Letters to the Editor

Evidence Supporting Niacin Therapy Is More Nuanced Than Article States

Original Article: Stable Coronary Artery Disease: Treatment

Issue Date: March 15, 2018

See additional reader comments at: https://www.aafp.org/afp/2018/0315/p376.html

To the Editor: This article states that "No data support the routine use of nonstatin drugs such as bile acid sequestrants, niacin, ezetimibe (Zetia), and fibrates as monotherapy. These medications lower [low-density lipoprotein (LDL)] cholesterol levels but do not reduce cardiovascular morbidity or mortality." As far as niacin is concerned, this is not true.

The first large niacin trial, the Coronary Drug Project, showed a 27% decrease in nonfatal myocardial infarction in patients with coronary artery disease who were treated with niacin for six years, and a 6.2% absolute mortality benefit nine years after the study was completed.[1] Since then, more trials have compared niacin with placebo and as add-on therapy for statins and other cholesterol-lowering agents in various combinations. Meta-analyses of these studies have drawn wildly divergent conclusions depending on which studies were included, from a 47% reduction in any cardiovascular event (cardiac death, nonfatal myocardial infarction, revascularization procedure, hospitalization for acute coronary syndrome, or stroke),[2] to no effect on any outcome.[3]

Although the two latest niacin trials did not show a benefit for niacin, it has been suggested that different trial protocols (e.g., dyslipidemia types, dosing and timing of niacin, niacin formulation) could have led to different results.[4] It is safe to conclude that in patients with very low levels of LDL cholesterol and apolipoprotein B who are already receiving statins and/or ezetimibe, the incremental addition of niacin does not further reduce cardiovascular events.

So the truth may be more nuanced: niacin monotherapy reduces cardiovascular events in patients with coronary artery disease and high LDL cholesterol levels, whereas a combination of niacin and a statin or other lipid-lowering agent has no effect in patients with low LDL cholesterol levels, and niacin may have some benefit in patients whose LDL cholesterol level is still too high despite maximal statin therapy.[5]

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In Reply: Thank you for your well-thought-out question regarding our article. As Dr. Pisarik pointed out, the article stated that "No data support the routine use of nonstatin drugs such as bile acid sequestrants, niacin, ezetimibe (Zetia), and fibrates as monotherapy. These medications lower LDL cholesterol levels but do not reduce cardiovascular morbidity or mortality." We stand by this statement.

We purposely added the phrase "as monotherapy" to the end of the sentence because trials have

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not consistently shown niacin to reduce morbidity or mortality when used alone.[1-3] In addition, numerous studies have noted that niacin combined with statin therapy does not reduce cardiovascular morbidity or mortality.[4,5] The Cochrane review you cited reviewed 23 randomized controlled trials published between 1968 and 2015 that included 39,195 participants. The review concluded that moderate- to high-quality evidence shows that niacin does not reduce overall mortality (risk ratio [RR] = 1.05; 95% confidence interval [CI], 0.97 to 1.12), cardiovascular mortality (RR = 1.02; 95% CI, 0.93 to 1.12), noncardiovascular mortality (RR = 1.12; 95% CI, 0.98 to 1.28), fatal or nonfatal myocardial infarctions (RR = 0.93; 95% CI, 0.87 to 1.00), or fatal or nonfatal strokes (RR = 0.95; 95% CI, 0.74 to 1.22).[4]

The other articles you cite show that patients benefitted the most from incorporating niacin in their treatment regimen when they had elevated LDL cholesterol (above target) and triglyceride levels and reduced high-density lipoprotein cholesterol levels. These studies used niacin as add-on therapy to a statin, not as monotherapy. There may still be a role for niacin in certain populations. However, in general, niacin alone does not have the same supportive data for reducing cardiovascular outcomes as first-line therapy like statins.

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The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. government.

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Does Niacin Have Cardiovascular Benefits in Patients with Dyslipidemia?

