Dyslipidemia and the Use of Statins

Troy L Randle, DO, FACC, FACOI
Objective:

- Identify CV risk.

- Determine what dyslipidemia (dyslipoproteinemia) is...

- Decrease CV risk and optimize lipid levels for your patients at higher risk – using statins.
Characteristics of Plaques Prone to Rupture

- Fibrous cap
- Lumen
- Media
- Lipid core
- "Vulnerable" plaque
  - T-lymphocyte
  - Macrophage foam cell (tissue factor *)
  - "Activated" intimal SMC (HLA-DR+)
  - Normal medial SMC

"Stable" plaque

Atherothrombosis: A Progressive Process

- Normal
- Fatty Streak
- Fibrous Plaque
- Occlusive Atherosclerotic Plaque

- Plaque Rupture/Fissure & Thrombosis
- Unstable Angina
- MI
- Stroke
- Critical Leg Ischemia

Increasing Age

Clinically Silent
Effort Angina
Claudication

Courtesy of P Ganz
Lesion growth
Mechanism of Plaque Disruption in Atherothrombosis
Thrombotic occlusion

Final Result

Normal blush
Framingham Risk Score (FRS) for 10 yr CHD Risk

Qx Calculate


Dysmetabolic Syndrome
Cardio-Metabolic Syndrome (MetS)
Refining Risk Assessment

- Coronary artery calcium, ankle-brachial index, high-sensitivity CRP (hs CRP), and family history were independent predictors of incident CHD/CVD in intermediate-risk individuals.

- Coronary artery calcium provided superior discrimination and risk reclassification compared with other risk markers.

### NCEP III Guidelines: Clinical ID of the Metabolic Syndrome*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal Obesity</strong></td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;40 in</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;35 in</td>
</tr>
<tr>
<td><strong>Triglycerides (TG)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 150mg/dL</td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50mg/dL</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>&gt;130/&gt;85mmHg</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td>&gt;100mg/dL</td>
</tr>
</tbody>
</table>

*Diagnosis is dependent on 3 or more factors

Metabolic Pathways Underlying Pre-Diabetes and Metabolic Syndrome

Grundy, S. M. J Am Coll Cardiol 2012;59:635-643
Interrelationship Between Insulin Resistance and Atherosclerosis

Insulin Resistance

- Hypertension
- Endothelial dysfunction
- Hyperinsulinemia
- Hyperglycemia
- Hypertriglyceridemia
- Small, dense LDL
- Low HDL-C
- Impaired fibrinolysis
- Hypercoagulability

Atherosclerosis
Secondary Prevention Guidelines*

- Recently updated by the AHA & ACC.
- First update since 2001 based on new evidence that intensive therapy can significantly reduce recurrent events and CVA.


www.sjhg.org: → Heartbeats
How to read a lipid panel in 6 quick steps

1. Look at the triglyceride (TG) level. If it is >500 mg/dL, treatment is indicated, and TG reduction takes precedence over all other lipid concentrations. If TG is <500 mg/dL, go to Step 2.

2. Look at the low-density lipoprotein cholesterol (LDL-C) level. If it is >190 mg/dL, drug therapy is indicated regardless of other findings. At lower levels, the need for therapy is based on the patient’s overall risk of cardiovascular disease (CVD). Therapeutic lifestyle changes (TLC) recommendations are always indicated.

3. Look at high-density lipoprotein cholesterol (HDL-C). Increased risk is present if it is <50 mg/dL, the threshold for women and <40 mg/dL in men. Do not assume that high HDL-C always means low CVD risk.
How to read a lipid panel in 6 quick steps

4. Calculate the total cholesterol (TC)/HDL-C ratio (a surrogate of apoB/apoA-I ratio). Increased risk is present if it is >4.0.
5. Calculate the non-HDL-C level (TC minus HDL-C). If it is >130 mg/dL or >100 mg/dL in very-high-risk patients, therapy is warranted. Newer data reveal that this calculation is always equal to, or better than, LDL-C at predicting CVD risk. Non-HDL-C is less valuable if TG is >500 mg/dL.
6. Calculate the TG/HDL-C ratio to estimate the size of LDL. If the ratio is >3.8, the likelihood of small LDL is 80%. (Small LDL usually has very high LDL-P.)
Cholesterol Management
...per NCEP III Guidelines

PRIMARY GOAL:
LDL-C

SECONDARY GOAL:
Non HDL-C

LDL-C

• LDL-C is the number one surrogate for Apo B (the transport vehicle that gets cholesterol into the vessel wall)...per NCEP ATP III guidelines (If Apo B is controlled it is unlikely that atherogenesis can occur).

