Niacin or Ezetimibe for Patients with, or at Risk of Coronary Heart Disease

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Abstract: Coronary heart disease treatment with HMG-CoA reductase inhibitors has been very successful. There is increasing interest in adding other lipid lowering therapy, primarily as additional therapy onto HMG-CoA reductase therapy. This paper will examine two of the more popular secondary agents, ezetimibe and niacin, and describe their research data and potential for usefulness in further reducing cardiovascular events.

Keywords: niacin, ezetimibe, coronary heart disease
**Introduction**

Coronary Heart Disease (CHD) remains the most significant health problem in the US and the developed world. Overall Cardiovascular Disease (CVD), which includes cardiac along with cerebrovascular disease like stroke, has been the leading cause of US mortality every year since 1900, except for 1918 in the midst of the severe flu epidemic. Indeed, data shows that, in the most recently reported year of 2004, CVD accounted for 36.3% of all US deaths.

While CVD is multifactorial in origin, we have been able to identify and to treat certain prominent risk factors, including hypertension and hyperlipidemia. Indeed, these and other comprehensive treatments have produced a significant and persistent decline in cardiovascular mortality rates for several decades.

Of the various cardiovascular risk factors in the prevention and management of CHD, hyperlipidemia, or elevated blood cholesterol, is one of the more treatable issues in this problem.

Interest in the treatment of elevated cholesterol began in the 1970’s with the Coronary Drug Project, or CPD. This trial in high risk men used Clofibrate, the original fibric acid agent, in some patients or high dose niacin (3 grams daily) in a different group of patients. The treatment with high dose niacin showed no reduction in total or cardiac mortality, with only a minor improvement in a secondary endpoint of non-fatal Myocardial Infarction (MI). However, a European study with clofibrate also showed a reduction only in non-fatal MI but not a reduction in mortality.

A different US trial, the LRC-CPPT trial, evaluated cholestyramine, a resin binding agent, in primary patients, those with high risk but without pre-existing disease. This study did show a significant reduction in the primary end-point of fatal and non-fatal MI. The final early cholesterol study was the Helsinki Heart Study, evaluating gemfibrozil, a different fibrate, in high risk men who were without pre-existing heart disease. This study also had no reduction in total or cardiac mortality, but only a reduction in non-fatal MI.

The modest and equivocal results of these early studies led many to question whether cholesterol treatment would reduce coronary heart disease. However, the next generation of studies, with the newer agents, the HMG-CoA Reductase Inhibitors, or statins, showed that significant cholesterol reduction could reduce a wide range of cardiovascular events.

**HMG-CoA Reductase Inhibitors**

The HMG-CoA reductase inhibitors, or “statins” as they are frequently called, have revolutionized the management of cardiovascular disease. Their mechanism of action involves the inhibition of the HMG reductase step in the production of cholesterol in the liver. This leads to a reduction of hepatic cholesterol levels, thus stimulating the Low Density Lipoprotein, or LDL-C, receptor sites on the hepatic cells. The stimulated LDL-C receptors increase their binding of LDL-C in the blood stream, lowering the serum LDL-C levels. The degree of LDL-C lowering differs within the statin class, with the original agents, pravastatin and lovastatin having the least LDL-C lowering and rosuvastatin having the greatest.

| Statin therapy      | Effect on lipids | Indirect cardiac markers | Cardiac event reductions |
|---------------------|------------------|--------------------------|--------------------------|
| HMG-CoA reductase Inhibitors “Statins” | | | |
| All agents | ↓LDL-C 20%–63% | Yes, rosuvastatin | Reductions seen with all agents and all Patient groups |
| | ↑HDL-C 3%–10% | Others N/A | None proven |
| | ↓ or no effect | atorvastatin | |
| Ezetimibe | ↓LDL-C 18% | Unsuccessful | No clear evidence |
| | ↑HDL-C 3% | | marginal evidence in two studies |
| Niacin | ≤1000 mg - LDL-C | ↓Carotid intimal wall thickening | No clear evidence |
| | No effect; ↑HDL-C 10%–15% | | |
| | 2000 mg - ↓LDL-C 15% | | |
| | ↑HDL-C 20% | | |

