Clinical Trials Overview
Lipid Intervention Trials

- Interpretation of clinical trials
- Early clinical trials
- Niacin trials
- Fibric acid derivative trials
- Omega-3 fatty acid trials
- Statin trials
- Ezetimibe trials
- Recent clinical trials
- Ongoing trials
Chapter 1

Study Designs and Epidemiologic Concepts
Evidence-based Medicine

- Integrates individual clinical experience (and patient values) with best available external clinical evidence to guide decisions about diagnosis, prognosis and treatment
  - Observational and laboratory research
  - Patient-centered clinical research
  - Outcomes studies to evaluate the efficacy and safety of therapeutic and preventive therapies


Types of Clinical Evidence

- Case series (no control group)
- Analytic (exposed vs. unexposed)
  - Cross-sectional surveys
  - Case-control
    - Single point in time
    - Nested within a cohort
  - Cohort (longitudinal follow-up)
- Intervention (clinical trials)

Each design has situations for which it may be the most appropriate approach, but each has its own strengths and weaknesses.
Hierarchy of Evidence (Low to High)

- Anecdotes/expert opinion
- Case series
- Cross-sectional
- Case-control
- Longitudinal observation
- Randomized clinical trials
  - Special considerations
    - Subgroup analyses in clinical trials
    - Meta-analyses (observational and RCTs)
      - Depend on the quality of the underlying data
Clinical Intervention Studies

• The randomized, controlled trial is the “gold standard” for evaluation of medical interventions
  – Exposure is assigned
  – Least susceptible to known and unknown sources of bias and confounding
  – Best for minimizing selection bias, but is prone to other types of biases

• Validity and generalizability rely on:
  – Appropriate selection of study participants
  – Random subject assignment to treatments
  – Blinding and use of a placebo or sham intervention where practical
Elements of a Clinical Trial

- Explicit, focused research question
- Objective outcomes
- Established and accepted methods
  - Sufficient control(s)
  - Blinding (where possible)
  - Accurate measurement tools
  - Adequate statistical power

Types of Hypotheses

• Superiority
  – $A > B$

• Non-inferiority
  – $A \geq B$

• Equivalence
  – $A = B$
Analysis Sets

• Intent-to-treat analysis
  – Analysis based on the initial treatment intent, not on the treatment eventually administered
  – All subjects randomized are analyzed
  – Subjects are part of their assigned group whether or not they actually received the treatment, adhered to the treatment regimen, or even received the opposite treatment
Interpretation of Study Results

Three main factors should be assessed in the interpretation of study results:

1. **Chance**
   - Was this a random chance finding?

2. **Bias**
   - Was there a non-random error that resulted in an incorrect estimate of the effect of the exposure?

3. **Confounding**
   - Is it possible that an observed association between the exposure and the response was due to the effects of differences other than the exposure under study?
P-Values and Confidence Intervals
(Assessment of Chance)

• P-value represents the probability that an association occurred due to chance
  – P = 0.05 = 5% or 5/100 chance that the association occurred due to random variation (be careful about dichotomous thinking)

• Confidence interval
  – 95% CI = range within which one can be 95% confident that the true value lies
  – Smaller 95% CI indicates greater precision in the point estimate of the effect (large sample size, many events)
Statistical Power and Sample Size

• Type I statistical error
  – Finding “significance” when a relationship is due to random variation (false positive)

• Type II statistical error
  – Failing to find significance when it is truly present
  – Insufficient power (false negative)

• Statistical power
  – Likelihood of finding significance if it is truly present
  – 1 – power = likelihood of a type II error
  – Power usually set at 80% or 90% for a 2-sided p-value of 0.05 for a given set of assumptions when planning a study (10-20% chance of a type II error)
Statistical Power and Sample Size

• Ways to increase statistical power
  – Increase sample size
  – Increase precision of measurements
    • Dual x-ray absorptiometry vs. skin-folds for body fat
    • Average values from multiple days to minimize the influence of biological variation (e.g., hs-CRP, TG, fibrinogen)
      – LDL-C example: 19%, 10%, 9% SD
  – Study a higher risk population
    • A greater number of events will increase power in clinical event studies
Measures of Association

• Odds ratio
  – Odds of exposure in cases/odds of exposure in controls; odds of exposure = yes/no
    • Obesity in DM cases vs. non-DM controls
    • OR = (80/20)/(20/80) = 4/0.25 = 16.0
  – Odds ratios are typically used for non-longitudinal studies, but can be calculated for longitudinal studies (not incorrect to do so)

• Relative risk (RR) or hazard ratio (HR) is calculated as the ratio of the incidence of those exposed to the incidence of those not exposed
  – RR uses cumulative incidence
  – HR uses incidence rates (person-time units of observation)

\[
\text{RR or HR} = \frac{\text{Incidence in those Exposed}}{\text{Incidence in those Not Exposed}}
\]
Prevalence and Incidence

- **Prevalence** – the fraction of a sample or population that has the characteristic of interest

- There are two types of incidence measures:
  - **Cumulative Incidence** – the proportion of people who become diseased during a specific *time period*
  - **Incidence Rate** – the number of new cases of a disease per total *person-time* of observation
    - Person-time refers to the sum of all individuals' time under observation
    - Following 1,000 women for 5 years provides 5,000 woman-years
    - Following 5,000 women for 1 year provides 5,000 woman-years
Evolution of NHLBI Supported Guidelines

- **NCEP ATP I**
  - 1988
  - Framingham
  - MRFIT
  - LRC-CPPT
  - Coronary Drug Project
  - Helsinki Heart Study
  - CLAS

- **NCEP ATP II**
  - 1993
  - Angiographic trials
    - (FATS, POSCH, SCOR, STARS, Ornish, MARS)
  - Meta-analyses
    - (Holme, Rossouw)

- **NCEP ATP III**
  - 2001
  - 4S
  - WOSCOPS
  - CARE
  - LIPID
  - AFCAPS/TexCAPS

- **NCEP ATP III Update 2004**
  - HPS
  - PROVE-IT
  - ASCOT-LLA
  - PROSPER
  - ALLHAT-LLT

- **AHA/ACC Update 2006**
  - TNT
  - IDEAL
  - ACCORD

NHLBI = National Heart, Lung, and Blood Institute
NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel
AHA = American Heart Association
ACC = American College of Cardiology

Evolution of NHLBI Supported Guidelines

NCEP ATP I 1988
NCEP ATP II 1993
NCEP ATP III 2001
NCEP ATP III Update 2004
AHA/ACC Update 2006

More Intensive Treatment Recommendations

Framingham
MRFIT
LRC-CPPT
Coronary Drug Project
Helsinki Heart CLAS

Angiographic trials
(FATS, POSCH, SCOR, STARS, Ornish, MARS)
Meta-analyses
(Holme, Rossouw)

4S
WOSCOPS
CARE
LIPID
AFCAPS/TexCAPS

HPS
PROVE-IT
ASCOT-LLA
PROSPER
ALLHAT-LLT

TNT
IDEAL
ACCORD

NHLBI = National Heart, Lung, and Blood Institute.
NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.
AHA = American Heart Association.
ACC = American College of Cardiology.

