THE GOAL OF PREVENTIVE CARDIOLOGY is to maximize event reduction in patients with, or at risk for, heart disease. A wealth of epidemiologic evidence is available on risk factors, causes of heart disease, and interventions to prevent heart disease. Optimal management of cardiac risk factors includes early, sustained, clinical goal optimization, compliance with medication, and non-pharmacological measures. Clinical goal optimization is achieving nationally accepted guideline values for blood pressure, glucose, and lipids.

Almost everyone in American society needs non-pharmacologic measures to reduce cardiac risk factors. When patients need additional help reaching their goals, drug therapy is important. Drug selection should be based, first and foremost, on evidence of impact on morbidity and mortality outcomes. In addition to efficacy, safety, cost, and practical patient related concerns need to be considered.

Atherosclerosis begins silently in the teenage years. It starts with a thickening of the endothelial layer of the blood vessel. The process of ongoing changes and lipid accumulation within the blood vessel continues throughout a person’s lifetime. By the third decade of life, a person may have perceptible thickening of the artery wall. As the process continues untreated, an advanced atherosclerotic lesion develops that may rupture, thereby forming a blood clot and obstructing blood flow that results in a heart attack or a stroke. Previously it was thought that patients could only be helped to survive a heart attack. With current evidence-based therapies, intervention can occur much earlier to slow the progression of atherosclerosis. Some data now suggest that the process can even be halted or reversed.

Major Cardiovascular Risk Factors

The four major risk factors for developing heart disease are hyperlipidemia, hypertension, cigarette smoking, and diabetes. Eighty-seven to 100 percent of patients in one study experiencing a fatal coronary event had at least one of these risk factors before dying.1 About 80 percent of patients with coronary heart disease have at least one of these four major risk factors contributing to their development.2 Most hypertensive patients have at least one additional risk factor and many have several other risk factors (Exhibit 1).2 For men, hypertension, plus an additional risk factor, occurs in 26 percent of patients. Hypertension plus two risk factors occur in 25 percent of males. Hypertension and three risk factors occur in 22 percent. A small
percentage of men have four risk factors. Multiple risk factors occur more often in women. Thus, it is unusual for patients to have hypertension alone. It appears that risk conferred by each individual risk factor is not just additive, but probably multiplicative as illustrated by data from the MRFIT intervention trial (Exhibit 2).  

Dyslipidemia is one of the cardiac risk factors for which much success in reducing cardiac events has been achieved. The lower low-density cholesterol (LDL-C) that is achieved, the lower the cardiovascular event rate, regardless of age, gender, history of heart attack, or starting cholesterol values. This relationship between LDL-C lowering and cardiovascular event reduction from large, randomized, well-designed trials is shown in Exhibit 3.  

**Implications of Switching Statins**

As statins become widely available generically, many managed care plans have revised their lipid-lowering agent formularies. When these changes are made, several issues in addition to efficacy need to be addressed, including actual overall costs of switching thousands of patients’ therapy, compliance issues, and comparative safety of the various statins.

Switching formulary agents results in more expense than just medication costs. A managed care plan must also consider the cost of additional medical visits and laboratory tests likely to occur as the result of any switch. Many clinicians will want to see a patient after a switch is made and run lipid profile and liver function tests to ensure the patient is effectively and safely

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**Exhibit 1: Most Hypertensive Patients Have Additional Risk Factors**

Framingham Offspring (Ages 18 to 74 Years) with Hypertension Were Likely to Have Additional Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN +1 RF</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>HTN +2 RFs</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td>HTN +3 RFs</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>HTN +4 or more RFs</td>
<td>8%</td>
<td>12%</td>
</tr>
</tbody>
</table>

RF=risk factor

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**Exhibit 2: Impact of Elevated Systolic BP and Total Cholesterol on CHD Mortality—MRFIT**

Age-Adjusted CHD Death Rates Per 10,000 Person-years

<table>
<thead>
<tr>
<th>Cholesterol Quintile (mg/dL)</th>
<th>MRFIT N=202,619</th>
</tr>
</thead>
<tbody>
<tr>
<td>245+</td>
<td>34</td>
</tr>
<tr>
<td>221-244</td>
<td>21</td>
</tr>
<tr>
<td>203-220</td>
<td>17</td>
</tr>
<tr>
<td>182-202</td>
<td>12</td>
</tr>
<tr>
<td>&lt;182</td>
<td>11</td>
</tr>
<tr>
<td>&lt;118</td>
<td>14</td>
</tr>
</tbody>
</table>

