Statins
Introduction

- What is the role of statin therapy in the management of dyslipidemia and prevention of CVD?
- What are starting statin doses, dosage ranges, metabolic effects, and main considerations?
- How should statin treatment be monitored?
- What is the major evidence supporting the use of statin therapy?

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
• In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. \(^1\)

• On the basis of morbidity and mortality outcome trials, statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals. \(^2\)

• For clinical decision-making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2D associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction. \(^3\)

• Certain benefits associated with statin therapy may not be due to their LDL-C-lowering effect, but rather associated with pleiotropic benefits, such as reduced inflammation in the vasculature, kidney, and bone. \(^4\)

ASCVD = atherosclerotic cardiovascular disease;
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes.

Statin Therapy in the AACE ASCVD Risk Factor Modification Algorithm

**Even more intensive therapy might be warranted.**

Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HTN = hypertension; Hx = history; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; OM3 = omega-3; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Rx = prescription; TG = triglyceride

Statins, ASCVD Risk Categories, and LDL-C Treatment Goals

- In high-risk individuals, further LDL-C lowering beyond established targets with statins results in additional ASCVD event reduction and may be considered in:
  - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or with T2D plus ≥1 additional risk factor should be treated with statins to target a reduced LDL-C goal of <70 mg/dL
  - Extreme-risk individuals should be treated with statins to a LDL-C treatment goal of <55 mg/dL
- Combination therapy with lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually statin) does not achieve therapeutic goal.

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Statin Therapy

• Inhibits HMG-CoA reductase, a key rate-limiting enzyme in hepatic cholesterol synthesis
  • Triggers increased expression of hepatic LDL receptors and increased LDL-C clearance
• Decreases plasma LDL-C in a dose-dependent fashion by 20%-55%
• Exerts modest lowering effects on VLDL-C, IDL-C, and TG (10%-30%)
• Raises HDL-C by 2%-10%
• Improves LDL subfraction profiles (atorvastatin and rosvastatin)
  • Larger clinical trials necessary to confirm effect of statins on LDL particle size and density

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; IDL = intermediate-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

Representative Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With LDL-C ≥160 mg/dL and ≤250 mg/dL (N=2431)

- The lipid-lowering effects of statins in these studies are representative of other controlled trials, with one exception: pravastatin had a slightly greater TG-lowering effect in the CARE, WOSCOPS, and LIPID trials.
- Lovastatin and fluvastatin data are from the 8-week CURVES trial, a comparison of the effects of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin in patients with LDL-C 192-244 mg/dL (N=534); these data do not represent head-to-head analyses.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage range, daily (mg/dL)</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20-80</td>
<td>↓ 21 to ↓ 36</td>
<td>↓ 29 to ↓ 48</td>
<td>↑ 4.6 to ↑ 8.0</td>
<td>↓ 12 to ↓ 13</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-40</td>
<td>↓ 15 to ↓ 22</td>
<td>↓ 20 to ↓ 30</td>
<td>↑ 3.2 to ↑ 5.6</td>
<td>↑ 8 to ↓ 13</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10-80          a</td>
<td>↓ 20 to ↓ 33</td>
<td>↓ 28 to ↓ 46</td>
<td>↑ 5.2 to ↑ 6.8</td>
<td>↓ 12 to ↓ 18</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10-40</td>
<td>↓ 13 to ↓ 19</td>
<td>↓ 17 to ↓ 23</td>
<td>↑ 0.9 to ↑ 3.0</td>
<td>↓ 5 to ↓ 13</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80</td>
<td>↓ 27 to ↓ 39</td>
<td>↓ 37 to ↓ 51</td>
<td>↑ 2.1 to ↑ 5.7</td>
<td>↓ 20 to ↓ 28</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10-40</td>
<td>↓ 33 to ↓ 40</td>
<td>↓ 45 to ↓ 55</td>
<td>↑ 7.7 to ↑ 9.6</td>
<td>↓ 20 to ↓ 26</td>
</tr>
</tbody>
</table>

a Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

CARE=Cholesterol and Recurrent Events; CURVES=Comparative Dose Efficacy of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LIPID=Long-Term Intervention With Pravastatin in Ischemic Disease; TC=total cholesterol; TG=triglycerides; WOSCOPS=West of Scotland Coronary Prevention Study.

