Examining the Impact of Cardiovascular Safety with Emerging Treatments for Type 2 Diabetes
Educational Objectives

• Recognize the rationale for cardiovascular outcome trials (CVOTs) in T2DM and review data from recent CVOTs of anti-hyperglycemic agents
• Examine alignment of managed care T2DM treatment algorithms with recent CVOT data
• Implement patient-centered strategies to minimize cardiovascular risk in patients treated in a managed care setting
• Discuss the potential impact of CVOT results on benefit design strategies
Examining the Impact of Cardiovascular Safety with Emerging Treatments for Type 2 Diabetes
Type 2 Diabetes and Cardiovascular Outcomes Trials (CVOTs)

Jennifer Green, MD
Associate Professor of Medicine
Duke University Medical Center
Chief, Endocrine Section
Durham VA Medical Center
Learning Objective

• Recognize the rationale for cardiovascular outcomes trials (CVOT) in T2D and review data from recent CVOT of anti-hyperglycemic agents
Diabetes is Associated with Significant Loss of Life Years

On average, a 50-year-old individual with diabetes and no history of vascular disease will die 6 years earlier compared to someone without diabetes.

Pathophysiologic Progression of Type 2 Diabetes and Its Vascular Complications

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus

Cardiovascular Outcomes: Recent Trials
• As part of the approval process for antidiabetic medications...

“...a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.

This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.
FDA Guidance on Conduct of CVOTs

- Patient selection
  - Focus on high-risk populations including those with advanced disease, elderly and those with renal impairment
- Duration
  - At least 2 years of CV safety data
- Endpoints
  - A prospective independent adjudication of CV events in phase 2 and 3 studies must also be performed including CV mortality, myocardial infarction (MI) and stroke, and possibly hospitalization for ACS, and urgent revascularization

Possible Statistical Scenarios for Drug Approval Based on CVOT Results

• Possible scenarios for approval of new glucose lowering drugs depending on the hazard ratio (HR) for CV risk
• An upper bound of the two-sided 95% confidence interval (CI) for the estimated increased risk above the non-inferiority (NI) boundary of 1.3 as well as underpowered studies prevents FDA approval

# Large CVOTs Are Underway or Recently Completed Since 2008

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Trial</th>
<th>Drug</th>
<th>Primary Endpoint</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>MACE + UA</td>
<td>14,671</td>
</tr>
<tr>
<td></td>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin</td>
<td>MACE</td>
<td>16,492</td>
</tr>
<tr>
<td></td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>MACE</td>
<td>5,380</td>
</tr>
<tr>
<td></td>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>MACE + UA</td>
<td>6,000</td>
</tr>
<tr>
<td></td>
<td>CARMELINA</td>
<td>Linagliptin</td>
<td>CV risk</td>
<td>8,300</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>LEADER</td>
<td>Liraglutide</td>
<td>MACE</td>
<td>9,340</td>
</tr>
<tr>
<td></td>
<td>SUSTAIN-6</td>
<td>Semaglutide</td>
<td>MACE</td>
<td>3,297</td>
</tr>
<tr>
<td></td>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>MACE</td>
<td>6,068</td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>MACE</td>
<td>14,000</td>
</tr>
<tr>
<td></td>
<td>ITCA 650</td>
<td>Exenatide</td>
<td>MACE</td>
<td>4,000</td>
</tr>
<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>MACE</td>
<td>9,622</td>
</tr>
<tr>
<td></td>
<td>HARMONY</td>
<td>Albiglutide</td>
<td>MACE</td>
<td>9,400</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>EMPA-REG</td>
<td>Empagliflozin</td>
<td>MACE</td>
<td>7,020</td>
</tr>
<tr>
<td></td>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>MACE</td>
<td>4,407</td>
</tr>
<tr>
<td></td>
<td>DECLARE-TIMI 58</td>
<td>Dalagliflozin</td>
<td>MACE</td>
<td>17,150</td>
</tr>
<tr>
<td></td>
<td>VERTIS CV</td>
<td>Ertugliflozin</td>
<td>MACE</td>
<td>8,000</td>
</tr>
<tr>
<td>Insulin</td>
<td>DEVOTE</td>
<td>Degludex</td>
<td>MACE</td>
<td>7,500</td>
</tr>
</tbody>
</table>

MACE = major adverse cardiac events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke)  
UA = hospitalization for unstable angina

COVT Completion Dates

- SAVOR-TIMI
- EXAMINE
- DEVOTE
- SUSTAIN-6
- CAROLINA
- CARMELINA
- ITCA
- EXSCEL
- CANVAS
- ELIXA
- TECOS
- EMPA-REG
- LEADER
- REWIND
- HARMONY
- DECLARE
- VERTIS

Legend:
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist
- Insulin
Results
Interpretation, Comparison and Application of the Results: Caveats and Limitations

- Results may only be valid for the particular patient groups enrolled in the studies
  - Thus far, focus has been on high CV risk patients with T2DM
- It is unclear how translatable the results are to the general patient population
- Comparison among results is difficult and is limited by significant variation in
  - Study design
  - Patient selection criteria including patient age, disease duration, baseline blood glucose levels
  - Definition of cardiovascular risk and manifestations of CV disease at baseline
  - Baseline and achieved A1C levels
  - Study endpoints
  - Statistical analysis

CVOTs: DPP-4 Inhibitors
SAVOR TIMI-53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in MI

