Lipid management: approach and advances

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Disclosures

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• Event adjudicator Siemens
• Site PI for study sponsored by MERCK
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• Dr. Christie Ballantyne
• Dr. Salim Virani
Objectives

• Approach towards lipid management
• Focus on statin intolerant patient
• PCSK 9 inhibitors
• Treatment of Triglycerides
• Which cholesterol parameter is the best predictor of adverse cardiovascular events?
Friedewald equation

- Total cholesterol = HDLc + LDLc + TG/5
Lipoprotein Subclasses

http://www.med.unibs.it/~marchesi/lipoprot.html
Atherogenic Particles

MEASUREMENTS:
Apolipoprotein B
Non-HDL-C (TC – HDL)

TG-rich Lipoproteins:
- VLDL
- VLDL_R
- IDL
- LDL
- Sm-Dense LDL

TG-rich Lipoproteins
Elevated Triglycerides Are Associated With Increased Small, Dense LDL Particles

Fewer Particles

More Particles

Correlates with:

- TC 198 mg/dL
- LDL-C 130 mg/dL
- TG 90 mg/dL
- HDL-C 50 mg/dL
- Non–HDL-C148 mg/dL

Correlates with:

- TC 210 mg/dL
- LDL-C 130 mg/dL
- TG 250 mg/dL
- HDL-C 30 mg/dL
- Non–HDL-C180 mg/dL

Am J Cardiol. 2002;90:22i-29i.
Table 6. Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL–C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or trans fats, weight gain, anorexia</td>
<td>Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity, pregnancy*</td>
</tr>
</tbody>
</table>

*Cholesterol and triglycerides rise progressively throughout pregnancy (81); treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

LDL–C indicates low-density lipoprotein cholesterol. Adapted with permission from Stone et al (81).
Figure 2. Major recommendations for statin therapy for ASCVD prevention

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

- Adults age >21 y and a candidate for statin therapy
- Clinical ASCVD

- Yes: Age ≤75 y
  - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
- Yes: Age >75 y OR if not candidate for high-intensity statin
  - Moderate-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%

- LDL-C ≥190 mg/dL
  - Yes: High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No: Moderately effective statin
Figure 2. Major recommendations for statin therapy for ASCVD prevention

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

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

LDL-C ≥190 mg/dL

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

No
Diabetes Type 1 or 2
Age 40-75 y

Yes

Moderate-intensity statin

No

Yes

Estimated 10-y ASCVD risk ≥ 7.5%*

High-intensity statin

Estimate 10-y ASCVD Risk with Pooled Cohort Equations*

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

Yes

Moderate-to-high intensity statin

No

ASCVD prevention benefit of statin therapy may be less clear in other groups
In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment
Diabetes Type 1 or 2, Age 40-75 y

Yes

Moderate-intensity statin

No

Estimate 10-y ASCVD Risk with Pooled Cohort Equations

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

Yes

Moderate-to-high intensity statin

No

ASCVD prevention benefit of statin therapy may be less clear in other groups. In selected individuals, consider additional factors influencing ASCVD risk, and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.
• Estimates of 10-year risk for ASCVD are based on data from multiple community-based populations and are applicable to African-American and non-Hispanic white men and women 40 through 79 years of age.

• For other ethnic groups, use of the equations for non-Hispanic whites recommended, though these estimates may underestimate the risk for persons from some race/ethnic groups, especially American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans).
Pooled Cohort Risk Estimate

- Enter the following information in the free, downloadable Excel spreadsheet at http://my.americanheart.org/cvrisk calculator
  - Sex M/F
  - Age
  - Race (AA vs WH/other)
  - Total cholesterol and HDL-cholesterol
  - Systolic BP
  - Treatment for HTN Y/N
  - Diabetes Y/N
  - Smoker Y/N
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable range of values</th>
<th>Optimal values</th>
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<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>M or F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td></td>
<td>20-79</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans) or WH (for whites or others)</td>
<td>AA or WH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>130-320</td>
<td>170</td>
<td></td>
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<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>20-100</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>90-200</td>
<td>110</td>
<td></td>
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<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
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<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
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<tr>
<td>High-Intensity Statin Therapy</td>
<td>Moderate-Intensity Statin Therapy</td>
<td>Low-Intensity Statin Therapy</td>
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<tr>
<td>------------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
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<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
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<tr>
<td>Atorvastatin (40)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td>Lovastatin 20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20–40 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Fluvastatin XL 80 mg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
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</tr>
</tbody>
</table>
Testing With Statins:
Baseline Labs

• Prior to starting statin:
  – Fasting lipid panel*, AST/ALT
    *If LDL ≥190 or triglycerides ≥500 mg/dL, evaluate for secondary causes
  – CK only if at high risk for muscle side effects
    • History of previous statin intolerance
    • History of muscle disorders
    • Impaired kidney or liver function
    • Concurrent therapy that raises risk (i.e., fenofibrate)
Testing with Statins: During Therapy

• For effect:
  – Check fasting lipids 1-3 months after starting
  – If at goal, monitor every 3-12 months
  – Goal is to ensure medication is working at reducing LDL by goal % from untreated baseline
  – **Goal is NOT to achieve a certain target LDLc**
  – Consider lowering statin dose if LDLc <40 mg/dL x2

• For side effects:
  – Measure AST/ALT if symptoms of hepatotoxicity occur
  – Screen for diabetes as per routine
Adverse effects of statins

- 0.1 cases of DM per 100 subjects treated with moderate intensity statin
- 0.3 cases of DM per 100 subjects treated with high intensity statin
- ~0.01 cases of myopathy/hemorrhagic stroke per 100 subjects treated with statins
- Category X in pregnancy
Non statin lipid lowering medication in whom and side effects
3. In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

Higher-risk individuals include:
- Individuals with clinical ASCVD‡ <75 years of age.
- Individuals with baseline LDL–C ≥190 mg/dL.
- Individuals 40 to 75 years of age with diabetes mellitus.

Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.

4. In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
## Safety of Niacin

1. Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every 6 months thereafter.  

   | B (Moderate) |

2. Niacin should not be used if:
   - Hepatic transaminase elevations are higher than 2 to 3 times ULN.  
   - Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur.  
   - New-onset atrial fibrillation or weight loss occurs.  

   | A (Strong)  
   | B (Moderate)  
   | C (Weak)  

3. In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy.  

   | E (Expert) |
4. To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to:

- Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated.
- Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms.
- If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over 4 to 8 weeks, with the dose of extended-release niacin increasing not more than weekly.
- If immediate-release niacin is chosen, start at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2 or 3 doses.
## Safety of BAS

1. BAS should not be used in individuals with baseline fasting triglyceride levels $\geq 300$ mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.)

   C (Weak)

2. It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL.

   E (Expert)

## Safety of Cholesterol-Absorption Inhibitors

1. It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations $>3$ times ULN occur.

   C (Weak)
<table>
<thead>
<tr>
<th>Safety of Fibrates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.</td>
<td>B (Moderate)</td>
</tr>
<tr>
<td>2. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are &gt;500 mg/dL, are judged to outweigh the potential risk for adverse effects.</td>
<td>E (Expert)</td>
</tr>
</tbody>
</table>
| 3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.  
  • Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², is present.  
  • If eGFR is between 30 and 59 mL/min per 1.73 m², the dose of fenofibrate should not exceed 54 mg/day.  
  • If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m², fenofibrate should be discontinued. | B (Moderate) |
| Safety of Omega-3 Fatty Acids                                                  |  |
| 1. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding. | C (Weak) |
The Expert Consensus

- Incorporate newer clinical trial data on niacin, ezetimibe, and the recently approved PCSK9 inhibitors to evidence base established by 2013 guideline.

