“WHAT ABOUT AIM-HIGH?”
“WHERE DID WE GO WRONG--OR DID WE?”


Funded by NHLBI, Abbott Laboratories (Kos), Merck, Inc.
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Northwest Lipid and Diabetes Research Laboratories.
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ClinicalTrials.Gov Registration Nos.:
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Jeffrey L. Probstfield, MD

FACULTY DISCLOSURE DECLARATION

FINANCIAL OR OTHER RELATIONSHIP(S) DISCLOSURE:

Dr. Probstfield has indicated that he has had financial or other relationships with commercial interests, related to this presentation, within the past 12 months as follows:

- Consulting/Speaking/Teaching: Sanofi Aventis, Lilly, Amylin
- Grant/Research Support: NHLBI, NCRR, Sanofi, Abbott, Lilly
- Advisory Committees or Review Panels: Sanofi, Genentech, Amylin
- Stocks: None
- Board of Director’s: None
AIM-HIGH - HYPOTHESIS

Among patients selected for clinically manifest atherosclerotic coronary, carotid, and/or peripheral arterial disease, and with low HDL-C, moderately elevated TG’s, and LDL-C < 180 mg/dl (<4.7 mmol/L), the combination of niacin and simvastatin will reduce defined clinical cardiovascular event frequency by at least 25%, relative to the event frequency in those treated with simvastatin monotherapy.
Objective

To determine whether the residual risk associated with low levels of HDL-C in patients with established CHD whose LDL-C therapy was optimized with statins ± ezetimibe would be mitigated with extended-release niacin vs. placebo during long-term follow-up
Background

- The direct relationship between increased LDL-C levels and increased CV risk is firmly established, as is the important role of statins in reducing CV events by 25%-35%.

- Residual risk persists despite achieving recommended levels of LDL-C on statin therapy.

- A significant, inverse relationship exists between low levels of HDL-C and incident CV events.
Framingham Study

*Risk of coronary heart disease over 4 years of follow-up for men ages 50 to 70.

Adapted from Castelli WP. *Can J Cardiol* 1988;4 Suppl A:5A-10A.
OR OF MI FOR INCREASING DECILES OF VARIOUS LIPID OR LIPOPROTEIN RATIOS

<table>
<thead>
<tr>
<th>Decile Medians overall I (cases+controls)</th>
<th>Decile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB/ApoA Ratio</td>
<td></td>
<td>0.43</td>
<td>0.53</td>
<td>0.60</td>
<td>0.66</td>
<td>0.72</td>
<td>0.78</td>
<td>0.85</td>
<td>0.93</td>
<td>1.04</td>
<td>1.28</td>
</tr>
<tr>
<td>LDL/HDL Ratio</td>
<td></td>
<td>1.37</td>
<td>1.87</td>
<td>2.22</td>
<td>2.52</td>
<td>2.82</td>
<td>3.13</td>
<td>3.49</td>
<td>3.92</td>
<td>4.55</td>
<td>5.93</td>
</tr>
<tr>
<td>TC/HDL Ratio</td>
<td></td>
<td>2.74</td>
<td>3.37</td>
<td>3.82</td>
<td>4.23</td>
<td>4.64</td>
<td>5.08</td>
<td>5.58</td>
<td>6.21</td>
<td>7.15</td>
<td>9.20</td>
</tr>
</tbody>
</table>
### Events* in Major Prevention Trials 1994 - 1998

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th># of Events Placebo</th>
<th># of Events Statin</th>
<th>RR Reduction</th>
<th>% Events Not Avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>622</td>
<td>431</td>
<td>34</td>
<td>66</td>
</tr>
<tr>
<td>WOS</td>
<td>6595</td>
<td>248</td>
<td>174</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>274</td>
<td>212</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6605</td>
<td>215</td>
<td>163</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>715</td>
<td>557</td>
<td>24</td>
<td>76</td>
</tr>
</tbody>
</table>

*Nonfataal MI/CHD death
Evidence from Prior Placebo-Controlled Trials Supporting Niacin or Fibrate Benefit

• **Coronary Drug Project (1975) 5-year follow-up**
  – Immediate-release niacin (3,000 mg/day)
  – Reduced CHD Death/MI by **14%**
  – Reduced non-fatal MI by **26%**
  – Reduced stroke/TIA by **21%**