**Study Design**
- **Patients** with T2D and CVD or CVD risk (n=16,492)
- **Randomization**
  - Saxagliptin: n=8,280
  - Placebo: n=8,212
- **Superiority study** with provision to test for noninferiority
- **Primary endpoint**: Composite of CV death, nonfatal MI, or nonfatal ischemic stroke
- **Secondary endpoint**: CV death, nonfatal MI, nonfatal ischemic stroke, hospitalization for HF, coronary revascularization, or unstable angina

**Key Results**
- Median follow-up: 2.1 years
- Endpoint A1C
  - Saxagliptin: 7.7% ± 1.4% (P<0.001 vs placebo)
  - Placebo: 7.9% ± 1.5%
- CV outcomes
  - Primary: HR 1.00 (95% CI 0.89 to 1.12); P=0.99 for superiority; P<0.001 for noninferiority
  - Secondary HR: 1.02 (95% CI 0.94 to 1.11); P=0.66 for superiority
- **Higher incidence of HF hospitalization w/saxagliptin**
- No difference between groups in incidence of acute/chronic pancreatitis; fewer cases of pancreatic cancer w/ saxagliptin; more cases of nonfatal angioedema w/saxagliptin (8 vs 1)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

SAVOR TIMI-53: Clinical Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>1.00 (0.89-1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>1.02 (0.94-1.11)</td>
<td>0.66</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.11 (0.96-1.27)</td>
<td>0.15</td>
</tr>
<tr>
<td>CV death</td>
<td>1.03 (0.87-1.22)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal ischemic stroke; †CV death, nonfatal MI, nonfatal ischemic stroke, hospitalization for HF, coronary revascularization, or unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

SAVOR TIMI-53: Individual Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>0.95 (0.80-1.12)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.11 (0.88-1.39)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1.19 (0.89-1.60)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td><strong>1.27 (1.07-1.51)</strong></td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Hospitalization for coronary revascularization</td>
<td>0.91 (0.80-1.04)</td>
<td>0.18</td>
</tr>
<tr>
<td>Renal endpoint*</td>
<td>1.08 (0.88-1.32)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hospitalization for hypoglycemia</td>
<td>1.22 (0.82-1.83)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Doubling of creatinine, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL.

CI, confidence interval; CV, cardiovascular; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

SAVOR TIMI-53: Characteristics and Risk of HF Hospitalization

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≤ 60 mL/min</td>
<td>1.36 (1.07-1.71)</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR &gt; 60 mL/min</td>
<td>1.16 (0.89-1.51)</td>
<td>0.27</td>
</tr>
<tr>
<td>No prior heart failure</td>
<td>1.30 (1.03-1.65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>1.23 (0.94-1.59)</td>
<td>0.13</td>
</tr>
<tr>
<td>No risk factors*</td>
<td>1.15 (0.81-1.63)</td>
<td>0.45</td>
</tr>
<tr>
<td>1 risk factor</td>
<td>1.35 (1.06-1.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>2 risk factors</td>
<td>1.22 (0.86-1.73)</td>
<td>0.27</td>
</tr>
<tr>
<td>Highest quartile NT-proBNP (333-46,627 pg/mL)</td>
<td>1.31 (1.04-1.66)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*EgFR ≤ 60 mL/min or history of previous HF.

HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; Q, quartile; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

SAVOR TIMI-53: Risk of Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>No. excess HHF events in patients treated with saxagliptin vs placebo per 1000 pt-y</th>
<th>eGFR (mL/min)</th>
<th>HF history</th>
<th>No. HF risk factors†</th>
<th>NT-proBNP quartiles (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;60</td>
<td>≤60</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>n =</td>
<td>11,637</td>
<td>4,855</td>
<td>14,387</td>
<td>2,105</td>
</tr>
<tr>
<td>2</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>3</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>8</td>
<td>1%</td>
<td>0.6%</td>
<td>1.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Saxagliptin vs placebo.
† eGFR ≤60 mL/min or history of previous HF.
HF, heart failure; HHF, hospitalizations for heart failure.
EXAMINE: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

**Study Design**
- **Patients** with T2D and ACS (n=5,380)
- **Randomization**
  - Alogliptin: n=2,701
  - Placebo: n=2,679
- **Noninferiority study**: prespecified HR margin = 1.3 for primary endpoint
- **Primary endpoint**: Composite of CV death, nonfatal MI, or nonfatal stroke
- **Secondary endpoint**: CV death, nonfatal MI, nonfatal stroke, urgent revascularization for unstable angina

**Key Results**
- Median follow-up: 18 months
- Least squares mean difference in A1C: -0.36% (95% CI -0.43 to -0.28; P<0.001) for alogliptin vs placebo
- CV outcomes
  - Primary: HR 0.96 (upper boundary of the one-sided repeated CI, ≤1.16); P=0.32 for superiority; P<0.001 for noninferiority
    - Secondary: HR 0.95 (upper boundary of the one-sided repeated CI, ≤1.14*); P=0.26 for superiority
- No difference between alogliptin and placebo in incidence of acute and chronic pancreatitis, cancer, renal impairment, angioedema, or severe hypoglycemia
- NS increased risk HHF

*Upper boundary of 1-sided repeated CI, alpha level 0.01.
CI, confidence interval; CV, cardiovascular
EXAMINE: Clinical Outcomes

<table>
<thead>
<tr>
<th>Primary composite</th>
<th>0.96 (≤1.16)*</th>
<th>0.32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint components</td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>CV death</td>
<td>0.79 (0.6-1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.08 (0.88-1.33)</td>
<td>0.47</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.91 (0.55-1.50)</td>
<td>0.71</td>
</tr>
<tr>
<td>Primary secondary endpoint†</td>
<td>0.95 (≤1.14)*</td>
<td>0.26</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.66-1.10)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Upper boundary of 1-sided repeated CI, alpha level 0.01.
†CV death, nonfatal MI, nonfatal stroke, urgent revascularization for unstable angina.
CI, confidence interval; CV, cardiovascular; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI, myocardial infarction.

TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin

**Study Design**

- **Patients** with T2D and CVD (n=14,671)
- **Randomization**
  - Sitagliptin: n=7,332
  - Placebo: n=7,339
- **Noninferiority study**: 1.3 marginal upper boundary of 2-sided 95% CI. Testing for superiority also performed
- **Primary endpoint**: Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
- **Secondary endpoint**: Composite of CV death, nonfatal MI, or nonfatal stroke

**Key Results**

- Median follow-up: 3.0 years
- Least squares mean difference in A1C: -0.29% (95% CI -0.32 to -0.27) for sitagliptin vs placebo
- Noninferior to placebo for cardiovascular outcomes
  - Primary: HR 0.98 (95% CI 0.88 to 1.09); \( P < 0.001 \) for noninferiority
  - Secondary: HR 0.99 (95% CI 0.89 to 1.11); \( P < 0.001 \) for noninferiority
- Superiority not demonstrated
- No difference between sitagliptin and placebo in incidence of infections, cancer, renal failure, hypoglycemia, or noncardiovascular death

TECOS: Primary and Other Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.98 (0.88-1.09)</td>
<td>&lt;0.001 (NI)</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.99 (0.89-1.11)</td>
<td>&lt;0.001 (NI)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>1.80 (0.86-3.76)</td>
<td>0.12</td>
</tr>
<tr>
<td>Any cancer (except nonmelanoma skin cancer)</td>
<td>0.93 (0.78-1.10)</td>
<td>0.38</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>0.91 (0.37-2.25)</td>
<td>0.85</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>1.13 (0.89-1.44)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.
†Secondary composite: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
NI=non-inferiority

TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

TECOS: Individual Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>1.03 (0.89-1.19)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.90 (0.70-1.16)</td>
<td>0.42</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.95 (0.81-1.11)</td>
<td>0.49</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.97 (0.79-1.19)</td>
<td>0.76</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.01 (0.90-1.14)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1.00 (0.83-1.20)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hospitalization for heart failure or CV death</td>
<td>1.02 (0.90-1.15)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Favors sitagliptin

TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.
CVOTs: SGLT2 Inhibitors
EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

**Study Design**

- **Patients** with T2D and CVD (n=7,020)
- **Randomization**
  - Empagliflozin: n=4,687
  - Placebo: n=2,333
- **Noninferiority study**: prespecified HR margin = 1.3 for primary endpoint
- **Primary endpoint**: composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke
- **Secondary endpoint**: composite of CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina

**Key Results**

- Median follow-up: 3.1 years
- Week 206 A1C, difference from placebo
  - Empagliflozin 10 mg: -0.24% (95% CI, -0.40% to -0.08%)
  - Empagliflozin 25 mg: -0.36% (95% CI, -0.51% to -0.20%)
- CV outcomes (pooled empagliflozin 10 mg + 25 mg)
  - Primary: HR 0.86 (95.02% CI 0.74 to 0.99); \( P < 0.001 \) for noninferiority
  - Secondary: HR 0.89 (95% CI 0.78 to 1.01); \( P = 0.08 \) for noninferiority
- Significantly lower rates of all-cause death, CV death, and HF hospitalization with empagliflozin
- Increased rates of genital infections in empagliflozin-treated patients

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

EMP A-REG: Clinical Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

EMPA-REG: Cardiovascular Outcomes and Death From Any Cause

### EMPA-REG: Renal Outcomes Over 3.2 Years

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or CV death</td>
<td>0.61 (0.55-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>0.61 (0.53-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>0.62 (0.54-0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45</td>
<td>0.56 (0.39-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.45 (0.21-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death</td>
<td>0.54 (0.40-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria*</td>
<td>0.95 (0.87-1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*In patients with normal albuminuria at baseline.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine.

CVOTs: GLP-1 Receptor Agonists
ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome

**Study Design**

- **Patients** with T2D and recent ACS event (n=6,068)
- **Randomization**
  - Lixisenatide: n=3,034
  - Placebo: n=3,034
- **Noninferiority study**: prespecified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
- **Primary endpoint**: composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina
- **Secondary endpoint**: composite of the primary end point and hospitalization for heart failure, or coronary revascularization procedures

**Key Results**

- Duration of follow up: 2 years
- **CV Outcomes**
  - Primary: HR 1.02 (95% CI 0.89 to 1.17); \( P < 0.001 \) for noninferiority; \( P = 0.81 \) for superiority
  - Secondary: There were no significant differences in the rate of hospitalization for HF (HR 0.96; 95% CI, 0.75 to 1.23) or the rate of death (HR 0.94; 95% CI, 0.78 to 1.13)
  - Findings were similar in those with a history of heart failure
  - Modest weight gain benefit favoring lixisenatide: -0.6 kg with lixisenatide vs. -0.0 kg for placebo (\( p < 0.001 \))
  - Hospitalization for heart failure: 4.2% vs. 4.0%

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

**Study Design**
- **Patients** with T2D and high CVD risk (n=9,340)
- **Randomization**
  - Liraglutide: n=4,672
  - Placebo: n=4,668
- **Noninferiority study**: prespecified margin = 1.3 for upper bound of 95% CI of the HR for primary endpoint
- **Primary endpoint**: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
- **Secondary endpoint**: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