Statin Starting Doses and Dosage Ranges

<table>
<thead>
<tr>
<th>Statin</th>
<th>Recommended Starting Daily Dose</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin¹</td>
<td>20 mg</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Pravastatin²</td>
<td>40 mg</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Simvastatin³</td>
<td>20-40 mg</td>
<td>5-80 mg&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluvastatin⁴</td>
<td>40 mg</td>
<td>20-80 mg</td>
</tr>
<tr>
<td>Atorvastatin⁵</td>
<td>10-20 mg</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Rosuvastatin⁶</td>
<td>10 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5-40 mg</td>
</tr>
<tr>
<td>Pitavastatin⁷</td>
<td>2 mg</td>
<td>2-4 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Simvastatin 80 mg not approved for therapy unless individual has been on treatment for >1 year without myopathy; Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

<sup>b</sup> Consider 5 mg starting dose in Asian patients; Crestor (rosuvastatin calcium) [PI]; 2010.

¹ Mevacor (lovastatin) [PI]; 2012. ²Pravachol (pravastatin sodium) [PI]; 2016. ³Zocor (simvastatin) [PI]; 2018. ⁴Lescol (fluvastatin sodium) [PI]; 2017. ⁵Lipitor (atorvastatin calcium) [PI]; 2017. ⁶Crestor (rosuvastatin calcium) [PI]; 2010. ⁷Livalo (pitavastatin) [PI]; 2016.
Main Considerations

- Conduct liver function testing prior to therapy and as clinically indicated thereafter.
- Myalgias and muscle weakness present in some individuals.
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, such as cyclosporine, warfarin, and protease inhibitors, and multiple other medications.
- Myopathy/rhabdomyolysis in rare cases; increased risk with co-administration of some drugs (see product label).
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for ≥12 months without muscle toxicity.
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine.
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups.

New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with metabolic syndrome, may be less common with pravastatin and possibly pitavastatin, and occurs to a lesser extent overall than the associated decrease in ASCVD.

ASCVD = atherosclerotic cardiovascular disease;
MetS = metabolic syndrome.

Monitoring Statin Therapy

• Reassess individuals’ lipid status 6 weeks after therapy initiation and again at 6-week intervals until treatment goal is achieved.

• While on stable lipid therapy:
  • Individuals should be tested at 6- to 12-month intervals.
  • The specific testing interval should depend on individual adherence to therapy and lipid profile consistency
  • If adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment.

ASCVD = atherosclerotic cardiovascular disease.

• More frequent lipid status evaluation is recommended in the following situations:
  • Deterioration of diabetes control
  • Use of a new drug known to affect lipid levels
  • Progression of atherosclerotic disease
  • Considerable weight gain
  • Unexpected adverse change in any lipid parameter
  • Development of a new ASCVD risk factor
  • Convincing new clinical trial evidence or guidelines that suggest stricter lipid goals

• CK levels should be assessed and statins discontinued if patients report clinically significant myalgias or muscle weakness on statin therapy.

ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase.

Establishing the Efficacy, Safety, and Benefits of Statin Therapy

Statins: The evidence
Numerous large clinical trials have established the efficacy and safety of statin therapy, and the cardiovascular benefits of LDL-C reduction with statin therapy in both primary and secondary prevention.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Inclusion criteria (mg/dL)</th>
<th>Mean baseline values (mg/dL)</th>
<th>Mean achieved values (mg/dL)</th>
<th>Relative risk reduction</th>
<th>Experimental event rate %±2</th>
<th>Control event rate %</th>
<th>Absolute risk reduction %</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS 0% Female</td>
<td>Pravastatin</td>
<td>---</td>
<td>155-232</td>
<td>192</td>
<td>30%</td>
<td>5.5% at 5.0 y</td>
<td>7.9%</td>
<td>2.4%</td>
<td>42</td>
</tr>
<tr>
<td>AFCAPS 15% Female</td>
<td>Lovastatin</td>
<td>≤400</td>
<td>130-190</td>
<td>150</td>
<td>40%</td>
<td>4.0% at 5.2 y</td>
<td>6.8%</td>
<td>1.2%</td>
<td>83</td>
</tr>
<tr>
<td>ASCOT-LLA 19% Female</td>
<td>Atorvastatin</td>
<td>&lt;400</td>
<td>TC &lt;250</td>
<td>134</td>
<td>37%</td>
<td>1.9% at 3.3 y</td>
<td>3.0%</td>
<td>1.1%</td>
<td>91</td>
</tr>
<tr>
<td>CARD 32% Female</td>
<td>Atorvastatin</td>
<td>&lt;600</td>
<td>≤160</td>
<td>118</td>
<td>35%</td>
<td>3.0% at 4.0 y</td>
<td>4.6%</td>
<td>1.6%</td>
<td>63</td>
</tr>
<tr>
<td>JUPITER 38% Female</td>
<td>Rosuvastatin</td>
<td>&lt;500</td>
<td>&lt;130°</td>
<td>108°</td>
<td>44%</td>
<td>1.6% at 1.9 y±2°</td>
<td>2.8%</td>
<td>---</td>
<td>95f</td>
</tr>
</tbody>
</table>

AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HDL-C = high-density lipoprotein cholesterol; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; NNT = number needed to treat; PBO = placebo; TG = triglycerides; WOSCOPS = West of Scotland Coronary Prevention Study.

## Secondary ASCVD Prevention With Statin Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Inclusion criteria (mg/dL)</th>
<th>Mean baseline values (mg/dL)</th>
<th>Mean achieved values (mg/dL)</th>
<th>Relative risk reduction</th>
<th>Experimental event rate %</th>
<th>Control event rate %</th>
<th>Absolute risk reduction %</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S 19% Female</td>
<td>Simvastatin, 20-40 mg vs. PBO</td>
<td>≤225</td>
<td>TC = 215-315</td>
<td>190</td>
<td>35%</td>
<td>8.2% at 5.4 y</td>
<td>11.5%</td>
<td>9.2%</td>
<td>11</td>
</tr>
<tr>
<td>CARE 14% Female</td>
<td>Pravastatin, 40 mg vs. PBO</td>
<td>&lt;350</td>
<td>115-74</td>
<td>139</td>
<td>23%</td>
<td>10.2% at 5.0 y</td>
<td>13.2%</td>
<td>3.0%</td>
<td>33</td>
</tr>
<tr>
<td>LIPID 17% Female</td>
<td>Pravastatin, 40 mg vs. PBO</td>
<td>&lt;445</td>
<td>TC = 155-271</td>
<td>150</td>
<td>23%</td>
<td>12.3% at 6.1 y</td>
<td>15.9%</td>
<td>3.6%</td>
<td>28</td>
</tr>
<tr>
<td>HPS 25% Female</td>
<td>Simvastatin, 40 mg vs. PBO</td>
<td>--</td>
<td>TC = 135</td>
<td>129</td>
<td>26%</td>
<td>8.7% at 5.0 y</td>
<td>11.8%</td>
<td>3.1%</td>
<td>32</td>
</tr>
<tr>
<td>TNT 19% Female</td>
<td>Atorvastatin, 80 mg vs. atorvastatin, 10 mg</td>
<td>≤600</td>
<td>&lt;130</td>
<td>98</td>
<td>21% in favor of atorvastatin, 80 mg</td>
<td>6.9% at 4.9 y</td>
<td>8.7%</td>
<td>1.8%</td>
<td>56</td>
</tr>
<tr>
<td>PROVE IT–TIMI 22% Female</td>
<td>Atorvastatin, 80 mg vs. pravastatin, 40 mg</td>
<td>--</td>
<td>TC ≤240 or TC ≤200 on therapy</td>
<td>106 (median)</td>
<td>17% in favor of atorvastatin</td>
<td>8.3% at 2 y</td>
<td>10.0%</td>
<td>1.7%</td>
<td>59</td>
</tr>
<tr>
<td>A to Z 25% Female</td>
<td>Simvastatin, 40/80 mg vs. PBO/simvastatin, 20 mg</td>
<td>--</td>
<td>TC ≤250*</td>
<td>112</td>
<td>11% in favor of simvastatin, 40/80 mg</td>
<td>14.4% at 2 y</td>
<td>16.7%</td>
<td>---</td>
<td>77%</td>
</tr>
</tbody>
</table>

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Trial; HDL-C = high-density lipoprotein cholesterol; HPS = Heart Protection Study; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; NNT = number needed to treat; PBO = placebo; PROVE IT–TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction; TG = triglycerides; TNT = Treating to New Targets.

AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides; HDL-C = high-density lipoprotein cholesterol; HPS2 THRIVE = Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid lowering; IMPROVE-IT = IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; LDL-C = low-density lipoprotein cholesterol; NNT = number needed to treat; PBO = placebo; TG = triglycerides.

