Despite substantial risk reductions targeting low-density lipoprotein cholesterol with statins, there remains significant residual risk as evidenced by incident and recurrent cardiovascular disease (CVD) events among statin-treated patients. Observational studies have shown that low levels of high-density lipoprotein cholesterol (HDL-C) are associated with increased CVD risk. It remains unclear whether strategies aimed at increasing HDL-C in addition to background statin therapy will further reduce risk. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial, which compared combined niacin/simvastatin with simvastatin alone, failed to demonstrate an incremental benefit of niacin among patients with atherosclerotic CVD and on-treatment low-density lipoprotein cholesterol values <70 mg/dl, but this study had some limitations. Previously, small randomized, clinical trials of niacin plus statins showed that modest regression of carotid atherosclerosis is possible in individuals with CVD, CVD risk equivalents, or atherosclerosis. This viewpoint summarizes these imaging trials studying niacin and places them in the context of the failure of AIM-HIGH to support the HDL-C-increasing hypothesis. (J Am Coll Cardiol 2012;59:2058–64) © 2012 by the American College of Cardiology Foundation

3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are the standard of care for the management of dyslipidemia. Although statins provide 25% to 40% reductions in cardiovascular disease (CVD) risk, there is considerable residual risk in persons who receive this therapy. Two mechanistically distinct adjunctive treatment options include efforts to further reduce low-density lipoprotein cholesterol (LDL-C) or attempts to increase high-density lipoprotein cholesterol (HDL-C). Triglyceride lowering (and, thus, further apolipoprotein B lowering) is also important, and non–HDL-C is a secondary target goal in the Adult Treatment Panel III guidelines.

No agent solely increases HDL-C. Fibric acid derivatives (peroxisome proliferator-activated receptor X agonists) up-regulate >60 genes and decrease triglyceride levels. Cholesteryl ester transfer protein (CETP) inhibitors markedly increase HDL-C, but certain CETP inhibitors also lower LDL-C by 25% to 40% and lower triglycerides. The full mechanism of action of niacin is still unclear (1,2). Niacin increases HDL-C by approximately 20% and also lowers LDL-C, triglycerides, and lipoprotein(a).

In a few previous studies, niacin therapy led to clinically significant relative risk reductions in clinical events and either stabilization or modest regression of atherosclerosis (3–5). However, the HATS [HDL Atherosclerosis Treatment Study] (3) (simvastatin-niacin vs. placebo with or without antioxidants) and FATS [Familial Atherosclerosis Treatment Study] (4) (lovastatin-colestipol vs. niacin-colestipol vs. conventional therapy) trials did not have a statin-only group. The number of clinical endpoints in HATS and FATS was modest, although there was a reduction in the CVD primary endpoint in HATS with simvastatin-niacin versus placebo when antioxidants were not used. HATS also showed a reduction in the progression of coronary stenosis with the niacin–simvastatin combination compared with placebo (Table 1).
The Coronary Drug Project was a pre-statin era secondary prevention trial that randomized 1,119 subjects to clofibrate or niacin. Nine years after termination of the Coronary Drug Project, niacin still conferred an 11% reduction in all-cause mortality compared with placebo (p = 0.0004) (5). A recent meta-analysis supported the benefit of niacin alone or in combination with other lipid-lowering drugs in reducing CVD events and atherosclerosis, although most of the studies in this meta-analysis were conducted before statin therapy (6). Thus, whether a strategy to increase HDL-C using adjunct pharmacotherapy to a background of statin treatment confers additional risk reduction remains unknown.

Several small randomized controlled trials (RCTs) (ARBITER [Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol] [7,8], HALTS [9], Oxford Niaspan [10], and NIA [National Institute on Aging] Plaque [11]) tested the effect of adding niacin to statin therapy on the surrogate endpoint of carotid atherosclerosis among individuals with coronary heart disease (CHD) or risk equivalents (Table 1). These trials studied a relatively modest number of patients over a relatively short treatment period. Therefore, RCT’s powered for clinical endpoints are required to determine whether combined niacin/statin therapy is more effective than statin monotherapy alone. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Cardiovascular Events) trial [12] reported disappointing results, whereas the larger HPS2-THRIVE (Treatmen of HDL to Reduce the Incidence of Vascular Events) trial is still under way. This viewpoint summarizes some of the surrogate imaging trials using niacin/statin combination therapy and places them in the context of the AIM-HIGH findings.