Table 1. Evidence for cholesterol reduction therapies.
lowering, while the newer statins, rosuvastatin and atorvastatin, produce the most potent lowering of LDL-C. In addition to lowering LDL-C by anywhere from 20% to 63%, the statins also lower total cholesterol and triglycerides by different amounts. All of the statins except atorvastatin also increase High Density Lipoprotein, or HDL-C, also in amounts that vary between the agents. Atorvastatin can also lower HDL-C, an anomaly that is not completely understood.\(^6\)

In a series of landmark clinical trails, the statins showed an unsurpassed ability to reduce a wide range of cardiovascular clinical events, including cardiovascular mortality and even total mortality. These trials cover both patients without previous cardiac disease ("primary prevention") and those with pre-existing cardiac disease ("secondary prevention"). The original statin trial was the 4S trial. 4S studied over 4000 Scandinavian men with pre-existing coronary heart disease ("secondary prevention") with simvastatin 20 or 40 mg versus placebo.\(^7\) The statin treated patients had significant reductions in a wide variety of cardiovascular end points including total mortality, fatal and non-fatal MI, and even stroke. Two subsequent pravastatin studies, CARE and LIPID, showed reductions in MI in secondary prevention patients with mid-range cholesterol.\(^8,9\)

The Heart Protection Study, or HPS, was an extraordinarily important British study. HPS enrolled over 20,000 men and women with coronary or other vascular disease, diabetes mellitus, or very high risk hypertension.\(^10\) However, HPS enrolled patients based on their risk rather than on their LDL-C, and treated patients with simvastatin 40 mg or placebo. Patients receiving simvastatin had significant reductions in total mortality, cardiovascular mortality, fatal or non-fatal MI, and stroke. These benefits were seen in all groups of patients, regardless of their baseline LDL-C.\(^10\) This extraordinary study led to recommendations that all high risk patients should receive aggressive statin therapy.

In "Primary Prevention" trials, the original study was the West of Scotland, or WOSCOPS, study, which evaluated over 6500 Scottish men with markedly elevated LDL-C and no previous coronary disease.\(^11\) Pravastatin 40 mg versus placebo produced significant reductions in first MI and fatal MI, and nearly a significant reduction in total mortality. A US trial, the AFCAPS/TEXCAPS study, evaluated US men and women with mid range LDL-C (about 150 mg/dl median) but with lower HDL-C.\(^12\) Lovastatin 20 or 40 mg versus placebo produced significant reductions in cardiac events, with a more significant reduction in patients with HDL-C <40 mg/dl at baseline.\(^12,13\) This trial therefore extended the benefit of statin treatment to patients with only moderate LDL-C elevations, and it also showed that statin monotherapy treatment is an effective therapy in patients with low HDL-C syndrome.

Furthermore, the ASCOT-LLA demonstrated that LDL-C reduction alone produced significant reduction in cardiac events. In ASCOT-LLA, over 10,000 men and women without heart disease were given atorvastatin 10 mg versus placebo.\(^14\) The dose of atorvastatin used produced a 36% reduction in LDL-C but did not lead to an increase in HDL-C as we had seen in all the previous statin studies. The atorvastatin treatment led to a significant reduction in fatal and non-fatal MI, along with a reduction in stroke, further supporting the LDL-C hypothesis.

JUPITER, the most recent statin study, was so successful that it was stopped early to avoid continuing to treat the placebo patients with only placebo. JUPITER enrolled low to medium risk primary prevention patients with an LDL-C of <130 mg/dl, but with a moderate elevation (>2 mg/dl) in the Hs-CRP inflammation marker, and treated them with rosuvastatin 20 mg versus placebo. The rosuvastatin treated patients had marked reductions of their LDL-C into the range of 55 mg/dl, compared to LDL-C levels of about 110 mg/dl in the placebo treated patients. The rosuvastatin treated patients had very significant reductions in cardiac events, reductions often of around 50%, without significant side effects from the very low LDL-C.\(^15\)

