From human genetics to new therapeutics for dyslipidemia and cardiovascular disease

Mendelian Randomization Meeting
Bristol, UK
June, 2015

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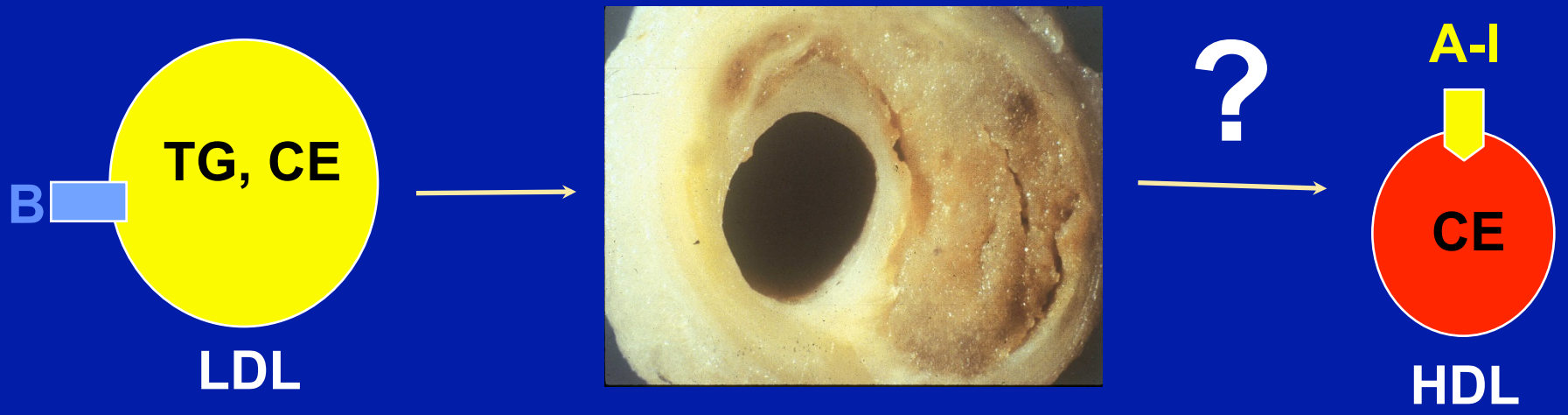
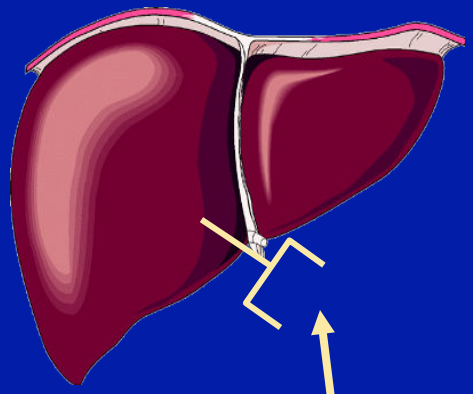
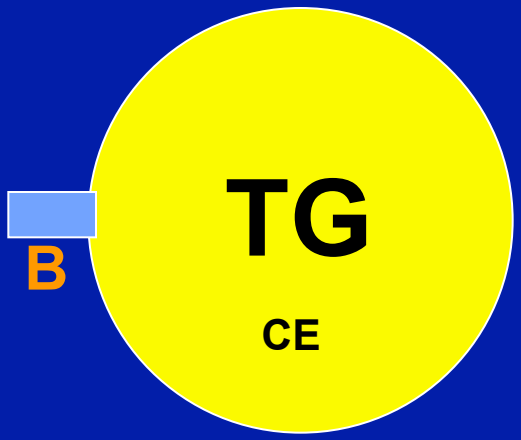
Lipoproteins and CAD

