# High Density Lipoprotein (HDL) Related Therapy:

## *Where we are now*

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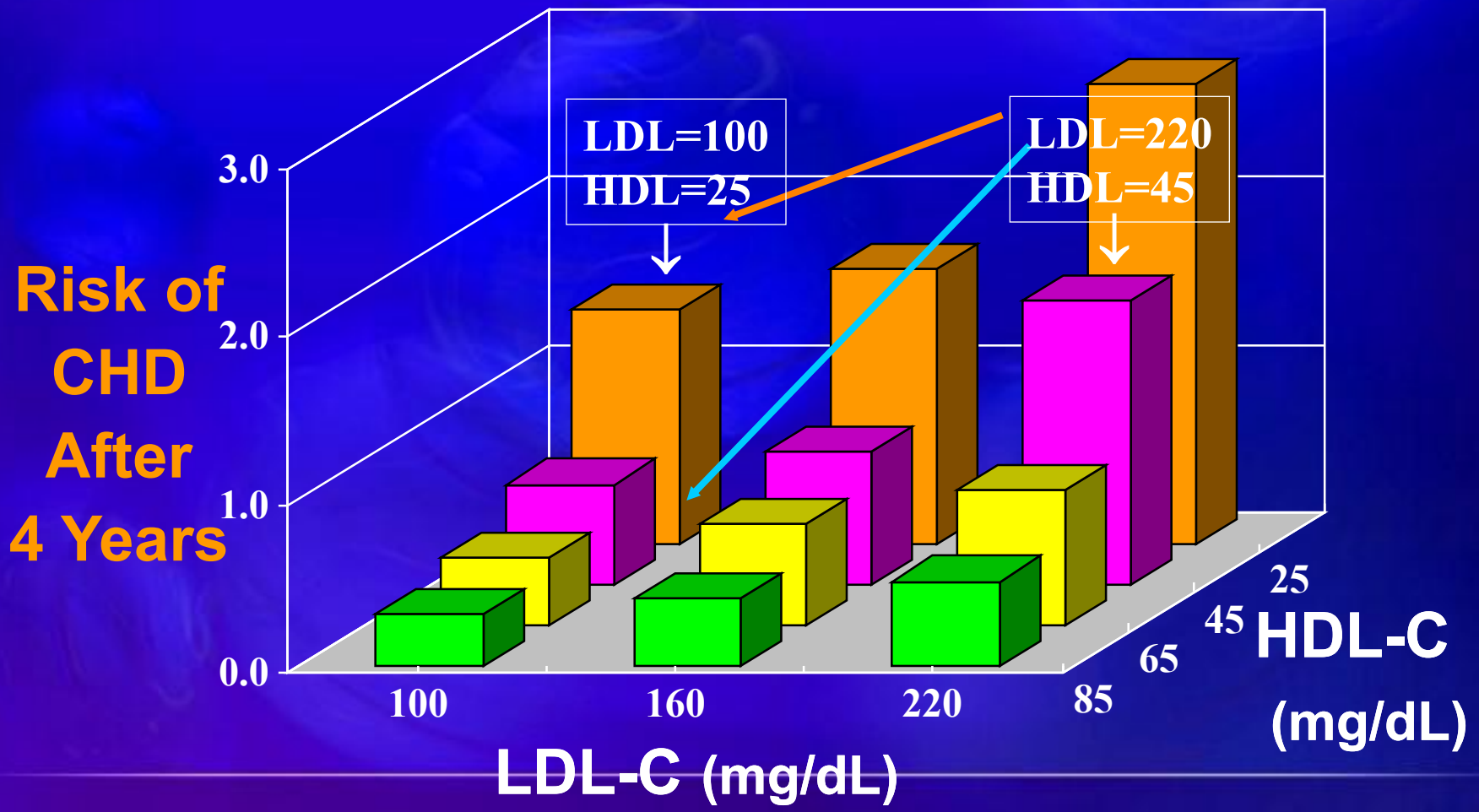
# Coronary Heart Disease Risk

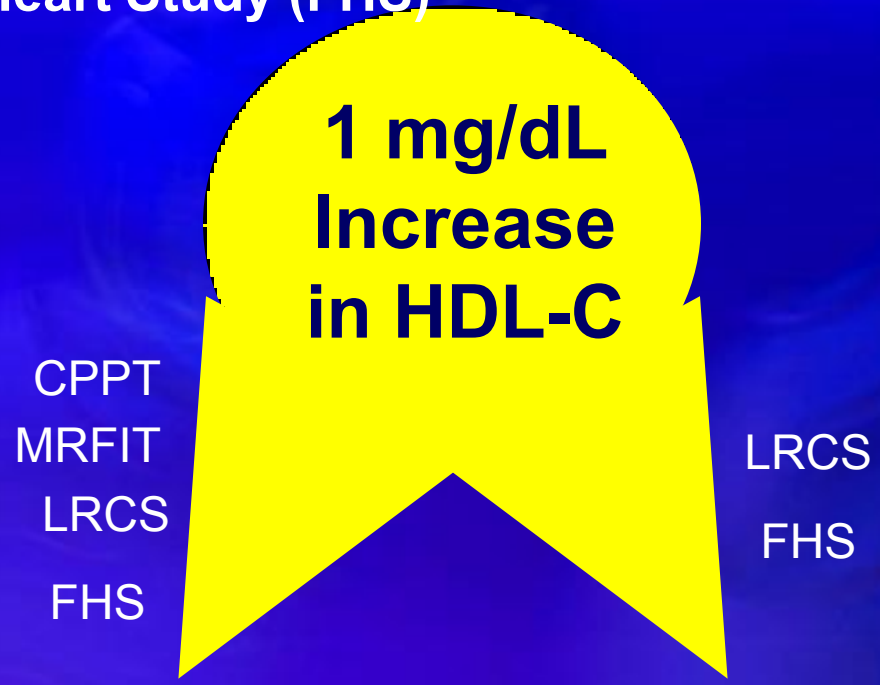
## HDL-C vs. LDL-C as a Predictor in Framingham Study



