Biological Janus:

# CETP inhibitor

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# ILLUMINATE study

## Torcetrapib

Wall Street *Journal,* Dec 4th
The Lancet, Dec 7th, 2006

- One of the most promising new approaches in cardiovascular medicine hit the buffers on Dec 2 when Pfizer announced the stopping of its phase III clinical trial development of torcetrapib.

- This trial was a large international randomised study of torcetrapib plus atorvastatin versus atorvastatin alone in 15 000 patients with or at risk of coronary heart disease. There had been 82 deaths in the torcetrapib plus atorvastatin group, compared with 51 deaths in the group taking atorvastatin.

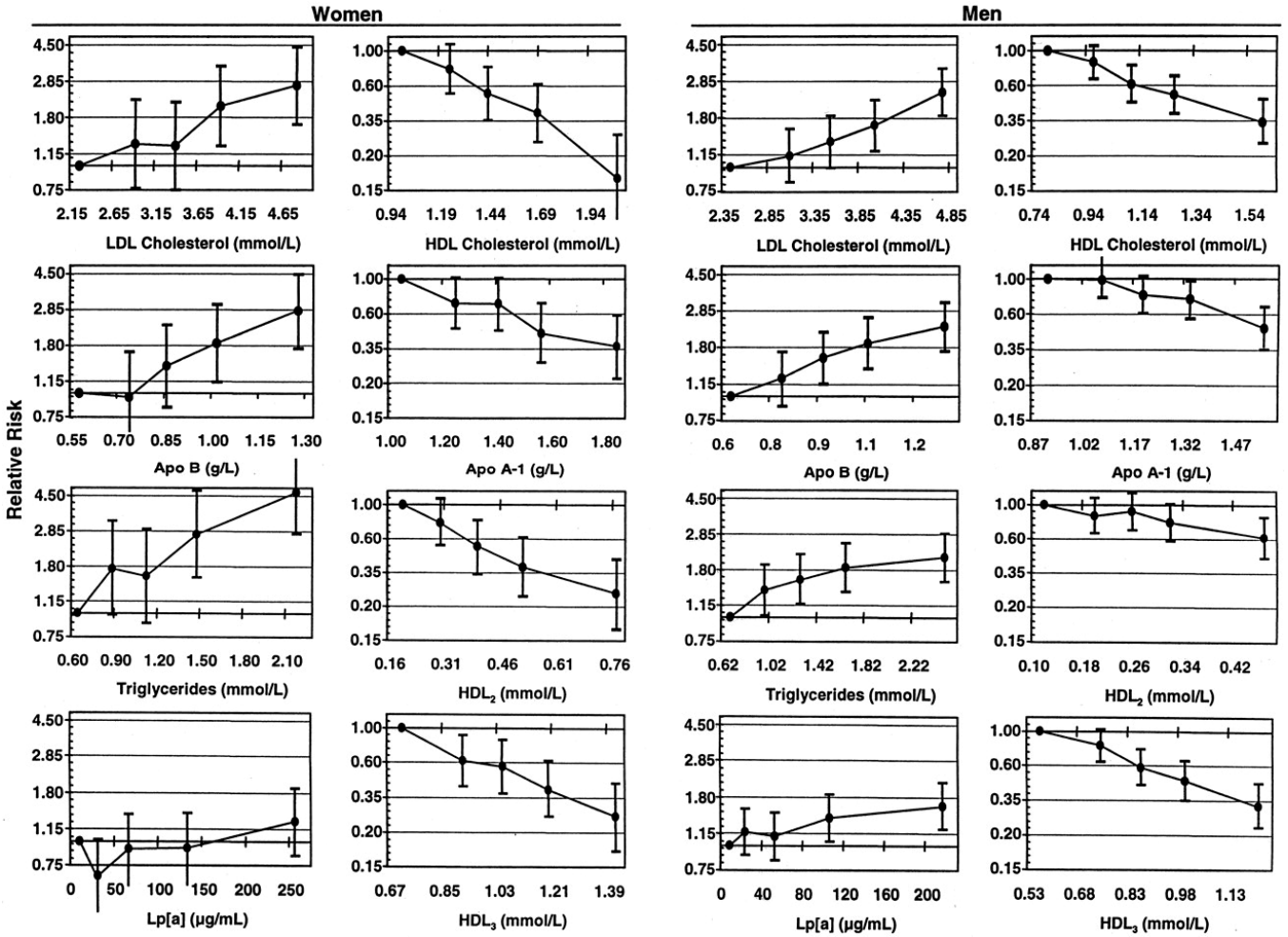
# The reasons for the failure are still unknown.

Possible reasons

- Hypertension
- Dysfunctional HDL
- Other unknown reason?

# HDL and cardiovascular risk

RR of CHD for lipid factor quintiles in ARIC study




*Sharrett, AR et al. Circulation 2001;104:1108*

**Table 3.** Randomized Controlled Clinical Trials of Pharmacological Therapies that Modify HDL and Affect Clinical or Surrogate Outcomes of Atherosclerotic Burden

| Source | Specific Agent(s) | Patients Receiving Treatment, No./Total (%) | Increase in HDL-C Levels, % | Follow-up Duration, y | Outcomes[a] |
|---|---|---|---|---|---|
| | | Nicotinic Acid | | | |
| Clinical outcome studies | | | | | |
| CDP,[44] 1975 | Niacin | 1119/8341 (13.4) | NR | 6 | Decreased (27%) nonfatal MI |
| CDP follow-up,[50] 1986 | Niacin | 1119/8341 (13.4) | NR | 15 | Decreased (11%) death |
| Stockholm,[51] 1988 | Niacin + clofibrate | 279/555 (50.3) | NR | 5 | Decreased (26%) death; decreased (36%) CAD death |
| HATS,[48] 2001 | Niacin + simvastatin | 38/160 (23.8) | 26 | 3 | Decreased (90%) first death, MI, stroke, or revascularization |
| AFREGS,[56] 2005 | Niacin + gemfibrozil + cholestyramine | 71/143 (49.7) | 36 | 2.5 | Decreased (13%) composite clinical outcome of angina, MI, TIA, stroke, death, and cardiovascular procedures; decreased focal coronary stenosis (secondary outcome) |
| Imaging studies | | | | | |
| CLAS I,[46] 1987 | Niacin + colestipol | 94/188 (50.0) | 37 | 2 | Decreased coronary atherosclerosis |
| CLAS II,[52] 1990 | Niacin + colestipol | 75/138 (54.3) | 37 | 4 | Decreased coronary atherosclerosis |
| FATS,[49] 1990 | Niacin + colestipol | 48/146 (32.9) | 43 | 2.5 | Decreased coronary atherosclerosis; decreased death, MI, or revascularization (secondary outcome) |
| CLAS Fem,[45] 1991 | Niacin + colestipol | 80/162 (49.4) | 38 | 2 | Decreased femoral atherosclerosis |
| CLAS IMT,[47] 1993 | Niacin + colestipol | 39/78 (50.0) | 38 | 4 | Decreased carotid IMT (regression also observed at 1 and 2 y) |
| SCRIP,[53] 1994 | Niacin + colestipol + gemfibrozil + lovastatin + aggressive lifestyle modification | 145/300 (48.3) | 12 | 4 | Decreased coronary atherosclerosis; decreased frequency of new coronary lesion formation |
| ARBITER 2,[55] 2004 | Niacin + statin | 87/167 (52.1) | 21 | 1 | Decreased carotid IMT ($P > .05$) |
| ARBITER 3,[54] 2006 | Niacin + statin | 87/167 (52.1) | 23 | 2 | Decreased carotid IMT |

