

# Attainment of Combined Optimal Lipid Values With the Use of Niacin

## Has AIM-HIGH Closed the Book on This Debate?

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### Abstract and Introduction

#### Abstract

The AIM-HIGH study results have provided new information for the clinical question regarding the potential benefit of the attainment of optimal lipid values to reduce residual cardiovascular risk in patients on optimal statin therapy. At first glance, it would seem that the early termination of this study owing to the perceived clinical futility of niacin therapy has effectively closed the debate on this topic. However, it is imperative that the clinician probes deeper into the study design and results before coming to this conclusion. This report will review the AIM-HIGH results and the impact on the clinical practice of adding niacin to optimized statin therapy in order to reduce residual cardiovascular risk.

### Revisiting the Concept of Residual Cardiovascular Risk

There is an abundance of data showing that statins reduce cardiovascular risk in high-risk patients; however, despite use of high-dose statin therapy, this population still has an elevated cardiovascular event rate. For example, the TNT trial investigators observed a 6.7% adverse cardiovascular event rate in the atorvastatin 80 mg daily treatment arm during the mean 4.9-year follow-up period.<sup>[1]</sup> Recently published active comparator trials have shown high-dose statin therapy to provide additional relative risk reductions compared with low- to moderate-dose statin therapy; however, it is important to note that the absolute reductions in these trials were small.<sup>[1-3]</sup> This cardiovascular risk that exists despite the use of aggressive statin therapy is termed 'residual risk'.

The larger absolute and relative risk reductions observed with combination therapy, when compared with those observed with statin monotherapy, show the potential for this approach to address this residual cardiovascular risk.<sup>[4-9]</sup> provides the relative and absolute risk reductions of several statin monotherapy and niacin combination trials. The small sample sizes of the previously published investigations of statin–niacin combination therapy and the use of surrogate markers for primary end points (e.g., imaging of plaque volume) were major limitations, which prompted the initiation of larger studies with clinical primary end points, such as the AIM-HIGH investigation.

**Table 1. Comparison of absolute and relative risk reductions with statin monotherapy and niacin combination therapy in high-risk populations.**

Study	Treatment group	Comparator group	Randomized study patients (n)	Mean/median duration of study (years)	ARR in major cardiovascular events, % (event rate in treatment vs comparator group)	RRR in major coronary events, % (95% CI)	Ref.
<b><i>Placebo-controlled statin monotherapy studies</i></b>							
4S	Simvastatin 20 mg daily	Placebo	4444	5.4	6.7 (15.9 vs 22.6)	34 (25–41)	[27]

ASCOT-LLA	Atorvastatin 10 mg daily	Placebo	10,305	3.3	1.1 (1.9 vs 3.0)	36 (17–50)	[28]
CARDS	Atorvastatin 10 mg daily	Placebo	2838	4.0	3.2 (5.8 vs 9.0)	37 (17–52)	[29]
CARE	Pravastatin 40 mg daily	Placebo	4159	5.0	3.0 (10.2 vs 13.2)	24 (9–36)	[30]
HPS	Simvastatin 40 mg daily	Placebo	20,356	5.0	3.1 (8.7 vs 11.8)	27 (21–33)	[31]
WOSCOPS	Pravastatin 40 mg daily	Placebo	6595	4.9	2.5 (6.8 vs 9.3)	31 (17–43)	[19]
<b>Statin active-comparator studies</b>							
TNT	Atorvastatin 80 mg daily	Atorvastatin 10 mg daily	10,001	4.9	1.6 (6.7 vs 8.3)	20 (8–31)	[1]
PROVEIT-TIMI 22	Atorvastatin 80 mg daily	Pravastatin 40 mg daily	4162	2.0	3.9 (22.4 vs 26.3)	16 (5–26)	[3]
IDEAL <sup>†</sup>	Atorvastatin 40–80 mg daily	Simvastatin 20–40 mg daily	8888	4.8	1.1 <sup>‡</sup> (9.3 vs 10.4)	11 (-1–22)	[2]
SEARCH	Simvastatin 80 mg daily	Simvastatin 20 mg daily	6031	6.7	0.6 <sup>‡</sup> (19.7 vs 20.3)	4 (-4–11)	[32]
<b>Niacin combination therapy studies</b>							
FATS	Colestipol plus niacin	Placebo	100	2.5	15.0 (4.2 vs 19.2)	Not reported for comparison between colestipol plus niacin and placebo treatment arms <sup>§</sup>	[4]
HATS	Simvastatin (dose adjusted to maintain LDL-C 40–90 mg/dl) plus niacin (dose titrated to achieve a 10-mg/dl increase in HDL-C)	Placebo	76	3.2	29 (2.6 vs 31.6)	91.8	[5]
AFREGS	Cholestyramine plus gemfibrozil plus niacin	Placebo	143	2.0	13.7 (12.7 vs 26.4)	51.8 <sup>¶</sup>	[8]