- Provide practical guide for use of non-statin drugs for risk reduction in situations not covered by the 2013 ACC/AHA guideline.

- The process did not involve formal systematic reviews/evidence grading → consensus statement.
FIGURE 4  Patients Age 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*  

NO

1. Address statin adherence.  
2. Intensify lifestyle (may consider phytosterols).  
3. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.†  
   Consider referral to lipid specialist if statin intolerant.  
4. Control other risk factors.  

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*  

NO

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)  
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)  
3. Patient preferences (see Table 4)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first; BAS second-line.‡

For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
Patients with clinical ASCVD with comorbidities,*

- No statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.†
   - Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 4)

Decision for no additional medication

Optional non-statin medications to consider

- Consider ezetimibe first.§

Consider adding or replacing with PCSK 9 inhibitor second.¶

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
Mechanism of action: Inhibits Niemann-Pick C1 like 1 (NPC1L1) protein; reduces cholesterol absorption in small intestine.

FDA-approved indication(s): As adjunct to diet to (1) primary hyperlipidemia, alone or in combination with a statin; (2) mixed hyperlipidemia in combination with fenofibrate;

Dose: PO daily, with or without food.

Mean % reduction in LDL-C (per PI): Monotherapy—18%; combination therapy with statin (incremental reduction)—25%

Adverse effects: overall safe, well tolerated

CV Outcomes Trials: IMPROVE-IT, SHARP

Prescribing considerations: Generally well tolerated. Brand only.
No Standard Definition of Statin Intolerance

• Inability to tolerate a dose of statin required to reduce a person’s risk sufficiently from their baseline risk\(^1\)

• Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins:
  – 1 statin at the lowest starting daily dose AND
  – Another statin at any daily dose
  – Due to:
    • Either objectionable symptoms (real or perceived)
    • Abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded\(^2\)

2. Guyton, et al. Journal Clinical Lipidology; 2014: 8; S72-S81
Statin discontinuation

- Study of over 100,000 patients in 2 academic medical centers
- Over 50% of patients had temporary discontinuations
- Statin-related AEs reported in 17.4% (18,774 pts) and 59% (11,124) stopped statin
- 4545 (24%) were not rechallenged within 12 months
- 6579 (35%) rechallenged

• More than 40% (2721 out of 6579) were rechallenged with the same statin to which the statin-related event was documented.
• Nearly one half (1295 out of 2721) of these patients were taking the same statin 12 months after the statin-related event.
• More than one third (996 out of 2721) were taking the original statin at the same or a higher dose.
Reasons for Stopping Statin Use: USAGE

<table>
<thead>
<tr>
<th>Reason for stopping</th>
<th>% of former users (n=1220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>17</td>
</tr>
<tr>
<td>Side effects</td>
<td>62</td>
</tr>
<tr>
<td>Efficacy</td>
<td>12</td>
</tr>
</tbody>
</table>

Diminishing statin side effects: new guideline recommendations
<table>
<thead>
<tr>
<th>DIMINISHING STATIN SIDE EFFECTS</th>
<th>GRADE OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use moderate intensity statin if high risk features present * or Asian ancestry/ hemorrhagic stroke</td>
<td>A</td>
</tr>
<tr>
<td>Don’t measure CK routinely</td>
<td>A</td>
</tr>
<tr>
<td>Okay to measure if high risk</td>
<td>E</td>
</tr>
<tr>
<td>If muscle symptoms okay to measure CK</td>
<td>E</td>
</tr>
<tr>
<td>Measure ALT before starting statin</td>
<td>B</td>
</tr>
<tr>
<td>During statin therapy okay to measure ALT if signs/ symptoms of hepatotoxicity</td>
<td>B</td>
</tr>
<tr>
<td>Decrease statin dose for 2 LDLc &lt;40 mg/dL</td>
<td>C</td>
</tr>
<tr>
<td>Simvastatin 80 mg harm</td>
<td>B</td>
</tr>
<tr>
<td>Caution in age &gt;75, solid organ transplant, retroviral meds</td>
<td>E</td>
</tr>
<tr>
<td>Memory changes: evaluate other causes as well</td>
<td>E</td>
</tr>
</tbody>
</table>

* · Multiple or serious comorbidities, including impaired renal or hepatic function.
· History of previous statin intolerance or muscle disorders.
· Unexplained ALT elevations >3 times ULN.
· Patient characteristics or concomitant use of drugs affecting statin metabolism.
· >75 years of age.
Statins and the muscle
# Myalgia, myopathy, myositis

<table>
<thead>
<tr>
<th>Condition</th>
<th>FDA</th>
<th>NLA</th>
<th>ACC/AHA/NHLBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>CK at least 10 fold increase</td>
<td>Myalgia + CK increase</td>
<td>Any muscle disease, myalgia, weakness</td>
</tr>
<tr>
<td>Myositis</td>
<td></td>
<td></td>
<td>Myopathy + increase in CK</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>50 fold increase in CK with end organ injury</td>
<td>CK &gt;10,000 IU/L</td>
<td>CK &gt;10 fold increase + increase in serum creatinine</td>
</tr>
</tbody>
</table>
Statin: muscle side effects prevalence

- Myalgias: ~10% (clinical studies suggest lesser/some other studies more)

- Myositis: muscle symptoms with CK
  - ~2.5%

- Rhabdomyolysis: <0.1%
N-of-1 (Single-Patient) Trials for Statin-Related Myalgia

Tisha R. Joy, MD; Alaa Monjed, MD; Guang Yong Zou, PhD; Robert A. Hegele, MD; Charlotte G. McDonald, MD, MSc; and Jeffrey L. Mahon, MD, MSc

Background: Statin-related myalgia is difficult to distinguish from other conditions causing myalgia and may often lead to statin discontinuation.

Objective: To compare the effect of statin rechallenge with placebo in patients with prior statin-related myalgia and to determine whether patients resumed statin therapy after evaluating the results.

Design: N-of-1 trial with 3 double-blind, crossover comparisons separated by 3-week washout periods. (Clinicaltrials.gov: NCT01259791)

Setting: Tertiary care lipid clinic.

Patients: Patients with prior statin-related myalgia with or without mild elevation of creatine kinase levels.

Intervention: Rechallenge with the statin that was previously associated with myalgia within 3 weeks of open-label use versus matching placebo.

Measurements: Weekly visual analogue scale (VAS) scores for myalgia and specific symptoms (VAS myalgia score and symptom-specific VAS score, respectively), pain interference scores, and pain severity scores were recorded during the 3-week periods when patients were receiving placebo or statin. The primary outcome was the VAS myalgia score (range, 0 to 100 mm).

Results: Eight patients (mean age, 66 years [SD, 8 years]; 88% women, all with high 10-year Framingham cardiovascular risk) participated in n-of-1 trials. Seven patients completed 3 treatment pairs, and 1 completed 2 treatment pairs. For each n-of-1 trial, no statistically significant differences were seen between statin and placebo in the VAS myalgia score, symptom-specific VAS score, pain interference score, and pain severity score. Five patients resumed open-label statin treatment, with a median posttrial follow-up of 10 months.

Limitation: Results are limited by the small sample size and cannot be extended to patients with longer onset of myalgia after statin initiation.

