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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 $_{apoB, HDL, TG}$, given that lowering LDL ↓ risk of cardiovascular events, including death
- Previous Related Evidence, Analysis and Trials
  - CTT MA [4] has shown a RRR of 21% in major vascular events for with statin therapy (1mmol/L ↓LDL)
  - 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
  - **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, βB, ACEi/ARB, or statin (HDL not reported)
  - **VA-HIT** MC, DB, RCT(6): gemfibrozil 600mg BID ↓ non-fatal MI/CHD death 22% ARR 4.4% at 5yrs in men with CHD low HDL/normal LDL ΔHDL 6% (0.98→1.07mmol/L)
  - **ACCORD Lipid** DB, MC, RCT(7): high-risk T2DM; simvastatin ~20mg ± fenofibrate 160mg/day (f/u 4.7yrs) no difference primary outcome nonfatal MI, nonfatal stroke, or death from CV causes (HR 0.92, NS ARR 0.17%/yr)
  - **TNT** MC, DB, RCT(8): ↓LDL 2.5→2.0mmol/L with intensive statin therapy atorvastatin 80mg showed ↓22% ARR2.2% 5yr 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 with established CVD & atherogenic dyslipidemia
  - 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 91 sites: US, CAN superiority RCT (funded by NLHBI & Abbott, medications provided by Abbott & Merck)
- **Simvastatin + ER-Niacin NIASPAN 1500-2000mg/day** n=1,718 vs. **Simvastatin + Placebo** n=1,696
  - simvastatin dosed to achieve LDL 1-2.1 mmol/L (**avg dose 40mg** **80mg**: 17.5 v **24.7%**); added ezetimibe 10mg/day if needed to achieve LDL target n=515, 9.5 v 21.5%
  - ≥4wk run-in phase to demonstrate tolerability of at least 1500mg niacin ER (titrated by 500mg weekly) 80% enrolled; 50mg niacin in placebo tablets to maintain double blind recommended use of low-fat snack and/or ASA 325mg to reduce flushing

POPULATION

- N=3,414 patients aged ≥45 with established vascular disease CAD: multi-vessel, MI; cerebrovascular (ischemic stroke); carotid dx, symptomatic PAD or atherogenic dyslipidemia not on statin: LDL ≤4.1 mmol/L; HDL ≤1 ♂ or ≤1.3 ♀; TG ≥1.7 & ≤4.5 mmol/L; on statin: LDL adjusted based on expected effect of current statin, HDL <1.1 ♂/1.4 ♀, TG 1.1-4.5 mmol/L
  - Exclusion: ACS or PCI within 4wk, CABG within 1year, unstable angina symptoms on maximal medical therapy, left main stenosis >50%, stroke within 8wk, fasting glucose >10mmol/L or A1C>9% niacin can ↑glucose, EF<30% or unresponsive HF, BP >200/100mmHg despite treatment, SCr >220umol/L, AST or ALT >2x ULN, CYP3A4 inhibitors, unable to discontinue lipid therapy statin, fibrate, niacin, bile acid seq, ezetimibe, fatty acids
- Baseline Characteristics: Age_{mean}=64, men 85%, Caucasian 92%, CAD 92%, HTN 71%, DM 34%, metabolic sx 81%; previous MI 56%; carotid dx 12%; PAD 11%; LDL 1.84 mmol/L, HDL 0.9 mmol/L off all lipid agents except statin/ezetemibe x4week; ASA 92%; BB 80%; ACEi/ARB 74%; statin 93%, niacin 20%

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

Clinical Endpoints	Niacin ER + Simvastatin (n=1696)	Placebo + Simvastatin (n=1718)	Hazard Ratio (95% CI)	Comments
1°: first event of: CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS, symptom-driven coronary/cerebral revasc.	16.4% (6.15%/year)	16.2% (6.08%/year)	1.02 (0.87-1.21), NS	**NS** for main endpoint and individual components
2°: CHD death, non-fatal MI, ischemic stroke, high-risk ACS	10%	9.3%	1.08 (0.87-1.34), NS	
3°: All deaths from CHD	2.2%	2.0%	1.10 (0.96-1.75), NS	
3°: Non-fatal MI	6.1%	5.5%	1.11 (0.84-1.47), NS	
3°: Hospitalization for ACS	4.2%	4.8%	0.87 (0.63-1.19), NS	
3°: Symptom-driven coronary or cerebral revascularization	9.7%	9.9%	0.99 (0.80-1.22), NS	
3°: Ischemic Stroke	1.7%	1.1%	1.61 (0.89-2.61), NS	
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	
- $LDL_{mmol/L}$ (mean)	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 ≥1.02 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**]
- 2° endpoint was originally the 1° 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%], especially with the modest changes in HDL and background medical therapy patients received [in addition to the 25% rate of premature discontinuation]
- (Unusually) 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 [niacin] vs 18 [placebo]
  - Most likely chance finding as no other RCTs or MA have found a similar signal (MA showed ↓stroke OR 0.74, p=0.007), no plausible biological mechanism known, no statistical adjustment done for multiplicity of testing of components of the 1° 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 [cholesterol ester transfer proteins: dalcetrapib (dal-OUTCOMES), anacetrapib (REVEAL) (studies ongoing)]
♦ 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 [NIASPAN] as an add-on to statin therapy in a stable 2° 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 duration of the trial.
- 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 [statins]
- A larger [n=25,000], international [Europe, China] trial [HPS2-Thrive] of high dose ER-niacin [with simvastatin 40mg] 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

A1C=haemoglobin A1C **ACEi**=angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **apoB**=apolipoprotein B **ARB**=angiotensin receptor blocker **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **AST**=aspartate aminotransferase **ALT**=Alanine transaminase **BB**=beta blocker **BP**=blood pressure **CABG**=coronary artery bypass graft **CAD**=coronary artery disease **CHD**= coronary heart disease **CTT MA**=cholesterol therapy trialists meta-analysis **CV**=cardiovascular **CVD**=cardiovascular disease **DB**=double blind **DSMB**=Data&Safety Monitoring Board **Dx**=disease **F/u**=follow-up **EF**=ejection fraction **ER**=extended release **HDL**=high density lipoprotein **HF**=heart failure **HR**=hazard ratio **IR**=immediate release **LDL**=low density lipoprotein **LFT**=liver function test **MA**=meta-analysis **MC**=multicentre **MI**=myocardial infarction **NNT**=number needed to treat **NS**=non-significant **PAD**=peripheral artery disease **PC**= placebo controlled **PCI**=percutaneous coronary intervention **RCT**=randomized controlled trial **RRR**=relative risk reduction **SCr**=serum creatinine **Sx**=syndrome **T2DM**=type 2 diabetes mellitus **TG**=triglycerides **TIA**=transient ischemic attack **ULN**=upper limit of normal **♂=male ♀=female △=change**

Links to RxFiles: **- Lipid Lowering Chart:** http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents.pdf
- Lipid Landmark Trials: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf

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