ARBITER 2	Any statin plus niacin ER 1000 mg daily	Any statin plus placebo	167	1.0	5.8 <sup>‡</sup> (3.8 vs 9.6)	60.4 <sup>¶</sup>	[7]
ARBITER 6-HALTS	Any statin plus niacin ER 2000 mg daily	Any statin plus ezetimibe 10 mg daily	325	1.2	4.2 (1.3 vs 5.5)	76.4 <sup>¶</sup>	[9]

<sup>†</sup>Atorvastatin dose was reduced to 40 mg if the patient had an adverse event on 80 mg daily; the dose of simvastatin could be increased to 40 mg daily if LDL-C was >190 mg/dl after 24-week treatment with simvastatin 20 mg daily.

<sup>‡</sup>The difference in event rates was not statistically significant.

<sup>§</sup>The FATS investigation included three treatment arms: colestipol plus niacin, colestipol plus lovastatin and finally placebo. The investigators found a 73% RRR (95% CI: 23–90%) in event rate in the two combination treatment arms versus placebo. The investigators did not report RRRs with comparisons between colestipol plus niacin versus placebo treatment arms.

<sup>¶</sup>RRR was calculated using event rates reported in the study. Major cardiovascular events equaled nonfatal cardiovascular events and fatal coronary events.

ARR: Absolute risk reduction; ER: Extended-release formulation (Niaspan®); HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; RRR: Relative risk reduction.

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## Atherogenic (Mixed) Dyslipidemia Confers Additional Cardiovascular Risk

Atherogenic dyslipidemia, defined as a combination of suboptimal lipoprotein levels, is a marker for elevated VLDL-cholesterol, which contributes to atherosclerosis and plaque formation, and risk of adverse cardiovascular events. Non-HDL-cholesterol (HDL-C), calculated to determine VLDL-cholesterol levels, should be a secondary target (after LDL-cholesterol [LDL-C] targets are attained) when triglyceride levels are ≥200 mg/dl, according to the National Cholesterol Education Program (NCEP) Expert Panel and the American Heart Association/American College of Cardiology Foundation practice guideline for secondary prevention of atherosclerotic vascular disease.<sup>[10,11]</sup> These guideline panels recommend lowering non-HDL to 30 mg/dl above a patient's LDL-C; this means a patient with a LDL-C goal of <100 mg/dl would have a non-HDL-C goal of <130 mg/dl.

The results of a recently published meta-analysis provide additional data demonstrating increased risk of cardiovascular events with elevated non-HDL-C levels.<sup>[12]</sup> The investigators observed statin-treated patients with LDL-C levels of <100 mg/dl and non-HDL levels of >130 mg/dl to have a 32% increased risk of a major cardiovascular event (hazard ratio: 1.32; 95% CI: 1.17–1.50), compared with patients with LDL-C and non-HDL-C levels of <100 mg/dl and <130 mg/dl, respectively. Study results have also shown statin-treated patients with optimal LDL-C levels to be at increased risk of cardiovascular events when HDL-C levels are low. The findings of a *post-hoc* analysis of the TNT investigation showed low HDL-C levels to be associated with increased cardiovascular risk in patients on high-dose atorvastatin (80 mg daily), including patients with LDL-C levels less than 70 mg/dl.<sup>[13]</sup>

Owing to niacin's ability to raise HDL-C and lower levels of triglycerides, as well as other atherogenic lipoproteins such as lipoprotein(a), it has been hypothesized to be an ideal agent for use in combination statin therapy in patients with elevated non-HDL-C.

