New opportunities for targeting multiple lipid pathways

Michel FARNIER, DIJON, FRANCE
Lipid lowering drug therapy

- 60s and 70s
  - nicotinic acid
  - resins
- 70s to 90s
  - fibrates
- the 90s
  - statins
Coronary heart disease (CHD) event rates in secondary prevention trials are directly proportional to the on-treatment LDL-C levels.

\[ y = 0.1629 \times - 4.6776 \]

\[ R^2 = 0.9029 \]

\[ p < 0.0001 \]

O'Keefe et al. JACC 2004; 43: 2142-6
Previous lipid intervention strategies for preventing/reversing atherosclerosis

- Reduce LDL-C - statins
- Increase HDL-C - fibrates, niacin
Event rates in subjects treated with statins or fibrates are up to 35% lower than in those on placebo.

But events are by no means eliminated by the therapy.

The challenge now is to devise therapies that can reduce events by much more than can be achieved by the existing medications.
Lipid lowering drug therapy

- 60s and 70s
  - nicotinic acid
  - resins

- 70s to 90s
  - fibrates

- the 90s
  - statins

- the new millennium
  - combination with novel agents
Future Research in Hyperlipidemia

What are the major targets of new LRD?

- Effect on single risk factor
  - LDL
  - HDL

- Effect on multiple risk factors
  - Atherogenic Lipid Profile (ALP)
  - Type 2 diabetes, Metabolic Syndrome

- Effect on atherogenesis
Combination therapy in hyperlipidemia

What are the present / near future options in clinical practice?

- **Effect on single risk factor**
  - → LDL
  - → HDL

- **Effect on multiple risk factors**
  - → ↑ TG, ↓ HDL, ↑ small dense LDL

- **Effect on atherogenesis**
What are the present / near future options in clinical practice?

- Effect on single risk factor
  - LDL → Statin + BAS (resin)
  - HDL → Statin + Ezetimibe
Regulation of intestinal Cholesterol Absorption

(NPC1L1 = Niemann-Pick C1 Like 1 Protein)

LXR

Fatty Acids

TG

Fatty Acids

ACAT 2

MTP

ABCG5

ABCG8

NPC1L1

Protein

LXR

Chylomicrons

Blood

Cholesterol

Plant Sterols

Enterocyte

Intestinal Lumen

Intestinal Lumen

Lymph

MTP

apo B-48

Cholesterol

Plant Sterols

Fatty Acids

Blood

Cholesterol

Plant Sterols

ABCG5

ABCG8

NPC1L1

Protein

Altmann et al., Science 2004;303:1204
Regulation of intestinal Cholesterol Absorption

- Intestinal Lumen
  - ABCG5
  - ABCG8
  - Ezetemibe
  - Micelles
  - Plant Sterols
  - NPD-L1 Protein

- Enterocyte
  - LXR
  - Fatty Acids
  - TG
  - MTP
  - ACAT 2
  - Cholesterol
  - Plant Sterols

- Lymph
  - apo B-48
  - ns
  - Chylomicrons

- Circulation of Cholesterol and Fatty Acids
  - Micelles
  - Plant Sterols
Dual Inhibition: Ezetimibe and Statin

- Dietary cholesterol
- Cholesterol
- Bile
- Intestine
- Synthesis of Cholesterol
- LDL-C absorption
- Ezetimibe
- Excretion

Statin
LDL-C Reduction in Usual Doses

Eze/Simva 10/20 mg (n=86)

- 51%*

Simvastatin 20 mg (n=89)

-35%

* p < 0.001 vs. Simvastatin

Percentage of patients reaching target levels of LDL-Cholesterol < 100 mg/dl at a typical dose of Eze/Simva 10/20

- EZE/Simva 10/20 mg (n=108) - 83%*
- Simvastatin 20 mg (n=246) - 46%

* p < 0.001 vs. Simvastatin 20 mg

Data on file MSD and Schering-Plough
Combination therapy in hyperlipidemia

**What are the present / near future options in clinical practice?**

- **Effect on single risk factor**
  - LDL
  - HDL
Established and emerging HDL raising approaches

