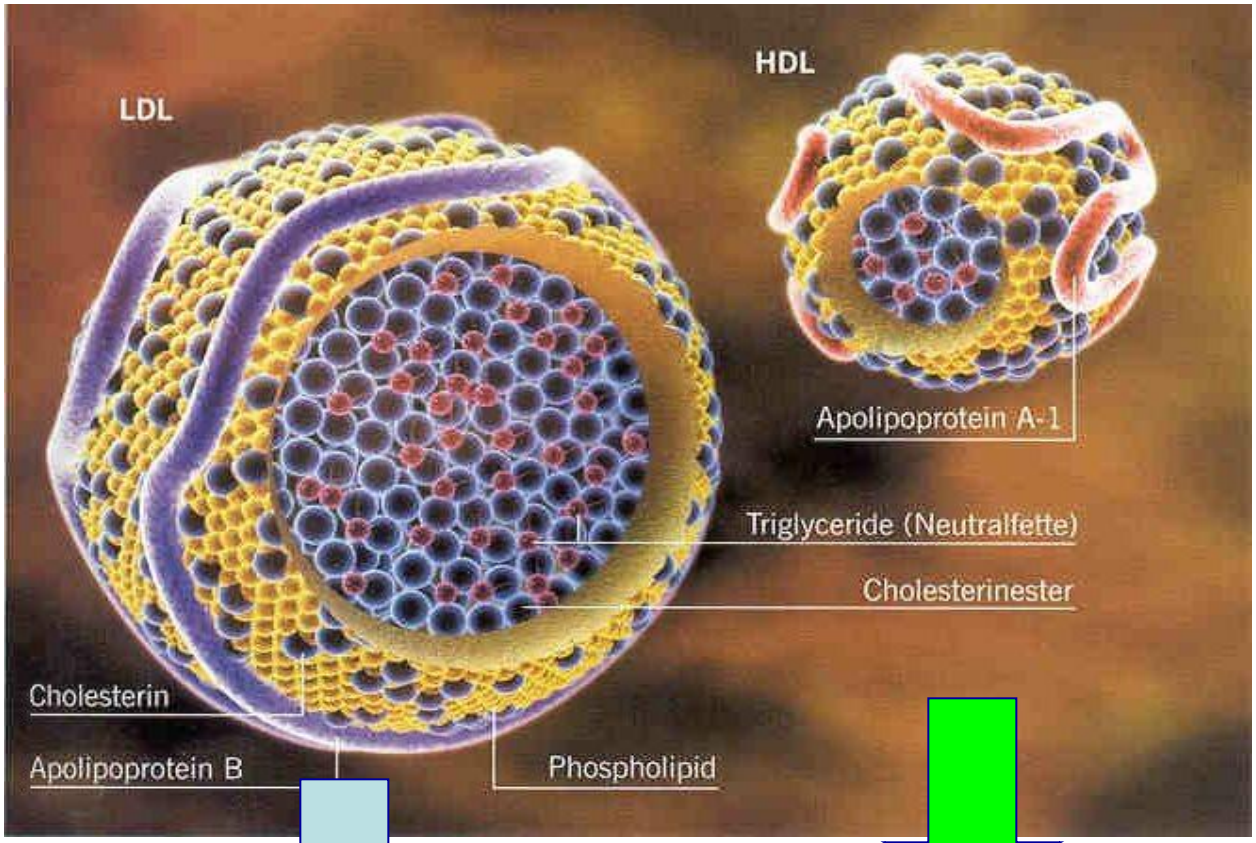
Lipid managment

HDL-Cholesterol – an enigma ?

Ulf Landmesser, MD

Chairman, Department of Cardiology,
Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin

HDL and coronary disease – an enigma ?



Statin therapy

HDL ?

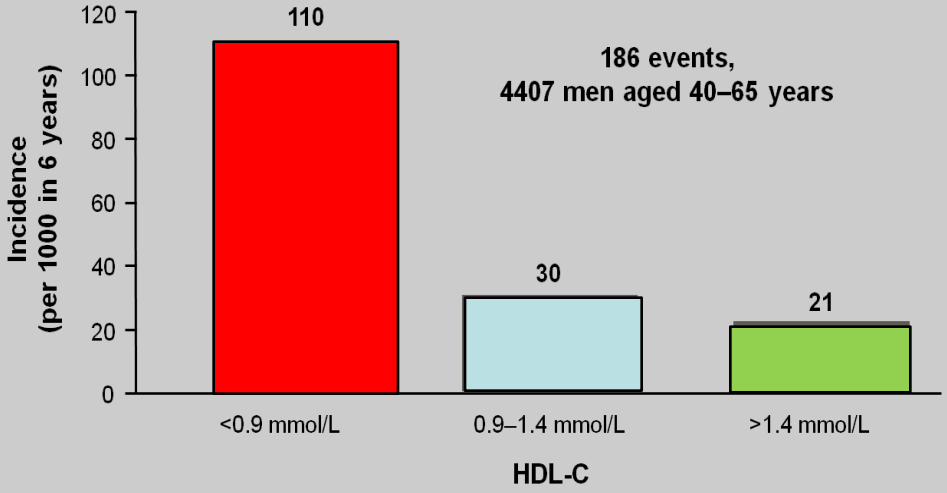
HDL-cholesterol and coronary disease – an enigma ?

1. **HDL-cholesterol – the hypothesis**

2. **HDL-cholesterol in cardiovascular disease**
   - Clinical trials
   - HDL function
   - HDL-C and genetic studies

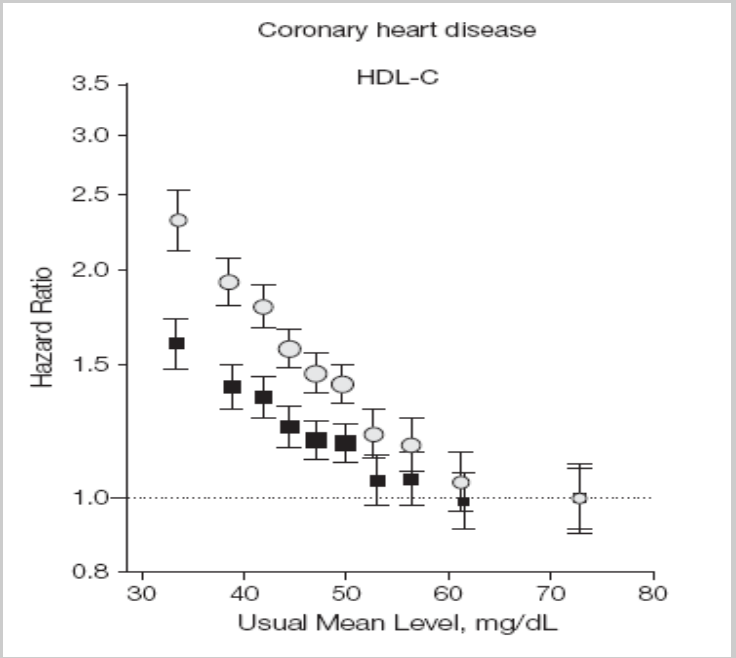
3. **Implications for therapeutic strategies**

HDL-cholesterol and risk of coronary disease



PROCAM Study:
HDL-C is An Independent Predictor of CHD Risk

Assmann G, Schulte H. Lipid Metabolism Disorders and Coronary Heart Disease. 2nd ed. Munich: Medizin, 1993

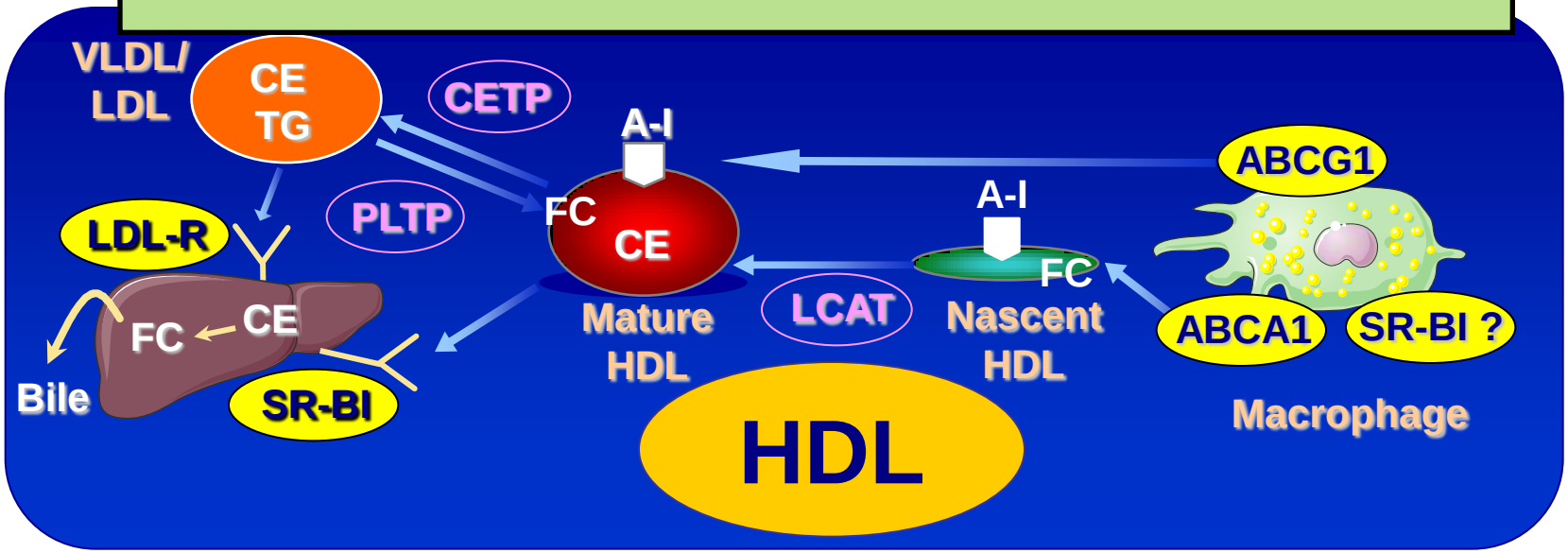


Emerging Risk Factors Collaborations:
Incidence of CHD

Di Angelantonio E et al.; JAMA 2009

HDL: proposed anti-atherogenic effects

1. HDL-mediated promotion of macrophage cholesterol efflux



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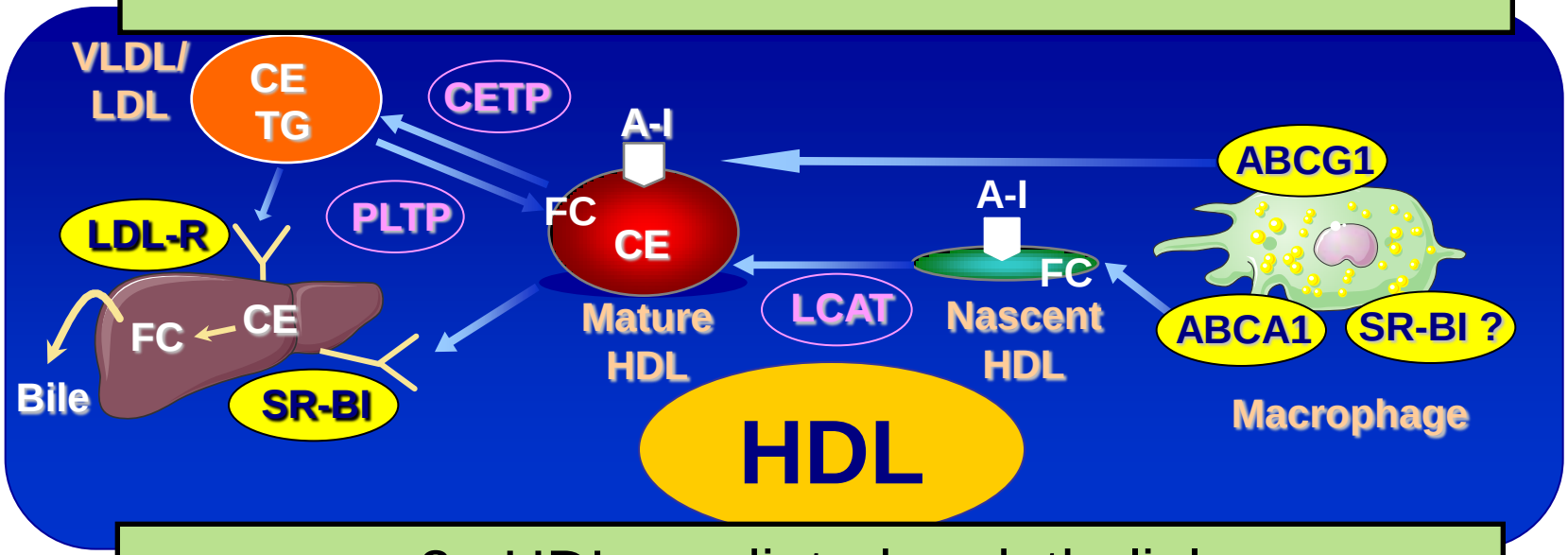
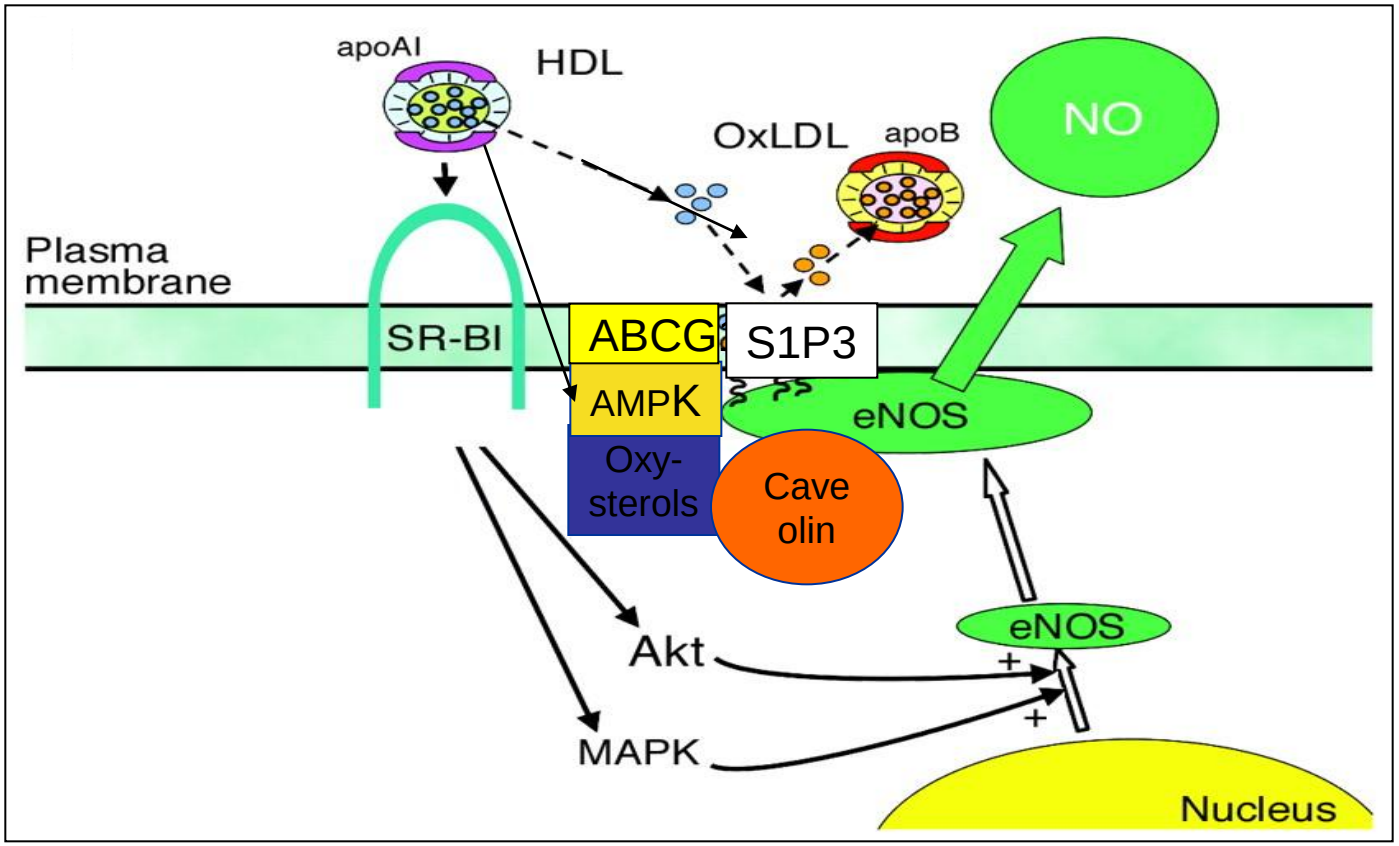


2. HDL-mediated endothelial athero-protective effects

- **Endothelial anti-apoptotic effects**
- **Promotion of endothelial repair**
- **Endothelial NO production**
- **Anti-inflammatory effects**
- **Anti-thrombotic effects**

Besler C, Lüscher T, Landmesser U. ***EMBO Mol Medicine 2012***; 4: 251-68

Mechanisms of effects of HDL on endothelial cell nitric oxide (NO) production



Yuhanna IS et al.; *Nat Med 2001*
Mineo e al.; *J Biol Chem*. 2003
Nofer et al.; *J. Clin. Invest.* 2004

Terasaka N et al.; *J. Clin. Invest.* 2008
Terasaka N et al.; *Arterioscler Thromb Vasc Biol.* 2010
Li D et al. *Arterioscler Thromb Vasc Biol.* 2010

HDL-cholesterol and coronary disease – an enigma ?

1. HDL-cholesterol – the hypothesis

2. **HDL-cholesterol in cardiovascular disease**
   - **Clinical trials**
   - **HDL function**
   - **HDL-C and genetic studies**

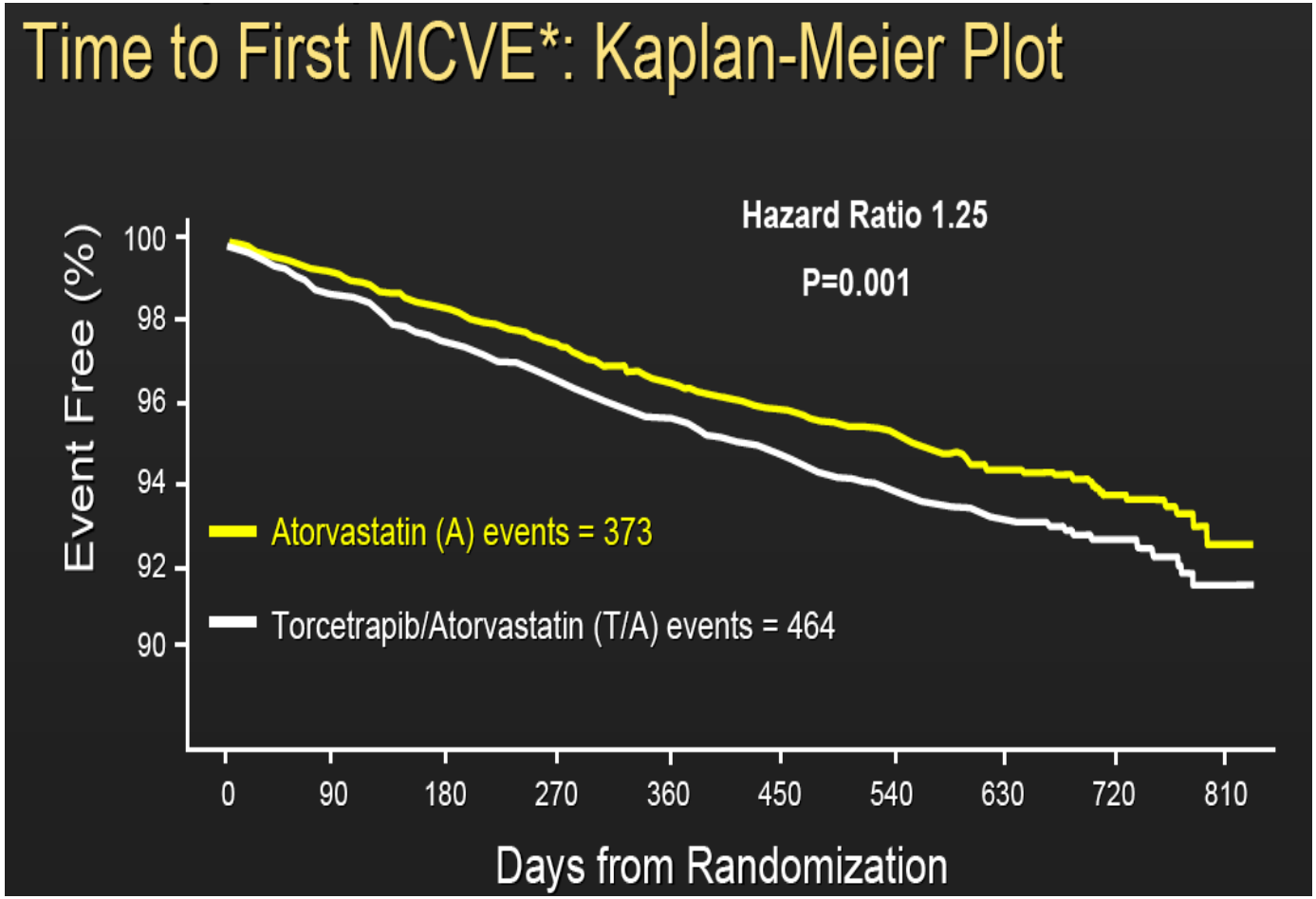
3. **Implications for therapeutic strategies**

CETP-Inhibition with Torcetrapib: marked lipid changes

	Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Lipids (percent change) — %			
Cholesterol			
Total	+2.2±14.5	+7.0±17.7	<0.001
High-density lipoprotein	+1.8±14.0	+72.1±34.7	<0.001
Low-density lipoprotein	+3.0±23.7	−24.9±28.5	<0.001
Triglycerides			
Median	+1	−9	<0.001
Interquartile range	−18 to 25	−27 to 13	

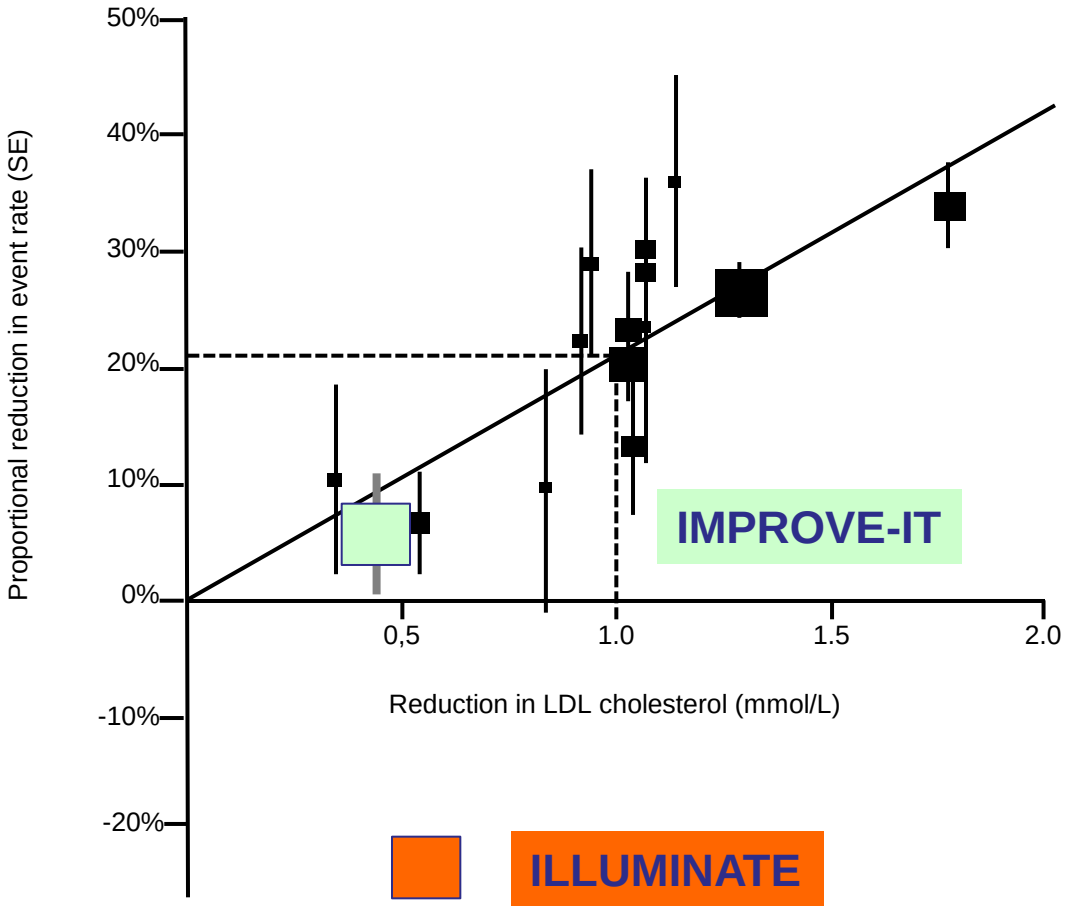
Barter et al., *N Engl J Med* 2007; 357: 2109-2122

CETP-Inhibition with Torcetrapib: *increase of major cardiovascular events in patients at high risk of coronary events*



Barter et al., ***N Engl J Med* 2007**; 357: 2109-2122

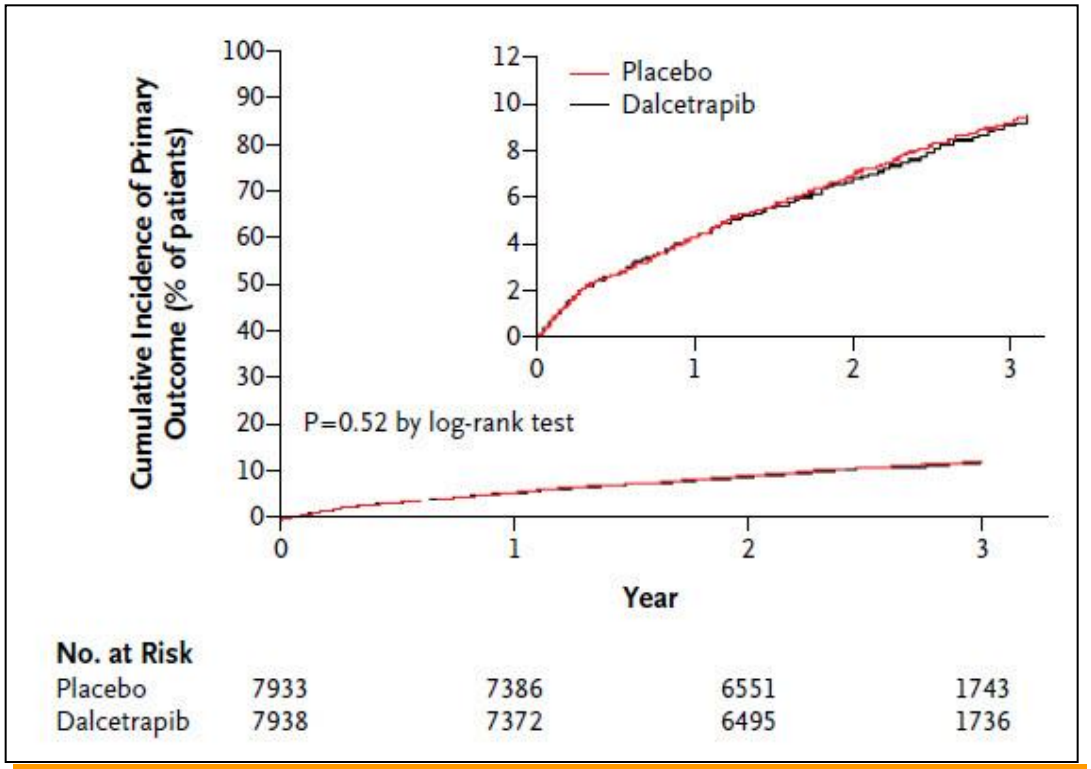
LDL-C reduction and cardiovascular events



The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2012;367:2089-99.
DOI: 10.1056/NEJMoa1206797

ORIGINAL ARTICLE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome



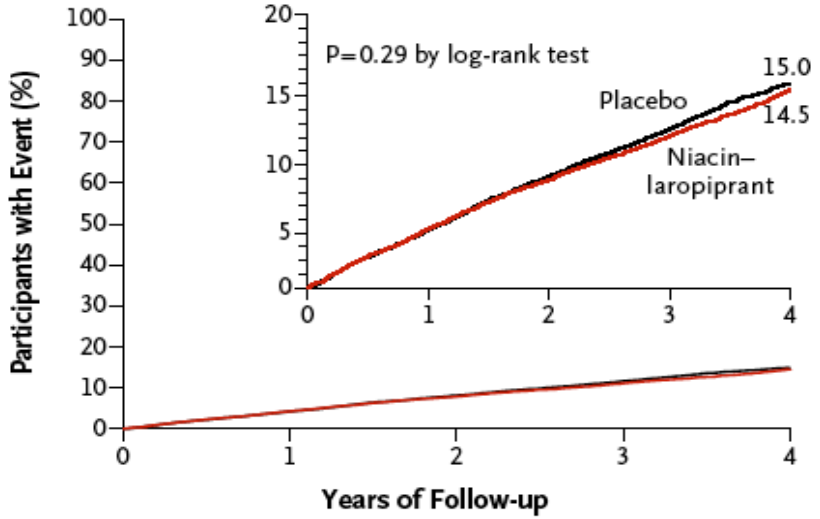
Incidence of the Primary Efficacy End Point.

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*



No. at Risk

Niacin–laropiprant	12,838	12,232	11,517	7672	4978
Placebo	12,835	12,247	11,523	7643	5036
Benefit per 1000 participants assigned to niacin–laropiprant		0±3	3±3	5±5	5±7

HDL-cholesterol and coronary disease – an enigma ?

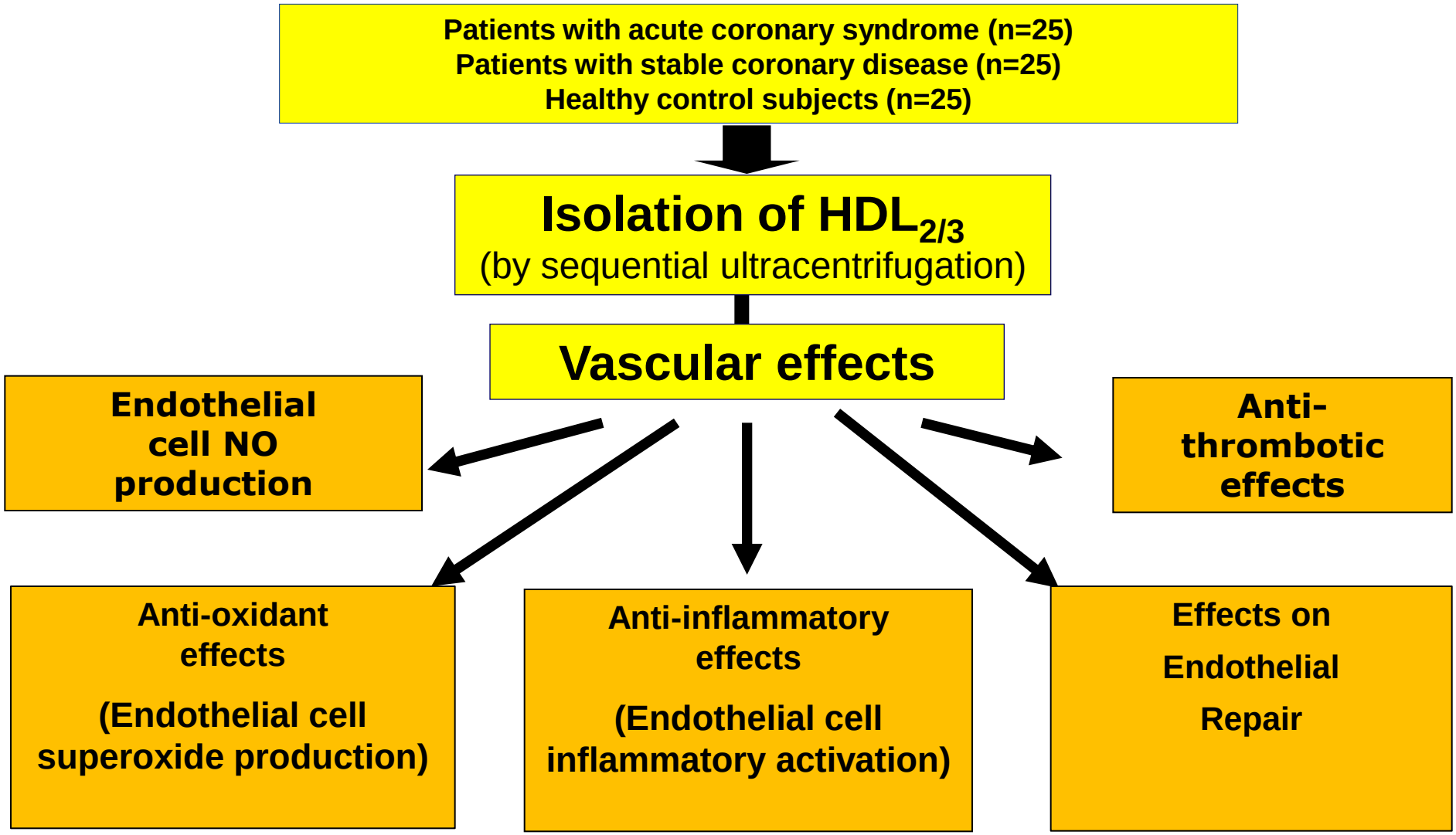
1. HDL-cholesterol – the hypothesis

2. **HDL-cholesterol in cardiovascular disease**
   - Clinical trials
   - **HDL function and**
   - **HDL-C and genetic studies**

3. **Implications for therapeutic strategies**

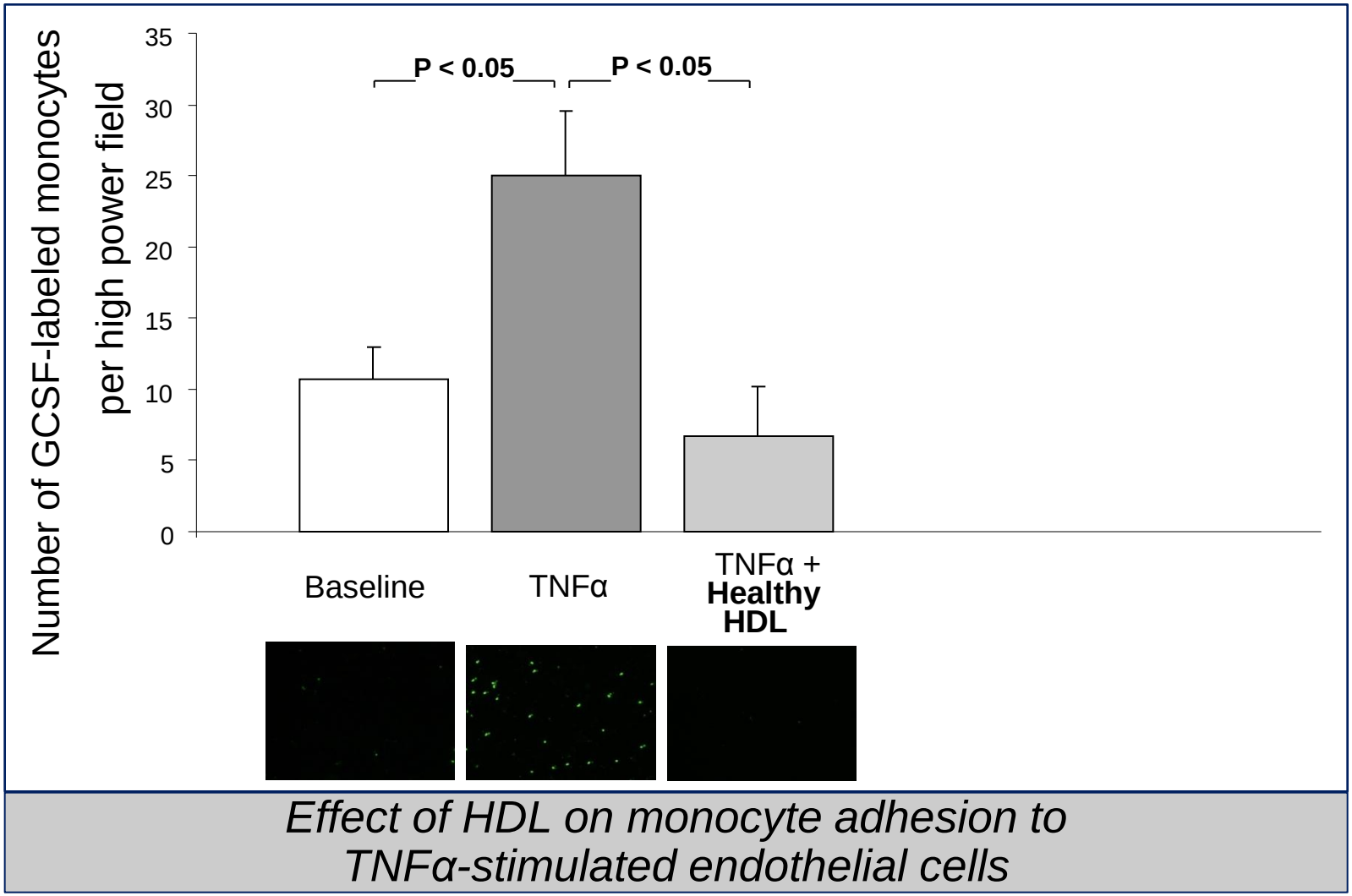
Vascular effects of HDL in patients with coronary disease as compared to healthy subjects ?

Endothelial effects of HDL - endothelial bioassays



Role of HDL function versus HDL cholesterol levels ?

Different effects of HDL from patients with CAD



Effect of HDL on monocyte adhesion to TNFα-stimulated endothelial cells

Besler C et al. & Landmesser U. *J Clin Invest* 2011;121: 2693-708

Role of HDL function versus HDL cholesterol levels ?

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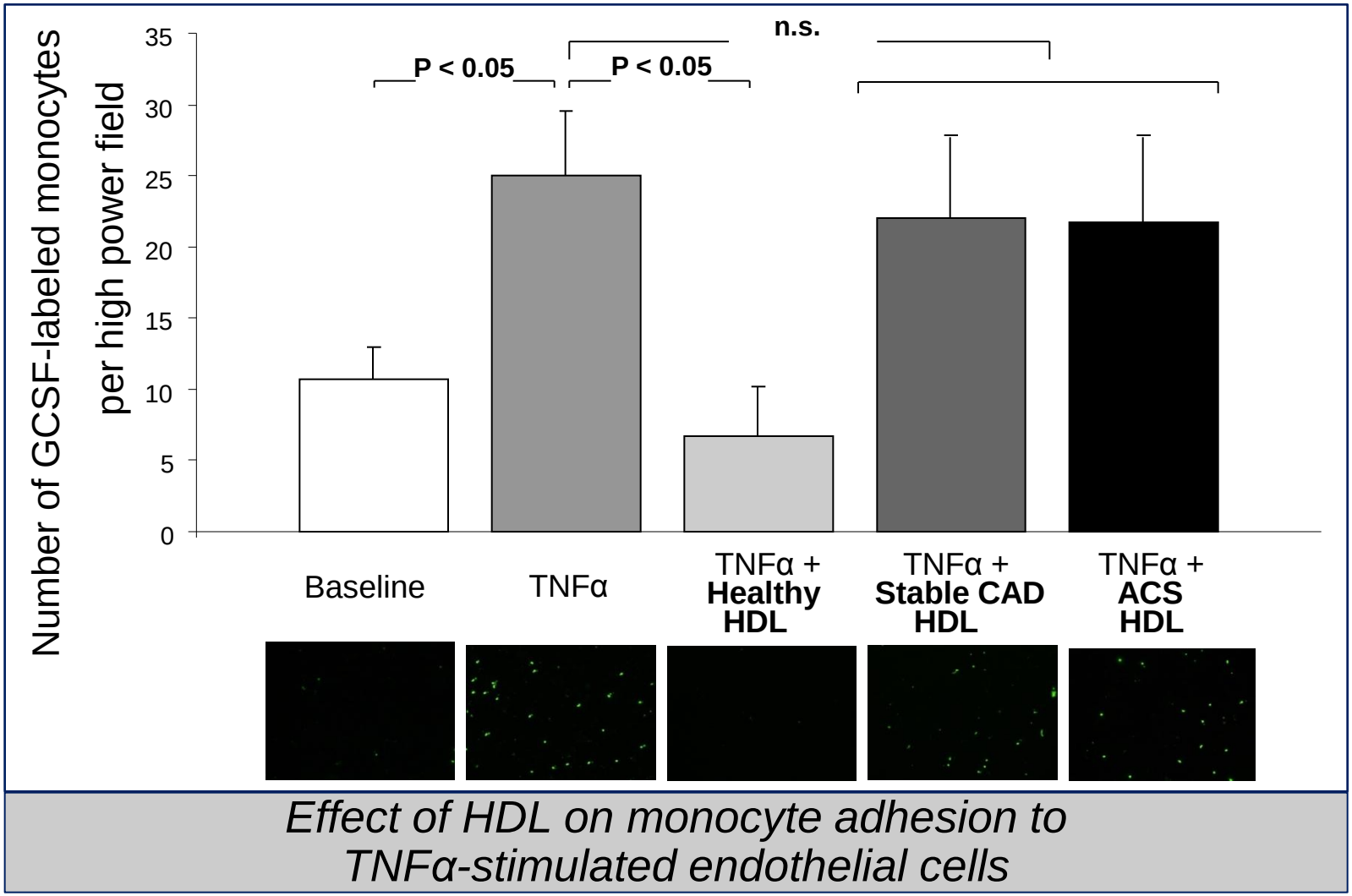


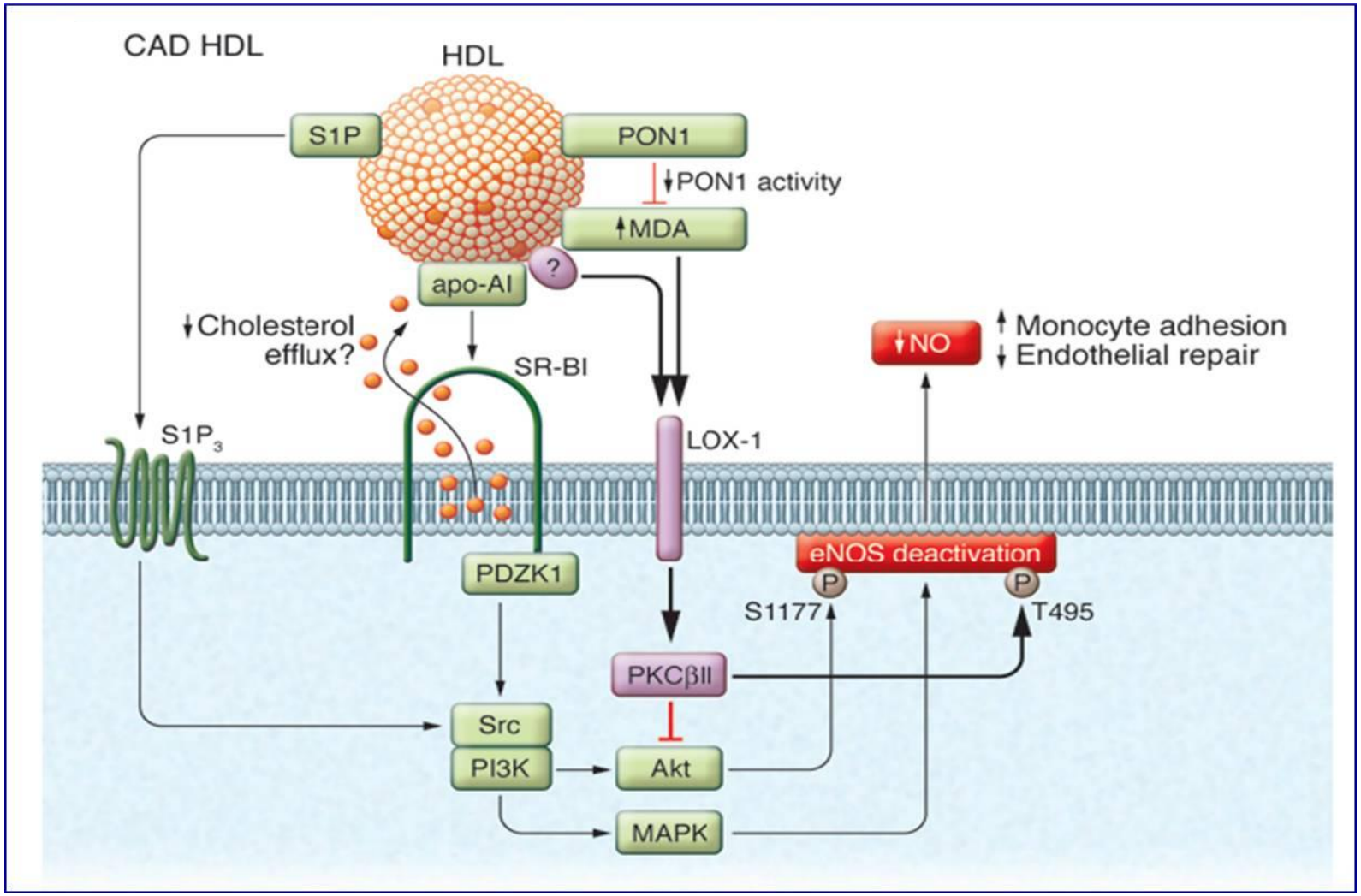
Effect of HDL on monocyte adhesion to TNFα-stimulated endothelial cells

Besler C et al. & Landmesser U. *J Clin Invest* 2011;121: 2693-708

HDL function (vascular effects)

Which changes of HDL are mediating differences in HDL‘s vascular effects ?

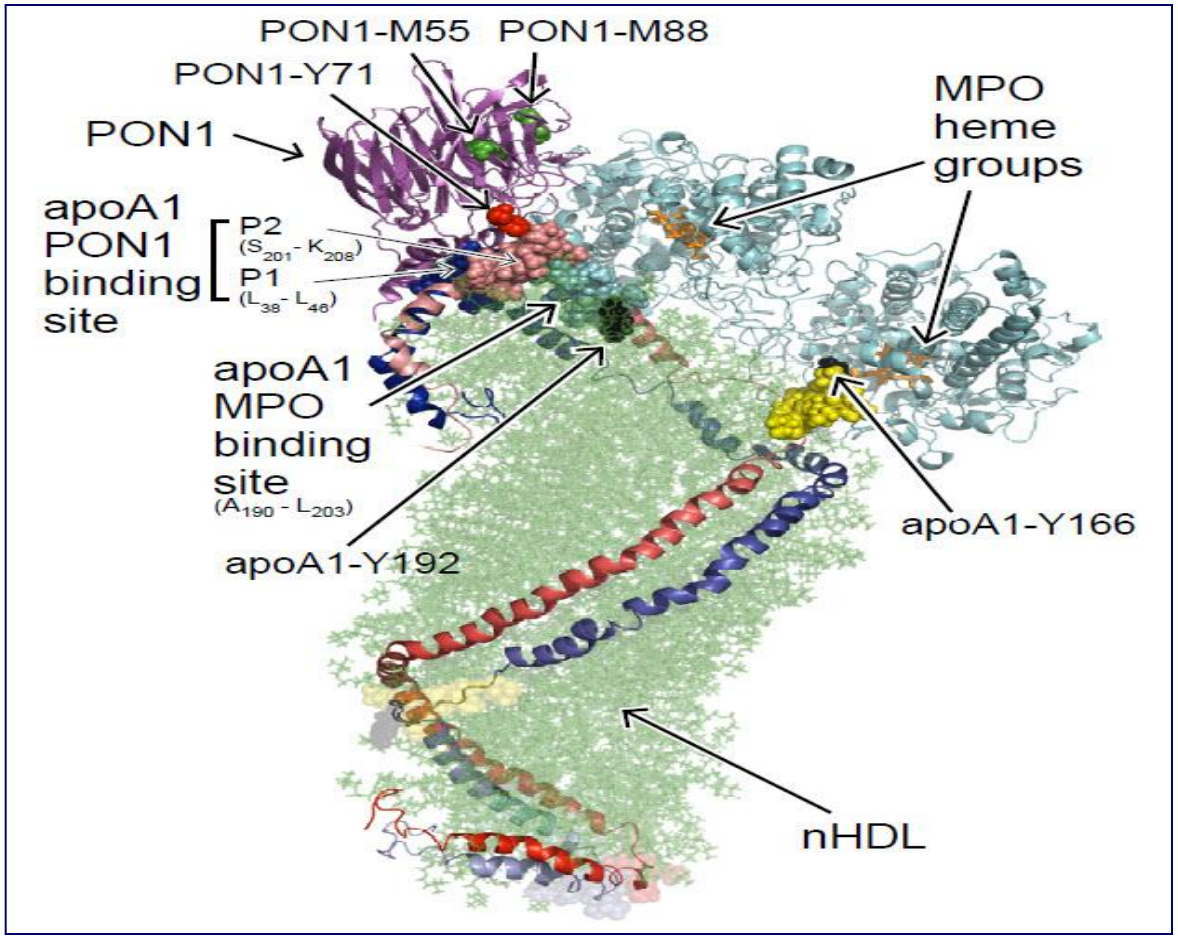
Mechanisms leading to altered effects of HDL on endothelial nitric oxide availability in CAD



Mineo C & Shaul PW. *J Clin Invest* 2011

Myeloperoxidase leads to oxidative inactivation of paraoxonase-1 (PON-1) – analysis in coronary disease:

A functional ternary complex of MPO-PON-1-HDL

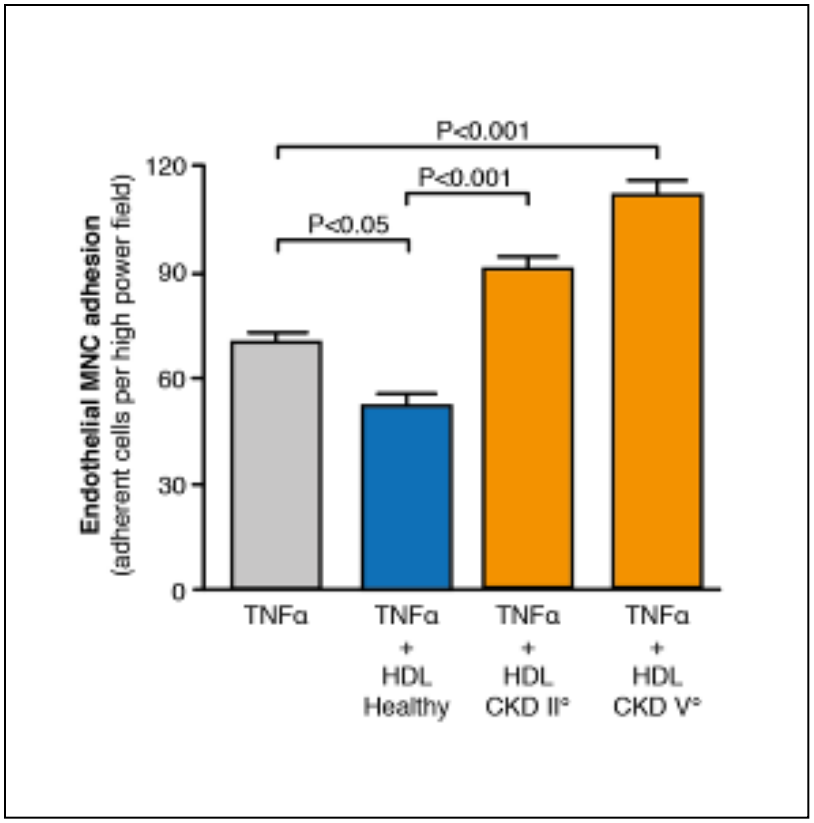


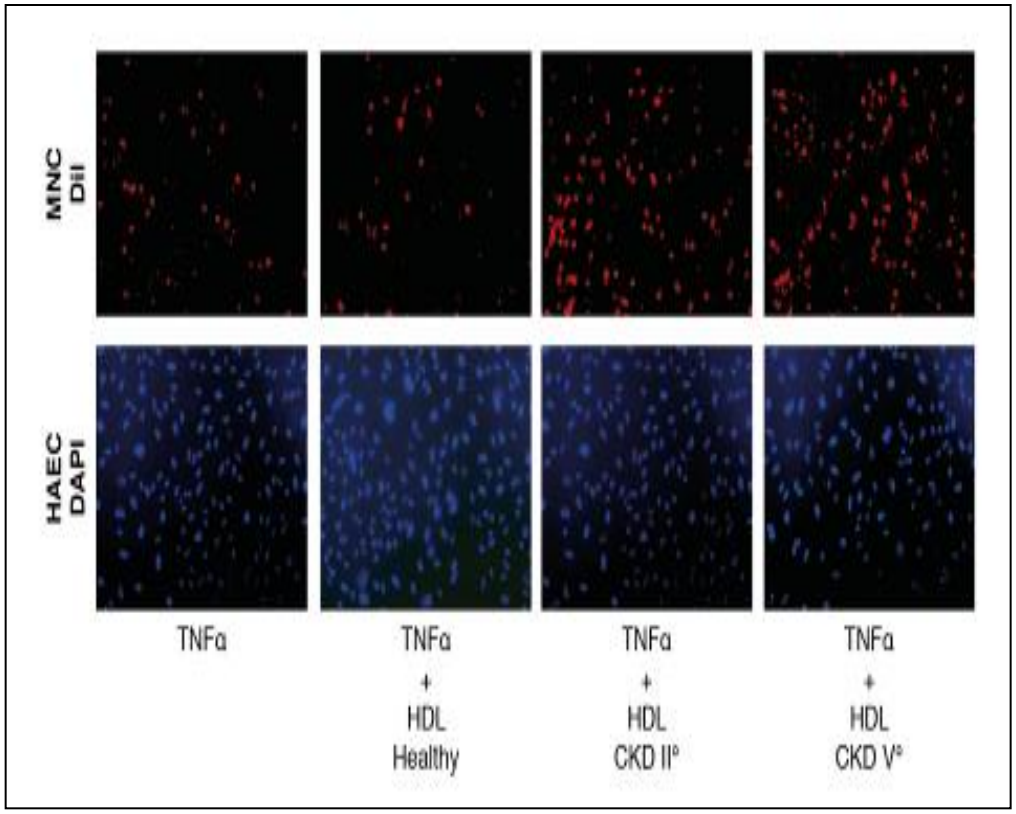
PON-1 partially inhibits MPO activity

MPO inactivates PON-1
- oxidizes PON-1 on Tyrosin-71

Huang Y, et al. & Landmesser U, Hazen S. ***J Clin Invest*** **2013**

HDL from patients with chronic kidney disease (CKD) promotes endothelial inflammatory activation:





Speer T,* Rohrer L* et al. *Immunity* 2013; 38(4):754-68.

Shroff R et al.; *J Am Soc Nephrol*. 2014 Nov;25(11):2658-68.

Dysfunctional HDL Takes Its Toll in Chronic Kidney Disease

Kathryn J. Moore[1,*] and Edward A. Fisher[1]
[1]Marc and Ruti Bell Vascular Biology and Disease Program, Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY 10029, USA
*Correspondence: kathryn.moore@nyumc.org
http://dx.doi.org/10.1016/j.immuni.2013.03.006

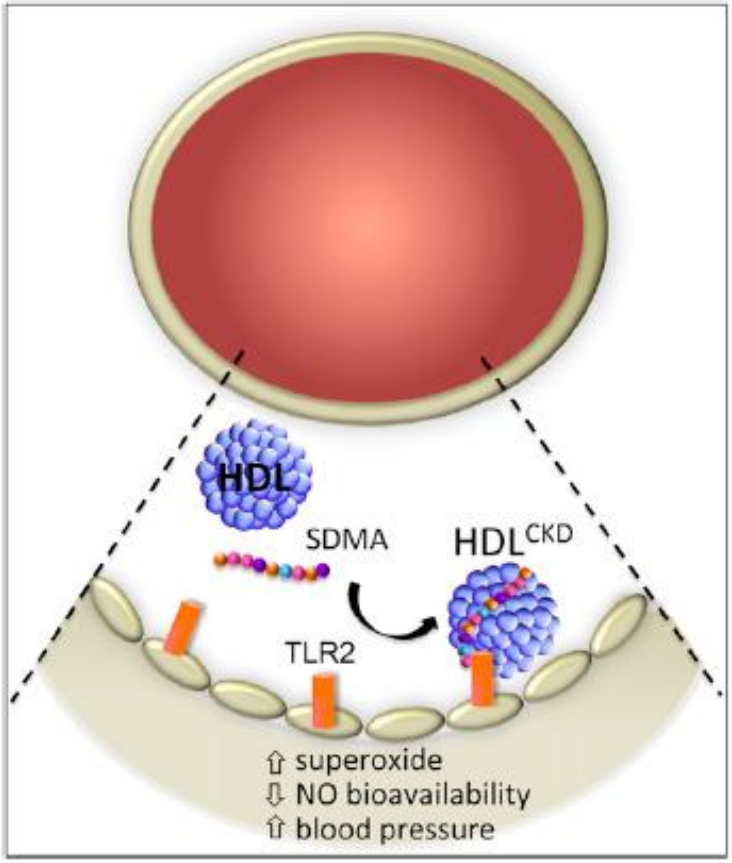
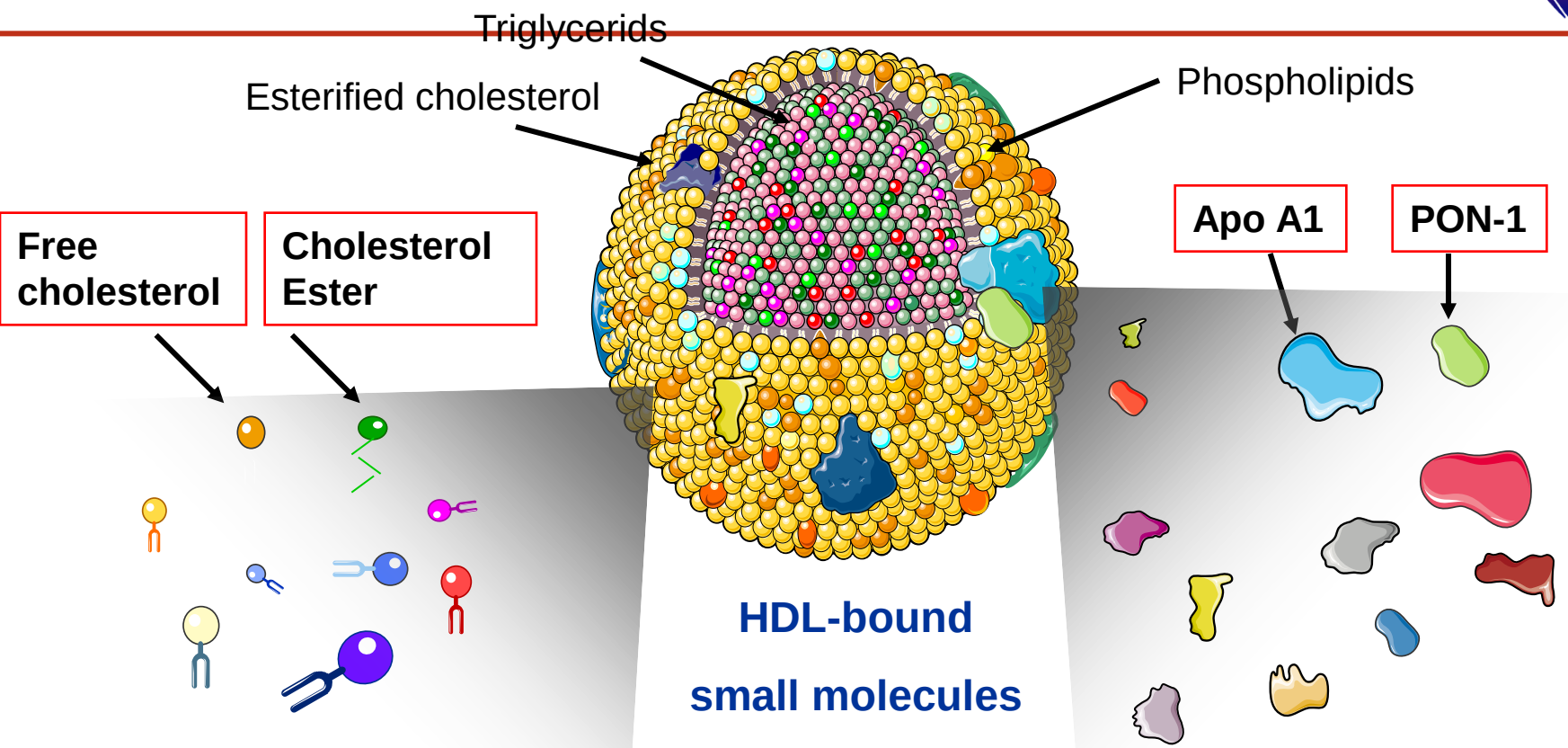


Figure 1. Elevated SDMA in Chronic Kidney Disease Generates Dysfunctional HDL

The complexity of the HDL-lipoprotein



> 1000 different lipids

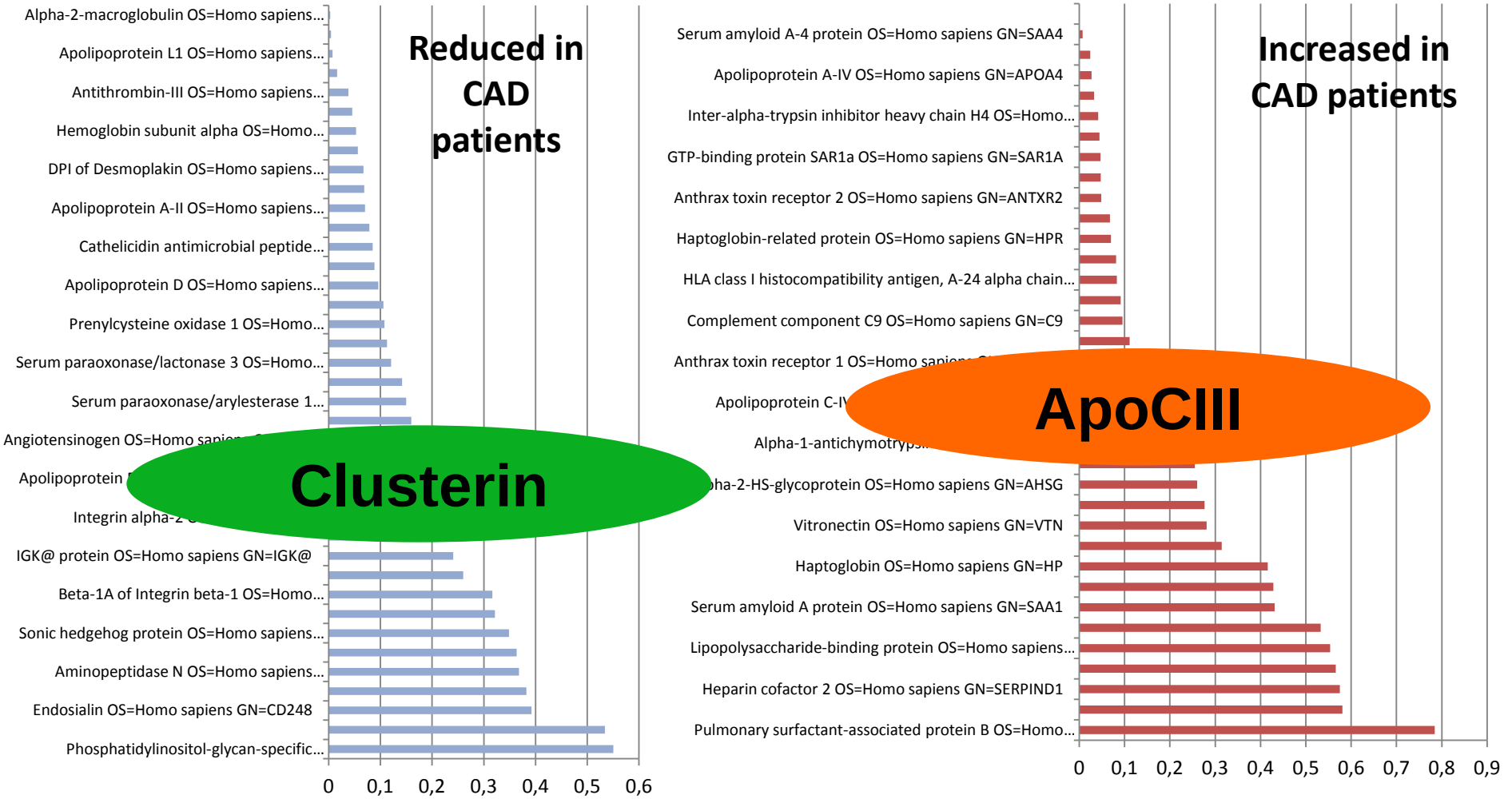
(Phospholipid species, Cholesterol Ester, Trigylcerides, …)

➢70 different proteins

(ApoA1, **PON-1**, ApoA2, ApoCIII, ApoE, **ApoH, ...)**

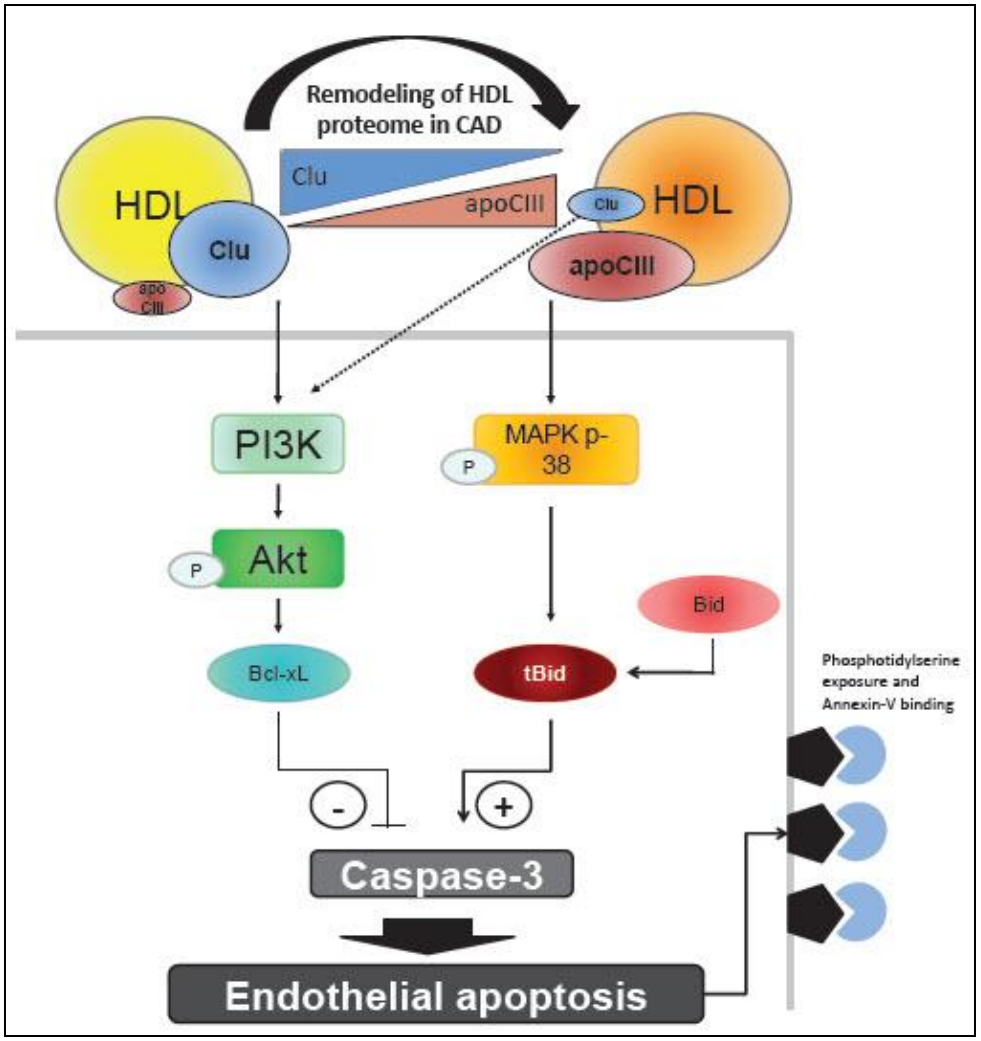
Changes in **composition** and **modification** of both, lipids and proteins of HDL in cardiovascular disease results in altered HDL „function“

HDL proteome alterations in patients with coronary disease



Riwanto M et al. & *Circulation* 2013; 127(8):891-904

Potential mechanisms leading to altered effects of HDL on endothelial apoptosis in CAD



Riwanto M et al. & *Circulation* 2013; 127(8):891-904

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

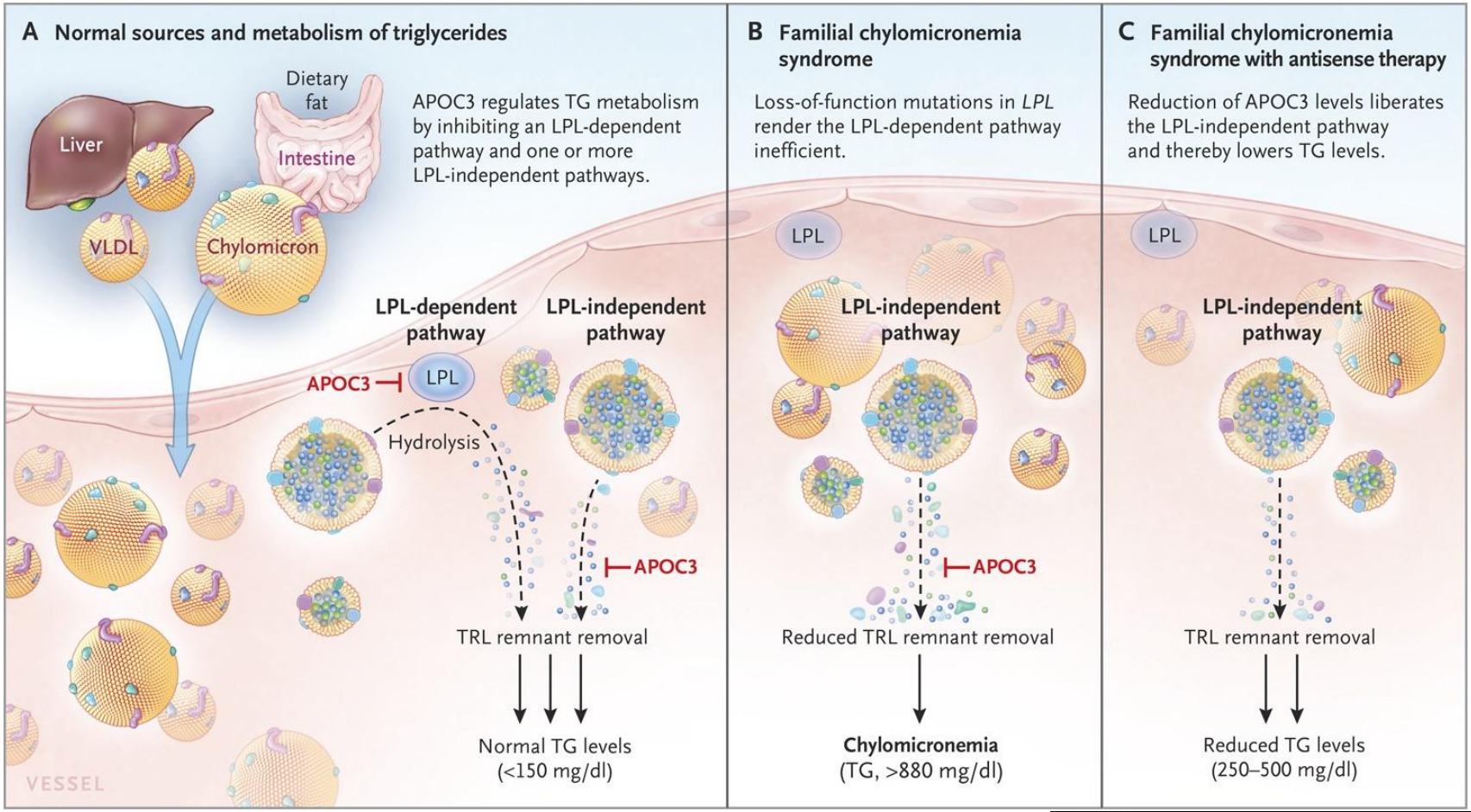
The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

- **Exome sequencing** in 3734 persons: identification of several rare coding-sequence variants of *APOC3.*
- **Carriers of an *APOC3* mutation had**
  - Triglyceride levels that were 39% lower
  - HDL cholesterol levels that were 22% higher
  - LDL cholesterol levels that were 16% lower
  - Circulating APOC3 levels that were 46% lower

Risk of coronary heart disease reduced by 40%

N Engl J Med. 2014 Jul 3;371(1):22-31.

Role of APOC3 in lipid metanbolism



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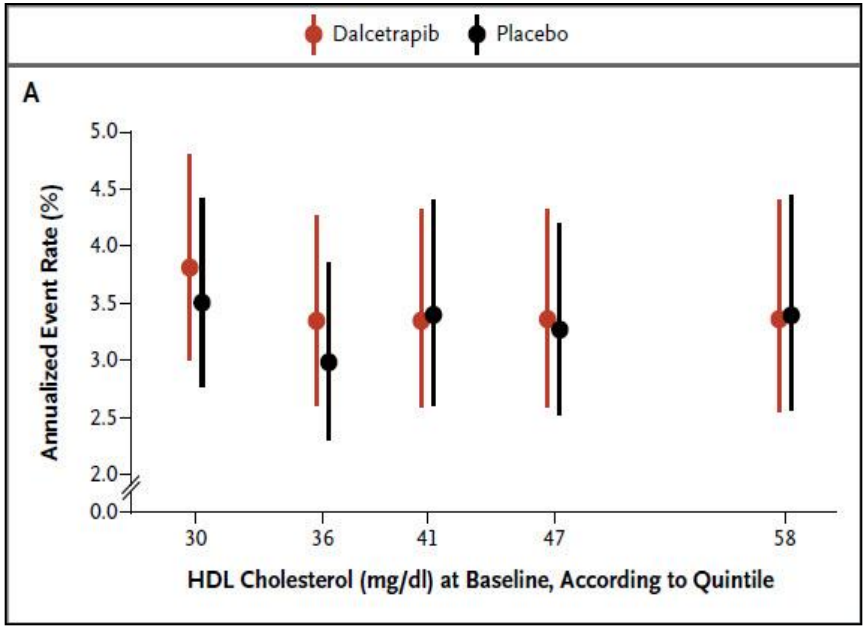
Gaudet D et al. N Engl J Med 2014;371:2200-2206

Association of baseline HDL cholesterol levels and risk of cardiovascular events in patients with a *recent acute coronary syndrome* on statin therapy ?

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2012;367:2089-99.
DOI: 10.1056/NEJMoa1206797

ORIGINAL ARTICLE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome



There was no significant association in either group between the baseline HDL cholesterol level (i.e., the level measured at randomization) and the risk of the primary end point

N Engl J Med 2012, 367(22):2089-99

ORIGINAL ARTICLE

HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events

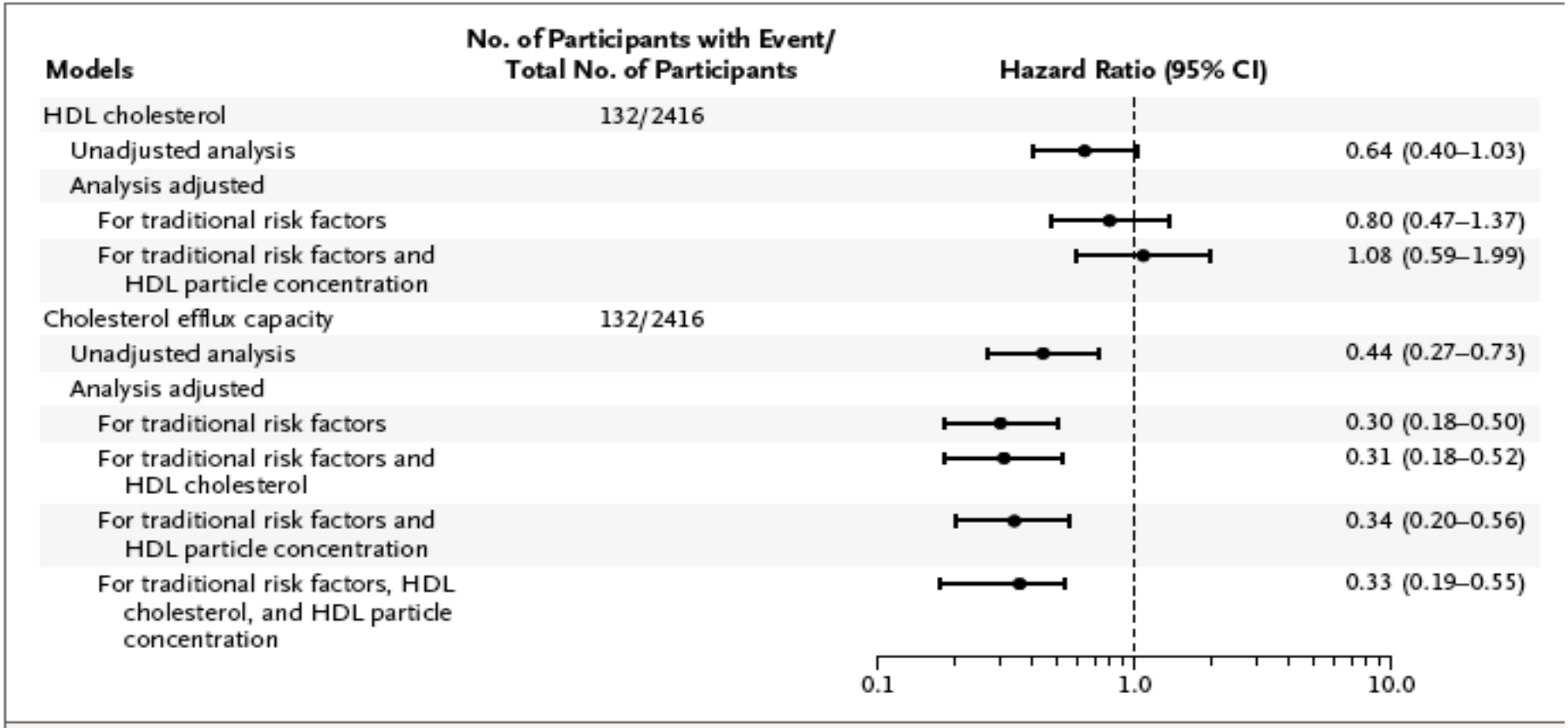


Figure 1. Atherosclerotic Cardiovascular Disease Events, According to Models Based on High-Density Lipoprotein (HDL) Cholesterol Level and Cholesterol Efflux Capacity.

N Engl J Med. 2014 Dec 18;371(25):2383-93

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

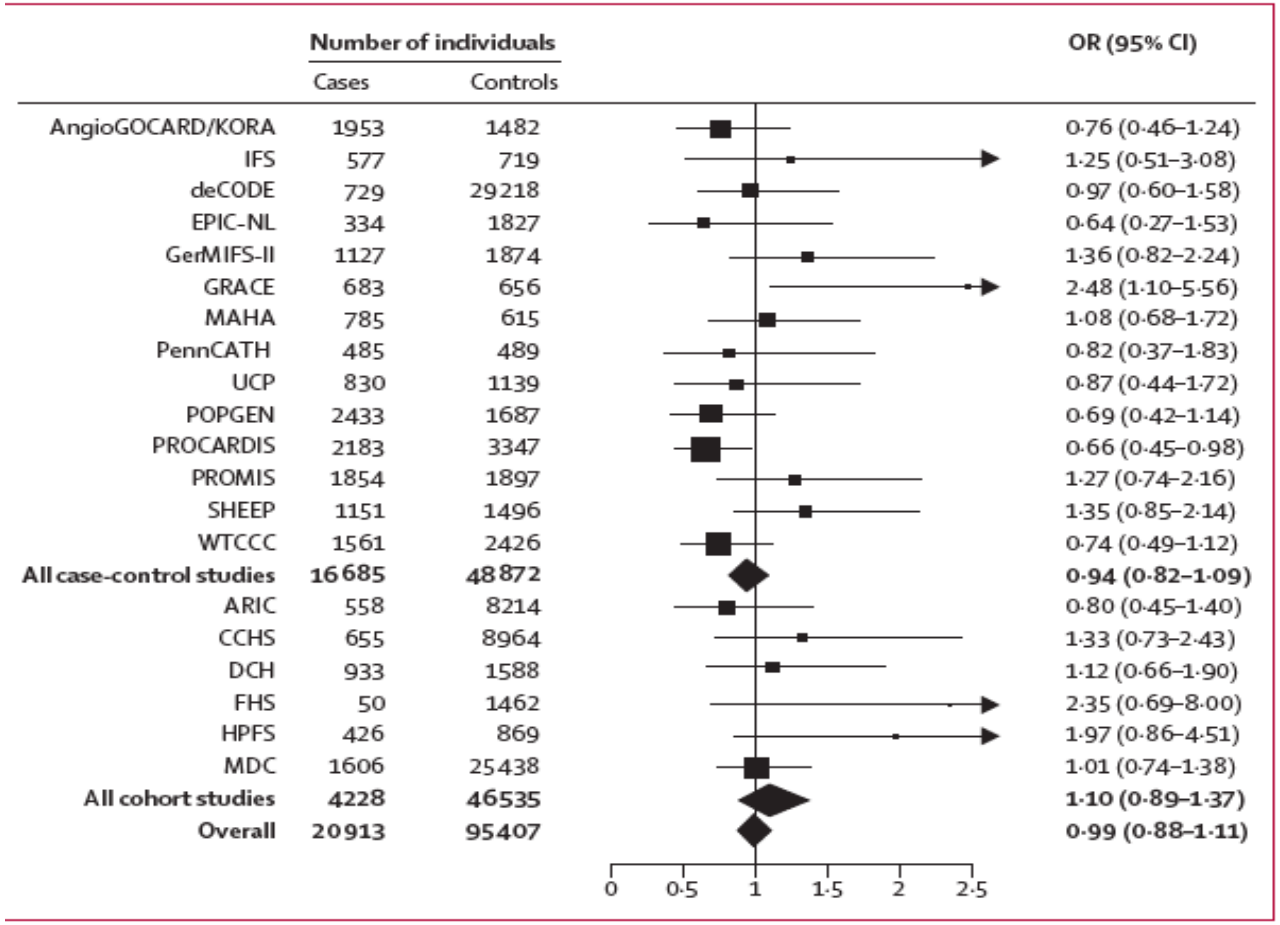


Figure 2: Association of *LIPG* Asn396Ser with myocardial infarction in 116 320 participants from 20 studies
In each study, the HDL-cholesterol-raising serine allele was modelled.

Lancet. 2012 Aug 11; 380(9841): 572–580

HDL-C – association with myocardial infarction in genetic studies ?

	Chromosome	Gene(s) of interest within or near associated interval	Major allele, minor allele (minor allele frequency)*	Modelled allele	Effect of modelled allele on plasma HDL cholesterol (mmol/L)*	Effect of modelled allele on plasma triglycerides (mmol/L)*	Effect of modelled allele on plasma LDL cholesterol (mmol/L)*	Sample size (MI cases/ MI-free controls)	For modelled allele, observed change in MI risk (%; 95% CI)	For modelled allele, p value for association with MI
rs17482753	8p21	*LPL*†	G, T (0·10)	T	0·08	−0·24	..	19 139/50 812	−12% (−16 to −7)	4×10^{-7}†
rs17321515	8q24	*TRIB1*†	A, G (0·45)	G	0·02	−0·11	−0·05	19 139/50 812	−7% (−9 to −4)	2×10^{-6}*†
rs6589566	11q23	*APOA1-APOC3-APOA4-APOA5*†	A, G (0·07)	A	0·05	−0·27	−0·09	18 310/49 897	−10% (−15 to −5)	8×10^{-5}†
rs4846914	1q42	*GALNT2*†	A, G (0·40)	A	0·02	−0·03	..	19 139/50 812	−3% (−6 to −1)	0·02†
rs2967605	19p13	*ANGPTL4*†	C, T (0·16)	C	0·05	−0·07	..	13 595/16 423	−5% (−10 to −1)	0·03†
rs3764261	16q13	*CETP*†	C, A (0·32)	A	0·10	..	−0·03	16 503/46 576	−4% (−7 to 0)	0·04†
rs61755018 (Asn396Ser)	18q21	*LIPG*	A, G (0·015)	G	0·14‡	..	..	17 165/49 077	−6% (−18 to 9)	0·41
rs17145738	7q11	*MLXIPL*	C, T (0·11)	T	0·03	−0·15	..	19 139/50 812	−1% (−4 to 3)	0·61
rs3890182	9q31	*ABCA1*	G, A (0·14)	G	0·03	..	0·05	19 139/50 812	−1% (−5 to 4)	0·76
rs2338104	12q24	*MMAB, MVK*	G, C (0·46)	G	0·03	..	..	19 139/50 812	0% (−3 to 3)	0·85
rs471364	9p22	*TTC39B*	T, C (0·12)	T	0·03	..	..	15 693/47 098	0% (−5 to 5)	0·97
rs2271293	16q22	*LCAT*	G, A (0·11)	A	0·03	..	..	19 139/50 812	4% (−1 to 8)	0·10
rs174547	11q12	*FADS1-FADS2-FADS3*	T, C (0·33)	T	0·03	−0·06	..	19 139/50 812	3% (−1 to 6)	0·11
rs1800588	15q22	*LIPC*	C, T (0·22)	T	0·05	0·07	..	17 917/49 514	4% (0 to 7)	0·04
rs16988929	20q13	*HNF4A*	C, T (0·01)	T	0·01	..	..	17 041/20 137	31% (12 to 54)	9×10^{-4}

*Data presented from a meta-analysis of seven cohorts (n up to 19 840) as presented in reference 16; the effect of each SNP on a lipid trait was modelled if the association of the SNP with a plasma lipid trait exceeded nominal significance (p<0·05). †Loci and SNPs that exceeded nominal significance (p<0·05) for association of modelled allele with MI; all modelled alleles increased HDL cholesterol. ‡Effect size presented is from the Atherosclerosis Risk in Communities Study.

