Combination Therapy versus Monotherapy for Dyslipidemia: Are 2 Pills Better than 1?

Accumulating clinical trial evidence and recently updated national guidelines support more aggressive efforts to reduce levels of circulating atherogenic lipoproteins. To meet the new, intensified low-density lipoprotein cholesterol goals issued by the Third Adult Treatment Panel of the National Cholesterol Education Program, dyslipidemic patients at high cardiovascular risk may require reductions in low-density lipoprotein cholesterol levels that exceed 50%. Combination drug therapy can help in reaching greater decreases in low-density lipoprotein cholesterol than monotherapy and improve other lipid parameters, including triglycerides and high-density lipoprotein cholesterol. However, it may also increase the side effects and costs, and reduce compliance. The initial choice of an effective statin may be an important first step in planning safe, aggressive, and cost-effective lipid reductions.

Accumulating evidence suggests that intensive lipid lowering produces greater clinical benefit than more moderate therapy. In a meta-analysis of 58 placebo-controlled, lipid-lowering trials (involving both statin and nonstatin therapy), mean decreases in low-density lipoprotein cholesterol (LDL-C) of 20, 40, and 62 mg/dL were associated with reductions in ischemic heart disease events of 20%, 31%, and 51%, respectively. Recent clinical trials of statin therapy have explored how already low LDL-C levels can be safely reduced even further in high-risk patients, and to what extent aggressive lipid lowering will mitigate cardiovascular risk. Results indicate that intensive statin therapy safely reduces LDL-C to levels that are even lower than those originally proposed in the 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. Moreover, the cardiovascular benefits of aggressive lipid lowering include significant reductions in major coronary events, as well as decelerated progression and even stabilization of coronary atheroma.

In response to these findings, the NCEP issued an update to the ATP III guidelines in 2004. They reiterated their recommendation of less than 100 mg/dL as the LDL-C goal in high-risk persons, suggested the same goal as a therapeutic option in moderately high-risk persons, and recommended a target of less than 70 mg/dL in very-high-risk individuals (Table 1). Persons at high risk for cardiovascular events include those with coronary heart disease (CHD) or CHD risk equivalents (ie, symptomatic carotid artery disease, peripheral vascular disease, abdominal aortic aneurysm, diabetes...
mellitus, and multiple CHD risk factors conferring a 10-year risk for CHD of >20%). Patients at “very high risk” are those with many poorly controlled major risk factors, especially diabetes, or a recent acute coronary syndrome, such as unstable angina or myocardial infarction.

To help improve compliance and success rates in achieving these new, intensified ATP III LDL-C targets, physicians can prescribe more effective statins and therapeutic lifestyle regimens, increase statin dosages more aggressively, and monitor patients more closely. When near-maximum or maximum-dose monotherapy falls short of the goal, a strategy of growing popularity (and one incorporated in ATP III algorithms) is to add a second or even a third lipid-lowering agent. Although combined drug therapy may indeed reduce LDL-C further, perhaps by as much as 20%, questions remain regarding side effects, compliance, and added costs.

This review examines the options for aggressive management of dyslipidemia, including titrating statin doses, choosing a more effective statin, or trying combination therapy when an initial strategy fails to achieve desired goals. The advantages of statin monotherapy and the rationale behind trying effective statin monotherapy before resorting to combination therapy are also discussed.

**Recommendations of the ATP III Guidelines**

The ATP III guidelines lay out an algorithm for starting and intensifying LDL-lowering drug therapy in patients with elevated LDL-C (Figure). The usual first-line drug, in conjunction with new or existing diet therapy, is a statin. If, after 6 weeks, the patient does not achieve the LDL-C goal, the options are to increase the dose of statin monotherapy or add a bile acid sequestrant or nicotinic acid. Once the LDL-C goal is met, attention should turn to other lipid risk factors that may be present, particularly when triglyceride levels are 200 mg/dL or higher, which often coexist with low levels of high-density lipoprotein cholesterol (HDL-C) and small, dense LDL particles (ie, atherogenic dyslipidemia).

