Managing Cardiovascular Risk in Patients with Type 2 Diabetes: Emerging Concepts
Ashlyn Smith, PA-C

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  - Secretary on the board of directors for the American Society of Endocrine Physician Assistants
  - Adjunct Assistant Professor at Midwestern University

- Disclosures: Speaker’s Bureau and Advisory Board for Abbott nutrition

- AAPA received independent educational grants from AstraZeneca and Novo Nordisk to support the development of this activity
Managing Cardiovascular Risk in Patients with Type 2 Diabetes: Emerging Concepts

At the end of this module, you’ll be able to:

• Describe the pathophysiology of type 2 diabetes and CVD.
• Review the results of previous strategies addressing cardiovascular risk through glucose control.
• Identify the role of the rosiglitazone controversy in ushering in a new era of CV outcome studies mandated by the FDA for type 2 diabetes agents.
• Summarize the results of recent cardiovascular outcome trials.
• Differentiate among agents based on their cardiovascular profile as new data emerge from trials.
• Select an appropriate second agent based on a patient’s cardiovascular risk profile.
Diabetes and Cardiovascular Disease in United States

**Diabetes**
- 23.4 diagnosed
- 7.6 undiagnosed
- 81.6 pre-diabetes

**CVD**
- 92.1 million

- CVD more common in people with diabetes than those without


Cardiovascular Disease and Diabetes

- When CVD present, more aggressive course with worse prognosis
- Adults with diabetes 2 to 4 times more likely to die from CVD than adults w/o diabetes
- Middle-aged individuals with diabetes and no CVD same risk for MI as individual w/o diabetes and CVD history

Modifiable Diabetes, Dyslipidemia, Hypertension, Obesity/overweight, Smoking

Nonmodifiable Family history, Age, Sex

Pathophysiology of Type 2 Diabetes and CVD
Hyperglycemia, other cardiometabolic factors promote
- macrovascular complications
- microvascular complications
Alterations in vascular homeostasis promote proinflammatory, prothrombotic state
Macro- and microvessels differ
- size
- architecture
- cellular components
- function

Pathophysiology: Vasculature

Macrovascular Disease Complications

- Cerebrovascular Disease
- Peripheral Artery Disease
- Coronary Heart Disease
Macrovascular complications include:

- Atherosclerosis
  - Dyslipidemia
  - Atherosclerotic plaque
- Endothelial dysfunction
- Oxidative stress

- Up to 97% of patients with diabetes dyslipidemic
- Predominantly small, dense LDL
  - Susceptible to oxidation
  - Triggers immune response that generate atherosclerotic plaque

- Early indicator of diabetic vascular disease
- Reflects imbalance of regulators of vascular tone and blood fluidity
- Most cardiometabolic factors contributing to development of endothelial dysfunction in diabetes impact oxidative stress

Microvascular Disease Complications

Retinopathy

Nephropathy

Neuropathy
Diabetes and the Microvasculature

- Microvessels maintain blood pressure, deliver nutrients
- Regulatory systems in microcirculation can adapt flow to local metabolic needs
- Diabetes-induced changes include alterations in capillary basement membrane → microvessel thickening and abnormal function
- Diabetes causes defects in autonomic nervous system, worsening microvascular disease
  - Cardiovascular autonomic neuropathy (CAN) associated with impaired autoregulation of blood flow in various vascular beds, including in heart
  - CAN → higher CV mortality rates

Pivotal Trials: Intensive Glycemic Control and CVD Risk
Landmark Trials Assessing Intensive Glycemic Control

Series of trials comparing intensive versus standard therapy for glycemic control

- Diabetes Control and Complications Trial (DCCT) (1993)
- United Kingdom Prospective Diabetes Study (UKPDS) (1998)
- Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD) (2008)
- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial (ADVANCE) (2008)
- Veterans Affairs Diabetes Trial (VADT) (2009)
DCCT and UKPDS

**DCCT (N = 1,441)**
- Primary endpoint: appearance and progression of background retinopathy
- Baseline A1C 8.9%, fell to ~7% at 6 mos, maintained with intensive therapy (INT)
- At mean 6.5 years F/U, intensive therapy reduced risk of developing retinopathy by 76% and slowed progression by 54%
- No significant changes in macrovascular endpoints

**UKPDS (N = 3,867)**
- Primary endpoint: reduction of risk of microvascular and macrovascular complications
- Over 10 years, median A1C reduced 11% with INT (7.0% vs. 7.9%; p < 0.0001)
- Risk in INT 12% lower for any diabetes-related endpoint (p = 0.029)
- No significant reductions in macrovascular endpoints

Results led ADA to recommend A1C target of <7% as reasonable goal for nonpregnant adults with type 2 diabetes.