**Key Results**
- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1C: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: 2.3 kg (95% CI, 2.5 to 2.0 kg)
  - SBP: 1.2 mm Hg (95% CI, 1.9 to 0.5 mm Hg)
- CV outcomes
  - Primary: HR 0.87 (95% CI 0.78 to 0.97); *P*=0.01 for superiority
  - Secondary HR: 0.88 (95% CI 0.81 to 0.96); *P*=0.005 for superiority
- Significantly lower rates of all-cause death and CV death with liraglutide
- Increased rates of GI events in liraglutide-treated patients
- Lower numerical incidence of pancreatitis in liraglutide group (not statistically significant)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

LEADER: Clinical Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.87 (0.73-1.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>Nephropathy‡</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF; ‡Defined as new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 mL/min/1.73 m², the need for continuous renal-replacement therapy, or death from renal disease

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

LEADER: Clinical Outcomes

*CV death, nonfatal MI (including silent MI), or nonfatal stroke.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

**Study Design**
- **Patients** with T2D (n=3,297) age ≥50 years with established CVD or stage ≥3 CKD or age ≥60 years with at least one CV risk factor
- **Randomization**
  - Semaglutide: n=3,034
  - Placebo: n=3,034
- **Noninferiority study**: prespecified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
- **Primary endpoint**: first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke
- **Secondary endpoints**: first occurrence of an expanded composite CV outcome (death from CV causes, nonfatal MI, nonfatal stroke, revascularization [coronary or peripheral], and hospitalization for UA or HF), an additional composite outcome (death from all causes, nonfatal MI, or nonfatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy

**Key Results**
- **Duration of follow up**: 2 years
- **CV Outcomes**
  - Primary: HR 0.74 (95% CI 0.58 to 0.95); *P*<0.001 for noninferiority; *P*=0.02 for superiority
  - Secondary:
    - Nonfatal MI: HR 0.74 (95% CI, 0.51 to 1.08; *P*=0.12)
    - Nonfatal stroke: HR 0.61 (95% CI, 0.38 to 0.99; *P*=0.04)
    - Rates of CV-related death were similar
    - Rates of new/worsening nephropathy were lower in the semaglutide group
    - Rates of retinopathy complications were significantly higher in the semaglutide group; HR 1.76 (95% CI, 1.11 to 2.78); *P*=0.02

SUSTAIN-6: Cardiovascular Outcomes

### Summary of Completed CVOT Trials

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>SAVOR TIMI-53</th>
<th>EXAMINE</th>
<th>TECOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor</td>
<td>Neutral*</td>
<td>Neutral*</td>
<td>Neutral*</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>Beneficial</td>
<td>Neutral</td>
<td>Beneficial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>ELIXA</td>
<td>SUSTAIN-6</td>
</tr>
<tr>
<td>SLGT2-Inhibitor</td>
<td>Beneficial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Although the DPP-4 inhibitor trials were neutral, there was no increase in the number of patients hospitalized for heart failure with sitagliptin (TECOS trial). Saxagliptin (SAVOR TIMI-53 trial), showed an increase in heart-failure events. Alogliptin (EXAMINE trial) showed a trend toward an increased risk of heart-failure events in T2DM patients.*
Summary

- Diabetes is a significant contributor to cardiovascular disease risk
- In 2008, the FDA mandated that all new therapies for diabetes must be rigorously assessed for CV safety
  - Majority of CVOTs have been designed to compare effects of antihyperglycemic agent to placebo, thus lack head-to-head comparisons
  - Methodological differences between trials and a focus on high risk populations, limits generalization of the results
- Seven CVOTs of have been completed; 3 show a reduction in CV risk (LEADER, SUSTAIN-6 and EMPA-REG) and 4 were neutral (eg, demonstrated noninferiority to placebo)
Aligning Managed Care Type 2 Diabetes Treatment Algorithms with Recent Cardiovascular Outcomes Trial Data

John Fox, MD, MHA
Vice President, Associate Chief Medical Officer
Medical Affairs
Priority Health
Learning Objective

- Examine alignment of managed care type 2 diabetes treatment algorithms with recent cardiovascular outcomes trial data
Standards of Medical Care in Diabetes—2017

- Annual update from the American Diabetes Association (ADA)
- Includes new guidance multiple topics including
  - Glycemic targets
  - Pharmacologic approaches to achieving glycemic targets
  - Cardiovascular disease risk management
  - Lifestyle management
  - Patient-centered care

<table>
<thead>
<tr>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 50% of patients fail to meet targets for A1C, blood pressure (BP),</td>
</tr>
<tr>
<td>or lipids</td>
</tr>
<tr>
<td>Only 14% of patients meet targets for all A1C, BP, lipids, and nonsmoking</td>
</tr>
<tr>
<td>measures</td>
</tr>
<tr>
<td>CVD risk factor reduction continues to be a public health priority</td>
</tr>
<tr>
<td>Care delivery remains fragmented</td>
</tr>
<tr>
<td>Data on comparative effectiveness of treatment alternatives is limited</td>
</tr>
</tbody>
</table>

Achieving A1C Treatment Goals: 2010-2015

Screening for A1C in Commercial Plans 2010-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>87.6%</td>
<td>88.5%</td>
<td>88.7%</td>
<td>88.6%</td>
<td>88.4%</td>
<td>89.5%</td>
</tr>
</tbody>
</table>

