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
Medical expenditures for people with DM are 2.3 times higher than those without DM.

The primary driver of increased cost is the increasing prevalence of DM.

Despite the introduction of new classes of medications for DM treatment, anti-diabetic agents and supplies only account for 12% of medical expenditures.

DM = diabetes mellitus.

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

Prediabetes Treatment Algorithm

- Weight-loss agents orlistat, 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% - 30%
  - Use for prediabetes is off-label
  - Both are safe, confer CVD risk benefit; metformin is well tolerated
- TZDs prevented progression to T2DM in 60% - 75% of patients in clinical trials
  - Associated with adverse outcomes
- GLP-1 receptor agonists may be as effective as TZDs
  - Promote weight loss, but inadequate safety data
- TZDs and GLP-1 RAs reserved for patients not responding to conventional therapies or at highest risk for T2DM

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

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%
For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
Approach to Management of Hyperglycemia

Glycemic Management of Type 2 Diabetes: Treatment Goals

Lowering A1C

Preventing Hypoglycemia

Individualized Algorithm
UKPDS: Benefits of Glycemic Control

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

Decrease was statistically significant for all comparisons shown.


PVD=Peripheral Vascular Disease
Main Pathophysiological Defects in T2DM

“The Ominous Octet”

Islet β-cell
- Impaired insulin secretion

Decreased incretin effect

Islet α-cell
- Increased glucagon secretion

Increased hepatic glucose production

Increased lipolysis

Increased glucose reabsorption

Decreased glucose uptake

Neurotransmitter dysfunction

Decline in β-Cell Function with Diabetes Progression: UKPDS

Rx: Insulin, Metformin, Sulfonylurea

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.

Hepatic Insulin Resistance: Increased Hepatic Glucose Output


FPG=Fasting Plasma Glucose
Current Antihyperglycemic Medications

12 groups with different mechanisms of action

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

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 \( \uparrow \) PP and FPG, GLP-1 if \( \uparrow \uparrow \) PP, TZD if metabolic syndrome or NAFLD, AGI if \( \uparrow \) 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

**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></td>
<td>Glinides</td>
<td>Biguanides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td></td>
<td>TZDs</td>
<td>Colesevelam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td>Amylin</td>
<td>GLP-1 RA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TZDs</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>SGLT-2 inhibitors</td>
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</tr>
</tbody>
</table>

**Glucose**

- Production
- Uptake
- Release
- Absorption
- Sensitivity
- Reabsorption
- 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

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**

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

| Efficacy      | Moderate           |

| Advantages    | Strong short term efficacy |

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

| Contraindications | Avoid in severe hepatic and renal impairment |

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.

# Alpha-Glucosidase Inhibitors

**Acarbose, Miglitol**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↓ Rate of gut polysaccharide breakdown, thereby slowing absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%-1.0%), PPG lowering</td>
</tr>
<tr>
<td>Advantages</td>
<td>Weight-neutral, non-systemic drug, targets post-prandial glucose</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Bloating, flatulence, diarrhea – ↓ w/slow titration, frequent dosing</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Severe renal impairment, diabetic ketoacidosis, malabsorption, obstruction, inflammatory bowel, or conditions aggravated by gas production</td>
</tr>
</tbody>
</table>

Combinations available with sulfonylureas

A1C = glycated hemoglobin; PPG = post-prandial glucose

## Dopamine Receptor Agonist

### Bromocriptine QR

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Exact mechanism of action unclear, believed to reduce sympathetic tone, inflammation, and insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>May decrease cardiovascular risk</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Hypotension, syncope, hypoglycemia, nausea</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of psychosis or during breastfeeding. Use caution with renal or hepatic impairment.</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; QR = quick-release

## 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

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
Inhibition of DPP-4 Increases Active Incretin Levels, Enhancing Downstream Incretin Actions

- Increased insulin secretion
- Decreased glucagon release

Glucose control improved

GIP = glucose-dependent insulino tropic peptide

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>
</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

Comparative Efficacies of DPP-4s

Placebo-corrected Change From Baseline In A1C: Monotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mean ΔHbA1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin1</td>
<td>12.5mg</td>
<td>-0.56</td>
</tr>
<tr>
<td></td>
<td>25mg</td>
<td>-0.59</td>
</tr>
<tr>
<td>Linagliptin2</td>
<td>5mg</td>
<td>-0.6</td>
</tr>
<tr>
<td></td>
<td>5mg</td>
<td>-0.7</td>
</tr>
<tr>
<td>Saxagliptin2</td>
<td>5mg</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>5mg</td>
<td>-0.6</td>
</tr>
<tr>
<td>Sitagliptin2</td>
<td>100mg</td>
<td>-0.6</td>
</tr>
<tr>
<td></td>
<td>100mg</td>
<td>-0.6</td>
</tr>
<tr>
<td>Vildagliptin3</td>
<td>50mg BID</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td>50mg</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

The current DPP-4s have comparative efficacy

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.
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

