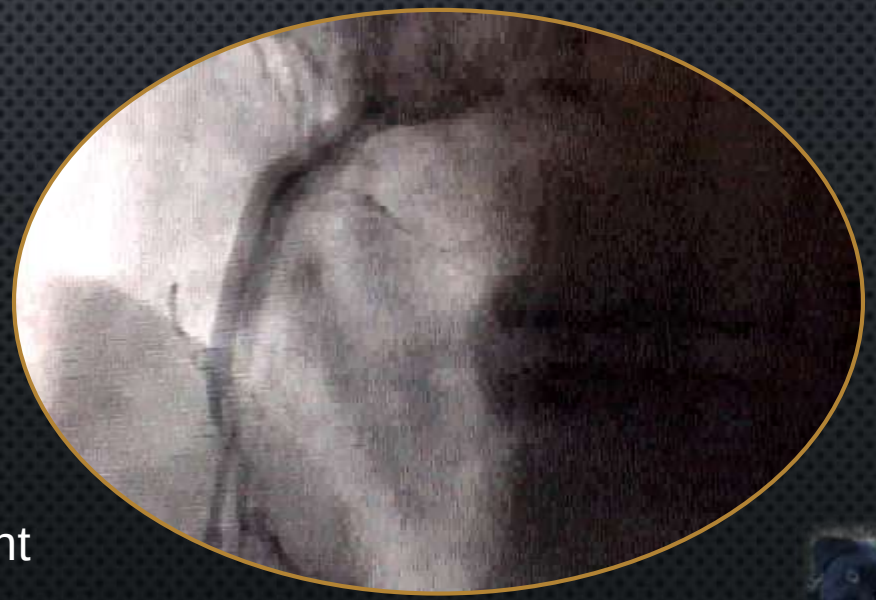
ATHEROSCLEROSIS: OMICS TO FUTURE CLINICAL CHALLENGES

Highest technologies available we still have unacceptable recurrent **acute coronary events** after treatment with **secondary** prevention…..10-20% in first 12 months

Eur Heart J. 2015;36:1163–1170
N Engl J Med. 2009;361:1045



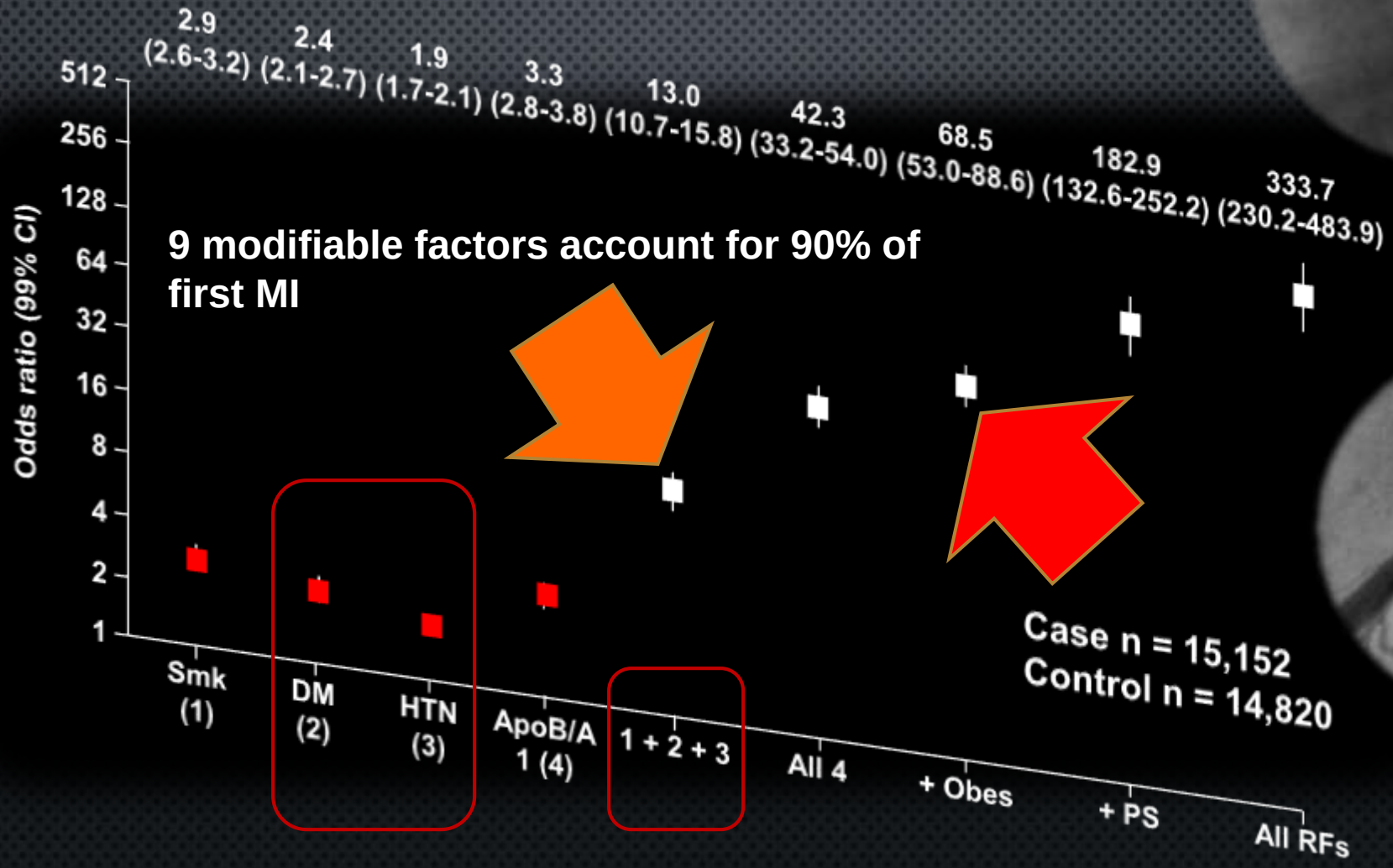
Professor Robert Chilton
University of Texas Health Science Center
San Antonio, Texas
Director of Cath Lab
Director clinical proteomics center

43 y/o male
Recent stent placement
ASA, Plavix, Statins

CONFLICTS: YES

- Research
- Clinical trials
- International advisory boards

INTERHEART: IMPACT OF MULTIPLE RISK FACTORS ON CV RISK

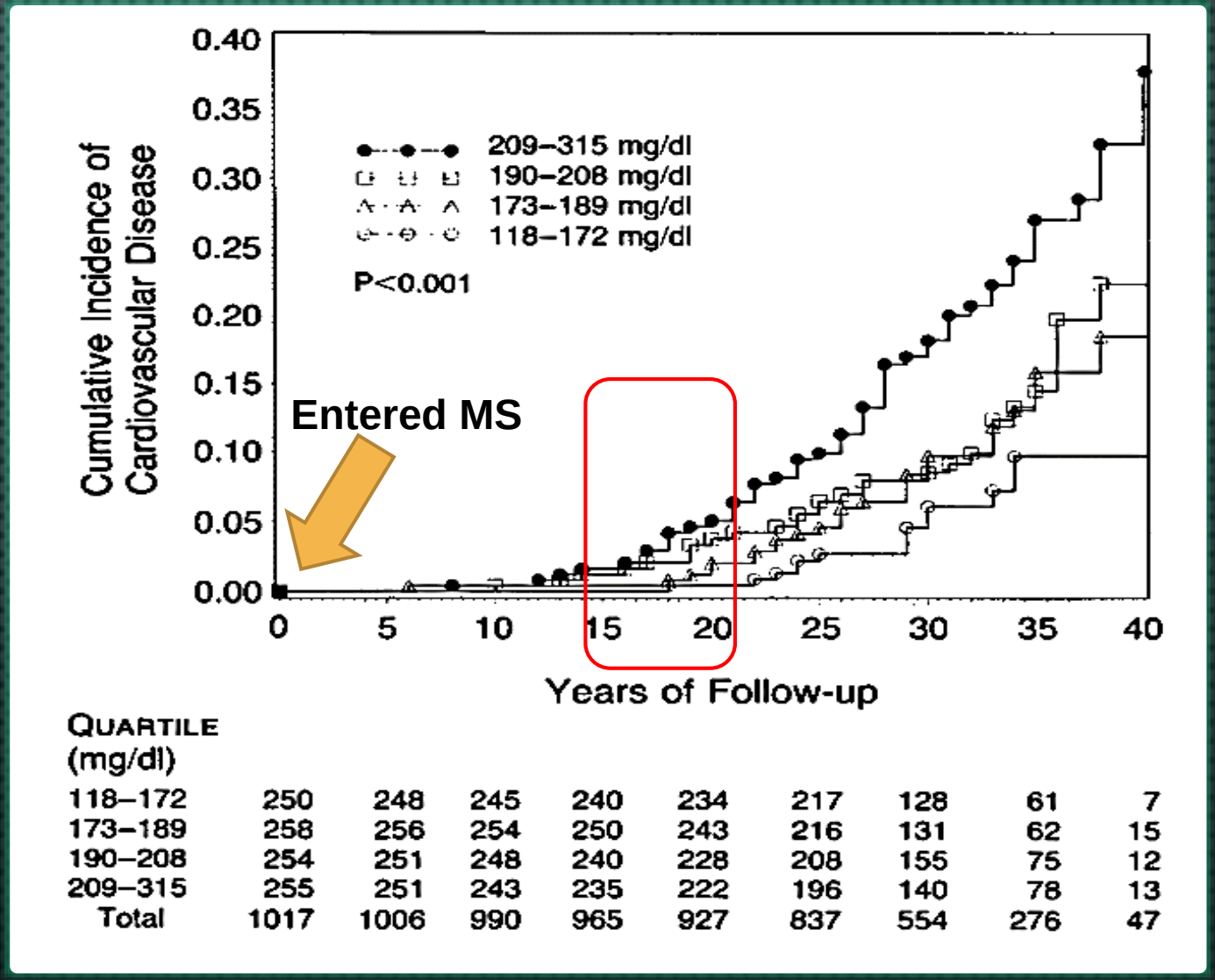


Yusuf S, et al. *Lancet.* 2004;364(9438):937-952.

NOTE: IT STARTS MAINLY AFTER 15-20YRS

Johns Hopkins: medical students cholesterol and risk of CV disease

Prospective study
N=1017 young men
Mean age 22

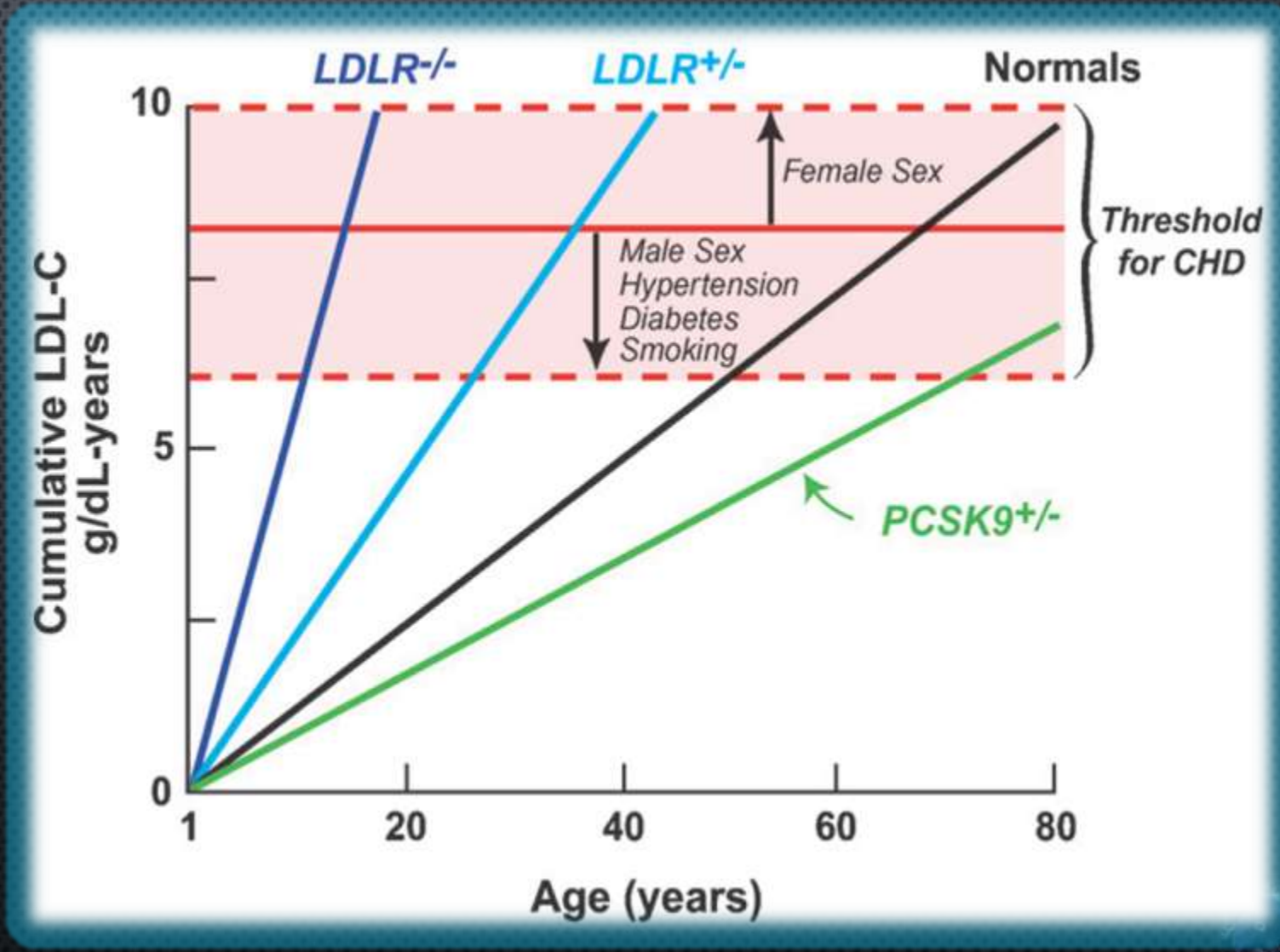


Quartile (mg/dl)									
118–172	250	248	245	240	234	217	128	61	7
173–189	258	256	254	250	243	216	131	62	15
190–208	254	251	248	240	228	208	155	75	12
209–315	255	251	243	235	222	196	140	78	13
Total	1017	1006	990	965	927	837	554	276	47

NEJM 1993;328:313

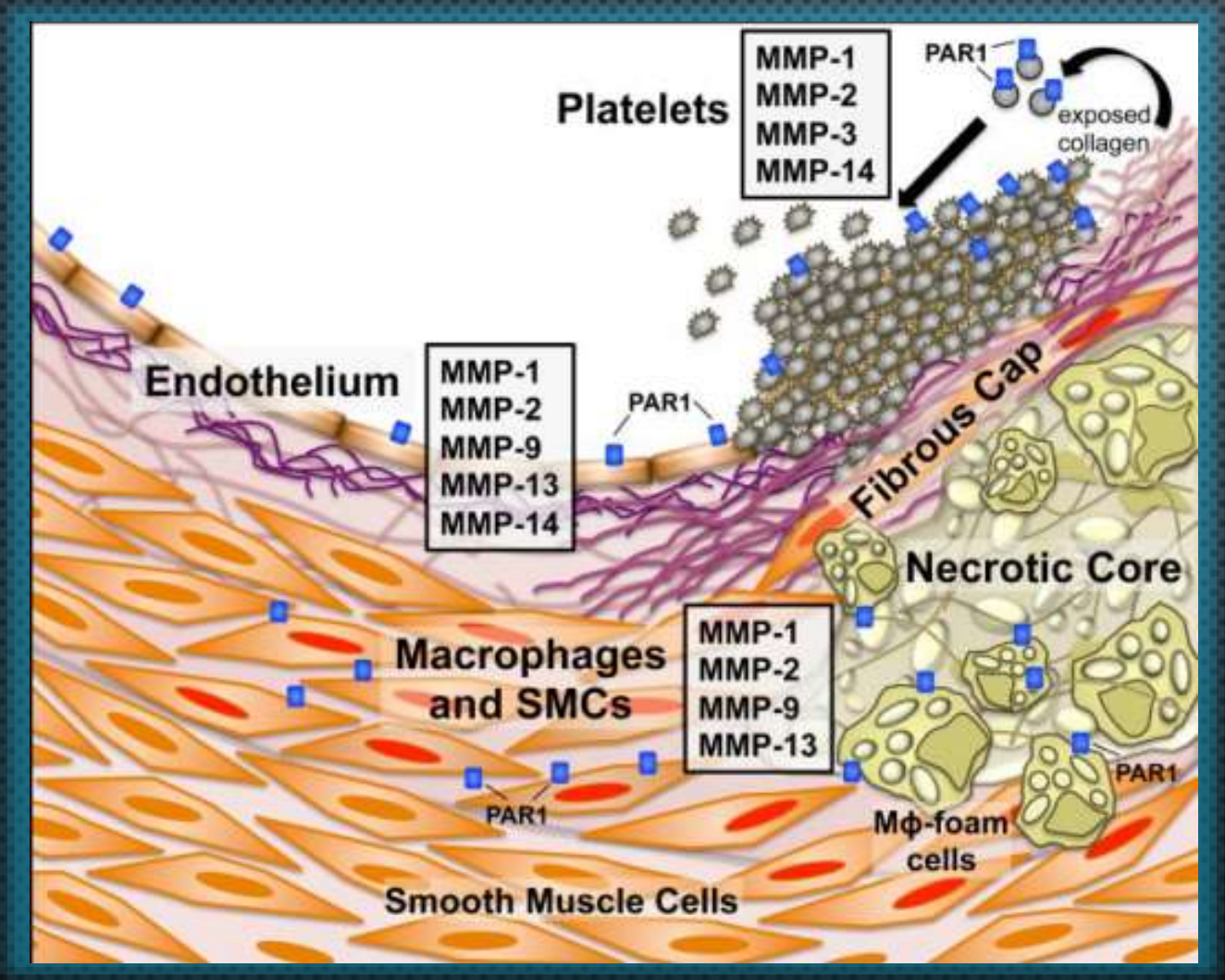
CUMULATIVE LDL EXPOSURE (EXPRESSED AS GRAMS OF CHOLESTEROL PER YEAR) OVER A LIFETIME IN PATIENTS