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)

Randomized, double-blind, placebo-controlled study of statin therapy (rosuvastatin 20 mg) in patients (N=17,802) with moderate to low LDL-C (<130 mg/dL) and elevated hsCRP (≥2.0 mg/L)
Median follow-up, 1.9 years; maximal follow-up, 5 years

- Primary endpoint: first occurrence of MACE (nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization, or CV death)
- Trial was suspended due to unequivocal evidence of reduced CV morbidity and mortality in the statin group vs placebo
- At 12 months, median LDL-C, TG, and hsCRP levels were 50%, 17%, and 37% lower, respectively, in the rosuvastatin vs placebo groups
- Relative MACE hazard reduction of 44% in the rosuvastatin group (95% CI, 0.46-0.69; P<0.00001)

CV = cardiovascular; CVA = cerebrovascular attack; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction; TG = triglycerides.

JUPITER: Lower Risk of CV Events With LDL-C <50 mg/dL

- Rosuvastatin participants achieving LDL-C <50 mg/dL had lower risk of CV events without increased AEs.
- Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes were not significantly different among rosuvastatin participants with/without LDL-C <50 mg/dL.

*All hazard ratios are vs placebo

A 2010 meta-analysis of major vascular events (coronary death, MI, coronary revascularization, and ischemic stroke) in RCTs with ≥1,000 patients and ≥2 years of more- vs less-intensive statin therapy, and/or statin vs control (N=169,138); 5 years’ follow-up

- Confirmed benefit of LDL-C lowering with statin therapy
- **A 1 mmol/L (38.7 mg/dL) reduction in LDL-C resulted in:**
  - 22% decrease in major vascular events (nonfatal MI or ASCVD death)
  - 25% reduction in coronary revascularizations
  - 16% reduction in CVA

ASCVD = atherosclerotic cardiovascular disease; CVA = cerebrovascular event;
LDL-C = low-density lipoprotein cholesterol;
MI = myocardial infarction; RCT = randomized-controlled trial.

Cholesterol Treatment Trialists’ Collaboration: Benefit of Intensive LDL-C Lowering

• Compared to standard regimens, more intensive statin therapy showed a significant 15% further reduction in major vascular events.¹

• Data suggest that reducing LDL-C by 2-3 mmol/L (~77 to 116 mg/dL) would reduce the risk of major vascular events by 40%-50%.²

• The primary goal for individuals at high risk of occlusive vascular events should be to achieve the largest possible LDL-C reduction without increasing myopathy risk, rather than setting an LDL-C target goal.³

LDL-C = low-density lipoprotein cholesterol; RR = relative risk.

Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosage): Patients Who Achieved Very Low LDL-C Levels Had Lower Risk for Major CV Events

**Adjusted* Hazard Ratio for Major CV Events**

*Adjusted for sex, age, smoking, diabetes, SBP, HDL-C, and trial*

**Cutoffs: LDL-C, ApoB, non-HDL-C**

**Achieved On-Trial Atherogenic Cholesterol and Lipoprotein Concentration, mg/dL**

- LDL-C
- Apo B
- Non-HDL-C

Apo = apolipoprotein; CV = cerebrovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Imaging Studies Assessing the Impact of Statin Therapy on Coronary Atherosclerosis Regression and Progression

Statins: Imaging Studies
Several studies have applied imaging techniques to assess the effect of statin therapy on coronary atherosclerosis regression and progression.

- **MARS**: In lesions with ≥50% stenosis at baseline, lovastatin 80 mg/day resulted in a significant mean reduction of 4.1% vs 0.9% with placebo ($P=0.005$).\(^1\)
- **REVERSAL**: Intravascular ultrasonography showed that intensive therapy (atorvastatin, 80 mg daily) resulted in a significantly lower progression rate of both atheroma volume and % atheroma volume compared with moderate therapy (pravastatin, 40 mg daily).\(^2\)
- **ASTEROID**: Rosuvastatin (40 mg daily for 24 months) resulted in a mean atheroma volume reduction of 0.98% and a mean change in atheroma volume of 6.1 mm\(^3\) in the most diseased 10-mm\(^3\) segment.\(^3\)
- **HATS**: The combination of simvastatin (titrated to 13±6 mg per day) and niacin decreased proximal stenosis by 0.4% vs an increase of 3.9% with placebo.\(^4\)


