Is CETP Inhibition An Important Potential Strategy for Reducing Cardiovascular Events?

— Pro —

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Talk Outline

• Cholesteryl Ester Transfer Protein (CETP)
  – What is its role in lipid metabolism?
  – What is its role in atherosclerosis?

• CETP-Inhibition: good or bad?
  – Torcetrapib: why *harmful*?
  – Dalcetrapib: why *not* beneficial?
  – Anacetrapib and Evacetrapib: what are their chances of benefit and approval?

• Summary
Central Role of CETP in Plasma Lipid Transport

Liver

VLDL

LDL

HDL

CETP

FFA

Adipose tissue

Adipose and other tissues

LDL receptor

New synthesis

Peripheral Cell

Bile

FC

CE

TG

FC

CE

TG

CE

TG

CE

CE

FC

LCAT

www.lipid.org
Central Role of CETP in Plasma Lipid Transport

Liver

FC → CE → TG

CE → CE

FC Λ CE

FFA

Adipose tissue

VLDL

LPL

FFA

Adipose and other tissues

LDL

LDL receptor

LDL receptor

Liver

CETP

TG → CE

CE

CE

New synthesis

Peripheral Cell

HDL

LCAT

Liver

Bile

CETP

TG → CE

CE

FC
Central Role of CETP in Plasma Lipid Transport

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- FC → CE
- CE → TG
- TG

FFA

Adipose tissue

Bile

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LPL

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Adipose and other tissues

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Central Role of CETP in Plasma Lipid Transport

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Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT

Peripheral Cell

Bile

LCAT
CETP Action: Likely Mechanisms of Apo A-I loss and HDL Shrinkage

Normal HDL

TG-enriched HDL

Very small (globular?) Lipid-poor Apo A-I

Apo A-I loss by glomerular filtration

Small, dense HDL
CETP Action: Likely Mechanism of LDL Shrinkage

Normal LDL

TG-enriched LDL

TGR-Lp

CE

TG

CETP

CE

TG

CE

HL

FFA

TG

CE

Small, dense LDL

www.lipid.org
CETP-Deficient Mutations: 
*Increased* HDL-C and *Decreased* CAD

- Per-allele odds ratio for coronary disease associated with CETP variants in the current analysis
- Odds ratio for observed per-allele increase in HDL-C levels in prospective studies

**Variant**
- TaqIB (rs708272)
- I405V (rs5882)
- -629C>A (rs1800775)

**Overall Odds Ratio (95% CI)**

Thompson, A; JAMA 2008;299:2777-88
CETP-Deficient HDL Promotes Cholesterol Efflux Better than HDL from Normal Subjects

Matsuura, F JCI 2006;116:1435
CETP-Deficient HDL w/ Apo E Promotes Cholesterol Efflux (ABCG1 Transporter)

Matsuura, F JCI 2006;116:1435
CETP Inhibition May Reduce “Futile Cycle” in Reverse Cholesterol Transport

Liver

- Hepatic Cholesterol
- Bile Salts

CETP

LDL and VLDL

LDL-R

SR-B1

CE

TG

HDL

Bile

Futile Cycle

Free Cholesterol (FC) in Extrahepatic tissues
## Lipid Effects of CETP-Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>HDL-C</th>
<th>Apo A-I</th>
<th>LDL-C</th>
<th>Lp(a)</th>
<th>TG</th>
<th>CETP Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalcetrapib* 600 mg/d</td>
<td>↑29%</td>
<td>↑13%</td>
<td>↑7%</td>
<td>ND</td>
<td>↑9%</td>
<td>Partial (~↓50%)</td>
</tr>
<tr>
<td>Anacetrapib** 100 mg/d</td>
<td>↑138%</td>
<td>↑45%</td>
<td>↓40%</td>
<td>↓36%</td>
<td>↓7%</td>
<td>Very high</td>
</tr>
<tr>
<td>Evacetrapib*** 100 mg/d</td>
<td>↑79%</td>
<td>ND</td>
<td>↓11%</td>
<td>ND</td>
<td>↑1%</td>
<td>High</td>
</tr>
</tbody>
</table>

All results are with background statin therapy.
ND=no data

Cholesterol Efflux Capacity of HDL Increases with CETP-Inhibition

Yvan-Charvet, L; ATVB 2010;30:1430
Anti-Inflammatory Effects of HDL Increase with CETP-Inhibition (partly independent of ABCA1 & ABCG1)

Yvan-Charvet, L; ATVB 2010;30:1430
CETP Inhibitors: 2 Down, 2 Remain

Torcetrapib: ~80% HDL-C increase, but CVD (off-target), OK HDL function
Evacetrapib: ~80% HDL-C increase
Anacetrapib: ~138% HDL-C increase, +/- anti athero
Dalcetrapib: ~30% HDL-C decrease, *No CVD, OK HDL function

*Dalcetrapib development stopped May 7, 2012 due to lack of efficacy in the Dal-Outcomes CVD endpoint trial.

