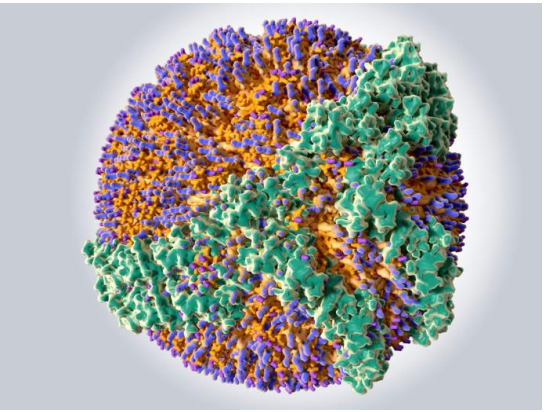


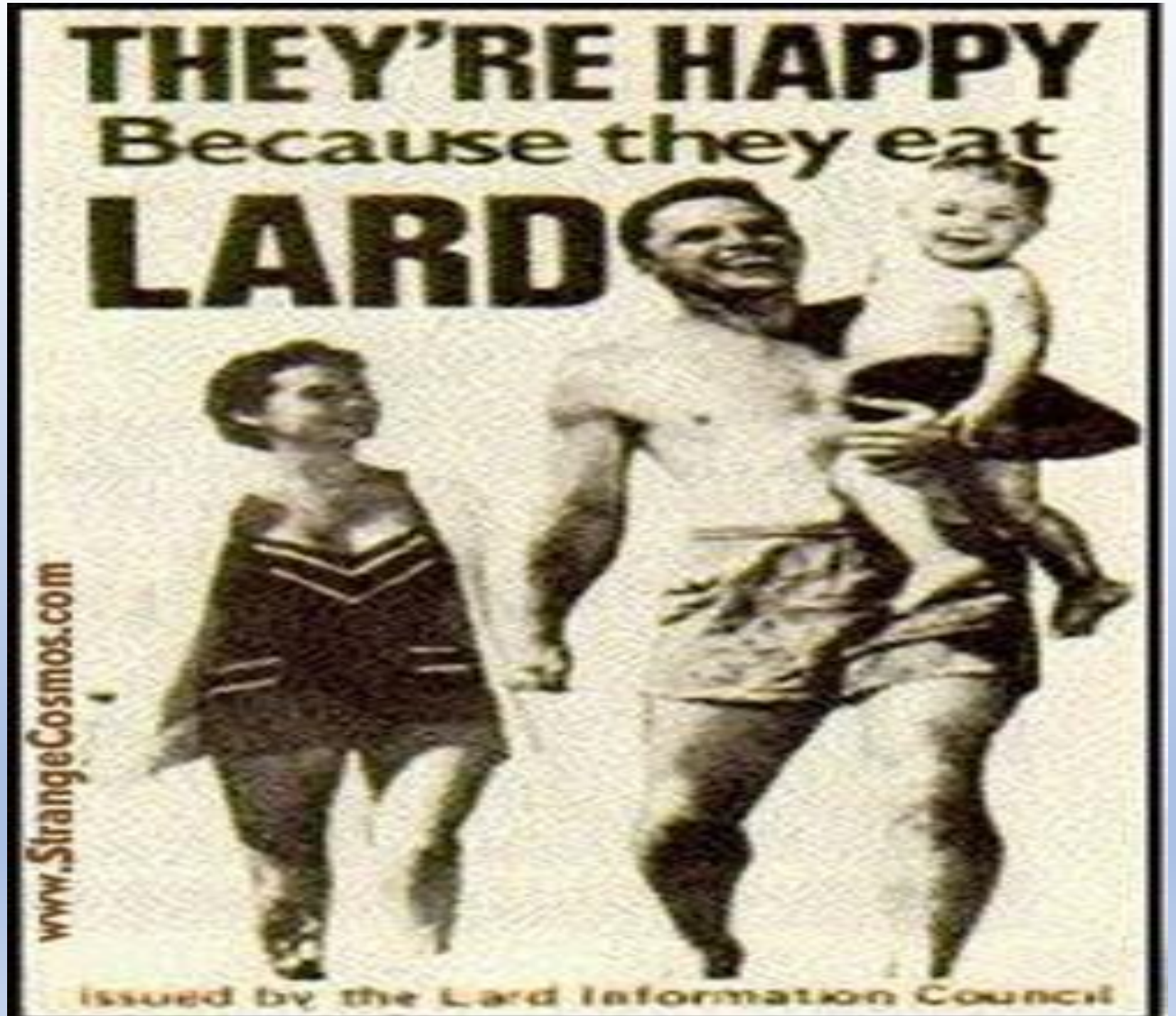
HDL: The Misunderstood Lipoprotein

Rob Greenfield MD FACC FAHA FNLA
Clinical Associate Prof. UCI (retired)
California Heart Associates (retired)
Emeritus Dir. Lipidology:
Orange Coast Memorial

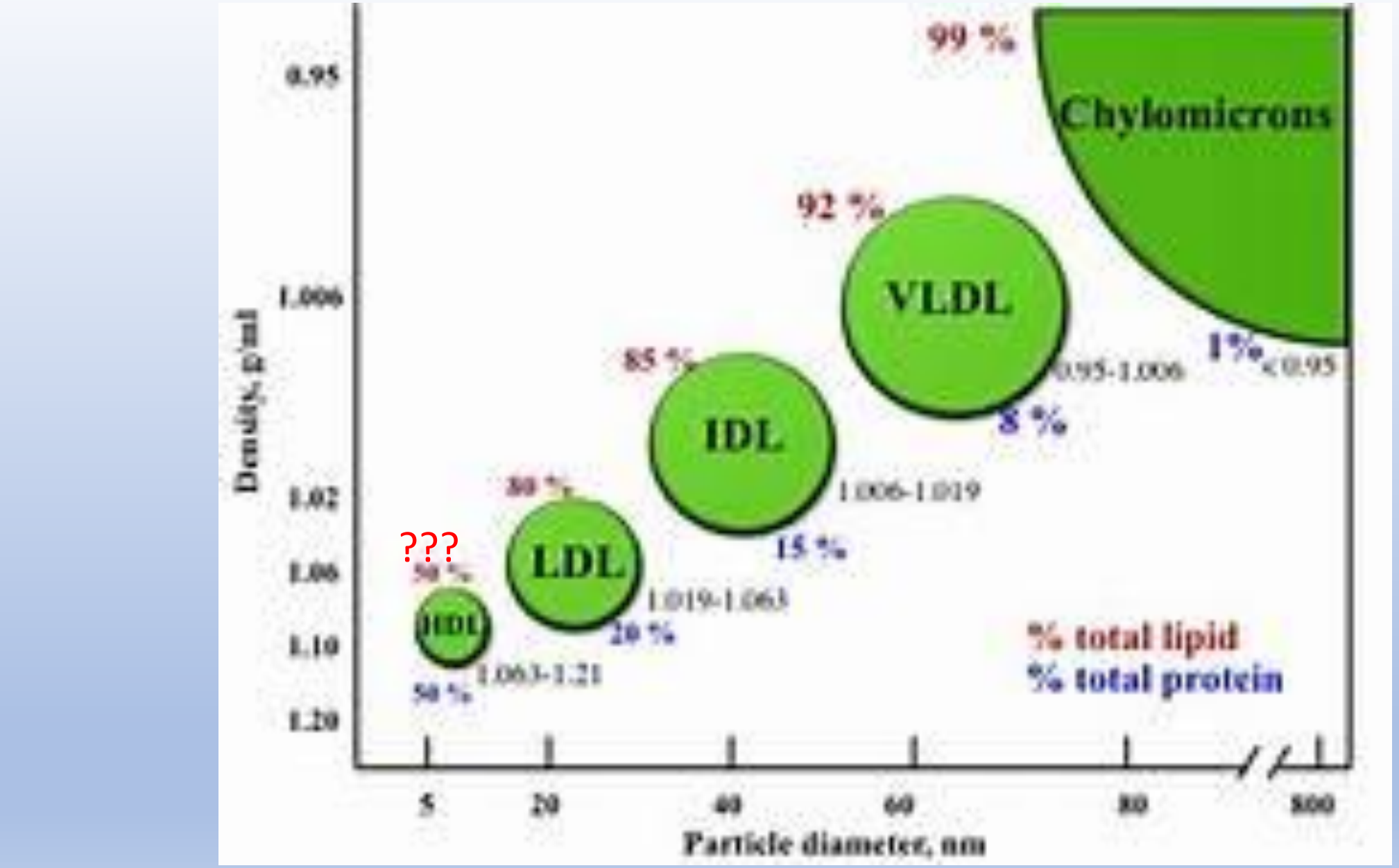
Disclosures

- No Disclosures…

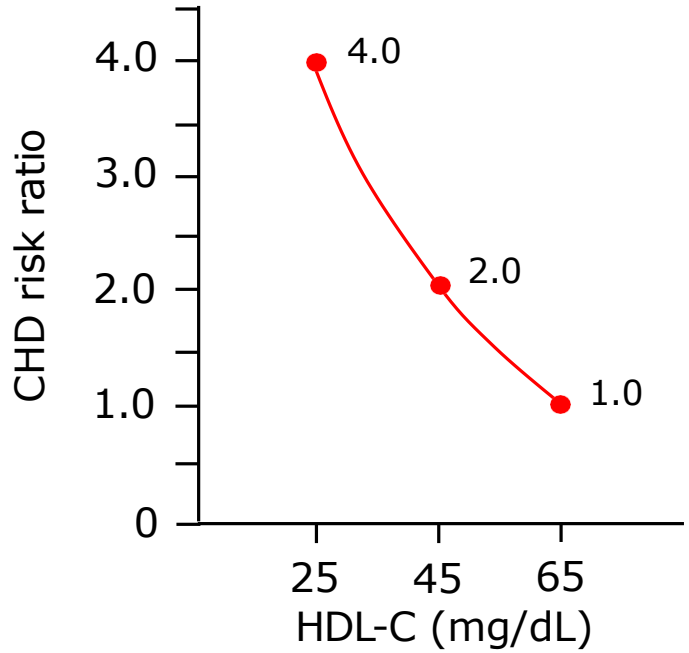
Before the discovery of lipoproteins …..
What did we know ???


THEY'RE HAPPY
Because they eat
LARD
www.StrangeCosmos.com
issued by the Lard Information Council

What did we know about HDL in the 1960's ?


99 %
Chylomicrons
92 %
VLDL
1%
<0.95
0.95-1.006
8 %
85 %
IDL
1.006-1.019
15 %
80 %
???
LDL
1.019-1.063
20 %
50 %
IDL
1.063-1.21
50 %
% total lipid
% total protein
Density, g/ml
0.95
1.006
1.02
1.06
1.10
1.20
5
20
40
60
80
800
Particle diameter, nm

CHD RISK ACCORDING TO HDL-C LEVELS FRAMINGHAM STUDY



Kannel WB. Am J Cardiol 1983;52:9B–12B

1980

- **HDL-cholesterol: the negative risk factor for coronary heart disease**
- M H Tan
- PMID: 7018364

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2011 VOL. 365 NO. 24

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

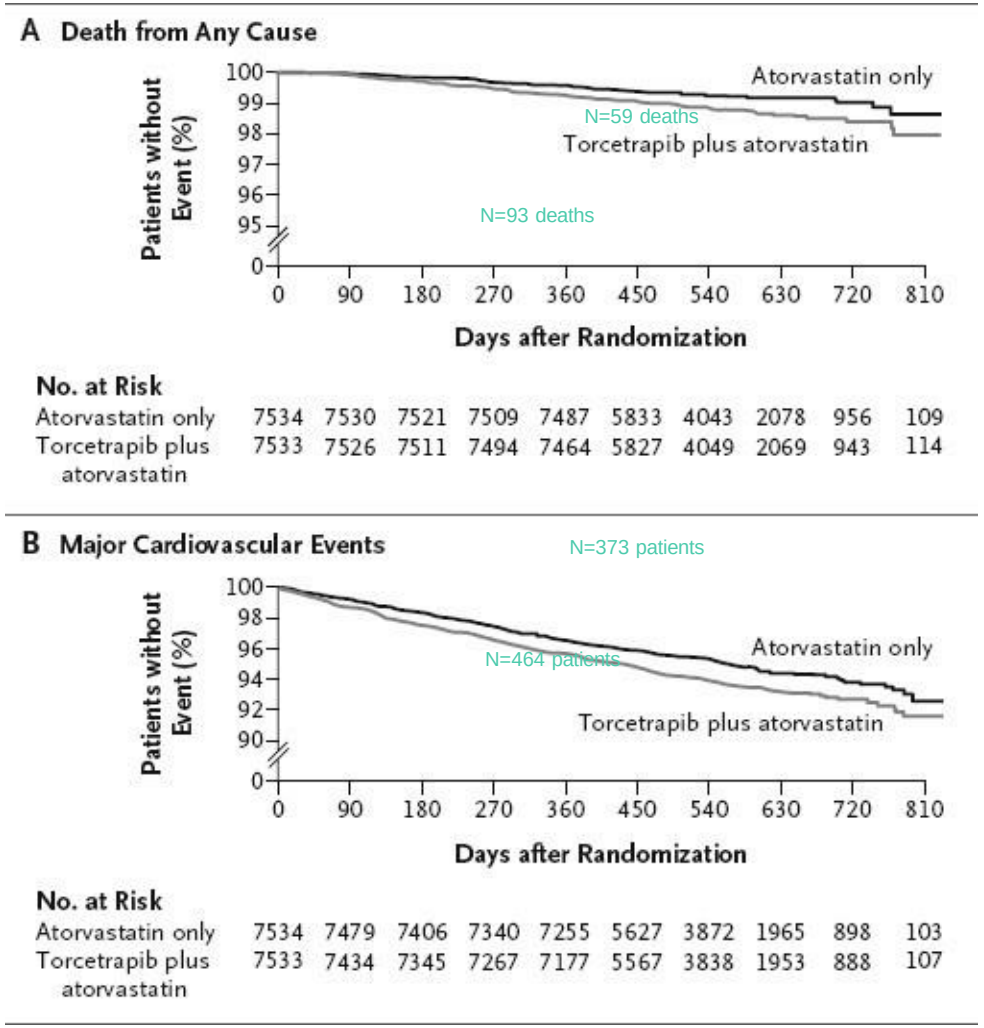
ESTABLISHED IN 1812 JULY 17, 2014 VOL. 371 NO. 3

Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

The HPS2-THRIVE Collaborative Group*

ILLUMINATE: TORCETRAPIB INCREASES EVENTS

- **N=15,067 patients**
  - Mean age 61 years
  - 73% male, 93% white
  - CVD or DM
  - Planned F/U 4.5 years
- **Treatment arms:**
  - Atorva
  - Atorva + torcetrapib
    - HDL-C increased 72%
    - LDL-C decreased 25%
- **Trial stopped after 18 m due to harm**
  - Increased CV and non-CV deaths
  - ? Off-target effect on aldosterone secretion

