

## Improving Cholesterol Control in Managed Care Populations

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### **Presentation Summary**

Cholesterol management has clearly emerged as a top priority for prevention-oriented management of coronary artery disease, and National Cholesterol Education Program (NCEP) guidelines provide the best treatment targets for these efforts. However, even in the highest risk patients, where managed care organizations naturally tend to focus their prevention budgets, the

percentage of patients attaining NCEP targets is dismal. To improve success rates in patients requiring pharmacologic therapy, more effective use of new and existing drug therapies may be required. This article provides an update on current options for lipid-modifying drug therapy and offers examples of combination regimens that may assist practitioners in attaining target lipid levels.

All integrated health systems and managed care organizations (MCOs) now acknowledge the benefits of lowering elevated low-density lipoprotein cholesterol (LDL-C) levels. With their protocols for cholesterol screening and risk assessment, member education programs on diet and exercise, and sanctioned formularies for lipid-lowering drug therapy, managed care groups are in many ways leading today's prevention-based fight against coronary heart disease (CHD). In fact, the value of cholesterol reduction is now so deeply imbedded in the definition of quality medical care that the Health Plan Employer and Data Information Set (HEDIS) has established standardized measures to assist purchasers in comparing the

cholesterol management performance of competing plans.<sup>1</sup>

### **The Managed Care Perspective**

The broad goal of cholesterol control is universally accepted. This widespread acceptance has its origins in 2 main lines of evidence: the first is the epidemiologic evidence showing that total and LDL-C are important risk factors in cardiovascular disease,<sup>2</sup> and the second is the resounding evidence from clinical trials showing that reduction of LDL-C (especially with statins) significantly reduces CHD.<sup>3-8</sup> One general rule is that each 10% reduction in LDL-C translates into a 15% reduction in CHD risk within 5 years of treatment.<sup>9</sup> Given the tremendous direct costs of hospitalization and cardiac interventions

associated with CHD,<sup>10</sup> the decision to reimburse for treatment related to cholesterol reduction seems justifiable economically—to a point.

The exact point at which cholesterol reduction remains cost effective is debatable. In the managed care setting, with its natural emphasis on shorter term returns on investment, the most aggressive treatment approaches for hyperlipidemia are still usually reserved for patients with established CHD and for primary prevention patients with a “CHD risk-equivalent,” such as is seen in patients with diabetes and those with multiple risk factors. For low- and intermediate-risk patients, primary prevention efforts are usually based on lifestyle modification, including a low saturated fat diet. This intuitive bias toward a risk-stratified cholesterol reduction is supported by some pharmacoeconomic analyses. Recently, secondary prevention with a statin was shown to be cost effective for all risk subgroups and cost saving in some of the highest risk subgroups.<sup>11</sup> However, in primary prevention, the study found statins to be cost effective only in patients with multiple risk factors.

The results of all such cost analyses are highly dependent on the study's perspective, the patient population, the time horizon, the institutional direct costs, and the assumptions regarding treatment efficacy, safety, and drug costs. These issues are so intertwined and changeable that accurate and up-to-date cost analysis is extremely difficult.

For example, a new pharmaceutical purchasing contract that reduces the acquisition price for a lipid-lowering drug may greatly influence the overall cost-effectiveness equation,<sup>12</sup> especially in the primary prevention setting, where drug costs constitute about 90% of total treatment costs.<sup>11</sup> Similarly, cost-related treatment decisions may be influenced by the long-term safety profile of the therapy

selected; for example, the level of drug side effects tolerated in an older, high-risk patient may prove unacceptable as primary prevention in a young, intermediate-risk health maintenance organization member.<sup>13</sup>

The pharmacy and therapeutics committees in most health systems lack the resources for the customized local pharmacoeconomic analyses that would be required to support and update decisions affecting clinical protocols or formularies. This makes guidance from the literature and the consensus statements of various national expert committees valuable, and it is exactly the role currently filled by the lipid treatment initiation and target levels defined and promulgated by the National Cholesterol Education Program (NCEP).<sup>14</sup> The current NCEP guidelines are widely accepted and have influenced treatment decisions since their release in 1993. A new set of NCEP treatment guidelines, which will incorporate the considerable evidence base that has accumulated since 1993, is under development and scheduled for release in the spring of 2001.

