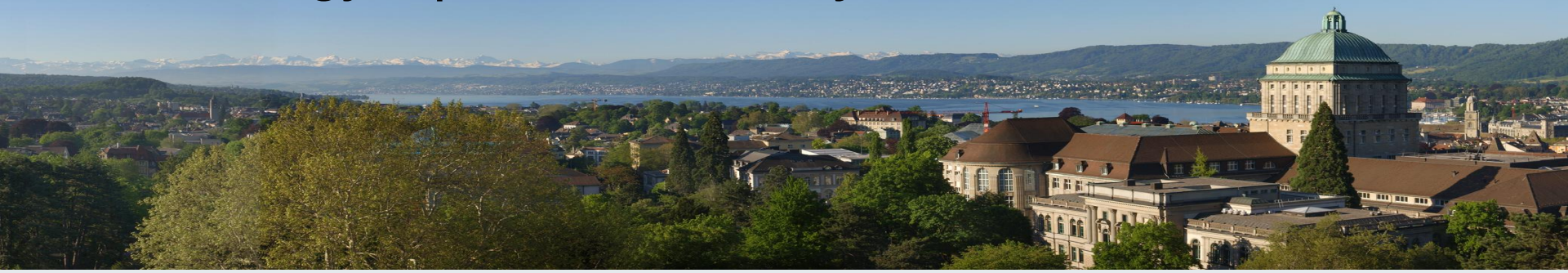
Cardiology Update, February 10 – 15 2013, Davos



Lipids: Current practice and future targets:
HDL dysfunction and CETP inhibition?

Ulf Landmesser, MD
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University Hospital Zürich, Switzerland

UniversityHospital Zurich

University of Zurich[UZH]

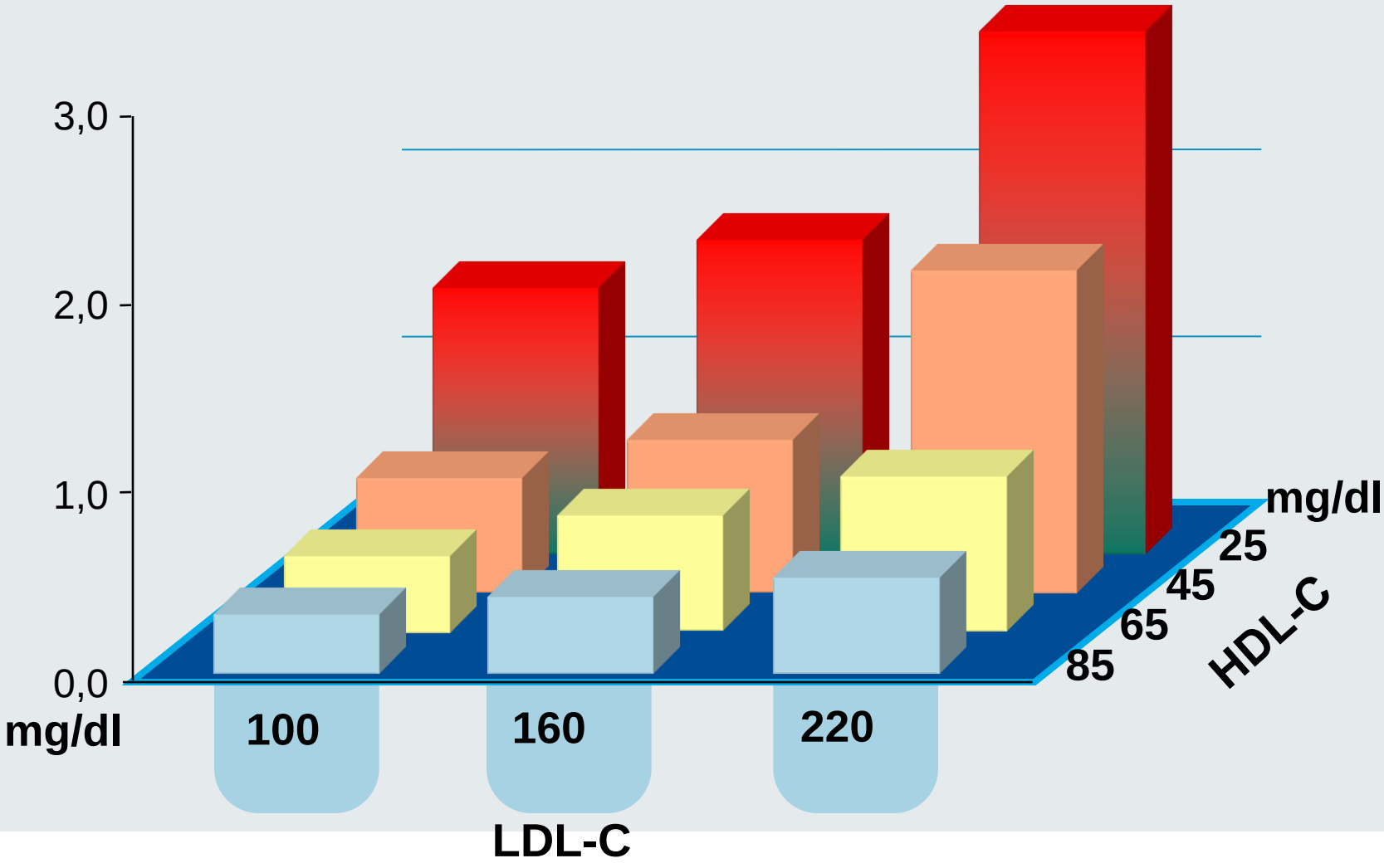
HDL dysfunction and CETP inhibition ?

1. The HDL cholesterol hypothesis

2. HDL dysfunction

3. Novel therapeutic interventions - CETP inhibition ?

LDL and HDL-Cholesterol and risk of coronary disease: *Framingham Heart Study*



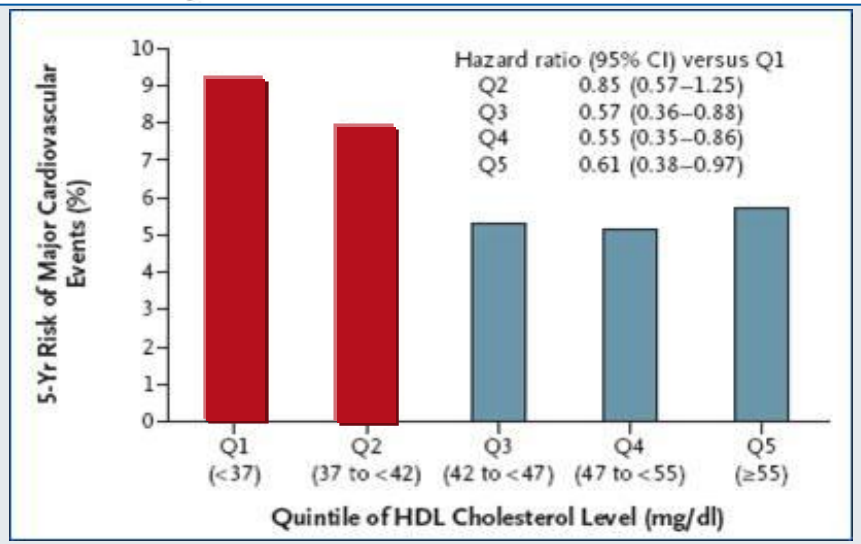
Gordon T et al. Am J Med 1977;62:707-714

Low HDL as predictor of cardiovascular events in patients with *stable CAD* and low LDL-C levels on statin therapy ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events



"*HDL cholesterol levels were predictive of major cardiovascular events in patients treated with statins*.
This relationship was also observed among *patients with LDL cholesterol levels below 70 mg per deciliter*."

N Engl J Med 2007; 357(13):1301-10

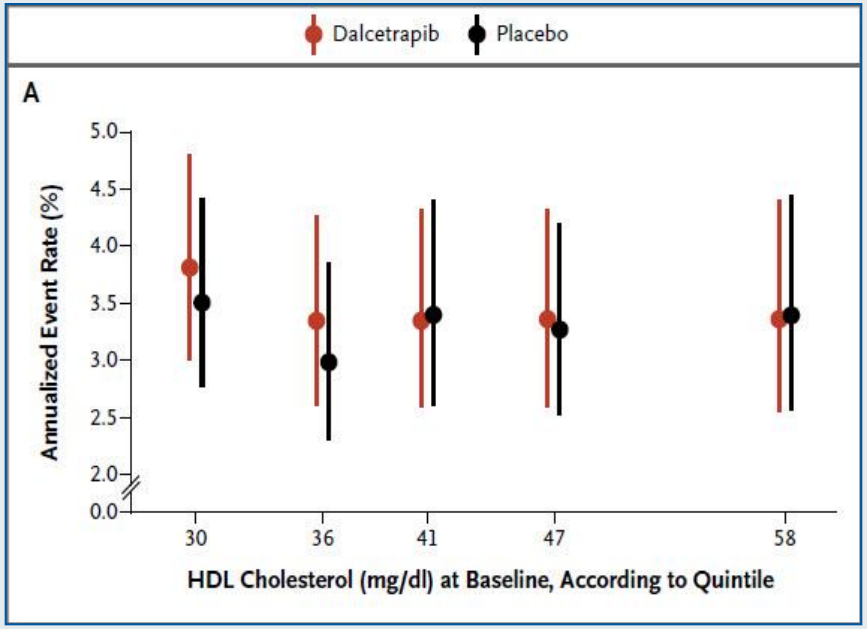
Association of baseline HDL cholesterol levels and risk of cardiovascular events in patients with a *recent acute coronary syndrome* on statin therapy ?

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



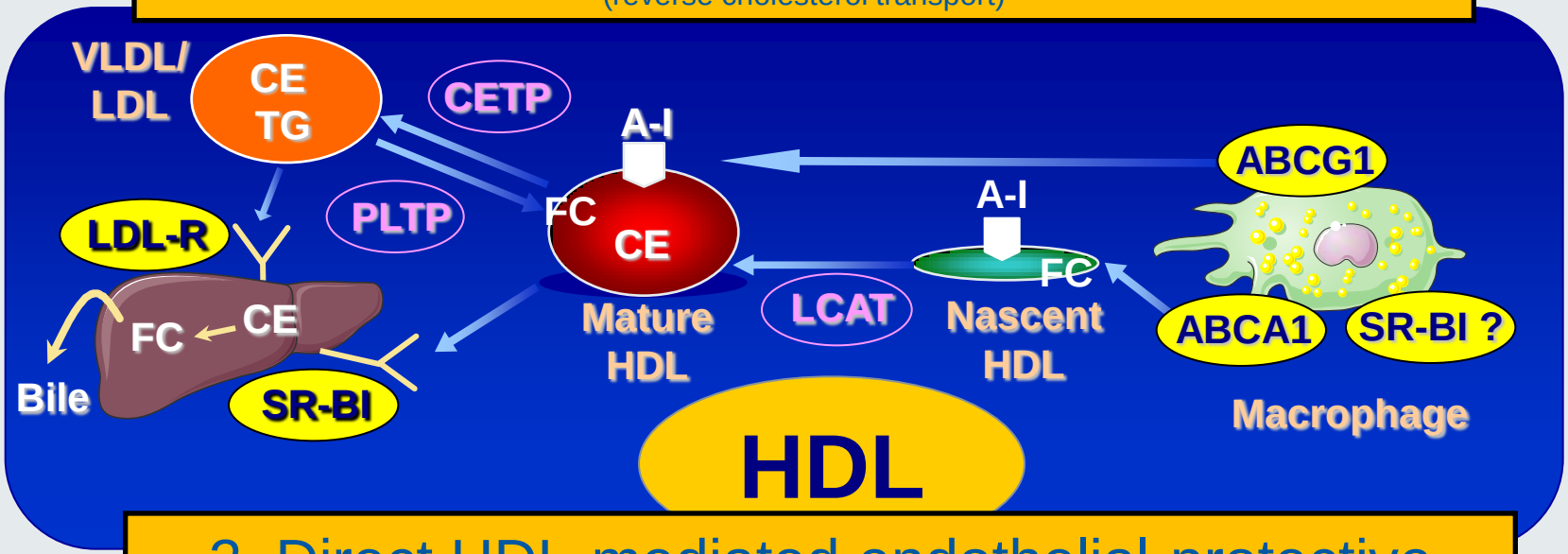
There was no significant association in either group between the baseline HDL cholesterol level (i.e., the level measured at randomization) and the risk of the primary end point

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

HDL: proposed anti-atherogenic effects

1. HDL-mediated promotion of RCT

(reverse cholesterol transport)

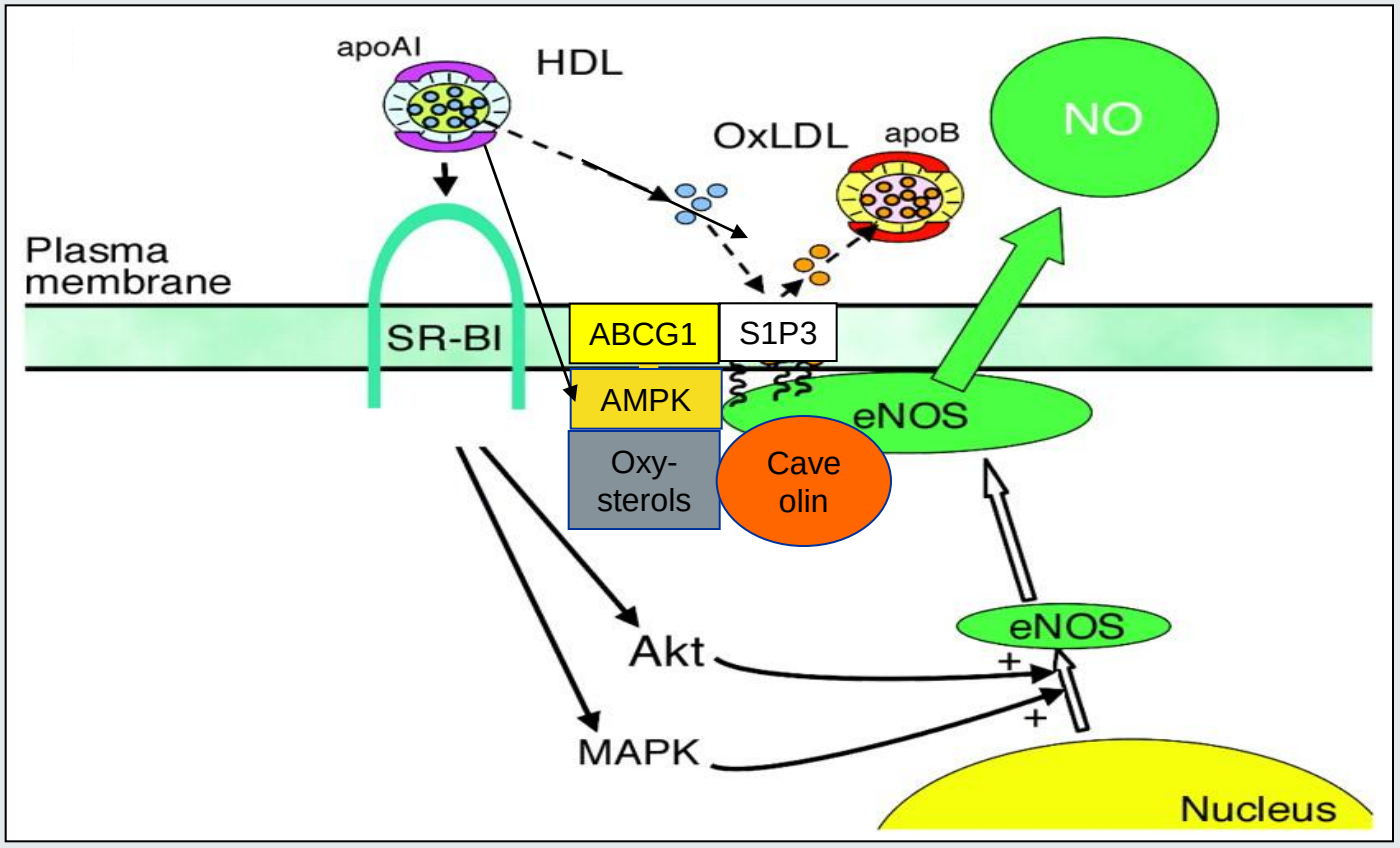


2. Direct HDL-mediated endothelial-protective potential anti-atherogenic effects

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

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

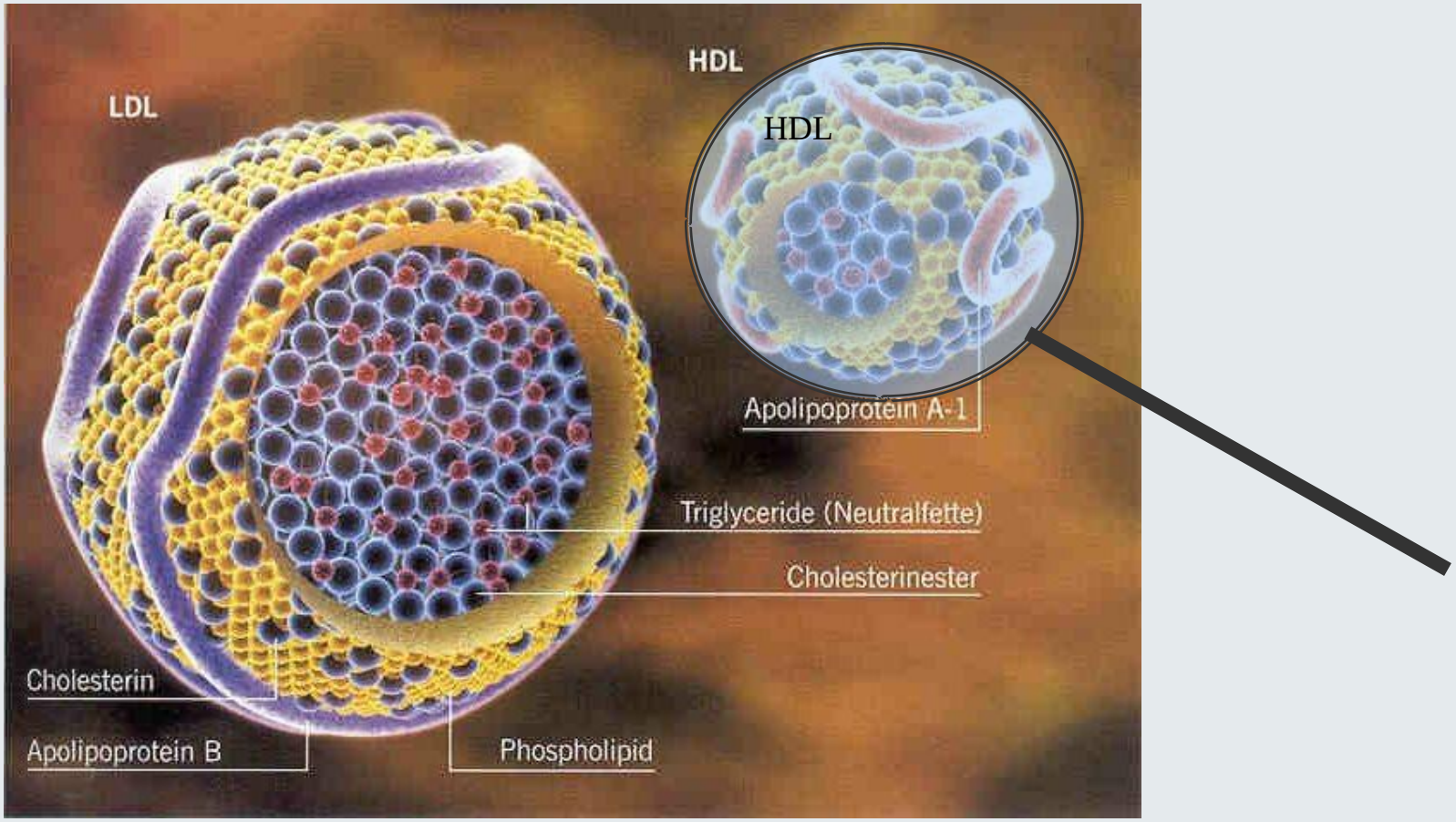
Mechanisms of vasoprotective effects of HDL: Endothelial cell nitric oxide (NO) production



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 - a therapeutic target in cardiovascular prevention ?



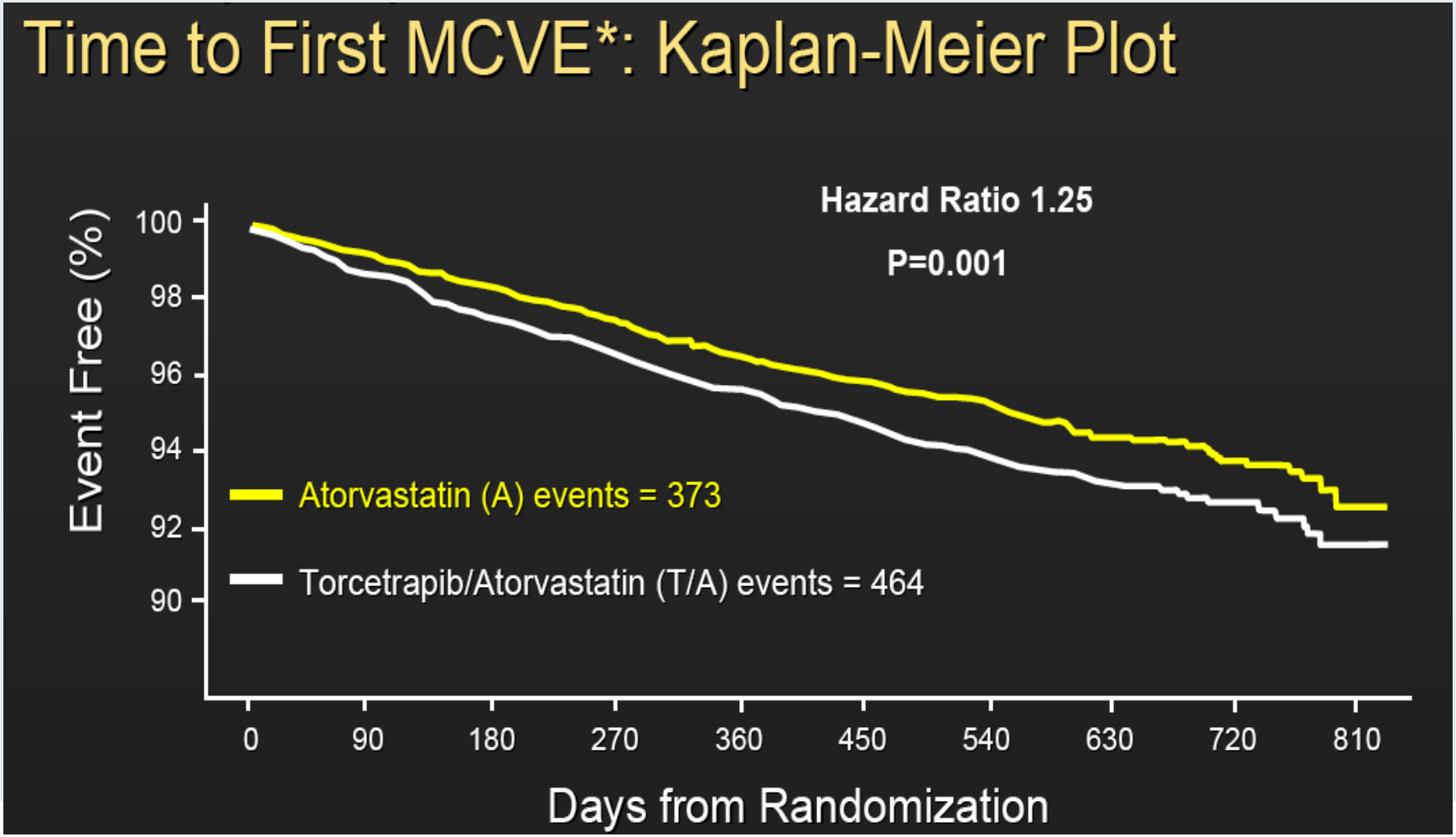
Should we raise the “good“ cholesterol ?