## ILLUMINATE: Deaths Paralleled Aldosterone w/ Torcetrapib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Decrease/Increase Related to Median</th>
<th>No. of patients</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium (decrease)</td>
<td>≥ 0.1 mmol/L</td>
<td>3709</td>
<td>54 (1.46%)</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bicarbonate (increase)</td>
<td>&gt; 0.7 mmol/L</td>
<td>3669</td>
<td>54 (1.47%)</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*vs. 1.23% A+T and 0.78% A only.
Post-hoc Exploratory Analyses in the Torcetrapib/Atorvastatin Group

Similar inverse relationship seen between on-study HDL-C and coronary athero by IVUS

ILLUMINATE: Summary of Torcetrapib Effects

• Torcetrapib rapidly increases:
  – Fatal + non-fatal CVD (↑MI, USA, TIA, CHF, but no △ CVA or sudden death, ↓PAD)
  – *Fatal* cancer
  – *Fatal* infection

• The increase in CVD was
  – Related to ↑BP and ↑aldosterone
  – *Not* predicted by IVUS or CIMT (unchanged)

• HDL appeared to remain *functional*

• Curious *benefits*
  – ↑Glycemic control (↓glucose, ↓insulin resistance)
  – ↑Renal function (↓serum creat. and ↑GFR)?
Dalcetrapib Phase III CVD Event Trials—Discontinued May 7, 2012

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Projected End Date</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Study Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2008</td>
<td>May 2013</td>
<td>N=15,600, acute coronary syndrome (ACS, clinically stable)</td>
<td>MACE</td>
<td>dal-OUTCOMES-I No benefit—all dal-HEART Trials D/C’d</td>
</tr>
<tr>
<td>Feb 2012</td>
<td>Oct 2016</td>
<td>N=20,000 chronic CHD (standard 2° prevention)</td>
<td>MACE</td>
<td>dal-OUTCOMES-II (stopped early in recruitment)</td>
</tr>
</tbody>
</table>

Cause of Dalcetrapib failure remains unknown

Dalcetrapib Increases HDL-C and Apo A-I but Does Not Reduce LDL-C or Apo B (dal-VESSEL)

Luscher, TF Eur Heart J 2012;33:857.
Dalcetrapib Did *Not* Improve Endothelial Function (Brachial Artery Dilatation in dal-VESSEL)

Also no anti-oxidant or anti-inflammatory effects were seen

Luscher, TF Eur Heart J 2012;33:857.
Dalcetrapib: Why *No* Benefit?

- No decr in pro-atherogenic particles: LDL-C and Lp(a)
- Few/no anti-athero mechanism benefits:
  - No incr endoth function
  - No anti-inflam effects
  - No anti-oxidation effects
- Odd MoA
  - Covalent binding to CETP, but
  - Poor inhibition (max ~50% even at 10x lethal doses)
- Unidentified metabolites (possible adverse effects?)
- dal-OUTCOMES was *only* in ACS population
- Incr in HDL-C too modest?
# Does Anacetrapib Reduce CVD Events? DEFINE Results

## Cardiovascular Events During the Treatment Phase of the Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Anacetrapib (N = 808)</th>
<th>Placebo (N = 804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified, adjudicated cardiovascular safety end point</td>
<td>16 (2.0)</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>4 (0.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>6 (0.7)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1 (0.1)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>11 (1.4)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>8 (1.0)</td>
<td>28 (3.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>6 (0.7)</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (0.2)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

“Hard” CVD
No net \( \Delta \) (\( \downarrow 23\% \)?)