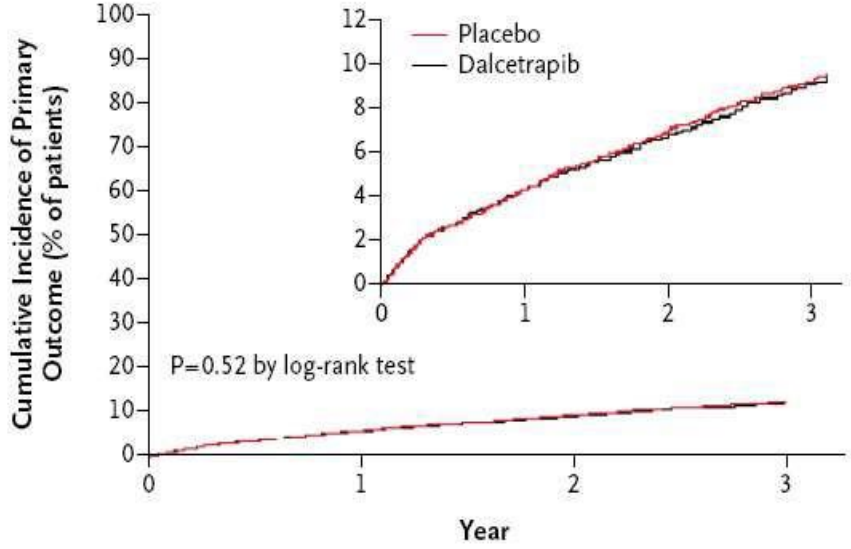


NEJM 2007; 357:2109-22

DAL-OUTCOMES: NO BENEFIT WITH DALCETRAPIB

- **N = 15,871**
- **Recent ACS**
- **Dalcetrapib 600 mg daily vs. placebo**
- **Background statin therapy**
- **BL: HDL-C 42, LDL-C 76**
- **1º EP: composite of CHD death, nonfatal MI, ischemic stroke, UA, or cardiac arrest with resuscitation**

Placebo: HDL-C +4% to +11%
Dalcetrapib: HDL-C +31% to +40%

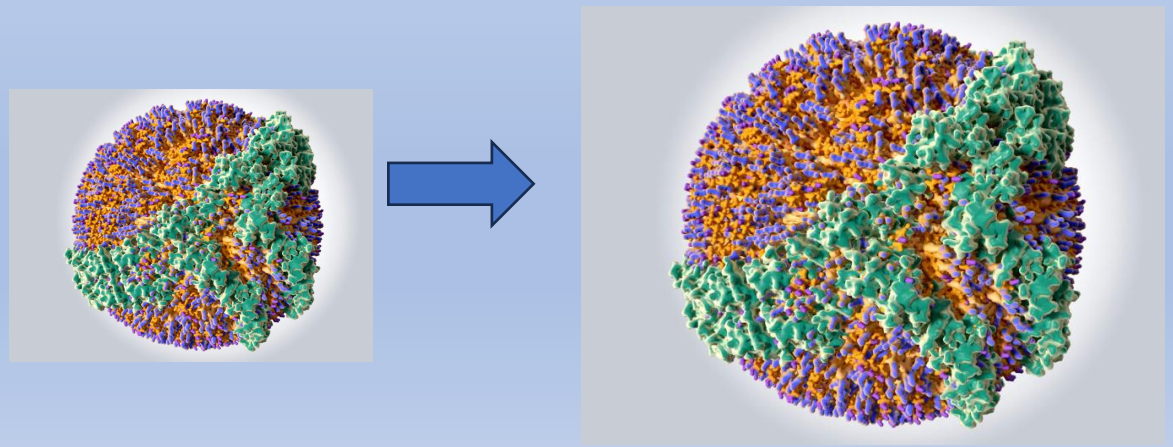


No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

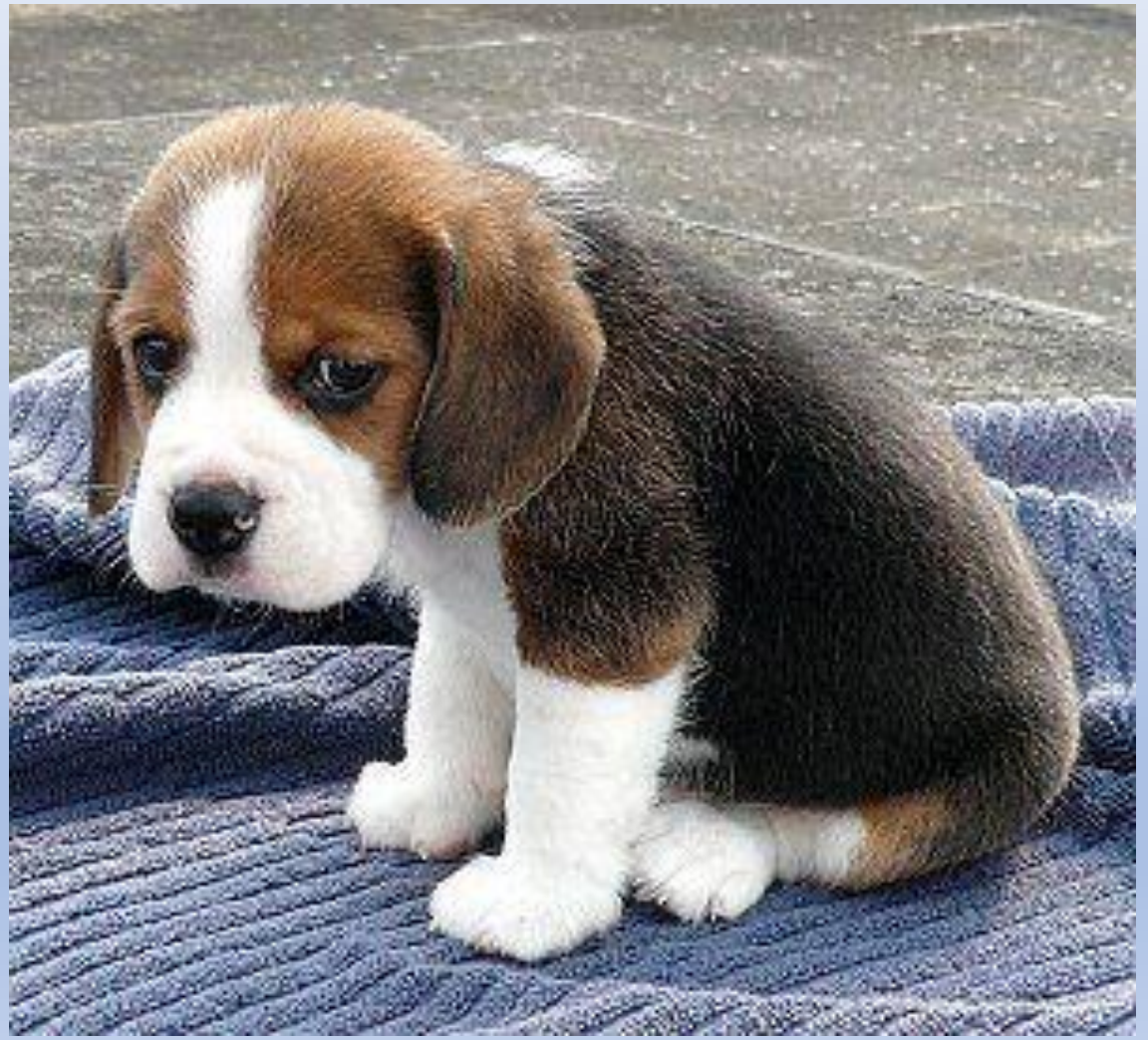
Schwartz GG et al. N Engl J Med 2012;367:2089-99

Increasing HDL-C :

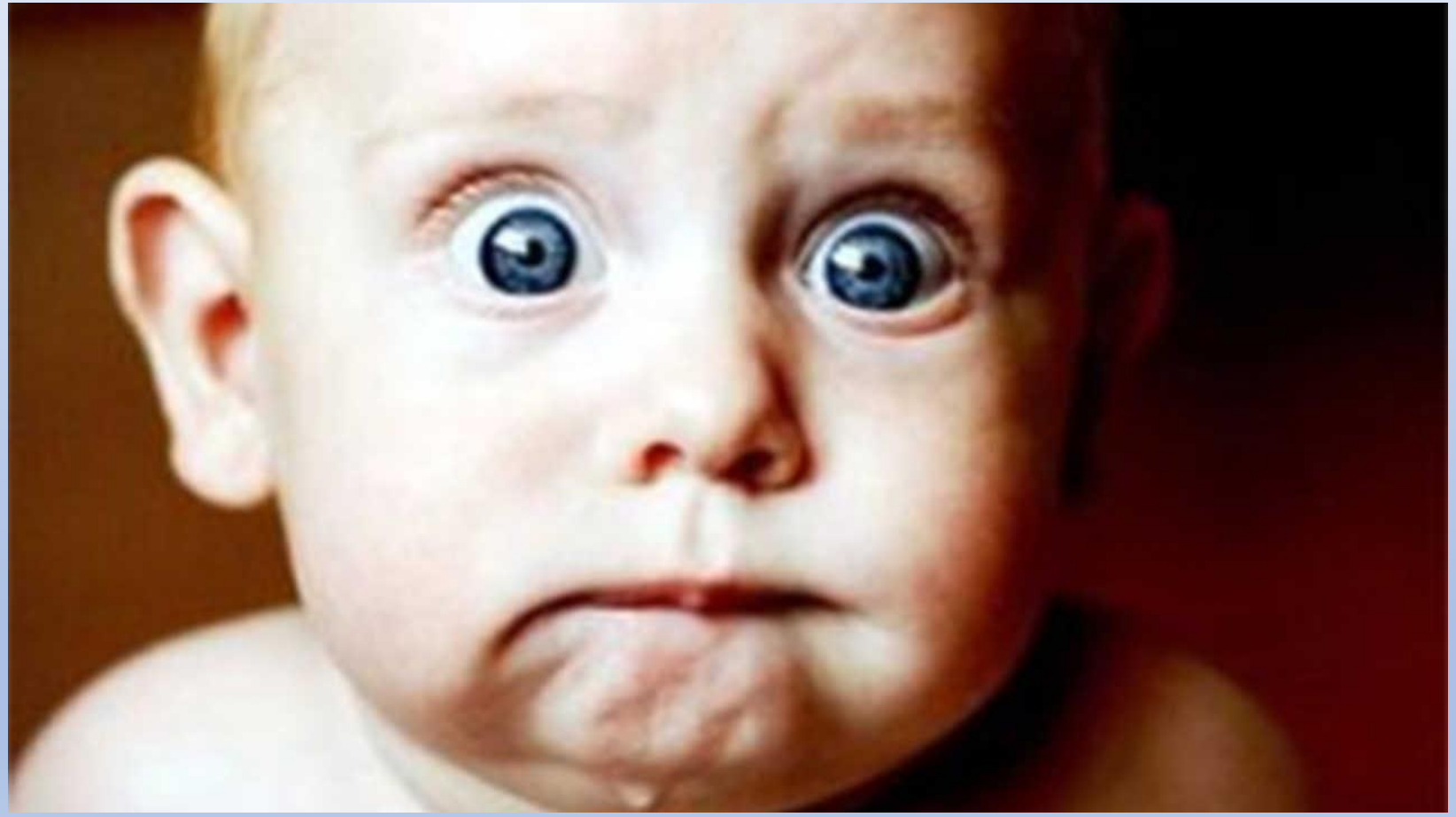
- **Clinical trials with pharmacological therapies that only increase the cholesterol content of the HDL particles have failed to establish this approach as an effective strategy for preventing CV events**



So, What Do You Think About HDL-C Now ?

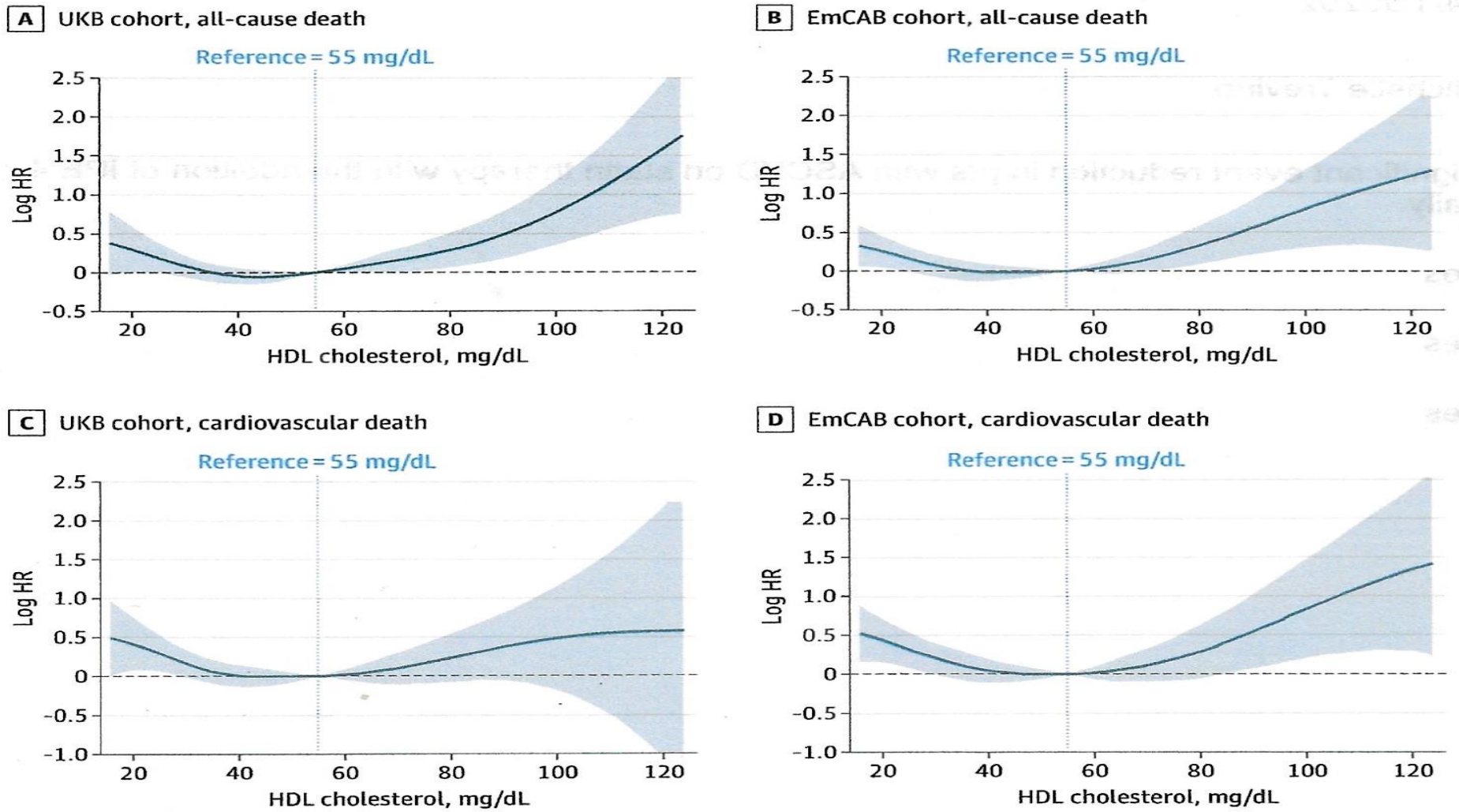


And if the wasn’t enough…..



