

# AIM - HIGH

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The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes



# Background

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- ❑ Arthrogenic Dislipidemia linked with cardiovascular risk
- ❑ Statins have been mainstay but aggressive LDL lowering results in 30-35% reduction
- ❑ Beneficial effect seen in some studies with fibrates but not all
- ❑ Earlier trials with niacin showed benefit against placebo – Pre-statin



# Objective

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- to evaluate the effect of extended-release niacin in subjects with established atherosclerotic cardiovascular disease and atherogenic dyslipidemia, whose LDL-C is optimally treated.

Am Heart Journal 2010;161(3)

# Inclusion Criteria

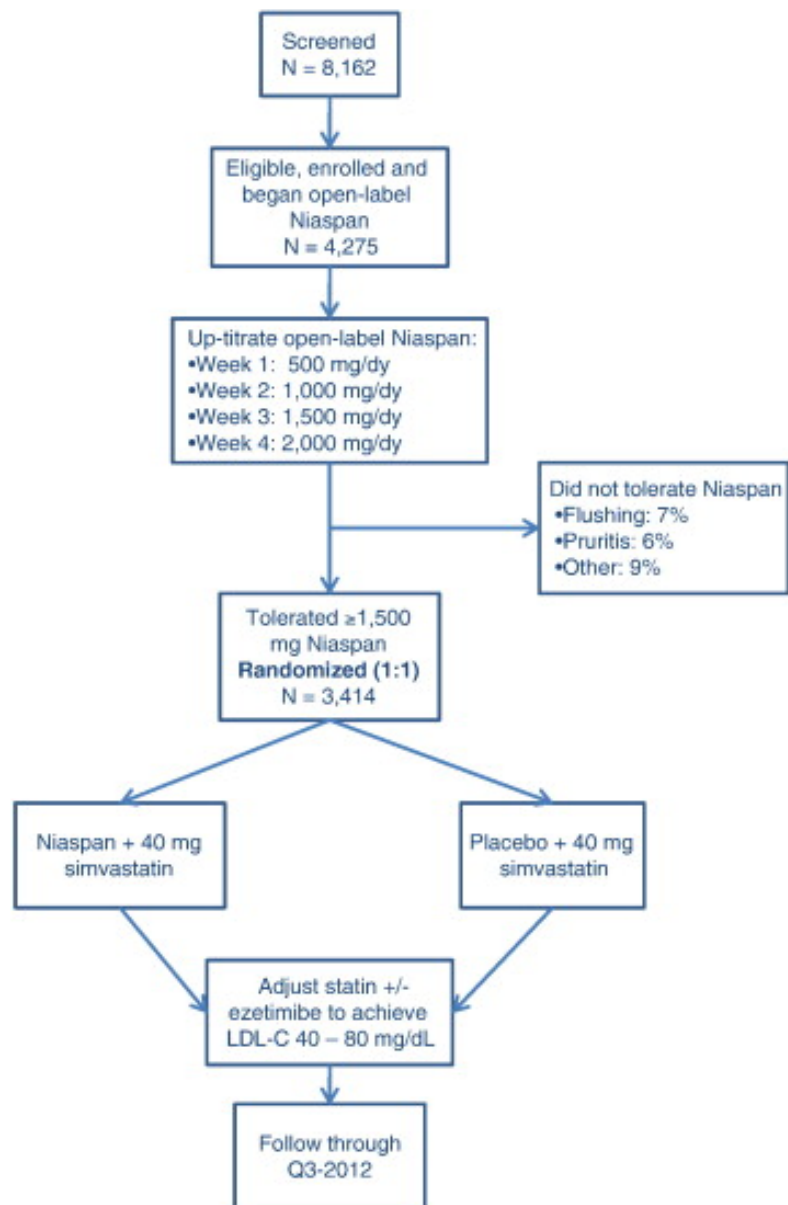
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- Men and women aged 45 y and older with:
  - established vascular disease
    - Documented CAD
    - Documented Cerebrovascular disease or carotid disease
  - atherogenic dyslipidemia
    - Off statins - LDL  $\leq$  4.7 mmol/L; HDL  $\leq$  1.0 mmol/L men or  $\leq$  1.3 mmol/L women; TG 1.7-4.5 mmol/L
    - On statin – HDL  $\leq$  1.1mmol/L men and  $\leq$  1.4 mmol/L women; TG 1.1 – 4.5 mmol/L

