Pharmacy Drug Class Review

December 19, 2008

Disclaimer: Specific agents may have variations

PHARMACY DRUG CLASS REVIEW

STATIN REVIEW PART II – HDL FOCUS

INCLUDING NIACIN AND OTHER DRUGS WITH A SIGNIFICANT IMPACT ON HDL

What do ATP III guidelines say in regards to HDL specifically?

True or False? All statins minimally elevate HDL to the same degree?

What are PRIMARY causes of low HDL?...What are SECONDARY causes of low HDL?

True or False? Flushing from niacin CAN be prevented, but NOT acutely relieved?

True or False? Tolerance to flushing from niacin develops over time?

True or False? Niacin should NOT be used in diabetics due to plasma glucose increases?

At what dose is Niaspan® ER most effective? Any significant benefit in dosing beyond 500 mg/day?

What are some cost-effectiveness considerations in regards to HDL elevation?

How significant is the benefit of exercise in regards to HDL elevation?

True or False? The goal HDL for both men and women is >40 mg/dL?

What are the proposed benefits (direct or indirect) of HDL?

What is meant by ‘functional HDL’?...What about Pro-Inflammatory HDL?

What is the current status of the CETP inhibitors drug class? (i.e., Torcetrapib from Pfizer)

Do HDL and C-Reactive Protein (CRP) have any significant relationship?

Does residual cardiovascular risk exist if HDL is not at goal even if LDL-C is below 70 mg/dL?

Highlights: The Quick Read Information

- Statins have variable and limited efficacy in elevating HDL, ranging from increases of 2 – 16%
  - The most effective HDL elevating statins appear to be Crestor® (rosuvastatin) and Zocor (simvastatin)
- The most potent HDL elevating monotherapy is niacin (Niaspan® ER), 2000mg providing up to 35% HDL increase in naïve patients.
  - Dose should be titrated as 500 mg/day only provides an expected increase of about 9 – 15%
  - In addition, it may take 12 – 18 months before maximal lipid benefit from niacin is observed
- The least potent HDL elevating monotherapy (among typical cholesterol medications) are Bile Acid Resins and Zetia® (ezetimibe).
- Per ATP III, high HDL (>60 mg/dL) removes 1 risk factor, it does NOT offset high LDL.
- ATP III does NOT account for differences in HDL levels between men and women.
- Framingham and other studies suggest that for every decrease of 1 mg/dL in HDL; increase of 2 – 3% in risk of CHD.
- Reduced level of HDL (<40 mg/dL in men, <50 mg/dL in women) found to be an independent predictive risk factor for CAD, even in statin-treated patients, irrespective of their LDL-C levels.
- In the Coronary Drug Project, a significant (p=0.0012) 11% reduction in total mortality in patients treated with nicotinic acid compared with placebo. This present after 15 years of follow-up (only first 6 years were active follow up) all BEFORE statins available (1966 – 1975).
- Extensive data from clinical trials and post-marketing safety surveillance indicated a very low incidence (<1%) of elevated LFTs with prolonged release niacin (Niaspan®ER), when given either alone or in combination with statins and NO increase in incidence of myopathy (when used in combination w/statin) compared with statin alone.
- Tolerance to flushing due to niacin DOES develop over time. In addition it CAN be acutely relieved with analgesic doses of NSAIDs.
- Do NOT utilize product called ‘flushless’ niacin (inositol hexanicotinate), as it does NOT contain any free niacin.
- In the STRRIDE trial, HDL increased 4 mg/dL w/intense AND frequent exercise vs. +0.7 mg/dL in low intensity AND low frequency.
- Per AACE, “niacin therapy is safe and effective in this patient population [diabetes mellitus]”.
- Beta-blockers have been shown to significantly decrease HDL levels by about 4 – 5 mg/dL.
Mechanism of Action: Statins inhibit endogenous cholesterol synthesis through selective, competitive inhibition of HMG-CoAReductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, a precursor of cholesterol. Statins also lead to an up-regulation of LDL receptors on hepatic cells, which causes increased hepatic uptake of cholesterol from the circulation, ultimately reducing levels of circulating cholesterol.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Available?</th>
<th>Brand Name®</th>
<th>Available Strengths (mg)</th>
<th>Half – Life (hrs)</th>
<th>IHA Tier</th>
<th>Tablet Splitting?</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>N</td>
<td>Lipitor®</td>
<td>10, 20, 40, 80</td>
<td>14</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>N</td>
<td>Lescol®</td>
<td>20, 40</td>
<td>&lt; 3</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>N</td>
</tr>
<tr>
<td>fluvastatin XL</td>
<td>N</td>
<td>Lescol X®</td>
<td>80</td>
<td>~ 9</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>N (can’t)</td>
</tr>
<tr>
<td>lovastatin</td>
<td>Yes</td>
<td>Mevacor®</td>
<td>10, 20, 40</td>
<td>0.5 – 2.3</td>
<td>Generic-1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>lovastatin ER</td>
<td>N</td>
<td>Altoprev®</td>
<td>20, 40, 60</td>
<td>4.7</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>N (can’t)</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>NDA submit</td>
<td></td>
<td>1, 2, 4</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pravastatin</td>
<td>Yes</td>
<td>Pravachol®</td>
<td>10, 20, 40, 80</td>
<td>2.6 – 3.2, metab ~ 77</td>
<td>Generic-1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>N</td>
<td>Crestor®</td>
<td>5, 10, 20, 40</td>
<td>19 – 20.8</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; (Jan ’09)</td>
<td>N</td>
</tr>
<tr>
<td>simvastatin</td>
<td>Yes</td>
<td>Zocor®</td>
<td>5, 10, 20, 40, 80</td>
<td>4.2 – 4.9</td>
<td>Generic-1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Tablet Splitting Program: Details on copay and qty/day supply to write rx for

IHA – 1 copay for a 2 month supply, Rx written as #30 for a 60 day supply

<table>
<thead>
<tr>
<th>Combination Products</th>
<th>Available?</th>
<th>Brand Name®</th>
<th>Available Strengths (mg)</th>
<th>Half – Life (hrs)</th>
<th>IHA Tier</th>
<th>Tablet Splitting?</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine/atorvastatin</td>
<td>N</td>
<td>Caduet®</td>
<td>Numerous</td>
<td>30-50 / 14</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>N</td>
</tr>
<tr>
<td>niacin ER/lovastatin</td>
<td>N</td>
<td>Advicor®</td>
<td>500/20, 750/20, 1000/20, 1000/40</td>
<td>4.5 – 2.3</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>N (can’t)</td>
</tr>
<tr>
<td>niacin ER/simvastatin</td>
<td>N</td>
<td>Simcor®</td>
<td>500/20, 750/20, 1000/20</td>
<td>4.2 – 4.9</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>N (can’t)</td>
</tr>
<tr>
<td>ezetimibe/simvastatin</td>
<td>N</td>
<td>Vytorin®</td>
<td>10/10, 10/20, 10/40, 10/80</td>
<td>22 / 4.2 – 4.9</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>N</td>
</tr>
</tbody>
</table>

`Statin` Equipment Dosing

<table>
<thead>
<tr>
<th>LDL Reduction</th>
<th>Lovastatin (Mevacor®)</th>
<th>Lovastatin ER (Altoprev®)</th>
<th>Pravastatin (Pravachol®)</th>
<th>Fluvastatin (Lescol, Lescol X®)</th>
<th>Simvastatin (Zocor®)</th>
<th>Atorvastatin (Lipitor®)</th>
<th>Rosuvastatin (Crestor®)</th>
<th>Pitavastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 – 30%</td>
<td>20mg</td>
<td>20mg</td>
<td>20mg</td>
<td>40mg</td>
<td>10mg</td>
<td>1mg</td>
<td>1mg</td>
<td></td>
</tr>
<tr>
<td>30 – 40%</td>
<td>40-80mg</td>
<td>40mg</td>
<td>40 – 80mg</td>
<td>80mg XL</td>
<td>20mg</td>
<td>10mg</td>
<td>4mg</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
<tr>
<td>40 – 45%</td>
<td>Advisor 1000/20mg-1500/40mg</td>
<td>60mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note:</td>
<td>Adding Zetia to any statin generally decreases LDL up to an additional 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adding Niacin to any statin WILL provide variable additional LDL lowering, most of benefit from elevating HDL and decreasing TGs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Adjustments with Renal Dysfunction: Adjust for Reduced GFR (mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>60-90</th>
<th>15-59</th>
<th>&lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>No adjustment</td>
<td>Per product package insert; start at 5mg and monitor, NKF = unknown</td>
<td></td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>No adjustment</td>
<td>Reduce dose by 50% in patients with GFR &lt; mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>No adjustment</td>
<td>Per product package insert; Not tested in doses &gt;40mg/day in severe renal impairment, NKF = unknown</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>No adjustment</td>
<td>Per package insert; starting dose 5mg/d and NOT to exceed 10mg/d in patients with CrCl&lt;30 mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>No adjustment</td>
<td>Per package insert; starting dose 5mg/d</td>
<td>No adjustment</td>
</tr>
</tbody>
</table>

### Typical Cholesterol Medications (RX only)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>IHA Tier Info</th>
<th>% HDL Increase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic Acid</td>
<td>Niaspan® ER 500mg (tab) qhs</td>
<td>2</td>
<td>+ 10%</td>
<td>Most effective agent to increase HDL-C, not only ↑ HDL but preferentially ↑ larger more buoyant HDL w/ ApoAI. Also, when added to statin, favorably alters LDL particle distribution.</td>
</tr>
<tr>
<td></td>
<td>1000mg (tab) qhs</td>
<td></td>
<td>+ 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1500mg (dose) qhs</td>
<td></td>
<td>+ 22 to 26%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000mg (dose) qhs</td>
<td></td>
<td>+ 30 to 35%</td>
<td></td>
</tr>
<tr>
<td>Combo</td>
<td>Niacin ER /Lovastatin (Advicor®)</td>
<td>3</td>
<td>+20 to 33% up</td>
<td>Combines powerful LDL lowering and most effective HDL raiser.</td>
</tr>
<tr>
<td></td>
<td>Niacin ER/Simvastatin (Simcor®)</td>
<td>2</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>*Gemfibrozil 600mg bid</td>
<td>Generic-1st</td>
<td>+ 6 to 20%</td>
<td>FIELD study showed only 2% ↑ in HDL fenofibrate monotherapy. ACCORD trial - statin/fibrate combo any better than either alone</td>
</tr>
<tr>
<td></td>
<td>*Fenofibrate – 48 to 200mg qd</td>
<td>Generic-1st</td>
<td>+2 to 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (Crestor®) qd</td>
<td>2 (Jan '09)</td>
<td>+ 8 to 10%</td>
<td>Major mechanism is LDL lowering, making it difficult for trials to tease out benefit due to any HDL increase. Rosuvastatin and Simvastatin generally considered most effective at raising HDL</td>
</tr>
<tr>
<td></td>
<td>*Simvastatin (Zocor®) qhs</td>
<td>Generic-1st</td>
<td>+ 5 to 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Pravastatin (Pravachol®) qhs</td>
<td>Generic-1st</td>
<td>+ 3 to 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Lovastatin (Mevacor®) qhs</td>
<td>Generic-1st</td>
<td>+ 5 to 8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atorvastatin (Lipitor®) qd</td>
<td>Generic-1st</td>
<td>+ 2 to 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin (Lescol XL®) qhs</td>
<td>2</td>
<td>+ 3 to 6%</td>
<td></td>
</tr>
<tr>
<td>Bile Acid Resins</td>
<td>*Cholestyramine (Questran®)</td>
<td>Generic-1st</td>
<td>+ 3 to 5%</td>
<td>Increase intestinal production of ApoAI but effect on HDL negligible compared to effects on LDL. many GI effects, frequent dosing, drug interactions</td>
</tr>
<tr>
<td></td>
<td>Colestipol (Colestid®)</td>
<td>Generic-1st</td>
<td>+ 3 to 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colesevelam (Welchol®)</td>
<td>2</td>
<td>+ 3 to 5%</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Ezetimibe (Zetia®) 10mg qd</td>
<td>2</td>
<td>+ 1 to 5%</td>
<td>Effect on HDL negligible compared to LDL, few side effects, few drug interactions.</td>
</tr>
<tr>
<td>Omega-3’s</td>
<td>Lovaza® 1 gram two bid</td>
<td>2</td>
<td>+ 9.1%</td>
<td>Primarily for TG lowering, modest HDL increase in combo w/statin (minimal LDL increase)</td>
</tr>
<tr>
<td>(Rx only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other Drugs That Increase HDL (not indicated for cholesterol therapy)

| TZDs               | Pioglitazone (Actos®) qd              | 2             | + 5 to 13%     | No trials showing impact on hard endpoints such as mortality. Rosiglitazone can raise LDL! Pioglitazone also lowers TGs as well.          |
|                   | Rosiglitazone (Avandia®) qd           |               |                |                                                                                                                                     |
| SERMs             | Raloxifene (Evista®) qd               | 2             | - 2% to +14%   | RUTH trial evaluating 10,101 post-menopausal women at high CHD risk for cardioprotection (w/raloxifene)                                 |
| HRT (estrogen only)| *Estradiol and various estrogens     | Generic-1st   | + 7 to 13%     | Raises HDL and lowers LDL, However, WHI showed increased cardiovascular complications                                                  |
| Phenytoin         | *Phenytoin (Dilantin®)                | Generic-1st   | + 10 to 13%    | Anticonvulsant, drug interactions, many serious adverse effects. Interesting to note that in a onestudy it reduced aortic atherosclerosis |

### OTC Products and NON-RX Methods to Increase HDL

| Omega-3’s (OTC)   | Various products with varying Amounts of EPA and DHA | Not covered OTC | Variable increase | Can’t be certain of EPA and DHA content, Lovaza much more potent and FDA approved                                             |
| EtOH              | Moderate amount, especially Red wine                | N/A            | + 7 to 12%       | Not a routine recommendation. Increases availability of ApoAI, stimulates cellular cholesterol efflux. AHA does not recommend EtOH for cardiovascular reasons. |
| Exercise          | VERY intense – 90kg subject jogging for 20miles/wk at 65 to 80% of peak O2 consumption | FREE !!!       | + 4 mg/dL about 10% | Only limited benefit from VERY intense, VERY frequent exercise                                                                 |

IHA Tier:
1. Tier 1: Highest priority, should be tried first.
2. Tier 2: Good choice but used less often.
3. Tier 3: Occasionally used but not considered a standard therapy.
Points of Interest

HDL Terminology Updates

**ApoA1** - Apolipoprotein A-I, the main protein in HDL that accounts for about 70% of the total HDL protein. Atheroprotective lipoprotein; important function in promoting the efflux of cholesterol from cells, and has anti-oxidant and anti-inflammatory properties.

**ApoA1 milano** - A variant of apoA-I with potent cholesterol efflux capacity.

**ApoB** - Apolipoprotein B-100, major lipoprotein of LDL, IDL and VLDL (all atherogenic cholesterol)

**Lipoprotein (a)** - A genetic variant of low-density lipoprotein. An increased level is associated with increased risk of heart disease.

**CETP** - Cholesterol ester transfer protein, facilitates net transfer of cholesterol esters from HDL to TGRLPs and reciprocal transfer of TGs from VLDL to LDL and HDL

**SR-B1** - Scavenger receptor B1, an HDL receptor present mainly in the liver (as well as extraheptic tissue), that promotes selective uptake of HDL cholesterol.

**ABCA1** - ATP-binding cassette A1 transporter. It is a cell membrane transporter that exports cholesterol and phospholipids from cells onto lipid poor apolipoproteins that are the precursors for HDL particles. It is important to note that ABCA1 requires poorly lipidated apolipoproteins to promote cholesterol efflux, and that processes favoring the incorporation of lipid-free apolipoproteins into HDL or other lipoproteins will inhibit cholesterol efflux by this pathway.

- Mutations in ABCA1 cause severe HDL deficiency characterized by deposition of cholesterol in tissue macrophages and prevalent CVD.

**LCAT** - Lecithin:cholesterolacyltransferase; an enzyme that catalyses the esterification of cholesterol in HDL, and accounts for most of the cholesteryl esters that circulate in the plasma. Plays a major role in the metabolism & remodeling of HDL.

**LXR** – Liver X receptors. LXR alpha and LXR beta are master regulators of whole-body cholesterol homeostasis, intermediary metabolism and energy balance, and the integration of metabolic and inflammatory signaling. Each are equally effective in promoting reverse cholesterol transport from macrophages; they activate members of the ABC superfamily of membrane transporters (i.e., ABCA1, ABCG1), which transfer cholesterol to HDL particles.

**Beta-glucans** - These compounds are a form of a dietetic hydrosoluble fiber. They are polysaccharides that are found in yeast, oat and barley as well as in some medicinal mushrooms. They have demonstrated a significant 30% increase in HDL with addition of beta-glucans to the diet³. The effects on HDL are dose-dependent and evidence in very early stages.

What do ATP III guidelines say in regards to HDL specifically? [Link]

- High HDL (>60 mg/dL) removes 1 risk factor, however, it does NOT offset high LDL
- It treats men the same as women (though do mention possible difference)
- “Suggestive evidence” that elevating HDL decreases CHD risk
- “Uncertain whether increased HDL, independent of other changes in lipid and/or nonlipid risk factors will decrease CHD risk”
- However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and non-lipid risk factors should be encouraged.

2004 ATP III Update [Link]

- “Although the potential benefit of HDL-raising therapy has evoked considerable interest, current documentation of risk reduction through controlled clinical trials is not sufficient to warrant setting a specific goal value for raising HDL-C. Recent lipid-lowering drug trials provide no new evidence in this regard.”
- “Post-hoc analysis of several clinical trials with fibrates indicates that they reduce risk for CHD events in patients with high triglycerides and low HDL-C, especially when the patients have diabetes or characteristics of the metabolic syndrome.”
- “Several clinical trials support the efficacy of nicotinic acid for reduction of CHD risk, both when used alone and in combination with statins.”
- “Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.”
**Pharm.D. Interpretation:**
ATP III was last updated in 2004. At that time the authors do acknowledge that “suggestive evidence” that elevating HDL decreases CHD risk and that potential benefit of HDL-raising therapy evoked considerable interest. In addition, the authors seem to feel the difference in regards to sufficient HDL levels between men and women is fairly insignificant. Furthermore, in apparent disagreement (or via incomplete analysis?), ATP III indicates that high HDL (>60 mg/dL, with no designation between men and women) is beneficial and indicates that its presence removes one risk factor. What’s more, ATP III states that TLC to modify low HDL (among other factors) should be utilized to modify this risk factor regardless of LDL level. Yet, ATP III falls completely short of providing even remotely as strong a recommendation to treat patients with pharmacologic measures proven to significantly modify low HDL (among other factors).

- The last 4 words of this 2004 update statement (“removes one risk factor”) are in complete contradiction to ATP III’s statement that it’s uncertain whether increased HDL, independent of other changes in lipid and/or non lipid risk factors will decrease CHD risk.
- e.g., I would argue that ATP III is inconsistent in its recommendations regarding HDL, as far as acceptable levels as well as therapy targeting HDL.

Numerous clinical trials and analyses of varying design and size have supported that the benefits from HDL are indeed independent from the benefits of lower LDL and in fact, are additive. In addition, data indicating clear differences between acceptable HDL levels in men versus women have been present since before ATP III 2004 update and continue to emerge.

- The very notion that a difference in acceptable HDL levels between men and women presents a limitation, or need to re-assess, numerous studies evaluating benefit of HDL targeting therapies. General expert consensus indicates that acceptable HDL-C levels are >40 -45 mg/dL in men and >50 – 55 mg/dL in women.
- This means that a 10 point (~20-25%) difference exists between men and women. Thus, studies setting an arbitrary HDL target of >40 mg/dL to assess benefit likely greatly underestimate benefit for women and possibly for men (if more accurate number turns out to be >45 mg/dL).
- Further complicating matters, in many early HDL targeting studies HDL-C goal was much lower, typically 35 mg/dL.
- What does appear certain is that low HDL carries significant risk, regardless of LDL-C level and vice versa.

Clarification of HDL, as well as LDL, targets will likely become clearer via further study of the particles themselves. Both HDL and LDL each come in a spectrum of sizes and contain numerous products that can either increase or decrease their benefit or risk. They are more like vehicles (dumptrucks), than simple particles. Thus, it may not be LDL-C or HDL-C that we measure and target, but rather more specific HDL or LDL particles and/or vehicle contents (its cargo). Or we use HDL simply as a vehicle, to deliver anti-inflammatory, anti-oxidant compounds directly to the tissue?

**True or False? All statins minimally elevate HDL to the same degree?**
False. Statins, as a class, are limited in their ability to elevate HDL. Prospective statin comparison studies such as STELLAR and CURVES indicate that rosuvastatin and simvastatin are generally the most potent in regards to HDL elevation compared with other statins.

- See comparative chart above [Link]

**Note:** A recent meta-analysis published in Lancet from the Cholesterol Treatment Trialists (CTT) Collaborators found that diabetes patients (18,686 in 14 randomized controlled trials) with a low level of HDL cholesterol remain at increased cardiovascular risk, despite statin therapy7. Vascular event rates were 50% higher in statin patients with low HDL.

**What are PRIMARY causes of low HDL?**
- ApoA1:
  - Complete deficiency
  - ApoA1-mutations (ie.milano)
- LCAT:
  - Complete deficiency
  - Partial LCAT deficiency (fish-eye disease)
- ABC1:
  - Tangier disease (homo/heterozygous)
  - Familial hypoalphalipoproteinemia
- Unknown generic etiology:
  - Metabolic syndrome
  - Combined hyperlipidemia w/ low HDL

**What are SECONDARY causes of low HDL?**
- Elevated serum TGs
- Overweight and obesity (visceral fat)
- Physical inactivity
- Cigarette smoking
- Very-low-fat diet, very-high-carbohydrate intakes (>60% of total energy intake)
  - i.e., among vegetarians
- Type II DM
- Beta-blockers (much of data from atenolol)
- Androgenic steroids, Androgenic progestins
**True or False? Flushing from niacin CAN be prevented, but NOT acutely relieved?**

False. Flushing due to niacin CAN be prevented, AND treated acutely.

Flushing has NOT appeared to represent a serious health risk of any kind. It is viewed as an annoyance or nuisance rather than a health risk. Given that significant health benefits have been demonstrated; communicating to and educating patients regarding flushing due to niacin, methods of its prevention, methods of acute relief, that it’s short-lived, AND that tolerance develops are of the utmost importance.

- The graph to the right is from a small but randomized study (n=22) shows the reduction of flushing (on a visual analog scale), AND that sufficient doses (i.e., ASA 325 mg) were required to demonstrate statistically significant reduction.
- Flushing is caused primarily by a prostaglandin, PGD2, which acts through the DP1 pathway to cause vasodilation in the skin and flushing symptoms.
- A DP1 inhibitor has been developed and numerous trials demonstrating efficacy in flushing reduction have been conducted and a large prospective outcomes trial for niacin ER/laropiprant, termed the HPS-2 THRIVE, is currently underway.

**More on Niacin Metabolism and ADRs:**
Niacin undergoes saturable first pass metabolism via 2 pathways. The flushing pathway appears to be a low affinity, high capacity conjugative pathway.
- This means that immediate release niacin formulations will quickly saturate the non-conjugative metabolic pathway, forcing a large fraction of niacin to be metabolized by the conjugative system, resulting in flushing.
- Very slowly absorbed long-acting formulations will be preferentially absorbed down the non-conjugative pathway potentially resulting in hepatotoxicity.

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**Strategies for improving adherence and managing flushing with niacin**

- Long-term adherence with niacin is dependent on patient awareness and education
  - i.e., flushing harmless, short-lived, preventable, treatable, describe it as ‘prickly heat’ typically occurring on face & upper body
- Patients should be instructed to avoid interrupting niacin therapy whenever possible
- Initiate therapy using small doses, taken with meals (or snack – NOT hot, spicy or fatty), and then slowly titrate upward over several weeks to achieve treatment goals
  - Note: It may take 12 – 18 months for maximum lipid benefit to be apparent with niacin therapy
- Advise patients to take an adult (325mg) aspirin (or any NSAID) 30 minutes before niacin dose (if not contraindicated)
  - Note: Enteric coating will delay absorption/benefit from aspirin, thus advisable to take earlier
- Recommend that patients avoid spicy/fatty foods and/or hot (including coffee) or alcoholic beverages near niacin dose
- Use intermediate release (Niaspan®ER) rather than immediate release formulation to minimize flushing and maximize adherence
  - Note: Extended release formulations WILL minimize flushing, however, WILL also increase risk associated with liver toxicity.
- Analgesic doses of NSAIDs (aspirin 650mg, ibuprofen 400mg, etc) can be utilized for acute treatment if flushing does occur and is intolerable (if not contraindicated)
- Do NOT utilize product called ‘flushless’ niacin (inositol hexanicotinate), as it does NOT contain any free niacin and does NOT have evidence of significant benefit

Adapted from Davidson M. Niacin Use and Cutaneous Flushing: Mechanisms and Strategies for Prevention. Am J Cardiol. 2008;101(suppl):14B-19B.
True or False? Tolerance to flushing from niacin develops over time?  

In the Open-label evaluation of the safety and efficacy of a Combination of Niacin ER and Simvastatin in patients with dyslipidemia (OCEANS) study demonstrated reduction in flushing over time (max of 12 weeks follow up). Treatment with Niacin ER/simvastatin (NER/S) was well tolerated:

- 71% of patients experienced flushing and 92% of flushing episodes were mild or moderate in intensity.
- Overall, 61% of patients experienced flushing episodes that were rated as mild or moderate in intensity.
- **Flushing decreased over time** <40% of those who had flushing during titration experienced flushing during the final 12 weeks.
- A total of 20% of patients discontinued treatment because of a treatment-related adverse event
  - Note: only 7% of these discontinued because of flushing.

An early study (1998), evaluated the long term efficacy and safety of Niaspan® (niacin ER) and demonstrated not only that flushing was common, but that tolerance to flushing developed over time and that after 4 weeks of therapy patients had about 3.3 flushes/month and by 48 weeks <1 flush/month.

> In this study, only 6% discontinued therapy due to flushing.

Additional studies of niacin or niacin ER, alone and in combination with statins or other lipid modifying drugs have generally provided similar results as the aforementioned studies.

True or False? Niacin should NOT be used in diabetics due to plasma glucose increases?  

False. Multiple lines of evidence and expert consensus are below. As an aside, at least one study has indicated that higher HDL has been associated with reductions in albuminuria in patients with long standing type 1 diabetes (though not necessarily from niacin therapy).

**From ATP III:**

- “Nicotinic acid reduces insulin sensitivity, and higher doses (>3 g/day) often worsen hyperglycemia in persons with type 2 diabetes. Recent studies suggest that lower doses do NOT unduly worsen hyperglycemia.”
- “Nicotinic acid also has a favorable effect on diabetic dyslipidemia. Recent clinical trials in persons with diabetes indicated that low doses (<3 grams/day) of nicotinic acid are accompanied by only modest deterioration in glucose control with no changes in HbA1C levels.”

**Per Goldberg et al review in Mayo Clinic Proceedings (2008):**

- “Retrospective and observational studies, case reports, and case studies were excluded. On the basis of our analysis, the effects of niacin (<2.5 g/d), alone or in combination with statins, on fasting glucose (an increase of 4%-5%) and hemoglobin A1C levels (an increase of <=0.3%) are modest, transient or reversible, and typically amenable to adjustments in oral hypoglycemic regimens without discontinuing niacin.”
- “Niacin therapy was infrequently associated with incident diabetes or the need for new insulin prescriptions.”
- “Studies showed important clinical benefits of niacin or niacin-statin regimens despite modest effects on glucose control.”
- “On a population basis, significant reductions in incidences of cardiovascular events and the degree of atherosclerotic progression associated with long-term niacin (or niacin-statin) therapy in patients with diabetic dyslipidemia outweigh the typically mild effects of this therapy on glycemic regulation.”
**Per Bays H. (2005):**
From the standpoint of CAD outcomes, analyses have suggested that the greatest benefits of niacin may be in patients with glucose levels ≥6.99426 mmol/L (126 mg/dL), compared with patients with lower glucose levels.

![Figure to the left:](image)

The Coronary Drug Project (CDP) at 6 years: myocardial infarction by baseline fasting plasma glucose level (1 mg/dL=0.05551 mmol/L). The z value for interaction was 0.44 (p =0.66), indicating homogeneity of treatment effects across all levels of fasting plasma glucose. The greatest degree of percentage benefit of niacin in reducing atherosclerotic coronary artery disease events (over that of placebo) occurred at glucose levels ≥6.99426 mmol/L (126 mg/dL).

**Per National Lipid Association (2007):**
Minor (4-5%) increases in glucose [on fasting glucose] result from niacin-induced insulin resistance, but these increases are often clinically insignificant or readily treated.

**Per AHA/ADA (2007):** Not entirely accurate; as studies have included diabetic patients and subgroup-analyses have been published (i.e., NAUTILUS, Department of Veterans Affairs Study, etc.)

Both recognize niacin as the most effective available drug for raising HDL-C and state that clinical trials suggest CV risk reduction with niacin, although no trials of niacin in patients with DM have been performed. At higher doses, niacin can worsen hyperglycemia.

**Per AHA (2007):**
Niacin can significantly elevate blood glucose at high doses. However, at modest doses (750mg to 2 grams/day), significant lipid/lipoprotein benefits are accompanied by only modest alterations in glucose that are typically amenable to adjustment of anti-diabetes regimens.

**Per AACE (2007):**
“Although use of niacin in patients with diabetes mellitus has been limited because of associated increased hyperglycemia, niacin therapy is safe and effective in this patient population.”

**Per European Consensus Panel (2005):**
Niacin at clinically recommended doses (≤2 grams/day) is an acceptable therapeutic alternative for patients with type 2 DM, as well as people with the metabolic syndrome, at elevated risk of CAD.

**At what dose is Niaspan® ER most effective? Any significant benefit in dosing beyond 500 mg/day?**

In the figure to the right, using niacin study data from Mckenney et al\(^{10}\), and Goldberg et al\(^{11}\), we can see that a 500 mg/day of immediate release (IR) niacin and extended release (ER) niacin provides a range of 7 – 10% HDL increase and that maximum benefit likely occurs somewhere around 2000 mg/day at a range of 30 – 40% HDL increase.

In addition, the HDL-C raising effect associated with niacin has a creep effect, ie, HDL-C levels continue to climb for months after initiation of niacin therapy, even if daily doses remain the same.

- The elevation in HDL-C associated w/ 1000 mg daily of ER niacin in the ARBITER 2 trail was 10% after 3 months of therapy, 13% after 6 months, and 21% after 12 months.

**Pharm.D. Interpretation:**
Given that you’re unlikely to have started Niacin in a patient only needing a 10% increase in HDL in order to achieve goals (given that most statins would provide about this much), it would be very unlikely that stopping the dose titration at 500mg would be enough to get your patient to HDL-C goal.
What are some cost-effectiveness considerations in regards to HDL elevation?

The chart below presents a unique perspective on drug costs. When Piepho R. did his original analysis for publication in 2000 it was clear that Niacin ER was the least costly per 1% rise in HDL-C. My own updated cost analysis shows that fenofibrate is least costly Rx, and in general the more potent the HDL increase, the least costly per 1% HDL rise.

Clearly there are other factors in cost/outcome (compliance, maximum allowable costs with generics, copays, multi-variate outcomes, etc). Further pharmaco-economic analyses are needed. Combination of niacin ER plus a statin appears to be low end in cost/hdl rise in addition to much greater likelihood to reach not only HDL goals, but TG and LDL goals as well.

This topic will be discussed further in the next review, ‘Statins Part III – Comprehensive Lipid Management’.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose (mg)</th>
<th>Max HDL Increase (%)</th>
<th>AWP/day (as of 12/2008)</th>
<th>Cost/1% HDL rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin IR</td>
<td>2000</td>
<td>24.4</td>
<td>$0.14</td>
<td>$0.006 LOW</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>160</td>
<td>20.0</td>
<td>$2.38</td>
<td>$0.12</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>1200</td>
<td>13.3</td>
<td>$2.50</td>
<td>$0.19</td>
</tr>
<tr>
<td>Simcor® (simvastatin/niacin ER)</td>
<td>2000/40</td>
<td>41.0 – possibly greater with time</td>
<td>$8.40</td>
<td>$0.20</td>
</tr>
<tr>
<td>Crestor® (rosuvastatin)</td>
<td>40</td>
<td>16.0</td>
<td>$3.97</td>
<td>$0.25</td>
</tr>
<tr>
<td>Advicor® (lovastatin/niacin ER)</td>
<td>1000/40</td>
<td>33.0 – 41.0 (after 52 wks)</td>
<td>$8.54</td>
<td>$0.26</td>
</tr>
<tr>
<td>Niacin ER</td>
<td>2000</td>
<td>29.5</td>
<td>$8.40</td>
<td>$0.28</td>
</tr>
<tr>
<td>Lipitor® (atorvastatin)</td>
<td>40</td>
<td>13.8</td>
<td>$4.50</td>
<td>$0.33</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>80</td>
<td>12.0</td>
<td>$4.79</td>
<td>$0.40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>80</td>
<td>12.0</td>
<td>$4.90</td>
<td>$0.41 V</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>80</td>
<td>9.5</td>
<td>$8.54</td>
<td>$0.90 HIGH</td>
</tr>
</tbody>
</table>


How significant is the benefit of exercise in regards to HDL elevation?

See the chart above for the effect of various non-pharmacologic methods to increase HDL. [Link]

While exercise is very important as a general cardiovascular risk intervention, it has only limited efficacy in increasing HDL-C levels, being modestly effective only in the setting of elevated triglycerides and in response to frequent and intense exercise as evidenced by the HERITAGE trial.

The Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE) trial was a randomized, controlled clinical study, found that beneficial effects of exercise on the lipid parameters were related more to the frequency of exercise than the intensity of exercise. It is important to note that the group with the greatest benefit in this trial was the high frequency, high intensity exercise group (jogging 20 miles/week at 65 – 80 percent of peak oxygen consumption).

Figure to the right from STRRIDE trial:

- + 4 mg/dL in high frequency, high intensity group
- - 0.6 mg/dL in sedentary control group, (p=0.015)

Note: The max benefit seen here was 4 mg/dL increase, which was about a 10% increase.

In addition, the average baseline HDL-C’s in each group were all above 40 mg/dL, i.e., NOT considered low HDL for men or women.

Can your high risk patients with cardiovascular disease maintain moderate to intense exercise for extended periods of time? Is 10% increase in HDL enough to get them above 40 or 50 mg/dL? Exercise is clearly beneficial; however, it is likely that most patients with low HDL should be encouraged to exercise IN ADDITION to a pharmacologic measure to maintain optimal HDL lipid parameters.
**True or False? The goal HDL for both men and women is >40 mg/dL?**

False. There is a distinct difference between men and women for acceptable levels of HDL-C supported by a number of studies and expert consensus. In addition, physiologically, estrogens do positively affect HDL-C levels; whereas, androgens negatively affect HDL-C levels.

- Recently, the worldwide consensus on Metabolic Syndrome by the International Diabetes Federation suggests a different threshold value: 40 mg/dL for men and 50 mg/dL for women.\(^2\)
- Prior to this consensus, the International Task Force for Prevention of Coronary Heart Disease and NCEP ATP2 utilized 35 mg/dL for men and 45 mg/dL for women as cutoffs for low HDL-C.
- In addition, the Pan-European Survey utilized HDL cut-offs of 40 mg/dL for men and 50 mg/dL for women to establish the prevalence of low HDL among the European population.\(^2\)

**In regards to age AND gender differences and HDL-C levels:**

Landi F, et al. recently analyzed data from the Aging and Longevity Study in the Sirente geographic area (ilSIRENTE Study), consisting of a cohort of 359 persons aged 80 years or older for 2 years of follow-up.

- **Men**
  - Mean HDL 36.7 mg/dL among those that died
  - Mean HDL 43.4 mg/dL among survivors

- **Women**
  - Mean HDL 42.2 mg/dL among those that died
  - Mean HDL 49.3 mg/dL among survivors

**General information regarding acceptable HDL-C levels:**

- AFCAPS/TexCAPS provided evidence supporting that the definition of low HDL used by ATP 2 be increased. In this study, there was a marked difference between patients with lower levels of HDL from 34 to 39 mg/dL and patients with levels higher than 40mg/dL, because the first group derived greater benefit from lovastatin treatment than the second group.
  - i.e., a ‘hidden’ demonstration of benefit to elevating HDL even while lowering LDL?

**What is meant by ‘functional HDL’?...What about Pro-Inflammatory HDL?**

As mentioned above lipoproteins (HDL and the like) are like transport vessels with varying functions, that are largely dependent upon their protein content, their shape and their size. As such, it has become apparent that alterations in size and/or content of lipoproteins can alter their functions.

- Alterations can happen in multiple directions, i.e., functional may become pro-inflammatory and pro-inflammatory may revert back to functional. This has been observed with respect to HDL.
- For example, during inflammation HDL can acquire proteins that may have both beneficial and harmful effects on the artery wall.
  - i.e., HDL becomes enriched in amyloid A from the liver during inflammation, which can promote trapping of HDL particles in the artery wall and their conversion to atherogenic lipoproteins.

**Functional HDL** – basically, carries ‘good’ cargo, and/or is of optimal size and shape to interact with receptors and enzymes promoting anti-atherogenic pathways.

**Pro-Inflammatory HDL** – basically, carries ‘bad’ cargo and/or is of a size and shape making it less able to interact with anti-atherogenic pathways and possibly enhance its interaction with atherogenic pathways.

- All of the factors pushing HDL one way or the other are NOT completely understood at this point. In addition, all of the effects of various pharmacologic agents on HDL, even of those currently available, aren’t entirely understood.
- LDL is not devoid of particle size and cargo differences either. We’ve apparently identified a great intervention, in statins, that has good overall effects on various LDL particles. It is interesting to note that there are differences amongst statins in effects on resulting LDL particle distributions, meaning of which is still uncertain.
- It did take about 20 years of basic science and clinical studies to demonstrate that lowering LDL cholesterol had beneficial effects on atherosclerotic vascular disease in humans and that it as the discovery of the LDL receptor and statin family of drugs that was critical to the success of this approach.
- It’s hard to say exactly where we are in this process with the HDL approach; however, we do have a few drugs that we know significantly increase HDL and have been shown to decrease CV risk beyond that expected with statin only and LDL benefit alone (i.e., statins and fibrates, possibly omega-3s).
At the present, the anti-inflammatory ('functional') and pro-inflammatory ('dysfunctional') properties of HDL can be characterized using various in-vitro assays that measure the impact of HDL on various steps in vascular inflammation.

- MCA (monocyte chemotaxis assay) – quantifies LDL-induced incorporation of monocytes within a co-culture of endothelial and smooth muscle cells. Allows a calculation of an 'inflammatory index'.
- CFA (cell-free assay) – model of LDL oxidation that evaluates the effect of HDL on phospholipid oxidation in the presence of a potent oxidant using a fluorescent signal.
- Another assay evaluates the impact of HDL on expression of particular adhesion molecules.

The point here is that we are quickly moving toward better understanding of the functionality of HDL (and other particle), which should in turn lead toward better therapies for CV risk reduction in short time.

The 2 figures below illustrate functional and dysfunctional HDL and various effects from the research of Ansell B et al.¹⁴
**HDL and Reverse Cholesterol Transport (RCT)**

HDL is believed to protect against atherosclerosis at least in part through the process of reverse cholesterol transport, whereby excess free cholesterol (FC) is removed from cells in peripheral tissues, such as macrophages within the arterial wall, and returned to the liver for excretion in the bile. FC is generated in part by the hydrolysis of intracellular cholesteryl ester (CE) stores. Promotion of this pathway could in theory help reduce atherosclerosis.

Several key molecules play roles in reverse cholesterol transport, including:

- ATP-binding cassette protein A1 (ABCA1) – deals more with ApoA1 and immature HDL
- ATP-binding cassette protein G1 (ABCG1) – deals more with mature alpha HDL
- lecithin:cholesterolacyltransferase (LCAT)
- scavenger receptor class-B, type I (SR-BI)

![Diagram of HDL and Reverse Cholesterol Transport](image)

**Excess cholesterol stored in macrophages in arterial walls contributes to atherogenesis.**

In reverse cholesterol transport, cholesterol ester hydrolase (CEH) releases free cholesterol from cholesterol ester (CE) stores.

The ABCA1 transporter facilitates the efflux of cellular cholesterol to lipid-poor apo A-I to form nascent pre-β-HDL. Apo A-I is produced in the liver and intestine, and is also generated upon catabolism of mature HDL.

Lecithin-cholesterol acyltransferase (LCAT) esterifies free cholesterol in nascent pre-β-HDL to cholesterol ester, converting nascent β-HDL to mature α-HDL (HDL₆ and HDL₇).

**Interconversion of mature α-HDL subspecies (HDL₆ and HDL₇) can occur in the arterial wall and in plasma. These interconversions are mediated by hepatic lipase (HL), endothelial lipase (EL), and LCAT.**

**Indirect Pathway of Hepatic Cholesterol Uptake**

Cholesterol ester transfer protein (CETP) facilitates the exchange of CE in HDL for triglycerides (TG) in TG-rich apo B particles (LDL, VLDL).

**Direct Pathway of Hepatic Cholesterol Uptake**

CE is taken up via SR-B1 receptors on hepatocytes that recognize apo A-I as a ligand.

*C. Lynch*

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ABCA1 indicates adenosine triphosphate–binding cassette transporter A1; ABCG1, adenosine triphosphate–binding cassette transporter G1; apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-R, LDL receptor; LPL, lipoprotein lipase; SR-B1, scavenger receptor type B1; VLDL, very low-density lipoprotein.
What are the proposed benefits (direct or indirect) of HDL?

These benefits are from HDL assumed to be ‘functional HDL’.

1) **Reverse Cholesterol Transport (RCT)**
   - Described in text and figure above in great detail.

2) **Antioxidant**
   - Inhibits oxidation of LDL (oxidized LDL attracts monocytes leading to foam cell formation)
   - This effect may be either direct or due to high content of antioxidants. Among other antioxidants, HDL carries paraoxonase (PON) which hastens degradation of oxidized LDL.
   - PON and other antioxidants carried by HDL also limit the level of ‘seeding molecules’ which are required for oxidation of lipid species.

3) **Anti-inflammatory**
   - Experimental evidence suggests that HDL may be directly anti-inflammatory, shown to reduce certain anti-inflammatory markers

4) **Anti-apoptotic**
   - May help maintain population of endothelial cells by preventing their cell death by preventing their death by oxidized LDL and other activators of apoptosis
   - Limits cell damage and necrosis resulting from the complement system

5) **Anti-thrombotic**
   - Inhibits interaction of monocytes with endothelial and smooth muscle cells
   - In a study of hypercholesterolemic men, serum HDL was shown to be a significant independent predictor of platelet thrombus formation
   - In vitro, HDL has been shown to enhance inactivation of coagulation factor Va
   - ApoA1 and A2 have been shown to activate fibrinolysis

6) **Anti-infectious**

7) **Endothelial function enhancement**
   - Promotes eNOS activation and NO release, with resulting vasorelaxation

What is the current status of the CETP inhibitors drug class? (i.e., Torcetrapib from Pfizer)

How CETP (cholesteryl ester transfer protein) inhibition as a target to reduce CV risk came about:

- It was shown over 15 years ago that Japanese subjects with loss-of-function mutations in CETP had elevated levels of both HDL cholesterol and ApoA1 in association with longevity and decreased incidence of CVD.
- It was then observed that lab animals that lacked CETP, such as mice, had much higher HDL levels and are more resistant to diet-induced atherosclerosis than those that express CETP, such as hamsters or rabbits.
- These and other observations and studies supported suppressing CETP activity to reduce CV risk, however, as studies accumulated it became apparent that CETP activity in relation to CV risk was more complicated than originally thought.
- Consequently, compounds were identified that are potent CETP inhibitors and investigations ensued.
Treatment with torcetrapib has both mechanism-based and off-target effects that may have contributed to an increased rate of adverse cardiovascular and non-cardiovascular outcomes. The drug inhibits cholesteryl ester transfer protein (CETP), blocking the transfer of cholesteryl esters to lipoproteins containing apolipoprotein B (ApoB), such as low-density lipoprotein (LDL), resulting in increased levels of high-density lipoprotein (HDL) cholesterol and enlarged HDL particles.

Although HDL cholesterol can be taken up directly by the liver through the HDL scavenger receptor, class B, type I (SR-BI), inhibition of CETP may reduce the rate of return of HDL cholesterol to the liver, thus impairing reverse cholesterol transport and increasing cardiovascular risk.

The potential that torcetrapib has off-target effects that contributed to an increased risk of non-cardiovascular events is possible but remains speculative.

- The change in HDL composition could conceivably impair immune function associated with HDL, thus increasing non-cardiovascular risks such as infection and cancer.
- On the other hand, the molecule torcetrapib clearly has the off-target effects of elevating levels of aldosterone and blood pressure, changes that probably contributed to the increased cardiovascular risk.
- Finally, CETP inhibition has the potentially beneficial effects of increasing cholesterol efflux from macrophages mediated by ATP-binding cassette transporter G1 (ABCG1) (which could increase the rate of physiologically relevant reverse cholesterol transport from macrophages) and of increasing the uptake of LDL cholesterol by the liver (which reduces LDL cholesterol levels), effects that could be important for CETP inhibitors that do not have the off-target effects of torcetrapib.

**Brief Information on the trials that brought down Torcetrapib:**

**ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events)**
- Large, prospective randomized trial of CVD patients treated w/ torcetrapib in combination w/statin or a statin alone
- Abruptly halted due to an increased in deaths (82 compared with 51 in the statin only groups), heart failure, angina, and other problems
- Earlier torcetrapib studies had indicated that it increased SBP, though modest increases in these studies
- Later it was found that some patients exhibited MUCH greater increases in SBP (15 mmHg)
- It appears unlikely that the SBP increase was a result of CETP inhibition, as persons with CETP loss-of-function mutations do not exhibit elevated SBP
- Some suggest that perhaps the type of HDL generated by CETP inhibition may have been a pro-atherogenic type

**RADIANCE (Rating Atherosclerotic Disease change by Imaging A new CETp inhibitor)**
- Large, prospective randomized trial of 850 patients with heterozygous familial hypercholesterolemia undergoing beta- ultrasonography to evaluate changes in carotid intima media thickness (CIMT) after torcetrapib/atorvastatin or atorvastatin alone treatment, average follow up of 2 years.
- Despite a large increase in HDL cholesterol levels (+ 51.9% vs atorvastatin alone) and a substantial decrease in levels of LDL cholesterol (- 20.6% vs atorvastatin alone) and triglycerides, no significant difference in CIMT could be demonstrated.
- It is difficult to assess the relevance of this imaging study of patients with normal HDL and VERY elevated LDL cholesterol to the general population.
- In this study, the inhibition of CETP by torcetrapib actually INCREASED plasma levels of CETP.
- In this study, the possibility that HDL may have lost its anti-inflammatory potential is illustrated by the observation that torcetrapib did NOT affect levels of C-reactive protein.

**ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation)**
- This study addressed some of the applicability to general public concerns by evaluating patients with CAD who were treated with atorvastatin until they reached LDL less than 100 mg/dL before being randomized to torcetrapib/atorvastatin or atorvastatin alone group. Again a 2 year follow up.
- Conclusion was that torcetrapib was associated w/substantial increase in HDL-C (61%) & decrease in LDL-C (20%)
- It was also associated with an INCREASE in SBP (4.6 mmHg), and there was NO significant decrease in the progression of coronary atherosclerosis.
At least 2 other CETP inhibitors continue to be studied. These compounds have NOT demonstrated the off-target effects seen with torcetrapib. Results of studies of these compounds should shed significant light on CETP and HDL.

- JTT-705
- anacetrapib

Do HDL and CRP have any significant relationship?  

- Recently (2008), Alber H et al confirmed this association with a large cohort (n = 5641) undergoing coronary angiography for evaluation of CAD in a multivariate analysis. Alber et al demonstrated CRP independently predicted association but NOT severity of CAD (independently of other risk factors). Alber et al demonstrated CRP independently predicted association but NOT severity of CAD (independently of other risk factors).  
- However, their study DID demonstrate independent association AND severity of CAD with HDL-C levels (inverse).
- Interestingly, among the cohort LDL-C was similar in overall CAD and non-CAD patients
  - 124.5 mg/dL vs. 126.0 mg/dL, P=NS

**Pharm.D. Interpretation:**
Given that HDL has been shown to have anti-inflammatory, anti-oxidant and other properties it seems likely that a significant relationship between HDL and CRP would exist. Alber et al found that both HDL and CRP were independent predictors of CV risk. This finding indicates that non-lipid related inflammation certainly represents CV risk (likely in the form of HTN, renal disease, etc).

It is important to note that HDL predicts BOTH incidence AND severity of CAD, whereas CRP only incidence.

**Does residual cardiovascular risk exist if HDL is not at goal even if LDL-C is below 70 mg/dL?**

- This question will again be explored in further detail in the Part III of drug class review (focusing residual CV risk and comprehensive lipid therapy).
- The short answer is YES, and significantly. Statins have contributed a great deal to reducing CV-related events. Despite significant improvement, CV-related deaths are still atop the mortality rate lists. We’re well rehearsed by now in targeting LDL-C and getting patients on statins whenever possible to reduce risk, now we must build on this success and construct an approach that does NOT leave out other significant and treatable risk factors such as HDL or TGs and now CRP. An update to ATP III is necessary in the near future.
  - Meta-analysis of 90,056 patients in statin studies showed that patients with a low level of HDL (<35 mg/dL) had up to 60% higher risk of further cardiovascular events than patients with higher HDL levels (>42.5 mg/dL) and statin treatment did NOT affect this risk.

**Miscellaneous HDL-related Notes:**

****C-Reactive Protein (CRP) – Some Significant Details**
Does Red Yeast Rice have efficacy data from reliable trials?

Red yeast rice (RYR) – General Information:

The following 2 studies are the only studies cited as good or excellent quality in Natural Standard® database:

Lin et al 20

- HDL cholesterol and apo B levels did NOT change significantly.

Is alternate daily dosing or twice weekly dosing of particular statins effective?

- A few studies have emerged that suggest statins (generally those with longer half-lives) may retain efficacy if given as alternate day (i.e., every other day) or even as infrequent as twice weekly administration.
- This approach appears to be useful in patients who have difficulty tolerating low daily doses of statins due to myalgias, however NO apparent benefit in regards to HDL-C.

Gadarla M, et al 28

This was a retrospective chart review of 40 patients treated with rosuvastatin 5 or 10 mg twice weekly (Mon and Thurs) for greater than 3 weeks, who had no other changes in their lipid medications. Concomitant lipid medications were listed and notably, 2 were taking Chinese red rice and ezetimibe.

Results:

✓ TC decreased by 19%, LDL-C by 26%, and TGs by 14%.
✓ HDL did not change
✓ 54% achieved their LDL-C goals
✓ 20% discontinued treatment due to recurrence of muscle-related symptoms (no mention as to whether any of these patients were those taking Chinese red rice or other particular lipid medication).

NOTE:

✓ These authors conducted a similar study, utilizing atorvastatin every other day, and obtained similar results.

Some Key references:

27. Wallace A, Chinn D, Rubin G. Taking simvastatin in the morning compared with in the evening: randomised controlled trial. BMJ. 2003;327(7418).