Diabetes and Cardiovascular Risk Management
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Presenter Disclosure Information
In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Kenneth Ligaray, MD

Disclosed no conflict of interest
Learning Objectives

• Demonstrate screening recommendations for early detection
• Identify antihypertensive treatment approaches for adults with diabetes and hypertension
• Cite ADA lipid treatment guidelines
• Summarize the CV risk reduction noted in clinical trials of certain antihyperglycemic agents

Atherosclerotic Cardiovascular Disease

• Leading cause of morbidity and mortality in diabetes.
  – Coronary heart disease
  – Cerebrovascular disease
  – Peripheral arterial disease presumed to be of atherosclerotic origin
Focus on ASCVD

- Early assessment and targeted intervention needed to treat and prevent all ASCVD and diabetes risk factors
- Common conditions coexisting with type 2 diabetes are clear risk factors for ASCVD
  - Hypertension and dyslipidemia
  - Diabetes itself confers independent risk

Hypertension

Goals for most people with diabetes and hypertension

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>&lt;140 mmHg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>&lt;90 mmHg</td>
</tr>
</tbody>
</table>

Lower targets (<130 mmHg, <80 mmHg) may be appropriate for certain individuals if it can be achieved without undue treatment burden.
Lipid Management

Intensify lifestyle therapy and optimize glycemic control in patients with:

- Triglycerides ≥150 mg/dL; and/or
- Low HDL cholesterol
  - <40 mg/dL for men
  - <50 mg/dL for women


Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD</th>
<th>Recommended statin intensity* and combination treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>No</td>
<td>None†</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#</td>
</tr>
<tr>
<td>≥40 years</td>
<td>No</td>
<td>Moderate‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)</td>
</tr>
</tbody>
</table>

* In addition to lifestyle therapy. †For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. ‡Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.
High- and Moderate-Intensity Statin Therapy

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

Note: Once-daily dosing. XL = extended release


Case Study

**Introduction**

- Mrs. M is a 47-year-old music teacher.
- She has diabetes and a 1-pack-week smoking history.
- Her HDL is 35 mg/dL and her LDL is 145 mg/dL.
- She has tried with little success to control her cholesterol with diet, she is not physically active and continues to smoke a pack a week.

Continued...
Case Study (cont’d)

Discussion Question
What are Mrs. M’s CV risks factors and what would you recommend to curb her risk of ASCVD?
A. Smoking. Enroll her in a smoking cessation program
B. LDL ≥100 mg/dL and high intensity statin therapy
C. Age, gender and presence of diabetes. Recommend lifestyle therapy.
D. A, B and C
E. Family history, hypertension and obesity. Prescribe high intensity statin therapy.

Think-Pair-Share

• If Mrs. M was 52-years-old and had a father who suffered a stroke at age 65 years, how would this information alter your treatment recommendations?
Antiplatelet Agents

• Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD

• For patients with ASCVD and aspirin allergy, clopidogrel (75 mg/day) should be used.

• Dual antiplatelet therapy (aspirin + P2Y12 inhibitor) is reasonable for a year after acute coronary syndrome and may have benefits beyond this period.


Antiplatelet Agents

• Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with T1DM or T2DM at increased cardiovascular risk and not at increased risk of bleeding

• Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

Coronary Artery Disease

Screening:
- In asymptomatic patients, routine screening for CAD isn’t recommended and doesn’t improve outcomes, provided ASCVD risk factors are treated. A
- Consider investigations for CAD with:
  - Atypical cardiac symptoms
  - Signs/symptoms of associated vascular disease
  - EKG abnormalities E

Pre-2008 Working Hypothesis
- DM → ↑ micro and macrovascular complications
- ↑ glucose is major physiologic problem in DM
- Therefore ↓ glucose will improve DM and ↓ micro and macrovascular risk
- So, 1st goal of DM therapy to ↓ glucose, regardless of mechanism
- True for microvascular complications and supported by T1DM data
2018 Working Hypothesis

- Common conditions coexisting with T2D (e.g., hypertension, dyslipidemia) are clear risk factors for ASCVD
- Diabetes itself confers independent risk
- Control individual cardiovascular risk factors to prevent/slow CVD in people with diabetes
- Systematically assess all patients with diabetes for cardiovascular risk factors

CVD Risk in Type 2 Diabetes: Summary of RCTs

<table>
<thead>
<tr>
<th>Intensive vs less intensive glycemic control</th>
<th>Cardiovascular events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>UKPDS</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>VADT</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Individual glucose-lowering drug vs placebo (since 2008 FDA guidance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53 (DPP4i - saxagliptin)²</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>EXAMINE (DPP4i - alogliptin)³</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>TECOS (DPP4i - sitagliptin)⁴</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>ELIXA (GLP-1 RA - lixisenatide)⁵</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME (SGLT2i – empagliflozin)⁶</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LEADER (GLP-1RA – liraglutide)⁷</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>CANVAS (SGLT2i—canagliflozin)⁸</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
New 2018 Recommendations from ADA

- In patients with T2DM and established ASCVD, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse CV events and CV mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A

- In patients with T2DM and established ASCVD, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse CV events, based on drug-specific and patient factors. C

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Dual Therapy

Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. 575 and Table 8.1)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
    - Consider Triple Therapy
Are Complications Reversible?

