**BACKGROUND**

Cardiology Dyslipidemia has been clearly associated with CAD coronary heart disease risk. Therapeutic Intervention studies have demonstrated that cholesterol modification, especially reduction in low-density lipoprotein cholesterol (LDL-C) levels, is associated with favorable effects on reduction in coronary heart disease events and in many cases, stroke events, especially in patients at high risk for CHD. Cholesterol-lowering guidelines have had LDL-C as the primary target for lipid modification.

NCEP guidelines were evidence based, used CHD risk assessment for the recommended LDL-C targets and were relatively simple for health care providers, patients, and payers to understand.

ATP III update recommendations of 2004 recommended a LDL-C goal lower than 100 mg/dL for high-risk patients, with an optional goal of lower than 70 mg/dL for very high-risk patients. This update also recommended the initiation of dietary therapy and LDL-C–lowering drugs for all patients over goal, with a planned LDL-C reduction of 30% to 40%. Heart Protection Study (HPS), evaluated the effects of simvastatin, 40 mg daily, versus placebo in a group of 20,536 patients aged 40 to 80 years at high risk for CHD followed for a 5-year period. Pravastatin or Atorvastatin Evaluation and Infection–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) was designed to test noninferiority of a less aggressive cholesterol-lowering regimen. Intensive LDL-C level lowering with atorvastatin, 80 mg daily, reduced cardiovascular risk more than standard drug therapy with pravastatin, 40 mg, in a group of high-risk patients hospitalized for acute coronary syndromes. The mean LDL-C level attained was 95 mg/dL with pravastatin and 62 mg/dL with atorvastatin. The study demonstrated a 16% reduction in the composite cardiovascular end point in the atorvastatin group compared with the pravastatin group ($P < 0.005$).

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Arm (ALLHAT-LTT), and Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) also influenced the ATP III revised guidelines trial that evaluated two antihypertensive regimens and a lipid-lowering arm with atorvastatin. AHA/ACC guidelines for secondary prevention of CHD released in 2006 placed more weight behind the optional goal of LDL-C lower than 70 mg/dL in high-risk patients with CHD, based on data accrued from the Treat to New Targets (TNT) and Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trials.

Risk models such as the Framingham risk score are used in risk adjustment. Framingham risk score does not include some of the newer markers such as high-sensitivity C-reactive protein (hsCRP) or albuminuria. hsCRP is associated with increased risk for CHD, even when adjustments are made for other risk factors. Current guidelines suggest that hsCRP be used to help in risk assessment in patients who have intermediate risk for CHD.

**LIPID LOWERING: NON-PHARMACOLOGICAL THERAPY**

**Therapeutic Lifestyle Changes: Diet Recommendations**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>25%-35% of total calories</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>Less than 7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
</tr>
<tr>
<td>Trans fat</td>
<td>&lt;1% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/day</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50%-60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20-30 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Total calories (energy)</td>
<td>Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain.</td>
</tr>
</tbody>
</table>

- Consume diet rich in fruits and vegetables.
- Choose whole-grain, high-fiber foods.
- Consume fish, especially oily fish, at least twice a wk.
- Avoid fish with potential for mercury contamination.
- Minimize intake of beverages and foods with added sugars.
- Choose and prepare foods with little or no salt.
diminish inflammation by decreasing plasma low-density lipoprotein (LDL) cholesterol and removing pro-inflammatory modified LDL from the artery wall. However, in vitro studies suggest that statins may have non-LDL anti-inflammatory effects. For example, statins also decrease cholesterol-independent isoprenoids and prevent activation of the proinflammatory rho kinase. The correlations between changes in LDL and CRP are small among individuals within any single study, the intraindividual variation in the measurement of these variables can cloud any true relationships.

A novel use of meta-analysis techniques assessed the relationship between group changes in LDL cholesterol and CRP from a variety of statin and nonstatin interventions designed to lower LDL cholesterol. This analysis clearly revealed a strong relationship between the change in LDL cholesterol and change in CRP, a marker of inflammation in atherosclerosis. The principal reason that single studies rarely show a correlation between change in LDL and CRP among individual subjects is that any correlation is obscured by measurement error that is largely related to the intraindividual variation in LDL and CRP. High correlation between changes in LDL and CRP (r = 0.80) strongly support a causal link between changes in LDL and arterial inflammation in atherosclerosis, and complements histopathological studies in animals and humans using a variety of statin and nonstatin therapies. Across a range of LDL reduction typically seen with statin therapy (20% to 60%), 90% or more of the change in CRP was related to LDL reduction and 10% or less was related to non-LDL effects of statins.