- 80 Y/O COULD HAVE HAD 10 G/DL-YEARS EXPOSURE TO LDL
- <20 YEARS OF AGE FH PATIENT WOULD HAVE ALREADY HAD 10 G/DL-YEARS EXPOSURE TO LDL



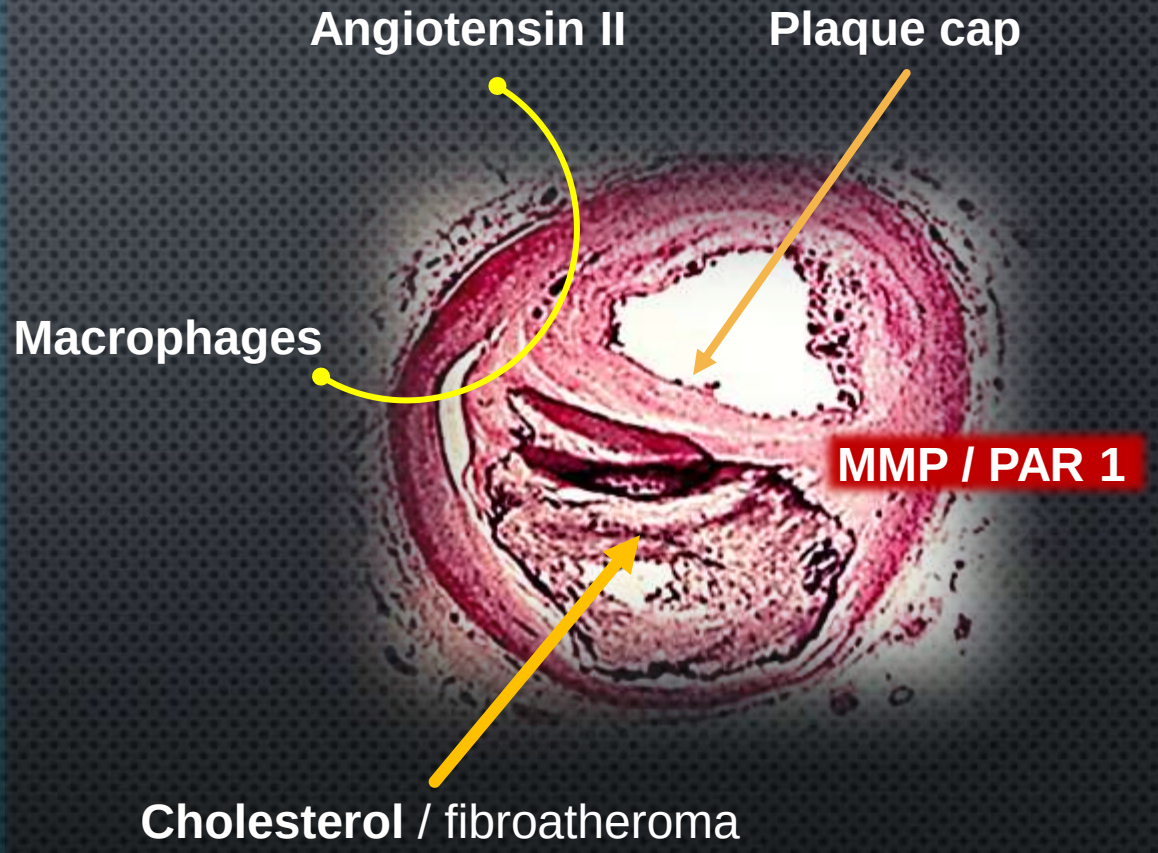
J. Lipid Res. 2009. 50: S172 – S177

Hematologic importance in plaque rupture



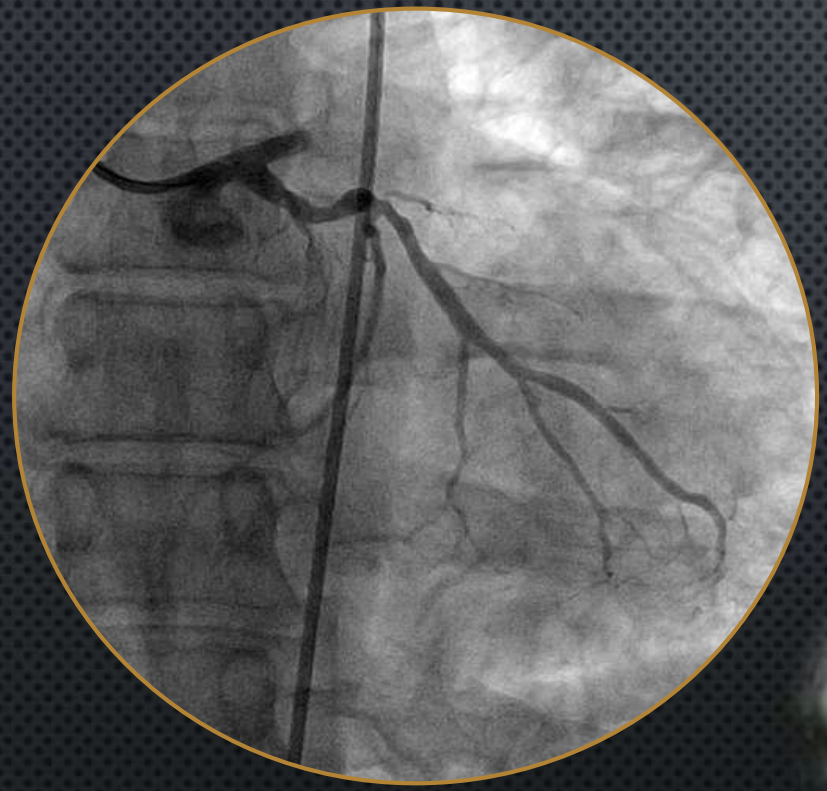
Translational biology of atherosclerosis

43 Lfull blood PAR1 MMP+++++.pdf

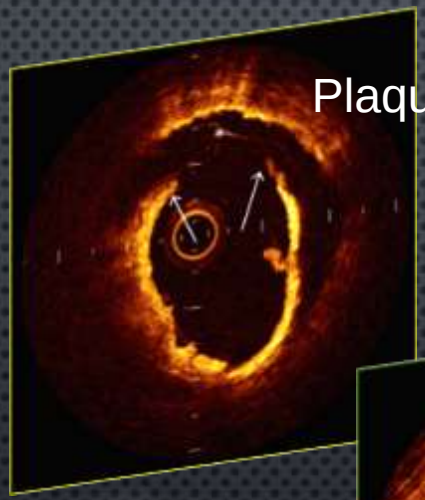


Nature medicine 2013;19:1094
Austin et al Blood 2013;121:431

ACUTE CORONARY SYNDROME CHARACTERISTIC'S BY OCT

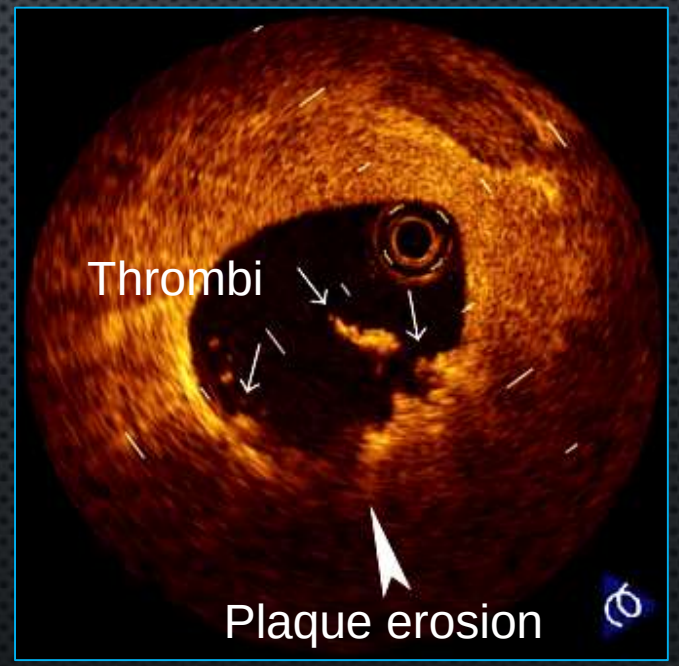


Biomarkers?



Plaque rupture

Thrombus

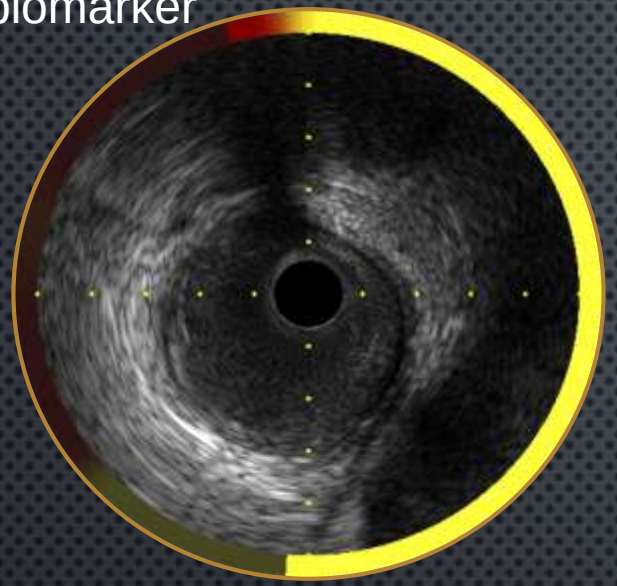


Thrombi

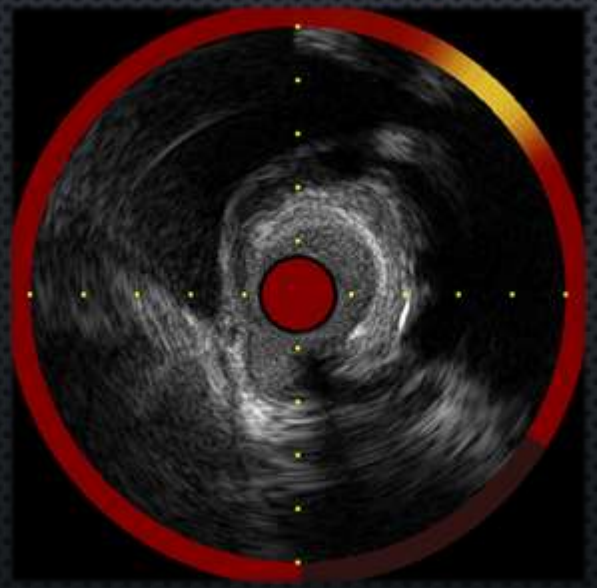
Plaque erosion

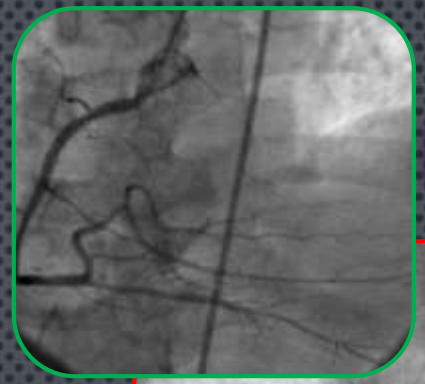
Cardiology Research and Practice: doi:10.4061/2011/312978

Imaging biomarker

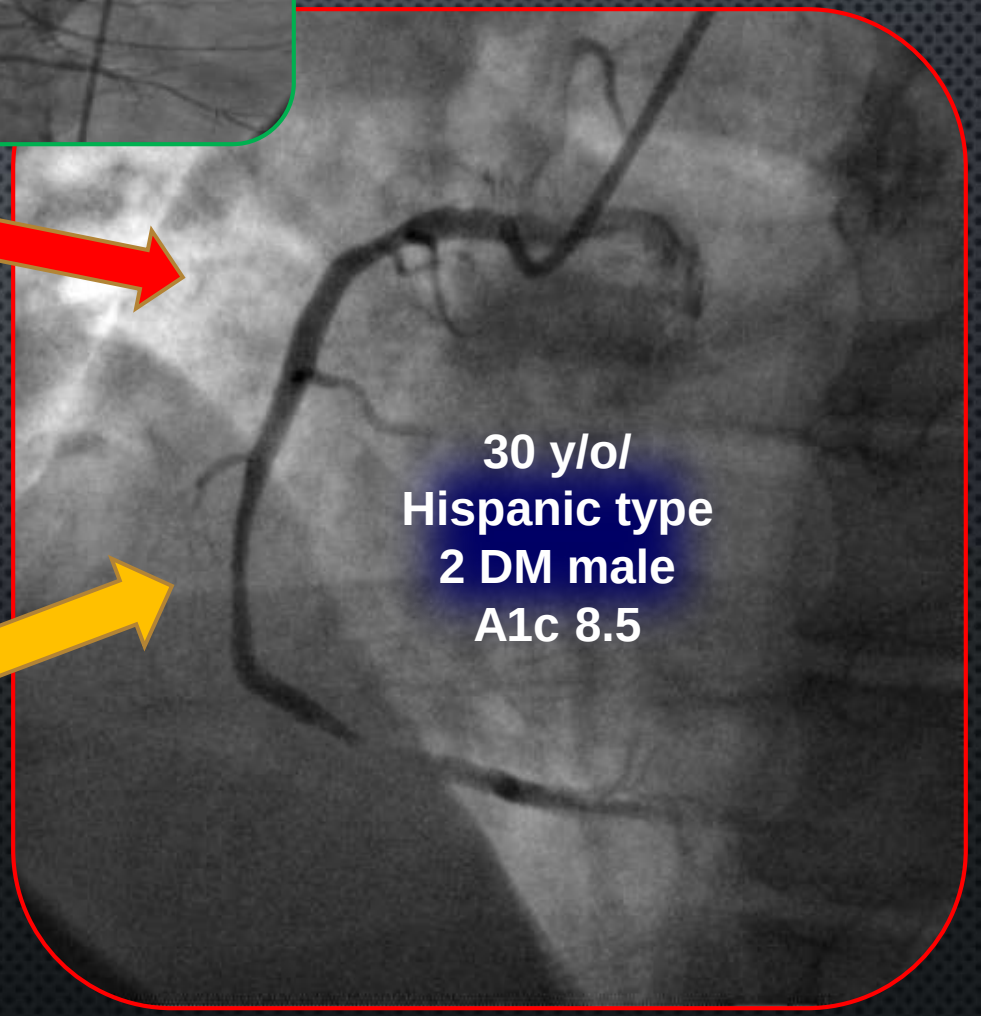


NIRS-IVUS





8 months before

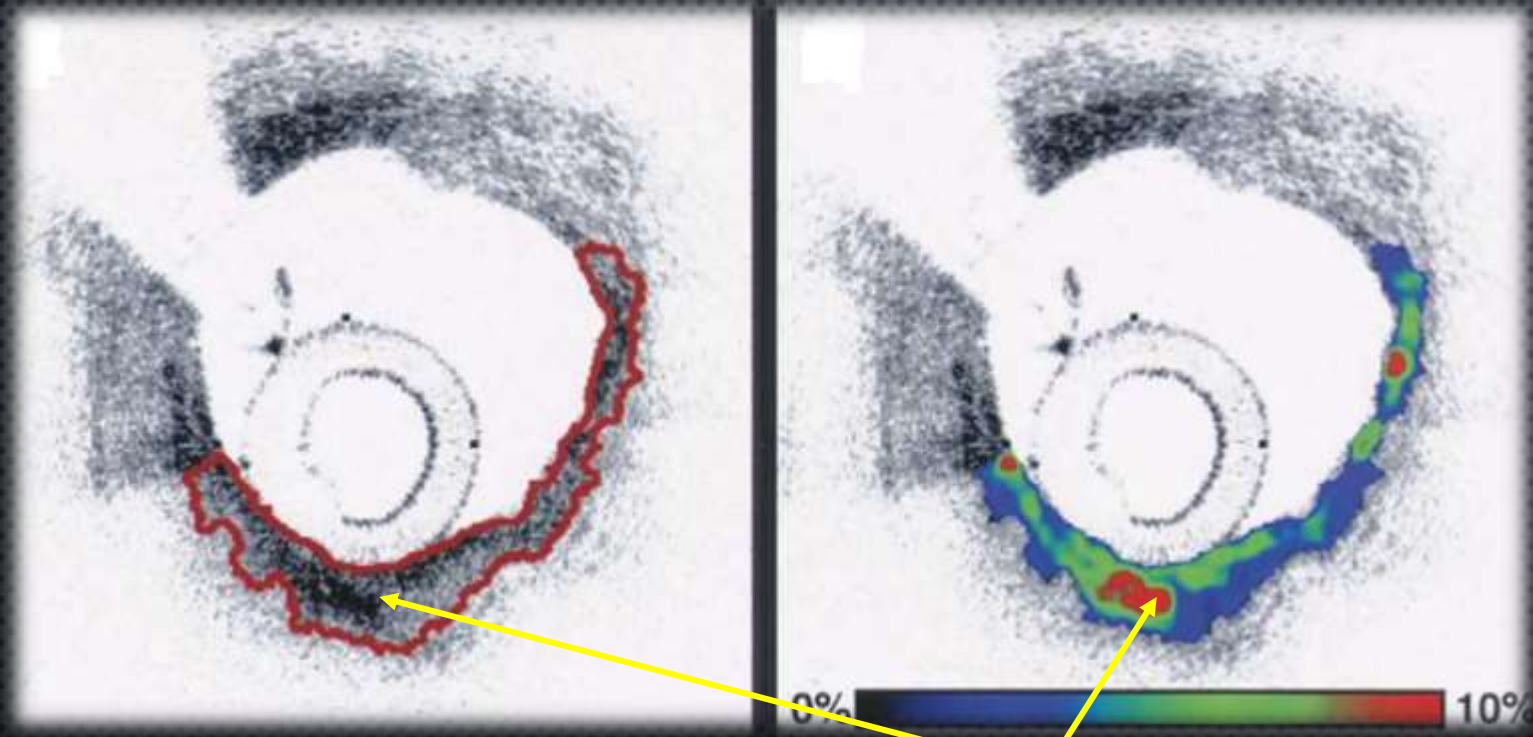


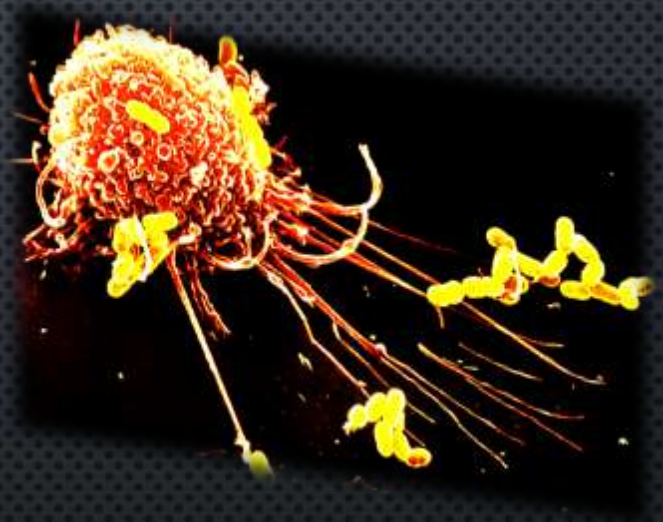
30 y/o/
Hispanic type
2 DM male
A1c 8.5

Acute coronary syndrome

OCT CAN ESTIMATE MACROPHAGE (INFLAMMATION) ACCUMULATION WITHIN fiBROUS CAPS

Imaging biomarkers





Macrophages

Humans with unstable angina (Red outlines: fibrous cap of the OCT image)