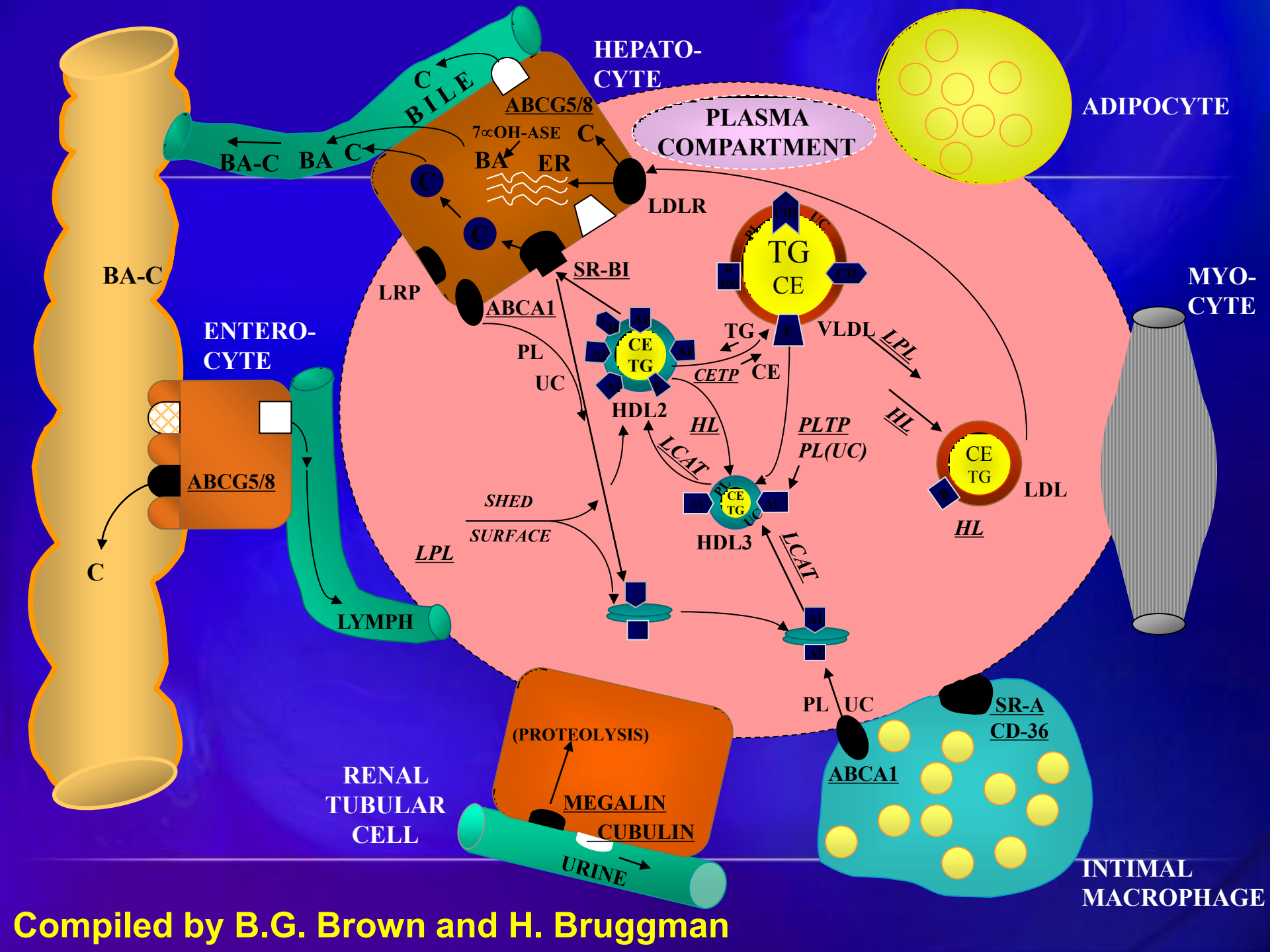

*Am J Med 1977;62:707-714*

# Meta-Analysis: Predictive Value of HDL-C

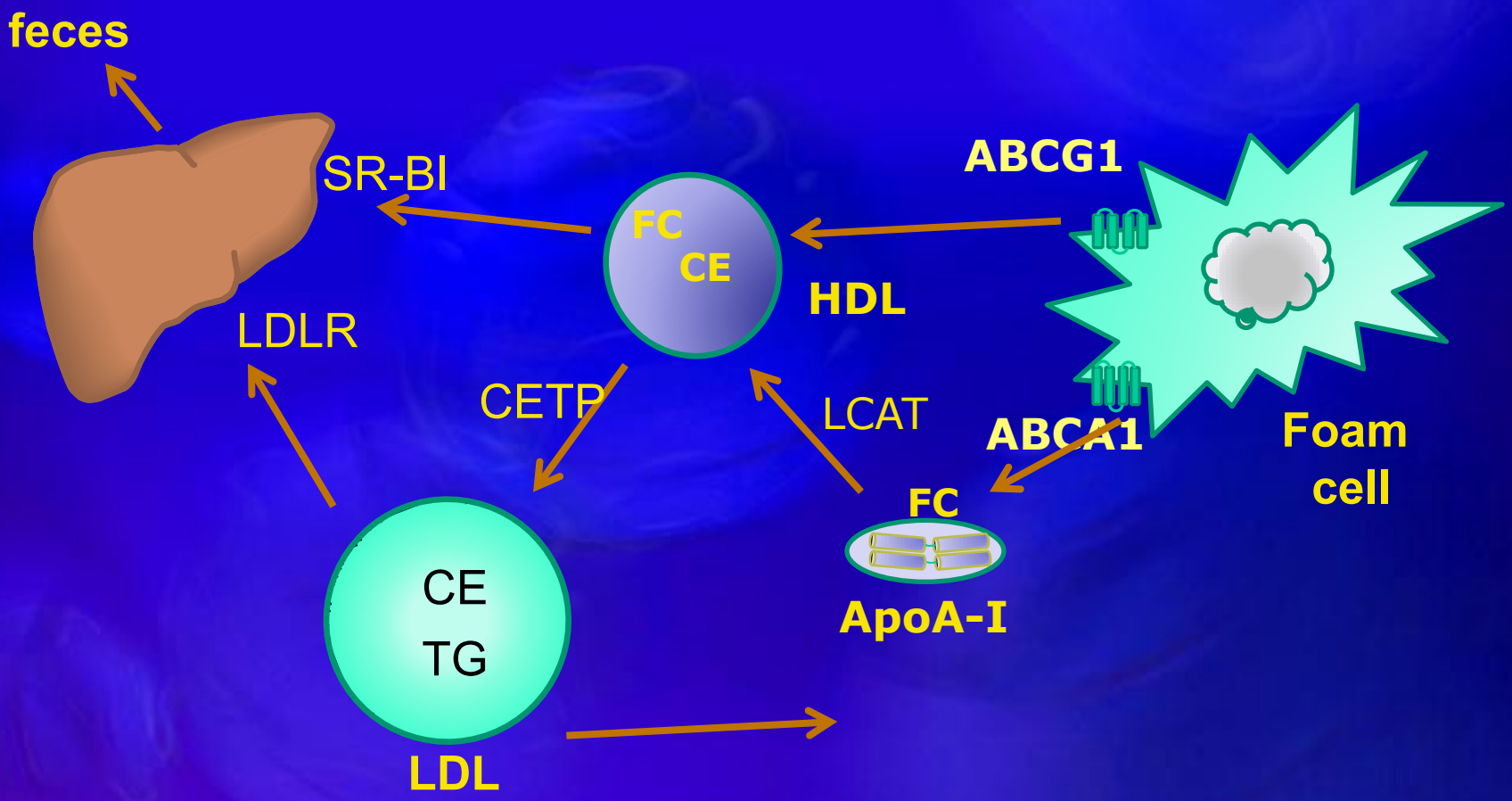
- Coronary Primary Prevention Trial (CPPT)
- Multiple Risk Factor Intervention Trial (MRFIT)
- Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCS)
- Framingham Heart Study (FHS)



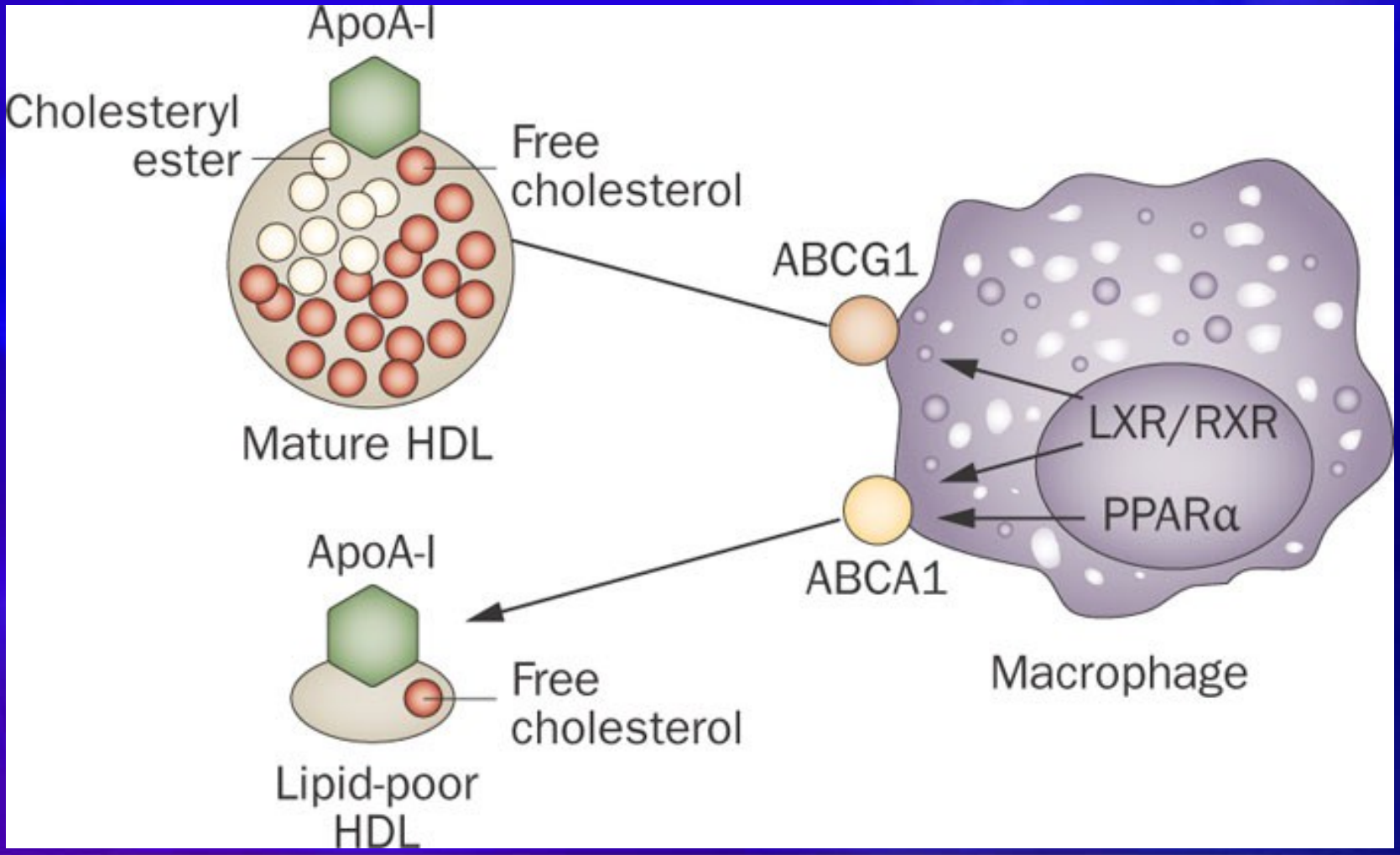

Gordon DJ, et al. *Circulation.* 1989;79:8-15.


HEPATO-
CYTE
ADIPOCYTE
PLASMA
COMPARTMENT
BILE
C
ABCG5/8
7∝OH-ASE
BA
ER
BA-C
BA
C
LDLR
SR-BI
LRP
ABCA1
BA-C
ENTERO-
CYTE
MYO-
CYTE
TG
CE
VLDL
LPL
TG
CE
CETP
HDL2
PL
UC
HL
PLTP
PL(UC)
LCAT
HL
CE
TG
LDL
HL
HDL3
SHED
SURFACE
LPL
LCAT
ABCG5/8
C
LYMPH
PL
UC
SR-A
CD-36
ABCA1
(PROTEOLYSIS)
MEGALIN
CUBULIN
URINE
RENAL
TUBULAR
CELL
INTIMAL
MACROPHAGE
Compiled by B.G. Brown and H. Bruggman

# Reverse Cholesterol Transport



# Cholesterol Efflux: the 1st Step in Reverse Cholesterol Transport



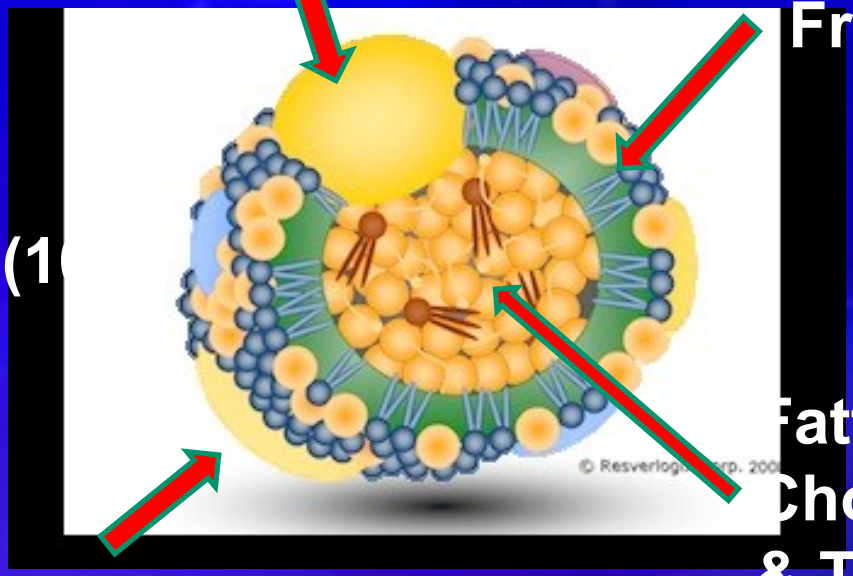

*Nature Reviews Cardiology* **6**, 455-463 (July 2009)

# High Density Lipoprotein (HDL) Structure

Apolipoproteins (Apo) A-II (20%)

