Diabetes & Cardiovascular Disease Risk Reduction

CAPT Judy Thompson PharmD, BCPS, CDE, BC-ADM
CDR Brittany L. Keener PharmD, MPH, BCPS

Disclosure

- CAPT Thompson and CDR Keener have nothing to disclose.
Objectives

• Recognize cardiovascular disease and risk management strategies in patients with diabetes.
• Identify goals for hypertension and lipid management.
• Review which diabetes medications are proven to reduce major adverse cardiovascular events.

Cardiovascular Disease

• Also known as heart disease
  – Atherosclerotic Cardiovascular Disease (ASCVD)
  – Coronary Artery Disease (CAD)
  – Atherosclerosis: when plaque builds up in the walls of the arteries
• Heart failure
• Arrhythmia
• Valve problems
• Others
Atherosclerotic Cardiovascular Disease (ASCVD)

- Coronary heart disease, cerebrovascular disease, or peripheral artery disease presumed to be of atherosclerotic origin.
- Leading cause of morbidity and mortality in patients with diabetes.
- Results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes.

Cardiovascular Disease Risk Factors

- Hypertension
- Hyperlipidemia
- **Diabetes**
  - Unhealthy diet
  - Physical inactivity
  - Obesity
  - Excessive alcohol consumption
  - Tobacco use
Cardiovascular Disease

• About **610,000 people** die of heart disease in the United States every year—that’s **1 in every 4 deaths**.

• Heart disease is the leading cause of death for both men and women. **More than half** of the deaths due to heart disease in 2009 were in men.

• Coronary heart disease (CHD) is the most common type of heart disease, killing over **370,000 people** annually.

• Every year about **735,000 Americans** have a heart attack. Of these, 525,000 are a first heart attack and 210,000 happen in people who have already had a heart attack.
Cardiovascular Disease

Heart Disease Death Rates, 2014-2016
Adults, Ages 65+, by County

Stroke Death Rates, 2014 - 2016
Adults, Ages 65+, by County

Risk Calculation

ASCVD Risk Estimator Plus

So our patient is at risk, now what?

- Lifestyle/behavior changes or modifications
- Medications
- Surgical procedures
- Assess risk factors at least annually
**Hypertension**

- Blood pressure should be measured at every routine clinical visit. High readings should be confirmed using multiple readings, including measurements on a separate day to diagnose hypertension.

- Hypertensive patients with diabetes should monitor blood pressure at home.

- Blood pressure targets should be individualized
  - For those with a higher CV risk: target of <130/80 mmHg may be appropriate if it can be safely attained
  - For those with a lower CV risk: target of <140/90 mmHg

- Lifestyle interventions
  - Weight loss if overweight/obese
  - DASH diet
  - Moderation of alcohol intake
  - Increased physical activity

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**Statin and Combination Treatment for Adults with Diabetes**

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD or 10-year ASCVD risk &gt;20%</th>
<th>Recommended statin intensity and combination treatment</th>
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</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>Yes</td>
<td>High</td>
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<tr>
<td></td>
<td></td>
<td>In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)</td>
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<tr>
<td>≥40 Years</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥40 Years</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)</td>
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</tbody>
</table>
Statin Intensity

<table>
<thead>
<tr>
<th>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</th>
<th>Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
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<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
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<tr>
<td>Simvastatin 20–40 mg</td>
<td>Simvastatin 20–40 mg</td>
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<tr>
<td>Pravastatin 40–80 mg</td>
<td>Pravastatin 40–80 mg</td>
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<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
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<tr>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastatin 2–4 mg</td>
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</tbody>
</table>

Lipid Management

- Lifestyle modifications
  - Weight loss if overweight/obese
  - Mediterranean or DASH diet; reduction of saturated/trans fats; increasing n-3 fatty acids, viscous fiber & plant stanols/sterols
  - Increased physical activity

- Intensify lifestyle therapy & optimize glycemic control for those with elevated TG (≥150 mg/dL) and/or low HDL (<40 mg/dL for men or <50mg/dL for women).

- For those not taking statins or other lipid-lowering therapy, obtain a lipid profile at the time of diabetes diagnosis, at initial medical evaluation, and every 5 years (if under the age of 40) or more frequently if indicated.

- Obtain a lipid profile at initiation of statin or other lipid-lowering therapy, 4-12 weeks after initiation or dose change, and annually thereafter to monitor response/adherence.
Lipid Management

- Statins and ezetimibe
- Statins and PCSK9 Inhibitors
- Statins and fibrates
- Statins and niacin

Antiplatelet Therapy

- Aspirin 75-162mg/day for secondary prevention.
- Clopidogrel 75mg/day if aspirin allergy.
- Dual antiplatelet therapy may be used for 1+ year after acute coronary syndrome.
- Aspirin 75-162mg/day may be considered for primary prevention in those at increased CV risk.
Diabetes Medications proven to reduce ASCVD

A review of Cardiovascular Outcome Trials (CVOTs)

Completed and Ongoing CVOTs

Diabetes Care 2018;41:14–31 | https://doi.org/10.2337/dci17-0057
Summary of CVOTs

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
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<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
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<td>Comparator</td>
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<tr>
<td>N</td>
<td>16,500</td>
<td>14,000</td>
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<td>2016</td>
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<td>placebo</td>
</tr>
<tr>
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<td>14,000</td>
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<td>5,400</td>
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<tr>
<td>Results</td>
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<td>2015</td>
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<td>2018</td>
<td>2019</td>
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<td>SGLT2-i</td>
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<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
<td></td>
</tr>
</tbody>
</table>

DPP-4 Inhibitors CVOTs Summary

- Five trials enrolling 49,618 patients have been designed to evaluate the CV safety of DPP-4 inhibitors.