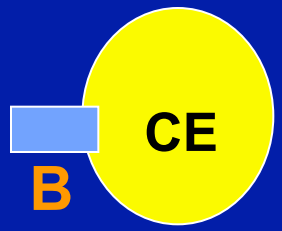


ApoC-III inhibits lipoprotein lipase

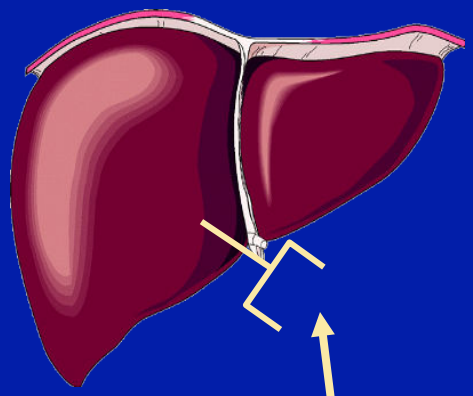


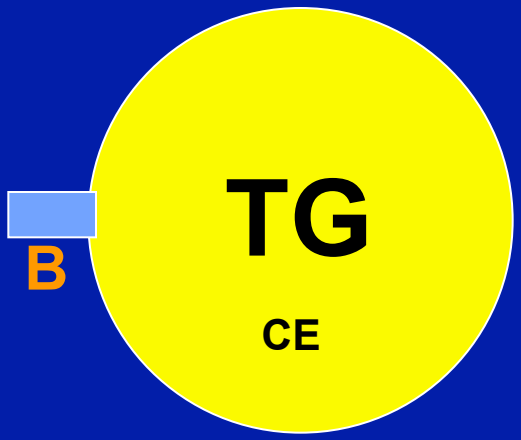


LPL ⊣ apoC-III



ApoC-III as a novel therapeutic target

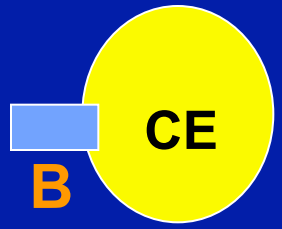




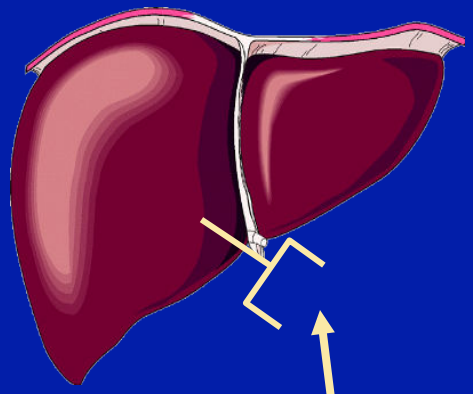
LPL

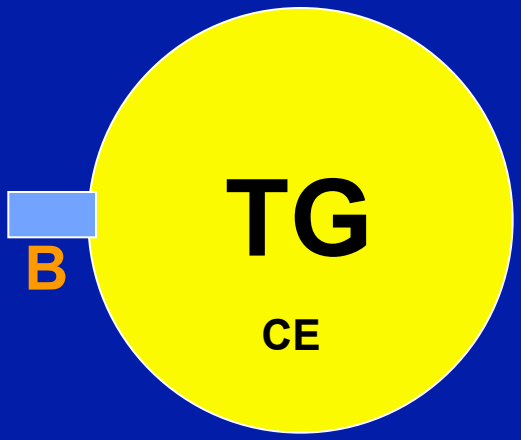
apoC-III

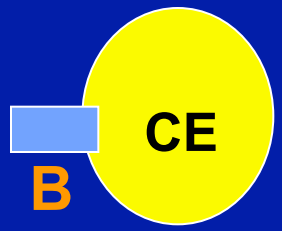
Inhibitor



Lipoprotein lipase is a nodal pathway for new therapeutic development







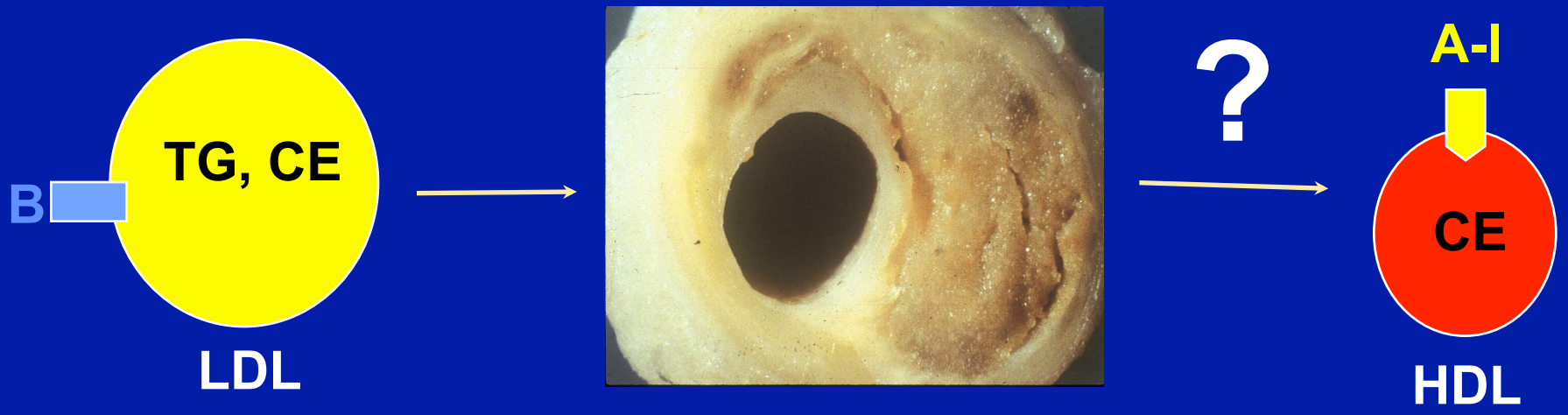
LPL

apoC-III
ANGPTL4
ANGPTL3

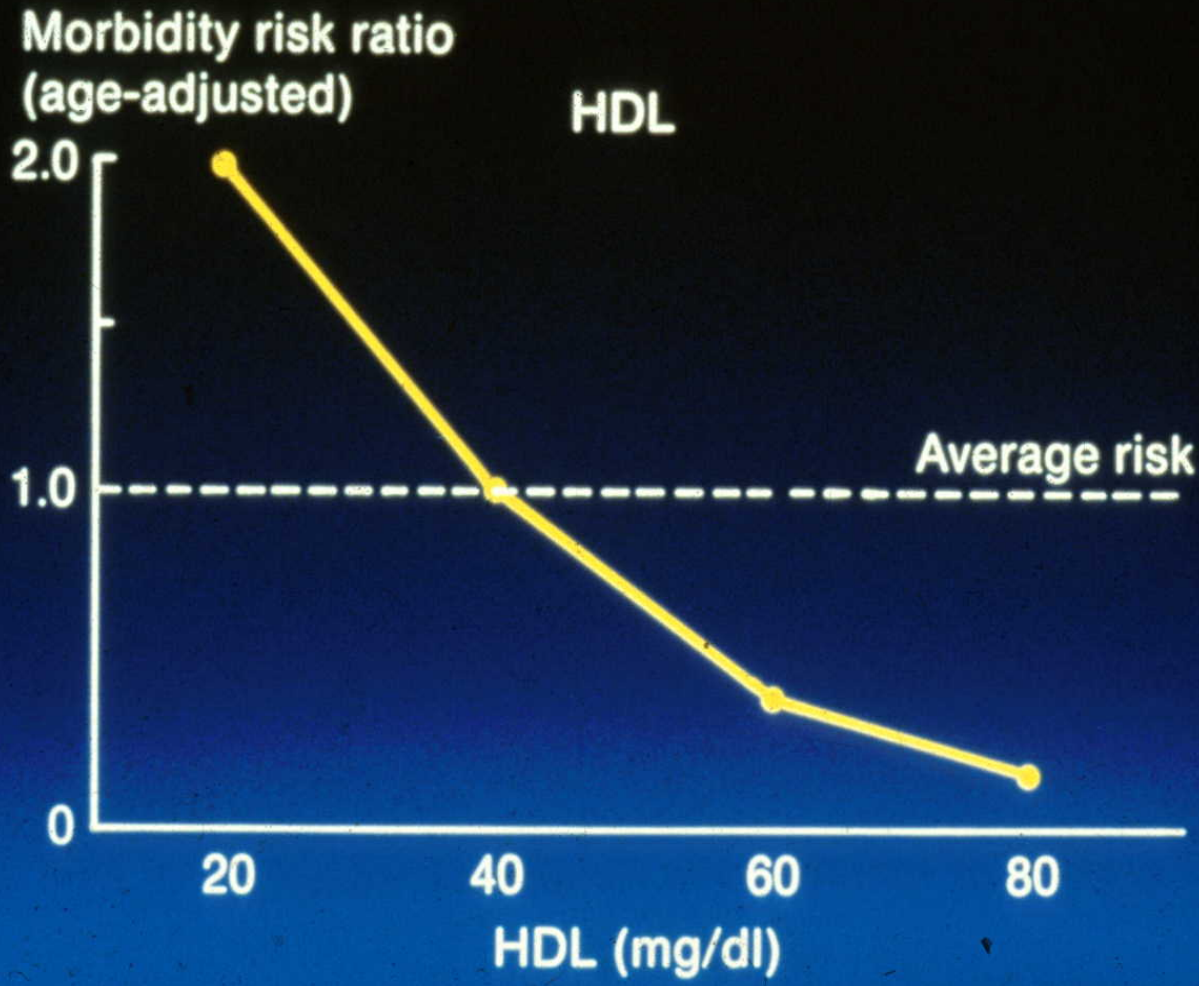
ANGPTL8

apoA-V

Lipoproteins and Atherosclerosis



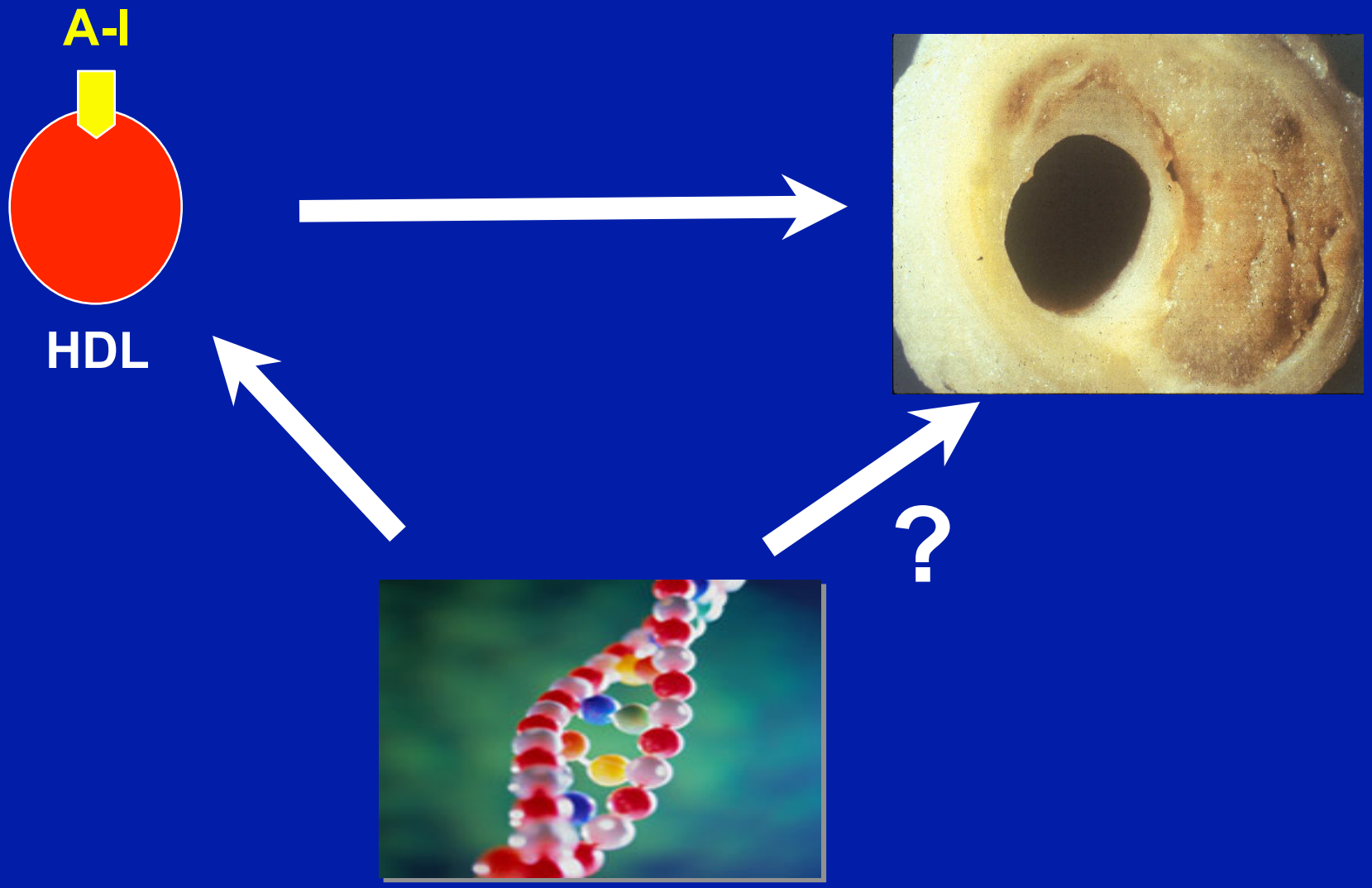
HDL-CHOLESTEROL AND CHD RISK (Men in Framingham, MA)



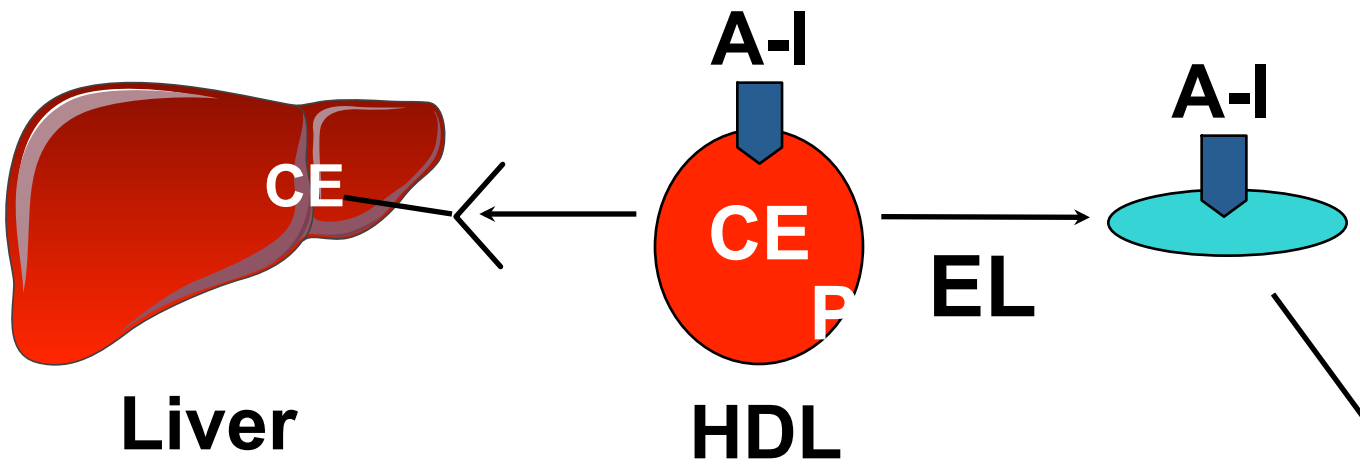
The HDL-C hypothesis

Raising plasma HDL-C levels will reduce CV events.

