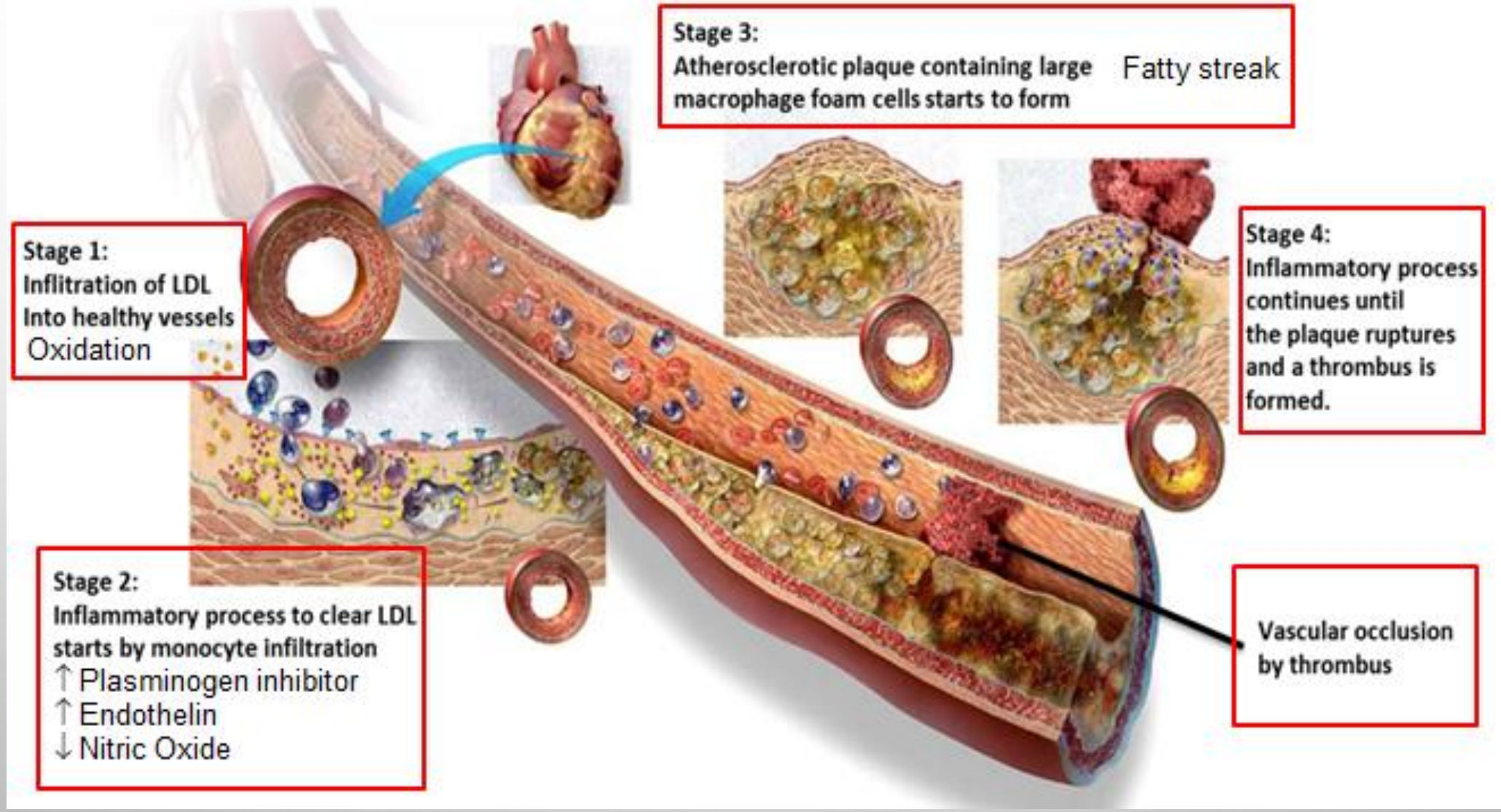
IL LABORATORIO

Elda Favari

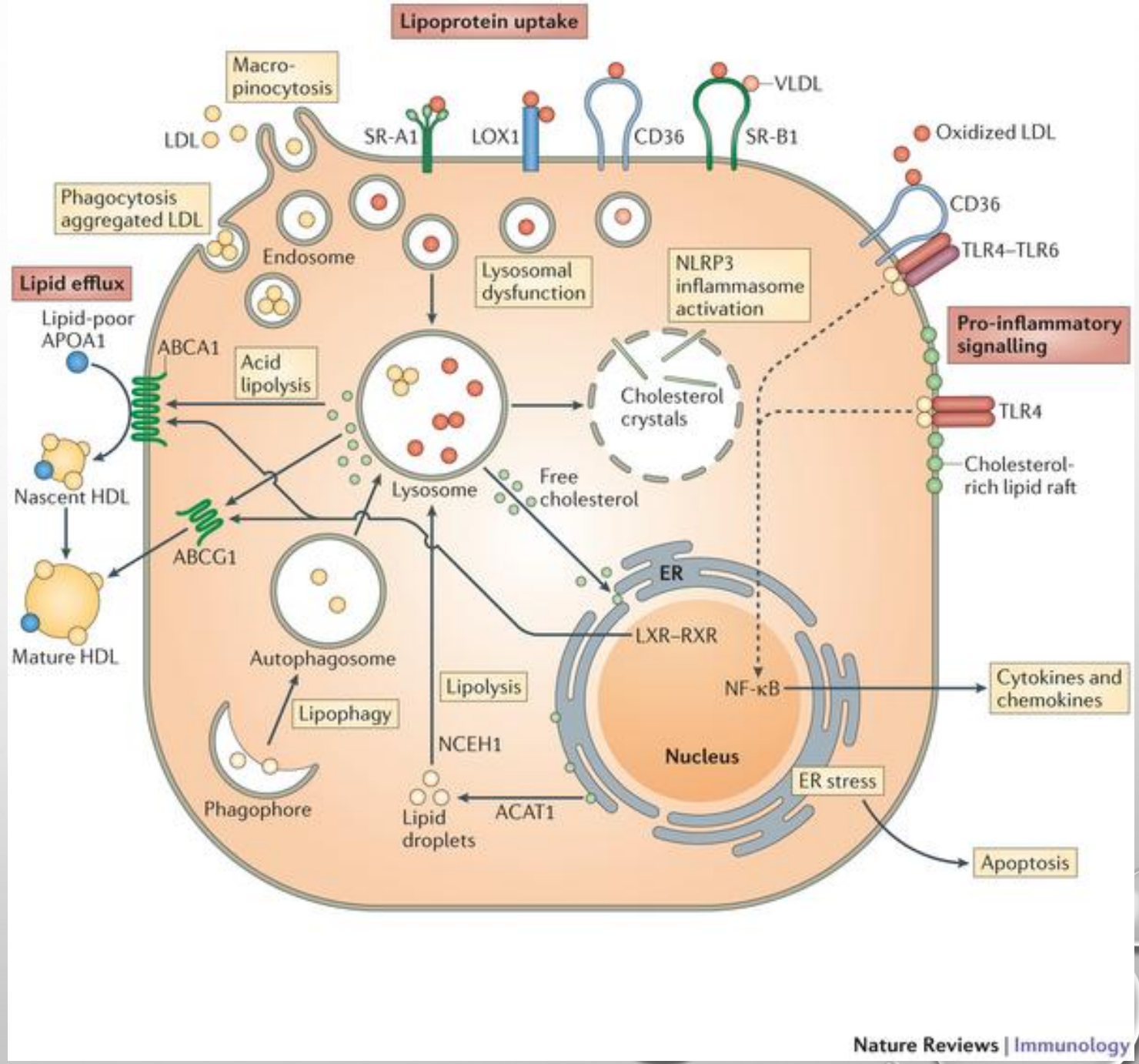
Department of Food and Drug

University of Parma, Italy

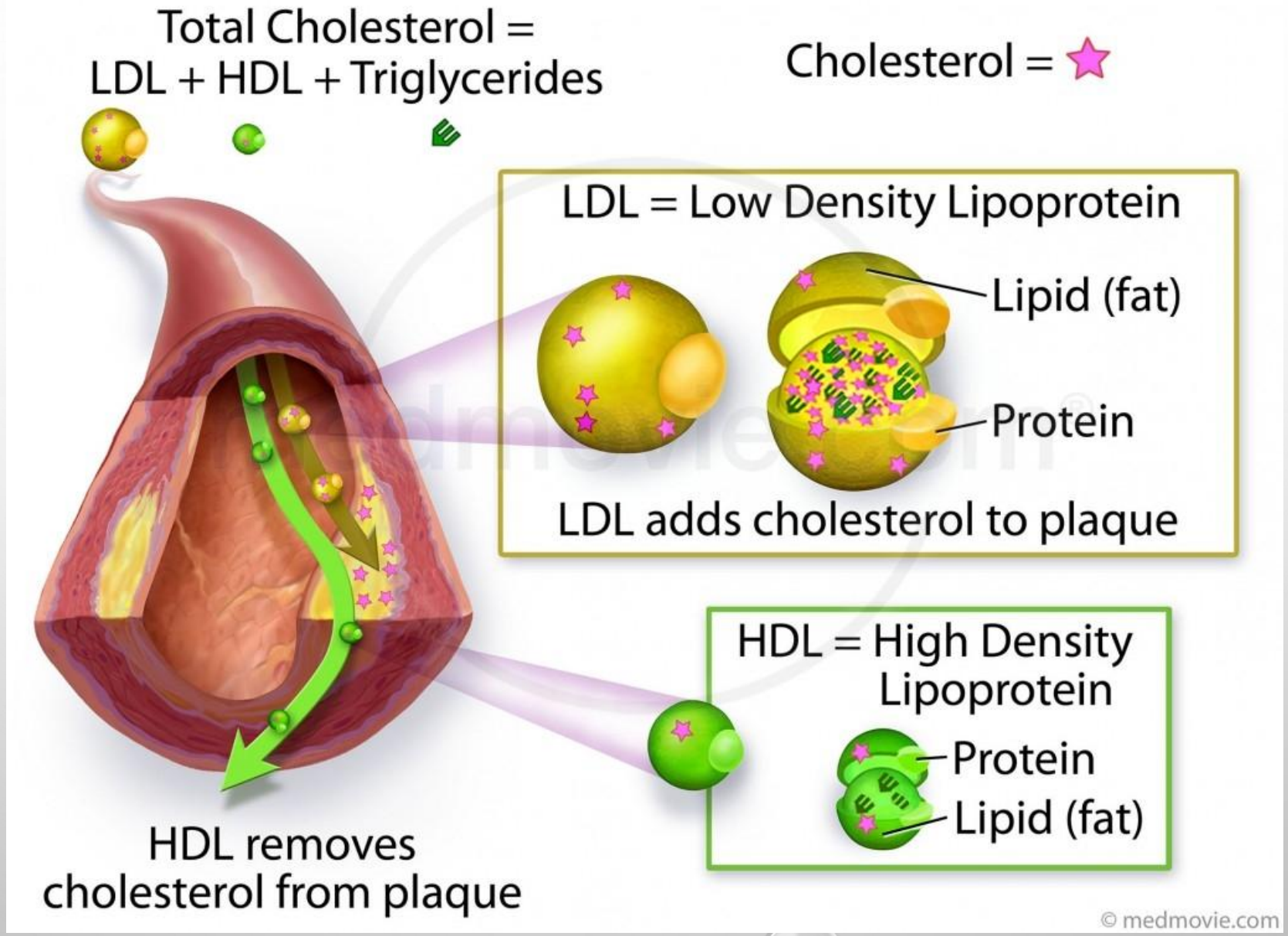
Roma, 4 maggio 2017


Stage 3:
Atherosclerotic plaque containing large macrophage foam cells starts to form
Fatty streak
Stage 1:
Inflitration of LDL
Into healthy vessels
Oxidation
Stage 4:
Inflammatory process continues until the plaque ruptures and a thrombus is formed.
Stage 2:
