A Practical Approach to Integrating the New Dyslipidemia Guidelines for People with Diabetes

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  - Please refer to learning goals and objectives
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours
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Objectives

1. Compare current dyslipidemia guideline recommendations as they apply to people with diabetes
2. Develop a risk assessment approach to determine management strategies for dyslipidemia
3. Apply the 2018 ACC/AHA treatment recommendations to participant case examples

Top 7 Leading Causes of Death

- Cardiovascular
- Cancer
- Injury
- Resp. Disease
- Stroke
- Alzheimer
- Diabetes

Atherosclerotic Cardiovascular Disease (ASCVD) includes:
- Myocardial infarction
- Stroke/Transient ischemic attack
- Peripheral Artery Disease
- Angina
- Arterial revascularization

66% of deaths are due to cardiovascular disease
Friedewald Equation for LDL-C

Calculated LDL-C = Total Cholesterol – TG/5-HDL-C

- Elevated Triglycerides (TGs) falsely lowers LDL-C
- Ignore low calculated LDL-C in the presence of high TGs
  - Inaccurate calculation starting at TGs ≥ 200 mg/dL
  - Invalid calculation once TGs reach 400 mg/dL
- Persistently elevated TGs is a risk enhancing feature commonly found in people with diabetes (PWD)
- Consider using Non-HDL-C for risk assessment
  - Non-HDL-C = total cholesterol – HDL-C

Cholesterol Treatment Guidelines

Goals: Treatment Targets or Percent LDL-C Reduction?

ATP III Update

<table>
<thead>
<tr>
<th>2004 Guideline Gap</th>
<th>2013</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
</table>

ACC/AHA

% LDL-C Reduction

2013 ACC/AHA “Statin Guidelines”

- Clinical ASCVD
  - Moderate-intensity statin (Age >75)
  - High-intensity statin (Age ≤75)
- LDL-C ≥190 mg/dL
  - High-intensity statin
- Diabetes
  - Moderate-intensity statin
  - High-intensity statin if 10-y risk ≥7.5%
- 10-y risk ≥7.5%
  - Moderate-to-high intensity statin

Atorvastatin 10-20 mg
Rosuvastatin 5-10 mg
Simvastatin 20-40 mg
Lovastatin 40 mg
Pravastatin 40-80 mg
Pitavastatin 1-4 mg

Atorvastatin 40-80 mg
Rosuvastatin 20-40 mg

Statin dose intensity and % LDL-C reduction

Moderate-intensity (LDL-C reduction 30-49%)
High-intensity (LDL-C reduction ≥50%)

Statin Treatment for Eligible Patients with Diabetes in the United States

Primary Prevention
Secondary Prevention

Care Gap
Care Gap

Statin
No Statin
Statin
No Statin

58.2%
42.8%
43.1%
66.9%

National Diabetes Statistics Report, 2017

AACE/ACE 2017 ASCVD Risk Factors

Risk Assessment includes:
• 10-year Risk Calculation and Assessment of Risk Factors

Major risk factors
Additional risk factors
Nontraditional risk factors

Advancing age
Total serum cholesterol level
LDL-C
Non-HDL-C
Diabetes mellitus
Hypertension
Stage 3 or 4 chronic kidney disease
Cigarette smoking
Family history of ASCVD

Family history of hyperlipidemia
Apo B
LDL particle concentration
Fasting/postprandial
hypertriglyceridemia
PCOS
Dyslipidemic triad (High TGs + Low HDL + small dense LDL)

Lipoprotein (a)
Clotting factors
Inflammation markers
(hsCRP, Lp-PLA2)
Homocysteine levels
Apo E4 isoform
Uric acid
TG-rich remnants

Abreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome.

### AACE/ACE 2017 “Lower is Better”

Comparing Past Guidelines

**ACC/AHA 2013**
- Statin focused
- No guidance for non-statin agents
- Treatment goal: % LDL-C reduction based on statin intensity
- Recommended lipid monitoring
  - 4-12 weeks for change in therapy
  - 4-12 months for stable patients

**AACE/ACE 2017**
- Comprehensive guideline
- Statin and non-statin recommendations
- Treatment goal: Targets
  - LDL-C, Non-HDL, Apo-B
- Recommended lipid monitoring
  - 6 weeks for change in therapy
  - 6-12 months for stable patients

2018 ACC/AHA Blood Cholesterol

- Lifestyle Therapies
  - Heart healthy diet
  - Physical activity
- Four (4) Statin Benefit Groups
  - Moderate- or high-intensity statins
- Myocardial infarction (MI)
- Stroke/TIA
- Peripheral arterial disease (PAD)
- Revascularization

