DIABETES DAY
FOR PRIMARY CARE PHYSICIANS

THIS ACTIVITY IS INTENDED FOR MDS, DOS, NPS, PAS, RNS, CDES, PHARMACISTS AND OTHER INTERESTED HEALTH CARE PROVIDERS

This activity is co-sponsored by American Association of Clinical Endocrinologists and Postgraduate Institute for Medicine.
New Paradigm in the Management of 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 and contraindications, and associated comorbidities.

• 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.
LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

LIFESTYLE STUDIES

• Finnish Diabetes Prevention Study
• US Diabetes Prevention Program
  • Goals: 7% weight loss, 150 minutes/week of moderately strenuous walking
• Chinese Da Qing Study
Diabetes Prevention Lifestyle Studies

The Finnish Diabetes Prevention Study: Lifestyle Modifications

- **Control (n=250)**
- **Diet Intervention (n=256)**

Increase of Diabetes Cases (Cases/100 Person-Years)

- **Control**: 87
- **Diet Intervention**: 37
- **Decrease**: 58%

Diabetes Prevention Program: Progression to Type 2 Diabetes

- **Control**
- **Intensive Lifestyle**

Cases/100 Person-Years

- **Control**: 13
- **Intensive Lifestyle**: 7
- **Decrease**: 58%

*All pairwise comparisons significantly different by group; sequential log-rank test.

Da Qing IGT and Diabetes Study

- **Control**
- **Diet**
- **Exercise**
- **Diet and Exercise**

% 6-Year Incidence of NIDDM

- **Control**: 37
- **Diet**: 23
- **Exercise**: 22
- **Diet and Exercise**: 19
- **Decreases**:
  - Diet: 31%
  - Exercise: 46%
  - Diet and Exercise: 42%

*p<.03
p<.0005
p<.005

**Adjusted for BMI and fasting glucose.

**Prediabetes Treatment Algorithm**

- Weight-loss agents lorcaserin and phentermine/topiramate can prevent progression to T2DM
  - Improve BP, triglycerides, and insulin sensitivity

- Metformin and acarbose can reduce progression to T2DM by 25% to 30%
  - Well tolerated, safe, confer CVD risk benefit

- TZDs prevented progression to T2DM in 60% to 75% of patients in clinical trials
  - Associated with adverse outcomes

- GLP-1 receptor agonists may be as effective as TZDs
  - Inadequate safety data
  - Promote weight loss

- TZDs and GLP-1 RAs reserved for patients not responding to conventional therapies or at highest risk for T2DM

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T2DM = type 2 diabetes mellitus; BP = blood pressure; CVD = cardiovascular disease; TZD = thiazolidinedione; GLP-1 = glucagon-like peptide-1; RA = receptor agonist

A1c ≤ 6.5%
For healthy patients without concurrent illness and at low hypoglycemic risk

A1c > 6.5%
Individualize goals for patients with concurrent illness and at risk for hypoglycemia
AACE Diabetes Algorithm

- **Guide therapy based on A1C level**
  - Focus on lifestyle intensification at all levels

- **Important tenets:**
  - Target A1C is <6.5%
    - Based on associated lower risk of micro- and macrovascular complications
    - Recommend monitoring A1C quarterly, along with fasting and postprandial blood glucose, with intensification of therapy until goal A1C is achieved
    - Individualize A1C target based on comorbidities
    - Patient should monitor fasting and postprandial blood glucose levels
  - Use agents with maximal efficacy, associated with lowest risk of hypoglycemia
    - Sulfonylureas are therefore much lower in algorithm
    - Earlier use of incretin mimetics and DPP-4 inhibitors to stimulate insulin secretion without hypoglycemia

A1C = glycated hemoglobin; DPP-4 = dipeptidyl-peptidase 4

Algorithm for Adding/Intensifying Insulin

START BASAL (long-acting insulin)

- **A1c < 8%**
  - TDD: 0.1–0.2 U/kg

- **A1c > 8%**
  - TDD: 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 4 U
  - FBG 140–180 mg/dL: add 2 U
  - FBG 110–139 mg/dL: add 1 U
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

Glycemic Control Not at Goal**

INTENSIFY (prandial control)

- **Add GLP-1 RA or DPP4-i**

- **Add Prandial Insulin**
  - TDD: 0.3–0.5 U/kg
  - 50% Basal Analog
  - 50% Prandial Analog
  - Less desirable: NPH and regular insulin or premixed insulin

Insulin titration every 2–3 days to reach glycemic goal:
- Increase basal TDD as follows:
  - Fixed regimen: Increase TDD by 2 U
  - Adjustable regimen:
    - FBG > 180 mg/dL: add 4 U
    - FBG 140–180 mg/dL: add 2 U
    - FBG 100–139 mg/dL: add 1 U
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

** Glycemic Goal:**
- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.
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
  - Hypoglycemic unawareness
  - Limited life expectancy
  - Severe comorbidities

Clinical Considerations

- Combining therapeutic agents with different modes of action may be advantageous

- Use insulin sensitizers such as metformin and/or TZDs as part of the therapeutic regimen in most patients (unless contraindicated or intolerance to these agents has been demonstrated)