• In patients with ↑ TG (> 130mg/dL) or low HDL-C (< 40mg/dL) - **TG/HDL axis disorders**, LDL-C is simply not as good a surrogate for Apo B as non-HDL-C.
Non-HDL-C

- Provides a measure of all the cholesterol in atherogenic particles including LDL-C, Apo B, LP(a) and TG-rich particles in VLDL, VLDL remnants and intermediately dense lipoproteins.

- Introduced as the secondary target of therapy in patients with high TG (> 200mg/dL) per NCEP ATP III guidelines.

NCEP III Non HDL-C Goal

- Non-HDL-C = TC - HDL-C
- Goal Non-HDL-C is 30mg > LDL-C goal

Must be remembered that LDL-C and non HDL-C goals are NCEP surrogates for the number 1 lipid risk factor which is Apo B lipoprotein. Neither non-HDL-C or especially LDL-C approaches Apo B or LDL-P (via NMR) measurements as the most accurate predictors of risk.
Non HDL-C

- When TG are elevated, non HDL-C is a much better surrogate of the all important Apo B level than is LDL-C.

- LDL-C is a calculation (TC-[HDL-C + VLDL-C] and VLDL-C is estimated by labs using a formula TG/5).
Non HDL-C

- Among statin-treated patients, on-treatment levels of LDL-C, non-HDL-C, and apoB were each associated with risk of future major cardiovascular events.

- The strength of this association was greater for non-HDL-C than for LDL-C and apoB.

*JAMA* June 21 2012;307(12):1302-1309
Abnormalities of the TG/HDL-C Axis

- Increasing prevalence (T2DM/MetS).
- Treatment errors are frequently made by looking only at the LDL-C level (particularly in diabetics) which are frequently normal or only slightly elevated and subsequently not treated.
- Frequently associated with elevated Apo B and increased LDL-C particle (LDL-P) concentrations if the LDL particles are small.
Bottom Line

- NCEP states: Normalize LDL-C and non-HDL-C to appropriate goals based on risk...the higher the risk the more aggressive the therapy.

- If you don’t want to risk your patient’s lives on lipid surrogates, order an apoB or the NMR lipid profile for the LDL-P (particle number).

- Perfect world:

  Framingham offspring study goals.
Cholesterol: How low?

- Lower seems to be better but how far is yet to be determined. Studies continue to show improved outcomes the lower we go.
## Statin Therapy in a Large Cross Section of Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Efficacy Parameters</th>
<th>Outcomes (All Significant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Protection Study (HPS; n=20,536)</td>
<td>±CHD + risk factors 40-80 yrs (25% women)</td>
<td>Simvastatin 40 mg ± antioxidants vs. placebo ± antioxidants</td>
<td>Morbidity + mortality</td>
<td>All-cause mortality ↓13%, major vascular events ↓24%, coronary death rate ↓18%, nonfatal MI + coronary death ↓27%, nonfatal or fatal stroke ↓25%, CV revascularization ↓24%</td>
</tr>
<tr>
<td>Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT*; n=4,162)</td>
<td>ACS avg 58 yrs (22% women)</td>
<td>Atorvastatin 80 mg vs. pravastatin 40 mg</td>
<td>Death + major CV events</td>
<td>All-cause mortality ↓28%, coronary death rate ↓30%, nonfatal MI + coronary death ↓18%, nonfatal or fatal stroke ↓9%, CV revascularization ↓14%</td>
</tr>
<tr>
<td>Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL*; n=654)</td>
<td>CHD, dyslipidemia, 30-75 yrs (28% women)</td>
<td>Atorvastatin 80 mg vs. pravastatin 40 mg</td>
<td>Progression of atherosclerosis</td>
<td>Intensive Rx led to less disease progression, total atheroma volume, change in % atheroma volume, and change in atheroma volume in the most severely diseased 10 mm vessel subsegment</td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA; n=10,305)</td>
<td>HTN + ≥3 CHD risk factors 40-79 yrs (19% women)</td>
<td>Atorvastatin 10 mg + anti-HTN vs. placebo + anti-HTN</td>
<td>CHD death + nonfatal MI</td>
<td>Combined endpoint ↓36%, total CV events ↓21%, total coronary events ↓29%, nonfatal or fatal stroke ↓27%, CV revascularization ↓14%</td>
</tr>
<tr>
<td>Treating to New Targets (TNT; n=10,003)</td>
<td>CHD, 30-75 yrs (19% women)</td>
<td>Atorvastatin 10 mg vs. 80 mg (LDL-C~100 vs. ~75 mg/d)</td>
<td>Time to major CV events</td>
<td>All major CV events ↓22%, nonfatal MI ↓22%, all stroke ↓25%, major coronary event ↓20%, any CV event ↓19%, hospitalization for HF ↓26%</td>
</tr>
<tr>
<td>Incremental Decreases in Endpoints through Aggressive Lipid Lowering (IDEAL*; n=8,888)</td>
<td>CHD, LDL-C varied ≤80 yrs</td>
<td>Atorvastatin 80 mg vs. simvastatin 20-40 mg</td>
<td>Coronary + vascular death + CV events</td>
<td>Any CHD event ↓16%, major CV event ↓13%, any CV event ↓16%, nonfatal MI ↓17%, CV revascularization ↓23% (Primary outcome of any major coronary event was ↓11% but was not significant.)</td>
</tr>
</tbody>
</table>

