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Review Article

Niacin and heart disease prevention: Engraving its tombstone is a mistake

Harold Robert Superko, MD, FAHA, FACC*, Xue-Qiao Zhao, MD, FACC, Howard N. Hodis, MD, John R. Guyton, MD

Cholesterol, Genetics, and Heart Disease Institute (501c3), Mercer University School of Pharmaceutical Sciences, Carmel, CA, USA (Dr Superko); Clinical Atherosclerosis Research Lab, Division of Cardiology, University of Washington, Seattle, WA, USA (Dr Zhao); Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA (Dr Hodis); and Division of Endocrinology, Metabolism, and Nutrition, Duke University Medical Center, Durham, NC, USA (Dr Guyton)

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Abstract: Niacin (nicotinic acid) has been used for primary and secondary coronary heart disease prevention for over 40 years. Until recently clinical trials incorporating niacin as part of an intervention strategy consistently demonstrated reduction in clinical events and lesion improvement, including ≥6% absolute mortality reduction. Two large clinical event trials in 2011 (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) and 2014 (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) concluded that niacin added to statin therapy did not provide clinical event benefit over statin alone. This has prompted some individuals to call for an end to the use of niacin in statin-treated patients and the US Food and Drug Administration to halt marketing of statin/niacin combination tablets. There are significant differences between the earlier clinical trials that revealed cardiovascular benefit of niacin and the 2 trials that failed to demonstrate a benefit. These differences include dyslipidemia types, niacin formulation, dosing, and timing. In general, the patient population that benefits the most from incorporating niacin in their treatment regimen can be defined by elevations in low-density lipoprotein cholesterol and triglycerides, and reduced high-density lipoprotein cholesterol. The niacin formulation and dose should be capable of achieving adequate lipoprotein change. Mealtime dosing of niacin, as opposed to bedtime dosing, may avoid a counter-regulatory hormone response, including catecholamines, because of altered fuel supply potentially leading to unexpected cardiovascular outcomes.
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Publication and analysis of the 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 and Impact on Global Health Outcomes (AIM-HIGH) investigations has generated some controversy and confusion among the public and medical community regarding the evidence for efficacy of niacin (nicotinic acid) as a drug for dyslipidemia and vascular disease treatment.[1,2] Most recently, the US Food and Drug Administration has announced

* Corresponding author. Cholesterol, Genetics, and Heart Disease Institute, 24953 Outlook Lane, Carmel, CA 93923, USA.
E-mail addresses: highhdl@mac.com; rsuperko@alumni.ucsd.edu
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withdrawal of previously approved indications for the use of extended-release (ER) niacin co-administered with a statin, commenting that existing evidence does not support that reducing triglycerides or raising of high-density lipoprotein cholesterol (HDL-C) with any drug improves cardiovascular (CV) risk in patients on statins.[3] A prominent physician stated, "There is no evidence for any meaningful benefit for addition of niacin or fibric acid derivatives to statins. There are also significant harms associated with these drugs. In the absence of benefits, there remain only harms."[4] In this review, we contend that the justification for this statement pertaining to niacin is specific only to the unique characteristics of HPS2-THRIVE and AIM-HIGH.[1,2] There is abundant evidence to support the use of niacin in combination with a statin or bile acid–binding resin when niacin is administered appropriately to the right patient populations. To appreciate evidence for niacin benefit and to avoid discarding a component of effective treatment for some patients, it is useful to understand important differences between successful studies using niacin and the lack of overall clinical event benefit in HPS2-THRIVE and AIM-HIGH. The current confusion creates the risk to patient care of avoiding beneficial treatment in specific patient groups that may benefit from niacin therapy. In regard to clinical utility, we call to attention 7 relevant points: (1) statin therapy alone is not sufficient to defeat coronary atherosclerosis in many patients; (2) niacin has provided benefit in randomized clinical trials that differed in critical ways from AIM-HIGH and HPS2-THRIVE; (3) recent discoveries about non-lipoprotein effects of niacin should guide understanding of clinical effects; (4) successful niacin clinical trials used higher doses of niacin compared with the unsuccessful studies and achieved greater blood lipid change; (5) studies powered for arteriographic change, and using niacin, reported both significant arteriographic benefit and clinical event benefit; (6) niacin has a greater effect on atherogenic dyslipidemia, a component of the metabolic syndrome, compared with statin treatment; and (7) there is a diversity of niacin preparations.