CETP-Inhibition with Torcetrapib: lipid changes

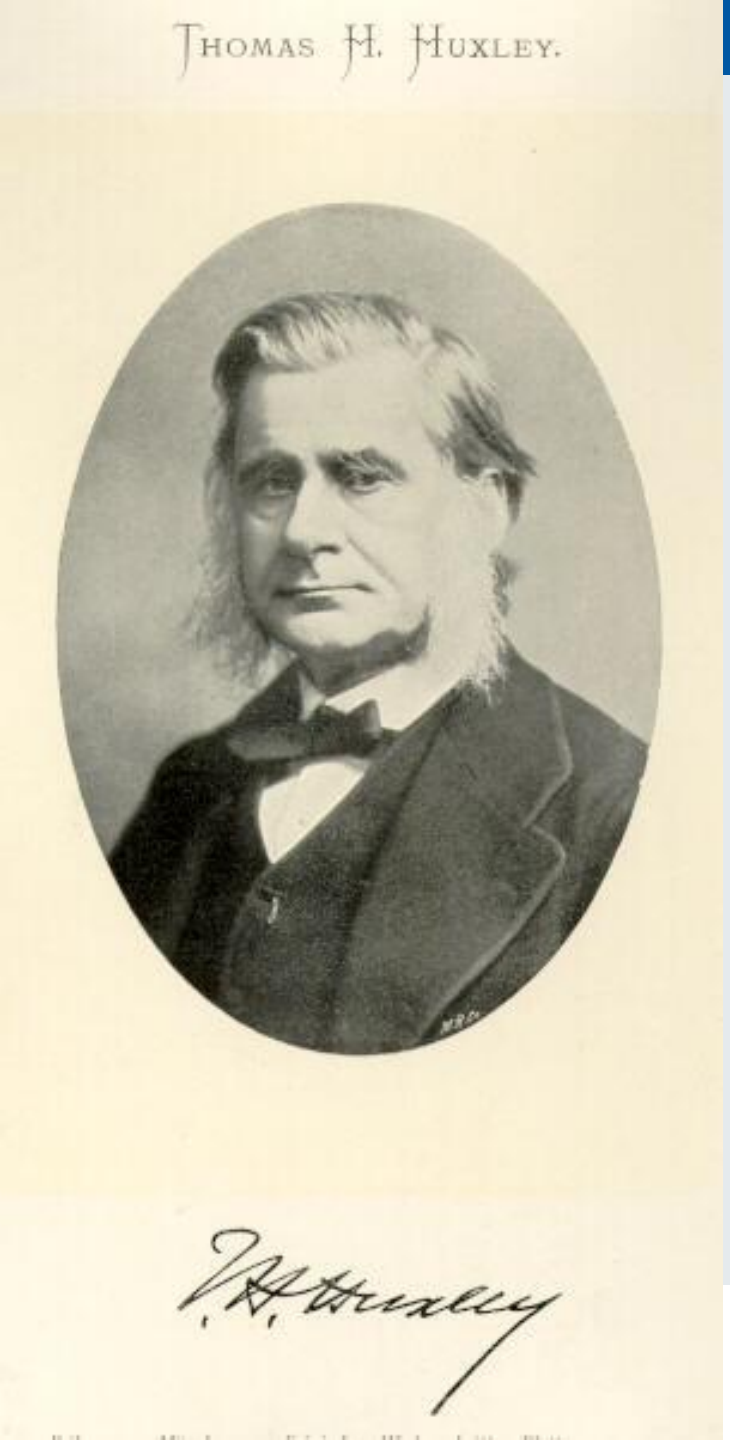
	Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Lipids (percent change) — %			
Cholesterol			
Total	+2.2±14.5	+7.0±17.7	<0.001
High-density lipoprotein	+1.8±14.0	+72.1±34.7	<0.001
Low-density lipoprotein	+3.0±23.7	−24.9±28.5	<0.001
Triglycerides			
Median	+1	−9	<0.001
Interquartile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

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

CETP-Inhibitor - Torcetrapib - Clinical Outcome Study: ILLUMINATE



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



The deepest sin against the human mind is to believe things without evidence.

Thomas H. Huxley

(1825 - 1895)

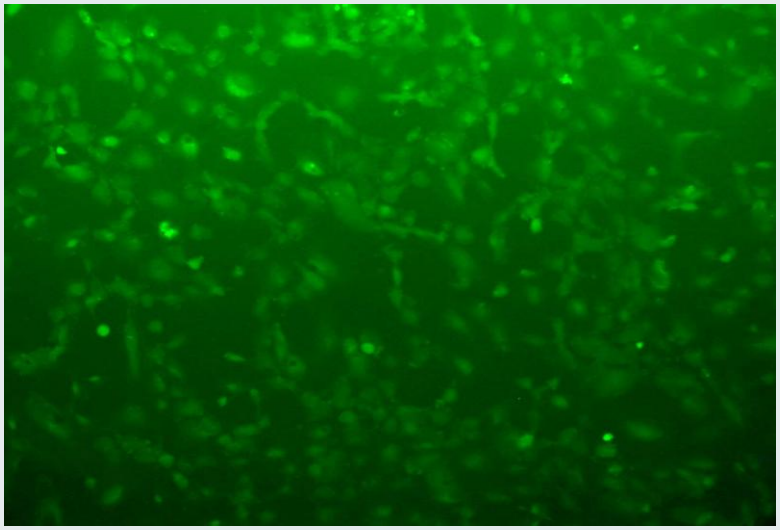
HDL dysfunction and CETP inhibition?

1. The HDL cholesterol hypothesis

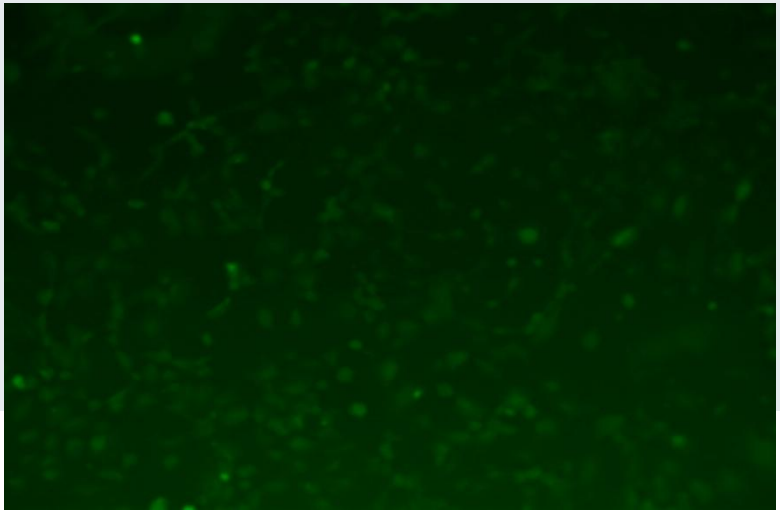
2. HDL dysfunction

3. Novel therapeutic interventions - CETP inhibition ?

Effect of HDL on endothelial cell nitric oxide production in coronary disease ?



HDL from Healthy subject



HDL from CAD patient

30 minutes

Vascular effects of HDL in patients with stable coronary disease or acute coronary syndrome as compared to healthy subjects ?

Study design:
Endothelial effects of HDL - endothelial bioassays

Patients with acute coronary syndrome (n=25)
Patients with stable coronary disease (n=25)
Healthy control subjects (n=25)

Isolation of $HDL_{2/3}$
(by sequential ultracentrifugation)

Vascular effects

Endothelial Function
(Endothelial cell NO production and vasoreactivity)

ESR spectroscopy
Organ chamber

Anti-thrombotic effects

Tissue factor Arterial thrombosis

Anti-oxidant effects
(Endothelial cell superoxide production)

Anti-inflammatory effects
(Endothelial cell inflammatory activation)

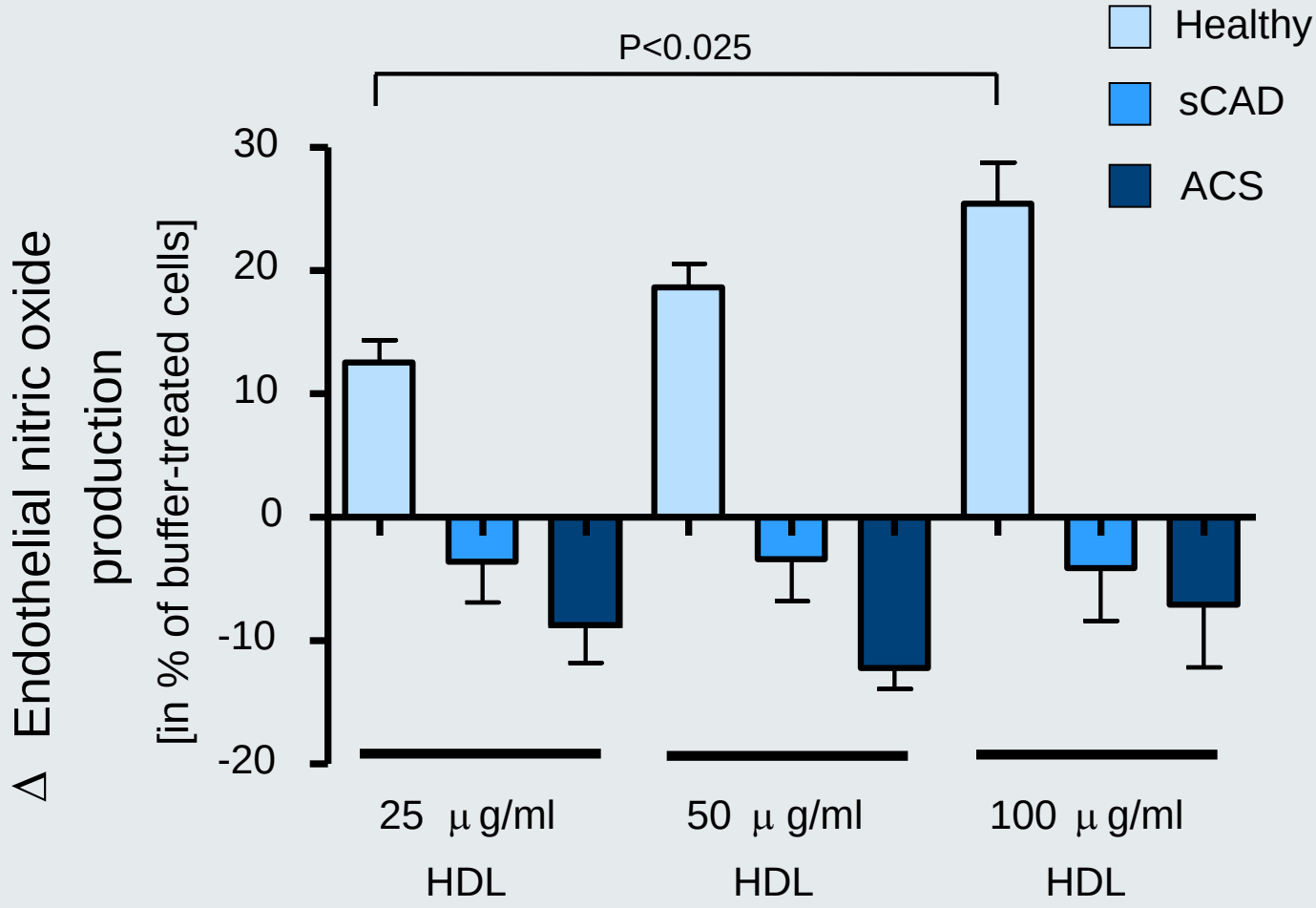
Effects on Re-Endothelialization

ESR spectroscopy

Monocyte adhesion
VCAM-1 expression

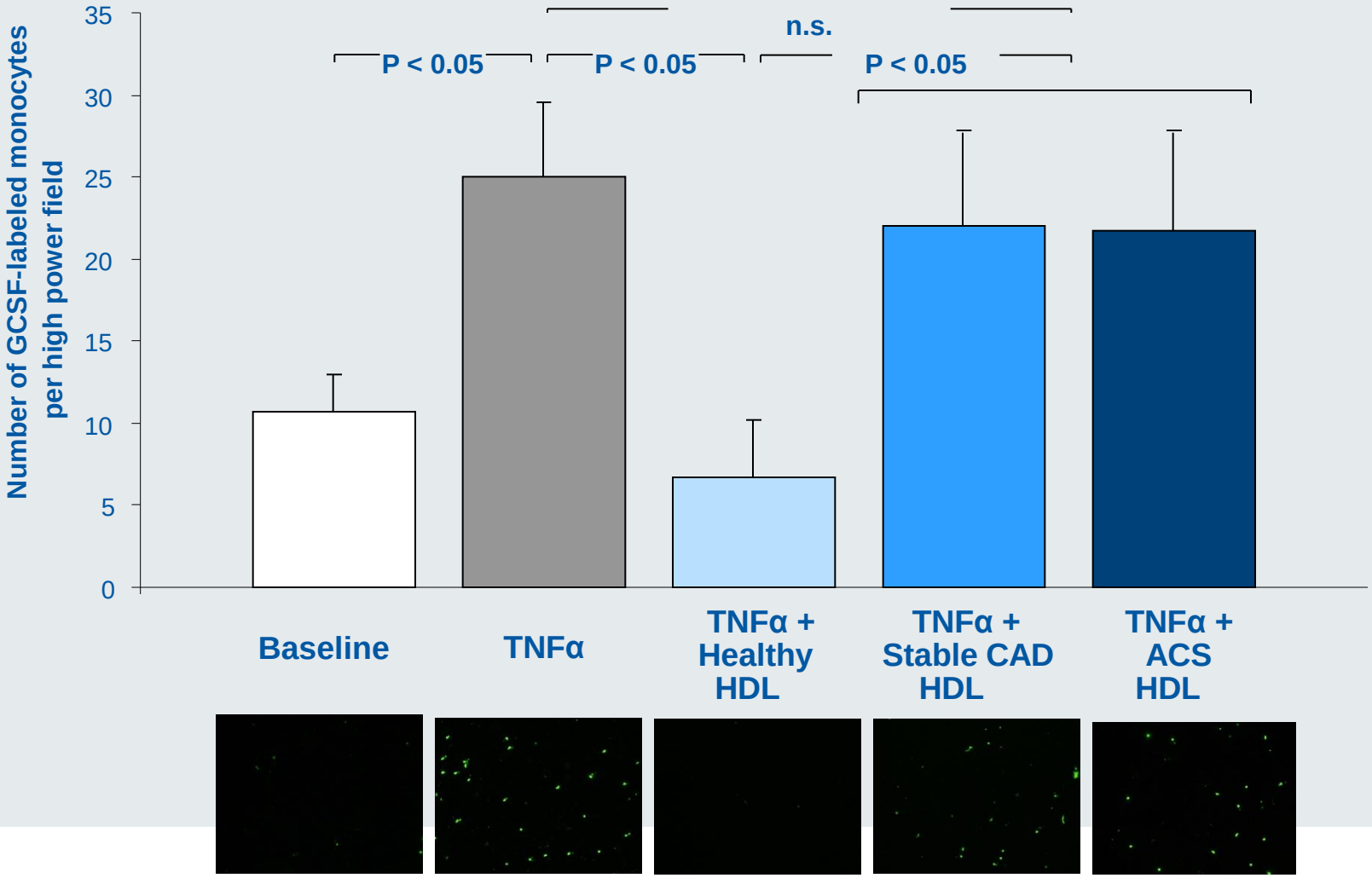
Carotid artery injury model in nude mice

HDL –effects on endothelial cell nitric oxide production in patients with CAD



Besler C et al. & Lüscher T, Landmesser U. *J Clin Invest* 2011;121(7):2693-708

Effects of HDL on vascular inflammation: *Monocyte adhesion on TNFα-stimulated endothelial cells*

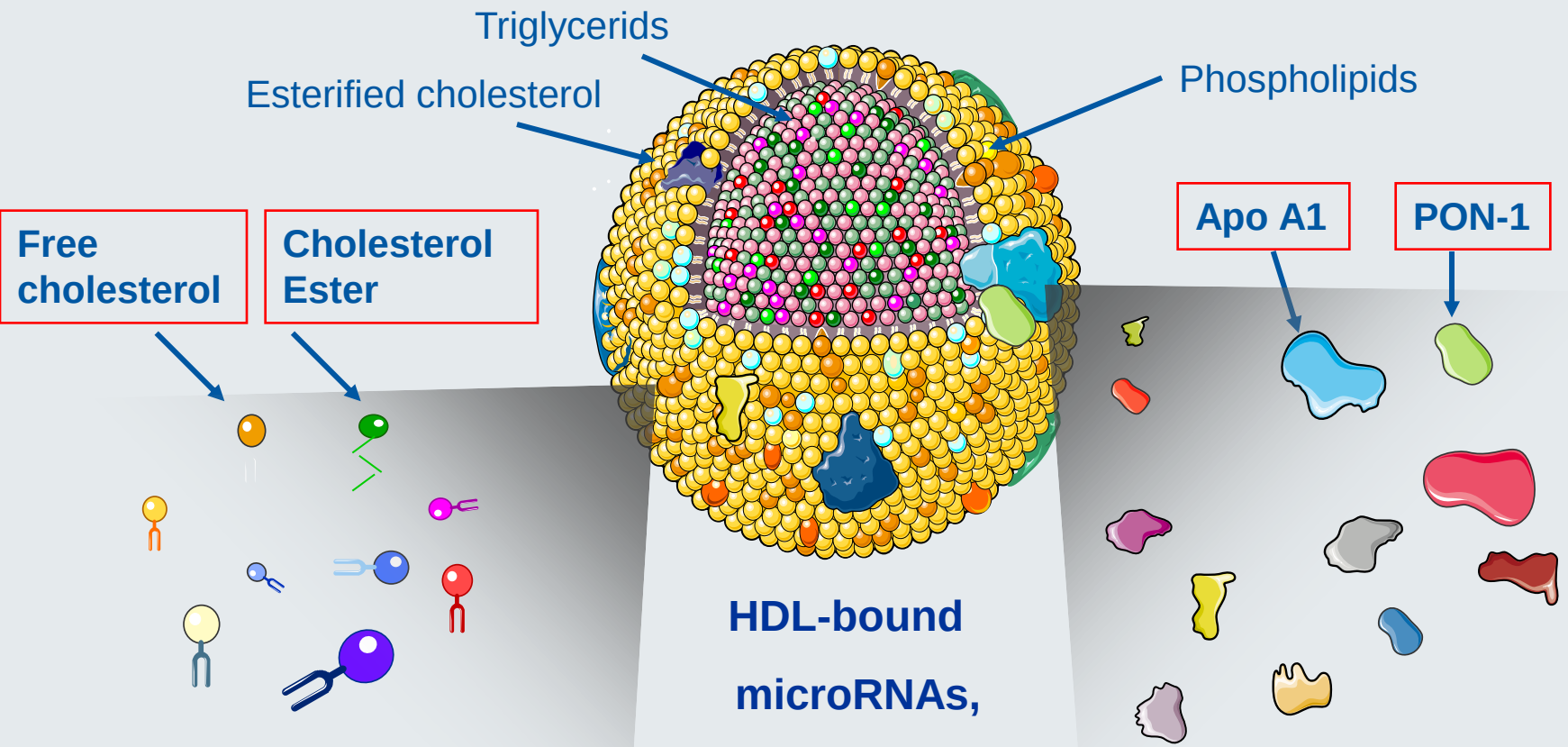


Besler C et al. & Lüscher T, Landmesser U. *J Clin Invest* 2011;121(7):2693-708

HDL function
(vascular effects)