Review of the Niacin RCTs With Surrogate Endpoints

The ARBITER-2 and -3. ARBITER-2 tested 1,000 mg extended-release niacin (ERN) versus placebo on top of background statin therapy on the change in mean common carotid intima-media thickness (cIMT) measured by B-mode ultrasound (7). Niacin-treated patients without insulin resistance experienced reduced cIMT progression compared with those treated with placebo. Extended out to 24 months in ARBITER-3, combined niacin/statin therapy conferred cIMT regression (8). Clinical endpoints were few in ARBITER-2 and not significantly different between groups.

The HALTS trial. The HALTS trial (9) compared the effects of 2 adjunctive lipid-lowering medications, ezetimibe and ERN, added to background statin therapy. At 14 months, assignment to niacin conferred a significant average reduction of cIMT, whereas the cIMT measurements in the ezetimibe group were unchanged. The incidence of CVD events was lower in the niacin group (2 [1%] vs. 9 [5%], p = 0.029), although the study was not powered for clinical endpoints (9). In an exploratory analysis, increasing niacin exposure resulted in a further reduction in cIMT, whereas increased cumulative ezetimibe exposure was associated with cIMT progression (13).

The implications of the HALTS trial were provocative, but raised a few concerns. First, ~10% withdrew because of side effects, with a differential dropout in the niacin and ezetimibe groups (27 vs. 9). Individuals less able to handle the side effects of niacin might also be less compliant with other secondary prevention measures. Removing these potentially less compliant subjects could be a source of bias; however, the authors did show that the baseline characteristics and 2-month lipid changes were similar between “completers” and “withdrawers.”

Unfortunately, the HALTS trial results do not allow us to conclude that all HDL-C-increasing therapies are superior to LDL-C-lowering therapies. For example, despite substantial increases in HDL-C levels conferred by treatment with the CETP inhibitor torcetrapib, this did not translate to any benefit (rather increased harm) in the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial, although blood pressure increases related to increased aldosterone may have negated the favorable changes in lipids (14).

The Oxford Niaspan study. The Oxford Niaspan study (10) was a smaller (N = 71) RCT of modified-release niacin (target 2,000 mg/day) versus placebo added to baseline statin therapy on the primary endpoint of change in common carotid artery wall area by magnetic resonance imaging at 1 year. Like the HALTS trial, there was a differential dropout related to side effects. Only 22 niacin-treated and 29 placebo-treated participants completed the study (63% vs. 81% study completion, respectively). After 12 months, there was carotid wall area regression in the niacin group compared with progression in the placebo group. Thus, the regression of carotid plaque seen with niacin was concordant with the findings of the HALTS trial.

The NIA Plaque study. On the other hand, the results of the NIA (National Institute on Aging) Plaque study (11) did not suggest a benefit of the addition of niacin to statin therapy among well-treated older participants with high vascular risk but higher mean HDL-C levels. Regression of carotid plaque was seen with aggressive standard medical therapy including statins, but a similar degree of regression occurred in both the niacin and placebo arms. Final conclusions regarding this study must be ultimately deferred until the full article is published.
Table 1  Niacin + Statin Imaging RCTs