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## Previous Studies of Statin–Niacin Combination Therapy

The HATS study, conducted by Brown and colleagues, showed that simvastatin–niacin combination therapy provided a large reduction in cardiovascular risk compared with placebo.<sup>[4]</sup> The small population (n = 76) limited the generalizability of these results, and the short duration of follow-up (38 months) prevented observations on the persistence of the clinical benefits. Moreover, this study compared the statin–niacin combination with placebo, so the results do not provide insight into the

clinical benefit of adding niacin to statin therapy versus maintaining statin monotherapy. Although there are limitations when comparing HATS results with other placebo-controlled statin monotherapy studies (e.g., differences in patient populations and baseline lipid levels), the larger reductions in clinical events seen with the HATS trial provide additional evidence supporting the strategy of combination therapy with statin and niacin.

The ARBITER clinical trials series has also contributed to the body of evidence supporting the use of statin–niacin therapy. The ARBITER 2 trial found statistically significant improvements in carotid intima–media thickness in the combination treatment group compared with the statin monotherapy group.<sup>[5]</sup> However, while the investigators found numerically fewer clinical events in the combination treatment group, this difference was not statistically significant (3.8 vs 9.6%;  $p = 0.23$ ). Once again, the small sample size ( $n = 363$  participants enrolled and 208 completed the study), short duration of follow-up (14 months) and the use of nonclinical, surrogate primary end points were limitations of this study.

The ARBITER 6-HALTS trial results showed that in statin-treated patients at high risk of adverse cardiovascular events who had acceptable LDL-C levels ( $<100$  mg/dl), the strategy of adding niacin to background statin therapy provides greater clinical benefit than the strategy of adding ezetimibe to background statin therapy.<sup>[7]</sup> There were greater reductions in carotid intima–media thickness and statistically significant reductions in the major adverse cardiovascular event rate in the statin–niacin group (1.3 vs 5.5%;  $p = 0.04$ ). In addition, while the  $p$ -value suggests a statistically significant difference in the event rate, this finding must be interpreted with caution, as multiple comparisons can increase the risk of committing a type I error (erroneously finding statistically significant differences). The same limitations of a small sample size and the use of surrogate primary end points described with the previous investigations apply to this study too.

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## AIM-HIGH Study Summary

### Inclusion Criteria

AIM-HIGH was a multisite investigation (92 sites were involved throughout the USA and Canada) that attempted to determine if the combination of statin–niacin would provide a greater cardiovascular risk reduction in patients with coronary heart disease and atherogenic dyslipidemia (low HDL-C and high triglyceride levels) compared with statin monotherapy.<sup>[14]</sup> Patients were at least 45 years of age with established cardiovascular disease (defined as stable coronary heart disease, cerebrovascular or carotid artery disease, or peripheral artery disease), low HDL-C levels (defined as HDL-C level  $< 40$  mg/dl for men and  $<50$  mg/dl for women) and elevated triglyceride levels (defined as triglyceride level between 150 and 400 mg/dl). Statin-naïve patients with baseline LDL-C levels of  $<180$  mg/dl and patients on statin and/or other lipid-lowering therapies were allowed to enroll, as long as they met the HDL-C and triglyceride criteria.