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

The complexity of the HDL-lipoprotein



> 1000 different lipids

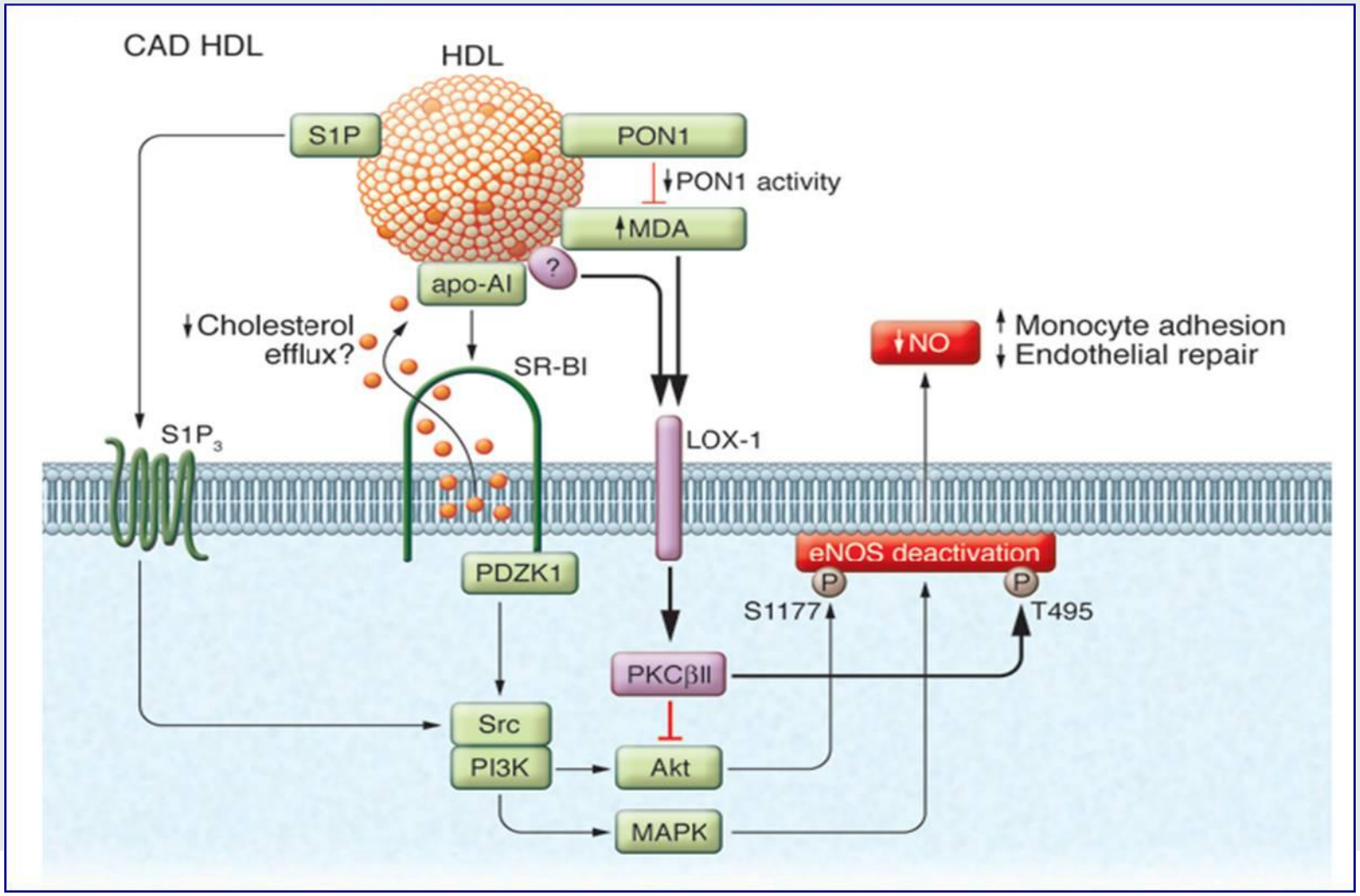
(Phospholipid species, Cholesterol Ester, Trigylcerides, …)

➢70 different proteins

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

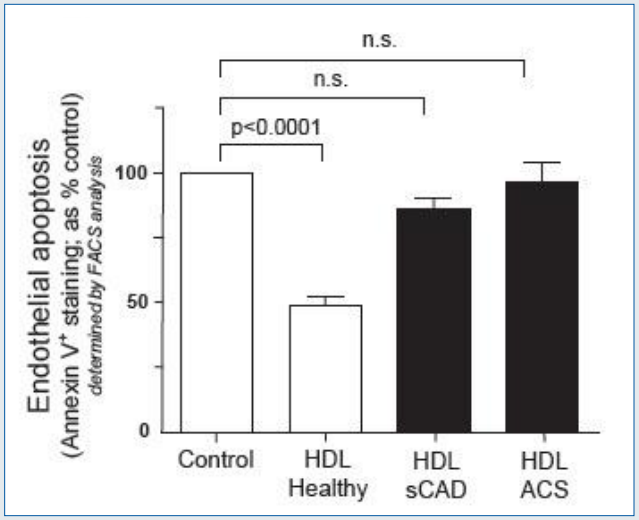
Changes in **composition** and **modification** of both, lipids and proteins of HDL in cardiovascular disease results in altered HDL „function“

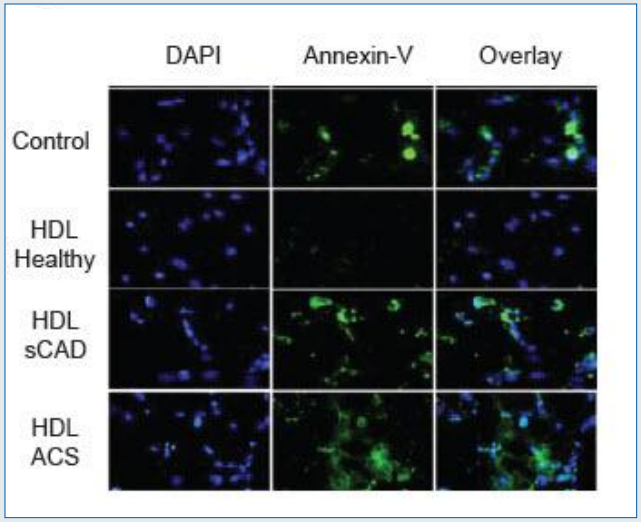
Mechanisms leading to altered effects of HDL on endothelial nitric oxide availability in CAD

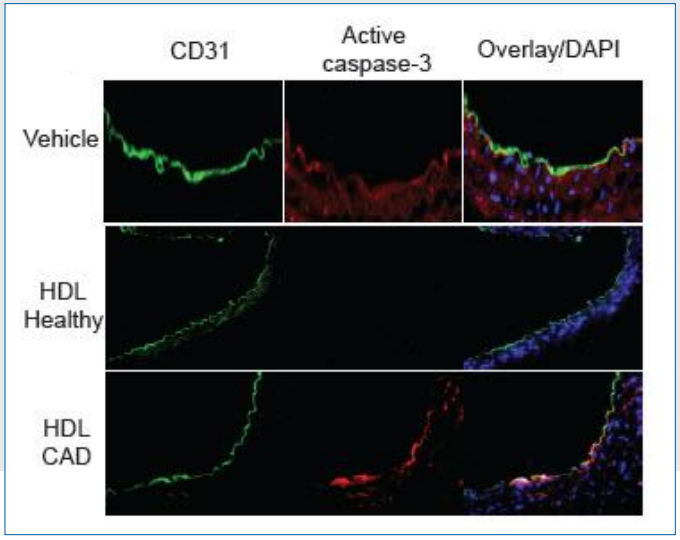


Mineo C & Shaul PW. *J Clin Invest* 2011

Effects of $HDL_{Healthy}$, HDL_{sCAD} or HDL_{ACS} on endothelial apoptosis *in vitro* and *in vivo*

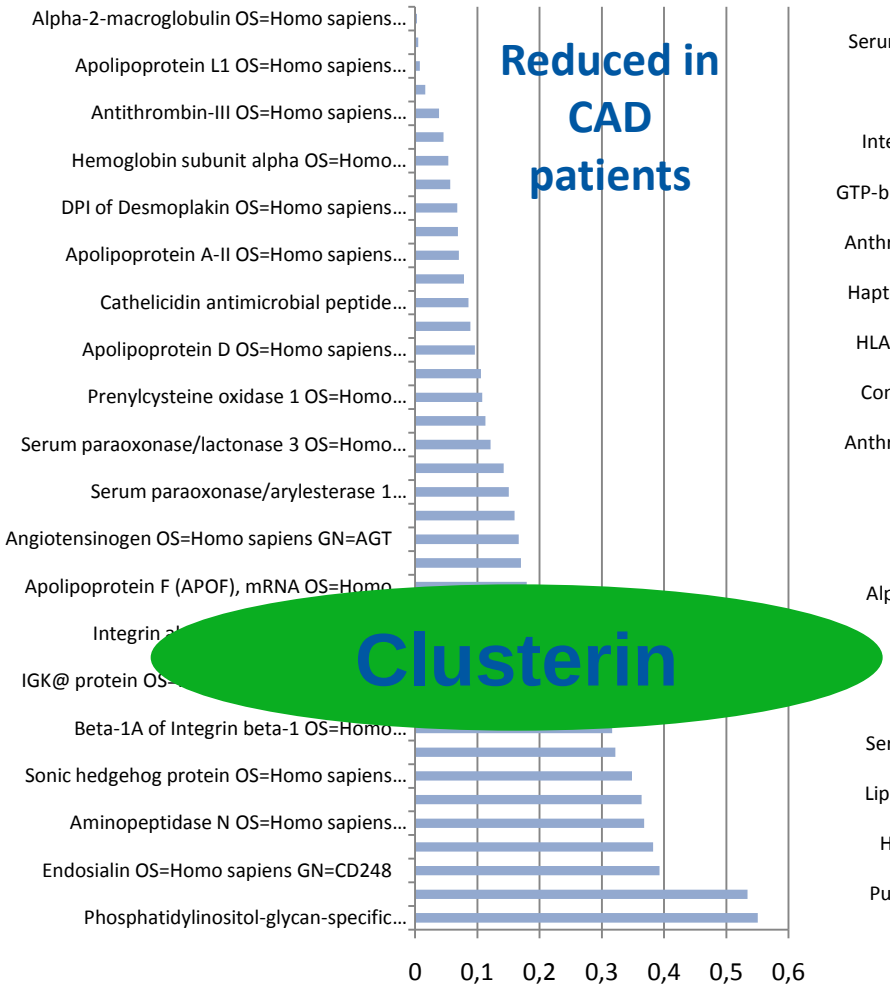


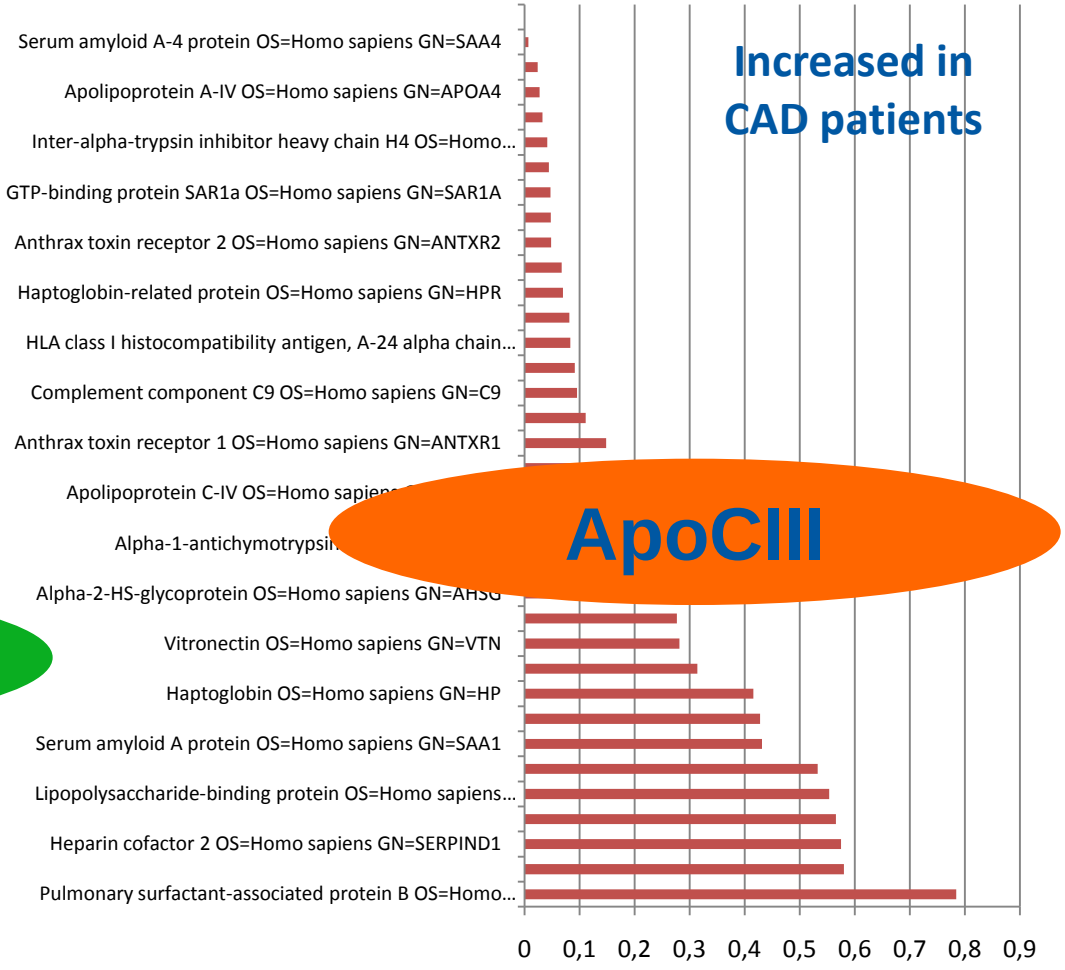




Riwanto M et al. & Lüscher T, Landmesser U. *Circulation* 2013 (in press)

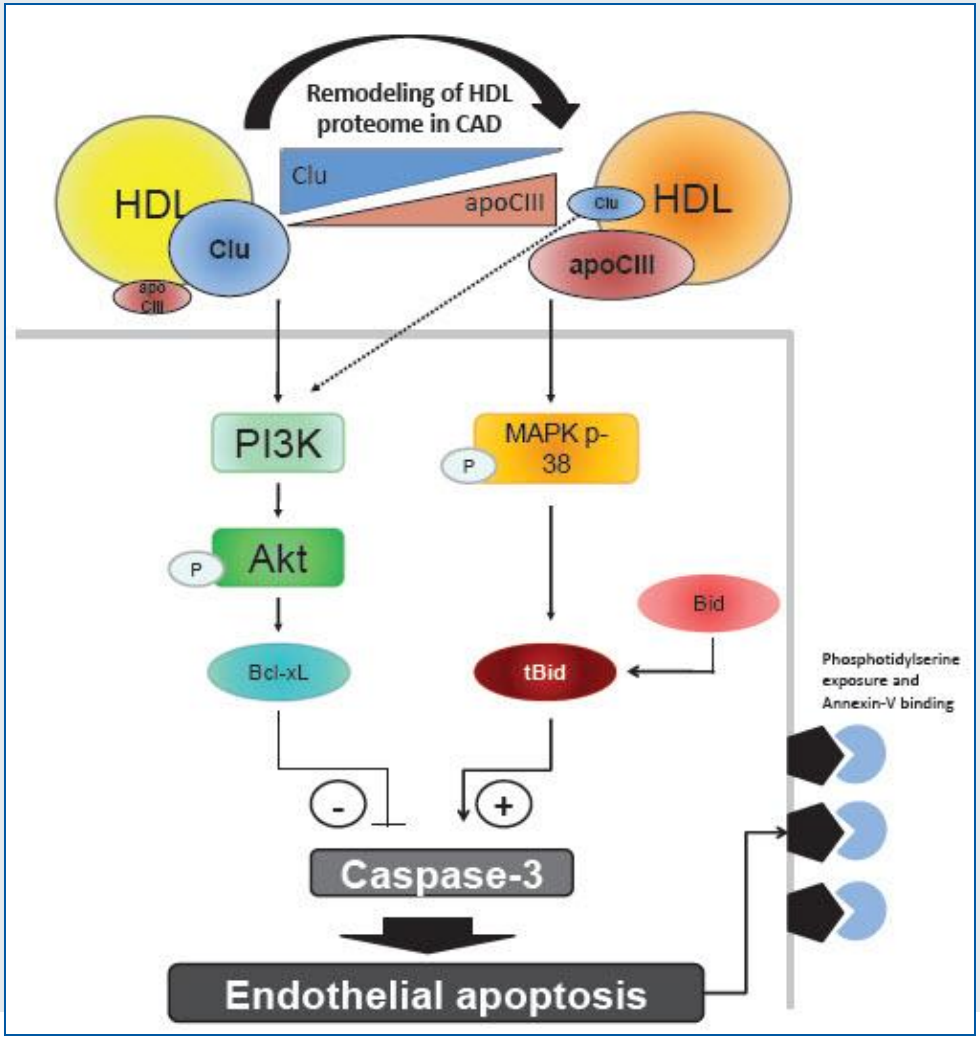
HDL proteome alterations in patients with coronary disease





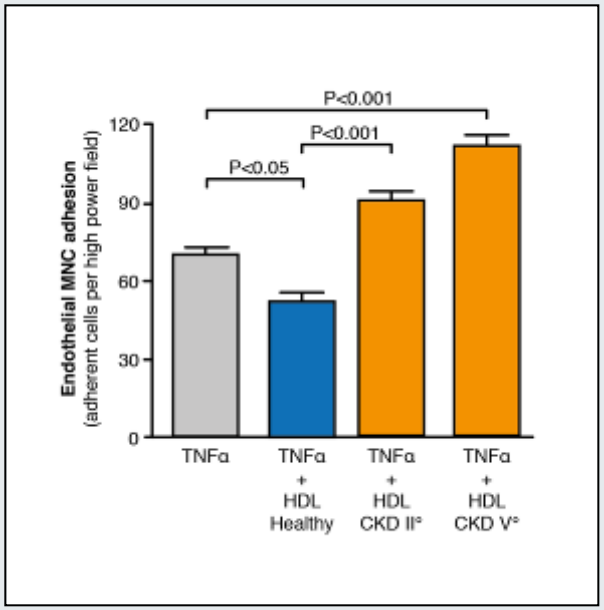
Riwanto M et al. & Lüscher T, Landmesser U. *Circulation* 2013 (in press)

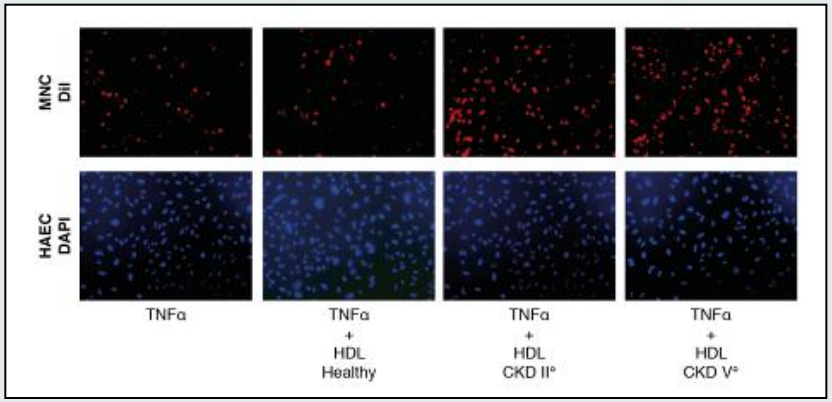
Summary of mechanisms leading to altered effects of HDL on endothelial apoptosis in CAD

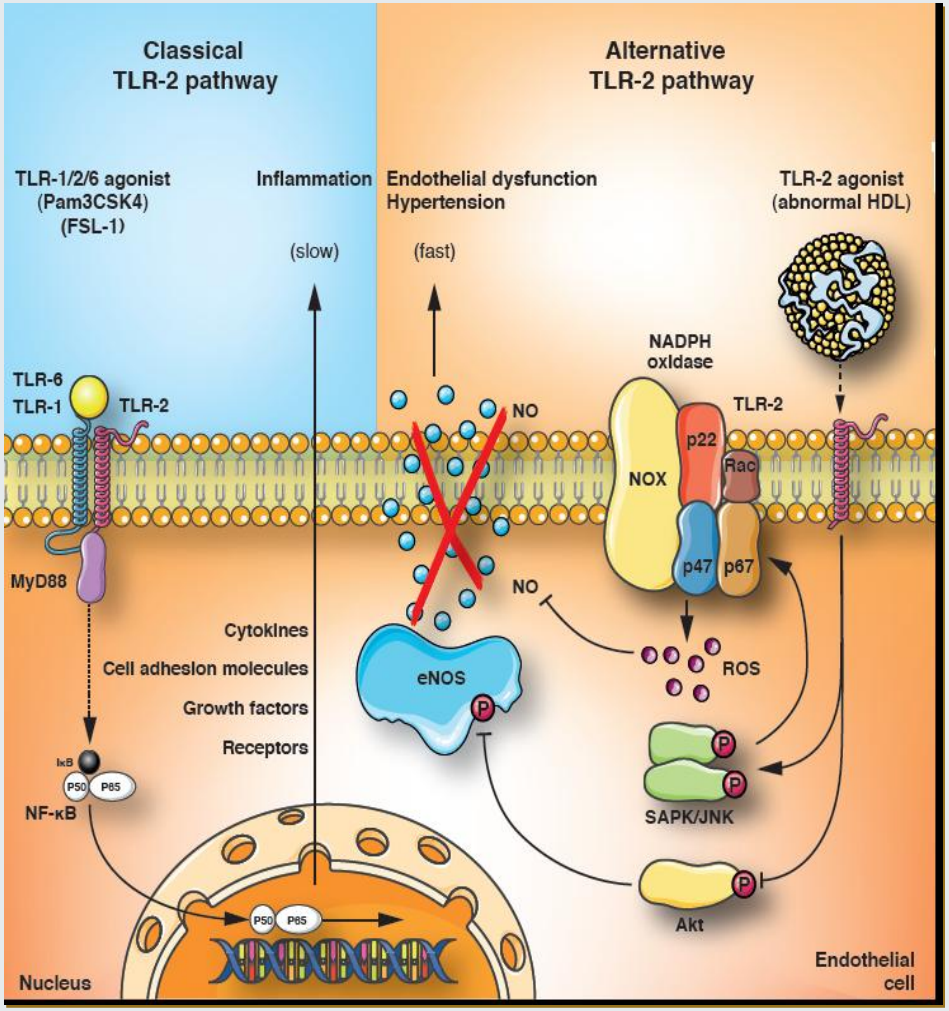


Riwanto M et al. & Lüscher T, Landmesser U. *Circulation* 2013 (in press)

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







Speer T et al.& Deanfield J, Lüscher TF, Fliser D, Landmesser U. *Immunity* 2013 (in press)

HDL dysfunction and CETP inhibition?

