Introduction

Coronary heart disease (CHD) remains a major cause of death in the United States, and despite continued improvements in cardiovascular care, CHD rates remain unacceptably high. Furthermore, coronary heart disease affects African Americans disproportionately. The most recent data from the Centers for Disease Control and Prevention (CDC) reveals that African Americans have earlier and higher mortality rates from CHD than do either Whites, American Indian/Alaska Natives, Asian/Pacific Islanders, or Hispanics (figure 1). Elevated low density lipoprotein cholesterol (LDL-C) is an important, pervasive, and undertreated risk factor for the development of CHD. Dietary recommendations are typically the first-line approach to reducing LDL-C. However, the average cholesterol reduction from changes in diet alone is roughly 5%, and many individuals require much more LDL-C reduction. Therefore, while dietary modification is an important part of a cholesterol management and CHD risk reduction program, pharmacological intervention has an indispensable role. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with considerable reductions in LDL-C and have revolutionized the treatment of hypercholesterolemia. In addition, results from large-scale, randomized, controlled clinical trials have shown that these drugs are associated with dramatic decreases in cardiovascular risk. Moreover, statins lower LDL-C and CHD risk with a very favorable adverse event profile. This expert report will summarize currently available data on the history of statins, the clinical utility of statins, the safety profile of statins and statin use in African Americans.

History of statins

In the 1950s and 1960s, the benefits of cholesterol reduction were becoming apparent and cholesterol-lowering agents were introduced into clinical use. These agents were modestly effective in cholesterol reduction but had several unpleasant side effects such as gastrointestinal upset, flushing, and unpalatability. In 1971, a Japanese biochemist named Akiro Endo and his colleagues were searching for new antibiotics. Because many microorganisms require cholesterol for growth, the group was hoping to identify novel factors that would inhibit the rate-limiting enzyme in cholesterol biosynthesis—HMG-CoA-reductase—thus hoping to develop these compounds as antibiotics. Ultimately, Endo isolated several inhibitors of HMG-CoA reductase, including one—Mevastatin—from the mold Penicillium citrinum. This compound was found to be a potent agent for the reduction of serum cholesterol. The pharmaceutical company, Merck began similar research in 1976, and isolated Lovastatin from the mold Aspergillus terreus. By 1990, several statins drugs such as
Lovastatin, Pravastatin, and Simvastatin were derived and marketed in the United States and across the world. The initial agents in the class—Lovastatin, Pravastatin and Simvastatin—are all derivatives of a fungal compound. Eventually, synthetic statins were developed. They include atorvastatin, fluvastatin, rosuvastatin, and the statin which was withdrawn from clinical use—cerivastatin. (Figure 2). The chemical structure of fungally-derived statins is quite similar, while the structures of the synthetic statins differ somewhat (Figure 3).

**Statin Efficacy**

**Lipoprotein effects**

Statins have generally similar effects on plasma lipids (Table 1). The main effect of statins is the decrease of serum level of low-density lipoprotein (LDL) cholesterol, due to the inhibition of intracellular cholesterol biosynthesis which brings about an upregulation of LDL receptors. Two separate studies have directly compared statin efficacy on lipoprotein parameters and have found Rosuvastatin and Atorvastatin to be the most
potent statins for total cholesterol and LDL-C reduction at currently available doses. These are followed (in order of LDL-C lowering potency) by Simvastatin, Lovastatin, Pravastatin, and Fluvastatin. The more effective a statin is in decreasing LDL-C, the more effective it also is in decreasing serum triglycerides. As such, the most potent triglyceride lowering statins are Rosuvastatin and Atorvastatin, followed, in order, by Simvastatin, Lovastatin, Pravastatin and Fluvastatin. Statins typically afford only a modest increase in high density lipoprotein cholesterol (HDL-C), and this increase appears to be independent of LDL-C lowering efficacy. Simvastatin, Rosuvastatin, and Pravastatin are the most potent HDL-C raising agents. Simvastatin raises HDL-C 12–16%; Rosuvastatin 12–14%; and Pravastatin 8–12%. Atorvastatin, Fluvastatin and Lovastatin offer up to 9% HDL-C increases. None of the statins decreases Lp(a). In fact, statin therapy is typically associated with an approximately 30% increase in Lp(a).