DCCT and UKPDS

- No benefit in macrovascular complications
- Was patient population too young and healthy?

<table>
<thead>
<tr>
<th>Patients in these trials older with existing CV disease or risk</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>A1C (intensive vs. conventional)</td>
<td>1 year: 6.4% vs. 7.5%</td>
<td>5-year F/U: 6.5% vs. 7.3%</td>
<td>5.6-year F/U: 6.9% vs. 8.4%</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Trial stopped early at 3.7 years because INT significantly increased all-cause and CV mortality</td>
<td>Significant reductions in microvascular but not macrovascular complications</td>
<td>No significant differences in endpoints, including microvascular complications</td>
</tr>
</tbody>
</table>

Hypoglycemia with INT in all trials

ACCORD, ADVANCE, and VADT results
• No macrovascular benefit
• Increased mortality in ACCORD
• Hypoglycemia significantly affected morbidity in these patients

ADA/EASD position statement
• Treatment and goals should be more patient centered
• Take individual factors into consideration

For older patients and patients with CV risk, less stringent target A1C (7.5%-8.0% or higher) may be appropriate.
After treatment ended, the protective effects of more intense glycemic control endured, producing a legacy effect, referred to as metabolic memory.

**DCCT/EDIC**

- Year 11 of EDIC (2004): A1C difference 0.1% but risk of CVD event ↓ by 42%, risk of nonfatal MI/stroke/CV death ↓ by 57%.
- Year 18 of EDIC (30 years after DCCT started): A1C 8% in both groups; risk of CVD event ↓ by 30%

**UKPDS**

- 10-year post-interventional study: between-group A1C differences gone, INT therapy continued to produce greater risk reduction in any diabetes-related endpoint (which included both microvascular and macrovascular events)

Metabolic Memory...Lapses?

**VADT**

- At 5.6 years → nonsignificant reduction in macrovascular outcomes for patients on intensive therapy
- At 10 years → significant 17% reduction in macrovascular events for patients on intensive therapy, demonstrating a legacy effect
- At 15 years → A1C levels converged; cardioprotective effect diminished to nonsignificant 9% risk difference

Conclusion: Persistent glucose lowering is needed to maintain cardioprotection.

Rosiglitazone and Cardiovascular Outcomes
Rosiglitazone Meta-analysis

- TZD approved in 1999
- Meta-analysis published in 2007
  - Rosiglitazone vs. active comparators ➔ CV outcomes
  - 42 trials, 27,847 patients
  - MI: 86 vs. 72
  - Deaths from CV causes: 39 vs. 22
- Possible reason: rosiglitazone increased LDL levels, possibly precipitated HF in susceptible patients
- Because of short trial duration, authors speculated rosiglitazone may be capable of provoking MI or CV death after a short time

Rosiglitazone Warning

A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

- FDA issued black box warning in November 2007
  - Rosiglitazone could increase risk of MI and angina
- New data emerged that rosiglitazone did not increase MI risk
- FDA removed black box warning entirely in 2013
FDA Guidance Document

- Issued December 2008
- Sets expectations for the development of antidiabetes agents
- Focused on CV safety in acknowledging burden of CVD in type 2 diabetes
- FDA guidance documents not legally enforceable BUT tend to be followed as FDA is the U.S. authority to approve or decline new pharmacological agents
### FDA Guidance Document: CVOT Components

<table>
<thead>
<tr>
<th>Independent Cardiovascular Endpoints Committee</th>
<th>Appropriately Design Phase II and III Clinical Trials for Meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>To prospectively adjudicate, in a blinded fashion, CV events during all phase II/III trials</td>
<td>Designed so a meta-analysis can be performed at study completion</td>
</tr>
<tr>
<td>Protocol should describe statistical methods for the proposed meta-analysis, including endpoints that will be assessed</td>
<td>Should include patients at higher risk of CV events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Methods for Proposed Meta-analysis</th>
<th>Perform Meta-analysis of Important CV Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform a meta-analysis of the important CV events across phase II/III clinical trials</td>
<td>Explore similarities and/or differences in subgroups</td>
</tr>
</tbody>
</table>

CVOT = cardiovascular outcomes trial

Clinical Trials: Research Papers

- Constructed to conform to universal guidelines and style
- Predictably organized
- Reader can apply consistent approach to reading and evaluating
  - Individually or compare multiple papers/trials
- Title and abstract summarize overall trial
  - May be enough information to determine whether the article is of value to be read in full
- Is article peer-reviewed?

