPP-4 inhibition on incretin levels and glucose control.]

- **Active GIP**
  - Increased insulin secretion
  - Decreased glucagon release

- **Inactive GIP**

- **Active GLP-1**

- **Inactive GLP-1**

**DPP-4**

**DPP-4 inhibitor**

**Glucose control improved**

GIP = glucose-dependent insulino tropic peptide

Umpierrez et al. Endocrine Practice 2014
GLP1-RA Increase Active Incretin Levels

Normal Physiology

Active GLP-1

DPP-4

Inactive GLP-1

GLP-1 RA

DPP-4 inhibitor

Resistance

Increased circulating GLP-1 levels

- Increased insulin secretion
- Decreased glucagon release

Glucose control improved

GLP-1 = glucagon-like peptide-1; GLP1-RA = glucagon-like peptide-1 receptor agonist; DPP-4 = dipeptidyl peptidase 4

Umpierrez et al. Endocrine Practice 2014
# Characteristics of DPP-4 Inhibitors

**Alogliptin, Linagliptin, Saxagliptin, Sitagliptin**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Inhibit enzymatic degradation of GLP-1 and GIP; glucose-dependent</th>
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</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Decrease A1C levels 0.6%–0.9%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once daily</td>
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<tr>
<td><strong>Side effects</strong></td>
<td>Headaches, nasopharyngitis</td>
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<tr>
<td><strong>Main risk</strong></td>
<td>Viral infection; long-term safety unknown</td>
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A1C = glycated hemoglobin; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1

## Summary of DPP-4 Inhibitors

### Average A1C Change in Clinical Trials

<table>
<thead>
<tr>
<th>DPP-4 Inhibitor</th>
<th>Mono-therapy</th>
<th>Initial with Metformin</th>
<th>Add-on to Metformin</th>
<th>Add on to SU</th>
<th>Add on to TZD</th>
<th>Initial with TZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>-0.59</td>
<td>--</td>
<td>-0.60</td>
<td>-0.53</td>
<td>--</td>
<td>-1.71</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>-0.44</td>
<td>-1.6</td>
<td>-0.49</td>
<td>-0.72 (SU + Met)</td>
<td>--</td>
<td>-1.06</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>-0.46</td>
<td>-2.5</td>
<td>0.69</td>
<td>--</td>
<td>-0.94</td>
<td>--</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>-0.67</td>
<td>-1.9</td>
<td>0.67</td>
<td>--</td>
<td>-1.4</td>
<td>--</td>
</tr>
</tbody>
</table>

Nesina (alogliptin) prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2013.
## Summary of DPP-4 Inhibitors

Alogliptin, Linagliptin, Saxagliptin, Sitagliptin

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A1C = glycated hemoglobin; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1

Efficacy of SGLT2 Inhibitors as Monotherapy

![Graph showing the efficacy of SGLT2 inhibitors as monotherapy. The graph compares the change in A1C (% Δ A1C) for different drugs (CANA, DAPA, EMPA) at various dosages (100, 300, 5, 10, 10, 25) against placebo (PBO). All treatments show a statistically significant reduction in A1C (P < 0.001 vs PBO for all).](image)

P < 0.001 vs PBO for all

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*a* Phase 3 trials, BL A1C 7.8% to 8.1%, 24-26 weeks.
Weight Effects with SGLT2 Inhibitors\textsuperscript{a} as Monotherapy

\textbf{CANA}\textsuperscript{1}

- PBO: \(-0.5\)
- 100: \(-2.5^b\)
- 300: \(-3.4^b\)

\textbf{DAPA}\textsuperscript{2}

- PBO: \(-2.2\)
- 5: \(-2.8\)
- 10: \(-3.2\)

\textbf{EMPA}\textsuperscript{3}

- PBO: \(-0.3\)
- 10: \(-2.3^{b,c}\)
- 25: \(-2.5^{b,c}\)

\textsuperscript{a} None of the agents listed are approved for weight reduction.\textsuperscript{4}

\textsuperscript{b} Greater than PBO (\(P < .05\)).

\textsuperscript{c} Greater than SITA (\(P < .05\)).


\textsuperscript{3} Ferrannini E et al. \textit{Diabetes Care}. 2010;33:2217-2224.

\textsuperscript{4} US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.
Renal Glucose Transport in Type 2 Diabetes

- With increasing plasma glucose, filtered glucose increases in linear relationship
- When transport system becomes saturated, excess glucose is excreted in urine
- Renal threshold for glucose is 180 mg/dL in normal glucose-tolerant individuals
- In patients with type 2 diabetes, transport maximum for glucose increases and glucosuria occurs at more elevated glucose levels
- Glucose reabsorption is enhanced, leading to worsening hyperglycemia
SGLT2 Inhibitors

• Mechanism of action:
  – Decrease re-absorption of glucose in the proximal convoluted tubule
  – Decrease renal threshold so urinary glucose excretion occurs at lower plasma glucose concentration

• FDA-approved
  – Canagliflozin
  – Dapagliflozin
  – Empagliflozin

FDA = U.S. Food and Drug Administration; SGLT-2 = sodium-dependent glucose cotransporters-2.

Bays, H. Diabetes Therapy, 2013.
SGLT 2 Inhibition: Meeting Unmet Needs in Diabetes Care

Corrects a Novel Pathophysiologic Defect

Reduces A1C

Promotes Weight Loss

Improves Glycemic Control and CVRFs

Complements Action of Other Antidiabetic Agents

Reduces Blood Pressure

No Hypoglycemia

Reversal of Glucotoxicity

CVRF=Cardiovascular Risk Factor
# SGLT2 Inhibitors

Canagliflozin, Dapagliflozin, Empagliflozin

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Inhibits sodium-glucose transport protein subtype 2 (SGLT2) which is responsible for at least 90% of glucose reabsorption in the kidney causing blood glucose is eliminated in the urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest ((\downarrow) A1C 0.8-1.2%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>Insulin-independent glucose reduction, Low risk of hypoglycemia, Weight loss (to 4% BW), Blood pressure-lowering</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Osmotic diuresis causing Polyuria and lightheadedness, Bacterial urinary tract infections (≈5%), Fungal genital infections (≈10%), Increased LDL cholesterol, Hyperkalemia (canagliflozin), Bladder cancer concerns (dapagliflozin)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of genital fungal infections, caution in chronic kidney disease</td>
</tr>
</tbody>
</table>

SGLT2 Inhibitors Safety: Adverse Reactions

- The most frequent adverse effects of SGLT2 inhibitors (occurring in ≥5% patients) are female genital mycotic and urinary tract infections.

- Patients may also experience increased urination, dehydration, or nasopharyngitis.

SGLT2 = sodium-glucose cotransporter-2
SGLT2 Inhibitors Safety: Warnings and Precautions

• SGLT2 inhibitor use may be associated with hypotension, ketoacidosis, impaired renal function, hypoglycemia, and increased LDL-C
  – Patients should be closely monitored, particularly those with a history of, or at risk for, these conditions

• Dapagliflozin should not be used in patients with a history of bladder cancer

• Canagliflozin may be associated with hyperkalemia and bone fracture
  – Bone fracture risk should be considered before use, and potassium levels should be monitored during use

LDL-C = low-density lipoprotein cholesterol; SGLT2 = sodium-glucose cotransporter-2