*Singh, IM et al. JAMA 2007;298:786-798.*

# Why CETP ?

**Table 1.** Effect of Lifestyle Modifications on HDL-C Levels and HDL Components

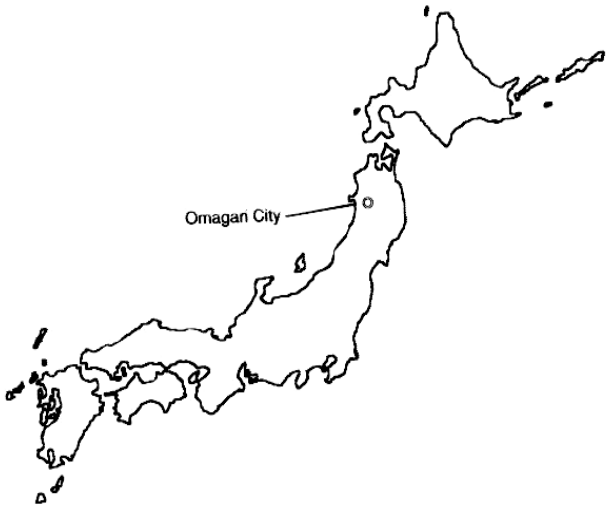
| Therapeutic In | | | |
|---|---|---|---|
| Aerobic exercise | | | |
| Tobacco cessati | | | |
| Weight loss[28-32] | | | |
| Alcohol consump | | | |
| Dietary factors (n<br>n-6 PUFAs, M | | | |

Abbreviations: ABC
cholesterol ester
ferase; LDL-C, lo
polyunsaturated
SI conversion factor: To convert HDL-C to mmol/L, multiply by 0.0259.

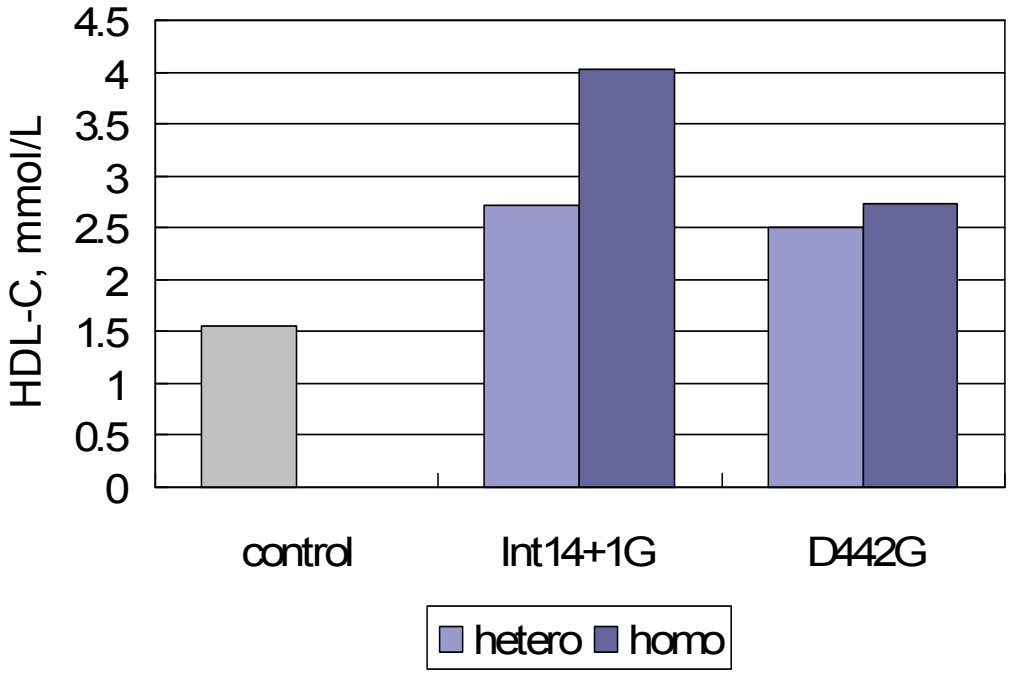
| Class of Agent | Specific Agents | Increase in HDL-C Levels, % | Mechanism of Action |
|---|---|---|---|
| Nicotinic acid (vitamin $B_3$)[44-56] | Niacin: 1-2 g 2 or 3 times/d<br>Niacin (ER): 1-2 g nightly<br>Niacin (SR): 250-750 mg/d or twice daily[a] | 20-30 | Increases pre-β-HDL<br>Decreases DGAT2 and hepatic apo A-I catabolism |
| Fibric acid derivatives[44,57-67] | Fenofibrate (Micronase): 43-200 mg/d<br>Fenofibrate: 48-145 mg/d<br>Gemfibrozil: 600 mg twice daily | 10-20 | Increases PPAR-α, hepatic apo A-I synthesis, apoC-III, and LPL<br>Decreases DGAT |
| Statins[68-75] | Atorvastatin: 10-80 mg/d<br>Fluvastatin: 20-40 mg nightly<br>Fluvastatin (ER): 80 mg nightly<br>Lovastatin: 10-60 mg nightly<br>Pravastatin: 10-80 mg/d<br>Rosuvastatin: 5-40 mg/d<br>Simvastatin: 5-80 mg/d | 5-10 | Increases hepatic apo A-I synthesis, PPAR-α, and mRNA synthesis<br>Decreases CETP |
| Cannabinoid-1 receptor blocker[31,32b] | Rimonabant: 5-20 mg/d | 5-10 | Increases adiponectin expression and production, apo A-I |
| Thiazolidinediones[76-78] | Pioglitazone: 2-8 mg/d or twice daily<br>Rosiglitazone: 15-45 mg/d | 5-10 | Increases PPAR-γ, ABCG1, and cholesterol efflux |
| Combination pill[79] | Lovastatin + niacin: 20/500 mg to 20/1000 mg nightly | 20-25 | As for individual agents |