Conclusion: In selected patients with a history of statin-related myalgia whose symptoms are difficult to evaluate, n-of-1 trials may be a useful method for determining statin tolerability.

Primary Funding Source: Western University, London, Ontario, Canada.

For author affiliations, see end of text.
The study duration was 33 wk. After the baseline assessment at time 0, patients had 3 pairs of active drug (3 wk) and placebo (3 wk) exposures. Randomly assigned treatment pairs comprised 2 treatment periods (active therapy or placebo) separated by a 3-wk washout period. Treatment pairs were also separated by washout periods. A complete n-of-1 trial comprised 3 treatment pairs. Clinic visits occurred at baseline and at the end of each treatment period (solid arrows). Baseline scores for the visual analogue scales and Brief Pain Inventories were collected at time 0. Patients then completed these questionnaires at days 7, 14, and 21 in each treatment period.
Table 3. Differences in Pain Measures During Statin Treatment and Receipt of Placebo in Individual N-of-1 Trials

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>VAS Myalgia Score, mm</th>
<th>Symptom-Specific VAS Score, mm</th>
<th>PSS</th>
<th>PIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI)*</td>
<td>Mean (95% CI)*</td>
<td>Mean (95% CI)*</td>
<td>Mean (95% CI)*</td>
</tr>
<tr>
<td>1</td>
<td>2.3 (−14.0 to 18.6)</td>
<td>1.9 (−16.6 to 20.4)</td>
<td>1.0 (−1.2 to 3.2)</td>
<td>0.5 (−1.3 to 2.4)</td>
</tr>
<tr>
<td>2</td>
<td>2.8 (−6.5 to 12.0)</td>
<td>3.2 (0.8 to 5.6)</td>
<td>0.029</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>−8.1 (−102.7 to 86.5)</td>
<td>−8.0 (−93.7 to 77.7)</td>
<td>0.73</td>
<td>−1.1 (−8.2 to 6.1)</td>
</tr>
<tr>
<td>4</td>
<td>5.9 (−16.6 to 28.4)</td>
<td>5.0 (−13.7 to 23.7)</td>
<td>0.37</td>
<td>1.1 (−2.6 to 4.7)</td>
</tr>
<tr>
<td>5</td>
<td>1.8 (−25.2 to 28.7)</td>
<td>−5.4 (−61.2 to 50.3)</td>
<td>0.72</td>
<td>0.2 (−2.0 to 2.5)</td>
</tr>
<tr>
<td>6</td>
<td>9.4 (−33.6 to 52.5)</td>
<td>18.1 (−13.4 to 49.5)</td>
<td>0.132</td>
<td>0.7 (−0.4 to 1.9)</td>
</tr>
<tr>
<td>7</td>
<td>−0.2 (−2.8 to 2.3)</td>
<td>0.2 (−2.4 to 2.9)</td>
<td>0.75</td>
<td>−0.02 (−0.1 to 0.06)</td>
</tr>
<tr>
<td>8</td>
<td>21.0 (−100 to 100)</td>
<td>12.8 (−100 to 100)</td>
<td>0.84</td>
<td>0.6 (−10 to 10)</td>
</tr>
</tbody>
</table>

PIS = pain interference score; PSS = pain severity score; VAS = visual analogue scale.

* Means and 95% CIs were calculated for statin-minus-placebo differences for completed pairs. A positive mean indicates greater muscle symptoms (muscle pain for VAS myalgia score and muscle pain, weakness, or cramping for symptom-specific VAS score) while receiving statin therapy versus placebo, whereas a negative mean indicates greater muscle symptoms while receiving placebo. A positive mean for PSS or PIS indicates greater muscle pain severity or intensity, respectively, while receiving statin therapy versus placebo, whereas a negative mean indicates greater muscle pain severity or intensity, respectively, while receiving placebo. A 13-mm change in VAS score and a 1-point change in PSS or PIS were considered to be clinically significant (21–23).
Statin muscle side effects

Genetic/ statin factors

Patient Factors
Leading mechanisms for statin muscle toxicity include:

1) decreased sarcolemmal cholesterol

2) mitochondrial dysfunction secondary to decreases in coenzyme Q

3) depletion of isoprenoids, cholesterol synthetic by-products that normally reduce rates of apoptosis.
### Statins and CYP3A4 Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (25 cases)</th>
<th>Simvastatin (118 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CYP3A4 inhibitor</td>
<td>2.4</td>
<td>38.4</td>
</tr>
<tr>
<td>Without CYP3A4 inhibitor</td>
<td>3.1</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Rhabdomyolysis cases per 10 million prescriptions

### TABLE 2. Clinical pharmacokinetics of HMG-CoA reductase inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>2–3</td>
<td>0.4–2.1</td>
<td>2–4</td>
<td>0.6–0.8</td>
<td>0.9–1.6</td>
<td>3</td>
<td>1.3–2.4</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>27–66</td>
<td>45–66</td>
<td>10–20</td>
<td>35–63</td>
<td>45–55</td>
<td>37</td>
<td>10–34</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>12</td>
<td>24</td>
<td>5</td>
<td>80</td>
<td>18</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Lipophilicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>80–90</td>
<td>&gt;98</td>
<td>&gt;95</td>
<td>96</td>
<td>43–55</td>
<td>88</td>
<td>94–98</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP3A4</td>
<td>Limited</td>
<td>Sulfation</td>
<td>Limited</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Active (minor)</td>
<td>Inactive</td>
<td>Active (minor)</td>
<td>Active</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>15</td>
<td>1.2</td>
<td>2.9</td>
<td>10–11</td>
<td>1.3–2.8</td>
<td>19</td>
<td>2–3</td>
</tr>
<tr>
<td>Urinary excretion (%)</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>NA</td>
<td>20</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Fecal excretion (%)</td>
<td>70</td>
<td>90</td>
<td>83</td>
<td>90</td>
<td>71</td>
<td>90</td>
<td>58</td>
</tr>
</tbody>
</table>

Data are based on a 40-mg oral dose. Table is adapted from data in Refs. 55–61. HMG-CoA, 3-Hydroxy-3-methylglutaryl coenzyme A; NA, not available; $T_{\text{max}}$, time after administration of a drug when the maximum plasma concentration is reached; $C_{\text{max}}$, maximum plasma concentration of a drug; $T_{1/2}$, time taken for the plasma concentration of a drug to be reduced by 50%.
Simvastatin FDA Drug Safety Communication

• FDA issued a Drug Safety Communication (8 June 2011)
• In SEARCH patients, myopathy (muscle weakness/pain with CK >10⊕ULN) in 52 (0.9%) on 80 mg vs 1 (0.02%) on 20 mg; rhabdo (muscle weakness/pain with CK >40⊕ULN) in 22 (0.4%) on 80 mg vs 0 on 20 mg; no fatalities
• In SEARCH, risks for myopathy and rhabdo with simvastatin 80 mg were highest in the 1st year, 5/1000 and 2/1000 person-years, and decreased to 1/1000 and 0.4/1000 person-years after that
• Older age and female sex both increased risk for myopathy
• Risk for myopathy was ~2-fold in patients taking CCBs, particularly diltiazem
• New patients should not be started on simvastatin 80 mg; patients taking simvastatin 80 mg should be maintained on current dose only if already taken ≥1 year without evidence of muscle toxicity