- New PPARα agonists (fibrates)
- CETP inhibitors
- LXR agonists
- Endothelial lipase inhibitors
- HDL mimetics
- Niacin receptor agonists
<table>
<thead>
<tr>
<th>Drug target</th>
<th>Class of protein</th>
<th>Expected biochemical mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin receptor agonists</td>
<td>GPCR (PUMA-G, HM74)</td>
<td>TG lowering, HDL increase</td>
</tr>
<tr>
<td>LXR agonists</td>
<td>Nuclear receptor</td>
<td>↑ ABCA1 expression, cholesterol efflux and HDL formation</td>
</tr>
<tr>
<td>CETP-inhibitors</td>
<td>Lipid transfer protein</td>
<td>↓ HDL clearance</td>
</tr>
<tr>
<td>Endothelial lipase inhibitors</td>
<td>Enzyme</td>
<td>↓ HDL clearance</td>
</tr>
<tr>
<td>Infusion of peptides related to ApoA1</td>
<td></td>
<td>Increased removal of cholesterol from atheroma</td>
</tr>
</tbody>
</table>
Combination therapy in hyperlipidemia

→ What are the present / near future options in clinical practice?

- Effect on single risk factor
  → LDL
  → HDL → Statin + CETP inhibitor
CETP inhibitors

- Drugs in development:
  - Torcetrapib or CP-529, 414
  - JTT 705
The reverse cholesterol transport route

Liver

HDL

ApoA1 interaction

SRB1 interaction

CETP

Peripheral tissues (ABC-A1, ABC-G1/G4 transporters)

VLDL

LPL

HL

Macrophage

Small dense LDL

LDL receptor
CETP inhibition as an anti-atherogenic strategy

How strong is the evidence base for CETP inhibition and its relationship to atherosclerosis?
Effect of CETP on Atherogenicity

Transgenic Mice

- No endogenous CETP expression in wild-type mice
- High background HDL levels
- No athero without diet or transgenic induction
- Introduction of CETP lowers HDL-C

Effect of CETP Inhibition on Atherogenicity

Rabbits

- High endogenous CETP expression
- Cholesterol diet induces atherosclerosis
- CETP inhibition elevates HDL-C
JTT-705, a CETP inhibitor:

- inhibits CETP activity by forming a disulphide bond
- in cholesterol-fed rabbits, increases HDL-C, decreases non-HDL-C and induces a 70% decrease of aortic arch lesions

Torcetrapib Treatment Inhibits CETP Activity in Rabbits


CE Transfer (RFU/sec) vs. Weeks of Treatment

- Control
- CP-529414-Treated

~ -75%
**Effect of Torcetrapib on Lipids and Atherosclerosis in Rabbits**

**Torcetrapib Increases HDL—No Change in Non-HDL**

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Control</th>
<th>Torcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>422 ± 75</td>
<td>450 ± 68</td>
</tr>
<tr>
<td>LDL</td>
<td>224 ± 41</td>
<td>239 ± 43</td>
</tr>
<tr>
<td>HDL</td>
<td>57 ± 6</td>
<td>208 ± 32</td>
</tr>
</tbody>
</table>

Lipoprotein values in mg/dl

**Torcetrapib Reduces Aortic Atherosclerosis**

* p = 0.001

~ - 60%*

From: Morehouse et al. AHA 20004.
Effects of a CETP inhibitor in normal subjects

Clark et al. ATVB 2004; 24 : 490-497
Torcetrapib: Dose-dependent CETP Inhibition, HDL Raising and LDL Lowering in Healthy Individuals

Lipid Profile during Treatment with Torcetrapib versus Placebo for 14 days

Adapted from Clark et al. ATVB 2004, 24:1-9
Efficacy of Torcetrapib (with or without Atorvastatin) in subjects with low HDL-C