*Singh, IM et al. JAMA 2007;298:786-798.*

# CETP mutation and HALP

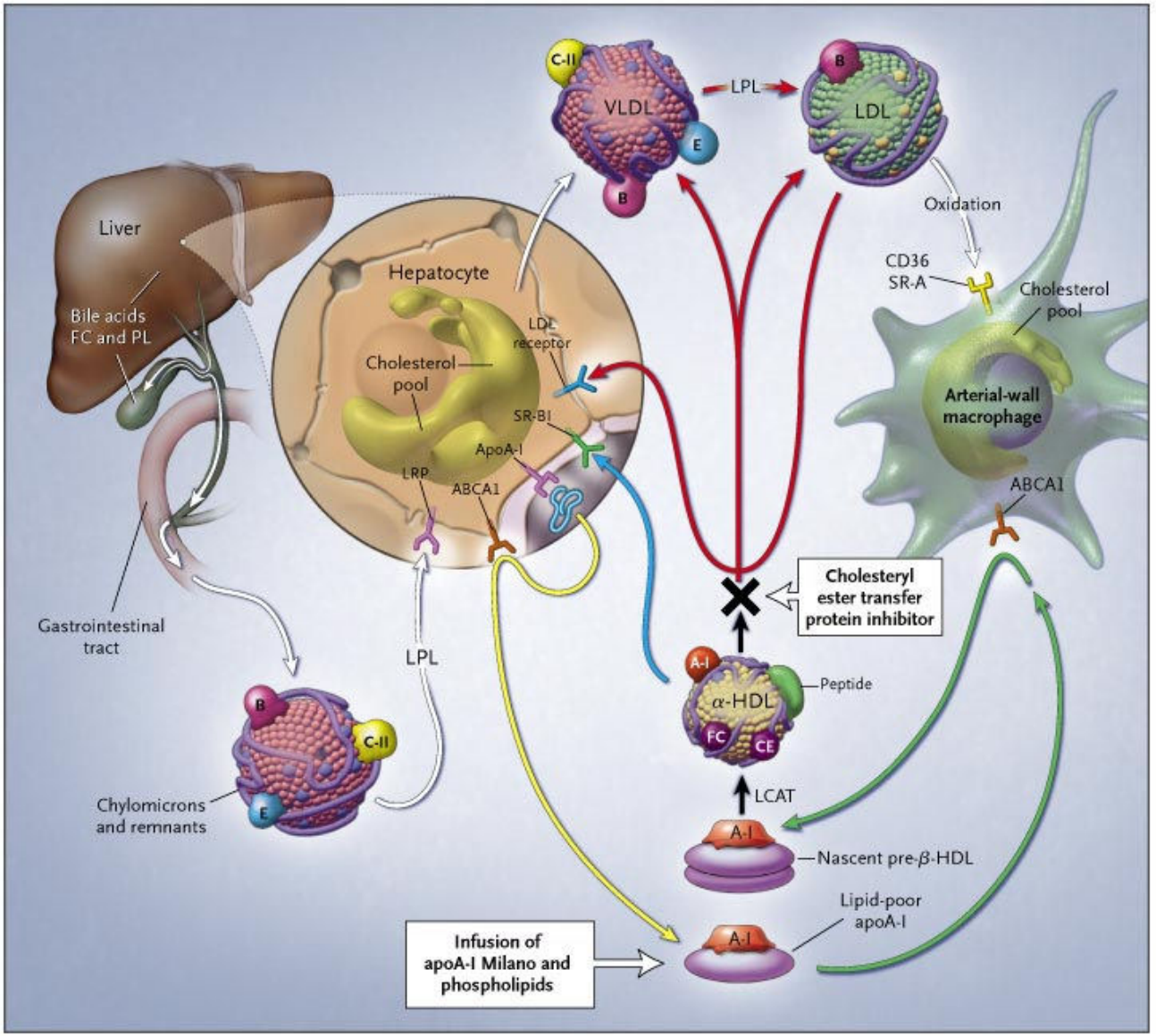



27% of people in the Omagari area of Japan has G to A mutation at the +1 of intron 14




*J Atheroscler Thromb. 2004;11:110*

# HDL & CETP




*N Eng J Med 2004;350:1491*

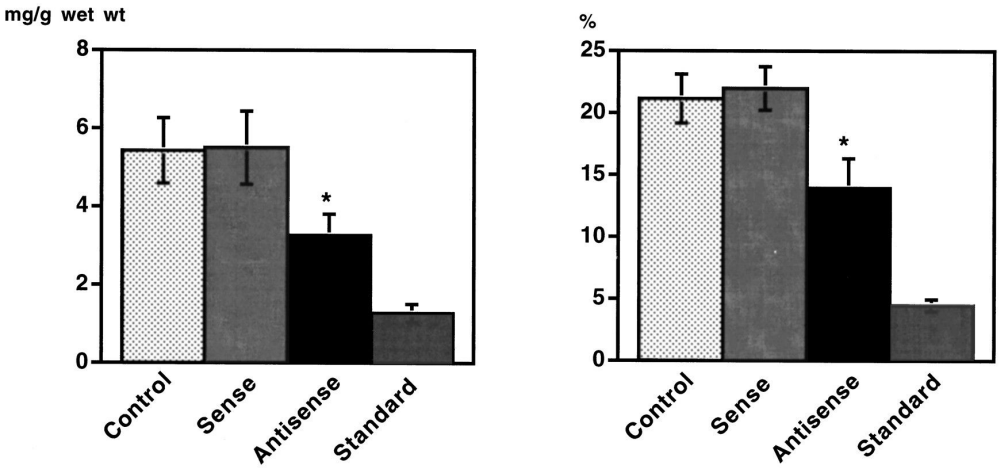
# CETP

- Facilitate hepatic cholesterol transport (additional route for delivery of HDL-derived CE via VLDL and LDL)
- Promote cholesterol removal from peripheral cells
- Involved in the generation of lipid poor pre-β-HDL particle
- May directly stimulate hepatic uptake of cholesterol esters from HDL

# Do we have enough evidences that CETP inhibition reduce CAD ?

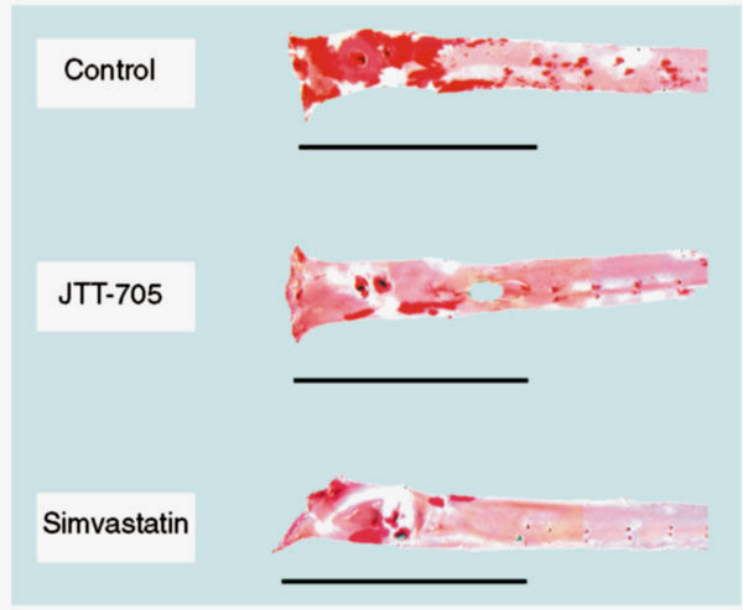
# CETP and atherosclerosis

## Inhibition of CETP in rabbit




CETP inhibition with antisense ODNs against CETP inhibit the atherosclerosis possibly by decreasing the plasma LDL + VLDL cholesterol in cholesterol-fed rabbits.

*JBC. 1988;273:5033*

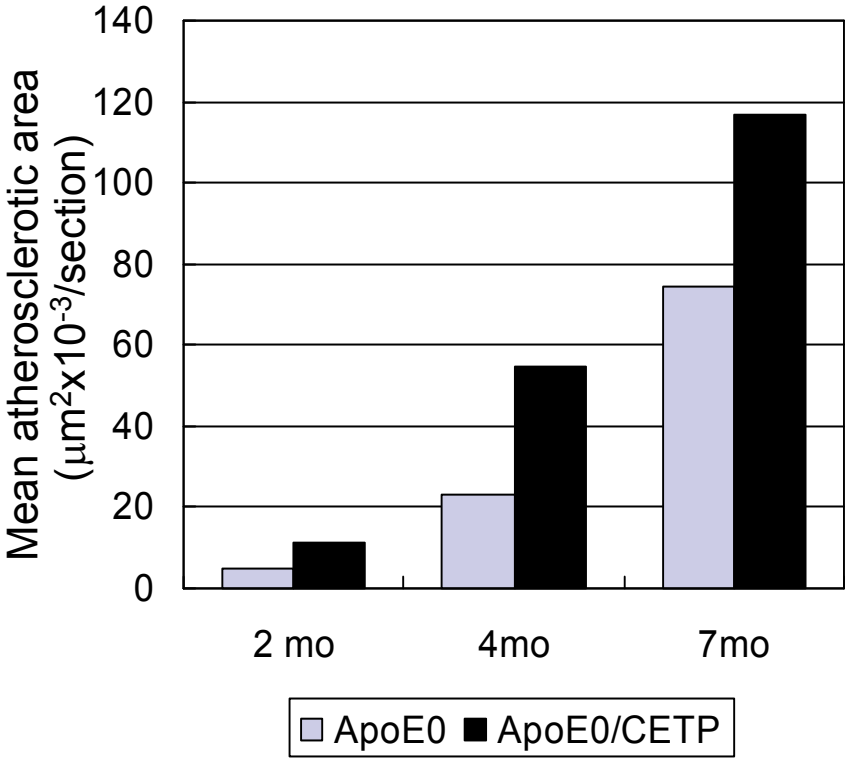



CETP inhibitor (JTT-705) that increases HDL cholesterol and inhibits the progression of atherosclerosis in rabbits.