Inflammatory process to clear LDL starts by monocyte infiltration
↑ Plasminogen inhibitor
↑ Endothelin
↓ Nitric Oxide
Vascular occlusion by thrombus

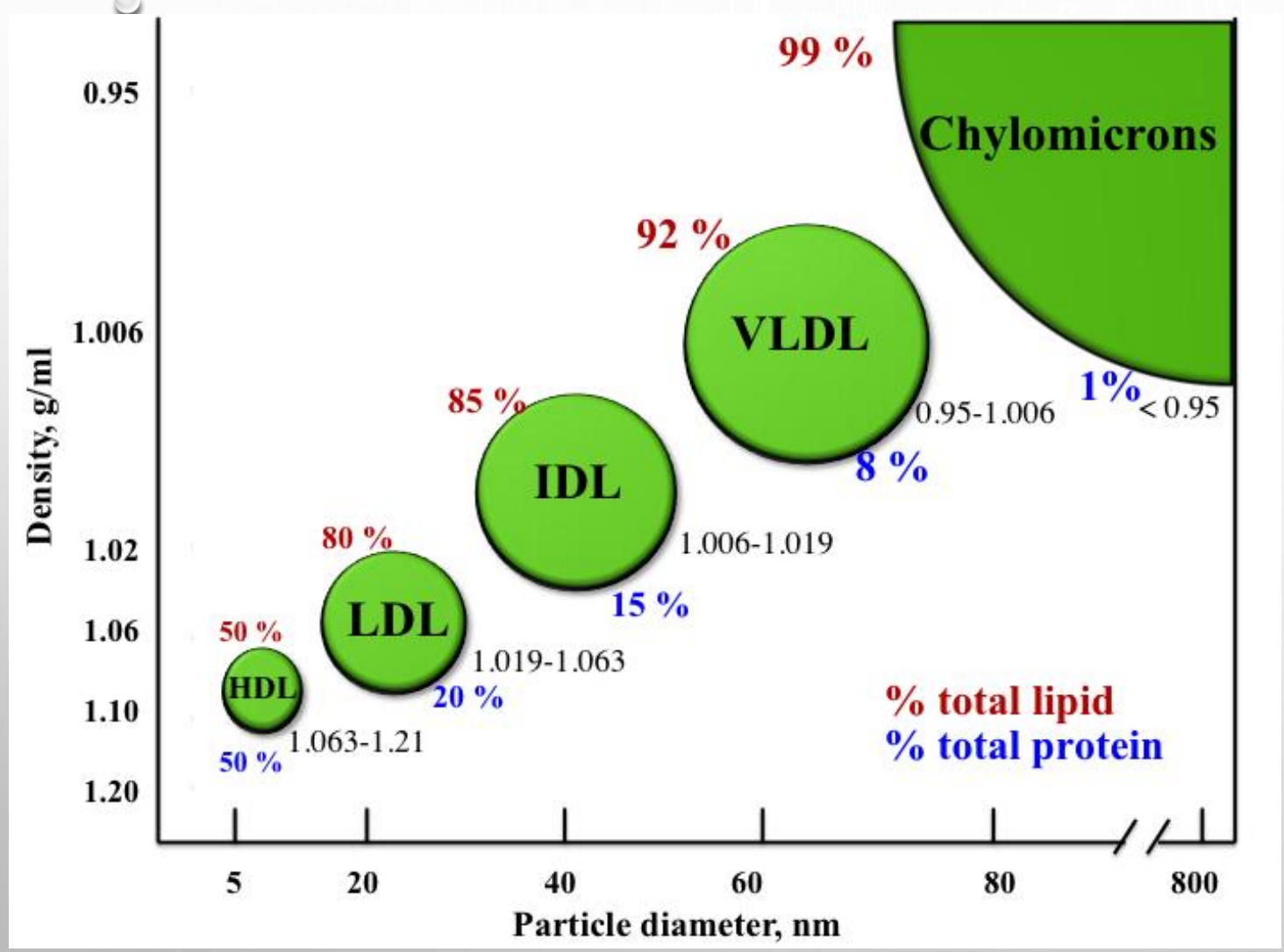
Cholesterol metabolism and "*foam cells*" formation

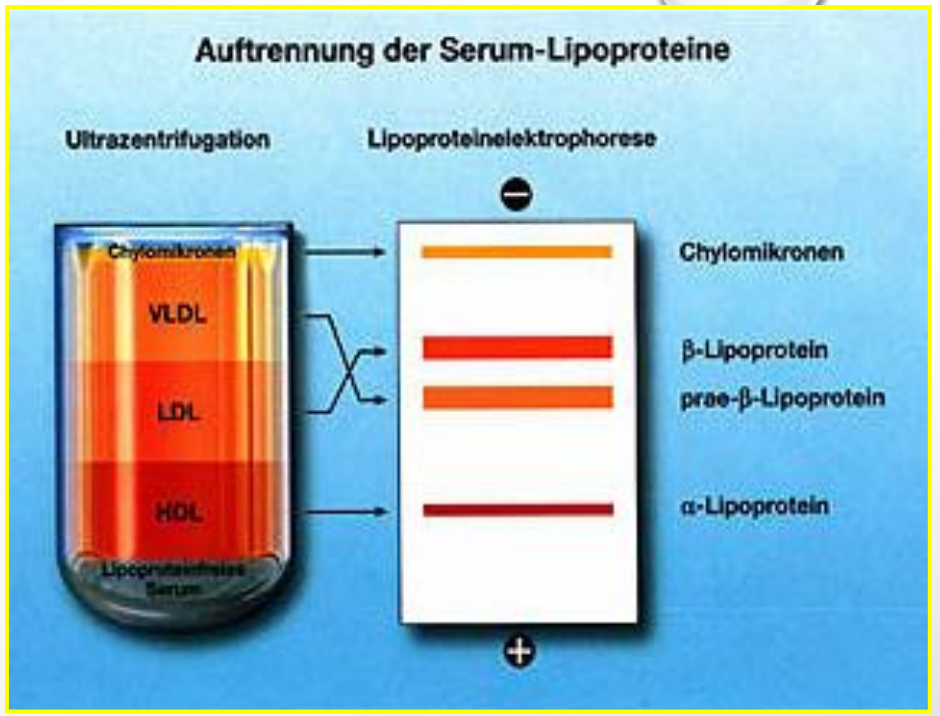


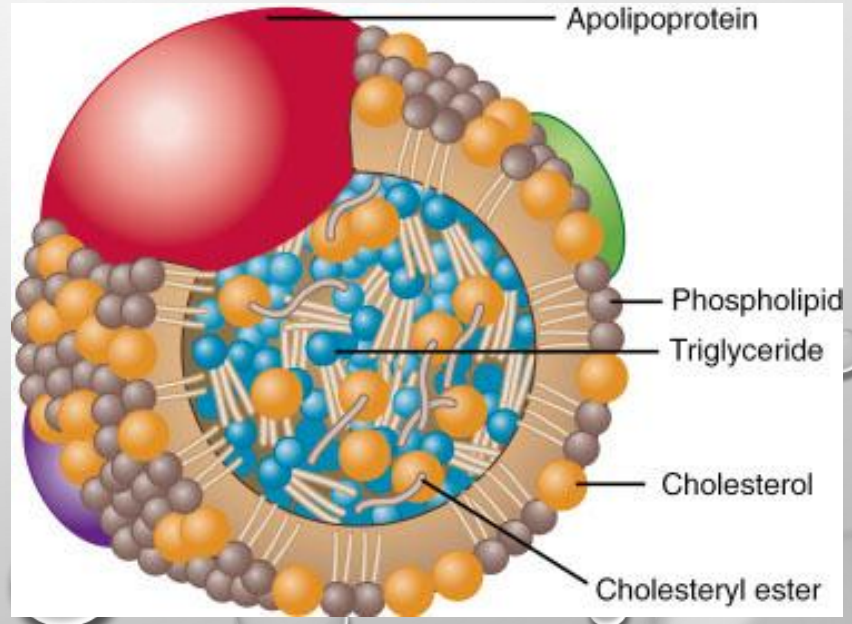
Roma, 4 maggio 2017



Roma, 4 maggio 2017







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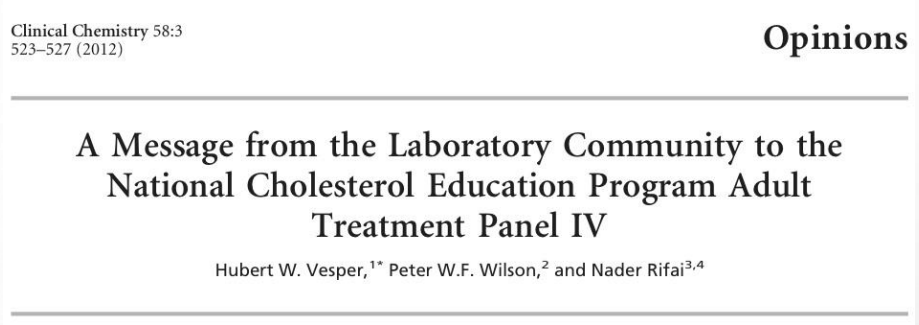
Serum lipoproteins are measured by enzymatic reactions