For patients with this disorder, the secondary target of lipid reduction becomes non–HDL-C (defined as total cholesterol minus HDL-C or LDL-C plus very-low-

---

**Table 1**

Lipid-lowering drug therapy: updated NCEP ATP III risk categories, LDL-C cut points, and LDL-C goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Consider drug therapy, LDL-C, mg/dL</th>
<th>LDL-C goal, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk*</td>
<td>&gt;100</td>
<td>&lt;100 (optional in very-high-risk persons)</td>
</tr>
<tr>
<td></td>
<td>• CHD or CHD risk equivalents†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10-year risk &gt;20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Very high risk: CVD + multiple major risk factors‡</td>
<td></td>
</tr>
<tr>
<td>Moderate high risk*</td>
<td>&gt;130</td>
<td>&lt;130 (therapy optional)</td>
</tr>
<tr>
<td></td>
<td>• 2+ risk factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10-year risk 10-20%</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&gt;160</td>
<td>&lt;130 (therapy optional)</td>
</tr>
<tr>
<td></td>
<td>• 2+ risk factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10-year risk &lt;10%</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&gt;190</td>
<td>&lt;160 (therapy optional)</td>
</tr>
<tr>
<td></td>
<td>• 0-1 risk factor</td>
<td></td>
</tr>
</tbody>
</table>

*In these persons, intensity of therapy should be sufficient to achieve at least a 30% to 40% reduction in LDL-C.
†Noncoronary clinical atherosclerotic disease, diabetes, and multiple CHD risk factors with 10-year CHD risk >20%.
‡For example, patients with diabetes who have multiple poorly controlled risk factors or patients with a recent acute coronary syndrome.

ATP = Adult Treatment Panel; CHD = coronary heart disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program.

density lipoprotein cholesterol), with a goal of 30 mg/dL above the LDL-C goal. If the initial statin dose is not sufficiently powerful to also lower non–HDL-C, a higher dose is recommended to reach the non–HDL-C goal, with the addition of a fibrate or nicotinic acid if necessary.6,8 As demonstrated in the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial, atorvastatin calcium (Lipitor) and rosuvastatin calcium (Crestor) used as monotherapy yielded reductions in non–HDL-C of 34% to 48% and 42% to 51%, respectively, across their established dosing ranges.6

The ATP III update notes that for moderate- and high-risk patients, initial statin therapy should be aggressive enough to reduce LDL-C by at least 30% to 40%.6 However, if high-risk patients—who may, for example, have baseline LDL-C levels of more than 130 mg/dL or even more than 200 mg/dL—are to attain a goal of less than 70 mg/dL, reductions of 46% and much more may be needed. This is a tall order: lowering LDL-C by more than 50% is difficult with most statins, even at high doses or with added drugs.6 Reductions of this magnitude are usually possible only with maximum doses (40-80 mg/day) of atorvastatin, the starting to maximum doses (10-40 mg/day) of rosvuastatin, or the maximum dose (80 mg/day) of simvastatin (Zocor).9,11,12

Titrating Statin Doses

Although the NCEP ATP III treatment algorithm advocates increasing statin doses if LDL-C goals are not met, doubling the statin dose produces only about a 6% additional reduction in LDL-C.8 Moreover, although statins are considered generally safe, higher doses are associated with increased rates of toxicity, especially myopathy and elevated serum transaminase levels.13 In the A to Z trial, for example, treatment with simvastatin, 80 mg/day after an acute coronary syndrome was associated with a significantly higher rate of myopathy (0.4%) compared with lower doses of 20 or 40 mg/day (0%；P = .02).4 In both the Pravastatin and Atorvastatin Evaluation and Infection Therapy (PROVE IT) and Treating to New Targets (TNT) trials, high-risk patients treated with atorvastatin, 80 mg/day, had persistently elevated liver enzymes (3.3% vs 1.1% with pravastatin sodium [Pravachol], 40 mg/day；P < .001, and 1.2% vs 0.2% with atorvastatin, 10 mg/day；P < .001, respectively).3,5 The increased risk of side effects at higher statin doses may be one reason physicians are reluctant to titrate statins, as shown in a study of 2829 high-risk patients with dyslipidemia who were treated mainly with simvastatin and atorvastatin.14 Only 14% of the 1464 patients who fell short of their LDL-C goal (ie, <100 mg/dL) with the initial statin dose were up-titrated during 6 months of follow up. Other reasons include increased cost and the need for additional follow up, two factors that may foster patient noncompliance.15