*Involves intensive lipid-lowering. ACS=acute coronary syndrome; CHD=coronary heart disease; CV=cardiovascular; HF=heart failure; HTN=hypertension; MI=myocardial infarction
PROVE IT / TIMI 22 - Lipid Lowering Results

Trial Design: PROVE IT was a multi-center, randomized, blinded 2 x 2 factorial trial of standard lipid lowering with pravastatin (40 mg/day; n=2,063) or aggressive lipid lowering using atorvastatin (80 mg/day; n=2,099) in patients hospitalized for an acute coronary syndrome (ACS). Primary endpoint was composite of death, MI, unstable angina requiring rehospitalization, revascularization, and stroke at mean follow-up of 24 months.

Results
- LDL ↓ from 106 mg/dl at baseline in each group to 95 mg/dl in standard-dose pravastatin group and 62 mg/dl in high-dose atorvastatin group (p<0.001 for difference in change between treatment groups)
- Median CRP ↓ from 12.3 mg/l at baseline to 2.1 mg/l for pravastatin and 1.3 mg/l for atorvastatin (p<0.001)
- Primary composite endpoint ↓ in aggressive lipid lowering group (Figure)
- Mortality trended ↓ atorvastatin arm (Figure)
- ALT ≥3x ULN ↑ in atorvastatin arm (3.3% vs 1.1%, p<0.001)

Conclusions
- Among patients hospitalized for an ACS, use of an aggressive lipid lowering strategy was associated with a reduction in the primary composite endpoint compared with standard lipid lowering strategy
- First large-scale trial to demonstrate an added clinical benefit of a more intensive lipid lowering therapy in post-ACS patients beyond current guidelines of LDL<100 mg/dL

Early and Late Benefit of High-Dose Atorvastatin in Patients with Acute Coronary Syndromes

Hazard Ratio = 0.76 (CI 0.66, 0.88)  
P = 0.0002

Number of Patients at Risk
2063  1748  1635  1555  962  Pravastatin
2099  1811  1691  1633  1045  Atorvastatin
## REVERSAL:
Main Primary and Secondary Endpoint Results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Atorvastatin 80 mg (n=253)</th>
<th>Pravastatin 40 mg (n=249)</th>
<th>P for difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % change in atheroma volume</td>
<td>-0.4 (no change)</td>
<td>+2.7 (progression)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median change in total atheroma volume (mm³)</td>
<td>-0.9 (no change)</td>
<td>+4.4 (progression)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median change in total percent atheroma volume (mm³)</td>
<td>+0.2 (no change)</td>
<td>+1.6 (progression)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
IDEAL: Incremental Decrease in Clinical Endpoints through Aggressive Lipid Lowering

Major coronary event
HR 0.89
p=0.07

Nonfatal MI
p=0.02

Any CHD event
p<0.001

- Atorvastatin
- Simvastatin
TNT (Treating to New Targets)

- Designed to test the “lower is better” concept.
- Intensive lipid-lowering therapy with atorvastatin (80mg vs 10mg) in patients with stable CHD resulted in a 25% CV event risk reduction.
- No difference between the two treatment groups in overall mortality.

TNT: Results

Major CV event
HR 0.78
p<0.001

MI
HR 0.78
p=0.004

Fatal or nonfatal stroke
HR 0.75
p=0.02

% 15
10
5
0
8.7 10.9

% 8
4
0
4.9 6.2

% 5
4
2
3.1
2.3

Atorvastatin 80 mg
Atorvastatin 10 mg
TNT and IDEAL: Effect of Aggressive Statin Therapy on Overall and Noncardiovascular Mortality

**TNT**
- Overall mortality: 5.7% (High Dose), 5.6% (Standard Dose), p=0.92
- Noncardiovascular mortality: 3.2% (High Dose), 2.5% (Standard Dose), p=0.06

**IDEAL**
- Overall mortality: 8.2% (High Dose), 8.4% (Standard Dose), p=0.81
- Noncardiovascular mortality: 3.2% (High Dose), 3.5% (Standard Dose), p=0.47

Legend:
- **High Dose**
- **Standard Dose**
Effect of Atorvastatin on Left Ventricular Systolic Function in Nonischemic Heart Failure