Achievement of ADA A1C Targets in Commercial Plans 2010-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;7%</th>
<th>&lt;8%</th>
<th>&gt;9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>35%</td>
<td>37%</td>
<td>31%</td>
</tr>
<tr>
<td>2011</td>
<td>56%</td>
<td>58%</td>
<td>56%</td>
</tr>
<tr>
<td>2012</td>
<td>39%</td>
<td>58%</td>
<td>34%</td>
</tr>
<tr>
<td>2013</td>
<td>36%</td>
<td>56%</td>
<td>34%</td>
</tr>
<tr>
<td>2014</td>
<td>37%</td>
<td>55%</td>
<td>34%</td>
</tr>
<tr>
<td>2015</td>
<td>35%</td>
<td>51%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Management Strategies to Improve Diabetes Outcomes

• Early screening/prompt diagnosis

• Early intervention with agents supported by evidence-based treatment guidelines

• Intensify treatment to achieve and maintain glycemic goals

• Manage relevant comorbidities

• Tailor treatment decisions to patient preferences, prognosis, and goals

• Foster strong therapeutic relationships between the patient and physician

Achieving Glycemic Goals
# Recommended A1C Goals for Adults

<table>
<thead>
<tr>
<th>Population</th>
<th>A1C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant adults</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Patients with</td>
<td></td>
</tr>
<tr>
<td>• Short duration of diabetes</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>• Type 2 diabetes treated with lifestyle or metformin only</td>
<td></td>
</tr>
<tr>
<td>• Long life expectancy</td>
<td></td>
</tr>
<tr>
<td>• No significant cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Patients with</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>• History of severe hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>• Limited life expectancy</td>
<td></td>
</tr>
<tr>
<td>• Advanced microvascular or macrovascular complications</td>
<td></td>
</tr>
<tr>
<td>• Extensive comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>• Long-standing diabetes in whom the goal is difficult to achieve</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Intensification to Achieve and Maintain Appropriate Glycemic Levels

- Intensification approach should be individualized to match the needs of each patient and characteristics of the disease

Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent → A1C 7%</th>
<th>Less stringent ←</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Relevant comorbidities</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
</table>

Improving Glycemic Levels With Lifestyle Interventions

- Lifestyle modifications form the foundation of anti-glycemic care
- Activities include
  - Diabetes self-management
  - Weight optimization
  - Following a healthy diet
  - Increased physical activity levels
  - Smoking cessation
  - Routine immunization
  - Diagnosis and management of psycho-social conditions

Pharmacologic Therapy for Type 2 Diabetes: General Principles

• Goal: Reduce blood glucose levels and minimize side effects (especially hypoglycemia)
• Develop a treatment plan and set therapeutic goals
  • Drug choice is based on patient, disease, drug characteristics, and patient preference
• Start aggressively and taper (if necessary)
  • Assume each medication will improve HgA1c by 1%
  • Always add new agent first, titrate to get control, then stop first agent
• Cost-effectiveness models have suggested that some newer agents may be of relatively lower clinical utility based on high cost and moderate glycemic effect

<table>
<thead>
<tr>
<th>Oral Agents</th>
<th>Injectable Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Insulin</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Amylin analogs</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>GLP-1 agonists (incretin)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DPP-4 inhibitors (incretin)</td>
</tr>
</tbody>
</table>

T2DM Treatment Algorithm

- General ADA recommendations for antihyperglycemic therapy in type 2 diabetes

T2DM Treatment Algorithm: Use of Insulin

- General ADA recommendations for use of combinations of injectable therapies
- Consider initiating when blood glucose is $\geq 300$ mg/dL or A1C is $\geq 10\%$ or if symptoms of hyperglycemia are present
- Regimens may be simplified as glucose targets are approached
CVOT Results and Diabetes Treatment Guidelines
The relationship between glycemic control and CVD has been examined in several trials completed prior to the FDA-mandated initiation of CVOTs.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>Trend toward lower risk of CVD events with intensive control (type 1)</td>
</tr>
<tr>
<td>EDIC</td>
<td>57% reduction in risk of nonfatal MI, stroke, or CVD death (type 1)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Nonsignificant reduction in CVD events (type 2)</td>
</tr>
<tr>
<td>ACCORD, ADVANCE, VADT</td>
<td>Suggested no significant reduction in CVD outcomes with intensive glycemic control (type 2)</td>
</tr>
</tbody>
</table>

# Overview of CVOTs with Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Trial</th>
<th>Drug</th>
<th>Primary Endpoint</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptan</td>
<td>MACE + UA</td>
<td>14,671</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin</td>
<td>MACE</td>
<td>16,492</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>MACE</td>
<td>5380</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>CAROLINA</td>
<td>Linagliptan</td>
<td>MACE + UA</td>
<td>6000</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>CARMELINA</td>
<td>Linagliptan</td>
<td>CV risk</td>
<td>8300</td>
<td>Completed</td>
</tr>
<tr>
<td><strong>GLP-1 RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>Liraglutide</td>
<td>MACE</td>
<td>9340</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>SUSTAIN-6</td>
<td>Semaglutide</td>
<td>MACE</td>
<td>3297</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>MACE</td>
<td>6068</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>MACE</td>
<td>14,000</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>ITCA</td>
<td>Exenatide</td>
<td>MACE</td>
<td>4000</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>MACE</td>
<td>9622</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>HARMONY</td>
<td>Albglutide</td>
<td>MACE</td>
<td>9400</td>
<td>Completed</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMPA-REG</td>
<td>Empagliflozin</td>
<td>MACE</td>
<td>7020</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>MACE</td>
<td>4407</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>DECLARE-TIMI-58</td>
<td>Dapagliflozin</td>
<td>MACE</td>
<td>17,150</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>DEVOTE</td>
<td>Degludec</td>
<td>MACE</td>
<td>7500</td>
<td>2018</td>
</tr>
</tbody>
</table>