# Methods

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- Double – blind, randomized controlled trial
- Open – label run in period with niacin
- All received simvastatin +/- ezetimibe (1.0 – 2.1 mmol/L)
- randomized to long-acting niacin 1500-2000mg or placebo spiked with 50mg niacin





# Primary Endpoints

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- CHD death
- Non-fatal MI or stroke
- Hospitalizations for ACS
- Symptom driven Revascularization



# Results

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- 3, 414 participants
  - 85% men
  - Mean age 65
  - 34% DM
  - 71% HTN
  - 81% metabolic syndrome
  - 74% current or former smokers



# Results

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- Median Baseline LDL - 1.84mmol/L
- Median Baseline HDL - 0.9 mmol/L
- Median Baseline TG – 1.84 mmol/L
- 94% statins (at entry)
- 80% BB
- 90% ASA

# Results

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- Trial started Sept 2005
- The average follow-up was to be 4.6 years (30 months – 7 years)
- Trial stopped after 32 months of follow-up
  - Participants on niacin had increased HDL levels but did not have reduced primary endpoint
  - Results also showed increase in stroke with participants on niacin (1.6% vs 0.7%)



# What does it all Mean?

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- Increased risk of stroke?
  - Nine strokes occurred in participants who had stopped taking their niacin for at least 2 months and up to 4 years before their stroke.
- Benefit?

# Risk of Incident Diabetes with Intensive-Dose compared with Moderate-Dose Statin Therapy

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A Meta-Analysis

JAMA June 2011; 305(24)

# Background

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- WOSCOPS (2001)– less diabetes with pravastatin
- Jupiter (2008)– modest but significant increase in DM and A1c
- Meta-Analysis – Lancet 2010
  - Pravastatin, lovastatin – no increase
  - Simvastatin, rosuvastatin, atorvastatin - yes



# Objective

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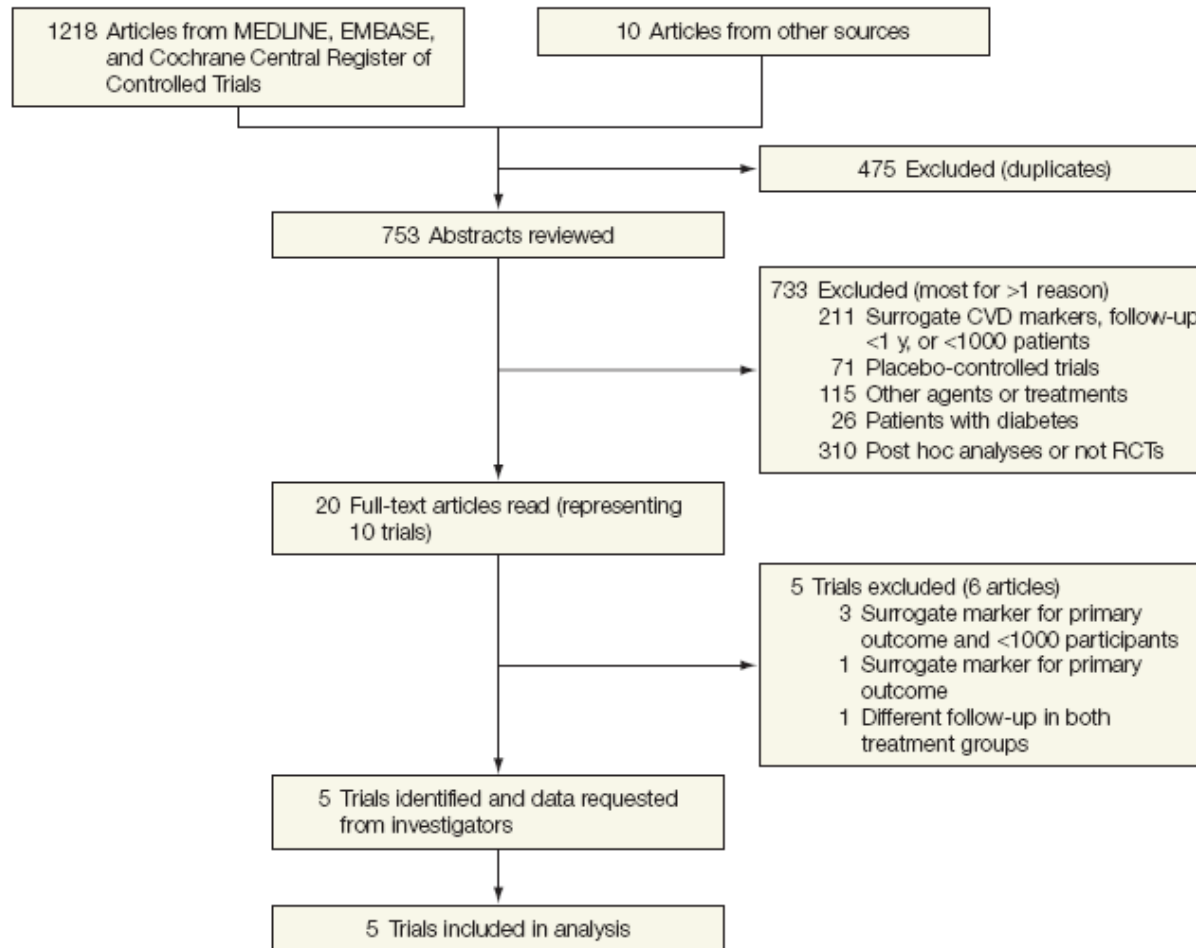
- To investigate whether intensive-dose statin therapy is associated with increased risk of new-onset diabetes compared with moderate-dose statin therapy.