Sodium Glucose Co-Transporter 2

Reabsorption of glucose is mediated by SGLTs in proximal convoluted tubule

- Independent of insulin

- SGLT2 and SGLT1
  - located on luminal surface of epithelial cells lining proximal convoluted tubule

- SGLTs in other organs
  - 2: liver
  - 1: small intestine

90% glucose is reabsorbed in S1 by SGLT2

  - Low affinity, high capacity transporter

10% reabsorbed in S3 by SGLT1

  - High affinity, low capacity transporter

Bays, H. Diabetes Therapy, 2013
Efficacy of SGLT2 Inhibitors as Monotherapy

<table>
<thead>
<tr>
<th></th>
<th>CANA</th>
<th>DAPA</th>
<th>EMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>100</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Δ A1C, %</td>
<td>0.14</td>
<td>-0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>PBO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>-0.77</td>
<td>-0.77</td>
<td>-0.66</td>
</tr>
<tr>
<td>300</td>
<td>-1.03</td>
<td>-0.89</td>
<td>-0.78</td>
</tr>
</tbody>
</table>

$P<0.001$ vs PBO for all

Phase 3 trials, BL A1C 7.8% to 8.1%, 24-26 weeks.

Weight Effects with SGLT2 Inhibitors\textsuperscript{a} as Monotherapy

- US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.

\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 (\(P < .05\)).
SGLT 2 Inhibition: Meeting Unmet Needs in Diabetes Care

Corrects a Novel Pathophysiologic Defect

Reduces A1C

Promotes Weight Loss

Complements Action of Other Antidiabetic Agents

Improves Glycemic Control and CVRFs

No Hypoglycemia

Reduces Blood Pressure

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 (↓ 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>
Clear Findings from EMPA-REG

• EMPA-REG studied a high-risk group of people
  - Mean age 63 years
  - Type 2 diabetes X 10 years; mean A1C 8.1%
  - Proven CV disease with prior heart failure in 10%
  - eGFR between 30-60 mL/min in 20%
  - Cardioprotective Rx (statins 77%, ACEi 81%, ASA 83%)
  - MACE event rate ~ 4%/year, CV death rate ~ 1.8%/year

• In 7,020 such people, empagliflozin (10 or 25 mg/day)
  - Clearly reduces CV death and heart failure hospitalization
  - Starts to reduce these outcomes within 3 months

• There is no clear MI or stroke effect over 3 years of treatment
  - The “composite” outcome may not be relevant
  - The effect on its 3 components appears heterogeneous

ASA = aspirin; ACEi = angiotensin-converting enzyme inhibitors; CV = cardiovascular; eGFR = estimated glomerular filtration rate; MACE = Major Adverse Cardiac Events; MI = myocardial infarction.

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
Empagliflozin/Jardiance®PI 2016.; Dapagliflozin/Farxiga® @ PI 2016.; Canagliflozin/Invokana® @ PI 2016.
Landmark 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

Reasons for Death in UKPDS Intensive Treatment Arm: 10-Year Follow-Up

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal MI or SD</td>
<td>231</td>
<td>(8.4%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>120</td>
<td>(4.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>74</td>
<td>(2.9%)</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>43</td>
<td>(1.6%)</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>16</td>
<td>(0.6%)</td>
</tr>
<tr>
<td>Accidents</td>
<td>5</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>PVD</td>
<td>2</td>
<td>(0.07%)</td>
</tr>
<tr>
<td>Hypo- or Hyperglycemia1</td>
<td></td>
<td>(0.04%)</td>
</tr>
</tbody>
</table>

Accidents, PVD, Hypo- & Hyperglycemia:
- Accidents: 15%
- PVD: 24%
- Hypo- & Hyperglycemia: 2.5%
- Renal: 3.3%
- MI or SD: 47%
- Other: 8.7%
- Stroke: 3.3%

## CVD Outcomes in ACCORD, ADVANCE, and VADT

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td>Intensive</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1%</td>
<td>8.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Final</td>
<td>6.4%</td>
<td>7.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>CVD/year</td>
<td>2.1%</td>
<td>2.3%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

**ACCORD** = The Action to Control Cardiovascular Risk in Diabetes study; **ADVANCE** = The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial; **CVD** = cardiovascular disease; **VADT** = Veterans Affairs Diabetes Trial
Meta-analysis: Cardiovascular Outcomes Trials in Diabetes
Effect of Intensive Control of Glucose on Cardiovascular Outcomes and Deaths in Patients with Diabetes Mellitus