<table>
<thead>
<tr>
<th>Trial, Year Published (Ref. #)</th>
<th>Drug Therapy</th>
<th>Participants</th>
<th>Mean Baseline Lipids, mg/dl</th>
<th>Length of Follow-Up, Months</th>
<th>Lipid Changes During Trial</th>
<th>Surrogate Endpoint</th>
<th>Clinical Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>HATS, 2001 (3)</td>
<td>Simvastatin-niacin (doses titrated) vs. placebo; with or without antioxidants</td>
<td>N = 160; known CHD, low HDL (&lt;35 mg/dl), and LDL (&lt;145 mg/dl)</td>
<td>LDL ~130, HDL ~32</td>
<td>36</td>
<td>LDL decreased 42% and HDL increased 26% with simvastatin-niacin compared with placebo. Results attenuated with antioxidants</td>
<td>On coronary angiography; the average coronary stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (p = 0.16), and 0.7% with simvastatin-niacin plus antioxidants (p = 0.004) and regressed by 0.4% with simvastatin-niacin alone (p &lt; 0.001)</td>
<td>9 events in the placebo arm vs. 1 event in the niacin-simvastatin arm (without antioxidants), 90% reduction (p = 0.03); however, events (n = 6) in the niacin-simvastatin with antioxidants group not significantly reduced</td>
</tr>
<tr>
<td>ARBITER-2, 2004 (7)</td>
<td>ERN (1,000 mg/day) vs. placebo</td>
<td>N = 167; known CHD; low HDL (&lt;45 mg/dl)</td>
<td>LDL 89 ± 20, HDL 40 ± 7</td>
<td>12</td>
<td>HDL increased 21% in niacin group</td>
<td>Overall, no difference in cIMT progression between niacin and placebo (p = 0.08); among subjects without insulin resistance, niacin reduced cIMT progression (p = 0.026)</td>
<td>No difference in clinical CVD events; events occurred in 3 niacin (3.8%) and 7 placebo (9.6%) patients; p = 0.20</td>
</tr>
<tr>
<td>ARBITER-3, 2006 (8)</td>
<td>ERN 1,000 mg/day</td>
<td>N = 130; ARBITER-2 participants who either continued on or crossed over (from placebo) to ERN</td>
<td>LDL 82 ± 23, HDL 42 ± 9</td>
<td>12-24</td>
<td>HDL increased 8 mg/dl on average</td>
<td>Among 57 participants treated with ERN for 24 months, there was regression of cIMT of ~0.041 ± 0.021 mm (p = 0.001 vs. placebo)</td>
<td>N/A</td>
</tr>
<tr>
<td>HALTS, 2009 (9)</td>
<td>ERN (target 2,000 mg/day) vs. ezetimibe</td>
<td>N = 363; documented CVD or risk equivalents. LDL &lt;100 mg/dl and low HDL-C (&lt;50 [men]/&lt;55 [women]) mg/dl</td>
<td>LDL 82 ± 23, HDL 42 ± 9</td>
<td>14 (study stopped early after 208 completed trial)</td>
<td>Both niacin and ezetimibe reduced LDL (10 vs. 18 mg/dl lower on average, respectively) (p = 0.01). HDL was increased in niacin (8 mg/dl on average), whereas HDL decreased in ezetimibe (~3 mg/dl) groups (p &lt; 0.001)</td>
<td>Niacin conferred average reduction of ~0.014 ± 0.004 mm in the common cIMT (p = 0.001) and ~0.018 ± 0.005 mm in maximum cIMT (p = 0.001), whereas cIMT in the ezetimibe group was unchanged (p = 0.8)</td>
<td>Fewer CVD events in the niacin group compared with ezetimibe (2 [1%] vs. 9 [5%], p = 0.04)</td>
</tr>
<tr>
<td>Oxford, 2009 (10)</td>
<td>Modified-release niacin (target 2,000 mg/day) vs. placebo; background statin therapy</td>
<td>N = 71; CHD or risk equivalent; low HDL (&lt;40 mg/dl)</td>
<td>LDL ~85, HDL ~38</td>
<td>12</td>
<td>Niacin increased HDL by 23% and lowered LDL by 19%</td>
<td>Compared with placebo, niacin significantly reduced carotid wall area on MRI (~1.64 mm², p = 0.03)</td>
<td>N/A</td>
</tr>
<tr>
<td>NIA, 2009 (11)</td>
<td>ERN (1,500 mg/day) vs. placebo; background statin therapy</td>
<td>N = 145; age ≥65 yrs with high vascular risk; HDL-C &lt;125 mg/dl; no HDL-C cutoff for entry</td>
<td>LDL ~87, HDL ~55</td>
<td>18</td>
<td>Compared with placebo, ERN resulted in significantly lower LDL (67 vs. 77 mg/dl, p = 0.03) and higher HDL (58 vs. 49 mg/dl, p &lt; 0.001)</td>
<td>Using carotid wall volume measured by MRI, regression of carotid plaque was seen with aggressive standard medical therapy including statins, but a similar degree of regression occurred in both the niacin and placebo arms</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; cIMT = carotid intima-media thickness; CVD = cardiovascular disease; ERN = extended-release niacin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; N/A = not available; RCT = randomized, clinical trial.
Reconciling Differences Between the Surrogate Studies

Although the HALTS trial (9) and the Oxford Niaspan Study (10) suggested niacin conferred more regression of carotid disease (cIMT or wall area) compared with ezetimibe or placebo, preliminary data from NIA Plaque study (11) showed that in an older, generally well-treated group, the addition of niacin failed to offer incremental benefit over statin therapy. Differences between the study results may be due: 1) the site imaged; 2) differences in the primary outcome; 3) differences in baseline HDL-C values; or 4) differences in LDL-C achieved on therapy.

