Diabetes and Cholesterol Management: Digesting Recent Treatment Guidelines

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Disclosures

Erin Raney, Pharm.D, BCPS, BC-ADM has no financial disclosures or conflicts of interest.
Learning Objectives

• Describe the updated approach to cardiovascular risk assessment according to the 2018 ACC/AHA Multisociety Guideline on the Management of Blood Cholesterol

• Recommend and monitor individualized lipid lowering medication regimens

• Compare and contrast the ACC/AHA Multisociety Guideline with other expert guidelines on the management of lipids in individuals with diabetes
The Connection Between Diabetes and Cardiovascular Disease

Adults with diabetes are 2-4 times more likely to die from heart disease than adults without diabetes.

68% of people age 65 and older with diabetes die from heart disease.

The ABC’s of Diabetes

A1C

Blood Pressure

Cholesterol


• Serves as an update to the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
• Provides recommendations for both primary and secondary prevention
• Reintroduces LDL treatment goals for some patient groups
• Incorporates specific recommendations for special populations
  • Racial/ethnic groups
  • Women
  • People with diabetes
  • People with chronic kidney disease
  • People with chronic inflammatory conditions or HIV
  • Older adults
  • People with hypertriglyceridemia

http://www.onlinejacc.org/content/early/2018/11/02/j.jacc.2018.11.003?_ga=2.266845514.593286583.1556770043-500181620.1556770043
Assessment of Cardiovascular Risk

• Focus on risk assessment using ASCVD risk calculator to estimate 10-year risk [http://static.heart.org/riskcalc/app/index.html#/baseline-risk](http://static.heart.org/riskcalc/app/index.html#/baseline-risk)

• Calculator incorporates the following traditional risk considerations: gender, age, race, cholesterol (total, LDL, HDL), systolic blood pressure, treatment for hypertension, history of diabetes, current smoker, aspirin therapy.

• New guidelines also incorporate assessment of “risk enhancers” in patients ages 40 to 75 years and the measurement of coronary artery calcium to determine treatment plans for some patients with intermediate risk.

CVD Risk Enhancers

- Family history of premature ASCVD (men <55 years old, women <65 years old)
- Persistently elevated LDL-C ≥ 160 mg/dl
- Metabolic syndrome
- Chronic kidney disease
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, psoriasis, HIV)
- History of early menopause or pregnancy-associated risks (e.g., preeclampsia, gestational HTN, gestational DM, preterm deliveries)
- High-risk ethnicity (e.g., South Asian Ancestry, Native American/Alaskan, Black Women)
- High lipid biomarkers
  - Triglycerides ≥175 mg/dL
  - High-sensitivity C-reactive protein ≥2.0mg/dL
  - Elevated lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L
  - Elevated apolipoprotein B ≥130 mg/dL
  - Ankle-brachial index (ABI) < 0.9

http://www.onlinejacc.org/content/early/2018/11/02/j.jacc.2018.11.003?_ga=2.266845514.593286583.1556770043-500181620.1556770043
Role of Lifestyle Modifications

• Lifestyle modifications are recommended at all risk levels

• New guidelines support the recommendations made in the 2013 ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk (Circulation 2014;129:S76–S99)

• Diet emphasizing intake of vegetables, fruits, whole grains, fish/seafood, legumes, healthy proteins

• Diet limiting sweets, sugar-sweetened beverages, and red meat

• Physical activity including aerobic activity 3-4 times per week (~40 minutes per session)

• Special emphasis on lifestyle management of the metabolic syndrome
  • At least 3 out of 5 of the following risk factors: elevated waist circumference, elevated triglycerides, low HDL, elevated BP, elevated fasting glucose

http://www.onlinejacc.org/content/early/2018/11/02/j.jacc.2018.11.003?_ga=2.266845514.593286583.1556770043-500181620.1556770043
## General Statin Treatment Approach

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk stratification</th>
<th>Recommendation for statin</th>
<th>LDL target (if not met consider additional therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0-19 yrs</td>
<td>If familial hypercholesterolemia</td>
<td>Consider statin</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 20-39 yrs</td>
<td>If family history of premature ASCVD and LDL ≥ 160</td>
<td>Consider statin</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40-75 yrs</td>
<td>High risk (10-yr ASCVD risk at least 20%)</td>
<td>High intensity</td>
<td>≥50% reduction</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (10-yr ASCVD risk 7.5 - &lt;20%)</td>
<td>Moderate intensity</td>
<td>30-49% reduction</td>
</tr>
<tr>
<td></td>
<td>Borderline risk (10-yr ASCVD risk 5-&lt;7.5%)</td>
<td>Moderate intensity (if risk enhancers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low risk (10-yr ASCVD risk &lt;5%)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>LDL ≥ 190 mg/dL</td>
<td>None needed</td>
<td>High intensity</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Clinical ASCVD (secondary prevention)</td>
<td>Very-high risk (multiple ASCVD events or ASCVD plus other high risk conditions)</td>
<td>High intensity</td>
<td>&lt;70 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Other risk</td>
<td>High intensity (age ≤ 75)</td>
<td>&lt;70 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate-High (age &gt; 75)</td>
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</tbody>
</table>