2018 ACC/AHA Blood Cholesterol

2018 ACC/AHA Blood Cholesterol

• Monitoring
  – Adherence to lifestyle and LDL-C lowering therapies
  – 4 to 12 weeks after statin initiation or dose adjustment
  – 3 to 12 months thereafter

Case 1:
• HB is a 67-year-old African American male here for diabetes management
• PMH: T2DM, HTN, previous MI (2016)
• Meds:
  • lisinopril 40 mg/d
  • carvedilol 12.5 mg BID
  • aspirin 81 mg/d
  • metformin 1000 mg BID
  • empagliflozin 10 mg/d
  • rosuvastatin 40 mg/d

Lipid panel

| Total Chol. | 171 mg/dL |
| TG | 133 mg/dL |
| HDL-C | 42 mg/dL |
| LDL-C | 94 mg/dL |

Vitals
• BP: 126/68 mm Hg
• HR: 67 bpm
• Weight: 193 lbs.
• BMI: 27.6 kg/m²
• FBG: 113 mg/dL

What changes would you make to HB’s lipid therapy?
2018 ACC/AHA Blood Cholesterol

- Myocardial infarction (MI)
- Stroke/TIA
- Peripheral arterial disease (PAD)
- Revascularization

High-intensity statin

Moderate-intensity statin

2018 ACC/AHA: Secondary Prevention

- “Very-high risk” group
  - Very-high risk includes: ≥2 major ASCVD events or major ASCVD event + multiple high-risk conditions

<table>
<thead>
<tr>
<th>Major ASCVD events</th>
<th>High-risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS within previous 12 months</td>
<td>Prior revascularization (CABG, PCI) outside of ASCVD event</td>
</tr>
<tr>
<td>Prior MI or ischemic stroke</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Symptomatic PAD, previous peripheral revascularization/amputation, or claudication with ABI &lt;0.85</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Prior revascularization (CABG; PCI) outside of ASCVD event</td>
<td>Current smoking</td>
</tr>
<tr>
<td>eGFR 15-59 ml/min/1.73m²</td>
<td>LDL-C ≥100 mg/dL (despite maximally tolerated statin + ezetimibe)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>Heterozygous Familial Hypercholesterolemia</td>
<td>Congestive heart failure</td>
</tr>
</tbody>
</table>

2018 ACC/AHA: Secondary Prevention

Goal: reduce LDL-C ≥50%

Moderate-intensity if unable to tolerate high-intensity statin

Lifestyle + high-intensity statin

Lifestyle + moderate-intensity statin

Lifestyle + moderate-intensity statin

Reasonable to add ezetimibe

Reasonable to add PCSK9i

Reasonable to add PCSK9i

Very-high ASCVD risk

≥70 years not very-high risk

#AADE
Non-statins for Secondary Prevention

- Ezetimibe
  - ↓ LDL-C 20-25%
  - Once-daily oral pill
  - Generic available

- PCSK9-inhibitors
  - ↓ LDL-C 45-65%
  - Bi-weekly SQ injection
  - Brand only
    - ~$14,000/yr (2018)
    - ~$6,000/yr (2019)

Case 1:

- HB is a 67-year-old African American male here for diabetes management
- PMH: T2DM, HTN, previous MI (2016)
- Meds:
  - lisinopril 40 mg/d
  - carvedilol 12.5 mg BID
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  - metformin 1000 mg BID
  - empagliflozin 10 mg/d
  - rosuvastatin 40 mg/d

- Vitals
  - BP= 126/68 mm Hg
  - HR= 67 bpm
  - Weight= 193 lbs.
  - BMI= 27.6 kg/m²
  - FBG= 113 mg/dL

Lipid panel

- Total Chol. 171 mg/dL
- TG 153 mg/dL
- HDL-C 42 mg/dL
- LDL-C 64 mg/dL

What changes would you make to HB's lipid therapy?

Reasonable to add ezetimibe 10 mg daily to current therapy

ADA 2019: Lipids

- Lifestyle modifications (diet & physical activity) should be recommended to improve the lipid profile and reduce the risk of ASCVD in patients with diabetes (A)
ADA 2019: Reducing ASCVD Risk

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD or 10-year ASCVD risk &gt;20%</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>Yes</td>
<td>High-intensity statin*</td>
</tr>
<tr>
<td>No</td>
<td>None*</td>
<td></td>
</tr>
<tr>
<td>≥40 years</td>
<td>Yes</td>
<td>High-intensity statin*</td>
</tr>
<tr>
<td>No</td>
<td>Moderate-intensity statin*</td>
<td></td>
</tr>
</tbody>
</table>

Maximally tolerated statin dose if unable to tolerate recommended intensity.

