AIM-HIGH: Niacin NIASPAN Plus Statin to Prevent Vascular Events 1-3
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes

TRIAL BACKGROUND
• Coronary heart disease remains a leading cause of morbidity and mortality despite use of ASA, β-blockers, ACEI/ARB and statin therapies
• Current 2009 Canadian Dyslipidemia Guidelines recommend targeting LDL cholesterol before other alternate targets, given that lowering LDL ↓ risk of cardiovascular events, including death
• Previous Related Evidence, Analysis and Trials
  o CTT MA 4 has shown a RRR of 21% in major vascular events for with statin therapy [1mmol/L ↓LDL]
  o Epidemiological studies have demonstrated that low HDL is associated with ↑ CHD events independent of LDL cholesterol, however it has not been shown that raising HDL is associated with ↓ CV events
  o Coronary Drug Project MC, RCT(5): niacin 3g/day ↓ non-fatal MI 27% ARR 3.3% & fatal/non-fatal stroke 24% ARR 2% but not overall mortality at 5yrs in men with CHD Caveat: not treated with ASA, BB, ACEI/ARB, or statin (HDL not reported)
  o VA-HIT MC, DB, RCT(6): gemfibrozil ↓ non-fatal MI/CHD death 22% ARR 4.4% at 5yrs in men with CHD low HDL/normal LDL (HDL 0.94mol/L)
  o ACCORD Lipid MC, DB, RCT(7): no difference primary outcome but showed ↓ 22% 1892% Syr rate of major CV events; those in highest HDL quintile with LDL <1.8 had a greater reduction, thus it was proposed that HDL may have prognostic value independent of LDL

• AIM-HIGH was designed to determine whether raising HDL with niacin, while (optimally) lowering LDL with statin therapy, would ↓ CV events in those established CVD & atherogenic dyslipidemia
  o Niacin’s mechanism of action on lipids is not well understood, but generally lowers TG 20-35%, raises HDL 15-35%

TRIAL DESIGN
• DB, PC, double-dummy, MC Q1 sites: US, CAN, Superiority RCT (funded by NHLBI & Abbott, medications provided by Abbott & Merck)
  o Simvastatin + ER-Niacin NIASPAN 1500-2000mg/day n=1,718 vs. Simvastatin + Placebo n=1,696
    o simvastatin dosed to achieve LDL 1.2-2.1 mmol/L (avg dose 40mg 80ng; 17.5 ± 24.7%);
      added ezetimibe 10mg/day if needed to achieve LDL target
    o 4wk run-in phase to demonstrate tolerability of at least 1500mg niacin ER (titrated by 500mg weekly) 80% enrolled
    o 50mg niacin in placebo tablets to maintain double blind

POPULATION
• N=3,414 patients aged ≥45 with established vascular disease  
  CAD: multi-vascular, MI; cerebrovascular (ischemic stroke); carotid dx, symptomatic PAD or other vascular dyslipidemia  
  Exclusion: ACS or PCI within 4wk, fasting glucose >10mmol/L or A1c>9%, nonstatin, niacin can’t tolerate symptoms of maximal medical therapy, left main stenosis >50%, stroke within 8wk, statin, fibrin, niacin, bile acid seq, ezetimibe, fatty acids
• Baseline Characteristics: Age mean=64, men 85%, Caucasian 92%, CAD 92%, HTN 71%, DM 34%, metabolic sx 91%, previous MI 56%, carotid dx 12%, PAD 31%, LDL 1.84 mmol/L, HDL 0.9 mmol/L

RESULTS - mean follow-up 32 mo (planned 4.6yrs)

