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.
Evidence-based Medicine

- Integrates individual clinical experience (and patient values) with best available external clinical evidence to guide decisions about diagnosis, prognosis and treatment


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

Hierarchie of Evidence

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)**
  – $95\% \text{ CI} =$ range within which one can be $95\%$ confident that the true value lies
  – Smaller $95\% \text{ CI}$ 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):
  \[ RRR = \frac{(control \text{ event rate}) - (treatment \text{ event rate})}{(control \text{ event rate})} \]

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

• 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: 15%
- Drug X: 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
2013
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 Ila: Benefits >> Risk
  – Class Ilb: 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

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></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></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><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

**RRR:** 24%
P<0.0001

**ARR:** 5.4%

**NNT:** 19

### 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>(10,269)</td>
<td>(10,267)</td>
<td></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>STATIN better</td>
</tr>
<tr>
<td>100 to 129</td>
<td>670</td>
<td>881</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/L)</td>
<td>1087</td>
<td>1365</td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></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)

- 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


Pravastatin 40 mg (26.3%)

Atorvastatin 80 mg (22.4%)

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

![Graph showing LDL-C value and major CV event rates for Atorvastatin 10 mg and 80 mg]

- **Mean LDL-C Value (mg/dL)**
- **Patients with Major CV Event (%)**

- **P<0.001**

- **RRR:** 22%
  - **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

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<0.001)
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

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

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
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


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)

**CIMT Results at 14 months**

P=0.003

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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

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Progression of Coronary Lesion</th>
<th>Regression of Coronary Lesion</th>
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<tbody>
<tr>
<td>Conventional Therapy</td>
<td>46</td>
<td>11</td>
</tr>
<tr>
<td>Colestipol + Lovastatin</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Colestipol + Niacin</td>
<td>25</td>
<td>39</td>
</tr>
</tbody>
</table>

www.lipid.org
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


*CVD Events

*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

**Placebo  Niacin+Simvastatin  Niacin+Simvastatin+VIT**
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:

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

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

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


www.lipid.org
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 standardize 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%

- 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)

RRR: 20%
P=0.0006
ARR: 4.4%
NNT: 23
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

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

5 Years or 500 CHD Events

- Primary endpoint: CHD event

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

15.1

Placebo  
13.0

Fenofibrate

Patients With Dyslipidemia†

14% Reduction  
P=0.06

16.3

Placebo  
14.0

Fenofibrate

*<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></td>
<td></td>
<td>Placebo</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>

• 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 \((\geq 204 \text{ mg/dL})\) and a low baseline HDL-C \((\leq 34 \text{ mg/dL})\) \((P=0.057)\)
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 rosvastatin 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)
  - Secondary endpoint of CV hospitalizations were with rosvastatin vs 46.6% with placebo (P<0.001)

# 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></td>
<td>• Atorvastatin 20 mg daily vs placebo for 4 years</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></td>
<td>• Rosuvastatin 10 mg daily vs placebo for 3.8 years</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>0.8</td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td>Ezetimibe/Simvastatin better</td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td>Placebo better</td>
</tr>
</tbody>
</table>

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

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