<table>
<thead>
<tr>
<th></th>
<th>Single Blind</th>
<th>Double Blind</th>
<th>Triple Blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Author</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Editor</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Assessing Trials: Patient Population

- Review inclusion/exclusion criteria
- Compare demographics of trial patients to practice patients
  - Older? Healthier? Heavier?
  - Different comorbid conditions?
- Factors may change trial and real-world experience

<table>
<thead>
<tr>
<th></th>
<th>UKPDS</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>3,867</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Age, mean (yrs)</td>
<td>53.3</td>
<td>62.2</td>
<td>66</td>
<td>60.4</td>
</tr>
<tr>
<td>Female (%)</td>
<td>39</td>
<td>38.5</td>
<td>42.4</td>
<td>3</td>
</tr>
<tr>
<td>White (%)</td>
<td>81</td>
<td>64.4</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>Newly diagnosed</td>
<td>10</td>
<td>7.9</td>
<td>11.5</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.08</td>
<td>8.1</td>
<td>7.51</td>
<td>9.4</td>
</tr>
</tbody>
</table>

**UKPDS** patients: younger, newly diagnosed with diabetes

**VADT** patients: fewer in number, overwhelmingly male, much higher baseline A1C
Assessing Trials: Study Design

- Methods section outlines design
  - Subject allocation
  - Treatment, support, follow-up protocols
  - Blinding helps reduce bias
- Clinical trial phases provide additional information about design and endpoints

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Determine safety of drug; dosing to use in later trials; short-term side effects (first-in-man trials)</td>
</tr>
<tr>
<td>II</td>
<td>Learn whether drug initially works and more about safety; refine dosing</td>
</tr>
<tr>
<td>III</td>
<td>Answer central question how drug works versus standard treatment; monitor safety and side effects</td>
</tr>
<tr>
<td>IV</td>
<td>Provide additional information about treatment, risks, benefits, and best use (post-marketing following FDA approval)</td>
</tr>
</tbody>
</table>

Assessing Trials: Endpoints and Comparisons

• Endpoints should be detailed and defined
  • Measurement reproducible and precise?
  • Clinically meaningful to real-world patients?
• Primary outcomes (e.g., event recurrence) more meaningful than surrogate measures (e.g., biomarkers)
• Scientific question should dictate whether a trial intends to prove superiority, equivalence, or noninferiority
  • If a trial intended to show superiority and did not (suggesting the treatment is not effective), investigators could not simply switch to an equivalence study as sample size would be inappropriate and the acceptable difference would not have been defined in advance
• In the CVOTs, most trials powered to show noninferiority
  • Clarified whether finding of superiority was truly supported by the patient population numbers to qualify as such
Assessing Trials: Results

- Articles should provide as much data as possible to demonstrate depth, breadth of effects
  - Help determine applicability, generalizability
- Statistically significant p value usually interpreted to mean presence of an important effect
  - Statistically, p value combines effect size (difference between 2 groups) and precision (variation of that difference seen in the confidence interval)
  - As study gets smaller in size, so does precision
  - Most trials consider p < 0.05 to be statistically significant
- Confidence intervals indicate reliability of an estimate or sampling
  - A 95% CI level means that 95% of intervals computed would include the true value

Achieving Noninferiority and Superiority

Noninferiority
- Upper CI bound typically <1.3*
- Study drug no worse than comparator
- CV safety demonstrated

Superiority
- Upper CI bound typically <1.0*
- Study drug reduced CV outcomes relative to comparator
- CV efficacy demonstrated

*Criteria may vary with study design.

McAlister FA. CMAJ. 2008;179:549-53.
Cardiovascular Outcomes Trials
Since FDA issued guidance >25 CVOTs have launched.

CVOTs differ from glycemic efficacy trials, add different information to the decision-making process.

Primary endpoint: major adverse cardiac events (MACE).

