USE OF COMBINATION THERAPY IN MIXED DYSLIPIDEMIA

Peter P. Toth, MD, PhD, FAAFP, FNLA, FAHA, FCCP, FACC
Director of Preventive Cardiology
CGH Medical Center
Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois
Professor of Clinical Medicine
Michigan State University
East Lansing, Michigan

Lipid Goals in NCEP ATP III Guidelines

- Non-HDL-C is currently a secondary target for lipid-modifying therapy when TG > 200 mg/dL.
  - Non-HDL-C goal: 30 mg/dL higher than the LDL-C goal

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Non-HDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 risk factor</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Multiple risk factors with 15-year CHD risk &gt; 20%</td>
<td>&lt;130 mg/dL</td>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td>CHD or CHD equivalent (15-year CHD risk &gt; 30%)</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Very high risk*</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

*Defined as the presence of established cardiovascular disease plus (1) multiple major risk factors (smoking, diabetes, hypertension, and obesity), (2) severe and poorly controlled risk factors (severely elevated triglycerides exceeding 500 mg/dL), (3) multiple risk factors of the metabolic syndrome (systolic blood pressure > 140, triglycerides > 200, HDL-C < 40 mg/dL, and abdominal obesity or any two in the remaining four risk factors).

Ref: Cholesterol Guideline, American Heart Association, 2001; 2002; 2004

Non–HDL-C Was a Better Predictor of CHD Risk Than LDL-C Was: Framingham Heart Study

Adjusted for age, gender, study, smoking status, systolic blood pressure, and prevalent diabetes (at baseline).

*Adapted for age, gender, study, smoking status, systolic blood pressure, and prevalent diabetes (at baseline).

Non-HDL-C Was A Better Predictor of CVD Mortality Than LDL-C: Lipid Research Clinics Program Study

Comparison of lipid levels in predicting CVD mortality in men and women

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>( \chi^2 ) for addition to model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.13 (1.11 to 1.15)</td>
<td>24.3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.11 (1.03 to 1.22)</td>
<td>9.0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.77 (0.69 to 0.86)</td>
<td>23.2</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.13 (1.08 to 1.19)</td>
<td>8.5</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.08 (0.94 to 1.24)</td>
<td>1.2</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.77 (0.69 to 0.86)</td>
<td>18.5</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Non–HDL-C was a better predictor of cardiovascular disease mortality by third lipid level when added to age only models.

*Non–HDL-C level was adjusted for age at baseline in a continuous and following Cox proportional hazard models.


EZETIMIBE PLUS STATIN

Ezetimibe use Equivalent to Three Titration Steps of a Statin

ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) Trial

- **Study Population:**
  - Primary endpoint: change from baseline in the mean cIMT
  - Treatment Duration: 24 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>cIMT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Simvastatin (n=230)</td>
<td>139</td>
<td>46</td>
<td>0.8</td>
</tr>
<tr>
<td>Simvastatin + EZE (n=293)</td>
<td>124</td>
<td>54</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Definitive of the mean of the far-wall IMT of the right and left CCA, control bulks, and internal carotid arteries.

*P-value for change in cIMT between treatment arms

CASHMERE (Carotid Atorvastatin Study In Hyperlipidemic Post-Menopausal Women)

- Population:
  - Postmenopausal women ≥50 years old (N=399), LDL-C = 130 to 190 mg/dL, TG < 4 g/L, "Normal" baseline cIMT (0.69 mm)
  - No LLT within 6 weeks of randomization

- Treatment Duration: 12 months
- Primary outcome: change in mean cIMT of a given arterial wall

Mean cIMT

<table>
<thead>
<tr>
<th>Tx arm</th>
<th>Baseline (mm ±SD)</th>
<th>12 mo (mm ±SD)</th>
<th>Change (%A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (n=182)</td>
<td>0.55 ±0.10</td>
<td>0.60 ±0.12</td>
<td>−4.0</td>
</tr>
<tr>
<td>Placebo (n=187)</td>
<td>0.60 ±0.11</td>
<td>0.62 ±0.13</td>
<td>−3.3</td>
</tr>
</tbody>
</table>

Tx arm

- Baseline
- 12 mo
- Change (%A)

Overall Arterial Rigidity Study

- Population:
  - Mexican patients 40 – 72 years of age with 10-year absolute risk for CD or MI >20% (N=90)
  - Majority of patients on prior low-dose statins
  - No prior use of ezetimibe