Statin therapy alone is not sufficient to defeat coronary atherosclerosis

Although abundant evidence exists that statin therapy can statistically significantly reduce clinical events, statin therapy alone leaves substantial residual risk and will not defeat coronary atherosclerosis in many patients. Statistical significance does not necessarily mean clinical relevance for all patients. The 25% relative risk reduction (RRR) attributed to statin therapy is actually only a 3% absolute risk reduction (ARR) and reflects the need to go beyond therapy designed to primarily reduce low-density lipoprotein cholesterol (LDL-C).[5,6] For example, in a meta-analysis of 5 statin clinical trials, in 30,817 men and women, a 31% RRR in coronary heart disease (CHD) events was reported.[7] However, this represents the difference between 2042 events (13.3%) in the placebo group and 1490 events (9.7%) continuing to occur in the statin treatment group. This reflects an ARR of only 3.6% over a 5- to 6-year period. To achieve this degree of event reduction, approximately 30 subjects had to be treated to prevent 1 event. This can be compared with clinical trials that used niacin combined with an LDL-C lowering medication and reported that approximately 10 subjects had to be treated to prevent 1 event.[6] The most recent large statin study, JUPITER, treated 17,802 normolipemic primary prevention subjects with elevated high-sensitivity C-reactive protein blood levels with rosuvastatin or placebo and achieved a 50% reduction in LDL-C and a statistically significant reduction in the primary CV endpoint.[8] However, of the 8901 subjects in the placebo group, 251 (2.8%) had an event and of the 8901 rosuvastatin subjects, 142 (1.6%) still had an event. Unfortunately, many patients on statin therapy experience a CV event and thus have "failed" on statin therapy for its primary intent of preventing CV events. Recent evidence from JUPITER has revealed that residual small LDL independently predicts CV events.[9] Niacin is effective at reducing small LDL.[10]

Niacin has provided benefit in randomized clinical trials that differed in critical ways from AIM-HIGH and HPS2-THRIVE

Niacin has a long history of clinical use for treatment of dyslipidemia by clinicians and researchers dating back to the Coronary Drug Project report of 1975.[11] Reviews abound that discuss the reputedly beneficial pharmacotherapeutic effects of niacin and lipoprotein disorders that it can modify.[12–15]

The most striking benefit in any large atherosclerosis risk reduction trial was 6.2% absolute mortality benefit ($P = .0004$) for the niacin group in a 15-year follow-up of the Coronary Drug Project.[11] The small Stockholm Ischemic Heart Disease study echoed this result, showing 7.8% absolute mortality benefit ($P = .035$) over 5 years for combination niacin-clofibrate therapy vs no lipid medication.[16] In comparison, the best absolute mortality benefit from any statin trial was 3.5% ($P = .0003$) in the Scandinavian Simvastatin Survival Study.[17]

Two randomized trials with arteriographic primary endpoints, comparing placebo treatment vs combination drug regimens including niacin, found unexpectedly large reductions of combined CV events. In the HDL Atherosclerosis Treatment Study (HATS) RRR was 70% and ARR 20% over 3 years.[18] The Armed Forces Regression Study (AFREGS) found RRR of 48% and ARR of 14% over 2.5 years.[19]

In the trials cited previously mentioned, control patients did not receive statins. The presence of statin background therapy is generally suggested as the reason for lack of benefit for niacin in AIM-HIGH and HPS2-THRIVE. However, there are other major differences between these 2 trials and earlier ones. We will give attention to differing patient populations and to bedtime vs mealtime dosing of niacin.

Historically, niacin has been prescribed, either alone or in combination with other lipid medications, for patients

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