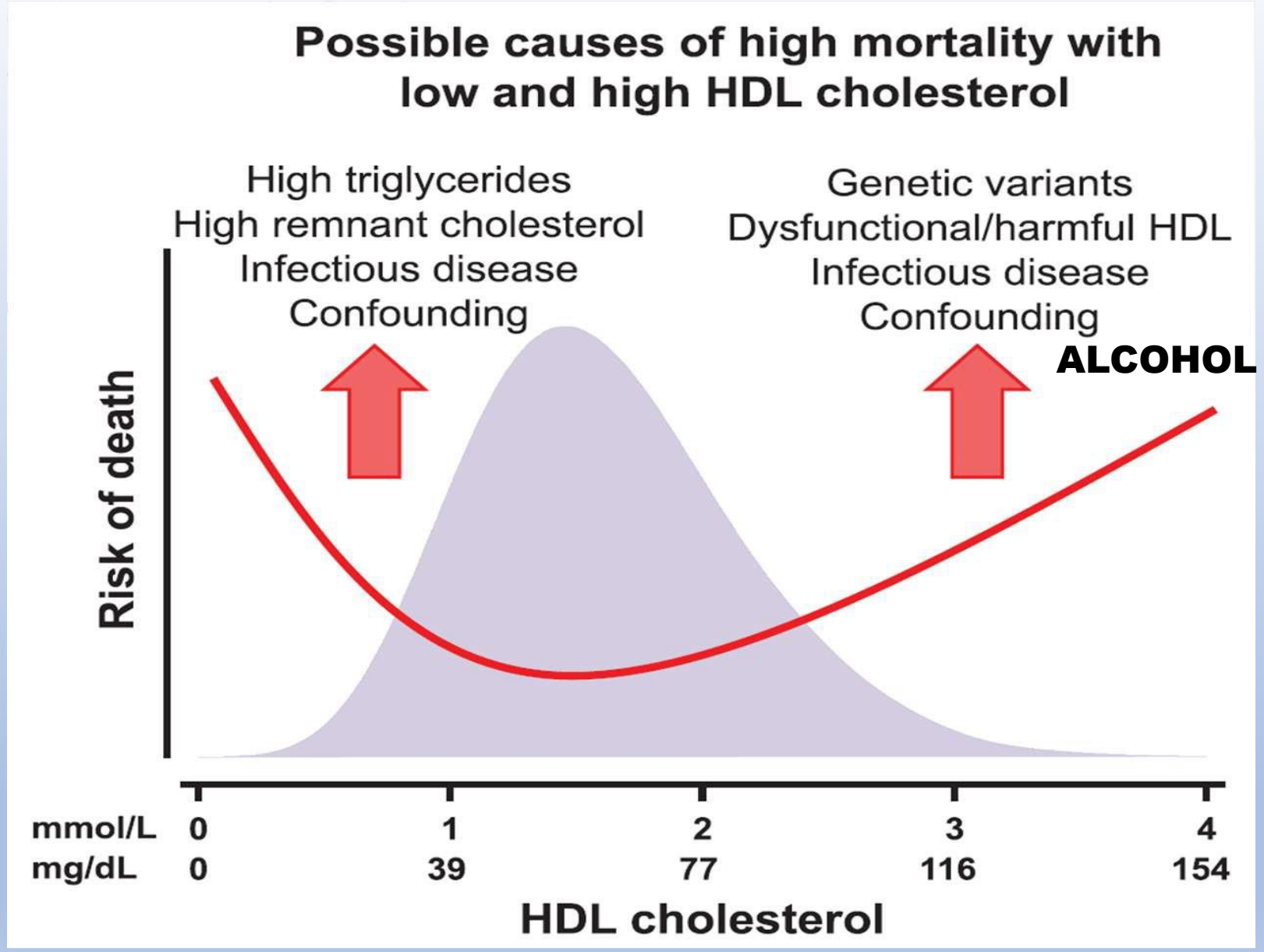
20,000 participants with CAD enrolled in either the UK Biobank or the Emory Biobank with HDL-C levels > 80 mg/dl had a 96% higher risk of all cause mortality and 71% higher risk of cardiovascular mortality after adjustments for covariates

Figure 1. Nonlinear Association Between High-Density Lipoprotein (HDL) Cholesterol Levels and Adverse Outcomes



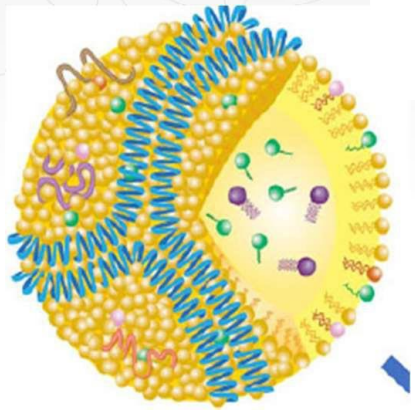
UK Biobank (UKB) coronary arter disease cohort model of all-cause death (A) and cardiovascular deat (C) adjusted for age, sex, race and ethnicity, body mass index, hypertension, diabetes, smoking, triglycerides, low-density lipoprot (LDL) cholesterol, stroke history, heart attack history, estimated glomerular filtration rate (eGFR), and frequent alcohol use (defined alcohol consumption ≥3 times pe week). Emory Cardiovascular Biobank (EmCAB) model of all-ca death (B) and cardiovascular deat (D) adjusted for age, sex, race and ethnicity, body mass index, hypertension, diabetes, current/former smoking, triglycerides, LDL cholesterol, hea failure history, myocardial infarcti history, eGFR, frequent alcohol us (defined as ≥8 alcohol beverages per week), statin use, aspirin use, β-blocker use, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. HR indicate hazard ratio.

Liu C. et al JAMA Cardiol. 2022;7



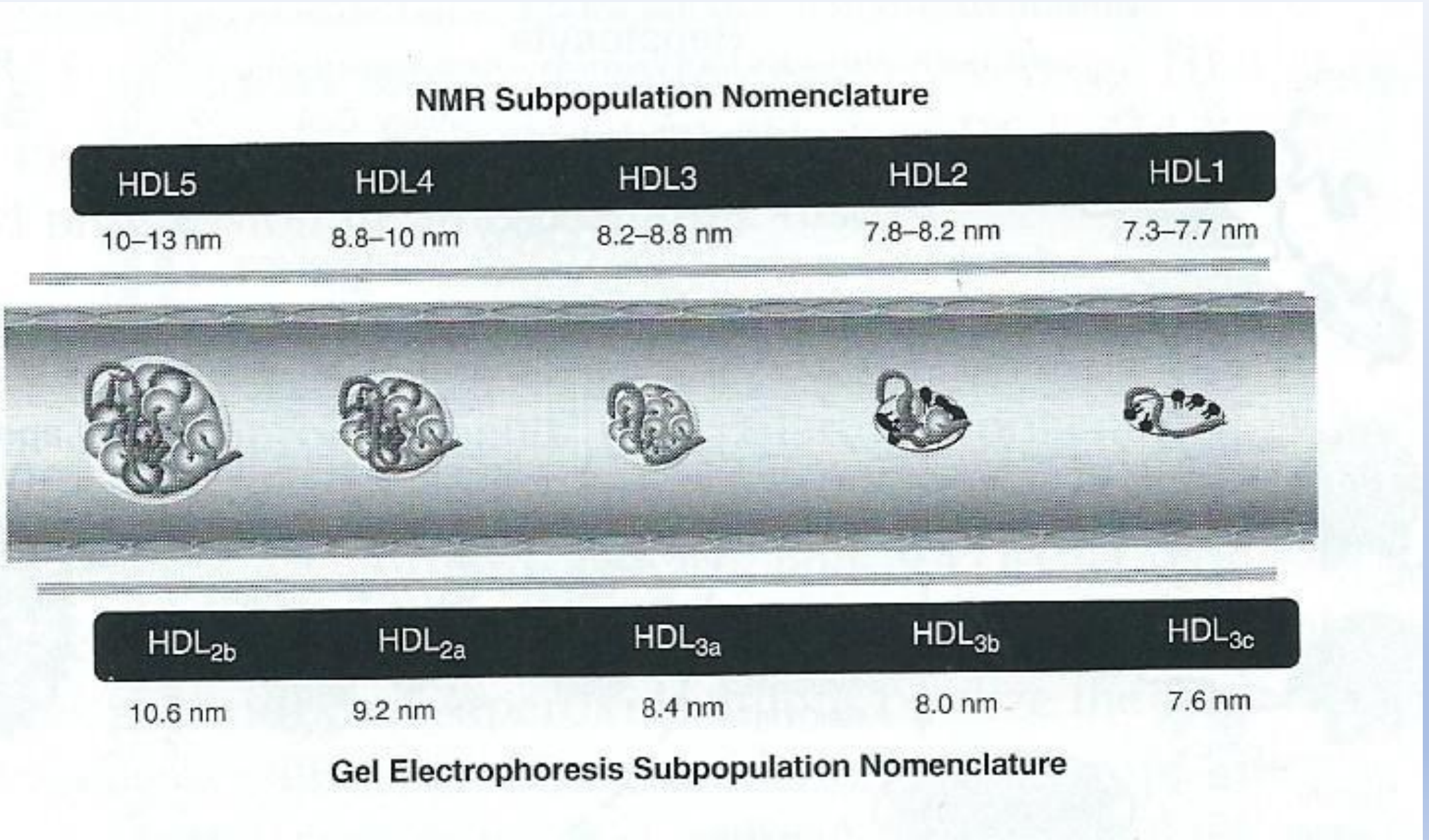
Madsen and Nordestgaard. Arterioscler Thromb Vasc Biol. 2018;38:484-486

TAKE HOME POINTS



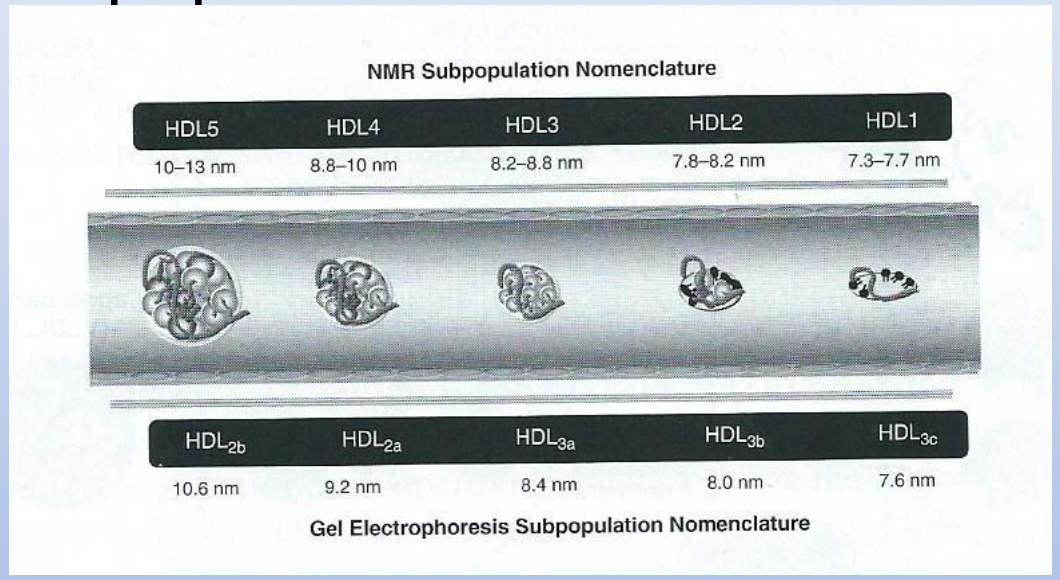
Von Eckardstein, EHJ 2022;1-14

- **HDL-C ≠ HDL**
- **Low HDL-C predicts poor outcomes, high HDL-C may not be protective for ASCVD**
- **No reduction in ASCVD events by raising HDL-C with**
  - **Niacin or fibrates on statin background**
  - **Estrogens**
  - **Most CETP inhibitors**
- **Need to focus on HDL function, not only on HDL-C concentration**


NMR Subpopulation Nomenclature
HDL5
HDL4
HDL3
HDL2
HDL1
10–13 nm
8.8–10 nm
8.2–8.8 nm
7.8–8.2 nm
7.3–7.7 nm
HDL2b
HDL2a
HDL3a
HDL3b
HDL3c
10.6 nm
9.2 nm
8.4 nm
8.0 nm
7.6 nm
Gel Electrophoresis Subpopulation Nomenclature

Increasing the Cholesterol Content of the HDL-C Lipoprotein…

- 1- HDLs are really exist as many subpopulations that differ in their:
- A- composition
- B- metabolism
- C- cellular interactions
- D- functional properties

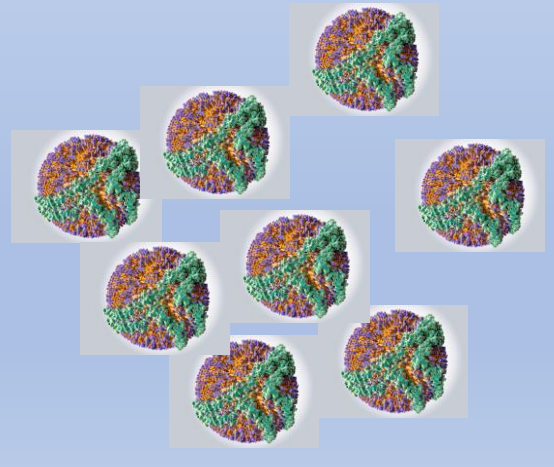


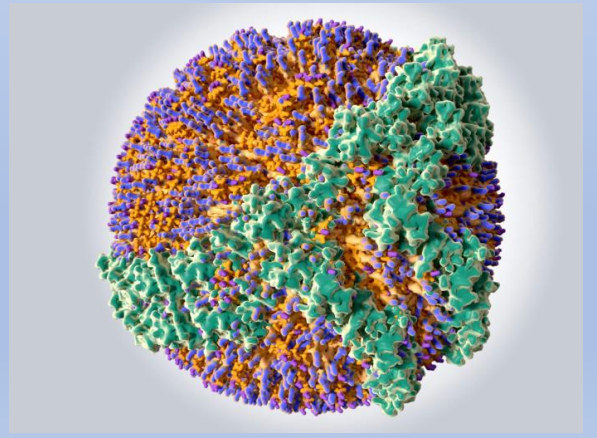
- Expansion of the cholesterol content of the HDL particle may interfere with cholesterol efflux, and alter the HDL protein mix to render it less effective in its antioxidant and anti-inflammatory properties

Otvos et al. Circ. 2000;101 Mackey et al. JACC 2012;60

- **SO EVIDENCE IS SUGGESTING THAT HDL PARTICLE CONCENTRATION (HDL-P) IS A BETTER CARDIOVASCULAR RISK MARKER THAN THE MEASUREMENT OF HDL-C."**