**MACE** = major adverse cardiac events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); **UA** = hospitalization for unstable angina

Inclusion of CVOT Data in the 2017 Update of the Treatment Guidelines

ADA guidelines include a brief review of 2 CVOTs that demonstrated benefits in high-risk patients with type 2 diabetes

**Empagliflozin**
- Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)

**Liraglutide**
- Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-Term Evaluation (LEADER) trial
EMPA-REG Results: Primary Endpoint

- Primary composite outcome
  - Death from cardiovascular causes
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Key secondary composite outcome
  - Hospitalization for unstable angina
- Conclusion
  - Type 2 diabetes patients at high risk for CV events treated with standard care empagliflozin had a lower rate of CV outcomes and death from any cause

HR: 0.62
(95% CI 0.49, 0.77)
P=0.0001
N=7020

LEADER Results: Primary Endpoint

- Primary composite outcome
  - Death from cardiovascular causes
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Key secondary composite outcome
  - Hospitalization for unstable angina or heart failure
- Conclusion
  - Rate of first occurrence of death from CV causes, nonfatal MI, and nonfatal stroke was lower with liraglutide vs placebo

What Effect will CVOT Results Have on Clinical Practice Guidelines?

- There are now 7 completed CVOTs involving 3 classes of drugs
  - DDP-IV inhibitors (3 trials)
  - GLP-1 receptor antagonists (3 trials)
  - SGLT2 inhibitors (1 trial)
- Results from these trials provide evidence of the overall cardiovascular safety of incretins and SGLT2 inhibitors
  - Results from specific agents may not be applicable to other members of the same class

The goal of antihyperglycemic treatment is to reduce blood glucose levels and minimize side effects (especially hypoglycemia).

The 2017 ADA treatment guidelines provide recommendations on diabetes care delivery including updated glycemic targets and antihyperglycemic pharmacotherapy.

Results from 2 of 7 large CVOT trials are included in the revised guidelines.

- Results from these trials provide evidence of the overall cardiovascular safety of the incretins and SGLT2 inhibitors.

Specific treatment recommendations based on the results of these and future CVOTs trials is anticipated in future editions of the guidelines.
CVOT Results and Plan Benefit Designs: Maximizing Value for Emerging Type 2 Diabetes Therapies

Vanita Pindolia, PharmD, BCPS
Vice President, Ambulatory Clinical Pharmacy Programs
Henry Ford Health System/Health Alliance Plan of Michigan
Learning Objective

- Discuss the potential impact of CVOT results on benefit design strategies
CVOT in Diabetes: Perspective

- Seventeen CVOT clinical trials involving >140,000 subjects have been completed or are ongoing in accordance with the FDA guidance issued in 2008\(^1\)

- The 7 completed trials involve three different drug classes (SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors)\(^1-5\)
  - Each has met their primary objective to exclude an unacceptable level of ischemic CV risk (as defined in the FDA guidance)\(^1-5\)
  - One trial found an increased risk of hospitalization for heart failure (SAVOR-TIMI 53\(^2\)) while 3 others demonstrated a reduction in cardiovascular death (EMPA-REG\(^3\), LEADER\(^4\), SUSTAIN-6\(^5\))

- To date, a heightened risk of CV ischemic events has not been demonstrated across several classes of new diabetes drugs

**How will these data impact the diabetes pharmacy benefit?**

Nearly 28 Million Americans Have Type 2 Diabetes*

*Nearly 1 in every 10 Americans carries a diagnosis of type 2 diabetes

*7.7 Million Americans with type 2 diabetes remain undiagnosed

Diabetes Increases Risk of CV Morbidity and Mortality

Meta-analysis of 102 clinical trials evaluating the risk of CV events due to T2DM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>26,505</td>
<td>2.00 (1.83-2.19)</td>
<td>64 (54-71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05-2.60)</td>
<td>41 (24-54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
<td>1.82 (1.64-2.03)</td>
<td>37 (19-51)</td>
</tr>
<tr>
<td>Stroke subtypes*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95-2.65)</td>
<td>1 (0-20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19-2.05)</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59-2.13)</td>
<td>33 (12-48)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51-1.98)</td>
<td>0 (0-26)</td>
</tr>
</tbody>
</table>

Diabetes mellitus significantly increases the risk of adverse CV events

Diabetes is the Most Expensive Traditional Therapy Class When Ranked by PMPY

Finding a Balance Between Cost Shifting and Patient Adherence is a Challenge

Patients Receiving More Generous Benefits Had Significantly Greater Adherence

Tenets of a Diabetes Benefit Plan Design

Manage costs by restricting utilization of resources

Cost-sharing frequently used to influence utilization patterns

- Patient cost-share related to acquisition cost of service or product
- Assumes inelastic demand or willingness to pay

Common Components of Diabetes Benefit Design

Cost Management

- Drug discounts
- Channel management
- Rebates
- Benefit design options

Utilization Management

- Medical necessity review, including recent CVOT data
- Clinical management via algorithms, eligibility criteria, duration of therapy
- PA, step therapy, quantity limits
- Formulary tiers, utilization caps, etc

Management Strategies to Consider for Diabetes Pharmacy

**Incentive Programs**
- **Member**
- **Provider**

**Coordination/Collaboration**
- Data management and routine use of IT

**Active, Focused Case Management**

**Patient Support Programs**
- Mandatory?
- Developed in-house?
Benefit Design Strategies to Consider for Diabetes Pharmacy