J Am Coll Cardiol 2004;44:972–9

BIOMARKERS TO IMPROVE THE PREDICTION OF DEATH FROM CARDIOVASCULAR CAUSES

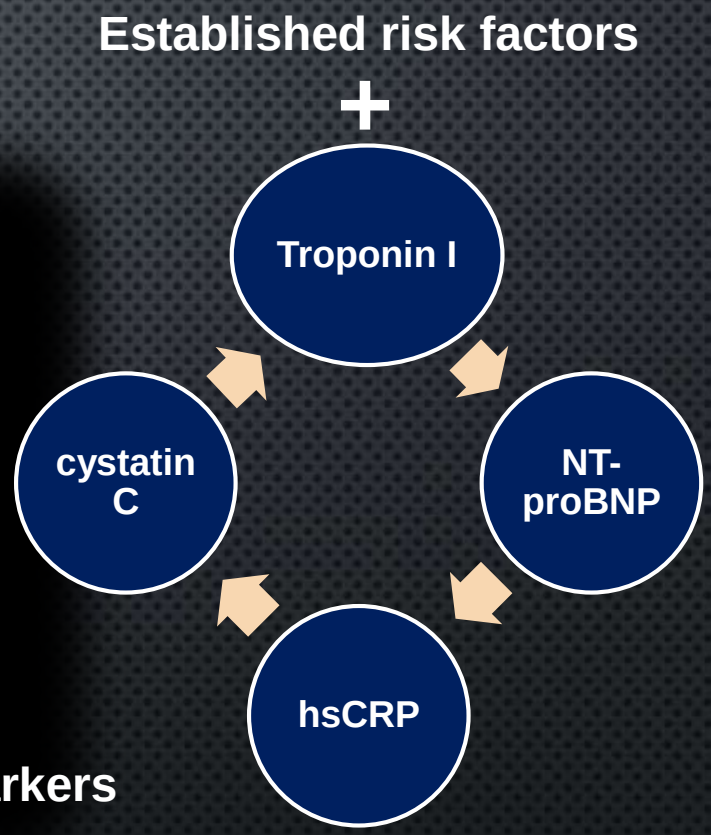
- Uppsala Longitudinal Study of Adult Men (ULSAM): cohort of elderly men (mean age 71)
- Hypothesis: can biomarkers improve risk stratification for CV events vs conventional?
- N= 1135
  - 136 deaths were cardiovascular
- four biomarkers (troponin I, NT-pro-BNP, C-reactive protein, and cystatin C) improved risk stratification for death from cardiovascular causes

C statistic improved significantly with four biomarkers

0.766
Biomarkers

P<0.001

0.664
Without biomarkers

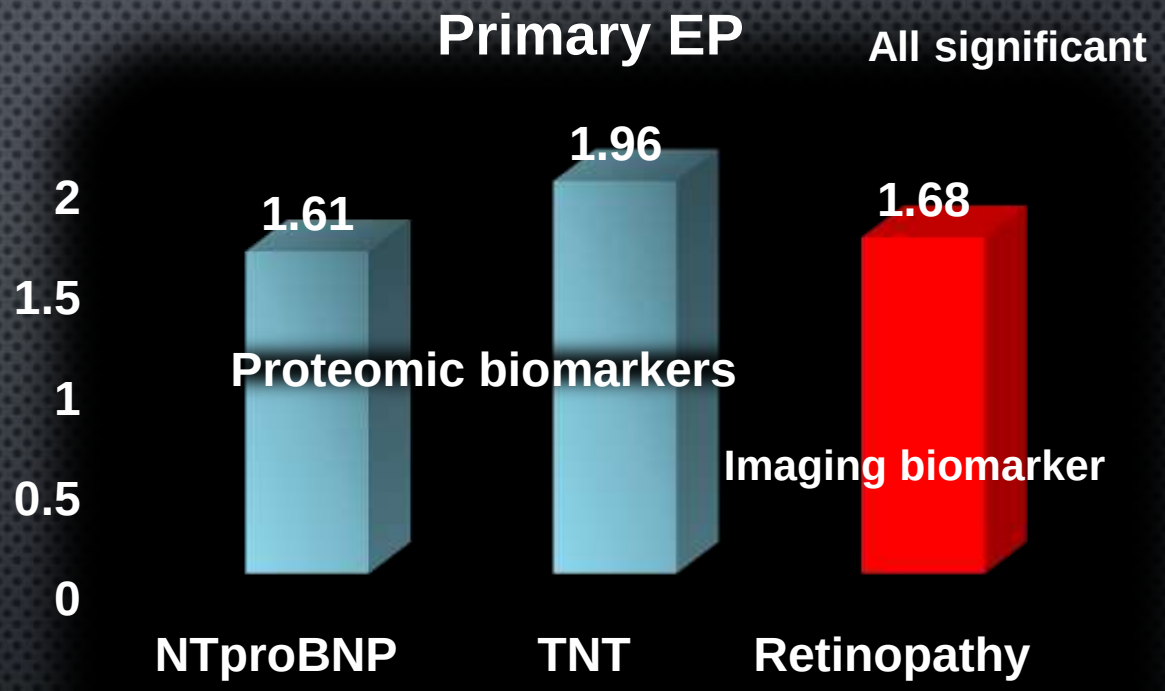


Uppsala, Sweden

N Engl J Med 2008;358:2107-16

THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY: DIABETES LOOK

- ARIC STUDY - PROSPECTIVE OBSERVATIONAL STUDY OF THE NATURAL HISTORY OF ATHEROSCLEROTIC DISEASES AND CARDIOVASCULAR RISK FACTORS
- MIDDLE-AGED (45 – 64 YEARS)(N=11,656)
- PARTICIPANTS WITHOUT PREVALENT CVD, WITH FURTHER CATEGORIZATION ACCORDING TO THE PRESENCE (N =1,510) OR ABSENCE (N = 6,892) OF DIABETES



Kaplan-Meier curves for probability of fatal and nonfatal cardiovascular events. HRs are adjusted for demographic characteristics and cardiovascular risk factors. DM, diabetes.

NTproBNP cutoff value of 125 pg/mL

Diabetes Care 2016;39:677 – 685

Microbiome

Future

New CV agents that lower BS

Introduction-translational cardio-metabolics

↓ LDL

Statins

Myositis

BET inhibitors

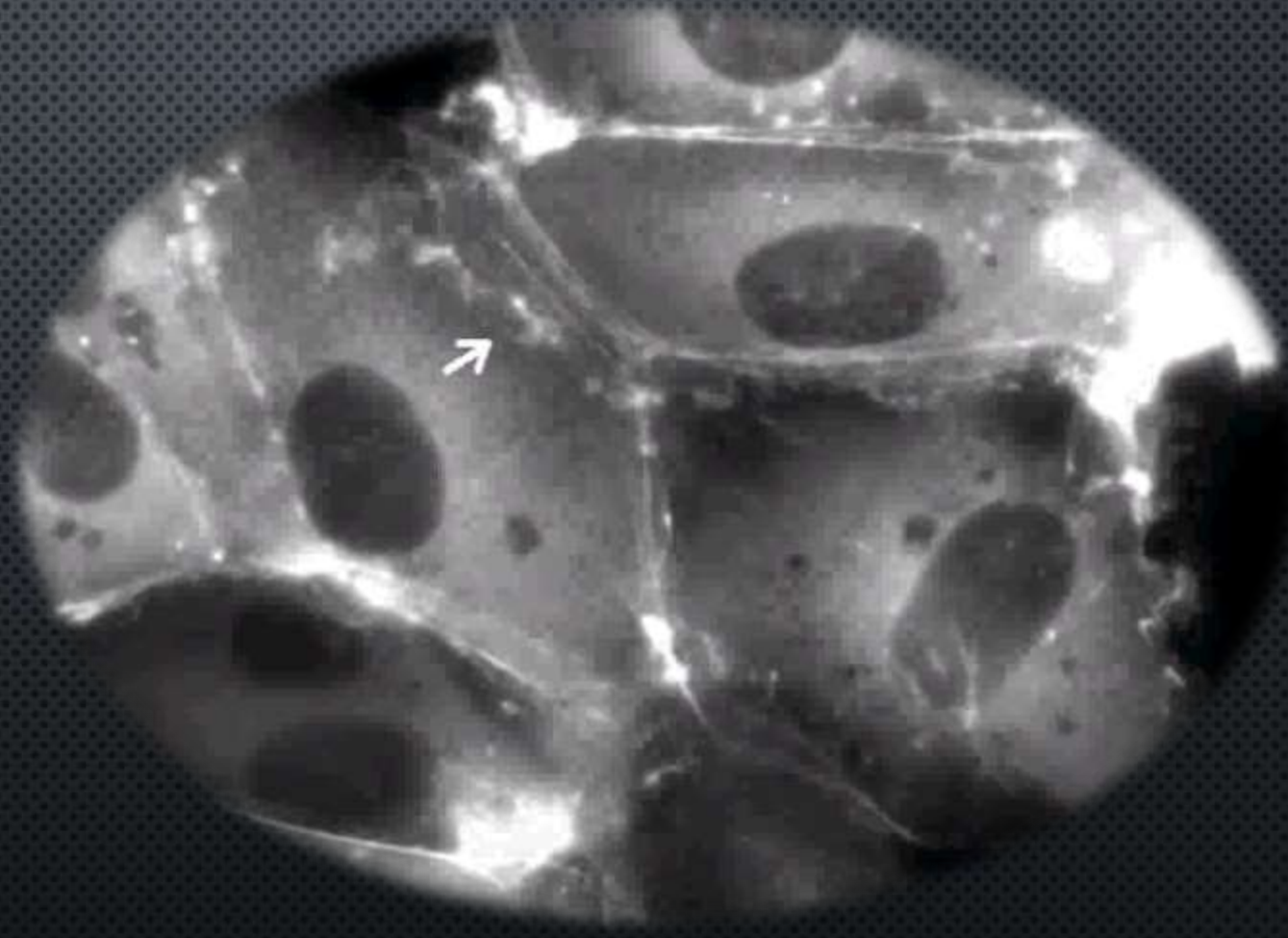
PCSK9

European Heart Journal
doi:10.1093/eurheartj/ehr224

Outline

Maestro of the CV system

Live imaging of endothelial cells at 600x magnification



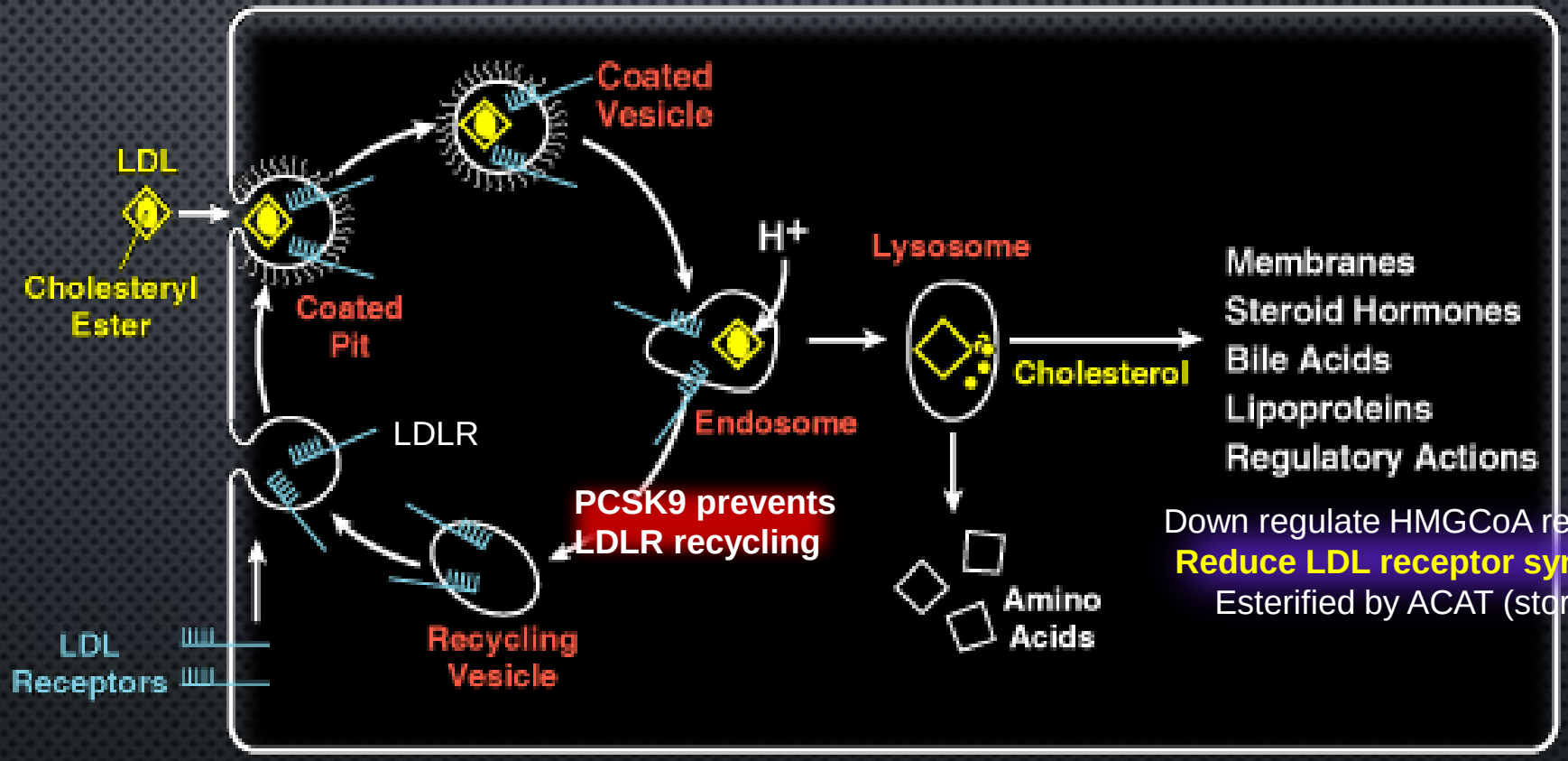
Endothelial cell health

Co-shared risk factors

Cardiovascular health

Courtesy of Jerome Breslin

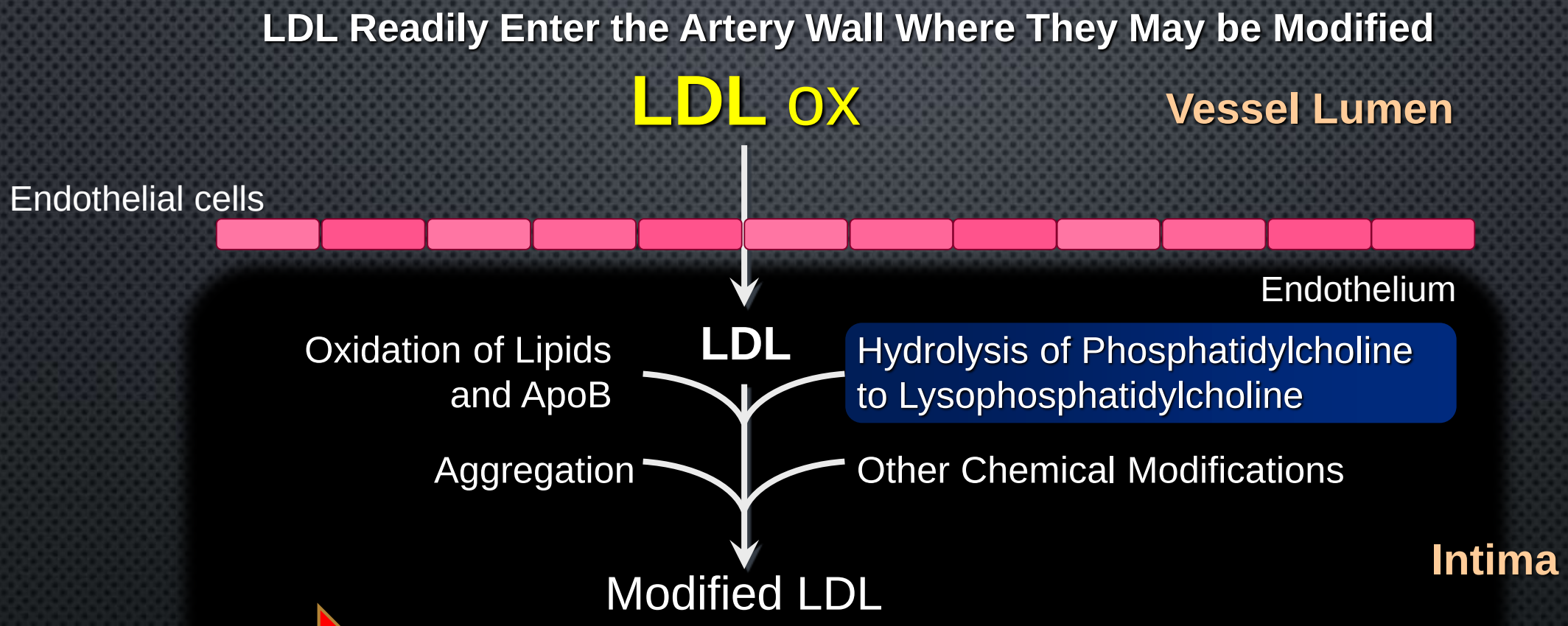
LDL RECEPTOR PATHWAY



Down regulate HMGCoA reductase
Reduce LDL receptor synthesis
Esterified by ACAT (storage)