Phopholipids & Free cholesterol

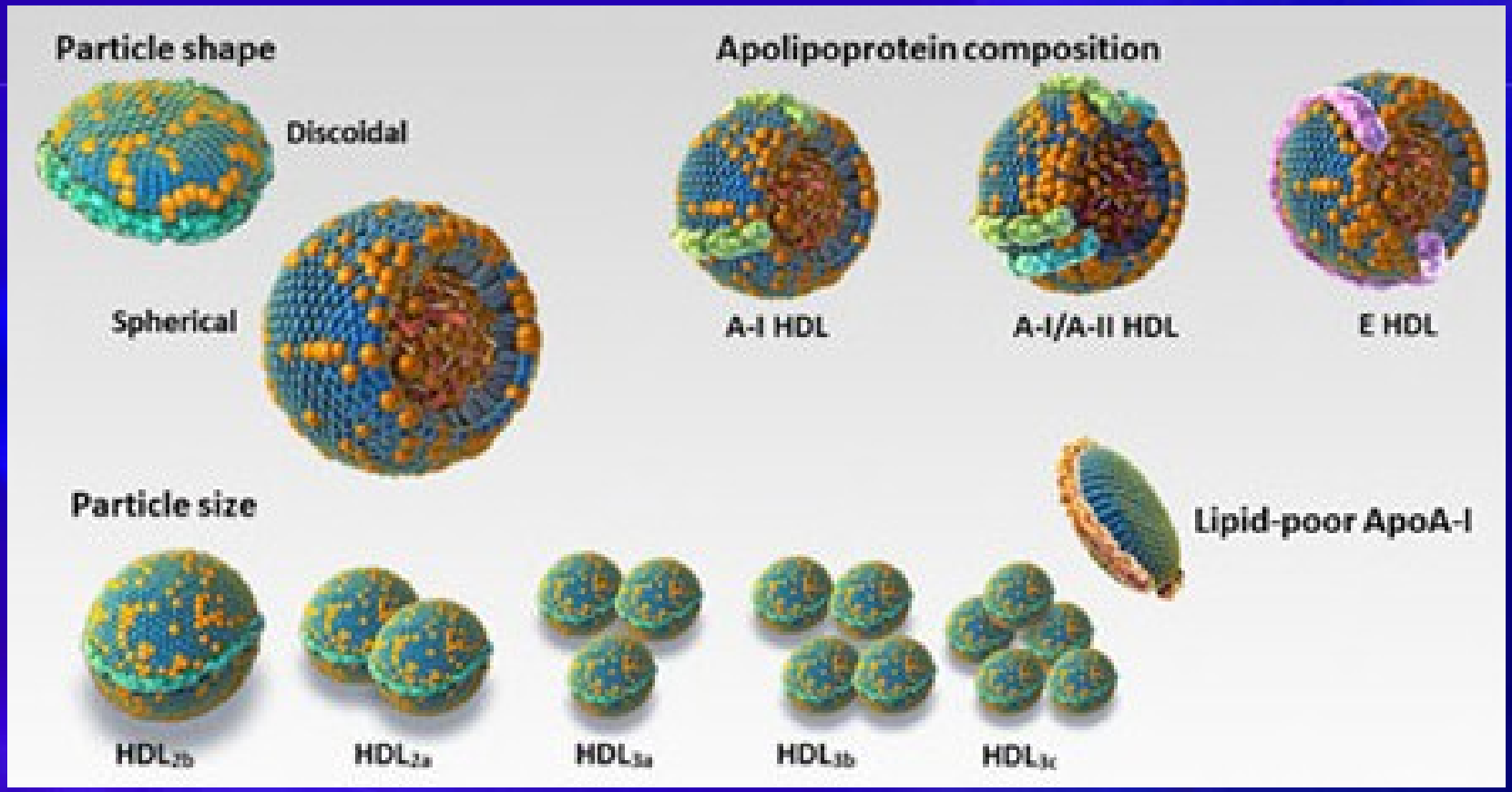
Other Proteins (1



Fatty core with Cholesteryl esters & Triglycerides (TG)

Apolipoproteins (Apo) A-I (70%)

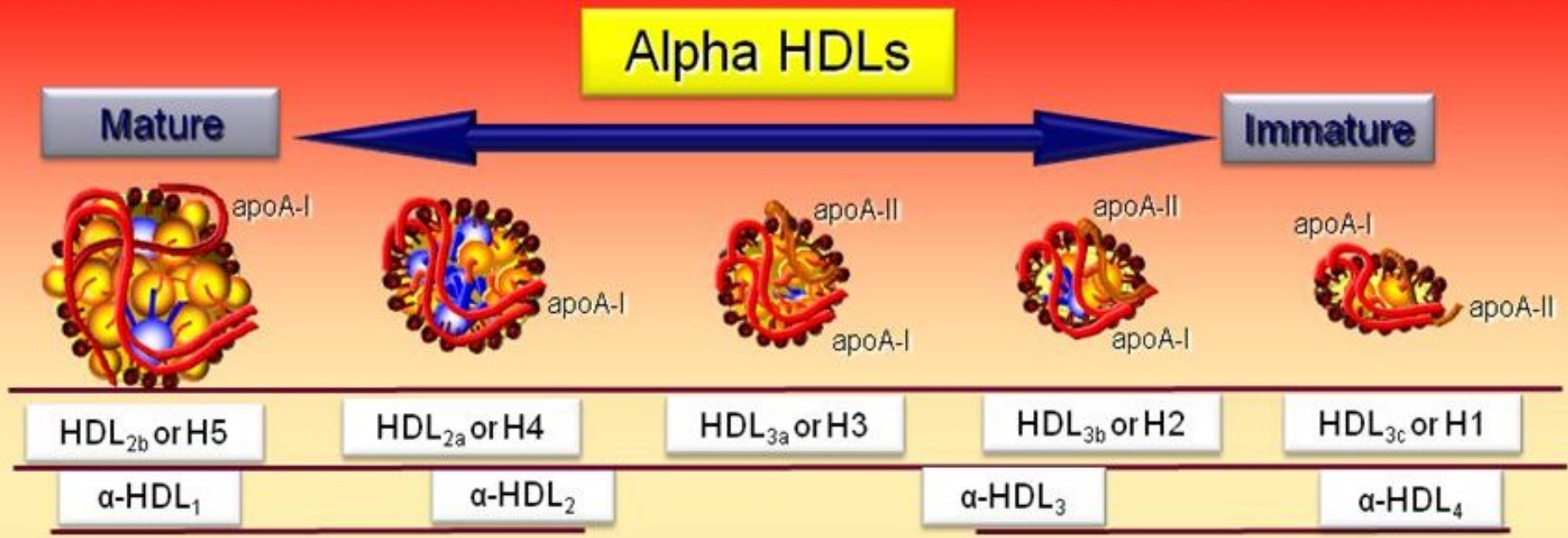
# Complex Particles




***The presence of CAD is more strongly associated with abnormalities in HDL particle distribution than with low HDL-C levels.***

**Cheung** MC, ***Brown* BG, *AC. Wolf, and . Albers JJ.*** J. ***Lipid Res. 1991.* 32: 383-394.**
**Cheung** MC, **Zhao XQ, . *Brown* BG. *ATVB 2001;21:1320-1326.***

# HDL Particle Size




## Prebeta HDLs

Unlipidated apoA-I or phospholipidated prebeta-1 & 2 HDL

***The ↑ in ApoA-1 in large alpha-1 HDL was significantly (p<0.01) related to lack of progression or regression of coronary stenosis in HATS***

***If alpha-1 HDL apoA-I is ↑ to > 20mg, there was net regression, provided LDL-C <80mg/dl***

Asztalos BF, *ATVB* 2003;23(5):847–852. Schaefer EJ, et al. Curr Opin Lipid. 2010;21(4):289-297

# HDL Particles and CV Event in HPS
## *(2% coronary event risk per year)*

**After adjustment for LDL particle number, HR for major occlusive coronary event per one SD higher level were:**

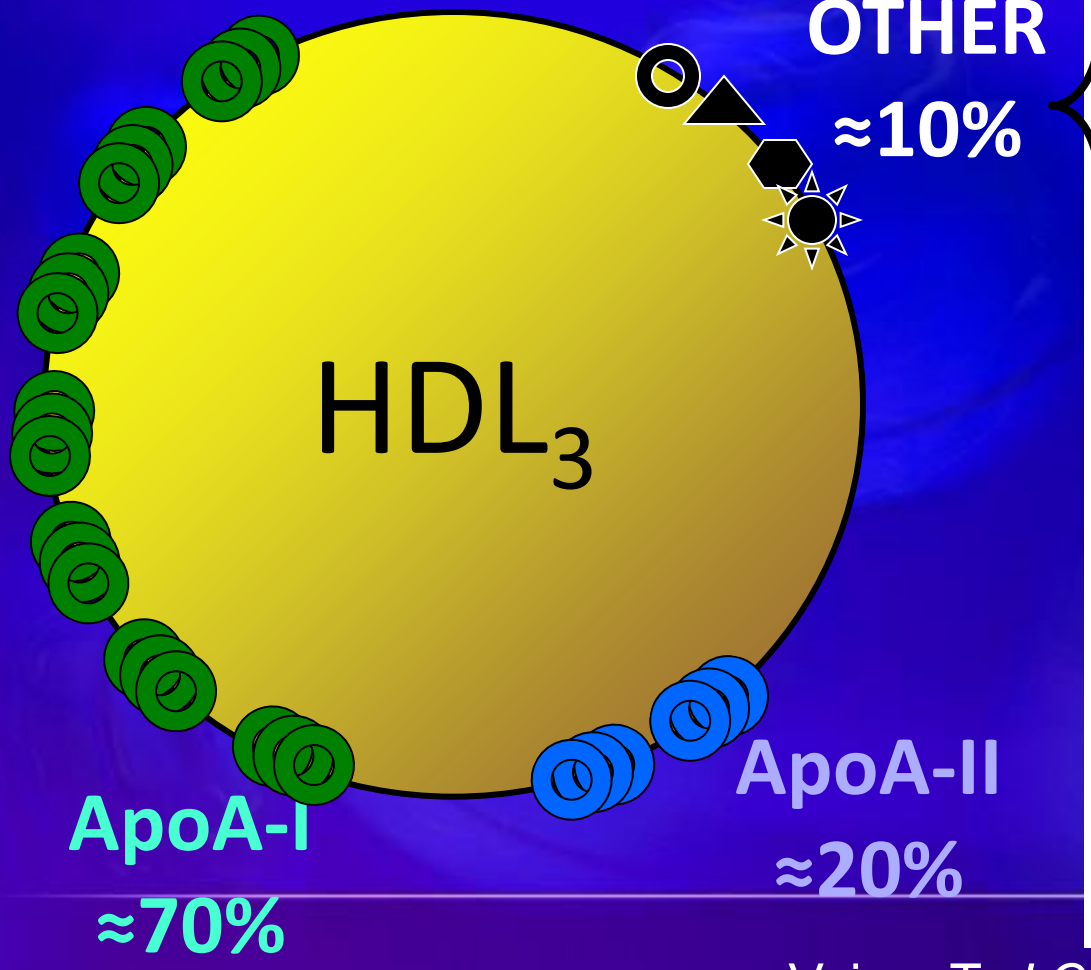
- **HDL-cholesterol: 0.91 (95%CI 0.86-0.96)**
- **HDL particle number: 0.89 (0.85-0.93)**