LIPID LOWERING: STATIN THERAPY

Statin use results in a 20% to 60% decrease in LDL-C levels, with more modest increases in HDL-C and decreases in triglyceride levels. The curve of cholesterol lowering versus risk reduction is therefore probably best understood as a direct logarithmic relationship as shown in the figure. To date, the lower limit of cholesterol that still results in risk reduction is unknown, although many experts have theorized that it may be at a LDL-C level of 40 mg/dL.

Studies of the so-called pleiotropic effects of statins have suggested that they may also improve endothelial function, have antioxidant and anti-inflammatory effects, and stabilize atherosclerotic plaque. High-dose statin has become part of standard care for patients presenting with acute coronary syndrome, based in part on the results of the PROVE-IT trial.

CRP, LDL-C LOWERING AND STATINS

Inflammation plays a central role in the progression and destabilization of atherosclerosis that herald cardiovascular events. Modest elevations of plasma markers of inflammation, such as C-reactive protein (CRP), are associated with future risk of cardiovascular disease. Statins can diminish inflammation by decreasing plasma low-density lipoprotein (LDL) cholesterol and removing pro-inflammatory modified LDL from the artery wall. However, in vitro studies suggest that statins may have non-LDL anti-inflammatory effects. For example, statins also decrease cholesterol-independent isoprenoids and prevent activation of the proinflammatory rho kinase. The correlations between changes in LDL and CRP are small among individuals within any single study, the intraindividual variation in the measurement of these variables can cloud any true relationships.

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HIGH C-REACTIVE PROTEIN AND NORMAL LDL CHOLESTEROL: IMPLICATIONS FROM THE JUPITER STUDY

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized, double-blind, placebo-controlled trial aimed to determine whether statin treatment can lower cardiovascular events in men and women with normal low-density lipoprotein (LDL) cholesterol and elevated C-reactive protein levels. 17,802 subjects from 1315 sites in 26 countries with LDL cholesterol < 130 mg/dL, high-sensitivity C-reactive protein (hs-CRP) level of 2.0 mg/L, and triglycerides < 500 mg/dL randomized to either rosuvastatin 20 mg daily or placebo. After a median follow-up of 1.9 years, patients in the rosuvastatin group had a 44% lower rate of the combined endpoint than the placebo group. Rosuvastatin decreased LDL cholesterol by 50% and hs-CRP by 37%. No increase in myopathy or cancer was noted in the rosuvastatin group, although there was a higher incidence of physician-reported diabetes. Further analysis of the 15,548 initially healthy men and women participating in the JUPITER trial (87% of full cohort) was recently released. It prospectively assessed the effects of rosuvastatin 20 mg versus placebo on rates of non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularisation, or cardiovascular death (prespecified endpoints) during a

Nutrient  Recommended Intake

Consume alcohol in moderation. Men, two drinks/day; women, one drink/day
When eating food prepared outside the home, follow the American Heart Association diet and lifestyle recommendations.


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maximum follow-up of 5 years (median 1–9 years), according to on-treatment concentrations of LDL cholesterol (≥1 8 mmol/L or <1 8 mmol/L) and hsCRP (≥2 mg/L or <2 mg/L).

In the Jupiter study, participants allocated to rosvastatin who achieved LDL cholesterol less than 1 8 mmol/L had a 55% reduction in vascular events (hazard ratio 0.45, p<0.0001), and those achieving hsCRP less than 2 mg/L a 62% reduction (HR 0.38, p<0.0001). Although LDL cholesterol and hsCRP reductions were only weakly correlated in individual patients (r values <0.15), a 65% reduction in vascular events was recorded in participants allocated to rosvastatin who achieved both LDL cholesterol less than 1 8 mmol/L and hsCRP less than 2 mg/L versus a 33% reduction in those who achieved one or neither target. In participants who achieved LDL cholesterol less than 1 8 mmol/L and hsCRP less than 1 mg/L, a 79% reduction was noted (HR 0.21, p<0.0001). Achieved hsCRP concentrations were predictive of event rates irrespective of the lipid endpoint used, including the apolipoprotein B to apolipoprotein AI ratio.

To address whether the use of alternative lipid cutoffs might the study findings, the above analyses was repeated with an LDL cholesterol target of less than 1.4 mmol/L (<55 mg/dL) (the median on-treatment LDL cholesterol concentrations within JUPITER) rather than the clinical target of LDL cholesterol less than 1.8 mmol/L. In this sensitivity analysis, participants who achieved the targets of LDL cholesterol less than 1.4 mmol/L and hsCRP less than 2 mg/L had better clinical outcomes than did those who did not.

Despite the pathophysiological evidence, in low-risk primary prevention populations with raised LDL cholesterol or hsCRP, initial interventions should remain lifestyle recommendations for dietary restriction, exercise, and smoking cessation. However, for people choosing to start pharmacological prophylaxis, reductions in both LDL cholesterol and hsCRP are indicators of the success of treatment with statin therapy.

REFERENCES