**Benefit Design**

- **Tiers**
  - Evaluating out-of-pocket expenses

- **Biosimilars**
  - First biosimilar insulin (insulin glargine) approved in January 2016

**Application of Guidelines, Algorithms, and Disease Management**
### Patient Behavior Considerations for Diabetes Pharmacy

<table>
<thead>
<tr>
<th>Disease and Treatment Variables</th>
<th>Health Care Delivery Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complex therapy</td>
<td>• Patient awareness/education</td>
</tr>
<tr>
<td>• Treatment tolerability</td>
<td>• Strengthening patient-</td>
</tr>
<tr>
<td>• Multiple comorbidities</td>
<td>provider relationships</td>
</tr>
<tr>
<td>• CV disease</td>
<td>• Patient empowerment</td>
</tr>
<tr>
<td>• Kidney disease</td>
<td>• Integrated communication</td>
</tr>
<tr>
<td>• Obesity</td>
<td>channels</td>
</tr>
<tr>
<td></td>
<td>• Medication therapy</td>
</tr>
<tr>
<td></td>
<td>management</td>
</tr>
<tr>
<td></td>
<td>• Medication reminders</td>
</tr>
<tr>
<td></td>
<td>• Telephone/email counseling</td>
</tr>
</tbody>
</table>

- **CV** disease
- **Kidney disease**
Formulary Management Considerations for Diabetes Pharmacy

More Formulary Control

- Assessment of recent data (eg, CVOT results)
- Identification of data gaps (eg, comparative trials)
- Prior authorization
- Quantity limits
- Start/stop rules

Contracting

- Outcomes-based shared risk
- Net effective pricing
Moving Away From *Volume* and Toward *Value*

- Payment/delivery paradigm emphasis is on rewarding value instead of volume
  - Value-based benefit design: shared savings, gain-sharing, bundled payments, capitation, etc
- Incentives driven by CMS are being implemented to coordinate care among/across providers
  - CMS Quality Strategy
  - CMS EHR incentive program
- Establishment of organizational infrastructure that promotes actual and virtual integration
  - Accountable care organizations (ACOs), medical homes, home-based chronic care management, community health teams, health care innovation zones
Key Elements of an Value-Based Design

- Benefit Design
- Clinical Evidence & Performance Metrics
- Consumer and Provider Engagement
- Transparency

VBID=value-based insurance design
Patient-centered Benefit Plan Designs

- Development guided by principles of value-based insurance design
  - Set cost shares that consider cost and value while prioritizing primary care and frequently needed care for management of chronic comorbidities including cardiovascular disease
  - Set fixed copays as much as possible; limit coinsurance to less frequently used benefits or services with high variability in cost as necessary to meet required actuarial values
  - Apply a stair-step approach for setting member cost shares for a service across each tier
- Reassess benefits each year based on emergence of new clinical trial data (eg, CVOT results) and patient experience related to access and cost
Summary

- Managed care will be required to develop novel solutions to meet the continued growth of the diabetes population
- Limited resources challenge patients, providers, and payers
- Diabetes pharmacy is a current and future concern for plan sponsors and patients
- Current plan designs often do not consider recent clinical trial data and thus, may not apply to the ongoing and future needs of diabetes pharmacy
- Benefit design should be reassessed annually and consider new clinical trial data (eg, CVOT results) as well as patient experience related to access and cost
- Newer approaches should be implemented that consider the needs of all stakeholders including patients, physicians, managed care organizations, industry, and payers
Patient-Centered Strategies to Minimize Cardiovascular Risk in Patients in a Managed Care Setting

Curtis Triplitt, PharmD, CDE
Texas Diabetes Institute, University Health System
Associate Professor of Medicine, Clinical/Division of Diabetes
University of Texas Health Science Center at San Antonio
Learning Objective

• Implement patient-centered strategies to minimize cardiovascular risk in patients treated in a managed care setting
CVD Risk in T2DM: More Risks = Higher Mortality

Mortality from Cardiovascular Disease*

- None: 6.8%
- Diabetes: 15.6%
- History of MI: 16.8%
- History of CVA: 16.1%
- Diabetes + MI: 32.0%
- Diabetes + CVA: 32.5%
- MI + CVA: 32.8%
- All 3: 59.5%

*Mortality per 1000 person years adjusted to age 60; N=689,300; Baseline surveys conducted 1960-2007; mortality follow up to 2013; 128,843 deaths
MI=myocardial infarction; CVA=cerebrovascular accident

More Than Two-Thirds of Adults With T2DM Die From CV Disease

More than two-thirds of patients with T2DM die from cardiovascular disease

Glycemic control takes a long time for CVD risk reduction; We are often too glucocentric in diabetes

Diabetes Becomes More Difficult to Treat Over Time

Disease Progression

More Chronic Conditions & Comorbidities ➔ More medications indicated ➔ Over- and under-prescribing ➔ Worse adherence ➔ More adverse events ➔ Increased hospitalization ➔ Increased readmissions ➔ Increased mortality

ADA Recommendations for When Goals Are Not Met: Treatment Intensification

- Patient and disease features dictate the intensity of therapy
- Patients with high baseline A1C or at high risk for complications often require intensive treatment
  - Monotherapy is often insufficient
  - Consider initiating combination therapy

---

Achieving Cardiovascular Risk Reduction in Diabetes Patients Remains Challenging

Achievement of A1C, BP, and LDL-C Treatment Goals Among Patients with Diabetes (2007-2010)*

*Data from the National Health and Nutrition Examination Survey, 2007-2010.
N=4926 adults (≥20 years) with self-reported diabetes.
BP=blood pressure; LDL-C=low density lipoprotein cholesterol.

