Role of Niacin in Current Clinical Practice: A Systematic Review

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ABSTRACT

BACKGROUND: Niacin, a potent high-density lipoprotein cholesterol-raising drug, seems an attractive approach to reduce cardiac events in patients with or at risk of atherosclerotic cardiovascular disease. However, previous evidence for niacin has been challenged recently by negative outcomes in 2 large, randomized, controlled trials comparing niacin to placebo with background statin therapy. We studied the currently available evidence for the role of niacin treatment for reducing the risk of cardiovascular events in current practice.

METHODS: A systematic review of randomized controlled trials in the MEDLINE, EMBASE, CINAHL, and Cochrane databases comparing niacin alone or combined with statin therapy was performed. We extracted trial level data, including basic characteristics and number of patients enrolled, duration of follow up, occurrence of adverse events, and cardiovascular-related outcomes. Random effects meta-analysis was conducted to estimate the risk ratio (RR) for individual trial endpoints.

RESULTS: Thirteen trials (N = 35,206) were selected for final analysis. The mean follow-up duration was 32.8 months. Overall, niacin led to significant increases in serum high-density lipoprotein cholesterol levels from baseline trial enrolment by 21.4%, 9.31 (95% confidence interval [CI] 5.11-13.51) mg/dL. However, we did not observe any differences in all-cause mortality rates (RR 0.99; 95% CI 0.88-1.12) between niacin and control arms. Further, niacin treatment was associated with a trend toward lower risk of cardiovascular mortality (RR 0.91; 95% CI 0.81-1.02), coronary death (RR 0.93; 95% CI 0.78-1.10), nonfatal myocardial infarction (RR 0.85; 95% CI 0.73-1.0), revascularization (coronary and noncoronary) (RR 0.83; 95% CI 0.65-1.06), and stroke (RR 0.89; 95% CI 0.72-1.10), compared with control.

CONCLUSION: Niacin therapy does not lead to significant reductions in total or cause-specific mortality or recurrent cardiovascular events among persons with or at risk of atherosclerotic cardiovascular disease. © 2016 Elsevier Inc. All rights reserved. ● The American Journal of Medicine (2017) 130, 173-187

KEYWORDS: Cardiovascular risk; High-density lipoprotein cholesterol; Niacin

Atherosclerotic cardiovascular disease (ASCVD) remains a huge burden on global health, despite decades of focused research and intervention. In large epidemiologic studies and subsequent analyses, low high-density lipoprotein cholesterol (HDL-C) and high low-density lipoprotein cholesterol (LDL-C) levels have been independently associated with an increased risk of cardiovascular disease (CVD). The causal association of LDL-C with
cardiovascular risk has been well validated in large, randomized, controlled trials. In meta-analyses of patient-level data from statin trials, the Cholesterol Treatment Trialists’ collaborators group observed a 5%-6% reduction in vascular events for every 10-mg/dL decrease in serum LDL-C levels. On the basis of these and other findings, major international cardiology and lipid associations recommend statins as the first-line agent for managing dyslipidemia as a risk factor for ASCVD. However, notwithstanding significant interindividual variations in response seen with statin therapy, guidelines recommend that the utilization of beneficial nonstatin drugs may be considered in patients with intolerance or less than anticipated response to statins. Furthermore, there are accumulating data that despite aggressive LDL-C targeted therapy with high-intensity statins, residual cardiovascular burden persists.

Several studies have shown an independent prognostic value of HDL-C levels with a strong inverse relation to HDL-C with incident major cardiac events, even among patients achieving very low levels of LDL-C with statin therapy. Thus, targeting HDL-C has been proposed as a potential approach to mitigate a sizeable residual risk of CVD. In clinical use for the past several decades, niacin is one of the most effective agents currently available to increase serum levels of HDL-C. It exerts multiple other lipid-modulating effects, including decreases in total cholesterol (TC), LDL-C, triglycerides, and lipoprotein (a) levels. In addition, in prior studies niacin has been shown to significantly reduce cardiovascular events. However, 2 recent clinical trials have demonstrated an increase in adverse events with no ischemic benefit (coronary events, stroke, or revascularization) with the addition of niacin to effective statin therapy. Thus, in the present meta-analysis, we specifically investigated the cumulative evidence for the effects of niacin on different serum cholesterol fractions and several clinical endpoints.