[ACC/AHA Multisociety Guideline](http://www.onlinejacc.org/content/early/2018/11/02/j.jacc.2018.11.003?_ga=2.266845514.593286583.1556770043-500181620.1556770043)
<table>
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<th>Recommendation for statin</th>
<th>LDL target (if not met consider additional therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (40-75 years old)</td>
<td>If LDL ≥ 70 (regardless of ASCVD risk)*</td>
<td>Moderate intensity</td>
<td>30-49% reduction in LDL</td>
</tr>
<tr>
<td>Diabetes (40-75 years old)</td>
<td>High risk (with DM-specific risk enhancers)**</td>
<td>High intensity</td>
<td>≥ 50% reduction in LDL</td>
</tr>
<tr>
<td></td>
<td>10-year ASCVD ≥20%</td>
<td>High intensity (or maximally tolerated statin plus ezetimibe, if needed)</td>
<td></td>
</tr>
<tr>
<td>Diabetes &gt; 75 years old</td>
<td>Continue statin if already on statin and tolerating If not on statin, consider statin therapy with shared decision making</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ASCVD risk calculator can be used to stratify risk further for treatment decisions
Diabetes Specific Risk Enhancers**

Type 2 for 10 years or more
Type 1 for 20 years or more
Ankle Brachial Index < 0.9
Albuminuria ≥ 30 mcg albumin/mg creatinine
Neuropathy
eGFR < 60
Retinopathy
## Statin Intensity

<table>
<thead>
<tr>
<th>High intensity (lowers LDL by at least 50%)</th>
<th>Moderate Intensity (lowers LDL by 30-50%)</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></td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
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<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
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<tr>
<td></td>
<td>Pitavastatin 1-4 mg</td>
</tr>
</tbody>
</table>
Case Scenario #1

A 48 year old Hispanic woman with Type 2 DM diagnosed at age 40 is taking metformin 1000 mg BID and lisinopril 10 mg once daily. She establishes with a new PCP who evaluates her risk for CVD. She is a non-smoker.

Recent labs/exam reveal A1C 7.6%, BMI 31 kg/m², BP 144/88, TC 230, LDL 134, HDL 39.

ASCVD 10-year risk 6.6%

Is statin therapy recommended, and if so, what intensity?
Case Scenario #1, cont’d

What if the same patient had this profile instead...

A 48 year old Hispanic woman with Type 2 DM diagnosed at age 40 is taking metformin 1000 mg BID and lisinopril 10 mg once daily. She establishes with a new PCP who evaluates her risk for CVD. She smokes cigarettes (1 ppd).

Recent labs/exam reveals A1C 9.6%, BMI 35 kg/m², BP 154/88, TC 240, LDL 154, HDL 30, eGFR 55 ml/min

ASCVD 10-year risk 31.1%

Is statin therapy recommended, and if so, what intensity?
## Statin Treatment Approach for Diabetes

### ACC/AHA Multisociety Guideline

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk stratification</th>
<th>Recommendation for statin</th>
<th>LDL target (if not met consider additional therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (20-39 years old)</td>
<td>Risk enhancers:</td>
<td>Consider moderate intensity statin therapy with shared decision making</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>ABI &lt;0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albuminuria ≥ 30 mcg albumin/mg creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 2 for 10 years or more</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Type 1 for 20 years or more</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>eGFR &lt; 60</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Retinopathy</td>
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<td></td>
</tr>
</tbody>
</table>

Case Scenario #2

A 33 year old man with type 2 diabetes diagnosed 3 years ago is taking liraglutide 1.2 mg once daily and metformin 1000 mg BID:

Recent labs/exam reveal A1C 6.6%, BMI 29 kg/m2, BP 122/78, TC 199, LDL 102, HDL 44, eGFR >100 ml/min, albumin/creatinine ratio <4 mcg/gm.

