Understanding Lipid Goals and Managing the Resistant Patient

John Devlin, MD, MPH, FACP

Prevalence of clinically defined cardiovascular risk factors, based on a correction of self-reported data in the BRFSS (Behavioral Risk Factor Surveillance System) 2009–2010 and shaded by quintile of national ranking, are shown.

Figure Legend:
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Stone NJ, et al. 
Circulation 2014;129:S1-S45
Important to Note

• ‘No Evidence’ could be
  • There is no evidence, or
  • The existing evidence is inconclusive

• We treat people not populations

• Goal-setting and use of other lipid modifying Rx is not precluded
  • It’s just not evidence-based

Eckel R, ADA Annual Meeting, 2015
Four Major Statin Benefit Groups

1) Individuals with clinical ASCVD

1) Individuals with LDL >190

2) Individuals with DM, 40-75 y.o. with LDL 70-189 and without clinical ASCVD

3) Individuals without clinical ASCVD or DM with LDL 70-189 and estimated 10-year ASCVD risk >7.5%
Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Risk Factors for ASCVD

- Gender: Male, Female
- Systolic BP: mmHg
- Age: years
- Race: White or other
- Receiving treatment for high blood pressure (if SBP > 120 mmHg): No, Yes
- Diabetes: No, Yes
- Smoker: No, Yes
- Total Cholesterol: mg/dL
- HDL Cholesterol: mg/dL

[Buttons: Reset, Calculate]

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
Figure 1. Comparison of observed event rates with event rates predicted by new ACC/AHA risk prediction algorithm in three external validation primary prevention cohorts: the Women’s Health Study, the Physicians’ Health Study, and the Women's Health Initiative Observational Study.

Paul M Ridker, Nancy R Cook

1. Patients with clinical ASCVD

- Defined by the inclusion criteria for the secondary prevention statin RCT
- Coronary artery disease or peripheral artery disease
- Acute coronary syndromes
- Coronary or other arterial revascularization
- Stroke or TIA
- PVD presumed to be atherosclerotic
Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

LDL–C ≥190 mg/dL

Diabetes Type 1 or 2 Age 40-75 y

Estimate 10-y ASCVD Risk with Pooled Cohort Equations

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Moderate-to-high intensity statin

Age ≤75 y

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Age >75 y OR if not candidate for high-intensity statin

Moderate-intensity statin

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Moderate-intensity statin

Estimated 10-y ASCVD risk ≥7.5%* High-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)

High: Daily dose lowers LDL–C by approx. ≥50% 
Moderate: Daily dose lowers LDL–C by approx. 30% to <50%
Questions?

- What is the role of statin therapy in the elderly ...
  - for Primary Prevention?
  - for Secondary Prevention?
3. Patients with diabetes, age 40-75 years

- All have indication for statin
  - Level of intensity of statin treatment depends on calculated 10 year risk.
The ADA Dyslipidemia/Lipid Management Recommendations: Statins

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended dose</th>
<th>Monitoring</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>
</tr>
<tr>
<td></td>
<td>CVD risk factors*</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>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>None</td>
<td>Moderate</td>
<td>As needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td>Moderate of high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

* CVD risk factors include LDL-C ≥ 100, HTN, smoking, and overweight/obesity
** includes those with previous CV events or ACS
Don’t Forget Healthy Lifestyle

• Healthy diet
• Regular exercise
• No tobacco
• Maintain healthy weight
Fed up with how her diet is going, Charlene takes a more serious aim at her target weight.
Randomized Groups in PREDIMED
(n=7,447 individuals at high risk for CVD)

<table>
<thead>
<tr>
<th>Diet Advice</th>
<th>Control</th>
<th>Med Diet + Extra-Virgin Olive Oil (EVOO)</th>
<th>Med Diet + Nuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce fat,</td>
<td>Reduce fat, discourage olive</td>
<td>Mediterranean Diet</td>
<td>Walnuts: 15 g/d</td>
</tr>
<tr>
<td>discourage olive</td>
<td>oil and nuts</td>
<td></td>
<td>Almonds: 7.5 g/d</td>
</tr>
<tr>
<td>oil and nuts</td>
<td>Non-food items</td>
<td>&gt; 4 Tbsp of EVOO/d</td>
<td>Hazelnuts: 7.5 g/d</td>
</tr>
</tbody>
</table>

Estruch, PREDIMED, NEJM 2013: 1279
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
Individuals not in a statin benefit group

