Niacin Use in Patients with Low HDL-Cholesterol Receiving Intensive Statin Therapy

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Co-Principal Investigators
on behalf of the AIM-HIGH Investigators

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AIM-HIGH Trial

Atherothrombosis

Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes
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
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
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
Hypothesis

Combination dyslipidemic therapy with high-dose extended-release niacin (1,500-2,000 mg/day), when added to intensive LDL-C lowering therapy, will be superior to intensive LDL-C lowering therapy alone in reducing the risk of CV events in patients with established atherosclerotic cardiovascular disease and low baseline levels of HDL-cholesterol.
Entry Criteria

❖ Patients Age ≥ 45 Years with
  • Coronary Heart Disease (CHD), or
  • Cerebrovascular Disease (CVD), or
  • Peripheral Arterial Disease (PAD)

❖ And Dyslipidemia
  • Low Levels of Baseline HDL-C
    <40 mg/dL for men; < 50 mg/dL for women;
  • Triglycerides 150-400 mg/dL;
  • LDL-C < 180 mg/dL
Open-Label Run-In: Up-Titrate Niacin from 500mg to 2,000mg/day
4-8 weeks

ER Niacin + 40-80 mg/day simvastatin
Placebo + 40-80 mg/day simvastatin

Adjust simva to LDL 40 – 80 mg/dL

Follow to end of study

Months Relative to Randomization

-2 -1 0 1 2 3 6 12
Study Population

Screened
N=8,162

Began Open Label Run-in
N=4,275

Randomized
N=3,414

Niaspan + Simvastatin 40-80mg
N=1,718

Placebo + Simvastatin 40-80mg
N=1,696
Endpoints

❖ **Primary Outcome Composite (Time to First Occurrence):**
  - Coronary Heart Disease Death
  - Non-Fatal MI
  - Ischemic (Non-Hemorrhagic) Stroke
  - Hospitalization for ACS
  - Symptom-Driven Revascularization

❖ **Secondary Composite Endpoints:**
  - CHD Death, Non-Fatal MI, Ischemic Stroke, or Hospitalization for High-Risk ACS
  - CHD Death, Non-Fatal MI or Ischemic Stroke
  - Cardiovascular Mortality
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><strong>Duration of Statin Therapy</strong></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%*
<table>
<thead>
<tr>
<th>Lipid</th>
<th>On Statin (n=3,196)</th>
<th>Off Statin (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>71</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C (mean)</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Triglycerides (median)</td>
<td>161</td>
<td>215</td>
</tr>
<tr>
<td>Non-HDL (mean)</td>
<td>107</td>
<td>165</td>
</tr>
<tr>
<td>Apo-B (mean)</td>
<td>81</td>
<td>111</td>
</tr>
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</table>
### Simvastatin Dose and Ezetimibe Use

<table>
<thead>
<tr>
<th>Simva Dose:</th>
<th>Mono-therapy</th>
<th>Combination Therapy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 mg/day</td>
<td>11%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>40 mg/day</td>
<td>50%</td>
<td>50%</td>
<td>0.018</td>
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<tr>
<td>&gt; 40 mg/day</td>
<td>25%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>On Ezetimibe</td>
<td>22%</td>
<td>10%</td>
<td>&lt; 0.001</td>
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</table>
HDL-C at Baseline & Follow-up

- Combination Therapy
- Monotherapy

P < 0.001

Baseline | Year 1 | Year 2 | Year 3
---|---|---|---
25 | 35 | 40 | 45

* Indicates statistical significance (P < 0.001)
Triglycerides at Baseline and Follow-up

- **Combination therapy**
- **Monotherapy**

Baseline Year 1 Year 2 Year 3

mg/dL

P < 0.001
LDL-C at Baseline & Follow-up

Combination Therapy
Monotherapy

P < 0.001

Baseline Year 1 Year 2 Year 3

mg/dL

50 55 60 65 70 75 80
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>1.02</td>
<td>0.87, 1.21</td>
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<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

Time (years)
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 worse
Niacin better

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.

- The unexpected 9.8% increase in HDL-C in placebo-treated patients could have minimized between-group event rate differences.
Interpretation of Study Findings and Therapeutic Implications

- ? 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

- 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.
# Study Organization

<table>
<thead>
<tr>
<th>Executive Committee:</th>
<th>Clinical Events Committee:</th>
<th>DCC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.E. Boden (Co-Chair)</td>
<td>B.R. Chaitman (Chair)</td>
<td>J. L. Probstfield (Co-Dir.)</td>
</tr>
<tr>
<td>J.L. Probstfield (Co-Chair)</td>
<td>D. Anderson</td>
<td>R. McBride (C-Dir.)</td>
</tr>
<tr>
<td>T. Anderson</td>
<td>R. Bach</td>
<td>J. Kaiser</td>
</tr>
<tr>
<td>B.R. Chaitman</td>
<td>S. Cruz-Flores</td>
<td>K. Seymour</td>
</tr>
<tr>
<td>P. Desvigne-Nickens</td>
<td>G. Gosselin</td>
<td>S. Claire</td>
</tr>
<tr>
<td>J. Fleg</td>
<td>S. Nash</td>
<td>B. Ricker</td>
</tr>
<tr>
<td>M. Kashyap</td>
<td>C. Sila</td>
<td>C. Wallum</td>
</tr>
<tr>
<td>S. Marcovina</td>
<td><strong>DSMB:</strong></td>
<td><strong>ECG Core Lab:</strong></td>
</tr>
<tr>
<td>R. McBride, PhD</td>
<td>J. Wittes (Chair)</td>
<td>B. R. Chaitman</td>
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<tr>
<td>M. McGovern</td>
<td>D. Arnett</td>
<td>Northwest Lipid Metabolism &amp; Diabetes Research Lab:</td>
</tr>
<tr>
<td>K.K. Teo</td>
<td>J. LaRosa</td>
<td>S. Marcovina</td>
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<tr>
<td>W.S. Weintraub</td>
<td>E. Meslin</td>
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<tr>
<td></td>
<td>T. Orchard</td>
<td></td>
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<td></td>
<td>K. Watson</td>
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</table>
Participating Centers
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 efficacy. At 3 years, niacin, though not significantly increased the median HDL level...