Genetic predisposition
Myopathy with Statins: Genetic Predisposition

- GWAS using ~300,000 markers (and additional fine-mapping)
- 85 subjects with definite or incipient myopathy and 90 controls, all taking simvastatin 80 mg/d as part of SEARCH
- Strong association of myopathy with the rs4363657 SNP located within \textit{SLCO1B1} on chromosome 12 (P=4x10^{-9}); \textit{SLCO1B1} encodes OATP1B1, shown to regulate hepatic uptake of statins
- Noncoding rs4363657 SNP in nearly complete LD with nonsynonymous rs4149056 SNP (r^2=0.97), linked to statin metabolism
- Prevalence of rs4149056 C allele in the population was 15%
- Odds ratio for myopathy: 4.5 (95% CI, 2.6 to 7.7) per copy of the C allele, 16.9 (95% CI, 4.7 to 61.1) in CC compared with TT homozygotes
- >60% of the myopathy cases could be attributed to the C variant

Clinical and Pharmacogenetic Predictors of Circulating Atorvastatin and Rosuvastatin Concentrations in Routine Clinical Care

Marianne K. DeGorter, PhD; Rommel G. Tirona, PhD; Ute I. Schwarz, MD, PhD; Yun-Hee Choi, PhD; George K. Dresser, MD, PhD; Neville Suskin, MBChB, MSc; Kathryn Myers, MD; GuangYong Zou, PhD; Otito Iwuchukwu, PhD; Wei-Qi Wei, MMed, PhD; Russell A. Wilke, MD, PhD; Robert A. Hegele, MD; Richard B. Kim, MD

Background—A barrier to statin therapy is myopathy associated with elevated systemic drug exposure. Our objective was to examine the association between clinical and pharmacogenetic variables and statin concentrations in patients.

Methods and Results—In total, 299 patients taking atorvastatin or rosuvastatin were prospectively recruited at an outpatient referral center. The contribution of clinical variables and transporter gene polymorphisms to statin concentration was assessed using multiple linear regression. We observed 45-fold variation in statin concentration among patients taking the same dose. After adjustment for sex, age, body mass index, ethnicity, dose, and time from last dose, SLCO1B1 c.521T>C (P<0.001) and ABCG2 c.421C>A (P<0.01) were important to rosuvastatin concentration (adjusted R^2=0.56 for the final model). Atorvastatin concentration was associated with SLCO1B1 c.388A>G (P<0.01) and c.521T>C (P<0.05) and 4β-hydroxycholesterol, a CYP3A activity marker (adjusted R^2=0.47). A second cohort of 579 patients from primary and specialty care databases were retrospectively genotyped. In this cohort, genotypes associated with statin concentration were not differently distributed among dosing groups, implying providers had not yet optimized each patient’s risk–benefit ratio. Nearly 50% of patients in routine practice taking the highest doses were predicted to have statin concentrations greater than the 90th percentile.

Conclusions—Interindividual variability in statin exposure in patients is associated with uptake and efflux transporter polymorphisms. An algorithm incorporating genomic and clinical variables to avoid high atorvastatin and rosuvastatin levels is described; further study will determine whether this approach reduces incidence of statin myopathy. (Circ Cardiovasc Genet. 2013;6:400-408.)
Algorithm for statin prescription based on genotypes and age

<table>
<thead>
<tr>
<th>SLCO1B1 c.521</th>
<th>ABCG2 c.421</th>
<th>Dose (mg)</th>
<th>SLCO1B1 c.388</th>
<th>Dose (mg)</th>
</tr>
</thead>
</table>
| TT
| CC           | 40          | AA        | 80            |
| CA           | 20          | AG        | 80            |
| AA           |             | GG        | 40            |
| TC
| CC           | 40          | AA        | 80            |
| CA           | 20          | AG        | 40            |
| AA           | 10          | GG        | 20            |
| CC
| CC           | 20          | AA        | 80            |
| CA           | 20          | AG        | 40            |
| AA           | 10          | GG        | 20            |

**Age (years)**

20 | 40 | 60 | 80

---

**Atorvastatin**

20 | 40 | 60 | 80
An approach towards caring for the statin intolerant subject
What the Clinician Needs to Consider

- Hypothyroidism
- Vitamin D deficiency
- Other drugs
  - Fibrates,azole anti-fungals, cyclosporine, macrolides, diltiazem, HIV protease inhibitors
- Genetic differences in drug-metabolizing enzymes, e.g. OATP1B1
  - SLCO1B1, CYP2D2, 3A4
- Neuromuscular diseases
  - Mitochondrial myopathy, McArdles disease, myotonic dystrophy, polymyositis

Statin Myalgia Clinical Index Score

- **Regional distribution pattern**
  - Symmetric hip flexors/thigh aches 3
  - Symmetric calf aches 2
  - Symmetric upper proximal aches 2
  - Non-specific asymmetric 1

- **Temporal pattern**
  - Symptoms onset <4 weeks 3
  - Symptoms onset 4-12 weeks 2
  - Symptoms onset >12 weeks 1

  **Probable** 9-13

  **Possible** 7-8

- **Dechallenge**
  - Improves on withdrawal (<2 weeks) 2
  - Improves on withdrawal (<2 weeks) 1
  - Does not improve on withdrawal (>4 weeks) 0

  **Unlikely** <7

- **Challenge**
  - Same symptoms on rechallenge <4 weeks 3
  - Same symptoms on rechallenge 4-12 week 1

Options

• Consider alternate drug options
• Consider alternate dosing regimens
• Consider ways to mitigate muscle pain
Asymptomatic CK in high risk patients only

CK measured: < 5 x normal

Mildly Symptomatic Symptoms worse: repeat CK & Stop or Reduce Statin Dose

Symptoms gone: CK ↓ & creat↓

Moderate to Severely Symptomatic Stop Statin: CK measured, hydrate if creatinine ↑

Ezetimibe and/or BAS

Fluvastatin or pravastatin, 20 mg per night or every other night

Fluvastatin XL 80 mg per night

Rosuvastatin 5 mg daily, every other day, or weekly

Red yeast rice, 600-1800 bid

Patient Types

Diagnostic Strategies

Therapeutic Options

PCSK 9 inhibitors
Mechanism of action: Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL –R available to clear circulating LDL.

FDA-approved indication(s): Alirocumab and evolocumab: Adjunct to diet and maximally tolerated statin therapy to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction. Evolocumab: Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction.

Dose and route of administration: sq injections 1-2 times monthly.

Mean % LDL-C reduction (per PI): up to 70% LDL-C reduction when added to statins.

Adverse effects: overall well tolerated (injection site reactions).

CV Outcomes Trials: Currently in progress. Post-hoc analysis of long term trials suggested decreased events.