**CLINICAL SIGNIFICANCE**

- Niacin therapy leads to a significant increase in high-density lipoprotein cholesterol levels.
- Among patients with or at high-risk of atherosclerotic cardiovascular disease, niacin does not reduce mortality.
- Treatment with niacin is not associated with significant reduction in recurrent cardiovascular events such as myocardial infarction, stroke, or revascularizations.
- Niacin is associated with increased risk of new-onset or worsening diabetes or skin, gastrointestinal, and musculoskeletal adverse effects.

**METHODS**

**Study Selection**

We performed a systematic literature search for studies testing niacin in comparison with a control agent in the MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science, and Cochrane databases. The review was conducted in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.

**Statistical Analysis**

Statistical analyses were performed according to the recommendations from the Cochrane Collaboration using Review Manager version 5.1 (2008; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).
Figure 1  The PRISMA flow chart for the trial selection process.

Table 1  Baseline Patient Characteristics in the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Niacin (n)</th>
<th>Control (n)</th>
<th>Follow-Up (mo)</th>
<th>Age (y)</th>
<th>Male (%)</th>
<th>DM (%)</th>
<th>HTN (%)</th>
<th>BL LDL-C (mg/dl)</th>
<th>Final LDL-C (mg/dl)</th>
<th>BL HDL-C (mg/dl)</th>
<th>Final HDL-C (mg/dl)</th>
</tr>
</thead>
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<td>CDP</td>
<td>3908</td>
<td>1119</td>
<td>2789</td>
<td>60</td>
<td>44</td>
<td>100</td>
<td>40</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CLAS</td>
<td>188</td>
<td>94</td>
<td>94</td>
<td>24</td>
<td>54</td>
<td>100</td>
<td>0</td>
<td>39</td>
<td>171</td>
<td>97</td>
<td>44.6</td>
<td>60.8</td>
</tr>
<tr>
<td>STOCKHOLM</td>
<td>555</td>
<td>279</td>
<td>276</td>
<td>60</td>
<td>60</td>
<td>80</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>USCF-SCOR</td>
<td>72</td>
<td>40</td>
<td>49</td>
<td>26</td>
<td>42</td>
<td>43</td>
<td>NA</td>
<td>15</td>
<td>283</td>
<td>172</td>
<td>47</td>
<td>59</td>
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<tr>
<td>FATS</td>
<td>100</td>
<td>48</td>
<td>52</td>
<td>30</td>
<td>47</td>
<td>100</td>
<td>NA</td>
<td>36</td>
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<td>129</td>
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<tr>
<td>HATS</td>
<td>67</td>
<td>33</td>
<td>34</td>
<td>36</td>
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<td>87</td>
<td>16</td>
<td>49</td>
<td>132</td>
<td>75</td>
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<td>ARBITER 2</td>
<td>149</td>
<td>78</td>
<td>71</td>
<td>12</td>
<td>67</td>
<td>91</td>
<td>27</td>
<td>75</td>
<td>87</td>
<td>85</td>
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<td>AFREGS</td>
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<td>72</td>
<td>30</td>
<td>63</td>
<td>92</td>
<td>NA</td>
<td>71</td>
<td>126</td>
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<tr>
<td>GUYTON</td>
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<td>391</td>
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<td>57</td>
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<tr>
<td>SANG</td>
<td>108</td>
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<td>56</td>
<td>12</td>
<td>71</td>
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<td>67</td>
<td>106</td>
<td>76</td>
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<td>63</td>
</tr>
<tr>
<td>ARBITER 6-HALTS</td>
<td>208</td>
<td>97</td>
<td>111</td>
<td>14</td>
<td>65</td>
<td>80</td>
<td>35</td>
<td>85</td>
<td>80.5</td>
<td>70.5</td>
<td>42.5</td>
<td>50.0</td>
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<tr>
<td>AIM-HIGH</td>
<td>3414</td>
<td>1718</td>
<td>1696</td>
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<td>85</td>
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<td>71</td>
<td>74</td>
<td>65</td>
<td>34.5</td>
<td>44.0</td>
</tr>
<tr>
<td>HPS2-THRIVE</td>
<td>25,673</td>
<td>12,828</td>
<td>12,835</td>
<td>43</td>
<td>65</td>
<td>83</td>
<td>32</td>
<td>NA</td>
<td>64</td>
<td>54</td>
<td>44</td>
<td>50</td>
</tr>
</tbody>
</table>