<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Primary endpoint parameter</th>
<th>Patients, n</th>
<th>Mean baseline lipid values, mg/dL</th>
<th>Mean achieved lipid values, mg/dL</th>
<th>Mean experimental % change, primary endpoint</th>
<th>Mean control % change, primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>F/U, y</td>
<td>LDL-C</td>
<td>HDL-C</td>
</tr>
<tr>
<td><strong>STATINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARS</td>
<td>Lovastatin, 80 mg (experimental) vs. PBO (control)</td>
<td>Percent diameter stenosis measured by QCA</td>
<td>247</td>
<td>23</td>
<td>2.2</td>
<td>157(^a)</td>
<td>43</td>
</tr>
<tr>
<td>HATS (imaging arm)</td>
<td>Simvastatin + niacin (experimental) vs. PBO (control)</td>
<td>Percent diameter stenosis measured by QCA</td>
<td>139</td>
<td>21</td>
<td>3.2</td>
<td>125</td>
<td>31</td>
</tr>
<tr>
<td>REVERSAL</td>
<td>Atorvastatin, 80 mg (experimental) vs. pravastatin, 40 mg (control)</td>
<td>Atheroma volume measured by coronary IVUS</td>
<td>362</td>
<td>140</td>
<td>1.5</td>
<td>150</td>
<td>42</td>
</tr>
</tbody>
</table>

F = female; F/U = follow-up; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasonography; LDL-C = low-density lipoprotein cholesterol; M = male; MARS = Monitored Atherosclerosis Regression Study; PBO = placebo; QCA = quantitative coronary angiography; REVERSAL = Reversing Atherosclerosis with Aggressive Lipid Lowering; TG = triglycerides.

### Major Statin Imaging Studies (2/4)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Primary endpoint parameter</th>
<th>Patients, n</th>
<th>Mean baseline lipid values, mg/dL</th>
<th>Mean achieved lipid values, mg/dL</th>
<th>Mean experimental % change, primary endpoint</th>
<th>Mean control % change, primary endpoint</th>
<th>Most diseased subsegment Overall</th>
<th>Most diseased subsegment Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATINS</td>
<td></td>
<td></td>
<td></td>
<td>LDL-C</td>
<td>HDL-C</td>
<td>TG</td>
<td>LDL-C</td>
<td>HDL-C</td>
<td>TG</td>
</tr>
<tr>
<td>ASTEROID</td>
<td>Rosuvastatin, 40 mg no control group</td>
<td>Atheroma volume measured by coronary IVUS</td>
<td>245 104</td>
<td>245</td>
<td>104</td>
<td>2</td>
<td>130</td>
<td>43</td>
<td>152</td>
</tr>
<tr>
<td>Schmermund</td>
<td>Atorvastatin, 80 mg (experimental) vs. atorvastatin, 10 mg (control)</td>
<td>Coronary artery calcification measured by EBCT</td>
<td>149 217</td>
<td>149</td>
<td>217</td>
<td>1</td>
<td>155±8</td>
<td>50±8</td>
<td>208±8</td>
</tr>
<tr>
<td>ENHANCE</td>
<td>Simvastatin, 80 mg + ezetimibe, 10 mg (experimental) vs. simvastatin, 80 mg + placebo (control)</td>
<td>Carotid-artery intima-media thickness measured by carotid ultrasound</td>
<td>370 350</td>
<td>370</td>
<td>350</td>
<td>2</td>
<td>319</td>
<td>46.7</td>
<td>157</td>
</tr>
</tbody>
</table>

**Note:**
- ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; EBCT = electron-beam computed tomography; ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; F = female; F/U = follow-up; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasonography; LDL-C = low-density lipoprotein cholesterol; M = male; TG = triglycerides.