Considerations in prescribing: Cost, SQ administration, CV outcomes trials not completed, burdensome prior authorization process.
Hepatic LDL Receptors Play a Central Role in Cholesterol Homeostasis

The LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood\(^1\-^3\)

Affinity of hepatic LDLR for apoB on LDL enables LDLRs to clear plasma LDL effectively\(^4\)

Recycling of LDL-Receptors Enables Efficient Clearance of LDL Particles

- The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL levels

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Is a Regulator of LDL-R Recycling

- PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation
- PCSK9 is highly expressed in the liver, small intestine, and kidney

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels


PCSK9 Gain of Function (GOF) = Less LDL-Rs$^{1,3,5}$

PCSK9 Loss of Function (LOF) = More LDL-Rs$^{2,4,5}$

1-3% of population$^{6,7}$
# Approaches to PCSK9 Inhibition

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Drug</th>
<th>Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCSK9 binding:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Alirocumab</td>
<td>Sanofi/Regeneron</td>
<td>3</td>
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<tr>
<td></td>
<td>Evolocumab</td>
<td>Amgen</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Bococizumab</td>
<td>Pfizer</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>LY3015014</td>
<td>Eli Lilly</td>
<td>3 (terminated)</td>
</tr>
<tr>
<td></td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>LGT209</td>
<td>Novartis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (terminated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (terminated)</td>
</tr>
<tr>
<td>**Modified binding protein (adnectin)</td>
<td>BMS-962476</td>
<td>Bristol-Myers Squibb/Adnexus</td>
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<tr>
<td><strong>PCSK9 synthesis:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RNA interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
<td>1</td>
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<tr>
<td><strong>LNA antisense oligonucleotide</strong></td>
<td>SPC-5001</td>
<td>Santaris</td>
<td>1</td>
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<td></td>
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<td>1 (terminated)</td>
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<tr>
<td><strong>RNA antisense</strong></td>
<td>BMS-844421</td>
<td>Isis/Bristol-Myers Squibb</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (terminated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>PCSK9 inhibitor</th>
<th>Population; n</th>
<th>Treatment groups</th>
<th>Change versus placebo (LSM%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL-C</td>
<td>Lp(a)</td>
</tr>
<tr>
<td>McKenney et al.</td>
<td>Alirocumab</td>
<td>LDL-C level ≥100 mg/dl with stable-dose atorvastatin; 183</td>
<td>50mg, 100mg, or 150mg every 2 weeks 200mg or 300mg every 4 weeks</td>
<td>-34.5 to -67.3</td>
</tr>
<tr>
<td>Roth et al.</td>
<td>Alirocumab</td>
<td>LDL-C level ≥100 mg/dl with atorvastatin; 92</td>
<td>150mg every 2 weeks plus atorvastatin 1.0 mg daily 150mg every 2 weeks plus atorvastatin 80mg daily</td>
<td>-48.9</td>
</tr>
<tr>
<td>Stein et al.</td>
<td>Alirocumab</td>
<td>LDL-C level ≥100 mg/dl with a statin, with or without ezetimibe; 77</td>
<td>150mg every 2 weeks 150mg, 200mg, or 300mg every 4 weeks</td>
<td>-57.2</td>
</tr>
<tr>
<td>LAPLACE-TIMI 57 trial</td>
<td>Evolocumab</td>
<td>LDL-C level ≥85 mg/dl with a statin, with or without ezetimibe; 631</td>
<td>70mg, 105mg, or 140mg every 2 weeks 280mg, 350mg, or 420mg every 4 weeks</td>
<td>-41.8 to -66.1</td>
</tr>
<tr>
<td>MENDEL trial</td>
<td>Evolocumab</td>
<td>LDL-C level ≥100 mg/dl and ≤190 mg/dl without lipid-lowering therapy; 406</td>
<td>70mg, 105mg, or 140mg every 2 weeks 280mg, 350mg, or 420mg every 4 weeks</td>
<td>-37.3 to -47.2</td>
</tr>
<tr>
<td>RUTHERFORD trial</td>
<td>Evolocumab</td>
<td>Heterozygous FH, LDL-C level ≥100 mg/dl with a statin, with or without ezetimibe; 167</td>
<td>350mg every 4 weeks 420mg every 4 weeks</td>
<td>-43.8</td>
</tr>
<tr>
<td>GAUSS trial</td>
<td>Evolocumab</td>
<td>Statin intolerant (no statin therapy), LDL-C level &gt;ATP III target; 236</td>
<td>280mg, 350mg, or 420mg every 4 weeks 420mg every 4 weeks plus ezetimibe 10 mg daily</td>
<td>-26.0 to -35.9</td>
</tr>
</tbody>
</table>

Phase II studies of bococizumab have been completed, and presented in abstract form, but full reports have not yet been published in peer-reviewed journals. Phase II studies of LY3015014 are ongoing. *Change versus atorvastatin 80 mg monotherapy in Roth et al.; change versus ezetimibe 10 mg monotherapy in GAUSS trial. Median. Abbreviations: ATP III, US National Cholesterol Education Program Adult Treatment Panel III; FH, familial hypercholesterolemia; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); LSM, least-squares mean; NA, not available; Tg, triglyceride.

From Dadu R, Ballantyne CM: Nature Rev Cardiology; 2014: 11; 563-75
# PCSK9 Inhibitor Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Amgen</td>
<td>Sanofi / Regeneron</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td>FOURIER</td>
<td>ODYSSEY Outcomes</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>22,500</td>
<td>18,000</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>MI, stroke or PAD</td>
<td>4-52 wks post-ACS</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>Atorva ≥20 mg or equiv</td>
<td>Evid-based med Rx</td>
</tr>
<tr>
<td><strong>LDL-C mg/dL (mmol/L)</strong></td>
<td>≥70 (≥1.8)</td>
<td>≥70 (≥1.8)</td>
</tr>
<tr>
<td><strong>PCSK9i Dosing</strong></td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke</td>
<td>CHD death, MI, ischemic stroke, or hosp for UA</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>Reported</td>
<td>Reported</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov
Fourier Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (∓ ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

RANDOMIZED DOUBLE BLIND

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Summary of Effects of PCSK9i Evolocumab

- **LDL-C by 59%**
- **First CV outcomes in patients on statin**
  - Safe and well-tolerated

Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl) vs. Placebo

<table>
<thead>
<tr>
<th></th>
<th>LDL-C Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolocumab</td>
<td>59% reduction</td>
</tr>
<tr>
<td>Placebo</td>
<td>Absolute ↓ 56 mg/dl</td>
</tr>
</tbody>
</table>

**KM Rate (%) at 3 Years**

- **HR 0.85 (0.79-0.92)**
  - P<0.0001

- **HR 0.80 (0.73-0.88)**
  - P<0.0001

CVD, MI, stroke

ODYSSEY outcomes: Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Key Exclusion Criteria

- Uncontrolled hypertension
- NYHA class III or IV heart failure; LVEF <25% if measured
- History of hemorrhagic stroke
- Fasting triglycerides >400 mg/dL (4.52 mmol/L)
- Use of fibrates other than fenofibrate or fenofibric acid
- Recurrent ACS within 2 weeks prior to randomization visit
  - Coronary revascularization performed within 2 weeks prior to randomization visit, or planned after randomization
- Liver transaminases >3 · ULN; hepatitis B or C infection
- Creatine kinase >3 · ULN
- eGFR <30 mL/min/1.73 m²
- Positive pregnancy test

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal
Treatment Assignment

Post-ACS patients (1 to 12 months)

Run-in period of 2–16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin

At least one lipid entry criterion met

Randomization

Alirocumab SC Q2W

Placebo SC Q2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Randomized 18,924 patients

1955 patients experienced a primary endpoint
726 patients died

Follow-up*: median 2.8 (Q1–Q3 2.3–3.4) years
8242 (44%) patients with potential follow-up ≥3 years

Alirocumab (N=9462)
Placebo (N=9462)

1343 (14.2%)
730 (7.7%)
14

1496 (15.8%)
Not applicable
9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

- Premature treatment discontinuation
- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
- Patients lost to follow-up (vital status)
# Baseline Lipid-Lowering Therapy

