Landmark Clinical Trials
Learning Objectives

• Discuss clinical trials and their role in lipid and lipoprotein treatment in cardiovascular prevention.
• Review the clinical trials of lipid-altering drug therapies used in cardiovascular disease prevention.
• Apply basic principles of statistics to enhance understanding of clinical trials related to lipid management.
Outline

• Overview of Basic Study Design and Biostatistics
• Prominent Landmark Clinical Trials:
  – Statin trials
  – LDL-C focused nonstatin trials
  – Mixed lipid modification focused nonstatin trials
  – Triglyceride/HDL-C focused nonstatin trials
• Other Landmark Trials
• Trials on the Horizon
Randomized controlled trials with definitive results

Randomized controlled trials with non-definitive results

Cohort Studies

Case-Control Studies

Cross Sectional Surveys

Case Reports

Systematic Reviews and Meta-Analyses

Clinical Trials: Endpoint Analysis

- **Primary Endpoints:**
  - Prospectively determined outcome
  - Main purpose of study, basis of power calculation
  - Results should be definitive

- **Secondary Endpoints:**
  - Prospectively determined outcome
  - Study may not have power to detect a difference
  - Results not designed to definitive

- **Subgroup Analyses:**
  - Results are speculative and hypothesis generating
Significance of Study Findings

Statistical Significance

• **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

• **Confidence Interval** (CI)
  – 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

Clinical Significance

• Difference is meaningful to patient care
Interpreting Study Results

• Relative risk reduction (RRR):
\[
RRR = \frac{(\text{control event rate}) - (\text{treatment event rate})}{(\text{control event rate})}
\]

• Absolute risk reduction (ARR):
\[
ARR = (\text{control event rate}) - (\text{treatment event rate})
\]

• Number Needed to Treat (NNT):
  – Number of patients that must be treated with studied therapy to prevent one event/endpoint
\[
NNT = \frac{1}{ARR}
\]

*Number needed to harm can be calculated to assess serious adverse effects*
Example Clinical Trial

Patients with Primary Endpoint (%)

Placebo Drug X

| Patients with Primary Endpoint (%) | 15 | 10 |

RRR = \(\frac{15\%-10\%}{15\%}\) = 33%

ARR = 15\%-10\% = 5%

NNT = \(\frac{1}{5\%}\) = \(\frac{1}{0.05}\) = 20
Evolution of Guidelines and Landmark Trials

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

NCEP ATP II
1993
- Angiographic Trials (FATS, POSCH, SCORE, STARTS, Ornish, MARS)
- Meta-analyses (Holmes Rossouw)

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

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

ACC/AHA, IAS, NLA
2013/2014
- TNT
- IDEAL
- ACCORD
- JUPITER
- CTT Meta-analyses
- ENHANCE
- SHARP
- AURORA
- CORONA

Expanded/Modified Treatment Recommendations

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
IAS = International Atherosclerosis Society
EXAMPLE: ACC/AHA Evidence-Based Recommendation Ranking Format

• **Class of Recommendations**
  – Class I: Benefits >>> Risk
  – Class IIa: Benefits >> Risk
  – Class IIb: Benefit ≥ Risk

• **Level of Evidence**
  – Level A: Multiple populations; data from multiple RCTs or meta-analyses
  – Level B: Limited populations and single RCT or non-controlled studies
  – Level C: Very limited populations; consensus opinion

Statin Trials

- AFCAPs/TexCAPs
- 4S
- HPS
- PROVE-IT
- ASCOT-LLA
- WOSCOPS
- CARE
- LIPID
- MEGA
- A to Z
- REVERSAL
- ASTEROID
- CARDS
- TNT
- JUPITER
- SEARCH
- METEOR
- IDEAL
- SPARCL
- ALLHAT-LLT
- PROSPER
- 4D
- MIRACLE
- AURORA
- CORONA
2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups

Clinical ASCVD

LDL-C ≥190 mg/dL

Diabetes Type 1 or 2 age 40-75 y

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups

**Clinical ASCVD**

- **LDL-C**
  - ≥190 mg/dL

- **Diabetes**
  - Type 1 or 2
  - Age 40-75 y

- **≥7.5% estimated 10-y ASCVD risk and age 40-75 y**

Scandinavian Simvastatin Survival Study (4S)