Lyon Diet Heart Study

![Graph showing event rates for Death (24 vs. 14), Cardiac Mortality (19 vs. 6), Non Fatal MI (25 vs. 8), and Cancer (17 vs. 7).](image)

Numbers in bars are # of events
POSCH Trial

Effect of Partial Ileal Bypass Surgery on Mortality and Morbidity from Coronary Heart Disease in Patients with Hypercholesterolemia

Figure 1. Total Plasma Cholesterol Levels in the Control and Surgery Groups.

Values are means with 95 percent confidence intervals. The difference between the groups at each follow-up interval was significant (P<0.0001).

Figure 2. Confirmed Myocardial Infarction and Death Due to Atherosclerotic Coronary Heart Disease as a Combined End Point (“Event”) in the Study Groups.

The difference between the groups was significant (P<0.001). The numbers of patients at risk for an event are shown at two-year intervals.

Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

3806 men aged <60 yr with total cholesterol ≥265 mg/dL and high LDL-C, initially free of coronary disease

Followed 7.4 yr

Cholestyramine 24 g/day vs. placebo

LDL-C –20.3%
HDL-C +1.6%

19% reduction in CHD death and/or nonfatal MI

Chapter 2

Overview of Key Lipid Trials — Part 1
Coronary Drug Project

• The Coronary Drug Project was a randomized, double-blind, placebo-controlled trial (1966–1974)
• 5 lipid-modifying agents
  • Low-dose estrogen
  • High-dose estrogen
  • Dextrothyroxine
  • Clofibrate
  • Niacin

Coronary Drug Project. JAMA. 1975;231:360-381.
Coronary Drug Project

- Participants 8341 men with previous MI and hypercholesterolemia
- Only the clofibrate and niacin groups completed the study (total follow-up ranged from 5 to 8.5 years per patient; mean follow-up was 6.2 years)
- There were 2789 patients in the placebo group and 1119 patients in the niacin group
- The primary endpoint was total mortality
- Total mortality was similar in the two groups at 5 years (24.4% with niacin versus 25.4% with placebo, $P = NS$)
- Niacin did provide a significant reduction in recurrent nonfatal MI (27% reduction, $P < 0.004$)
- Follow-up 9 years after end of trial: 11% lower total mortality in niacin (3 g daily) group

Coronary Drug Project. JAMA. 1975;231:360-381.
Familial Atherosclerosis Treatment Study (FATS)

• Angiographic trial to assess the effect of combination lipid-influencing therapy in patients with a history of CAD
• 146 men (aged ≤ 62 yr) with CAD and family history of CAD (average stenosis: 34%)
• Apo B >125 mg/dL

Treatment Groups
• Lovastatin 20 mg BID + colestipol 10 g TID
• Niacin 1 g QID + colestipol 10 g TID
• Conventional therapy

FATS: LDL-C and Other Lipid Changes with Combination therapy

Note: All changes for niacin plus colestipol were statistically significant compared to baseline


www.lipid.org
Familial Atherosclerosis Treatment Study (FATS): Angiographic Results

N = 120 men with CAD

- Conventional Therapy: 46 patients, 11 with progression, 35 with regression
- Colestipol + Lovastatin: 21 patients, 32 with regression
- Colestipol + Niacin: 25 patients, 39 with regression

*P < 0.005 versus conventional therapy


2.5 year follow-up
FATS: 10-Year Follow-Up with Triple Therapy Clinical End Points

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Event Rate, %</th>
<th>Reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Care (n = 101)</td>
<td>19.8</td>
<td>93%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Colestipol + Lovastatin + Niacin (n = 75)</td>
<td>18.8</td>
<td>67%</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

HDL-Atherosclerosis Treatment Study (HATS)

- 160 patients with measurable CAD by angiography
- HDL-C ≤35 mg/dL and LDL-C ≤145 mg/dL
- Randomized to 4 treatment groups
  - Placebo (PLAC)
  - Antioxidant vitamins (E, C, β-carotene, selenium) (VIT)
  - Simvastatin 10-20 mg + niacin 2-4 g (St/N)
  - VIT + St/N
- Repeat quantitative angiography after 3 years

HDL-Atherosclerosis Treatment Study (HATS): Clinical End Points

Quantitative Coronary Angiography

CVD Events

*P ≤ 0.005 vs. placebo
Mean dose of simvastatin was 13 mg/day
Mean dose of niacin was 2400 mg/day

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 $\geq 45$ 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
Study Design

Open-Label Run-In: Up-Titrate Niacin from 500mg to 2,000mg/day in 4-8 weeks

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

www.lipid.org
**AIM-HIGH: Niacin Plus Statin to Prevent Vascular Events**

**Inclusion Criteria**

- Age ≥45
- History of vascular disease
- Atherogenic dyslipidemia
  - LDL-C ≤160 mg/dL
  - HDL-C ≤40 mg/dL men or ≤50 mg/dL women
  - TG ≥150 mg/dL ≤400 mg/dL
- For patients entering the trial on a statin
  - HDL-C ≤42 mg/dL men or ≤53 mg/dL women
  - TG ≥125 mg/dL ≤400 mg/DL

**Primary Endpoint**

Composite Endpoint for first
- CHD death
- nonfatal MI
- ischemic stroke
- hospitalization for high-risk non-STEMI ACS