However, even the narrowest interpretation of existing treatment guidelines indicates that cholesterol-lowering medications are underutilized,<sup>15</sup> with fewer than one third of patients with CHD receiving drug therapy according to NCEP guidelines.<sup>16</sup> (See the Introduction to this supplement for more details.) Full acceptance of the NCEP guidelines would have major economic implications for MCOs,<sup>16</sup> so it is natural to expect an incremental and risk-based expansion of cholesterol treatment benefits.

To assist in this search for improved treatment approaches, this article reviews the current pharmaceutical options for cholesterol reduction and introduces potential new options. Various combination therapies are highlighted as examples of

new strategies for reaching NCEP goals or for treating mixed dyslipidemias. Of course, it must be understood that these treatment approaches are built on a strong foundation of lifestyle modification.

### Current Strategies for Cholesterol Treatment

The 4 main categories of cholesterol-lowering medications are the bile acid-binding resins, fibric acid derivatives, nicotinic acid, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Whereas the statins provide the backbone of lipid-lowering therapy today, many patients cannot tolerate statins or fail to achieve their target level on tolerable doses of this class. Thus, awareness of the full range of lipid-lowering options—as alternatives or potential adjuncts to the statins—is essential to those shaping formulary policies. As awareness of the current huge population of “half-treated” patients spreads and more high-risk patients need to be treated, a willingness to deploy the full range of pharmaceutical options becomes increasingly important.

*Bile Acid Sequestrants.* Bile acid resins block the normal enterohepatic circulation of bile acids by binding to them in the intestine. This action promotes conversion of cholesterol in hepatic cells into bile acids to replenish the depleted pool. The subsequent reduction in the hepatic cholesterol concentration leads to an upregulation of hepatic LDL receptors and enhanced removal of LDL-C from the circulation. Unfortunately, a conjoint increase in HMG-CoA reductase activity and cholesterol synthesis somewhat limits the reduction in hepatic cholesterol levels. In addition, the increased cholesterol synthesis also leads to an increase in the secretion of very low-density lipoprotein (VLDL) into the circulation, which may raise serum triglyceride levels,

especially in patients who are prone to hypertriglyceridemia.

The 2 oldest commercially available bile acid sequestrants, cholestyramine and colestipol, effectively reduce LDL-C by about 10% to 35%.<sup>17</sup> This class of agents was used in the first clinical trial to demonstrate a benefit from cholesterol reduction: the 7-year Lipid Research Clinics Coronary Primary Prevention Trial.<sup>18</sup> In fact, the significant reductions in fatal and nonfatal myocardial infarction seen in this pioneering trial led directly to the formation of the NCEP in 1985, the first set of cholesterol treatment guidelines in 1987, and the establishment of bile acid sequestrants as first-line agents for LDL-C reduction.

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The bile acid resins are nonsystemic and considered to be extremely safe. Because MCOs generally are still reluctant to endorse long-term statin therapy as primary prevention in low-to-moderate risk patients with elevated cholesterol, dietary changes and monotherapy with low-dose bile acid sequestrants are often recommended.<sup>13</sup> These agents are also a consideration in the management of women who are pregnant or lactating or in patients with impaired renal or hepatic function. They are also frequently used in combination with other lipid-modifying agents to further reduce LDL-C.

However, the use of bile acid resins has been limited by the common adverse effects of constipation and flatulence. Other limitations include

the potential for drug interactions, interference with fat absorption and fat-soluble vitamins, and dosage formulations (granules and extremely large tablets) that are unpalatable to patients. In treating a chronic condition that is essentially asymptomatic, such tolerance issues and patient preferences are of paramount importance. Because of the intolerance, cholestyramine and colestipol are often limited to use as adjuncts with statins or nicotinic acids or in patients with mildly elevated cholesterol.