Systolic BP Quintile (mm Hg)

- <118
- 118-124
- 125-131
- 132-141
- 142+
- 145+

MRFIT=Multiple Risk Factor Intervention Trial
managed on the new agent. An example of estimates of switch-related costs are presented in Exhibit 4. This analysis used a national plan coverage policy as a basis for cost determination and a commercial payment rate (140 percent of the 2006 Medicare Physician Fee Schedule). Based on six additional services occurring because of a switch (two physician visits, cholesterol panel, liver function test, and venipuncture), this analysis projects that for every 10,000 patients switched from one statin to another, the average cost would be greater than $800,000. These estimated initial medical costs have to be weighed against the potential cost savings of any statin change.

Another issue to be addressed is the impact on compliance and persistence. One study conducted in a managed care setting attempted to determine the effect of switching medications on the compliance and persistence of new statin users. A retrospective analysis of a pharmacy claims database provided by a large PBM was conducted. The study sample consisted of 38,000 new statin users age 18 to 65 receiving atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), or simvastatin (Zocor). Rosuvastatin (Crestor) was not available at the time of this study. Compliance was assessed by the medication possession ratio, and persistence was measured by the time to discontinuation. The switching rates were derived from the proportion of patients filling a prescription other than the initial statin. Patients who were switched were less compliant by about 19 percent. Statin switchers were less persistent by 20.9 percent to 48.3 percent (P<0.001), depending on the gap length used to define discontinuation. Although derived from only one study in one type of setting, these data are of concern because of the small, but real incidence of statin-withdrawal effects. Acute coronary syndrome in the few months after stopping a statin abruptly has been reported. The authors of this study note that patients who change medications should be given special care to ensure compliance.

Another consideration in developing a statin formulary are safety and dosing restrictions. These issues tend to vary for each statin. Two adverse effects associated with statins, and of most concern, are liver dysfunction and muscle-related side effects. Both appear to be dose-related adverse effects and may occur more commonly with some statins than with others. Most studies have shown that as statin dosage is increased, particularly to the highest available dose, the incidence of adverse events increases. The adverse event rates, although still low, are increased at the higher end of the dosage range. An important consideration is whether a statin chosen for formulary inclusion can be used safely at high doses to reach clinical goals.

Because of the particular enzyme pathways used to metabolize certain statins, such as lovastatin and simvastatin, are more prone to be involved in significant drug interactions. Other agents are less prone to drug interactions. Metabolic drug interactions can lead to elevated statin levels in the body, which increase the risk of drug-related adverse effects.
Exhibit 4: National Average Costs of Each Task and Aggregate Cost for the Health Plan

<table>
<thead>
<tr>
<th>Unit</th>
<th>Cost/Unit</th>
<th>No. of Patients</th>
<th>Total (000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two Physician Visits</td>
<td>$51.66</td>
<td>10,000</td>
<td>$516,600</td>
</tr>
<tr>
<td>Cholesterol Panel</td>
<td>$8.51</td>
<td>10,000</td>
<td>$85,120</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>$20.47</td>
<td>10,000</td>
<td>$204,680</td>
</tr>
<tr>
<td>Venipuncture</td>
<td>$4.20</td>
<td>10,000</td>
<td>$42,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$848,400</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Cost/Unit represents national average
- Every state has a specific Cost/Unit
- The 10,000 patient sample was arbitrarily chosen

Commercial payment is calculated as a percentage of 2006 Medicare physician and clinical laboratory fees. All Medicare data are derived from the 2006 Medicare Physician Fee Schedule Final Rule published in the Federal Register on Sept. 30, 2005, and Nov. 21, 2005. All physician fees are based on services performed in the physician office (nonfacility) setting. Data on file. Pfizer Inc.; New York, N.Y.

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Conclusion

For optimal management of dyslipidemia, goal optimization and compliance with medications and non-drug measures are critical. Drug selection should be primarily based on evidence of impact on morbidity and mortality outcomes in addition to safety, overall costs, and practical patient-related concerns. The evidence is clear that aggressive, early, sustained, goal-optimized management of cardiac risk factors is beneficial and generally safe for the majority of patients. From a formulary perspective, switching statins can create a need for more physician visits, more laboratory monitoring, and reduced compliance, leading to additional costs. JMCM

Karol E. Watson, MD, is assistant professor of Medicine/Cardiology, co-director, UCLA Program in Preventive Cardiology at the Geffen School of Medicine at UCLA.

References