Diabetes and Cardiovascular Risk Management
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Disclosures

• No disclosures
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
• ADA’s ASCVD guidelines endorsed by American College of Cardiology
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

Patients with Diabetes and Hypertension

- Individualize targets through shared decision-making that addresses CV risk, potential adverse effects of antihypertensive medications, and patient preferences. C
- For those patients at higher CV risk (existing ASCVD or 10-year ASCVD risk >15%), a BP target of <130/80 mmHg may be appropriate, if it can be safely attained. C
- For those patients at lower risk for CV disease (10-year ASCVD risk <15%), treat to a blood pressure target of <140/90 mmHg. A
- In pregnant patients with diabetes and preexisting hypertension who are treated with antihypertensive therapy, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. E
### RCT - Intensive v. Standard Hypertension Treatment Strategies – ACCORD BP

<table>
<thead>
<tr>
<th>Population</th>
<th>Intensive</th>
<th>Standard</th>
<th>Outcomes</th>
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</table>
| 4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors | Systolic blood pressure target: <120 mmHg | Systolic blood pressure target: 130–140 mmHg | • No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death  
• Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment  
• Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities |

*Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg*  
*Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg*


### RCT - Intensive v. Standard Hypertension Treatment Strategies – ADVANCE BP

<table>
<thead>
<tr>
<th>Population</th>
<th>Intensive</th>
<th>Standard</th>
<th>Outcomes</th>
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</thead>
</table>
| 11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors | Intervention: a single-pill, fixed-dose combination of perindopril and indapamide | Control: placebo | • Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)  
• 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant |

*Achieved (mean) systolic/diastolic: 136/73 mmHg*  
*Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg*


### RCT - Intensive v. Standard Hypertension Treatment Strategies – HOT

<table>
<thead>
<tr>
<th>Population</th>
<th>Intensive</th>
<th>Standard</th>
<th>Outcomes</th>
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</table>
| 18,790 participants, including 1,501 with diabetes | Diastolic blood pressure target: ≤80 mmHg      | Diastolic blood pressure target: ≤90 mmHg     | • In the overall trial, there was no cardiovascular benefit with more intensive targets  
  • In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events |


### RCT - Intensive v. Standard Hypertension Treatment Strategies – SPRINT

<table>
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<tr>
<th>Population</th>
<th>Intensive</th>
<th>Standard</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 9,361 participants without diabetes | Systolic blood pressure target: <120 mmHg     | Systolic blood pressure target: <140 mmHg     | • Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, HF, and death due to CVD)  
  • Intensive target reduced risk of death 27%  
  • Intensive therapy increased risks of electrolyte abnormalities and AKI |
|                                | Achieved (mean): 121.4 mmHg                    | Achieved (mean): 136.2 mmHg                   |                                                                                            |

Hypertension Treatment

- For patients with BP>120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese, a DASH-style dietary pattern, moderation of alcohol intake, and increased physical activity. **B**

- Patients with confirmed office-based BP≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve BP goals. **A**

- Patients with confirmed office-based BP≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with diabetes. **A**

- Treatment for hypertension should include drug classes demonstrated to reduce CV events in patients with diabetes (ACE inhibitors, ARBs, thiazide-like diuretics, or dihydropyridine calcium channel blockers). **A**
Hypertension Treatment

- Multiple-drug therapy is generally required to achieve BP targets. However, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs with direct renin inhibitors should not be used. A

- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, is recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine A or 30–299 mg/g creatinine. B If one class is not tolerated, the other should be substituted. B

- For patients treated with an ACE inhibitor, ARB, or diuretic, serum creatinine/eGFR and serum potassium levels should be monitored at least annually. B

- Patients with hypertension not meeting BP targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. B


Lipid Management

Lifestyle Modification

- Weight loss (if indicated)
- Mediterranean or DASH diet
- Reduction of saturated fat and trans fat
- Increase of n-3 fatty acids, viscous fiber, and plant stanols/sterols intake
- Increased physical activity