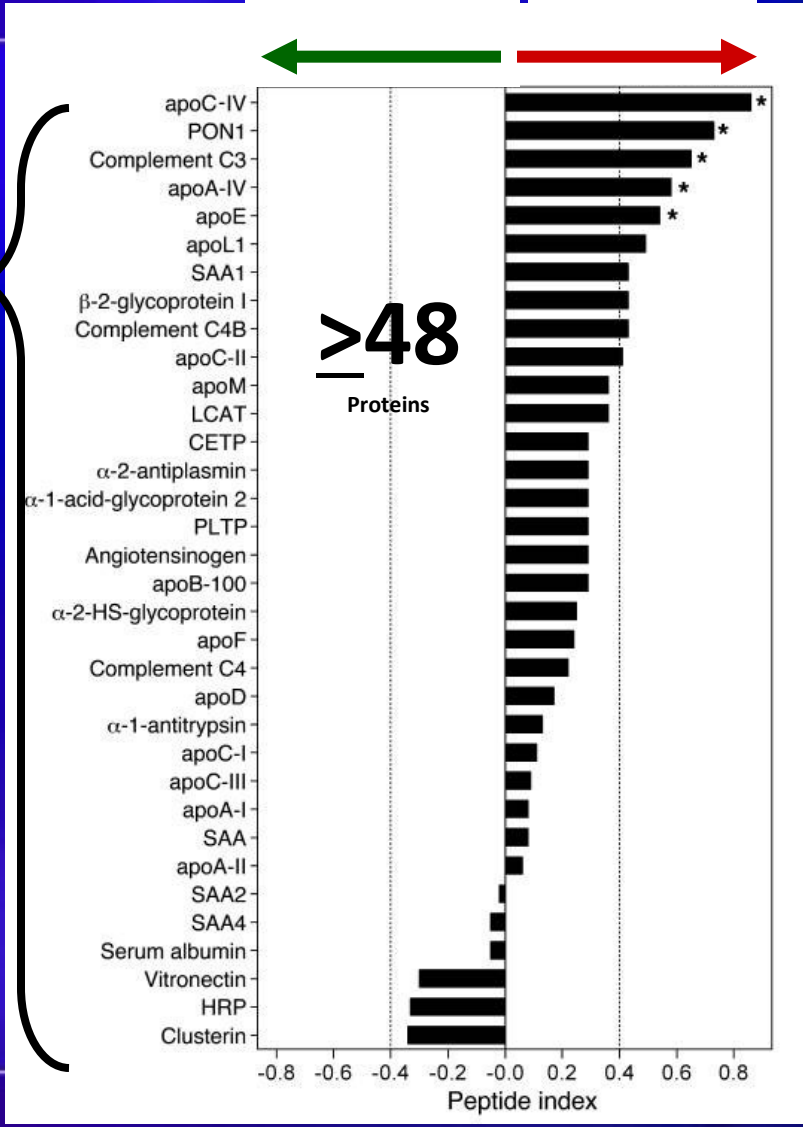
**Hazard ratios for other cardiac events were:**

- **Total HDL particle #: 0.84 (95%CI 0.79-0.90)**
- **Small HDL-particle #: 0.82 (95%CI 0.76-0.89)**
- **HDL-cholesterol: 0.94 (95%CI 0.88-1.00)**

Heart Protection Study Collaborative Group: *Lipids, lipoproteins and vascular events. Circulation May 2012*