While many patients and practitioners express concern about the safety of the statin agents, a careful examination of the research shows that, as a class, they are extraordinarily safe. They can produce modest elevation in liver enzymes, but there has never been a clearly documented case of liver failure produced by a statin, in contrast to a number of cases of liver failure from acetaminophen.\(^16-18\) While there is a risk of muscle problems with the statins, this risk is modest and usually manageable. The actual rate of true myalgia from statins is not clear, but it is probably relatively low and it is often confused with the
is important, since it emphasizes that many of the muscle aches attributed to statin therapy are also seen at the same rate in comparable patients who are not on statin therapy, representing the “background” level of muscle aches seen in patients who need statin therapy. Myopathy, a more serious condition with a CK > 10 times normal and muscle pain, is seen much less frequently than the less serious myalgia. In the HPS study myopathy occurred in about 10 cases per 10,000 patients treated with simvastatin, as opposed to 4 cases per 10,000 patients in the placebo treated group. The risk of myopathy appears to increase significantly with the 80 mg doses of each of the stains, indicating that it is clearly related to the milligrams of statin used. Rhabdomyolysis, a very severe muscle breakdown syndrome which can be fatal in as much as 50% of cases, is fortunately very rare, seen in only about one case per every seven million US statin prescriptions. Therefore, the statin class is, overall, extremely safe even in the widespread use that we are seeing at this time.

In summary, the statin treatment trials show that this class of agents is extremely successful in reducing heart attack and other cardiovascular events in at-risk patients. Clearly, much of this benefit is mediated through the lowering of LDL-C. However, whether the same degree of benefit would be seen with agents from the medication classes other than the statins is unproven and therefore a point of debate and conjecture.

Other Lipid Reduction Therapies
There are several other classes of agents, including the fibrates, resin absorption inhibitors, ezetimibe, and niacin, that are available to treat lipid disorders. These agents are used as monotherapy and also in combination with statin therapy. This paper will discuss the pharmacology and clinical usefulness of two of them, ezetimibe, a cholesterol absorption inhibitor, and niacin, a B-vitamin.

Ezetimibe
Ezetimibe has been marketed in combination with simvastatin as Vytorin®, and also as Zetia® for use as monotherapy or to be taken along with other therapy such as other statins or even other lipid reducing agents.
Financially, Zetia® and Vytorin® have been significant success stories. In 2009, both Zetia® and Vytorin® each achieved over four hundred million dollars in sales in the US alone. However, recently, concern about whether the lowering of lipid values with ezetimibe will actually produce the same level of reduction of cardiac events seen with the statins has been raised. While the utilization of ezetimibe has been assumed to produce the same degree of reduction of cardiac events as statin therapy, that assumption remains unproven at this time. In this section, I will review the data on ezetimibe and try to place its use in its proper scientific place.

**Mechanism of Action**
Ezetimibe has a completely different mechanism of cholesterol lowering than do the statins. Ezetimibe reduces cholesterol by inhibiting cholesterol absorption in the intestines. Ezetimibe targets the NPC1L1 sterol transporter, located in the brush border epithelium of the small intestine. Inhibition of this sterol transporter reduces intestinal absorption of cholesterol by 54%. This reduced cholesterol absorption leads to a reduction of intestinal cholesterol being transported into the liver, lowering hepatic cholesterol. Lowering of hepatic cholesterol stimulates the clearing of cholesterol from the blood, with this final mechanism being similar to the mechanism of action with the statins.

**Effects on Lipid Levels**
This action by ezetimibe results in a noticeable improvement in the serum lipids, with the total cholesterol reduced by 13%, the LDL-C by 19%, triglycerides reduced by 8%, and with the HDL-C increased by 3%. Since this mechanism is completely different from the cholesterol reduction of the statins, the effects of ezetimibe are additive to statin effects in the reduction of cholesterol fractions. Similar effects are also seen when ezetimibe is combined with fenofibrate.

**Preparations of Ezetimibe**
Ezetimibe is available in a 10 mg dosage form, either as monotherapy or, probably more commonly, as additive therapy on top of statin medication. It is also available in multiple dosage preparations as combination therapy with simvastatin, marketed as Vytorin®, at simvastatin doses of 10 mg (Vytorin 10®), 20 mg (Vytorin 20®), 40 mg (Vytorin 40®) or 80 mg (Vytorin 80®).