- In those not clearly in 1 of 4 statin benefit groups, additional factors may inform treatment decision-making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥ 160 mg/dL
  - hs-CRP ≥ 2.0 mg/L
  - Subclinical atherosclerosis
    - CAC score ≥ 300 or ABI < 0.9

- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences

Eckel R. ADA Annual Meeting, 2015
No longer treat to goal

- “Treatment goal is a treatment threshold”
  - 48% of patients with DM, age 40-75, not on a statin

Robinson J. ADA Annual Meeting, 2015
Testing the new paradigm: 2013 ACC/AHA cholesterol guideline outperforms NCEP ATP 3

• 2013 ACC/AHA – Treatment based on risk will prevent more CVD events
  – Dallas Heart Study – identified more high risk patients
  – U.S. NHANES – would prevent 450,000 more ASCVD events/10 years

• Why? No correlation LDL-C levels with plaque
  – Removing LDL-C cut-points improves accuracy of NCEP ATP 3
ADA 2014 Lipid Management Recommendations for Patients with Diabetes

• Providers may need to adjust intensity of statin therapy based on individual response to medication (E)
  – Adverse effects, tolerability, LDL-C levels

• Cholesterol laboratory testing may be helpful in monitoring adherence to therapy, but may not be needed once patients is stable on therapy (E)

• Combination therapy has not been shown to provided additional CVD benefit above statin therapy alone and is not generally recommended (A)
After maximizing statin therapy, there is a role for non-statins

- Prefer non-statins shown to reduce ASCVD events
  - Added to statin
    - Ezetimibe (IMPROVE-IT)
    - ? Fenofibrate (ACCORD – low HDL, high TG, p 0.06; HR increased in women)
  - As monotherapy (statin intolerant)
    - Niacin (Coronary Drug Project)
    - Gemfibrozil (VA-HIT)
    - Fenofibrate (FIELD)
    - Bile acid sequestrants (Lipid Research Clinics)
IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome
Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

- **Simvastatin** 40 mg
- Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

N=18,144

- Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

*3.2mM
**2.6mM

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
## LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
<td></td>
</tr>
</tbody>
</table>

Median Time avg 69.5 vs. 53.7 mg/dL

### Graph

- **Mean LDL-C (mg/dL)**
- **Time since randomization (months)**

Number at risk:
- EZ/Simva: 8990, 8889, 8230, 7701, 7264, 6864, 6583, 6256, 5734, 5354, 4508, 3484, 2608, 1078
- Simva: 9009, 8921, 8306, 7843, 7289, 6939, 6607, 6192, 5684, 5267, 4395, 3387, 2569, 1068
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT= 50

7-year event rates

Event Rate (%) vs. Time since randomization (years)
Major Pre-specified Subgroups

- Male: 34.9 vs 33.3
- Female: 34.0 vs 31.0
- Age < 65 years: 30.8 vs 29.9
- Age ≥ 65 years: 39.9 vs 36.4
- No diabetes: 30.8 vs 30.2
- Diabetes: 45.5 vs 40.0
- Prior LLT: 43.4 vs 40.7
- No prior LLT: 30.0 vs 28.6
- LDL-C > 95 mg/dl: 31.2 vs 29.6
- LDL-C ≤ 95 mg/dl: 38.4 vs 36.0

†7-year event rates

*p-interaction = 0.023, otherwise > 0.05
Conclusions

• IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - **YES:** Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
  - **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
  - **YES:** Confirms ezetimibe safety profile

• Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

• Results could be considered for future guidelines
Comparison of ACCORD subgroup results with those from prior fibrate studies

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (Gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG &gt; 200 mg/dl LDL-C/HDL-C &gt; 5.0</td>
<td>-71% (0.005)</td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 200 mg/dl</td>
<td>-39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 204 mg/dl HDL-C &lt; 42 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl</td>
<td>-31%</td>
</tr>
</tbody>
</table>
Diabetes Risk on Statins

- NNH = 1000 for both moderate- and high-intensity statin therapy
  - Based on 3 excess cases of incident diabetes per 100 individuals treated with statins for 10 years

Robinson J.  ADA Annual Meeting, 2015
Assumes a 35% relative risk reduction in ASCVD. NNT to prevent 1 ASCVD event varies by baseline estimated 10-y ASCVD risk. The NNH is based on 1 excess case of incident diabetes per 100 individuals treated with statins for 10 y. ACC/AHA = American College of Cardiologists/American Heart
Triglycerides