• Double-blind trial in 4444 men and women 35 to 70 years of age with prior MI and/or angina pectoris and total cholesterol (TC) of 212-309 mg/dL
• Randomized to simvastatin 20 mg daily or placebo; simvastatin increased to 40 mg daily if TC > 200 mg/dL
• Median duration was 5.4 years

• Primary Endpoint: All cause mortality

4S Primary Endpoint

4S: Changes in Lipoprotein Levels

4S: Results of Key End-points

Heart Protection Study (HPS)

- Double-blind trial in 22,536 patients, age 40-80 years, at 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
- Total cholesterol was >3.5 mmol/L (>135 mg/dL)
- Randomized to simvastatin 40 mg daily or placebo
- Scheduled 5 year treatment period

- Primary Endpoint: Major vascular events

HPS: Primary Endpoint Results by Group

<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>(10,269)</td>
<td>(10,267)</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>RRR: 24%</td>
</tr>
<tr>
<td>PVD</td>
<td>327 (24.7%)</td>
<td>420 (30.5%)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>276 (13.8%)</td>
<td>367 (18.6%)</td>
<td>ARR: 5.4%</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>NNT: 19</td>
</tr>
</tbody>
</table>

## HPS: Primary Endpoint Results 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>(10,269)</td>
<td>(10,267)</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 (2.6 mmol/L)</td>
<td>285</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>100 to 129</td>
<td>670</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/L)</td>
<td>1087</td>
<td>1365</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042</td>
<td>2606</td>
<td></td>
</tr>
</tbody>
</table>

(19.9%) (25.4%)

Het$\chi^2 = 0.8$

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

• Double-blind trial in 4162 patients hospitalized for ACS within 24 hours of acute coronary syndrome (ACS)
• Randomized to pravastatin 40 mg or atorvastatin 80 mg daily within 10 days of ACS for a mean of 24 months

• Primary endpoint: Composite of all cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization, stroke

PROVE IT – TIMI 22: Lipid Results

• Median starting LDL-C was 106 mg/dL
• Median treated LDL-C values were:
  – Atorvastatin 62 mg/dL
  – Pravastatin 95 mg/dL (P<0.001)

• ACS response lowers LDL-C from the true baseline and 25% of patients were receiving statins before ACS event
PROVE IT: Primary Endpoint

![Graph showing the comparison between Pravastatin 40 mg (26.3%) and Atorvastatin 80 mg (22.4%) with related statistics: RRR: 16%, P=0.005, ARR: 3.9%, NNT: 26.]

Treating to New Targets (TNT): Study Design

- Double-blind controlled trial in 10,001 men and women age 35-75 years
- All patients had clinically evident CHD and LDL-C <130 mg/dL while taking atorvastatin 10 mg daily
- Patients randomized to atorvastatin 80 mg or 10 mg
- Median duration was 4.9 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

Mean LDL-C Value (mg/dL)

Patients with Major CV Event (%)

P<0.001

RRR: 22%
P<0.001
ARR: 3.2%
NNT: 31

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

- Randomized, double-blind trial in 4731 patients with stroke or TIA in past 1 to 6 months
- Randomized to atorvastatin 80 mg daily or placebo
- Mean follow-up 4.9 years
- Primary endpoint: Stroke

Cholesterol Treatment Trialists’ (CTT) Collaboration

• Meta-analysis of large (n>1000), randomized clinical trials that were at least 2 yrs in duration
  – More vs. Less intensive statin therapy:
    • 5 trials (n=39,612), median 5 yr follow-up
  – Statin vs. control:
    • 21 trials (n=129,526), median 4.8 yr follow-up
• Average CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year after randomization were calculated

CTT Collaboration: More vs. Less Statin Therapy

- Weighted mean further reduction in LDL-C was 0.51 mmol/L (~19 mg/dL)

<table>
<thead>
<tr>
<th>Further Event Reduction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Vascular Events</td>
<td>15% (P&lt;0.001)</td>
</tr>
<tr>
<td>CHD Death or Non-Fatal MI</td>
<td>13% (P&lt;0.001)</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>19% (P&lt;0.001)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>16% (P=0.005)</td>
</tr>
</tbody>
</table>

- CV event reductions proportionate to LDL-C reductions, even when baseline LDL-C was <2 mmol/L (77 mg/dL)