1. The HDL cholesterol hypothesis

2. HDL dysfunction

3. Novel therapeutic interventions - CETP inhibition ?

Niacin (vitamin B3): clinical outcome studies in combination with statin therapy

AIM-HIGH trial

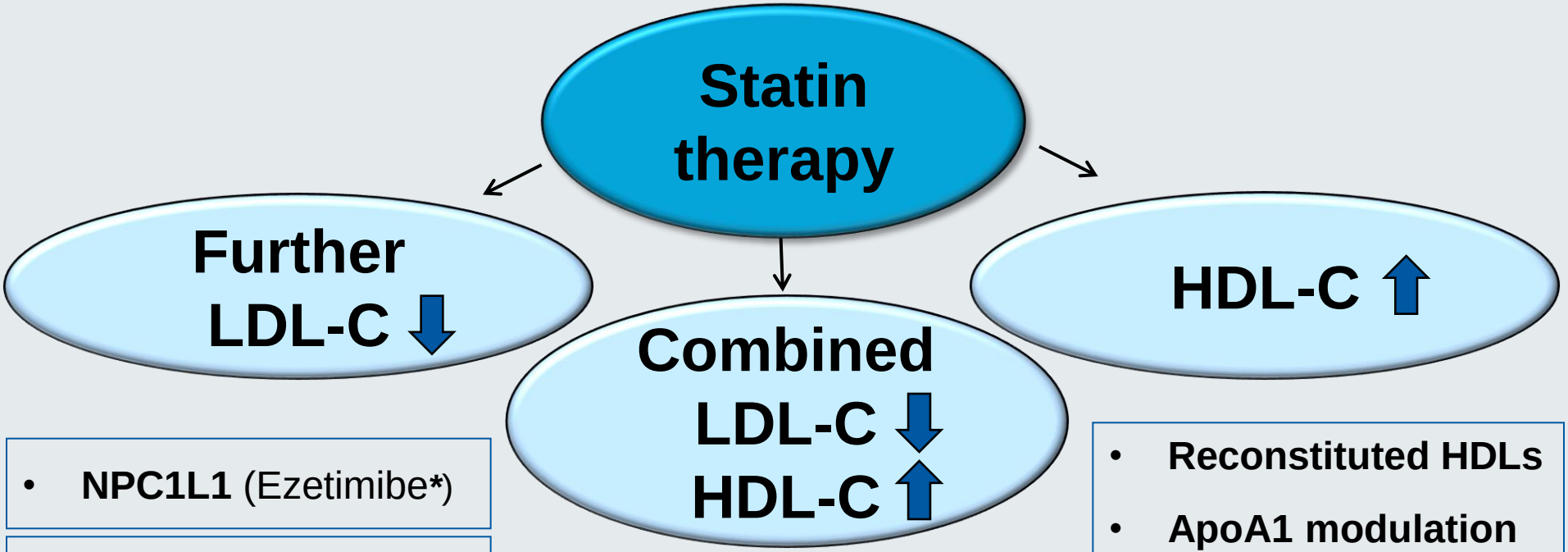
- Pre-randomisation phase with niacin (1.5/2g) ➡ exclusion: 20.1 %
- Aiming to have similarly low LDL-C in both treatment groups (simvastatin 40-80 mg)
  ➡ **LDL: - 5.5 %, HDL: + 13.2 %**
  ➡ **Cave: More patients increased statin dose and/or added ezetimibe in control-group**
- Randomization (n): 1718 vs. 1696 patients
- Mean FU - 3 years (556 events)

HPS2-THRIVE trial

- Pre-randomisation phase with ER-niacin (2g)/ laropiprant (40 mg) ➡ exclusion: 25.4 %
- No further adjustment of LDL-C levels after randomization (simvastatin 40 mg)
  ➡ **LDL: -19.9 %; HDL + 16.9 %**
  ➡ **Cave: Cardiovascular effects of PGD_2 receptor DP_1 antagonist laropiprant ?**
- Randomization (n): 12838 vs. 12835 patients
- Mean FU - 4 years (? events)

Eur Heart J 2013 (in press)

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



- **NPC1L1** (Ezetimibe*)

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

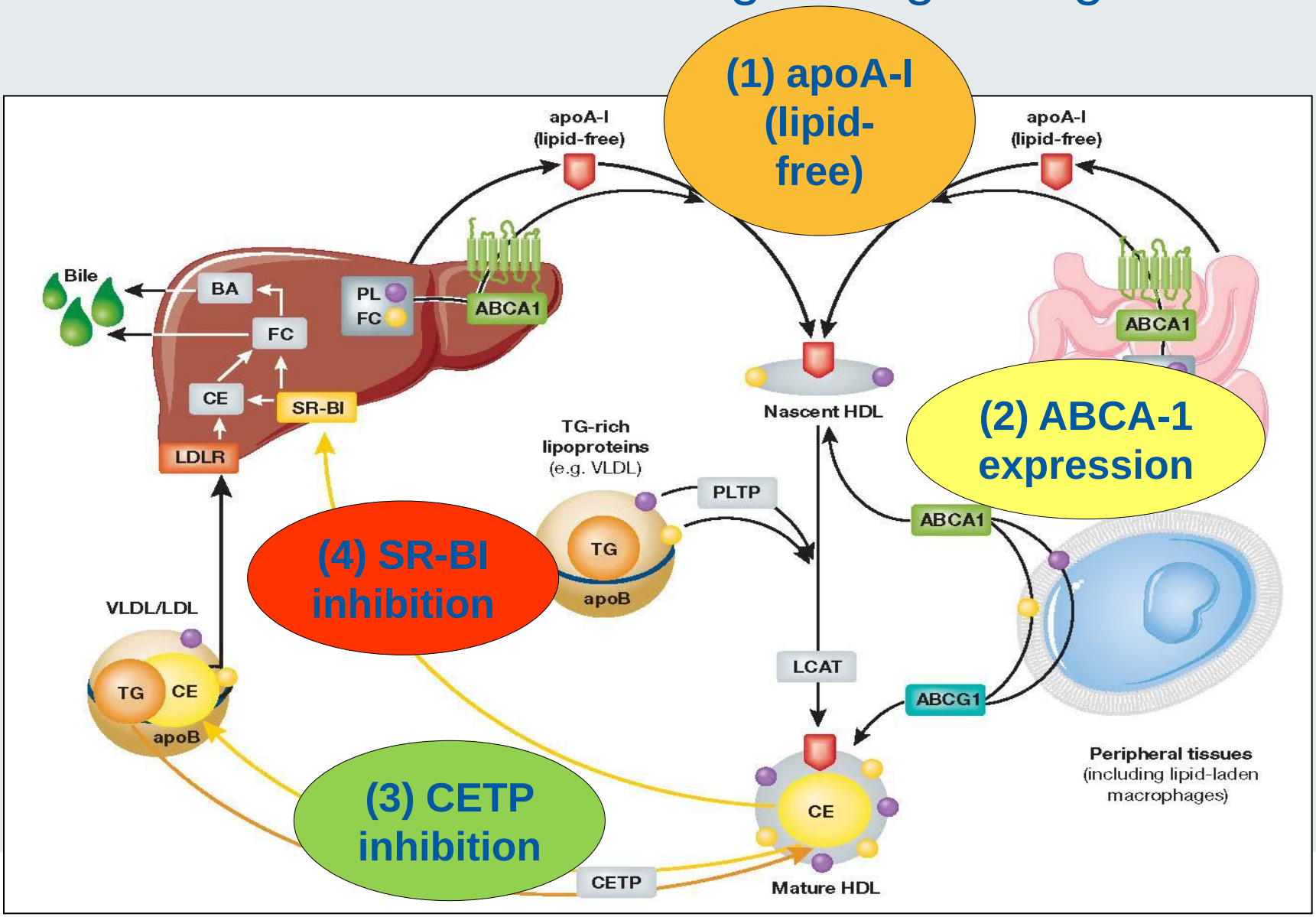
- **CETP inhibition** (Anacetrapib*, Evacetrapib*)

- **Reconstituted HDLs**
- **ApoA1 modulation**

**Clinical outcome trials ongoing*

Eur Heart J 2013 (in press)

HDL metabolism – different targets regulating HDL-C

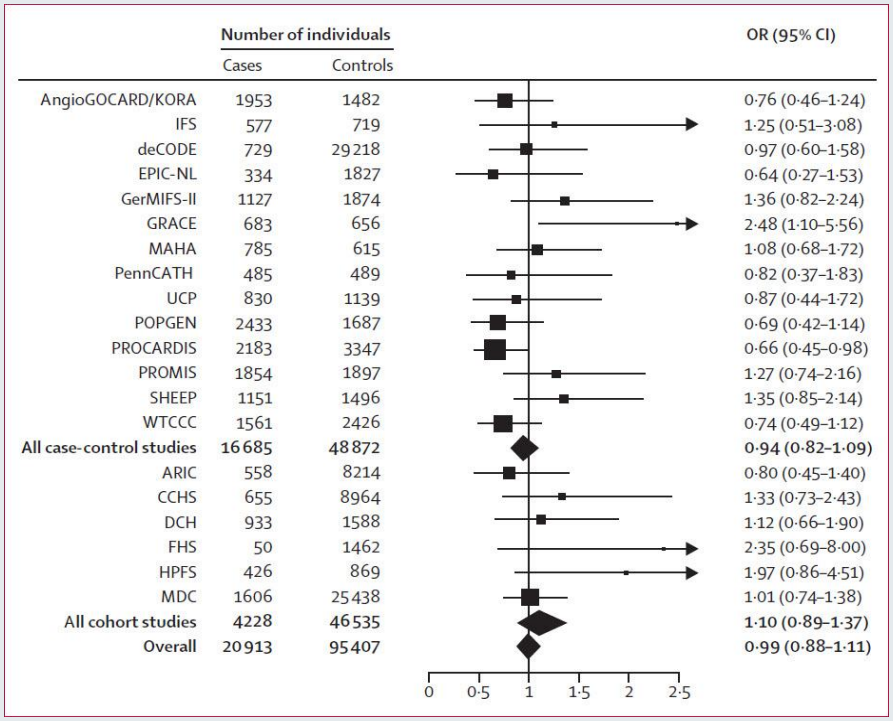


Besler C, Lüscher T, Landmesser U. *EMBO Mol Med 2012*; 4: 251-68

Genetic link with increased HDL cholesterol (endothelial lipase SNP), but not associated with myocardial infarction

Lancet 2012; 380: 572–80

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



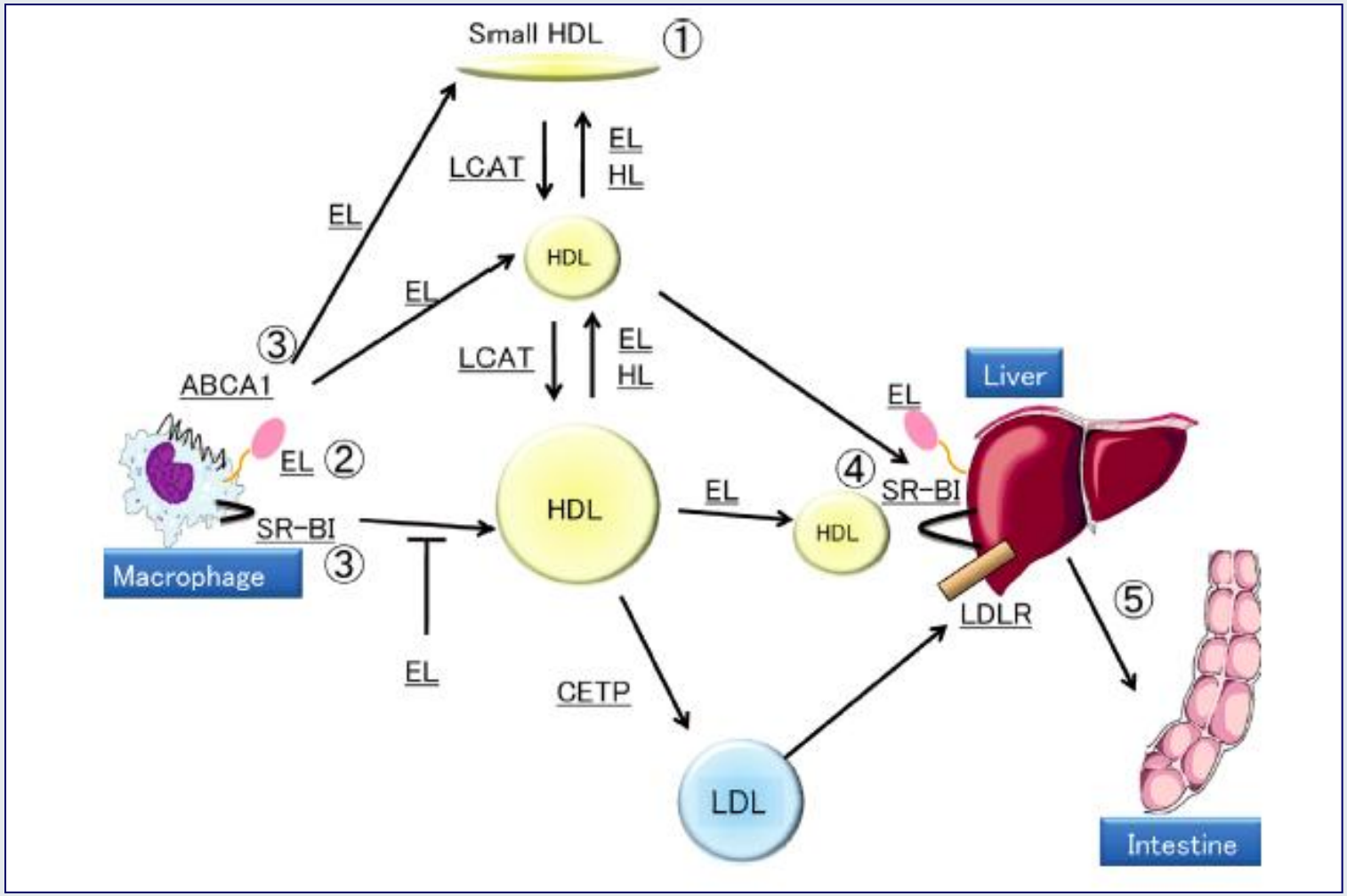
	Number of individuals		OR (95% CI)
	Cases	Controls	
AngioGOCARD/KORA	1953	1482	0·76 (0·46–1·24)
IFS	577	719	1·25 (0·51–3·08)
deCODE	729	29 218	0·97 (0·60–1·58)
EPIC-NL	334	1827	0·64 (0·27–1·53)
GerMIFS-II	1127	1874	1·36 (0·82–2·24)
GRACE	683	656	2·48 (1·10–5·56)
MAHA	785	615	1·08 (0·68–1·72)
PennCATH	485	489	0·82 (0·37–1·83)
UCP	830	1139	0·87 (0·44–1·72)
POPGEN	2433	1687	0·69 (0·42–1·14)
PROCARDIS	2183	3347	0·66 (0·45–0·98)
PROMIS	1854	1897	1·27 (0·74–2·16)
SHEEP	1151	1496	1·35 (0·85–2·14)
WTCCC	1561	2426	0·74 (0·49–1·12)
All case-control studies	**16 685**	**48 872**	**0·94 (0·82–1·09)**
ARIC	558	8214	0·80 (0·45–1·40)
CCHS	655	8964	1·33 (0·73–2·43)
DCH	933	1588	1·12 (0·66–1·90)
FHS	50	1462	2·35 (0·69–8·00)
HPFS	426	869	1·97 (0·86–4·51)
MDC	1606	25 438	1·01 (0·74–1·38)
All cohort studies	**4228**	**46 535**	**1·10 (0·89–1·37)**
Overall	**20 913**	**95 407**	**0·99 (0·88–1·11)**

"Some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction.
These data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions in risk of myocardial infarction.

Association of ***LIPG* Asn396Ser** with myocardial infarction in 116 320 participants from 20 studies

Lancet 2012; 380: 572-80

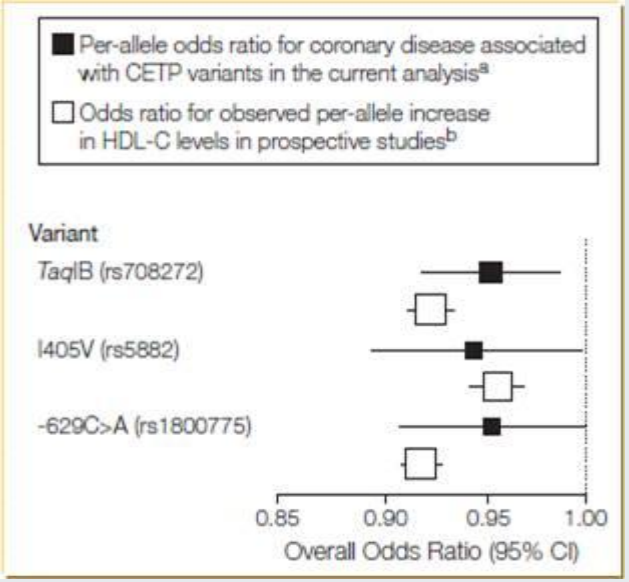
Endothelial lipase and reverse cholesterol transport



Circ J 2010;**74:** 2263–2270

CETP – genetic association with coronary disease: a meta-analysis

Association of Cholesteryl Ester Transfer Protein Genotypes With CETP Mass and Activity, Lipid Levels, and Coronary Risk



Odds Ratios for Coronary Disease for 3 CETP variants

Three CETP genotypes that are associated with moderate inhibition of CETP activity (and higher HDL-C levels) show weakly inverse associations
with coronary risk.

46 studies had data on 27,196 coronary cases and 55,338 controls

JAMA 2008; 299(23):2777-88

CETP – genetic association with ischemic cardiovascular events in Copenhagen City Heart Study

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http://dx.doi.org/10.1016/j.jacc.2012.07.045

Cardiometabolic Risk

Genetic Inhibition of *CETP*, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects

Trine Holm Johannsen, MD, PhD,*† Ruth Frikke-Schmidt, MD, DMSc,*† Jesper Schou, MSc,*† Børge G. Nordestgaard, MD, DMSc,†‡§ Anne Tybjærg-Hansen, MD, DMSc*†§

Genotype		Participants (n)	Myocardial Infarction Events (n)	Myocardial Infarction Incidence rate (95% CI)	Myocardial Infarction Hazard Ratio (95% CI)	Myocardial Infarction P for Trend	Ischemic Stroke Events (n)	Ischemic Stroke Incidence rate (95% CI)	Ischemic Stroke Hazard Ratio (95% CI)	Ischemic Stroke P for Trend
-629	CC	2709	308	47 (42-52)			243	36 (32-41)		
	CA	5084	478	39 (35-42)		<0.001	370	30 (27-33)		0.004
	AA	2468	205	34 (30-39)			178	29 (25-34)		
*Taq*1B	GG	3203	364	47 (42-52)			279	35 (31-40)		
	GA	5057	466	38 (35-41)		<0.001	375	30 (27-34)		0.003
	AA	2001	161	33 (28-38)			137	28 (23-33)		

J Am Coll Cardiol. 2012; 60(20):2041-8

CETP – genetic association with myocardial infarction ?

	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	..	19139/50 812	−12% (−16 to −7)	4×10^{-7}†
rs17321515	8q24	*TRIB1*†	A, G (0·45)	G	0·02	−0·11	−0·05	19139/50 812	−7% (−9 to −4)	2×10^{-6}†
rs6589566	11q23	*APOA1-APOC3-APOA4-APOA5*†	A, G (0·07)	A	0·05	−0·27	−0·09	18310/49 897	−10% (−15 to −5)	8×10^{-5}†
rs4846914	1q42	*GALNT2*†	A, G (0·40)	A	0·02	−0·03	..	19139/50 812	−3% (−6 to −1)	0·02†
rs2967605	19p13	*ANGPTL4*†	C, T (0·16)	C	0·05	−0·07	..	13595/16 423	−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‡	..	..	17165/49077	−6% (−18 to 9)	0·41
rs17145738	7q11	*MLXIPL*	C, T (0·11)	T	0·03	−0·15	..	19139/50 812	−1% (−4 to 3)	0·61
rs3890182	9q31	*ABCA1*	G, A (0·14)	G	0·03	..	0·05	19139/50 812	−1% (−5 to 4)	0·76
rs2338104	12q24	*MMAB, MVK*	G, C (0·46)	G	0·03	..	..	19139/50 812	0% (−3 to 3)	0·85
rs471364	9p22	*TTC39B*	T, C (0·12)	T	0·03	..	..	15693/47098	0% (−5 to 5)	0·97
rs2271293	16q22	*LCAT*	G, A (0·11)	A	0·03	..	..	19139/50 812	4% (−1 to 8)	0·10
rs174547	11q12	*FADS1-FADS2-FADS3*	T, C (0·33)	T	0·03	−0·06	..	19139/50 812	3% (−1 to 6)	0·11
rs1800588	15q22	*LIPC*	C, T (0·22)	T	0·05	0·07	..	17917/49514	4% (0 to 7)	0·04
rs16988929	20q13	*HNF4A*	C, T (0·01)	T	0·01	..	..	17041/20137	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

CETP – genetic association with longevity and reduced dementia

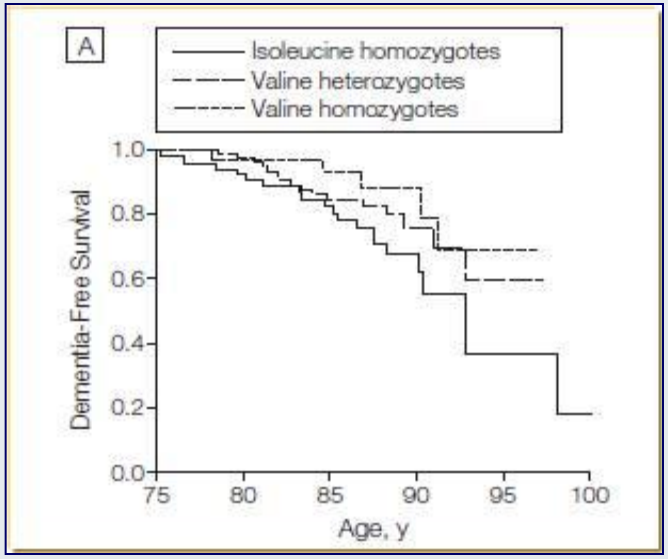
Unique Lipoprotein Phenotype and Genotype Associated With Exceptional Longevity

Barzilai N et al. *JAMA* 2003 Oct 15;290(15):2030-40

CETP Valine homozygosity occurred in 24.8% of centenarians compared with 8.6% among controls

Association of a Functional Polymorphism in the Cholesteryl Ester Transfer Protein (*CETP*) Gene With Memory Decline and Incidence of Dementia

Sanders AE et al., *JAMA* 2010; 303(2):150-8

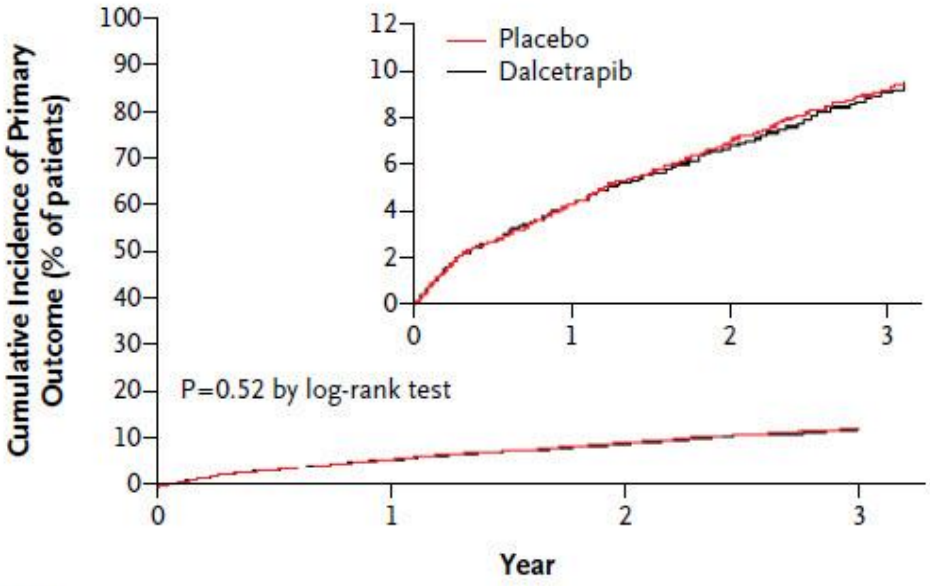


The NEW ENGLAND JOURNAL of MEDICINE

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



No. at Risk

Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

Incidence of the Primary Efficacy End Point.