*Nature. 2000;406:203*

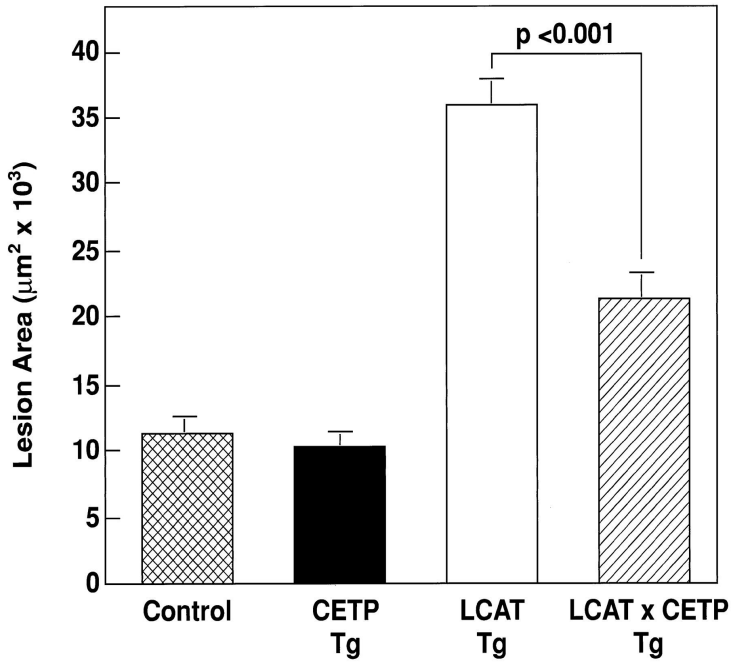
# CETP and atherosclerosis

## Expression of CETP in Transgenic Mice




CETP increases the extent of atherosclerosis in the apoE0 background

*ATVB 1999;19:1105*




Aortic lesion area in control, CETP-Tg, LCAT-Tg, and LCATxCETP-Tg mice after 16 weeks on an atherogenic HFHC diet.

*JBC 1999;274:36912*

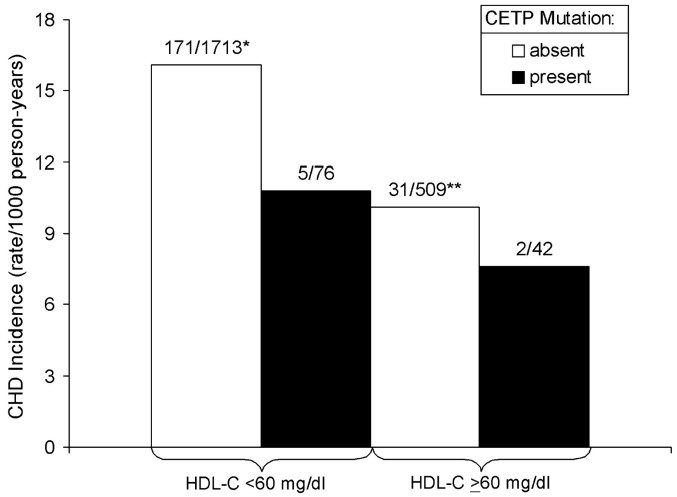
# CETP and atherosclerosis

## Human observational study

- Subjects with very high HDL levels (HDL-C ≥ 80 mg/dl) as well as mild-to-moderate HDL elevations (60-79 mg/dl) appear to be protected against CHD, whether or not they have CETP deficiency, a genetic cause of elevated HDL.

*Moriyama et al. Prev Med. 1998;27:659*

- Prospective study of HDL-C and cholesteryl ester transfer protein gene mutations and the risk of CHD in the elderly: suggestion of a lower rate of coronary events in those with a CETP mutation and a high HDL-C

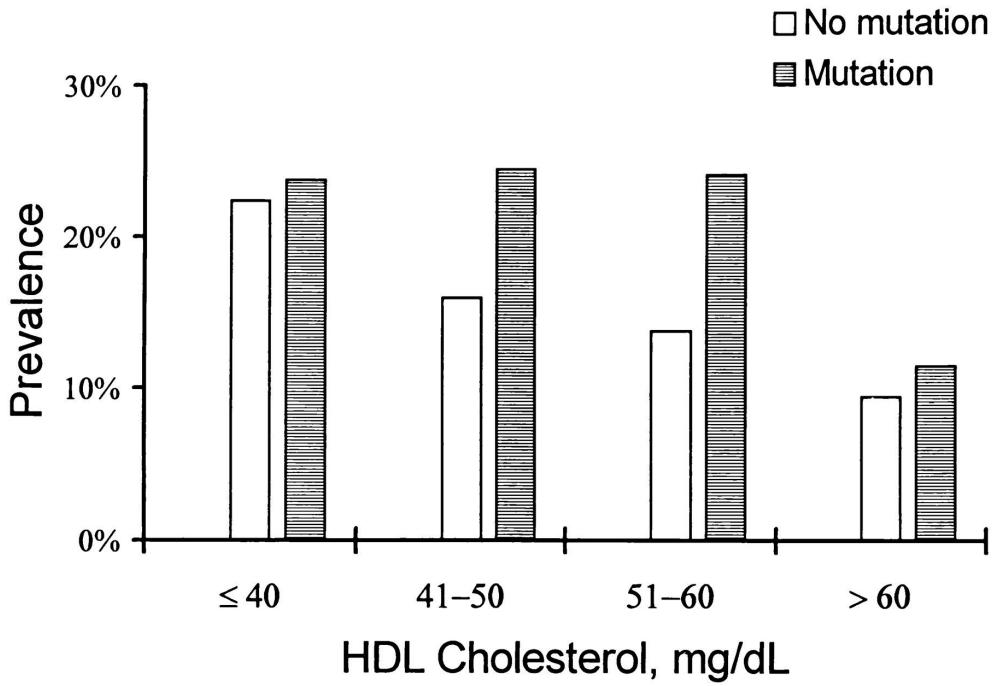



*J Lipid Res. 2004;45:948*

# CETP and atherosclerosis

## Human observational study

**Increased CHD in Japanese-American men with mutation in the CETP gene despite increased HDL levels**




Prevalence of men with definite coronary heart disease among four strata of HDL cholesterol for two groupings of men with and without a CETP mutation. HDL strata cut-points are approximately equal to quartiles.

*JCI 1996;97: 2917*

# CETP and atherosclerosis

## Clinical Trials

**Table 3.** Randomized Controlled Clinical Trials of Pharmacological Therapies that Modify HDL and Affect Clinical or Surrogate Outcomes of Atherosclerotic Burden (cont)

| Drug Class | Specific Agent(s) | Patients Receiving Treatment, No./Total (%) | Increase in HDL-C Levels, % | Follow-up Duration, y | Outcomes[a] |
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| ILLUSTRATE,[81] 2007 | Torcetrapib + atorvastatin | 591/1188 (49.7) | 61 | 2 | No decrease in coronary atherosclerosis progression by IVUS |
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| RADIANCE 2,[4] 2007 | Torcetrapib + atorvastatin | 377/752 (50) | 63 | 1.8 | No change in maximum intima-media thickness |
| | | **Apo A-I–Directed Therapies** | | | |
| Apo A-I Milano,[83] 2003 | ETC-216 | 45/57 (78.9) | NR | 5 wk | Decreased coronary atheroma volume on IVUS |
| ERASE,[84] 2007 | Reconstituted HDL (CSL-111) | 111/183 (60.7) | NR | 6 wk | No decrease in coronary atheroma volume on IVUS |

Abbreviations: AFREGS, Armed Forces Regression Study; apo A-1, apolipoprotein A-I; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP, Bezafibrate Infarction Prevention Study; CAD, coronary artery disease; CDP, Coronary Drug Project; CLAS, Cholesterol Lowering Atherosclerosis Study; CLAS Fem, femoral atherosclerosis group of CLAS; CLAS IMT, carotid ultrasound group of CLAS; DAIS, Diabetes Atherosclerosis Intervention Study; ERASE, Effect of rHDL on Atherosclerosis-Safety and Efficacy Trial; FATS, Familial Atherosclerosis Treatment Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes Study; HATS, HDL-Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; ILLUSTRATE, Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation Trial; IMT, intima-media thickness; IVUS, intravascular ultrasound; LEADER, Lower Extremity Arterial Disease Event Reduction Trial; LOCAT, Lopid Coronary Angiography Trial; MI, myocardial infarction; NR, not reported; RADIANCE, Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor Trial; SCRIP, Stanford Coronary Risk Intervention Project; TIA, transient ischemic attack; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; WHO, World Health Organization.