### Study Interventions

Patients on lipid-lowering therapies other than a statin or ezetimibe (i.e., niacin, fish oils or fibrates) prior to study enrollment underwent a minimum 4-week wash-out period prior to the obtaining of baseline lipid levels. Patients assigned to the statin–placebo group received simvastatin, with the dose adjusted in order to maintain the LDL-C levels of 40–80 mg/dl. In order to mask patients' treatment assignments, the placebo contained 50 mg of niacin to elicit the flushing side effect; patients assigned to statin–placebo received a total daily dose of 100–200 mg of immediate-release niacin. Patients assigned to the statin–niacin group also received simvastatin at a dose to maintain LDL-C level (40–80 mg), and extended-release niacin (Niaspan®) at 1500–2000 mg daily. Those patients unable to tolerate at least 1500 mg of niacin during the 4–8-week run-in period did not undergo study randomization. To maintain desired LDL-C levels, patients in either treatment group were given ezetimibe, according to the study's treatment protocol. In summary, the two treatment arms were niacin–simvastatin plus ezetimibe when needed to maintain LDL-C levels between 40 and 80 mg/dl and placebo–simvastatin plus ezetimibe when needed to maintain LDL-C between 40 and 80 mg/dl.

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## Results

### Patient Demographics

The majority of patients were white (93%) and male (85%), and the average age was 64 years. A total of 34% of participants had diabetes, which was well-controlled in many of the participants, as evidenced by a mean hemoglobin A1c level of 6.7% at baseline. The majority of patients were on standard-of-care medication therapies for secondary cardiovascular prevention at

the time of study enrollment: 95% were on statin therapy; 80% were on  $\beta$ -blocker therapy; 74% were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker; and 98% were on aspirin or another antithrombotic agent. summarizes the baseline and follow-up lipid levels in each treatment group.

**Table 2. Baseline and follow-up lipid levels of participants in the AIM-HIGH study.**

Lipid parameters	Placebo plus statin		Niacin ER plus statin	
	Baseline (n = 1696)	Year 3 of follow-up (n = 873)	Baseline (n = 1718)	Year 3 of follow-up (n = 865)
LDL-C (mg/dl)	76	68	76	65
HDL-C (mg/dl)	35	39	35	44
Triglycerides (mg/dl) <sup>†</sup>	162	152	164	120
Non-HDL-C (mg/dl)	112	102	113	93

All lipid levels are group means, except as noted.

<sup>†</sup>Median values provided.

ER: Extended-release formulation (Niaspan®); HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol.

### Primary End Points

During the mean 3-year follow-up period, the occurrence of the primary end point, the composite of the first event of death from coronary heart disease, nonfatal myocardial infarction or ischemic stroke, a hospital stay for at least 24 h for an acute coronary syndrome, coronary revascularization or cerebral revascularization, was statistically similar between the two groups: 282 participants in the niacin–statin group (16.4%) and 274 participants in the placebo–statin group (16.2%); the hazard ratio with niacin was 1.02 (95% CI: 0.87–1.21). Moreover, there were no differences between the two treatment groups in the occurrence of the individual components of the composite end point. A trend of an increased incidence of ischemic strokes in the niacin–statin group was disclosed at the time the public was informed of the study's early termination; however, subsequent statistical analyses showed that this increase was not statistically significant and may have been a chance finding: the niacin–statin group had 28 participants (1.6%) versus the placebo–statin group with 18 participants (0.9%; hazard ratio: 1.61; 95% CI: 0.89–2.90;  $p = 0.11$ ).

### Treatments

summarizes the statin doses the participants were taking at the 12-month follow-up visit. Use of simvastatin 80 mg daily and use of ezetimibe were higher in the simvastatin–placebo group. More patients in the statin–niacin group discontinued the study drug after randomization (25.4 vs 20.1%;  $p < 0.001$ ); on average, 8.4% of patients each year stopped niacin therapy. Adherence, assessed by pill counts, was at least 75% in the vast majority (>90%) of patients in each treatment arm.

