Dyslipidemia Management and PCSK9 Inhibition: Do Women Have an Equal Opportunity?

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Gender equality allows both men and women to do and have opportunities as each other. Men and women should have equal rights; times are changing and although most still have the idea that women are inferior to men it is not true. Women are capable of getting an education, good jobs, and working outside of the house.

C. Michael Valentine, MD, FACC
New ACC/AHA Cholesterol Guideline:

- Personalized
- Patient-Centered Care
- New Treatment Options
The full-text guidelines are also available on the following Web sites: ACC (www.acc.org) and AHA (professional.heart.org)
2018 Cholesterol Guidelines

Top 10 Take-Home Messages
1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.
Key Point for Very High Risk Patients:

- If LDL remains > 70 mg/dL adding ezetimibe first is reasonable
- or non-HDL > 100 mg/dL
- adding PCSK9 inhibitor is reasonable
The Cost of PCSK9 Inhibition Is Improving

Odyssey Outcomes (economics analysis)

• Cost Effectiveness Analysis
• $6,319 per year at the $100,000 willingness to pay threshold
• Over 18,000 patients (60/40 men/women)
• Elevated LDL despite max tolerated statin

Key Point

• The higher the baseline LDL, the higher the value of alirocumab appeared to be
4. In patients with severe primary hypercholesterolemia (LDL-C level \( \geq 190 \) mg/dL\([\geq 4.9 \text{ mmol/L}])\) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains \( \geq 100 \) mg/dL \((\geq 2.6 \text{ mmol/L})\), adding ezetimibe is reasonable

- If the LDL-C level on statin plus ezetimibe remains \( \geq 100 \) mg/dL \((\geq 2.6 \text{ mmol/L})\) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

• the presence of risk-enhancing factors (see No. 8);
• the potential benefits of lifestyle and statin therapies;
• the potential for adverse effects and drug–drug interactions;
• the consideration of costs of statin therapy; and
• the patient preferences & values in shared decision-making.
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 yrs);
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include
- apolipoprotein B ≥130 mg/dL
- high-sensitivity C-reactive protein ≥2.0 mg/L
- ankle-brachial index <0.9 and I
- lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

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- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

• Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
• In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).
## Recommendations for Issues Specific to Women

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Clinicians should consider conditions specific to women, such as premature menopause (age &lt;40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered.</td>
</tr>
</tbody>
</table>
Statins continue to be a stable to ASCVD preventive care
Lifestyle for everyone
Enhancing Factors
The power of a 0 CAC score
Collect Pregnancy and Menopause History
Improved PCSK9 affordability
The Statin Discussion

How Can We Select the Right Statin and Help our Patients Stay on Therapy Long-Term.
## Selecting the Appropriate Statin

### Table 3. High-, Moderate-, and Low-Intensity Statin Therapy*

<table>
<thead>
<tr>
<th>LDL-C lowering†</th>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Low Intensity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>≥50%</td>
<td>30%–49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Statins</td>
<td>Atorvastatin (40 mg‡) 80 mg</td>
<td>Atorvastatin 10 mg (20 mg)</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 20 mg (40 mg)</td>
<td>Rosuvastatin (5 mg) 10 mg</td>
<td></td>
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<td></td>
<td>...</td>
<td>Pravastatin 40 mg (80 mg)</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lovastatin 40 mg (80 mg)</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pitavastatin 1–4 mg</td>
<td></td>
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</tbody>
</table>

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice (S3.2.1-2).
†LDL-C lowering that should occur with the dosage listed below each intensity.

What Do We Do for Statin Side Effects?

Am J Cardiovasc Drugs
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REVIEW ARTICLE

Management of Statin Intolerance in 2018: Still More Questions Than Answers

Peter P. Toth¹,² · Angelo Maria Patti³ · Rosaria Vincenza Giglio³ · Dragana Nikolic³ · Giuseppa Castellino³ · Manfredi Rizzo³ · Maciej Banach⁴,⁵,⁶

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Abstract Statin therapy is generally well tolerated and very effective in the prevention and treatment of cardiovascular disease, regardless of cholesterol levels; however, it can be associated with various adverse events (myalgia, myopathy, rhabdomyolysis, and diabetes mellitus, among others). Patients frequently discontinue statin therapy without medical advice because of perceived side effects and consequently increase their risk for cardiovascular

Key Points

Statins are the gold standard for managing dyslipidemia in patients with elevated cardiovascular risk. Discontinuation of statin therapy is associated with an increase in cardiovascular events.
Definitions of Statin Intolerance

You have tried 2 Statins

- Low Dose Daily
- A second statin at any dose

- The patient describes symptoms (real or perceived)
- Abnormal Laboratory values may be present,
- Stop the statin (symptoms improve) and re-challenge but the symptoms continue
The Role of Biomarkers

• CK
• Statin Associated Liver Abnormalities
  – ALT > 3x normal
  – 1:1,000,000 chance of serious liver disease
  – 10-30% patients don’t receive statins for fear liver disease
• Emerging markers (sTn1, FABP1, CKM, MYL3)

Use of statins prevents 33% of major CVD events compared to placebo. Compared to 1/1,000,000 chance of serious liver disease

Toth et al. Am J Cardiovasc Drugs https://doi.org/10.1007/s40256-017-0259-7
Statin Intolerance Management

- Most important - need to continue statin therapy
- Complete statin intolerance affects <5% of statin intolerance patients
- Considerations
  - Dechallenge (step by step approach to decrease the dose)
  - Intermittent dosing (alternate day statin dosing)
  - Hydrophilic (pravastatin and rosuvastatin)
    - Can switch if on a lipophilic
    - Better tolerance in the elderly

Toth et al. Am J Cardiovasc Drugs https://doi.org/10.1007/s40256-017-0259-7
There’s an App for That!

Use LDL-C Manager App for next steps:

- ASCVD Risk Estimator
- LDL Lowering Therapy Decision Making
- Statin Intolerance
Thank You

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