What should be considered when assessing his need for a statin?
# Statin Considerations

<table>
<thead>
<tr>
<th>Select Adverse Effects</th>
<th>Factors Associated with Risk</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin associated muscle symptoms (myalgias, myositis,</td>
<td>Age, female, low BMI, drug interactions, Asian descent, alcohol use, physical activity,</td>
<td>Patient-reported symptoms CK (creatinine kinase) if symptoms</td>
</tr>
<tr>
<td>rhabdomyolysis)</td>
<td>HIV, renal failure, thyroid conditions, pre-existing myopathy</td>
<td>Renal function if symptoms</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Metabolic syndrome, high statin doses</td>
<td>Serum BG (screen prior to initiating statin)</td>
</tr>
<tr>
<td>Liver disease (increased liver enzymes, liver failure)</td>
<td></td>
<td>Liver function tests if symptoms</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td></td>
<td>Cognitive symptoms</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Pregnancy</td>
<td>If childbearing age and sexually active, counsel on contraception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If planning pregnancy, stop statin 1-2 months before attempting</td>
</tr>
</tbody>
</table>
## Non-Statin Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Groups</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>Clinical ASCVD on max statin with LDL ≥ 70 mg/dL</td>
<td>Well tolerated</td>
</tr>
<tr>
<td></td>
<td>Severe hypercholesterolemia on max statin with LDL ≥ 100 mg/dL</td>
<td>Relatively inexpensive oral drug</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>Clinical ASCVD on max statin plus ezetimibe with LDL ≥ 70 mg/dL</td>
<td>Injectable formulations only</td>
</tr>
<tr>
<td></td>
<td>Severe hypercholesterolemia on max statin plus ezetimibe with LDL ≥ 100 mg/dL</td>
<td>Relatively expensive</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Severe hypercholesterolemia on max statin plus ezetimibe who haven’t reached at least 50% reduction in LDL</td>
<td>Not as well tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not appropriate if high TG levels</td>
</tr>
</tbody>
</table>
Focus on Hypertriglyceridemia

• Adults 20 years and older with TG 175-499 mg/dL, address secondary causes and lifestyle factors
  • Obesity, metabolic syndrome, alcohol use
  • Medications associated with elevated triglycerides
  • Secondary factors such as uncontrolled blood glucose, chronic liver disease, chronic kidney disease, hypothyroidism

• Adults 40-75 years with moderate to severe hypertriglyceridemia and ASCVD risk ≥ 7.5 %, consider statin therapy if still elevated after addressing lifestyle and secondary causes

• Adults 40-75 years with TG ≥ 500 mg/dL (esp. ≥ 1000 mg/dL), address lifestyle and secondary causes as above and consider (in addition to statin):
  • Very low fat diet, avoidance of refined carbohydrates, avoidance of alcohol
  • Addition of omega-3 fatty acids
  • Fibrate therapy

http://www.onlinejacc.org/content/early/2018/11/02/j.jacc.2018.11.003?_ga=2.266845514.593286583.1556770043-500181620.1556770043
Comparison with ADA Standards of Medical Care in Diabetes - 2019
ADA Cardiovascular Risk and Risk Management

• Supports lifestyle management at all risk levels
  • Mediterranean or DASH eating plan
  • Reduced of saturated/trans fat
  • Increased dietary omega-3 fatty acids, viscous fiber, plant stanols/sterols
  • Increased physical activity

• Supports the use of the AHA/ACC ASCVD risk calculator to assess 10-year cardiovascular risk
  • Notes that this risk calculator does not account for duration of diabetes, diabetes complications, or diabetes control

• Recommends statins as primary agent for cholesterol management

• Generally recommends against the use of the following treatment combinations:
  • Statin/fibrate
  • Statin/niacin

http://care.diabetesjournals.org/content/42/Supplement_1
# Statin Treatment Approach

<table>
<thead>
<tr>
<th>Group</th>
<th>Statin</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes and ASCVD (any age)</td>
<td>High intensity</td>
<td>Consider adding ezetimibe or PCSK9 inhibitor if LDL not below 70 with treatment</td>
</tr>
<tr>
<td>Diabetes and ASCVD risk &gt;20% (any age)</td>
<td>High intensity</td>
<td>As above</td>
</tr>
<tr>
<td>Diabetes age &lt; 40 years with additional ASCVD risk factors</td>
<td>Consider moderate intensity</td>
<td></td>
</tr>
<tr>
<td>Diabetes age 40-75 years (primary prevention)</td>
<td>Moderate intensity</td>
<td>Consider high intensity if multiple ASCVD risk factors</td>
</tr>
<tr>
<td>Diabetes &gt; 75 years (primary prevention)</td>
<td>Moderate intensity</td>
<td>Consider high intensity if multiple ASCVD risk factors</td>
</tr>
</tbody>
</table>

**ASCVD RF:** LDL ≥100, HTN, Smoking, CKD, Albuminuria, Family history of premature CVD

ADA Standards of Medical Care

http://care.diabetesjournals.org/content/42/Supplement_1
Case Scenario #3

A 77 year old man with type 2 diabetes for 12 years presents to clinic for a routine check-up. He is taking glipizide 10 mg once daily, metformin 1000 mg BID, atorvastatin 40 mg once daily, and losartan 100 mg once daily. He is a nonsmoker (quit 10 years ago). He has no history of clinical ASCVD.

Today’s labs/exam reveal A1C 6.1%, BMI 24 kg/m2, BP 100/68, TC 168, LDL 62, HDL 41, eGFR 40 ml/min.