• **VA-HIT (1999) 5-year follow-up**
  – Gemfibrozil vs. placebo (no statin therapy)
  – Reduced CHD Death/MI by **22%**

• **HATS (2001) 3-year follow-up**
  – niacin + simvastatin
  – regression of angiographic coronary stenoses and reductions in clinical events
HATS: QCA RESULTS BY DM/IFG

Mean Change in Proximal Stenosis Severity ($\Delta \%S$)

Reg’n

Progression

Normo-Glycemic
n = 112

Diabetes or IFG
n = 34

-0.1 (P<0.001)

1.1 (P<0.05)

2.2

4.8

SN(-)

SN(+)
HATS: PRIMARY CLINICAL ENDPOINT

Relative Risk = 0.40
p = 0.02

% Free of Event

Relative Risk = 0.40
p = 0.02

Brown, BG NEJM 2001;345:1583-92
MULTIVARIATE ANALYSIS RELATIONSHIP BETWEEN MAJOR CVD EVENTS AND QUINTILES OF HDL-C

EFFECTS OF LDL-C AND HDL-C CHANGES: 29 LIPID TRIALS ON 1RY CLINICAL TRIAL OUTCOME

Reduction During Trial in 1\textsuperscript{st} CV Event Rate, vs Placebo (%)

### NIACIN STUDIES
META-ANALYSIS – CORONARY EVENTS

**E. Bruckert et al. / Atherosclerosis 210 (2010) 353–361**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER-6-HALTS</td>
<td>2/187</td>
<td>9/176</td>
<td>0.25 [0.08, 0.84]</td>
</tr>
<tr>
<td>Guyton JR et al</td>
<td>1/676</td>
<td>1/272</td>
<td>0.35 [0.02, 7.56]</td>
</tr>
<tr>
<td>AFREGS</td>
<td>0/71</td>
<td>1/72</td>
<td>0.14 [0.00, 6.92]</td>
</tr>
<tr>
<td>ARBITER-2</td>
<td>2/87</td>
<td>2/80</td>
<td>0.92 [0.13, 6.65]</td>
</tr>
<tr>
<td>HATS</td>
<td>1/38</td>
<td>5/38</td>
<td>0.24 [0.05, 1.26]</td>
</tr>
<tr>
<td>UCSF_SCOR</td>
<td>0/48</td>
<td>1/49</td>
<td>0.14 [0.00, 6.96]</td>
</tr>
<tr>
<td>STOCKHOLM</td>
<td>72/279</td>
<td>100/276</td>
<td>0.61 [0.43, 0.88]</td>
</tr>
<tr>
<td>CLAS</td>
<td>1/94</td>
<td>5/94</td>
<td>0.25 [0.05, 1.29]</td>
</tr>
<tr>
<td>CDP</td>
<td>287/1119</td>
<td>839/2789</td>
<td>0.81 [0.69, 0.94]</td>
</tr>
</tbody>
</table>

**Total**
- Test for heterogeneity: $P = 0.24$, $I^2 = 23.0\%$
- Test for overall effect: $P < 0.0001$

Subtotal excluding CDP
- $P = 0.53 [0.38, 0.73]$
## NIACIN STUDIES
### META-ANALYSIS - STROKE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guyton JR et al</td>
<td>0/676</td>
<td>1/272</td>
<td>0.03 [0.00, 2.33]</td>
</tr>
<tr>
<td>AFREGS</td>
<td>0/71</td>
<td>2/72</td>
<td>0.14 [0.01, 2.18]</td>
</tr>
<tr>
<td>ARBITER-2</td>
<td>0/87</td>
<td>1/80</td>
<td>0.12 [0.00, 6.27]</td>
</tr>
<tr>
<td>HATS</td>
<td>0/38</td>
<td>2/38</td>
<td>0.13 [0.01, 2.15]</td>
</tr>
<tr>
<td>STOCKHOLM</td>
<td>6/279</td>
<td>5/276</td>
<td>1.19 [0.36, 3.92]</td>
</tr>
<tr>
<td>CDP</td>
<td>95/1119</td>
<td>311/2789</td>
<td>0.75 [0.60, 0.94]</td>
</tr>
</tbody>
</table>

**Total**
- Test for heterogeneity: P = 0.27, I² = 21.9%
- Test for overall effect: P = 0.007

**Subtotal excluding CDP**

0.51 [0.20, 1.35]
AIM-HIGH - DESIGN

Patients: 3300 men and women with vascular disease, HDL ≤40 (50 F), TG 150-400 and LDL-C ≤180 mg/dl, if off (or as estimated off) statins. A 3-7 year follow-up.