- ACCORD – BP and lipid normalization also did not result in event reduction.
- LOOK AHEAD – no benefit of lifestyle change and weight loss!
- Above interventions may have been started too late.
- Therefore early intervention is better.
- BUT – When is disease reversible? At diagnosis?

The Look AHEAD Trial: Study Design

- Patients:
  - 5,145 individuals with T2DM, aged 45–74 years, with BMI >25 kg/m² (>27 kg/m² if taking insulin).
- Treatment:
  - An intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared with a diabetes support and education (DSE) condition.
The Look AHEAD Trial: Results

- Participants assigned to ILI lost an average 8.6% of their initial weight vs. 0.7% in DSE group.
- Mean fitness increased in ILI by 20.9% vs. 5.8% in DSE.
- A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medicines.
- Mean A1C dropped from 7.3 to 6.6% in ILI vs. from 7.3% to 7.2% in DSE.
- Systolic and diastolic pressure, triglycerides, HDL cholesterol, and urine albumin-to-creatinine ratio improved significantly more in ILI than in DSE.

Look AHEAD: Benefits of Weight Loss

- “Magnitude of weight loss at 1 year was strongly (p<0.0001) associated with improvements in glycemia, blood pressure, triglycerides, and HDL cholesterol, but not with LDL cholesterol.”
- Improvement was greater with weight loss of 10-15%.
- Conclusions:
  - Even modest weight loss of 5-10% is associated with significant improvements in cardiovascular risk factors.
  - No impact on MI, stroke, death
Impact of Baseline Smoking on Myocardial Infarction in T2DM: UKPDS

<table>
<thead>
<tr>
<th></th>
<th>Hazards ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.08 (0.75 - 1.54)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.58 (1.11 - 2.25)</td>
</tr>
</tbody>
</table>

Case Study

**Introduction**
- Mr. J 54 year old Hispanic male
- Dx with T2D 5 years ago with FBG of 136 and 153
- BMI 32, BP 148/96
- Saw CDE and RD at time of diagnosis (DSME)
- Rarely tests blood glucose (SMBG)
- Sedentary lifestyle
- Former smoker, quit 8 years ago
Case Study

• Labs:
  – A1C 9.2%
  – TC 195, TG 216, HDL 30, LDL 110
  – GFR, serum creatinine normal
  – Minor elevation of LFT’s
  – Urine albumin normal
• No history of ASCVD, renal disease, or retinopathy; notes history of peripheral neuropathy and NAFLD
• FH significant for T2D, MI in mother
• Current medications: Metformin 1000 mg BID, Glipizide extended release 10 mg daily

Case Study

• Address ASCVD risk
  – Modifiable
    • Apparent HTN
    • Abnormal lipid profile
    • Former smoker
    • Sedentary lifestyle
  – Non-modifiable
    • Positive family history
    • Over age 50
Case Study

- **Aspirin**: if no contraindications, start 81 mg daily
- **Hypertension**: (absence of albuminuria)
  - If BP between >140/90 and <160/100, monotherapy with ACEI, ARB, thiazide diuretic, or dihydropyridine calcium channel blocker
  - Target <140/90 (more aggressive individual targets, i.e., 130/80 if can be done without undue treatment burden)
  - Home monitoring

Case Study

- **Lipids**: Over age 40 with risk, moderate intensity (or maximally tolerated) statin
- **Sedentary lifestyle**:
  - Refer for DSME/S, consider exercise prescription
  - Tobacco relapse prevention
- **Blood glucose**: improve control
  - additional non insulin agent or basal insulin
What if this patient had ASCVD?

- **HTN:**
  - β-Blockers may be used for the treatment of prior MI, active angina, or heart failure
  - Consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events.

- **Lipids:**
  - High dose statin or maximally tolerated statin
  - If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

What if this patient had ASCVD?

- **Antihyperglycemics:** consider agents with proven ASCVD reduction
  1. Liraglutide
  2. Empagliflozin
  3. Canagliflozin
  - Continue metformin unless contraindicated
Summary: Cardiovascular Risk

• Assess a patient’s cardiovascular risk at least annually in all patients with diabetes
• Antihypertensive therapy can reduce ASCVD events, heart failure, and microvascular complications
• Statin therapy has beneficial effects on ASCVD outcomes
• Aspirin is effective in reducing CV morbidity and mortality in high-risk patients with previous MI/stroke
• Certain antihyperglycemic therapies can reduce major adverse CV events and mortality

Helpful Resources
Professional Education

- Free online continuing education on cardiovascular risk – including hypertension self-assessment program

Professional.Diabetes.org/CE

Thank You!