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The Current State of Niacin in Cardiovascular Disease Prevention

A Systematic Review and Meta-Regression

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Objectives This study sought to assess the efficacy of niacin for reducing cardiovascular disease (CVD) events, as indicated by the aggregate body of clinical trial evidence including data from the recently published AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial.

Background Previously available randomized clinical trial data assessing the clinical efficacy of niacin has been challenged by results from AIM-HIGH, which failed to demonstrate a reduction in CVD event incidence in patients with established CVD treated with niacin as an adjunct to intensive simvastatin therapy.

Methods Clinical trials of niacin, alone or combined with other lipid-altering therapy, were identified via MEDLINE. Odds ratios (ORs) for CVD endpoints were calculated with a random-effects meta-analyses. Meta-regression modeled the relationship of differences in on-treatment high-density lipoprotein cholesterol with the magnitude of effect of niacin on CVD events.

Results Eleven eligible trials including 9,959 subjects were identified. Niacin use was associated with a significant reduction in the composite endpoints of any CVD event (OR: 0.66; 95% confidence interval [CI]: 0.49 to 0.89; $p = 0.007$) and major coronary heart disease event (OR: 0.75; 95% CI: 0.59 to 0.96; $p = 0.02$). No significant association was observed between niacin therapy and stroke incidence (OR: 0.88; 95% CI: 0.5 to 1.54; $p = 0.65$). The magnitude of on-treatment high-density lipoprotein cholesterol difference between treatment arms was not significantly associated with the magnitude of the effect of niacin on outcomes.

Conclusions The consensus perspective derived from available clinical data supports that niacin reduces CVD events and, further, that this may occur through a mechanism not reflected by changes in high-density lipoprotein cholesterol concentration. (J Am Coll Cardiol 2013;61:440–6) © 2013 by the American College of Cardiology Foundation

Extensive epidemiological data have established elevated low-density lipoprotein cholesterol (LDL-C) as a major predictor of cardiovascular disease (CVD) risk. Current national CVD prevention guidelines strongly reflect this observation, focusing on lipid intervention strategies primarily targeting LDL-C (1–3). This approach is supported by considerable evidence derived from randomized controlled trials (RCTs) of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy demonstrating a reduction in CVD event rate proportional to the achieved absolute reduction in LDL-C (4). Recent analyses indicate that this quantitative relationship between LDL-C and CVD risk persists throughout even very low LDL-C concentrations, suggesting that as many as 40% of CVD events may be prevented by intensive statin therapy (5,6). While validating the incremental benefit of aggressive statin use, however, a review of recent RCTs revealed a substantial CVD event rate in those treated to achieve even the most stringent LDL-C targets (7–11). Recognition of this sizable residual risk has intensified efforts to identify novel therapeutic interventions.

Current understanding of the pathophysiology underlying atherosclerosis suggests a complex, multifactorial mechanism, only partially modulated by the most prominent target of statins, LDL-C. Niacin, a broad-spectrum lipid-regulating agent, has been shown to exert multiple favorable effects on cholesterol metabolism, including reduction of total cholesterol, triglycerides, very low-density lipoprotein, LDL-C, lipoprotein (a), and augmentation of high-density lipoprotein cholesterol (HDL-C) (12,13). It has also been

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recently suggested that niacin may exert nonlipid-mediated atheroprotective effects (13,14). As such, niacin has been in clinical use for many decades for the prevention of CVD. Previous clinical trials evaluating the efficacy of niacin treatment in cardiovascular outcomes yielded promising results. The Coronary Drug Project, a randomized, placebo-controlled secondary prevention trial, demonstrated a significant reduction in CVD events in the niacin intervention arm compared with that in placebo-treated subjects (15). Subsequent trials examining the combined effect of niacin added to statin therapy reported similar benefit with respect to various surrogate endpoints (16–21).

These somewhat limited empirical data supporting niacin's clinical efficacy have been challenged by the recently published results of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial) (22). Cosponsored by the National Heart, Lung, and Blood Institute, AIM-HIGH was designed to evaluate the addition of extended-release niacin to intensive statin therapy in patients with established CVD and atherogenic dyslipidemia (characterized by low HDL-C, elevated triglycerides, and small, dense LDL-C), compared with statin use alone. The study was stopped prematurely after an interim analysis revealed futility with respect to the primary clinical endpoint and a trend toward increased stroke incidence in niacin-treated subjects.