Presence of multiple biases



Clinical Chemistry 58:3
523–527 (2012)

Opinions

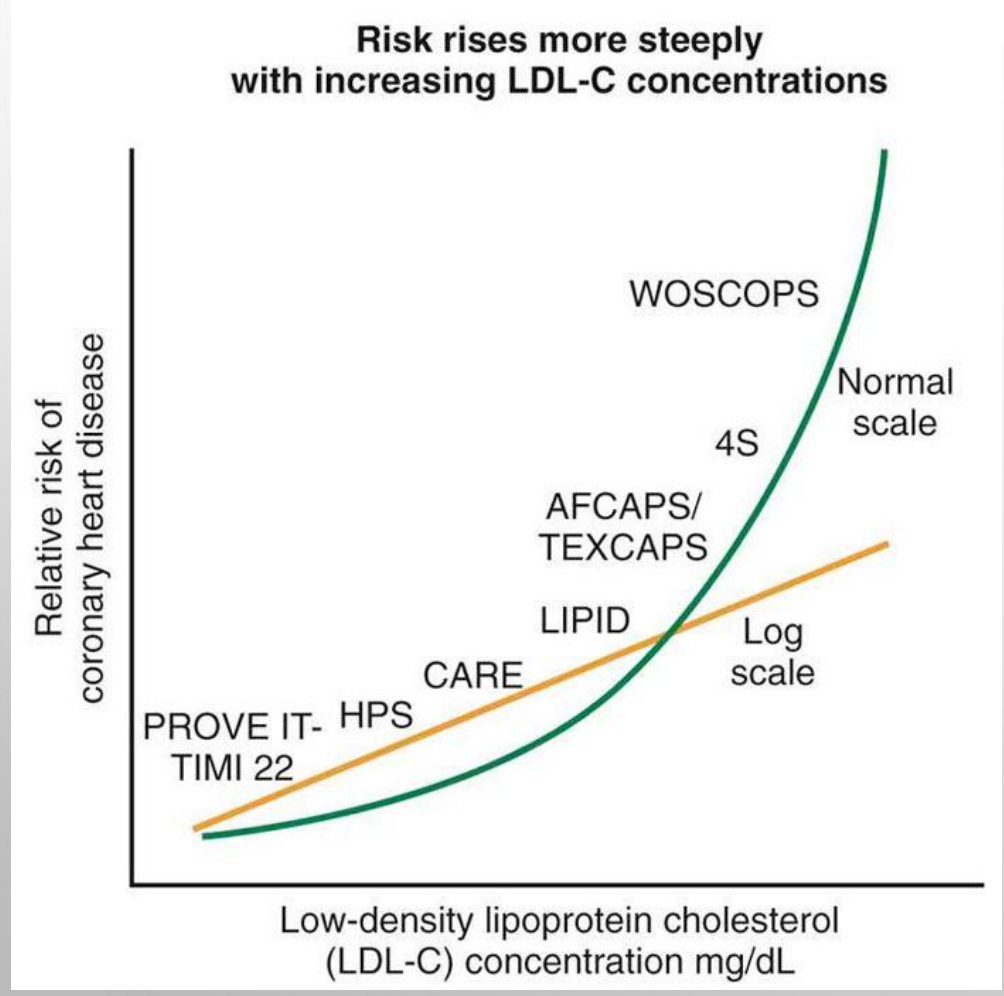
A Message from the Laboratory Community to the National Cholesterol Education Program Adult Treatment Panel IV

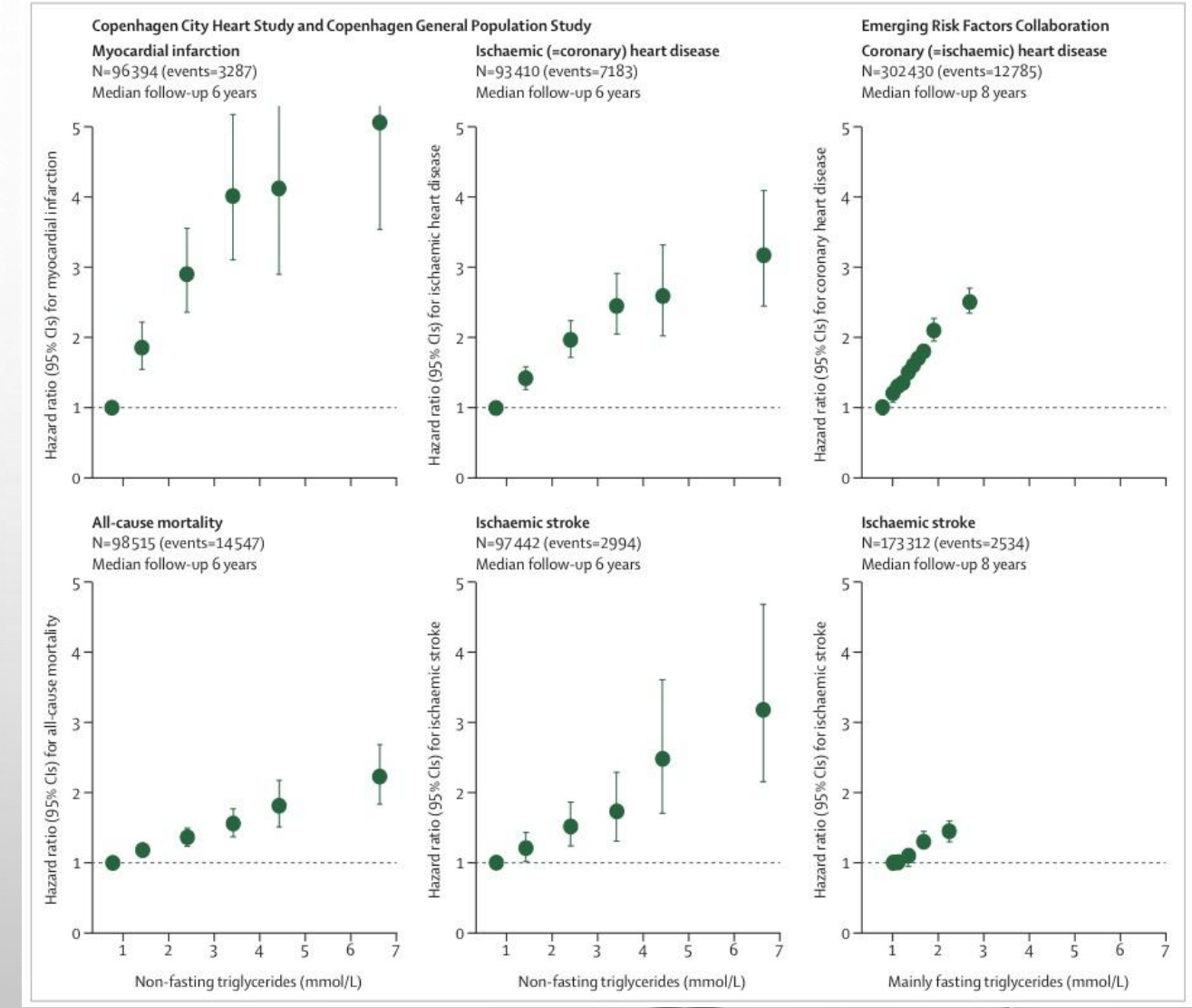
Hubert W. Vesper,[1*] Peter W.F. Wilson,[2] and Nader Rifai[3,4]

Valori lipidici	Basso (mg/dl)	Borderline Basso (mg/dl)	Accetabile (mg/dl)	Borderline Alto (mg/dl)	Alto (mg/dl)
Colesterolo Totale	-	-	<200	200-239	**>240**
LDL	-	-	<130	130-159	**>160**
Non-HDL	-	-	<150	150-189	**>190**
HDL	**<40**	40-44	>45	-	-
Trigliceridi	-	-	<150	150-199	**>200**