“Soft” CVD events \( \downarrow 74\% \)

Anacetrapib and Evacetrapib
Ongoing Development
• N=30,000, prior CVD; recruiting in North America, Europe, and Asia
• Background LDL-C lowering with atorvastatin
• Randomized to anacetrapib 100 mg/d vs placebo
• Scheduled follow-up: 4 years (started 6/2011, estimated completion 1/2017)
• Primary outcome: Cor. death, MI, or cor. revasc.

www.revealtrial.org
http://clinicaltrials.gov/ct2/show/NCT01252953?term=anacetrapib&rank=4
ACCELERATE: CVD Endpoint Trial of Evacetrapib

- N=11,000 with:
  - ACS (30-365 days earlier), or
  - CVA, or PAD, or
  - DM-2 with CAD
- Background LDL-C lowering with statin
- Rx: evacetrapib 130 mg/d (new formulation)
- Minimum 18 months f/u (starting 2H 2012, completion ??)
- Endpoint composite: CV death, non-fatal MI, CVA, hosp for USA, revasc.
Summary: CETP-Inhibition for CVD Prevention

- HDL *can* (but does not *always*) prevent atherosclerosis and CVD events
- CETP-I *can* (but does not *always*) dramatically raise HDL-C and significantly reduce Lp-B (LDL, Lp(a))
- CETP-I *may* also facilitate reverse cholesterol transport (reduce futile cycling)
- CETP-I does *not* necessarily:
  - Impair HDL function, or otherwise
  - Promote atherosclerosis/CVD
- Two CETP-I continue in clinical development (one has suggestive prelim. data re: ↓CVD)
- CETP-I seems to be a reasonable approach to ↓CVD and…

“You miss 100% of the shots you don’t take.”

--Wayne Gretzky
Back-up/Rebuttal Slides
Coronary heart disease Inversely Predicted by HDL-C
(Independent of other factors)

N = 302,430

CHD Hazard Ratio

Adjusted for age and gender only
Adjusted for multiple factors

Statin Treatment Does *Not* Alter Inverse Relationship Between HDL-C and CVD

Yellow circles indicate patients who are receiving statin interventions, and orange circles indicate patients who are receiving a nonstatin control.

Interpretation Some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction. These data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions in risk of myocardial infarction.

Note that both the LIPG gene and the SNP panel altered only HDL-C but HDL-C rarely varies in isolation.

Is HDL-C just a marker of CVD risk and not causally protective? If so, is this relevant to potential CVD benefits of CETP-Inhibitors? I believe the answer to both questions is NO!
Potential Antiatherogenic Actions of HDL

- Antioxidative Activity
- Antithrombotic Activity
- Anti-infectious Activity
- Endothelial Repair
- Cholesterol Efflux
- Sterol Transport
- Reverse Cholesterol Transport
- Anti-inflammatory Activity
- Anti-apoptotic Activity
- Vasodilatory Activity

HDL Infusion Decreases Atherosclerosis (Carotid Collar Rabbit)

Effects of apoA-I vs LDL Interventions on Coronary Atherosclerosis by IVUS

Intensive Statin Treatment
Up to 53% reduction LDL-C for 2 years

Median Change in % Atheroma Volume

apoA-I Milano or r-HDL
for 4-5 weeks

Intensive Statin Treatment

REVERSAL
pravastatin 40 mg
540 days

Progression

ASTEROID
rosuvastatin 40 mg
720 days

ERASE
apoA-I milano
JAMA 2003

Delipidated HDL

Mean LDL-C


Courtesy of Dr. Jan Johansson
There is substantial evidence that HDL is directly atheroprotective, but… “the devil is in the details”
Diversity of HDL Subpopulations

**Particle Shape**
- Discoidal
- Spherical
- Globular

**Apolipoprotein Content**
- A-I HDL
- A-I/A-II HDL
  - +other apos: A-IV, C, D, E, etc.
  - +non-apo proteins: inflam, thromb, etc.

**HDL Particle Size/Electrophoretic Mobility**
- HDL$_{2b}$
- HDL$_{2a}$
- HDL$_{3a}$
- HDL$_{3b}$
- HDL$_{3c}$

- Lipid-poor apoA-I
  - Globular
  - Discoidal

- Alpha-migrating
- Pre-beta-migrating
The HDL Proteome

- Lipid Metabolism
  - CETP
  - LCAT
  - apoC-I
  - apoC-II
  - apoC-III
  - apoC-IV
  - apoA-1
  - apoA-II
  - apoE
  - apoD
  - apoL-I
  - apoM
  - apoF
  - Clusterin
  - apoA-IV
  - apoH
  - PON1
  - PON3
  - SAA4
  - SAA2
  - SAA1
  - apoA-1

- Complement Regulation
  - C3
  - C4A
  - C4B
  - C9
  - VTN

- Proteinase Inhibitor
  - AGT
  - SERF2
  - SERF1
  - HRP
  - AMP
  - KNG1
  - AHSG
  - SERA1

- Acute-phase Response
  - ORM2
  - TTR
  - ITIH4
  - RBP4
  - TF
  - FGA
  - HPX

How to measure HDL benefits? How to treat to increase them?