### CV Outcomes Versus Glycemic Efficacy Trials

<table>
<thead>
<tr>
<th>Glycemic Efficacy Trial</th>
<th>CVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Drug efficacy</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>~300-600</td>
</tr>
<tr>
<td>Duration</td>
<td>26-104 weeks</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo or active comparator</td>
</tr>
<tr>
<td>CV Risk</td>
<td>Low or minimal</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Glycemic endpoints (HbA1C, blood glucose)</td>
</tr>
</tbody>
</table>

- **3-point MACE** = cardiovascular death, nonfatal myocardial infarction, nonfatal stroke
- **4-point MACE** = 3-point MACE + additional CV endpoint (acute coronary syndrome or hospitalization for heart failure or unstable angina)


DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors ("gliptins")

- Block DPP-4, an enzyme that inactivates incretins; this action
  - Increases incretin
  - Increases insulin secretion, thereby lowering blood glucose levels
### DPP-4 Inhibitor CVOTs: Primary Endpoint

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent</th>
<th>Saxagliptin</th>
<th>Alogliptin</th>
<th>Sitagliptin</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>7.3</td>
<td></td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXAMINE</td>
<td>11.3</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TECOS</td>
<td>11.4</td>
<td></td>
<td>11.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARMELINA</td>
<td>12.4</td>
<td></td>
<td>12.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All p < 0.001 for noninferiority

DPP-4 Inhibitors: Heart Failure Risk

- Significantly more patients taking saxagliptin in SAVOR-TIMI 53 hospitalized for heart failure (HHF)
- Investigators delved into HHF data and found
  - Patients in SAVOR-TIMI 53 who were HHF were significantly sicker at baseline and had higher NT-proBNP levels
  - EXAMINE found alogliptin increased risk for HHF in patients with no history of HF at baseline
- FDA conducted safety review and determined medicines containing saxagliptin and alogliptin may increase HF risk
  - In April 2016, required updated warning labeling for saxagliptin or alogliptin
  - In August 2017, added warning to sitagliptin and linagliptin labeling (despite no trial signals); suggesting concern this may be a class effect

Linagliptin is being investigated in another CVOT

**CAROLINA** (N = 6,103)
- Type 2 diabetes and increased CV risk
- Randomized to linagliptin or glimepiride
  - Active – not placebo – controlled
- Primary endpoint: 4-point MACE (+ hospitalization for unstable angina)
- Key secondary endpoints
  - 3-point MACE
  - Maintenance of A1C ≤7% without severe hypoglycemia or weight gain
  - Need for rescue medicine
- Expected completion: March 2019

Glucagon-like peptide-1 (GLP-1) receptor agonists

- Non-insulin injectable medications
- Act like incretin hormones such as GLP-1 (“incretin mimetics”)
- Bind to GLP-1 receptors and activate GLP-1 receptors in many tissues → stimulate glucose-dependent insulin release, suppress appetite, and inhibit glucagon secretion
GLP-1 Receptor Agonist CVOTs: Primary Endpoint

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>p for Noninferiority</th>
<th>p for Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>13%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>14.9</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>LEADER</td>
<td>Albiglutide</td>
<td>13%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>Exenatide</td>
<td>22%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Semaglutide</td>
<td>26%</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>Liraglutide</td>
<td>7%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

## GLP-1 Receptor Agonists: Completed Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Inclusion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA (Lixisenatide)</td>
<td>Patients with an acute coronary event within 180 days prior to screening</td>
<td>Significant clinical and metabolic effects (A1C, body weight, systolic blood pressure)</td>
</tr>
<tr>
<td>LEADER (Liraglutide)</td>
<td>Patients &gt;50 years with established CVD or &gt;60 years with at least 1 CV risk factor</td>
<td>FDA approved indication to reduce CV risk in patients with T2DM and CVD</td>
</tr>
<tr>
<td>SUSTAIN-6 (Semaglutide)</td>
<td>Evaluated 2 dosages of semaglutide in high CV risk patients with established CVD, chronic HF, and/or CKD</td>
<td>Significant clinical and metabolic effects (A1C, body weight, systolic blood pressure)</td>
</tr>
<tr>
<td>EXSCEL (Exenatide)</td>
<td>Pragmatic trial design to enhance generalizability (various levels of CV risk, open-label medications for diabetes treatment)</td>
<td>Authors thought possible reasons for lack of CV efficacy might have been shorter follow-up and treatment exposure</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>Patients ≥40 years of age with type 2 diabetes, an A1C level &gt;7.0%, and established CVD</td>
<td>Median follow-up was only 1.6 years and albiglutide no longer on market</td>
</tr>
</tbody>
</table>