**Efficacy of Ezetimibe**
The question as to whether ezetimibe therapy, either as dual therapy along with statin treatment or as monotherapy, will reduce MI and other cardiovascular events remains a difficult and controversial question. Ezetimibe was brought to the market, and enjoyed considerable sales success, on the assumption that the LDL-C lowering it produced would reduce cardiovascular events to the same degree as seen with statin therapy. However, assumptions are not facts, and medicine is frequently not logical, but instead is scientific. Therefore, we would need direct evidence of ezetimibe’s ability to reduce cardiac events before we can assure our patients that taking it will reduce their risk of heart attack. There are many examples of logic being proven wrong in medicine, such as homocysteine.

As we remember, elevated homocysteine levels are associated with higher risk for cardiovascular disease. However, numerous studies have shown that lowering homocysteine to normal levels with folic acid has no effect on the risk for cardiovascular events. Without any completed studies that would resolve whether ezetimibe therapy will lower cardiovascular events, we are forced to look at studies that utilize other measurements to estimate the efficacy of ezetimibe. There have been several studies recently that utilized B-mode ultrasound measurements of carotid intima-media thickening as a surrogate for coronary artery risk. These studies need to be approached with caution, since there is no clear evidence that changes in carotid intima-media thickening might be predictive of cardiovascular risk.

ENHANCE was the first longer term study of ezetimibe use. ENHANCE enrolled and randomized 720 men and women with familial hypercholesterolemia, with untreated LDL-C of about 318 mg/dL, to either simvastatin 80 mg with ezetimibe 10 mg versus simvastatin 80 mg and placebo. The study used B-mode ultrasound to measure the intima-media thickening in the carotid and femoral arteries. The patients receiving ezetimibe in addition to simvastatin did have markedly lower LDL-C than those receiving simvastatin alone, with LDL-C of
141 mg/dL versus 192 mg/dL. However, the addition of ezetimibe therapy did not show an improvement in intima thickening, which actually showed a non-significant worsening in the ezetimibe group. The overall meaning of this study is unclear, at best, but it created some doubts as to the efficacy of ezetimibe to improve cardiovascular outcomes.

The second study was SEAS, which enrolled 1873 patients with aortic stenosis but without known coronary heart disease. Patients had a baseline LDL-C of 139 mg/dL, well above the average LDL-C seen in the JUPITER trial. They were randomized to simvastatin 40 mg plus ezetimibe 10 mg, versus placebo. Surprisingly, the simvastatin/ezetimibe patients did not show a reduction in the primary combined end point, meaning that the study was not successful. This lack of success is particularly surprising, since one would have thought that, based on the Heart Protection Study, simvastatin 40 mg alone should have reduced cardiac events.

The final study looking at ezetimibe was the ARBITER 6—HALTS trial. This trial, published in November of 2009, is somewhat difficult to interpret. The study enrolled 363 men and women, with known coronary heart disease or its risk equivalent (including diabetes mellitus, a 20% or more MI risk from the Framingham calculation, or an elevated coronary calcium score). The patients were already on background statin therapy, predominantly simvastatin and atorvastatin, and their LDL-C must have been <100 mg/dL, with an HDL-C of <50 mg/dL in men and <55 mg/dL in women. The patients were randomized to 10 mg of ezetimibe or extended release niacin, initially 500 mg at bedtime, to be titrated toward a target dose of 2000 mg at bedtime.

Ezetimibe therapy did reduce the LDL-C further, with an average reduction of 19.2%, with an accompanying reduction of HDL-C of 2.8 mg/dL (6.5%).

Extended release niacin reduced LDL-C by only 12.4%, but it increased the HDL-C by 7.5 mg/dL (17.6%).

The primary endpoint, the change in the thickness of the mean carotid intima, was significantly improved in the niacin group as compared to the ezetimibe patients. Essentially, the carotid intima was basically unchanged by ezetimibe therapy, while it was improved by extended release niacin therapy. There was a reduction in cardiovascular events in the niacin group as compared to the ezetimibe group, but the overall numbers of cardiovascular events was small (9 in 165 ezetimibe patients against 2 in 160 niacin patients). Adverse events were somewhat more common in the niacin patients, and there were three times as many patients withdrawing for medication side effects in the niacin group than in the ezetimibe group (3 versus 17).