*moderate-low intensity may be considered if additional ASCVD risk factors present (LDL-C ≥100 mg/dL, high blood pressure, smoking, family history of premature ASCVD, CKD, or albuminuria).

* LDL-C ≥250 mg/dL on maximally tolerated statin, consider additional LDL-C lowering therapy (icosabia/PCSK9-I).

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Case 2:

- GN is a 63-year-old non-Hispanic female here for initial visit.
- PMH: T2DM, HTN, CKD
- SH: Smokes 8-12 cig/d
- Meds: amlodipine 5 mg/d, losartan 100 mg/d, metformin 1000 mg BID
- Vital signs: BP= 132/78 mm Hg, HR= 82 bpm, BMI= 28.6 kg/m²
- Labs:
  - eGFR 56 ml/min/1.73m²
  - Total Chol. 194 mg/dL
  - UACR 69 mcg/mg
  - TG 156 mg/dL
  - FBG 124 mg/dL
  - HDL-C 44 mg/dL
  - LDL-C 116 mg/dL
  - HgbA1C 7.2%

Would you recommend statin therapy for GN?

2018 ACC/AHA Blood Cholesterol

1. Clinical ASCVD
   - Myocardial infarction (MI)
   - Stroke/TIA
   - Peripheral arterial disease (PAD)
   - Revascularization

2. Severe hypercholesterolemia
   - LDL-C ≥190 mg/dL

3. Patients with diabetes mellitus and LDL-C ≥270 mg/dL

4. Age ≥75 years with DM and LDL-C ≥200 mg/dL and 10-year ASCVD risk ≥7.5%
Primary Prevention in Patients with Diabetes Mellitus (DM)

- Recommendations for adult patients with diabetes mellitus and LDL-C 70-189 mg/dL
  - 20-39 years
  - 40-75 years
  - >75 years


Reasonable to calculate 10-year ASCVD risk

- Multiple ASCVD risk factors
- 10-year ASCVD risk ≥20%
- Age 50-75 years

Primary Prevention in Patients with DM

Age 40-75 years

Reasonable to calculate 10-year ASCVD risk

Moderate-intensity statin

High-intensity statin

Ezetimibe to achieve ≥50% LDL-C reduction

ADA 2019: Reducing ASCVD Risk

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<td>≥40 years</td>
<td>Yes</td>
<td>High-intensity statin*</td>
</tr>
<tr>
<td>≥40 years</td>
<td>No</td>
<td>Moderate-intensity statin*</td>
</tr>
</tbody>
</table>

Maximally tolerated statin dose if unable to tolerate recommended intensity

*Moderate-high-intensity may be considered if additional ASCVD risk factors present (LDL-C ≥100 mg/dL, high blood pressure, smoking, family history of premature ASCVD, or albuminuria).

1. LDL-C ≥70 mg/dL on maximally tolerated statin, consider additional LDL-C lowering therapy (ezetimibe/PCSK9-I).
10-year ASCVD Risk Calculator

- 57 y/o AAF with diabetes
  - BP = 138/78 mmHg (treated)
  - TC = 234 mg/dL; HDL-C = 48 mg/dL
- 51 y/o Hispanic male with diabetes and current smoking
  - BP = 126/68 mmHg (treated)
  - TC = 208 mg/dL; HDL-C = 44 mg/dL
- 61 y/o non-Hispanic male with diabetes
  - BP = 144/68 mmHg (untreated)
  - TC = 185 mg/dL; HDL-C = 46 mg/dL

Case 2:

- GN is a 63-year-old non-Hispanic female here for initial visit.
- PMH: T2DM, HTN, CKD
- SH: Smokes 8-12 cig/d
- Meds:
  - amiodipine 5 mg/d
  - losartan 100 mg/d
  - metformin 1000 mg BID
- Vitals
  - BP = 132/78 mm Hg
  - HR = 82 bpm
  - BMI = 28.6 kg/m²

<table>
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<tr>
<th>Labs</th>
<th>10-year Risk</th>
<th>Is lipid-lowering medication recommended for GN?</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 96 ml/min/1.73m²</td>
<td>Total Chol. 194 mg/dL</td>
<td>High-intensity statin</td>
</tr>
<tr>
<td>UACR 69 mg/g</td>
<td>TG 196 mg/dL</td>
<td></td>
</tr>
<tr>
<td>FBG 124 mg/dL</td>
<td>HDL-C 44 mg/dL</td>
<td></td>
</tr>
<tr>
<td>HgbA1C 7.2%</td>
<td>LDL-C 116 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