N Engl J Med 2012

Summary and conclusion

1. The HDL-cholesterol hypothesis is derived largely from epidemiological studies in primary prevention and experimental studies using HDL from healthy subjects.

2. Vascular effects of HDL are heterogenous and are altered in patients with coronary disease (i.e. HDL dysfunction). One may speculate that this could lead to divergent effects of HDL-C raising strategies in different patient populations.

3. Therapeutic strategies leading to increased HDL cholesterol levels may have anti- or pro-atherogenic effects. HDL cholesterol alone is therefore not a reliable surrogate marker.

4. Whereas the ILLUMINATE and dal-HEART programm were halted, genetic studies of CETP variants are promising. The results of the ongoing HPS3-TIMI 55 (anacetrapib) and ACCELERATE (evacetrapib) study are expected.

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Aldon Lusis, PhD

UCL, London, UK

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Seattle, USA

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Cleveland Clinic, USA

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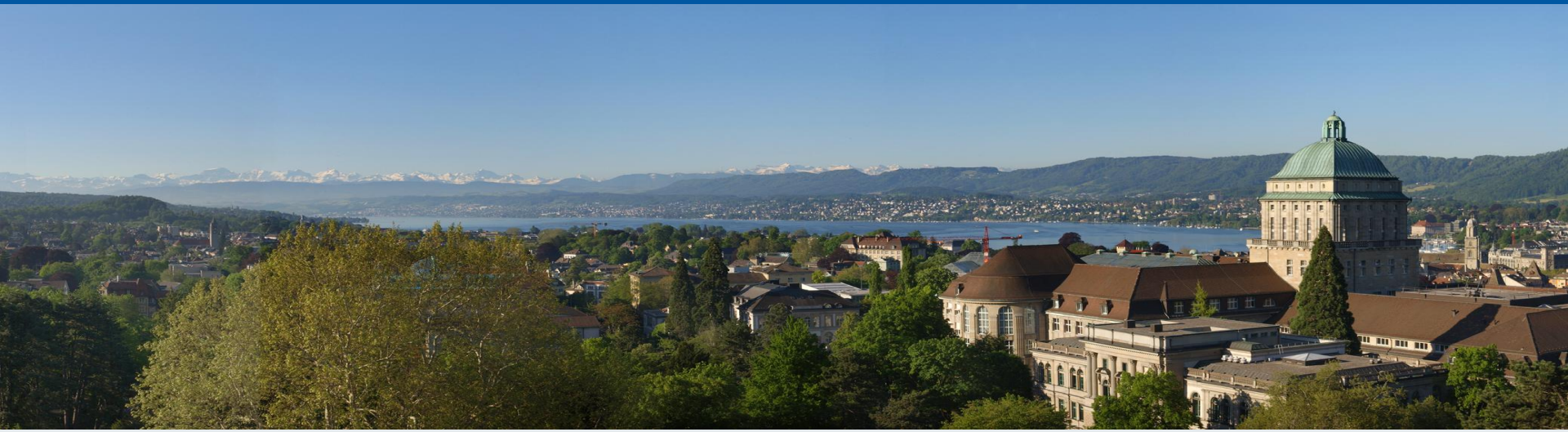
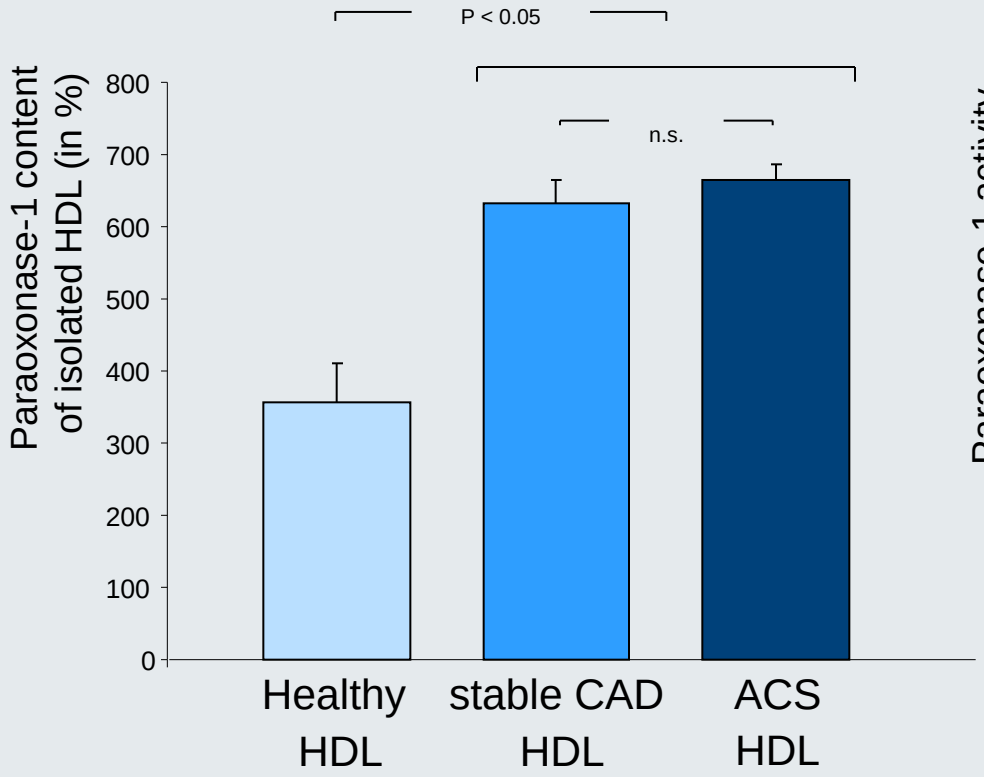


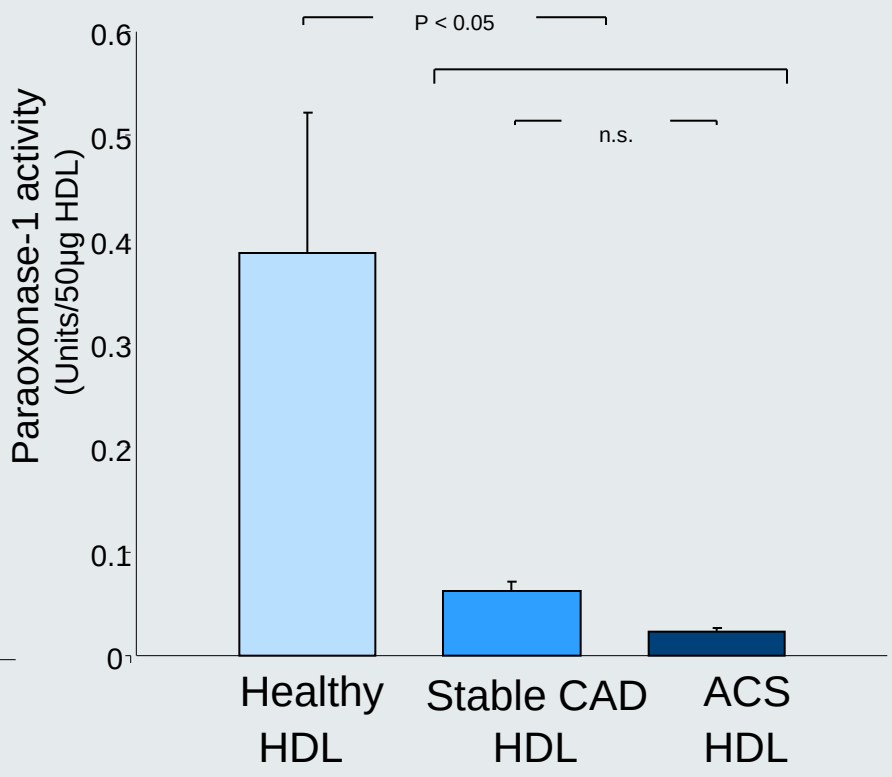
Thank you

HDL-associated paraoxonase activity and content

Paraoxonase-1 content

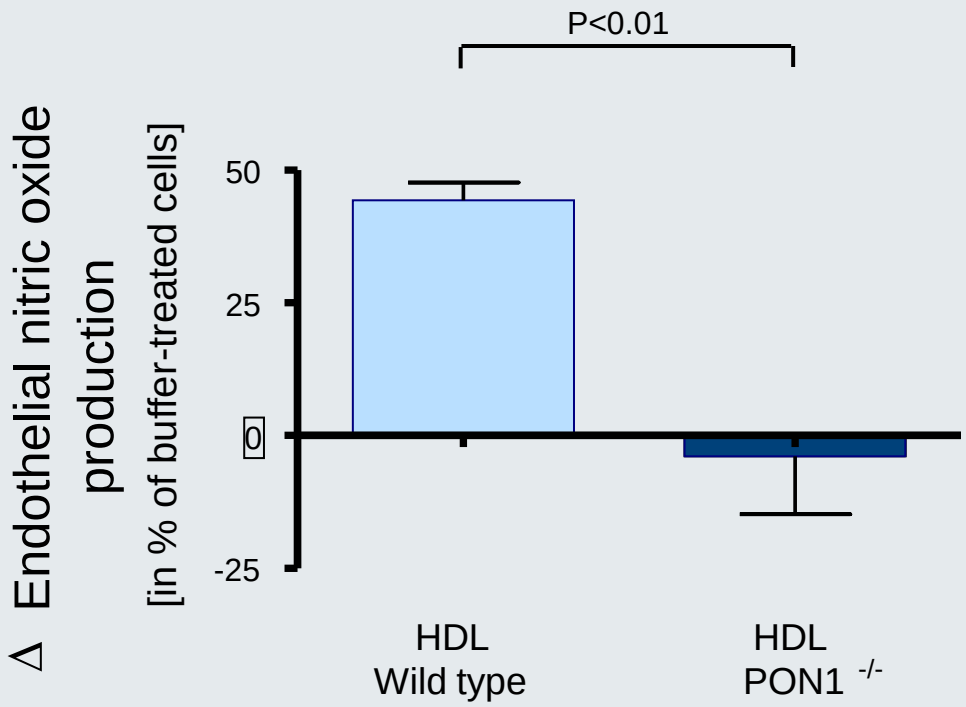


Paraoxonase activity



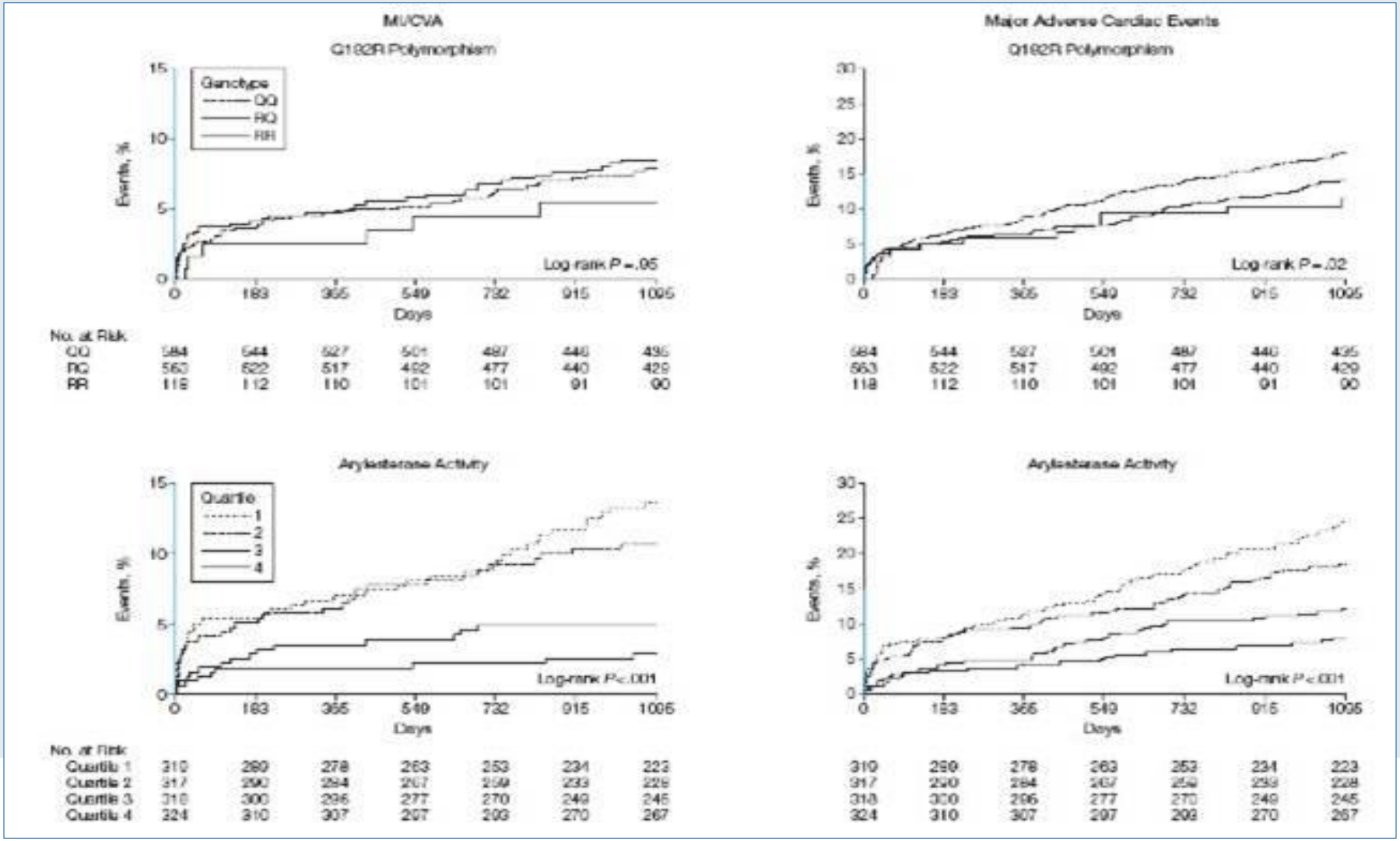
Besler C et al. & Landmesser U. *J Clin Invest* 2011;121(7):2693-708

HDL from paraoxonase-1 deficient mice did not stimulate endothelial NO production



Besler C et al. & Landmesser U. *J Clin Invest* 2011;121(7):2693-708

Paraoxonase gene polymorphisms, functional activity and cardiovascular risk

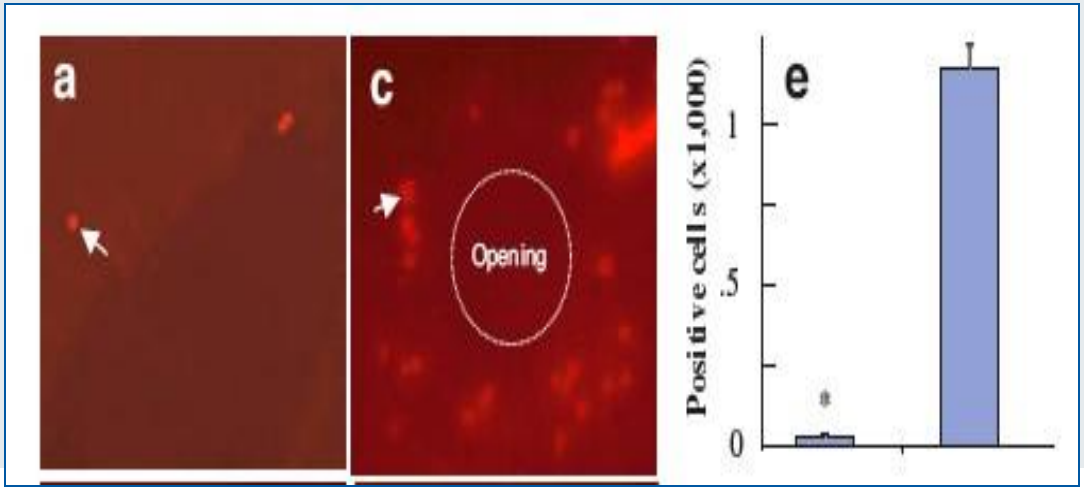


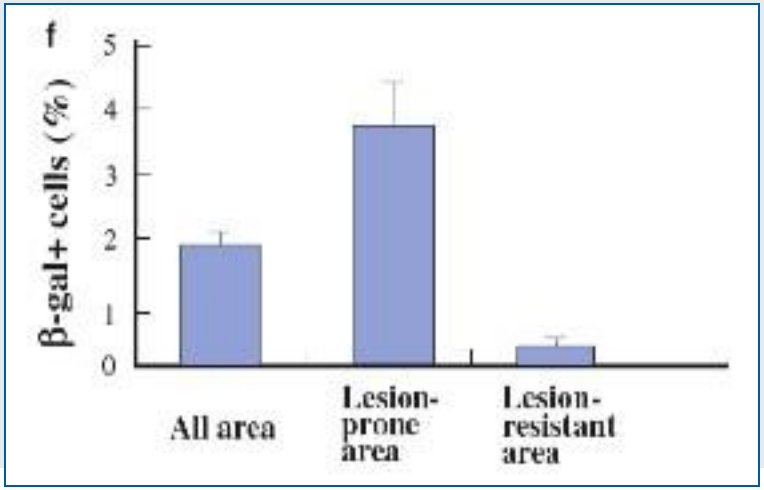
Bhattacharyya T et al.; *Jama* 2008

High endothelial cell turnover in atherosclerosis - prone areas

Rapid Endothelial Turnover in Atherosclerosis-Prone Areas Coincides With Stem Cell Repair in Apolipoprotein E–Deficient Mice

Georgios Foteinos, PhD*; Yanhua Hu, MD*; Qingzhong Xiao, PhD;
Bernhard Metzler, MD; Qingbo Xu, MD, PhD





Circulation. 2008;117(14):1856-63.

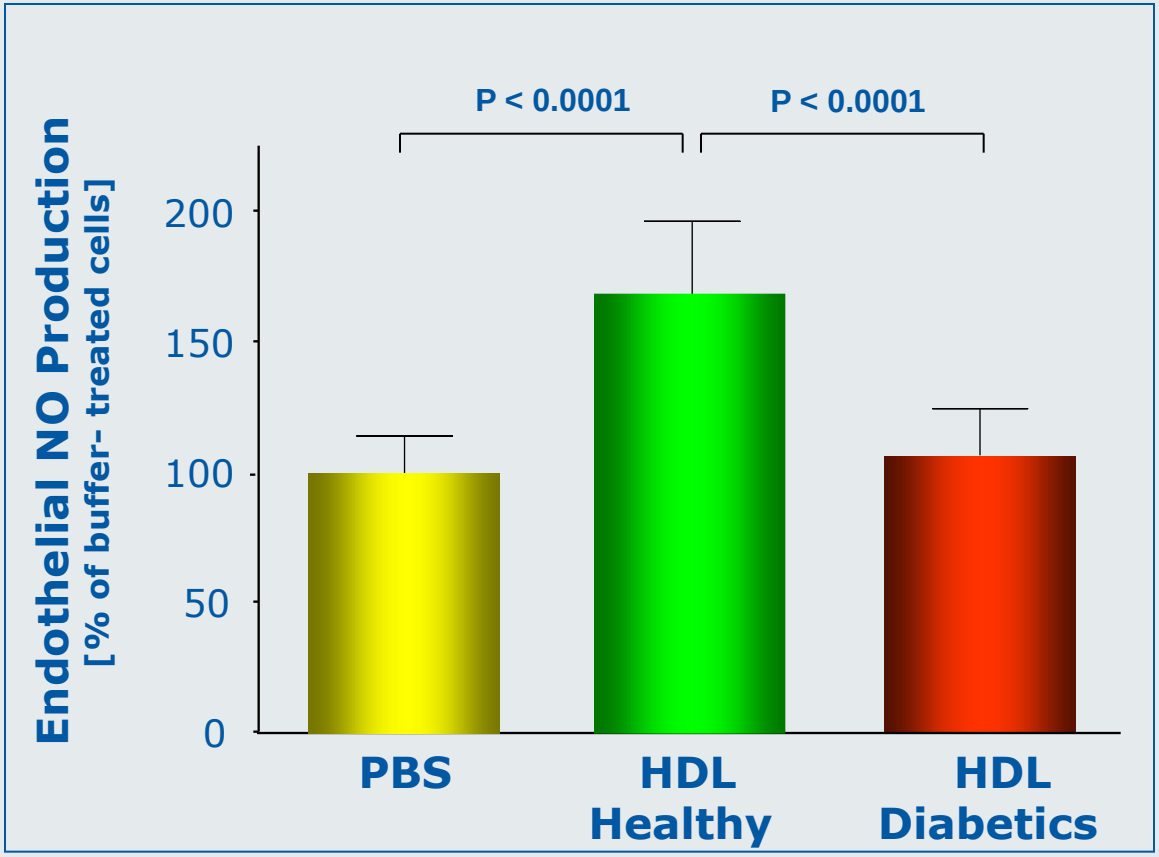
Characteristics of Type-2 Diabetic Patients and Healthy Subjects

	Healthy Subjects (n=10)	Diabetic Patients (n=33)	*P*
Age, y	65±10	60±11	0.22
Sex, male/female	8/2	28/5	0.71
Body mass index, kg/m^2	27±3	33±4	0.0007
Waist circumference, cm	91±11	116±13	<0.0001
Mean arterial pressure, mm Hg (metabolic syndrome under antihypertensive therapy)	95±8	97±10	0.58
Hemoglobin A_{1c}, %	5.4±0.5	6.6±1.0	0.0003
Fasting glucose, mg/dL	93±18	128±34	0.009
LDL cholesterol, mg/dL (metabolic syndrome under statin therapy)	145±26	110±27	0.001
HDL cholesterol, mg/dL	53±22	36±6	0.02
Triglycerides, mg/dL	168±94	225±213	0.41
HDL composition			
Cholesterol, mg/dL	20.4±6.3	14.9±7.6	0.05
Triglycerides, mg/dL	2.1±2.9	4.3±3.1	0.07
Protein, mg/dL	65.5±22.1	57.4±12.2	0.22

Values are expressed as mean±SD or number of patients.