AFREGS = Armed Forces Regression Study; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ARBITER 2 = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ARBITER 6-HALTS = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies; BL = baseline; CDP = Coronary Drug Project; CLAS = Cholesterol-Lowering Atherosclerosis Study; DM = diabetes mellitus; FATS = Familial Atherosclerosis Treatment Study; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; HPS2-THRIVE = Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; UCSF-SCOR = University of California, San Francisco, Arteriosclerosis Specialized Center of Research.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention Arm</th>
<th>Control Arm</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDP (1975)</td>
<td>Randomized, double-blind, multicenter</td>
<td>Niacin</td>
<td>Lactose placebo</td>
<td>1) History of documented MI before &gt;3 mo; 2) Age 30-64 y; 3) Male gender</td>
<td>1) NYHA &gt;2; 2) Not worsening of coronary disease or major illnesses</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>CLAS (1987)</td>
<td>Randomized, double-blind, single center</td>
<td>Niacin + colestipol</td>
<td>Placebo</td>
<td>1) Documented CAD with CABG &gt;3 mo; 2) Age 40-59 y; 3) Male gender; 4) Nonsmokers; 5) Total cholesterol 185-350 mg/dL</td>
<td>1) Diabetes mellitus; 2) Uncontrolled hypertension (diastolic blood pressure &gt;115 mm Hg); 3) Thyroid disease; 4) Renal insufficiency; 5) Fasting blood immunosuppressive levels &gt;500 mg/dL; 6) Congestive heart failure; 7) Major arrhythmia; 8) QRS width &gt;0.12 s; 9) Weight exceeding 1.5× ideal weight</td>
<td>Angiographic evaluation of atherosclerosis</td>
</tr>
<tr>
<td>STOCKHOLM (1988)</td>
<td>Randomized, unblinded, single center</td>
<td>Niacin + clofibrate</td>
<td>Conventional treatment</td>
<td>1) Consecutive survivors to myocardial infarction 2) Age &lt;70 y</td>
<td>1) Insulin-dependent diabetes; 2) Myocardial insufficiency, grade 4 NYHA; 3) Diastolic blood pressure &gt;120 mm Hg; 4) Extreme hyperlipidemia requiring treatment; 5) Kidney or liver failure; 6) Malignant disease; 7) Disabling diseases; 8) Other complicating diseases; 9) Psychosocial reasons</td>
<td>Total plus ischemic heart disease mortality</td>
</tr>
<tr>
<td>FATS (1990)</td>
<td>Randomized, double-blind, multicenter</td>
<td>Niacin + colestipol</td>
<td>Placebo + colestipol</td>
<td>1) Documented CAD with &gt;50% stenosis; 2) Apo-B &gt;125 mg/dL; 3) Family history of CAD; 4) Age &lt;62 y</td>
<td>1) Diabetes; 2) Uncontrolled hypertension; 3) Liver disease; 4) Renal disease; 5) Thyroid disease; 6) Declined participation</td>
<td>Change in severity of disease in proximal coronary arteries</td>
</tr>
<tr>
<td>UCSF-SCOR (1990)</td>
<td>Randomized, multicenter</td>
<td>Niacin + colestipol</td>
<td>Placebo ± colestipol</td>
<td>1) Documented coronary stenosis &gt;10%; 2) Heterozygous familial hypercholesterolemia with xanthomas, LDL &gt;200 mg/dL; 3) Triglycerides &lt;275 mg/dL; 4) Age 18-72 y</td>
<td>1) Previous CABG; PCI; multiple infarcts; 2) Planned revascularization for unstable lesions; 3) Systemic disease other than atherosclerosis or hypertension</td>
<td>Mean change in percent area stenosis</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention Arm</td>
<td>Control Arm</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Primary Endpoint</td>
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<tr>
<td>HATS (2001)</td>
<td>Randomized, double-blind, single center</td>
<td>Niacin + simvastatin</td>
<td>Placebo</td>
<td>1) Documented coronary disease with &gt;3 stenosis of 30% or 1 stenosis 50%;</td>
<td>1) Previous CABG; 2) Uncontrolled hypertension; 3) Uncontrolled DM; 4) Renal disease; 5) Thyroid disease</td>
<td>Mean change in percent stenosis of most severe coronary artery; time to first composite CVD event</td>
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<td>2) HDL &lt;35/40 mg/dL for male/female;</td>
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<td>3) LDL &lt;145 mg/dL; 4) TG &lt;400 mg/dL;</td>
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<td>5) Age &lt;63 y</td>