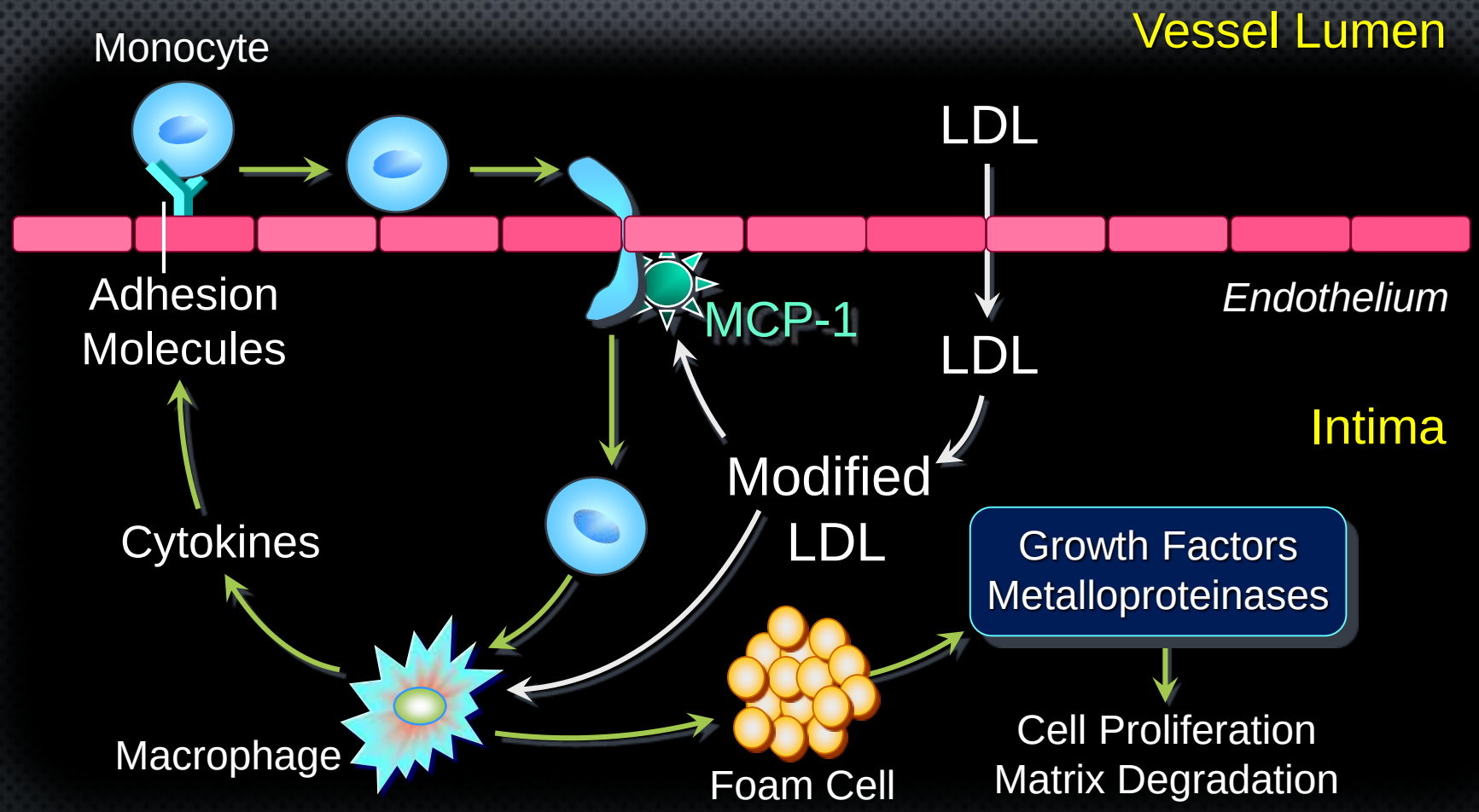
Statins: **High CV risk patient high potency statin**

LDL AND ATHEROGENESIS



Steinberg D et al. *N Engl J Med* 1989;320:915-924

MACROPHAGES AND FOAM CELLS EXPRESS GROWTH FACTORS AND PROTEINASES



Ross R. *N Engl J Med* 1999;340:115-126

C V RISK CONTINUES EVEN WITH STATIN THERAPY

Trial	Statin treatment	Clinical events*	
		Risk reduction vs placebo	Remaining risk
WOSCOPS** (6595)	Pravastatin 40 mg	31%	69%
AFCAPS/TexCAPS** (6605)	Lovastatin 20 or 40 mg	40%	60%
ASCOT-LLA** (10,305)	Atorvastatin 10 mg	38%	62%
4S** (4444)	Simvastatin 20 mg	26%	74%
CARE*** (4159)	Pravastatin 40 mg	24%	76%
LIPID*** (9014)	Pravastatin 40 mg	24%	76%
HPS*** (20,536)	Simvastatin 40 mg	27%	73%
PROSPER*** (5804)	Pravastatin 40 mg	24%	76%

*Nonfatal myocardial infarction and coronary death; **Primary prevention trial; ***Secondary prevention trial

QUESTION:

- **ARE RELATIVE RISK REDUCTIONS IN CV EVENTS WITH STATIN THERAPY ---RELATED TO BASELINE LEVELS OF LDLC?**

N Engl J Med 2008;359:2195-207

Genetic studies suggest that even lower LDLC levels are likely to confer cardiovascular benefits regardless of starting cholesterol levels

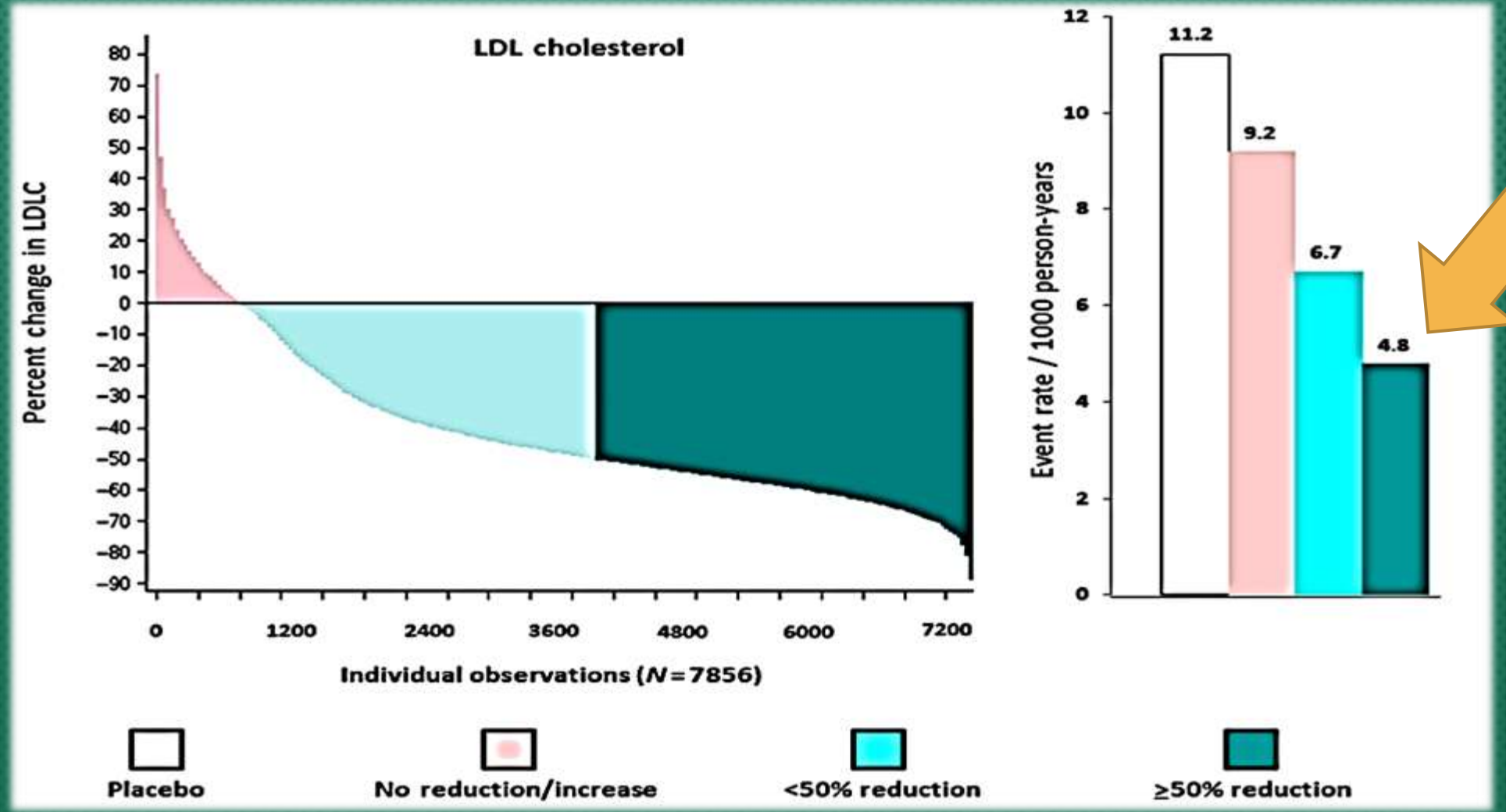
Am Coll Cardiol 2012;60:2631-9

JUPITER primary prevention trial high-intensity statin regimen, the magnitude of percentage change in LDLC was directly related to subsequent event rates.

Eur Heart J 2016;37:1373-9

THE LARGER PERCENTAGE CHANGE IN LDL THE GREATER THE CV BENEFIT

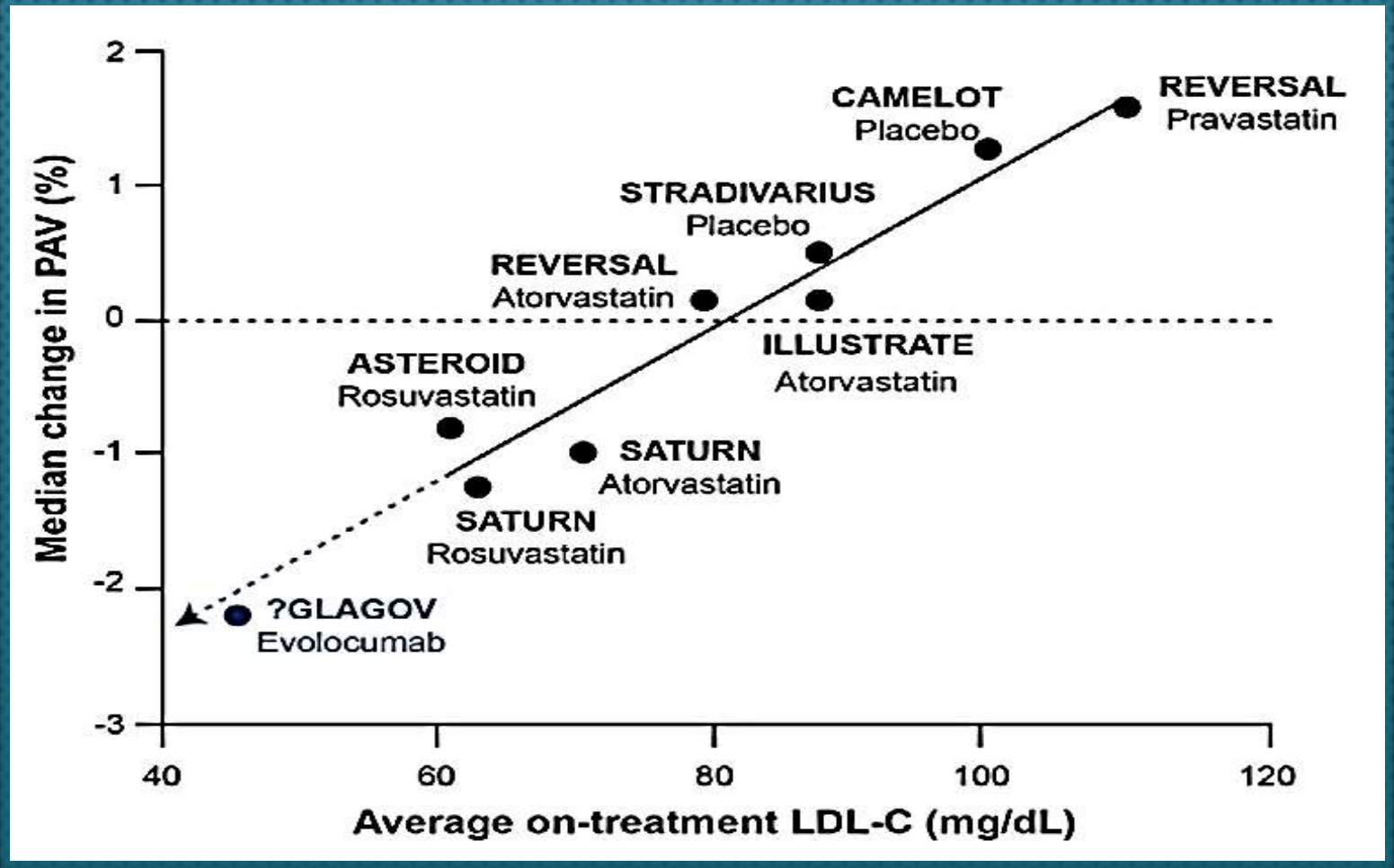
JUPITER



Jupiter 2016nker.pdf

European Heart Journal (2016) 37, 1373–1379

IVUS FINDS LOWER IS BETTER FOR CHANGING PLAQUE ATHEROMA VOLUME



glagov.pdf

Am Heart J 2016;176:83-92

PCSK9 (proprotein convertase subtilisin-kexin type 9)(GENE)

TRANSLATIONAL BIOLOGY OF PCSK9

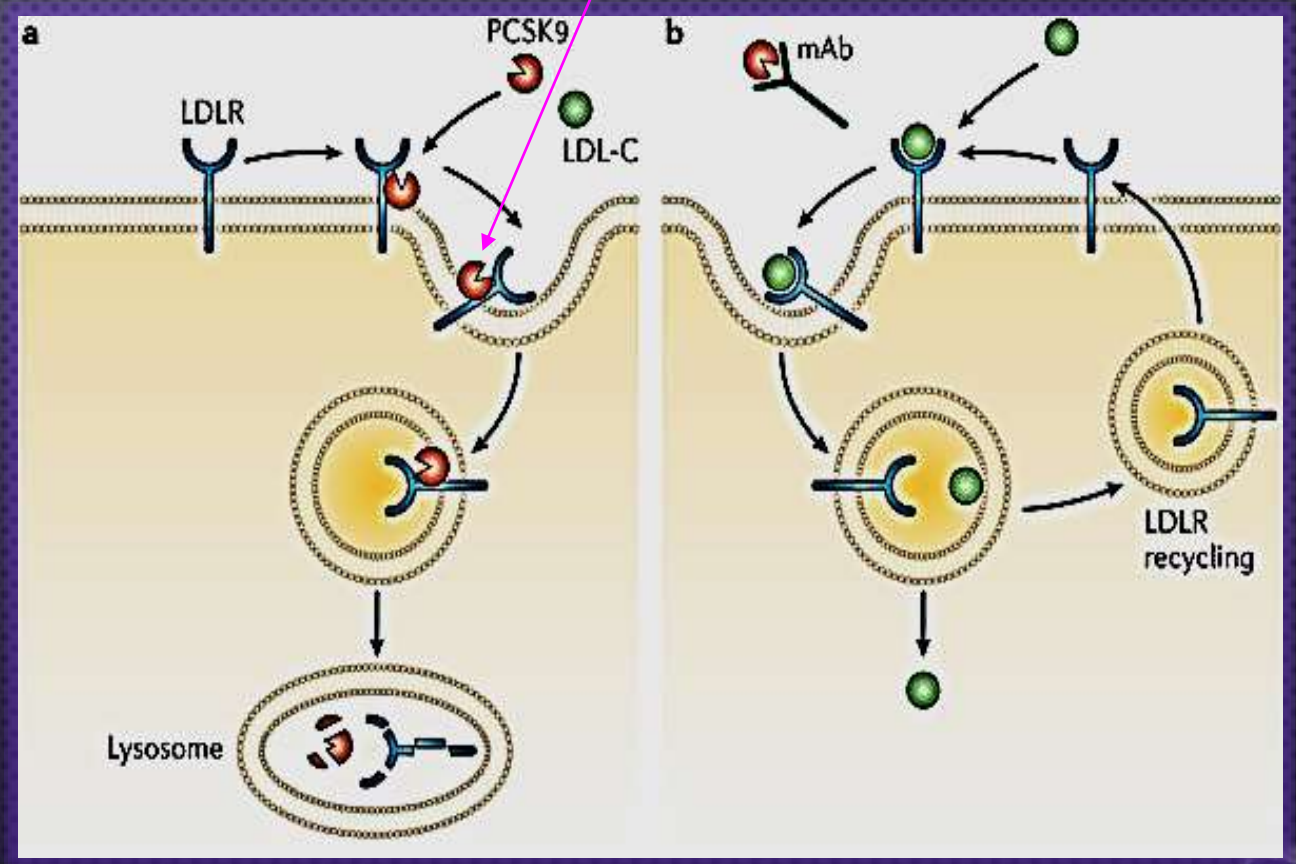
Atherosclerosis Risk in Communities Study, a missense mutation (pcsk9) in the prodomain (R46L), was associated with a 15% reduction in LDL-C and a 46% reduction in CHD