Statins’ Varied Efficacies

Statins vary in efficacy per milligram dose and therefore also differ in starting dose (as well as in the standard dose—the dose associated with a 30%-40% reduction in LDL-C).5,6 As shown in Table 2, the less efficacious statins—fluvastatin (Lescol), lovastatin (Mevacor), pravastatin, and simvastatin—have starting doses of 20 to 40 mg/day. The recommended starting doses of atorvastatin and rosuvastatin are 10 mg/day.11,12,17-20
Combination Therapy versus Monotherapy for Dyslipidemia

Using a lower initial dose of a less effective statin may set the stage for failing to reach and maintain intensive LDL-C goals.\textsuperscript{21} In contrast, very effective statins that produce large LDL-C reductions at low initial doses can help patients achieve their LDL-C goals and reduce the need for titration or additional agents.\textsuperscript{22}

In a study of 5 statins—atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin initiated at starting doses and titrated as necessary to reach LDL-C goals, atorvastatin produced significantly greater LDL-C reductions than the other statins (36% at 6 weeks and 42% at 54 weeks; \(P < .01\)), enabling more patients to reach their LDL-C goals.\textsuperscript{21} Of note, the LDL-C reduction at the starting dose for any statin strongly correlated with the proportion of patients who maintained goal levels (\(r = -.84\)). Similarly, in the STELLAR trial, 53% of patients taking the usual starting dose of rosvuvasatin (10 mg/day) reached LDL-C levels of less than 100 mg/dL within 6 weeks, compared with 18% of those taking the starting dose of atorvastatin (10 mg/day) and 14% of those taking the starting dose of simvastatin (20 mg/day; \(P < .002\) vs rosvuvasatin for both comparisons).\textsuperscript{10} ATP III LDL-C goals were achieved by 82% to 89% of STELLAR patients treated with rosvuvasatin, 10 to 40 mg/day, compared with 69% to 85% of those treated with atorvastatin, 10 to 80 mg/day; 51% to 82% of those treated with simvastatin, 10 to 80 mg/day; and 31% to 55% of those treated with pravastatin, 10 to 40 mg/day.\textsuperscript{25}

### Switching Statins

Changing therapy to improve efficacy may serve patients well. A study conducted at a Veterans Affairs medical center found that an institutionwide conversion from pravastatin to a similar dose of simvastatin (mean dose, approximately 25 mg/day) increased the LDL-C goal achievement rate from 44% to 69% (\(P < .001\)), with higher-risk patients having the greatest success rate.\textsuperscript{24} In another group of high-risk patients, substituting atorvastatin (10 mg/day) for usual doses of pravastatin (20-40 mg/day) and simvastatin (20 mg/day) resulted in greater or equal reductions in LDL-C and higher rates of goal achievement (all at an annual cost savings of >$550 per patient).\textsuperscript{26} Likewise, a switch to rosvuvasatin from usual starting doses of atorvastatin, simvastatin, or pravastatin significantly boosted goal achievement for high-risk patients.\textsuperscript{25} Changing from one statin to another in these studies was well tolerated. The potential to reduce the risk of statin-related adverse effects may be an important factor when considering a switch to lower doses of more effective statins.

### Combination Therapy

The recent increase in the prevalence of obesity, the metabolic syndrome, and diabetes in the United States has led to a higher incidence of mixed dyslipidemias, which usually require treatment with more than 1 agent.\textsuperscript{7,22}
resident & staff physician
and rosuvastatin alone
among elderly patients taking

experimental findings suggest that gemfibrozil

pravastatin is not significantly me-

in one study, coadministration of rosu-

combination therapy would likely reduce compliance further.