- Treatment Duration: 12 months
- Primary endpoint: change in mean cIMT

Mean cIMT

<table>
<thead>
<tr>
<th>Tx arm</th>
<th>Baseline (mm ±SD)</th>
<th>12 mo (mm ±SD)</th>
<th>Change (%A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin ± EZE (n=30)</td>
<td>0.75 ±0.12</td>
<td>0.95 ±0.14</td>
<td>−26.7</td>
</tr>
<tr>
<td>Simvastatin 40/80 mg (n=30)</td>
<td>0.95 ±0.14</td>
<td>1.15 ±0.16</td>
<td>−17.8</td>
</tr>
<tr>
<td>Simvastatin 20/40 mg + EZE (n=30)</td>
<td>1.15 ±0.16</td>
<td>1.35 ±0.18</td>
<td>−17.4</td>
</tr>
</tbody>
</table>

For all groups: *P<0.01 vs placebo

A: EZE added in month 2 if goal was not attained
B: Simvastatin titrated to 80mg in month 2 if goal was not attained
C: EZE/Simvastatin titrated to 10/40mg in month 2 if goal was not attained

Mean cIMT

Change in CIMT at 36 Months: Standard vs Aggressive Therapy Subgroups

- Standard group (S)
- Aggressive group (S+)
- No-recombinant group (S−)


*P<0.001 vs standard group

**ITT: Effects on Major Atherosclerotic Events**

- **Mean LDL cholesterol difference between treatment groups (mg/dL):**
  - 0%
  - 10%
  - 20%
  - 30%

- **Regression reduction in atherosclerotic event risk:**
  - 17% risk reduction

- **SHARP:**
  - More vs Less (3 trials)
  - Statin vs control (22 trials)

**Achievement of LDL-C, non-HDL-C and ApoB Targets**

- **Subjects with CHD**
  - LDL-C < 70 mg/dL (~<1.8 mmol/L)
  - non-HDL-C < 100 mg/dL (~<2.6 mmol/L)
  - Apo B < 80 mg/dL

- **% achieved by clinical trial:**
  - Statin: 4.8, 6.5, 22.4, 5.6, 4.7, 7.3, 19.4, 4.9, 3.8, 5.4, 25.4, 4.1
  - Statin + Ezet: 6.3, 7.8, 16.6, 7.5, 7.1, 12.1, 19.1, 4.9, 3.8, 5.4, 25.4, 4.1

**MIRACL and PROVE-IT: Benefit Of Statins**

- **Post ACS, but Considerable Residual Risk**
  - Residual risk with Atorvastatin 80
Why do we need add-on or combination therapies?

**Remaining Medical Need**

1. Strategies to increase likelihood of achieving LDL-C and non-HDL-C goals in patients on maximal statin therapy
2. Strategies to decrease residual risk linked to HDL / TG abnormalities (atherogenic dyslipidemia)
3. Specific strategies for patients with intolerance to statin therapy

**Metabolic Syndrome: NCEP ATP III Criteria**

Identifies a constellation of symptoms of which none alone has been shown to be a categorical risk factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td>&gt;40 inches</td>
</tr>
<tr>
<td>(waist circumference)</td>
<td>&gt;35 inches</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td></td>
</tr>
</tbody>
</table>

**Framingham Heart Study**

Risk of Coronary Artery Disease in Men Aged 50-70 by LDL and HDL Cholesterol Levels
Effects of LDL-C and HDL-C Changes in 28 Lipid Trials on Primary Clinical Trial Outcomes

![Graph showing reduction in CV event rates vs placebo for different treatments.](image)

Compiled by Greg Brown, Am J. Cardiol, 2006

NIacin Plus Statin

ER-Nicotinic acid: A Broad Spectrum Lipid-Modulating Agent

![Graph showing change in lipid levels with different dosages of ER-nicotinic acid.](image)
AIM HIGH: Baseline Lipids (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>On Statin (n=3,196)</th>
<th>Off Statin (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>71</td>
<td>119</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>

AIM-HIGH Primary Outcome

- **Combination Therapy** vs **Monotherapy**
  - HR 1.02, 95% CI 0.87, 1.21
  - Log-rank P value = 0.79

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Monotherapy at risk</th>
<th>Combination Therapy at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1901</td>
</tr>
<tr>
<td>2</td>
<td>1581</td>
<td>1366</td>
</tr>
<tr>
<td>3</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>4</td>
<td>910</td>
<td>428</td>
</tr>
</tbody>
</table>

Effect of High Risk Groups on Primary Outcome

- **TG ≥ 200 and HDL < 33**
  - Yes: 48 (17.0), 54 (22.4)
  - No: 224 (16.3), 220 (15.1)
  - Hazard Ratio: 0.74 (0.50, 1.09), 0.073

- **TG ≥ 198 and HDL < 33**
  - Yes: 40 (16.7), 50 (25.0)
  - No: 242 (16.2), 224 (15.0)
  - Hazard Ratio: 0.83 (0.40, 0.98), 0.017

- **Log HR and 95% CI**
  - 0.4, 0.5, 0.7, 1.0, 1.5

*Highest tertile of TG and lowest tertile of HDL-C  **Heterogeneity by treatment
The numbers of patients and % of category confused me. These appear to be for ERN vs placebo, but which group is which should be clarified. Same color coding should be used as in prior slide.