![Graph showing the effect of Atorvastatin on ejection fraction over time. The x-axis represents time in months (0, 6, 12), and the y-axis represents ejection fraction. The graph compares placebo (red triangle) and Atorvastatin (green square) groups. At baseline (0 months), the ejection fraction is similar for both groups (0.33). At 6 months, the ejection fraction for the Atorvastatin group increases to 0.37 (n = 46), while the placebo group decreases to 0.31 (n = 46). At 12 months, the ejection fraction for the Atorvastatin group remains at 0.37 (n = 46), and the placebo group decreases further to 0.27 (n = 43). Significant differences are indicated by * (p < 0.05) and † (p < 0.01).]
Effect of Statin Therapy before PCI on Contrast-Induced Nephropathy

Contrast-induced nephropathy

- Preprocedure statins: 4.37%
- No preprocedure statins: 5.93%
  \( p < 0.0001 \)

Nephropathy requiring dialysis

- Preprocedure statins: 0.32%
- No preprocedure statins: 0.49%
  \( p = 0.03 \)
Low-density lipoprotein cholesterol (LDL-C) levels of trials comparing high-dose to standard-dose statin therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>Event Rates No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR, 0.84 (0.77-0.91)</td>
<td></td>
</tr>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>-17% 147/2099 (7.0)</td>
<td>172/2063 (8.3)</td>
</tr>
<tr>
<td>A-to-Z</td>
<td>-15% 205/2265 (9.1)</td>
<td>235/2232 (10.5)</td>
</tr>
<tr>
<td>TNT</td>
<td>-21% 334/4995 (6.7)</td>
<td>418/5006 (8.3)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>-12% 411/4439 (9.3)</td>
<td>463/4449 (10.4)</td>
</tr>
<tr>
<td>Total</td>
<td>-16% 1097/13798 (8.0)</td>
<td>1288/13750 (9.4)</td>
</tr>
</tbody>
</table>

High-dose better   High-dose worse
**SPARCL**

**Trial Design:** SPARCL was a randomized, double-blind trial of atorvastatin (80 mg daily, n=2365) or placebo (n=2366) in patients with prior stroke or TIA. Primary endpoint was fatal or nonfatal stroke at a median follow-up of 4.9 years.

**Results**
- At 1 month, LDL levels ↓ from 133 mg/dl at baseline to 61.3 mg/dl in atorvastatin group (p<0.0001) but no change in placebo group (133.5 mg/dl)
- Primary endpoint of stroke ↓ in atorvastatin group vs placebo (Figure)
- Reductions in 2° endpoints of TIA (6.5% vs 8.8%, p=0.004), major coronary event (Figure), major CV event (14.1% vs 17.2%, p=0.005) also ↓ for atorvastatin
- No difference in mortality (9.1% for atorvastatin vs 8.9% for placebo, p=0.77)
- Persistent ALT/AST elevations ↑ in atorvastatin group (2.2% vs 0.5%, p<0.001)

**Conclusions**
- Among patients with prior stroke or TIA, treatment with atorvastatin was associated with reduction in recurrent stroke compared with placebo, as well as reductions in major coronary events
- Prior studies such as 4S, CARE, and CARDs showed ↓ coronary events with atorvastatin in patients with coronary heart disease
- Present trial extends findings to setting of cerebrovascular disease

www.cardiosource.com

*N Engl J Med 2006;355:549-59*
ASTEROID:

- A study to evaluate the effect of rosuvastatin (40mg) on intravascular ultrasound-derived atheroma burden after 2 years of tx.
- Resulted in mean LDL-C ↓ from 130mg/dL to 60mg/dL and a mean ↑ of HDL-C from 43mg/dL to 49mg/dL (15% ↑).
- Resulted in significant plaque regression (Reversal).

JAMA 2006; 295: 1556-65.
Modifications to NCEP ATP III

- TLC was re-emphasized.

- Use of the Framingham CAD risk calculator was recommended.

*Circulation* July 13 2004; 110: 227-239
### Modifications to NCEP ATP III

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk:</strong> CHD, PAD, Carotid vasc. Dx, AAA or CHD risk equivalents (DM or 10-yr CHD risk &gt; 20%)</td>
<td>&lt; 100mg/dL. Optional goal &lt; 70mg/dL (CAD)</td>
</tr>
<tr>
<td><strong>Very High Risk:</strong> Above plus having multiple risk factors including DM, tobacco dependence, MetS or severe or poorly controlled risk factors (eg HBP or recent MI, ACS or recurrent CAD symptoms on Tx and CKD.</td>
<td>Optional goal &lt; 70mg/dL. Strongly Rec</td>
</tr>
<tr>
<td><strong>Moderate Risk:</strong> Two or more risk factors (10-yr risk &lt; 10%)</td>
<td>&lt; 130mg/dL.</td>
</tr>
<tr>
<td><strong>High Moderate Risk:</strong> Two or more risk factors (10-yr risk &gt; 10%)</td>
<td>Optional goal &lt; 100mg/dL.</td>
</tr>
</tbody>
</table>

Safety Analysis of Intensive Tx

- Among subjects treated with intensive statin therapy following ACS, there were lower rates of clinical events in those patients who achieved LDL-C < 60 mg/dL (or < 40 mg/dL) compared with those in the > 80-100 mg/dL range.