SMALL HDL PARTICLES



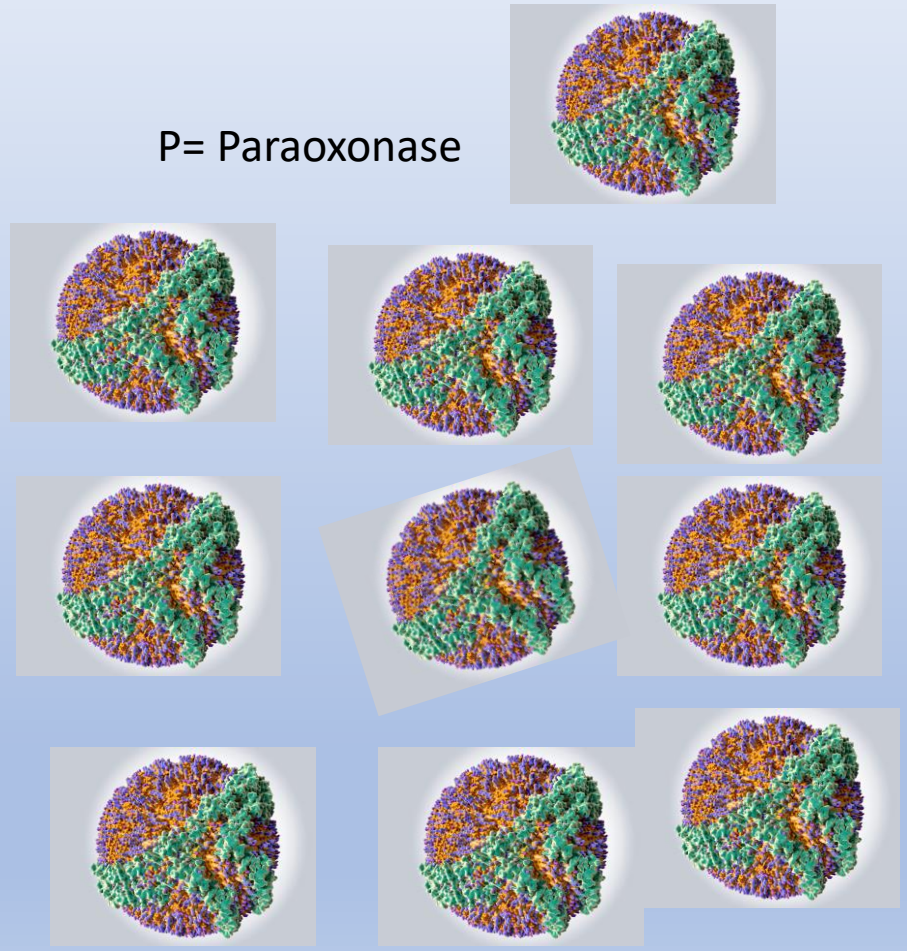


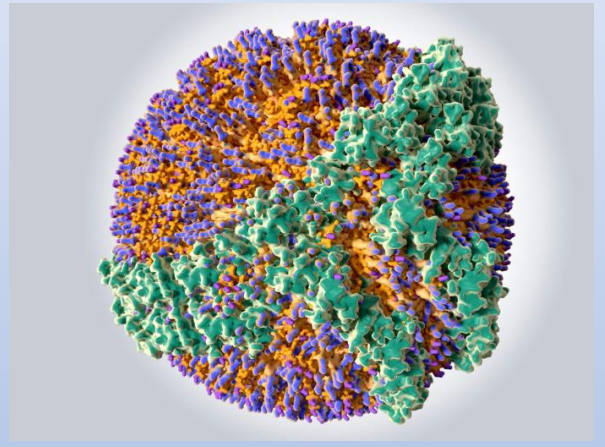
Large HDL PARTICLES

Otvos Circ. 2000 Mackey JACC 2012

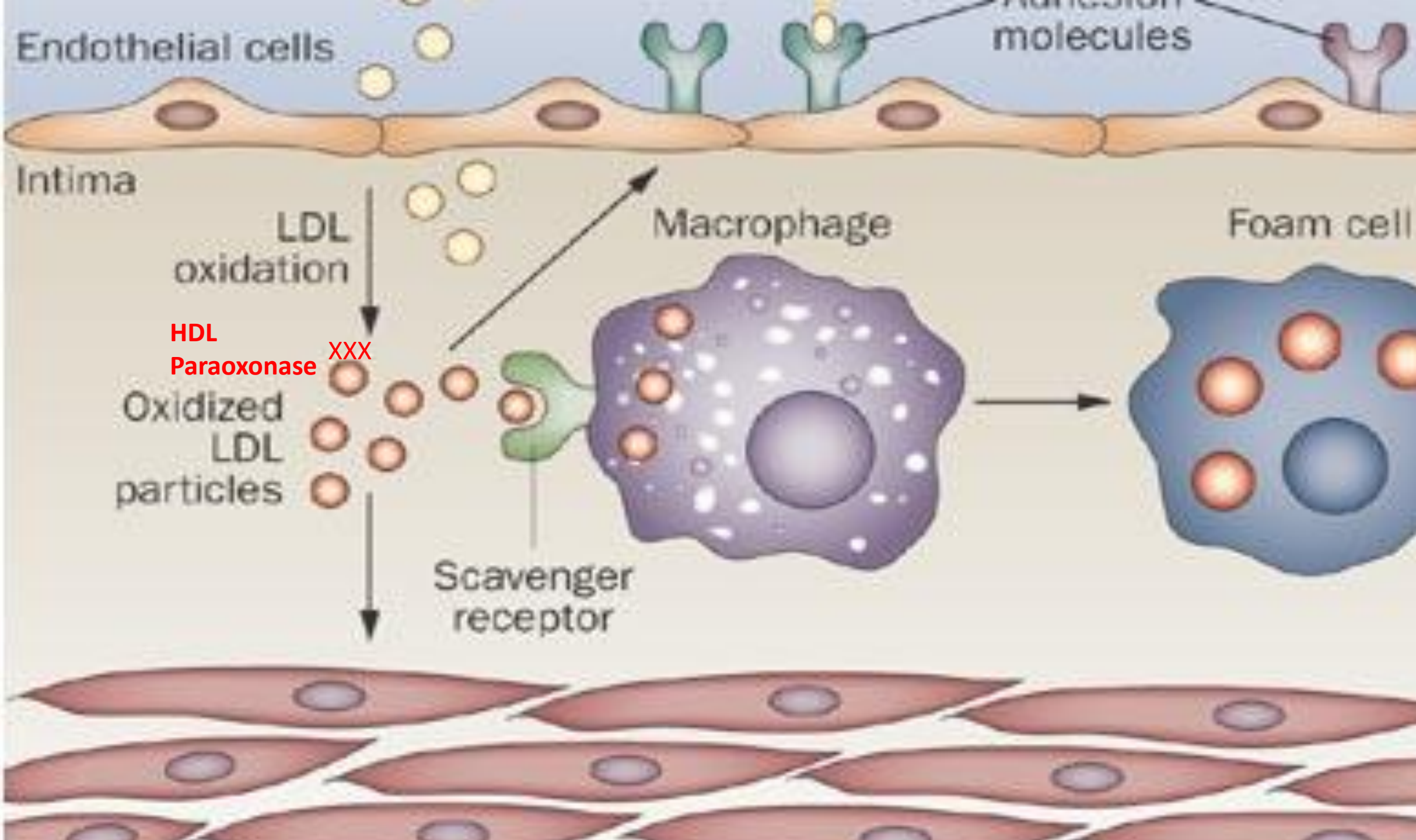
HDL-P vs. HDL-C

P= Paraoxonase

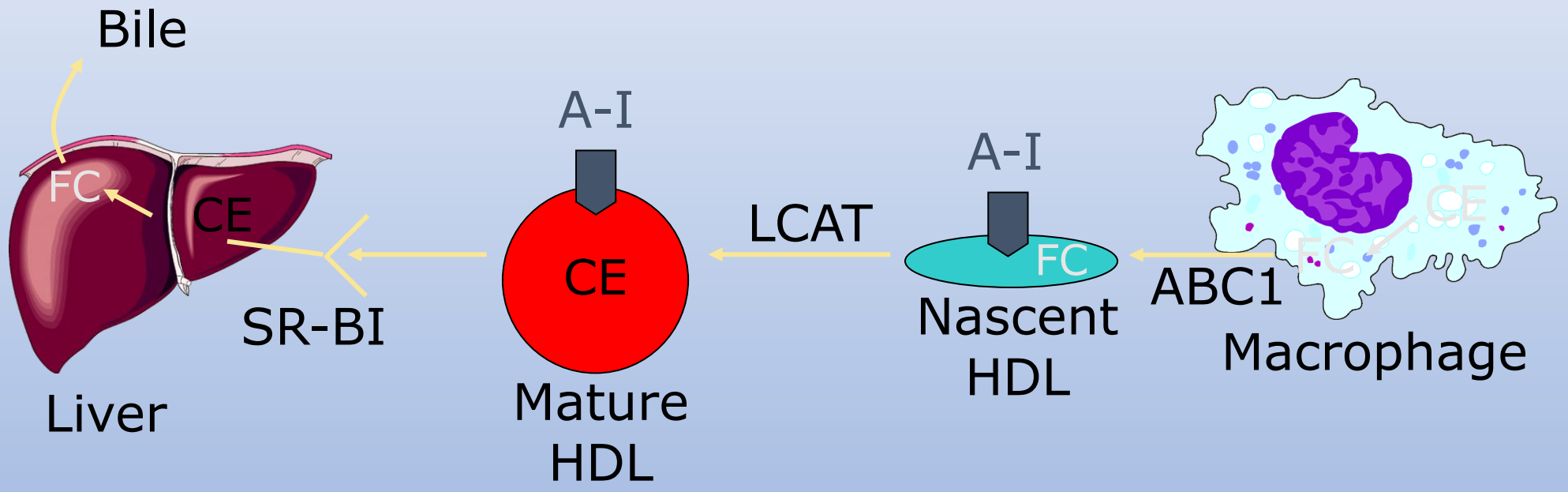




Adapted from Davidson MH. et al. Therapeutic Lipidology . Humana Press 2007

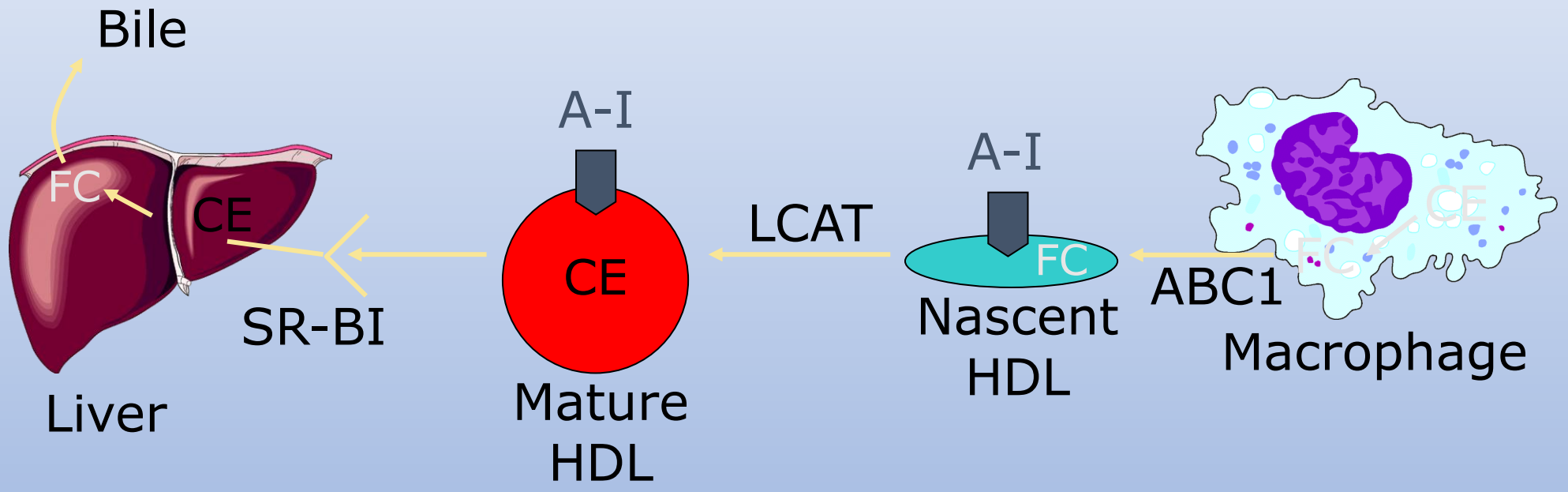

Endothelial cells
molecules
Intima
LDL
oxidation
HDL
Paraoxonase
XXX
Oxidized
LDL
particles
Macrophage
Foam cell
Scavenger
receptor

HDL Metabolism and Reverse Cholesterol Transport



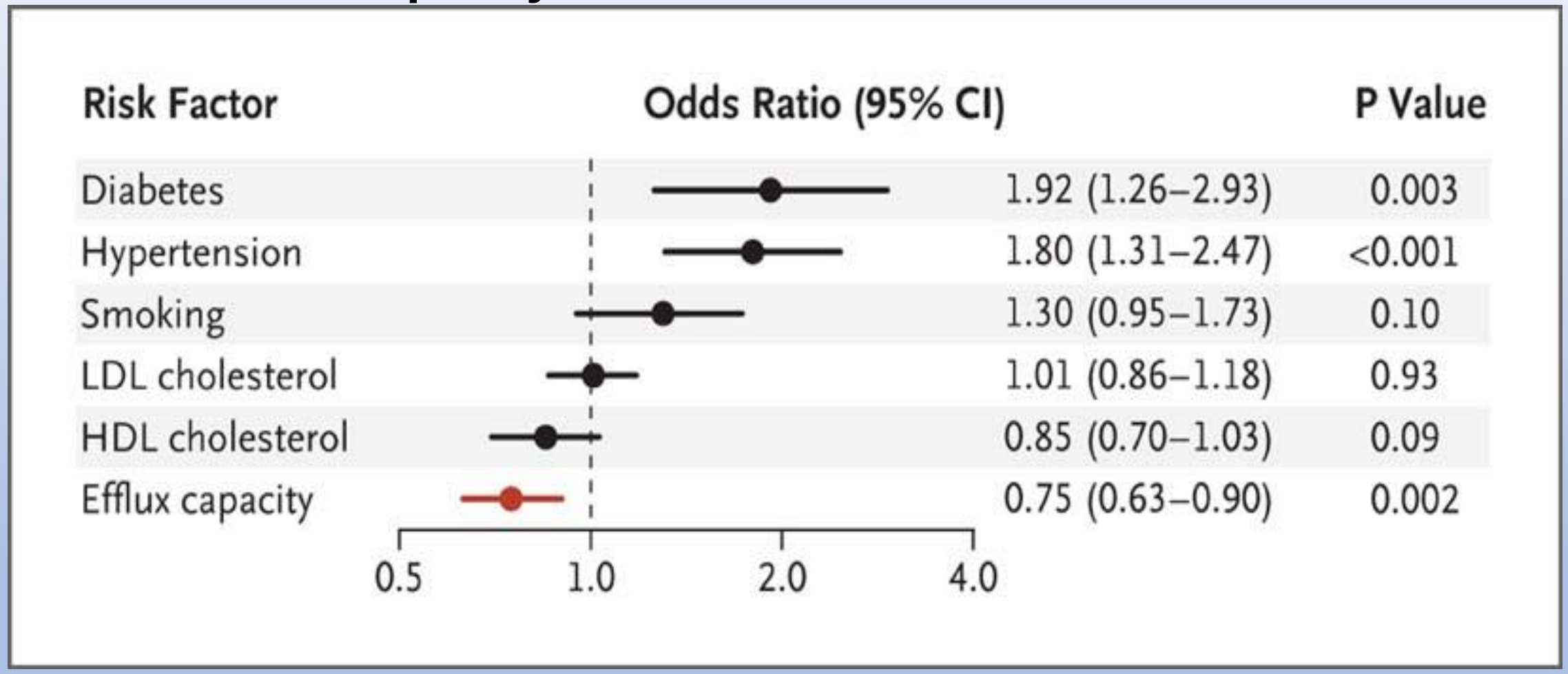
ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI

HDL Metabolism and Reverse Cholesterol Transport



ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI

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

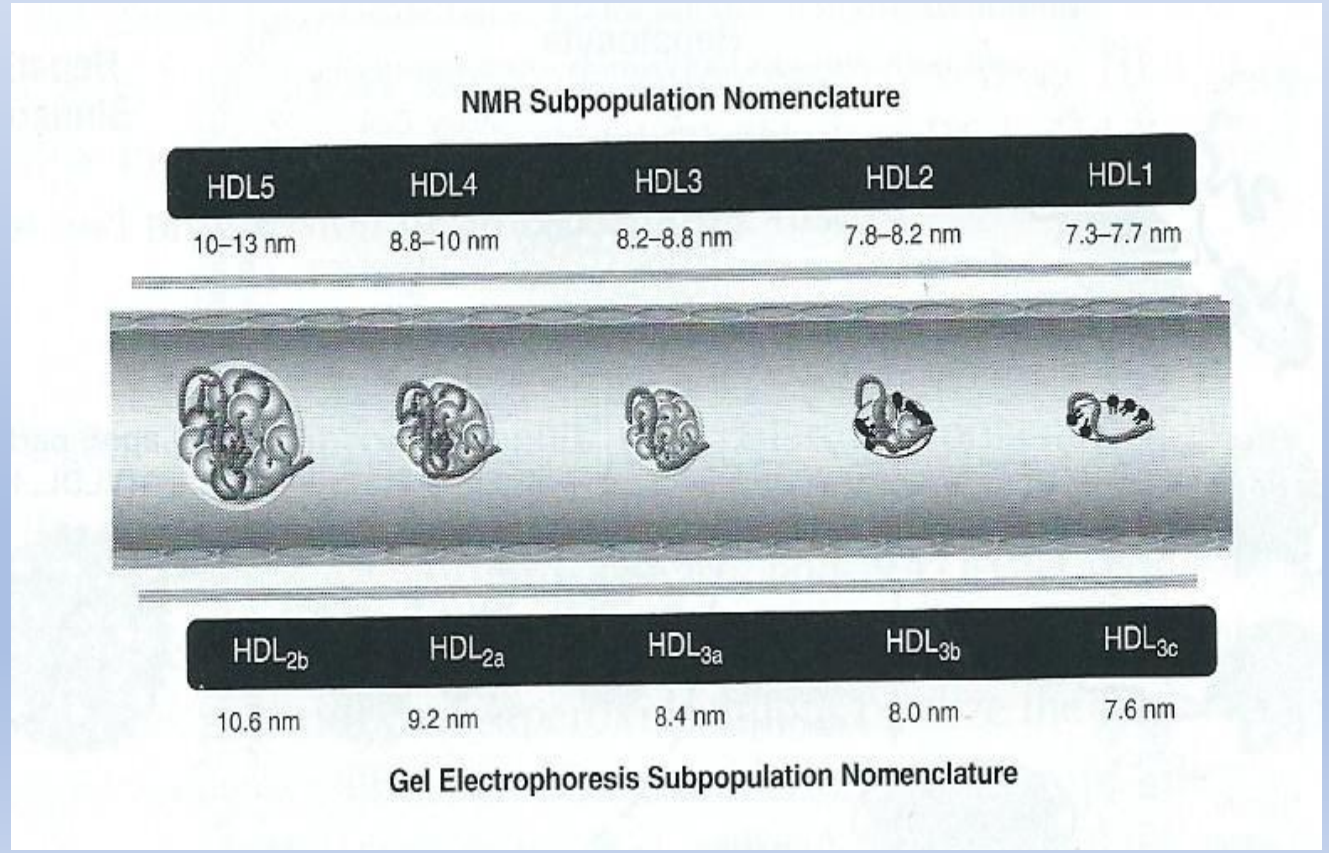


Khera AV et al. N Engl J Med 2011;364:127-135

The NEW ENGLAND JOURNAL of MEDICINE

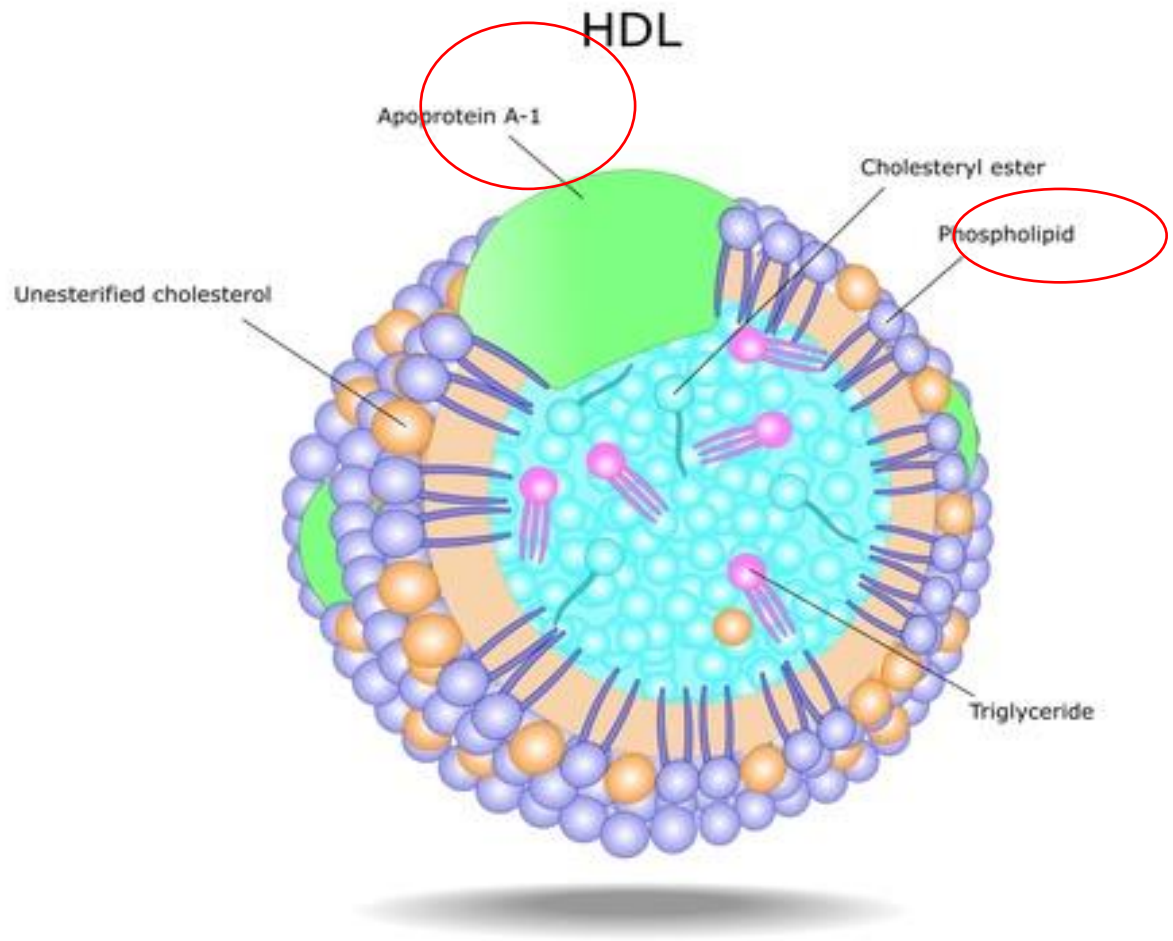
HDL: Structure-Function Relationship:
CHOLESTEROL EFFLUX IS ENRICHED IN THE SMALL HDL PARTICLES (HDL3)

- Cholesterol efflux
- anti-oxidative
- antithrombotic
- anti-inflammatory
- anti-apoptotic



Rosenson R. ATVB 2016 36 777-782

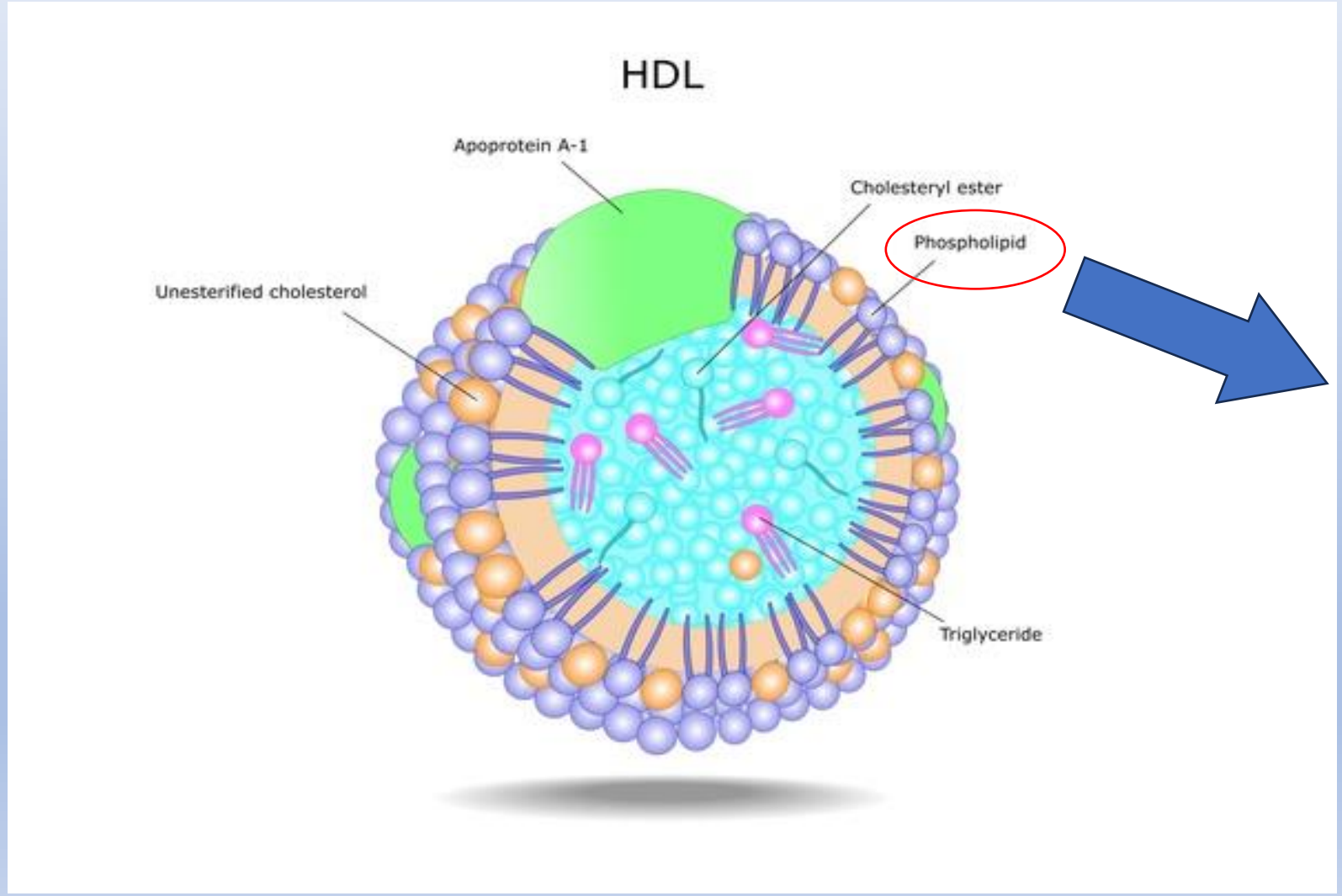
The Structure of HDL Determines the Function of HDL !

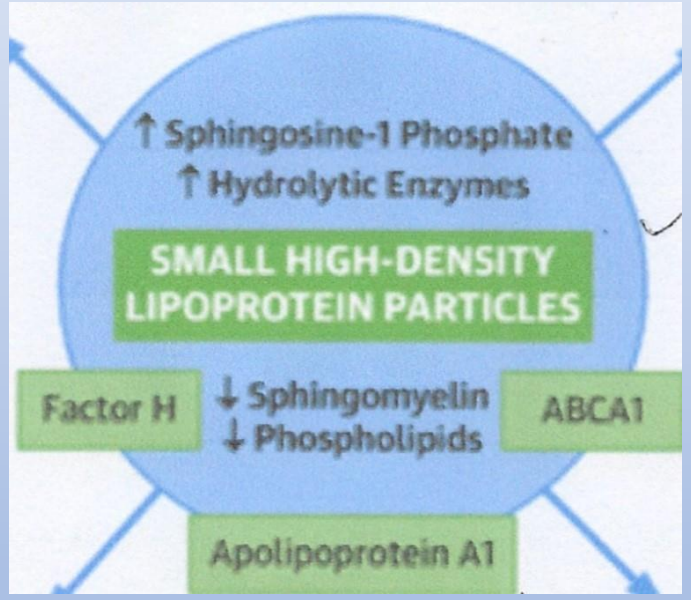


ADAPTED FROM Hunter WG et al. JACC 2019;73(2)

1- Phospholipids are a major component of HDL
2- Cholesterol efflux was increased in small dense HDL3 and correlated with the HDL phospholipid. (phosphosphingolipodome)

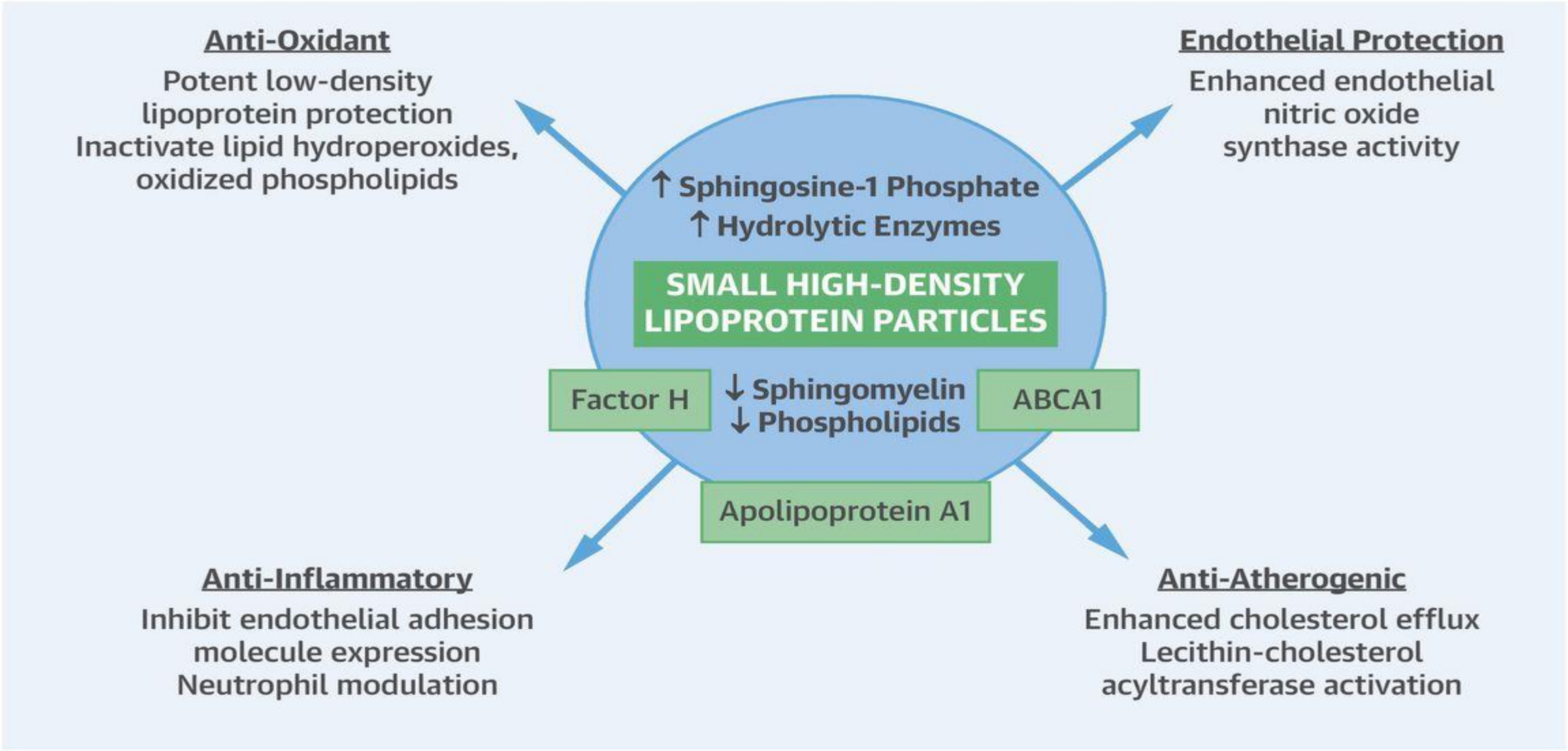
The Structure of HDL determines the Function of HDL





