A New Age of Dyslipidemia Treatment: Role of Non-Statin Therapies

BRODY MAACK, PHARMD, BCACP, CTTS
Objectives

1. Review current guidelines regarding use of statin medications in the treatment and prevention of ASCVD.

2. Discuss the clinical use and available evidence of PCSK-9 inhibitors and ezetimibe.

3. Identify methods to recognize patients who may benefit from lipid lowering therapy.

4. Design a lipid lowering regimen based on a patient’s ASCVD risk profile.
Disclosures

None.
Heart Disease and Stroke Statistics—2015 Update
Deaths attributable to cardiovascular disease
Heart Disease and Stroke Statistics—2015 Update
Prevalence of cardiovascular disease

Dariush Mozaffarian et al. Circulation. 2015;131:e29-e322
WHY WOMEN LIVE LONGER THAN MEN

1. Because of stuff like this:
THIS IS WHY WOMEN

LIVE LONGER THAN MEN
Out with the Old…

2004 NCEP ATP III

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk CHD or CHD Risk Equivalents</td>
<td>&lt;100 mg/dL; optional &lt;70 mg/dL</td>
<td>≥ 100 mg/dL</td>
<td>≥ 100 mg/dL</td>
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<tr>
<td>10-year risk &gt;20%</td>
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</tr>
<tr>
<td>Moderately High Risk 2+ risk factors</td>
<td>&lt; 130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL</td>
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<tr>
<td>10-year risk 10-20%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Risk 2+ risk factors</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>10-year risk &lt;10%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lower risk 0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
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</tbody>
</table>
Landmark Statin Trials: The History

NCEP ATP I (1988)
- Framingham
- MRFIT
- LRC-CPPT
- Coronary Drug Project
- Helsinki Heart CLAS

NCEP ATP II (1993)
- FATS
- POSCH
- SCORE
- STARTS
- Ornish
- MARS

NCEP ATP III (2001)
- 4S
- WOSCOPS
- CARE
- LIPID
- AFCAPS/TexCAPS

NCEP ATP II Update (2004)
- HPS
- PROVE-IT
- ASCOT-LLA
- PROSPER
- ALLHAT-LLT

ACC/AHA Guideline (2013)
- TNT
- IDEAL
- ACCORD
- JUPITER
- CTT
- ENHANCE
- SHARP
- AURORA
- CORONA
“The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.”
4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥ 190 mg/dL
- Diabetes
  Age 40-75
- Age 40-75
  10-year ASCVD risk
  ≥ 7.5%
4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥ 190 mg/dL
- Diabetes
  - Age 40-75
- Age 40-75
  - 10-year ASCVD risk
    ≥ 7.5%
What is Clinical ASCVD???

**Coronary Heart Disease (CHD)**
- ACS, Hx MI, Stable/Unstable Angina, Coronary revascularization

**Stroke/TIA**

**Peripheral Arterial Disease (PAD)**
Clinical ASCVD Group

Patients < 75 years old: **High Intensity** Statin therapy (IA)

If high intensity inappropriate, use **moderate intensity** statin therapy (IA)

Patients > 75 years old: Risk vs benefit for moderate-high intensity statin; Reasonable to continue current statin if tolerating (IIaB)
## Statin Intensities

<table>
<thead>
<tr>
<th>High Dose Statin Therapy</th>
<th>Moderate Dose Statin Therapy</th>
<th>Low Dose Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL-C by ~50%</td>
<td>Lowers LDL-C by ~30-50%</td>
<td>Lowers LDL-C by &lt; 30%</td>
</tr>
<tr>
<td><em><em>Atorvastatin (40</em>)-80 mg</em>*</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td><strong>Rosuvastatin 20-(40) mg</strong></td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin 40 mg BID</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td></td>
</tr>
</tbody>
</table>

1. Statins in bold are supported by RCT CV outcomes data
2. Atorvastatin 40 mg for patients not able to tolerate 80 mg
3. Doses in (parentheses) were not tested in RCTs, but may be used if needed
4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥ 190 mg/dL
- Diabetes
  Age 40-75
- Age 40-75
  10-year ASCVD risk ≥ 7.5%
LDL ≥ 190 mg/dL Group

Patients ≥ 21 years with untreated LDL-C ≥ 190 mg/dL: High intensity statin therapy (IB)

If high intensity inappropriate, use maximum tolerated statin therapy (IB)

Reasonable to intensify statin therapy to achieve ≥ 50% LDL-C reduction (IIaB)

After maximum intensity statin dose achieved, may consider adding non-statin drug to further lower LDL-C (IIbC)
4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥ 190 mg/dL
- Diabetes
- Age 40-75
- Age 40-75
- 10-year ASCVD risk ≥ 7.5%
Primary Prevention in DM Group