Fleg, Jerome L (NIH/NHLBI), 10/29/2012
Baseline LIPIDS on statin-based therapy in HPS-2 THRIVE

Mean (SD) baseline

<table>
<thead>
<tr>
<th></th>
<th>mg/dL</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>128 (22)</td>
<td>3.32 (0.57)</td>
</tr>
<tr>
<td>Direct-LDL</td>
<td>63 (17)</td>
<td>1.64 (0.44)</td>
</tr>
<tr>
<td>HDL</td>
<td>44 (11)</td>
<td>1.14 (0.29)</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>125 (74)</td>
<td>1.43 (0.84)</td>
</tr>
</tbody>
</table>

*64% fasted for >8 hours

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29

FENOFIBRATE PLUS STATIN
Elevated Triglycerides Are Associated With Altered Metabolism of LDL and HDL Particles

SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia
Reduction in CV events*: fibrate studies

<table>
<thead>
<tr>
<th>Study (fibrate)</th>
<th>Primary endpoint (all patients)</th>
<th>Lipid criteria (mmol/L)</th>
<th>Primary endpoint (Lipid subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (fenofibrate/simvastatin)</td>
<td>-8% (p=0.32)</td>
<td>TG 2.3 + HDL-C 0.88</td>
<td>-31%</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>-11% (p=0.16)</td>
<td>TG 2.3 + Low HDL-C</td>
<td>-27% (p=0.005)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>-7.3% (p=0.24)</td>
<td>TG 2.3 + HDL-C 0.9</td>
<td>-38.5% (p=0.02)</td>
</tr>
<tr>
<td>HHS (gemfibrozil)</td>
<td>-34% (p=0.02)</td>
<td>TG &gt;2.3 + LDL/HDL &gt;5.0</td>
<td>-71% (p&lt;0.003)</td>
</tr>
</tbody>
</table>

*Comparator treatments: simvastatin in ACCORD Lipid and placebo in other studies; 
§§ §§ <1.03 in men and <1.29 in women.

FIELD: Rapid Onset of Retinal Benefits Within 8 Months of Treatment Allocation
First Laser Treatment for Diabetic Retinopathy

OMEGA-3 PLUS STATIN
Japan EPA Lipid Intervention Study (JELIS)

**Major Coronary Events**

Control

EPA

Hazard ratio = 0.81 (0.69–0.95)

P = 0.011

Cumulative Incidence, %

0 1 2 3 4 5 Years

Control EPA

–19%

Hazard ratio = 0.81 (0.69–0.95)

P = 0.011

Major Coronary Events

EPA

Control

Japan EPA Lipid Intervention Study (JELIS)

Effects of EPA on MCE incidence for the high TG/low HDL-C Group

HR: 0.47

95% CI: 0.23–0.98

p = 0.043

Cumulative Incidence of major coronary events (%)

2013 ACC/AHA Blood Cholesterol Guidelines

1. The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further ASCVD events. In addition, identification of any RCTs that assessed ASCVD outcomes in statin-intolerant patients was not found.

2. Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a nonstatin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with LDL–C ≥190 mg/dL and individuals with diabetes.

1. 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.

2. BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.)

3. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.

1. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effects.

2. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

3. Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every 6 months thereafter.

CONCLUSIONS

1. The majority of patients with high and very high risk do not attain their risk stratified targets; many require combination therapy in order to do so.

2. Both NCEP and ESC/EAS Guidelines note that combination therapy is frequently required with statins and fibrates and/or nicotinic acid therapy in order to help normalize all components of the lipid profile.

3. Outcomes data supporting the use of combination therapy have shown decidedly mixed results to date; however, most of these trials did not enroll appropriate patients with mixed or atherogenic dyslipidemia.

4. Trials that enroll high risk patients with atherogenic dyslipidemia are needed in order to further substantiate or refute the efficacy of combination therapy in patients with residual risk.