# HDL Protein Composition:
## *Percentage and Numbers*



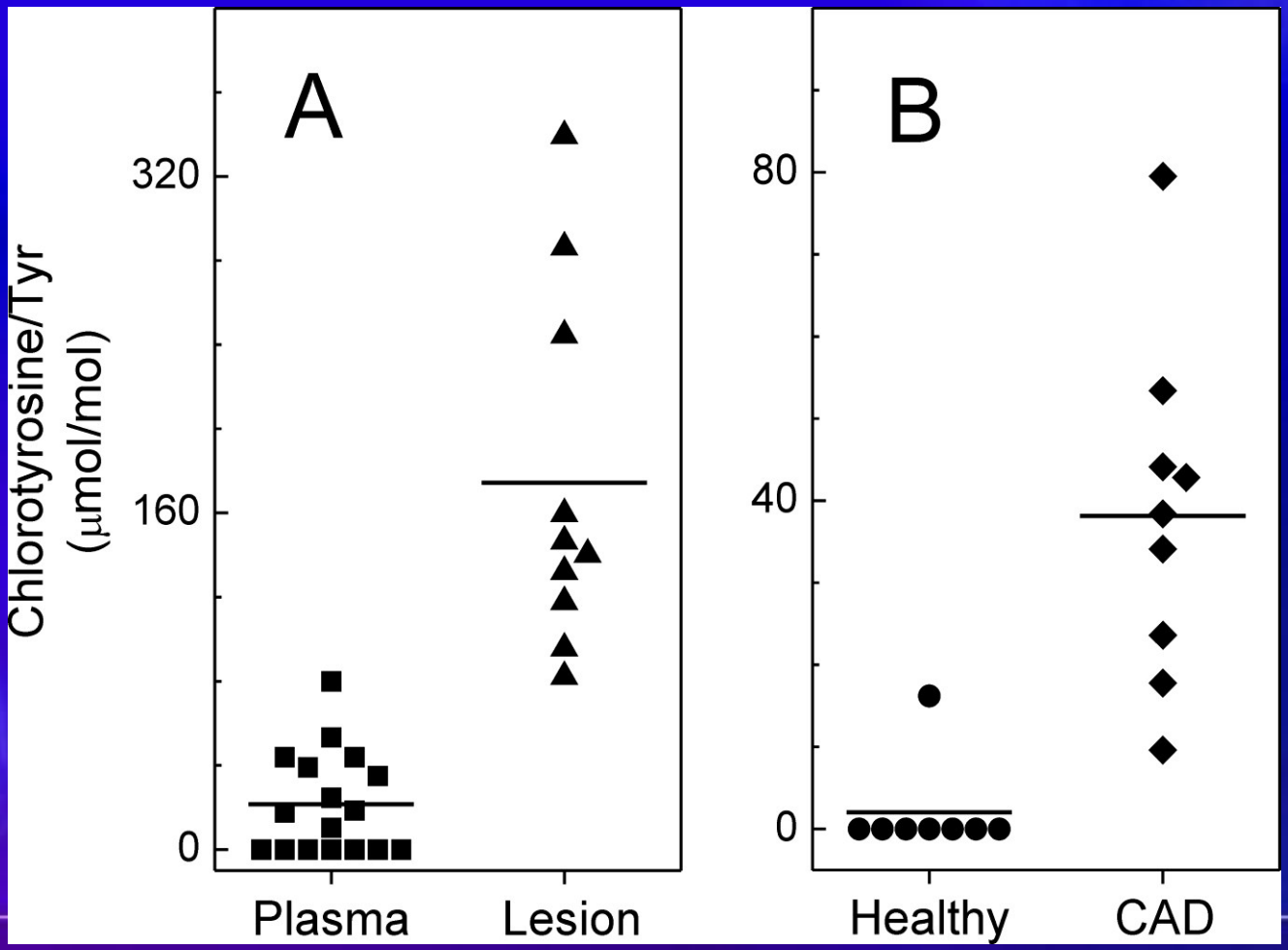




Vaisar T, *J Clin Invest* 2007; 117(3):746–756

# HOCl modification of HDL:

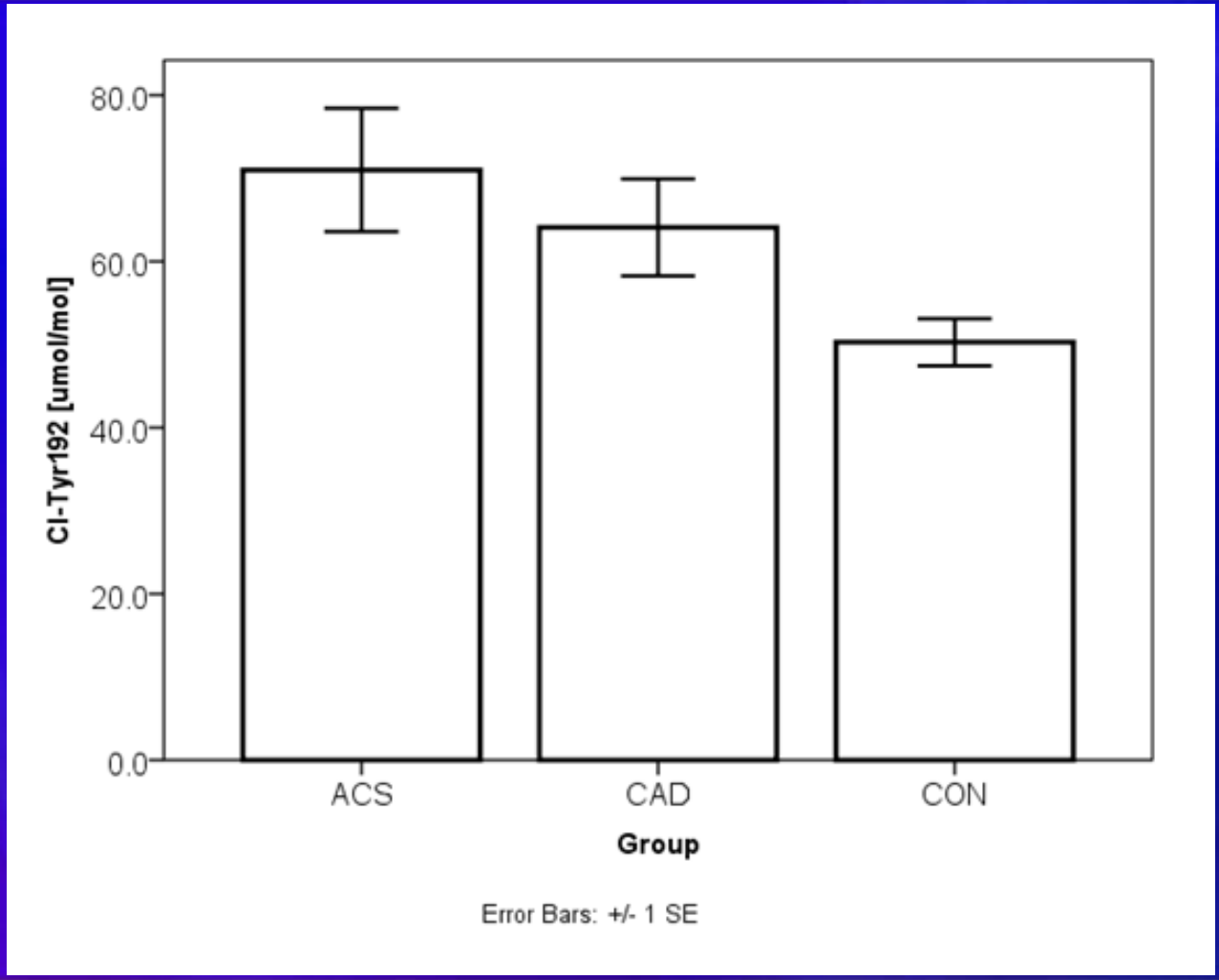
## *Plasma vs. Carotid Artery; Healthy vs. CAD*

CAD: Plasma vs. Lesion  Plasma: Healthy vs. CAD




Bergt C, *Proc Natl Acad Sci USA* 118:1259, 2008

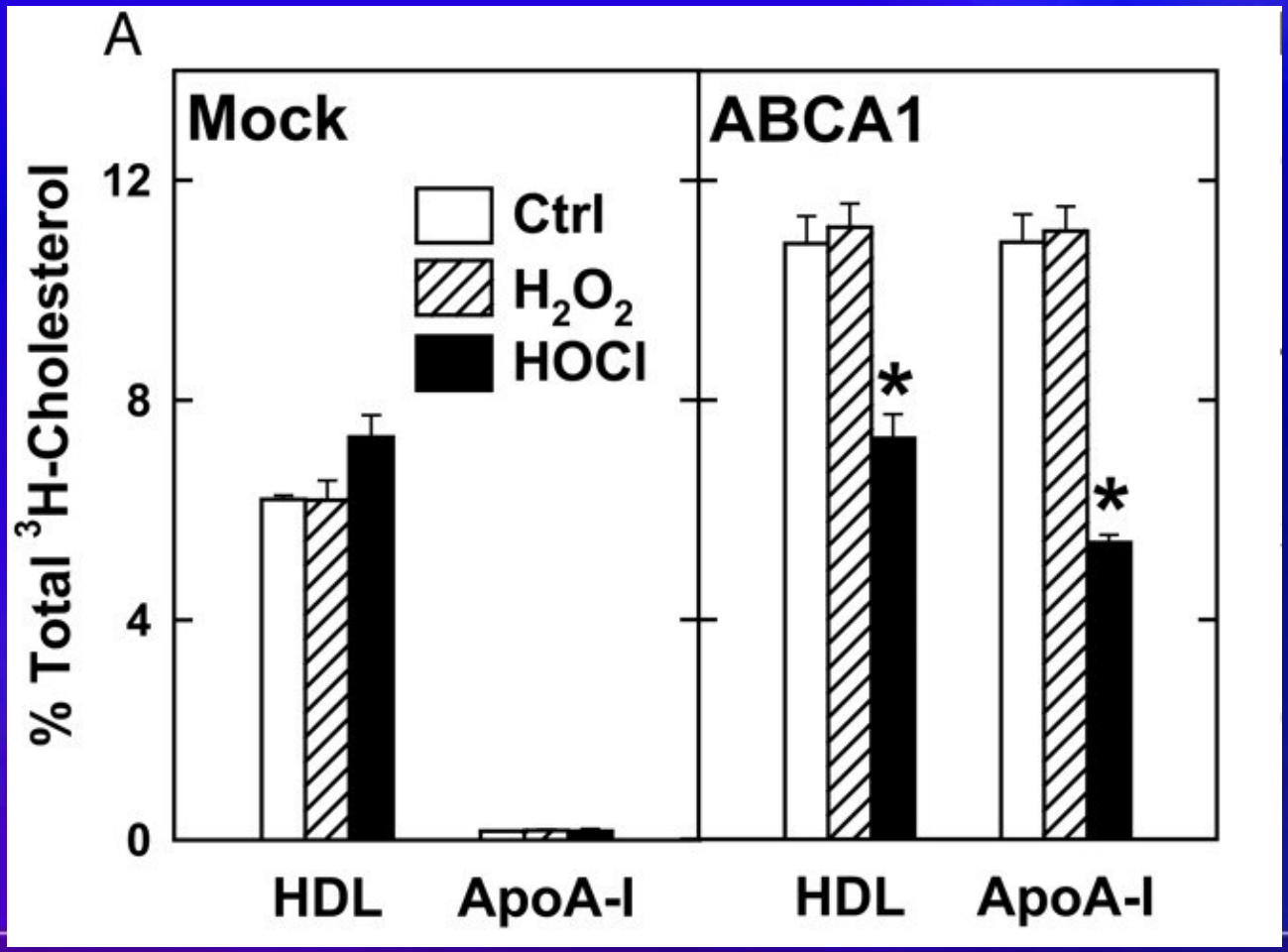
# Levels of 3-chloroTyr192 are higher in CAD and ACS