Trends Biochem. Sci. 32: 71

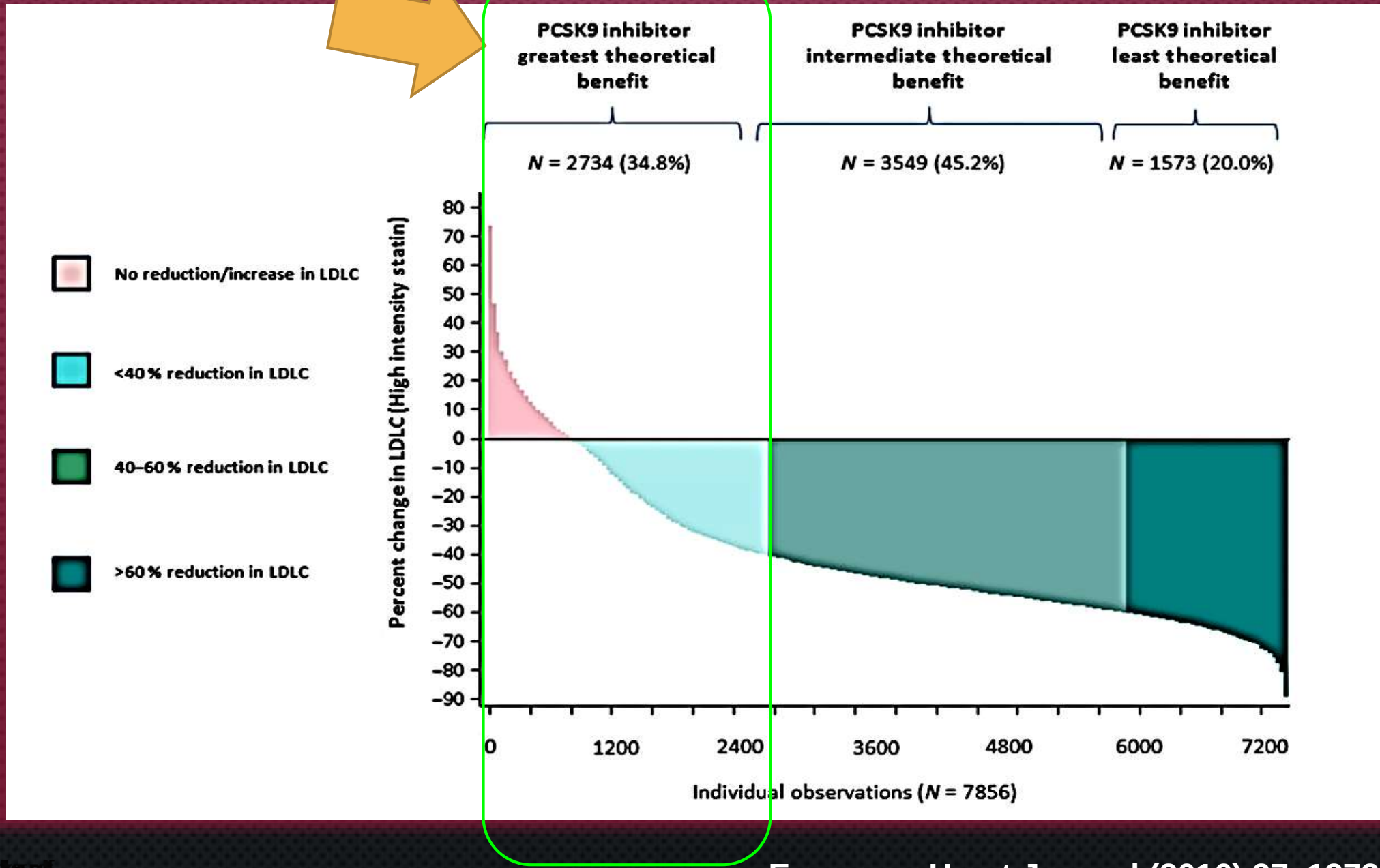
2-nonsense mutations (Y1423 and C6793), present in 2% of African-Americans, caused a 28% reduction in LDL-C and an 88% reduction in CHD

N Engl J Med 2006;354:1264-72

When PCSK9 binds to an LDLR, the receptor is **destroyed** along with the LDL particle



Nature reviews



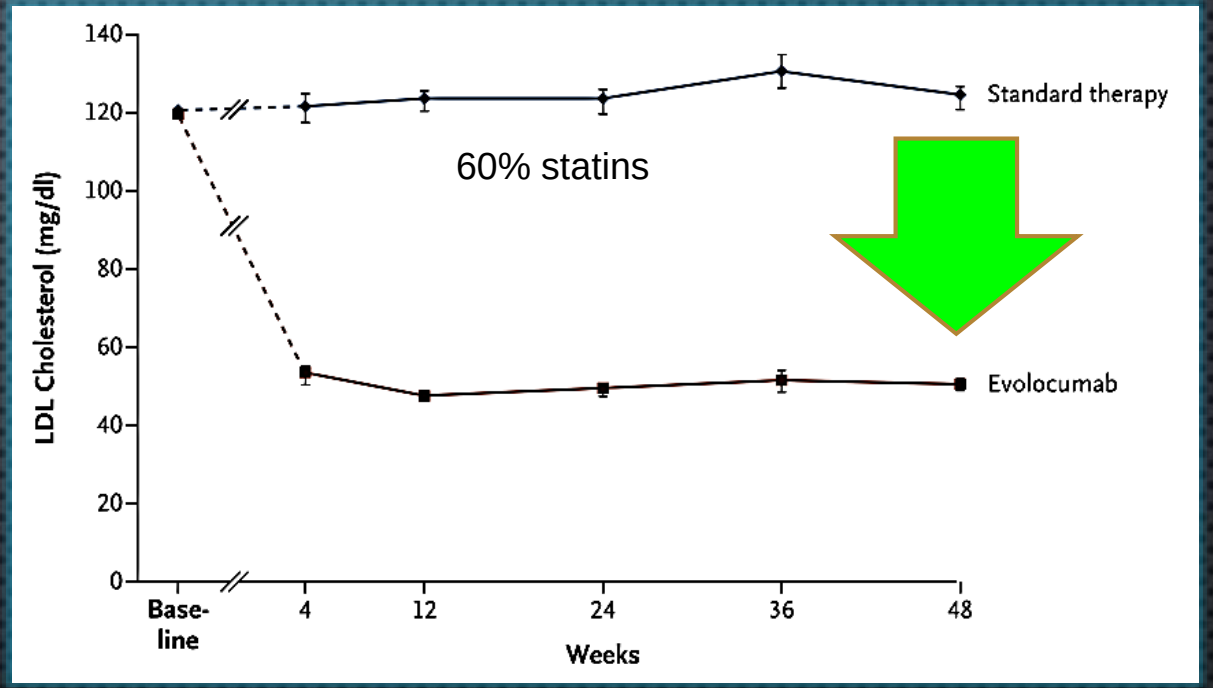
Jupiter 2016nrdkr.pdf

European Heart Journal (2016) 37, 1373–1379

FURTHER CARDIOVASCULAR OUTCOMES RESEARCH WITH PCSK9 INHIBITION IN SUBJECTS WITH ELEVATED RISK (FOURIER)

- DB, Randomized: Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy In Patients With Clinically Evident Cardiovascular Disease
- (N = 27,500), 5 years
- Primary endpoint: cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization whichever occurs first

OSLER trial N=1359



Enrollment:	27564
Study Start Date:	February 2013
Estimated Study Completion Date:	November 2016
Estimated Primary Completion Date:	November 2016

AHA?

N engl j med 2015;372:1500
Am Heart J 2016;173:94-101
Clinical trials.gov Sept 2016

ODYSSEY OUTCOMES: EVALUATION OF CARDIOVASCULAR OUTCOMES AFTER AN ACUTE CORONARY SYNDROME DURING TREATMENT WITH ALIROCUMAB

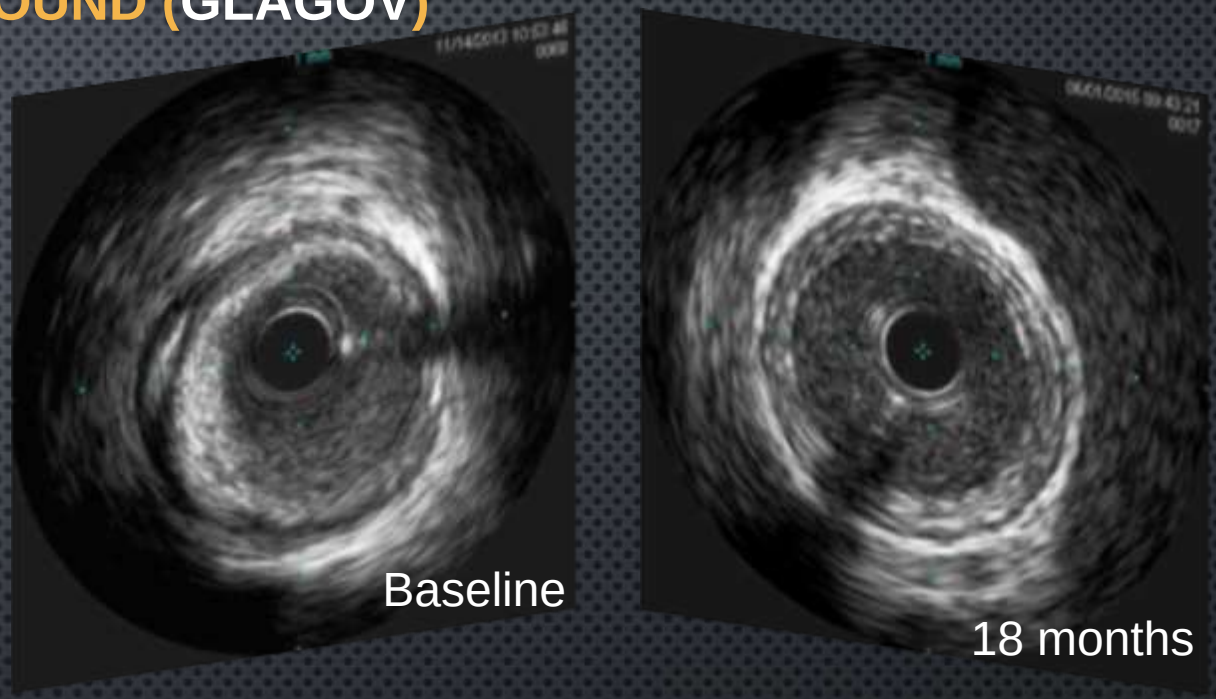
- PRIMARY: CHD DEATH, ANY NON-FATAL MI, FATAL AND NON-FATAL ISCHEMIC STROKE, UNSTABLE ANGINA REQUIRING HOSPITALIZATION
- F/U 64 MONTHS

Estimated Enrollment:	18600
Study Start Date:	October 2012
Estimated Study Completion Date:	February 2018
Estimated Primary Completion Date:	December 2017 (Final data collection date for primary outcome measure)

Clinical trials.gov Sept 2016

GLOBAL ASSESSMENT OF PLAQUE REGRESSION WITH A PCSK9 ANTIBODY AS MEASURED BY INTRAVASCULAR ULTRASOUND (GLAGOV)

- Impact of PCSK9 inhibition on coronary atheroma progression
- Phase 3, multicenter, double-blind, randomized, placebo-controlled trial evaluating the impact of
- Coronary atheroma volume: baseline to week 78 post randomization, as determined by intravascular ultrasound (IVUS)
- Randomized to the Evolocumab (AMG 145) arm will receive Evolocumab (AMG 145) subcutaneously every 4 weeks
- Regression (any reduction from baseline) in PAV (atheroma volume)[78 weeks]



Enrollment:	**970**
Study Start Date:	**May 2013**
Study Completion Date:	**July 2016**
Primary Completion Date:	**July 2016**

Inclusion Criteria:

Subjects already taking statin therapy, niacin or ezetimibe at screening must have been on a stable dose for at least 4 weeks prior to screening LDL-C. Fasting LDL-C ≥ 80 mg/dL (with or without additional risk factors)

glagov.pdf

Am Heart J 2016;176:83-92
Clinical trials.gov Sept 2016

COMPARISON OF OUTCOMES PCSK9 CLINICAL TRIALS

First to report

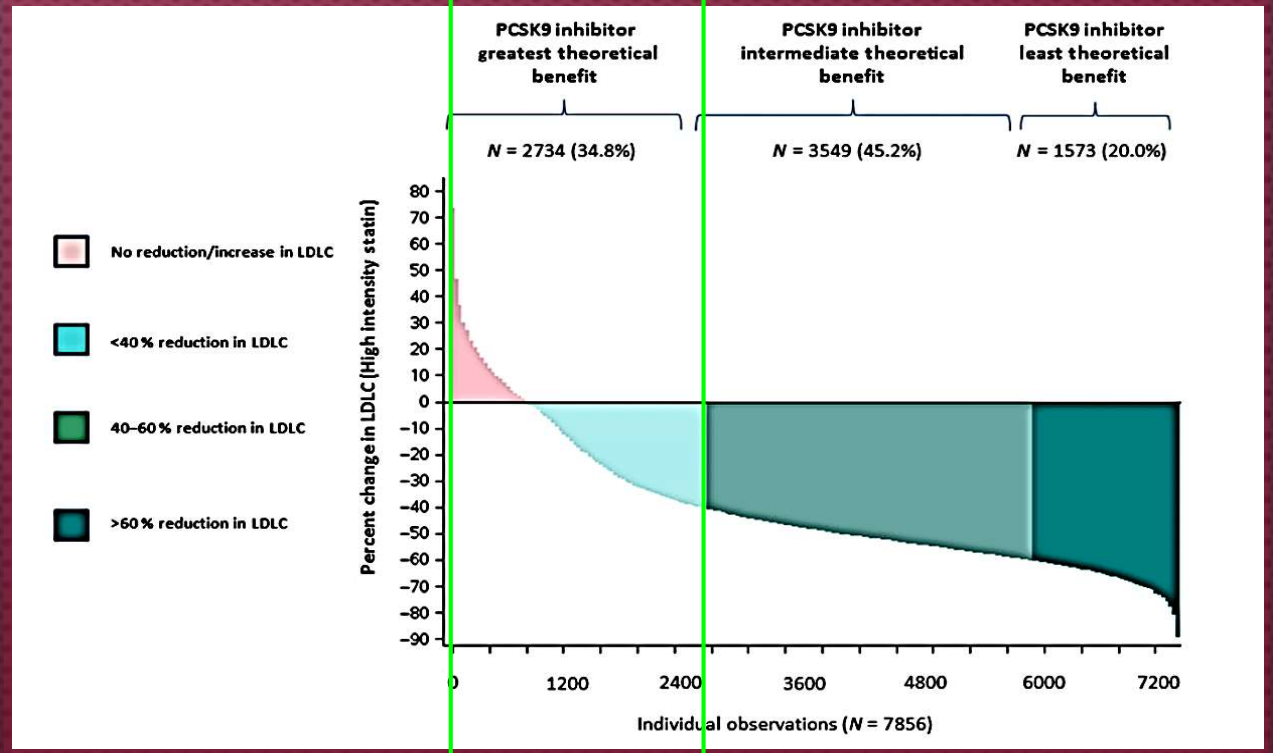
	SPIRE 1 (n = 17,000)	SPIRE 2 (n = 11,000)	FOURIER (n = 27,500)	ODYSSEY Outcomes (n = 18,000)
Monoclonal antibody	Bococizumab (humanized) 150 mg Q2W	Bococizumab (humanized) 150 mg Q2W	Evolocumab (human) 140 mg Q2W 420 mg Q4W	Alirocumab (human) 75-150 mg Q2W
Entry LDLC (mg/dL)	≥70	≥100	≥70	≥70
Statin requirement	Atorvastatin 40 or 80 mg Rosuvastatin 20 or 40 mg Simvastatin 40 mg (or 80 mg if >1 year) or documented intolerance to high intensity statin (SPIRE-1 and SPIRE 2) or documented complete statin intolerance (SPIRE-2)*		High-intensity statin preferred, minimum dose atorvastatin 20 mg or equivalent	Atorvastatin 40 or 80 mg Rosuvastatin 20 or 40 mg or the maximum tolerated dose of one of these agents
High-risk secondary prevention	Yes	Yes	Yes	Yes
High-risk primary prevention	Yes	Yes	No	No

*Allowed not to be taking statin if intolerant to any 2 statins (one at lowest dose) or a history of statin-induced rhabdomyolysis.

SPIRE trial.pdf

HIGHLIGHTS OF STATINS AND PCSK9

- STATINS PROVEN TO WORK AND LOWER APPEARS TO BE BETTER
- PCSK9 WITH STATINS MAY REDUCE CV EVENTS EVEN MORE….BUT WILL NEED TO WAIT UNTIL FOURIER REPORTS OUT THIS YEAR OR EARLY 2017
- POSSIBLY 30% OF PATIENT MIGHT HAVE ADDITIONAL BENEFIT FROM PCSK9 BUT WILL NEED TO WAIT UNTIL CV ENDPOINT TRIALS ARE COMPLETED



WHAT IS THE CORRECT LDL NUMBER OR JUST HIGH INTENSITY STATIN?