We sought to assess the impact of these results on the collective body of evidence evaluating the clinical efficacy of niacin. Described here is a systematic analysis of niacin RCTs that report CVD outcome data.

Methods

Trial inclusion. A MEDLINE search identified trials of niacin therapy, alone or in conjunction with additional lipid-altering interventions, published in the English language literature between January 1966 and December 2011. Eligible studies were of randomized, controlled design reporting clinical CVD event data with a minimum of 6 months of follow-up. The electronic search strategy included the terms *niacin*, *niaspan*, *nicotinic acid*, *acipamox, vitamin B3*, and *vitamin pp*. Citations were limited using the terms *human*, *English language*, and *randomized controlled trial*. To ensure a comprehensive identification of appropriate trials, we conducted a supplemental manual review of citations from all eligible studies and relevant systematic analyses (23,24).

Data extraction and quality assessment. All citations were screened at the abstract level, and full articles of eligible trials were independently reviewed. The following variables were collected from the published article of each eligible study as available: baseline demographic characteristics of study participants (sample size, age, sex, diabetes, smoking status, and body mass index); baseline and on-treatment serum HDL-C, LDL-C, total cholesterol, and triglyceride levels; and the occurrence of clinical CVD events (cardiac death, nonfatal myocardial infarction, hospitalization for acute coronary syndrome, stroke, or revascularization). In the event of multiple active treatment arms, analysis was limited to the 2 groups from each trial least confounded with respect to niacin use. This was achieved by exclusion of subjects receiving non-niacin therapy in the intervention arms of 2 trials (15,25), those assigned to treatment with antioxidant vitamins in another (16), and the niacin monotherapy arm of a fourth study in which control subjects received combination therapy with ezetimibe and simvastatin (26).

Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

OR = odds ratio

RCT = randomized controlled trial

The quality of individual trial design and execution was assessed via evaluation of randomization methods, concealment of treatment allocation, and description of withdrawals and dropouts, which was quantified using Jadad's scale (27).

Analysis. Our pre-specified primary analysis estimated the summary effect of niacin, as either monotherapy or an adjunctive lipid-modifying intervention, on the composite endpoint of any CVD event (defined as cardiac death, nonfatal myocardial infarction, hospitalization for acute coronary syndrome, stroke, or revascularization procedure). Two secondary endpoints were also analyzed: major coronary heart disease (CHD) event, (defined as nonfatal myocardial infarction or cardiac death), and stroke (ischemic or hemorrhagic). A pre-specified subgroup analysis evaluated the effect of niacin as an adjunct to statin therapy on each of the primary and secondary clinical outcome measures (16,17,19,22,26). An additional analysis was performed limited to trials in which the lipid-modifying intervention differed only with respect to the presence of niacin therapy between treatment and control arms (15,17,22,26).

An exploratory meta-regression analysis was performed examining a potential association between the difference in HDL-C concentration between trial arms with the calculated effect size of each respective trial for the primary endpoint of any CVD event.

Statistical methods. Measures of effect size with respect to the prespecified clinical endpoints for each included study are presented as odds ratios (ORs). The I^2 statistic was calculated to quantify the proportion of inconsistency observed across trials. Given the variation in baseline population characteristics and lipid-modifying regimens used within the included studies, a random-effects model (DerSimonian and Laird) was chosen to estimate the pooled effect of all trials for each prespecified clinical endpoint. To determine the extent to which inclusion of the 2 largest trials influenced the overall findings, sensitivity analyses

JACC Vol. 61, No. 4, 2013
January 29, 2013:440–6

were performed excluding the Coronary Drug Project (15) or AIM-HIGH (22).

Exploratory analyses designed to assess the role of HDL-C as a predictor of between-study variation in clinical outcome was limited to the primary composite endpoint of any CVD event due to constraints in requisite data availability. The natural log-transformed OR was modeled as a linear function of the trial-specific on-treatment difference in HDL-C concentration between study arms via inverse variance-weighted random-effects meta-regression for the outcome of interest.

Statistical analyses were performed using the Review Manager (RevMan) software package version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark; the Cochrane Collaboration, 2011) and SPSS 19.0 (SPSS, Inc., Chicago, Illinois). The threshold for statistical significance was set at the 2-tailed alpha level of 0.05.

