Diabetes and Cardiovascular Risk Management
Denise M. Kolanczyk, PharmD, BCPS-AQ Cardiology
Disclosures

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

NAME OF PRESENTER:

• Denise M. Kolanczyk, PharmD, BCPS-AQ Cardiology
Learning Objectives

• Define cardiovascular risk and assess the non-modifiable and modifiable risk factors
• Describe the benefits of early intervention
• Identify methods for early identification and management of risk factors
Focus on Cardiovascular Risk

• A comprehensive approach to patient care
• Multiple disease pathways and risk factors considered to facilitate earlier intervention
• Early assessment and targeted intervention needed to treat and prevent all risk factors associated with cardiovascular diseases (CVD) and diabetes
Cardiovascular Disease

• Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in diabetes.
  – Acute coronary syndromes (ACSs), a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, peripheral arterial disease presumed to be of atherosclerotic origin

• Common conditions coexisting with type 2 diabetes are clear risk factors for ASCVD.
  – Hypertension and dyslipidemia
  – Diabetes itself confers independent risk
More or less stringent goals may be appropriate for individual patients.
Hypertension

Goals for people with diabetes and hypertension

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

<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>

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
Case Study

Introduction

• Mrs. M is a 47-year-old music teacher.
• She has diabetes and a 20-pack-year 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 day.
Discussion Question

What are Mrs. M’s cardiovascular risks factors and what would you recommend to curb her risk of ASCVD?

A. Smoking and she should be enrolled in a smoking cessation program
B. LDL ≥100 mg/dL and high intensity statin therapy
C. Age, gender and presence of diabetes and she should be recommended lifestyle therapy
D. A, B and C
# Statin Therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
<th>Monitoring with lipid panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
<td>Annually or as needed to monitor adherence</td>
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<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
<td></td>
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<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
<td></td>
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</table>

*With lifestyle therapy  
**LDL ≥100 mg/dL, ↑BP, smoking, chronic kidney disease, albuminuria, family history of premature ASCVD

### Statin Therapy (cont’d)

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<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
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<tbody>
<tr>
<td>40-75 years</td>
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<td>Moderate</td>
<td>As needed to monitor adherence</td>
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<tr>
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<td>ASCVD risk factor(s)**</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or history of ASCVD but cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
<td></td>
</tr>
</tbody>
</table>

*With lifestyle therapy

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<th>Recommended statin intensity*</th>
<th>Monitoring with lipid panel</th>
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</thead>
<tbody>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
<td>As needed to monitor adherence</td>
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<tr>
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<td>ASCVD risk factor(s)**</td>
<td>Moderate to high</td>
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<tr>
<td>ASCVD</td>
<td>ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or history of ASCVD but cannot tolerate high-dose statins</td>
<td>High</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*With lifestyle therapy

**LDL ≥100 mg/dL, ↑BP, smoking, chronic kidney disease, albuminuria, family history of premature ASCVD
# 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 &lt;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
Impact of Diabetes on Cardiovascular Mortality

**Number of risk factors**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>50</td>
<td></td>
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<tr>
<td>40</td>
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<tr>
<td>30</td>
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<td></td>
</tr>
<tr>
<td>20</td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Mortality per 1,000 persons

- **Patients with diabetes**
- **Patients without diabetes**

* Risk factors analyzed were smoking, dyslipidemia, and hypertension

Observations: History of T2DM

- Insulin sensitivity
- Insulin secretion
- Associated risk factors:
  - Hypertension
  - Dyslipidemia
- Atherogenesis
- Complications
- Microvascular
- Fasting blood glucose

Cardiometabolic risk

Age (years)

Fasting blood glucose

- Euglycemia
- Impaired fasting glucose
- Diabetes

Type 2 Diabetes

### Risk Factors

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Overweight/obesity</td>
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<tr>
<td>Race/ethnicity</td>
<td>Inflammation, hypercoagulation</td>
</tr>
<tr>
<td>Gender</td>
<td>Smoking</td>
</tr>
<tr>
<td>Family history</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td></td>
<td>Unhealthy diet</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Abnormal lipid metabolism</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Inflammation, hypercoagulation: This refers to conditions that increase the risk of blood clots, which can lead to heart attacks and strokes. Insulin resistance: This occurs when the body produces insulin but the cells do not respond to it. Abnormal lipid metabolism: This involves issues with cholesterol and triglycerides in the blood. Hypertension: High blood pressure can lead to heart disease, kidney damage, and stroke.
Cardiometabolic Risk

Global diabetes/CVD risk

Abnormal lipid metabolism
- LDL
- ApoB
- HDL
- Triglycerides

Overweight/obesity

Insulin resistance syndrome
- Genetics
- Age

Insulin resistance
- Lipids
- BP
- Glucose

Smoking, physical inactivity, unhealthy eating

Hypertension

Age, race, gender, family history

Inflammation, hypercoagulation

Early Treatment and CVD Risks
Diabetes: Not Always CVD Risk Equivalent


CHD equivalence threshold

~ 8-10 years' duration

Age

CHD risk

Diagnosis
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

- Consider aspirin therapy (75–162 mg/day) in people not at increased risk for bleeding
- As a primary prevention strategy in those with T1DM or T2DM at increased cardiovascular risk
- 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 (onset under age 55 in a male relative or 65 in a female relative)
  - 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.