**Secondary Endpoint**

- composite of CHD death, nonfatal MI, or ischemic stroke out to common date

**ER niacin 500/1000/1500/2000 mg and simvastatin 40 mg**

4-8 week run-in with niacin dose increased each week

**ER niacin 2000 or 1500 mg and simvastatin 20/40/80 mg***

3-5 years

* dependent on LDL-C levels, ezetimibe 10 mg may be added as well

[www.lipid.org](http://www.lipid.org)
# Baseline Lipids (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>On Statin</th>
<th>Off Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>(n=3,196)</td>
<td>(n=218)</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>
</tbody>
</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>
</tr>
<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>
</tr>
</tbody>
</table>
## AIM-HIGH Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Plus Statin (N = 1696)</th>
<th>Extended-Release Niacin Plus Statin (N = 1718)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (N = 1696)</td>
<td>Baseline (N = 1718)</td>
</tr>
<tr>
<td></td>
<td>Year 1 (N = 1554)</td>
<td>Year 1 (N = 1561)</td>
</tr>
<tr>
<td>LDL-C (Mean mg/dL)</td>
<td>75.8±24.3</td>
<td>76.2±25.7</td>
</tr>
<tr>
<td></td>
<td>70.4±18.9</td>
<td>66.4±19.9</td>
</tr>
<tr>
<td>Triglycerides (Median mg/dL)</td>
<td>162</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>121</td>
</tr>
<tr>
<td>HDL-C (Mean mg/dL)</td>
<td>35.3±5.9</td>
<td>34.8±5.9</td>
</tr>
<tr>
<td></td>
<td>38.4±7.6</td>
<td>43.6±10.9</td>
</tr>
<tr>
<td>Apolipoprotein AI (Mean mg/dL)</td>
<td>123.7±16.2</td>
<td>122.5±16.3</td>
</tr>
<tr>
<td></td>
<td>127.4±17.5</td>
<td>132.2±20.1</td>
</tr>
<tr>
<td></td>
<td>127.4±17.5</td>
<td>132.2±20.1</td>
</tr>
</tbody>
</table>

Primary Outcome

**Monotherapy**

**Combination Therapy**

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

Cumulative % with Primary Outcome

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>N at risk Monotherapy</th>
<th>N at risk Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>2</td>
<td>1381</td>
<td>1366</td>
</tr>
<tr>
<td>3</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>4</td>
<td>436</td>
<td>428</td>
</tr>
</tbody>
</table>

www.lipid.org
So What Happened?

• In this aggressively managed group of patients was there no residual risk, hence no need for niacin?
• Prior studies done with Niacin IR, perhaps Niacin ER ineffective?
• Placebo effect?
• Niacin did not lower Apo B or LDL-P?
• HDL raising not effective if LDL-P or Apo B at goal?
• Perhaps raising HDL-C with no impact on HDL-P with low ApoB/LDL-P levels is not effective?
• Diabetes risk??/CVD
• Stroke? No prior signals. ? AFIB?
• “The Surprising AIM-HIGH Results Are Not Surprising When Viewed Through a Particle Lens” (Otvos JCL 2011)
ARBITER* 2: Effect of ER-Niacin 1000 mg hs Added to Statin on Carotid IMT in CAD Patients

- 167 patients with known CAD, mean age 67 yr
- Extended-release niacin 1000 mg hs (at bedtime) vs. placebo added to background statin Rx (all participants on statin at baseline, average duration 4.8 ± 4.3 y, most on simvastatin ≥20 mg)
- Primary endpoint: change in CIMT at 1 year
- HDL-C 40 mg/dL → 47 mg/dL
- Baseline CIMT: 0.868 mm (placebo), 0.893 mm (niacin)

* Arterial Biology for Investigation of Treatment Effects of Reducing Cholesterol

Fibric Acid Derivative Trials

- Helsinki Heart Study
- VA-HIT
- DAIS
- FIELD
- ACCORD
Helsinki Heart Study

- 4,081 men aged 40-55 years with non-HDL-C ≥200 mg/dL, initially free of coronary disease
- LDL-C –11%, HDL-C +11%
- 34% reduction in CHD endpoints
- Greatest benefits when triglyceride high or HDL-C low
- LDL-C/HDL-C >5.0 and triglycerides >200 mg/dL: risk was reduced by 71%

Veterans Affairs HDL Intervention Trial (VA-HIT)

- 2,531 men with CAD
  - HDL-C ≤ 40 (mean 32)
  - LDL-C ≤ 140 (mean 111)
  - Triglycerides ≤ 300 (mean 161)
- 25% diabetic
- 57% hypertensive
- BMI 29 kg/m²

- Followed for MI or Coronary death over 5 years

- Gemfibrozil 600 mg bid
- Placebo


www.lipid.org
VA-HIT: Gemfibrozil vs. Placebo in Patients with Low HDL-C

Alternative Measures of LDL and HDL as Predictors of CHD Events in VA-HIT

Adjusted for treatment, age, hypertension, smoking, BMI, and diabetes

DAIS: Reduction of Angiographic Progression of CAD in Patients With Diabetes

**Placebo** (n = 211)

- 42% Reduced Progression
- \( P = 0.020 \)

**Fenofibrate** (n = 207)

- 25% Reduced Progression
- \( P = 0.171 \)
- 40% Reduced Progression
- \( P = 0.029 \)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)
Study Design

- 5-year study against a background of usual care, including the option to add other lipid-lowering therapies

Fenofibrate 200 mg/day, n = 4895
+Other lipid-lowering therapies

Placebo, n = 4900
+Other lipid-lowering therapies

9795 Type 2 Diabetes Patients
No clear indication for lipid-lowering therapy at baseline

5 Years or 500 CHD Events

# FIELD: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 4900)</th>
<th>Fenofibrate (n = 4895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>No Prior CVD, %</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Lipid parameters, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>195</td>
<td>195</td>
</tr>
<tr>
<td>LDL-C</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>TG</td>
<td>153</td>
<td>154</td>
</tr>
<tr>
<td>Dyslipidemic*, %</td>
<td>37</td>
<td>39</td>
</tr>
</tbody>
</table>

*TG >150 mg/dL and HDL-C <40 mg/dL for men or <50 mg/dL for women

**FIELD: Primary and Secondary Endpoints**

11% Reduction  
*Placebo: 5.9  
Fenofibrate: 5.2  
P = 0.16*

24% Reduction  
*Placebo: 4.2  
Fenofibrate: 3.2  
P = 0.01*

19% Increase  
*Placebo: 1.9  
Fenofibrate: 2.2  
P = 0.22*

11% Reduction  
*Placebo: 13.9  
Fenofibrate: 12.5  
P = 0.035*

21% Reduction  
*Placebo: 7.4  
Fenofibrate: 5.9  
P = 0.003*

*Nonfatal MI and CHD death  
†CHD events, stroke, CVD death, revascularizations*

FIELD: Total CVD Events in Patient Subgroups

Patients With Low HDL-C*

ARR = 2.1%
NNT = 48

14% Reduction
P = 0.02

Patients With Dyslipidemia†

14% Reduction
P = 0.06
NNT = 44

*<40 mg/dL (men) and <50 mg/dL (women) at baseline
†Triglycerides ≥150 mg/dL and low HDL-C at baseline