**Pleiotropic Effects of Statins**

Statins have been reported to possess a broad array of pleiotropic activities that almost certainly contribute to their ability to decrease cardiovascular risk. Some of these properties include reduction in inflammation, plaque st

---

**TABLE I. CHEMICAL AND BRAND NAMES OF STATINS AS WELL AS THE METHOD OF PRODUCTION**

<table>
<thead>
<tr>
<th>Statin Drugs</th>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Production Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>Pravachol</td>
<td>Fermentation-modified</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Zocor</td>
<td>Fermentation-modified</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Mevacor</td>
<td>Fermentation</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Lescol</td>
<td>Synthetic</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
<td>Synthetic</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Crestor</td>
<td>Synthetic</td>
<td></td>
</tr>
<tr>
<td>Cervastatin</td>
<td>Baycol</td>
<td>Synthetic-no longer available</td>
<td></td>
</tr>
</tbody>
</table>

---

**FIGURE 2. MOLECULAR STRUCTURES OF THE CURRENTLY AVAILABLE STATINS**
bilation, improvement of endothelial function, inhibition of smooth muscle proliferation, reduction in adhesion molecules, prevention of cholesterol esterification, reduction proteinases, inhibition of platelet aggregation, and reduction in thrombogenic factors. While these pleitropic effects are intriguing, they have not yet definitively been proven to contribute to the clinical benefits of statins, though evidence is accumulating. Furthermore, the extent to which such properties are independent of the lipid effects of statins is uncertain.

**Statin Safety**

Statins are generally very well tolerated and serious adverse effects are rare. Currently, there appears to be no discernible difference between the statins in the range or severity of adverse effects, although experience is more limited with Rosuvastatin. The most serious reported adverse effects are skeletal muscle toxicity and hepatotoxicity. Though most patients are aware of statin-associated hepatotoxicity, it is the less worrisome of these two adverse effects. As noted in the ACC/AHA/NHLBI advisory on the safety of statins, although transaminase elevations with statins may occur, whether or not this represents true hepatotoxicity has not been determined. They also note that progression to liver failure is exceedingly rare with statins, if in fact it ever happens. Skeletal muscle toxicity with statins is better established and was brought to public attention by the withdrawal of the drug Cerivastatin. There is a wide spectrum of muscle adverse events with statins, ranging from mild myopathy to frank rhabdomyolysis.

The total reported incidence of statin-associated myotoxicity ranges from between 1–7%. The risk of myopathy appears to be increased by high doses of statins, certain concomitant medications or the presence of renal impairment. Myalgia is the most common side effect with statins while rhabdomyolysis and myositis, the most serious of muscle effects, account for less than 0.1% of all statin-related adverse effects. Cerivastatin was a unique case with an incidence of myotoxicity that was more than ten times that of other statins (Table III). The majority of cases of rhabdomyolysis occurred with the highest dose of Cerivastatin (0.8 mg) and there was a particularly high incidence associated with the use of Cerivastatin in

---

**TABLE II. LIPOPROTEIN EFFECTS OF CURRENTLY AVAILABLE STATINS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>10–80mg</td>
<td>↓25–45%</td>
<td>↓35–60%</td>
<td>↑5–9%</td>
<td>↓19–37%</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>20–80mg</td>
<td>↓17–27%</td>
<td>↓22–36%</td>
<td>↑3–9%</td>
<td>↓12–23%</td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>10–80mg</td>
<td>↓16–34%</td>
<td>↓21–42%</td>
<td>↑2–9%</td>
<td>↓6–27%</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>10–80mg</td>
<td>↓16–27%</td>
<td>↓22–37%</td>
<td>↑2–12%</td>
<td>↓11–24%</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>5–40mg</td>
<td>↓33–46%</td>
<td>↓45–63%</td>
<td>↑8–14%</td>
<td>↓10–35%</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>5–80mg</td>
<td>↓19–36%</td>
<td>↓26–47%</td>
<td>↑8–16%</td>
<td>↓12–33%</td>
</tr>
</tbody>
</table>
combination with the fibric acid derivative gemfibrozil. The frequency of rhabdomyolysis reported with the currently available statins is less than one in 100,000 and is comparable for all currently available statins. Deaths due to rhabdomyolysis is even rarer with a reported incidence of <1:1,000,000. Renal adverse events is a relatively new concern with statin therapy. Mild proteinuria has recently been identified in patients treated with statins, and this has been seen with all of the currently available statins. The proteinuria seen has been described as being generally transient and reversible and has not been associated with any change in renal function, thus the significance of this finding is unknown. In fact, statin therapy has been shown in several trials to improve glomerular filtration rates.

In summary, the statins remain a remarkably safe and efficacious class of medications that have proven to be invaluable in the fight against heart disease. Statin drugs have been prescribed to millions of patients for nearly 20 years, thus there have been hundreds of millions’ patient-years of use with relatively few adverse effects, and untold benefits.