Roma, 4 maggio 2017

LDL and TG vs. Cardiovascular Risk





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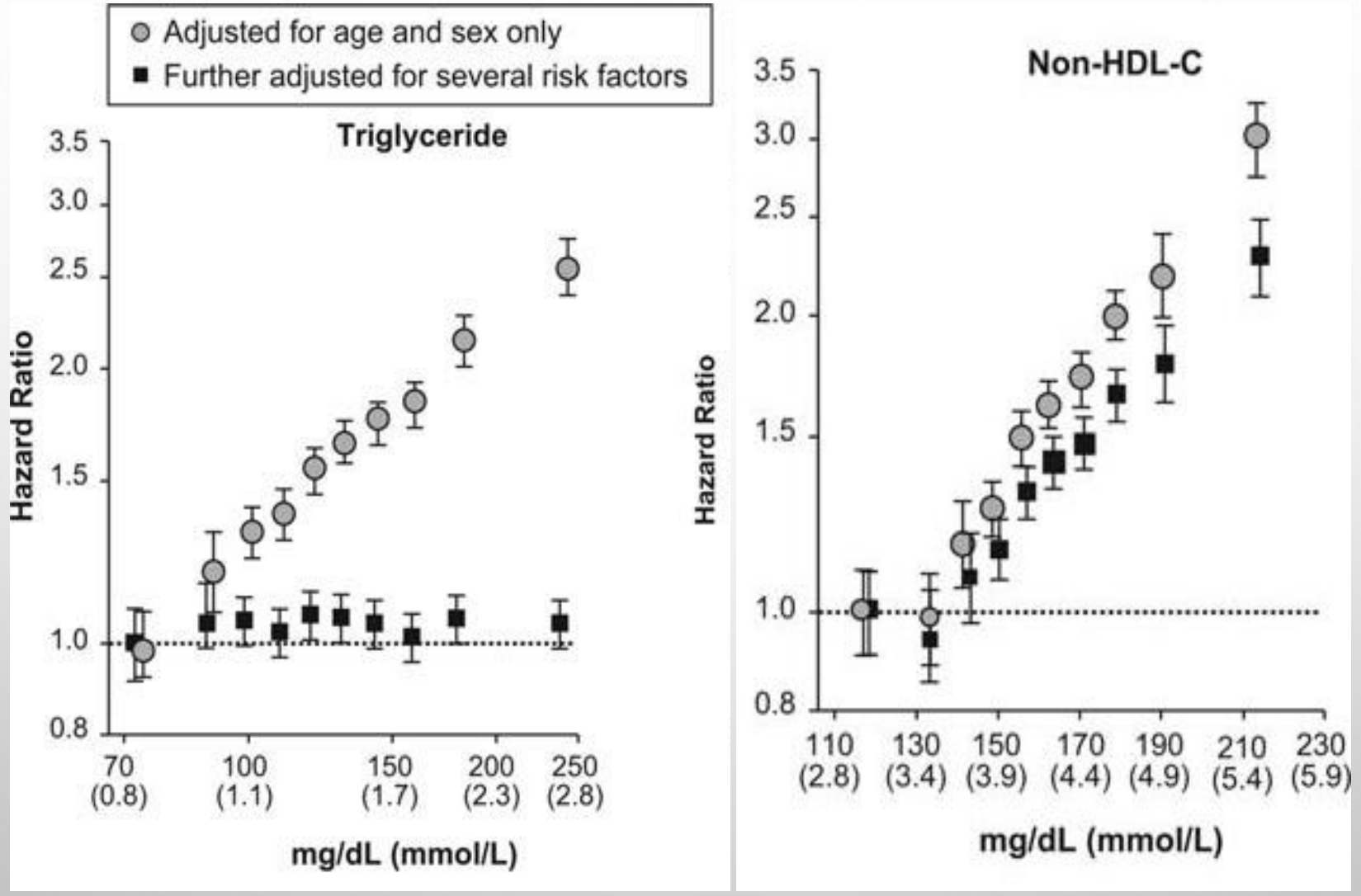


Roma, 4 maggio 2017

Lipid Metabolism and cardiovascular disease

Serum cholesterol efflux capacity (CEC)

Serum cholesterol loading capacity (CLC)

Roma, 4 maggio 2017

Atherosclerosis 251 (2016) 15–18

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lomitapide affects HDL composition and function

R. Yahya [a, 1], E. Favari [b, 1], L. Calabresi [c], A.J.M. Verhoeven [a], F. Zimetti [b], M.P. Adorni [b], M. Gomaraschi [c], M. Averna [d], A.B. Cefalù [d], F. Bernini [b], E.J.G. Sijbrands [a], M.T. Mulder [a], J.E. Roeters van Lennep [a, *]

[a] Department of Internal Medicine, Division Pharmacology, Vascular and Metabolic Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands
[b] Department of Pharmacy, University of Parma, Parma, Italy
[c] Centro Grosi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy
[d] Department of Internal Medicine and Medical Specialties – DIBIMIS, School of Medicine, University of Palermo, Palermo, Italy

The CLC of sera of the patients decreased by an average of 20% at maximum lomitapide dose in comparison to baseline (from 53.6 ± 18.0 to 42.8 ± 12.3 µg cholesterol/mg cell protein).

Atherosclerosis 242 (2015) 443–449

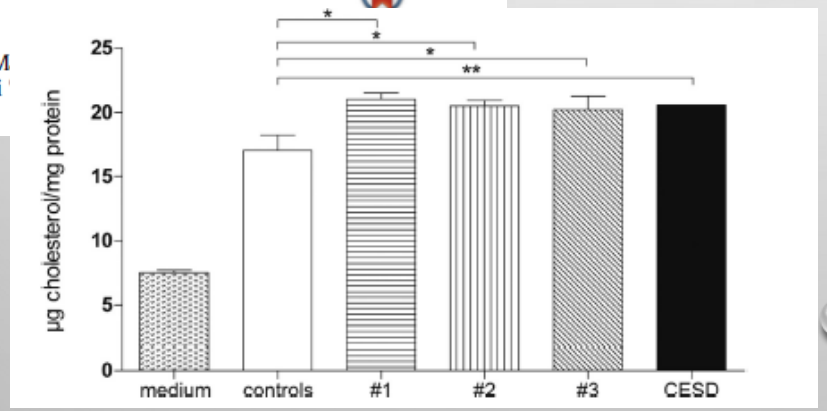
Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Cholesterol trafficking-related serum lipoprotein functions in children with cholesteryl ester storage disease

Francesca Zimetti [a, 1], Elda Favari [a, *, 1], Paola Cagliero [b], M
Nicoletta Ronda [a], Renato Bonardi [c], Monica Gomaraschi
Franco Bernini [a], Ornella Guardamagna [b]



Serum cholesterol loading capacity (CLC)

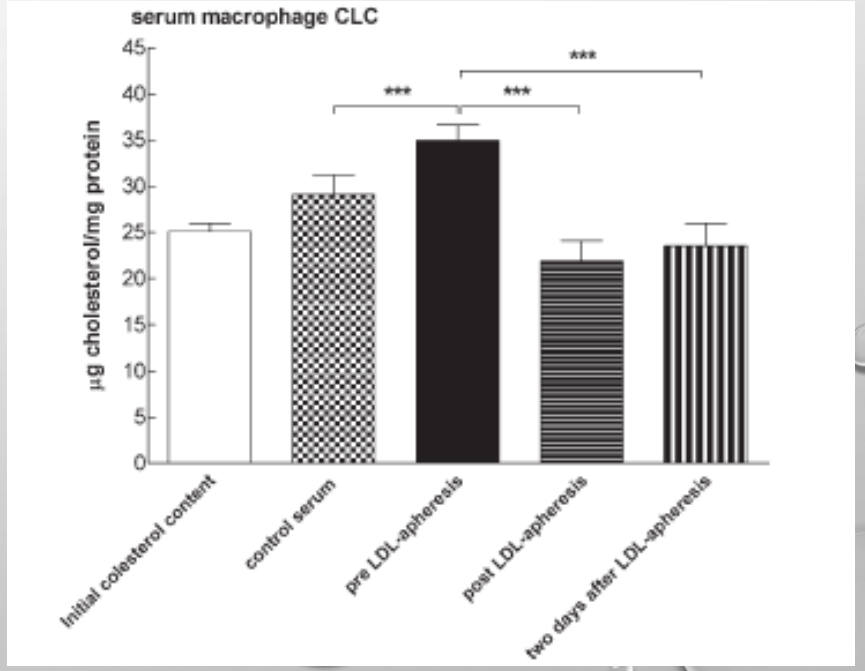
Supplemental Material can be found at: http://www.jlr.org/content/suppl/2012/03/12/jlr.P024810.DC1.html

patient-oriented and epidemiological research

Cellular cholesterol efflux and cholesterol loading capacity of serum: effects of LDL-apheresis§

M. P. Adorni,[1,*] F. Zimetti,[1,*] M. Puntoni,[†] F. Bigazzi,[§] F. Sbrana,[§] F. Minichilli,[†] F. Bernini,[2,*] N. Ronda,[*] E. Favari,[*] and T. Sampietro[†,§]

Department of Pharmacological and Biological Sciences and Applied Chemistries,* University of Parma, Parma, Italy; CNR Institute of Clinical Physiology,† Pisa, Italy; and Dyslipidemias and Atherosclerosis Laboratory,§ Fondazione Toscana Gabriele Monasterio, Pisa, Italy