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study

- **Question:** Would statin plus a fibrate as compared with statin monotherapy reduce CVD in diabetics at high risk for CVD?
- 5518 patients with type 2 DM treated with open label simvastatin were treated with either masked fenofibrate or placebo
- **Primary outcome measure:** nonfatal MI, nonfatal stroke, or death from CV causes
- **Follow-up:** 4.7 years

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study

• Results: Annual primary outcome was 2.2% in fenofibrate group and 2.4% in placebo group (NS)
• Annual rate of death was 1.5% in fenofibrate group and 1.6% in placebo group (NS)
• Prespecified subgroup analysis suggested heterogeneity in treatment according to sex, with a benefit for men and possible harm for women ($P = 0.01$ for interaction)
• Possible benefit seen in fenofibrate group if baseline triglycerides high (>204 mg/dL) and HDL-C low (<34 mg/dL): primary outcome rate 12.4% in fenofibrate group vs. 17.3% in placebo ($P = 0.057$ for interaction)

Primary Outcome & Total Mortality

Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Primary Outcome

Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Total Mortality

## Primary Outcome By Treatment Group and Baseline Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate % Events (# in grp)</th>
<th>Placebo % Events (# in grp)</th>
<th>Feno to Placebo Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.6% (2765)</td>
<td>11.3% (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-c Tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=84 mg/dl</td>
<td>9.4% (938)</td>
<td>12.2% (891)</td>
<td></td>
<td>0.1212</td>
</tr>
<tr>
<td>85-111 mg/dl</td>
<td>9.9% (934)</td>
<td>11.2% (922)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=112 mg/dl</td>
<td>12.4% (877)</td>
<td>10.6% (927)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-c Tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=34 mg/dl</td>
<td>12.2% (964)</td>
<td>15.6% (905)</td>
<td></td>
<td>0.2374</td>
</tr>
<tr>
<td>35-40 mg/dl</td>
<td>10.1% (860)</td>
<td>9.5% (866)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=41 mg/dl</td>
<td>9.1% (925)</td>
<td>9.0% (965)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride Tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=128 mg/dl</td>
<td>9.9% (891)</td>
<td>11.3% (939)</td>
<td></td>
<td>0.6422</td>
</tr>
<tr>
<td>129-203 mg/dl</td>
<td>10.5% (924)</td>
<td>9.9% (913)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=204 mg/dl</td>
<td>11.1% (934)</td>
<td>12.8% (888)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trig/HDL combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG204+/HDL&lt;=34</td>
<td>12.4% (485)</td>
<td>17.3% (456)</td>
<td></td>
<td>0.0567</td>
</tr>
<tr>
<td>All Others</td>
<td>10.1% (2264)</td>
<td>10.1% (2284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c &lt;= 8.0</td>
<td>8.7% (1324)</td>
<td>10.6% (1335)</td>
<td></td>
<td>0.2045</td>
</tr>
<tr>
<td>A1c 8.1+</td>
<td>12.2% (1435)</td>
<td>11.9% (1415)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statin Trials

- AFCAPs/TexCAPs
- 4S
- ALLIANCE
- HPS
- PROVE-IT
- ASCOT-LLA

- CARDS
- TNT
- EXPLORER
- METEOR
- JUPITER
- SEARCH
AFCAPS/TexCAPS Study Design

• **Design:**
  – Randomized, double-blind, placebo-controlled trial

• **Setting:**
  – Outpatient clinics in Texas

• **Participants:**
  – 5608 men and 997 women with baseline average TC (221 mg/dL) and LDL-C (150 mg/dL) and below-average HDL-C (37 mg/dL)

• **Intervention:**
  – Lovastatin (20-40 mg daily - to achieve an LDL-C of <110 mg/dL) or placebo in addition to a low-saturated fat, low-cholesterol diet

Primary Endpoint

• First Acute Major Coronary Event defined as:
  – Unstable Angina Pectoris*
  – Fatal or Non-fatal MI
  – Sudden Cardiac Death

*Unstable Angina Endpoint Criteria
Clinical history with hospitalization, reversible ischemic ECG changes, + thallium ETT, cardiac catheterization: > 90% stenosis in major epicardial coronary artery

Primary Endpoint ~ First Acute Major Coronary Event*

*Includes unstable angina, fatal and non-fatal MI & sudden cardiac death

37% Risk Reduction
(P < 0.001)

Scandinavian Simvastatin Survival Study (4S) Objectives

• To investigate whether long-term simvastatin therapy reduces total mortality and coronary events in post-MI and/or angina patients with elevated cholesterol

4S: Design

- Double-blind, randomized, placebo-controlled trial:
  - 94 centers in 5 countries
  - 4,444 men and women 35 to 70 years of age
  - **Inclusion criteria**: Prior MI and/or angina pectoris
  - **Total cholesterol**: 212-309 mg/dL
  - **Follow-up**: until 440 deaths occurred

4S: Treatment Schedule

Simvastatin 20 mg/day or matching placebo

Increased to 40 mg/day if TC exceeded 200 mg/dL

Study goal:
TC 116-200 mg/dL
4S Primary Endpoint: Overall Survival

4S: Changes in Lipoprotein Levels

Simvastatin vs. placebo at study end

4S: Summary of Key End-point Results

Simvastatin Better

- Total mortality
- CAD mortality
- Major coronary events
- PTCA/CABG
- Event-free survival

Placebo Better

Relative risk (95% CI)

- Reduced
- Increased

Total mortality: $P = 0.0003$
Major coronary events: $P < 0.00001$
PTCA/CABG: $P < 0.00001$
Event-free survival: $P < 0.00001$

Aggressive Lipid-Lowering Initiation Abates New Events (ALLIANCE): Study Design

• Usual care is the lipid treatment program prescribed by the patient’s primary care physician and could include diet, behavior modification, and antihyperlipidemic medication (including atorvastatin after 1997).
• Two thirds of patient were receiving lipid-lowering therapy at baseline.