A new agent in this class, colesevelam hydrochloride, is a nonabsorbed polymer with a high affinity and specificity for binding bile acids. This agent has not been associated with the severe constipating effects and many of the drug-drug interactions of the old bile acid sequestrants. In short-term trials, colesevelam effectively lowered LDL-C by 19% at a dose of 3.75 g/day.<sup>19</sup> Data from more than 1000 patients who received either placebo or colesevelam indicate that the rates of flatulence and constipation were 12% and 11%, respectively, in the colesevelam group versus 14% and 7%, respectively, in the placebo group (not significantly different at  $P > 0.05$ ).<sup>20</sup>

In one of the pivotal placebo-controlled trials for colesevelam, a dose of 3.8 g/day of colesevelam as monotherapy led to a sustained mean LDL-C decrease of 15% over a 24-week period ( $P < 0.0001$  versus placebo).<sup>20</sup> Over this same 6 months, the adherence rate for patients taking colesevelam ranged from 88% to 91% versus 92% for placebo. The rates of discontinuation because of adverse effects, including gastrointestinal intolerance, were 9% to 14% for the bile acid agent versus 6% for placebo. Triglycerides increased by about 5% to 10% in the colesevelam groups (versus 5% in the placebo group), and high-density lipoprotein cholesterol (HDL-C) also increased slightly. The

availability of this more tolerable and effective bile acid resin offers an alternative to statins in patients with low-to-moderate CHD risk who cannot achieve treatment goals with lifestyle modification alone or with the use of older bile acid-binding resins.

*Fibric Acid Derivatives.* Fibric acid derivatives include clofibrate, gemfibrozil, and fenofibrate. These agents have a complex and multifaceted mechanism of action. One principal action appears to involve activation of the nuclear transcription factor peroxisome proliferator-activated receptor alpha (PPAR alpha) that downregulates the expression of the apolipoprotein CII gene and upregulates the expression of apolipoprotein A1 gene. The former, coupled with an increase in fatty acid oxidation in the muscle by the drug, increases the activity of lipoprotein lipase, leading to enhanced hydrolysis of triglycerides from circulating lipoproteins. The latter PPAR alpha effect leads to an increase in HDL-C.

The chief clinical use of the fibrate class of drugs is to decrease triglyceride and increase HDL-C levels; it has a marginal or variable effect on LDL-C in the presence of hypertriglyceridemia. The Helsinki Heart Study in men without CHD (ie, primary prevention) has documented that fibrates effectively reduce coronary events (an overall 34% decrease in cardiovascular endpoints), with the greatest effects seen in patients with LDL-C levels greater than 175 mg/dL, triglyceride levels greater than 200 mg/dL, or HDL-C levels less than 35 mg/dL.<sup>21</sup> No difference was seen between treatment and placebo groups in total mortality or in cancer deaths, as had been observed in a previous clofibrate study.

More recently, the US Veterans Administration 5-year HDL Intervention Trial in males with CHD (ie, secondary prevention) demonstrated a 22% reduction in nonfatal

myocardial infarctions or deaths as a result of CHD ( $P = 0.006$ ) in patients receiving gemfibrozil compared with placebo.<sup>22</sup> Conversely, the 6-year Bezafibrate Infarction Prevention (BIP) study in patients with CHD reported a nonsignificant 9% reduction in fatal and nonfatal myocardial infarctions and sudden deaths. However, in a post-hoc analysis of a subgroup of BIP patients who had triglyceride levels greater than 200 mg/dL, a substantial 36% to 42% reduction in endpoints was observed, depending on whether the HDL-C was greater or less than 35 mg/dL.<sup>23</sup> These clinical trial results generally support the use of fibrates to reduce CHD risk, especially in patients with a mixed hyperlipidemic profile.