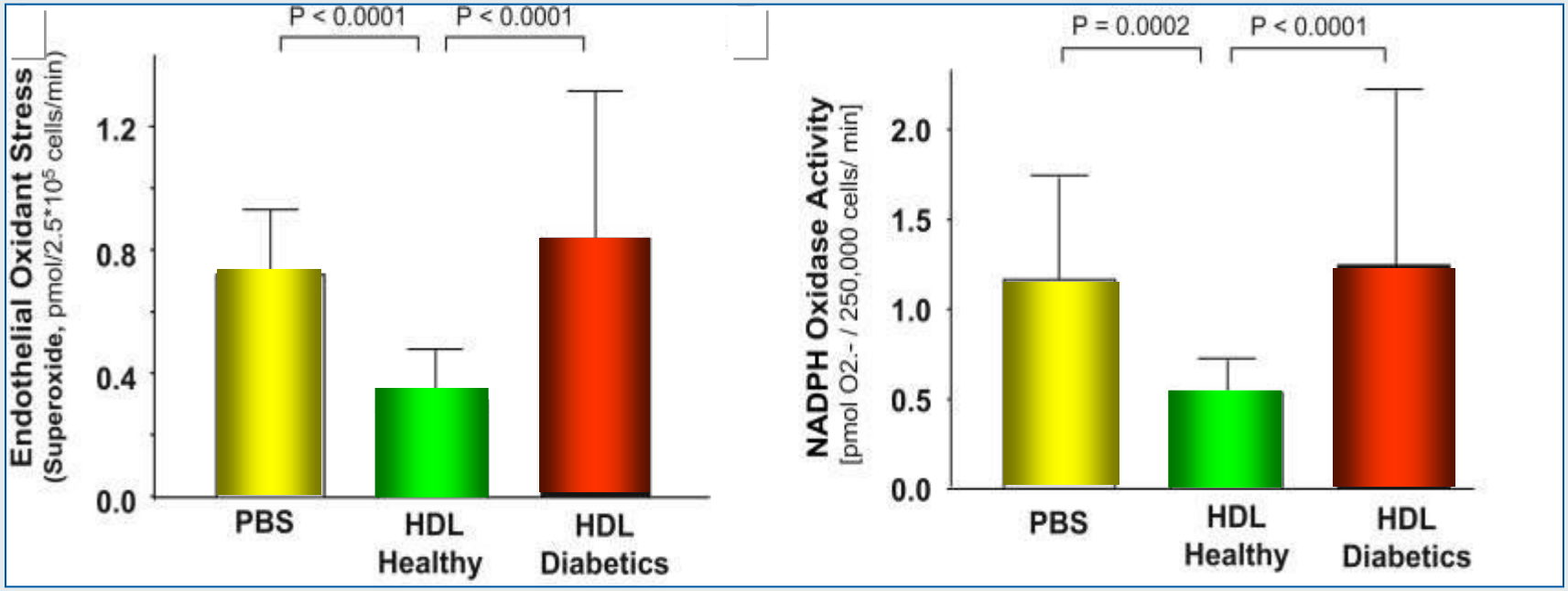
Sorrentino SA et al. & Landmesser U. *Circulation* 2010;121:110-122

Effects of HDL from patients with type-2 diabetes on endothelial NO availability



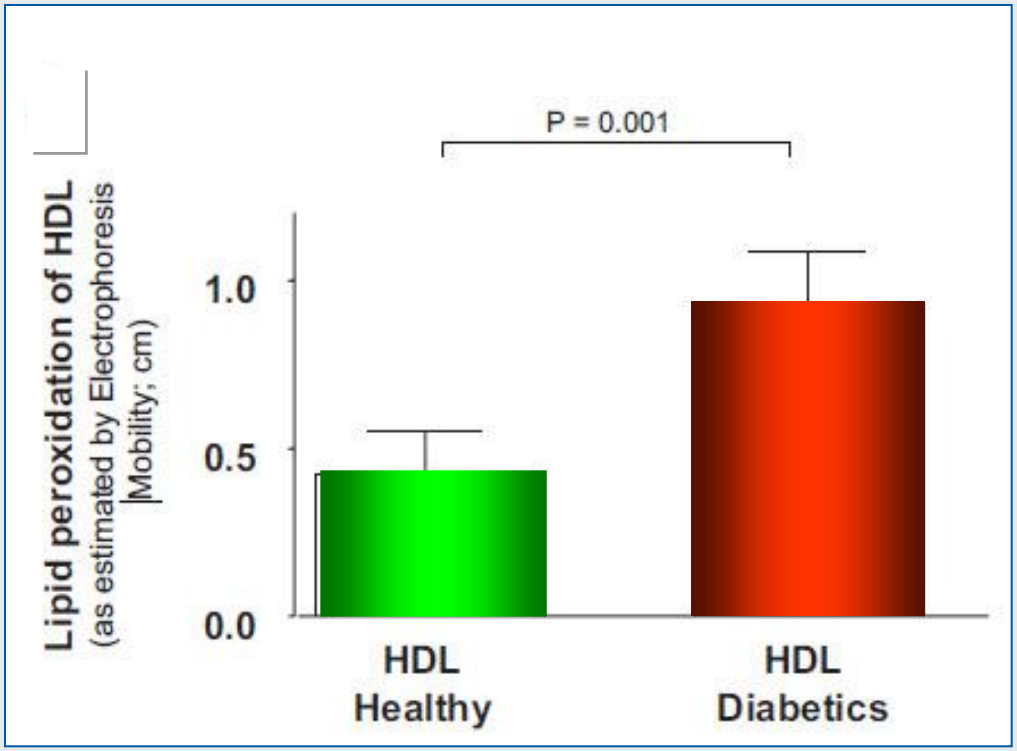
Sorrentino SA et al. & Landmesser U. *Circulation* 2010;121:110-122

Effects of HDL from patients with type-2 diabetes on endothelial oxidant stress



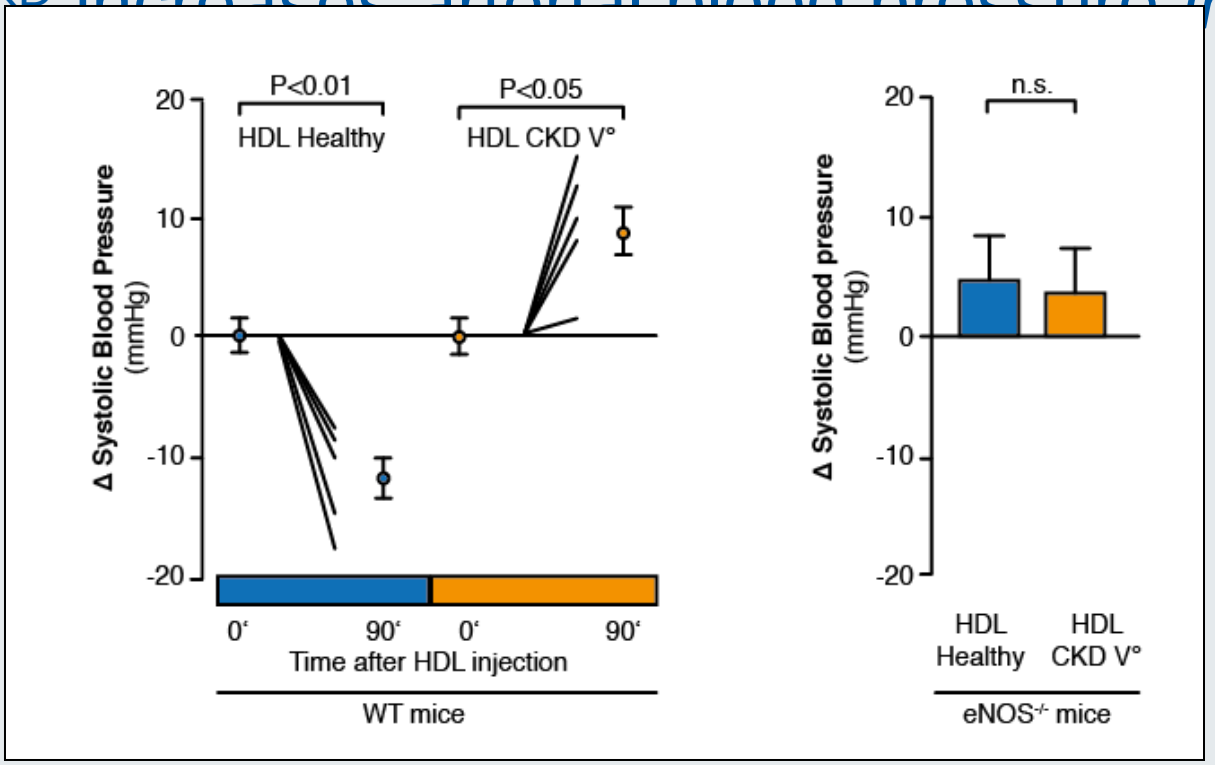
Sorrentino SA et al. & Landmesser U. *Circulation* 2010;121:110-122

Lipid oxidation of HDL from patients with type-2 diabetes and healthy subjects



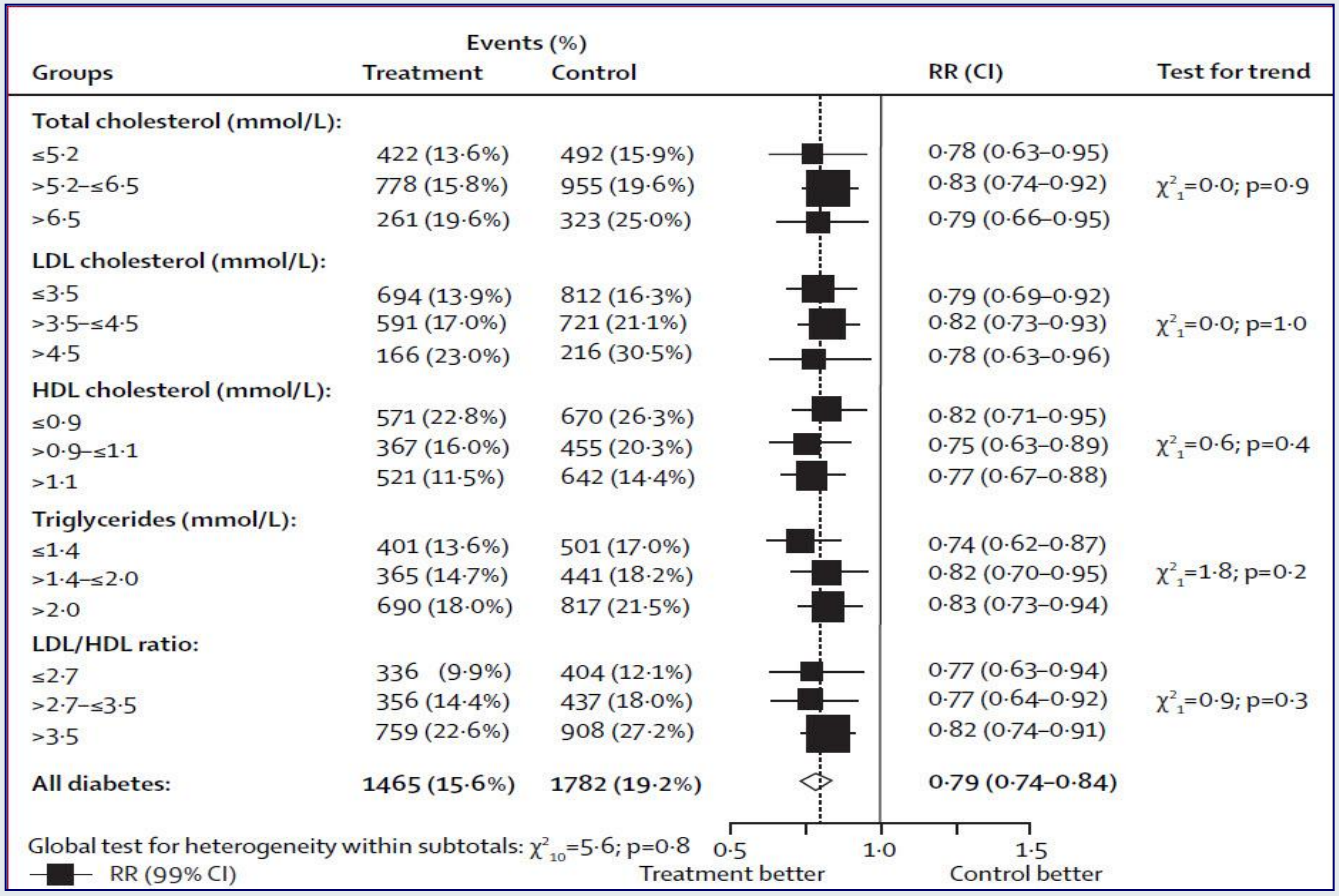
Sorrentino SA et al. & Landmesser U. *Circulation* 2010;121:110-122

HDL^{CKD} increases arterial blood pressure *in vivo*



Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Cholesterol Treatment Trialists' (CTT) Collaborators*



Groups	Events (%) Treatment	Control	RR (CI)	Test for trend
Total cholesterol (mmol/L):				
≤5·2	422 (13·6%)	492 (15·9%)	0·78 (0·63–0·95)	
>5·2–≤6·5	778 (15·8%)	955 (19·6%)	0·83 (0·74–0·92)	χ^2_1=0·0; p=0·9
>6·5	261 (19·6%)	323 (25·0%)	0·79 (0·66–0·95)	
LDL cholesterol (mmol/L):				
≤3·5	694 (13·9%)	812 (16·3%)	0·79 (0·69–0·92)	
>3·5–≤4·5	591 (17·0%)	721 (21·1%)	0·82 (0·73–0·93)	χ^2_1=0·0; p=1·0
>4·5	166 (23·0%)	216 (30·5%)	0·78 (0·63–0·96)	
HDL cholesterol (mmol/L):				
≤0·9	571 (22·8%)	670 (26·3%)	0·82 (0·71–0·95)	
>0·9–≤1·1	367 (16·0%)	455 (20·3%)	0·75 (0·63–0·89)	χ^2_1=0·6; p=0·4
>1·1	521 (11·5%)	642 (14·4%)	0·77 (0·67–0·88)	
Triglycerides (mmol/L):				
≤1·4	401 (13·6%)	501 (17·0%)	0·74 (0·62–0·87)	
>1·4–≤2·0	365 (14·7%)	441 (18·2%)	0·82 (0·70–0·95)	χ^2_1=1·8; p=0·2
>2·0	690 (18·0%)	817 (21·5%)	0·83 (0·73–0·94)	
LDL/HDL ratio:				
≤2·7	336 (9·9%)	404 (12·1%)	0·77 (0·63–0·94)	
>2·7–≤3·5	356 (14·4%)	437 (18·0%)	0·77 (0·64–0·92)	χ^2_1=0·9; p=0·3
>3·5	759 (22·6%)	908 (27·2%)	0·82 (0·74–0·91)	
All diabetes:	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

Global test for heterogeneity within subtotals: χ^2_{10}=5·6; p=0·8

RR (99% CI)

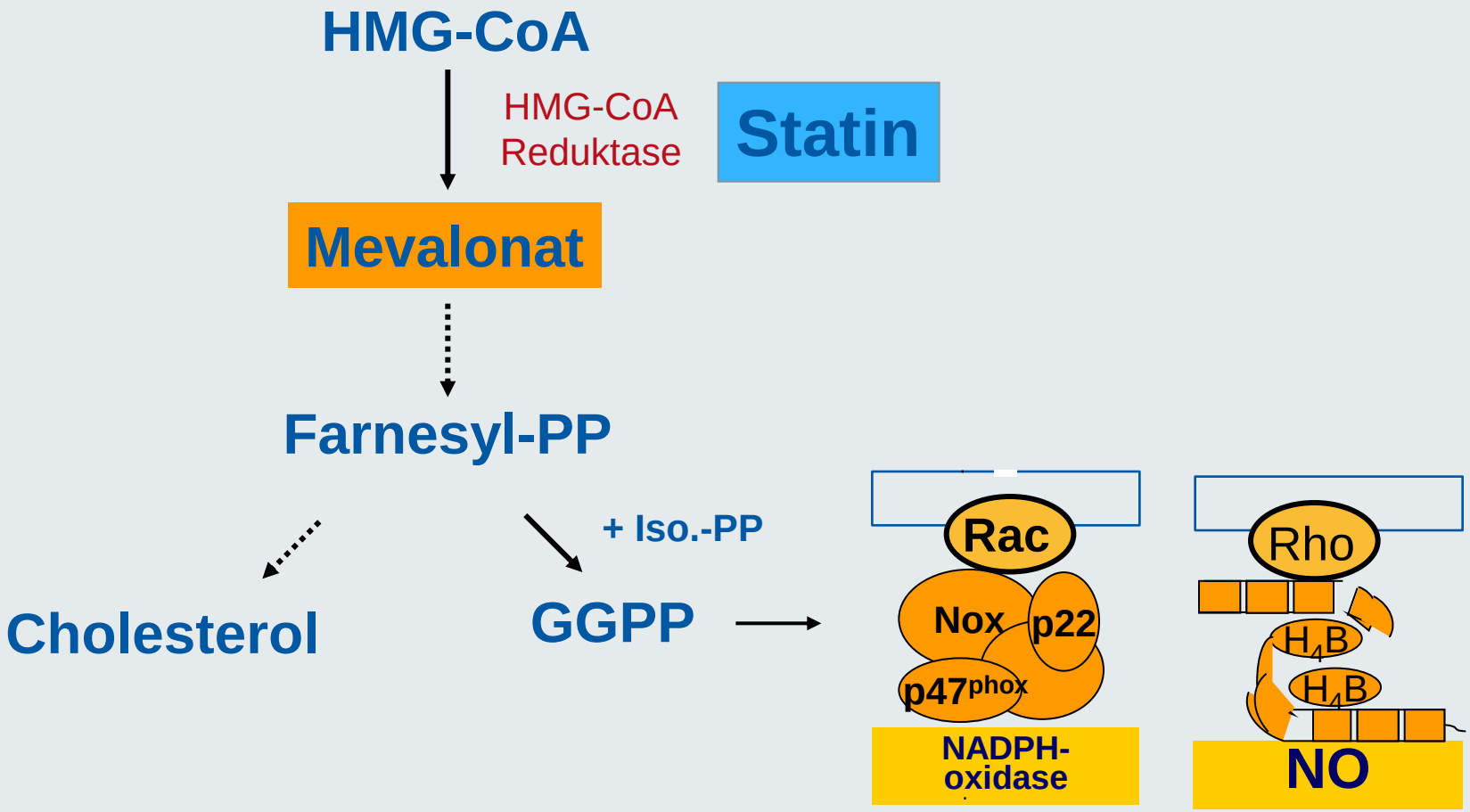
0·5 Treatment better

1·0

1·5 Control better

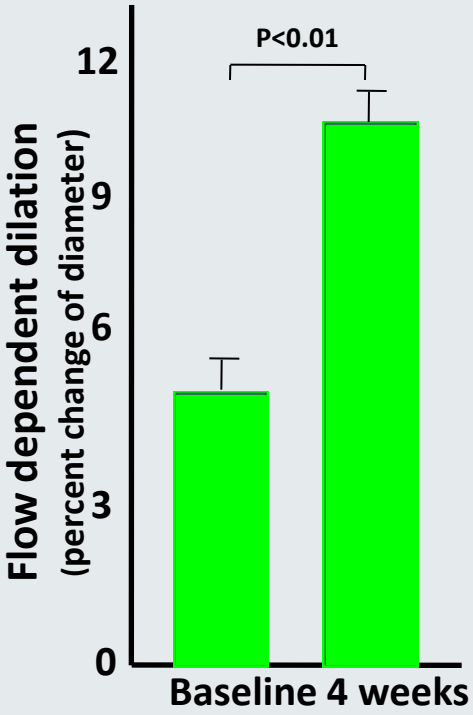
Lancet 2008; 371:317-321

Statins: pleioptropic endothelial effects

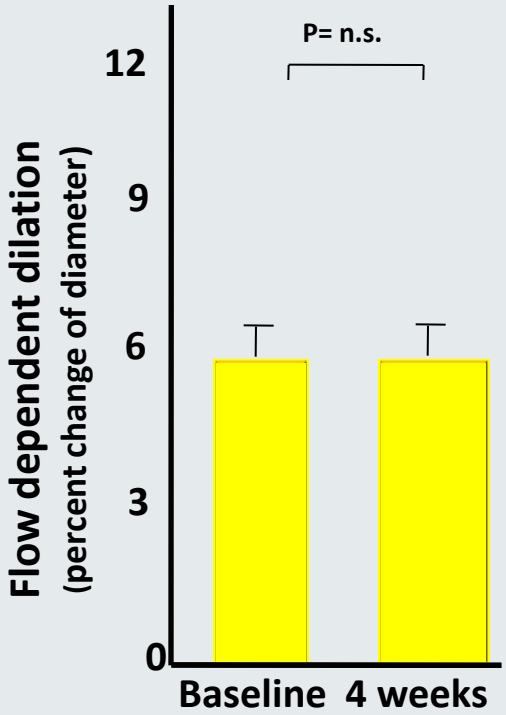


Sorrentino & Landmesser, *Curr Treat Opt*; 2005

Statins: pleioptropic effects on endothelial function



Simvastatin 10 mg group

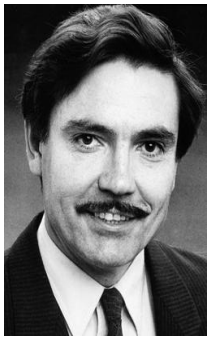


Ezetimibe 10 mg group

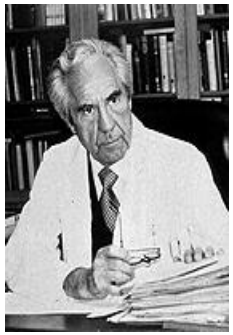
LDL-c reduction similar in both groups.