GLP-1 Receptor Agonists: Current Investigations

- **REWIND** (N = ~9,900)
  - Assess dulaglutide vs. placebo
  - Primary endpoint: 3-point MACE
  - Patient characteristics make results more generalizable
  - Completed: August 2018
  - Preliminary results: significant reduction in primary endpoint
  - Will be presented at 2019 ADA meeting

- **PIONEER 6** (N = 3,176)
  - Assess oral formulation of semaglutide vs. placebo
  - Primary endpoint: 3-point MACE
  - Completed: September 2018
  - Preliminary results: noninferiority versus placebo

SGLT2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors increase urinary glucose excretion by interfering with glucose reabsorption in the proximal renal tubule.

<table>
<thead>
<tr>
<th>MACE Trials</th>
<th>Heart Failure Secondary Trials</th>
<th>Renal Secondary Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME (Empagliflozin)</td>
<td>Dapa-HF (Dapagliflozin)</td>
<td>Dapa-CKD (Dapagliflozin)</td>
</tr>
<tr>
<td>CANVAS Program (Canagliflozin)</td>
<td>EMPEROR-Preserved (Empagliflozin)</td>
<td>CREDENCE (Canagliflozin)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 (Dapagliflozin)</td>
<td>EMPEROR-Reduced (Empagliflozin)</td>
<td></td>
</tr>
<tr>
<td>SCORED (Sotagliflozin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERTIS CV (Ertugliflozin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Completed: EMPA-REG OUTCOME, CANVAS; DECLARE-TIMI 58; others ongoing
### SGLT2 Inhibitor CVOTs: Primary Endpoint

#### CANVAS

<table>
<thead>
<tr>
<th></th>
<th>Study Drug</th>
<th>Placebo</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26.9</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.001 for noninferiority</td>
<td>p = 0.02 for superiority</td>
<td></td>
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</tbody>
</table>

#### DECLARE-TIMI 58

<table>
<thead>
<tr>
<th></th>
<th>Study Drug</th>
<th>Placebo</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death/HF Hospitalization</td>
<td>4.9</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>p = 0.005 for superiority</td>
<td></td>
<td></td>
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</table>

#### EMPA-REG OUTCOME

<table>
<thead>
<tr>
<th></th>
<th>Study Drug</th>
<th>Placebo</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.5</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.001 for noninferiority</td>
<td>p = 0.04 for superiority</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Percent

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>14%</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>17%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Participants per 1,000 Patient-years

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>10.5</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>8.8</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>26.9</td>
</tr>
</tbody>
</table>

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Amputations
• In CANVAS, canagliflozin increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; HR: 1.97; 95% CI: 1.41-2.75)
• Although amputations were primarily at the level of the toe or metatarsal, FDA added a black box warning to the drug’s label (May 2017)
• A 2018 meta-analysis of observational databases found no significant elevated risk for below-knee amputations with canagliflozin versus non-SGLT2 inhibitors

Fournier’s Gangrene
• FDA has identified 12 cases of necrotizing fasciitis of the perineum in patients taking an SGLT2 inhibitor
  • All patients required hospitalization and surgery
• Required a new warning added to labels of all SGLT2 inhibitors (August 2018)

CVD-REAL

- Retrospective, observational study of effects of SGLT2 inhibitors
- Reviewed records >1 million patients in U.S., U.K., Germany, Sweden, Norway, Denmark
- Propensity matched arms (n = 154,528 in each): SGLT2 inhibitor or other glucose-lowering drug
- Use of SGLT2 inhibitor significantly lowered all endpoints (all p < 0.001)
- No significant heterogeneity by country, suggesting class effect
- Similar results in CVD-REAL 2 patients in countries beyond US, Europe

VERTIS CV (N = ~8,000)
- 3rd of 9 planned phase III trials for the SGLT2 inhibitor ertugliflozin
- Primary endpoint: 3-point MACE; numerous secondary endpoints, including 4-point MACE
- Expected 6-year follow-up
- Expected completion: September 2019

SCORED (N = ~10,500)
- Currently recruiting for phase IIIb randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of sotagliflozin
- Primary endpoint: no increase in risk of 3-point MACE and reduction of risk of CV death or hospitalization for HF
- Secondary objectives include superiority for 3-point MACE
- Expected completion: March 2022

Renal outcomes trials: CANVAS-R, CREDENCE, and Dapa-CKD

Heart failure outcomes trials: Dapa-HF, EMPEROR-Preserved, and EMPEROR-Reduced
Choosing Agents Based on CV Risk Profile
Strategies to Reduce CV Risk

• With advances in research and clinical care, morbidity and mortality have significantly decreased in both type 1 and type 2 diabetes.