- Insulin and secretagogues are the only medications that cause significant hypoglycemia
  - However, when metformin, TZD, DPP-4 inhibitors, and/or incretin mimetics (GLP-1 agonists) are used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline

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!**
Table 1: Effect of Glucose-lowering Drugs on Patient Weight

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>A1C &lt;7.0%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>✓</td>
<td>↑</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>✓</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>✓</td>
<td>↑</td>
</tr>
<tr>
<td>Metformin&lt;sup&gt;7&lt;/sup&gt;</td>
<td>✓</td>
<td>↔</td>
</tr>
<tr>
<td>DPP-4 inhibitor&lt;sup&gt;8&lt;/sup&gt;</td>
<td>✓</td>
<td>↔</td>
</tr>
<tr>
<td>GLP-1 receptor agonist&lt;sup&gt;9&lt;/sup&gt;</td>
<td>✓</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors&lt;sup&gt;10&lt;/sup&gt;</td>
<td>✓</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

# Biguanides

## Metformin

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↓↓ Hepatic glucose production 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</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 |

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
### Characteristics of DPP-4 Inhibitors

**Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin**

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

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

# Characteristics of GLP-1 Agonists

**Exenatide, Liraglutide**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mimic prolonged action of GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 0.5%–2.0% (depends on entry of glucose into bloodstream from gut)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once- or twice-daily injection*</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, vomiting, weight loss</td>
</tr>
<tr>
<td>Main risk</td>
<td>C-cell thyroid tumors**, long-term safety unknown</td>
</tr>
<tr>
<td>Associated with</td>
<td>Pancreatitis possible</td>
</tr>
</tbody>
</table>

*Dosing depends on GLP-1 agonist
**With liraglutide, in rodents only

A1C = glycated hemoglobin; GLP-1 = glucagon-like peptide-1


Exenatide [package insert]. San Diego, CA; Amylin Pharmaceuticals; 2010.
# Sulfonylureas

Glipizide, Glimepiride, Glyburide

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Insulin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>↓ FPG</td>
</tr>
<tr>
<td></td>
<td>↓ PPG</td>
</tr>
</tbody>
</table>

| Efficacy           | Moderate          |

| Advantages         | Strong short term efficacy |

| Disadvantages      | Weight gain, hypoglycemia, tend to loose efficacy after several years |

| Contraindications  | Avoid in severe hepatic and renal impairment |

Combinations available with metformin, TZD

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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 = post-prandial glucose

### Synthetic Human Amylin Analog

**Pramlintide**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Amylin mimetic: ↓PPG, suppresses glucagon secretion, slows gastric emptying, promotes satiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No dosage adjustment required in renal impairment</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Nausea, headaches, anorexia, vomiting, abdominal pain, fatigue, dizziness, coughing, pharyngitis, risk of severe hypoglycemia with insulin</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Confirmed diagnosis of gastroparesis, hypoglycemia unawareness</td>
</tr>
</tbody>
</table>
Recent Glycemia Trials

• Action to Control Cardiovascular Risk in Diabetes (ACCORD)
• Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation (ADVANCE)
• Veterans Affairs Diabetes Trial (VADT)
• All conducted in:
  – “Older” patients (≥60 years of age)
  – Patients with cardiovascular disease (CVD; 1/3 to 1/2 of cohorts)
  or
  – ≥1 CVD risk factors

The Ticking Clock

Increased risk for both microvascular and macrovascular disease begins early **in the prediabetic state**

- Insulin resistance is already present in patients with NGT who later develop T2DM
- Patients with prediabetes already have high insulin resistance and significantly decreased beta-cell function
- Both diabetic retinopathy, peripheral neuropathy, and nephropathy occur in patients with prediabetes
- Patients with prediabetes have a 2 to 3-fold increase in CHD risk, similar to patients with diabetes

CHD = coronary heart disease; NGT = normal glucose tolerance; T2DM = type 2 diabetes mellitus
Implications for Clinical Care

• The lack of significant reductions in CVD events should not lead clinicians to abandon the general target A1C of <7.0% or <6.5%
  – There is still a proven reduction in microvascular complications!

• Patients with diabetes need comprehensive care involving lipids, BP, and glycemic control

• Severe and/or frequent hypoglycemia should be avoided
  – Hypoglycemia is associated with sequelae that increase mortality, such as arrhythmia caused by lengthened QT interval

A1C = glycated hemoglobin; BP = blood pressure; CVD = cardiovascular disease

UKPDS: Benefits of Glycemic Control

Every 1% decrease in A1C led to significant reductions in diabetes-related complications

- 14% decrease in risk of myocardial infarction
- 21% decrease in risk of diabetes-related death
- 37% decrease in risk of microvascular complications
- 43% decrease in risk of amputation or PVD death

Decrease was statistically significant for all comparisons shown

Glucose and Cardiovascular (CV) Risk In Advanced Type 2 Diabetes

- If other CV risk factor control is good, there is no additional CV benefit of lowering A1C from 8.4% to 6.9% in older people with advanced DM (VADT)

