Antioxidant Supplements and Simvastatin-Niacin Therapy

To the Editor:

This article1 attracted our attention first because of the wide implications and second because of the related editorial comments2 that sort of urged the physicians to "stop prescribing antioxidant vitamins to prevent and treat heart disease."

In these studies, subjects with coronary artery disease were divided into 4 treatment groups, namely (1) placebo group, (2) antioxidant group, (3) simvastatin-niacin group (S-N), and (4) simvastatin-niacin plus antioxidant group (S-N+A). The probability values for between-groups comparisons of changes from the individual values at the start and until the end of the study period (12 months) for several parameters (Table 2) indicate that there were no significant differences between the S-N group and the S-N+A group with respect to plasma cholesterol, plasma tri-glycerides, VLDL-C, IDL-C, LDL-C, HDL-C, HDL2-C, apo A-I, apo A-II, apo-B. However, the changes in HDL2-C values differed significantly between these two groups.

The intakes of simvastatin in these groups at the start of the studies ranged between 10 and 20 mg. During the course of the studies, intakes were raised to 20 to 40 mg for the subjects whose LDL cholesterol levels were not lowered to less than 90 mg/dL. Similarly, the intakes of niacin were increased from 2 g per day to 3 to 4 g per day for the subjects in whom the rise in HDL cholesterol level was less than 10 mg/dL. Evidently, some subjects failed to respond to the predetermined treatment, requiring modification of the treatment and thus creating subgroups who received higher levels of medications. Such subgroups should have been treated separately, and separate comparisons of the subgroups receiving higher levels of medications should have been made. Then again, the number of subjects in each group that required such interventions with an increased dosage of simvastatin and niacin would in itself become a relevant and essential parameter for interpreting the treatment effects. These aspects have not been considered in interpreting the data and are particularly important in evaluating the quantum of rise in HDL2-C, as it is quite possible that higher levels of HDL-C in the S-N group were related to higher intakes of niacin. Neglect of these several factors has possibly led to unwarranted conclusions.

The authors state “HDL-C and HDL2-C and apo A-I responses in several other studies.” This is not borne out by the probability value given in Table 2. None of these values are significantly different.

In face of these facts, the title of the article “Antioxidant Supplements Block the Response of HDL to Simvastatin-Niacin Therapy...” is highly misleading. Antioxidants, such as vitamin C, have been shown to increase HDL levels and lower total cholesterol in several other studies.3-5 It is worthwhile noting here that the recent studies in natural approaches to health have already challenged the traditional cholesterol theory of heart disease.6 Use of antioxidants has still been shown to directly improve atherosclerotic conditions.7 Several million people are in urgent need of the right type of medication for atherosclerotic conditions. With some statins withdrawn from the market and some others attracting adverse comments, it is likely that we may have to depend more and more on antioxidants either alone or in combination with lower doses of a few selected statins. It is therefore imperative that we should have incontrovertible evidence against the use of antioxidants before we stop using them.

In Response:

The combination of antioxidant supplements used in our study significantly blunted the specific response of HDL2-C-cholesterol and HDL particles containing apo A-I but not apo A-II [Lp(A-I)] to simvastatin-niacin therapy in subjects with coronary artery disease and low HDL. As HDL2 and these Lp(A-I) particles are considered to be the most protective components of total HDL, we do not believe that the title of the article is misleading.

Because the principal observed effect of antioxidants was to block the HDL2 response to simvastatin and niacin therapy, we performed the treatment subgroup analyses suggested by Netke et al on the HDL2 response; these analyses are provided in the Table. Thus, there were no significant effects of simvastatin or niacin dose on the HDL2 response to simvastatin-niacin therapy. The blunting effect of antioxidants was seen across the dose range. This subgroup analysis further supports our conclusion.

Regarding the putative dangerous effects of statin, the inclusion of this statement in their letter reflects the bias of Dr. Rath’s group against proven forms of therapy in favor of unproven ones. Statins have a much lower serious complication rate than aspirin. Furthermore, assuming one death in 4 years from rhabdomyolysis among 300,000 statin-treated patients (excluding cerivastatin), failing to treat 300,000 patients would result in an additional 4-year cardiovascular mortality of approximately 4000 patients. Is this group suggesting we should deny this risk-benefit ratio to individuals deserving therapy by current recommendations? We stand by our conclusion that antioxidant vitamins blunt the response of HDL2 and Lp(A-I) to combined simvastatin-niacin therapy.