% changes in HDL-C

<table>
<thead>
<tr>
<th></th>
<th>PLB</th>
<th>T10</th>
<th>T30</th>
<th>T60</th>
<th>T90</th>
</tr>
</thead>
<tbody>
<tr>
<td>T alone</td>
<td>0%</td>
<td>9%</td>
<td>28%</td>
<td>45%</td>
<td><em>55%</em></td>
</tr>
<tr>
<td>T + Atorva 20 mg</td>
<td>1%</td>
<td>8%</td>
<td>22%</td>
<td>33%</td>
<td><em>40%</em></td>
</tr>
</tbody>
</table>

* p = 0.0001

PLB = placebo
T = torcetrapib

Davidson et al. JACC 2005; 45 (Suppl A) : 394A
Efficacy of JTT-705 in Humans

A randomized phase II Dose-Response Study

CETP Activity, % of control

- Placebo n=50
- JTT 300mg n=48
- JTT 600mg n=47
- JTT 900mg n=52

HDL, mmol/l absolute changes

- Placebo n=50
- JTT 300mg n=48
- JTT 600mg n=47
- JTT 900mg n=52

* p < 0.0001 vs placebo  ** p < 0.001 vs placebo

Efficacy of JTT-705 in Humans

A randomized phase II Dose-Response Study

- Treatment with 900 mg JTT-705 for 4 weeks led to a:
  - 37% decrease in CETP activity ($p < 0.0001$)
  - 34% increase in HDL-C ($p < 0.0001$)
  - 7% decrease in LDL-C ($p < 0.017$)

Combination therapy in hyperlipidemia

What are the present/near future options in clinical practice?

- **Effect on single risk factor**
  - → LDL
  - → HDL

- **Effect on multiple risk factors**
  - → ↑ TG, ↓ HDL, ↑ small dense LDL → Statin + Fenofibrate
  - → Statin + Niacin
  - → Ezetimibe + Fenofibrate
Combination therapy in hyperlipidemia

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  - → Statin + Niacin
  - → Ezetimibe + Fenofibrate
Statin-Fibrate combination therapy

- **Rationale**
  Complementary metabolic effects of fibrates and statins

- **Efficacy**
  Combinations with usual doses of statins and fibrates led to:
  - reductions in LDL-C ≥ 40%, TG ≥ 50%
  - increase in HDL-C ≥ 20%

  *Farnier. Am J Cardiovasc Drugs 2003; 3: 169*

- **Targeted populations**
  - combined hyperlipidemia
  - type 2 diabetes or metabolic syndrome
Effectiveness and tolerability of Simvastatin plus Fenofibrate for Combined Hyperlipidemia: The SAFARI trial

12-week, double-blind, randomized study in 619 patients with combined hyperlipidemia (TG 150-500 mg/dl, LDL-C > 130 mg/dl)


Baseline

227    234

Baseline

213    213

Baseline

162    163

Baseline

43  44

% change from baseline

0

-10

-20

-30

-40

-50

20

10

0

-10

-20

-30

-40

-50

Baseline

227    234

Baseline

213    213

Baseline

162    163

Baseline

43  44

Simva 20 (n=207) Simva 20 + Feno 160 (n=411)

Simva 20 (n=207) Simva 20 + Feno 160 (n=411)

* p < 0.001

- 20.1

- 24.1

- 26.1

- 25.8

- 43.0*

- 49.1*

- 35.3*

- 31.2*

18.6 *

9.7 *
SAFARI Trial: effects on LDL-C particle subclasses

Proportion of total LDL-C particle subclasses

N = 618

- B (Small, Dense)
- AB (Intermediate)
- A (Larger, Buoyant)

* Significantly different pattern between the 2 treatments groups (p < 0.001)

Statin-Fibrate combination therapy

- Safety
  use restricted because of severe myopathy and rhabdomyolysis
  associated with statin-gemfibrozil combination therapy
  and with cerivastatin-fibrate combination therapy
# RESULTS: Number of reports of rhabdomyolysis for Fibrate/Statin therapies (1998 to 2002)