• Consider investigations for CAD with:
  - Atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort)
  - Signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication or PAD
  - EKG abnormalities (e.g. Q waves)

Long-Term Effects of Intensive Glucose in Newly Dx Patients


### Microvascular disease

**Intensive (SU/Ins) vs. Conventional glucose control**

- **HR = 0.76, p = 0.001**

**Intensive (metformin) vs. Conventional glucose control**

- **HR = 0.64, p = 0.30**

### Myocardial infarction

**Intensive (SU/Ins) vs. Conventional glucose control**

- **HR = 0.85, p = 0.014**

**Intensive (metformin) vs. Conventional glucose control**

- **HR = 0.73, p = 0.002**

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, 1° goal of DM therapy to ↓ glucose, regardless of mechanism
• True for microvascular complications and supported by T1DM data
2017 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

Mortality

HR = 1.22
(95% CI = 1.01-1.46)
p = 0.04
1.41% vs. 1.14% /yr

Primary outcome (composite nonfatal MI, nonfatal stroke, CVD death)

HR = 0.90
(95% CI = 0.78-1.04)
p = 0.16
2.3% vs. 2.1% /yr
<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive vs less intensive glycemic control ¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>←→</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>←→</td>
<td></td>
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<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>
</tbody>
</table>
EMPA-REG OUTCOME and LEADER

EMPA-REG OUTCOME
CV death, non-fatal MI, or non-fatal stroke

LEADER -
CV death, non-fatal MI, or non-fatal stroke

Pooled analysis of the UKPDS, ACCORD, ADVANCE, and VADT trials yielded a 16% overall reduction in nonfatal MI. The absolute overall risk reduction was 9 events per 1000 patients over 5 years of treatment.

In overall analysis, intensive glucose control had no significant effect on:

- CV mortality (relative risk 0.97 [95% CI, 0.76-1.24])
- all-cause mortality (relative risk 0.98 [95% CI, 0.84-1.15])
Before entering VADT intensive treatment arm

After entering VADT intensive treatment arm

Generation of a ‘bad glycemic legacy’

Drives risk of complications

Modelling the prior history of patients recruited in VADT illustrates the drawbacks of late intervention

Legacy of “Bad Metabolic Memory”

HbA1c (%)

Time since diagnosis (years)

6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5

6 7 8 9 10 11 12 13 14 15 16 17

Insulin Resistance
Case Study

Review

• Mrs. M is 47 years old.
• She has diabetes and a 20-pack-year 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 day.
Think-Pair-Share

• If Mrs. M had a BMI of 27 kg/m², how would this information alter your treatment plan?
Factors Affecting Insulin Resistance

- Overweight/fat distribution
- Age
- Genetic predisposition
- Activity level
- Medications
- Puberty
- Pregnancy
Insulin Resistance and CHD Mortality Paris Prospective Study


CHD mortality (per 1000)

\[\begin{align*}
\text{≤29} & : 0 \\
30-50 & : 1 \\
51-72 & : 2 \\
73-114 & : 2.5 \\
\geq115 & : 3
\end{align*}\]

Quintiles (pmol) of fasting plasma insulin

- Insulin sensitive
- Insulin resistant

\[p < .01\] (n = 943)
Multiple Factors Associated with Obesity Give Rise to Increased Risk of CVD

Waist Circumference Is Correlated with Visceral Adipose Tissue

(r = 0.80)

Abdominal Obesity Is Associated with Increased Risk of Coronary Heart Disease

- Waist circumference is independently associated with increased age-adjusted risk of CHD, even after adjusting for BMI and other CV risk factors.

- $p$ for trend = .007 (women)
- $p$ for trend = .001 (men)

Relative Risk

Quintiles of Waist Circumference

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.

“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
<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>
Inflammation/Hypercoagulation

• Proinflammatory/prothrombotic factors underlie cardiovascular risk.
• Inflammation is a major component of atherogenesis and other cardiovascular problems.
• Obesity in DM is associated with inflammation.

Summary: Cardiovascular Risk

- Assessing a patient’s cardiovascular risk is important to prevent ASCVD and T2DM.
  - Modifiable risk factors such as physical inactivity and smoking can be minimized.
  - Identification of these modifiable risk factors allows for the initiation of lifestyle and pharmacologic strategies.
- Early detection of risk factors allows for implementation of preventive strategies.
- **CVD risks are irreversible.**
- Early intervention and risk management can prevent and delay progression of T2DM.
Thank You!