Patients 40-75 years with LDL-C 70-189 mg/dL: **Moderate intensity** statin (IA)

Patients 40-75 years, LDL-C 70-189 mg/dL, **with 10-year ASCVD risk ≥ 7.5%**: **High intensity** statin (IIBa)

Patients younger or older than 40-75 years: Risk vs benefit and patient preference (IIBaC)
ASCVD Risk Estimation

Pooled cohort equations

- 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk
- Predicts 10-year risk in patients 40-79 years
- Predicts “Lifetime” risk (of MI/stroke) in patients 20-59 years

- Required parameters:
  - Age, gender, race, TC, HDL-C, SBP, taking BP med?, diabetes status, smoking status (current)
# ASCVD Risk Estimator*

## 10-Year ASCVD Risk

<table>
<thead>
<tr>
<th></th>
<th>Risk with Optimal Risk Factors**</th>
<th>Calculated Risk</th>
<th>Risk with Optimal Risk Factors**</th>
<th>Calculated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.1%</td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0%</td>
<td></td>
<td>8%</td>
</tr>
</tbody>
</table>

## Lifetime ASCVD Risk

**Intended for use if there is not ASCVD and the LDL cholesterol is <190 mg/dL.

**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker.

### Data Entry

- **Gender:** Male or Female
- **Age:** 52
- **HDL - Cholesterol (mg/dL):** 42
- **Total Cholesterol (mg/dL):** 230
- **Diabetes:** Yes or No
- **Treatment for Hypertension:** Yes or No
- **Systolic Blood Pressure:** 146
- **Smoker:** Yes or No

[Recommendation Based On Calculation]
4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥ 190 mg/dL
- Diabetes Age 40-75
- Age 40-75
  10-year ASCVD risk ≥ 7.5%
Primary Prevention Group (No DM)

Patients 40-75 years, with LDL-C 70-189 mg/dL, and 10-year **ASCVD risk > 7.5%**: Moderate to High intensity statin therapy (IA).

Patients 40-75 years, with LDL-C 70-189 mg/dL, and 10-year **ASCVD risk 5-7.5%**: “Reasonable to offer” moderate intensity statin therapy (IIaB).
What if I don’t fit in?

Patients with LDL-C < 190 mg/dL, not identified in a statin benefit group, or with uncertain ASCVD risk: Additional risk factors may be considered

- May then consider statin therapy based on ASCVD risk reduction benefit, adverse effects, drug interactions, patient preferences
What if I don’t fit in?

Patients with LDL-C < 190 mg/dL, not identified in a statin benefit group, or with uncertain ASCVD risk: **Additional risk factors** may be considered

- **LDL-C** > 160 mg/dL; **Family hx** ASCVD in father < 55 years or mother < 65 years; **hs-CRP** ≥ 2 mg/L; **CAC score** ≥ 300 Agatston units (or ≥ 75 percentile for age, sex, ethnicity); **ABI** < 0.9; Elevated ‘Lifetime’ risk of ASCVD
Non-statin Drugs

AIM-HIGH\(^1\)
- *No difference* between statin + placebo vs statin + niacin in reduction of composite CV events

ACCORD\(^2\)
- *No difference* between statin + fenofibrate vs statin + placebo in reduction of composite CV events

HPS2-THRIVE\(^3\)
- *No difference* between statin + niacin/laropiprant vs statin + placebo in reduction of major vascular events (more adverse effects seen in niacin/laropiprant group)

Non-statin Drugs

Recommendations

- **ACC/AHA**
  - Routine use of statins + non-statins *not supported* by data to reduce ASCVD events
  - Statin intolerant patients
  - LDL ≥ 190 mg/dL group

- **ADA**
  - *Generally not recommended* to use statin/niacin or statin/fibrate (no benefit above statin alone)
  - *Exception: Men (with DM), TG ≥ 204 mg/dL and HDL ≤ 34 mg/dL: Might consider statin + fenofibrate (grade B recommendation)*

- **NLA**
  - Statin intolerant patients
  - Add to statin to achieve lipid goals
Ezetimibe
<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin dose</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 for adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factor(s)</td>
<td>Moderate or high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
<td>As needed to monitor adherence</td>
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<td>CVD risk factors</td>
<td>High</td>
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<td></td>
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<td>High</td>
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<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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American Diabetes Association
Standards of Medical Care in Diabetes 2017

- Risk Factors:
  - Baseline LDL-C > 100 mg/dL
  - Hypertension
  - Smoking
  - Overweight/obesity
  - Family Hx premature ASCVD
Additional considerations:

- Patients aged 40 and older, with hx ACS + LDL > 50 mg/dL who cannot tolerate high intensity statin: Moderate intensity statin + Ezetimibe
KDIGO 2013