Is HDL-C causally associated with CAD?



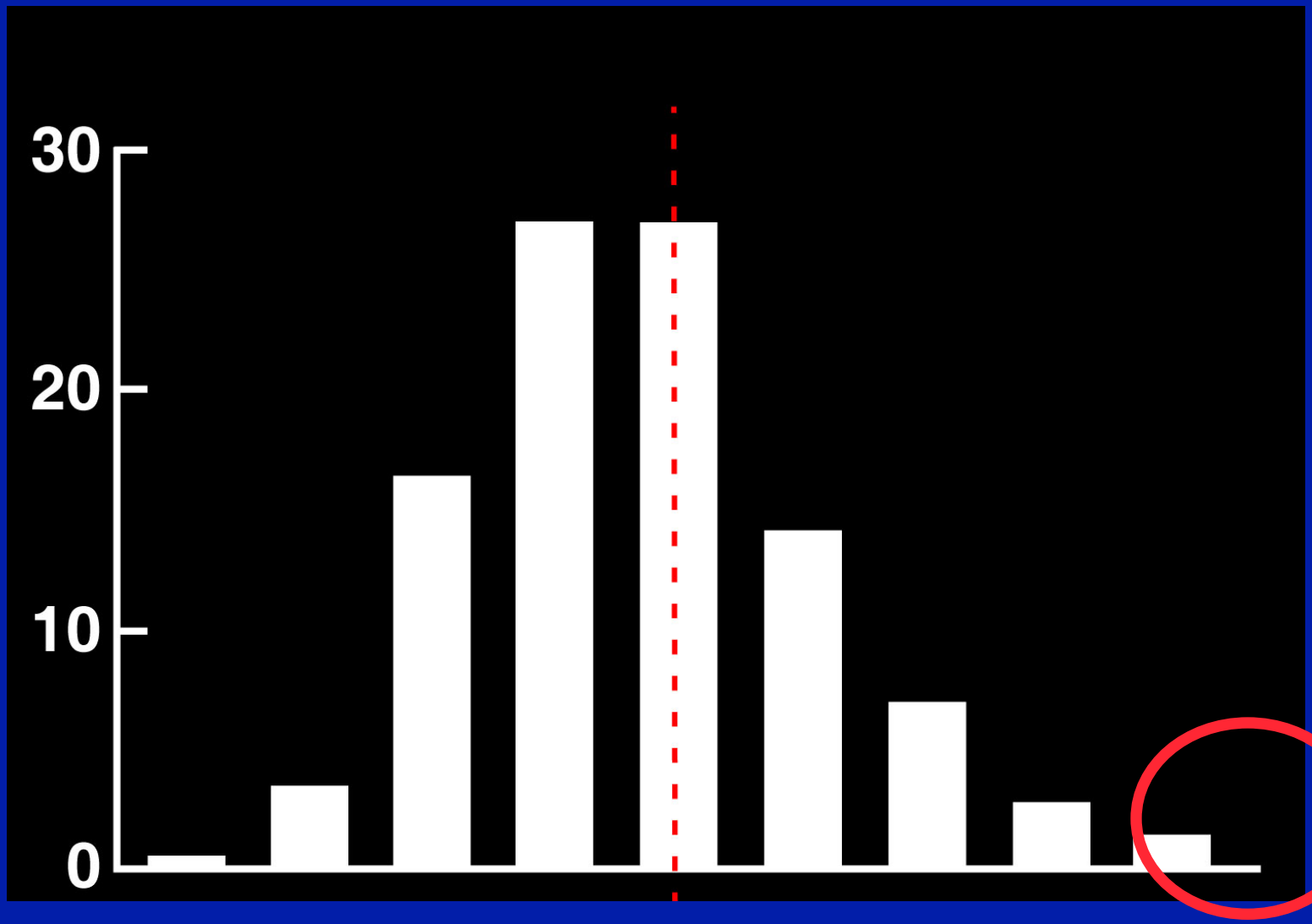
Endothelial Lipase (EL) promotes HDL catabolism and reduces HDL-C levels



Jaye et al, Nature Genetics 1999

Kidney

Do loss-of-function mutations in EL (*LIPG*) cause high HDL-C?



Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans

Andrew C. Edmondson,[1] Robert J. Brown,[1] Sekar Kathiresan,[2,3] L. Adrienne Cupples,[4] Serkalem Demissie,[4] Alisa Knodle Manning,[4] Majken K. Jensen,[5] Eric B. Rimm,[5,6] Jian Wang,[7] Amrith Rodrigues,[1] Vaneeta Bamba,[1] Sumeet A. Khetarpal,[1] Megan L. Wolfe,[1] Stephanie DerOhannessian,[1] Mingyao Li,[8] Muredach P. Reilly,[1,9] Jens Aberle,[10] David Evans,[10] Robert A. Hegele,[7] and Daniel J. Rader[1,9]

Edmondson, *J Clin Invest* 2009

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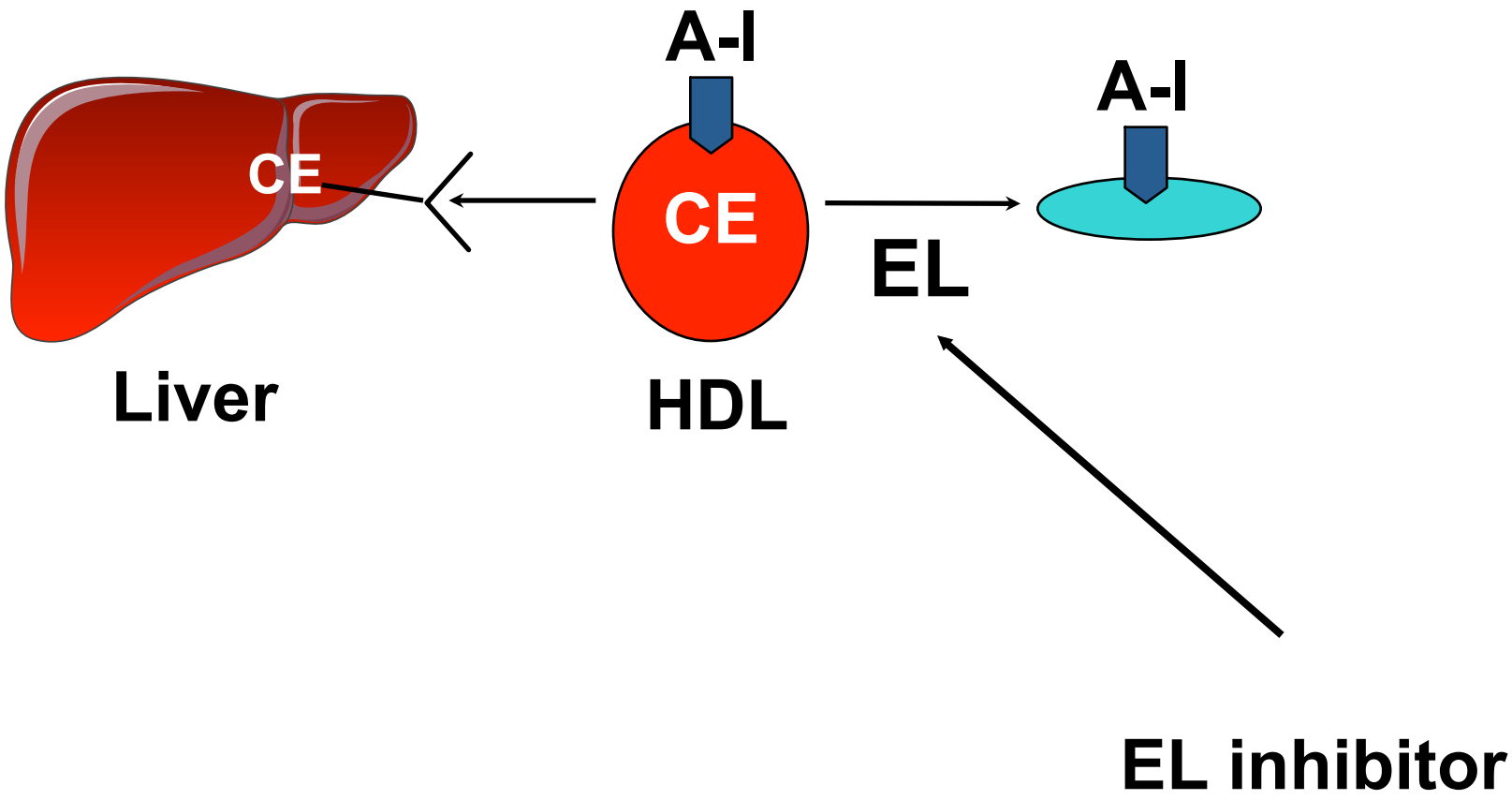
Endothelial lipase Asn396Ser