10-year ASCVD risk >20%
Primary Prevention in Patients with DM

Age 20-39
- Assess Diabetes-Specific Risk Enhancers
  - Long duration of DM
  - ≥20 years T1DM
  - ≥10 years T2DM
  - Retinopathy
  - Neuropathy
  - Albuminuria ≥30 mg albumin/creatinine
  - eGFR <60 mL/min/1.73 m²
  - ABI <0.9

Moderate-intensity statin

Age >75 years
- Already on statin
- Not on statin
- Reasonable to continue
- Clinician-patient discussion (Benefits vs Risks)

Primary Prevention in Patients without DM

Age 0-19 years
- Lipid screening for FH
- Promote lifestyle to reduce ASCVD risk

Age 20-39 years
- Assess lifetime ASCVD risk + risk factors
- Promote lifestyle to reduce ASCVD risk
- Consider statin if premature family history of ASCVD and LDL-C ≥160 mg/dL

Age 40-75 years (70-189 mg/dL)
- Assess 10-year ASCVD risk

Case 3:
- HL is a 48-year-old African American male here for pre-diabetes education
- PMH: HTN, pre-diabetes
- Meds: amlodipine 5 mg/d
- Vitals
  - BP: 137/74 mm Hg
  - HR: 72 bpm
  - BMI: 33.8 kg/m²
  - Waist circumference: 42.3”
- Labs
  - eGFR: 115 mL/min/1.73m²
  - Total Chol.: 214 mg/dL
  - UACR: 3 mcg/mg
  - CRP: 118 mg/dL
  - HDL-C: 36 mg/dL
  - LDL-C: 113 mg/dL
  - FBG: 118 mg/dL
- Is lipid-lowering medication recommended for HL?
Primary Prevention in Patients without DM

Age 40-75 years (LDL-C 70-189 mg/dL)

- **Assess 10-year ASCVD risk**
  - **"Low"** <5%
  - **"Borderline"** 5.0-7.4%
  - **"Intermediate"** 7.5-19.9%
  - **"High"** ≥20%

- **Promote lifestyle to reduce ASCVD risk**
- **Evaluate risk enhancers**
- **Moderate-intensity statin to reduce LDL-C 30-49%**
- **High-intensity statin to reduce LDL-C ≥50%**


Risk Enhancing Factors

<table>
<thead>
<tr>
<th>Family history of premature ASCVD</th>
<th>Lipid biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>Persistently elevated LDL-C (≥160 mg/dL)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Persistently elevated TG (≥175 mg/dL)</td>
</tr>
<tr>
<td>Ethnicity (South Asian)</td>
<td>hs-CRP ≥2.0 mg/L</td>
</tr>
<tr>
<td>Inflammatory diseases (RA, HIV, psoriasis)</td>
<td>Lipid profile</td>
</tr>
<tr>
<td>Preeclampsia &amp; premature menopause</td>
<td>Lp(a) 50 mg/dL or &gt;125 nmol/L</td>
</tr>
<tr>
<td>Ankle-brachial index &lt;0.9</td>
<td>ApoB ≥130 mg/dL</td>
</tr>
</tbody>
</table>

To guide decision to initiate statin therapy in "borderline" and "intermediate-risk" individuals age 40-75 with LDL-C ≥170 mg/dL.


Case 3:

- HL is a 48-year-old education
- PMH: HTN, pre-diabetes
- Meds: amlodipine 5 mg/d
- Vitals
  - BP= 137/74 mm Hg
  - HR= 72 bpm
  - BMI= 33.8 kg/m²
  - Waist circumference= 42.3"
- Labs
  - eGFR 115 ml/min/1.73m²
  - Total Chol. 214 mg/dL
  - UACR 3 mcg/mg
  - TG 234 mg/dL
  - HDL-C 38 mg/dL
  - HgbA1C 6.4%
  - LDL-C 113 mg/dL

Is lipid-lowering medication recommended for HL?