Centers: 90 centers (≈36 patients per center) in US and Canada (20 centers).

Funding: NHLBI, Abbott (Kos), Merck.

Therapy: Simvastatin vs Simva+Niaspan ± Ez. Post-randomiz. LDL-C titration target: 40-80 mg/dl (ave. 70 mg/dl).

1° Endpoint: 1st Occurrence:

- CHD Death,
- Nonfatal MI,
- Fatal or nonfatal stroke,
- ACS hospitalization (23 hr),
- Revascularization for progressive ischemia
AMENDMENT 5

• Primary endpoint (E5):
  – CAD Death
  – Non-fatal MI
  – Ischemic Stroke
  – Hospitalization for ACS
  – *Symptom driven* coronary or cerebral revascularization
AMENDMENT 5: ASSUMPTIONS

- Sample size 3,300 (actual)
- Enrolled over ~3.5 years (actual)
- One-sided test (alpha=0.025)
- Monotherapy event rate 0.065 (estimated based on blinded review of data in planning amendment)
- Hazard ratio 0.75
- Delay in treatment effect begins at 3 months, full effect at 6 months
- Rate of discontinuation of blinded therapy (active) 0.085 for 867 primary endpoint events
- Power 85%
**Study Design**

Open-Label Run-In: Up-Titrate Niacin from 500mg to 2,000mg/day

Adjust simva to LDL 40 – 80 mg/dL

ER Niacin + 40-80 mg/day simvastatin

Follow to end of study

Placebo + 40-80 mg/day simvastatin

**Months Relative to Randomization**

-2 -1 0 1 2 3 6 12
Statistical Analyses

• Event-driven trial with projected 800 primary outcomes; 2.5-7 year follow-up (mean 4.6 years)

• 85% power to detect a 25% reduction in the 5-component primary endpoint (one-sided test of significance; alpha level=0.025

• Pre-specified, conservative asymmetric boundaries for potential early stopping based on efficacy/lack of efficacy

• Trial stopped on 5/25/11: lack of efficacy and concern of ischemic stroke imbalance with niacin after a 36-month average follow-up
## Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomized</td>
<td>3,414</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>64±9</td>
</tr>
<tr>
<td>Male</td>
<td>85%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>92%</td>
</tr>
<tr>
<td>Current smokers</td>
<td>20%</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>71%</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>34%</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>81%</td>
</tr>
<tr>
<td>History of MI</td>
<td>56%</td>
</tr>
<tr>
<td>History of Cerebrovascular Disease</td>
<td>21%</td>
</tr>
</tbody>
</table>

*All baseline characteristics balanced between treatment groups*
Concomitant Medications at Entry

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>On a Statin</td>
<td>94%</td>
</tr>
<tr>
<td>Duration of Statin Therapy*</td>
<td></td>
</tr>
<tr>
<td>≥ 1 year</td>
<td>76%</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>40%</td>
</tr>
<tr>
<td>Prior Niacin Use</td>
<td>20%</td>
</tr>
<tr>
<td>ASA/Antiplatelet Therapy</td>
<td>98%</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>80%</td>
</tr>
<tr>
<td>ACEI / ARB</td>
<td>74%</td>
</tr>
</tbody>
</table>

*Use of all secondary prevention therapies was well-balanced between treatment groups

*Duration of statin therapy not ascertained in 6%
## Baseline Lipids (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>On Statin (n=3,196)</th>
<th>Off Statin (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C (mean)</strong></td>
<td>71</td>
<td>119</td>
</tr>
<tr>
<td><strong>HDL-C (mean)</strong></td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>161</td>
<td>215</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-HDL (mean)</strong></td>
<td>107</td>
<td>165</td>
</tr>
<tr>
<td><strong>Apo-B (mean)</strong></td>
<td>81</td>
<td>111</td>
</tr>
</tbody>
</table>
HDL-C at Baseline & Follow-up