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Niacin ER + Simvastatin (n=1,696)</th>
<th>Placebo + Simvastatin (n=1,718)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1st: first event of: CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS, symptom-driven coronary/cerebral revasc.</td>
<td>16.4% (6.15%/year)</td>
<td>16.2% (6.08%/year)</td>
<td>1.02 (0.87-1.21), NS</td>
<td>NS for main endpoint and individual components</td>
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<tr>
<td>2nd: CHD death, non-fatal MI, ischemic stroke, high-risk ACS</td>
<td>10%</td>
<td>9.3%</td>
<td>1.08 (0.87-1.34), NS</td>
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<tr>
<td>3rd: All deaths from CHD</td>
<td>2.2%</td>
<td>2.0%</td>
<td>1.10 (0.96-1.75), NS</td>
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<tr>
<td>4th: Non-fatal MI</td>
<td>6.1%</td>
<td>5.5%</td>
<td>1.11 (0.84-1.47), NS</td>
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<tr>
<td>5th: Hospitalization for ACS</td>
<td>4.2%</td>
<td>4.8%</td>
<td>0.87 (0.63-1.19), NS</td>
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<tr>
<td>6th: Symptom-driven coronary or cerebral revascularization</td>
<td>9.7%</td>
<td>9.9%</td>
<td>0.99 (0.80-1.22), NS</td>
<td></td>
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<tr>
<td>7th: Ischemic Stroke</td>
<td>1.7%</td>
<td>1.1%</td>
<td>1.61 (0.89-2.61), NS</td>
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Lipid Levels Achieved at Year 2 (% change)
- HDL_{mmol/L} (mean) | 1.09 (↑25%) | 1.00 (↑9.8%) | p<0.001 |
- TG_{mmol/L} (median) | 1.40 (↑29%) | 1.70 (↑8.1%) | NS |
- LDL_{mmol/L} (median) | 1.70 (↓12%) | 1.80 (↓5.5%) | NS |

Adverse Events
- LFT Abnormalities | 0.8% | 0.5% | NS |
- Muscle symptoms or myopathy | 0.3% | 0.3% | NS |

Discontinuation Rate | 25.4% | 20.1% | P<0.001 |

Adherence ≥75% | 90.0% | 93.3% | NS |
COMMENTS

- Data & Safety Monitoring Board (DSMB) recommended trial termination April 25, 2011 based on pre-specified boundary for lack of efficacy when 50% of events were reported. HR 21.02 with p<0.001 for futility
  - DSMB concluded that high dose, ER-niacin offered no benefit above statin therapy in reducing CV events; no evidence that continuation of trial would change results. Risk of ischemic stroke NOT reason for trial termination
  - 2nd endpoint was originally the 1st endpoint – changed due to low event rate on basis of blinded examination of data by the executive committee

- Lack of benefit with niacin despite expected increase in HDL & LDL TG (possibly due to at-target LDL/statin therapy) including non-lipid benefits along with other disease-modifying therapies: antiplatelet, BB, ACEI/ARB
  - Study was not underpowered, but did assume an ambitious treatment effect 25%
  - With the modest changes in HDL and background medical therapy patients received in addition to the 25% rate of premature discontinuation

(Usuually) high adherence and low discontinuation rates in niacin arm likely reflects removal of intolerant patients in run-in phase and high proportion of patients on niacin prior to the trial

- Uncertain mechanism by which niacin may contribute to imbalance in ischemic stroke risk (27 strokes as first event (1.6%) ER-Niacin vs. 12 (0.7%) placebo (including 9 patients who had stopped taking niacin for at least 2 months and up to 4 years) had a stroke, and 3 additional TIAs in the niacin group were re-classified as ischemic strokes post-hoc analysis); strokes on treatment: 21 vs 18 placebo
  - Most likely chance finding as no other RCTs or MA have found a similar signal (MA showed 1-stroke OR 0.74, p=0.007), no plausible biological mechanism known, no statistical adjustment done for multiplicity of testing of components of the 1st outcome

Strengths:
- Important clinical question
- Important clinical endpoints
- Well blinded
- Low loss to follow up

Limitations:
- Stopped early by DSMB and short planned follow-up
- Change in primary endpoint and power calculation
- Limited generalizability

Uncertainties:
- Benefit in statin-intolerant lower risk population or other subgroups, including those who can’t reach LDL targets
- Effect of IR vs ER formulation
- Whether stroke risk was causal
- Benefit of niacin in higher risk patients
- Benefit of other HDL-raising therapies in stable CVD
- Whether CV risk can be reduced beyond that conferred by statins in addition to other medical therapy

BOTTOM LINE:

- AIM-HIGH does NOT provide support for the use of ER-niacin as an add-on to statin therapy in a stable 2nd prevention population already treated with ASA, beta-blockers, ACEI or ARB’s & statins. However likely was not designed appropriately to answer this question since ambitious estimated risk reduction, and early stop/short of the duration.
- Results for AIM-HIGH raise questions regarding modifiable nature of residual risk in patients reaching LDL targets on a statin. Clinical relevance of previous studies ARBITER, ARBITER-6-HALTS examining carotid intima-media thickness with niacin unclear, as using this surrogate marker has shown inconsistent results even with proven event lowering therapies
- A larger international trial of high dose ER-niacin with simvastatin is ongoing with expected results in 2013, which may help to answer the question of niacin’s ability to reduce CV events in this population

References:

3. The AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. Am Heart J 2011;161:538-43.