- Results have been neutral, caveat HF signals with saxagliptin in SAVOR and a trend noted in EXAMINE with alogliptin.
GLP-1 Receptor Agonists CVOTs Summary

- The CV safety of GLP-1 receptor agonists has been assessed in eight trials enrolling 60,090 patients

- LEADER demonstrated the CV noninferiority, as well as the statistical superiority, of once-daily treatment with liraglutide.

- FDA approved a new indication for liraglutide “to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease”

SGLT-2 Inhibitors CVOTs Summary

- Nine trials enrolling 62,378 patients are evaluating the CV and renal safety of SGLT2 inhibitors.

- EMPA REG OUTCOME was the first trial to demonstrate the CV superiority of an antidiabetes drug, empagliflozin

- FDA approved a new indication for empagliflozin on 2 December 2016 “to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease”

- CANVAS also had positive results leading to an FDA indication stating “to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease”
9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019

Start with Monotherapy unless:
- A1C is greater than or equal to 9%
- A1C is greater than or equal to 10%
- Blood glucose is greater than or equal to 300 mg/dL
- Patient is markedly symptomatic

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin
- Lifestyle Management

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
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</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
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<td></td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>modest/less</td>
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</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>GI/nae underdoses</td>
<td></td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
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Dual Therapy

<table>
<thead>
<tr>
<th>SGLT2 Inhibitor</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Lifestyle Management</th>
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<tbody>
<tr>
<td>Efficacy*</td>
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<td>intermediate</td>
<td>high</td>
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<tr>
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</tr>
<tr>
<td>Side effects</td>
<td>hyperglycemia</td>
<td>hyperglycemia, thirst, fatigue, nausea</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Pharmacologic Approaches to Glycemic Treatment Diabetes Care Volume 42, Supplement 1, January 2019

Mark

- A1c 11.0%
- WT 150.3 KG
- BMI 46.9
- BP 132/74
- Cholesterol
  - Total 363
  - TG 514
  - HDL 32
  - LDL 264
Mark’s Diabetes therapies circa 2015

CURRENT LIST OF MEDICINES:
1. Insulin glargine 50 units b.i.d
2. insulin aspart 20-30 units TID AC (patient rarely uses)
3. Metformin 500 mg 2 twice a day.

Glucose-Lowering Medication in Type 2 Diabetes: Overall Approach

First-line therapy is METFORMIN and COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY) if A1C is above target proceed to tracks
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin

GLP-1 Receptor Agonist

- With proven CVD benefit
- liraglutide > semaglutide > exenatide extended release
- Essentially increases the "incretin hormone" available in a person's body
Incretin Hormone Role in the Body

Beta cells: Enhances glucose-dependent insulin secretion

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

GLP-1: Secreted upon the ingestion of food

Data from Nauck MA, et al. Diabetologia. 1996;39:1546-1553; Data from Drucker DJ. Diabetes. 1998;47:159-169

SGLT2i

• With proven CVD benefit
• evidence modestly stronger for empagliflozin > canagliflozin
Renal Handling of Glucose + SGLT2 Inhibitor

Mark's Diabetes therapies circa 2019

CURRENT LIST OF MEDICINES:
1. Insulin glargine 60 units QHS
2. liraglutide 1.8 mg Daily
3. Metformin 500 mg 2 twice a day
4. Empaglifozin 25 mg Daily
Nelson

- A1c 7.7%
- WT 135.6 KG (down ~32 lbs)
- BMI 41.8
- BP 120/84
- Cholesterol
  - Total 190
  - TG 201
  - HDL 48
  - LDL 119
WithOUT established ASCVD or CKD
WithOUT established ASCVD or CKD

**COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**

- **GLP-1 RA with good efficacy for weight loss**
- **SGLT2i**
- **GLP-1 RA with good efficacy for weight loss**
- **SGLT2i**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

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WithOUT established ASCVD or CKD

**COST IS A MAJOR ISSUE**

- **SU**
- **TZD**
- **TZD**
- **SU**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

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**If HbA1c above target**

- **Insulin therapy** basal insulin with lowest acquisition cost
- OR
  - Consider DPP-4i OR SGLT2i with lowest acquisition cost

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

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Post Presentation Questions

1. For patients with a lower CVD risk, an appropriate blood pressure target is ____________

2. Name one of the two high intensity statins

   Atorvastatin 40–80 mg
   Rosuvastatin 20–40 mg

3. What was the first diabetes medication to receive FDA approval for “to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease”

   Empagliflozin (Jardiance®)
References


Questions?

thank you
Cardiovascular Outcome Trials: Reported Studies to Date

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Cardiovascular events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI53</td>
<td>DPPIV - saxagliptin</td>
<td>←</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>DPPIV - albiglifase</td>
<td>←</td>
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<tr>
<td>TECOS</td>
<td>DPPIV - sitagliptin</td>
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<td>ELIKA</td>
<td>GLP-1 RA - lixisenatide</td>
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<td>LADEN</td>
<td>GLP-1 RA – liraglutide</td>
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<td>EXSCEL</td>
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<td>GLT-2 – empagliflozin</td>
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<td>CANVAS (SGLT-2)</td>
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