Your patient

1. Just give high risk patients high intensity statin (government guidelines)
2. Treat based on LDL number

You're the patient

1. Just give high risk patients high intensity statin (government guidelines)
2. Treat based on LDL number

CHROMATIN-BASED THERAPEUTICS FOR ATHEROSCLEROSIS

BET-**bromo** and extraterminal (family) proteins

Bromodomains (BRDs) are protein-interaction modules that are **selectively recruited to** lysine-containing sequences

BRDs nuclear proteins:
regulating transcription, chromatin modulators, and chromatin-modifying enzymes

control expression of genes that play key regulatory roles in

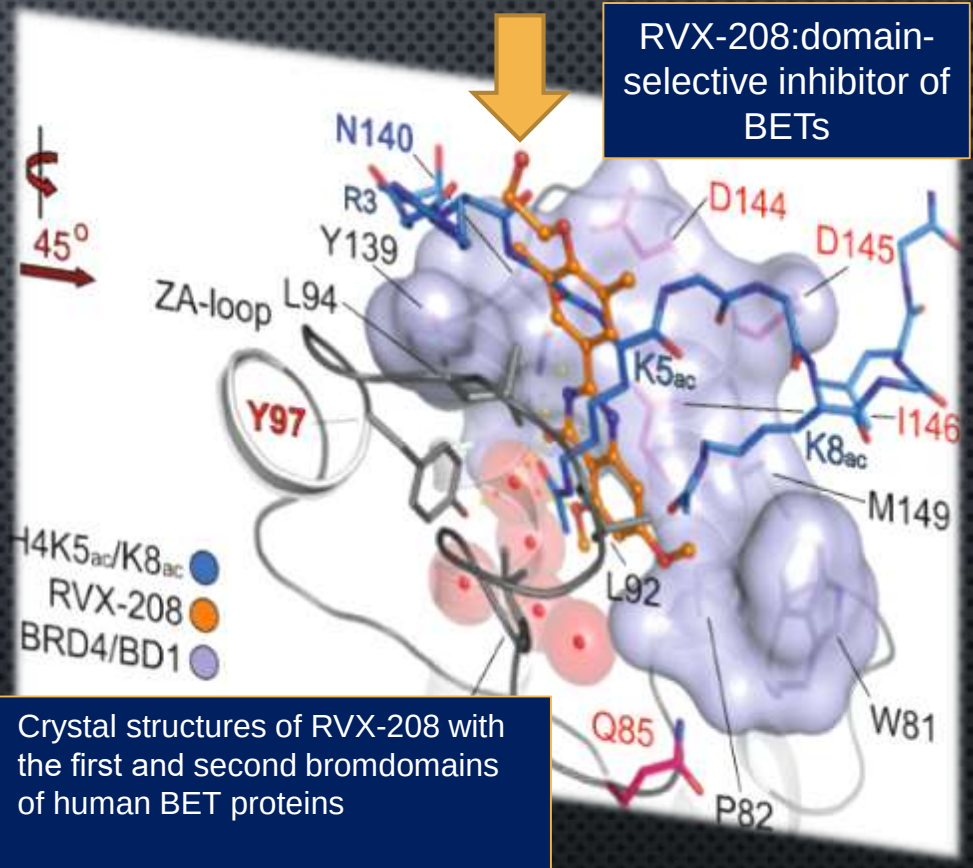
Cell proliferation

Apoptosis

Dysfunction of BET proteins develop tumors

BET inhibitors-raising HDL

RVX-208:domain-selective inhibitor of BETs



Crystal structures of RVX-208 with the first and second bromdomains of human BET proteins

Nature 468(7327):1067–1073

ENDOVASCULAR CONSIDERATIONS IN BIOMARKERS

Cholesterol flux biomarkers

Pathways known to mediate **cholesterol efflux** from macrophages

ABCA1, ABCG1, scavenger receptor B1

Odds Ratios for Coronary Artery Disease According to Efflux

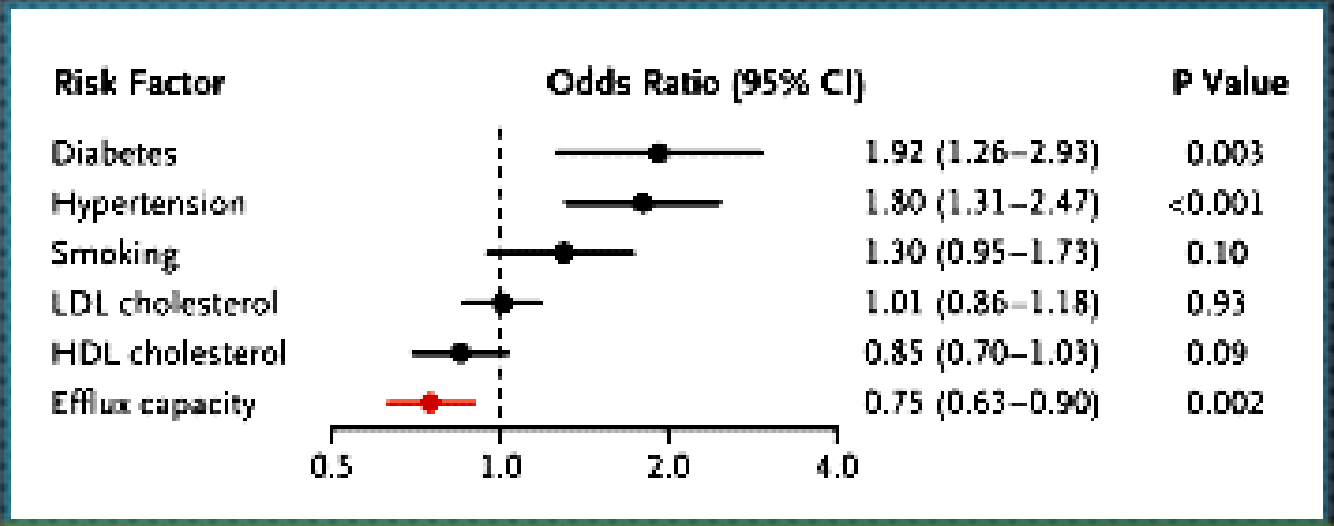


Table 4. Effect of Pharmacologic Interventions on Cholesterol Efflux Capacity.*

Pharmacologic Intervention	No. of Patients	Percent Change in Cholesterol Efflux Capacity (95% CI)	P Value vs. Baseline	P Value vs. Placebo
Thiazolidinedione				
Pioglitazone	16	11.3 (1.8 to 20.8)	0.02	0.04
Placebo	23	0.0 (−6.2 to 6.1)	0.99	
Statin				
Pravastatin, 40 mg	23	−0.4 (−6.5 to 5.6)	0.88	0.71
Atorvastatin, 10 mg	26	2.7 (−4.8 to 10.2)	0.47	0.81
Atorvastatin, 80 mg	25	−2.5 (−9.1 to 4.1)	0.45	0.38
Placebo	25	−1.1 (−6.5 to 4.2)	0.66	

N Engl J Med 2011;364:127-35

CHOLESTEROL EFFLUX CAPACITY, A NEW BIOMARKER WAS INVERSELY RELATED TO INCIDENCE OF CARDIOVASCULAR EVENTS

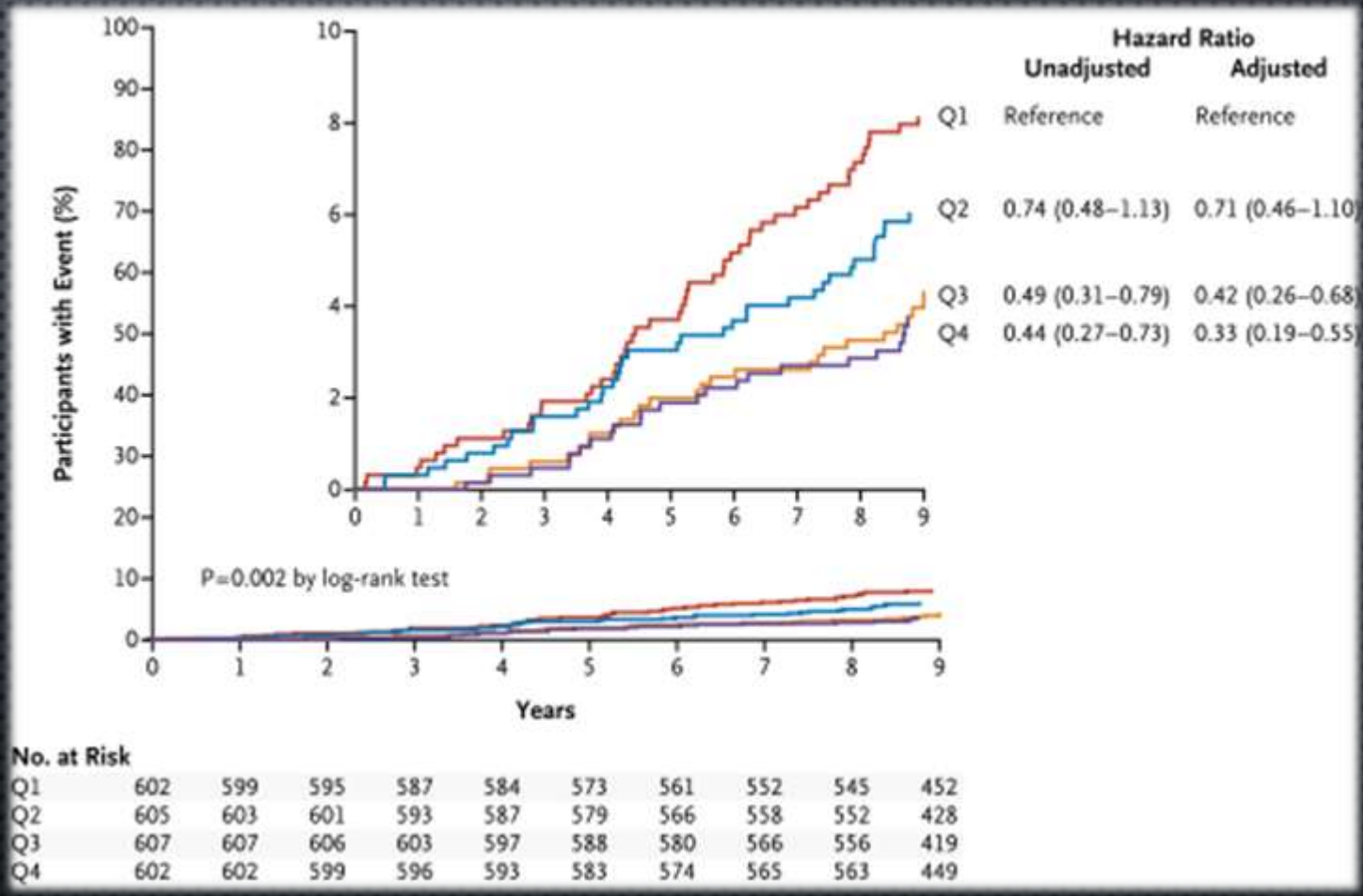
- POPULATION BASED COHORT
- BASELINE N=2924 ADULTS FREE FROM CARDIOVASCULAR DISEASE
- DALLAS HEART STUDY
- PRIMARY END POINT WAS ATHEROSCLEROTIC CARDIOVASCULAR DISEASE,
  - FIRST NONFATAL MYOCARDIAL INFARCTION, NONFATAL STROKE, OR CORONARY REVASCULARIZATION OR DEATH FROM CARDIOVASCULAR CAUSES
- FOLLOW UP 9.4 YEARS MEDIAN

End Point	All Participants (N=2416)	Cholesterol Efflux Capacity				Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)†
		Quartile 1 (N=602)	Quartile 2 (N=605)	Quartile 3 (N=607)	Quartile 4 (N=602)		
		no. of participants					
Primary end point: atherosclerotic cardiovascular disease	132	49	35	26	22	0.44 (0.27–0.73)	0.33 (0.19–0.55)
Myocardial infarction‡	28	11	6	4	7	—	—
Stroke‡	36	15	11	8	2	—	—
Coronary revascularization‡	26	14	7	2	3	—	—
Death from cardiovascular causes‡	42	9	11	12	10	—	—

N Engl J Med 2014;371:2383-93

CHOLESTEROL EFFLUX CAPACITY, A NEW BIOMARKER WAS INVERSELY RELATED TO INCIDENCE OF CARDIOVASCULAR EVENTS

- POPULATION BASED COHORT
- BASELINE N=2924 ADULTS FREE FROM CARDIOVASCULAR DISEASE
- DALLAS HEART STUDY
- PRIMARY END POINT WAS ATHEROSCLEROTIC CARDIOVASCULAR DISEASE,
  - FIRST NONFATAL MYOCARDIAL INFARCTION, NONFATAL STROKE, OR CORONARY REVASCULARIZATION OR DEATH FROM CARDIOVASCULAR CAUSES
- FOLLOW UP 9.4 YEARS MEDIAN

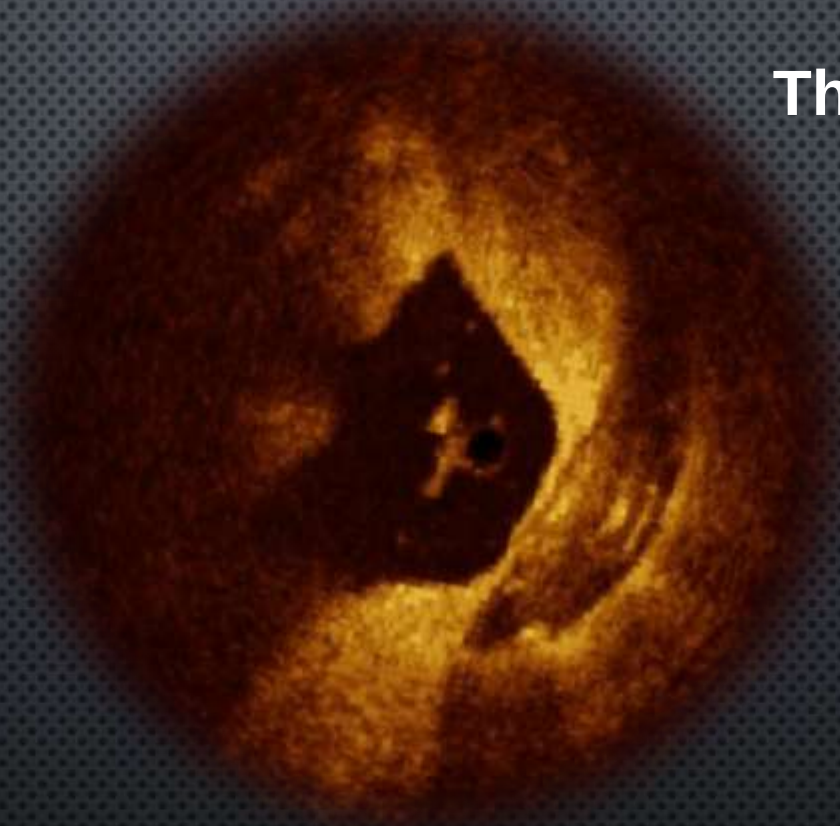


N Engl J Med 2014;371:2383-93

ACS have ↑↑↑ TCFA plaques

Thin-cap fibroatheroma

Optical coherence tomography



Diabetes vulnerable plaques

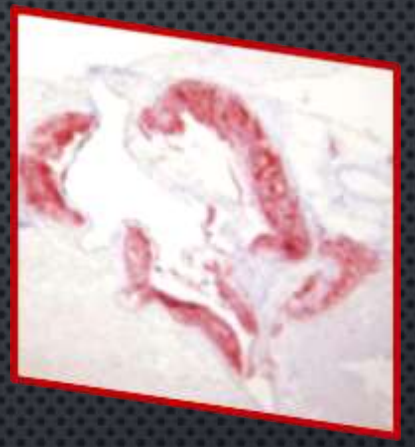
Lipids
↑Thin plaque cap & ↑ CRP
Increased macrophages

J Am Coll Cardiol Img 2009;2:339–49

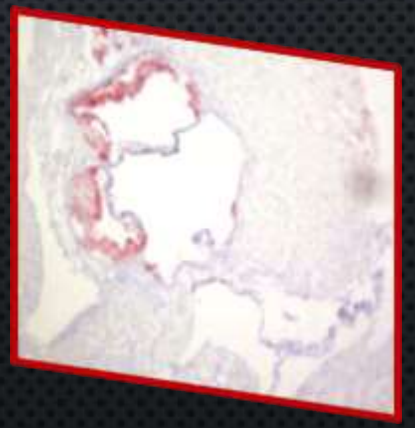
BET BROMODOMAIN INHIBITOR, RVX-208, SHOWS REDUCTION OF ATHEROSCLEROSIS IN HYPERLIPIDEMIC APOE DEfiCIENT MICE

Western diet≈Univ café food

- HDL REDUCES CVD RISK THROUGH A PROCESS THAT INVOLVES FORMATION OF PRE-BETA PARTICLES
  - FACILITATES THE REMOVAL OF CHOLESTEROL FROM THE LIPID-LADEN MACROPHAGES IN THE ARTERIES
- BET BROMODOMAIN ANTAGONIST, RVX-208
  - RAISE APOA-I AND INCREASE PRE B - HDL PARTICLES
- HYPERLIPIDEMIC APOE -/- KO MICE
- EVALUATED AORTIC ATHEROSCLEROSIS IN 12 WEEK STUDY
  - 2-FOLD INCREASES IN THE LEVELS OF CIRCULATING HDL-C, AND ~50% DECREASES IN LDL
  - NO SIGNIfiCANT CHANGES IN PLASMA APOA-I WERE OBSERVED