Use of Surrogate Endpoint to Predict Atherosclerotic CVD Events

Whether demonstration of a treatment effect of niacin on imaging measures translates to actual clinical benefit remains unknown. Controversy also exists about which marker of subclinical atherosclerosis is the best marker for predicting future CVD risk.

B-mode ultrasound imaging is a sensitive and reproducible method for the assessment of cIMT in the hands of an experienced technologist and investigator. In observational studies, cIMT predicts future CHD and stroke (15). However, surrogate markers of atherosclerosis from various vascular beds (coronary artery calcium, cIMT, ankle-brachial index) are only modestly correlated with each other, and coronary artery calcium is more strongly predictive of CHD events than cIMT (16). cIMT is only somewhat correlated with coronary atherosclerosis and may not fully mirror CHD events.

Other limitations to the use of surrogate markers include potential differential response to statins. For example, statin therapy does not slow the progression of another surrogate marker, coronary artery calcium. Foam cell accumulation in the carotid arteries, the principal pathological feature of an increased cIMT, is likely the main component that is capable of regression; direct comparisons of cIMT and magnetic resonance imaging–measured regression in the context of statins are not available.

In addition, it remains unclear whether a reduction in cIMT progression or actual regression obtained with a pharmacological treatment is necessarily followed by a decrease in coronary atherosclerosis and events. Hormone therapy and thiazolidinediones retard the progression of cIMT (17,18) but may be associated with adverse CVD events (19). Although cIMT has been deemed an acceptable surrogate endpoint for statin trials (20), a meta-analysis of 41 trials enrolling 18,307 participants suggested that regression or slowed progression of cIMT induced by cardiovascular drugs does not always reflect a decrease in cardiovascular events (21).

The final word on the additive power of niacin on top of aggressive statin therapy will only come from RCTs powered for clinical event endpoints, and the use of surrogate markers as reliable indicators of future CVD events should be viewed with healthy skepticism.

Review of the Niacin RCTs With Clinical Endpoints

The AIM–HIGH trial. The AIM–HIGH trial (12) was a double-blind RCT that enrolled patients with a history of CVD and atherogenic dyslipidemia (lipid entry criteria varied by sex and statin dose at screening). All participants received simvastatin (± ezetimibe) at a dose sufficient to maintain an LDL-C level of 40 to 80 mg/dl. There was an open-label niacin run-in phase to determine tolerance of at least 1,500 mg/day of niacin, and ~20% of those enrolled dropped out because of niacin intolerance. Niacin-tolerant participants (N = 3,414) were then randomized to ERN (at 1,500 to 2,000 mg/day) or placebo (which contained a 50-mg dose of immediate-release niacin to help ensure blinding).

The mean age was 64 ± 9 years, 85% were men, and 92% were white. Metabolic risk factors and vascular disease were highly prevalent (34% diabetes, 71% hypertension, 81% metabolic syndrome, and 92% coronary disease). Statin therapy was used by 94% of enrolled patients before enrollment. Before randomization, the mean LDL-C was 71 mg/dl, HDL-C was 34 mg/dl, and the triglyceride level was 161 mg/dl among statin-treated participants.

AIM–HIGH ended earlier than expected after a mean follow-up of 3 years after an interim analysis was conducted suggesting futility in proving its hypothesis. The on-treatment mean LDL-C was 65 ± 22 mg/dl and HDL-C values were 44 ± 11 and 39 ± 8 mg/dl in the niacin/simvastatin and placebo/simvastatin arms, respectively. Of the participants, 25% and 20% in the niacin and placebo arms, respectively, discontinued the study drug (p < 0.001).