MCHO = managed care organizations; VA = Veterans Administration facilitates database

ALLIANCE: Primary End Point* Reduced Versus Usual Care

*Time to composite end point of cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, or unstable angina requiring hospitalization

Heart Protection Study (HPS): Eligibility

- Increased risk of CHD death due to prior disease
  - MI or other CHD
  - Occlusive disease of non-coronary arteries, or
  - Diabetes mellitus or treated hypertension

- Age 40-80 years

- Total cholesterol >3.5 mmol/L (>135 mg/dL)

- Statin or vitamins not considered clearly indicated or contraindicated by patient’s own doctors

**HPS:**

Major Vascular Events by Prior Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>SIMVASTATIN</th>
<th>PLACEBO</th>
<th>Rate ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10269)</td>
<td>(10267)</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>999 (23.5%)</td>
<td>1250 (29.4%)</td>
<td>STATIN better</td>
</tr>
<tr>
<td>Other CHD (not MI)</td>
<td>460 (18.9%)</td>
<td>591 (24.2%)</td>
<td>PLACEBO better</td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>172 (18.7%)</td>
<td>212 (23.6%)</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>327 (24.7%)</td>
<td>420 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>276 (13.8%)</td>
<td>367 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

24% SE 3 reduction
(2P < 0.00001)

### HPS: Vascular Events by LDL-C

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>STATIN</th>
<th>PLACEBO</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10269)</td>
<td>(10267)</td>
<td>STATIN better</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td>STATIN worse</td>
</tr>
<tr>
<td>&lt; 100 (2.6 mmol/L)</td>
<td>285</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>≥ 100 &lt; 130</td>
<td>670</td>
<td>881</td>
<td>24% SE 2.6 reduction</td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/L)</td>
<td>1087</td>
<td>1365</td>
<td>(2P&lt;0.00001)</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042</td>
<td>2606</td>
<td></td>
</tr>
<tr>
<td>(19.9%)</td>
<td>(25.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Het\(\chi^2\) = 0.8

Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE IT –TIMI 22): Study Design

4162 patients with ACS <10 days prior

ASA + standard medical therapy

Double-blind

Standard therapy (Pravastatin 40 mg) Intensive therapy (Atorvastatin 80 mg)

2x2 factorial: gatifloxacin vs placebo

Duration: mean 2-year follow-up (>925 events)

Primary end point: death, MI, documented unstable angina requiring hospitalization, revascularization (>30 days after randomization), or stroke

ACS = acute coronary syndrome; ASA = aspirin

Changes in LDL-C may differ from previous trials
25% of patients were receiving statins before ACS event
ACS response lowers LDL-C from the true baseline

PROVE IT: All-Cause Death or Major Cardiovascular Events in All Randomized Subjects

ASCOT-LLA: The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm

Rationale:
Prior to the study, the potential benefit of adding lipid-lowering therapy to antihypertensive regimens in patients with low to moderately elevated cholesterol levels was not known.

Study Objective:
To compare the effects of atorvastatin 10 mg with placebo on the combined end point of nonfatal MI and fatal CHD in hypertensive patients with total cholesterol levels 250 mg/dL (6.5 mmol/L) or less

ASCOT-LLA: Primary End Point of Nonfatal MI and Fatal CHD

Atorvastatin reduced the risk of nonfatal MI and fatal CHD

- Atorvastatin 10 mg (100 events)
- Placebo (154 events)

36% relative risk reduction

HR = 0.64 (0.50–0.83)

P = .0005

Collaborative AtoRvastatin Diabetes Study (CARDS)

- Collaboration in the UK with BDA and NHS
- Type 2 diabetes
- No prior MI or CHD, CVA, or severe PVD
- LDL-C ≤160 mg/dL (4.4 mmol/L)
- TG ≤600 mg/dL (6.78 mmol/L)
- ≥1 additional RF
  - HTN
  - Retinopathy
  - Albuminuria
  - Smoker

- Primary end point: time to first major CV event (CHD death, nonfatal MI, revascularization, stroke)
- Secondary end points: total mortality, any cardiovascular end point, lipids, and lipoproteins

Atorvastatin 10 mg

Placebo

2,838 patients


BDA=British Diabetic Association; NHS=National Health Service; CVA= cerebrovascular accident; PVD=peripheral vascular disease; RF=risk factors; HTN=hypertension.
CARDS: Lipid Levels by Treatment

TC (mg/dL)
Average difference 26%
54 mg/dL (1.4 mmol/L) P<.0001

LDL-C (mg/dL)
Average difference 40%
46 mg/dL (1.2 mmol/L) P<.0001

0 1 2 3 4 4.5
Years of Study

0 80 120 160
TC (mg/dL)

0 40 80 120 160
LDL-C (mg/dL)

Placebo
Atorvastatin

CARDS: Effect of Atorvastatin on the Primary End Point of Major CV Events Including Stroke

Relative Risk Reduction 37% (95% CI, 17-52)  
*P*=.001

**Cumulative Hazard (%)**

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1410</td>
<td>1428</td>
</tr>
<tr>
<td>1</td>
<td>1351</td>
<td>1392</td>
</tr>
<tr>
<td>2</td>
<td>1306</td>
<td>1361</td>
</tr>
<tr>
<td>3</td>
<td>1022</td>
<td>1074</td>
</tr>
<tr>
<td>4</td>
<td>651</td>
<td>694</td>
</tr>
<tr>
<td>4.75</td>
<td>305</td>
<td>328</td>
</tr>
</tbody>
</table>

Treating to New Targets (TNT): Study Design

- 10,001 patients with clinically evident CHD and LDL-C <130 mg/dL while taking atorvastatin 10 mg daily
- Atorvastatin 80 mg vs. 10 mg, randomized, double-blind, placebo-controlled trial over 5 years
- Primary end point: time to first major CV event (CHD death, non-procedural myocardial infarction, resuscitation after cardiac arrest, or stroke)

Treating to New Targets (TNT): LDL-C Results and Primary Endpoint

EXPLORER

Examination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe vs. Rosuvastatin alone

- Six week open-label, randomized, multicenter, parallel-group study
- LDL \(\geq 160 \text{ mg/dL but} < 250 \text{ mg/dL}\)
- Patients were required to have history of CHD or clinical evidence of atherosclerosis or CHD equivalent (10-year CHD risk score of \(>20\%\))
- Fasting triglycerides \(<400 \text{ mg/dL}\)
- Rx: Rosuvastatin 40 mg/day or rosuvastatin 40 mg/day + ezetimibe 10 mg /day
- Primary end point: % patients achieving NCEP ATP III LDL-C goal

EXPLORER

Examination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe vs. Rosuvastatin alone

- Rosuvastatin + Ezetimibe (N = 239)
  - Baseline LDL-C: 189 mg/dL
  - % LDL-C drop: 70%
  - % achieved:
    - <100 mg/dL: 94.0%
    - <70 mg/dL: 79.6%