Results

Our search strategy yielded 560 citations that were screened at the abstract level, of which 173 were retrieved for detailed evaluation. On review of full-text articles, 11 trials were deemed eligible according to the aforementioned criteria for inclusion in the present analysis. There was a total of 4,365 subjects allocated to receive niacin intervention and 5,596 subjects allocated to the respective control arms of included trials. The mean duration of follow-up was 2.7 years (SD 1.7 years). Study quality, as quantified by the Jadad scale was ≥3 for each eligible trial. Of the 11 trials included in the primary meta-analysis, 8 were conducted in a double-blind fashion (15–17,22,25,26,28,29). Baseline demographic and clinical characteristics of study participations are provided in Table 1.

Meta-analysis. Among selected trials, 1 was excluded from analysis of major CHD event (25) and 4 from that of stroke incidence (19,25,28,29,31) due to the absence of reported events for these outcomes during the period of observation. In a summary analysis of all trials, the primary composite endpoint of any CVD event was significantly less frequent in niacin-treated patients compared with controls (OR: 0.66; 95% confidence interval [CI]: 0.49 to 0.89; p = 0.007; I^2 = 59%) (Fig. 1). A significant response to niacin treatment was also demonstrated in a similar analysis performed with respect to the secondary endpoint of major CHD events (OR: 0.75; 95% CI: 0.59 to 0.96; p = 0.02; I^2 = 31%) (Fig. 2). There was no significant difference in stroke risk between subjects allocated to niacin treatment compared with controls (OR: 0.88; 95% CI: 0.5 to 1.54; p = 0.65; I^2 = 41%) (Fig. 3). Pooled effect estimates were not significantly changed for any clinical endpoint on sensitivity analysis excluding the Coronary Drug Project, the largest single trial (15) (Online Appendix A). Sensitivity analysis excluding AIM-HIGH also resulted in a niacin-associated improvement in outcomes including a significant decrease in stroke incidence (Online Appendix B).

Table 1 Trial Design and Baseline Characteristics of Trials Included in the Current Analysis

Trial/First Author (Ref. #)	Year	n	Study Arm: Treatment	Study Arm: Control	Follow-Up, yrs	Age, yrs	Male, %	BMI, kg/m^2	Hypertension, %	Diabetes, %	Baseline LDL-C	Baseline HDL-C
CDP (15)	1975	3,908	Niacin 3 g	Placebo	6.2	44	100	—	—	40	—	—
HATS (16)	2001	76	Niacin 2.4 g + simvastatin 13 mg	Placebo	3	53	87	29	49	16	129.5	31.5
ARBITER-2 (17)	2004	167	Niacin 1 g + any statin	Any statin	1	67.5	91	NA	74.9	27.5	88.9	39.5
ARBITER-6 (19)	2009	363	Niacin 2 g + any statin	Ezetimibe 2 g + any statin	1.2	65	80	31	87.3	40	83.9	42.5
AIM-HIGH (22)	2011	3,414	Niacin 1.5–2 g + simvastatin 40–80 mg	Simvastatin 40–80 mg	3	63.7	85	31.2	71.1	33.9	76	35
FATS (25)	1990	100	Niacin 4 g + colestopol 30 g	Conventional therapy	2.7	47	100	26.4	35	0	181.8	38.4
Guyton et al. (26)	2008	948	Niacin 2 g + ezetimibe 10 mg + simvastatin 20 mg	Ezetimibe 10 mg + simvastatin 20 mg	0.5	56.8	49	29.9	63	15.3	156.4	50.7
AFREGS (28)	2005	143	Niacin 0.25–3 g + gemfibrozil 1.2 g + cholestyramine 2 g	Placebo	2.5	63.2	92	26.5	71	0	129.5	34.8
CLAS (29)	1987	188	Niacin 4.3 g + colestipol 29.7 g	Placebo	2	54.2	100	26.7	39	0	170	44.2
STOCKHOLM (30)	1988	555	Niacin 3 g + colfibrate 2 g	Conventional therapy	5	60	80	—	—	3	—	—
UCSF_SCOR (31)	1990	97	Niacin 0–7.5 g + colestipol 15–20 g	Conventional therapy	2.2	41.7	43	—	12.3	—	278.2	50.2

AFREGS = Armed Forces Regression Study; ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; BMI = body mass index; CDP = Coronary Drug Project; CLAS = Cholesterol-Lowering Atherosclerosis Study; FATS = Familial Atherosclerosis Treatment Study; HATS = HDL Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; UCSF_SCOR = University of California, San Francisco, Arteriosclerosis Specialized Center of Research.