Drug interactions are more likely to occur when combining agents that share the same metabolic pathway. For example, many drugs are metabolized in the liver by the cytochrome (cy) P450 family of enzymes; CYP3A4, the major isoenzyme of the CYP450 group, is involved in the metabolism of at least 150 known drugs, including atorvastatin, lovastatin, and simvastatin. The risk of myopathy increases when these statins are used with drugs that share and inhibit the CYP3A4 pathway (eg, azole antifungals, cyclosporine [Gengraf, Neoral, Sandimmune], macrolide antibiotics), potentially causing statin concentrations to rise to toxic levels. Pravastatin is not significantly metabolized by the cy enzyme system, and rosuvastatin does not depend on the CYP3A4 pathway but rather on CYP450 isoenzymes 2C9 and 2C19, whose inhibition may not be as clinically important.

Risk is also elevated when an added drug has its own myotoxic potential. The main example here is gemfibrozil (Lopid), which increases myopathy independently but most noticeably in combination with statins. Experimental findings suggest that gemfibrozil interacts with statins not through the CYP3A4 pathway but by inhibiting glucuronidation, a pathway needed for the clearance of active statin metabolites.

Fenofibrate (eg, Antara, Tricor, Triglide), however, has less of an impact on glucuronidation, which may explain this drug’s relative safety when combined with statins. In one study, coadministration of rosvastatin, 10 mg/day, and fenofibrate, 67 mg 3 times daily, for 7 days in healthy men caused no significant changes in plasma concentrations of either agent. In addition, the combination of simvastatin, 10 mg/day, and fenofibrate, 200 mg/day, evinced no interactions but improved triglyceride and HDL-C levels in patients with atherogenic dyslipidemia. However, statin–fenofibrate combinations may have little to add to LDL-C reductions if the statin monotherapy is sufficiently powerful.

Combining a statin with niacin addresses elevated LDL-C levels along with HDL-C and triglyceride abnormalities and thus is frequently used in patients with atherogenic dyslipidemia. The combination of simvastatin (mean, 13 mg/day) and slow-release niacin (mean, 2.4 g/day) reduced LDL-C by 42% and raised HDL-C by 26% (both comparisons, $P < .001$ vs baseline) in a study of patients with coronary disease and low HDL-C. This combination also lowered rates of coronary atheromatous plaque progression and major cardiovascular events during a 3-year period compared with placebo.

However, as with statin–fenofibrate therapy, statin–niacin combination therapy may not improve on effective statin monotherapy when the goal is LDL-C lowering. In a study of patients with atherogenic dyslipidemia, rosuvastatin 40 mg/day monotherapy reduced LDL-C significantly more (by 48%) than either rosuvastatin, 10 mg/day, plus extended-release niacin, 2 g/day (36% reduction; $P = .007$), or niacin alone (0.1% reduction; $P < .001$). Rosuvastatin alone was also better tolerated than the combined drugs or niacin alone, mainly because of niacin-induced flushing, pruritus, and rash.

Bile acid sequestrants are an effective addition to statin therapy for furthering LDL-C reduction, with the combination reducing LDL-C by as much as 70%. These drugs appear to lower the bioavailability of statins but not at the expense of efficacy or safety. Their chief drawback has always been gastrointestinal (GI) side effects, such as constipation. In a 6-week study, however, coadministration of the new bile acid sequestrant colesvelam HCl (WelChol), 2.3 or 3.8 g/day, and simvastatin, 10 or 20 mg/day, resulted in greater LDL-C reductions than with either drug alone, and GI side effects were generally mild.

The combination of a statin and ezetimibe (Zetia), a recently approved cholesterol absorption inhibitor, has reduced LDL-C more effectively than statin monotherapy in several comparisons. In a study comparing simvastatin alone with simvastatin plus ezetimibe, the combination decreased LDL-C by an additional 14% compared with the monotherapy ($P < .01$). In high-risk patients, ezetimibe, 10 mg/day, plus simvastatin, 10 to 40 mg/day, outperformed simvastatin, 20 mg/day

February 2006 resident & staff physician 5
alone, allowing significantly more patients to reach their LDL-C goal of less than 100 mg/dL (P < .001) after 5 weeks of treatment.\textsuperscript{2} A fixed-dose combination of simvastatin, 10, 20, 40, or 80 mg/day, and ezetimibe, 10 mg/day (Vytorin), was approved for marketing in 2004. Positive results have also been reported with ezetimibe plus atorvastatin, 10 mg/day; the combination was as effective as atorvastatin, 80 mg/day, with each regimen reducing LDL-C by half.\textsuperscript{3} In addition, after ezetimibe was given to high-risk, severely dyslipidemic patients (including patients with familial hypercholesterolemia) who were already receiving rosvastatin, 40 mg/day, the combination lowered LDL-C an additional 28% (P < .001).\textsuperscript{4}