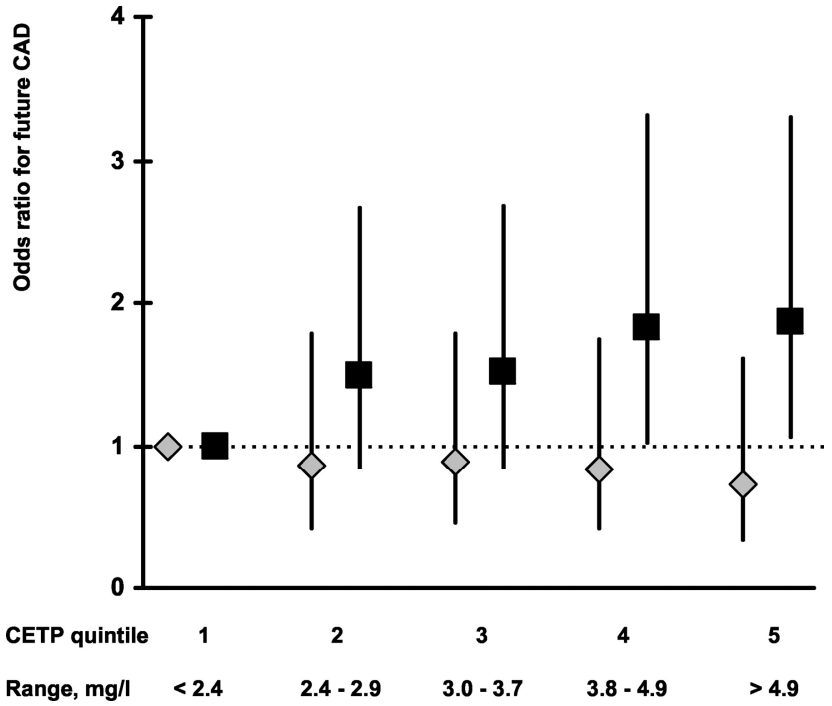
[a] Death indicates all-cause mortality.

*Singh, I. M. et al. JAMA 2007;298:786-798.*

# CETP activity and CAD

## Effect of plasma TG

The Prospective EPIC (European Prospective Investigation into Cancer and nutrition)–Norfolk Population Study




Increased concentrations of CETP are associated with an increasing risk of future CAD in healthy individual with elevated TG level (■ >1.7 mmol/L)

These prospective data support the hypothesis that pharmacological CETP inhibition may reduce the risk of CAD in humans, but only in those with high triglyceride levels.

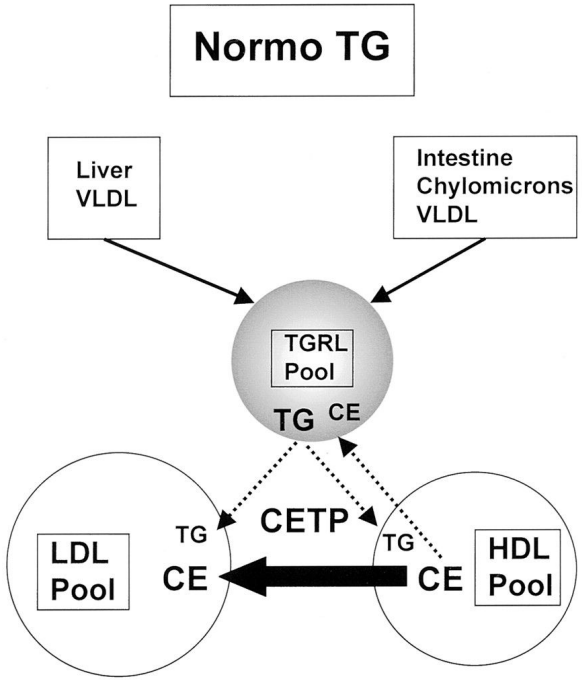
*Circulation. 2004;110:1418*

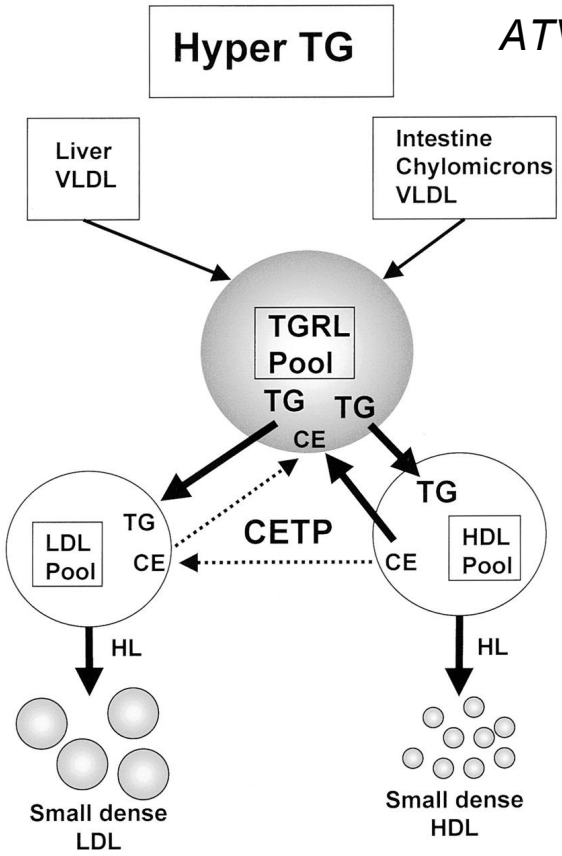
# CETP inhibition

Action mechanism

- Increase the HDL cholesterol?
  - Yes
- Increase the reverse cholesterol transport?