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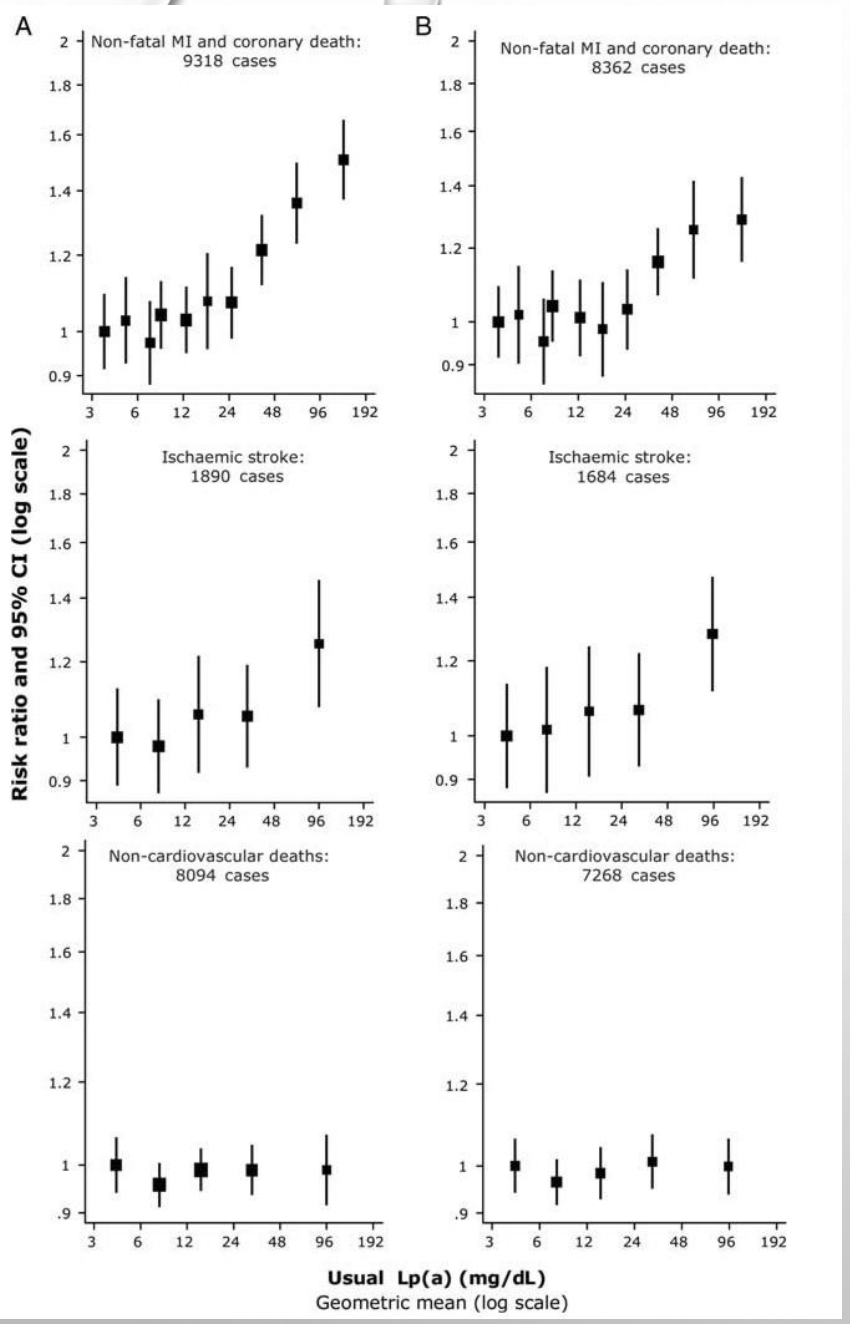
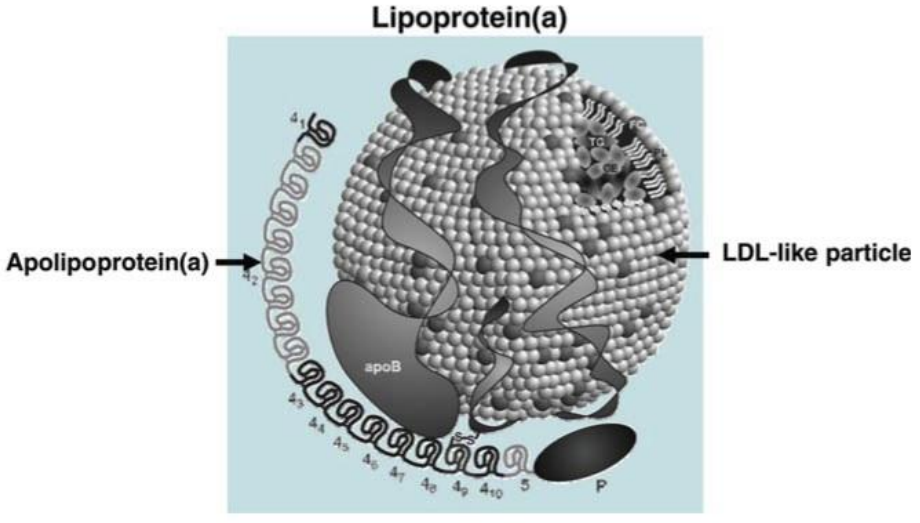


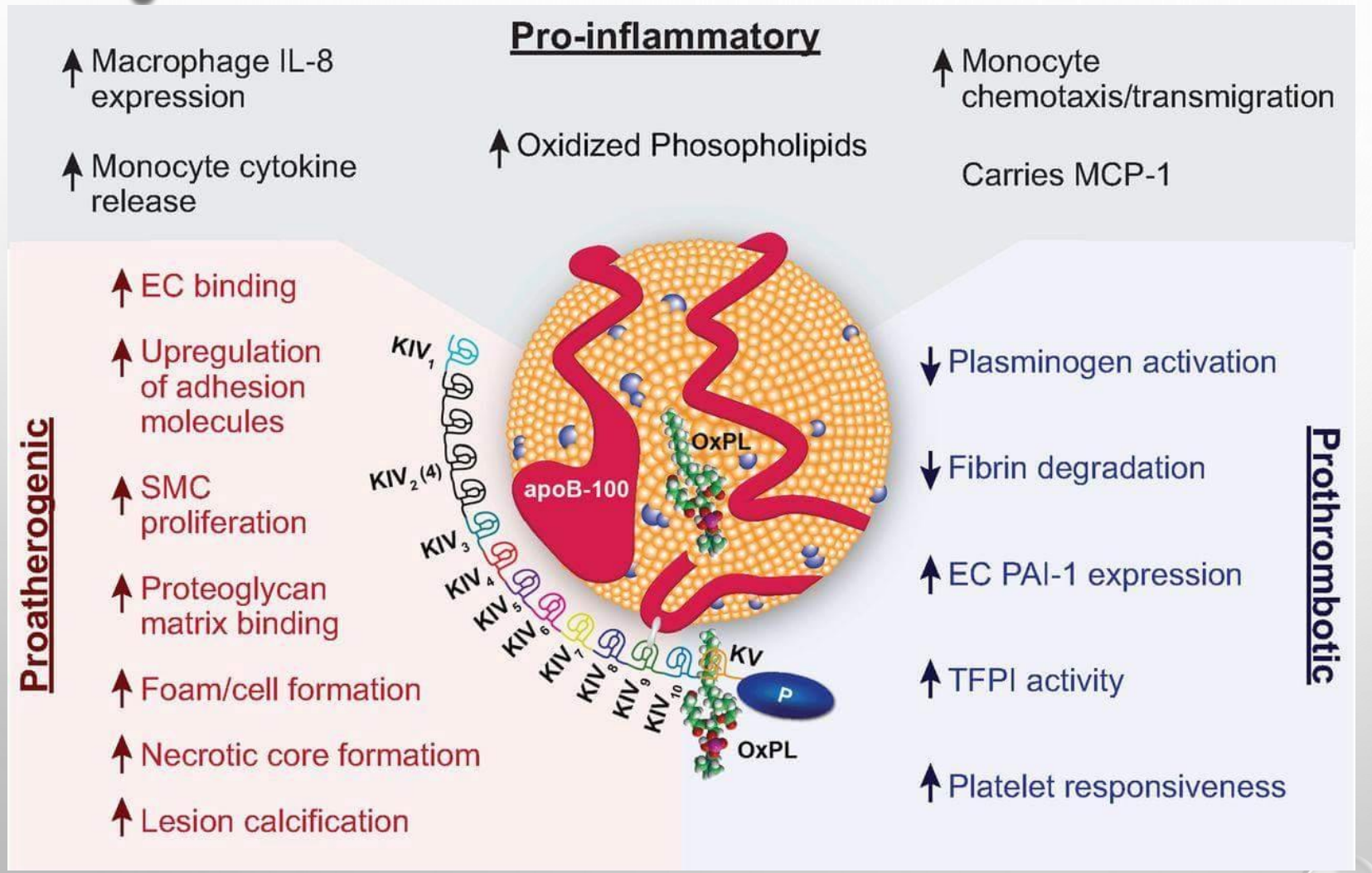


Whom to screen

We suggest that Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) ≥3% 10-year risk of fatal CVD according to the European guidelines,[35] and
(vi) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[36]

Repeat measurement is only necessary if treatment for high Lp(a) levels is initiated in order to evaluate therapeutic response.

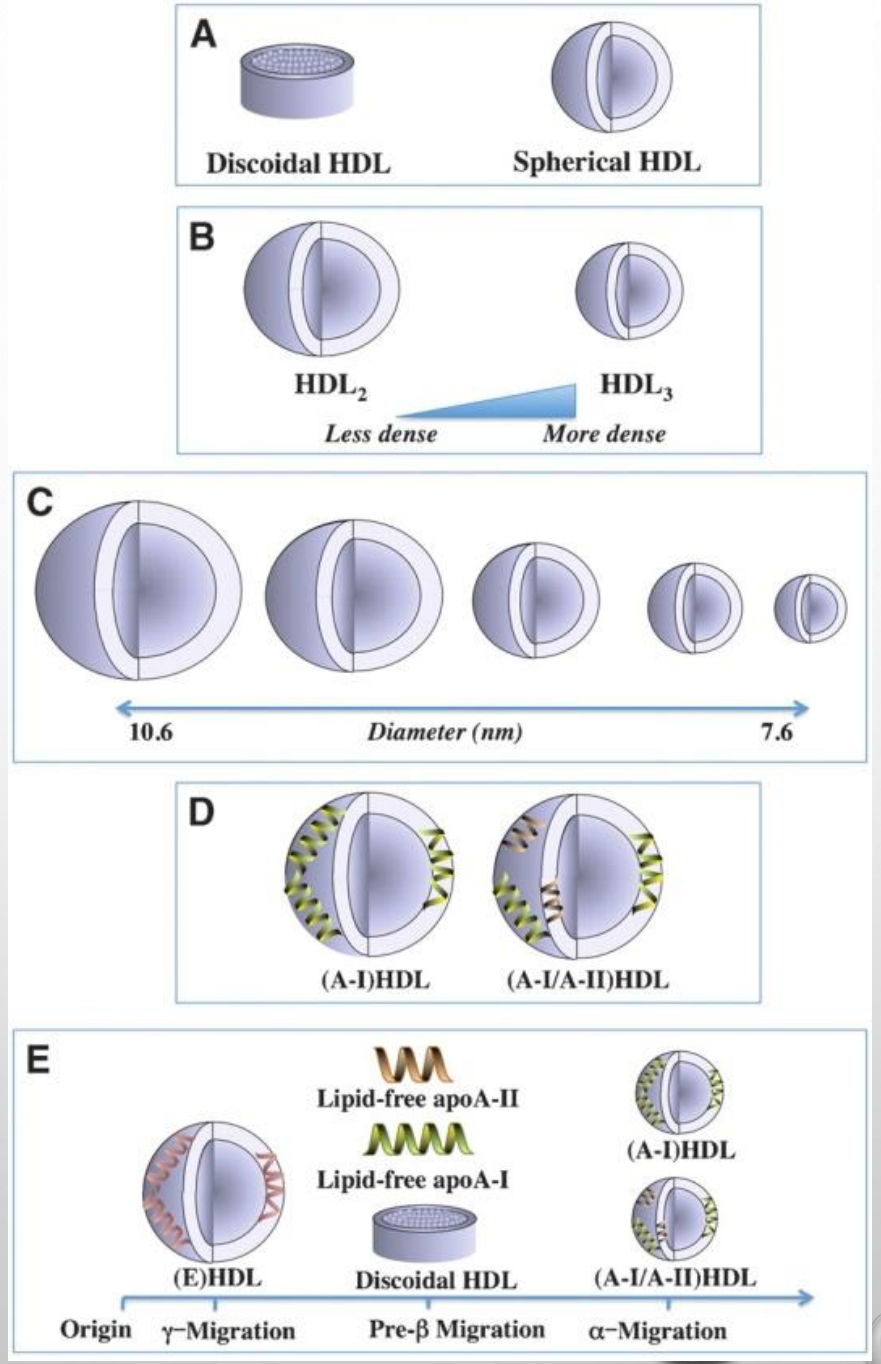


Serum cholesterol loading capacity (CLC)

- Is there a relationship between Lp(a) and CLC?
- If so, to wich isoforms of Lp(a)?