Intermediate-risk + MetS


#AAED
Hypertriglyceridemia

- VLDL particles = Increase ASCVD risk
- Persistent TG ≥175 mg/dL is a risk-enhancing factor


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Approach to Hypertriglyceridemia (HTG)

Moderate HTG 175-499 mg/dL
- Secondary disorders
  - Diabetes mellitus
  - Chronic liver disease
  - Chronic kidney disease and/or nephrotic syndrome
  - Hypothyroidism
  - Triglyceride-raising drugs
  - Lifestyle (obesity and metabolic syndrome)

Severe HTG >500 mg/dL
- Address Underlying Causes
  - Secondary disorders
  - Diabetes mellitus
  - Chronic liver disease
  - Chronic kidney disease and/or nephrotic syndrome
  - Hypothyroidism
  - Triglyceride-raising drugs
  - Lifestyle (obesity and metabolic syndrome)

ASCVD >7.5% ➔ moderate-intensity statin or intensify therapy

Prevention of Pancreatitis
- Especially if fasting TG ≥1000 mg/dL
- Very low-fat diet
- Avoid of refined carbohydrates and alcohol
- Consume omega-3 fatty acids
- Add fibrate therapy (avoid gemfibrozil if concurrent use of statin)


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Case 4:

- AD is a 66-year-old Hispanic female here for follow-up on diabetes and dyslipidemia.
- Meds:
  - Benazepril/HCTZ 20/25 mg/d
  - Atorvastatin 80 mg/d
  - Metformin ER 2g/d
  - Canagliflozin 300 mg/d
  - Linagliptin 1.8 mg/d
  - Aspirin 81 mg/d

What changes would you make to AD’s lipid lowering meds?

<table>
<thead>
<tr>
<th>Labs</th>
<th>Lipid panel</th>
<th>TC/ TG/ HDL-C/ LDL-C</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug. ’19</td>
<td>176/ 213/ 44/ 68</td>
<td>6.9%</td>
<td></td>
</tr>
<tr>
<td>May ’19</td>
<td>168/ 198/ 42/ 71</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Jan. ’19</td>
<td>182/ 226/ 43/ 75</td>
<td>7.5%</td>
<td></td>
</tr>
</tbody>
</table>


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REDUCE-IT

Patients with:
- Age ≥45 years + ASCVD or age ≥50 with DM + ≥1 risk factor
- On statin therapy & TG 135-499 mg/dL

Icosapent ethyl 2 g BID
Placebo (mineral oil) BID

N=8179
4.9 years follow-up

1° endpoint: CV death, non-fatal MI or stroke, coronary revascularization, unstable angina
2° endpoint: CV death, non-fatal MI or stroke

REDUCE-IT

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>IE (n=4089)</th>
<th>Placebo (n=4090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median) years</td>
<td>64.0</td>
<td>64.0</td>
</tr>
<tr>
<td>Male sex</td>
<td>71.6%</td>
<td>70.8%</td>
</tr>
<tr>
<td>History of ASCVD</td>
<td>70.7%</td>
<td>70.7%</td>
</tr>
<tr>
<td>Statin intensity (moderate or high)</td>
<td>93.4%</td>
<td>93.0%</td>
</tr>
<tr>
<td>Median LDL-C (mg/dL)</td>
<td>74.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Median TG (mg/dL)</td>
<td>216.5</td>
<td>216.0</td>
</tr>
<tr>
<td>Distribution of TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/dL</td>
<td>10.1%</td>
<td>10.5%</td>
</tr>
<tr>
<td>150-199 mg/dL</td>
<td>29.2%</td>
<td>29.1%</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>60.7%</td>
<td>60.4%</td>
</tr>
</tbody>
</table>

REDUCE-IT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IE (n=4089)</th>
<th>Placebo (n=4090)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° composite</td>
<td>17.2%</td>
<td>22.0%</td>
<td>0.75 (0.68-0.83)</td>
</tr>
<tr>
<td>CV death or non-fatal MI</td>
<td>9.6%</td>
<td>12.4%</td>
<td>0.76 (0.69-0.86)</td>
</tr>
<tr>
<td>Fatal non-fatal MI</td>
<td>6.1%</td>
<td>8.7%</td>
<td>0.69 (0.58-0.81)</td>
</tr>
<tr>
<td>Fatal non-fatal stroke</td>
<td>2.4%</td>
<td>3.3%</td>
<td>0.72 (0.55-0.93)</td>
</tr>
<tr>
<td>CV death</td>
<td>4.3%</td>
<td>5.2%</td>
<td>0.80 (0.66-0.98)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>6.7%</td>
<td>7.6%</td>
<td>0.87 (0.74-1.02)</td>
</tr>
</tbody>
</table>

1° composite = 4.6% ARR (NNT=21)
**ADA 2109 Recommendations**

- In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499 mg/dL), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. (A)

**Agents in development**

- Bempedoic acid
  - LDL-C lowering
- EPA/DHA carboxylic acids
  - TG-lowering in moderate hypertriglyceridemia
- Pemafibrate
  - TG-lowering in moderate hypertriglyceridemia