Unpublished data: Vaisar T, Heinecke JW, Zhao XQ , 2011, UW CARL

# HOCl modification of HDL:
# ABCA1 associated function

## *Cholesterol efflux activities*




*Bergt, Constanze et al. (2004) Proc. Natl. Acad. Sci. USA 101, 13032-13037*

# Sterol Efflux Capacity is Independent Predictor of CAD

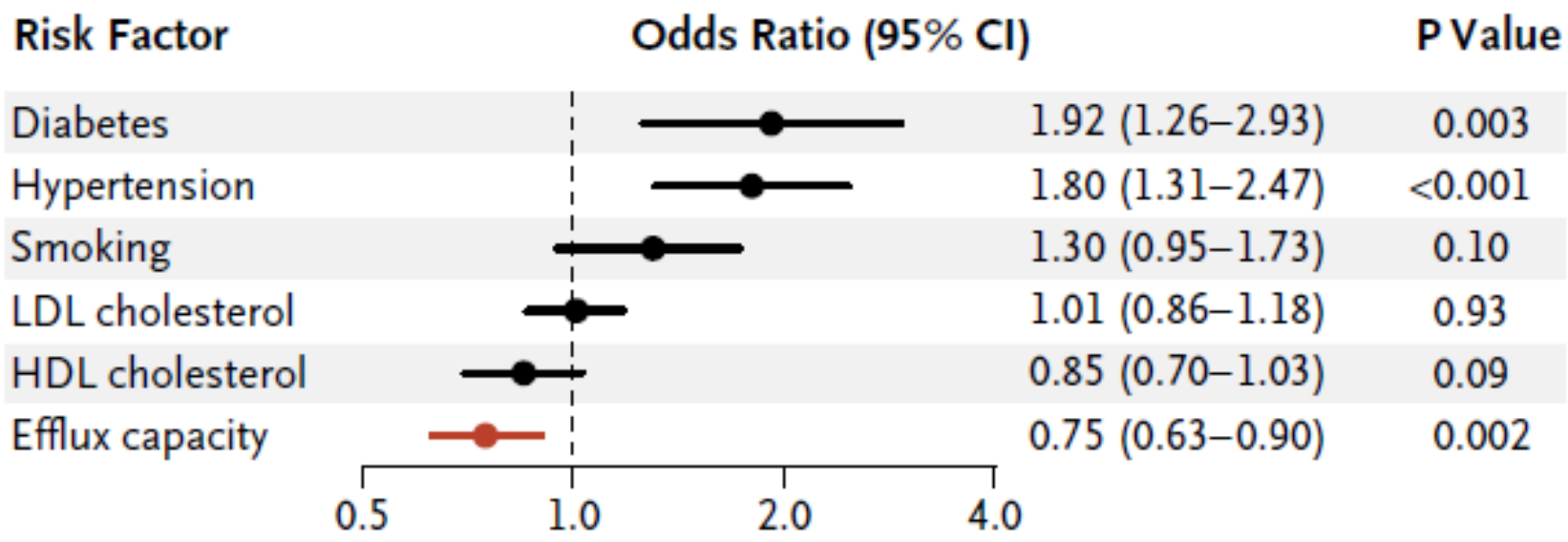


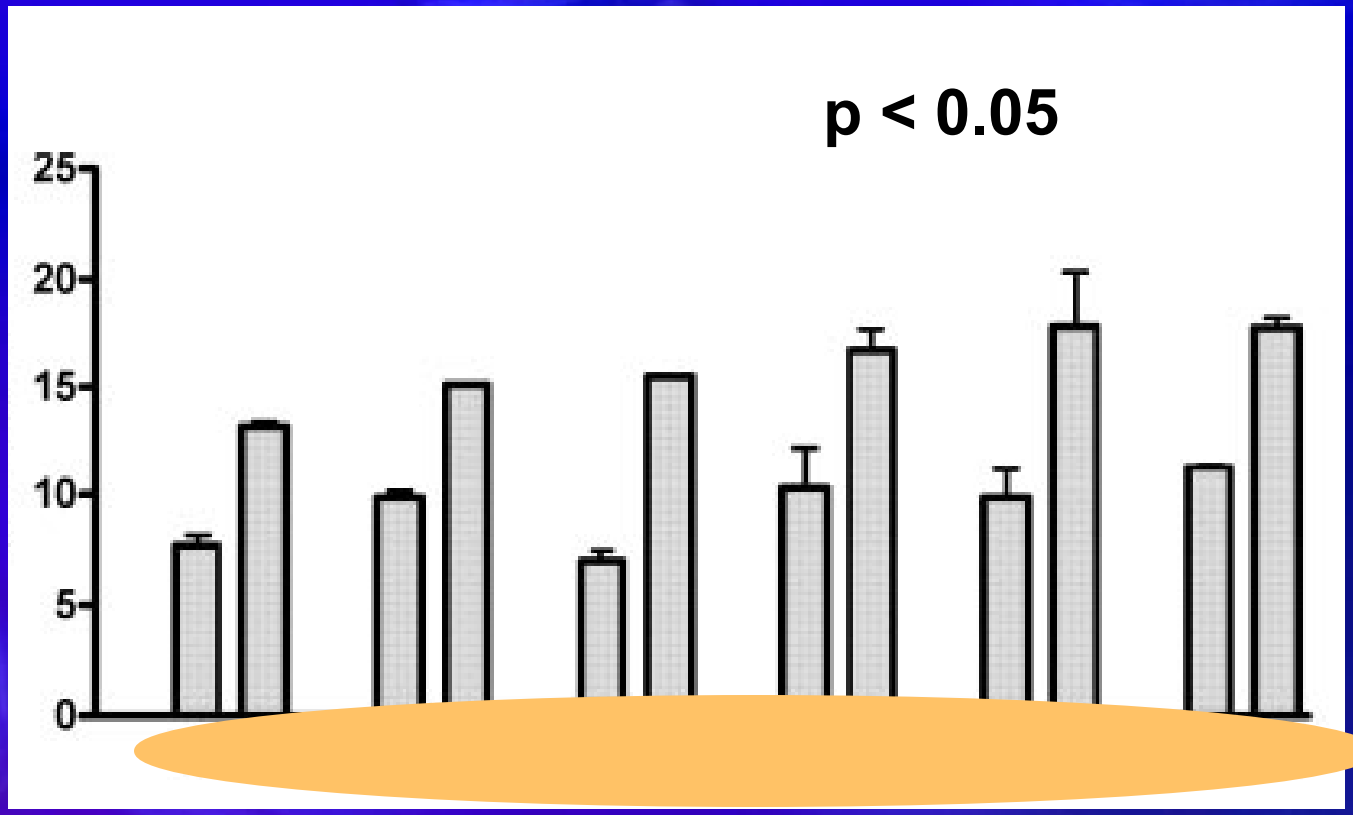

**Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.**

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Khera, Rader NEJM 2011

# HDL-C and Cholesterol Efflux

## HDL Cholesterol Efflux Capacity Is Independent Of HDL-C (D. Rader, U Penn)




La Moya *et al* ATVB 2010
Khera et al NEJM 2011

# Cholesterol Efflux Capacity in CAD

**20 ACS subjects – UWMC Cath Lab**

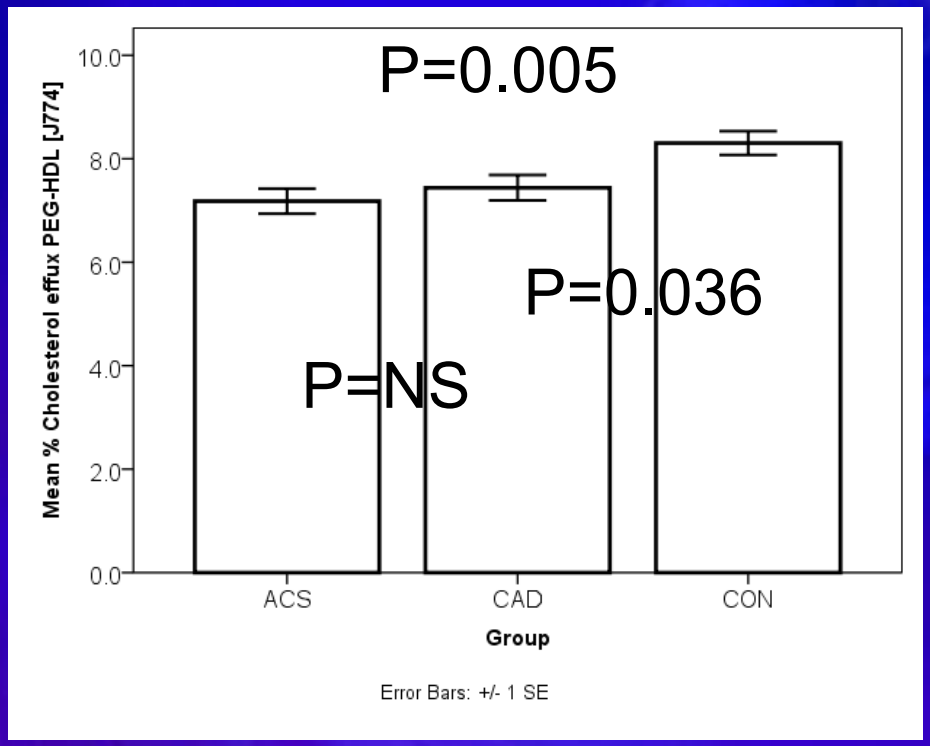
**20 stable CAD subjects – Research participants**

**20 controls – Screened for research studies**

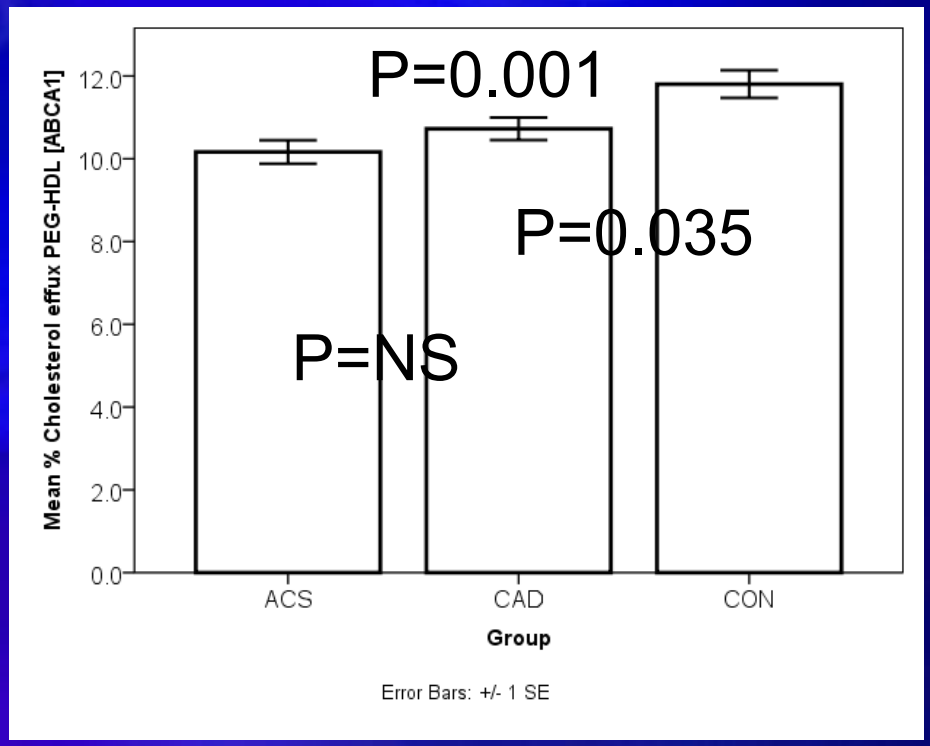
Unpublished data: Vaisar T, Sinha A, Heinecke JW, Zhao XQ , 2011.