<table>
<thead>
<tr>
<th>Therapy, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose atorvastatin/rosvastatin</td>
<td>8380 (88.6)</td>
<td>8431 (89.1)</td>
</tr>
<tr>
<td>Low-/moderate-dose atorvastatin/rosvastatin</td>
<td>830 (8.8)</td>
<td>777 (8.2)</td>
</tr>
<tr>
<td>Other statin</td>
<td>19 (0.2)</td>
<td>27 (0.3)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>269 (2.8)</td>
<td>285 (3.0)</td>
</tr>
<tr>
<td>No lipid-lowering therapy</td>
<td>87 (0.9)</td>
<td>91 (1.0)</td>
</tr>
</tbody>
</table>
## Guideline-Recommended Post-ACS Medications

<table>
<thead>
<tr>
<th>Medication, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>9050 (95.6)</td>
<td>9036 (95.5)</td>
</tr>
<tr>
<td><strong>P2Y\textsubscript{12} antagonist</strong></td>
<td>8296 (87.7)</td>
<td>8245 (87.1)</td>
</tr>
<tr>
<td><strong>ACE-I/ARB</strong></td>
<td>7356 (77.7)</td>
<td>7360 (77.8)</td>
</tr>
<tr>
<td><strong>Beta-blocker</strong></td>
<td>7998 (84.5)</td>
<td>7992 (84.5)</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker
**LDL-C: ITT and On-Treatment Analyses**

- **Placebo**
  - ITT
  - On-treatment*

- **Alirocumab**
  - ITT†
  - On-treatment*

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Number at Risk
Placebo 9462
Alirocumab 9462

Years Since Randomization
0 1 2 3 4

MACE (%) 0 3 6 9 12 15

HR 0.85 (95% CI 0.78, 0.93); P=0.0003
Primary Efficacy and Components

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
# Main Secondary Efficacy Endpoints: Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD event</strong></td>
<td>1199 (12.7)</td>
<td>1349 (14.3)</td>
<td>0.88 (0.81, 0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Major CHD event</strong></td>
<td>793 (8.4)</td>
<td>899 (9.5)</td>
<td>0.88 (0.80, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>CV event</strong></td>
<td>1301 (13.7)</td>
<td>1474 (15.6)</td>
<td>0.87 (0.81, 0.94)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Death, MI, ischemic stroke</strong></td>
<td>973 (10.3)</td>
<td>1126 (11.9)</td>
<td>0.86 (0.79, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>CHD death</strong></td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>240 (2.5)</td>
<td>271 (2.9)</td>
<td>0.88 (0.74, 1.05)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>334 (3.5)</td>
<td>392 (4.1)</td>
<td>0.85 (0.73, 0.98)</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*Nominal P-value
# Primary Efficacy in Main Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>Incidence (%)</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18924</td>
<td>9.5</td>
<td>11.1</td>
<td>0.85 (0.78, 0.93)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 Yr</td>
<td>13840</td>
<td>8.5</td>
<td>9.5</td>
<td>0.89 (0.80, 0.99)</td>
</tr>
<tr>
<td>≥ 65 Yr</td>
<td>5084</td>
<td>12.4</td>
<td>15.5</td>
<td>0.79 (0.68, 0.91)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4762</td>
<td>10.7</td>
<td>11.8</td>
<td>0.91 (0.77, 1.08)</td>
</tr>
<tr>
<td>Male</td>
<td>14162</td>
<td>9.2</td>
<td>10.9</td>
<td>0.83 (0.74, 0.92)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>5437</td>
<td>7.9</td>
<td>9.3</td>
<td>0.84 (0.70, 1.01)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>4175</td>
<td>9.1</td>
<td>10.0</td>
<td>0.90 (0.74, 1.09)</td>
</tr>
<tr>
<td>North America</td>
<td>2871</td>
<td>13.7</td>
<td>17.1</td>
<td>0.76 (0.65, 0.94)</td>
</tr>
<tr>
<td>South America</td>
<td>2588</td>
<td>9.1</td>
<td>9.7</td>
<td>0.94 (0.73, 1.21)</td>
</tr>
<tr>
<td>Asia</td>
<td>2293</td>
<td>7.7</td>
<td>7.6</td>
<td>1.03 (0.76, 1.38)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>1560</td>
<td>12.2</td>
<td>16.7</td>
<td>0.70 (0.54, 0.92)</td>
</tr>
<tr>
<td>Time from Index Event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 Months</td>
<td>6178</td>
<td>10.3</td>
<td>12.3</td>
<td>0.83 (0.71, 0.96)</td>
</tr>
<tr>
<td>2 - &lt;6 Months</td>
<td>9518</td>
<td>9.6</td>
<td>11.1</td>
<td>0.85 (0.75, 0.96)</td>
</tr>
<tr>
<td>≥ 6 Months</td>
<td>3228</td>
<td>8.0</td>
<td>8.7</td>
<td>0.90 (0.71, 1.14)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>7164</td>
<td>8.3</td>
<td>9.5</td>
<td>0.86 (0.74, 1.01)</td>
</tr>
<tr>
<td>80 - &lt;100</td>
<td>6128</td>
<td>9.2</td>
<td>9.5</td>
<td>0.96 (0.82, 1.14)</td>
</tr>
<tr>
<td>≥100</td>
<td>5629</td>
<td>11.5</td>
<td>14.9</td>
<td>0.76 (0.55, 0.97)</td>
</tr>
</tbody>
</table>

*P-values for interaction
Post hoc Analysis: All-cause Death by Prespecified Baseline LDL-C Subgroups

- **<80 mg/dL**
  - HR 0.89
  - (95% CI 0.69, 1.14)

- **80 to <100 mg/dL**
  - HR 1.03
  - (95% CI 0.78, 1.36)
Post hoc Analysis: All-cause Death by *Prespecified* Baseline LDL-C Subgroups

\[ P_{interaction} = 0. \]

- **<80 mg/dL**
  - HR 0.89
  - (95% CI 0.69, 1.14)

- **80 to <100 mg/dL**
  - HR 1.03
  - (95% CI 0.78, 1.36)

- **≥100 mg/dL**
  - HR 0.71
  - (95% CI 0.56, 0.90)
Efficacy: Subgroup with Baseline LDL-C $\geq 100$ mg/dL

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=2814)</th>
<th>Placebo (N=2815)</th>
<th>Absolute risk reduction</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td>324 (11.5)</td>
<td>420 (14.9)</td>
<td>3.4</td>
<td>0.76 (0.65, 0.87)</td>
</tr>
<tr>
<td><strong>CHD death</strong></td>
<td>69 (2.5)</td>
<td>96 (3.4)</td>
<td>0.9</td>
<td>0.72 (0.53, 0.98)</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>81 (2.9)</td>
<td>117 (4.2)</td>
<td>1.3</td>
<td>0.69 (0.52, 0.92)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>114 (4.1)</td>
<td>161 (5.7)</td>
<td>1.7</td>
<td>0.71 (0.56, 0.90)</td>
</tr>
</tbody>
</table>
## Safety (1)

<table>
<thead>
<tr>
<th>Treatment-emergent adverse events, n (%)</th>
<th>Alirocumab (N=9451)</th>
<th>Placebo (N=9443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>7165 (75.8)</td>
<td>7282 (77.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>2202 (23.3)</td>
<td>2350 (24.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt;3 · ULN, n/N (%)</td>
<td>212/9369 (2.3)</td>
<td>228/9341 (2.4)</td>
</tr>
<tr>
<td>Creatine kinase &gt;10 · ULN, n/N (%)</td>
<td>46/9369 (0.5)</td>
<td>48/9338 (0.5)</td>
</tr>
<tr>
<td>Neutralizing antidrug antibodies*, n</td>
<td>42</td>
<td>6</td>
</tr>
</tbody>
</table>

