New Treatments for Hypercholesterolemia

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Note that this paper should have an abstract, but does not. Otherwise it is a quite good paper.
Introduction

It is well known in the medical community that high LDL cholesterol levels can lead to complications such as atherosclerosis and eventually coronary artery disease [1-3]. These diseases lead to significant morbidity and mortality. With the increasing rate of obesity in the United States and with the higher LDL-C seen in more of the population, the number of patients who face the consequences of atherosclerosis is increasing. Due to the overwhelming amount of comorbidity in the US, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) has recently issued new, lower guidelines for cholesterol lowering [2].

These new, lower guidelines pose significant problems for practitioners [1]. The problem is that so many patients are now presenting with high cholesterol levels and multiple comorbid diseases [1]. Unfortunately, the commonly known cholesterol treatment drugs are not effective enough to lower cholesterol to the recommended levels in many people [2]. Part of the reason for this is the side effect profiles of commonly available drugs [2]. While the drug may have the potential to reach the goals, many people suffer adverse side effects to the drugs before they reach the dose necessary and are forced to discontinue the drugs [2].

In order for practitioners in this country to be able to decrease atherosclerosis and coronary heart disease, something must be done. With lower cholesterol level recommendations for many, there must be new advances in drug therapy [2]. Luckily, there are. Recently a new class of cholesterol medication was introduced: cholesterol
absorption inhibitors [4]. This new class of drugs works in the gut to inhibit the absorption of cholesterol from food [4]. Also, there has recently been released a new statin, that is more potent that those previously available [5]. In the past year there have also been several combination medications released. Other new classes of drugs are also being developed [1]. All of these advances will help enable practitioners to better meet guidelines for their patients, and hopefully, decrease the morbidity and mortality of the atherosclerosis.

**Body**

The recently issued ATPIII guidelines recommend even lower cholesterol goals than previously [4]. The new guidelines can be seen in Table 1 [4].

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Optimal</td>
</tr>
<tr>
<td>100-129</td>
<td>Near Optimal</td>
</tr>
<tr>
<td>130-159</td>
<td>Borderline High</td>
</tr>
<tr>
<td>160-189</td>
<td>High</td>
</tr>
<tr>
<td>≥ 190</td>
<td>Very High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL-C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Low</td>
</tr>
<tr>
<td>≥60</td>
<td>High</td>
</tr>
</tbody>
</table>

The ATPIII panel also provided additional risk factors for Coronary Heart Disease [4]. For those patients that are at increased risk for CAD, or have other risk factors, the cholesterol goal is even lower than for those patients that do not have any other risk factors [4]. Some risk factors that play a role in CAD, in addition to high cholesterol levels, include: smoking, high blood pressure, family history, age, male sex, and having
diabetes [4]. For those patients who have 0-1 of these risk factors the new LDL-C goal is <160, for those with 2 or more then goal is <130, and for those patients that already have CAD or an equivalent condition the new goal is <100 [4]. These new guidelines put intense pressure on medical practitioners to help their patients lower their cholesterol levels. Unfortunately, this was easier said than done, until the recent release of several new drugs within the past year or two. Up to this point, the most commonly prescribed cholesterol lowering agents were statins [2]. However, the previously available drugs were not strong enough at the most likely prescribed dose to help the patient reach their goals [2]. Because it is well known that the reduction in LDL cholesterol can lead to impressive drops in occurrence of CAD it is imperative to have drugs available that can help patients meet the new guidelines [3].

The first newly released drug is called Ezetimibe (trade name Zetia). Not only is this a new drug, but it is also the first drug released in a new class of drugs; cholesterol absorption inhibitors [5]. This class of drugs lowers cholesterol levels by acting in the gut [5]. The drug binds to the gut and will not allow cholesterol to be absorbed from food as it passes through the intestinal tract [5]. Ezetimibe has the potential of decreasing cholesterol absorption by 96% [5]. This is a huge breakthrough for those patients who have high cholesterol as a result of their diets. The side effect profile of this drug is also very good, being similar to a placebo in adverse effects [5]. In trials ezetimibe has been shown to lower LDL-C by 18.5% [6]. While it is able to lower LDL-C it is also able to increase HDL-C by 3.5% [6]. Another benefit of this drug is that within 2 weeks of beginning treatment with this drug its full potential has been reached, similar to the statins [6].
As with all drugs, ezetimibe does have its low points. The patient’s body will react to the decreased absorption of cholesterol from food by increasing the production of cholesterol from the liver [7]. Fortunately, statin drugs work to inhibit the production of liver cholesterol synthesis. Because statins and cholesterol absorption inhibitors work differently to lower cholesterol, cholesterol absorption inhibitors are great drugs to be given in combination with statins [7]. When given in combination cholesterol absorption inhibitors and statins increase each others effectiveness [7]. This increase in effectiveness can be seen in a trial where ezetimibe was given concurrently with pravastatin [8]. In this trial it was found that when compared with pravastatin administration only the coadministration patients reduced their LDL-C by an average of 38% compared to only 24% in the single drug group (p<0.01) [8]. The coadministration group also did better than if they were to take ezetimibe alone: 38% versus 19% (p<0.01) [8]. This points to future success for the new cholesterol absorption inhibitors. Another new drug recently introduced is Rosuvastatin (trade name Crestor). This drug is a new statin. Statins work by decreasing cholesterol production by the liver [9]. This is a different mechanism of action than the cholesterol absorption inhibitors. The statins that have been on the market for a while are the most used drugs to treat hypercholesterolemia. Unfortunately, statins do have some unwanted side effect. Common side effects of the drugs include pain (6%), pharyngitis (5%), myalgia (4%), and headache (3%) [10]. More serious side effects that can occur with statins are rhabdomyolysis, myopathy (0.2%), and death [9]. Many of the more common side effects occur at common doses of the previously available statins. The more serious complications are more likely to occur as the dose increases. For this reason a new drug
that could effectively reduce cholesterol levels and yet have decreased side effects is a welcomed addition to the drugs available to treat hypercholesterolemia. Rosuvastatin is the drug that could meet all of these criteria.