- Lipid levels well below the current guidelines were not associated with worse safety outcomes.

- Therefore, there is no need to reduce statin dosage if the LDL-C levels are below target goal.


Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients.

*Am J Cardiol.* 2006;97:61-67
“Very High Risk” Patients

The updated NCEP III definition of “high risk” requires established CVD plus:

- Multiple risk factors (especially diabetes).
- Severe and poorly controlled risk factors (especially continued cigarette smoking).
- Multiple risk factors for MetS (especially high TG >200; low HDL-C [< 40mg/dL]—i.e. non-HDL-C > 130mg/dL.).
- Patients with ACS or recurrent anginal symptoms.
- CKD

(Circulation September 5 2006; 114: 1083-1087).

GOAL LDL-C: < 70mg/dL

GOAL Non-HDL-C: < 100mg/dL
The Forgotten Cardiac Risk Factor: Noncompliance With Lipid-Lowering Therapy


- Will be even more difficult reaching LDL-C goals post update.

# MESA: Control of Dyslipidemia

<table>
<thead>
<tr>
<th>LDL-C &lt;ATP III drug treatment goal</th>
<th>Non-Hispanic White</th>
<th>Chinese</th>
<th>Black</th>
<th>Hispanic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>All MESA participants (%)</td>
<td>62.9</td>
<td>75.6</td>
<td>66.3</td>
<td>79.5</td>
<td>62.1</td>
</tr>
<tr>
<td>Participants with dyslipidemia (%)</td>
<td>39.7</td>
<td>57.5</td>
<td>35.9</td>
<td>61.2</td>
<td>32.7</td>
</tr>
<tr>
<td>On drug therapy (%)</td>
<td>76.4</td>
<td>86.2</td>
<td>77.1</td>
<td>82.5</td>
<td>68.5</td>
</tr>
</tbody>
</table>
## Available Lipid-Lowering Drugs

<table>
<thead>
<tr>
<th>Bile-Acid Sequestrants</th>
<th>Cholesterol Absorption Inhibitor</th>
<th>Fibric-Acid Derivatives</th>
<th>HMG-CoA Reductase Inhibitors</th>
<th>Niacin, Nicotinic Acid</th>
<th>Statin + Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Ezetimibe</td>
<td>Gemfibrozil</td>
<td>Atorvastatin</td>
<td>Immediate release</td>
<td>Lovastatin + niacin ER (Advicor)</td>
</tr>
<tr>
<td>Colestipol</td>
<td></td>
<td>Fenofibrate</td>
<td>Lovastatin</td>
<td>Sustained release</td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td></td>
<td></td>
<td>Pravastatin</td>
<td>Extended release</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluvastatin</td>
<td>(Niaspan)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rosuvastatin</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tbody>
</table>
Effect of Therapeutic Intervention on Lowering LDL

- **Statins**
  - Decrease LDL 18% - 55%

- **Bile Acid Sequestrants**
  - Decrease LDL 15% - 30%

- **Fibrates**
  - Decrease LDL 5% - 20%
<table>
<thead>
<tr>
<th>Available Statins</th>
<th>% LDL-C reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitavastatin (Livalo)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>5 mg</td>
</tr>
<tr>
<td>*Atorvastatin (Lipitor)</td>
<td>10mg</td>
</tr>
<tr>
<td>*Simvastatin (Zocor)</td>
<td>20mg</td>
</tr>
<tr>
<td>*Lovastatin (Mevocor)</td>
<td>40mg</td>
</tr>
<tr>
<td>*Pravastatin (Pravacol)</td>
<td>40mg</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>80mg</td>
</tr>
</tbody>
</table>

*Available in generic form*
## The Statin Class: Approximate LDL-C Lowering Efficacy at Different Doses

<table>
<thead>
<tr>
<th>Rosuva</th>
<th>Atorva</th>
<th>Simva</th>
<th>Pitava</th>
<th>Lova</th>
<th>Prava</th>
<th>Fluva</th>
<th>↓ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>NA</td>
<td>10</td>
<td>1</td>
<td>20</td>
<td>20</td>
<td>40</td>
<td>30%</td>
</tr>
<tr>
<td>NA</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>40 or 80</td>
<td>40</td>
<td>80</td>
<td>38%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>40</td>
<td>4</td>
<td>80</td>
<td>80</td>
<td>NA</td>
<td>41%</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>80*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>47%</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>55%</td>
</tr>
<tr>
<td>40</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>63%</td>
</tr>
</tbody>
</table>

*Restricted Dosing: Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80 mg dose of simvastatin, patients unable to achieve their LDL-C goal using the 40 mg dose of simvastatin should **not** be titrated to the 80 mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.
# The Statin Armamentarium: Individual Metabolism Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pitava</th>
<th>Rosuva</th>
<th>Fluva</th>
<th>Atorva</th>
<th>Simva</th>
<th>Lova</th>
<th>Prava</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption, %</td>
<td>80</td>
<td>50</td>
<td>98</td>
<td>30</td>
<td>60-85</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Bioavail, %</td>
<td>60</td>
<td>20</td>
<td>30</td>
<td>12</td>
<td>&lt; 5</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>T ½, h</td>
<td>10-13</td>
<td>20</td>
<td>1-3</td>
<td>7-20</td>
<td>2-5</td>
<td>2-5</td>
<td>1-3</td>
</tr>
<tr>
<td>CYP metabolism</td>
<td>2C9/2C8</td>
<td>2C9/2C19</td>
<td>2C9</td>
<td>3A4</td>
<td>3A4</td>
<td>3A4</td>
<td>None</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MDR1</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+/- = minimal metabolism by pathway

MDR1 = multidrug resistance protein 1; OATP1B1 = organic anion transporter polypeptide 1B1

## Effect of Statin Therapy on CHD: Clinical Events Trials

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Event* rate (%)</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (mg/dl)</td>
<td>↓ (%)</td>
<td>On Rx (mg/dl)</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>188</td>
<td>35</td>
<td>122</td>
<td>19.4</td>
<td>28.0</td>
</tr>
<tr>
<td>LIPID</td>
<td>150</td>
<td>25†</td>
<td>112</td>
<td>12.3</td>
<td>15.9</td>
</tr>
<tr>
<td>CARE</td>
<td>139</td>
<td>32</td>
<td>98</td>
<td>10.2</td>
<td>13.2</td>
</tr>
<tr>
<td>HPS</td>
<td>131</td>
<td>38</td>
<td>89</td>
<td>8.7</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>192</td>
<td>26</td>
<td>159</td>
<td>5.3</td>
<td>7.5</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>150</td>
<td>25</td>
<td>115</td>
<td>3.5</td>
<td>5.5</td>
</tr>
<tr>
<td>ASCOT</td>
<td>133</td>
<td>35†</td>
<td>87</td>
<td>1.9</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*Nonfatal MI or CHD death; also resuscitated cardiac arrest in 4S, angina and sudden cardiac death in AFCAPS
† vs. placebo

• Restores or improves endothelial function, especially through increased bioavailability of nitric oxide*

• Increases expression of tissue-type plasminogen activator

• Inhibits expression of endothelin-1, a potent vasoconstrictor and mitogen

• Promotes re-endothelialization

• Promotes plaque-stabilization through a combined reduction in lipids, macrophages, and proteolytic enzymes, such as matrix metalloproteinases (MMPs)

• Reduces oxidative stress (through cholesterol-independent anti-oxidative effects)

• Decreases the levels of inflammation markers, such as C-reactive protein, interleukin 6, and tumor necrosis factor alpha

• Reduces inflammation at the site of atherosclerotic plaque

• Inhibits tissue factor expression, leading to impaired activation of the blood coagulation cascade (as evidenced by a decrease in thrombin generation thereby potentially reducing the thrombotic potential of the vascular wall)

• Inhibits platelet aggregation

• Anticoagulant effects

* While cholesterol lowering alone may improve endothelial function, restoration of endothelial function has been shown to occur following initiation of statin therapy but before any significant reduction in serum cholesterol levels. This suggests statins have additional effects on endothelial function beyond that of cholesterol reduction.
Effect of Statins on CV Event Rate According to Reduction in LDL-C
Lancet 2010:376:1670-81

file:///C:/Documents%20and%20Settings/mario%20maiese/Desktop/Statins%20Is%20It%20Really%20Time%20to%20Reassess%20Benefits%20and%20Risks%E2%80%94%20NEJM_files/nejmp1203020_f1.jpeg
### A: More Statin vs. Less Statin (5 trials: 0.51 mmol/liter LDL difference)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>More Statin</th>
<th>Less Statin</th>
<th>Relative Risk per 1 mmol/liter (39 mg/dl) Reduction in LDL Cholesterol (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major coronary event</td>
<td>1725 (1.9)</td>
<td>1973 (2.2)</td>
<td>0.74 (0.65–0.85)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2250 (2.6)</td>
<td>2741 (3.2)</td>
<td>0.66 (0.60–0.73)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>572 (0.6)</td>
<td>663 (0.7)</td>
<td>0.74 (0.59–0.92)</td>
</tr>
<tr>
<td>5 Trials: any major vascular event</td>
<td>3837 (4.5)</td>
<td>4416 (5.3)</td>
<td>0.72 (0.66–0.78)</td>
</tr>
</tbody>
</table>