# Effects of CETP in Normo TG and Hyper TG




*ATVB 2003;23:160*

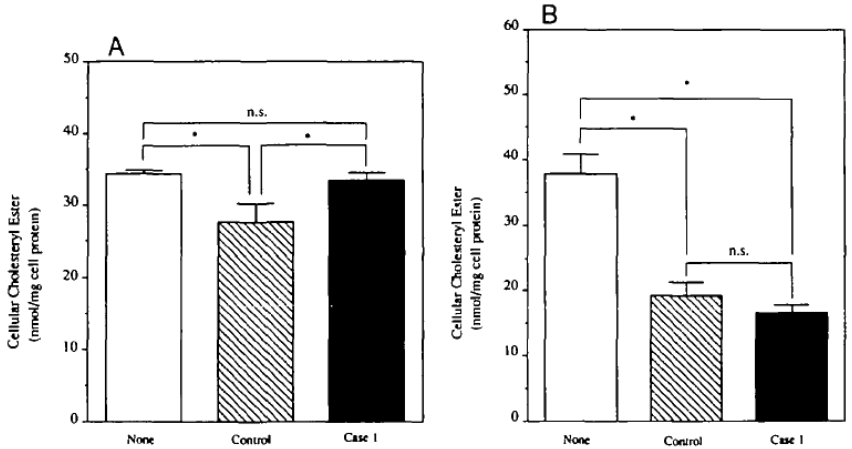
**CETP inhibition**

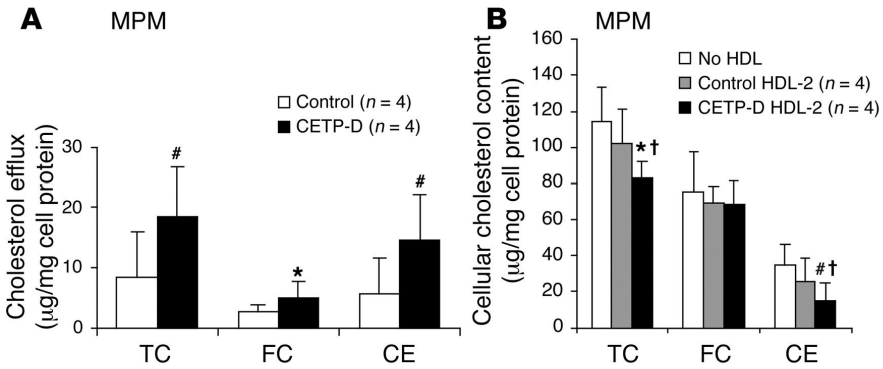
Affect RCT

Possibly reduce small dense LDL

# Effect of CETP in cholesterol efflux

$HDL_2$ | $HDL_3$ | Media | Cellular




Cholesterol efflux induced by HDL from MΦ

*Case: CETP deficiency

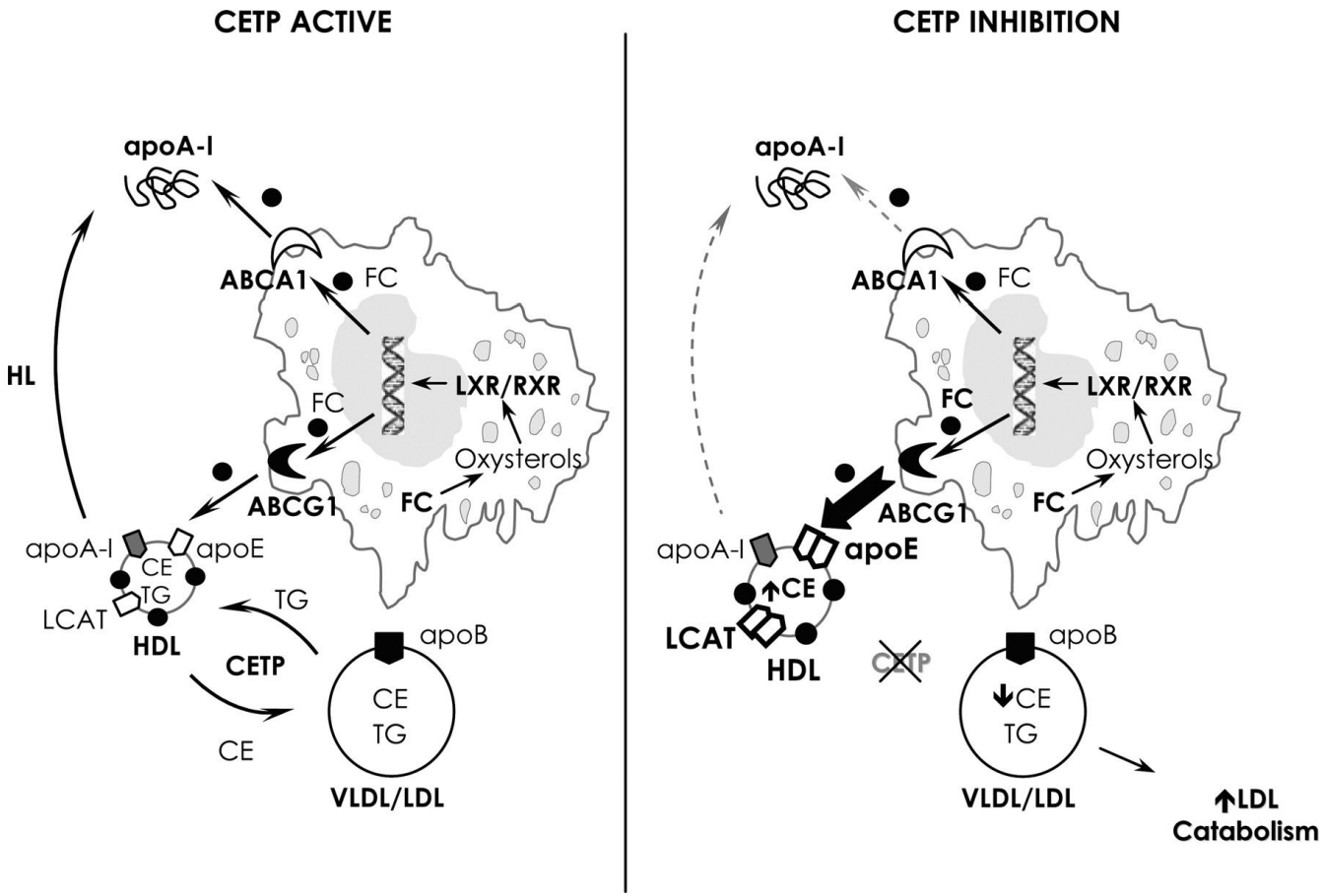
Homozygous CETP deficiency failed to promote CE efflux from cholesterol-loaded human MΦ ($HDL_2$)

HDL from CETP-deficient subjects shows enhanced CE efflux from MΦ (apoE- & ABCG1-dependent pathway)

*JBC 1994;116:257*

*J Clin Invest. 2006; 116: 1435*

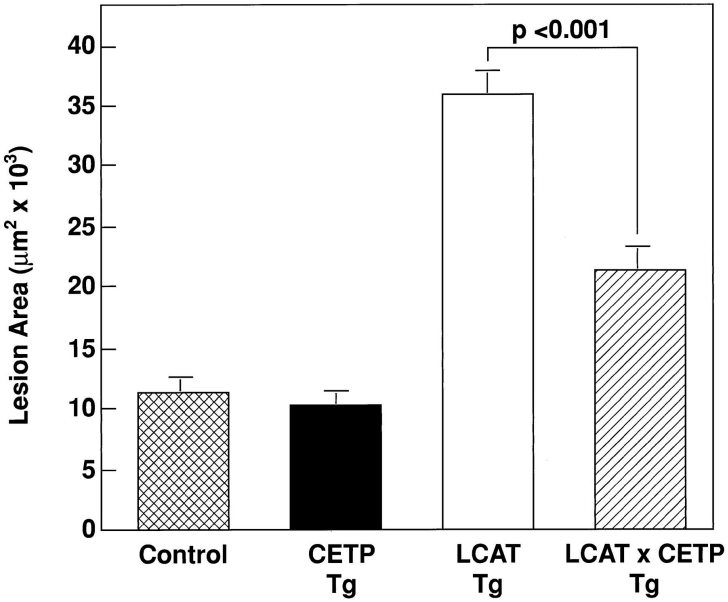
# Role of CETP in regulating macrophage cholesterol efflux via ABCA1 and ABCG1