We don’t know! (yet)
CETP Inhibition: Promise Unrealized

Benjamin Ansell, MD FACC, FACP, FNLA
Co-Director, Cholesterol, Hypertension, & Atherosclerosis Management Program (CHAMP)
Professor of Medicine/Cardiology and General Medicine
UCLA School of Medicine, Los Angeles, CA
Framingham Heart Study

Risk of coronary artery disease in men aged 50-70 according to HDL-C and LDL-C levels over four years of follow-up

Adapted from Castelli WP, et al. JAMA. 1986;256:2835-2838.
CETP-Inhibition: Epitaph of Failure

- Reverse epidemiology
- Epidemiology/genetic models
- Mechanism of action
- HDL “Functional” testing
- Clinical trials/imaging
HDL Metabolism: Role of CETP

A1=apolipoprotein A1
ABCA1=ATP-binding cassette transporter A1
CE=cholesterol ester
CETP=cholesterol ester transfer protein
FC=free cholesterol
LCAT=lecithin cholesterol acyltransferase
LDL=low-density lipoprotein
LDLR=LDL receptor
SR-BI=scavenger receptor class-B, type I
TG=triglyceride
VLDL=very low density lipoprotein

Liver
Bile

SR-BI
LDLR

CETP

VLDL/LDL

Macrophage

ABCA1

www.lipid.org
CETP Deficiency is Associated with Markedly Increased HDL-C Levels

A1=apolipoprotein A1
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CETP=cholesterol ester transfer protein
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LDLR=LDL receptor
SR-BI=scavenger receptor class-B, type I
TG=triglyceride
VLDL=very low density lipoprotein

HDL-C=high-density lipoprotein cholesterol
HDL Metabolism in CETP Deficiency

Delayed catabolism

A-I

CE

LCAT

A-I

FC

ABCA1

Macrophage

CETP

VLDL/LDL

B

CE

TG
CETP Deficiency

- Autosomal co-dominant; mutations in both alleles of CETP gene
- Markedly elevated levels of HDL-C and apoA-I
- Delayed catabolism of HDL cholesteryl ester and apoA-I
- HDL particles enlarged and enriched in cholesteryl ester
- No evidence of protection against atherosclerosis; possible increased risk of premature atherosclerotic vascular disease

CVD-Free Survival According to CETP Activity

Log rank p=0.0004

N= 1,978 from Framingham offspring cohort


Number at Risk

<table>
<thead>
<tr>
<th>CETP &lt; median</th>
<th>CETP &gt; median</th>
</tr>
</thead>
<tbody>
<tr>
<td>989</td>
<td>989</td>
</tr>
<tr>
<td>937</td>
<td>958</td>
</tr>
<tr>
<td>858</td>
<td>886</td>
</tr>
<tr>
<td>617</td>
<td>768</td>
</tr>
</tbody>
</table>
CETP-Inhibition: Epitaph of Failure

- Reverse epidemiology
- Epidemiology/genetic models
- Mechanism of action
- “Functional” testing
- Clinical trials/imaging
CETP-Inhibition: Historical Perspective

- Epidemiology of HDL-C
- Extrapolation from post hoc analyses of trials of other lipid-lowering agents
- Negative results from FIELD, ACCORD, AIM-HIGH
- Optimism even in context of known blood pressure effects of torcetrapib
Dalcetrapib (JTT-705) Attenuates Atherosclerosis in Rabbits

CETP-Inhibition: Historical Perspective

- Epidemiology of HDL-C
- Extrapolation from *post hoc analyses* of trials of other lipid-lowering agents
- Optimism even in context of known blood pressure effects of torcetrapib
## Lipid Effects of CETP Inhibitors/Modulators

### % Change from Baseline

<table>
<thead>
<tr>
<th>CETP Agent</th>
<th>Dose (Mg/day)</th>
<th>HDL-C (%)</th>
<th>LDL-C (%)</th>
<th>TG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>60</td>
<td>61</td>
<td>-24</td>
<td>-9</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>100</td>
<td>138</td>
<td>-40</td>
<td>-7</td>
</tr>
<tr>
<td>Evacetrapib</td>
<td>500</td>
<td>129</td>
<td>-36</td>
<td>-11</td>
</tr>
<tr>
<td>Dalcetrapib</td>
<td>600</td>
<td>31</td>
<td>-2</td>
<td>-3</td>
</tr>
</tbody>
</table>