### B: Statin vs. Control (21 trials: 1.07 mmol/liter LDL difference)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Statin</th>
<th>Control</th>
<th>Relative Risk per 1 mmol/liter (39 mg/dl) Reduction in LDL Cholesterol (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major coronary event</td>
<td>3380 (1.3)</td>
<td>4539 (1.7)</td>
<td>0.76 (0.73–0.79)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>3103 (1.2)</td>
<td>4066 (1.6)</td>
<td>0.76 (0.73–0.80)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1730 (0.7)</td>
<td>2017 (0.8)</td>
<td>0.83 (0.80–0.90)</td>
</tr>
<tr>
<td>21 Trials: any major vascular event</td>
<td>7136 (2.8)</td>
<td>8934 (3.6)</td>
<td>0.79 (0.77–0.81)</td>
</tr>
</tbody>
</table>

### C: More Statin vs. Less Statin and Statin vs. Control (26 trials)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Statin or More Statin</th>
<th>Control or Less Statin</th>
<th>Relative Risk per 1 mmol/liter (39 mg/dl) Reduction in LDL Cholesterol (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with type 1 diabetes</td>
<td>145 (4.5)</td>
<td>192 (6.0)</td>
<td>0.77 (0.58–1.01)</td>
</tr>
<tr>
<td>Patients with type 2 diabetes</td>
<td>2494 (4.2)</td>
<td>2920 (5.1)</td>
<td>0.80 (0.74–0.86)</td>
</tr>
<tr>
<td>Patients without diabetes</td>
<td>8272 (3.2)</td>
<td>10,163 (4.0)</td>
<td>0.78 (0.75–0.81)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>10,973 (3.2)</td>
<td>13,350 (4.0)</td>
<td>0.78 (0.76–0.80)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause-specific mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cardiac</td>
<td>3333 (0.9)</td>
<td>3384 (1.1)</td>
<td>0.84 (0.80–0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>483 (0.1)</td>
<td>501 (0.1)</td>
<td>0.96 (0.84–1.09)</td>
</tr>
<tr>
<td>Any vascular</td>
<td>4220 (1.2)</td>
<td>4794 (1.3)</td>
<td>0.86 (0.82–0.90)</td>
</tr>
<tr>
<td>Any nonvascular</td>
<td>2943 (0.8)</td>
<td>2994 (0.8)</td>
<td>0.97 (0.92–1.03)</td>
</tr>
<tr>
<td>All-cause mortality (any death)</td>
<td>7642 (2.1)</td>
<td>8327 (2.3)</td>
<td>0.90 (0.87–0.93)</td>
</tr>
</tbody>
</table>
Residual Risk:

Even with optimal statin treatment: 25-45% reduction in CV events with statins.

“There is 50% to 60% risk we’re not addressing”.
Residual Risk:

- Suggests responsibility of other risk factors, such as older age, male sex, hypertension, diabetes, cigarette smoking, and sedentary lifestyle.

- High-risk patients identified through measurement of lipid values and identification of other risk factors; other lipid-based risk factors include triglycerides, intermediate-density lipoproteins, and very low-density lipoproteins. (apoB lipoprotein or LDL-P { particle number})

- More sophisticated methods of identifying and addressing risk always being sought; maximal reduction of LDL known to be beneficial; new mechanisms of intervention still being identified, including ways of raising HDL and genetic research to help identify high-risk individuals.
Side Effects:
“The number one ‘side effect’ of statins is a >25% reduction in heart attacks and strokes.”
Side Effects:

- Statins are well tolerated and are believed to have minimal adverse effects.

- Most common adverse effects are myopathies, elevations of liver enzymes, and very rarely, rhabdomyolysis.

- Discontinuation or reduction in the dose of statin treatment usually leads to resolution of these side effects.
Side Effects:

- In February 2012, the U.S. Food and Drug Administration (FDA) concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective for detecting or preventing serious liver injury. Therefore, labels were revised to remove the need for routine periodic monitoring of liver enzymes.

- More recently, the debate has centered on whether use of statins causes cognitive decline, cancer, and/or diabetes mellitus.
Statin Benefits Offset Diabetes Risk


- The cardiovascular benefits of statin treatment for primary prevention outweighed the risk of developing diabetes, even among those at risk for the condition.

- Statin therapy prevented 134 cardiovascular events or deaths for every 54 cases of new-onset diabetes among participants with at least one risk factor for diabetes.

- "A major take-home message for the clinician involved in either primary or secondary prevention of cardiovascular disease is that all individuals on a statin who have major risk factors for diabetes, particularly impaired fasting glucose, need to be informed about the risk, monitored regularly for hyperglycemia, and advised to lose weight and take regular physical exercise to mitigate the emergence of diabetes."
• Physicians should stop prescribing a new 80-mg dose of simvastatin (Zocor).