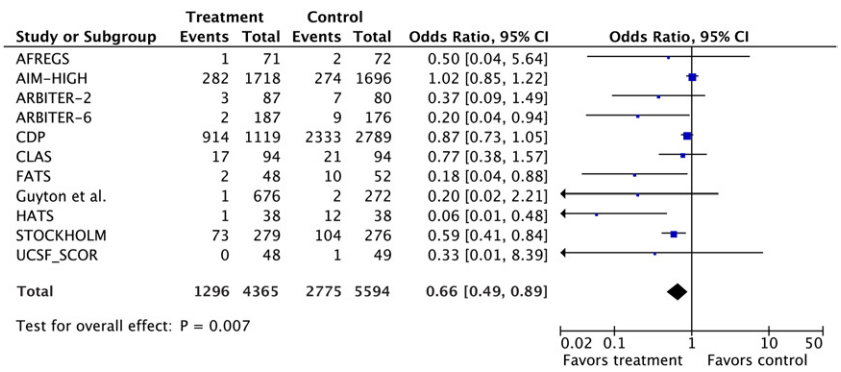

Figure 1 **Effect of Niacin Therapy on the Occurrence of Any Cardiovascular Disease Event**

Random-effects odds ratio shown. **Horizontal lines** represent 95% confidence intervals (CIs).

Including only those trials evaluating the efficacy of niacin in conjunction with statin use (16,17,19,22,26), a significant treatment effect was observed on the composite endpoint of any CVD event (OR: 0.31; 95% CI: 0.1 to 0.97; p = 0.04). No significant effect of niacin was observed on the outcomes of major CHD event or stroke (data not shown).

Analyses limited to trials in which treatment and control arms differed only with respect to the presence of niacin therapy (15,17,22,26) revealed a significantly decreased frequency of CHD events in niacin-treated patients (OR: 0.86; 95% CI: 0.75 to 0.98; p = 0.03), but no significant effect on all CVD events or stroke (data not shown).

Meta-regression. Of the 11 trials selected for the principal analysis reporting outcome data for the primary composite endpoint of any CVD event, 9 provided baseline and on-treatment measures of HDL-C and were thus included in the pre-specified secondary random-effects meta-regression analysis (16,17,19,22,25,26,28–31). No significant association was found between the magnitude of the difference between treatment arms in on-treatment HDL-C and the natural log-adjusted OR for any CVD event incidence (Beta = −0.0125, p = 0.86) (Fig. 4).

Discussion

Despite clear efficacy demonstrated by multiple clinical endpoint–driven studies, increasing appreciation of the considerable CVD risk that persists despite intensive statin therapy (4,5,32) has heightened interest in alternative therapeutic interventions. The consensus perspective derived from previously available data had suggested that niacin could be an effective agent in CVD risk prevention (23,24). Although clinical outcome data supporting its benefits largely predate the advent of statins, several recent trials showed niacin to be an effective adjunct to statin therapy with respect to surrogate measures of atherosclerosis progression (16–21). Contrasting evidence provided by results of the AIM-HIGH trial (22) recently called into question the appropriate role of niacin in clinical practice. The present study, taking in aggregate the cumulative body of relevant empirical clinical data, continues to support that niacin is an effective agent to reduce CVD risk.

In the present meta-analysis including a total of 9,959 subjects derived predominantly from secondary prevention trials, allocation to niacin treatment yielded relative odds

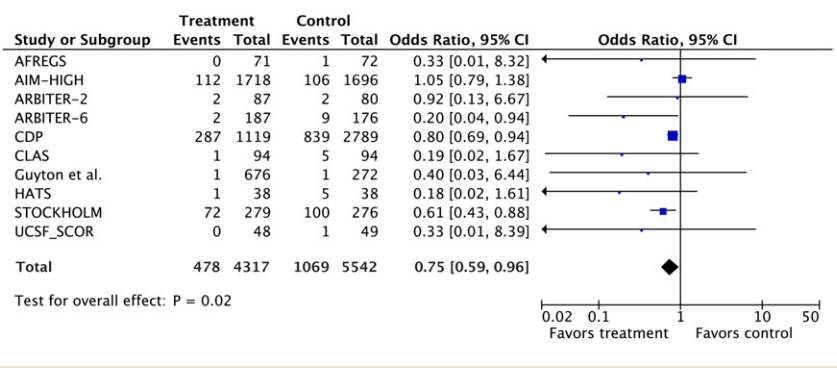

Figure 2 **Effect of Niacin Therapy on the Occurrence of Major CHD Events**

Random-effects odds ratio shown. **Horizontal lines** represent 95% confidence intervals (CIs).