Table 2: **Association of myocardial infarction (MI) with single nucleotide polymorphisms (SNPs) previously found to relate to plasma HDL cholesterol**

Voight BF et al *Lancet* 2012; 380: 572–80

HDL-cholesterol and coronary disease:

1. HDL-cholesterol – the hypothesis

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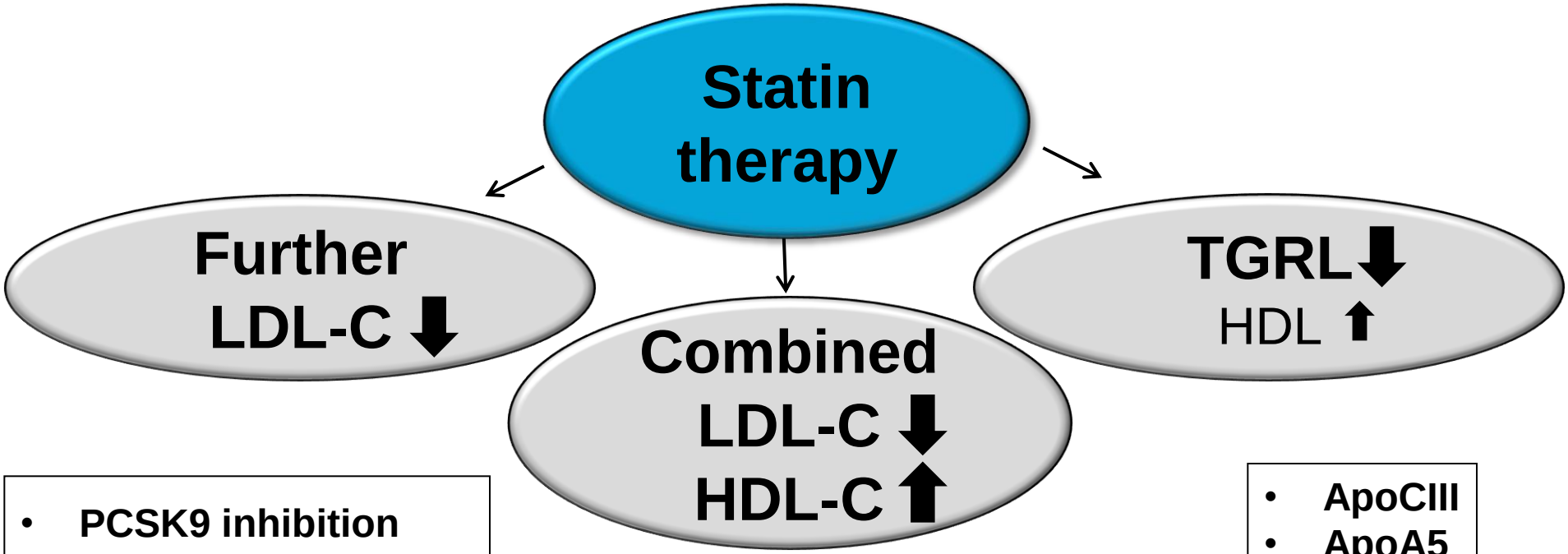
3. **Implications for therapeutic strategies**

Lipid-targeted Therapies – What should be added to statins in patients with high vascular risk ?



- **PCSK9 inhibition** (Monoclonal Ab*)
- ApoB-100 Antisense oligonucleotides

- **CETP inhibition** (Evacetrapib*, Anacetrapib*)

- **ApoCIII**
- **ApoA5**
- **LPL**

**Clinical outcome trials ongoing*

MODIFIED FROM Landmesser U. Eur Heart J 2013

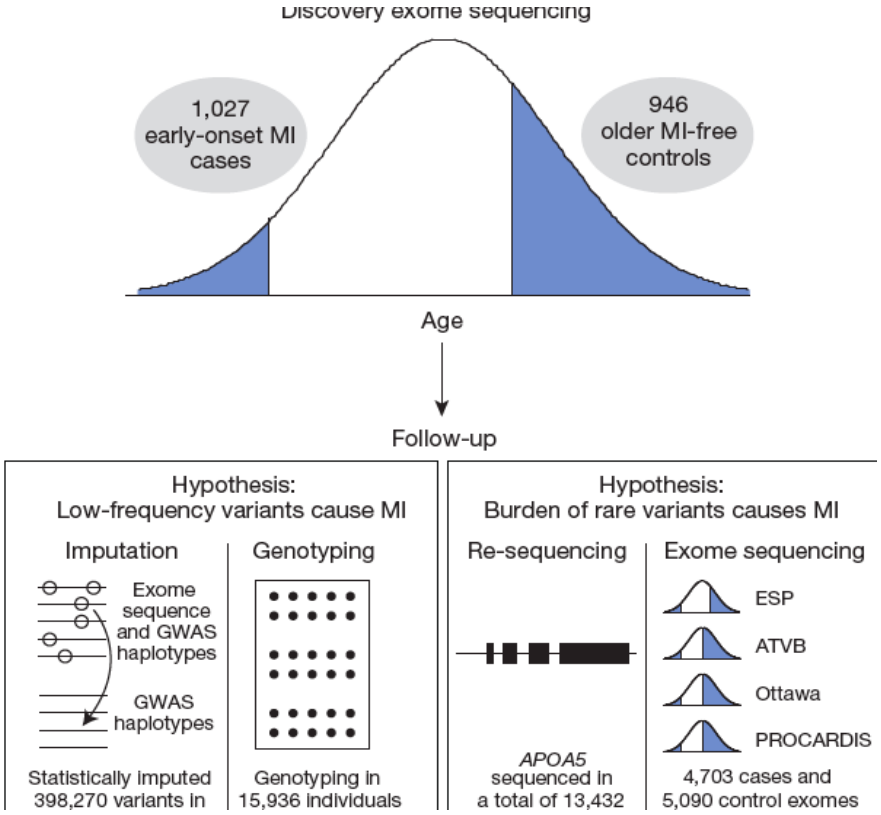
Exome Sequencing Project coordinated by the National Heart, Blood and Lung Institute

LETTER

doi:10.1038/nature13917

Exome sequencing identifies rare *LDLR* and *APOA5* alleles conferring risk for myocardial infarction

A list of authors and their affiliations appears at the end of the paper

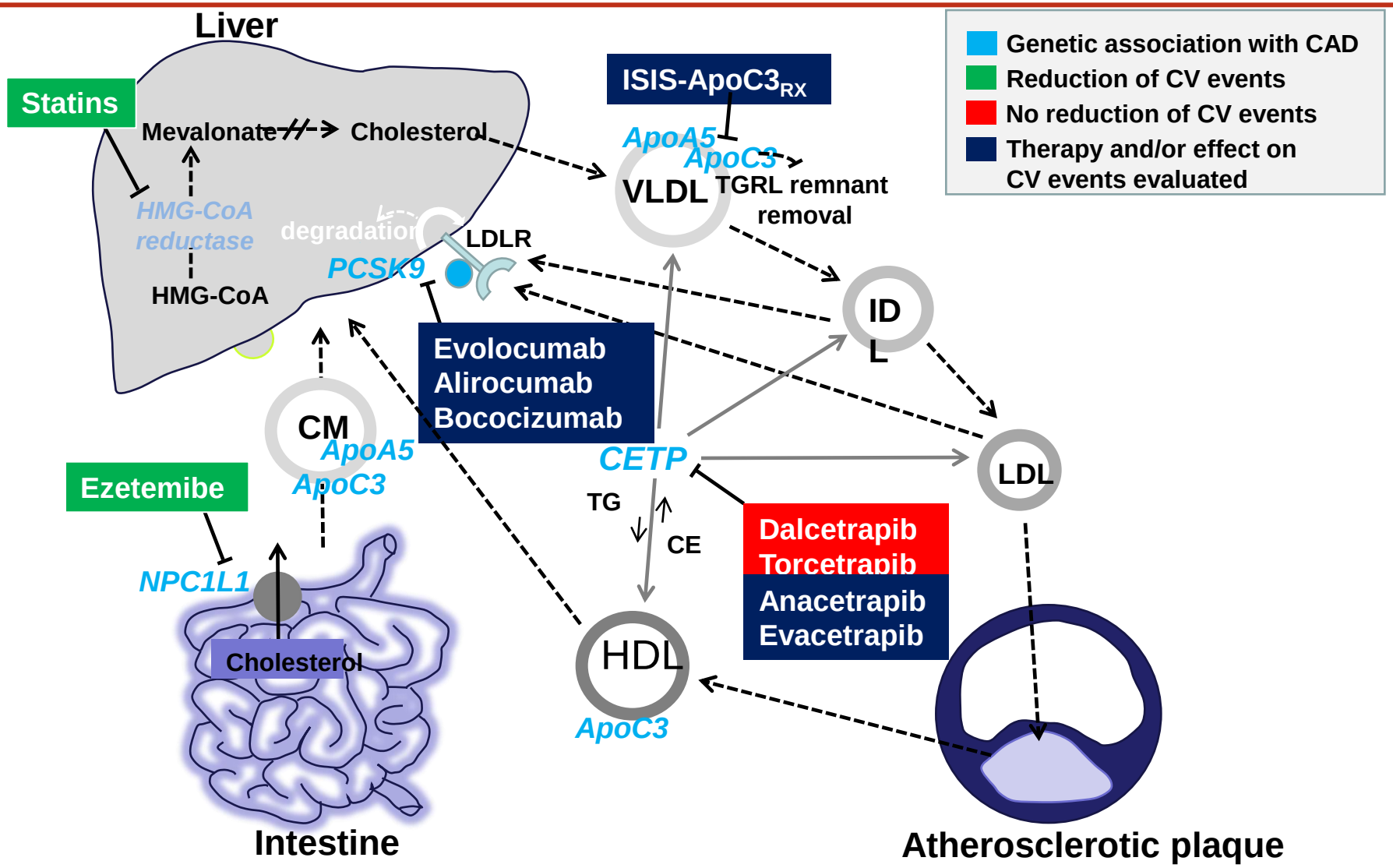


At apolipoprotein A-V **(APOA5)**, **carriers** of rare non-synonymous mutations were **at 2.2-fold increased risk for MI**.

Recent evidence has connected MI risk with coding-sequence mutations at **two genes functionally related to APOA5, namely lipoprotein lipase and apolipoprotein C-III**.

Nature. 2015 Feb 5;518(7537):102-6.

Lipid-targeted Therapies – genetic association with CAD and clinical outcome studies



Hewing, Landmesser U. In press

Summary and conclusion

1. The HDL-cholesterol hypothesis was derived largely from epidemiological studies in primary prevention and experimental studies testing vascular effects of HDL from healthy subjects.

2. The relation between HDL-C and cardiovascular events is at least attenuated in CAD. Vascular effects of HDL are heterogenous and are altered in patients with coronary disease and diabetes (i.e. HDL dysfunction).

3. HDL cholesterol is therefore not a reliable surrogate marker for therapeutic interventions. Genetic studies suggest that TRLs are on the causal pathway of CAD (LPL, ApoC3, ApoA5)

Thank you