The potential development of gallstones is a major limitation of fibrate therapy, although this was not noted with gemfibrozil in the Helsinki Heart Study. Other potential side effects include dyspepsia, myositis, renal dysfunction, and abnormal liver function tests. Overall, about 5% to 10% of patients experience side effects.<sup>17</sup> The combination of gemfibrozil with statins for treatment of mixed dyslipidemias, although theoretically desirable, is hampered by the potential for an increased risk of myositis. However, if this combination is restricted to low doses of both drugs and to patients with normal hepatic and renal function, the incidence of myositis appears to be very low. Whether the combination of fenofibrate with statins carries the same risk as gemfibrozil with statins remains to be demonstrated.

**Nicotinic Acid.** A variety of immediate- and extended-release niacin products are available, many of which are available over the counter. These agents inhibit the mobilization of free fatty acids from the peripheral fat stores and thereby decrease hepatic triglyceride synthesis as well as VLDL production.

On average, full doses of niacin reduce LDL-C by about 20% to 25% and triglycerides by about 50%. Most dramatically, niacin can increase HDL-C by 25% to 30%, even with rather modest daily doses (eg, 1000 to 1500 mg/day); the effects of niacin on HDL-C usually exceed those seen with gemfibrozil.<sup>24</sup> Several studies have documented a reduction in coronary events with niacin, either alone<sup>8</sup> or in combination with agents that bind bile acids.<sup>25</sup> Niacin is best used for treatment of patients with mixed (combined) hyperlipidemia and in combination with a bile acid resin or statin to extend the LDL-C lowering effects.

The main drawbacks of niacin are related to flushing and hepatic toxicity. In particular, the vasodilatory side effects associated with immediate-release products (ie, flushing, itching, headache, feeling of warmth) significantly reduce the number of patients who are willing to take this drug. The extended-release formulation of niacin may be associated with less vasodilatory symptoms but with a risk of hepatic toxicity, especially when daily doses exceed 2000 mg/day. Because of the potential for hepatotoxicity, frequent liver monitoring with sustained-release niacin is required.

**Statins.** The 6 statins currently on the market (atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, and fluvastatin) dominate today's management of hyperlipidemia. These agents are indicated for treating both hypercholesterolemia and hypertriglyceridemia. They work by competitively inhibiting the HMG-CoA reductase activity, which blocks synthesis of cholesterol in the liver and thereby leads to increased LDL receptor expression and enhanced removal of LDL-C and LDL-C precursors from the plasma.

The overall clinical effect is a decrease in total cholesterol, LDL-C,

triglycerides, and apolipoprotein B; the statins also produce a slight increase in HDL-C. The clinical benefits of these lipid actions have now been demonstrated in a broad range of patients.<sup>3,6,7,26,27</sup> The LDL-C reductions of 20% to 60% as well as perhaps the beneficial actions on triglycerides (especially with atorvastatin<sup>28</sup>) and HDL-C have now been associated with significant decreases in total and CHD mortality in both primary and secondary prevention trials. The weight of this clinical evidence, plus the recent work demonstrating the potential for regression of atherosclerosis with these agents, has made this class of drugs a top choice in most lipid management protocols, especially in patients with particularly high total or LDL-C levels.<sup>29</sup>

The statins are very safe. Even the major side effects associated with statin therapy, such as increases in hepatic enzymes and myopathy, rarely are problematic. Hepatic enzyme elevations are usually mild, asymptomatic, and self-limiting, even with continued therapy. No cases of hepatic failure or transplant resulting from statin therapy have been reported. Periodic monitoring of liver function (eg, annually) is recommended. Myositis occurs in less than 1% of patients and is quickly reversed by withdrawing statin therapy. The risk of myositis rises with an increase in the blood levels of the active drug or metabolite. High drug levels are mostly encountered when high doses are used or when the statin is coadministered with other drugs that interfere with statin metabolism or excretion, such as cyclosporine, erythromycin, azole antifungals, and fibrates.<sup>17</sup>