Analyses were conducted by intention-to-treat methods. During the 36-month follow-up period, the primary outcome occurred with 274 events in the placebo/simvastatin arm (16%) and 282 events in the niacin/simvastatin arm (16%) (hazard ratio: 1.02; 95% confidence interval: 0.87 to 1.21; p = 0.79). There was no significant subgroup interaction found including for those with a previous myocardial infarction or statin use at entry. A subgroup analysis of outcomes by baseline lipid status (such as LDL-C ≥70 mg/dl vs. <70 mg/dl) was not presented in the main paper.

The results of AIM–HIGH are disappointing. Perhaps in these predominantly statin–treated patients generally at lipid goals, coronary plaque might have already been depleted of its lipid core. The results of AIM–HIGH should not necessarily be extrapolated to other patient populations such as those with LDL-C >100 mg/dl for whom there still might be a role for niacin. With just 3,414 participants, AIM–HIGH was relatively small for a clinical trial in the modern era of background medical therapy. Designed for a
power to detect a 25% reduction in the primary outcome, anticipating 800 events was perhaps optimistic. With only 556 events, the study may have been underpowered to see a difference between the groups.

AIM-HIGH does not lend itself to a direct comparison of niacin versus placebo because the study design allowed titration of statin dosing and the addition of ezetimibe to keep LDL-C within a range of 40 to 80 mg/dl. Because niacin has LDL-C-lowering effects, this meant greater use of higher simvastatin doses in the placebo arm (25% of the placebo arm was taking simvastatin 80 mg vs. 18% of the niacin arm, \( p = 0.02 \)) and also more ezetimibe in the placebo arm (22% vs. 10%, \( p < 0.001 \)), which likely also confounded the results.

Finally, AIM-HIGH also does not necessarily negate the HDL-raising hypothesis. The difference in on-treatment median HDL-C between niacin and placebo was only modest (4 mg/dl); thus, results of AIM-HIGH cannot be extrapolated to other HDL-C-increasing therapies such as CETP inhibitors.

There is an ongoing substudy of AIM-HIGH with the primary outcome of change in mean plaque lipid composition assessed by carotid magnetic resonance imaging, which may shed light on the apparent discordance between surrogate endpoints using imaging and clinical events.

The HPS2-THRIVE trial. Despite AIM-HIGH, the verdict is not yet in for niacin because there is still a much larger niacin RCT in progress. HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) (niacin/laropiprant vs. placebo on a background of simvastatin 80 mg vs. 18% of the niacin arm, \( p = 0.02 \)) and also more ezetimibe in the placebo arm (22% vs. 10%, \( p < 0.001 \)), which likely also confounded the results.

Another non-niacin large RCTs recently completed or in progress. Both fibrates and omega-3 fatty acids have modest HDL-C-increasing properties and have also been studied as adjunctive agents to statin therapy. Although ACCORD (Action to Control Cardiovascular Risk in Diabetes) failed to show an incremental benefit of combined fenofibrate/simvastatin versus simvastatin alone among diabetics in the overall trial, subgroup analyses did suggest a benefit for those with marked dyslipidemia (triglycerides \( \geq 204 \) mg/dl and HDL \( \leq 34 \) mg/dl) (22). In the JELIS (Japan EPA Lipid Intervention Study) study, there was an incremental benefit of adding icosapentaenoic acid supplements to background statin therapy with a decrease in CVD events by 19% among patients with a history of CHD (23).

In contrast, the OMEGA (Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction) study failed to show any additional CVD benefit at 1 year of omega-3 fatty acids when combined with modern guideline-adjusted therapy after myocardial infarction (24).

Two CETP inhibitor drugs are also currently in phase III RCTs (2). Dal-OUTCOMES (\( N = 15,600 \)) randomized patients with acute coronary syndromes to dalcetrapib or placebo and is anticipated to be completed in 2013.

The baseline mean LDL-C in AIM-HIGH was lower than in the HALTS and Oxford studies, which may partially explain the lack of benefit for additional niacin therapy.