# Sterol Efflux is Significantly Suppressed in CAD and ACS subjects

## Total HDL Efflux (J774 cells)

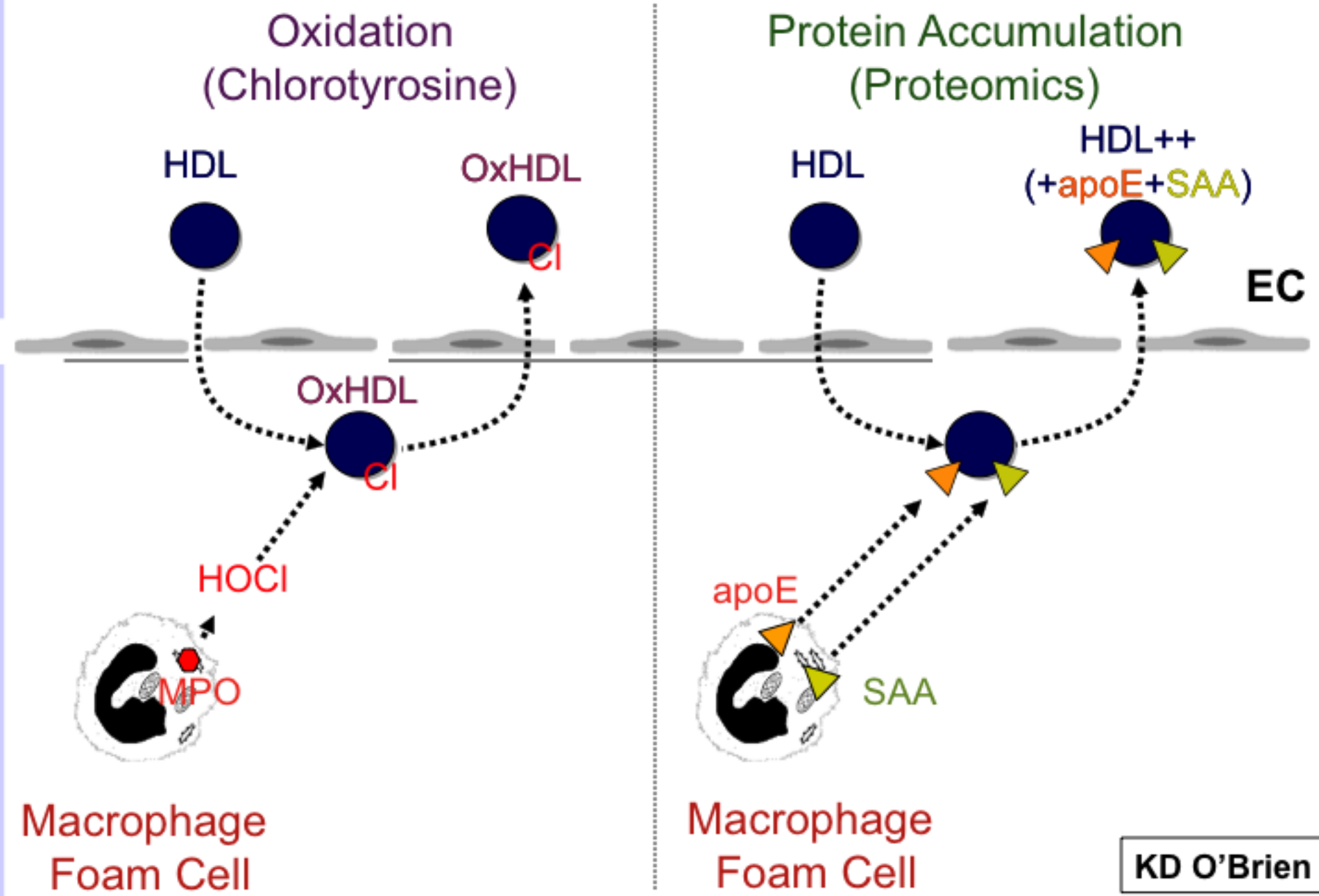



## ABCA1 Specific Efflux (ABCA1-BHK cells)

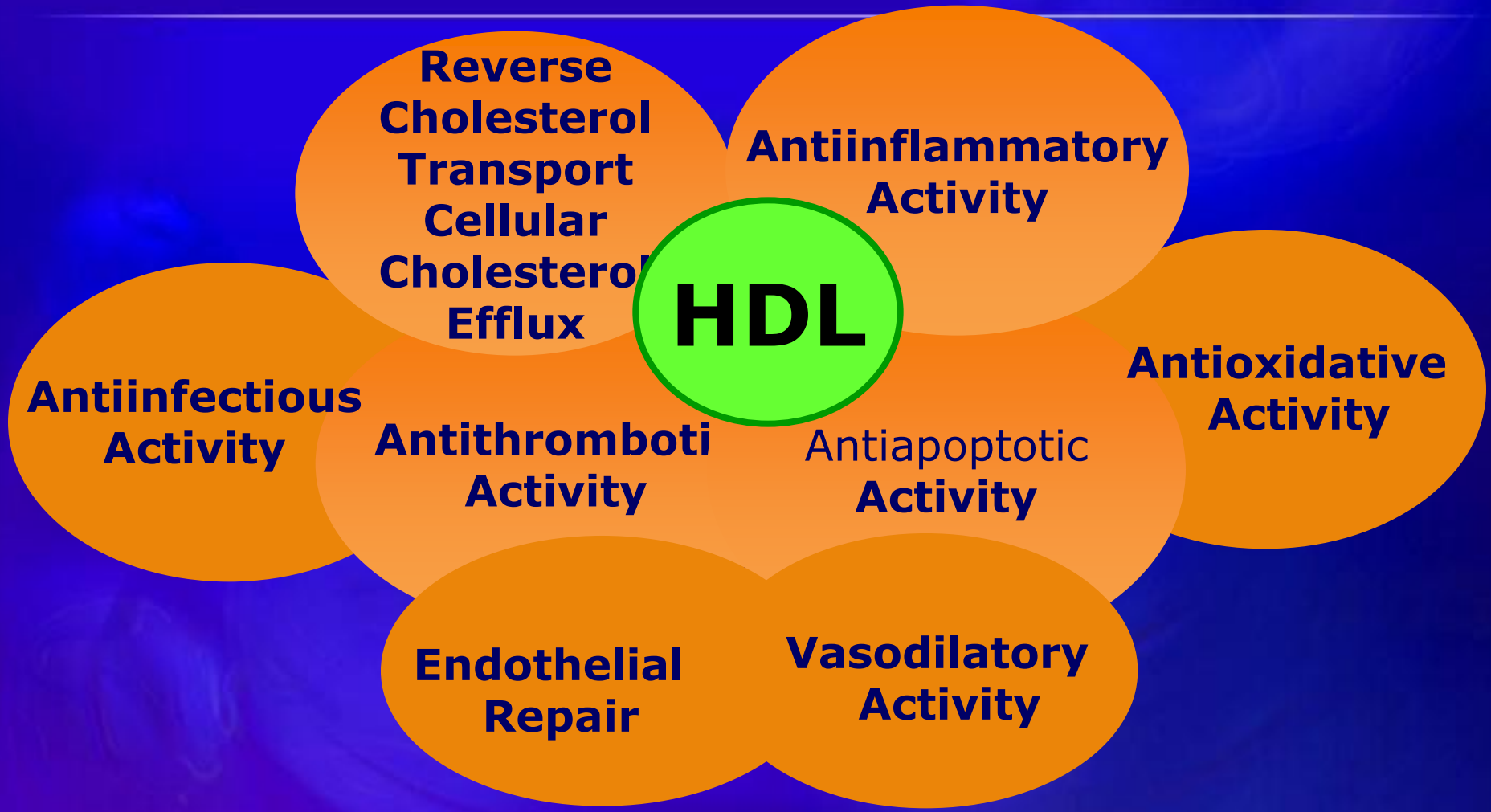



Unpublished data: Vaisar T, Heinecke JW, Zhao XQ , 2011, UW CARL

# HDL Modifications: Reflection of Plaque Biology?



# Anti-atherogenic Actions of HDL




Chapman MJ, et al. *Curr Med. Res Opin.* 2004,20:1253-1268.
Assmann G, et al. *Annu Rev Med.* 2003,53:321-41.

# Increasing HDL-C to Reduce Coronary Heart Disease???

# Linear Regression Analysis of % Coronary Stenosis

| Model | Variables In model | ß Coefficient (95% CI) | P value | $R^2$ |
|---|---|---|---|---|
| 1 | %Δ HDL-C | -0.133 (-0.305, 0.038) | 0.09 | 0.67 |
| 2 | %Δ LDL-C | +0.085 (0.007, 0.162) | 0.04 | 0.80 |
| 3* | %Δ HDL-C | -0.076 (-0.199, 0.046) | 0.12 | 0.96 |
| | %Δ LDL-C | +0.060 (-0.011, 0.132) | 0.07 | |

*: P value for overall model = 0.004

5400 patients from 18 reported trials

Brown BG, Stukovsky KH, Zhao X-Q: Current Opinion in Lipidology 2006,17:631-636

# Linear Regression Analysis of % Relative Event Rate

| Model | Variables In model | ß Coefficient (95% CI) | P value | $R^2$ |
|---|---|---|---|---|
| 4 | %Δ HDL-C | -0.1853 (-3.601, -0.104) | 0.04 | 0.53 |
| 5 | %Δ LDL-C | +1.211 (0.428, 1.994) | 0.01 | 0.70 |
| 6* | %Δ HDL-C | -1.288 (-2.095, -0.481) | 0.01 | 0.93 |
| | %Δ LDL-C | +0.971 (0.514, 1.428) | 0.003 | |

*: P value for overall model = 0.0001

83,000 patients from 23 reported trials

Brown BG, Stukovsky KH, Zhao X-Q: Current Opinion in Lipidology 2006,17:631-636

REVIEW | Annals of Internal Medicine

# Meta-analysis: Statin Therapy Does Not Alter the Association Between Low Levels of High-Density Lipoprotein Cholesterol and Increased Cardiovascular Risk

Haseeb Jafri, MD; Alawi A. Alsheikh-Ali, MD, MS; and Richard H. Karas, MD, PhD

**Background:** Low levels of high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk for myocardial infarction (MI). Although statins reduce the risk for MI, most cardiovascular events still occur despite statin treatment.

**Purpose:** Using meta-analysis of large randomized, controlled trials (RCTs) of statins to determine whether statins alter the relationship between HDL-C level and MI.

HDL-C levels and risk for MI in statin-treated patients and control participants. In Poisson meta-regressions, every 0.26-mmol/L (10-mg/dL) decrease in HDL-C was associated with 7.1 (95% CI, 6.8 to 7.3) and 8.3 (CI, 8.1 to 8.5) more MIs per 1000 person-years in statin-treated patients and control participants, respectively. The inverse association between HDL-C levels and MI did not differ between statin-treated patients and control participants ($P = 0.57$).