Original Article: Use of Niacin for Primary or Secondary Prevention of Cardiovascular or Cerebrovascular Events [Cochrane for Clinicians]

Issue Date: April 1, 2018

Available online at: https://www.aafp.org/afp/2018/0401/p436.html

To the Editor: In this Cochrane for Clinicians the authors concluded that niacin does not reduce myocardial infarction (MI), strokes, or overall mortality when used for primary or secondary prevention, either alone or in addition to statins. In 2016, the U.S. Food and Drug Administration withdrew its approval to use niacin in combination with statins to treat dyslipidemia, citing a lack of cardiovascular benefit based on the results of two trials that explored the possible benefits of adding niacin to high-intensity statin therapy.[1,2] However, both trials were poorly designed to capture the potential cardiovascular benefits of niacin. Not only was the selected patient population inappropriate, but dosing schedules and formulations were different from what was used in previous positive studies.[3]

In the pre-statin era, the Coronary Drug Project (1966-1975) tested the effect of 3 g of niacin per day on cardiovascular events in men with previous MI. Niacin treatment showed modest benefit in decreasing nonfatal recurrent MI but did not decrease total mortality.[4] However, a 15-year follow-up study, nearly nine years after termination of the original trial, found that mortality in the niacin group was 11% lower than in the placebo group (52.0% vs. 58.2%, respectively; $P = .0004$), a striking 6.2% absolute risk reduction.[5] By comparison, the greatest absolute risk reduction in any placebo-controlled statin trial was 3.5% in a study involving simvastatin (Zocor).[6]

Most other niacin trials included background statin therapy in both the study and placebo arms, which clouded the results because statins had become the standard of care.[3] Moreover, approval of new drugs showing clear cardiovascular benefits on top of statins, such as ezetimibe (Zetia) and proprotein convertase subtilisin/kexin type 9 inhibitors, has dampened further pharmaceutical interest in studying niacin. Nevertheless, based on available evidence, niacin (which is inexpensive and available over the counter)

should remain an option, especially for patients who refuse or are unable to tolerate statins.

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In Reply: We appreciate the thoughtful comments from Dr. Wójcik that advocate for keeping niacin as an option for the prevention of cardiovascular or cerebrovascular events in patients with dyslipidemia. However, we respectfully disagree with the letter's conclusions.

The two trials used by the U.S. Food and Drug Administration (i.e., Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE] and Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes [AIM-HIGH]) to withdraw approval for the use of niacin with statins were included in the Cochrane review.[1] However, another 21 randomized controlled trials carried about 40% of the weight of evidence used in the analysis, including the Coronary Drug Project.[2] A meta-regression analysis completed by the Cochrane authors did not find significant effect modification based on length of treatment, whether patients had baseline coronary heart disease, or the proportion of patients already taking statins.[1]

The four studies mentioned by Dr. Wójcik that show large benefits with niacin therapy and are cited in the Superko article[3] (i.e., Cholesterol Lowering Atherosclerosis Study [CLAS], Familial Atherosclerosis Treatment Study [FATS], HDL-Atherosclerosis Treatment Study [HATS], and Armed Forces Regression Study [AFREGS]) were all excluded from the Cochrane systematic review for lacking comparison of interest. Although this article does note a decrease in cardiovascular events for patients taking niacin in these studies, most of the cited benefits are disease-oriented, and there is little consideration of the harms of niacin therapy.[3] The average dosage of niacin in these trials was 3.4 g per day; it seems likely this was difficult to tolerate based on available evidence.[3]

The lower mortality rate seen in patients several years after completion of the Coronary Drug Project is interesting. Although the initial trial was included in the Cochrane review, it is unclear if the follow-up study was.[1,4] Still, the authors of this study believed that the benefit from niacin therapy was almost certainly due to lowering of serum cholesterol and not to any pleiotropic effect of niacin.[4] It is possible that the delay in mortality benefit could have been caused by concomitant harm from active niacin use; the mortality benefit in these patients was seen only after niacin had long been discontinued.[4] Although this result was very important before statins and other lipid-lowering options were available, it seems less so now. We suggest that niacin be retired from consideration for the prevention of cardiovascular or cerebrovascular events, given its lack of patient-oriented benefit in multiple high-quality studies.

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This work represents the views of the authors and does not represent the views of the U.S. government, the U.S. Army, the U.S. Air Force, or the Defense Health Agency.

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