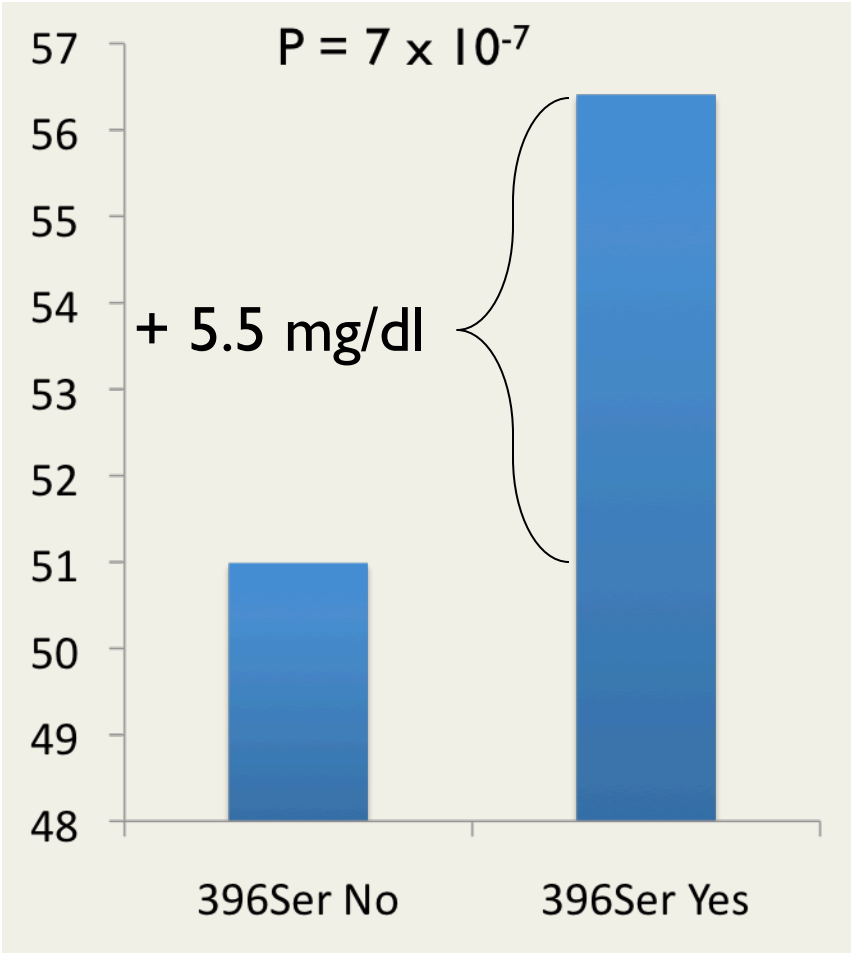
- Serine allele has marked reduced lipolytic function
- 1-2% of people carry the Serine allele
- They have significantly higher HDL-C and ApoA-1 levels
- No effect on other lipid fractions or MI risk factors

Edmondson, *J Clin Invest* 2009

Endothelial Lipase inhibition is predicted to raise HDL-C levels



After Testing in >110,000 Participants, EL N396S Variant *Not* Associated with MI



Odds Ratio for MI:

0.99

(0.88 – 1.11)