A Meta-analysis of Randomized Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th>UKPDS</th>
<th>PROactive</th>
<th>ADVANCE</th>
<th>VADT</th>
<th>ACCORD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>4620</td>
<td>5238</td>
<td>11140</td>
<td>1791</td>
<td>10251</td>
<td>33040</td>
</tr>
<tr>
<td><strong>Years</strong></td>
<td>10.1</td>
<td>2.9</td>
<td>5.0</td>
<td>5.6</td>
<td>3.5</td>
<td>4.95</td>
</tr>
<tr>
<td><strong>Patient-years</strong></td>
<td>46,237</td>
<td>15,059</td>
<td>55,700</td>
<td>10,030</td>
<td>35,879</td>
<td>162,905</td>
</tr>
<tr>
<td><strong>Control A1C</strong></td>
<td>7.9%</td>
<td>7.6%</td>
<td>7.3%</td>
<td>8.4%</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Intensive A1C</strong></td>
<td>7.0%</td>
<td>7.0%</td>
<td>6.8%</td>
<td>6.9%</td>
<td>6.4%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>
Probability of Non-fatal Myocardial Infarction Events with Intensive Glucose-lowering vs. Standard Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS&lt;sup&gt;4,7&lt;/sup&gt;</td>
<td>3071/1549, 221/141</td>
<td>21.8%</td>
<td>0.78 (0.62–0.98)</td>
</tr>
<tr>
<td>PROactive&lt;sup&gt;18–20&lt;/sup&gt;</td>
<td>2605/2633, 119/144</td>
<td>18.0%</td>
<td>0.83 (0.64–1.06)</td>
</tr>
<tr>
<td>ADVANCE&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5571/5569, 153/156</td>
<td>21.9%</td>
<td>0.98 (0.78–1.23)</td>
</tr>
<tr>
<td>VADT&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>892/899, 64/78</td>
<td>9.4%</td>
<td>0.81 (0.58–1.15)</td>
</tr>
<tr>
<td>ACCORD&lt;sup&gt;8&lt;/sup&gt;</td>
<td>5128/5123, 186/235</td>
<td>28.9%</td>
<td>0.78 (0.64–0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773, 743/754</td>
<td>100%</td>
<td>0.83 (0.75–0.93)</td>
</tr>
</tbody>
</table>

Non-fatal myocardial infarction

Probability of Coronary Heart Disease Events with Intensive Glucose-lowering vs. Standard Treatment

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td>UKPDS\textsuperscript{4,7}</td>
<td>3071/1549</td>
</tr>
<tr>
<td>PROactive\textsuperscript{18–20*}</td>
<td>2605/2633</td>
<td>164/202</td>
<td>20.2%</td>
</tr>
<tr>
<td>ADVANCE\textsuperscript{5}</td>
<td>5571/5569</td>
<td>310/337</td>
<td>36.5%</td>
</tr>
<tr>
<td>VADIT\textsuperscript{21,22}</td>
<td>892/899</td>
<td>77/90</td>
<td>9.0%</td>
</tr>
<tr>
<td>ACCORD\textsuperscript{8}</td>
<td>5128/5123</td>
<td>205/248</td>
<td>25.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1182/1136</td>
<td>100%</td>
</tr>
</tbody>
</table>

Coronary heart disease events

Probability of Stroke with Intensive Glucose-lowering vs. Standard Treatment

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS\textsuperscript{4,7}</td>
<td>3071/1549</td>
<td>160/78</td>
<td>5.2%</td>
</tr>
<tr>
<td>PROactive\textsuperscript{18-20*}</td>
<td>2605/2633</td>
<td>86/107</td>
<td>20.5%</td>
</tr>
<tr>
<td>ADVANCE\textsuperscript{5}</td>
<td>5571/5569</td>
<td>238/245</td>
<td>51.4%</td>
</tr>
<tr>
<td>VADT\textsuperscript{21,22}</td>
<td>892/899</td>
<td>28/36</td>
<td>6.8%</td>
</tr>
<tr>
<td>ACCORD\textsuperscript{8}</td>
<td>5128/5123</td>
<td>76/72</td>
<td>16.2%</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>588/539</td>
<td>100%</td>
</tr>
</tbody>
</table>

Probability of All-cause Mortality with Intensive Glucose-lowering vs. Standard Treatment

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS(4,7)</td>
<td>3071/1549</td>
<td>539/302</td>
<td>10.1%</td>
</tr>
<tr>
<td>PROactive(18-20^*)</td>
<td>2605/2633</td>
<td>177/186</td>
<td>21.5%</td>
</tr>
<tr>
<td>ADVANCE(5)</td>
<td>5571/5569</td>
<td>498/533</td>
<td>29.4%</td>
</tr>
<tr>
<td>VADT(21,22)</td>
<td>892/899</td>
<td>102/95</td>
<td>15.5%</td>
</tr>
<tr>
<td>ACCORD(8)</td>
<td>5128/5123</td>
<td>257/203</td>
<td>23.6%</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1573/1319</td>
<td>100%</td>
</tr>
</tbody>
</table>

All-cause mortality

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

Recent ACCORD Data

• The most recently published ACCORD data show significant decreases in CVD risk with intensive therapy.
  – Study included data on over 10,000 adults, ages 40 to 79, randomized to receive standard or intensive therapy
  – Patients received active therapy for a mean 3.7 years, further follow-up was 1-2 years

• Intensive therapy resulted in lowered 5-year incidence for:
  – Ischemic heart disease coronary revascularization (13%)
  – Coronary revascularization (16%)
  – Any myocardial infarction (19%)
  – Unstable angina (16%)
  – Non-fatal myocardial infarction (19%)

CVD = cardiovascular disease

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