*Preliminary data; last visit analysis pending.
### Safety (2)

<table>
<thead>
<tr>
<th>Event</th>
<th>Alirocumab (N=9451)</th>
<th>Placebo (N=9443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes worsening or diabetic complications: <em>pts w/DM at baseline</em>, n/N (%)</td>
<td>506/2688 (18.8)</td>
<td>583/2747 (21.2)</td>
</tr>
<tr>
<td>New onset diabetes; <em>pts w/o DM at baseline</em>, n/N (%)</td>
<td>648/6763 (9.6)</td>
<td>676/6696 (10.1)</td>
</tr>
<tr>
<td>General allergic reaction, n (%)</td>
<td>748 (7.9)</td>
<td>736 (7.8)</td>
</tr>
<tr>
<td>Hepatic disorder, n (%)</td>
<td>500 (5.3)</td>
<td>534 (5.7)</td>
</tr>
<tr>
<td>Local injection site reaction, n (%)*</td>
<td>360 (3.8)</td>
<td>203 (2.1)</td>
</tr>
<tr>
<td>Neurocognitive disorder, n (%)</td>
<td>143 (1.5)</td>
<td>167 (1.8)</td>
</tr>
<tr>
<td>Cataracts, n (%)</td>
<td>120 (1.3)</td>
<td>134 (1.4)</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>9 (&lt;0.1)</td>
<td>16 (0.2)</td>
</tr>
</tbody>
</table>

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Osler(^1)  (n=4465 pts, 48 weeks)</th>
<th>Odyssey Long Term(^2) (n=2341 pts, 78 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evolocumab</td>
<td>SOC</td>
</tr>
<tr>
<td>Any adverse events</td>
<td>69.2%</td>
<td>64.8%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>AE leading to DC of Rx</td>
<td>2.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>4.3%</td>
<td>NA</td>
</tr>
<tr>
<td>Transaminase &gt; 3x ULN</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Muscle-related/myalgia</td>
<td>6.4%</td>
<td>6.0%</td>
</tr>
<tr>
<td>CK &gt; 5x/&gt; 3x ULN</td>
<td>0.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Neurocognitive events/disorders</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

# Low LDL-C

Alirocumab-treated patients in the Global Safety Pool

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab n=3340</th>
<th>≥ 2 LDL-C &lt; 25 mg/dL n=796 (24%)</th>
<th>≥ 2 LDL-C &lt; 15 mg/dL n=288 (7%)</th>
<th>LDL-C ≥ 25 mg/dL n=2544 (76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and connective tissue</strong></td>
<td>24.2%</td>
<td>21.1%</td>
<td>20.1%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.9%</td>
<td>3.1%</td>
<td>3.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.9%</td>
<td>1.0%</td>
<td>1.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>17.0%</td>
<td>12.7%</td>
<td>10.1%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>3.0%</td>
<td>1.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td>14.9%</td>
<td>10.3%</td>
<td>9.0%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.6%</td>
<td>1.8%</td>
<td>1.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition</strong></td>
<td>6.9%</td>
<td>7.0%</td>
<td>7.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.2%</td>
<td>1.5%</td>
<td>2.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>4.6%</td>
<td>5.3%</td>
<td>6.9%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cataract</td>
<td>0.8%</td>
<td>1.5%</td>
<td>2.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>2.5%</td>
<td>2.8%</td>
<td>2.4%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
### New Onset DM or IFG in Patients Receiving Alirocumab in the Global Safety Pool

<table>
<thead>
<tr>
<th>Global Safety Pool</th>
<th>Placebo-Controlled Studies</th>
<th>Ezetimibe-Controlled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>New Onset Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline normoglycemia (FBG &lt; 100 mg/dL)</td>
<td>0.1% n=718</td>
<td>0.3% n=365</td>
</tr>
<tr>
<td>Baseline impaired fasting glucose (FBG 100-126 mg/dL)</td>
<td>5.7% n=865</td>
<td>3.8% n=420</td>
</tr>
</tbody>
</table>

**New Onset Impaired Fasting Glucose**

| Baseline normoglycemia (FBG < 100 mg/dL) | 31.2% n=718 | 26.6% n=365 | 26.5% n=223 | 24.1% n=174 |

**Reverted to Normoglycemia**

| Baseline impaired fasting glucose (FBG 100-126 mg/dL) | 20.6% n=865 | 18.1% n=420 | 28.2% n=333 | 31.7% n=243 |
Neurologic Events

Logic: Cholesterol is major component of cellular membranes and myelin. Indicators of Neurologic AE include central (unlikely b/c mAb unlikely to cross BBB) and peripheral neuropathies

<table>
<thead>
<tr>
<th>Global Safety Pool</th>
<th>Placebo-Controlled Studies</th>
<th>Ezetimibe-Controlled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab n=2476</td>
<td>Alirocumab n=864</td>
</tr>
<tr>
<td>Patients with a Neurologic TEAE</td>
<td>3.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td><strong>0.98 (0.68-1.41)</strong></td>
<td><strong>1.43 (0.76-2.69)</strong></td>
</tr>
<tr>
<td>Demyelination</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Guillain-Barre</td>
<td>3.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>DC due to neurologic AE</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Roberts MD. Alirocumab. BLA 125559. Clinical Safety Review. Presented to the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 9, 2015

# Neurocognition

<table>
<thead>
<tr>
<th></th>
<th>Global Safety Pool</th>
<th>Osler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any control n=2080</td>
<td>Evolocumab n=3946</td>
</tr>
<tr>
<td>Median exposure (mo)</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Neurocognition TEAE</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>DC due to TEAE</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>-</td>
<td>0.1%</td>
</tr>
<tr>
<td>Dementia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0.1%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

PCSK 9 i in those with muscle issues on statins
Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event

Cox model analysis:
HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042
HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P=0.096

GAUSS-3 Study Design: Two Double-Blind Phases

Phase A

- 511 patients enrolled at 53 centers with a history of intolerance to multiple statins due to muscle-related adverse effects.
- 10 weeks: Atorvastatin 20 mg → Placebo
- 10 weeks: Atorvastatin 20 mg → Placebo

Phase B

- Patients proceeded to Phase B only if they had *intolerable* muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during prior statin treatment.
- 24 weeks:
  - Monthly SC evolocumab 420 mg
  - Daily oral ezetimibe 10 mg

### Phase A: Study Drug Discontinuation Events

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
</tbody>
</table>

Bypassed Phase A due to CK elevation ≥ 10 x ULN   19 (3.9%)* 

*218 of these 228 eligible patients proceeded to Phase B

Phase B: Time to Any Muscle-Related Symptom

Cumulative Event Probability

Approved Indications

FDA (alirocumab and evolocumab)

- In combination with maximum tolerated statin in adults with heterozygous familial hypercholesterolemia and
- In combination with maximum tolerated statin therapy in patients with ASCVD, who require additional lowering of LDL-C
- In patients with homozygous familial hypercholesterolemia (evolocumab only)

European Commission (evolocumab)

- In combination with maximum tolerated statin therapy in patients unable to reach LDL-C goal
- Alone or in combination with other LLT in patients who are statin-intolerant or for whom a statin is contraindicated
- In patients with homozygous familial hypercholesterolemia
## NLA Recommended Candidates for PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Segment</th>
<th>Specific population</th>
<th>LDL-C (mg/dL) on maximally-tolerated statin (±ezetimibe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>Heterozygous FH patients without ASCVD</td>
<td>≥ 130</td>
</tr>
<tr>
<td>ASCVD</td>
<td>ASCVD</td>
<td>≥ 100</td>
</tr>
<tr>
<td></td>
<td>Selected ASCVD patients such as those with recurrent CV events</td>
<td>≥ 70</td>
</tr>
<tr>
<td>Statin Intolerance</td>
<td>High or very high risk patients who meet the NLA definition of statin intolerance</td>
<td>As above</td>
</tr>
</tbody>
</table>