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C ≥190 mg/dL
- Diabetes Type 1 or 2, age 40-75 y
- ≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Collaborative AtoRvastatin Diabetes Study (CARDS)

- 2838 primary prevention patients (no ASCVD) with type 2 diabetes
  - At least 1 other CV risk factor such as smoking, hypertension, retinopathy, or microalbuminuria
  - LDL-C levels ≤160 mg/dL and TG levels ≤600 mg/dL
- Randomized to placebo or atorvastatin 10 mg daily

- Primary endpoint:
  - Time to first major CV event (CHD death, nonfatal MI, revascularization, stroke)
- Trial stopped at a median of 3.9 years, 2 years early
CARDS: Primary End Point Results

• Mean baseline LDL-C 117 mg/dL reduced 40% with atorvastatin (P<0<0001)

Cumulative Hazard (%)

RRR: 36%
P=0.001
ARR: 3.2%
NNT: 31

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups

- Clinical ASCVD
- LDL-C \( \geq 190 \text{ mg/dL} \)
- Diabetes Type 1 or 2 age 40-75 y

\( \geq 7.5\% \) estimated 10-y ASCVD risk and age 40-75 y

AFCAPS/TexCAPS

• Randomized, double-blind trial in 5608 men and 997 women with no history of CHD (primary prevention)
  – Baseline LDL-C was 150 mg/dL
  – Baseline HDL-C was 37 mg/dL
• Randomized to lovastatin 20-40 mg daily (titrated to achieve an LDL-C of <110 mg/dL) or placebo
• Mean follow-up was 5.2 years

• Primary endpoint: First acute major coronary event (unstable angina pectoris, fatal or non-fatal MI, or sudden cardiac death)

AFCAPS/TexCAPS: Primary Endpoint Results

Lovastatin vs Placebo

Cumulative Incidence

Years of Follow-up

RRR: 37%
P<0.001
ARR: 4.1%
NNT: 24

Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA)

- Double-blind trial in 10,305 patients with multiple CV risk factors including diabetes mellitus, but not CHD
- Randomized to placebo or atorvastatin 10 mg daily

- Primary Endpoint was non-fatal MI and fatal CHD
- Treatment stopped after a median follow-up of 3.3 year
- Mean baseline LDL-C 133 mg/dL:
  - Reduced 33% to a mean LDL of 90 mg/dL
ASCOT-LLA: Primary End Point of Nonfatal MI and Fatal CHD

Proportion of Patients (%)  

Year

Placebo

Atorvastatin

RRR: 36%  
P=0.0005
ARR: 1.1%  
NNT: 91

Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)

- Randomized, open-label trial in primary patients age 40-70 years and TC 220-270 mg/dL
- Randomized to pravastatin 10-20 mg daily or placebo
- Mean follow-up 5.3 years
- Primary endpoint: Coronary heart disease

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

- Double-blind trial in 17,802 primary prevention men and women with LDL-C <130 mg/dL and hs-CRP ≥2 mg/L
- Randomized to rosuvastatin 20 mg or placebo

- Primary endpoint: Composite of CV death, MI, cerebrovascular event, arterial revascularization, or hospitalization for unstable angina
- Study halted after 1.9 years (maximum of 5 years)
- Rosuvastatin reduced LDL-C by 50% (hs-CRP by 37%)

JUPITER: Results

Cumulative Incidence of the Primary Endpoint

Follow-up (years)

RRR: 44%
P<0.0001
ARR: 1.2%
NNT: 83

The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further ASCVD events

- In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

LDL-C Focused Nonstatin Drug Therapies Clinical Trials

- Bile Acid Sequestrants (i.e., colesevelam, colestipol, cholestyramine)
  - LRC-CPPT

- Cholesterol Absorption Inhibitor (ezetimibe)
  - ENHANCE
  - SEAS
  - ARBITER-6
  - SHARP
Lipid Research Clinics
Coronary Primary Prevention Trial

• 3806 primary prevention men, <60 years old with TC ≥ 265 mg/dL, randomized, double-blind to cholestyramine 24 g/day or placebo

• Mean duration was 7.4 years

• Mean LDL-C was 216 mg/dL; reduced 20.3% with cholestyramine

• Primary Endpoint: CHD death + nonfatal MI

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- 720 patients with familial hypercholesterolemia
- Most (81%) previously treated with statins
- Randomized, double-blind to simvastatin 80 mg vs. ezetimibe/simvastatin 10/80 mg for 2 years