Patients ≥ 50 years with eGFR < 60 mL/min/1.73m², not on HD or transplant: Treat with statin or statin/ezetimibe (IA)

Patients ≥ 50 years with CKD and eGFR ≥ 60 mL/min/1.73m²: Treat with statin (IB)

Patients 18-49 years with CKD, not on HD or transplant: Treat with statin IF: (2A)
- Hx CAD
- Diabetes
- Hx ischemic stroke
- 10-year risk of CHD death or non-fatal MI > 10%
Patients on dialysis: *Do not* START statins or statin/ezetimibe (2A)

Patients ON a statin +/- ezetimibe when dialysis initiated: *OK to continue* (2C)

Kidney transplant patients: *Treat with statin* (2B)
Ezetimibe Evidence

IMPROVE-IT

- > 18,000 patients
- Patients post-ACS hospitalization with LDL-C 50-100 mg/dL (50-125 mg/dL if not on lipid lowering Tx)
- Simvastatin 40 mg + ezetimibe 10 mg VS Simvastatin 40 mg + placebo
- **ARR 2% in ezetimibe group (p = 0.016)** at 7 years

PCSK-9 Inhibitors
PCSK9 Inhibitors

- MOA: Proprotein convertase subtilisin-kexin type 9 is a protein which binds to LDL receptor, preventing them from being recycled to the cell surface after endocytosis of cholesterol.

- Evolocumab

- Alirocumab
PCSK9 Inhibitors

Alirocumab (Praluent®)

- Indications:
  - Add-on to max tolerated statin therapy for heterozygous FH
  - Add-on to max tolerated statin therapy for clinical ASCVD
PCSK9 Inhibitors

Alirocumab (*Praluent®*)

- **Efficacy**

  - **ODYSSEY LONG TERM Study**: 
    - HeFH (18%) & ASCVD (69%) patients
    - 58% further LDL reduction in addition to max tolerated statin

  - **ODYSSEY COMBO I Study**: 
    - ASCVD patients
    - 44% further LDL reduction in addition to max tolerated statin

PCSK9 Inhibitors

Alirocumab (Praluent®)

- **Efficacy**

- ODYSSEY COMBO II Study\(^1\):
  - ASCVD patients
  - 48% further LDL reduction in addition to max tolerated statin
  - 20% further LDL reduction in ezetimibe group (comparison group)

- FH I and FH II Studies\(^2\)
  - HefH patients (45% also had ASCVD)
  - 47% further LDL reduction in addition to max tolerated statin

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PCSK9 Inhibitors

Alirocumab (Praluent®)

- Push-button injection
- Medication and dosage label
  - Color-coded by dose
- Large inspection window
  - Turns yellow when injection is completed so you know full dose has been delivered
- Yellow safety cover
  - Keeps needle hidden throughout the entire injection

Image from: https://www.praluenthcp.com/administration
PCSKit9 Inhibitors

Evolocumab (Repatha®)

- Indications:
  - Add-on to max tolerated statin therapy for heterozygous FH
  - Add-on to max tolerated statin therapy for clinical ASCVD
PCSK9 Inhibitors

Evolocumab (Repatha®)

- **Efficacy**

  - **LAPLACE 2 Study¹:**
    - ASCVD patients
    - 63-77% (mean 71%) further LDL reduction in addition to max tolerated statin

  - **RUTHERFORD-2 Study²:**
    - HeFH patients (38% also had ASCVD)
    - 61% further LDL reduction in addition to max tolerated statin

PCSK9 Inhibitors

Evolocumab (Repatha®)

- **Safety**

- **EBBINGHAUS trial**
  - Substudy of FOURIER
  - 2000 participants
  - Trial to evaluate effect of evolocumab on cognitive function (d/t very low LDL)
  - *Noninferior* to placebo regarding cognitive adverse effects over 2 years
PCSK9 Inhibitors

CV Outcomes Study

- **FOURIER Trial** (Evolocumab)
  - ~27,500 patients with **ASCVD**, LDL 70 mg/dL or higher, already on statin
  - Primary outcome: **CV composite** (CV death, MI, stroke, hospitalization for UA, coronary revascularization)
  - At 48 weeks: 1° outcome reduced in Tx group (9.8%) vs placebo (11.3%) (p<0.001)
  - Injection site reactions only side effect > placebo

PCSK9 Inhibitors

Evolocumab (*Repatha®*)
PCSK9 Inhibitors

Guidelines
- 2016 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL lowering in management of ASCVD risk

- **Clinical ASCVD**, on max tolerated statin, <anticipated response:
  - Ezetimibe, *then* add/replace with PCSK-9 inhibitor