JCL 2015; 9:Suppl 6S: S1 – S122
Estimated cost of different LDL-cholesterol lowering regimens for patients with ASCVD within the Veterans Affairs System

Modelled Costs with Different LDL-C Lowering Regimens

- $2.08 Billion: Start evolocumab in all FOURIER-eligible pts
- $1.12 Billion: Titrate all pts on moderate statin to high-intensity statin, start ezetimibe in all pts not on ezetimibe
- $838 Million: Start evolocumab in pts with LDL-C ≥70 mg/dL
- $950 Million: Titrate statin and ezetimibe, start evolocumab in pts with LDL-C ≥70 mg/dL

- 631,855 pts with ASCVD, ~25% eligible for FOURIER, with LDL-C ≥70 mg/dL
- Only 48% on high-intensity statin, 2.6% on ezetimibe + statin

A Simplified Pathway to PCSK9i Use

**Clinical ASCVD**
1. ACS or history of myocardial infarction
2. Unstable or stable angina
3. Stroke or TIA (presumed to be atherosclerotic)
4. Coronary revascularization (PCI, CAGB, stent)
5. Peripheral arterial disease or revascularization

**Heterozygous FH**
1. LDL-C ≥190 mg/dL (LDL-C ≥180 mg/dL for ≤20 years)
   **AND any of the following:**
2. First-degree relative with premature coronary artery disease
3. First-degree relative with FH-range LDL-C
4. Positive genetic testing (LDL-receptor, apoB or PCSK9)

---

**Document in medical history**

**Is patient on maximally tolerated statin?**
- No
  - **Higher dose not tried**
  - **Increase dose**

- Yes
  - **Anticipated LDL-C reduction?**
    - Yes
      - ≥50% (LDL-C ≤100 mg/dL)
      - ≥50% (LDL-C ≤70 mg/dL)
    - **Reinforce lifestyle and adherence**
    - **Add nonstatin therapy**
      - (ezetimibe); reinforce lifestyle and adherence

    - **PCSK9 Inhibitors**
      - Evolocumab 140 mg every 4 weeks or 420 mg every 4 weeks
      - Alirocumab 75 mg every 2 weeks
      - Alirocumab 150 mg every 2 weeks
      - with other lipid therapies, heart-healthy diet, and exercise

  - No
    - **Rule out other causes of muscular complaints**
      - ≥2 trials of statin rechallenge (including less-frequent dosing or lower-dose regimen)
      - **Symptom free off statin?**
        - Yes
          - **Trial of nonstatin therapy**
            - (ezetimibe) + healthy diet and lifestyle adherence
        - No
          - **Anticipated LDL-C reduction?**
            - Yes
            - ≥50% (LDL-C ≤100 mg/dL)
            - ≥50% (LDL-C ≤70 mg/dL)
            - **No**
Triglycerides
Eruptive Xanthomas in Type 2 Diabetes
• Need to treat when triglycerides >400 mg/dL for pancreatitis risk
• Values less than that, a risk factor but no evidence as yet except in secondary analysis that treatment helps
• Lifestyle changes a cornerstone of treatment
**Safety of Fibrates**

1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.  
   - **Level**: B (Moderate)

2. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effects.  
   - **Level**: E (Expert)

3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.  
   - Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², is present.  
   - If eGFR is between 30 and 59 mL/min per 1.73 m², the dose of fenofibrate should not exceed 54 mg/day.  
   - If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m², fenofibrate should be discontinued.  
   - **Level**: B (Moderate)

**Safety of Omega-3 Fatty Acids**

1. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.  
   - **Level**: C (Weak)
Hypertriglyceridemia

Diet
Exercise
Glycemia control
Fibrates (Note: no gemfibrozil with statins; need to watch renal function and adjust dose)
Fish oil (omega fatty acid 3-5 gms)
Niacin
New Lipid Treatments

- HDL (?LDL) therapies (not approved, in research)
  CETP inhibitors (anacetrapib)
- PCSK 9 humanized monoclonal antibodies
  Alirocumab (approved), Evolocumab (approved), Bococizumab
- Antisense oligonucleotide (ASO) to apo B
  Mipomersen (approved)
- Microsomal triglyceride transfer protein (MTP) inhibitor
  Lomitapide (approved)
The REDUCE-IT (Reduction of Cardiovascular Events Outcomes trial): A multi-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effectiveness of Vascepa as an add-on to statin therapy, in reducing the first major cardiovascular event in an high-risk patient population compared to statin therapy alone. Patients enrolled in the study have elevated triglyceride levels and at least one other defined cardiovascular risk factor. The control arm of the study is comprised of patients on optimized statin therapy. The active arm of the study is comprised of patients on optimized statin therapy plus Vascepa. Entry requirements for participants in this study include elevated triglyceride levels and either coronary heart disease or risk factors for coronary heart disease. This study is being conducted at over 400 clinical sites in 11 countries with the largest number of sites located within the United States.
**Reduction of Cardiovascular Events With EPA—Intervention Trial (REDUCE-IT)**

- **Patients:** ~8000 men and women aged ≥45 years with
  - CVD or high CVD risk
  - hypertriglyceridemia
  - on statin therapy ≥4 wks

- **Intervention:** highly purified ethyl ester of eicosapentaenoic acid (AMR101) or placebo

- **Primary outcome measures:** Incidence of CV events, such as coronary revascularization

- **Secondary outcome measures:** incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as diabetic patients

- **Follow-up:** 4–6 years

- **Estimated primary completion date:** November 2016 (Final data collection date for primary outcome measure)

http://clinicaltrials.gov/ct2/show/NCT01492361
The Pemafibrate to Reduce cardiovascular Outcomes by reducing triglycerides IN diabetic patients (PROMINENT) Phase 3 K-877 cardiovascular outcomes trial will recruit an estimated 10,000 high-risk diabetic patients worldwide. All participants will receive aggressive, standard of care management of cardiovascular risk factors including treatment with high-intensity statins. In addition, patients will receive either K-877 or placebo. The trial will include diabetic patients with and without established cardiovascular disease and will test whether K-877 reduces the occurrence of heart attacks, hospitalizations for unstable angina requiring unplanned revascularization, stroke, or death from cardiovascular causes.
A Null Mutation in Human APOC3 Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,¹ Coleen M. Damcott,¹ Haiqing Shen,¹ Sandra H. Ott,¹ John Shelton,¹ Richard B. Horenstein,¹ Wendy Post,² John C. McLenithan,¹,³ Lawrence F. Bielak,⁴ Patricia A. Peyser,⁴ Braxton D. Mitchell,¹ Michael Miller,¹ Jeffrey R. O’Connell,¹ Alan R. Shuldiner¹,³

12 DECEMBER 2008 VOL 322 SCIENCE
Loss of Function Mutation (R19X) in Apo C III in the Amish

- Reduced Apo C III levels in heterozygotes by 50%
- Decreased fasting and postprandial TGs
- Decreased non HDL-C, LDL-C, VLDL-C, IDL-C
- Increased HDL-C, HDL-2, HDL-3
- Reduced coronary calcium scores
THANK YOU