Results: Primary Endpoint
- No significant difference in mean carotid intimal medial thickness (CIMT) (P=0.64)

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

- 1873 patients with mild/moderate aortic stenosis randomized to ezetimibe/simvastatin 10/40 mg daily or placebo for 52.2 months
- Primary endpoint: Composite of major CV events

- Results – ezetimibe/simvastatin vs. placebo:
  - Primary outcome: 35.3% vs. 38.2% (P=0.59)
  - Aortic valve events: 32.6% vs. 35.1% (P=0.73)
  - Ischemic CV events: 15.7% vs. 20.1% (P=0.02)

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 with LDL-C <100 mg/dL and HDL-C <50 mg/dL (men) or <55 mg/dL (women)
- Randomized to add either extended-release niacin (goal 2000 mg daily) or ezetimibe (10 mg daily)
- Primary Endpoint: Between-group difference in the change in CIMT at 14 months from baseline

ARBITER 6–HALTS - Results

- **HDL-C:**
  - Niacin increased by 7.5 mg/dL
  - Ezetimibe had no significant change

- **LDL-C:**
  - Ezetimibe had a greater lowering than niacin (17.6 vs 10.0 mg/dL)

The Study of Heart and Renal Protection (SHARP)

- 9438 patients with chronic kidney disease
  - Not on dialysis: elevated creatinine on 2 occasions \( \geq 1.7 \text{ mg/dL} \) (men) or \( \geq 1.5 \text{ mg/dL} \) (women)
  - On dialysis: hemodialysis or peritoneal dialysis
- Age \( \geq 40 \) years with no history of MI or coronary revascularization
- Randomized to ezetimibe/simvastatin10/20 mg daily, simvastatin 20 mg daily, or placebo for 1 year to assess safety; after 1 year, simvastatin monotherapy group randomized to one of the other two groups
- Total median follow-up was 4.9 years

SHARP - Primary Endpoint Results: Major Atherosclerotic Events

Placebo

Ezetimibe/Simvastatin

RRR: 17%
P=0.0021
ARR: 2.1%
NNT: 48

Mixed Lipid Modification Focused Nonstatin Drug Therapies Clinical Trials

- Niacin
  - Coronary Drug Project
  - FATS
  - HATS
  - AIM-HIGH
  - HPS2-THRIVE
Coronary Drug Project

- Randomized, double-blind, placebo-controlled trial in 8341 men with prior MI and hypercholesterolemia
- Tested 5 lipid-modifying agents: Low-dose estrogen, High-dose estrogen, Dextrothyroxine, Clofibrate, Niacin
- 2789 patients in the placebo group and 1119 patients in the niacin group followed for 5 to 8.5 yrs (mean 6.2 yrs)
- Results at follow-up:
  - Primary endpoint: Total mortality
    • 24.4% with niacin, 25.4% with placebo; P=ns
  - Secondary endpoint: Recurrent nonfatal MI
    • 10.2% with niacin, 13.8% with placebo; P<0.05

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

- 146 secondary prevention men aged ≤ 62 years with average stenosis of 34% and 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
- Primary endpoint: Arteriographic change in coronary stenosis

FATS: Angiographic Results at 2.5 years

N = 120 men with coronary artery disease
*P<0.005 vs conventional therapy

HDL-Atherosclerosis Treatment Study (HATS)

• 160 patients with measurable CAD by angiography
  – HDL-C ≤ 35 mg/dL and LDL-C ≤ 145 mg/dL
• Patients randomized to:
  – Placebo
  – Antioxidant vitamins (E/C/β-carotene/selenium) [VIT]
  – Simvastatin 10-20 mg + niacin 2-4 g
  – Simvastatin 10-20 mg + niacin 2-4 g + VIT
• Primary Endpoints: Arteriographic change in coronary stenosis and the occurrence of a first CV event
• Repeat quantitative angiography after 3 years

**HATS: Primary End Points**

- **Quantitative Coronary Angiography**

  - **Change in Stenosis (%)**
    - Placebo: 3.9
    - Niacin+Simvastatin: 0.7
    - Niacin+Simvastatin+VIT: 3.9

  - **Event Rate (%)**
    - Placebo: 24
    - Niacin+Simvastatin: 3
    - Niacin+Simvastatin+VIT: 14