Overall, 4% to 7% of patients who participate in clinical trials are withdrawn from statin therapy because of intolerable side effects.<sup>30</sup> In the clinical setting, where the drug is administered to patients who have numerous medical problems and are receiving

multiple drug therapies, this withdrawal rate is likely to be higher. Also, as doses of statins are increased to maximum levels, the relative risk of adverse effects increases. For example, an elevation in liver transaminase enzymes greater than 3 times the upper limit of normal has been reported in less than 1% of patients receiving 10 to 40 mg of atorvastatin daily but in greater than 2% of patients when 80 mg is used.<sup>31</sup> Similar trends have been reported with other statins. Concern for these dose-related adverse effects may be one reason for physicians' apparent lack of aggressiveness in achieving treatment goals.

In certain patients, adding a non-statin agent to the starting dose of the statin may be a better option for attaining the treatment goal than increasing the statin dose. The combination approach also provides new options for attacking mixed (combined) dyslipidemias.

### Strategies for Combination Therapy

As indicated in the introduction to this supplement, the majority of patients now receiving cholesterol-lowering therapy fail to meet NCEP targets. Health system administrators and clinicians in integrated health systems and MCOs often have large medical record databases that can help identify those higher risk patients who are undertreated, non-compliant, or failing to achieve NCEP goals.<sup>32</sup> The latest HEDIS guidelines also mandate follow-up checks of cholesterol, at least in the highest risk patients. Thus, as health systems become more aware of their treatment failure rates, new options for more aggressive therapy will need to be explored.

Because of the reluctance of many physicians to use higher doses of the cholesterol-lowering agents,<sup>13</sup> the concept of combination therapy may be an attractive alternative. Limiting

dose-related side effects while pushing LDL-C lower is one of the primary motivations for combination therapy. This is especially true for individuals with an LDL-C greater than 200 mg/dL who require a reduction beyond the 20% to 40% that is normally achievable with a single agent.<sup>17</sup> The opportunity to link complementary mechanisms and thereby favorably impact LDL-C as well as HDL-C, triglycerides, or other emerging CHD risk markers is another draw. A potential pitfall of combination therapy is the loss of dosing simplicity, a key factor in achieving high patient compliance and long-term cholesterol control.<sup>33</sup> The rationales and results of a few of the main combinations are described.

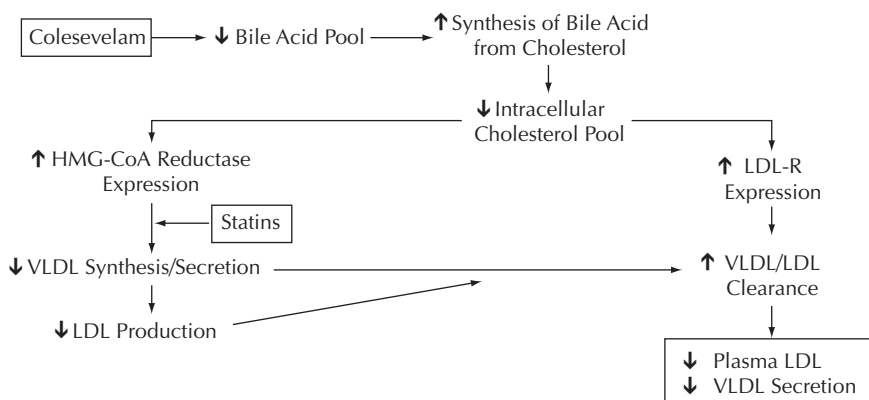
*Bile Acid Sequestrant Plus Niacin and/or Statin.* Because of their non-systemic and complementary modes of action, the bile acid sequestrants are often used in combination with nicotinic acid; such a combination can lower LDL-C levels by 45% to

60%.<sup>17,25</sup> Unfortunately, the side effects of niacin and the bile acid resin usually limit the use of the combination. Limiting the daily dose of niacin to 2 g or less and the resin to less than 12 g (3 packets) may provide a more tolerable regimen with reasonably good LDL-C lowering and HDL-C elevating effects.