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<td></td>
<td>1) Previous CABG; 2) Uncontrolled hypertension; 3) Uncontrolled DM; 4) Renal disease; 5) Thyroid disease</td>
<td>Mean change in percent stenosis of most severe coronary artery; time to first composite CVD event</td>
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<td>1) Liver disease or transaminases &gt;3 ULN;</td>
<td>Change in CIMT</td>
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<td>2) Known niacin intolerance</td>
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<td></td>
<td>1) Unstable CAD or cardiovascular event within 6 mo;</td>
<td>Change in global angiographic stenosis</td>
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<td>2) EF &lt;40%;</td>
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<td>3) Uncontrolled hypertension;</td>
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<td>4) Diabetes;</td>
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<td>5) Cardiac immunosuppressive;</td>
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<td>6) Thyroid disease;</td>
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<td>7) Liver disease;</td>
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<td></td>
<td>8. Creatinine &gt;2 mg/dL;</td>
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<td>9) Concomitant therapy with heparin, CCS, or immunosuppressive</td>
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<td></td>
<td></td>
<td>1) Metabolic or clinical instability;</td>
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<td>2) Thyroid disease;</td>
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<td>3) Creatinine &gt;2 mg/dL;</td>
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<td>4) CK &gt;2 × ULN;</td>
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<td></td>
<td></td>
<td></td>
<td>5) Transaminases &gt;1.5 × ULN</td>
<td></td>
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<td></td>
<td></td>
<td>1) Serious hepatic or kidney diseases;</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>2) Hemodynamic instability;</td>
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<td></td>
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<td>3) Tumor with an expected survival time of less than 1 y;</td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>4) Known intolerance or allergy to niacin or statins;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5) Administration of lipid-lowering drugs within the month before the inclusion</td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention Arm</td>
<td>Control Arm</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Primary Endpoint</td>
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</tr>
</tbody>
</table>
| ARBITER 6-HALTS (2009) | Randomized, open-label, multicenter | Niacin + any statin         | Ezetimibe + any statin  | 1) Documented CAD or CAD equivalent  
2) Statin therapy >3 mo;  
3) LDL <100 mg/dL;  
4) HDL <50/55 mg/dL for male/female;  
5) Age >30 y | NA | Change in CIMT |
| AIM-HIGH (2011)  | Randomized, double-blind, multicenter | Niacin + simvastatin         | Simvastatin           | 1) Documented CAD or PAD or cerebrovascular disease;  
2) HDL <40/50 mg/dL male/female  
3) LDL <180 mg/dL without statin therapy or “adjusted” level in statin therapy  
4) Triglycerides <400 mg/dL;  
5) Age >45 y | 1) Acute coronary event within 4 wk;  
2) Coronary revascularization within 4 wk or planned;  
3) Stroke within 8 wk;  
4) Fasting glucose >180;  
5) EF <30%  
6) AST/ALT >2 ULN;  
7) CKD (creatinine >2.5 mg/dL);  
8) Concomitant drugs with increased risk of hepatotoxicity or myopathy | Composite of CVD events* |
| HPS2-THRIVE (2013) | Randomized, double-blind, multicenter | Niacin ER + larpopirant + simvastatin | Simvastatin | 1) History of MI, stroke/TIA; PAD or DM with other symptoms of CAD;  
2) Age 50-80 y | 1) Cardiovascular event within 3 mo or planned revascularization;  
2) Liver disease or transaminase >1.5× ULN;  
3) Creatinine >2 mg/dL;  
4) Myositis or CK >3× ULN;  
5) Treatment with other statin or simvastatin >40 mg/d | Major vascular events† |