# Methods

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- Published and unpublished data
- Large randomized end point statin trials
  - Designed to assess effect of intensive vs moderate dose therapy
- Length of follow-up minimum 1 year
- Searched MEDLINE, EMBASE and Cochrane Central Register

**Figure 1.** Flow Diagram of the Literature Search



CVD indicates cardiovascular disease; RCTs, randomized controlled trials.

## 5 trials included

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- Treating to New Targets (TNT) trial
- Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial
- Aggrastat to Zocor (A to Z) trial
- PROVE IT- TIMI 22 trial
- Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial



# End Points

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- Considered to have developed Diabetes if
  - Adverse event report of newly diagnosed diabetes during trial
  - Commenced glucose lowering medication during trial
  - Had 2 FPG values of 7 or greater during the trial

# Results

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- 32,752 nondiabetic participants
- Mean follow-up 4.9 years
- 2749 participants (8.4%) developed diabetes
  - 1449 assigned intensive-dose therapy
  - 1300 assigned moderate-dose therapy
- 6684 (20.4%) experienced a major CV event
  - 3134 assigned intensive-dose therapy
  - 3550 assigned moderate-dose therapy

# Results

## Incident Diabetes

PROVE IT-TIMI 22,<sup>18</sup> 2004

A to Z,<sup>17</sup> 2004

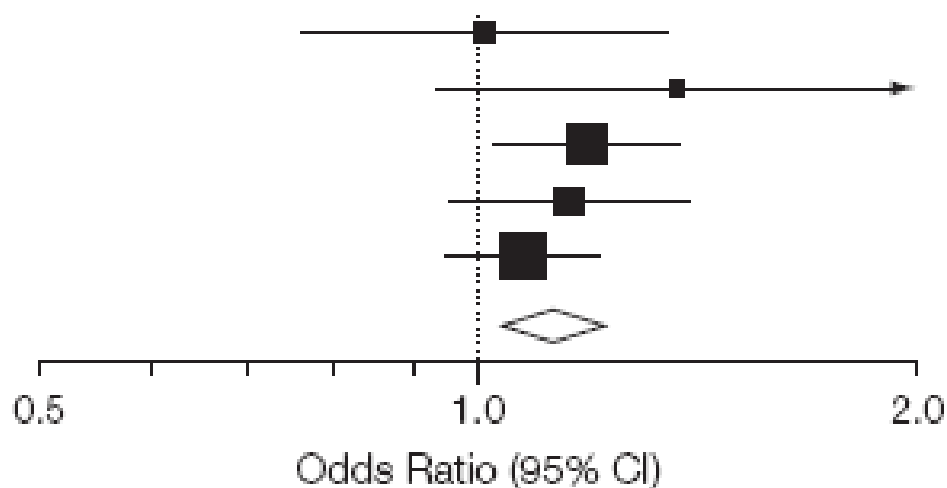
TNT,<sup>15</sup> 2005

IDEAL,<sup>16</sup> 2005

SEARCH,<sup>5</sup> 2010

Pooled odds ratio