- < 500 mg/dl → Statins to reduce CVD risk
- ≥ 500 mg/dl → Lower to < 500 mg/dl

1. Control diabetes HbA1c ≤ 7.5%
2. Rule out secondary causes
   - Hypothyroidism, renal disease
3. Improve lifestyle
   - Reduce refined carbohydrates, fats
   - Increase physical activity
   - Lose weight
4. Drug therapy
   - TG > 1000 mg/dl – usually start drug concurrently with lifestyle/diabetes control
Drug treatment of triglycerides > 500 mg/dl

- Statins to reduce ASCVD risk
  - High intensity statins ↓ 30% triglycerides
- Fenofibrate in statin-treated patients
  - Adjust dose for renal impairment
    - AVOID if GFR < 30 mg/min/1.73 m²
    - 48 mg/day if GFR 30-60 mg/min/1.73 m²
- Omega-3 fatty acids DHA+EPA = 3400 mg/day
  - 4 x 850 EPA+DHA/1000 mg fish or kelp oil concentrate
- Gemfibrozil – contraindicated with statins
- Niacin – use with caution – may worsen DM control
- Bile acid sequestrants – CONTRAINDICATED
- Ezetimibe – no effect on TG
Muscle or other symptoms
Most muscle and other symptoms are unrelated to statin

1. Stop statin
2. Wait until symptoms resolve
   - Statin-related symptoms resolving within 2 weeks of DC & completely resolved within 2 months
   - Symptoms persisting 2 months after statin DC – evaluate for other causes
3. Re-challenge with statin
   - Low dose of same statin or another statin
4. Try all 7 statins
   - Rosuvastatin 5-10 mg q week ↓ LDL-C 25%
PCSK9 monoclonal antibodies
Preliminary data – CVD event reduction

• Odyssey long term
  – Robinson JG. NEJM 2015;372:1489-99

• OSLER
  – Sabatine MS. NEJM 2015;372:1500-09
Background and Rationale

• Despite the widespread availability of statins, many patients fail to reach recommended LDL-C targets in clinical practice, even in combination with other lipid lowering agents

• In PCSK9 human population studies:
  – Gain-of-function mutations result in hypercholesterolemia
  – Loss-of-function mutations associated with low LDL-C and low prevalence of CHD events

• SAR236553/REGN727 is a highly specific, fully human monoclonal antibody (mAb) to PCSK9

LDL Receptor Function and Life Cycle

For illustration purposes only
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of an PCSK9 mAb on LDL Receptor Expression
Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.
Changes in TG, HDL-C, and Apo Al from Baseline to Week 12 by Treatment Group (mITT Population)

% Change from Baseline at Week 12

1 LS mean (SE)
2 median (Q1-Q3)
### PCSK9: Safety in Patients with T2 DM
Analysis of 4 evolocumab phase 3 trials

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo n = 95</th>
<th>Ezetimibe n = 74</th>
<th>Evolocumab n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>33 (34.7)</td>
<td>35 (47.3)</td>
<td>101 (40.7)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>4 (4.2)</td>
<td>3 (4.1)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Leading to DC of study drug</td>
<td>0</td>
<td>2 (2.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Non-serious</td>
<td>0</td>
<td>2 (2.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

Sattar N.  ADA Annual Meeting, 2015
57-year-old male developed diarrhea followed by rash on his arms, legs, and abdomen 9 days after receiving his first injection of SAR236553 300mg.

- Leukocytoclastic vasculitis diagnosed by biopsy
- Prednisone begun with full resolution
- No organ involvement per signs and symptoms
- No anti-drug antibodies 2 weeks before or after the incident
- ANA, IgG, IgA, IgM, IgE, tryptase, anti-dsDNA, complement 5 WNL
- Investigator considered this a “significant medical event” related to IP
DESCARTES: Conclusions

- Largest and longest double-blind, randomized placebo controlled trial reported to date, of a monoclonal antibody to PCSK9
- Evolocumab 420 mg QM reduced placebo adjusted UC LDL-C 57% from baseline in patients with a wide range of cardiovascular risk receiving background lipid lowering therapies ranging from diet alone to the combination of atorvastatin 80 mg/d and ezetimibe 10 mg/d
- Durable effect with consistent LDL-C reductions at weeks 12 and 52
- Similar AE profile in placebo and active treatment groups
- No adverse laboratory signals observed
- Cardiovascular outcome trial is ongoing