For full trial names, see Table 1 footnote.

ALT = alanine transaminase; AST = aspartate transaminase; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = corticosteroids; CIMT = carotid intimal media thickness; CK = creatine kinase; CKD = chronic kidney disease; DM = diabetes mellitus; EF = ejection fraction; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; TG = triglyceride; TIA = transient ischemic attack; ULN = upper limit of normal.

*Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 h) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

†Major coronary event (nonfatal myocardial infarction or death from coronary causes), stroke of any type, or coronary or noncoronary revascularization.
We conducted meta-analysis using the random-effects model of DerSimonian and Laird with inverse variance weighting. For each clinical endpoint, pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to assess the treatment effects of niacin compared with control/usual care. The pooled effect of niacin on different lipid fractions (TC, LDL-C, and HDL-C) was also estimated. Heterogeneity between studies was assessed using Cochrane’s Q test and the I² statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. Heterogeneity was considered significant if the P value was <.05.

RESULTS

Study Characteristics

The initial search identified a total of 1296 publications that were screened at the abstract level. Among these, 13 randomized clinical trials met the aforementioned inclusion criteria and were included in the final analysis (Figure 1). These studies included a total of 35,206 patients (with or at-risk of ASCVD), with 16,858 randomized to the niacin arm and 18,348 to the control arm. The mean duration of follow-up was 32.8 months (range, 6-74 months).

Baseline characteristics of subjects and included studies are shown in Tables 1 and 2, respectively. Patients included in the final analysis had a mean age of 58 years, and 81% were male. Five studies used placebo as the control arm, whereas 8 studies used either a statin or ezetimibe or “conventional” treatment in the control arm.

Clinical Outcomes

Results of the clinical outcomes with niacin versus control are summarized in Figures 2-7 and Table 3. Among the 34,810 subjects in 11 studies, 2841 patients (8.2%) died from any cause (Figure 2). We failed to observe any differences in all-cause mortality rates (RR 0.99; 95% CI 0.88-1.12) between the niacin and control arms, and there was no significant heterogeneity between the included studies for this endpoint (I² = 31.1%).

Cardiovascular mortality was reported in 1095 patients (11.8%) among 9 trials involving 9236 patients (Figure 3). Four trials, including 33,543 subjects, reported coronary death as a separate endpoint in 1523 patients (4.5%) (Figure 4). Compared with the control arm, niacin did not result in a significant reduction in cardiovascular related mortality (RR 0.91; 95% CI 0.81-1.02) or coronary death (RR 0.93; 95% CI 0.78-1.10).
Nine studies involving 34,251 patients reported the frequency of myocardial infarction (Figure 5). Among these, 1634 patients (4.8%) experienced this event. Niacin treatment was associated with a nonsignificant reduction in nonfatal myocardial infarction (RR 0.85; 95% CI 0.73-1.0). A total of 2088 patients (7%) underwent revascularization procedures among 29,842 patients across 8 studies (Figure 6). Niacin did not result in a significant risk reduction for revascularization (RR 0.83; 95% CI 0.65-1.06). Similarly, among 1417 cerebrovascular events (4.6%) in 30,428 patients, randomization to niacin did not affect this outcome (RR 0.89; 95% CI 0.72-1.10) (Figure 7). Finally, there was no significant heterogeneity between the included studies for each of the endpoints examined.