JACC Vol. 61, No. 4, 2013
January 29, 2013:440–6

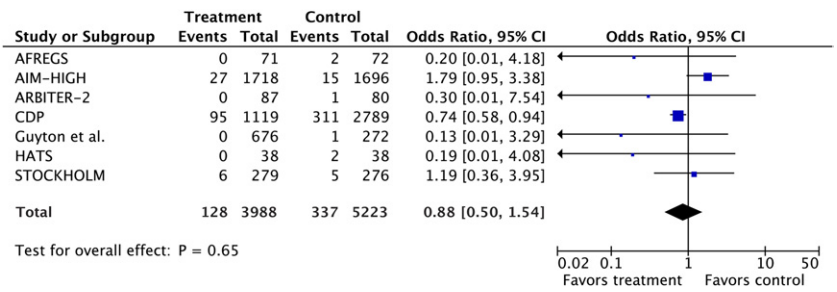

Figure 3 **Effect of Niacin Therapy on the Occurrence of Stroke**

Random effects odds ratio shown. **Horizontal lines** represent 95% confidence intervals (CIs).

reductions of 34% (p = 0.007) and 25% (p = 0.02) for the respective endpoints of any CVD event and major CHD event. Furthermore, a significant treatment effect remained in analysis limited to those trials evaluating the effect of niacin in combination with statin therapy for the largest composite clinical endpoint of any CVD event. Placing these findings in context, the Cholesterol Treatment Trialists' Collaboration recently reported 22% and 27% reductions in comparable clinical endpoints in statin-treated participants compared with a control population in a meta-analysis of 21 trials including 129,526 subjects (5).

While serving to place the recent results of AIM-HIGH in context with the total body of clinical trial evidence, the current analysis challenges prevalent notions surrounding the mechanism underlying the treatment effect of niacin. Widely recognized as the most potent currently available modulator of HDL-C, the potential benefit of niacin in mitigating CVD risk is often attributed to its impact on this target. The rationale for this hypothesis is derived from extensive epidemiological data establishing baseline low HDL-C as an independent marker of CVD risk (33–37). It is important to consider, however, that the pharmacological effects of niacin extend well beyond augmentation of HDL-C concentration. In the current study, meta-regression failed to demonstrate an association between on-treatment differences in HDL-C concentration and niacin-mediated improvement of outcomes. There are several ways in which this finding can be interpreted. One possibility is that the clinical efficacy of niacin may still result from its lipid effects, but that these are not captured in the standard lipid measurements reported in clinical trials. For example, niacin reduces lipoprotein (a) and exerts presumably favorable effects on both HDL-C and LDL-C particle size distribution, not reflected by typical lipoprotein analysis nor assessed in the current study (38). It is also possible that niacin's clinical benefit may result not from its lipid effects, but rather may be contingent on any of its several reported pleiotropic properties. As such, consideration should also be paid to expanding data delineating the various nonlipoprotein-mediated effects of niacin as a means to explain its efficacy. Niacin has been documented to exhibit anti-inflammatory properties as evidenced by a reduction in lipoprotein-associated phospholipase A_2 and C-reactive protein (38), suppress pro-atherogenic chemokines (39), and augment serum concentration of the atheroprotective hormone adiponectin (40,41), each of which could confer cardiovascular protection.

That niacin may attenuate atherosclerotic progression and vascular inflammation via measures independent of its effect on lipoprotein concentration is supported by observations in several animal models (42–44). Lukasova et al. (43) recently demonstrated a niacin-associated antiatherosclerotic effect in LDL-receptor knockout mice not accompanied by change in either HDL-C or total cholesterol.

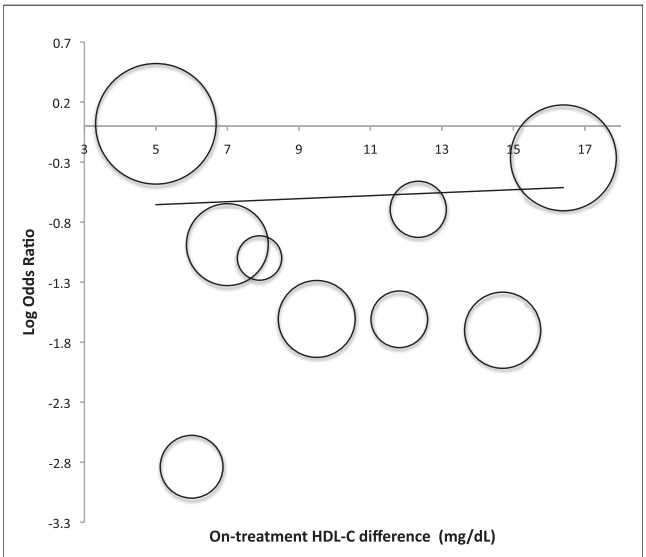

Figure 4 **Association Between On-Treatment HDL-C Difference Between Study Arms and Any CVD Event**