His baseline lipid panel before starting a statin 10 years ago was TC 220, LDL 141, HDL 30.

What is the appropriate statin treatment recommendation for him at this time?

Identify additional treatment considerations for his cardiometabolic health.
Focus on Hypertriglyceridemia

- If TG moderately elevated (175 – 499 mg/dL), address secondary causes and lifestyle factors
  - Obesity, metabolic syndrome, alcohol use
  - Medications associated with elevated triglycerides
  - Secondary factors such as uncontrolled blood glucose, chronic liver disease, chronic kidney disease, hypothyroidism

- If TG ≥ 500 mg/dL (especially > 1000 mg/dL), recommend evaluation for secondary causes and consider drug treatment to reduce pancreatitis risk in addition to lifestyle factors
  - Fibrates
  - Fish oil
  - Statins (if ASCVD risk is ≥ 7.5%)

- Recent REDUCE-IT trial showed a 25% reduction in CV risk in the diabetes cohort when given icosapent ethyl 2 grams BID versus placebo (N Engl J Med 2019;380:11-22)
  - LDL levels were < 100 mg/dL and TG were 150-499 mg/dL
Comparison with AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm- 2019
AACE/ACE Lipid Management Approach

• Supports lifestyle therapy (weight management, healthy eating, physical activity, smoking cessation)

• Suggests the most individuals with Type 2 Diabetes will need drug therapy for lipid management
  • Statin therapy preferred
  • Recommends addition of other agents when goals are not achieved with statins alone, or use alone when statin intolerance occurs
    • Ezetimibe
    • PCSK-9 inhibitors
    • Bile acid resins

# AACE/ACE Lipid Targets

<table>
<thead>
<tr>
<th>Risk</th>
<th>Description</th>
<th>Lipid Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤ 1 risk factor</td>
<td>LDL &lt; 160; non-HDL &lt; 190</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 2 risk factors and 10-year risk &lt; 10%</td>
<td>LDL &lt; 130; non-HDL &lt; 160</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2 risk factors and 10-year risk &gt; 10% -or- CHD risk equivalent (includes diabetes or CKD 3/4 with no other risk factors)</td>
<td>LDL &lt; 100; non-HDL &lt; 130; TG &lt; 150; Apo B &lt; 90</td>
</tr>
</tbody>
</table>
| Very High  | -Established or recent hospitalizations for ACS, coronary/carotid/peripheral vascular disease  
-Diabetes or CKD 3/4 with one or more risk factors  
-HeFH | LDL < 70; non-HDL < 100; TG < 150; Apo B < 80                                 |
| Extreme    | -Progressive ASCVD including unstable angina in patients after achieving LDL < 70  
-Established clinical ASCVD with DM, CKD 3/4, or HeFH  
-History of premature ASCVD (male < 55, female < 65) | LDL < 55; non-HDL < 80; TG < 150; Apo B < 70                                |

People with Type 2 Diabetes

Case Scenario #4

A 68 year old man with type 2 diabetes for 20 years was recently discharged from a hospitalization for acute coronary syndrome. Prior to the hospitalization, he was taking insulin glargine 26 units every evening, pravastatin 10 mg once daily, and HCTZ 25 mg once daily.

He is a non-smoker and has the following family history: maternal (COPD, died at age 60), paternal (unknown), brother (currently age 65, MI at age 50, type 2 DM)

Pre-hospital labs/exam reveal A1C 8.7%, BMI 35 kg/m², BP 162/78, TC 206, LDL 134, HDL 25, eGFR 45 ml/min, albumin/creatinine ratio 96 mcg/gm.

What is the appropriate statin treatment recommendation for him at this time?

What treatment goal and monitoring is recommended?

Would this differ if we were following the ACC/AHA Multisociety Guideline or ADA Standards of Care instead?
Focus on Hypertriglyceridemia

• If triglycerides are > 500 mg/dL, the following recommendations are made:
  • Improve blood glucose control
  • Reduce intake of refined carbohydrates, recommend very low fat diet
  • Initiate additional drug therapy
    • Fibrate
    • Niacin (must monitor for increased blood glucose during use)
    • Omega-3 fatty acids (prescription grade)
Summary

• Current cholesterol treatment guidelines recognize diabetes as a significant independent risk factor for cardiovascular disease.

• Lifestyle management through dietary and physical activity approaches remains the foundation of all treatment plans.

• Current risk assessment tools can be supplemented by additional risk modifiers to determine treatment plans for patients who do not fall within specific treatment groups.

• Statin therapy is supported as the first-line treatment approach by all current guidelines.

• Some non-statin therapies are appropriate in combination with statins for the highest risk individuals or those who have statin intolerance.

• Updated assessments of risk and treatment regimens is important over a patient’s lifespan.
Questions?