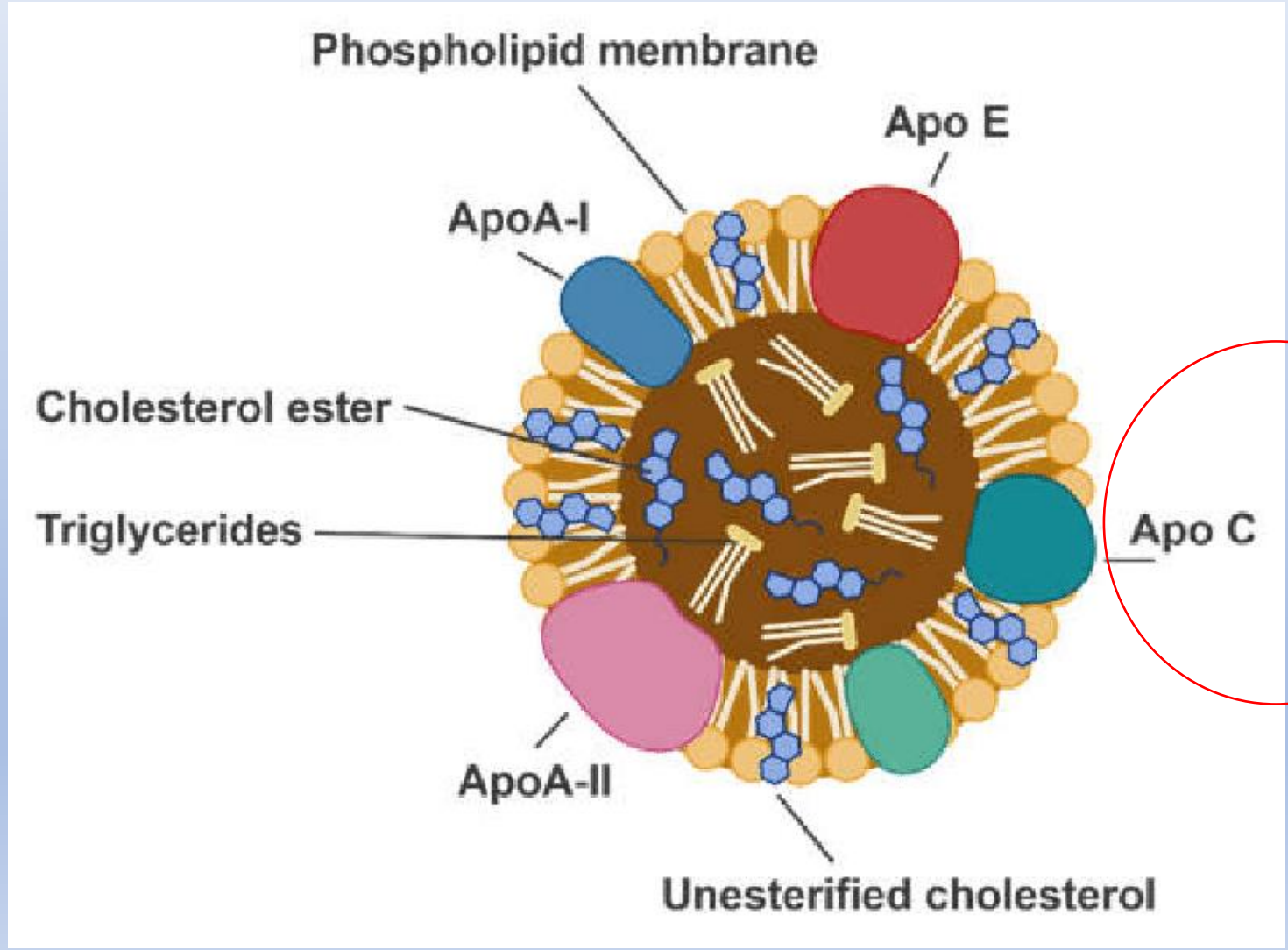
Hunter WG et al. JACC 2019;73(2)

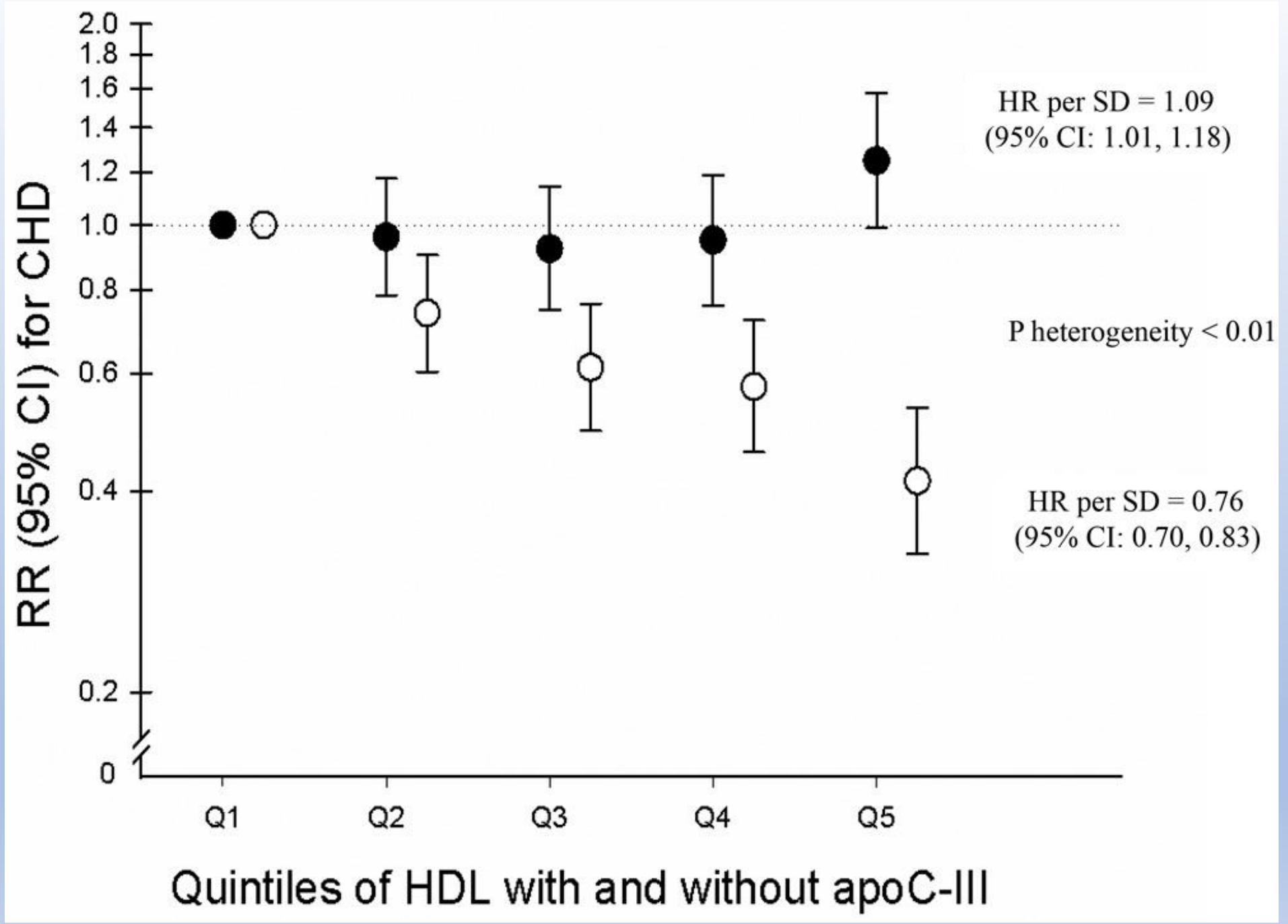
CENTRAL ILLUSTRATION: Proposed Protective Activities of Small High-Density Lipoprotein Particles



Hunter, W.G. et al. J Am Coll Cardiol. 2019;73(2):177–86.

APO C III


Phospholipid membrane
Apo E
ApoA-I
Cholesterol ester
Triglycerides
Apo C
ApoA-II
Unesterified cholesterol



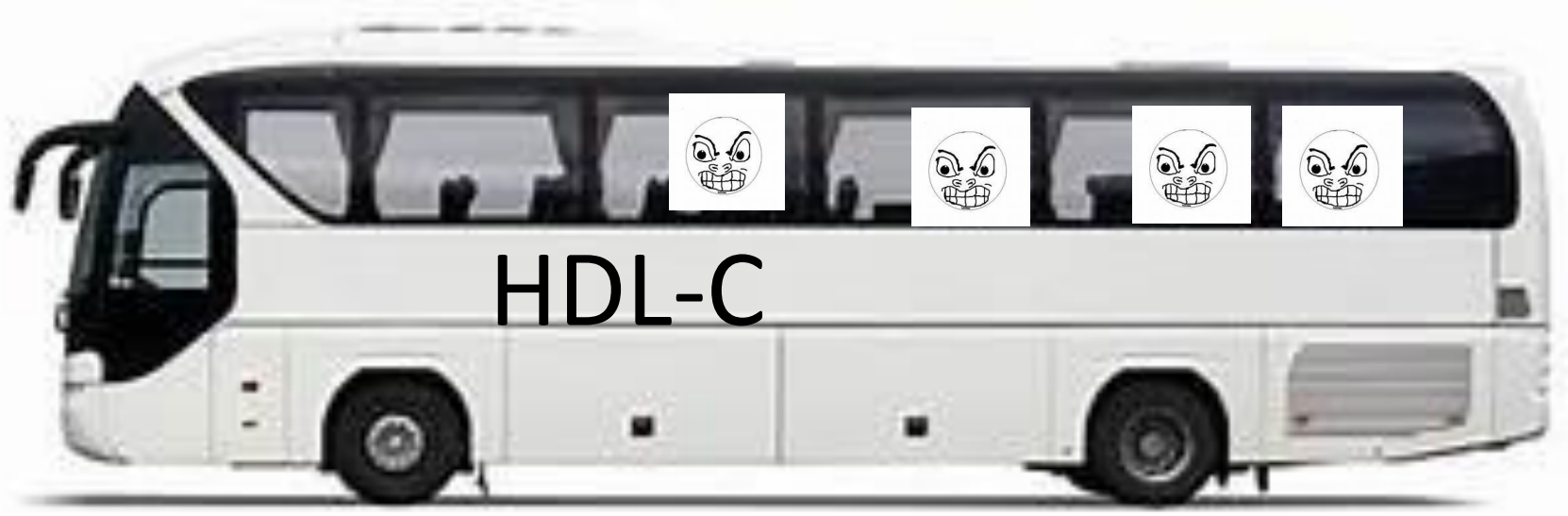
Jensen, Sacks Circ. March 2018

Who’s in the BUS?? Which passengers?

Who’s in the BUS??

1-Phospholipid 2- ApoA1 3-Paraoxonase
4- No ApoC3

Who's in the bus determines if HDL will be atheroprotective or pro-inflammatory



1-Serum Amyloid A

2- ApoC3

3 Apo J

4- CRP

5- IL-6

Reduced antioxidative activity and deminished cholesterol efflux capacity

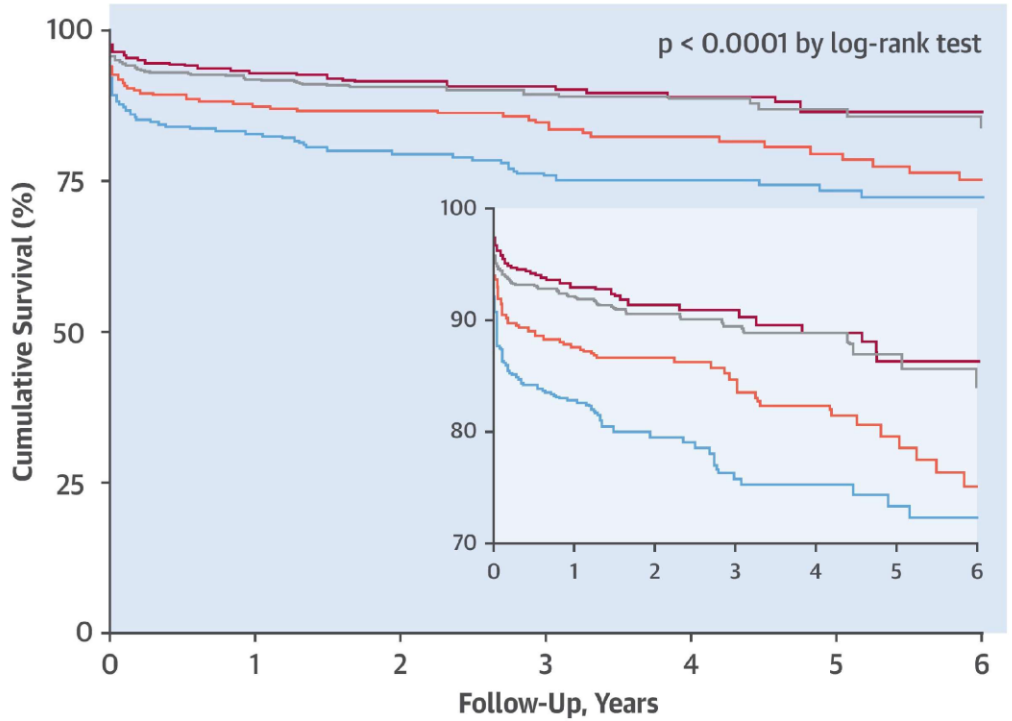
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 25, 2018

PUBLISHED BY ELSEVIER

Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction

Maryse Guerin, PhD,[a,*] Johanne Silvain, MD, PhD,[a,b,*] Julie Gall, PhD,[a] Maryam Darabi, PhD,[a] Myriam Berthet, PhD,[a] Eric Frisdal, PhD,[a] Marie Hauguel-Moreau, MD,[a,b] Michel Zeitouni, MD,[a,b] Mathieu Kerneis, MD,[a,b] Benoit Lattuca, MD,[a,b] Delphine Brugier,[a,b] Jean-Philippe Collet, MD, PhD,[a,b] Philippe Lesnik, PhD,[a] Gilles Montalescot, MD, PhD[a,b]