The supporters of niacin therapy were as delighted with the results of ARBITER-6 as the enthusiasts for ezetimibe were concerned. However, we all must maintain great caution to avoid over interpreting these results. First, whether changes of carotid intima thickening have any predictive value as a surrogate marker for cardiovascular events is totally unproven. Secondly, even though there were differences in cardiovascular events between the groups, the study was so small and short that the overall numbers of events were quite small, and therefore inconclusive. Finally, the absence of a placebo control group makes overall interpretation of this trial very difficult. While the study is suggestive, it remains a preliminary project that needs to be confirmed in a larger, longer trial to evaluate cardiovascular events and these therapies.

For ezetimibe, the crucial study will be the IMPROVE-IT study. IMPROVE-IT is a very large trial, recently with an expansion of its study group from 12,500 patients to 18,000 patients. IMPROVE-IT is an ongoing cardiac events trial that will enroll 18,000 patients with recent Acute Coronary Syndrome but with relatively low LDL-C values at baseline. Patients will be randomized to simvastatin 40 mg along with ezetimibe 10 mg versus simvastatin 40 mg and placebo. Enrollment has recently been extended to be more certain of enough events to determine if there is a significant reduction of cardiac events when ezetimibe is added to statin therapy. Thus, with enrollment expected to be completed by mid-summer of 2010, we will have to wait several years for a definitive answer to this most important question.

Finally there is the SANDS trial. SANDS was a long term trial in Type II diabetics, with the goal of using aggressive LDL-C lowering to <71 mg/dL to reduce carotid IMT. SANDS was designed to evaluate LDL-C lowering directly, producing it with statin alone if possible but with the addition of ezetimibe 10 mg when it was needed. The regression in carotid intima media thickening, or CIMT, was the same whether statin alone or statin plus ezetimibe produced the aggressive LDL-C lowering.
Thus, SANDS suggests that ezetimibe does not have specific negative or positive effects on CIMT regression/progression, which appears to be affected by the LDL-C achieved.30

In summarizing the evidence about the efficacy of ezetimibe to reduce cardiovascular events, the only clear conclusion is that, until the IMPROVE-IT trial is reported several years from now, we will not know whether ezetimibe therapy reduces cardiac events or not. Therefore, my opinion is that ezetimibe should not be utilized as routine therapy when aggressive statin therapy can achieve our LDL-C goals. In the small number of patients who do not achieve LDL-C therapy on maximal statin therapy, such as rosuvastatin 40 mg, then we could consider utilizing ezetimibe therapy. In my practice, I explain to my patients when I want to start ezetimibe that we do not know if ezetimibe will reduce their risk of cardiac events as it lowers their LDL-C.

**Side Effects of Ezetimibe**

In general, ezetimibe is well tolerated by most patients. Side effects are mild and generally self limited.22 Reported side effects do include modest elevations of liver enzymes, along with myopathy and even rhabdomyolysis.21

The most intriguing question about ezetimibe safety is whether ezetimibe might induce the development of malignancy. In the SEAS trial, there were an increased number of cancers and cancer deaths.26 A careful examination showed that there was no particular pattern to the malignancies, and no particular organ system involved. The FDA conducted a review of this question, reviewing SEAS, IMPROVE-IT, and a third study called SHARP. The FDA and independent researchers found no increased pattern of malignancy across the three studies.31,32 I think that this was just an unusual cluster of random cancers in one study, and that it does not represent a true risk factor for our patients.

**Conclusions**

In summary, the proper place of ezetimibe in our current treatment pattern of hyperlipidemia remains unclear. It was quite popular at the outset of its use, particularly when it was used in combination with simvastatin, as the commercial product Vytorin. However, it has not, at this time, been properly studied to document as to whether the LDL-C reduction that it produces actually results in reduction of cardiovascular events. In general, ezetimibe appears to be safe and well tolerated, with no clear safety issues.

This author has always felt that, since any cardiac benefit remains unproven, ezetimibe should be used only as adjunct therapy in addition to the maximal dose of the most potent statin, either rosvuvastatin or atorvastatin, to lower LDL-C that can not be lowered to goal without dual therapy. Whether the patient’s cardiovascular risk will be lowered by such therapy is unclear. We will not get an answer to this most important question until the IMPROVE-IT trial is completed and reported in the next several years.