*P≤0.005 vs. placebo; ** P=0.03 vs. placebo

Mean dose of simvastatin was 13 mg/day
Mean dose of niacin was 2400 mg/day

Niacin Plus Statin to Prevent Vascular Events (AIM-HIGH)

- 3414 patients age ≥ 45 years with ASCVD and dyslipidemia (low HDL-C, triglycerides 150-400 mg/dL, LDL-C < 180 mg/dL)
- Primary Endpoint: Composite of CV events
- Drug allocation:

  - 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*
  - simvastatin 20/40/80 mg*
  - 3-5 years
  - * dependent on LDL-C levels, ezetimibe 10 mg may be added as well

## AIM-HIGH: Results

<table>
<thead>
<tr>
<th>mean/median values (mg/dL)</th>
<th>Placebo + Statin (N = 1696)</th>
<th>ER Niacin + Statin (N = 1718)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (N = 1696)</td>
<td>Year 1 (N = 1554)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>162</td>
<td>155</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Apolipoprotein AI</td>
<td>123</td>
<td>127</td>
</tr>
</tbody>
</table>

AIM-HIGH: Primary Endpoint Results

HR 1.02
(95% CI 0.87-1.21; P=0.79)

ER Niacin with Laropiprant in High-Risk Patients: HPS2-THRIVE

- 25,673 patients with vascular disease randomized to extended-release niacin/laropiprant 2000/40 mg daily or placebo for a median of 3.9 years
- All patients treated with a standardized background of statin-based LDL-C lowering therapy
- Primary Endpoint: major vascular events
  - Niacin/laropiprant 13.2%
  - Placebo 13.7% \( (P = 0.29) \).
- Niacin–laropiprant associated with more serious adverse effects (glycemic control, gastrointestinal system, musculoskeletal system, skin, infection, and bleeding

Triglyceride/HDL-C Focused Nonstatin Drug Therapies Clinical Trials

• Fibric Acid Derivatives
  – Helsinki Heart Study
  – VA-HIT
  – FIELD
  – ACCORD
Helsinki Heart Study

- 4081 primary prevention men age 40-55 years with non-HDL-C ≥200 mg/dL
- Randomized, double-blind to gemfibrozil 600 mg twice daily or placebo for 5 years
- Results:
  - 34% reduction in the primary endpoint of CHD events (MI and CV death)
  - Gemfibrozil 27.3 per 1000
  - Placebo 41.4 per 1000
  - LDL-C reduced 11%, HDL-C increased 11%
  - Greatest benefits when triglyceride high or HDL-C low

Veterans Affairs HDL Intervention Trial (VA-HIT)

- Double-blind trial in 2531 men with coronary heart disease (CHD), age < 74 years, HDL-C ≤ 40 mg/dL, LDL-C ≤ 140 mg/dL years and triglycerides ≤ 300 mg/dL
- Randomized to gemfibrozil 1200 mg/day or placebo
- Mean lipid values were: LDL-C 111 mg/dL, HDL-C 32 mg/dL and triglycerides 161 mg/dL
- 25% had diabetes, 57% had hypertension, average body mass index was 29 kg/m²
- Median follow-up was 5.1 years

- Primary endpoint: nonfatal MI or fatal CHD
VA-HIT: Results

• Percentage of patients with primary endpoint:
  – Gemfibrozil    17.3%
  – Placebo       21.7%

<table>
<thead>
<tr>
<th></th>
<th>RRR: 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P=0.0006</td>
</tr>
<tr>
<td>ARR:</td>
<td>4.4%</td>
</tr>
<tr>
<td>NNT:</td>
<td>23</td>
</tr>
</tbody>
</table>

• Mean/median lipid values with gemfibrozil vs placebo
  – LDL-C         113 vs 113 mg/dL (P=ns)
  – HDL-C         34 vs 32 mg/dL  (P<0.001)
  – Triglycerides 113 vs 161 mg/dL (P<0.001)
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

Patients with Type 2 Diabetes (n=9795)