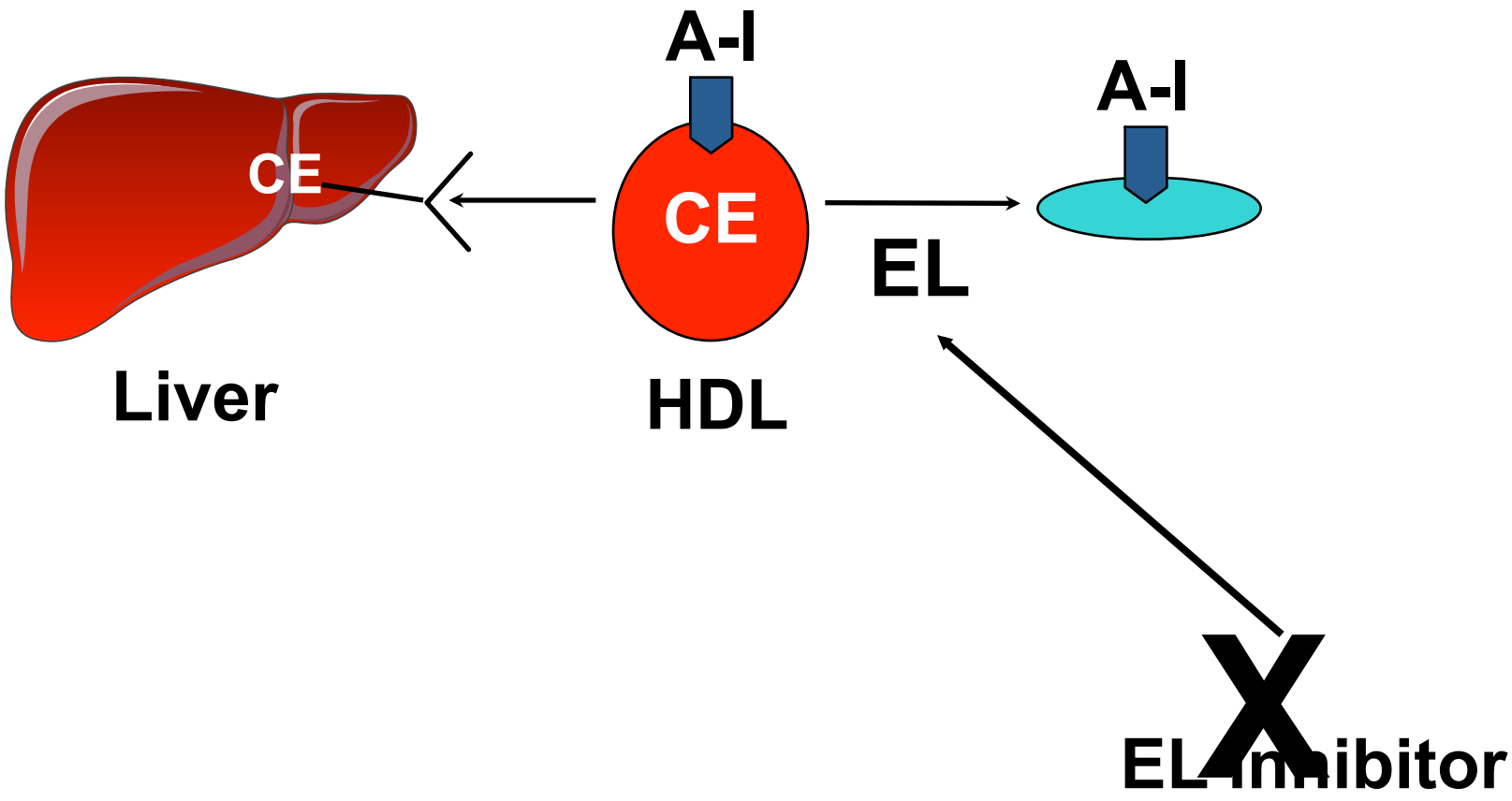
P=0.41

N=19,539 cases,

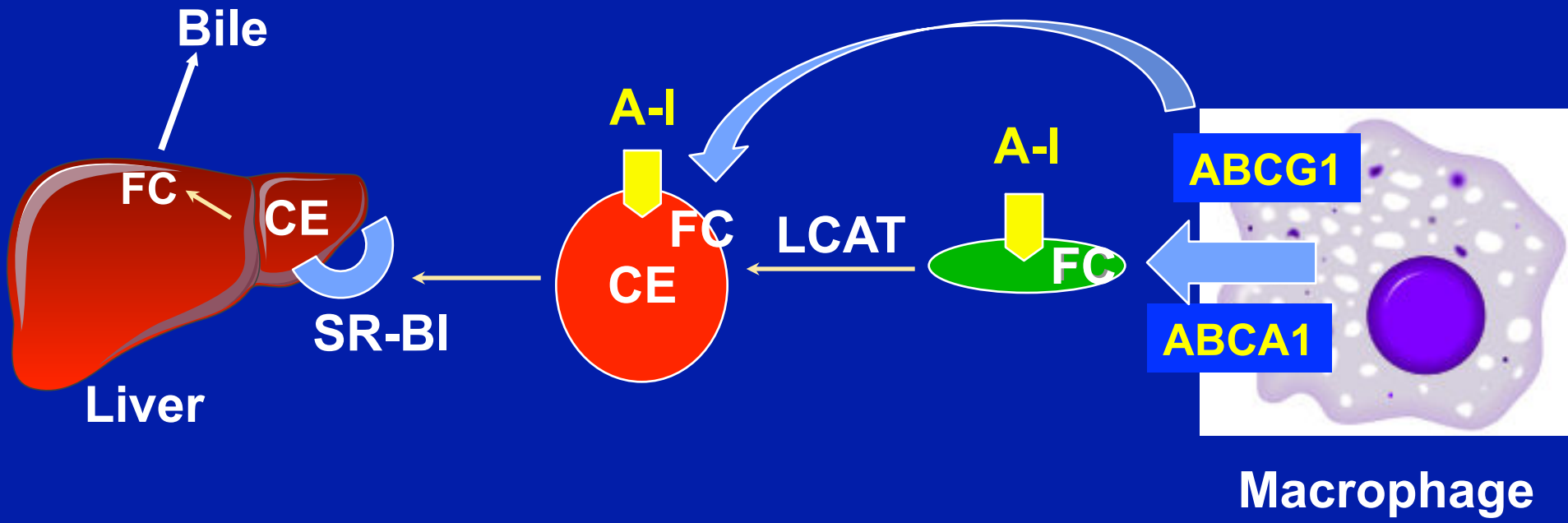
93,715 controls

Voight et al, Lancet 2012

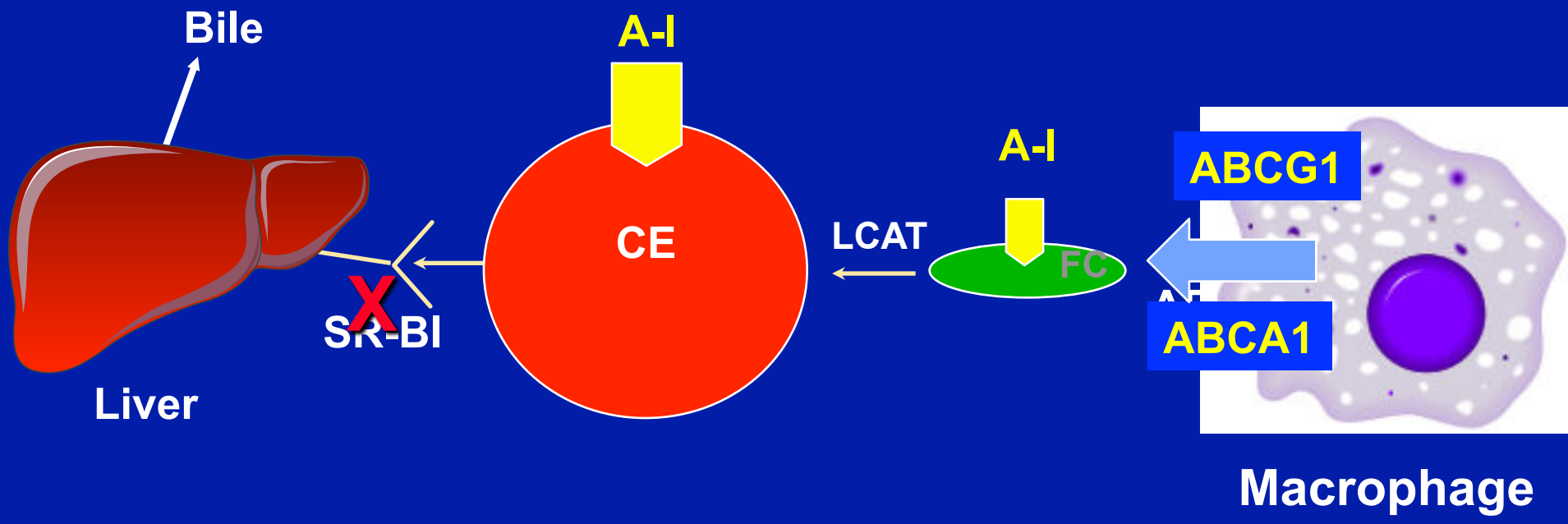
Endothelial Lipase inhibition is predicted to raise HDL-C levels but not reduce CAD



SR-BI and HDL metabolism

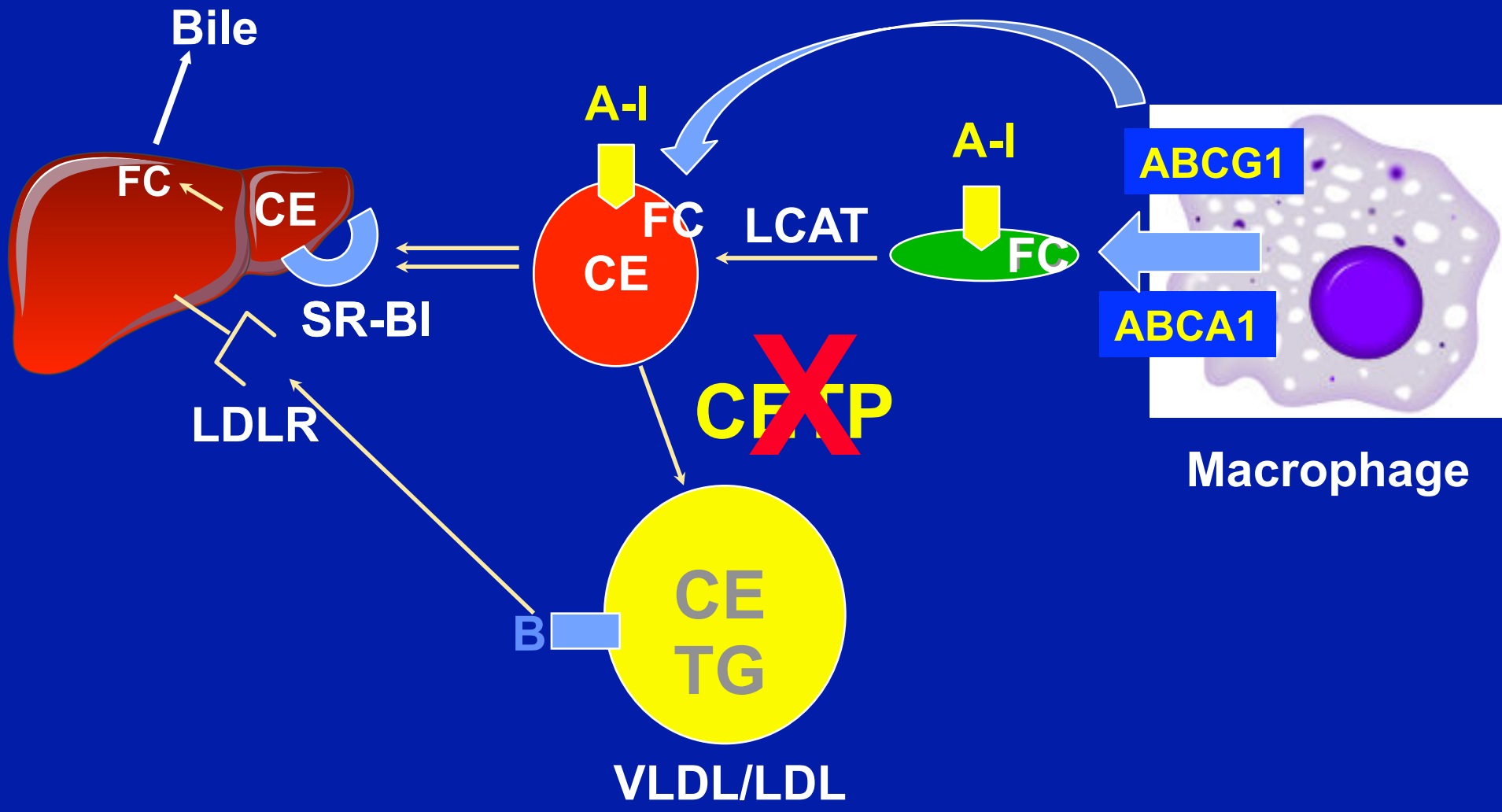


SR-BI knockout mice have elevated HDL-C levels but impaired RCT and increased atherosclerosis

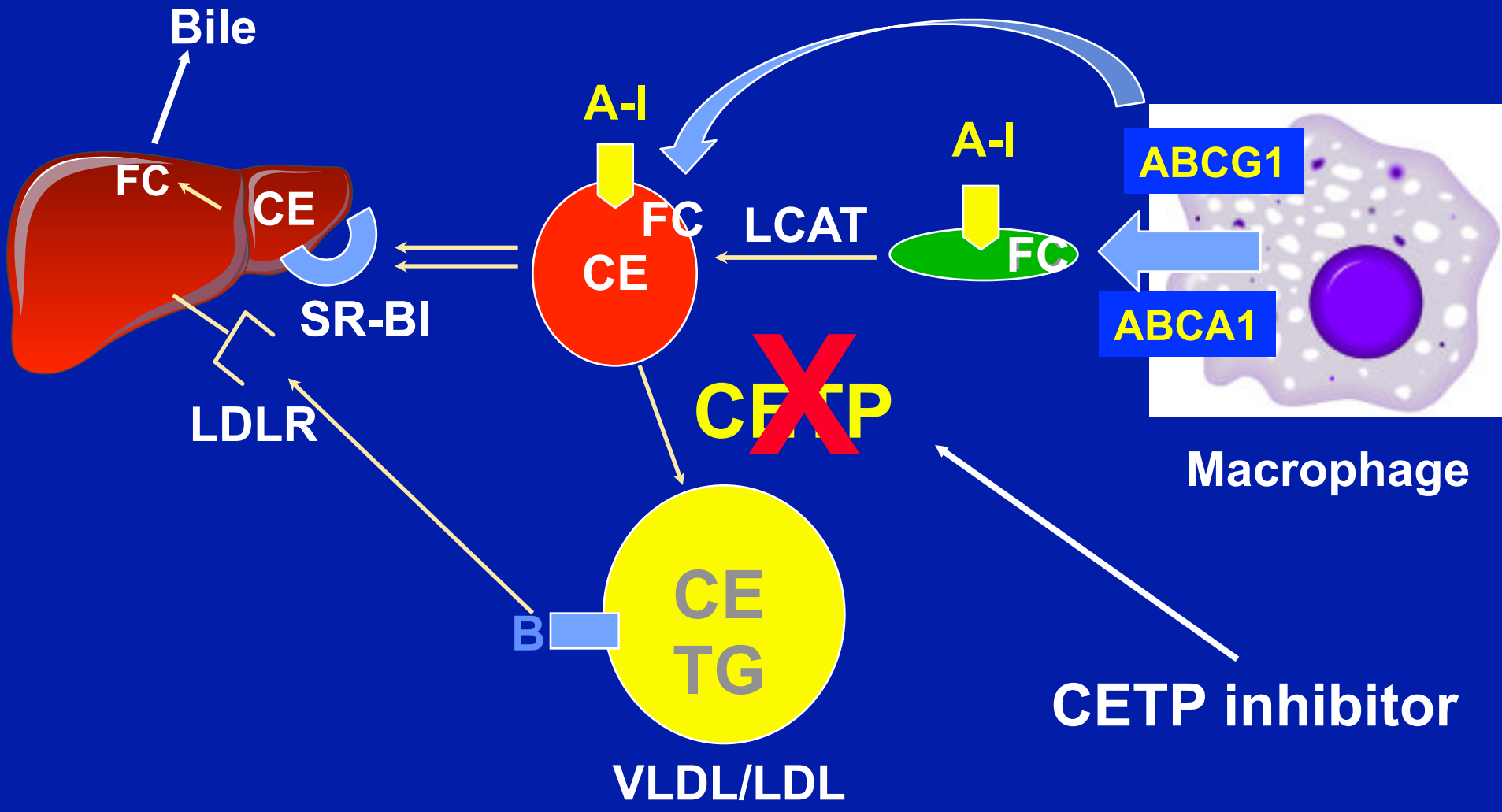


What is the contribution of SR-BI to HDL metabolism and atherosclerosis in humans?