**NIACIN**

Niacin, or nicotinic acid, is a B vitamin with cholesterol lowering properties. It has enjoyed varying levels of interest for its usefulness in managing lipid disorders. Its popularity appears to be on the rise, mainly because of suggestive results from the ARBITER-6 HALTS study, which was discussed previously. Whether this surge in popularity will turn out to be justified will hinge on the results of the AIM-HIGH study, now in progress, which will compare simvastatin/niacin (long acting) vs. simvastatin and placebo for the prevention of cardiovascular events.33

**Mechanism of Action**

In spite of its use for the treatment of hyperlipidemia for over 50 years, the actual mechanism whereby niacin affects lipid levels is not clear. It is not related to its effect as a B vitamin.

**Effects on Lipid Levels**

Niacin has noticeable effects on all of the significant lipid values. Also, the pattern of lipid effect is related to the dose level of niacin administered, with an increase in HDL-C beginning at lower doses and increasing with higher doses. Lowering of LDL-C, however, requires much more substantial doses, usually in the 1500–3000 mg range.34

While the expected effects will vary with the preparation used and the individual patient, the pattern of change in the lipid fractions include, for the 1000 mg dose, an increase in the HDL-C of about 10%–15%, a 20%–25% reduction in
triglycerides, along with insignificant effect on the LDL-C. At the 2000 mg daily dose, the HDL-C increase is about 20–30%, along with a 25%–30% reduction in triglycerides, and with about a 20% reduction in LDL-C. Lp(a) is reduced by 9% at 1000 mg up to 32% at the 2000 mg dose. Higher doses, even up to 3000–4000 mg have been used, with greater reductions in LDL-C, but they are not commonly used now that the statins are available, and because of the profound levels of side effects that one can see with higher dose niacin.

Preparations
Niacin comes in multiple preparations, including products that are sold over the counter as generic vitamin or nutritional supplements, along with several prescription preparations. If a physician or other health care prescriber is going to institute niacin therapy, I would recommend that they utilize one of the two major prescription preparations, Niaspan® or Slo-Niacin®. In using a prescription preparation, we are assured of the quality and accuracy of the FDA approved preparation, and this allows the practitioner to monitor and regulate the doses used.

Niaspan® is a long acting preparation that comes in 500 mg, 750 mg. and 1000 mg dose preparations. It is given at bedtime, usually at the 500 mg initial dose, and slowly titrated. Slo-Niacin® is a generic preparation with preparations in doses of 250 mg, 500 mg, and 750 mg, and it is dosed at bedtime or sometimes twice daily. Because of niacin’s very potent side effects, particularly flushing and itching, it needs to be initiated at a low dose and titrated up gradually.

Evidence of Efficacy
There is widespread confusion over the efficacy data, or lack thereof, around the uses of niacin in the prevention of cardiovascular events. Under careful examination, the data to support the use of niacin as add-on therapy in addition to statin therapy, as it is currently used, are essentially non-existent.

The original trial of niacin therapy to reduce coronary events was the Coronary Drug Project, a European trial published in the 1970’s. This trial took very high risk patients with known coronary artery disease, and evaluated several different potential treatments in different groups. In one arm of the study, niacin treatment of about 3500 mg daily, when compared to placebo, did not reduce total or coronary mortality, the primary endpoint. Niacin did reduce a single secondary endpoint, namely non-fatal myocardial infarction. However, since the overall study was not successful, it is not clear evidence of effectiveness to pull out one secondary endpoint to claim success. Therefore, the CDP does not provide proof of niacin’s effectiveness, even in this very high risk group. Also, since the study was completed over 35 years ago, when statin therapy was in the distant future, what does this unclear data say to us now? Unfortunately, there is no clear or usable evidence from this very old trial. Also, there was a secondary publication from this same trial that is even more confusing. Nine years after the study was completed and had stopped, the investigators went back to the study group and found that there was an 11% reduction in total mortality in the niacin group. However, since the study had been stopped and the therapy terminated nine years before the data was evaluated, no one can honestly draw any clear conclusion from this data.

Niacin was also a component in several trials of combination therapy. However, these studies also fail to give clear evidence of successful events reduction. Niacin was combined with simvastatin in the HATS study and the combination was compared against anti-oxidant vitamins or placebo. While the combination did reduce events versus vitamins or placebo, the absence of monotherapy arms for niacin or simvastatin alone failed to show whether the addition of niacin to simvastatin was at all beneficial in the reduction of cardiac events instead of the benefit being produced completely by the simvastatin.