MM project, University of Parma
KANEKA

Roma, 4 maggio 2017



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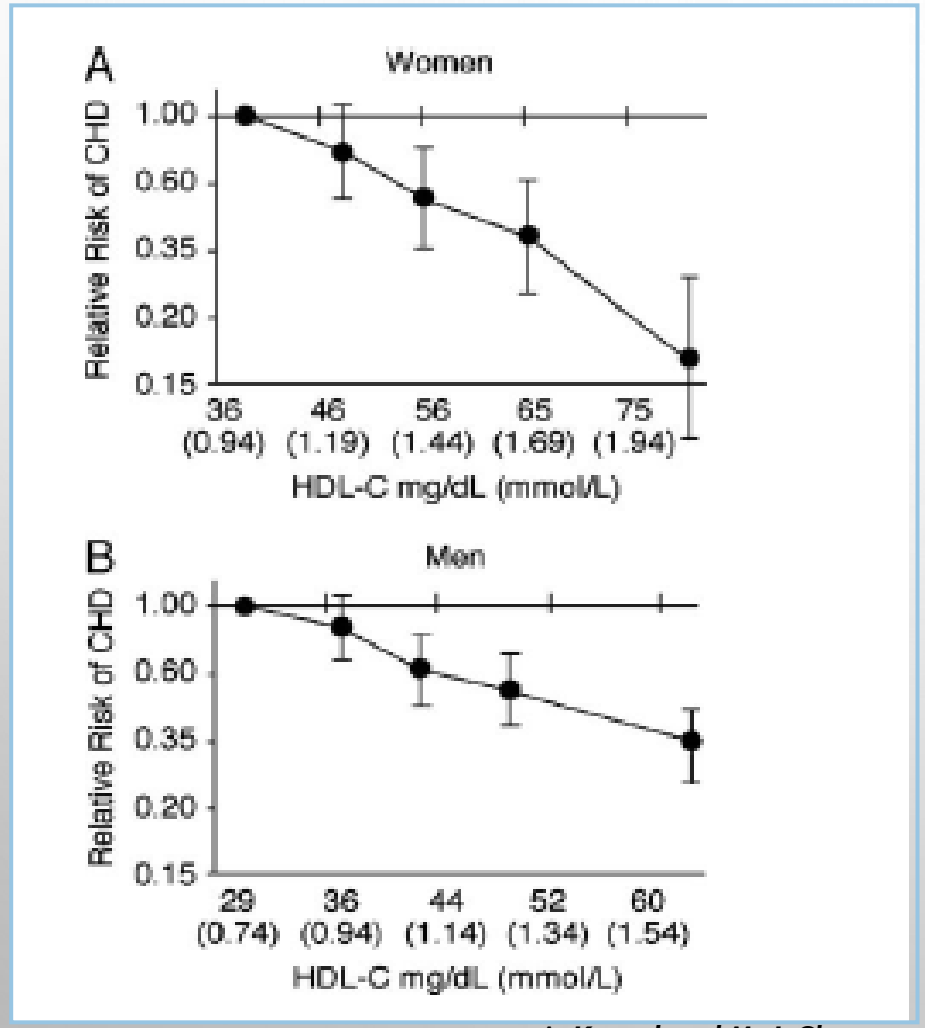
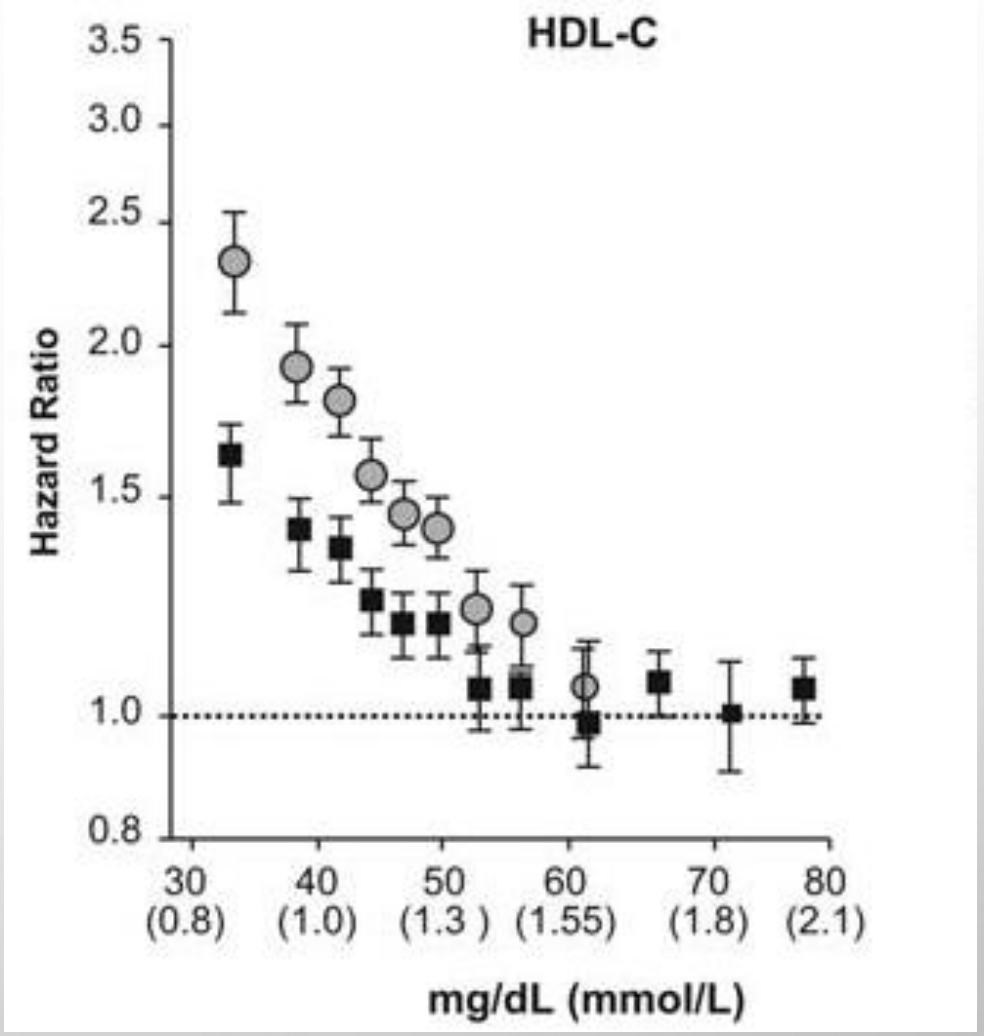
OBSERVATIONAL APPROACH





A. Kontush and M. J. Chapman
Pharmacol Rev. 2006

GENETIC APPROACH

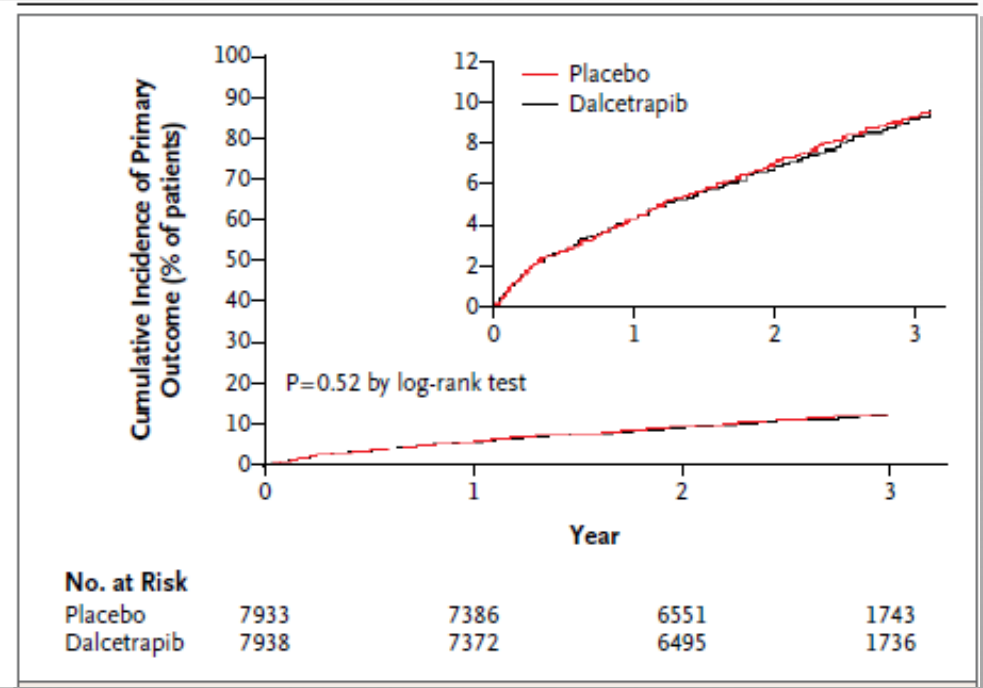
	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45–1·63)	2·13 (1·69–2·69), $p=2\times10^{-10}$
HDL cholesterol	0·62 (0·58–0·66)	0·93 (0·68–1·26), p=0·63