### Major Statin Imaging Studies (3/4)

**ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CLAS = Cholesterol Lowering Atherosclerosis Study; F=female; F/U = follow-up; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; M = male; METEOR = Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin; PBO = placebo; TG = triglycerides.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Primary endpoint parameter</th>
<th>Patients, n</th>
<th>Mean baseline lipid values, mg/dL</th>
<th>Mean achieved lipid values, mg/dL</th>
<th>Mean experimental % change, primary endpoint</th>
<th>Most diseased sub-segment</th>
<th>Most diseased sub-segment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METEOR</td>
<td>Rosuvastatin, 40 mg (experimental) vs. PBO (control)</td>
<td>Carotid-artery intima-media thickness measured by carotid ultrasound</td>
<td>588, 396, 2</td>
<td>LDL-C: 155 (rosuvastatin), 154 (PBO); HDL-C: 50 (rosuvastatin), 49 (PBO); TG: 126 (rosuvastatin), 134 (PBO)</td>
<td>LDL-C: 78, HDL-C: 53, TG: 98</td>
<td>-0.0014</td>
<td>NA</td>
<td>0.0131</td>
</tr>
<tr>
<td>Niacin-colestipol and/or combination</td>
<td>Extended-release niacin added to statin therapy</td>
<td>Mean carotid-artery intima-media change measured by ultrasound following up to 24 months of niacin use</td>
<td>120, 10, 1 or 2</td>
<td>LDL-C: 90.5, HDL-C: 39.2, TG: 180.4</td>
<td>LDL-C: 79.2 (1 year niacin use); HDL-C: 78.4 (2 years niacin use); TG: 48.5 (1 year niacin use); 48.6 (2 years niacin use)</td>
<td>120.5 (both 1 and 2 years niacin use)</td>
<td>-0.027 (12 months); -0.041 (24 months)</td>
<td>NA</td>
</tr>
<tr>
<td>ARBITER-3</td>
<td>Niacin + colestipol</td>
<td>Change in Global Coronary Change score based on combined coronary, femoral, and carotid angiograms</td>
<td>162, 0, 2</td>
<td>LDL-C: 171.0, HDL-C: 44.6, TG: 151.0</td>
<td>LDL-C: 97.0, HDL-C: 60.8, TG: 110</td>
<td>0.3</td>
<td>NA</td>
<td>0.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Primary endpoint parameter</th>
<th>Patients, n</th>
<th>M</th>
<th>F</th>
<th>F/U, y</th>
<th>Mean baseline lipid values, mg/dL</th>
<th>Mean achieved lipid values, mg/dL</th>
<th>Mean experimental % change, primary endpoint</th>
<th>Mean control % change, primary endpoint</th>
<th>Most diseased sub-segment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATINS</strong></td>
<td><strong>FATS</strong></td>
<td>Colestipol 30 g + niacin 4 g; Colestipol 30 g + lovastatin 40 mg</td>
<td>Percentage change in disease severity (proximal coronary artery lesion stenosis), measured by arteriography</td>
<td>146</td>
<td>0</td>
<td>2.5</td>
<td>189.9 (niacin + colesterol); 196.1 (lovastatin + colesterol)</td>
<td>193.8 (niacin + colesterol); 200.9 (lovastatin + colesterol)</td>
<td>128.9 (niacin + colesterol); 40.9 (lovastatin + colesterol)</td>
<td>137.2 (niacin + colesterol); 183.2 (lovastatin + colesterol)</td>
<td>-1.1% (niacin + colesterol); -0.3% (lovastatin + colesterol)</td>
</tr>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td><strong>GLAGOV</strong></td>
<td>Evolocumab, 420 mg (experimental) vs. PBO (control)</td>
<td>Nominal change in % atheroma volume, measured by intravascular ultrasound</td>
<td>699</td>
<td>269</td>
<td>6.5</td>
<td>92.6 (evolocumab); 92.4 (PBO)</td>
<td>117 (evolocumab); 124.5 (PBO)</td>
<td>36.6 (evolocumab); 51.0 (PBO)</td>
<td>105.1 (evolocumab)</td>
<td>-0.95</td>
</tr>
</tbody>
</table>

FATS = Familial Atherosclerosis Treatment Study; F = female; F/U = follow-up; GLAGOV = Global Assessment of Plaque Regression with a PCSK9 Antibody; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; M = male; PBO = placebo; TG = triglycerides.

Statin Combination Therapy
• Combination therapy of lipid-lowering agents should be considered when LDL-C/non-HDL-C levels are markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals.

Statins decrease plasma LDL-C in a dose-dependent fashion by 20%-55%.

Numerous clinical trials and imaging studies confirm the CV benefits of statin therapy.

Statin therapy should be monitored at 6-12 weeks and then periodically thereafter.

The benefits of intensive statin therapy for ASCVD risk reduction outweigh the associated increased risk of new-onset T2D.

Combination therapy should be considered when statin monotherapy does not achieve therapeutic targets.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes.