Coronary heart disease (CHD) is the leading cause of death in the US afflicting more than 16 million patients. It imposes a major burden on society in terms of morbidity, mortality and economic costs. According to the 2008 Heart and Stroke Statistics, the total (direct and indirect) cost of care for CHD in 2008 was estimated to be $156.4 billion. Of the total direct costs, hospital and nursing home costs account for $51.0 billion and $11.9 billion, respectively, and drugs/other medical durables for $9.7 billion.

Hyperlipidemia is a known risk factor for CHD. Lowering low-density lipoprotein cholesterol (LDL-C) slows the progression of coronary artery lesions and decreases coronary event rates. Several clinical trials have demonstrated reductions in morbidity and mortality with LDL-C lowering therapy in particular with HMG-CoA reductase (statins) inhibitors. Since 1988 the National Cholesterol Education Program (NCEP) has provided hyperlipidemia treatment guidelines. The guidelines seek to prevent or delay CHD events such as myocardial infarctions (MIs), revascularization procedures (i.e., angioplasty and bypass surgery), and acute coronary syndromes by modifying abnormal blood lipid levels. The expert panel from this program released its most recent report, the NCEP-Adult Treatment Panel (ATP) III, in May 2001. The ATP III provides guidelines for assessment of CHD risk and continues to emphasize LDL-C as the primary target of therapy. A 2004 update to the NCEP ATP III clinical practice guidelines suggested a more aggressive therapeutic option for patients at very high risk for CHD based on clinical trials. ATP IV is expected to be released Summer 2010.

### ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories with Proposed Therapeutic Options Based on recent Clinical Trials

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dl)</th>
<th>Initiate TLC^</th>
<th>Consider Drug Therapy (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk*</td>
<td>&lt;70</td>
<td>≥70</td>
<td>≥70</td>
</tr>
<tr>
<td>High Risk</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥100</td>
</tr>
<tr>
<td>2 or more risk factors‡</td>
<td>&gt;130</td>
<td>≥130</td>
<td>≥130</td>
</tr>
<tr>
<td>10-year risk 10% to 20%‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately High Risk‡</td>
<td>&lt;130</td>
<td>≥130</td>
<td>≥160</td>
</tr>
<tr>
<td>2 or more risk factors§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-year risk &lt;10%§</td>
<td>&lt;130</td>
<td>≥130</td>
<td>≥160</td>
</tr>
<tr>
<td>Lower Risk</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^TLC= Therapeutic lifestyle changes. *Very High Risk = Presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥200 mg/dl plus non-HDL-C ≥130 mg/dl with low HDL-C [<40 mg/dl]), and (4) patients with acute coronary syndromes. †CHD risk equivalents = Clinical manifestations of non-coronary forms of atherosclerotic diseases, diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%. ‡Risk Factors = Cigarette smoking, hypertension or on antihypertensive medication, low HDL cholesterol (<40 mg/dl), family history of premature CHD, and age (men >45 years; women >55 years).
Despite data from landmark trials and the NCEP guidelines, hyperlipidemia is often untreated or undertreated. National estimates indicate that only 35% of primary prevention patients needing therapy are receiving it.13

**Therapeutic Lifestyle Changes**

Reduction in LDL-C and thus, CHD risk, begins with the adoption of a healthy lifestyle. ATP III recommends therapeutic lifestyle changes (TLC) to achieve a healthy lifestyle. Many patients can achieve LDL-C goals by TLC alone. In most patients, TLC is implemented before initiating drug therapy. In high-risk and very high-risk patients, drug therapy and TLC may be initiated simultaneously. Wherever possible, patients should be referred to a registered dietitian or other qualified nutritionist for instruction and guidance on TLC.1,11,12 Components of TLC include

- Reducing intake of LDL-raisers – Saturated fats (< 7% of total calories), trans fats (<1% of total calories), and dietary cholesterol (< 200 mg/day)
- Increasing consumption of dietary adjuncts for enhancing LDL lowering: -- Plant stanols/sterols (2-3 g/day) and soluble fiber (5-10 g/day)
- Maintaining a desirable weight or reducing weight if overweight.
- Participating in regular physical activity – 30-60 minutes of moderate-intensity aerobic activity (e.g., brisk walking) on most, preferably all, days of the week

For patients with no evidence of CHD or a CHD equivalent, a minimum of 12 weeks is generally required to fully implement TLC. Patients are given 6 weeks to adopt the diet and physical activity before returning for the first follow-up appointment. At the 6-week visit, the TLC may be intensified as needed. At the next follow-up visit, typically 12 weeks after starting TLC, drug therapy may be started if the patient is not at the LDL-C goal.1,11,12

**Drug Therapy**

Currently, there are four different classes of agents used to lower LDL-C: HMG-CoA reductase inhibitors (statins), niacin, cholesterol absorption inhibitors and bile acid resins (BARs).

**Statins**

The HMG-CoA reductase inhibitors, or statins, can significantly lower both LDL-C and triglycerides and increase high-density lipoprotein cholesterol (HDL-C). Additionally, statin therapy has decreased the risk of morbidity and mortality in patients with or without established heart disease in numerous trials.3-10 Statins reduce LDL-C concentrations by 18% to 55%. Most of this reduction is seen with the initial dose; further LDL-C reduction of 6% to 7% is seen each time the dose is doubled thereafter. Generic statins provide cost-effective options whether a low-, mid- or high-potency product is needed to reach the LDL-C goal. Lovastatin (22%-32% LDL-C lowering), pravastatin (20%-30% LDL-C lowering) and simvastatin (22%-46% LDL-C lowering) are available generically. Statin therapy has been associated with elevated serum transaminases, myopathy, and rhabdomyolysis. The risk of myopathy/rhabdomyolysis is increased by high levels of statin activity in the plasma, such as, high statin doses and concomitant use with drugs that inhibit statin metabolism. Statins should not be used with strong CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin), telithromycin, HIV protease inhibitors and nefazodone. The benefits of statin therapy should be carefully weighed if co-administered with gemfibrozil, fibrates, niacin (≥1 g/day), danazol, amiodarone and verapamil since these combinations have also been associated with increased risk of myopathy/rhabdomyolysis. Other predisposing factors for myopathy/rhabdomyolysis include advanced age (≥65 years), uncontrolled hypothyroidism and renal impairment. Statins are contraindicated in active hepatic disease, unexplained, persistent elevations in serum transaminases, pregnancy and nursing mothers.11,14
Niacin
Nicotinic acid, or niacin, lowers LDL-C and triglyceride levels, and it effectively raises HDL-C. Niacin was the first antilipemic agent shown to reduce recurrent myocardial infarction (MI) and total mortality in a controlled clinical trial. Over-the-counter (OTC) immediate-release niacin reduces LDL-C levels by an average of 20% to 25% when dosed to 3 grams daily. Prescription extended-release niacin lowers LDL-C concentrations by 15% to 20% at its maximum dose of 2 grams daily. Both products raise HDL-C by 15% to 30% and reduce triglycerides by 20% to 35% at doses as low as 1 gram daily. The major limitation to niacin is its side effects, including flushing, with both immediate- and extended-release products. Flushing can be minimized by having the patient take aspirin 30 minutes before the morning dose of immediate-release niacin or the bedtime dose of extended-release niacin. Sustained-release niacin has also been associated with severe liver toxicity when given in doses above 2 grams daily.\textsuperscript{11,14}

Cholesterol Absorption Inhibitors
Ezetimibe is the only cholesterol absorption inhibitor currently available. It is approved for use as monotherapy or in combination with statins or fenofibrate for the treatment of hypercholesterolemia. The effects of ezetimibe given alone or in combination with a statin or fenofibrate on cardiovascular morbidity and mortality have not been established. As monotherapy, ezetimibe reduces LDL-C by 18%. When used in combination with a statin, LDL reductions range from 39% to 56% depending upon the statin used. The adverse effect profile for combined ezetimibe/statin therapy is similar to statin monotherapy, except for an increase in the incidence of hepatic enzyme elevations.\textsuperscript{14}

Bile Acid Resins
Bile acid resins (BARs) lower LDL-C by 15% to 30% and raise HDL-C by 3% to 5%. Triglycerides may increase or remain unchanged. The greatest advantage of BARs is their lack of systemic absorption, which provides a treatment option for patients in whom low systemic exposure is desired, such as young patients and women who are or may become pregnant. Colesevelam, the most recently marketed BAR, is also FDA-approved to improve glycemic control in adults with type 2 diabetes mellitus. The most commonly reported side effect with BARs is gastrointestinal intolerance, including bloating, gas, abdominal pain, and constipation. BARs also interfere with the absorption of some drugs (e.g., digoxin, thyroxine, iron, fat-soluble vitamins, and warfarin), necessitating their administration 1 hour before or 4 hours after the BAR is given.\textsuperscript{11,15,16}

Combination Drug Therapy
Many patients require aggressive treatment to reach LDL-C goals; thus, combination therapy is often warranted. Adding ezetimibe, a BAR or niacin to a low-dose statin regimen generally produces a LDL-C reduction similar to that achieved by quadrupling the statin dose. If statins cannot be used because of patient intolerance or contraindications, ezetimibe, niacin or a BAR is an effective regimen for lowering LDL-C levels.\textsuperscript{11,14} If further triglyceride lowering is needed, a fibrate or niacin can be added to statin therapy. However, extra monitoring for signs and symptoms of myopathy is needed with these combinations.\textsuperscript{1,11,14}

Conclusion
Comprehensive treatment of hyperlipidemia has the potential to help millions of people avoid disabling and life-shortening CHD events.

References:


15. Welchol (colesevelam) prescribing information. Daiichi Sankyo, Inc. Parsippany (NJ); October 2009.