Simvastatin: 15.6 %
Ezetimibe: 15.4%

Landmesser et al, Circulation 2005; 111(18): 2280-1



The New England Journal of Medicine

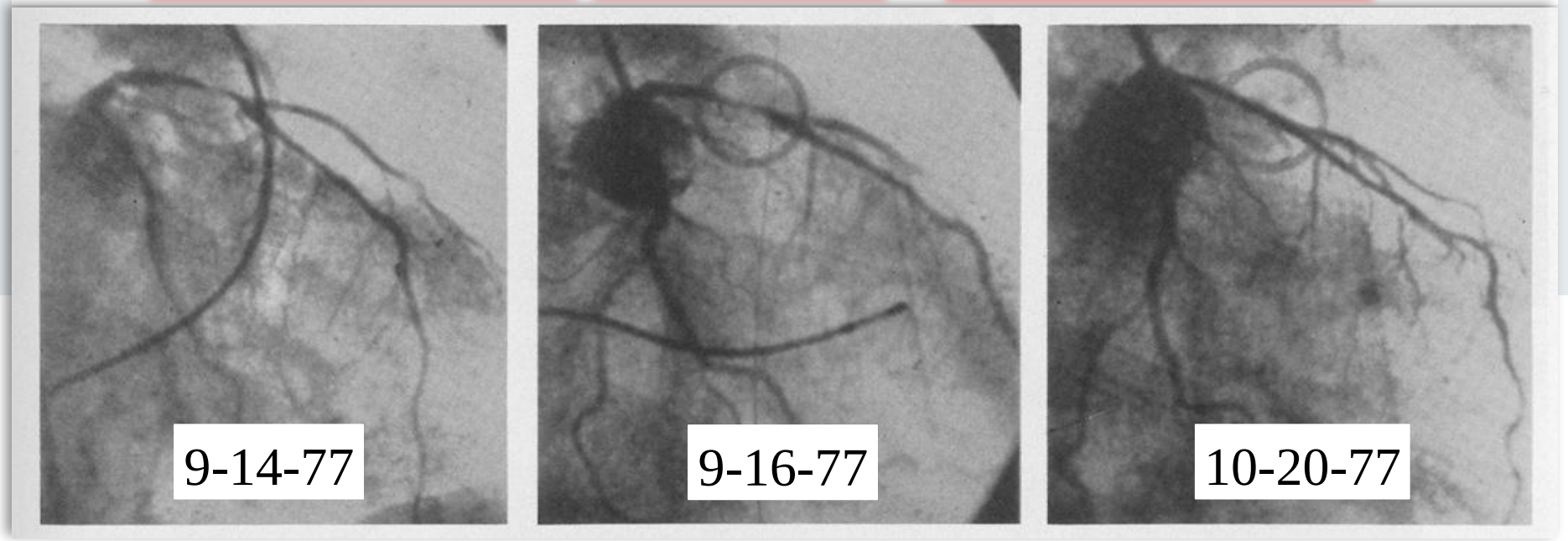


Volume 301 JULY 12, 1979 Number 2

NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

Percutaneous Transluminal Coronary Angioplasty

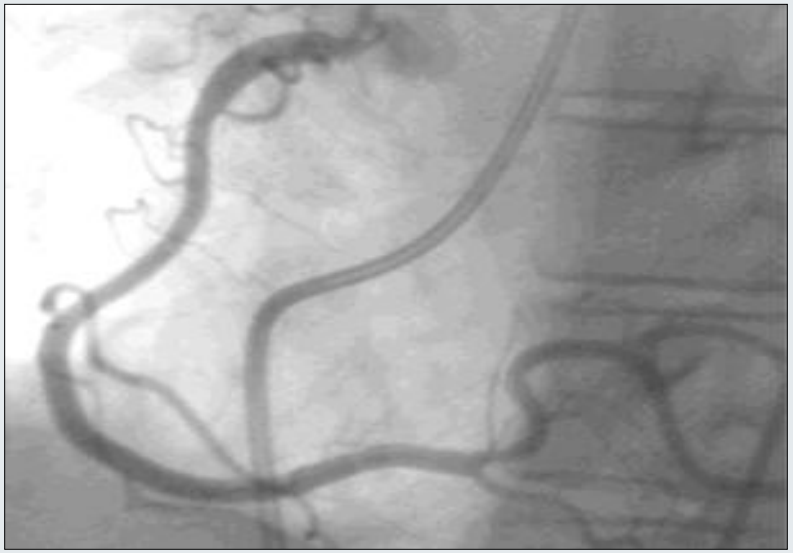
ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.



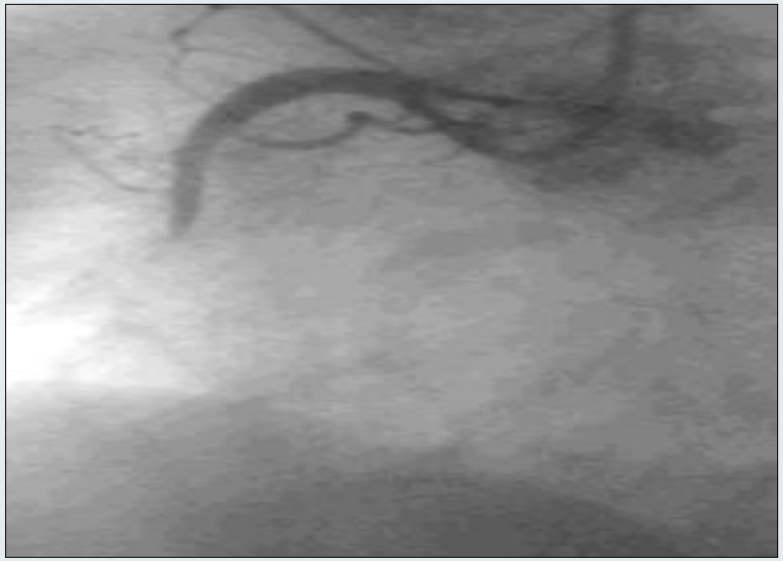
CASE EXAMPLE – Coronary disease
Acute coronary syndrome

2 Month later

Plaque in RCA

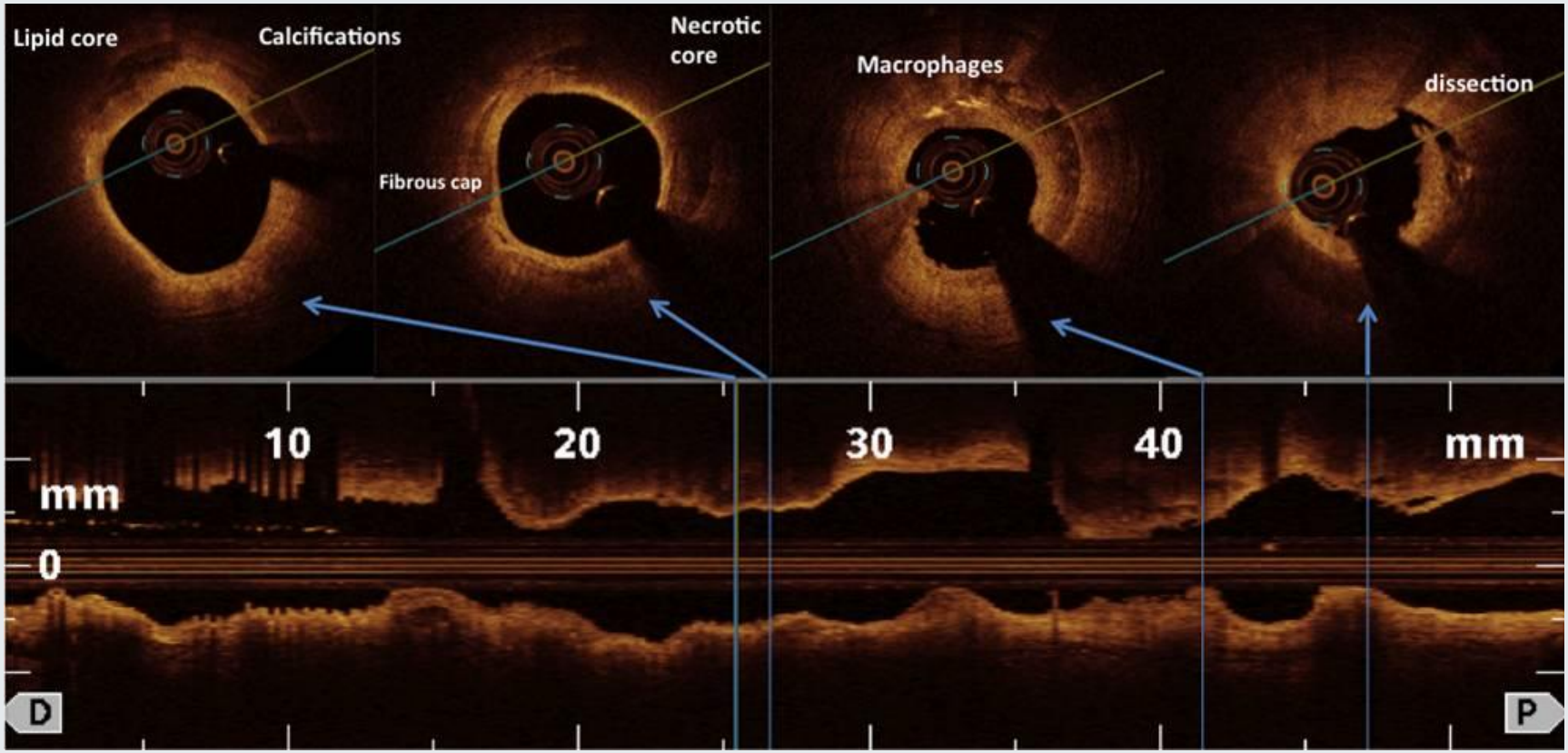


Acute occlusion of RCA

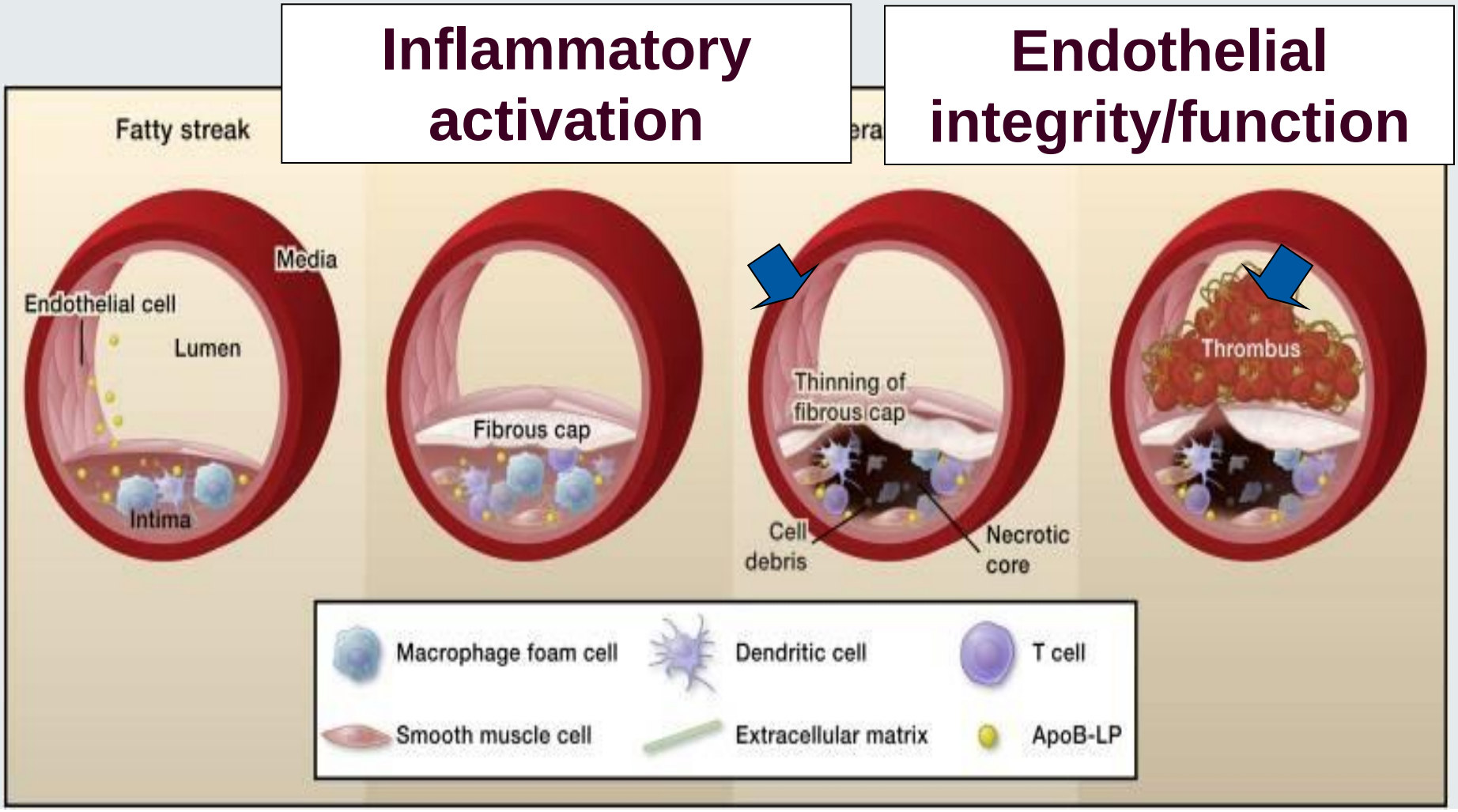


We need to target the underlying atherosclertic vascular disease

Coronary atherosclerosis by OFDI imaging: plaque characteristics

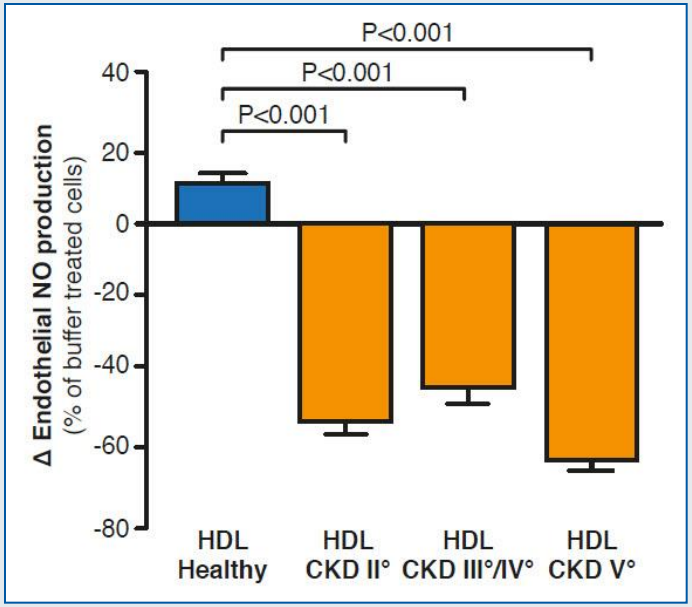


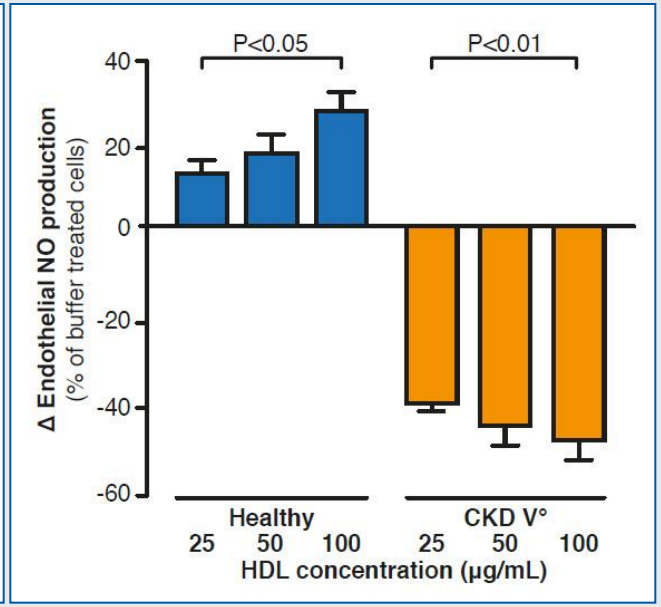
Atherosclerotic plaque progression

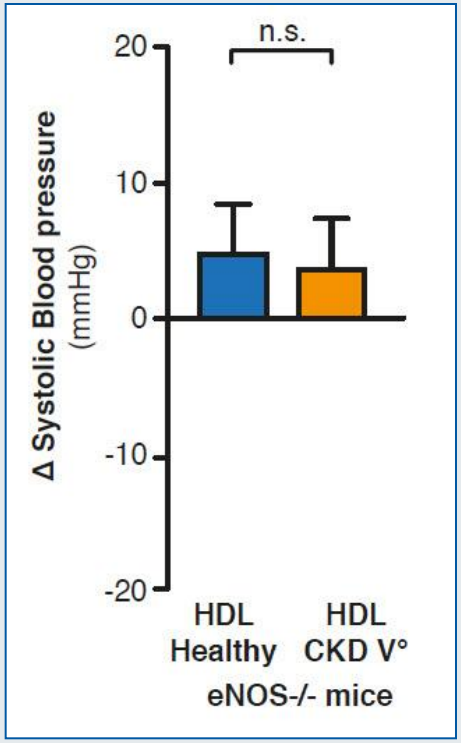


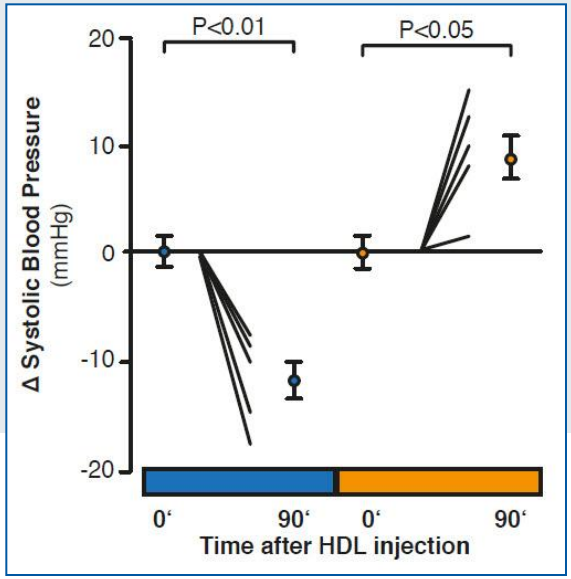
Moore K, Tabas. *Cell* 2011, 145(3):341-55

titel







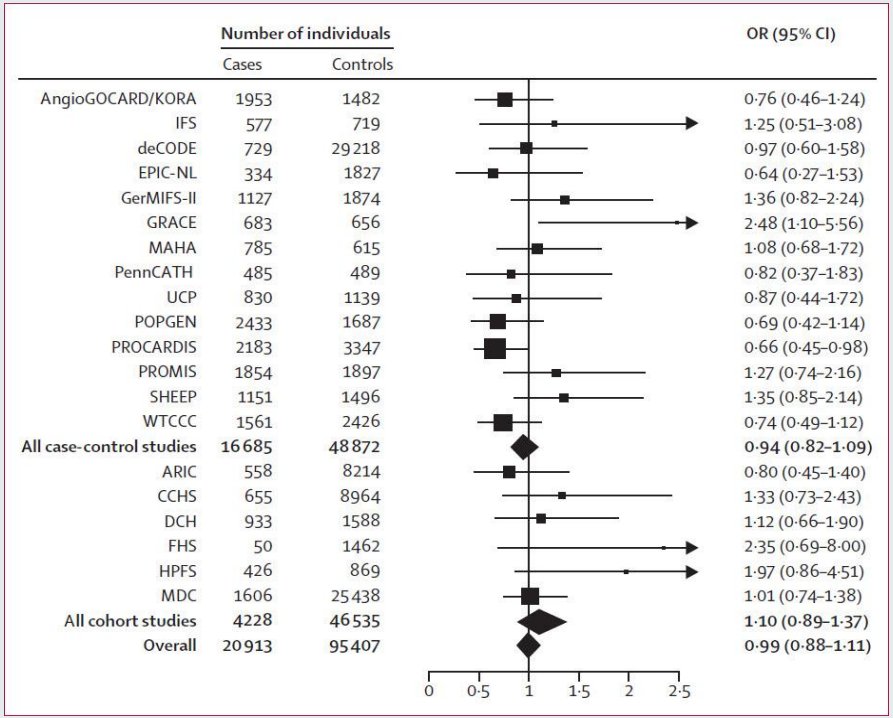


Speer T et al. (in revision)

Genetic link with increased HDL cholesterol (endothelial lipase SNP) not linked risk of myocardial infarction

Lancet 2012; 380: 572–80

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



"Some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction.
These data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions in risk of myocardial infarction.

Association of ***LIPG* Asn396Ser** with myocardial infarction in 116 320 participants from 20 studies

Lancet 2012; 380: 572-80

	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

	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.

Table 4: **Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments**

From observational epidemiology, an increase of 1 SD in usual LDL cholesterol was associated with raised risk of myocardial infarction (OR 1·54, 95% CI 1·45–1·63; appendix p 22). In a mendelian randomisation analysis, a 1 SD increase in LDL cholesterol due to genetic score was also associated with risk of myocardial infarction (OR 2·13, 95% CI 1·69–2·69, $p=2\times10^{-10}$; table 4). From observational epidemiology, a 1 SD rise in usual HDL cholesterol was associated with lowered risk of myocardial infarction (OR 0·62, 95% CI 0·58–0·66; appendix p 22). However, in mendelian randomisation analysis, a 1 SD increase in HDL cholesterol due to genetic score was not associated with risk of myocardial infarction (OR 0·93, 95% CI 0·68–1·26, p=0·63; table 4).

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

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Cardiometabolic Risk

Genetic Inhibition of *CETP*, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects

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Børge G. Nordestgaard, MD, DMSc,†‡§ Anne Tybjærg-Hanse

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EDITORIAL COMMENT

Will Cholesteryl Ester Transfer Protein Inhibition Succeed Primarily by Lowering Low-Density Lipoprotein Cholesterol?

Insights From Human Genetics and Clinical Trials*

Sekar Kathiresan, MD

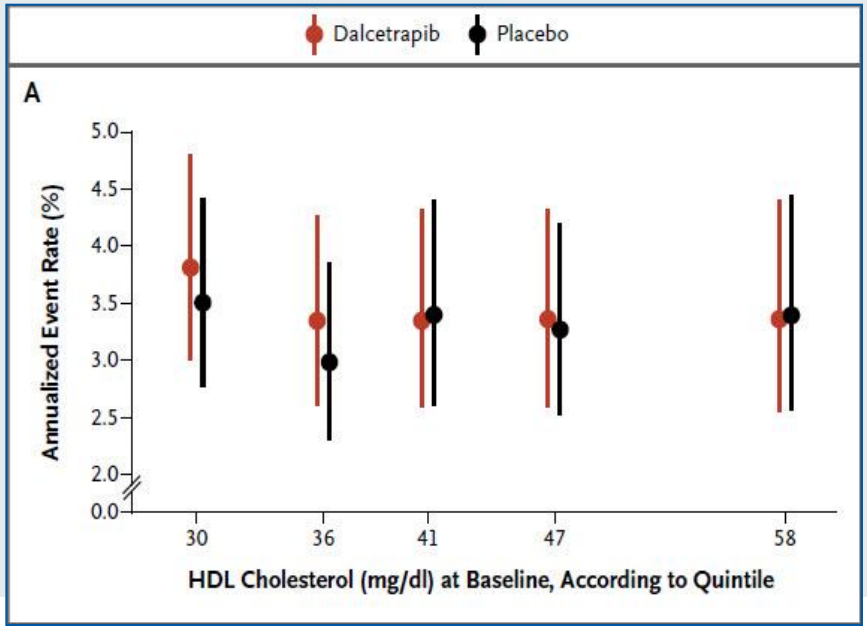
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2012;367:2089-99.
DOI: 10.1056/NEJMoa1206797

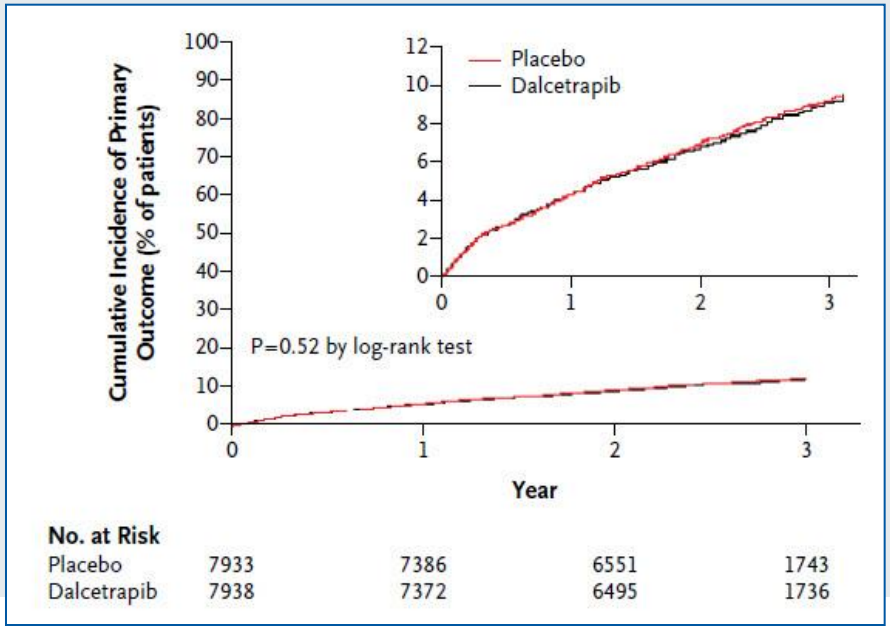
ORIGINAL ARTICLE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.D., Ph.D., Jochen Brumm, Ph.D., Bernard R. Chaitman, M.D., Ingar M. Holme, Ph.D., David Kallend, M.B., B.S., Lawrence A. Leiter, M.D., Eran Leitersdorf, M.D., John J.V. McMurray, M.D., Hardi Mundl, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Prediman K. Shah, M.D., Jean-Claude Tardif, M.D., and R. Scott Wright, M.D., for the dal-OUTCOMES Investigators*



Association between HDL Cholesterol Level
Dalcetrapib Placebo **and Risk of the Primary End Point**



Incidence of the Primary Efficacy End Point.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Altered Activation of Endothelial Anti- and Pro-Apoptotic Pathways by High-Density Lipoprotein from Patients with Coronary Artery Disease: Role of HDL-Proteome Remodeling

Meliana Riwanto, Lucia Rohrer, Bernd Roschitzki, Christian Besler, Pavani Mocharla, Maja Mueller, Damir Perisa, Kathrin Heinrich, Lukas Altwegg, Arnold von Eckardstein, Thomas F. Lüscher and Ulf Landmesser

Circulation. published online January 24, 2013;
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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Mild Renal Dysfunction and Metabolites Tied to Low HDL Cholesterol are Associated with Monocytosis and Atherosclerosis

Anjali Ganda, Martin Magnusson, Laurent Yvan-Charvet, Bo Hedblad, Gunnar Engström, Ding Ai, Thomas J. Wang, Robert E. Gerszten, Olle Melander and Alan R. Tall

Circulation. published online February 1, 2013;
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

LDL-Cholesterol/HDL-Cholsterol and risk of coronary disease

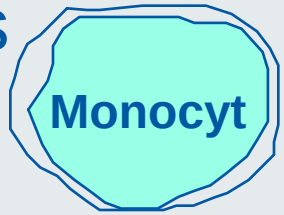
1% decrease in LDL-C: reduced CHD risk by 1%

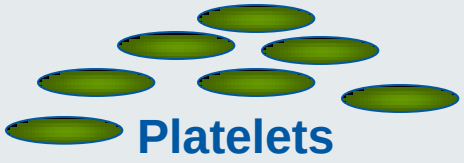
Statin Therapy

1% increase in HDL-C: reduced CHD risk by 2-3%

Therapeutic Opportunity ?

Endothelial NO production – anti-atherogenic effects





Inhibition of Leukocyte adhesion und -infiltration

Inhibition of Thrombocyte adhesion and -aggregation

Endothel

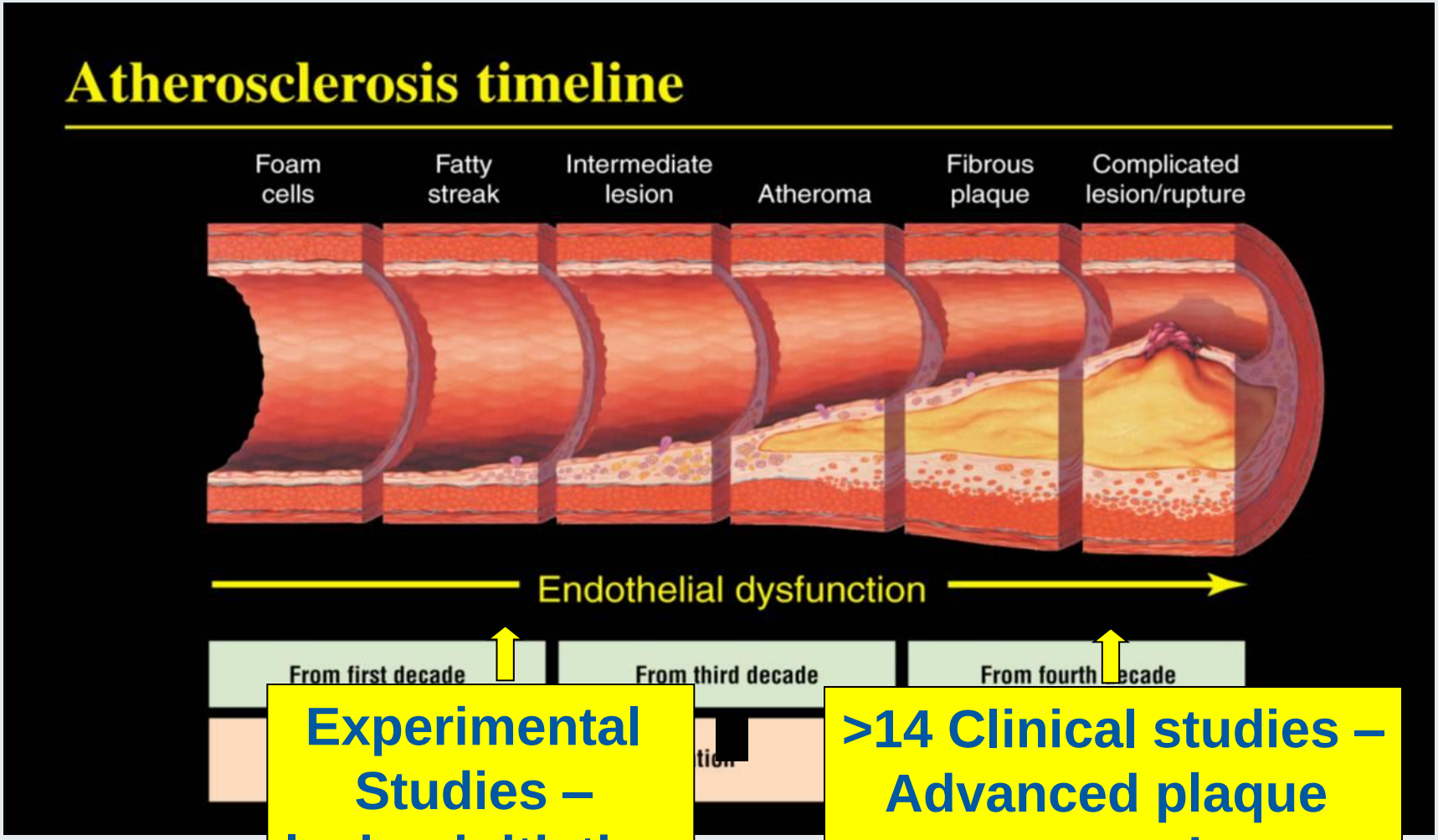
NO

Inhibition of VSMC proliferation

Vascular smooth muscle cell

Landmesser et al. *Circulation* 2004; 109(21 Suppl 1):II27-33

Endothelial dysfunction in atherosclerosis



Summarized in:

Landmesser et al. Circulation 2004; 109(21 Suppl 1):II27-33

High-Density Lipoprotein - vascular effects?

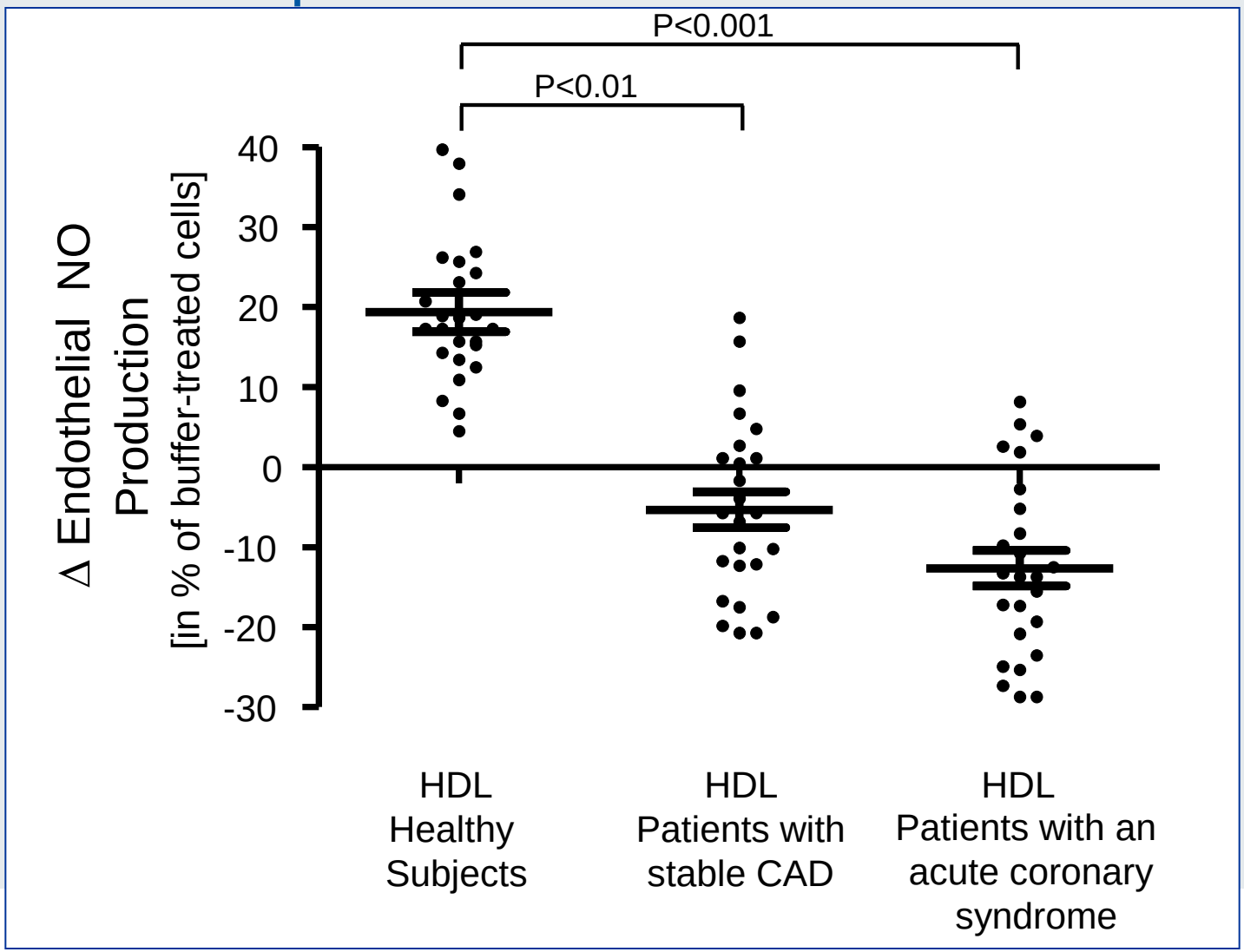
- **Anti-atherogenic effects of HDL ?**
- **“HDL function“ in coronary disease and diabetes ?**
- **HDL-targeted therapies ?**

Characteristics of the study population

	Healthy subjects (n=25)	Stable coronary artery disease (n=25)	Acute coronary syndrome (n=25)
Age (years)	54±5	56±6	54±6
Sex (male/female)	19/6	19/6	18/7
Body mass index (kg/m^2)	26±5	27±4	26±3
Total cholesterol (mmol/l)	5.3±1.0	5.4±0.9	5.1±0.7
HDL cholesterol (mmol/l)	1.4±0.4	1.2±0.3	1.2±0.3
LDL cholesterol (mmol/l)	2.9±0.9	2.7±1.0	2.8±0.6

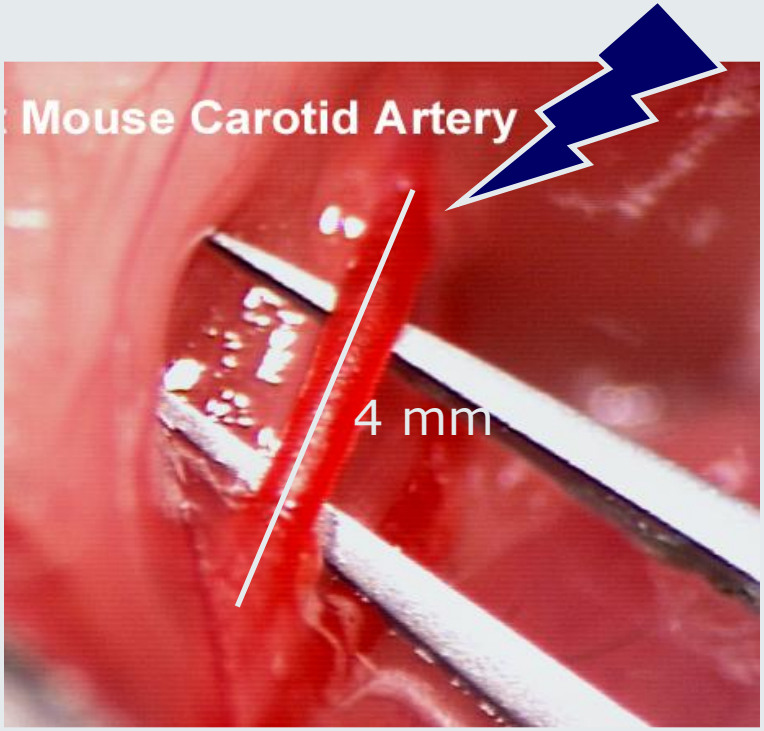
Besler C et al. & Landmesser U. *J Clin Invest* 2011;121(7):2693-708

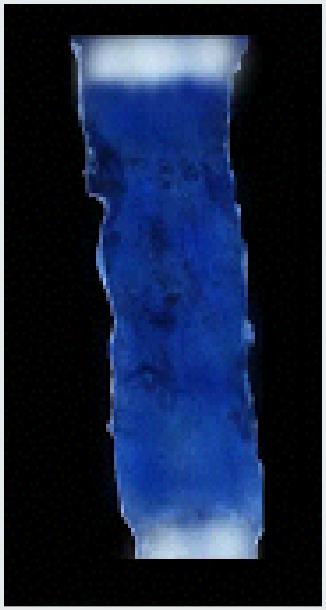
HDL –effects on endothelial cell nitric oxide production in patients with CAD



Besler C et al. & Landmesser U. *J Clin Invest* 2011;121(7):2693-708

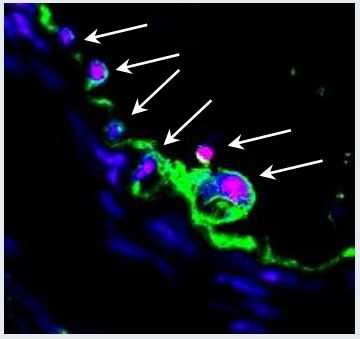
Carotid injury model to examine *in vivo* effect of HDL on endothelial repair

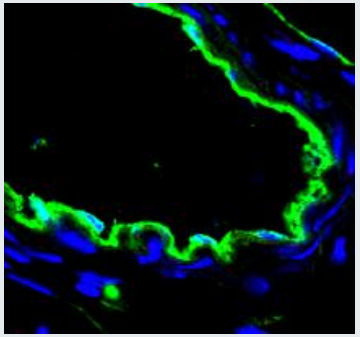




4 mm

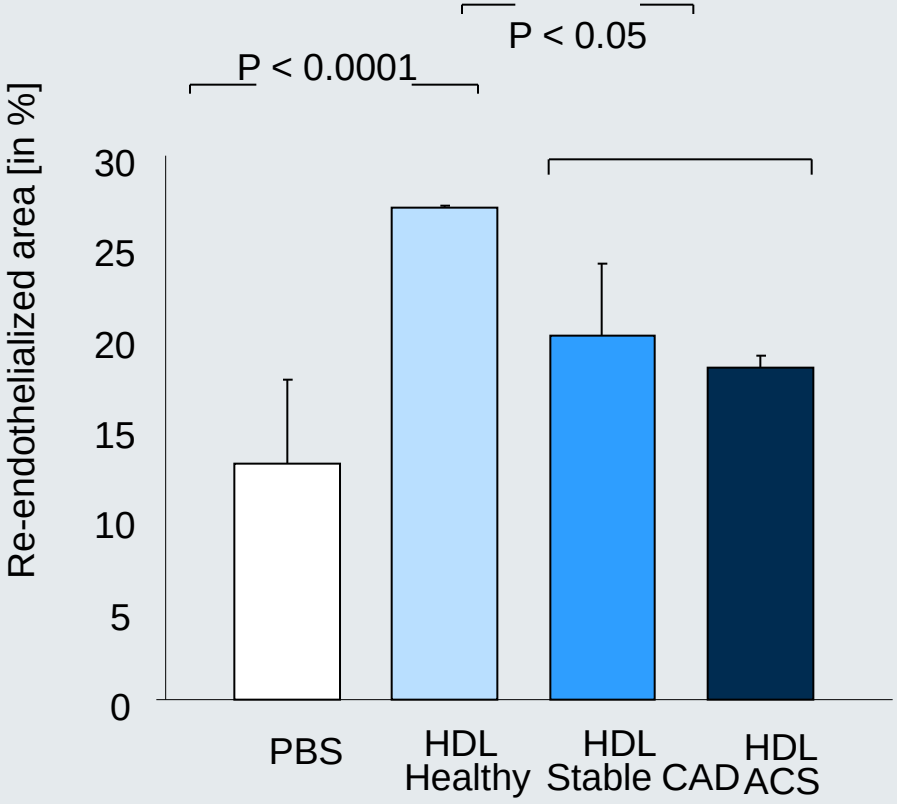
Evans blue staining

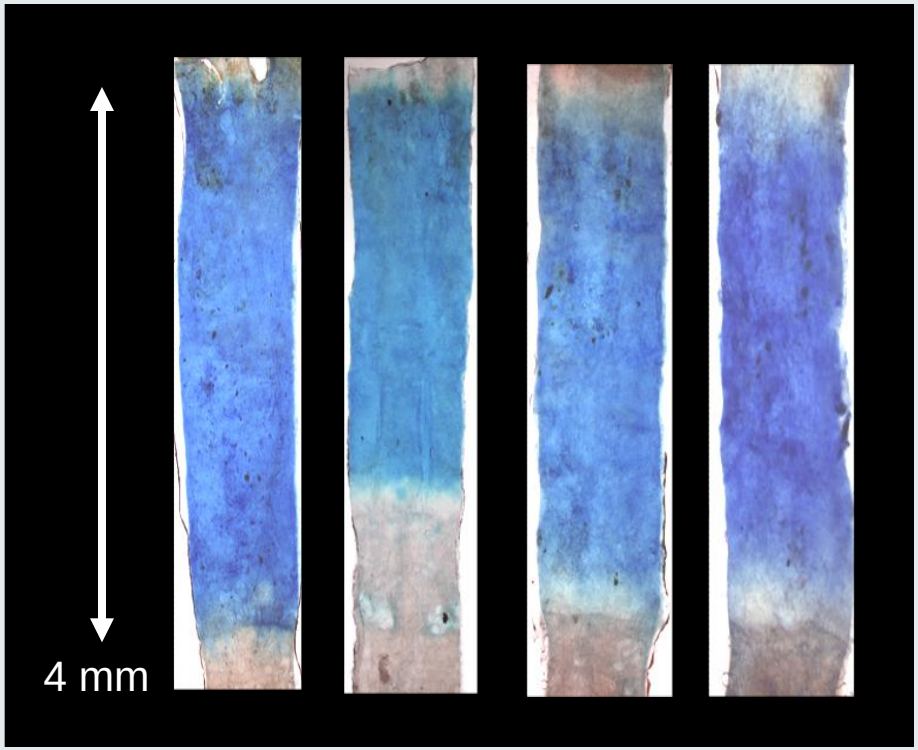




Sorrentino SA et al.; *Circulation* 2007; 116(2):163-73
Sorrentino SA et al.; *Circulation* 2010; 121(1):110-22
Giannotti G et al.; *Hypertension* 2010; 55:1389-97

Effects of HDL on endothelial repair in vivo after arterial injury





Quantification of re-endothelialized area 3 days after induction of carotid injury by Evan`s blue staining