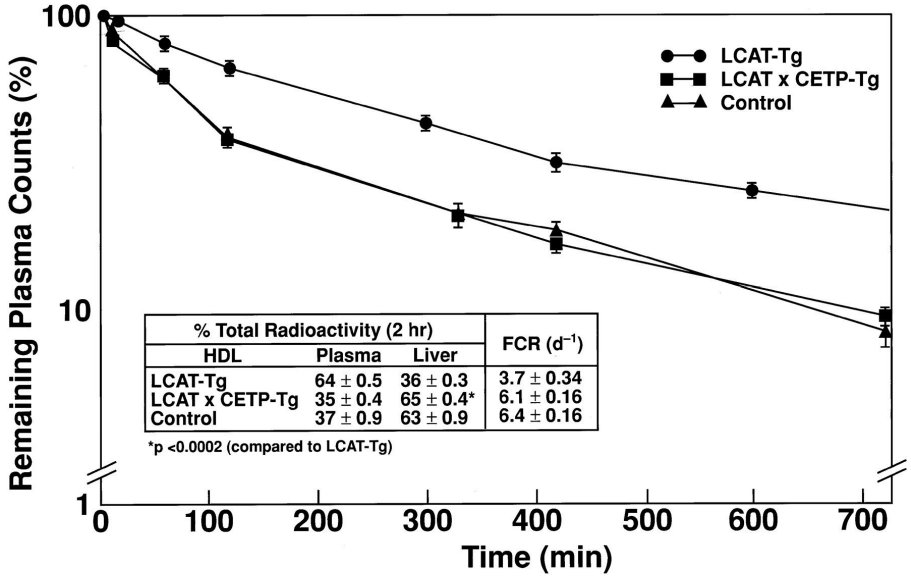

*ATVB 2007;27:257*

# CETP

## RCT: Animal experiments




Aortic lesion area in control, CETP-Tg, LCAT-Tg, and LCATxCETP-Tg mice after 16 weeks on an atherogenic high fat, high cholesterol diet.



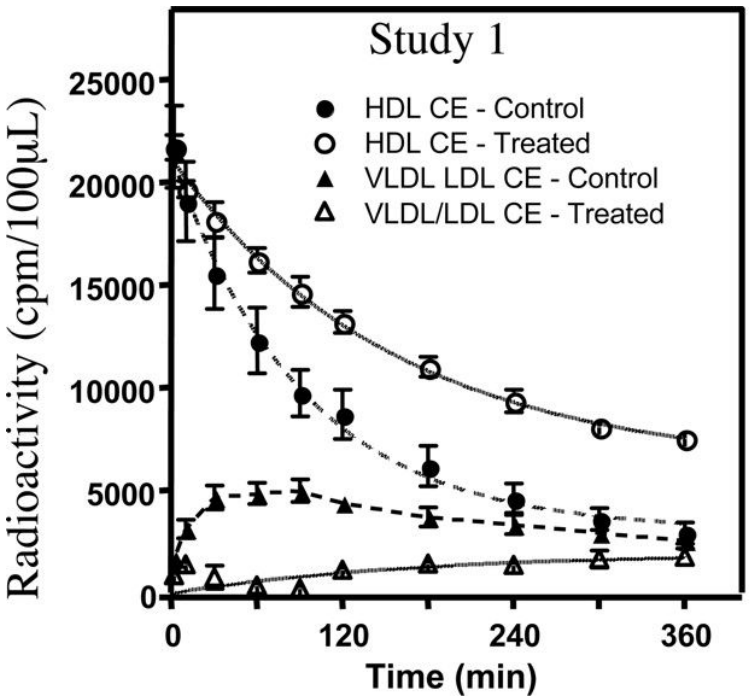

Plasma kinetics of [$^3$H]CE HDL from C57BL/6, LCAT-Tg, and LCATxCETP-Tg mice.

*JBC 1999;274:36912*

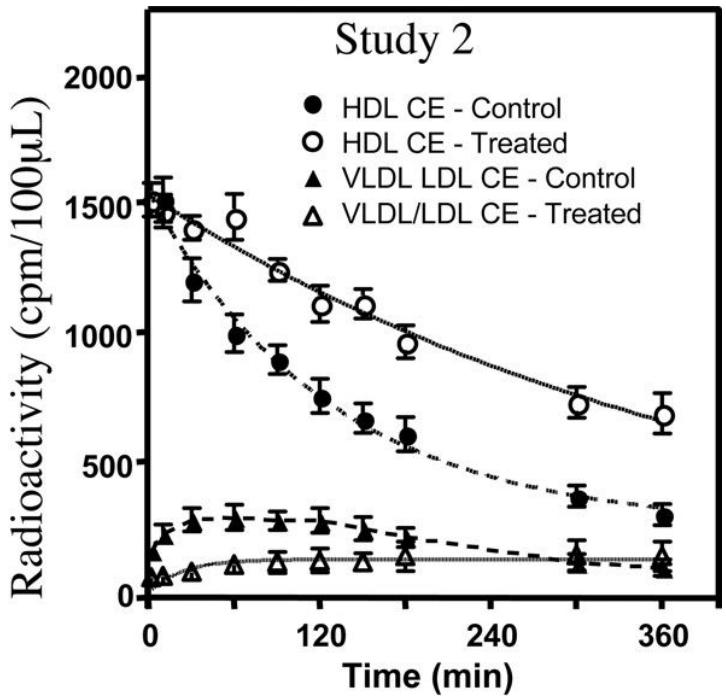
# Effect of Inhibiting CETP on the Kinetics of HDL CE Transport in Plasma

*ATVB 2006;26:884*

spherical rHDL as a tracer

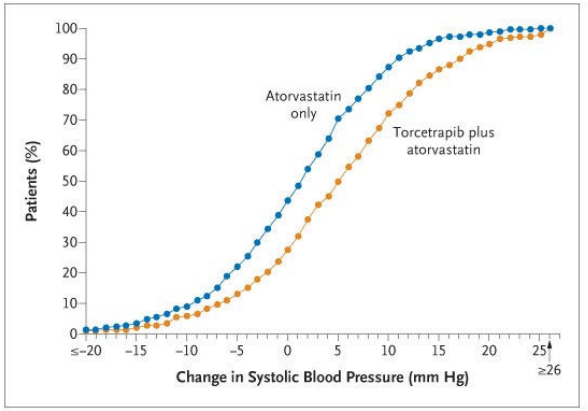



Native HDL as a tracer




Administration of the CETP inhibitor almost completely blocked the transfer of CE from HDL to the VLDL/LDL fraction. However, these effects were not accompanied by a reduction in the total flux of HDL CE, indicating that neither the rate of production nor the overall removal of HDL CE from plasma was compromised.