**Table 3. Treatments of participants in the AIM-HIGH study at the 12-month follow-up.**

Treatments <sup>†</sup>	Placebo plus statin (n = 1696)	Niacin ER plus statin (n = 1718)
Simvastatin 20 mg or less daily (%)	10.9	18.6
Simvastatin 40 mg daily (%)	50.2	49.5
Simvastatin 80 mg daily (%) <sup>*</sup>	24.7	17.5
Ezetimibe (%) <sup>**</sup>	21.5	9.5

<sup>†</sup>Doses listed are doses patients were taking after 12 month follow-up visit or after two consecutive follow-up visits with the same dose before the 12 month follow-up visit.

\*p = 0.02; \*\* p < 0.001ER: Extended-release formulation (Niaspan®).

## Considerations

Although the AIM-HIGH investigators did not report an additional cardiovascular risk reduction when niacin was added to statin therapy in patients with low LDL-C levels, the findings do not mean that the use of niacin to lower cardiovascular risk should be stopped in all patients. The clinician should bear several items in mind when making the decision to alter his or her practice of adding niacin to statin therapy.

### Power of the Study in Question

The estimated event rate was smaller than expected, which may have reduced the study's power to find a difference in event rates in the treatment arms. To address this problem, the investigators expanded the original primary composite end point of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke or hospitalization for high-risk acute coronary syndrome to include more clinical events, such as symptom-driven coronary or cerebral revascularization.<sup>[15]</sup> The investigators considered prolonging the follow-up period and increasing the sample size, but budgetary reasons precluded these approaches.

The differences between HDL-C levels after treatment were smaller than expected (5 mg/dl) because patients in the statin–placebo group had a mean increase in their baseline HDL-C level of approximately 10% (see ). This less than expected difference between the HDL-C levels in the two groups would attenuate the event reduction expected with the HDL-raising effects of niacin, thus diminishing the power of the study for finding a difference between the two treatment arms.

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ER: Extended-release formulation (Niaspan®); HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol.

Epidemiological studies have estimated that a 1-mg/dl increase in HDL-C levels provides a 2–3% decrease in cardiovascular risk.<sup>[16]</sup> Using this estimate, the statin–placebo group may have had an additional 8–12% risk reduction (mean HDL-C increased by 4 mg/dl) while the statin–niacin group may have had an additional 18–27% risk reduction (HDL-C increased by 9 mg/dl), resulting in a risk difference of 10–15%, below the calculated 25% risk reduction included in the power calculation. This means that more patients should have been randomized to show a difference in event rates between the two groups. It has been speculated that the use of low doses of niacin in the placebo group may have raised HDL-C levels, but this hypothesis is controversial.<sup>[14,17]</sup>

### Differences in Statin Doses Between the Two Study Groups

The AIM-HIGH protocol allowed for alterations in study drug doses and the addition of ezetimibe in order to attain a specific LDL-C level. Ultimately, using this approach resulted in statistically significant and clinically important differences in the

treatments between the two groups, as demonstrated by the fact that more patients were on 80 mg simvastatin and ezetimibe daily in the statin–placebo treatment arm. Ultimately, this investigation revealed similar cardiovascular risk reductions when a target LDL-C level between 40 and 80 mg/dl was achieved with the use of higher doses of simvastatin with or without ezetimibe compared with lower doses of simvastatin plus niacin, with or without ezetimibe. The study design confirms a cardiovascular risk reduction when very low LDL-C levels are attained. The titration of statin doses and the addition of ezetimibe limited the study's ability to observe any potential benefit of adding niacin therapy to a static statin regimen.