Random-effects meta-regression analysis depicting the relationship between the log-adjusted odds ratio for the composite endpoint of any cardiovascular disease (CVD) event and the difference in on-treatment high-density lipoprotein cholesterol (HDL-C) concentration between niacin treatment and control arms. Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis.

Similarly, regression of atherosclerosis burden and plaque stabilization have been documented in apolipoprotein E–deficient mice on niacin administration absent a significant change in lipid profile (44). Indeed, emerging evidence contesting the uniform viability of HDL-C as both a therapeutic target and surrogate marker of CVD risk suggests that attribution of niacin's clinical efficacy to augmentation of serum HDL-C may be misdirected. The dal-OUTCOMES trial (NCT00658515), designed to evaluate the efficacy of cholesterol ester transfer protein inhibition by dalcetrapib as an adjunct to existing standard of care in secondary prevention of CVD was recently halted due to a lack of clinically meaningful benefit despite increasing HDL-C in excess of 25% during phase II clinical trials (45,46). Moreover, Mendelian randomization analyses failed to establish a relationship between genetic polymorphisms associated with HDL-C levels and CHD event incidence (47). The present findings thus reinforce the potential significance of niacin's various pleiotropic actions and cautions against defining its clinical utility to be exclusively dependent on the validity of the HDL-C hypothesis.

Preliminary reports from AIM-HIGH raised substantial concern over the safety of niacin. Interim analysis of ischemic stroke in the treatment arm of AIM-HIGH demonstrated a trend toward increased risk, which importantly failed to reach statistical significance in the final intention-to-treat analysis. Of note, 8 patients included in the AIM-HIGH analysis, all of whom were assigned to niacin treatment, sustained a stroke between 2 months and 4 years after discontinuation of the study drug (22). Although not definitive, the absence of a similar association in the present analysis is both reassuring and consistent with that expected based on previous evidence (15).

Importantly, decades of clinical data have confirmed the overall safety of niacin therapy, particularly that of the prescription version used in the AIM-HIGH study. A recent review of the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System found prescription niacin to be associated with a lower rate of serious adverse events (defined as resulting in hospitalization or death), hepatotoxicity, and rhabdomyolysis compared with that of several other commonly used lipid-altering drugs including simvastatin, pravastatin, atorvastatin, gemfibrozil, and fenofibrate (48). Furthermore, the safety profile of niacin-statin combination therapy has been found comparable to that of either drug alone (48–50).

Study limitations. It is important to note that the present findings are not without limitation. The use of trial-level data as opposed to patient-level data represents a limitation, and access to individual patient data would allow a more robust analysis. Additionally, although clinical outcomes were adjudicated in individual trials, standardized adjudication was not possible across all included RCTs. Moreover, although random effects were assumed in the present statistical analysis, the mild to moderate variation across studies reflected in heterogeneity testing cannot be disregarded and represents a potential for confounding by factors such as between-trial variation in population characteristics, dosing, and comparators (including variable regimens of combination lipid-modifying therapy). The limited available clinical data largely confined to small trials of niacin therapy may also subject the present analysis to potential publication bias, which should be considered when interpreting the reported findings. Finally, although thought provoking, results of the meta-regression reflect an observation across trials and may be subject to confounding by individual trial and patient characteristics not captured in the current analysis.

Conclusions

Although potentially indicative of limited efficacy in select patients, the recently published findings of AIM-HIGH are insufficient to alter the aggregate available data supporting the clinical efficacy of niacin therapy as a means to reduce CVD risk. The present analysis demonstrates the summary effect of niacin across a broad clinical population to confer atheroprotection and cautions against the extension of recent isolated findings to substantially alter overall clinical practice. These results thus underscore the need for further analysis, including that offered by the ongoing HPS2-THRIVE (Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events) trial, to more clearly define the role of niacin in current practice.

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Key Words: cardiovascular disease ■ HDL cholesterol ■ lipids ■ niacin.

APPENDIX

For supplemental tables, please see the online version of this article.