# Effect on blood pressure

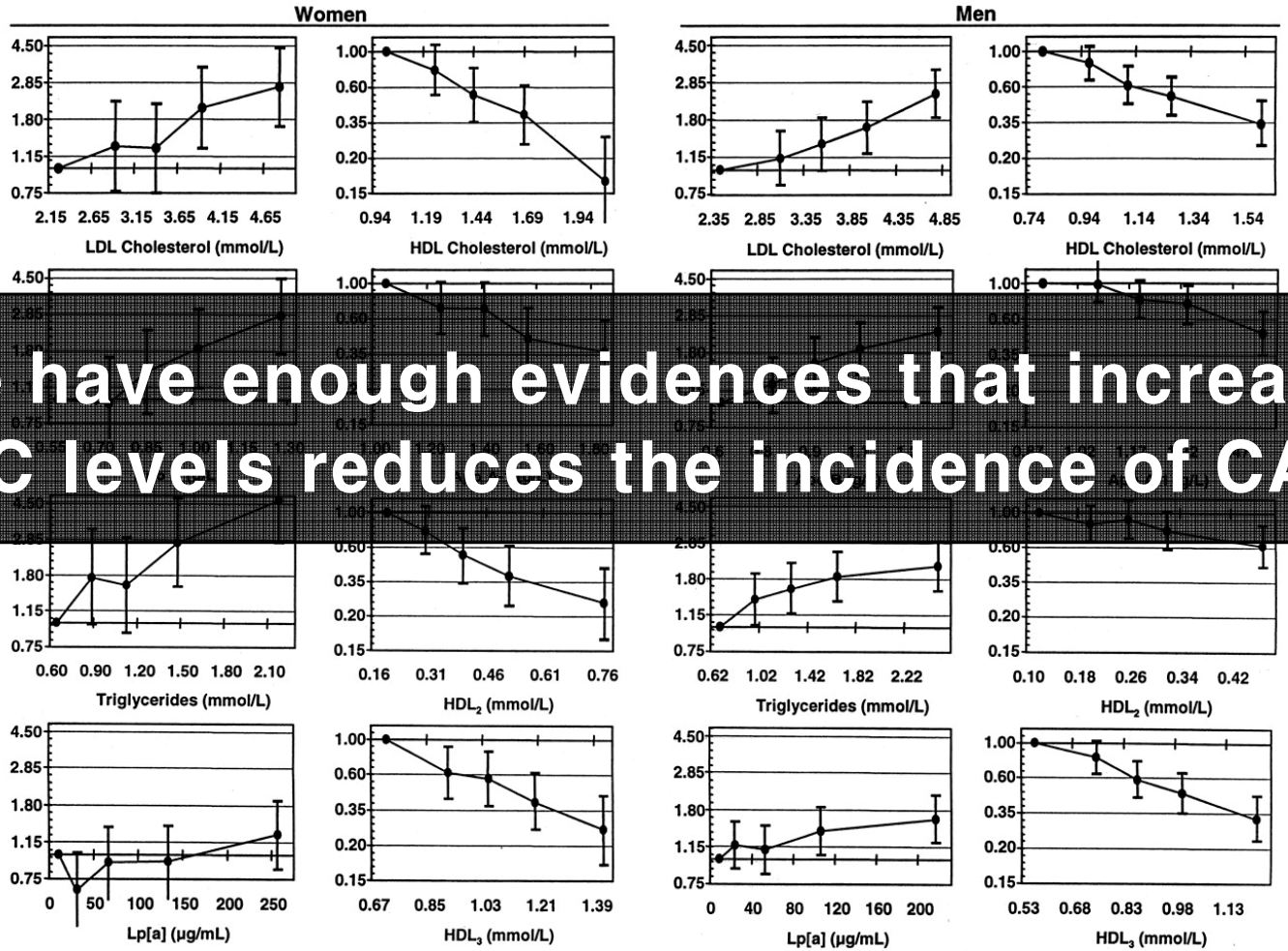



- ILLUMINATE trial
  - Patients in the torcetrapib–atorvastatin group had more hypertensive adverse events (23.7% vs. 10.6%) and more blood-pressure values greater than 140/90 mm Hg (21.3% vs. 8.2%). *NEJM 2007;356:1304*
- RADIANCE 2 study
  - The frequency at which systolic blood pressure was raised by 15 mm Hg or more was 20/377 (5%) in the combined-treatment group and 8/375 (2%) in controls (p=0.02).

*Lancet 2007;370:153*

# HDL and cardiovascular risk

RR of CHD for lipid factor quintiles with in ARIC study




**Do we have enough evidences that increasing HDL-C levels reduces the incidence of CAD?**

*Sharrett, A. R. et al. Circulation 2001;104:1108*

# Therapy targeted to HDL

## Clinical Trials

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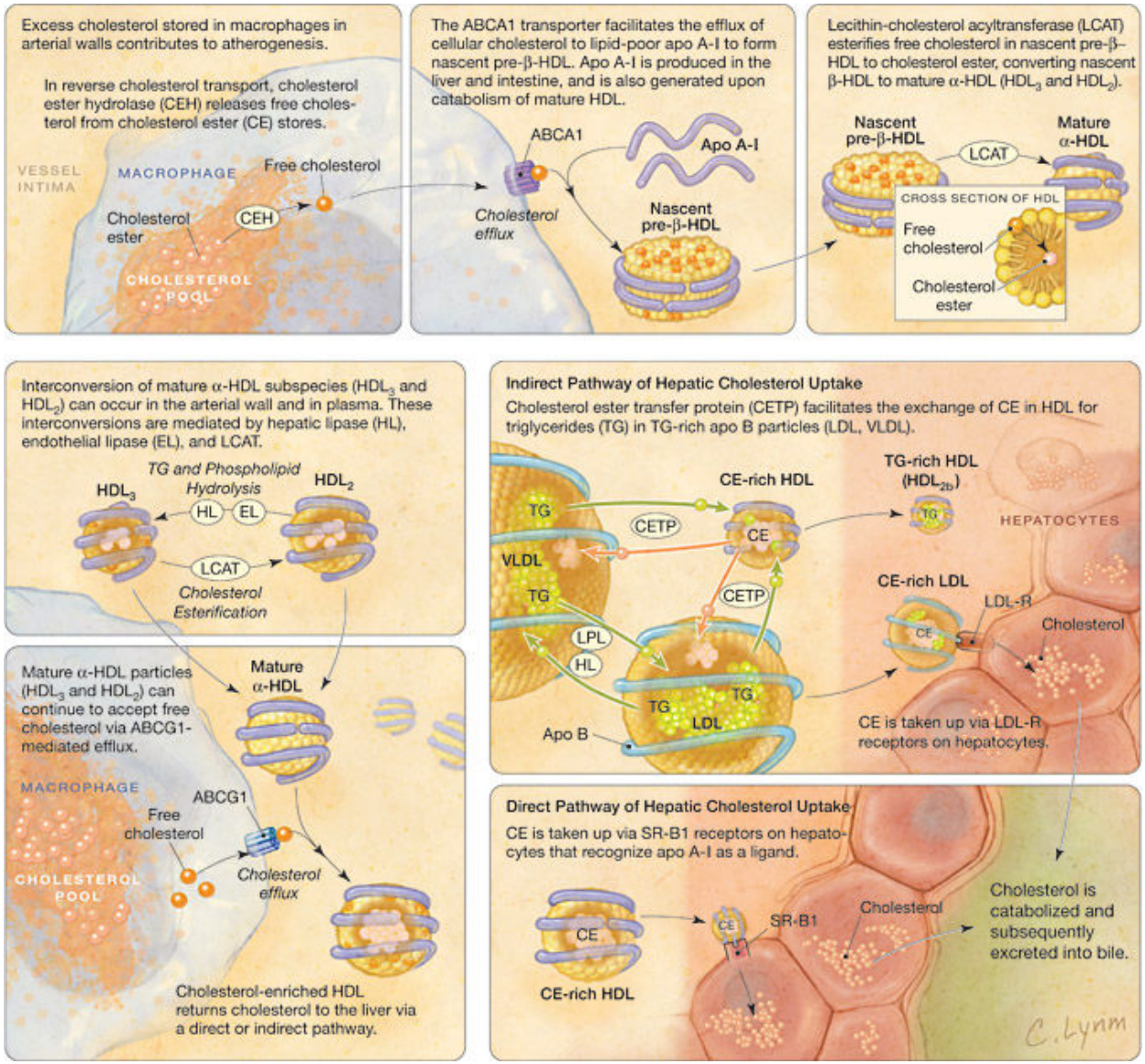
[a] Death indicates all-cause mortality.

*Singh, I. M. et al. JAMA 2007;298:786-798.*

# Summary

- The reason for the failure of torcetrapib : no clear answer yet.
- Possible mechanisms
  - No beneficial effect on RCT even with high HDL cholesterol: cholesterol efflux, hepatic uptake, etc.
  - Effect on blood pressure and vasculature
  - Chemical effect other than class effect?
- We should reconsider the efficacy of HDL-based therapy.

# Overview of RCT and HDL Metabolism

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