<table>
<thead>
<tr>
<th>Medications</th>
<th>No. Cases reported</th>
<th>No. Prescriptions dispensed</th>
<th>No. Cases reported per million prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fenofibrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with Cerivastatin</td>
<td>14</td>
<td>100 000</td>
<td>140</td>
</tr>
<tr>
<td>with other statins</td>
<td>2</td>
<td>3 419 000</td>
<td>0.58</td>
</tr>
<tr>
<td>Fenofibrate total</td>
<td>16</td>
<td>3 519 000</td>
<td>4.50</td>
</tr>
<tr>
<td><strong>Gemfibrozil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with Cerivastatin</td>
<td>533</td>
<td>116 000</td>
<td>4600</td>
</tr>
<tr>
<td>with other statins</td>
<td>57</td>
<td>6 641 000</td>
<td>8.60</td>
</tr>
<tr>
<td>Gemfibrozil total</td>
<td>590</td>
<td>6 757 000</td>
<td>87.00</td>
</tr>
</tbody>
</table>

1. Adverse Event Reporting System. U.S. Food and Drug Administration
2. National Prescription Audit Plus report, IMS Health
3. Concomitancy Report, VERISPAN LLC

Jones, Davidson. Am J Cardiol 2005; 95: 120-122
Number of cases of rhabdomyolysis in combination therapy with Statins other than cerivastatin

Fenofibrate

0.58

Gemfibrozil

8.6

15-Fold increase

No cases reported per million prescriptions

Comparative rates of gemfibrozil- and fenofibrate-associated rhabdomyolysis

OR 10.84
(95% CI 8.44 to 13.95)

Reports of rhabdomyolysis/one million prescriptions

OR 10.84
(95% CI 8.44 to 13.95)

Gemfibrozil

Fenofibrate

p < 0.000001

VA health care system comparison of Gemfibrozil to Fenofibrate

- 149 cases of rhabdomyolysis in 95,000 patients on statins plus gemfibrozil
  Rate of 0.16%
- No cases of rhabdomyolysis in 1500 patients on fenofibrate plus statins

Presented by Davidson, New York, July 2005
### Statin-Fibrate combination therapy: pharmacokinetic interactions

<table>
<thead>
<tr>
<th></th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>↑ in $C_{\text{max}}$ (expected)</td>
<td>No effect</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ in $C_{\text{max}}$ by 2 fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ in $C_{\text{max}}$ by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↑ in $C_{\text{max}}$ by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ in $C_{\text{max}}$ by 2.8-fold</td>
<td>Not available</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ in $C_{\text{max}}$ by 2-3-fold</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Statin-Fibrate interactions

Possible explanation = Glucuronidation

- Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of statins
- Gemfibrozil inhibits simvastatin, atorvastatin, rosvastatin and more prominently cerivastatin glucuronidation
- Fenofibrate has less inhibitory effect on statin glucuronidation

May explain the lack of significant drug interaction between fenofibrate and statins

Prueksaritanont et al. JPET 2002; 301: 1042-1051
DMD 2002; 30: 1280-1287
**ACCORD: NIH/NHLBI Trial**
Action to Control Cardiovascular Risk in Diabetes

- Does a therapeutic strategy that targets HbA1c < 6% reduce the rate of CVD versus a target of 7.5%?
- Does a therapeutic strategy of fibrate therapy *plus* statin therapy reduce CVD greater than statin therapy alone?

**Simvastatin 20mg + Fenofibrate 160mg**

<table>
<thead>
<tr>
<th>1450</th>
<th>1450</th>
</tr>
</thead>
</table>

**Simvastatin 20mg**

<table>
<thead>
<tr>
<th>1450</th>
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</tr>
</thead>
</table>

**Intensive Glycemia Control**

**Standard Glycemia Control**

http://www.clinicaltrials.gov/ct/gui/show
Combination therapy in hyperlipidemia

What are the present / near future options in clinical practice?