Effects on Adverse Events
Results for adverse events with niacin as compared with control are summarized in Figures 8-12. Among 4 studies reporting diabetes as an adverse event, patients assigned to niacin therapy were at significantly increased risk for this metabolic disorder compared with control (RR 1.44; 95% CI 0.65-1.06). Similarly, among 1417 cerebrovascular events (4.6%) in 30,428 patients, randomization to niacin did not affect this outcome (RR 0.89; 95% CI 0.72-1.10) (Figure 7). Finally, there was no significant heterogeneity between the included studies for each of the endpoints examined.

Effects on Serum Lipoproteins
Overall, niacin therapy resulted in a nonsignificant decrease in serum levels of TC (0.39 [95% CI 0.20, 0.98]) and LDL-C (0.43 [95% CI 0.05, 0.91]). There was a significant increase in levels of HDL-C from baseline by 21.4%, 9.31 (95% CI 5.11, 13.51) mg/dL, (0.67 [95% CI 0.86, 0.47]) with niacin compared with the control group.

DISCUSSION
Our results showed that the addition of niacin to statin therapy was associated with a significant increase in serum levels of HDL-C and nonsignificant decreases in TC and LDL-C compared with placebo. However, niacin therapy did not lead to significant reductions in all-cause mortality, mortality, CI 1.23-1.90) and musculoskeletal adverse events (RR 1.24; 95% CI 1.09-1.42), as compared with the respective control arms. Subjects receiving niacin therapy experienced a significantly higher risk of skin flushing (RR 18.59; 95% CI 2.52-137.29), whereas the risk of liver toxicity was not significantly elevated (RR 1.66; 95% CI 0.65-4.27) compared with those in the respective control groups.
cardiovascular-related mortality, myocardial infarction, revascularization, or stroke among patients with established or at-high risk of ASCVD.

Despite the widespread use of statins as first-line therapy, patients with established ASCVD remain at increased risk for adverse cardiovascular events.8,35 In the Framingham study cohort, an inverse relation between serum levels of HDL-C and cardiovascular events was observed.36 This was further supported by evidence from various clinical studies, which reported an improvement in both surrogate markers of atherosclerosis and the frequency of cardiovascular events with niacin, one of the most effective HDL-C-raising drugs.21,22,32 However, in the “statin era,” an independent relation of HDL-C with decreased cardiovascular risk has been difficult to demonstrate.37,38 Two large clinical trials, AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events), testing niacin in addition to background statin therapy, failed to show any reduction in cardiovascular events.23,24

To our knowledge the present meta-analysis is the largest to date, comprising 13 trials and including 35,206 patients with or at-risk of ASCVD. Because of heterogeneity in the definition and classification of the primary endpoint among the various trials included, we undertook pooling of individual endpoints to detect meaningful differences in outcomes. Our results showed no significant effect on several important clinical outcomes with the addition of niacin therapy. The Coronary drug project (1975), a 6-year prospective trial randomizing patients with established coronary artery disease to either niacin or placebo, showed lower incidence of myocardial infarction among patients on niacin.21 Furthermore, the 15-year follow-up of the Coronary drug project trial demonstrated that niacin was associated with benefits on long-term survival despite discontinuation after 5 years, thereby suggesting an alteration of ischemic risk.39 Subsequent randomized controlled trials were not adequately powered to detect significant differences in individual endpoints.27,28,30