CETP Deficiency Is Genetic Cause of Elevated HDL-C



CETP Inhibition Raises HDL-C Levels



Lipid efficacy of CETP inhibitors (% change from baseline)

CETP inhibitor	Dose mg/d	HDL-C %	LDL-C %	TG %
Torcetrapib	60	61	-24	-9
Dalcetrapib	600	31	-2	-3

Adapted from Cannon C, JAMA 306:2154; 2011

Lipid efficacy of CETP inhibitors (% change from baseline)

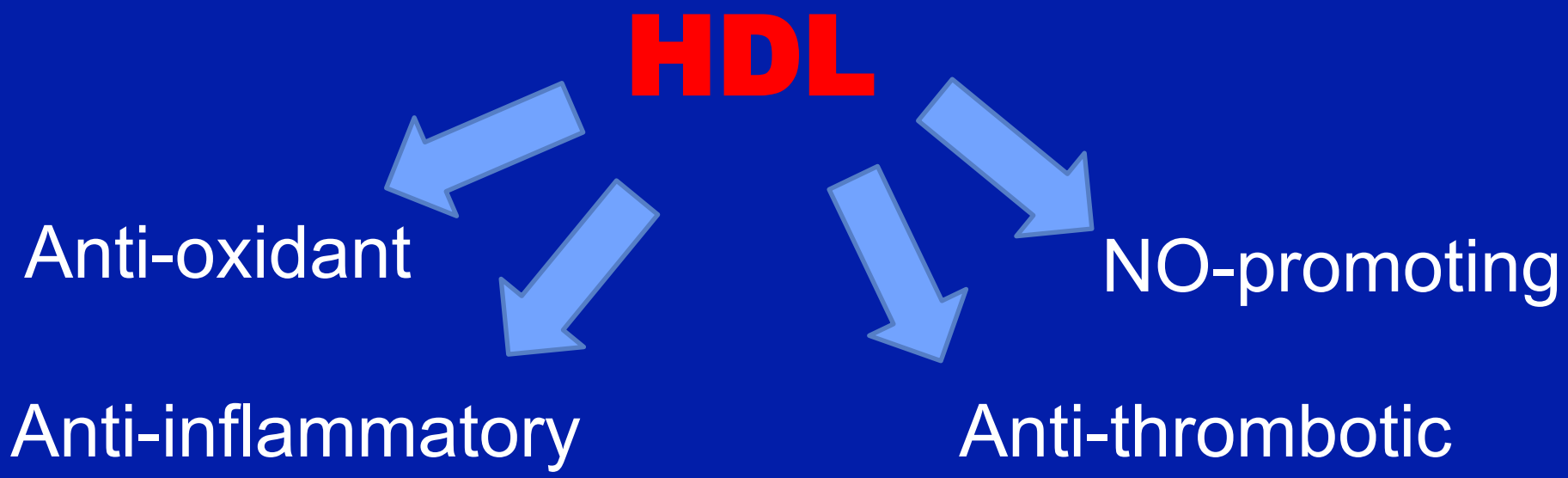
CETP inhibitor	Dose mg/d	HDL-C %	LDL-C %	TG %
Torcetrapib	60	61	-24	-9
Dalcetrapib	600	31	-2	-3
Anacetrapib	100	138	-40	-7
Evacetrapib	500	129	-36	-17

Adapted from Cannon C, JAMA 306:2154; 2011

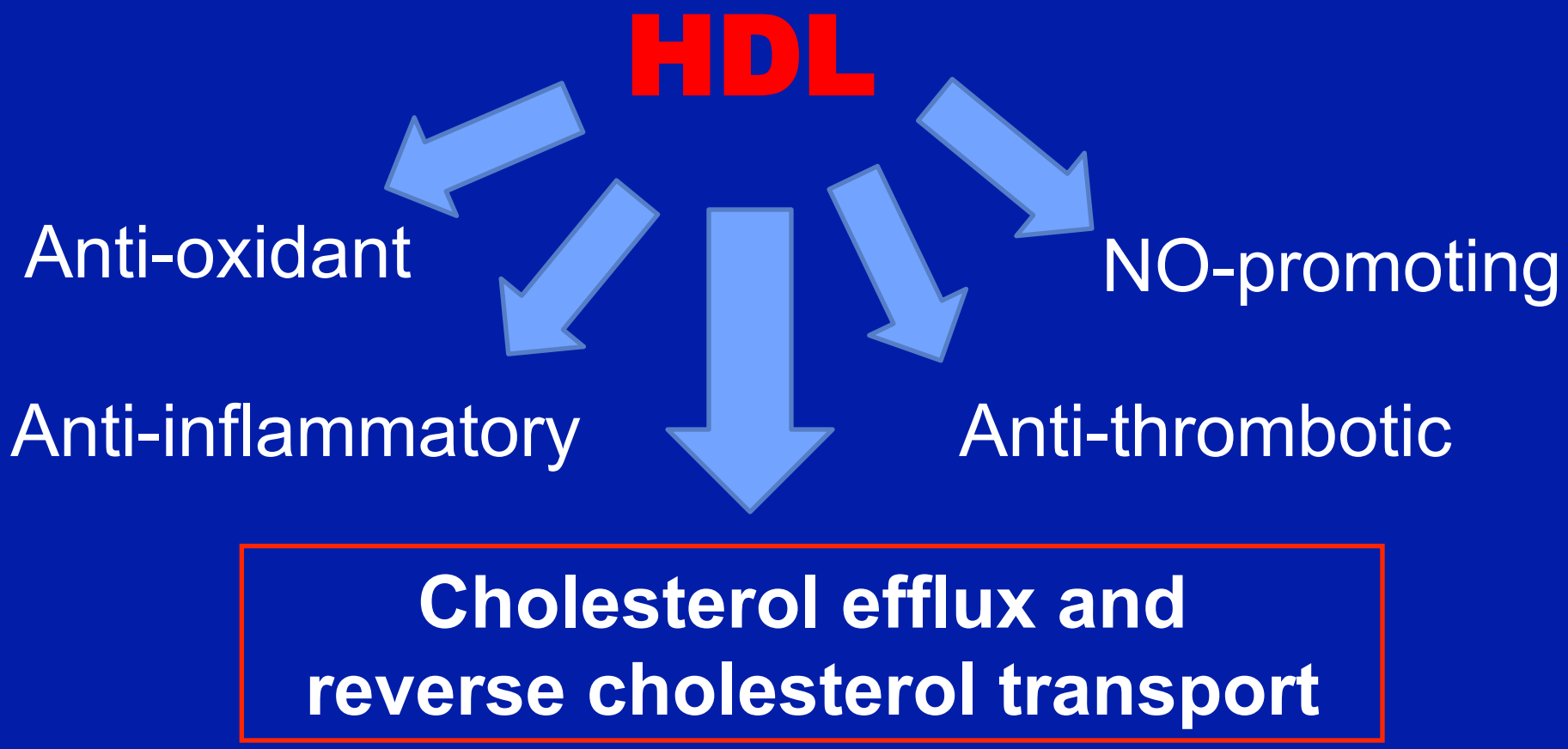
Time to retire the HDL-C hypothesis?

Raising plasma HDL-C levels will reduce CV events.