The CLAS study was an angiographic trial, which evaluated the effect of treatment on the progression of coronary artery lesions in patients with known disease. In CLAS, niacin was combined with colestipol, a resin binding agent with modest cholesterol lowering properties. The combination therapy did slow the progression of coronary lesions, but it did not reduce cardiac events, so the overall results are unclear. Niacin was shown to reduce cardiac events in one Swedish trial when it was combined with the fibrate clofibrate. Since clofibrate is now off the market, that data is not useful to us.

Finally, we have the previously mentioned ABITER-6-HALTS trial.
In ARBITER-6-HALTS, high risk patients who were already on statin therapy, with LDL-C <100 mg/dL and HDL <50 mg/dL in men and <55 mg/dL in women were studied. Patients had ezetimibe 10 mg or niacin (beginning at 500 mg at bedtime and aiming to titrate to 2000 mg at bedtime) added to the background statin therapy. Niacin additive therapy did reduce the primary endpoint of carotid artery intima-media thickening as measured by B-mode ultrasound when compared to ezetimibe therapy, and there was a significant reduction in cardiovascular events in the niacin group with two in the niacin group and nine in the ezetimibe group. As I said previously, the true importance of this study is unclear. It could suggest that adding niacin to background statin therapy will be protective against cardiac events, but it could also mean that adding ezetimibe to statin therapy increases events. Overall, this study is suggestive and interesting, but not conclusive. Also, tolerance of niacin was noticeably less than tolerance of ezetimibe in the study.

Overall, clear evidence for the potential benefit of niacin therapy in addition to statin therapy awaits the AIM-HIGH study. AIM-HIGH will compare simvastatin/niacin versus simvastatin/placebo in high risk individuals in a long term trial to evaluate cardiovascular events. When AIM-HIGH is reported, we should have much clearer information on whether niacin as additive therapy to statin therapy is beneficial.

Side Effects
Niacin’s side effects remain a considerable factor restricting niacin’s widespread use. Although niacin’s vitamin status allows it to be sold over the counter, it produces a widespread pattern of both symptomatic and metabolic side effects.

The major symptomatic side effect is flushing, with the attendant pruritis and other forms of skin discomfort that accompany it. The actual rates seen in clinical practice are unclear. The very recent trial comparing niacin add-on therapy to ezetimibe add-on therapy found that 36% of niacin treated patients reported flushing and skin symptoms.27 The long acting preparations are felt by many to have lower rates of skin symptoms, but that is unclear.40 However, one study, ARBITER-2 using Niaspan®, a long acting preparation, had 69% of niacin patients complain of skin flushing.41 The main benefit may be related to the traditional dosing of the long acting preparations at bedtime, allowing some lessening of the symptoms during sleep. Also, many practitioners think that a small dose of aspirin or an NSAID will reduce the dermatological symptoms, but this is also unclear.

The considerable metabolic side effects have the potential for more severe problems, and those of us prescribing niacin need to take them into consideration.

Liver dysfunction has the potential to be a serious side effect of niacin therapy, so that regular monitoring of hepatic enzymes is warranted. The actual rates of liver enzyme elevations are not clearly defined. They appear to be mild at lower doses but to become more prominent above 2000 mg daily.34 The combination of niacin with a statin can increase the rate of elevated liver enzymes.34,36

Glucose elevation is a well known side effect of niacin therapy, and it is also related to the niacin dose.34 This issue needs to be considered when niacin therapy is contemplated in diabetic or glucose intolerant patients.

Considerations about Combination Lipid Therapy
There is increasing interest in combinations of lipid lowering agents of different classes to treat complex hyperlipidemia. Combination therapy is widely used in treating many other disorders, such as multiple agents to lower blood pressure or several different antibiotics to treat infections. Since hyperlipidemia is different than hypertension and infections, we cannot safely assume that combination therapy with different lipid lowering classes will be safe and beneficial. Medicine is scientific not logical. Therefore, we should need scientific studies rather than intuition to drive our therapeutic decisions.