Adding a resin to statin therapy can also reduce LDL-C 40% to 50%.<sup>17</sup> A triple combination of bile acid resin with niacin plus a statin has been reported to decrease LDL-C by as much as 70%.<sup>34</sup> However, for these combinations to be maximally effective, daily doses of the bile acid resin, colestipol or cholestyramine, should be kept to a minimum to avoid at least some of the gastrointestinal side effects.

*Colesevelam Plus Statin.* The availability of a new bile acid sequestrant, colesevelam, which appears to be more tolerable, may allow clinicians to take full advantage of the complementary actions of statins or

**Figure 1.** Complementary Mechanisms of Action: Colesevelam Plus Statin



HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-R = low-density lipoprotein receptor; VLDL = very low-density lipoprotein.

niacin with bile acid resins. As shown in Figure 1, the upregulation of HMG-CoA reductase activity, which normally accompanies treatment with bile acid-binding agents, is blocked by the coadministered statin. This complementary action not only enhances plasma LDL-C reduction but may also limit the modest short-term increases in triglycerides associated with bile acid sequestrant monotherapy.<sup>17,19</sup>

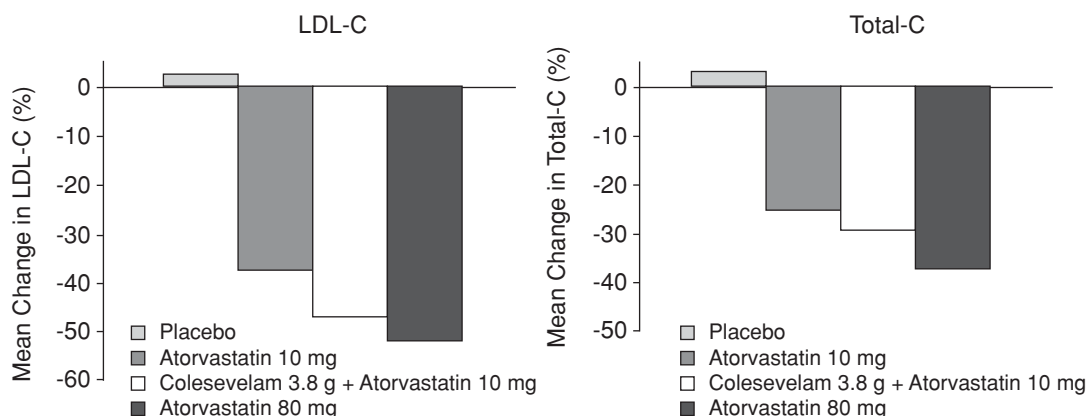
Colesevelam has been tested in combination with 3 statins: lovastatin, simvastatin, and atorvastatin.<sup>20</sup> Starting doses of each agent have produced impressive LDL-C reductions of 35% to 48%. The 48% reduction in LDL-C achieved with the starting doses of colesevelam (3.8 g) and atorvastatin (10 mg) was practically the same as the 53% reduction observed with atorvastatin 80 mg (Figure 2). In these colesevelam plus statin trials, the HDL-C was, in general, modestly increased and triglycerides were either modestly decreased or unchanged. There was no change in the adverse-event profile compared

with colesevelam monotherapy, that is, colesevelam was associated with substantially fewer gastrointestinal side effects than would have been anticipated with traditional bile acid sequestrants. The availability of colesevelam should provide an important alternative in designing effective LDL-C-reducing therapies for secondary prevention and high-risk primary prevention patients whose LDL-C goal is less than 100 mg/dL.