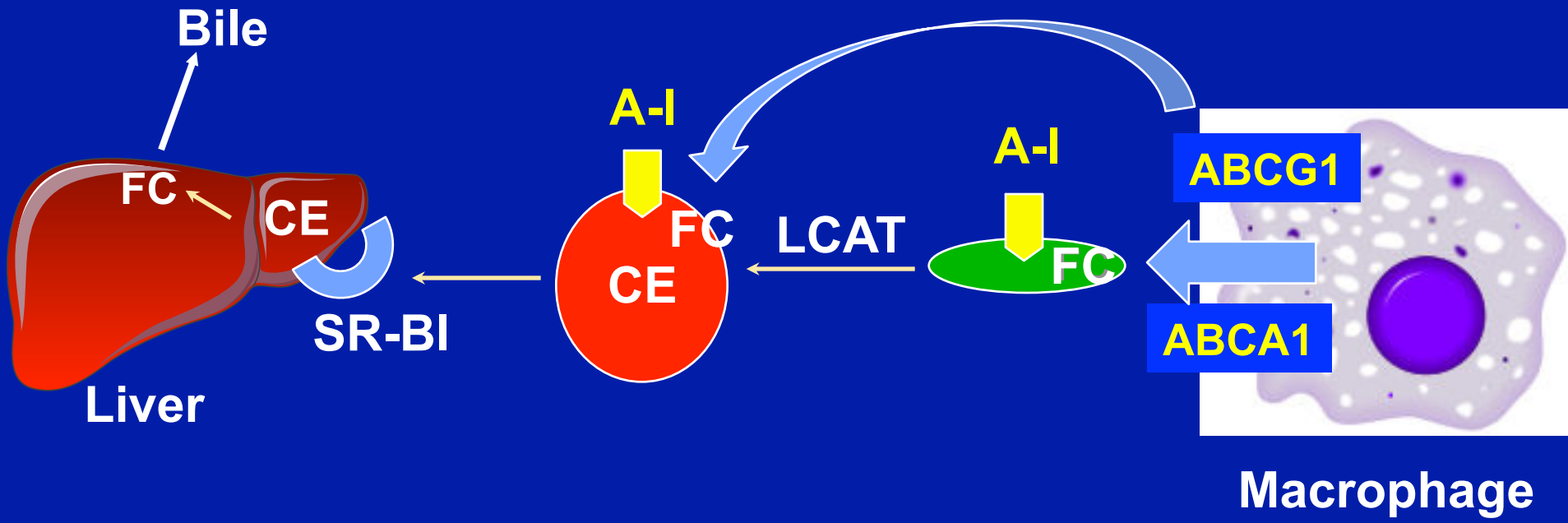
Anti-atherogenic HDL functions



Anti-atherogenic HDL functions



Reverse Cholesterol Transport



Quantitation of macrophage reverse cholesterol transport in vivo

Genetic and pharmacologic interventions

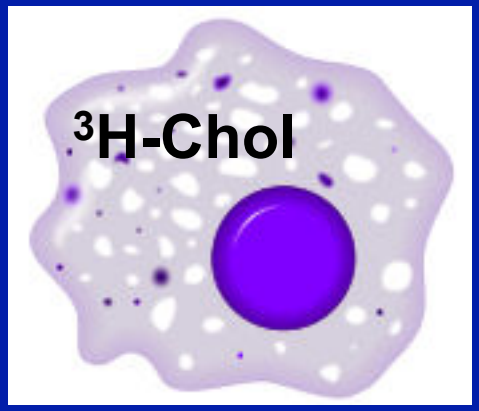
Feces ^{3}H-BA ^{3}H-FC

Bile ^{3}H-BA ^{3}H-FC

^{3}H-BA

^{3}H-FC

Plasma ^{3}H-chol



Macrophage

^{3}H-cholesterol, AcLDL

Macrophage RCT predicts atherosclerosis better than plasma HDL-C in mice

Genetic and pharmacologic interventions

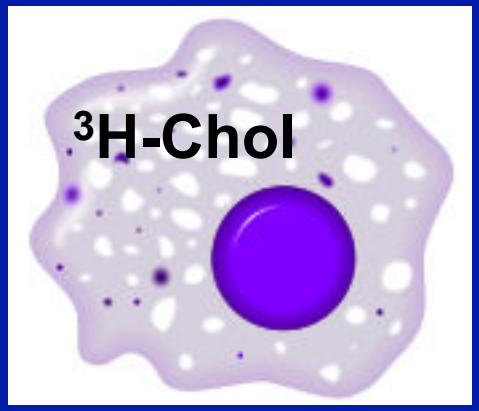
Feces ^{3}H-BA ^{3}H-FC

Bile ^{3}H-BA ^{3}H-FC

^{3}H-BA

^{3}H-FC

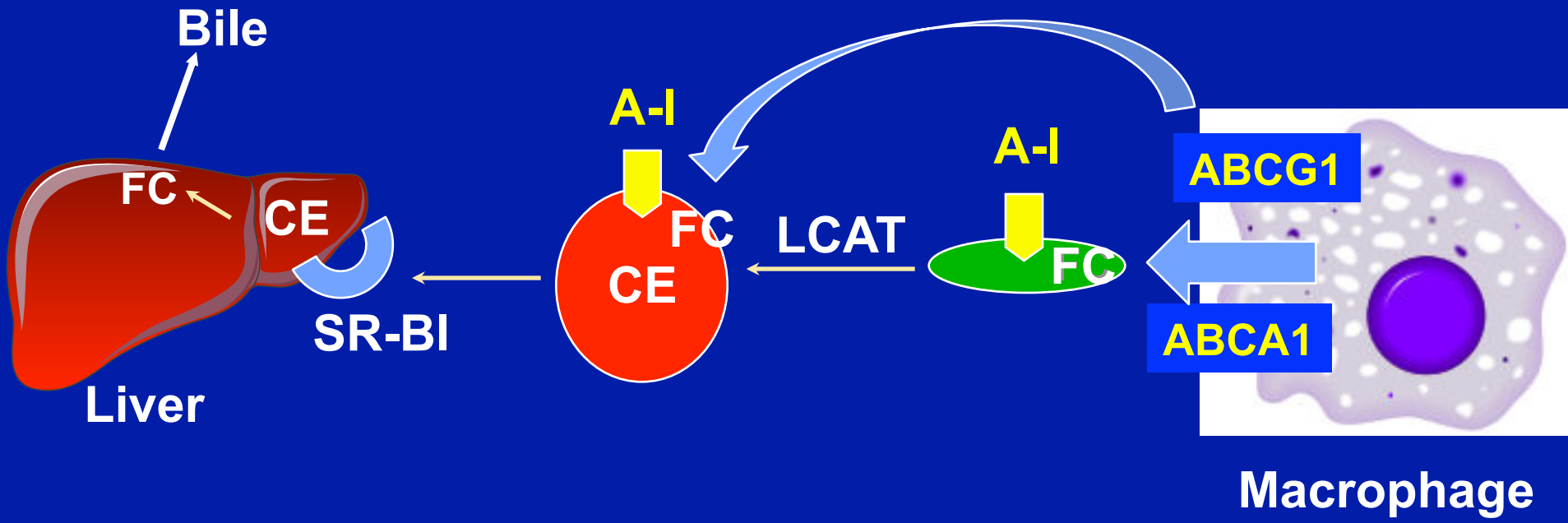
Plasma ^{3}H-chol



Macrophage

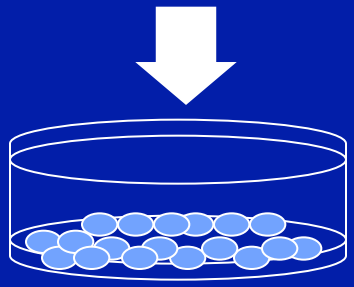
^{3}H-cholesterol, AcLDL

Measuring Steps of Reverse Cholesterol Transport in Humans



Measuring HDL Cholesterol Efflux Capacity in Humans

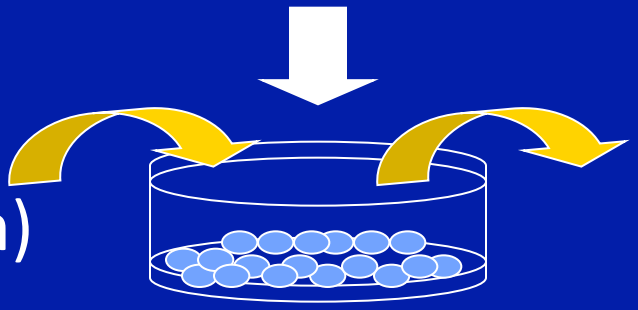
^{3}H-Cholesterol ± AcLDL



cAMP-treated J774 MACROPHAGES

cAMP

HDL (apoB-depleted serum)



% cholesterol efflux

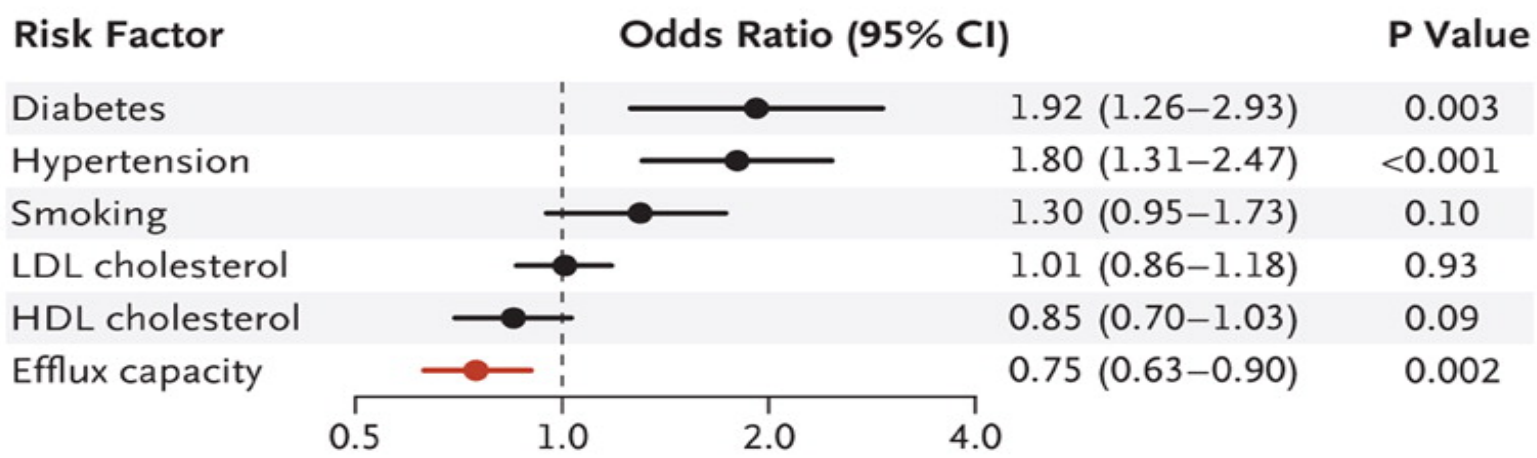
After George Rothblat, et al

Cholesterol efflux capacity is inversely correlated with carotid IMT and angiographic CAD after adjusting for HDL-C or apoA-I

Table 2. Beta Coefficients for the Association between Cholesterol Efflux Capacity and Carotid Intima–Media Thickness.