The lesson of torcetrapib is very important to remember. Torcetrapib was a CTEP inhibitor that produced increases in HDL-C of about 72% coupled with a further reduction of about 25% in LDL-C, when it was added to atorvastatin therapy. It was assumed that these striking effects on these important lipid fractions would drastically reduce cardiac disease. In fact, the addition of torcetrapib produced significant increases in MI and cardiac mortality.42 Therefore, we need to be certain that combining two or more lipid reducing agents is safe and furthermore, that it reduces cardiac...
Combination therapy with ezetimibe to lower LDL-C further than with maximum statin therapy has been discussed earlier in this paper. It will remain unknown until the IMPROVE-IT trial is reported, as to whether this combination offers further events reductions over statin therapy. Aggressive lowering of LDL-C into the range of 50–55 mg/dl with rosuvastatin therapy alone produced significant events reductions in the JUPITER study, so we should maximize our statin therapy initially before adding a secondary LDL-C lowering agent. High dose niacin, in doses of 2500 mg or more, or resin binding agents like cholestyramine or colestipol can be added to high dose statin therapy in very difficult to control patients. However, this additional therapy is also unproven to reduce events and frequently has unacceptable side effects.

Combination therapy with niacin to lower elevated triglycerides is attractive to many practitioners. However, caution here is also in order. While elevated triglycerides add to the risk of elevated LDL-C in patients that are not on statin therapy, secondary analyses of several of the statin trials indicate that lowering elevated LDL-C with statin therapy eliminates the risks of elevated triglycerides. Other studies have examined whether elevated triglycerides are actually an independent risk factor for increased cardiac events, and have determined that they are not a true risk once the other abnormal lipid fractions like lower HDL-C have been accounted for. Therefore, without at least strong evidence that lowering elevated triglycerides in addition to statin therapy actually reduces events, I recommend aggressive LDL-C lowering with maximal statin therapy and using low-fat, low-carbohydrate diet to reduce triglycerides.

Combination therapy with niacin to increase low HDL-C is the most popular and attractive target for niacin therapy as added onto statin therapy. Also, several studies have shown that, in contrast with elevated triglycerides, low HDL-C remains a risk factor for cardiac events even with most traditional levels of statin therapy. The one exception was from a recent secondary analysis from the JUPITER study, which lowered LDL-C levels down to the 50–55 mg/dL range. In that study, super lowering of LDL-C appears to have eliminated the additive risk of low HDL-C.

Previously, the AFCAPS-TEXCAPS trial had used lovastatin therapy alone to prevent initial cardiac events. In the subgroup of patients with HDL-C <40 mg/dl, lovastatin alone had reduced initial cardiac events by nearly one half.

Recently, interest has focused on adding niacin therapy onto statin treatment in patients with low HDL-C syndrome. The previously mentioned ARBITER-6 HATS and ARBITER-3 trials have shown that increasing HDL-C with niacin therapy can improve the surrogate end-point of reducing carotid arterial wall intima thickening. While these studies are interesting and intriguing, they do not offer the clear evidence as to whether this addition of niacin to statin therapy can actually further reduce cardiovascular events. This lack of complete clarity is emphasized by the older ARBITER-2 and the recently released NIA Plaque study. ARBITER-2 compared adding long acting niacin to statin treatment and found only a trend toward plaque regression as compared to placebo. NIA Plaque added niacin or placebo to patients with low HDL-C but whose LDL-C was already well controlled on statin therapy. In this study, there was no difference in regression of intima wall plaque from niacin or placebo. This study may support the JUPITER study suggestion that aggressive LDL-C lowering may remove the risk effect of low HDL-C.

The resolution of this controversy will await the AIM-HIGH study, comparing multi-year treatment with statin/niacin versus statin/placebo in patients with low HDL-C. At this point, the only conclusion that we can make based on clinical trials evidence is that aggressive statin therapy will reduce events in patients with low HDL-C lipids. Whether adding niacin will be additionally beneficial will remain to be seen in the future when AIM-HIGH will be reported.

Conclusion

While the temptation to add secondary agents like ezetimibe or niacin to statin therapy can be alluring, practitioners should remember the questions that we have discussed here. Adding either of these secondary agents has not been proven to reduce cardiac events in this add on role. They may be beneficial, but again they may not be. What can be said is that adding them will increase the cost of therapy (particularly for ezetimibe) or may significantly increase the risk of adverse effects, like the prominent itching and
skin discomfort from niacin. With definitive research in progress, it is prudent for practitioners to avoid starting these therapies until clear benefit has been demonstrated.

Disclosure
This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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