- Rosuvastatin Only (N = 230)
  - Baseline LDL-C: 190 mg/dL
  - % LDL-C drop: 57.1%
  - % achieved:
    - <100 mg/dL: 79.1%
    - < 70 mg/dL: 35.0%


Patients (n = 984)
Asymptomatic for CVD
Framingham risk score <10%
(excludes diabetes and CHD)
Maximum CIMT ≥1.2–<3.5 mm
Men 45–70 years
Women 55–70 years

Rosuvastatin 40 mg (n = 702)
(this is not an approved starting dose)

Placebo (n = 282)

Visit:  1  2  3  4  5  6  7  8  9  10  11  12  13
Week:  -6  -4  -2  0  6  13  26  39  52  65  79  91  104

Lipids  CIMT  Lipids  CRP  Lipids  CIMT  CIMT  Lipids  CIMT  Lipids

Run-in/eligibility  Safety

### METEOR: Changes in Lipid Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rosuvastatin 40 mg (n = 624)</th>
<th>Placebo (n = 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-48.8%</td>
<td>-0.3%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>8%</td>
<td>2.8%</td>
</tr>
<tr>
<td>TG</td>
<td>-15.7%</td>
<td></td>
</tr>
<tr>
<td>Total C</td>
<td>-33.7%</td>
<td></td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>-45.1%</td>
<td></td>
</tr>
</tbody>
</table>

*Time-weighted changes in lipid parameters during treatments were calculated; shown is the least squares mean change from baseline. All results rosuvastatin vs. placebo (P < 0.001).

Effect of Rosuvastatin 40 mg/day on Subclinical Carotid Atherosclerosis

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER)

- **Methods**: 17,802 men and women (38%) with LDL-C <130 mg/dL and hs-CRP ≥2 mg/L assigned to rosuvastatin 20 mg vs. placebo followed for occurrence of primary endpoint: Death from CV cause, MI, CVA, arterial revascularization, hospitalization for unstable angina

- **Results**: Study halted after 1.9 years (max 5.0). Rosuvastatin reduced LDL-C by 50% and hs-CRP by 37%, reduced primary endpoint by 44% ($P < 0.00001$)
  Reduced MI by 54% ($P = 0.0002$)
  Reduced stroke by 48% ($P = 0.002$)
  Reduced death from any cause by 20% ($P = 0.02$)
  Increased physician reported new diabetes 270 cases vs. 216 cases ($P = 0.01$) but no significant difference between groups in fasting glucose or glycosuria during the follow-up period.

Cumulative Incidence of Cardiovascular Events According to Study Group

A Primary End Point

B Myocardial Infarction, Stroke, or Death from Cardiovascular Causes

C Revascularization or Hospitalization for Unstable Angina

D Death from Any Cause

JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69

Placebo 251 / 8901
HR 0.56, 95% CI 0.46-0.69

P < 0.00001

Number Needed to Treat (NNT<sub>5</sub>) = 25

- 44 %

JUPITER

5-Year NNT Values for Primary Prevention of CVD

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER): Editorial

“The proportion of participants with hard cardiac endpoints (MI, CVA, death from CV disease) in JUPITER was reduced from 1.8% (157 of 8901 subjects) in the placebo group to 0.9% (83 of the 8901 subjects) in the rosuvastatin group; thus, 120 participants were treated for 1.9 years to prevent one event.”

“JUPITER provides yet more evidence about the effectiveness of statin therapy in reducing cardiovascular risk, even among persons who would not currently be considered for pharmacotherapy.”

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)

- **Population**: 12,064 MI survivors
- **Treatment**: Simvastatin 20 mg vs. 80 mg
  - Folic acid + vitamin B12 vs. placebo
- **Results**: no benefit from folic acid + vitamin B12
- 80 mg simvastatin lowered LDL-C 14 mg/dL more than the 20 mg dose; this resulted in a non significant 6% reduction in CV events
- **Myopathy**: 53 cases in 80 mg group vs. 3 in 20 mg group
Chapter 3

Overview of Key Lipid Trials — Part 2
ENHANCE Trial

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

John J.P. Kastelein, M.D., Ph.D., Fatima Akdim, M.D., Erik S.G. Stroes, M.D., Ph.D., Aeilko H. Zwinderman, Ph.D., Michiel L. Bots, M.D., Ph.D., Anton F.H. Stalenhoef, M.D., Ph.D., F.R.C.P., Frank L.J. Visseren, M.D., Ph.D., Eric J.G. Sijbrands, M.D., Ph.D., Mieke D. Trip, M.D., Ph.D., Evan A. Stein, M.D., Ph.D., Daniel Gaudet, M.D., Ph.D., Raphael Duivenvoorden, M.D., Enrico P. Veltri, M.D., A. David Marais, M.D., Ph.D., and Eric de Groot, M.D., Ph.D., for the ENHANCE Investigators*

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- 720 patients with familial hypercholesterolemia – most (81%) previously treated with statins randomly assigned to simvastatin 80 mg vs. simvastatin 80 mg + ezetimibe 10 mg for 2 years
- No difference in mean cIMT at the end of 2 years ($P = 0.64$)

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis (SEAS)

- 1873 patients with mild/moderate aortic stenosis
- Simvastatin 40 mg + ezetimibe 10 mg (s/e) vs. placebo (pl)
- Rx duration 52.2 months
- **Primary outcome:** Composite of major CV events including death from CV cause, aortic valve replacement, nonfatal MI, hospitalization for unstable angina, heart failure, CABG, PCI, nonhemorrhagic stroke

**Results:**
- **Primary outcome:** 333 (35.3%) s/e vs. 355 (38.2%) pl ($P = 0.59$)
- **Aortic valve replace:** 267 (28.3%) s/e vs. 278 (29.9%) pl ($P = 0.97$)
- **Ischemic CV events:** 148 s/e vs. 187 pl ($P = 0.02$)
- **Cancer:** 105 s/e vs. 70 pl ($P = 0.01$)

Stop Atherosclerosis in Native Diabetics Study (SANDS)

- 499 American Indian men and women aged 40 years or older with type 2 diabetes and no prior CVD events
- Randomized, open-label, blinded-to-end point, 3-year trial from April 2003-July 2007
- Primary end point was progression of atherosclerosis measured by common carotid artery intimal medial thickness (IMT)
- 2 treatment groups and targets (JNC VI)
  - Aggressive group (N=252)
    - SBP <115/75
    - LDL <70
  - Control group (N=247)
    - SBP<130/85
    - LDL <100

---

# SANDS

<table>
<thead>
<tr>
<th></th>
<th>Baseline A</th>
<th>Baseline S</th>
<th>36-month A</th>
<th>36-month S</th>
<th>A vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>104</td>
<td>104</td>
<td>72</td>
<td>104</td>
<td><em>P&lt;0.001</em></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128</td>
<td>133</td>
<td>117</td>
<td>129</td>
<td><em>P&lt;0.001</em></td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.808</td>
<td>0.797</td>
<td>0.796</td>
<td>0.837</td>
<td><em>P&lt;0.001</em></td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>41.2</td>
<td>40.5</td>
<td>38.9</td>
<td>39.4</td>
<td><em>P=0.03</em></td>
</tr>
</tbody>
</table>

Categorical Change in CIMT in SANDS Subgroups

Copyright ©2008 American College of Cardiology Foundation. Restrictions may apply.
SANDS - Summary

• Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes.