The ezetimibe–statin combinations were well tolerated in all these comparisons, and a small study of ezetimibe plus rosvastatin, 10 mg/day, found no evidence of pharmacokinetic interactions between the drugs.\textsuperscript{5} However, there are case reports of the development of myopathy when ezetimibe was added to high doses of atorvastatin or fluvastatin,\textsuperscript{6} and in February 2005, a public advisory was issued in Canada regarding myopathy (as well as hepatitis, pancreatitis, and thrombocytopenia) associated with the use of ezetimibe. It is not clear whether a statin was coadministered in the cases prompting the advisory.\textsuperscript{7}

**Conclusion**

Given the weight of the evidence favoring intensification of lipid-lowering therapy, national guidelines have reduced LDL-C targets further, which has enlarged the pool of patients needing aggressive treatment. Reductions in LDL-C of more than 50% may be necessary, an objective hindered by barriers such as inadequate drug efficacy and use, concerns over side effects with high-dose therapy, or noncompliance with treatment. Solutions may be found in well-considered selection and dosing of statin monotherapy; some statins cannot produce recommended LDL-C reductions even at maximum doses, whereas more powerful statins have allowed patients to achieve their LDL-C goals at lower doses without the need for upward titration. Switching from a less-effective to a more-effective statin to intensify therapy is a rational and safe option. Combination therapy is a popular option for treating combined hyperlipidemia and atherogenic dyslipidemia. Uncertainties remain about the safety and tolerability of some combinations, even those that promise to lower rather than raise medication costs. Legitimate questions also remain about whether combinations of lipid-lowering drugs reduce cardiovascular event rates better than single-agent regimens. For now, physicians might best serve intensive-therapy goals by first exhausting the more effective choices in monotherapy.

**SELF-ASSESSMENT TEST**

1. Which of the following strategies is NOT appropriate for intensive lipid management?
   A. LDL-C goal of <100 mg/dL in high-risk patients
   B. LDL-C reductions of at least 30% to 40%
   C. Uptitration of statin doses
   D. Preference for combination therapy over effective monotherapy

2. Which of the following statements about the CYP450 enzyme pathway is true?
   A. It metabolizes only pravastatin among statin drugs
   B. If inhibited by coadministered drug(s), it may be responsible for drug interactions
   C. It is present only in men
   D. It metabolizes fewer than 10 types of therapeutic drugs

3. Which of the following options is NOT an LDL-C goal of the 2004 update to the NCEP ATP III guidelines?
   A. <100 mg/dL in high-risk persons
   B. <100 mg/dL in moderately high-risk persons
   C. <130 mg/dL in low-risk persons
   D. <70 mg/dL in very-high-risk persons

4. Which statin and dosage cannot achieve LDL-C reductions >50% as monotherapy?
   A. Atorvastatin, 80 mg/day
   B. Rosuvastatin, 10 mg/day
   C. Simvastatin, 80 mg/day
   D. Pravastatin, 40 mg/day

5. Which of the following statements about atherogenic dyslipidemia is NOT true?
   A. It is characterized by triglyceride levels >200 mg/dL and low HDL-C
   B. It is characterized by triglyceride levels >200 mg/dL and low HDL-C
   C. It calls for targeting non–HDL-C to 30 mg/dL above LDL-C goal
   D. It is treatable with statin alone or with statin plus fibrate or niacin

(Answers at end of reference list)

**References**

1. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low-density lipoprotein cholesterol, ischaemic heart disease, and
Combination Therapy versus Monotherapy for Dyslipidemia

32. Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. Am J Cardiol. 2002;90(suppl 1B):50K-60K.
44. Stein EA, Harris S, Schlieman M, et al, Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: effects on low-density lipoprotein cholesterol and C-reactive protein. Abstract presented at the American College of Cardiology Annual Scientific Sessions, March 6-9, 2005; Orlando, Fla.


February 2006 Resident & Staff Physician 7