With the advent of widespread statin use, the AIM-HIGH and HPS2-THRIVE trials investigated the strategy of niacin in patients already receiving effective statin therapy.23,24 The AIM-HIGH study, which enrolled patients with stable CHD with low levels of mean baseline LDL-C (74 mg/dL) and HDL-C (35 mg/dL) on statin treatment, found no significant decrease in cardiovascular events with niacin-statin combination despite a significant increase in HDL-C levels, as compared with the statin-only group.23 In the multicenter

Figure 4  Forest plot showing effect of niacin on coronary death. CI = confidence interval; RR = risk ratio. For full trial names, see Table 1 footnote.
HPS2-THRIVE study, which randomized more than 25,000 patients with stable cardiovascular disease receiving effective lipid-lowering therapy to niacin plus statin combination therapy or statins only over a mean follow-up of 3.6 years, the combination therapy with extended-release niacin and statin failed to significantly reduce the risk of major vascular events.24 Our results are in contrast to the findings from previous meta-analyses that evaluated the role of niacin therapy.40,41 However, these analyses included trials which predated the era of optimal statin therapy and did not include the AIM-HIGH and HPS2-THRIVE studies. A recently conducted meta-analysis of 39 clinical trials involving several HDL-C-directed therapies (niacin, fibrates, cholesteryl ester transfer protein inhibitors) demonstrated results consistent with our study.42 Additionally, 2 randomized trials that investigated the effects of niacin therapy in combination with statin therapy were not included in their analysis, thereby failing to study the cumulative evidence available.31,32 Further, in addition to the larger sample size of our meta-analysis, we attempted to include all the cardiovascular endpoints available in different studies, to broaden the interpretation of these studies, whereas the endpoints of cardiovascular mortality and revascularization have not been evaluated in previous meta-analyses.42,43 The present analysis is also unique in reporting the safety profile of niacin with respect to different adverse events. Consistent with prior evidence, we found significant increases in the niacin arm, compared with control, on the risks of skin, gastrointestinal, diabetes, and musculoskeletal adverse events. Most importantly, our study coincides with the recent withdrawal of approval by the US Food and Drug Administration for combination use of extended-release niacin with statin therapy based on results from the AIM-HIGH and HPS2-THRIVE trials. Our study demonstrated no improvement in clinical outcomes despite a significant increase in serum HDL-C levels with niacin therapy. This lack of clinical benefit could have several potential explanations. First, major weightage in our analysis was provided by the AIM-HIGH and HPS2-THRIVE trials, which recruited patients with highly optimized statin-based therapy maintaining below goal LDL-C levels (<70 mg/dL), which is not universally seen in clinical practice.13,44 This is in contrast with the trials conducted before effective LDL-C—reducing drugs were available.37,38 Furthermore, other trials investigating the role of niacin in combination with statins among patients with low serum levels of HDL-C studied surrogate endpoints and had a low number of clinical events.22,32 Second, with an evolving understanding of HDL composition and
function, it is being increasingly realized that HDL-C’s role and clinical effects may extend far beyond simply the concentration levels, and is more related to HDL particle number (HDL-P) and function. As seen in the AIM-HIGH trial, combination of niacin-statin therapy may not lead to a significant increase in HDL-P and thus cholesterol efflux, thereby explaining the negative results. Further, in a population-based cohort of subjects free from ASCVD, cholesterol efflux activity was inversely associated with incident cardiovascular events over a long-term follow-up of approximately 9 years. Indeed, the efficacy of niacin on the atheroprotective cholesterol efflux pathway is less certain owing to conflicting results in different studies. Third, niacin raises HDL-C through induction of apolipoprotein A-I (apoA-I) synthesis, a major constituent of the HDL molecule. In a meta-analysis of statin trials evaluating association of HDL-C and apoA-I with major adverse cardiovascular events in patients reaching LDL-C <70 mg/dL, a reduced incidence of cardiovascular events was seen only with apoA-I increase, but not HDL-C. Finally, although the effect of niacin in raising HDL-C is well known, it is unclear whether the observed reductions in cardiovascular events in previous studies were related solely to its favorable effect on the patient’s lipid profile. In a meta-regression analysis of 11 niacin trials, Lavigne et al failed to demonstrate an association of serum levels of HDL-C with a reduction in cardiovascular events. This finding could be due to an independent antiatherogenic effect of niacin through its anti-inflammatory and antioxidant properties.