Rosuvastatin binds to a specific site in the liver, but previous statins did not bind as specifically to one site [9]. By binding at this site it is able to significantly lower cholesterol synthesis in the liver [9]. In trials on mice Rosuvastatin was found to be much more potent than any of the other available statin drugs [9]. Rosuvastatin has been found to reduce LDL-C levels by 43-51% at the common starting dose up to 60-65% at the highest doses [9]. These reductions are significantly more than those found with the other statins [11]. When comparing Rosuvastatin 5mg and 10 mg with Atorvastatin (Lipitor) 10 mg, the reductions in LDL-C levels were 41.9% and 46.7% for Rosuvastatin 5mg and 10 mg compared to 36.4% for Atorvastatin 10mg [11]. These are statistically significant findings (p <0.001) [11].

Not only is Rosuvastatin effective in reducing LDL-C levels, it is also effective in lowering triglyceride levels and raising HDL-C levels [9]. Studies showed that Rosuvastatin can raise HDL-C levels by 8-12% compared to an average of 5% with other statins [9]. The percent rise in HDL-C levels by Rosuvastatin appears not to be related to the dose of the medicine given [10]. This is not the case with other statins [10]. While Rosuvastatin is capable of reducing triglyceride levels it appears that the reduction is similar to that seen with other statins [9]. All of these data are used to evaluate the efficacy of Rosuvastatin in helping patients achieve their new NCEP cholesterol goals [10]. Patients who took 20-40 mg of Rosuvastatin were the most likely to reach their new NCEP goals with 89% of patients reaching their goals [10]. Even 82% of patients
taking only 10 mg reached their goals [10]. The results of the group taking 10 mg of Rosuvastatin are comparable to that of the patients taking the maximum dose of Atorvastatin [10].

The safety of Rosuvastatin is comparable to the safety of other statins available [9]. However, because the dose of Rosuvastatin required to reach the new NCEP goals is likely to be much lower than the dosage of other statins, the chance of a patient experiencing an adverse effect is less. When looking at the ability of this new drug to lower cholesterol levels as well as its appealing side effect profile it is clear that Rosuvastatin is going to be a welcome and effective new medicine in the treatment of hypercholesterolemia.

Another drug released in the past few years is a combination drug with Lovastatin and Niacin (trade name Advicor). This is the first combination drug available for the treatment of hypercholesterolemia. Combination drugs are now common for the treatment of such diseases as hypertension. They allow for medication condensing so that patients don’t have as many drugs to take on a daily basis. Combination drugs are also beneficial in the battle against noncompliance. Patients are more likely to take one medicine rather than two. For these reasons Advicor is a beneficial drug and is appropriate for those patients whose cholesterol is slightly elevated.

An important step in treatment will also be patient education. Patients need to be made aware of the potential complications of poor health as well as poor diet. Educating the patients on these important issues before they reach the point of needing drug intervention could be the best treatment available. In many cases if the patient could alter their diet and exercise programs they could have a beneficial effect on their cholesterol
levels. Perhaps when told of the risks associated with elevated cholesterol levels patients may be more willing to adjust their lifestyle.

**Future**

With the lower guidelines recently released by NCEP the introduction of more potent and novel drugs to combat hypercholesterolemia are going to be required [12]. Although there has been the recent introduction of several new drugs these drugs will not be effective for everyone suffering from hypercholesterolemia. Fortunately, there are new drugs being researched as well as new classes of drugs.

As discussed above the cholesterol absorption inhibitors are a new class of drugs. Since absorption inhibitors have a different mechanism of action than statins, the two drugs can work together to further decrease cholesterol levels, i.e. a combination medicine with a statin and a cholesterol absorption inhibitor would be very beneficial [12]. Another new class of drugs called cholesterol ester transfer inhibitors is being researched [12]. This class of drugs would work by decreasing cholesterol accumulation in the walls of the arteries as well as decreasing cholesterol absorption [12]. One drug in this class, Avisimibe, is currently being studied and is showing promising results [12].

Another statin is currently being studied called Pitavastatin. Early data on this drug suggest that it may be more potent than Rosuvastatin [13]. Early results show that 2 mg of Pitavastatin can decrease total cholesterol by 31% and LDL-C by 40% [13]. It also shows good triglyceride lowering ability [13]. In early trials no significant side effects have been noted [13]. This drug also has the potential to be beneficial in treating hypercholesterolemia.

**Conclusion**
Heart disease is the number one killer in the United States resulting in more than 700,000 deaths in 1999 [14]. While these numbers are the result of many different causes, many of the causes can be treated. The medical community is becoming more and more aware of the potential benefits of aggressively lowering cholesterol levels. Studies have shown that aggressive cholesterol treatment following acute coronary syndromes reduces the future hazard ratio of the patients [15]. This study showed that treatment with a less effective statin resulted in 26.3% deaths at two years following the acute coronary syndrome as compared to 22.4% deaths in the group treated with a more potent statin [15]. These results along with the new updated NCEP guidelines for cholesterol lowering suggest that it would be very beneficial to patients to aggressively lower their cholesterol levels. Fortunately, new drugs have recently been introduced to help practitioners meet these goals, and more new drugs are on the way. The most important step in treatment should be patient education. Some patients may be willing to make lifestyle changes to avoid having to use medications. This would benefit their health in more ways than just lowering their cholesterol levels.

References:

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