- No clear indication for lipid-lowering therapy at baseline

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

5 Years or 500 CHD Events

Placebo (n=4900)
+ Other lipid-lowering therapies

- Primary endpoint: CHD event

## 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: Results

Primary Endpoint: CHD events (P=0.16)
- Placebo: 5.9%
- Fenofibrate: 5.2%

Secondary Endpoint: Total CVD (P=0.035)
- Placebo: 13.9%
- Fenofibrate: 12.5%

FIELD: Subgroup Analyses

Patients With Low HDL-C*

14% Reduction
P=0.02

Event Rate, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1</td>
<td>13.0</td>
<td></td>
</tr>
</tbody>
</table>

Patients With Dyslipidemia†

14% Reduction
P=0.06

Event Rate, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.3</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

*<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

- 5518 patients with type 2 diabetes treated with open label simvastatin randomized, double blind, to fenofibrate 160 mg daily (with renal adjustment) or placebo
- Primary outcome: nonfatal MI, nonfatal stroke, CV death
- Mean follow-up was 4.7 years

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>100.6</td>
<td>81.1</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>38.1</td>
<td>41.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>162</td>
<td>122</td>
</tr>
</tbody>
</table>
ACCORD: Results

- Subgroup analyses:
  - Possible heterogeneity in treatment according to sex, with benefit for men and harm for women (P=0.01)
  - Possible benefit in patients with both high baseline triglycerides (≥204 mg/dL) and a low baseline HDL-C (≤34 mg/dL) (P=0.057)
ACC/AHA 2013 Blood Cholesterol Guideline: Additional Recommendations

• The panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA Class II-IV ischemic systolic heart failure or in patients on maintenance hemodialysis.
Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

- 5011 patients ≥ 60 years of age with NYHA class II, III, or IV ischemic, systolic heart failure (mean EF 31%)
- Randomized, double-blind to rosuvastatin 10 mg daily or placebo for a median follow up of 32.8 months
- Results:
  - Primary endpoint of CV death or nonfatal MI or stroke
    - Rosuvastatin 27.5%
    - Placebo 29.3% (P=0.12)

Lipid-Lowering Therapy in Patients with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D:</td>
<td>Type 2 diabetes plus long-term hemodialysis (n=1255)</td>
<td>CV death, nonfatal MI, fatal/nonfatal stroke</td>
<td>0.92 (0.77–1.10)</td>
</tr>
<tr>
<td>• Atorvastatin 20 mg daily vs placebo for 4 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURORA:</td>
<td>Long-term hemodialysis (n=2776)</td>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>0.96 (0.84–1.11)</td>
</tr>
<tr>
<td>• Rosuvastatin 10 mg daily vs placebo for 3.8 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SHARP: Major Vascular Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ezetimibe/Simvastatin (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: No significant heterogeneity between non-dialysis and dialysis patients (P=0.25)

Schizophrenic Life of Ezetimibe

• 2002 – Approval of ezetimibe
• 2004 – Approval of ezetimibe/simvastatin combination
• 2005 – IMPROVE-IT study starts targeting 12,500 patients
• 2006 – ENHANCE published after 18 month delay
• 2008 – Excess cancer cases in the SEAS trial
• 2008 – IMPROVE-IT changes target enrollment to 18,000; completion delayed until 2012
• 2009 – FDA investigation concludes cancer risk unlikely
• 2010 – IMPROVE-IT completion delayed until 2013
• 2011 – SHARP Trial
• 2015 – Release of IMPROVE-IT results
IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

- Double-blind trial in 18,144 patients with an acute coronary syndrome, age ≥50 years with a high CV risk feature, and LDL-C 50-125 mg/dL (50-100 if on lipid-lowering therapy)
- Randomized to simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 4.9 years
- Primary endpoint: CV death, MI, hospital admission for unstable angina, coronary revascularization, or stroke
- Mean LDL-C values
  - Simvastatin alone 69.9 mg/dL
  - Ezetimibe /simvastatin 53.2 mg/dL

IMPROVE-IT: Results


Simvastatin — 34.7%
2742 events

Ezetimibe/Simvastatin — 32.7%
2572 events

RRR: 20%
P = 0.016
ARR: 2%
NNT: 50
RRR: 5.8%
Key Take-Away Messages: Landmark Clinical Trials

• Applying basic principles of clinical trials and statistics is needed when interpreting landmark clinical trials and applying findings to patient care
• Multiple landmark clinical trials have had a major influence on recommendations for treatment of dyslipidemia
• Statin-based landmark trials have consistently demonstrated reduced risk of CV events
• Nonstatin have been evaluated in landmark clinical trials with mixed results and various interpretations