Our analysis suggesting a lack of clinical benefit with niacin is in agreement with studies involving other HDL-raising drugs. Recently published trials investigating fibrates and cholesteryl ester transfer protein inhibitors have added to a growing consensus against the hypothesis that HDL-C—raising therapies would be atheroprotective. Notably, among statin-treated patients, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and dal-OUTCOMES (Study of the Effect of Dalcetrapib on Atherosclerotic Disease in Patients with Coronary Artery Disease) trials failed to show any reduction in recurrent cardiovascular events, with the addition of fenofibrate and dalcetrapib, respectively.

The major strength of the present analysis is individual pooling of important clinical outcomes from available randomized controlled trials comparing niacin with a control agent. In addition, we evaluated the cumulative adverse effect profile associated with niacin treatment. Our results did not show any benefit in terms of all-cause mortality or other cardiovascular events, while suggesting increased risk of several adverse events, with niacin therapy. Our study has
Table 3  Outcomes in Niacin Group Compared with Control

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Niacin (n = 16,858)</th>
<th>Control (n = 18,348)</th>
<th>Risk ratio (95% confidence interval)</th>
<th>( P_{\text{interaction}} )</th>
<th>Heterogeneity (( I^2 )) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1230/16,667</td>
<td>1611/18,143</td>
<td>0.99 (0.88-1.12)</td>
<td>.180</td>
<td>31</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>339/3880</td>
<td>759/5356</td>
<td>0.91 (0.81-1.02)</td>
<td>.628</td>
<td>0.1</td>
</tr>
<tr>
<td>Coronary death</td>
<td>590/15,947</td>
<td>933/17,596</td>
<td>0.93 (0.78-1.10)</td>
<td>.083</td>
<td>55</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>660/16,296</td>
<td>974/17,955</td>
<td>0.85 (0.73-1.0)</td>
<td>.188</td>
<td>28.9</td>
</tr>
<tr>
<td>Revascularization</td>
<td>987/14,932</td>
<td>1101/14,910</td>
<td>0.83 (0.65-1.06)</td>
<td>.098</td>
<td>42</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>599/14,385</td>
<td>818/16,043</td>
<td>0.89 (0.72-1.10)</td>
<td>.192</td>
<td>34.4</td>
</tr>
</tbody>
</table>

Figure 7  Forest plot showing effect of niacin on stroke. CI = confidence interval; RR = risk ratio. For full trial names, see Table 1 footnote.

Figure 8  Forest plot showing effect of niacin on new-onset or worse control of pre-existing diabetes mellitus (DM). CI = confidence interval; M-H = Mantel-Haenszel. For full trial names, see Table 1 footnote.
Figure 9  Forest plot showing effect of niacin on gastrointestinal (GI) adverse events. CI = confidence interval; M-H = Mantel-Haenszel. For full trial names, see Table 1 footnote.

Figure 10  Forest plot showing effect of niacin on musculoskeletal adverse events. CI = confidence interval; M-H = Mantel-Haenszel. For full trial names, see Table 1 footnote.

Figure 11  Forest plot showing effect of niacin on skin flushing. CI = confidence interval; M-H = Mantel-Haenszel. For full trial names, see Table 1 footnote.
several limitations. The dosages and comparators varied across the studies included, and we were not able to estimate the effect of niacin monotherapy. Although clinical outcomes were adjudicated in individual trials, standardized adjudication was not possible across all included randomized controlled trials included in the present analysis.

CONCLUSION
Niacin therapy does not lead to a significant reduction in total or cause-specific mortality or recurrent cardiovascular events, despite an improvement in serum HDL-C levels. Additional research is indicated to better understand HDL subfractions and their association with cardiovascular outcomes with targeted therapies, to increase only those subfractions associated with better cardiovascular outcomes.

References