Linear-Regression Covariates*	Beta Coefficient per 1-SD Increase in Efflux Capacity (95% CI)	P Value
Age and sex	–0.02 (–0.04 to –0.003)	0.02
Age, sex, and cardiovascular risk factors	–0.02 (–0.04 to –0.004)	0.02
Age, sex, cardiovascular risk factors, and high-density lipoprotein cholesterol	–0.03 (–0.06 to –0.01)	0.003
Age, sex, cardiovascular risk factors, and apolipoprotein A-I	–0.04 (–0.06 to –0.01)	0.005

* Cardiovascular risk factors were systolic blood pressure, glycated hemoglobin, and low-density lipoprotein cholesterol.



Khera AV, Cuchel M. NEJM. 2011; 364:127-35

Cholesterol Efflux Capacity is inversely associated with incident coronary events

- Dallas Heart Study
- EPIC-Norfolk

Cholesterol Efflux Capacity at baseline is inversely associated with incident coronary events in EPIC-Norfolk

Figure 2a

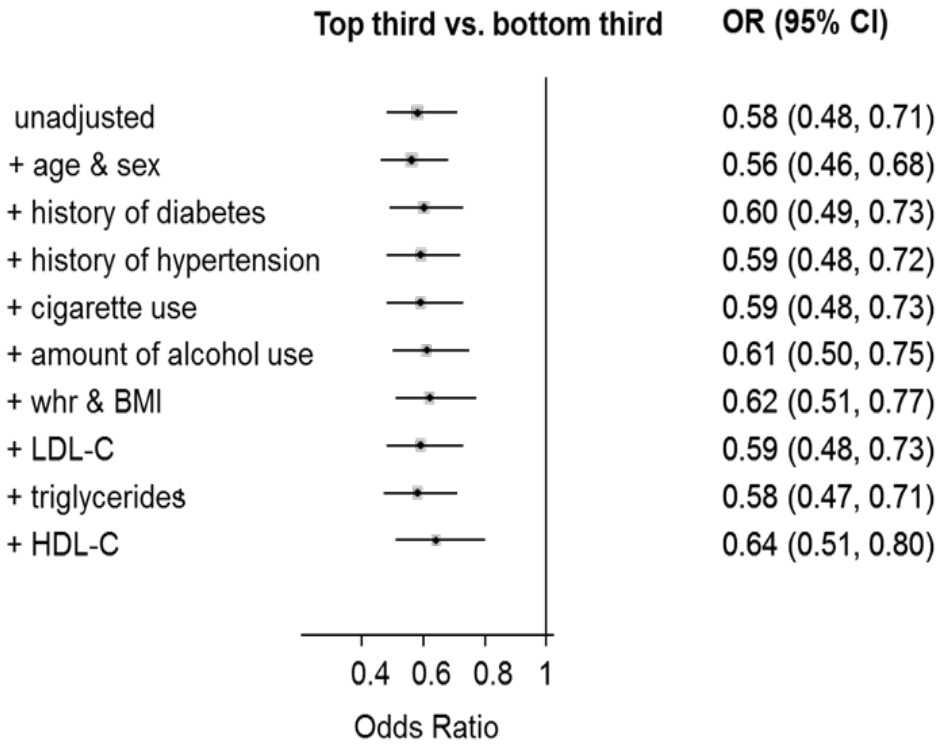
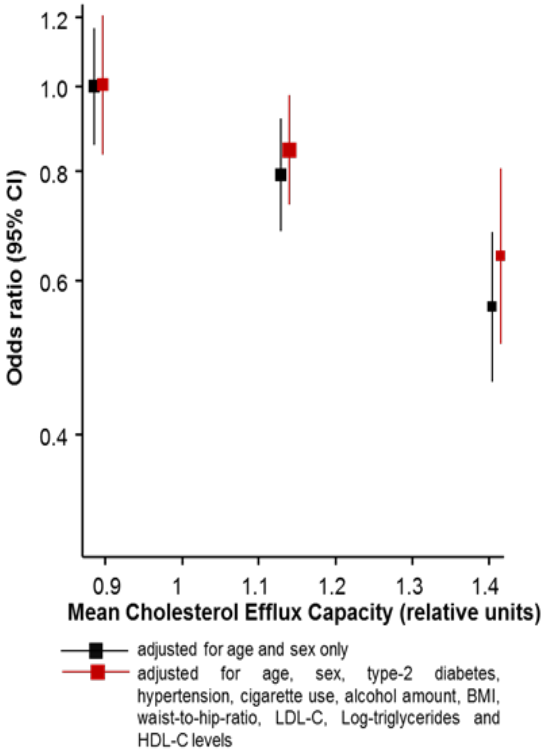


Figure 2b



Saleheen, et al. Lancet Diab Endo 2015

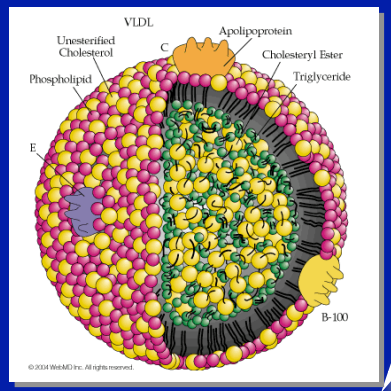
The HDL flux hypothesis

Promoting cholesterol efflux and RCT will reduce CV events.

Genetic variants

?

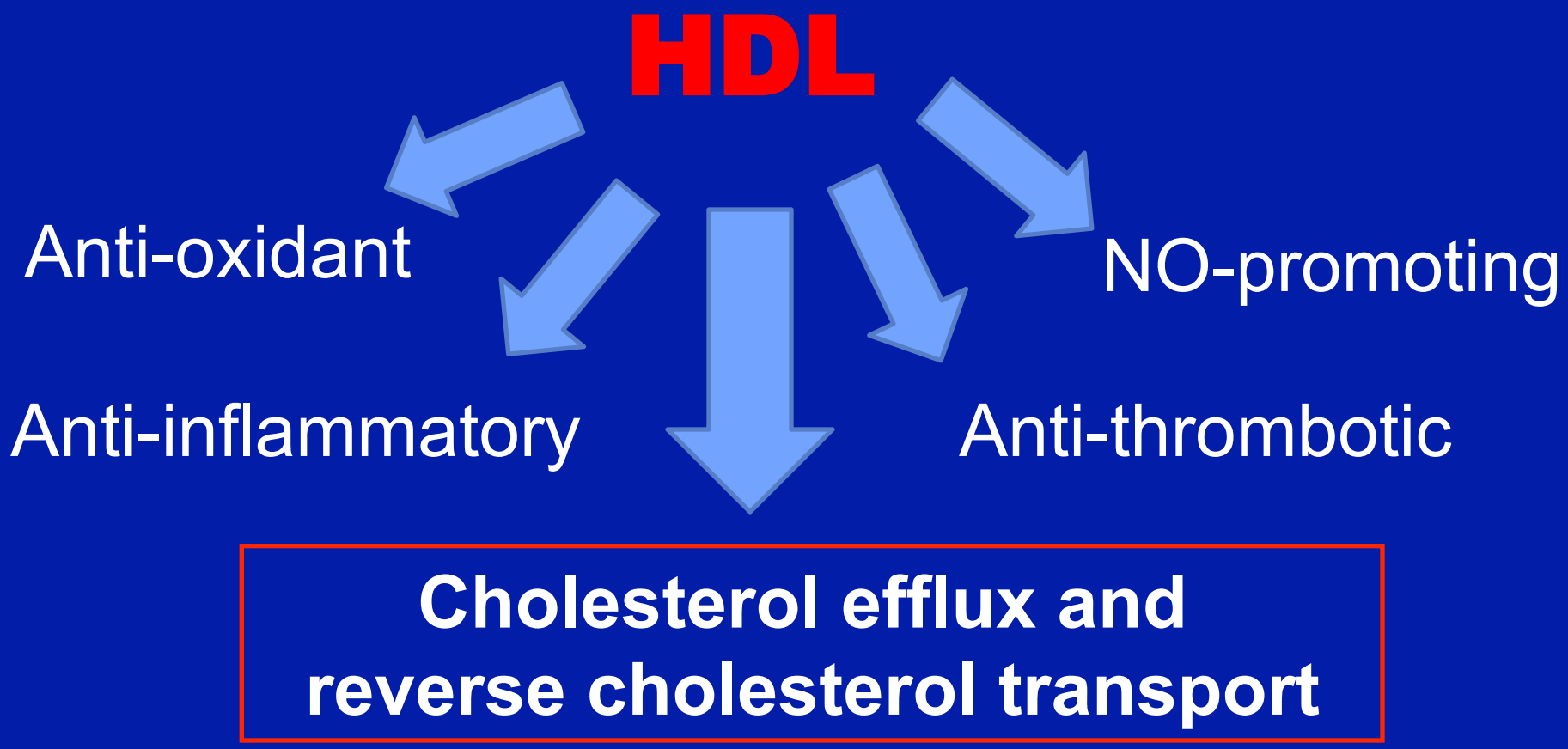
?



Cholesterol efflux capacity

Coronary disease

Anti-atherogenic HDL functions



Human genetics leading to smarter and faster development of new medicines