• However, patients with diabetes still have greater CV risk than patients without diabetes, increasing the urgency to devise strategies to reduce cardiovascular risk.

• As the CVOTs have demonstrated time and again, not all CV risk is the same nor is the response to various antidiabetes agents.

## Factors to Consider in Selecting Antihyperglycemic Treatment

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects ASCVD</th>
<th>CV Effects CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (potential for modest loss)</td>
<td>Potential benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Loss</td>
<td>Benefit: canagliflozin, empagliflozin</td>
<td>Benefit: canagliflozin, empagliflozin</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>High</td>
<td>No</td>
<td>Loss</td>
<td>Neutral: lixisenatide, Benefit: liraglutide &gt; semaglutide &gt; exenatide extended release</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Potential risk: saxagliptin, alogliptin</td>
</tr>
<tr>
<td>TZDs</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Potential benefit: pioglitazone</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Sulfonylureas (2nd generation)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin (Human, analog)</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

Monotherapy
- Lifestyle Management + Metformin
  - Initiate metformin if no contraindications

A1C at target after 3 months of monotherapy?
- Yes: Monitor A1C
- No: Consider dual therapy

Dual Therapy
- Without established ASCVD or CKD
  - Criteria for adding agents:
    - compelling need to minimize hypoglycemia
    - compelling need to minimize weight gain/promote weight loss
    - cost is a major issue

# Antihyperglycemic Therapy in Adults with T2 Diabetes and CVD

## Monotherapy
- **Lifestyle Management + Metformin**
  - Initiate metformin if no contraindications

## Dual Therapy
- **With established ASCVD or CKD**
  - Add agent proven to reduce MACE and/mortality
  - If A1C remains above target: Choose agents demonstrating CV safety

## ASCVD Predommates
- **Either/or**
  - GLP-1 receptor agonist with proven CVD benefit*
  - SGLT2 inhibitor with proven CVD benefit (if eGFR adequate)†

## HF or CKD Predominate
- **Preferably**
  - SGLT2 inhibitor with evidence of reducing HF and/or CKD (if eGFR adequate)‡
- **Or**
  - If SGLT2 inhibitor not tolerated or contraindicated or eGFR inadequate, add GLP-1 receptor agonist with proven CVD benefit*

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*Strongest evidence: liraglutide > semaglutide > exenatide ER

†Modestly stronger evidence: empagliflozin > canagliflozin

‡Equivalent evidence: empagliflozin and canagliflozin
Patient-Centered Approach to Hyperglycemic Management

ADA and EASD
Updated Position Statement

Emphasizes treatment should begin with an assessment of:
• CVD status
• Other comorbidities
• Patient preferences

Establishes goals of care:
• Prevent complications related to diabetes
• Improve quality of life
• Decrease CV risk

Patient-Centered Approach in Practice

• Consider patient and disease features that impact management
  • Hypoglycemia risk, disease duration, life expectancy, established vascular complications, etc.
• Determine the impact of such a feature on A1C goal and adjust therapeutic strategy accordingly
  • For instance, someone with newly diagnosed diabetes and a long life expectancy could handle – and benefit from – a more stringent management strategy
• Revisit and readjust strategy as factors change

Summary

• The interconnection of type 2 diabetes and cardiovascular disease manifests in macrovascular and microvascular complications that can affect management of both diseases.

• Pivotal trials using intensive therapy demonstrated benefits and risks of using such a strategy while helping shape a target goal for glucose management.

• The perceived cardiovascular risks associated with one antidiabetes agent, rosiglitazone, led the FDA to issue a guidance document calling for cardiovascular outcome trials for new drugs to at least demonstrate cardiovascular safety in patients with type 2 diabetes.

• New drug classes are demonstrating safety and, in some cases, efficacy in cardiovascular outcomes, helping to create greater differentiation among agents that can be used most effectively when choosing a second drug and accounting for a patient’s cardiovascular – and cardiometabolic – risk profile.
• Additional modules are available at AAPA Learning Central