The HPS2 THRIVE study will provide additional information to help answer this question. HPS2 THRIVE will include more patients and randomize patients to simvastatin monotherapy and simvastatin and niacin given with laropiprant (a prostaglandin antagonist given to block the flushing effect of niacin). Patients may be on simvastatin–ezetimibe if they were on a more potent statin prior to randomization. The study protocol does not describe the use of dose adjustments to maintain a specific LDL-C level, so it will allow for a better analysis of the addition of niacin to a static statin regimen.<sup>[101]</sup>

### **Baseline Triglyceride Levels Below Threshold for Targeting Non-HDL-C**

While the investigators attempted to study a population with atherogenic dyslipidemia, the baseline triglyceride level of 162 mg/dl is not reflective of the patient in whom niacin therapy generally would be considered, since treatment guidelines recommend targeting non-HDL when triglycerides are  $\geq 200$  mg/dl.<sup>[10,11]</sup> These baseline lipid levels are similar to those reported from the ACCORD trial, which also failed to show additional risk reduction when a fibrate was added to statin therapy.<sup>[18]</sup> It is important to note that combination therapy trended towards providing an additional risk reduction in the subgroup of patients with the lowest HDL-C level (mean: 30 mg/dl) and the highest triglyceride level (mean: 284 mg/dl) in the ACCORD trial; however, this subgroup was relatively small, comprising only 17% of the total study population (941 participants in the subgroup and 5518 in the total population), thus attenuating the generalizability of this finding. Perhaps a similar *post-hoc* subgroup analysis of the AIM-HIGH results will show a similar trend for greater risk reduction with combination therapy, but these results would be subject to limitations inherent in *post-hoc* analyses.

### **Was the Study's Follow-up Period Too Short to Find a Difference?**

The event rate observed in the Cholesterol and Recurrent Events investigation, a placebo-controlled study with pravastatin 40 mg daily, began to separate approximately 2 years after study initiation.<sup>[19]</sup> The Coronary Drug Project, a placebo-controlled study showing cardiovascular risk reduction with immediate-release niacin, did not show a separation in event rate curves until 5 years after study enrollment.<sup>[20]</sup> It is important to note that the Coronary Drug Project results may not be generalizable to current secondary prevention trials since this study took place prior to the existence of statin therapy and predates the current standard therapies that are now generally used. Conversely, one may argue that ARBITER 6-HALTS authors showed a separation in event curves after several weeks of therapy.<sup>[7]</sup> However, the limitation of the short follow-up period, which was noted for the other niacin trials that did show benefit, also extends to AIM-HIGH. Interestingly, the authors considered lengthening the original expected mean 4.6-year follow-up period in order to overcome the smaller than expected event rate, but the study's early termination further shortened the follow-up period (mean 3-year follow-up), potentially further compromising the study's power. However, the Kaplan–Meier curve for the primary end point showed no trend that the event rates were beginning to separate towards the end of the mean 3-year follow-up period, suggesting that additional follow-up may have yielded similar findings.

### **Statin Use Prior to Study Enrollment**

A vast majority (93.6%) of randomized patients were on statin therapy prior to study enrollment: 76.2 and 39% of the study patients were receiving statin therapy for at least 1 and 5 years, respectively. Pre-enrollment statin treatment may have contributed to the lower than expected event rates. Lipid-lowering therapy reduces plaque rupture and induces plaque stabilization by depleting atherogenic plaques of their lipid-rich core, so there may have been no room for further risk reduction by means of lipid modification.<sup>[21,22]</sup> A *post-hoc* analysis of the 218 patients not previously treated with a statin may provide additional insight into the contribution of prestudy statin use to the study's findings, but these results would be subject to limitations inherent in *post-hoc* analyses, and the small sample size would limit generalizability. Not surprisingly, the baseline lipid profiles of these 218 patients differed from the overall population (LDL-C: 124 vs 71 mg/dl in statin-treated patients; HDL-C: 33 vs 35 mg/dl; triglyceride level: 215 vs 161 mg/dl, respectively).<sup>[23]</sup>

## AIM-HIGH Results do not Mean all Patients on Niacin Should Discontinue Therapy

The failure of AIM-HIGH to show additional risk reduction when niacin was added to background statin does not mean that all patients on niacin should stop therapy. Niacin will continue to have a role in lipid management for patients who are unable to attain LDL-C goals on statins alone: ARBITER 6-HALTS results suggest that greater risk reductions may be attained with the addition of niacin to background statin therapy in patients with baseline LDL-C of approximately 80 mg/dl.<sup>[7]</sup> Moreover, the niacin–statin combination provides an option for patients who are unable to attain lipid goals because of intolerable side effects with high-dose statin therapy.