Concluding Thoughts

HDL-targeted therapeutics in a post-ILLUMINATE, post-AIM-HIGH era. ILLUMINATE (14) and AIM-HIGH (12) demonstrated that increasing HDL-C levels through pharmacotherapy is neither adequate nor necessary for predicting cardiovascular benefit. Low HDL-C levels may be simply a marker of risk, given its association with metabolic syndrome and insulin resistance, and not a causal factor. If this is the case, a strategy to increase HDL-C levels via pharmacotherapy may not translate to additional clinical benefit.

There are other therapeutic agents under investigation targeting HDL-C (2). Other oral medications include the CETP inhibitors, niacin receptor (GPR109A) agonists, liver X receptor agonists, peroxisome proliferator–activated receptor agonists, and oral apolipoprotein A-I mimetic peptides. Parenteral approaches include apolipoprotein A-I (Milano or wild type) phospholipid complexes, apolipoprotein A-I mimetic peptides, or delipidated autologous HDL.

Improving HDL-C function will be the focus of new therapies (2), particularly through enhancing reverse cholesterol transport but perhaps also through HDL-C’s proposed antithrombotic, antioxidant, and anti-inflammatory properties. These studies mandate improved standardized methods to assess HDL-C function.

Reaching the target LDL: statin monotherapy versus combination therapy. LDL-C remains the primary target of lipid therapy with non–HDL-C as the secondary target. It remains unknown whether more aggressive LDL-C reduction with a more potent statin would be more effective than adding a second lipid-modifying agent to a less potent statin or lower statin dose. For most high-risk patients, reduction of \( > 50\% \) of LDL-C is needed to achieve an LDL-C \( < 70 \) mg/dl and a non–HDL-C \( < 100 \) mg/dl. All of the subjects with established vascular disease or high risk of CVD in the surrogate endpoint RCTs and AIM-HIGH would have an optional LDL-C goal of \(< 70 \) mg/dl, but the mean LDL-C in these trials was \( > 70 \) mg/dl at enrollment. The baseline mean LDL-C in AIM-HIGH was lower than in the HALTS and Oxford studies, which may partially explain the lack of benefit for additional niacin therapy.
The SANDS (Stop Atherosclerosis in Native Diabetics Study) compared the effects of aggressive LDL-C-lowering strategy (target LDL-C goal <70 mg/dl) with those of a standard-treated group (LDL-C goal <100 mg/dl) (26). Among the aggressively treated group (with approximately one third taking the statin/ezetimibe combination), a similar regression of cIMT at 3 years was seen in subjects who attained equivalent LDL-C reductions from statin alone or a statin plus ezetimibe. The standard-treated group showed an increase in cIMT.

For adults with increased metabolic risk, intensified lifestyle changes remain an important target of therapy; weight loss can have substantial impact on triglyceride levels and inflammatory markers. In secondary prevention patients, the evidence supports initially increasing doses of a statin to reach LDL-C goals. If a patient cannot reach his or her lipid goals (i.e., LDL-C and non–HDL-C) with a potent statin alone, the choices remain a fibrate, niacin, bile acid sequestrant, phytosterols, or ezetimibe as add-on therapy. Unfortunately, the published studies to date do not provide a definitive answer as to which of these therapies should be chosen when LDL-C and non–HDL-C goals cannot be reached despite maximally tolerated statin therapy.

Summary

Although low HDL-C remains a marker of residual risk even among statin-treated individuals treated to reach aggressive lipid goals (27), after AIM-HIGH, there likely will be less enthusiasm for starting niacin therapy in patients with low HDL-C who have well-controlled LDL-C (<70 mg/dl). This does not necessarily mean that niacin lacks a role in lipid-modifying therapy. Pending different conclusions from the upcoming HPS2-THRIVE, there may remain a place for niacin in high-risk patients who cannot reach the LDL-C goal of <70 mg/dl despite maximally tolerated statin therapy or in statin-intolerant patients. At this time, there is no clear indication to withdraw niacin in patients receiving this therapy if further LDL-C reduction is needed.

Clinicians should await larger ongoing clinical trials such as HPS2-THRIVE, Dal-OUTCOMES, REVEAL, and IMPROVE-IT to determine whether there is benefit of the addition of lipid-modifying agents to background statin therapy. The role of niacin or other lipid-modifying agents among patients optimally treated with statin therapy remains uncertain, and time will tell whether HDL-C–targeted therapeutics will live up to their hype.

References


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Niacin Surrogate Trials and the AIM-HIGH Trial

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