• Clinical cardiovascular events were lower than anticipated: 1.6/100 person years in aggressive group and 1.5/100 person years in the standard group (P = 0.87; no significant difference). Further follow-up is needed to determine whether long term CVD event rates will be lower with aggressive treatment of LDL-C and SBP in diabetes.

Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol–6 HDL and LDL Treatment Strategies (ARBITER 6–HALTS)

- 208 patients with CHD or CHD risk equivalents on long-term statin therapy (mostly simvastatin or atorvastatin) with LDL-C <100 mg/dL (baseline = 82) and HDL-C <50 mg/dL (men) and <55 mg/dL (women), randomly assigned to add either extended-release niacin (goal 2000 mg/day) or ezetimibe (10 mg/day)

- **Outcome of interest**: between-group difference in the change in CIMT at 14 months from baseline

ARBITER 6–HALTS - Results

- Niacin had a greater impact on HDL-C (+7.5 ± 9.2 mg/dL vs. –2.8 ± 5.7 mg/dL on ezetimibe)
- Ezetimibe had a greater impact on LDL-C (–17.6 ± 20.1 mg/dL vs. –10.0 ± 24.5 mg/dL on niacin)
- The change in CIMT from baseline to 14 months was significantly different between the niacin group and the ezetimibe group ($P = 0.003$).
- Niacin was associated with a significant reduction in CIMT between 8 and 14 months; no change was seen in the ezetimibe group.

ARBITER 6-HALTS: CIMT Results at 14 Months

The Study of Heart and Renal Protection (SHARP): Eligibility

• History of chronic kidney disease
  – not on dialysis: elevated creatinine on 2 occasions
    • Men: ≥1.7 mg/dL (150 µmol/L)
    • Women: ≥1.5 mg/dL (130 µmol/L)
  – on dialysis: hemodialysis or peritoneal dialysis
• Age ≥40 years
• No history of myocardial infarction or coronary revascularization
• Uncertainty: LDL-C lowering treatment not definitely indicated or contraindicated
• Randomized to 10/20 mg Eze-Simv vs. placebo

Adapted from the SHARP slides available at www.sharpinfo.org from the presentation made by Colin Baigent and Martin Landray on behalf of the SHARP Investigators at the American Society of Nephrology, Denver November 20, 2010.
SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P = 0.0022

Adapted from the SHARP slides available at [www.sharpinfo.org](http://www.sharpinfo.org) from the presentation made by Colin Baigent and Martin Landray on behalf of the SHARP Investigators at the American Society of Nephrology, Denver November 20, 2010.
# SHARP: Major Vascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n = 4650)</th>
<th>Placebo (n = 4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Any revascularization</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>16.5% SE 5.4 reduction (P = 0.0022)</td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>45 (1.0%)</td>
<td>37 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Other major vascular events</td>
<td>207 (4.5%)</td>
<td>218 (4.7%)</td>
<td>5.4% SE 9.4 reduction (P = 0.57)</td>
</tr>
<tr>
<td>Major vascular event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td>15.3% SE 4.7 reduction (P = 0.0012)</td>
</tr>
</tbody>
</table>

Adapted from the SHARP slides available at [www.sharpinfo.org](http://www.sharpinfo.org) from the presentation made by Colin Baigent and Martin Landray on behalf of the SHARP Investigators at the American Society of Nephrology, Denver November 20, 2010.
Analyses of Cancer Data from Three Ezetimibe Trials

- **Background**: Increase cancer risk in SEAS
- Compared SEAS with data from SHARP and IMPROVE-IT
- **Results**: No overall increase in risk of cancer (313 active Rx vs. 326 control – no significant excess cancer at any particular site. Among patients assigned to ezetimibe there were more cancer deaths (not significant: 97 vs. 78 in control group; $P = 0.07$) but fewer cases of cancer (not significant: 216 vs. 254 in control group; $P = 0.08$)
- **Conclusion**: Currently available data do not provide credible evidence of any adverse effect of ezetimibe on cancer risk.

Effects of Torcetrapib in Patients at High Risk for Coronary Events (ILLUMINATE)

- 15,067 patients at high cardiovascular risk received either torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.

- **Results:** There was an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; \( P = 0.001 \)) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; \( P = 0.006 \)).

ILLUMINATE – Results

Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE)

- Anacetrapib treatment had robust effects on HDL-C, LDL-C, non HDL-C and Lp(a) with sustained effects over 18 months.
- Anacetrapib had an acceptable side-effect profile with no effects on blood pressure, electrolytes or aldosterone.
- Within the power of the study, anacetrapib did not exhibit adverse cardiovascular effects seen with a prior CETP inhibitor.
- The long term safety and efficacy of anacetrapib will now be tested in a large clinical outcomes trial.