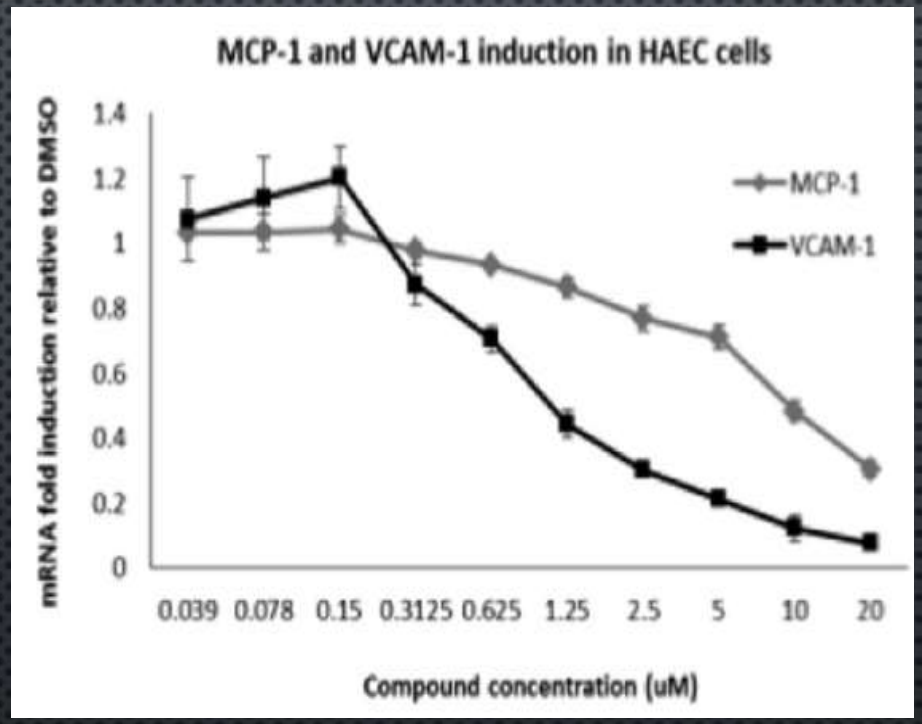
39% reduction

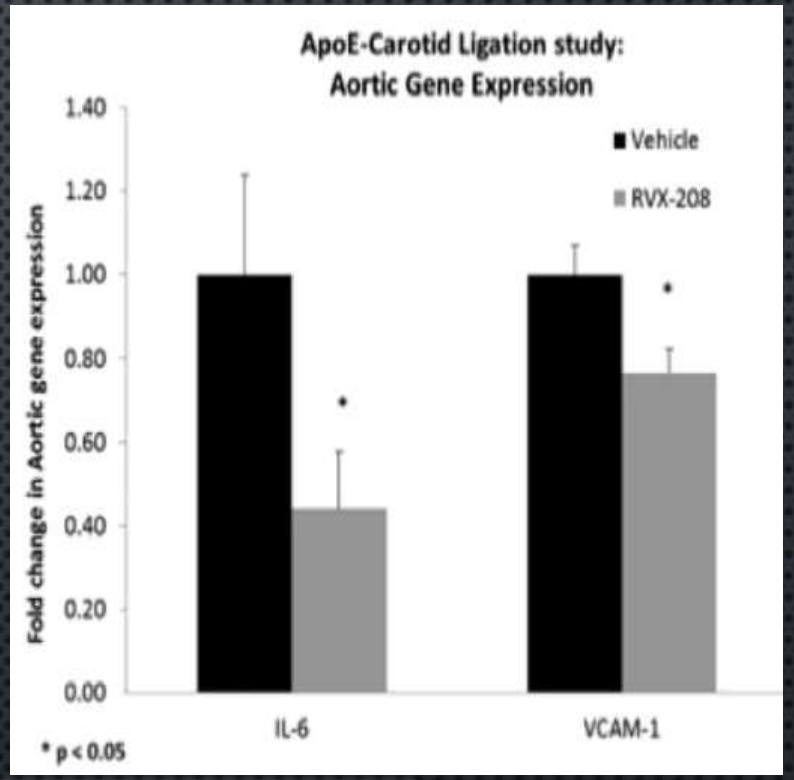


Atherosclerosis 236 (2014) 91e100

SUMMARY OF BASIC TRANSLATION RESEARCH RVX-208, BET INHIBITOR

- 2 FOLD INCREASE HDL
- REDUCES LDL BY 50%
- REDUCES INFLAMMATION
- REDUCES ADHESION MOLECULES





Mean levels of serum cytokines (ug/mL)		
Group	Haptoglobin	VCAM-1
Vehicle	128	2311
RVX-208	47	1911
p-value	0.001	0.004

betatherus.pdf

Atherosclerosis 236 (2014) 91e100

Humans

2 trials: total of 499 subjects-received either 100 mg b.i.d. of RVX-208 (n = 331) or placebo (n = 168)

No significant changes in metabolic parameters (blood pressure, high-sensitivity C-reactive protein [hsCRP] and glucose)

Clinical trials-early

CLINICAL HUMAN TRIALS WITH RVX-208 (BET INHIBITOR

- **SUSTAIN**: DOCUMENTED STABLE CORONARY ARTERY DISEASE
- **ASSURE** STUDY (IVUS) PATIENTS WERE SCHEDULED TO UNDERGO CORONARY ANGIOGRAPHY FOR A CLINICAL INDICATION
- BOTH DOUBLE BLIND RANDOMIZED TRIALS FOR 26 TO 28 WEEKS

Trials evaluated: lipid, inflammatory and metabolic biomarkers as
well as incidence of major adverse cardiac events (MACE) defined
as death, nonfatal myocardial infarction, coronary revascularization
and hospitalization for unstable angina or heart failure

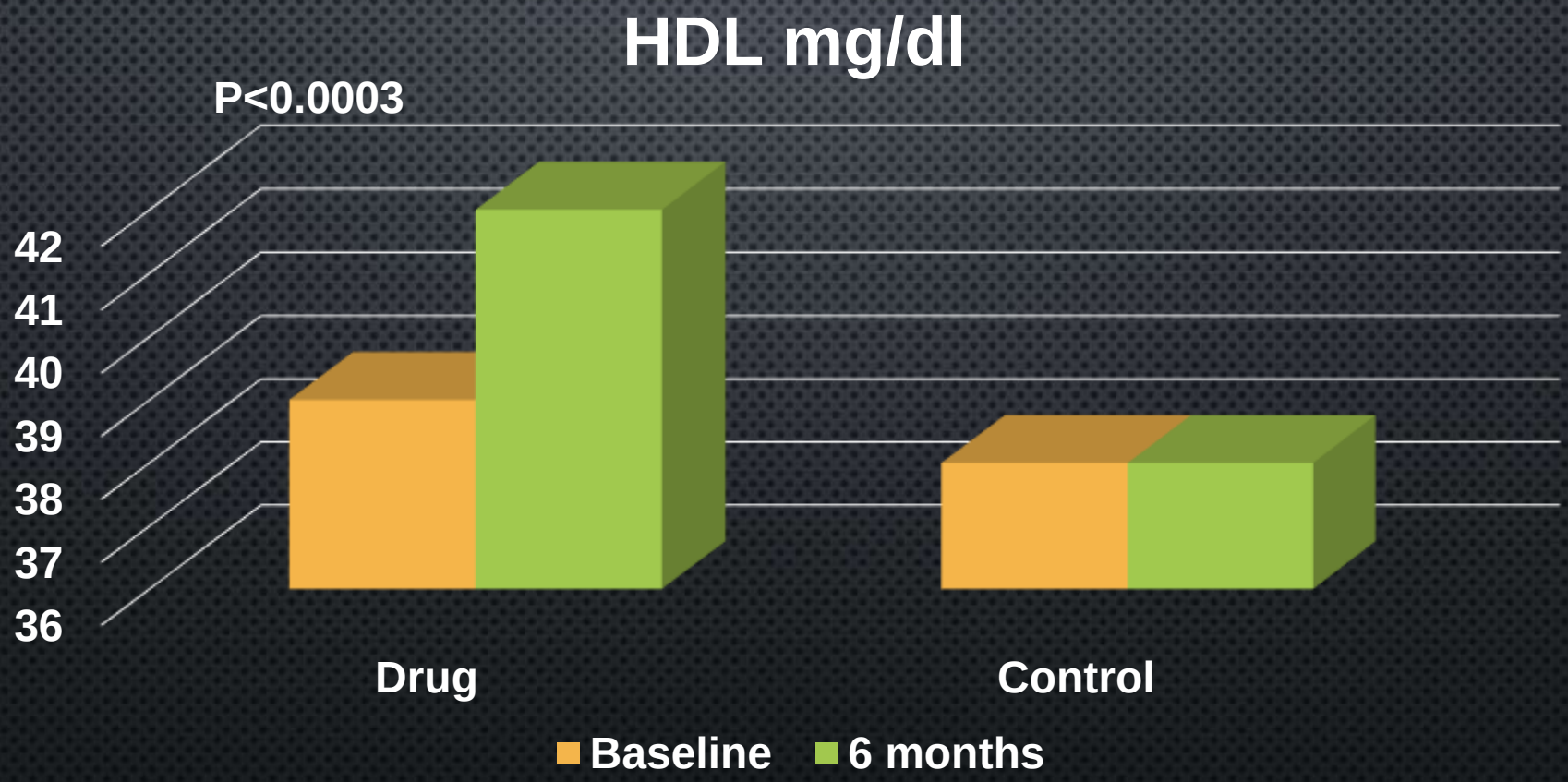
Secondary outcome:
HDL-c, ApoA-I and HDL-subclasses

The proApoA-I clinical data were collected in the SUSTAIN study

Primary human hepatocytes with microarrays

COMBINED TRIAL RESULTS

N=499



SUSTAIN
ASSURE

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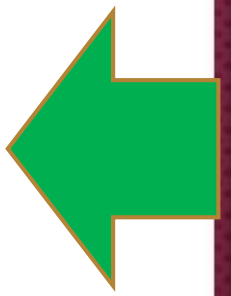
COMBINED TRIAL RESULTS

Table 1
Combined analysis of the ASSURE and SUSTAIN phase II trials.

Biomarker	RVX-208 (n = 331)		Placebo (n = 166)		p value vs placebo
	Baseline	Change from baseline (%▲)	Baseline	Change from baseline (%▲)	
HDL-cholesterol (mg/dL)	39.0	+3.0 (+7.69)	38.0	0.0 (0.0)	0.0003
ApoA-I (mg/dL)	119.2	+12.3 (+10.3)	118.1	+4.8 (+3.8)	0.005
Large HDL particles (μmol/L)	2.4	+0.8 (+30.7)	2.1	+0.1 (+4.11)	0.03
HDL particle size (nm)	8.7	+0.1 (+1.16)	8.7	0.0 (0.0)	0.049
Total HDL particles (μmol/L)	27.2	+1.9 (+6.51)	26.9	+0.1 (+0.40)	0.07
LDL-cholesterol (mg/dL)	2.4	−0.2 (−10.8)	2.3	−0.2 (−8.05)	NS
Glucose (mmol/L)	5.8	+0.1 (+2.08)	5.7	+0.2 (+3.57)	NS
hsCRP (mg/L)	2.3	−0.36 (−28.4)	2.5	−0.33 (−22.4)	NS



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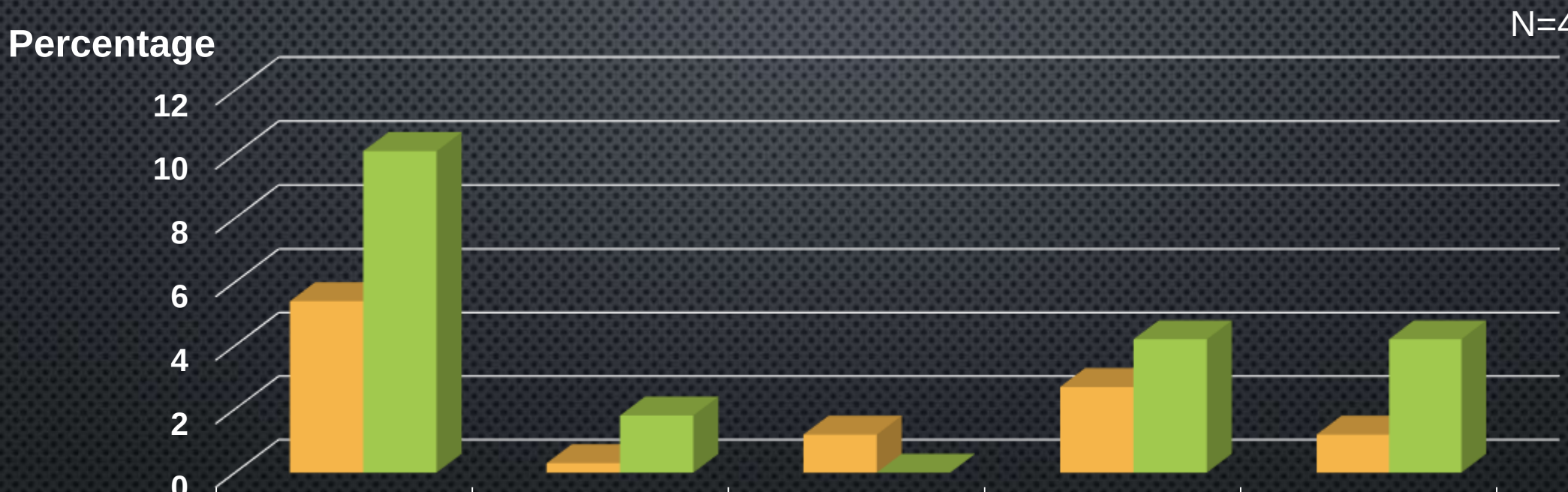
PHASE II RESULTS: SUSTAIN & ASSURE COMBINED



	MACE	Death	MI	Coronary revascularization	Hosp UA/HF
Drug	5.4	0.3	1.2	2.7	1.2
Control	10.1	1.8	0	4.2	4.2

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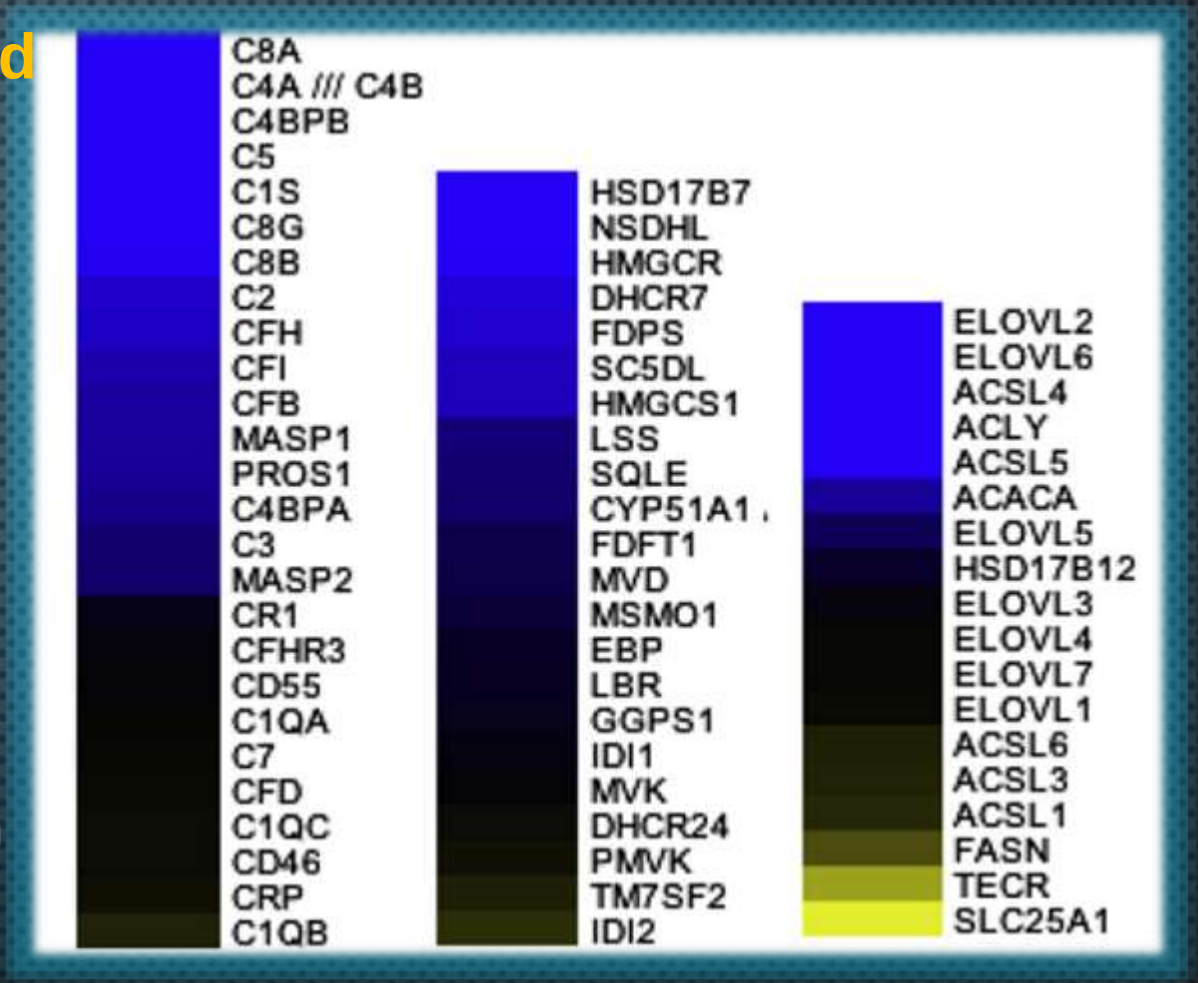
Microarray analysis of RVX-208-induced gene expression changes in primary human hepatocytes