Heterogeneity:  $I^2 = 0\%$ ;  $P = .60$



# Results

## Incident CVD

PROVE IT-TIMI 22,<sup>18</sup> 2004

A to Z,<sup>17</sup> 2004

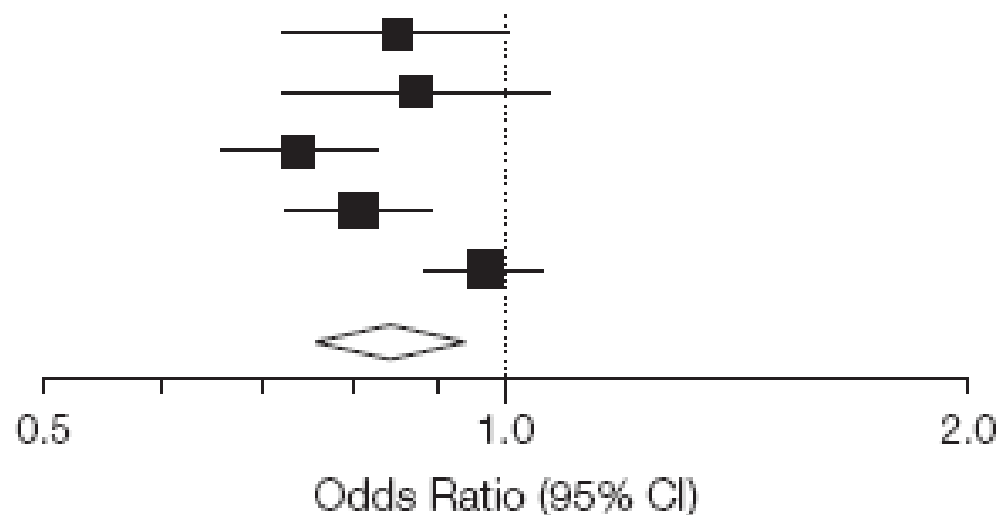
TNT,<sup>15</sup> 2005

IDEAL,<sup>16</sup> 2005

SEARCH,<sup>5</sup> 2010

Pooled odds ratio

Heterogeneity:  $I^2 = 74\%$ ;  $P = .00$



# Results

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- 2 additional cases of diabetes/1000 pt years
  - NNH 498
- 6.5 fewer CV events/1000 pt years
  - NNT 155
- 3 major CV events prevented for every 1 new case of diabetes

# Results

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- Subgroup analysis
  - Cardiovascular benefit consistent across all subgroups
    - Age, HDL, triglycerides, BMI, Fasting glucose
  - Odds of Developing Diabetes
    - Similar for Age, HDL, BMI and Fasting glucose
    - Higher in those with higher Triglycerides
    - Higher following ACS



# Mechanism? Questions?

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- May influence muscle or liver insulin action directly
- Animal studies – statin myopathy associated with development of muscle insulin resistance
- Generalized tendency or a specific group



# So What Does it Mean?

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- ❑ Not ready to put statins “in the water” just yet
- ❑ J-Predict trial
- ❑ Modest increase in CV risk in first decade of diabetes mixed with benefit of statin therapy still strongly favours statin therapy
- ❑ Will want to monitor glucose and A1c with use of statin (whether pt has diabetes or not)
- ❑ Adding adjunct lipid therapy



Questions?

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