- Effect on single risk factor
  - LDL
  - HDL

- Effect on multiple risk factors
  - TG, HDL, small dense LDL
    → Statin + Fenofibrate
    → Statin + Niacin
    → Ezetimibe + Fenofibrate
### Lipid-Altering effects of Statin-Niacin regimens

<table>
<thead>
<tr>
<th>Study /year</th>
<th>Statin/dose, mg/d</th>
<th>Niacin type/dose, g/d</th>
<th>∆ LDL %</th>
<th>∆ HDL %</th>
<th>∆ TG %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davignon et al. 1994</td>
<td>Pravastatin, 40</td>
<td>SR, 1.0-2.0</td>
<td>- 41</td>
<td>16</td>
<td>- 35</td>
</tr>
<tr>
<td>Jacobson et al. 1994</td>
<td>Fluvastatin, 20</td>
<td>IR, &lt; 3.0</td>
<td>- 40</td>
<td>28</td>
<td>- 30</td>
</tr>
<tr>
<td>Vacek et al. 1995</td>
<td>Lovastatin, 20</td>
<td>SR, 1.2</td>
<td>- 37</td>
<td>2</td>
<td>- 11</td>
</tr>
<tr>
<td>O 'Keefe et al. 1995</td>
<td>Pravastatin, 20</td>
<td>IR, 3.0</td>
<td>- 25</td>
<td>29</td>
<td>- 42</td>
</tr>
<tr>
<td>Gardner et al. 1996</td>
<td>Lovastatin, 20</td>
<td>IR, 1.5</td>
<td>- 30</td>
<td>27</td>
<td>- 19</td>
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<tr>
<td>Pasternak et al. 1996</td>
<td>Pravastatin, 40</td>
<td>SR, 1.5-3.0</td>
<td>5</td>
<td>- 3</td>
<td>- 26</td>
</tr>
<tr>
<td>Stein et al. 1996</td>
<td>Simvastatin, 10</td>
<td>SR, 1.5</td>
<td>- 29</td>
<td>31</td>
<td>- 36</td>
</tr>
<tr>
<td>Kashyap et al. 2000</td>
<td>Lovastatin, 40</td>
<td>ER, 0.5-2.0</td>
<td>- 47</td>
<td>30</td>
<td>- 42</td>
</tr>
</tbody>
</table>

ER : extended-release; IR : immediate-release; SR : sustained-release

Comparison of Niacin ER/Lovastatin with standard doses of Atorvastatin and Simvastatin: The Advicor Versus Other Cholesterol-modulating Agents Trial Evaluation (ADVOCATE)

**Study Design**

315 patients with
- LDL-C ≥ 160 mg/dl without CHD
- ≥ 130 mg/dl with CHD
- TG < 300 mg/dl
- HDL-C < 45 mg/dl (men)
- < 50 mg/dl (women)

<table>
<thead>
<tr>
<th>NIACIN ER / LOVASTATIN (mg)</th>
<th>(n= 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500/20</td>
<td></td>
</tr>
<tr>
<td>1000/40</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>(n= 78)</th>
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</thead>
<tbody>
<tr>
<td>500/20</td>
<td></td>
</tr>
<tr>
<td>1000/40</td>
<td></td>
</tr>
<tr>
<td>1500/40</td>
<td></td>
</tr>
<tr>
<td>2000/40</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATORVASTATIN (mg)</th>
<th>(n= 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIMVAVASTATIN (mg)</th>
<th>(n= 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Bays et al. Am J Cardiol 2003; 91: 667-72
Comparison of Niacin ER/Lovastatin with standard doses of Atorvastatin and Simvastatin

% change from baseline at week 16

-40 -30 -20 -10 0 10 20 30 40

LDL-C HDL-C TG Lp(a)

Niacin ER/Lovastatin 2000/40 mg
Atorvastatin 40 mg
Simvastatin 40 mg

* p ≤ 0.05 vs simvastatin
† p ≤ 0.05 vs atorvastatin
‡ p ≤ 0.05 vs niacin ER/lovastatin

Bays et al. Am J Cardiol 2003; 91: 667-72
Combination therapy in hyperlipidemia

What are the present / near future options in clinical practice?