- **Combination Therapy**
- **Monotherapy**

**P < 0.001**

*Significant difference*
LDL-C at Baseline & Follow-up

Baseline | Year 1 | Year 2 | Year 3
---|---|---|---
50 | | | 
55 | | | 
60 | | | 
65 | | | 
70 | | | 
75 | | | 
80 | | | 

Combination Therapy

Monotherapy

P < 0.001
<table>
<thead>
<tr>
<th>Primary &amp; Secondary Endpoints</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>1.02</td>
<td>0.87, 1.21</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD Death, MI, Ischemic Stroke, High-Risk ACS</td>
<td>1.08</td>
<td>0.87, 1.34</td>
</tr>
<tr>
<td>CHD Death, MI, Ischemic Stroke</td>
<td>1.13</td>
<td>0.90, 1.42</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>1.17</td>
<td>0.76, 1.80</td>
</tr>
</tbody>
</table>
Primary Outcome

- Cumulative % with Primary Outcome
  - Combination Therapy
  - Monotherapy

**HR 1.02, 95% CI 0.87, 1.21**
Log-rank P value = 0.79

- **N at risk**
  - Monotherapy: 1696, 1581, 1381, 910, 436
  - Combination Therapy: 1718, 1606, 1366, 903, 428

- **16.4%** for Combination Therapy
- **16.2%** for Monotherapy
Primary and Secondary Endpoints

Primary Endpoint
CHD Death
Non-fatal MI
Ischemic Stroke
Hospitalization for ACS
Symptom-Driven Coronary or Cerebral Revascularization

Original Primary Endpoint
(CHD death, non-fatal MI, ischemic stroke, hospitalization for high-risk ACS)

Composite of CHD Death, non-fatal MI or ischemic stroke
All Cardiovascular Death

Niacin better
Niacin worse

P = 0.11
Pre-Specified Subgroups

Overall

- Age ≥ 65 years
- Age < 65 years

Men
- Women

Diabetes
- No Diabetes

Metabolic Syndrome
- No Metabolic Syndrome

Prior MI
- No Prior MI

ON Statin at Entry
- OFF Statin at Entry

Niacin better
- Niacin worse
Interpretation of Study Findings and Therapeutic Implications

• Contemporary optimal medical therapy and aggressive secondary prevention (particularly with intensive LDL-C lowering therapy) may make it increasingly difficult to demonstrate incremental treatment superiority.

• Previous therapy in patients receiving statins (94%) and niacin (20%) may have limited our ability to demonstrate a favorable treatment effect with niacin.

• Intensive use of statin therapy for ≥1 year in ~ 75% of patients may have caused “delipidation” of lipid-rich necrotic cores, converting high-risk vulnerable plaques → stable, quiescent plaques.
Interpretation of Study Findings and Therapeutic Implications

- The unexpected 9.8% increase in HDL-C in placebo-treated patients could have minimized between-group event rate differences.

- Residual risk in AIM-HIGH patients during follow-up was appreciable (5.4% event rate/year), but was not mitigated by niacin.

- Whether niacin benefit might have been discerned during a longer follow-up remains uncertain.
Conclusions

• Among patients with stable, non-acute, cardiovascular disease and LDL-C levels of <70 mg/dL, there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up, despite significant improvements in HDL-C and triglycerides.

• AIM-HIGH reaffirms current NCEP ATP-III treatment guidelines for LDL-C lowering as the principal target of lipid treatment.

• Additional analyses will be required to determine if certain subsets of patients with low HDL-C in AIM-HIGH may benefit from niacin treatment.
RELEVANT ISSUES-1

- Should the trial have been stopped?
- Was AIM-HIGH underpowered?
- Did we test the HDL hypothesis?
- What proportion of the “at risk” population did we address?
- Is there a subgroup that might have benefited?
RELEVANT ISSUES-2

• Is there a theoretical ceiling effect, or maximum amount of risk reduction (~50%) that can be achieved with lipid modification (based on INTERHEART)?
• Why such a big increase in Placebo gp. HDL?
• Are the ischemic stroke results real?
• Do the participants in AIM-HIGH resemble those we would treat in practice?
HPS2-THRIVE (2004 – 2013)

- 25,000 history of CAD or diabetes
- UK, Scandinavia, and (~50%) China
- No lipid entry criteria other than LDL-C < 160 mg/dL
- Randomized to simvastatin 40 mg or simvastatin + extended release niacin/laropiprant
- Use of Zetia allowed
- No target LDL-C level
- No attempt to equalize LDL-C levels between groups
Differences: AIM-HIGH & HPS2-THRIVE

- **AIM-HIGH** conducted in USA/Canada. Nearly all patients previously treated with statin and well-controlled (baseline LDL-C ~ 73 mg/dl)

- **HPS 2 THRIVE** conducted in UK, Scandinavia, and (50%) in China. Previous treatment and length of treatment with a statin?