*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Benjamin F Voight et al, Lancet 2012

PHARMACOLOGICAL APPROACH

IN PATIENTS WHO HAD A RECENT ACUTE CORONARY SYNDROME, DALCETRAPIB INCREASED HDL CHOLESTEROL LEVELS (31-40%) BUT DID NOT REDUCE THE RISK OF RECURRENT CARDIOVASCULAR EVENTS (dal-OUTCOMES)



Schwartz GG et al, NEJM 2012

THERE WAS NO INCREMENTAL CLINICAL BENEFIT FROM THE ADDITION OF NIACIN TO STATIN THERAPY, DESPITE SIGNIFICANT IMPROVEMENTS IN HDL CHOLESTEROL (+25%) (AIM-HIGH STUDY)

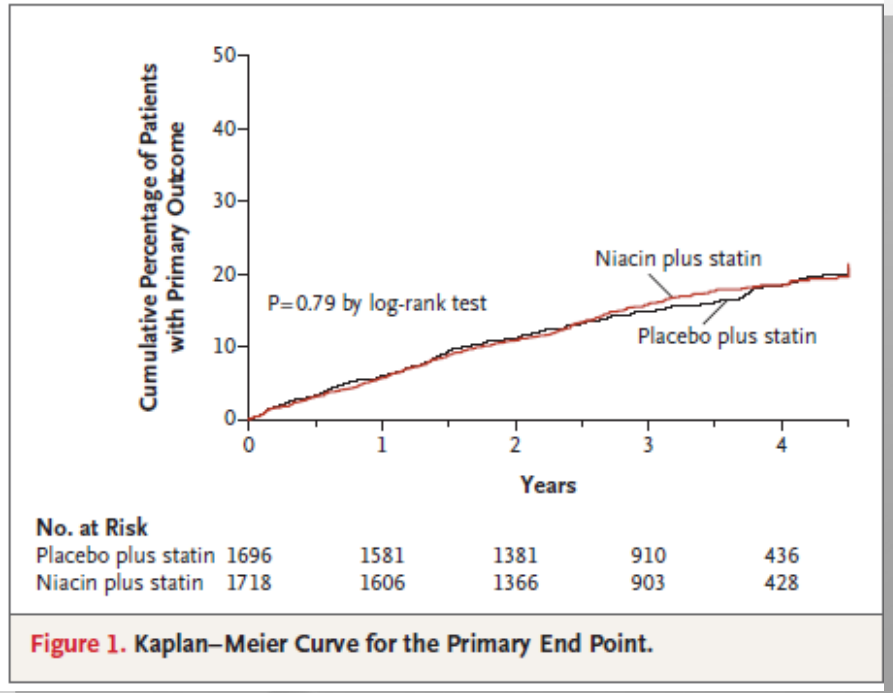


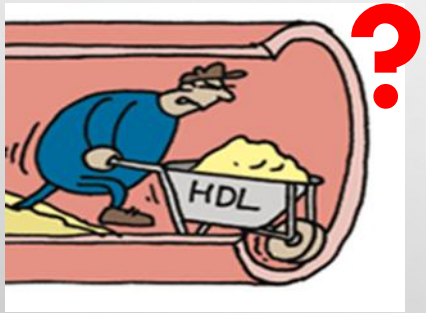
Figure 1. Kaplan–Meier Curve for the Primary End Point.

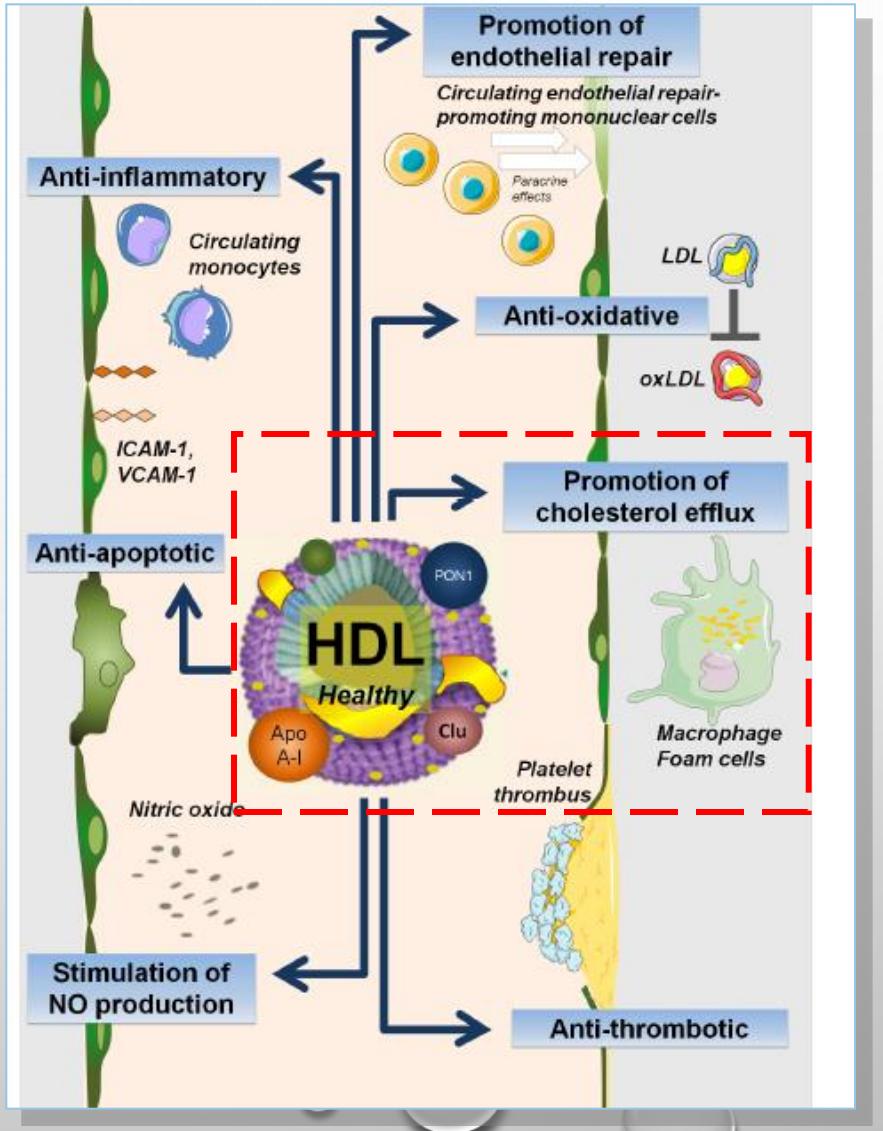
AIM-HIGH investigators N Engl J Med 2011

HDL FUNCTIONS

… HDL-C levels per se may not be the proper parameter to adequately assess the contribution of HDL to CVD risk.

Journal of Clinical Lipidology
2013 (7):484-525

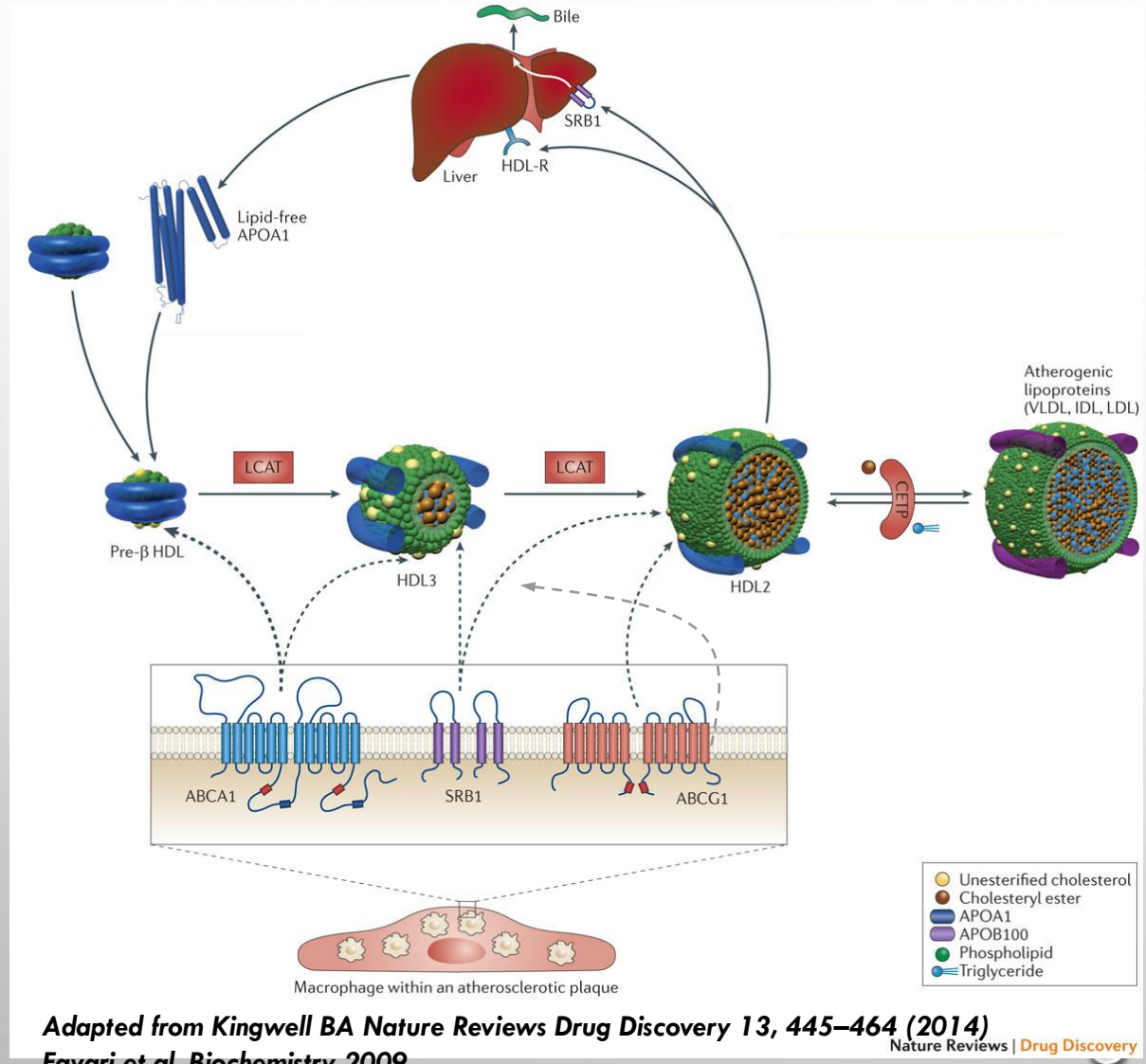




Riwanto, M. et al, JLR 2013

Roma, 4 maggio 2017

Cholesterol Efflux Capacity (CEC) and Reverse Cholesterol Transport (RCT)