Safety of Anacetrapib in Patients with or at Risk for Coronary Heart Disease

Effects on LDL-C and HDL-C

**LDL-C**

-39.8% (p<0.001)

**HDL-C**

+138.1% (p<0.001)

Anacetrapib Had No Effect on BP

Anacetrapib Had No Effect on Key Safety Parameters

<table>
<thead>
<tr>
<th>Safety Parameters</th>
<th>Anacetrapib n (%) n/N (%)</th>
<th>Placebo n (%) n/N (%)</th>
<th>Absolute Difference (%) 95% CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium &gt; ULN</td>
<td>86/800 (10.7)</td>
<td>84/797 (10.5)</td>
<td>0.2 (-2.8, 3.2) 0.89</td>
</tr>
<tr>
<td>Chloride &gt; ULN</td>
<td>23/800 (2.9)</td>
<td>27/797 (3.4)</td>
<td>-0.5 (-2.3, 1.2) 0.56</td>
</tr>
<tr>
<td>Bicarbonate &gt; ULN</td>
<td>11/800 (1.3)</td>
<td>17/797 (2.1)</td>
<td>-0.8 (-2.2, 0.6) 0.25</td>
</tr>
<tr>
<td>Potassium &lt; LLN</td>
<td>38/800 (4.8)</td>
<td>38/797 (4.8)</td>
<td>-0.0 (-2.2, 2.1) 0.99</td>
</tr>
<tr>
<td>Consecutive elevations of ALT /or AST ≥ 3x ULN</td>
<td>1/800 (0.1)</td>
<td>8/797 (1.0)</td>
<td>-0.9 (-1.9, -0.2) 0.019</td>
</tr>
<tr>
<td>CK ≥ 10*ULN</td>
<td>0/800</td>
<td>2/797 (0.3)</td>
<td>-0.3 (-0.9, 0.2) 0.16</td>
</tr>
<tr>
<td>Any muscle symptom</td>
<td>32 (4.0)</td>
<td>28 (3.5)</td>
<td>0.5(-1.4, 2.4) 0.61</td>
</tr>
<tr>
<td>Aldosterone change from baseline (median +/-SD)</td>
<td>15.0 ± 46.5</td>
<td>13.5 ± 48.4</td>
<td>2.0 (-3.0, 7.0) 0.27</td>
</tr>
</tbody>
</table>

Antisense ‘Shoots the Messenger’

- Receptor = RNA
- Drug = Oligonucleotide
- Drug Receptor Binding Motif = Watson-Crick Hybridization
- Post Receptor Binding Events = Degradation/Inhibition of Receptor
Antisense Apo B Synthesis Inhibitor: ISIS-301012

Phase: 3

Design: Placebo-controlled, randomized, double-blind with optional open-label extension

Dose: 200 mg/week (n = 100, 2:1 randomization)

Study Population: Subjects with heterozygous familial hypercholesterolemia, documented CAD, on stable lipid-lowering therapy with LDL-C >100 mg/dL and triglycerides <200 mg/dL

Treatment Duration: 26 weeks in primary study + 52 weeks in open-label extension

Primary Efficacy Endpoint: %LDL-C reduction at conclusion of primary study. After 26 weeks of treatment, an additional LDL-C reduction of 28% seen with ISIS-301012 ($P < 0.001$), with significant reductions in Apo B and Lp(a), but no significant change in HDL-C.

Thyroid Hormone Analogue: Eprotirome

• Early study evaluating the safety and efficacy of a thyromimetic compound, eprotirome, for lowering LDL-C in patients with hypercholesterolemia already receiving simvastatin or atorvastatin

• Patients received 25, 50, or 100 μg of study drug or placebo per day for 12 weeks.

# Serum LDL-C at Baseline and 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mg/dL)</th>
<th>Week 12 (mg/dL)</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>138 ± 27</td>
<td>127 ± 23</td>
<td>−11 ± 23</td>
</tr>
<tr>
<td>Eprotirome 25 μg</td>
<td>144 ± 21</td>
<td>113 ± 25</td>
<td>−32 ± 22</td>
</tr>
<tr>
<td>Eprotirome 50 μg</td>
<td>138 ± 16</td>
<td>99 ± 16</td>
<td>−39 ± 20</td>
</tr>
<tr>
<td>Eprotirome 100 μg</td>
<td>141 ± 25</td>
<td>94 ± 18</td>
<td>−47 ± 25</td>
</tr>
</tbody>
</table>

The ASSERT Study (RVX-208)

- RVX-208 is an oral inducer of Apo A-I synthesis.
- Enhanced Apo A-I synthesis should generate functional HDL particles that facilitate reverse cholesterol transport.
- In animals and healthy volunteers, RVX-208 treatment is associated with an increase in pre-β HDL and α1 particles, resulting in increased cholesterol efflux potential.
- Improved HDL quantity and quality may produce other non-lipid-related beneficial effects on inflammation and endothelial function.

Median Change in Apo A-I from Baseline (Did not reach primary outcome)

- Placebo: +0.9%
- 100 mg: +0.1%
- 200 mg: +3.8%
- 300 mg: +5.6%

*P = 0.09, #P = 0.10 and ¥P = 0.06 compared with placebo

HPS3-TIMI 55
Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)

- 30,000 patients with occlusive arterial disease in North America, Europe and Asia.
- Background LDL-C lowering with atorvastatin.
- Randomized to anacetrapib 100 mg vs. Placebo.
- Scheduled follow-up: 4 years.
- Primary outcome: Coronary death, myocardial infarction or coronary revascularization.
dal-OUTCOMES trial: Efficacy and Safety of Dalcetrapib in Patients with Recent Acute Coronary Syndrome

Rationale and Design

Major Trials In Progress

• **AIM-HIGH**: Additional Data pending including Lipoprotein and Lp(a) Sub-Analyses

• **IMPROVE-IT**: Simvastatin 40 mg vs ezetimibe 10 mg/simvastatin 40 mg in patients enrolled following acute coronary syndrome. Endpoint of major CV events.

• **HPS2-Thrive**: Simvastatin ER niacin/laropiprant CVD Endpoint, 20,000 patients 2° prevention 7000 with DM

• **HOPE-3**: 2 x 2 factorial trial, rosuvastatin 10 mg vs placebo, candesartan/HCTZ vs placebo. Enrolling people at average risk, without CHD. Endpoint of major CV events.
Key Take-Away Messages: Clinical Trials

- Over time, lowering LDL-C reaps great benefits in terms of reduction of cardiovascular events.
  - In fact, lowering LDL-C by 1% reduces cardiovascular risk by 1%.
- Clinical trials provide hope that novel therapies may provide additional benefits beyond LDL-C lowering.
Key Take-Away Messages: Clinical Trials

- Newer trials involving niacin, fibrates, and other novel agents such as CETP inhibitors give hope that by modifying HDL-C and triglyceride levels, CVD risk will be reduced.
- Clinical outcome trials are underway evaluating combination therapies to see if there is an incremental benefit modifying lipids beyond just LDL-C lowering.
Key Take-Away Messages: Clinical Trials

• Several novel agents are under investigation that affect different receptors in lipid metabolism, including:
  • Antisense drugs to reduce the production of Apo B
  • Thyromimetic therapies
  • Apo A1 enhancing therapies to improve the activity and amount of HDL in the plasma