*Gemfibrozil Plus Statin or Niacin.*

Patients with dyslipidemia and the metabolic syndrome marked by elevated triglycerides, low HDL-C, high LDL-C; diabetes; hypertension; and central obesity have a very high CHD risk. This syndrome is characterized by increased levels of LDL-C and triglycerides and low levels of HDL-C. These patients often have central obesity, hypertension, and glucose intolerance. Fibrates may be effective in these patients to lower plasma triglycerides, which are increasingly recognized as an independent risk factor

**Figure 2.** Additive Cholesterol-Lowering Effects in Combination Therapy: Colesevelam Plus Atorvastatin



\*P < 0.05 versus placebo. LDL-C = low-density lipoprotein cholesterol; total-C = total cholesterol. Source: Reference 20.



for CHD.<sup>35</sup> If fibrates are used alone in patients with high pretreatment triglycerides, however, LDL-C levels tend to increase. Thus, adding a statin with a fibrate to counter this tendency and to effectively lower elevated LDL-C levels as well as triglyceride levels is recommended. These combinations also increase HDL-C, sometimes substantially.

However, fibrate-statin combinations are also associated with an increased risk of myositis, so caution must be exercised when using these drugs together.<sup>17</sup> The combination should only be used in patients with normal hepatic and renal function and with no evidence of increased risk of myositis. Furthermore, the combination should be used in the lowest effective doses, for example, the starting dose of the statin and half the usual daily dose of the fibrate. Doses may be titrated upward to lipid goals. Some lipid experts have also advised that the doses of the statin and the fibrate be separated (eg, the fibrate in the morning and the statin at bedtime). Finally, fenofibrate may be the preferred fibrate to be used in combination with a statin because there are few reported cases of myositis (however, this may well be a function of less experience with its use in combination).

Although gemfibrozil is less commonly coadministered with niacin, this combination may have some synergistic triglyceride-lowering and HDL-C-raising effects<sup>36,37</sup>; actions that may improve outcomes independent of their effect on LDL-C.<sup>22</sup>

*Niacin Plus Statin.* An alternative to the fibrate-statin combination for the treatment of patients with the metabolic syndrome is niacin-statin. (The term metabolic syndrome will be prominent in the new cholesterol guidelines.) With this combination, the risk of myositis appears to be very low. However, the side effects of niacin limit its use. Additionally,

niacin may worsen the blood sugar of diabetic patients, who frequently have the metabolic syndrome, although this adverse effect may be overrated.<sup>38</sup> One way to use this combination is to keep daily niacin doses low, so the statin would provide the bulk of the LDL-C lowering and low-dose niacin would lower triglycerides and raise HDL-C.<sup>17</sup>

### Conclusion

MCOs with highly developed information systems and patient education programs are in an excellent position to improve their overall CHD outcomes. Although HEDIS guidelines suggest that an LDL-C less than 130 mg/dL may be acceptable in secondary prevention, managed care leaders need to be aware that most authorities feel that the more aggressive NCEP targets are justifiable. Health system managers should also be aware of the emerging concept of "CHD risk equivalent," which essentially means that certain primary prevention patients with multiple risk factors but no history of CHD may also require LDL-C lowering to less than 100 mg/dL. Finally, in terms of primary prevention, clinicians should recognize that the strong, continuous, and graded relationship between low cholesterol and longevity has now been extended to young men.<sup>39</sup> Clearly, the size of the population requiring either nondrug or drug therapy for high cholesterol is expanding.

With the NCEP guidelines as a target, managed care groups are uniquely equipped to use their data (ie, periodic monitoring of cholesterol levels) to motivate both physicians and patients to achieve the desired risk-reducing goals. Success will require an adequate investment in screening and monitoring of cholesterol in the member population, followed by ongoing plan-wide education on the connection between hyperlipidemia and CHD. Equipped with access to the full range of lipid therapies, clinicians

in these settings can improve the percentage of their patients who actually attain NCEP targets. As an awareness of the current shortfalls of cholesterol-lowering therapy grows, new strategies involving safe combination drug therapy may be needed.

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