**Conclusion: Statins do not alter the relationship between low HDL-C and CV risk**

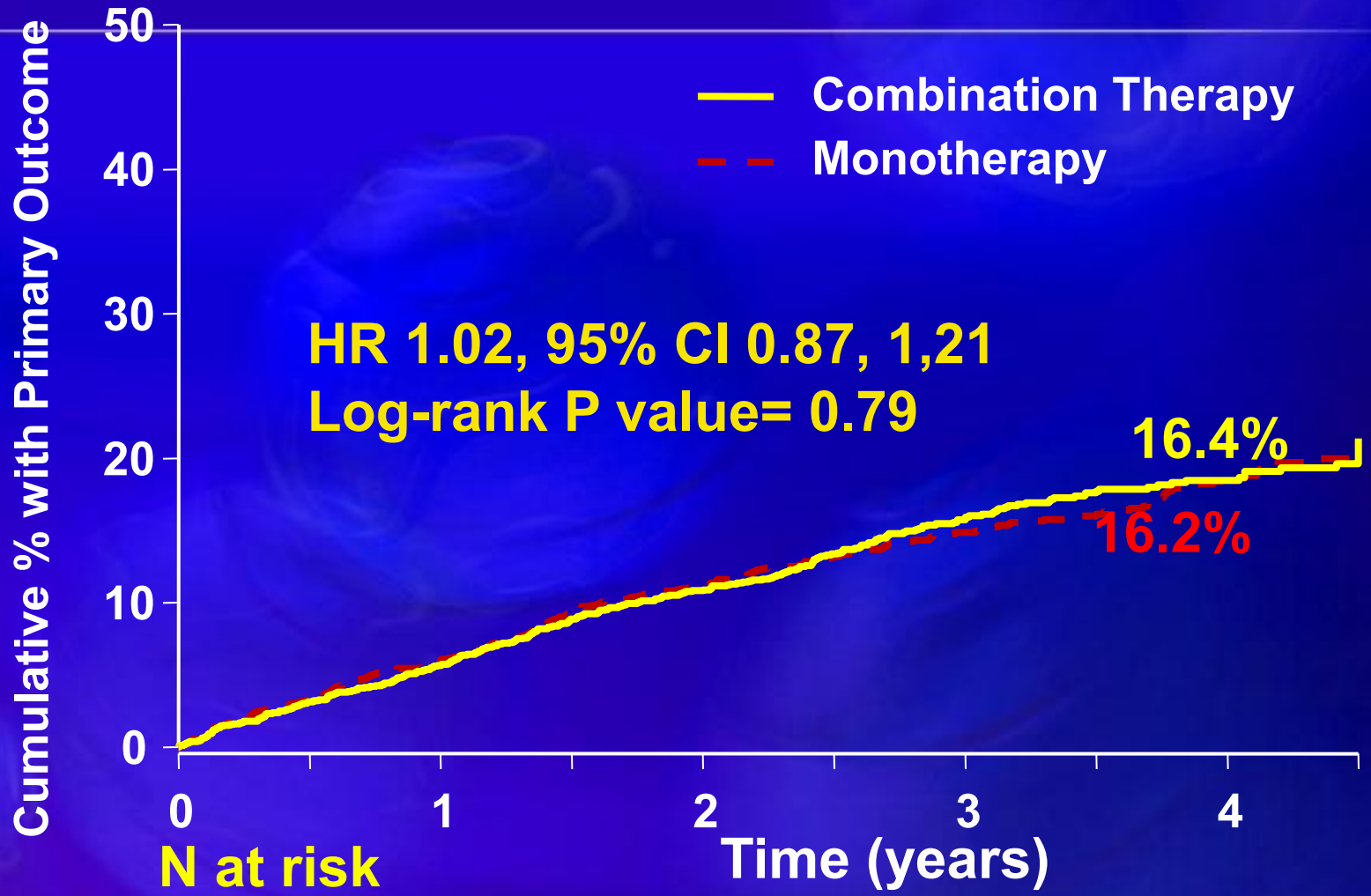
# Event Trials of Combined LDL-C-lowering and HDL-C-raising

| | Therapy | No. | F/U | Finish |
|---|---|---|---|---|
| **AIM-HIGH (NIH/Abbott) US & Canada** | Simva. vs. Simva/ER-niacin | 3400 +CVD +↑TG +↓HDL-C (Base. LDL-C @ 70th) | 4-5 yrs | Rx stopped May, 11 3 yrs* |
| **HPS-2 THRIVE (Merck) Europe & China** | Simva. vs. Simva/ER-niacin (flushing inhibitor) | 25,000 ±CVD -lipid | 4-5 yrs | 2013 |

# AIM-HIGH

- Trial stopped prematurely in May 2011 for futility
- Odds of observing the expected treatment effect (of a 25% reduction in risk of a major CV event in the Niaspan+ statin group versus the statin only group) were < 1 in 10,000
- In other words, there was no benefit of treatment with Niaspan on top of simva. in stable patients with optimal LDL-C

# Primary Outcome

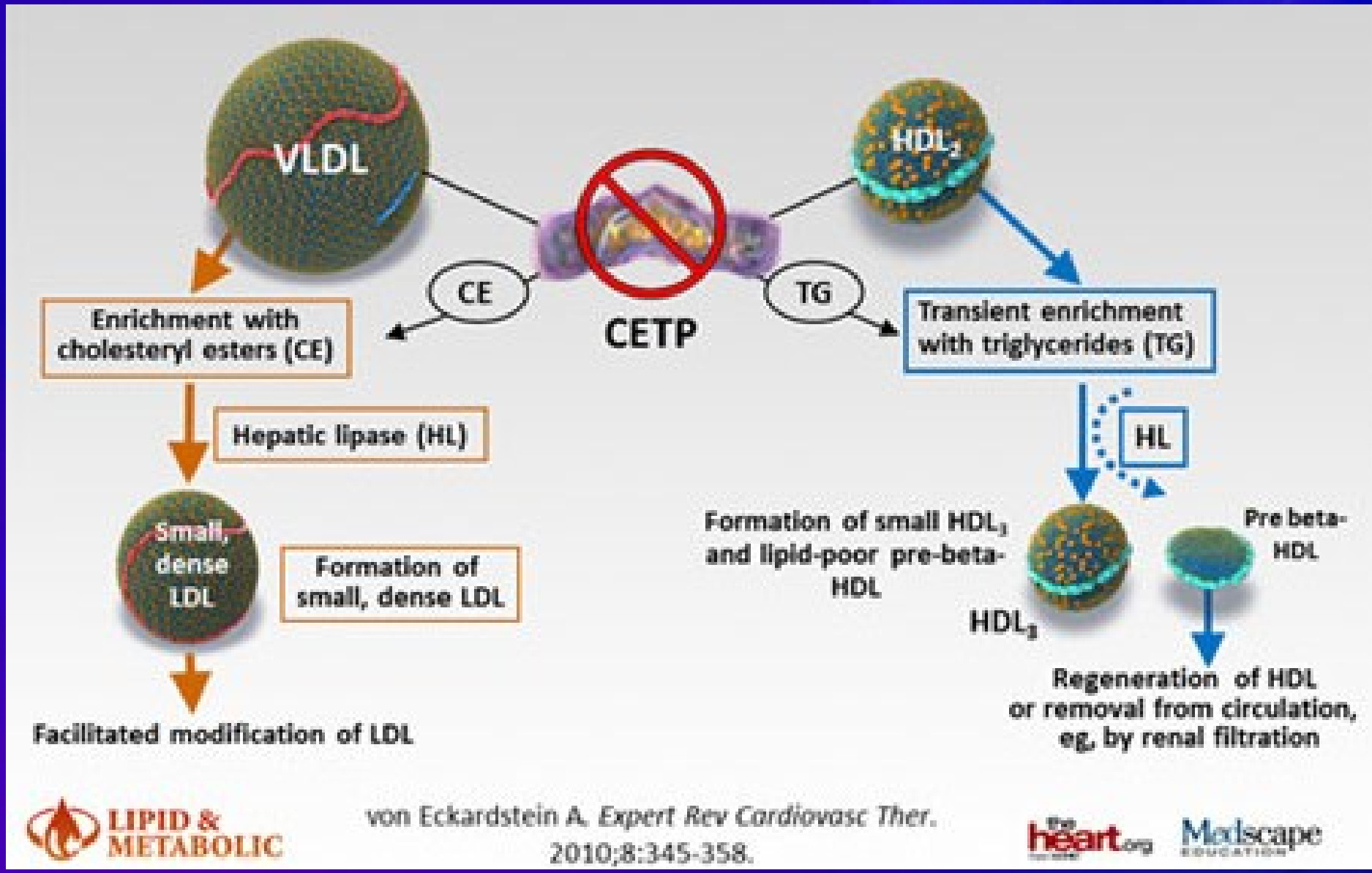



| N at risk | | | | | |
|---|---|---|---|---|---|
| Mono-Rx | 1696 | 1581 | 1381 | 910 | 436 |
| Combination-Rx | 1718 | 1606 | 1366 | 903 | 428 |

# HDL Therapy Target(s)

- HDL-modifying plasma enzymes and transfer proteins
  - LCAT, CETP, PLTP
- HDL associated apolipoproteins
  - ApoA-I, ApoA-IV and ApoE
- Cellular and cell surface proteins
  - ABC1 and SR-B1

# CETP Inhibition




LIPID & METABOLIC

von Eckardstein A. *Expert Rev Cardiovasc Ther.* 2010;8:345-358.

theheart.org Medscape EDUCATION

# CETP Inhibitors Development

| | Phase II | Phase III |
|---|---|---|
| Torceptrapib | ✔✔ | Stopped due to TOX |
| Dalceptrapib | ✔✔ | Stopped due to futility |
| Anaceptrapib, | ✔✔ | HPS-3 On-going |
| Evaceptrapib, | ✔✔ | Under design |

# What Is the Future of HDL Therapies?

HDL therapies do work in phase I and II:

- ApoAI Milano – IVUS study in humans
- ApoAI Milano – studies in mice and rabbits
- ApoAI gene transfer experiments in mice
- Overexpression of LCAT in transgenic rabbits
- CETP inhibitors (anaceptrapib, evacetrapib, dalceptrapib) in vitro and vivo atherosclerosis studies.

**Do HDL therapies work in phase III ????**

# HDL-C Level and MI Risk

## Endothelial Lipase Gene (*LIPG* Asn396Ser)

Carriers of the *LIPG* 396Ser allele (2.6% frequency) had higher HDL-C (0.14 mmol/L higher) but similar levels of other lipid and non-lipid risk factors for MI

Estimate of the association of genetically raised LDL-C or HDL-C and risk of MI using multiple genetic variants as instruments in 12 482 cases of MI and 41 331 controls

| | OR (95% CI) per SD ↑ in observational epidemiology* | OR (95% CI) per SD ↑ in conferred by genetic score† |
|---|---|---|
| LDL-C | 1.54 (1.45-1.63) | 2.13 (1.69-2.69), $p=2X10^{-10}$ |
| HDL-C | 0.62 (0.58-0.66) | 0.93 (0.68-1.26), p=0.63 |

*Published in Lancet. May 17, 2012*

# How Will We Evaluate HDL Therapies in the Future? Implications of AIM-HIGH

- Will we have to modify the types of patients we enroll in clinical outcome trials?
- What is the role of combination therapies in statin-naïve patients, or patients with acute coronary events (who were excluded in AIM-HIGH)?
- Special patient populations (e.g., statin intolerant)?

# Conclusions

- HDL is complex in terms its protein characteristics, particle size, oxidation, and …
- A better understanding of HDL and its function is important and needed
- HDL-C is an independent CV risk factor
- ⑩↑HDL-C has not been approved to be beneficial
  - Need to wait for results of HPS2-THRIVE and CETP inhibitor trials

# Conclusions

- The clinical trial landscape has dramatically changed after 20 years of statin availability and widespread use
- Effects of add-on therapies will be increasingly difficult to demonstrate
- Yet, there is a compelling clinical need for additional therapies, given the high residual risk  despite statin therapy