- **Baseline LDL ≥ 190 group**, on max tolerated statin, <anticipated response:
  - Ezetimibe (or BAS 2^{nd} line), *OR* PCSK-9 inhibitor
Treatment of FH

Initial Drug Monotherapy
• High Intensity Statin
• If LDL above “goal” after 3 months + good adherence, proceed to 2 drug regimen:

Two-drug Combination
• High Intensity Statin + Ezetimibe
• If LDL above “goal” after 3 months + good adherence, proceed to 3 drug regimen:

Three-drug Combination
• High Intensity Statin + Ezetimibe +
• PCSK9 Inhibitor (or BAS or Niacin)

Complex-therapy Combination
• Consider four-drug combination and LDL Apheresis

PCSK9 Inhibitors

Practice-based Recommendations/Observations
- Patients on max tolerated statins, with/without ezetimibe:
  - **ASCVD** + LDL ≥ 100 or non-HDL ≥ 130 = Add PCSK-9 inhibitor
  - **FH** + LDL ≥ 130 or non-HDL ≥ 160 = Add PCSK-9 inhibitor
Practical Approach to Identifying Patients

Family HealthCare ASCVD Risk Reduction Service

- APPE Student-driven
- Prospective chart review for upcoming medical visits
- 10-year ASCVD risk calculated, if appropriate
Practical Approach to Identifying Patients

Family HealthCare ASCVD Risk Reduction Service

- Statin/lipid-lowering recommendations provided
- Lab recommendations provided
- Suggestions for referral to PharmD service provided, based on modifiable risk factors
- Findings/recommendations entered as progress note in EHR and sent to PCP for visit prep
Sample Progress Note:

Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimation Service

Subjective: Patient’s chart reviewed for assessment of ASCVD risk.

Objective:

Race/Ethnicity (Black/Caucasian/Other): Caucasian
Total Cholesterol (highest on file/baseline): 185
HDL Cholesterol (from same panel as TC above): 32
Most Recent Systolic Blood pressure: 141
Treatment for hypertension: [X] Yes [ ] No
Diabetes: [ ] Yes [X] No
Smoker: [X] Yes [ ] No
Most recent LDL: 141

Assessment:

Next office visit: 4/24/17 with Dr. Strange
ASCVD 10 Year Risk: 18.8%
ASCVD 10 year risk with optimal risk factors: 3.6%
ASCVD Lifetime Risk: 89%
Lifetime ASCVD risk with optimal risk factors: 5%

Recommendation:

1) Might consider initiating moderate-high intensity statin therapy (e.g. atorvastatin 20-80 mg or rosuvastatin 5-40 mg daily)
2) Referral to PharmD for help with BP monitoring and tobacco cessation could be considered.

Rationale:

Patients age 40-75 with LDL 70-189 mg/dL with no diabetes and 10-year risk 7.5% or higher should be treated with moderate-high intensity statin therapy. Patient is currently on no lipid lowering therapy.

Disclaimer: These results and recommendations are provided to inform possible treatment recommendations for patients at increased risk of ASCVD. The guidelines these recommendations are based upon do not replace clinical judgment, and each patient should be evaluated on an individual basis. ASCVD risk estimation is calculated using the Pooled Cohort Equation, as suggested by 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol. Please contact Brody Maack, PharmD for further information and/or references.
Case Example

RD is a 63 yo Caucasian male with hx HTN, CAD (s/p CABG x 2 in 2014), Diabetes and gout. Currently prescribed metformin, Lisinopril, metoprolol XL, Atorvastatin 80 mg daily, and low-dose aspirin. He is 100% adherent to all his medications, and denies any adverse effects.

FH: Mother died at age 73 (cancer); Father died at age 44 (MI)

SH: No EtOH; Smokes 0.5 ppd cigarettes

Vitals: Ht: 73”, Wt: 254lbs, BMI: 33.5, T: 98.8°F, BP: 154/79 mmHg, HR: 70 BPM, RR: 17

Renal/hepatic function normal and stable. Lipid panel as follows:

TC: 174 mg/dL
LDL: 113 mg/dL
HDL: 34 mg/dL
TG: 132 mg/dL

What would you recommend for lipid lowering therapy?
Summary

All current guidelines recommend using **statins in fixed doses** first-line to treat patients based on ASCVD risk, while using a patient centered approach.

Non-statins lipid lowering agents are recommended primarily for those who are **intolerant to statins**, have **contraindications** to statins, for treatment of severely elevated **triglycerides**.

**Ezetimibe and/or PCSK-9 inhibitors** are recommended as add-on to statins for those with ASCVD or high ASCVD risk, not achieving adequate LDL response.

**LDL “goals”: will they be back?**
References/Guidelines