It has been hypothesized that this combination may provide additional benefit in acute coronary syndrome (when plaque rupture is a major contributor to risk of a subsequent cardiovascular event) relative to stable coronary disease, since aggressive lipid lowering contributes to plaque stabilization.<sup>[21,22]</sup> However, the early termination of the dal-OUTCOMES study may have cast doubt on this theory. This investigation, which included patients suffering an acute coronary syndrome 4–12 weeks prior to study randomization, was undertaken to determine the benefit of adding dalcetrapib, a CETP inhibitor that raises HDL-C, to current standard of care for secondary prevention.<sup>[24]</sup> Researchers studying CETP inhibitors attribute these findings to dalcetrapib's relatively weak HDL-C-raising capabilities compared with other agents in this pharmacologic class.

While these data will be difficult to extrapolate to niacin owing to differences in the mechanisms of action of these agents, this investigation and other investigations of CETP inhibitors should provide additional evidence regarding the approach of targeting other lipid parameters, in addition to LDL-C, for secondary cardiovascular prevention.

Finally, AIM-HIGH results did not show an increased risk of harm with niacin–statin combination, so continuation of this combination in willing patients is a reasonable option until the study results of investigations currently in progress are published.

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## Conclusion

For now, the debate regarding optimizing the complete lipid panel with the use of combination therapy with statin–niacin is still ongoing. AIM-HIGH's neutral findings may have been the result of limitations in the study design and will not be the final chapter in this debate. We will have to await results of HPS2 THRIVE and AIM-HIGH subgroup analyses to provide additional data on the clinical practice of targeting the complete lipid panel in patients with atherogenic dyslipidemia.

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## Future Perspective

Data continue to emerge to suggest that our current methods of evaluating cardiovascular risk may be improved by quantifying surface proteins such as apoA-I and apoB, and other lipoproteins such as lipoprotein(a). However, it is important to note that such data have been conflicting, but investigations in this area will continue to be conducted and the results of such investigations may help to improve our approach to estimating cardiovascular risk.<sup>[25]</sup> Moreover, while apoA-I and B and lipoprotein(a) may be associated with increased cardiovascular risk, evidence that modification of these lipid marker levels will reduce the risk of cardiovascular disease is lacking and will require further study.

Finally, the results of current clinical trials of the CETP inhibitors anacetrapib and evacetrapib may show these agents will provide additional cardiovascular risk reduction. The REVEAL investigation is a Phase III study currently in the recruitment stage, and is designed to determine if anacetrapib will lower cardiovascular risk in patients with established cardiovascular disease.<sup>[102]</sup> Evacetrapib may be promising as it has been shown in a Phase II investigation to increase HDL-C levels by as much as 130% while lowering LDL-C levels by up to 36%, without raising blood pressure (as was seen with torcetrapib, which was shown to increase adverse cardiovascular event rate).<sup>[26]</sup> For now, while it is unclear if niacin–statin combination therapy will reduce residual cardiovascular risk, there continues to be hope agents currently under investigation may prove effective for this purpose.

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## Sidebar

### Executive Summary



- The AIM-HIGH study results failed to demonstrate the use of niacin to raise HDL-cholesterol in order to reduce cardiovascular risk in statin-treated patients with good LDL-cholesterol levels.
- Smaller than expected between-group HDL-cholesterol differences may have compromised the power of this study to find a difference between the two treatment arms.
- The baseline HDL-cholesterol and triglyceride levels were not reflective of the lipid levels of the patient in whom combination therapy would be considered in clinical practice.
- The HPS2 THRIVE study, a larger study including more than 25,000 participants, will provide additional data on the effectiveness of statin–niacin combination therapy to reduce cardiovascular risk.

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Papers of special note have been highlighted as:

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