**Statin Use in African Americans**

Statin use in African Americans had been studied in subpopulations of broader trials and in two trials that have exclusively studied African Americans. In the Cholesterol Reduction in Seniors Program (CRISP) ninetyninety African Americans (out of a total cohort of 431 subjects) over the age of 65 were studied and the drug Lovastatin at a dose up to 40 mg per day was found to decrease LDL-C up to 25% and raise HDL-C up to 9%. In the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial, 459 African Americans (out of a total cohort of 8,245 subjects) were studied and the drug Lovastatin at a dose up to 40 mg twice a day was found to decrease LDL-C up to 38% and raise HDL-C up to 6%. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) there were a large number of African American subjects enrolled; of the 10,355 participants, 38% were African American. In this trial, the effects of pravastatin with “usual care and cardiovascular morbidity and mortality were assessed. Although in the overall cohort, only a nonsignificant decrease in the rates of MI and stroke were seen in the Pravastatin group. In the African American cohort, there was a significant reduction in events in those who were randomized to receive Pravastatin.

In the first trial to test statin therapy in an exclusively African American cohort, Jacobsen and colleagues studied 245 African Americans given the drug Pravastatin, and found it to decrease LDL-C 26% but also to decrease HDL-C 0.4% Finally, in the most recent of the statin trials conducted in an exclusively African American population, the African-American Rosuvastatin Investigation of Efficacy and Safety (ARIES) trial was designed to compare, head-to-head the effects of 2 statins in African Americans. ARIES compared the two statins, Rosuvastatin and Atorvastatin in 774 African Americans over the
course of 6 weeks. This study showed that after 6 weeks of therapy, on a mg-equivalent basis, the reductions in LDL-cholesterol with Rosuvastatin 10 mg or 20 mg (37% and 46%) were significantly greater than with Atorvastatin (32% and 39%). Significantly greater increases in HDL-cholesterol were also observed. These trials thus confirm that significant benefits can occur from statin use in African Americans. Despite this, however, statins remain underutilized in the African American population\(^2\), thus those that might stand to benefit most, are least likely to receive these life saving medications.

Since African Americans continue to suffer a disproportionate burden of CHD, statins should play a key role in overall risk reduction strategies for the African American population. Further efforts should be aimed at assuring adequate access and availability of statins to populations most at risk, including African Americans.

Conclusion

Statins were first introduced as a treatment for hypercholesterolemia, but since their introduction, they have been shown to provide a remarkable array of clinical benefits. The currently available statins, furthermore, have a very favorable safety profile. Since African Americans continue to suffer a disproportionate burden of CHD, statins should play a key role in overall risk reduction strategies for the African American population. Further efforts should be aimed at assuring adequate access and availability of statins to populations most at risk, including African Americans. The few cases of adverse events in patients being prescribed statin therapy has been unfairly exaggerated. Fortunately, the one compound (Cerivastatin) that was laden with side effects is no longer available. Statins should be prescribed with confidence. Significant reductions in total cholesterol and LDL and an increase in HDL with less than 1% of patients experiencing side effects makes this one of the safest compounds available.

ABC Expert Panel on the Safety and Efficacy of Statin Therapy:

- Karol Watson, M.D., Ph.D., Chair
- Boisey Barnes, M.D.
- Clinton Brown, M.D.
- Luther Clark, M.D.
- Aloysius Cuyjet, M.D., M.P.H.
- Keith Ferdinand, M.D.
- Icilma Fergus, M.D.
- Eric Vanderbush, M.D.

This article was supported by an unrestricted educational grant from AstraZeneca. Dr. Karol Watson reports having served as a consultant for AstraZeneca, Bristol-Myers Squibb, Pfizer, Merck/Schering-Plough, Sankyo, KOS and Takeda. Dr. Keith Ferdinand reports having received grant/research support from AstraZeneca, Pfizer and Merck. Dr. Aloysius Cuyjet reports having received grants/research support from Eli Lilly; consultant fees from Ortho-Biotech and lecture fees from Ortho-Biotech, and Boehringer Ingelheim. Dr. Luther Clark reports having received grants/research support from Eli Lilly; consultant fees from Ortho-Biotech and lecture fees from Merck and lecture fees from Merck/Schering-Plough. Dr. Eric Vanderbush reports having received research support from Bristol-Myers Squibb.

References

2. Centers for Disease Control and Prevention (CDC). Disparities in premature deaths from heart disease—50 States and the District of

continued on the next page