CENTRAL ILLUSTRATION: Cholesterol Efflux and Mortality in Myocardial Infarction: Kaplan-Meier Cumulative Survival Curve



No. at Risk		
Q1	303	54
Q2	324	59
Q3	341	51
Q4	344	65

	Hazard Ratio	
	Unadjusted	Adjusted*
Q4	0.40 (0.27-0.58)	0.54 (0.32-0.89)
Q3	0.45 (0.31-0.65)	0.76 (0.48-1.21)
Q2	0.71 (0.52-0.97)	0.84 (0.55-1.27)
Q1	Reference	Reference

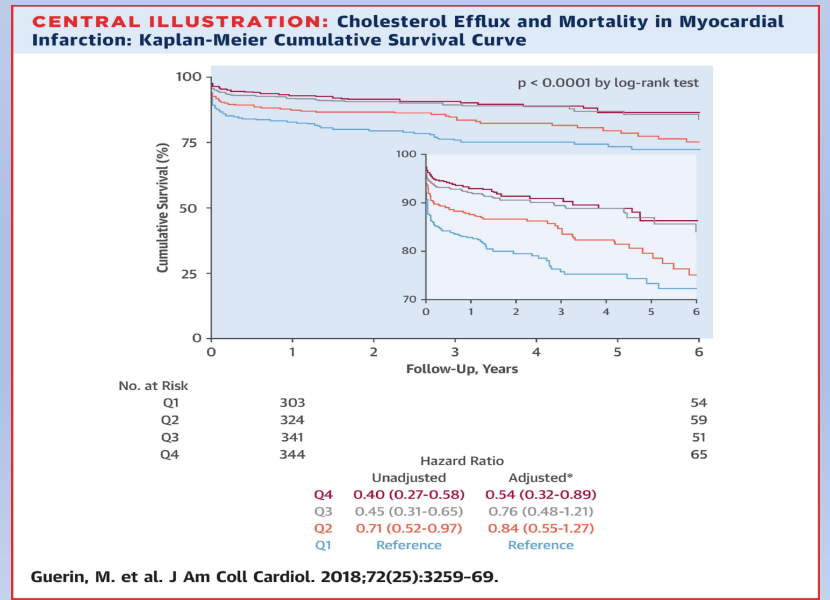
Guerin, M. et al. J Am Coll Cardiol. 2018;72(25):3259-69.

Significance?

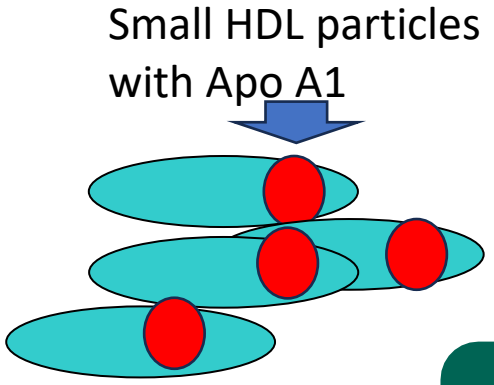
1- Cholesterol efflux capacity, a component of reverse cholesterol transport is independently associated with long term survival in MI patients.

2- Identify patients at higher risk of mortality after an acute coronary event

3- Independent of HDL-C



Cholesterol Efflux Hypothesis



CSL112 increases cholesterol efflux[1,2]
- Preclinical research data
- Clinical development program

Phase 2a[3]

Phase 2b/ AEGIS-I[4]

Increased cholesterol efflux in post-AMI patients[4,5]

Phase 3/ AEGIS-II[6]

Reduced risk of CV events[6]

Well characterized mechanism of action[1]
apoA-I (human) formulated with phospholipids that improve LCAT function

Appropriate dose[7]
Upper end of dose range

Patients at high risk of CV events during 90 days post AMI[6]
ACS patients with high event rates, multivessel disease, and established CV risk factors

Timely intervention[6]
Early post-ACS, when cholesterol efflux is impaired

1. Diditchenko S, et al. Arterioscler Thromb Vasc Biol. 2013;33:2202–11; 2. Gille A, et al. Arterioscler Thromb Vasc Biol. 2014;34:2106–114; 3. Tricoci P, et al. J Am Heart Assoc. 2015;4:e00271; 4. Gibson CM, et al. Circulation. 2016;134:1918–30; 5. Gibson CM, et al. Am Heart J. 2019;208:81–90; 6. Gibson CM, et al. Am Heart J. 2021;231:121–7; 7. Zheng B, et al. Br J Clin Pharmacol. 2021;87:2558–71.

HDL Particle Size and Structure Examined:

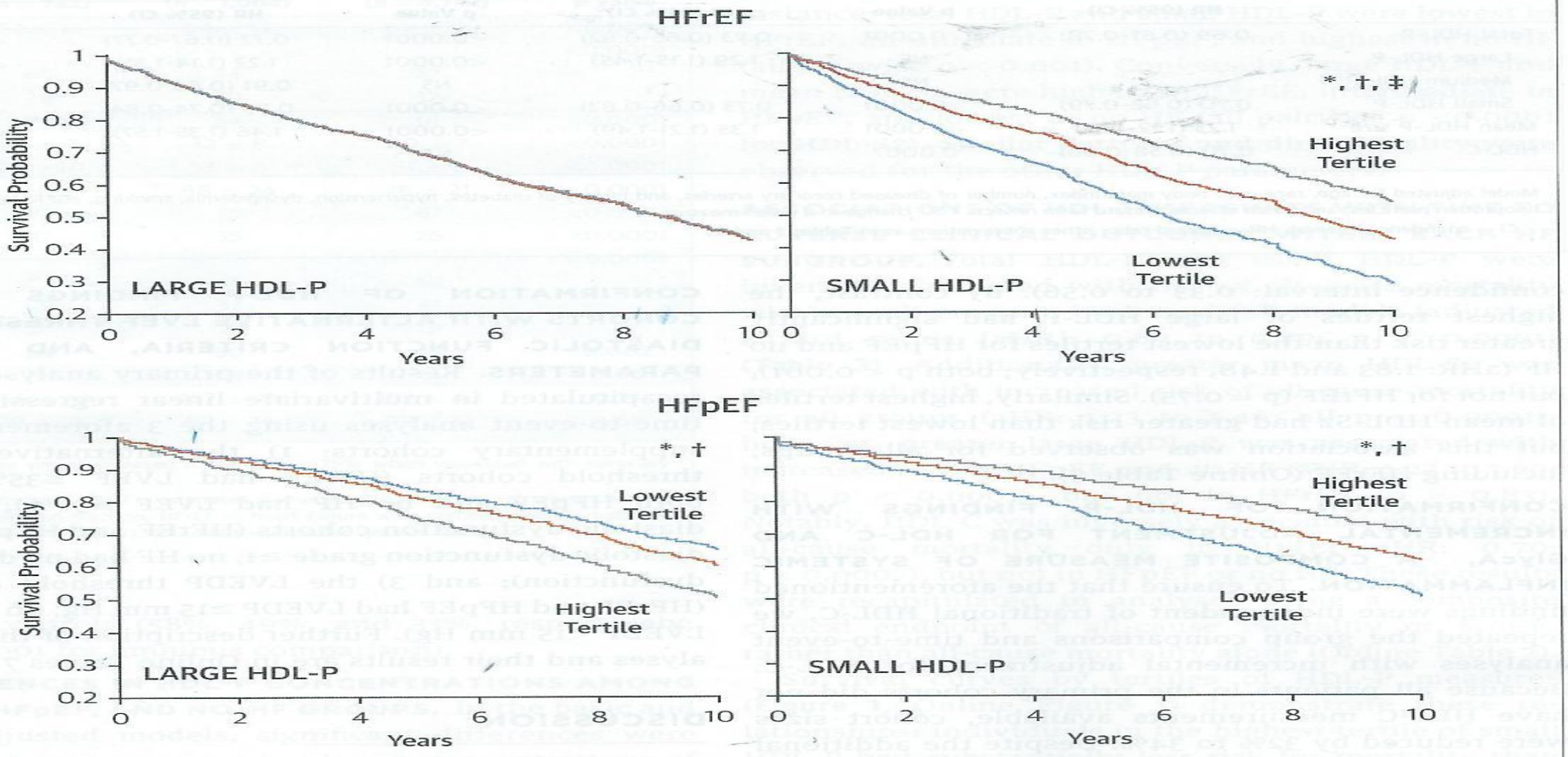
- 1- small particle size had greater efflux capacity, more anti-inflammatory, anti-oxidant, endothelial protective capacity than larger HDL particles
- 2- ***HDL subfractions modulate key pathways in heart failure as well !***

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 73, NO. 2, 2019

High-Density Lipoprotein Particle Subfractions in Heart Failure With Preserved or Reduced Ejection Fraction

Wynn G. Hunter, MD, MHSc,[a] Robert W. McGarrah III, MD,[b,c] Jacob P. Kelly, MD, MHS,[d] Michel G. Khouri, MD,[b] Damian M. Craig, MS,[c] Carol Haynes, AB,[c] G. Michael Felker, MD, MHS,[b,e] Adrian F. Hernandez, MD, MHS,[b,e] Eric J. Velazquez, MD,[b,e] William E. Kraus, MD,[b,c] Svati H. Shah, MD, MS, MHS[b,c,e]

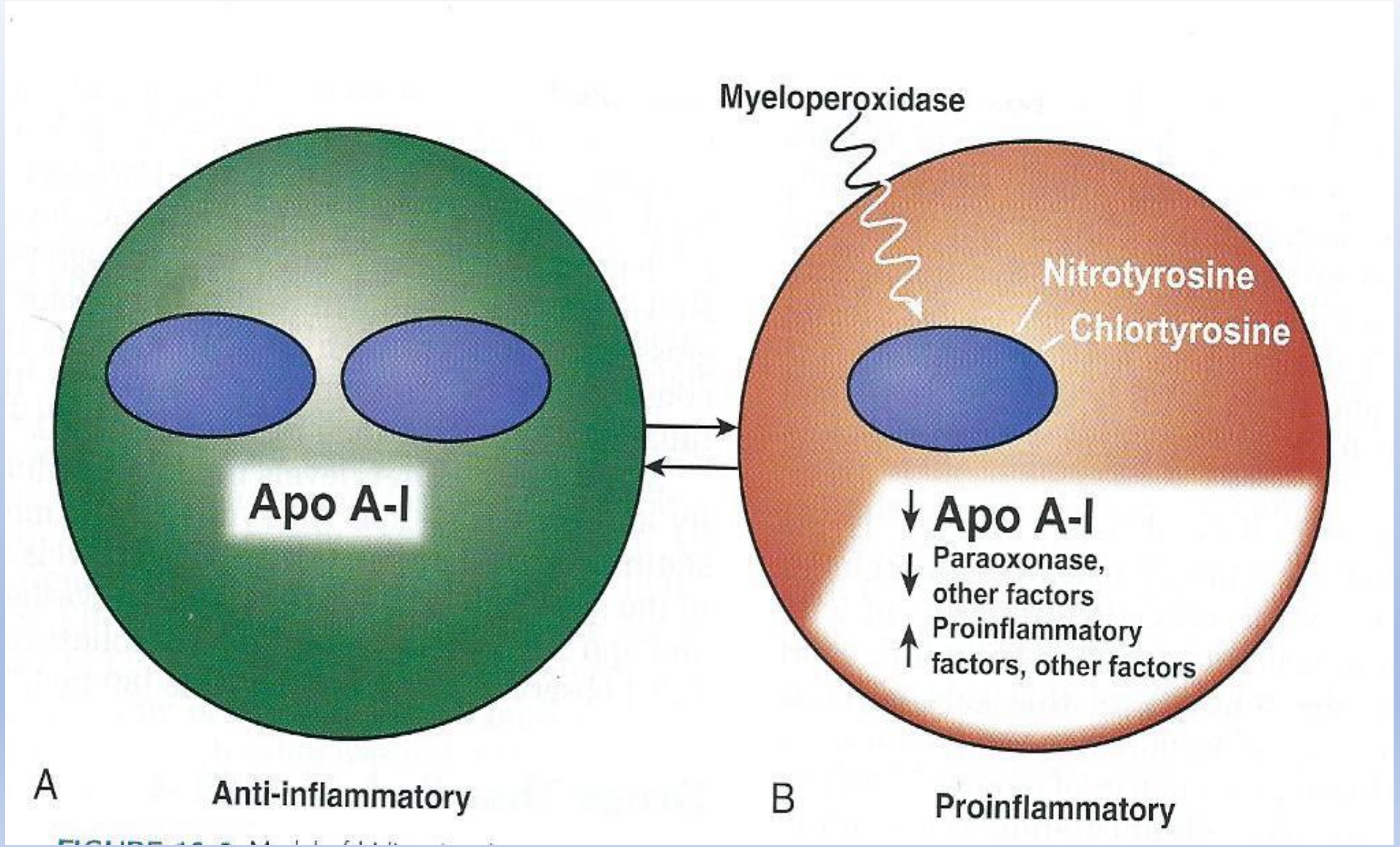
FIGURE 1 Multivariate Kaplan-Meier Survival Curves Showing Relationships Between Tertiles of HDL-P Subfractions and All-Cause Mortality in HFrEF and HFpEF



Adjusted for age, race, sex, body mass index, number of diseased coronary vessels (>75% stenosis), estimated glomerular filtration rate, history of hypertension, diabetes mellitus, smoking, dyslipidemia, low-density lipoprotein particles, and batch effects. Statistical significance ($p < 0.05$) denoted as follows: *Significant difference in all-cause mortality between the highest and lowest tertiles. †Middle and lowest tertiles. ‡Highest and middle tertiles. HDL-P = high-density lipoprotein particle(s); HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Cardiometabolic Diseases in Which HDL Metabolism is Perturbed, and in Which the Proteome and Functionality of HDL Particles May Be Altered:

1. CAD / ACS
2. Acute Systemic inflammation / Sepsis / Endotoxemia
3. Uremia


Myeloperoxidase
Nitrotyrosine
Chlortyrosine
Apo A-I
↓ Apo A-I
↓ Paraoxonase, other factors
↑ Proinflammatory factors, other factors
A
Anti-inflammatory
B
Proinflammatory