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Mean (Median) Percent Change in HDL2 With Simvastatin and Niacin +/- Antioxidants

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Simvastatin Dose</th>
<th>Niacin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤10 mg/d</td>
<td>&gt;10 mg/d</td>
</tr>
<tr>
<td>Simvastatin-niacin and placebo</td>
<td>(n=20) 77% (50%)</td>
<td>(n=18) 45% (33%)</td>
</tr>
<tr>
<td>Simvastatin-niacin and antioxidants</td>
<td>(n=28) 23% (0%)</td>
<td>(n=12) 19% (0%)</td>
</tr>
</tbody>
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Familial Combined Hyperlipidemia and Insulin Resistance

To the Editor:

In the last paragraph of this editorial (Arterioscler Thromb Vasc Biol. 2001;21:469–470), Dr Eckel mentions that assays for apo B remain less than optimal and quotes our article that deals with standardization of the DAIS Study.1 In fact, after the decision was made on a common International Federation of Clinical Chemistry/World Health Organization standard for the 2 laboratories involved in DAIS, there was very little bias in the apo B values (see Figure 5A of our article). Apo B assays have been standardized2–3 and reference values established in both the United States and Canada (for a review, see Bhatnagar et al).4

Plasma apo B concentration, a measure of LDL particle number, has been shown in both epidemiological studies and prospective, double-blind, placebo controlled clinical trials to be related to clinical outcomes.5–7 In the Quebec Cardiovascular Study,8 apo B was the single most important lipid parameter that predicted cardiovascular events. Similarly, data from AFCAPS/TEXCAPS9 have demonstrated that although LDL cholesterol, HDL cholesterol, and apo B predict cardiac outcomes before therapy is initiated, the lipid levels and their ratios did not predict outcome on treatment, whereas apo B and the ratio of apo B to apo A1 did. Similarly, on treatment, apo B and apo A1 were the significant predictors in a secondary prevention study of van Lennep et al.7 This also fits well with observational data by Moss and colleagues10 in 1045 postinfarction patients. Target values have been established and accepted by the Canadian Cardiovascular Society.11

Although apo B should not be the only parameter measured in the initial assessment of the risk of disease, it is, in addition to serum lipids, an excellent parameter for the follow-up of patients. In the most common type of dyslipidemia, namely, mild to moderate hypertriglyceridemia, low HDL cholesterol and higher numbers of small, dense LDL particles, measurement of apo B can distinguish between those at risk, ie, those with familial combined hyperlipidemia and those with familial hypertriglyceridemia (ie, those with “good” and “bad” hypertriglyceridemia).

In conclusion, apo B is a standardized, well-characterized, and validated measurement that could greatly simplify diagnosis and treatment of patients with dyslipidemia.

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In Response:

I would like to begin by thanking Drs Frohlich and Sniderman for their thoughtful letter in response to my recent editorial “Familial combined hyperlipidemia and insulin resistance: distant relatives linked by intra-abdominal fat.” Their predominant concerns relate to my recommendations as to when apo B determinations should be obtained and the technical quality of the assay for apo B.

When fasting plasma triglycerides are >200 mg/dL and the National Cholesterol Education Program (NCEP) treatment goal for LDL cholesterol has been achieved, ie, <160, <130, or <100 mg/dL, the secondary treatment goal outlined by the recent report of the NCEP is a non-HDL cholesterol level of <190, <160, or <130 mg/dL, respectively, not apo B.2 In fact, apo B was not recommended by the NCEP panel as a tool to assess coronary heart disease (CHD) risk under any circumstances. As stated by Drs Frohlich and Sniderman, non-HDL cholesterol may not be a perfect surrogate for apo B. However, the fact that the correlation coefficient is stronger between non-HDL cholesterol and total cholesterol than between non-HDL cholesterol and apo B is not surprising, considering the presence of total cholesterol in both of the correlation covariates (cholesterol and non-HDL cholesterol, the latter of which is total cholesterol minus HDL cholesterol).

Presumably, but not stated, is that the NCEP panel viewed (1) the clinical evidence in support of apo B as a better predictor of CHD than non-HDL cholesterol and/or (2) the assays available to measure apo B as sufficient to encourage the routine use of apo B. Although as noted in the letter by Drs Frohlich and Sniderman, some studies have shown the superiority of apo B in predicting CHD events, many studies either have not reported apo B data (WOSCOPS, 4S) or have not indicated the relative merit of 1 determinant versus the other (CARE)3 in predicting outcome. If the data were substantial to support the superiority of apo B and one could assume that all commercial assays for apo B had the accuracy and quality control of reference labs,4,5 I would strongly agree and extend my recommendations to patients with hypertriglyceridemia and LDL cholesterol levels >130 but ≤160 mg/dL. However, this certainty is not apparent. When LDL cholesterol levels are >160 mg/dL, I remain convinced that apo B is elevated and its measurement is redundant. Despite the progress in Canada to add apo B to their CHD risk assessment,6 it is interesting to note that lipid and lipoprotein measurements have not been eliminated.

Overall, my opinion that apo B has tremendous value in the assessment of cardiovascular risk in patients with hypertriglyceridemia is in agreement with the position of Drs Frohlich and Sniderman. Such an approach to risk assessment is used by few physicians in the United States, and I am confident that increasing and appropriate use of apo B in the assessment of patients with hypertriglyceridemia may improve therapeutic strategies and outcomes in at least some of these.
patients. However, the NCEP expert panel has stopped short of such recommendations. It will be interesting to see the rationale for this lack of enthusiasm when the complete report is released.

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