Ongoing Therapy and Monitoring

- In adults not taking statins or other lipid-lowering therapy, obtain a lipid profile at diagnosis, at initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. E
- Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. E


Statins and Combination Treatment

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD or 10-year ASCVD risk &gt;20%</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>• 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>
</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>
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<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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</table>

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>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
</tr>
<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>
</tr>
</tbody>
</table>

Note: Once-daily dosing. XL = extended release


Statins in Older Adults

• Meta-analysis including 186,854 participants
  – 14,483 older than 75
• Statin therapy showed benefits in secondary prevention even in age > 75
• Trend towards weaker benefits in primary prevention, but too few participants

Summary: Statins

- Known ASCVD: High intensity statin regardless of age
- Age < 40 and risk < 20%: no statin
- Age 40 and older and risk < 20%: moderate intensity statin

Lipid Management

- For patients with fasting triglyceride levels ≥500 mg/dL (5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C
- In adults with moderate hypertriglyceridemia (fasting or non-fasting triglycerides 175–499 mg/dL), address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. C
- Combination therapy (statin/fibrate) has not been shown to improve ASCVD outcomes and is generally not recommended. A
- Combination therapy (statin/niacin) has not been shown to provide additional CV benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A
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.

**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 and presence of diabetes. Recommend lifestyle therapy.
D. A, B and C
E. Family history, hypertension and obesity. Prescribe high intensity statin therapy.
Antiplatelet Agents

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

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

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


Antiplatelet Agents

• Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk and not at increased risk of bleeding. C

• 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 (e.g. unexplained dyspnea, chest discomfort)
  - 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
Step 1: Assess cardiovascular disease
Presence of cardiovascular disease is compelling indication

If ASCVD Predominates:
GLP-1 RA with proven cardiovascular benefit
  • Liraglutide > semaglutide > exenatide LAR

SGLT2-i with proven cardiovascular benefit
  • Empagliflozin > canagliflozin
### GLP-1RA and Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on cardiovascular mortality, nonfatal MI, or nonfatal CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>HR 0.87 after median 3.8y</td>
</tr>
<tr>
<td></td>
<td>13% vs 14.9%</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>HR 0.74 after median 2y</td>
</tr>
<tr>
<td></td>
<td>6.6% vs 8.9%</td>
</tr>
</tbody>
</table>


### SGLT2-i and Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on cardiovascular mortality, nonfatal MI, or nonfatal CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>HR 0.86 after 3y</td>
</tr>
<tr>
<td></td>
<td>10.5% vs 12.1%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>HR 0.86 after mean 3.6y</td>
</tr>
<tr>
<td></td>
<td>26.9% vs 31.5%</td>
</tr>
</tbody>
</table>

Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

**Rationale:** Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2-i trials

**Caveat:** trials were not designed to adjudicate heart failure

Majority of patients did not have clinical heart failure at baseline

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**Summary**

Consider the presence or absence of ASCVD, CKD and HF

Start with metformin if tolerated, then:

- In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended
- In patients with ASCVD and HF SGLT2-i is recommended
- In patients with CKD, with or without ASCVD consider an SGLT2-i
  - Agents with proven benefit are preferred
  - ASCVD, CKD and HF affects choice of additional glucose lowering medication
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>Smoking Status</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

- **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. Semaglutide
  3. Exenatide LAR
  4. Empagliflozin
  5. Canagliflozin
  – Continue metformin unless contraindicated
Summary: Cardiovascular Risk

• Assess a patient’s cardiovascular risk at least annually in all patients with diabetes
• Individualizing targets for 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 Resources

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

Professional.Diabetes.org/CE

Risk Calculator

The American College of Cardiology/ American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year ASCVD risk

tools.acc.org/ASCVD-Risk-Estimator-Plus
Thank You!