- If other CV risk factor control is good, there may be CV harm in lowering A1C from 7.5% to 6.4% in older people with advanced DM (ACCORD), perhaps due to hypoglycemia (VADT)

- Therefore, it is important to individualize A1C targets

A1C = glycated hemoglobin; ACCORD = The Action to Control Cardiovascular Risk in Diabetes study; CV = cardiovascular; DM = diabetes mellitus; VADT = Veterans Affairs Diabetes Trial

Other Therapies

Bromocriptine

Bile Acid Sequestrants (Colesevelam)

Both classes of drugs likely affect hepatic and peripheral insulin resistance

Sodium Glucose Co-Transporter 2 (SGLT-2) Inhibitors (Canagliflozin, Dapagliflozin)

Block reabsorption of glucose in the proximal tubules of the kidney
Bromocriptine QR: Proposed Mechanism of Action

Morning administration (within 2 hours of waking) → Low dopaminergic tone in hypothalamus in early morning in diabetes → Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)

- Increased sympathetic tone
- Increased HPA axis tone
- Increased hepatic gluconeogenesis
- Increased FFA and TG
- Increased insulin resistance
- Increased inflammation/hypercoagulation

Impaired glucose metabolism, hyperglycemia and insulin resistance
Adverse cardiovascular pathology

Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity) → Decreased sympathetic tone
Decreased HPA axis tone
Decreased hepatic gluconeogenesis
Decreased FFA and TG
Decreased insulin resistance
Decreased inflammation/hypercoagulation

Decreased postprandial glucose levels
Reduction in insulin resistance
Day-long reduction in plasma glucose, TGs, and FFAs

FFA = free fatty acid; HPA = hypothalamic-pituitary-adrenal; TG = triglyceride

Bromocriptine-QR (Quick Release)

• This dopamine receptor agonist is indicated as an adjunct to diet and exercise to improve glycemic control in adults with diabetes

• The specific mechanism by which bromocriptine mesylate improves glycemic control is not known

• Patients with type 2 diabetes should take bromocriptine mesylate within 2 hours of waking in the morning

• An initial daily dose of 0.8 mg should be titrated weekly until a maximum tolerated dose of 1.6 mg to 4.8 mg is achieved

• Possible decreased risk for cardiovascular events with bromocriptine

Bromocriptine Effect on A1C in Combination with Other Oral Hypoglycemic Agents (OHA)


Sodium Glucose Co-Transporter 2 Inhibitors

Inhibit sodium-glucose transport protein subtype 2 (SGLT2)
Responsible for at least 90% of glucose reabsorption in the kidney
Blood glucose is eliminated in the urine

Renal handling of glucose in a non-diabetic individual. Virtually all the glucose filtered is reabsorbed, and none appears in the urine. The locations for sodium-glucose co-transporter 2 (SGLT2) and SGLT1 are shown.

**SGLT2 Inhibitors**

**Canagliflozin and Dapagliflozin (under submission)**

### Potential advantages

- Insulin-independent glucose reduction (A1C ↓0.8% to 1.2%)
- Low risk of hypoglycemia
- Weight loss (to 4% BW)
- Blood pressure-lowering

### Potential disadvantages

- Osmotic diuresis
  - Polyuria and lightheadedness
- Bacterial urinary tract infections (≈5%)
- Fungal genital infections (≈10%)
- Increased LDL cholesterol
- Hyperkalemia
- Breast/bladder cancer concerns (dapagliflozin)

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A1C = glycated hemoglobin; BW = body weight; LDL = low-density lipoprotein

Glucose Control With Canagliflozin

<table>
<thead>
<tr>
<th>Treatment (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>ΔA1C (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.0</td>
<td>0.14</td>
<td>584</td>
</tr>
<tr>
<td>Monotherapy 26 Weeks¹</td>
<td>8.1</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Add-on to Metformin 12 Weeks²</td>
<td>8.0</td>
<td>-0.77</td>
<td>451</td>
</tr>
<tr>
<td>Add-on to Metformin + SU 52 Weeks³</td>
<td>7.8</td>
<td>-0.74</td>
<td>755</td>
</tr>
<tr>
<td>Add-on to OAs +/- Insulin in CKD* 26 Weeks⁴</td>
<td>7.6</td>
<td>-0.76</td>
<td>269</td>
</tr>
</tbody>
</table>

ΔA1C (%)

-0.8  -0.6  -0.4  -0.2  0  0.2

-1.2 -1  -0.8 -0.6 -0.4 -0.2  0  0.2

-1.03 ** -0.77 ** -0.76 ** -0.92 ** -0.66 -1.03 †

*Estimated glomerular filtration rate 30-50 mL/min/1.73 m²

**P<0.001 vs placebo. ***P<0.05 vs placebo.

†Met criteria for noninferiority and superiority (upper limit of confidence interval <0.0%)

Treatment of Type 2 Diabetes
What Have We Learned?

• Outlined the clinical considerations in the selection of pharmacotherapy for type 2 diabetes

• Discussed the role of combination therapy and when it should be initiated based on A1C goals

• Discussed modes of action and clinical potential of recently introduced agents in the management of patients with type 2 diabetes

• Explained the implications of recent clinical trials and meta-analyses on clinical practice decisions