• Do not exceed 10 mg of simvastatin daily with: amiodarone, verapamil or diltiazem.

• Do not exceed 20 mg of simvastatin daily with: amlodipine or ranolazine.

• Avoid large quantities of grapefruit juice.
Clues for higher risk

- ↑ LDL-C (per NCEP III).
- ↑ non HDL-C (TC - HDL-C) 30mg/dL higher than LDL-C goal - almost always indicates ↑ LDL-P.
- ↑ TG (> 150mg/dL)…probably > 100.
- ↓ HDL-C (< 40mg/dL) associated with ↑ apoB and small LDL-C.
- ↑ VLDL-C (TG/5) > 30mg/dL.
- TC/HDL-C > 4.
- TG/ HDL-C >3.8 (women) and > 4 (men) indicates a high chance of ↑ small dense LDL-C particles (↑ LDL-P per NMR LipoProfile)
Unlimited Resources...

If you don’t want to bet patients’ lives on NCEP lipid surrogates get an NMR LipoProfile from LipoScience which measures LDL-P (low density lipoprotein concentration and size which gives you an accurate reflection of apoB).

Not proven to decrease risk.

NMR LipoProfile can be obtained thru LabCorp

(LabCorp form request “884247” NMR LipoProfile)
No proven benefit of other lipid-lowering treatment after statins.
Be aggressive with combination therapies...after statin at maximum

In insulin resistant patients with abnormalities of the TG/HDL-C axis, a statin/ezetimibe/fenofibrate or Lovaza combination would solve the overwhelming majority of lipoprotein abnormalities seen in most patients (getting to LDL-C and non-HDL-C goals (apoB surrogate markers)...while also ↑ HDL-C &/or ↓ TG. Niaspan can also improve the numbers.
Generics

...can save millions
Cost Saver Message

• Millions saved by splitting statin tablets.

• No decrease in benefit.

Am J Cardiol 2005; 95: 1481-1483
Fenofibrates

- In combination with statins doesn’t interfere with catabolism & is less likely to increase risk of myopathy.
- Decreases TG and elevates HDL-C.
- Decreases small, dense LDL-C in favor of larger more buoyant LDL particles.
- Pleiotropic effects.
- Decreases cardio CRP.
Advantages of Combination Lipid Drug Treatment

- Additive effects for reducing LDL-C
  - Statin + BAS*
  - Statin + cholesterol absorption inhibitor (ezetimibe)
  - Statin + BAS or ezetimibe + niacin

- Additional benefit for reducing very high triglycerides
  - Fibrate + niacin
  - Fibrate or niacin + fish oil
  - Fibrate + niacin + fish oil

- Complementary benefit on mixed dyslipidemias (low HDL-C; high TG; small, dense LDL-C)
  - Statin + niacin or fibrate
  - BAS or ezetimibe + fibrate or niacin

- Reduction of elevated Lp(a)

- Use of lower doses of ≥2 drugs rather than maximum doses of 1, which can minimize adverse effects

*BAS=bile-acid sequestrants
Combination Therapy: Ezetimibe Plus Atorvastatin vs Atorvastatin Titration

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline at wk 12 (%)</td>
<td>-54.0</td>
<td>3.7</td>
<td>-31.0</td>
</tr>
<tr>
<td></td>
<td>-53.0</td>
<td>3.0</td>
<td>-31.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

- Placebo
- Atorvastatin 80 mg
- Ezetimibe 10 mg + atorvastatin 10 mg

Summary: Take Home Points

- Assess and Identify risk.
- Treat high risk aggressively...to specific goals.
- A statin should be part of the lipid-lowering treatment program. Intensive lipid lowering with high-dose statin therapy provides a significant benefit over standard-dose therapy for preventing predominantly non-fatal cardiovascular events.
- Always consider safety and cost as part of selection.
TLC (Therapeutic Lifestyle Changes)

...Cornerstone of therapy

- Diet (South Beach or Med)

- Exercise (30-60 min 5x/ wk minimum preferably daily).
The Problem:

“Will power only lasts 3 weeks and in addition it is alcohol soluble.”

....Don’t have a pill for diet & exercise.
Sample Case

- Male, age 62, overweight,
- BP 140/90

Original Lipid Panel:
- TC = 210, HDL-C = 25,
- LDL-C = 124, TG = 307
- Non HDL-C = 210 - 25 = 185
- FBS 110

Post Tx Lipid Panel on TriCor 145 mg and Lipitor 20mg
- TC = 148, HDL-C = 23, LDL-C = 67, TG = 291, Non HDL-C = 125

Access Risk:
CHD Risk calculation

Goals of therapy:
(Based on NCEP ATP III updated)
- Primary goal: LDL-C
- Secondary goal (TG > 200): Non-HDL-C

Treatment:
- TLC
- Meds