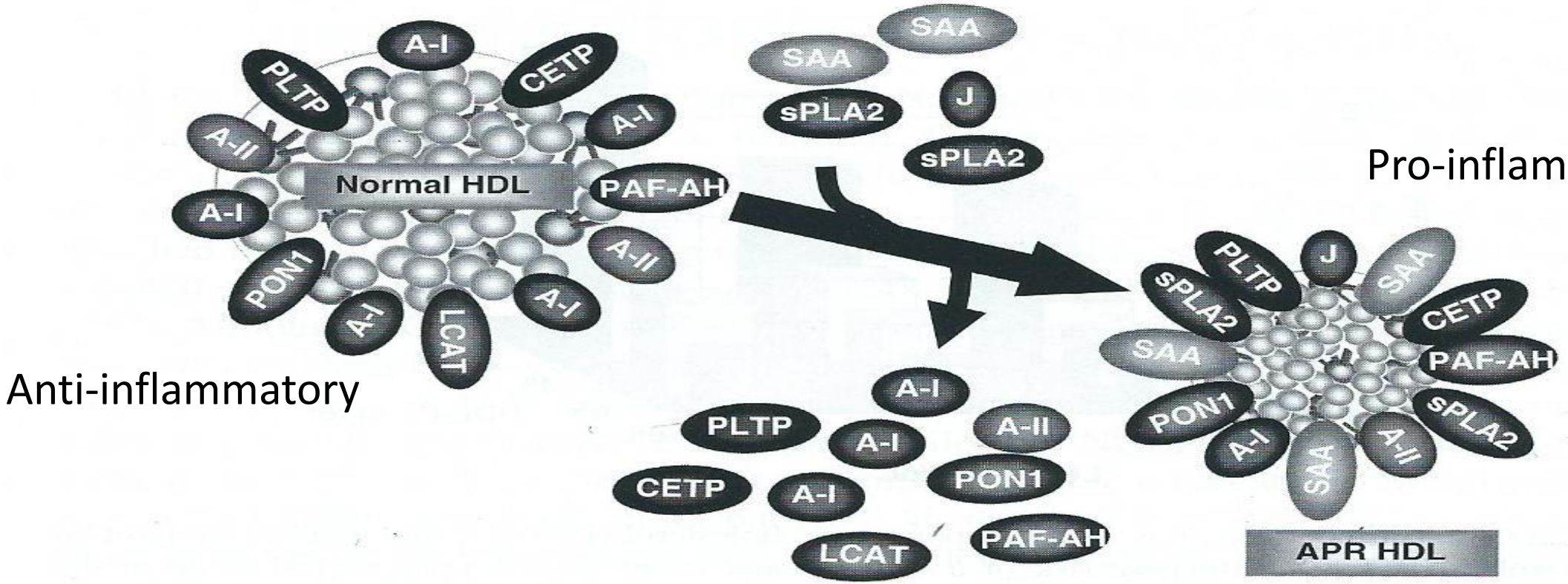
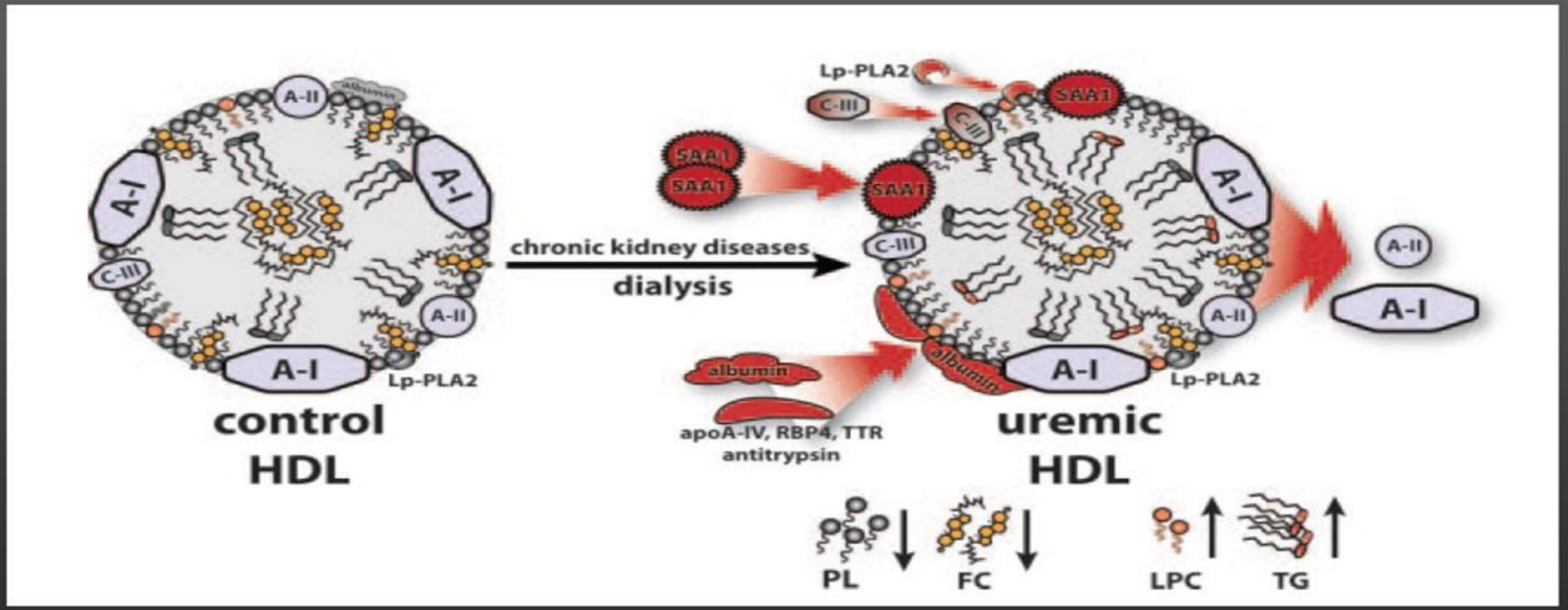


Fig. 5. Compositional alterations in high-density lipoprotein (HDL) during acute phase reactions. During an acute phase reaction, the expression of a large number of inflammatory mediators increases, including C-reactive protein, fibrinogen, serum amyloid A, and secretory phospholipase A2. The normal enzymatic and apoprotein constituents of HDL can dissociate and be replaced by apoJ, serum amyloid A, and phospholipase A2. This attenuates the ability of HDL to engage in reverse cholesterol transport and decrease oxidation and inflammation. A-I, apoprotein A-I; A-II, apoprotein A-II; J, apoprotein J; CETP, cholesteryl ester transfer protein; LCAT, lecithin:cholesteryl acyltransferase; PLTP, phospholipid transfer protein; PON1, paraoxonase 1; SAA, serum amyloid A; sPLA2, secretory phospholipase A2. Reproduced with permission from Ansell et al. *(82)*. (*see* Color Plate 4)

Davidson MH. et al. Therapeutic Lipidology . Humana Press 2007

3) HDL Remodelling in Uremic Patients



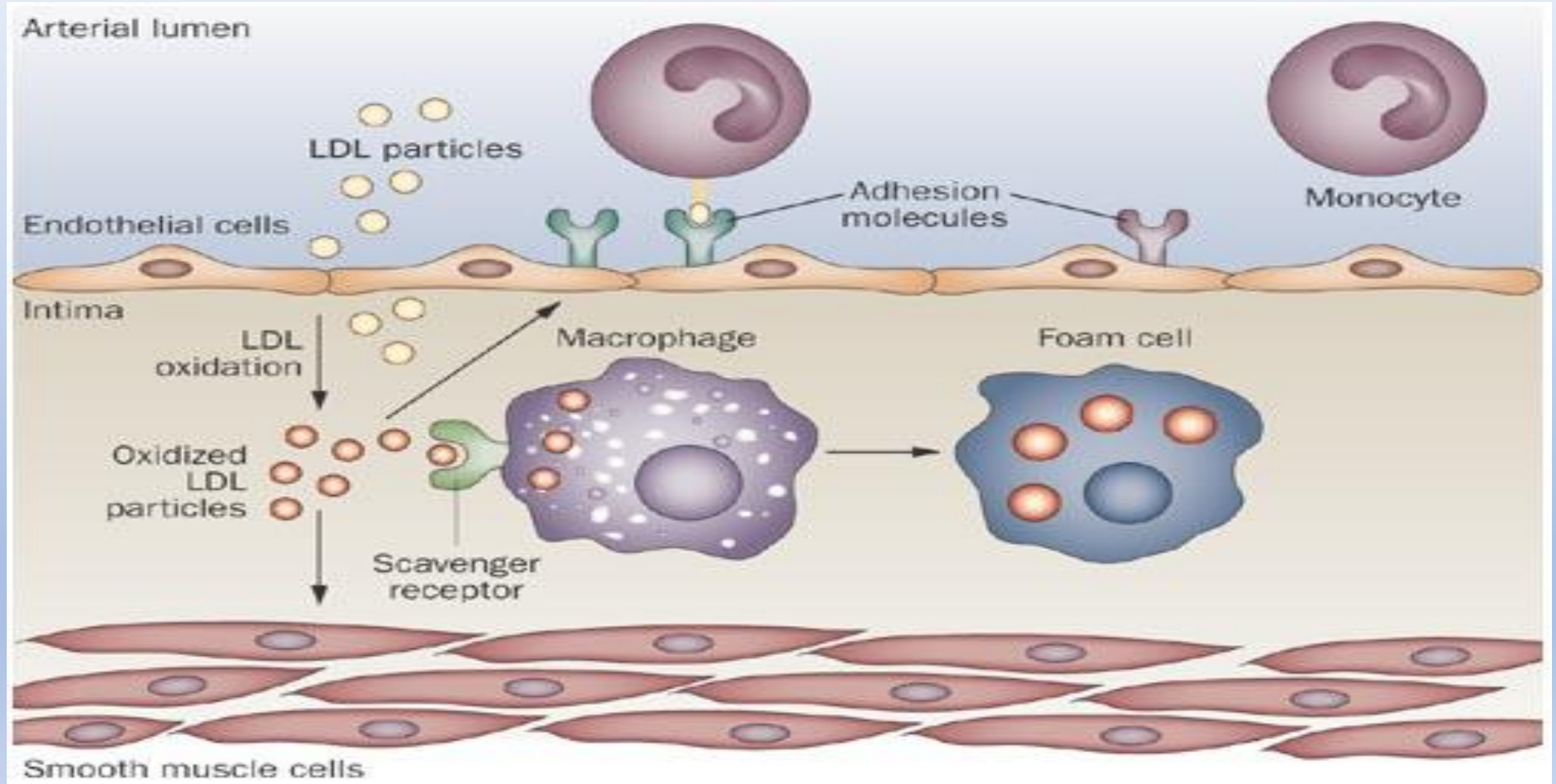
End-stage renal disease

Holzer M, et al. *J Am Soc Nephrol.* 2011;22(9):1631-1641.

THE LDL-C STORY…

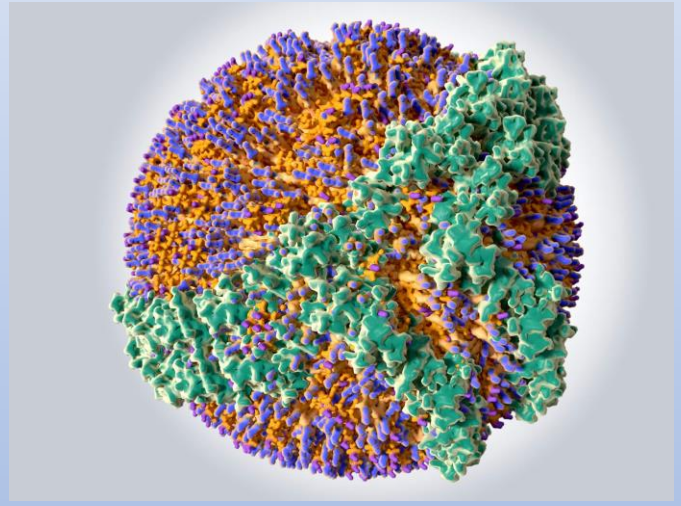
- The story we know the best……

THE LDL-C STORY….

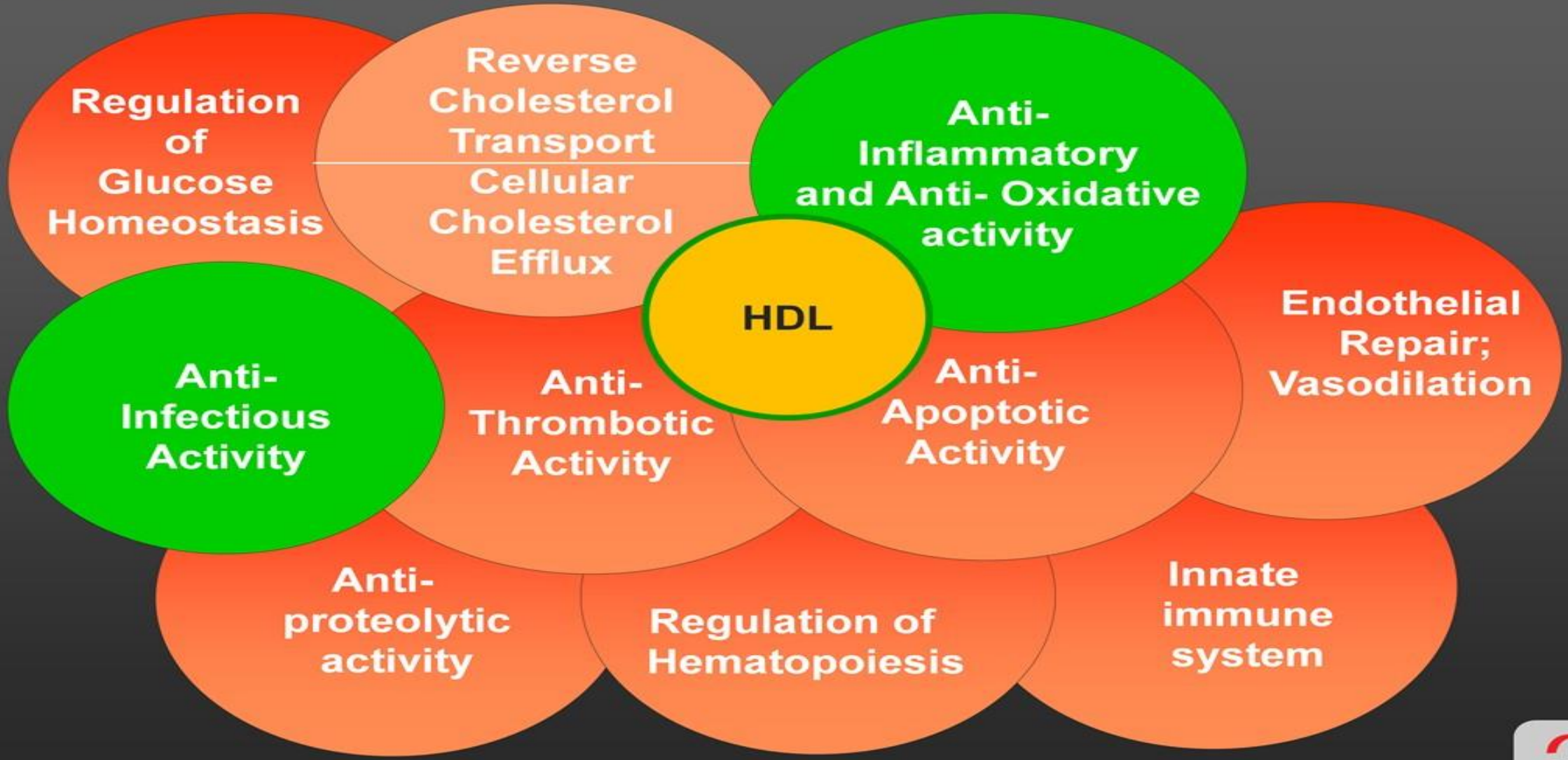


THE HDL STORY…

the story we know less !



Atheroprotective & Vasculoprotective Activities of HDL



Kontush A, Chapman MJ. *Pharmacol Rev.* 2006;58(3):342-374.

nla NATIONAL LIPID ASSOCIATION

THANK YOU FOR LISTENING!!