Organizing Care to Achieve Treatment Goals

- The ADA recommends prioritizing timely and appropriate treatment intensification of lifestyle and/or drug therapy for patients who have not achieved BP, lipid, or glucose goals.

- Strategies include
  - Explicit goal setting with patients
  - Identifying and addressing barriers to care
  - Integrating evidence-based guidelines
  - Incorporating care management teams

ADA Recommendations for When Goals Are Not Met: Adherence

- Address issues related to patient adherence
- Barriers to adherence may include
  - Patient factors (eg, remembering to obtain or take medications, fears, depression, and health beliefs)
  - Medication factors (eg, regimen complexity, multiple daily dosing, cost, side effects)
    - Simplifying a complex treatment regimen may improve adherence
  - System factors (eg, inadequate follow-up and support)

Considering the Patient’s Perspective

- What if my therapy fails?
- What happens if I forget to take my medicine?
- Why is lowering blood glucose so important?
- Do I need to use a needle to get my insulin?
- Don’t those drugs have bad side effects?
- I don’t feel bad... why do I have to take any medicine?
- How long do I have to take these drugs?
- Why do I have to take any medicine?
Patient-Centered Care

• You as provider or managed care expert:
  • You are the expert on diabetes information, treatments, algorithms, etc
  • Large amount of information you know on chronic diseases

• This will not help if the patient doesn’t know or won’t do it

• Patient
  • I follow the advice of my HCP, but I may trust my neighbor more than my HCP
  • I have a disease that is called “chronic”—I live with it everyday
  • No one knows me better than me
  • I already have most of the answers, but I may not have made the connection
  • Am I being non-adherent? Or is it a choice—something I am missing

• Finding common language, common ground, and partnering with your patients to succeed to “make the connections”
Strategies for Improving Diabetes Care: A Patient-Centered Approach

• “...providing care that is respectful of and responsive to individual patient preferences, needs, and values, ensuring that patient values guide clinical decisions”

• Underlying principles
  • Evidence-based care individualized based on disease characteristics and patient needs, goals and values
  • Encourages shared decision-making
  • Provides coordinated, multidisciplinary care
  • Continuity of care across the life span

Patient-Provider Interactions are Key to Individualizing Care

**Ideal Patient Behaviors**
- Actively engaged
- Provides his/her perspective
- Willing to contribute to the decision-making process

**Ideal Provider Behaviors**
- Active listening
- Negotiation-motivational interviewing
- Provides information when needed or in response to a question

---

*Ultimate control over:*
- Lifestyle changes
- Treatment adherence

*Joint decisions:*
- Drug therapy
- Glycemic targets

*Consider:*
How phenotype and patient/disease characteristics should drive drug choices
Delivering Patient-Centered Care Through the Medical Home

- Features of the patient-centered medical home (PCMH) that support better diabetes outcomes
  - Diabetes self-management education
  - Team-based care
  - Care coordination/case management
  - Specialty providers as members of the care team
  - Electronic record capabilities for tracking outcomes and performance improvement

Evidence for the Effectiveness of the PCMH in Diabetes Care is Encouraging

<table>
<thead>
<tr>
<th>Rank</th>
<th>Intervention</th>
<th>Number of Trials</th>
<th>Mean Difference in A1C (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Promotion of self-management</td>
<td>60</td>
<td>-0.57 (-0.83 to -0.31)</td>
</tr>
<tr>
<td>2</td>
<td>Team changes</td>
<td>47</td>
<td>-0.57 (-0.71 to -0.42)</td>
</tr>
<tr>
<td>3</td>
<td>Case management</td>
<td>57</td>
<td>-0.50 (-0.65 to -0.36)</td>
</tr>
<tr>
<td>4</td>
<td>Patient education</td>
<td>52</td>
<td>-0.48 (-0.61 to -0.34)</td>
</tr>
<tr>
<td>5</td>
<td>Facilitated relay of clinical data</td>
<td>32</td>
<td>-0.46 (-0.60 to -0.33)</td>
</tr>
<tr>
<td>6</td>
<td>Electronic patient registry</td>
<td>27</td>
<td>-0.42 (-0.61 to -0.24)</td>
</tr>
<tr>
<td>7</td>
<td>Patient reminders</td>
<td>21</td>
<td>-0.39 (-0.65 to -0.12)</td>
</tr>
<tr>
<td>8</td>
<td>Audit and feedback</td>
<td>8</td>
<td>-0.26 (-0.44 to -0.08)</td>
</tr>
<tr>
<td>9</td>
<td>Clinician education</td>
<td>15</td>
<td>-0.19 (-0.35 to -0.03)</td>
</tr>
<tr>
<td>10</td>
<td>Clinician reminders</td>
<td>18</td>
<td>-0.16 (-0.31 to -0.02)</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td></td>
<td><strong>120</strong></td>
<td><strong>-0.37 (-0.45 to -0.28)</strong></td>
</tr>
</tbody>
</table>

Summary

• Diabetes patients are at increased risk for CV morbidity and mortality

• We are often glucocentric in diabetes, yet 2/3 will die from CVD

• Achieving cardiovascular risk reduction in diabetes patients remains challenging

• Patient-centered care may help to address barriers to CV risk reduction by increasing patient involvement in the care decision-making process

• The PCMH provides a venue for increased patient engagement and improved diabetes care delivery