- **Effect on single risk factor**
  - → LDL
  - → HDL

- **Effect on multiple risk factors**
  - → ↑ TG, ↓ HDL, ↑ small dense LDL → Statin + Fenofibrate
  - → Statin + Niacin
  - → Ezetimibe + Fenofibrate
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

Study Design

![Study Design Diagram](image)

- **Placebo run-in wash-out period**
- **12-week double-blind placebo controlled phase**
- **48-week double-blind extension phase**

**Short-term**
- Placebo (n = 64)
- FENO 160 mg (n = 189)
- EZE 10 mg (n = 187)
- EZE 10 mg + FENO 160 mg (n = 185)

**Long-term**
- EZE 10 mg + FENO 160 mg
- FENO 160 mg

*Farnier et al. Eur Heart J 2005; 26: 897-905*  
*McKenney, Farnier, JACC, submitted*
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia (baseline: LDL-C 160 mg/dl, TG 275 mg/dl)

**LDL-C Response with Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent Change in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.2*</td>
</tr>
<tr>
<td>EZE 10 mg</td>
<td>-13.4*</td>
</tr>
<tr>
<td>FENO 160 mg</td>
<td>-5.5*</td>
</tr>
<tr>
<td>FENO 160 mg + EZE 10 mg</td>
<td>-20.4</td>
</tr>
</tbody>
</table>

Data are least square mean percent change (standard error); *p < 0.001 compared to FENO+EZE

Farnier et al. Eur Heart J 2005; 26: 897-905
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

**LDL-C Response by TG Subgroup**

Data are least square mean percent change (standard error); * p < 0.001 compared to FENO+EZE within TG strata.

- **TG ≤ 3.1 mmol/l**
  - Placebo (n = 61): -0.4*
  - EZE 10 mg (n = 173): -15.3*
  - FENO 160 mg (n = 179): -27.8
  - FENO 160 mg + EZE 10 mg (n = 175): -9.9*

- **TG > 3.1 mmol/l**
  - Placebo (n = 61): -0.2*
  - EZE 10 mg (n = 173): -11.5
  - FENO 160 mg (n = 179): -12.9
  - FENO 160 mg + EZE 10 mg (n = 175): -1.1*

_Farnier et al. Eur Heart J 2005; 26: 897-905_
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

Percent changes in HDL-C and TG

**Percent changes in HDL-C**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent change in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3,2</td>
</tr>
<tr>
<td>EZE 10 mg</td>
<td>3,9</td>
</tr>
<tr>
<td>FENO 160 mg</td>
<td>18,8 *</td>
</tr>
<tr>
<td>FENO 160 mg + EZE 10 mg</td>
<td>19,0 *</td>
</tr>
</tbody>
</table>

**Percent changes in TG**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent change in TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-9,2</td>
</tr>
<tr>
<td>EZE 10 mg</td>
<td>11,1</td>
</tr>
<tr>
<td>FENO 160 mg</td>
<td>-43,2 *</td>
</tr>
<tr>
<td>FENO 160 mg + EZE 10 mg</td>
<td>-44,0 *</td>
</tr>
</tbody>
</table>

* p < 0.001 vs Placebo and EZE,  # p = 0.021 vs FENO

Farnier et al. Eur Heart J 2005; 26: 897-905
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

* p < 0.001 vs Placebo and EZE

Farnier et al. Eur Heart J 2005; 26: 897-905
Conclusions (1)

- The use of combination therapy for the treatment of dyslipidemia is becoming increasingly important in the management of patients with CHD and multiple risk factors.

- High risk patients often require combined drug therapy to achieve LDL-C and non-HDL-C goals, and also to normalize HDL-C and TG.

- Ezetimibe together with a statin is a novel and beneficial approach, providing dual inhibition of two sources of cholesterol.
Conclusions (2)

- Combination therapy with fenofibrate may be of considerable value in combined/mixed hyperlipidemia, in diabetic patients and in patients with MS.
- The future of the combined therapies with niacin mainly depends of the tolerability of new forms in development.
- Clinical endpoint studies are required to validate the use of these combination therapies.