ILLUMINATE: Increased Cardiovascular and Non-cardiovascular Morbidity and Mortality with Torcetrapib

59% increase in all-cause mortality (P<0.001)

ILLUMINATE: Mortality by Treatment Assignment


<table>
<thead>
<tr>
<th>Event</th>
<th>Atorvastatin Only (N = 59)</th>
<th>Torcetrapib plus Atorvastatin (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular cause</td>
<td>35</td>
<td>49</td>
</tr>
<tr>
<td>Sudden death</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Fatal myocardial infarction (not procedure-related)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Embolic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not classified</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal heart failure</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other vascular-related cause</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fatal myocardial infarction (procedure-related)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other cardiac-related cause</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Any noncardiovascular cause</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Cancer</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Suicide or homicide</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other cause</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Reason unknown</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
DEFINE: Anacetrapib Had no Effect on BP

The dal-HEART Program tests a novel hypothesis that raising HDL through CETP inhibition will attenuate cardiovascular risk.

<table>
<thead>
<tr>
<th>dal-OUTCOMES 1</th>
<th>dal-VESSEL 2</th>
<th>dal-PLAQUE 3</th>
<th>dal-PLAQUE 2 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A double-blind, randomized, placebo-controlled study in 15,600 patients recently hospitalized for ACS</td>
<td>A double-blind, randomized, placebo-controlled study in 450 patients with CHD or CHD risk equivalent</td>
<td>A double-blind, randomized, placebo-controlled study in 130 patients with CHD</td>
<td>A double-blind, randomized, placebo-controlled study in 900 patients with CAD</td>
</tr>
<tr>
<td>Goal: To evaluate the effect of dalcetrapib on CV outcomes</td>
<td>Goal: To evaluate the effect of dalcetrapib on endothelial function and blood pressure, measured by FMD and ABPM</td>
<td>Goal: To evaluate the effect of dalcetrapib on inflammation, plaque size, and burden, measured by PET/CT and MRI</td>
<td>Goal: To evaluate the effect of dalcetrapib on atherosclerotic progression, assessed by IVUS and carotid B-mode ultrasound</td>
</tr>
</tbody>
</table>

**Trial design:** Clinically stable patients with coronary heart disease (CHD) or at high risk for CHD who were already on lipid-lowering therapy were randomized to either dalcetrapib or placebo. Patients were followed for 2 years.

**Results**

- 30.9% vs. 4%: increase in HDL for dalcetrapib vs. placebo. No difference in BP between the two arms.
- MRI: significant ↓ in total vessel area (average for carotid) with dalcetrapib vs. placebo at 24 months (-4.01 mm²; p = 0.04)
- $^{18}$F-FDG-PET/CT: most diseased segment mean of max target-to-background ratio unchanged after 6 months (-0.07; 95% CI -0.11 to 0.25; p = 0.51)

**Conclusions**

- Phase II trial indicating that dalcetrapib, a novel CETP inhibitor, is not associated with pro-inflammatory effects, with a slight reduction in carotid plaque volume on MRI

Fayad ZA, et al. Lancet 2011;Sep 12:[Epub]
**dal-OUTCOMES: Study Design**

- A double-blind, randomized, placebo-controlled, multicenter outcomes study in 15,600 patients with stable CHD after recent ACS
- Outcomes: coronary death, MI, or CVA

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**Pre-randomization phase**

- **Single-blind**
  - Placebo Run-in
  - 4-12 Weeks

**Double-blind**

- dalcetrapib 600 mg
- placebo

**Background of standard medication for ACS** (including aspirin, antihypertensives, and statins)

**Visit 1**

**Visit 2**

**Randomization**

**Visit 3**

**Follow up 1st year:** every 3 months

**Following years:** every 4 months

**At least 2 years**

**Until 1600 events occur, but at least a minimum of 2 years**

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Dal-OUTCOMES: Study Termination

- Study stopped May 7, 2012 “due to a lack of clinically meaningful efficacy.”
- No safety signals were reported from DSMB.
- Subsequent imaging and surrogate studies also terminated.

CETPi Clinical Trial Scorecard

- Torcetrapib
  - increased all-cause mortality
  - Increased both CV and non-CV mortality
  - neutral effect on imaging

- Dalcetrapib
  - No effect on primary endpoint
  - Modest improvement in imaging

- Anacetrapib
  - Trends toward decreased primary endpoint (DEFINE safety analysis) and revasc., but increased total and CV mortality
  - Await HPS-3 REVEAL

- Evacetrapib