Adapted from Kingwell BA Nature Reviews Drug Discovery 13, 445–464 (2014)
Favari et al. Biochemistry 2009

Serum
cholesterol efflux capacity
(CEC)

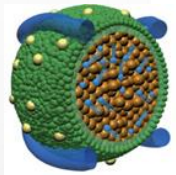
⇨HDL-CEC is a metric of HDL functionality in humans

⇨cell cholesterol efflux is the first limiting step of RCT

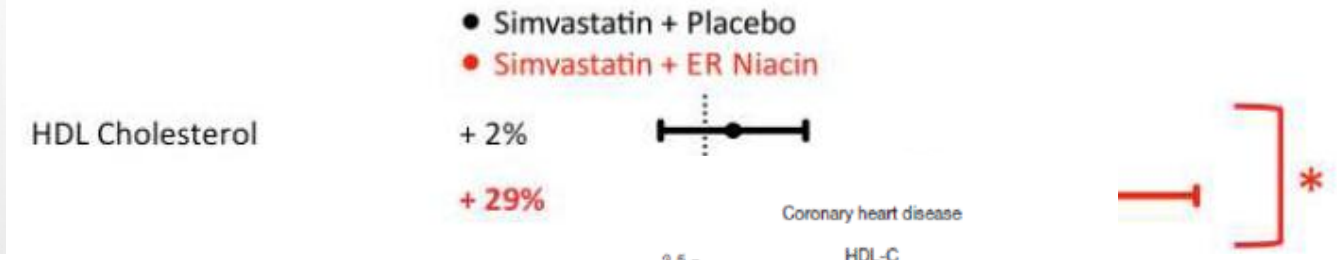
HDL functionality (CEC) determines the pharmacological effect

The Addition of Niacin to Statin Therapy Improves High-density Lipoprotein Cholesterol Levels but not Metrics of Functionality

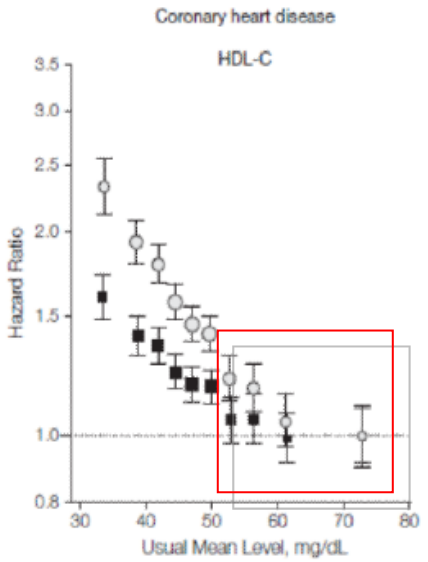
Amit V. Khera, MD, Parin J. Patel, MD, Muredach P. Reilly, MD, & Daniel J. Rader, MD



Serum cholesterol efflux capacity (CEC)

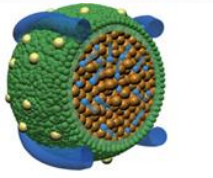


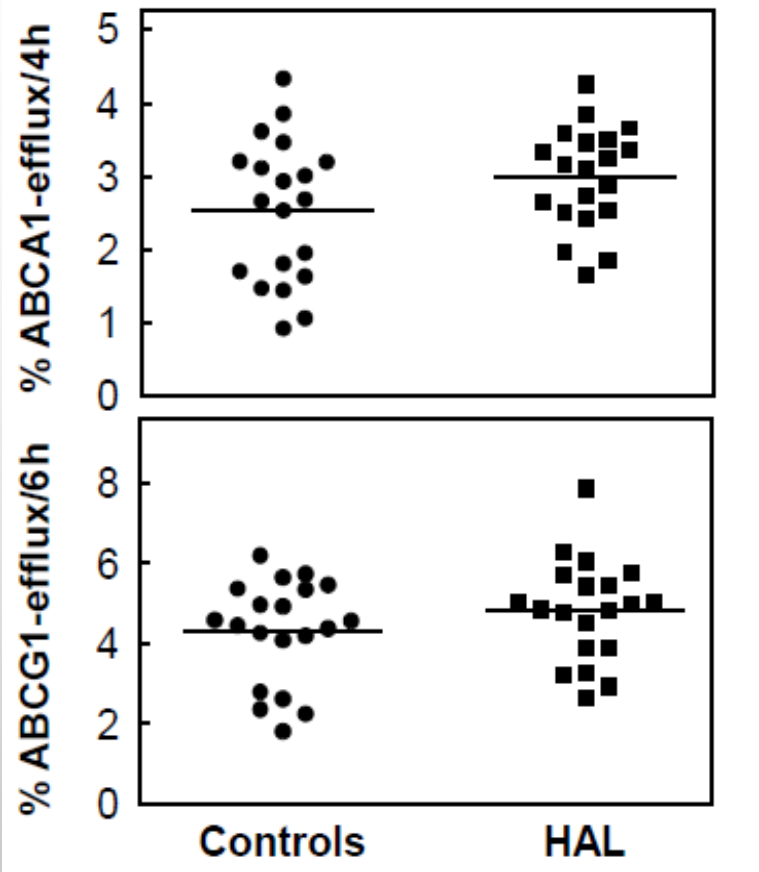
With a trial design where baseline HDL-cholesterol levels were 50 mg/dL, a 29% increase in HDL with niacin would increase levels to 65 mg/dL, but this is the flat part of the event curve

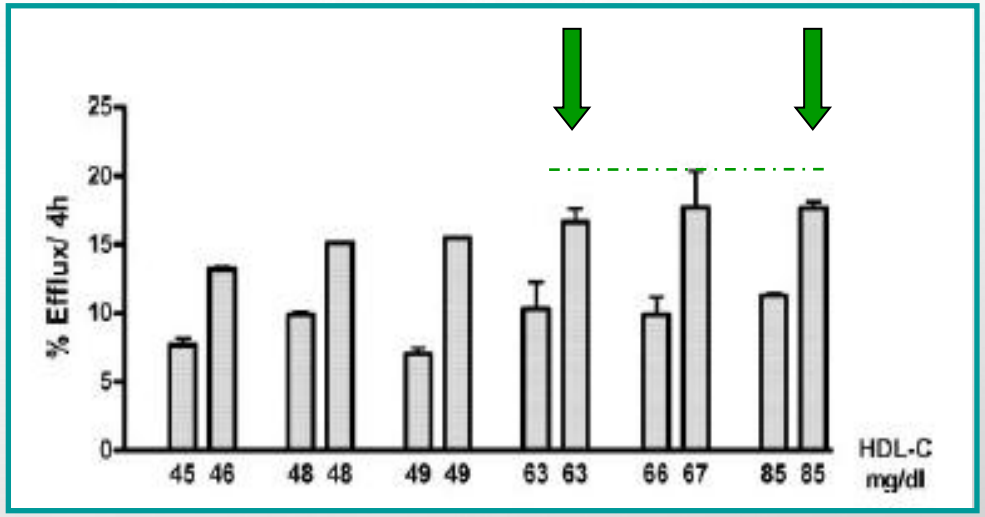


Journal of the American College of Cardiology (2013)

HDL functionality (CEC) overcomes the importance of HDL-C levels







Serum cholesterol efflux capacity (CEC)

G.B. Vigna et al. and E. Favari NMCD 2014

Roma, 4 maggio 2017

Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study

Danish Saleheen, Robert Scott, Sundas Javad, Wei Zhao, Amrith Rodrigues, Antonino Picataggi, Daniya Lukmanova, Megan L Mucksavage, Robert Luben, Jeffery Billheimer, John J P Kastelein, S Matthijs Boekholdt, Kay-Tee Khaw, Nick Wareham, Daniel J Rader

Summary

Background Although HDL cholesterol concentrations are strongly and inversely associated with risk of coronary heart disease, interventions that raise HDL cholesterol do not reduce risk of coronary heart disease. HDL cholesterol efflux capacity—a prototypical measure of HDL function—has been associated with coronary heart disease after adjusting for HDL cholesterol, but its effect on incident coronary heart disease risk is uncertain.

Lancet Diabetes Endocrinol 2015; 3: 507–13
Published Online May 27, 2015
http://dx.doi.org/10.1016/S2213-8587(15)00126-6

Interpretation HDL cholesterol efflux capacity might provide an alternative mechanism for therapeutic modulation of the HDL pathway beyond HDL cholesterol concentration to help reduce risk of coronary heart disease.

CURRENT OPINION

Modulating cholesterol efflux capacity to improve cardiovascular disease

Nicholas Brownell and Anand Rohatgi

Summary

The modification of cholesterol efflux capacity (CEC) by current medications and interventions has been investigated in both large randomized control trials and smaller observational cohorts. This review serves to compile the results of these studies and evaluate CEC modulation by commonly used medications. Altering CEC could be a novel therapeutic approach to improving cardiovascular risk profiles.

Serum cholesterol efflux capacity(CEC)

Roma, 4 maggio 2017

Take home messages

- ✓ **Not only QUANTITY but also QUALITY for serum LIPOPROTEINS**

⇩

- ✓ **LIPOPROTEIN QUALITY means FUNCTIONALITY**

⇩

- ✓ **CLC for atherogenic lipoproteins and CEC for anti-atherogenic lipoproteins is a metric of FUNCTIONALITY in humans**

Locandina Workshop Lipidology and Atherosclerosis.pptx