- **AIM-HIGH**: low HDL-C plus elevated TG

- **HPS2-THRIVE**: only LDL-C < 160 mg/dL

- No attempt to equalize LDL-C levels between-groups in HPS-2 THRIVE
What Is the Future of HDL Therapies?

• Need to wait for results of HPS2-THRIVE (25,000 patients versus 3,400 patients in AIM-HIGH)

• Ongoing CETP inhibitor morbidity/mortality trials

• ? Role of combination therapy in statin-naïve patients?
### Lipid Effects of CETP Inhibitors

#### Table. Lipid Changes Following Treatment With Cholesterol Ester Transfer Protein Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Change From Baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dalcetrapib, 600 mg/d</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>+31</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>+11</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>-2</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>+4</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+8</td>
</tr>
</tbody>
</table>

Data are adapted from Barter et al., Cannon et al., and Fayad et al. As monotherapy.
ILLUMINATE: Torcetrapib

- Inclusion criteria: High-risk of vascular disease
- Sample size: 15,067
- Recruitment: 2004-05
- Intervention: Torcetrapib vs. placebo
  - Lipid effects: LDL-C ↓ 25% (12 months) HDL-C ↑ 72%

- Results: Stopped early due to INCREASED Major CV events (coronary death, non-fatal MI, stroke, unstable angina), and increased total mortality
- BP noted to be 5/2 mm Hg Higher with torcetrapib, increase aldosterone levels – potentially an “off target” toxicity
- HDL functionality also questioned
Kaplan–Meier Curves: Death Any Cause and Primary Composite Outcome.

Study Organization

**Executive Committee:**
- W.E. Boden (Co-Chair)
- J.L. Probstfield (Co-Chair)
- T. Anderson
- B.R. Chaitman
- P. Desvigne-Nickens
- J. Fleg
- M. Kashyap
- S. Marcovina
- R. McBride, PhD
- M. McGovern
- K.K. Teo
- W.S. Weintraub

**Clinical Events Committee:**
- B.R. Chaitman (Chair)
- D. Anderson
- R. Bach
- S. Cruz-Flores
- G. Gosselin
- S. Nash
- C. Sila
- J. Wittes (Chair)
- D. Arnett
- J. LaRosa
- E. Meslin
- T. Orchard
- K. Watson

**DCC:**
- J. L. Probstfield (Co-Dir.)
- R. McBride (Co-Dir.)
- J. Kaiser
- K. Seymour
- S. Claire
- B. Ricker
- C. Wallum

**DSMB:**

**EGC Core Lab:**
- B. R. Chaitman

**Northwest Lipid Metabolism & Diabetes Research Lab:**
- S. Marcovina
Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

ABSTRACT

BACKGROUND
In patients with established cardiovascular disease, residual cardiovascular risk persists despite the achievement of target low-density lipoprotein (LDL) cholesterol levels with statin therapy. It is unclear whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol is superior to simvastatin alone in reducing such residual risk.

METHODS
We randomly assigned eligible patients to receive extended-release niacin, 1500 to 2000 mg per day, or matching placebo. All patients received simvastatin, 40 to 80 mg per day, plus ezetimibe, 10 mg per day, if needed, to maintain an LDL cholesterol level of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). The primary end point was the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

RESULTS
A total of 3414 patients were randomly assigned to niacin (1718) or placebo (1696). The trial was stopped after a mean follow-up period of 3 years owing to a lack of difference in the primary end point between niacin and placebo. At 3 years, niacin therapy significantly increased the median HDL cholesterol level by 0.43 mmol per liter (16.7 mg per deciliter), compared with placebo (P<0.001). In this subgroup analysis, a benefit of niacin over placebo was observed in reducing the primary end point. However, the absolute risk reduction was not clinically meaningful (relative risk, 0.89; 95% confidence interval, 0.72 to 1.12).

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