Diabetes microarrays

Cryopreserved human hepatocytes were treated with 30mM RVX-208

Reduce GI absorption of glucose-? SGLT 1
No change in incretins levels

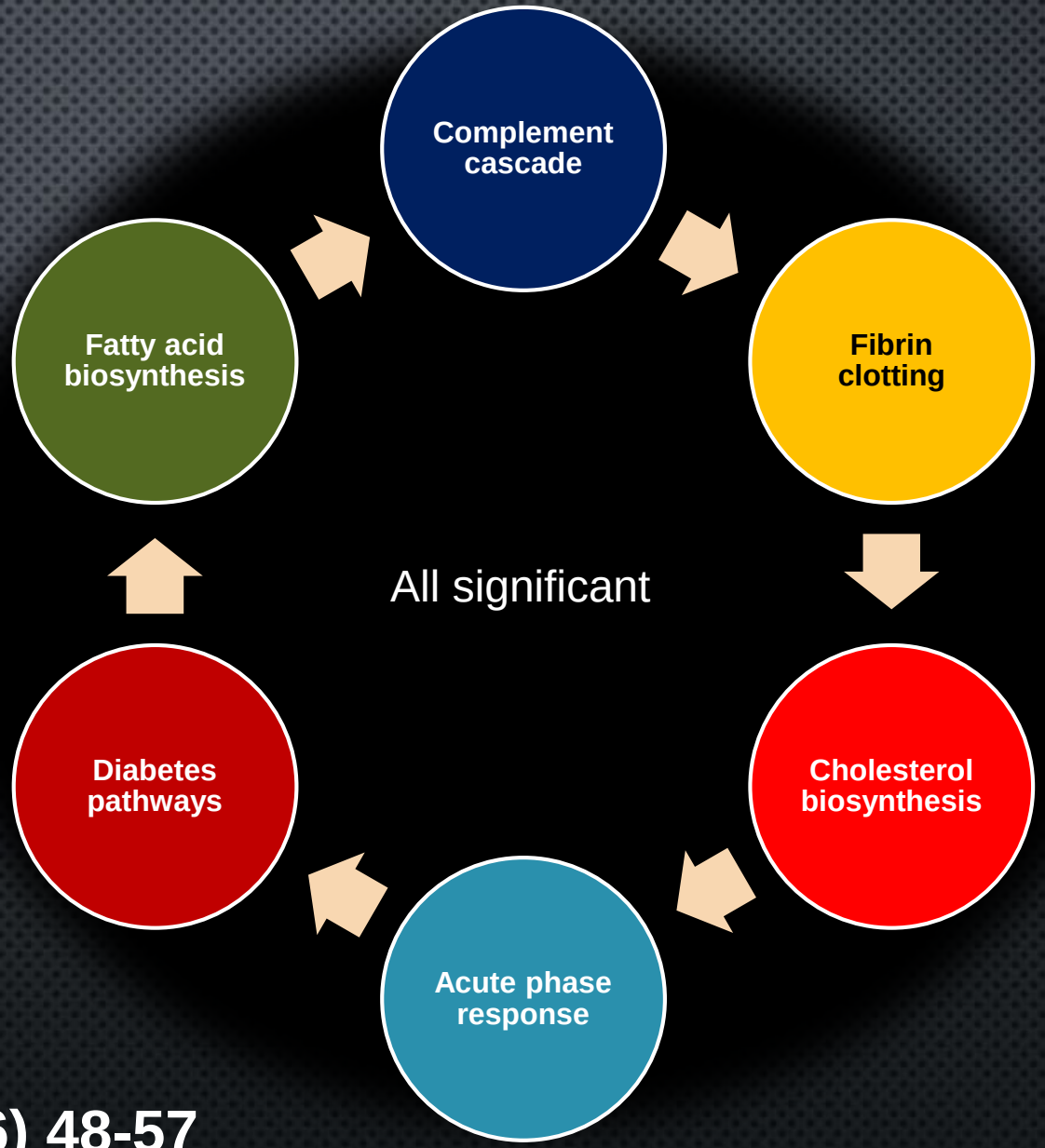


Complement Cascade | **Cholesterol Biosynthesis** | **Fatty Acyl CoA Biosynthesis**

j.metabol.2016.03.002
Atherosclerosis 247 (2016) 48-57

REACTOME PATHWAYS IMPACTING MACE

Microarrays from cryopreserved primary human hepatocytes



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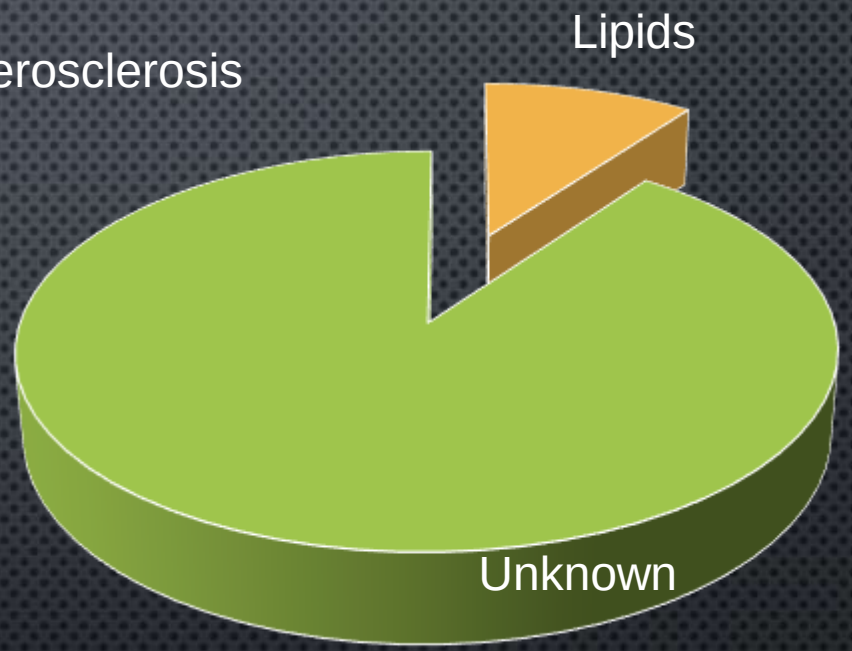
IVUS RESULTS-ASSURE TRIAL

- Elevated liver enzymes was observed in RVX-208-treated patients (7.1 vs. 0%, P = 0.009)
- Primary endpoint, the change in percent atheroma volume
  - Control arm: decreased 0.30% (P = 0.23 compared with baseline)
  - RVX-208: 11.1% (P < 0.001 compared with baseline)
  - LDL-C decreased by 17.9% vs placebo (P < 0.001 compared with baseline)

No greater increase in apoA-I or HDL-C or incremental regression of atherosclerosis than administration of placebo

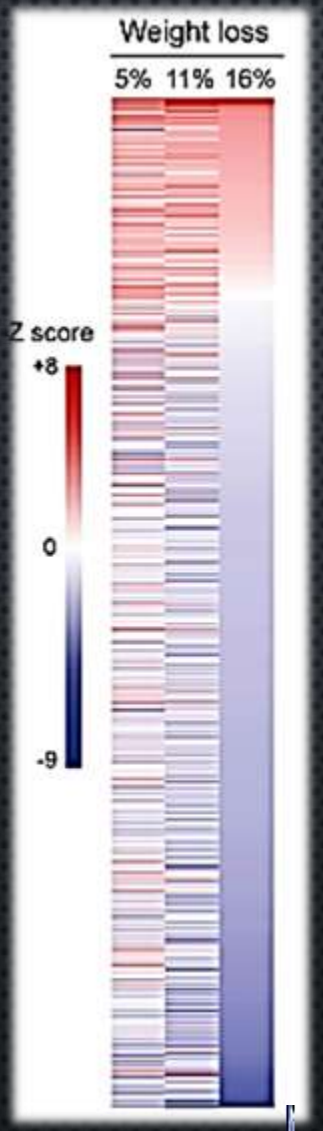
ClinicalTrials.gov identifier-NCT01067820.



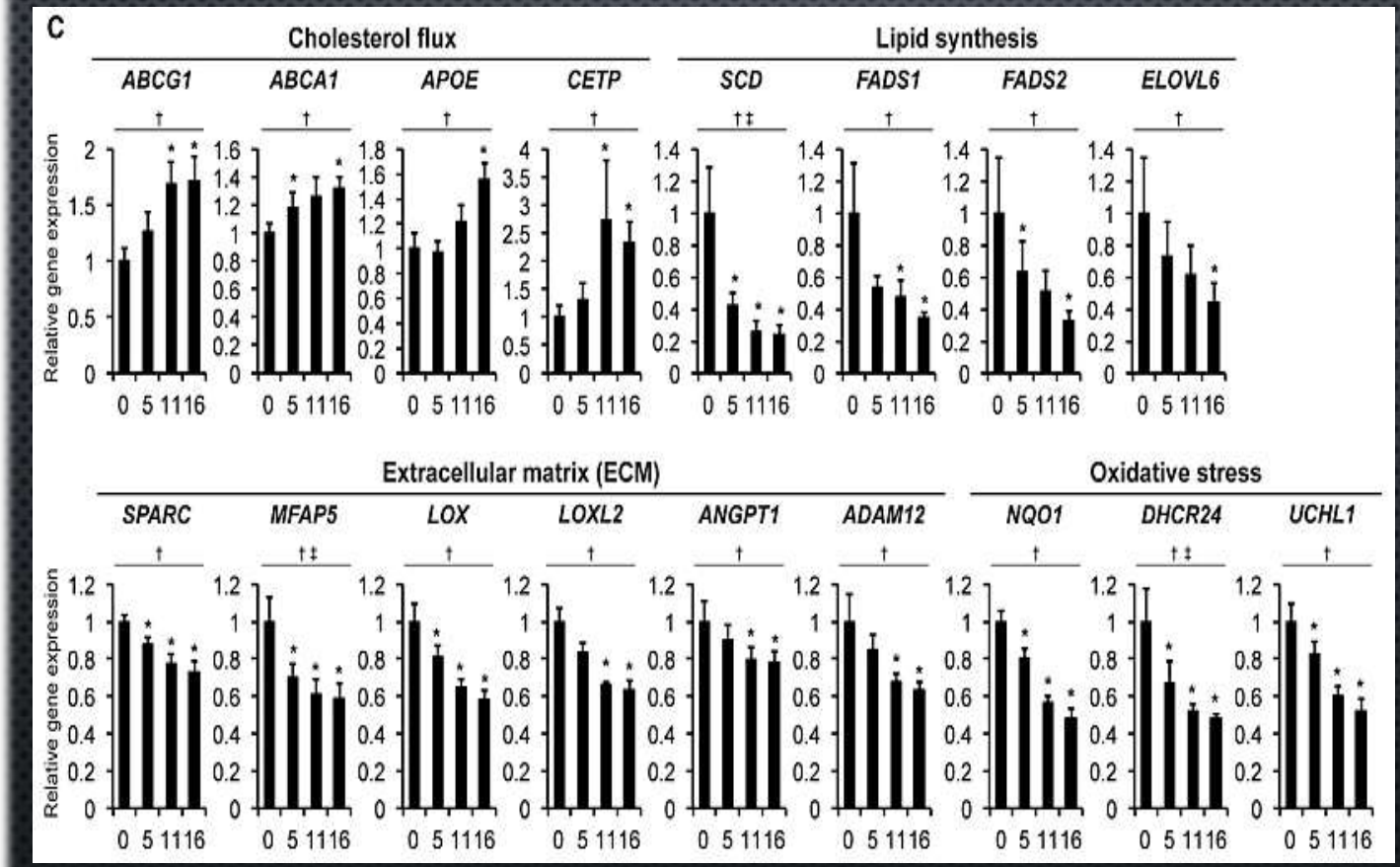
Closing comments

Weight loss in humans

40 Humans subjects



Adipose tissue gene expression

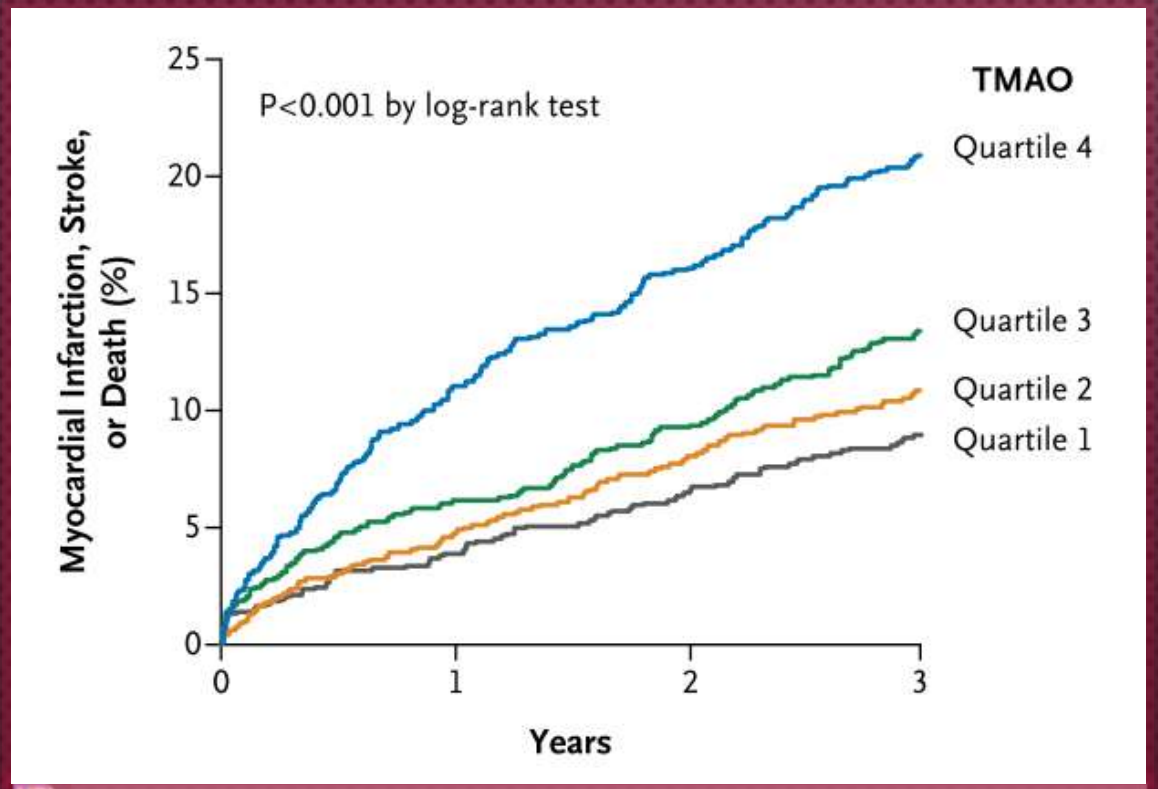


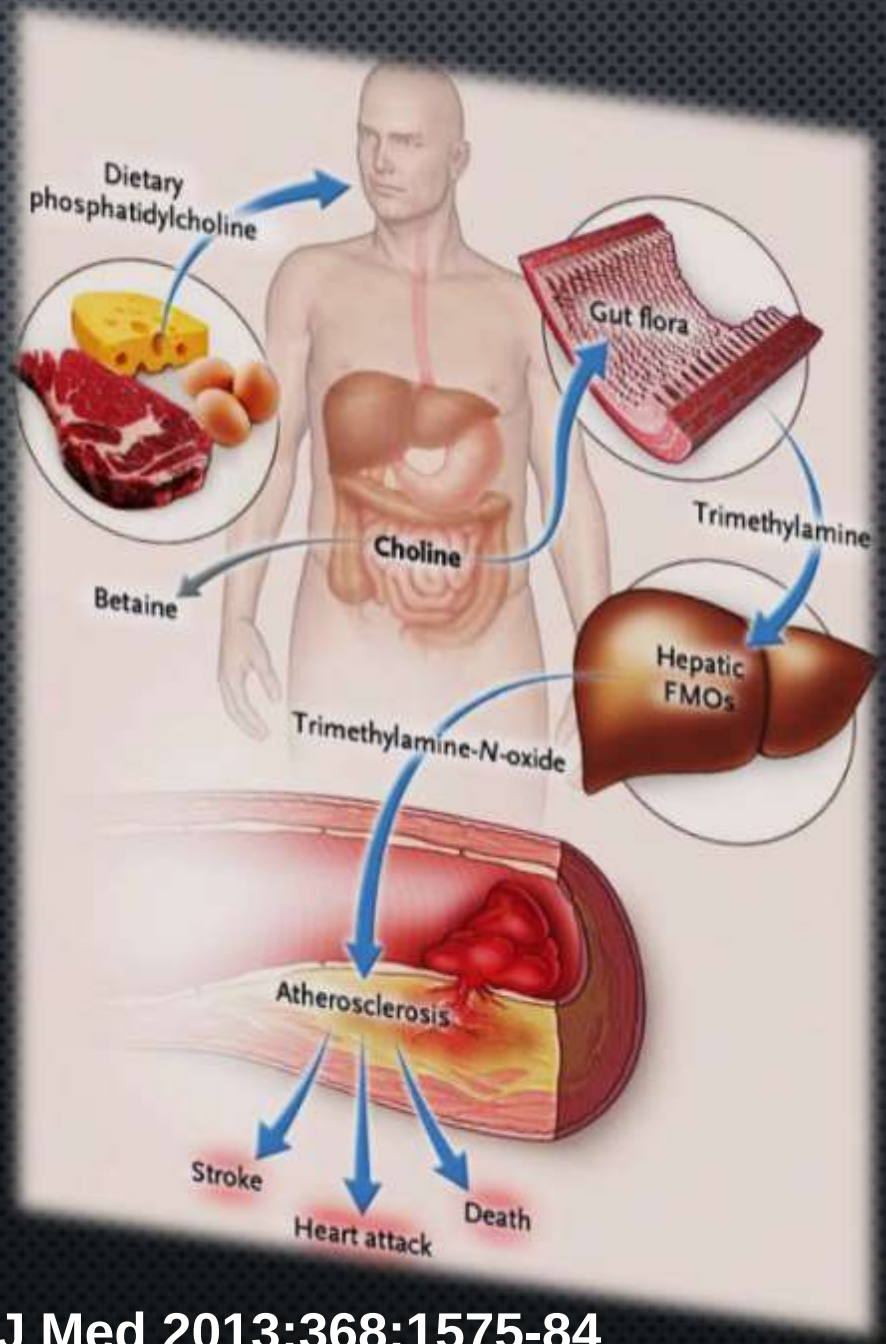
% weight loss

Magkos et al., April 2016, Cell Metabolism 23, 591–601

INTESTINAL MICROBIAL METABOLISM OF PHOSPHATIDYLCHOLINE AND CARDIOVASCULAR RISK

4007 adults undergoing cath



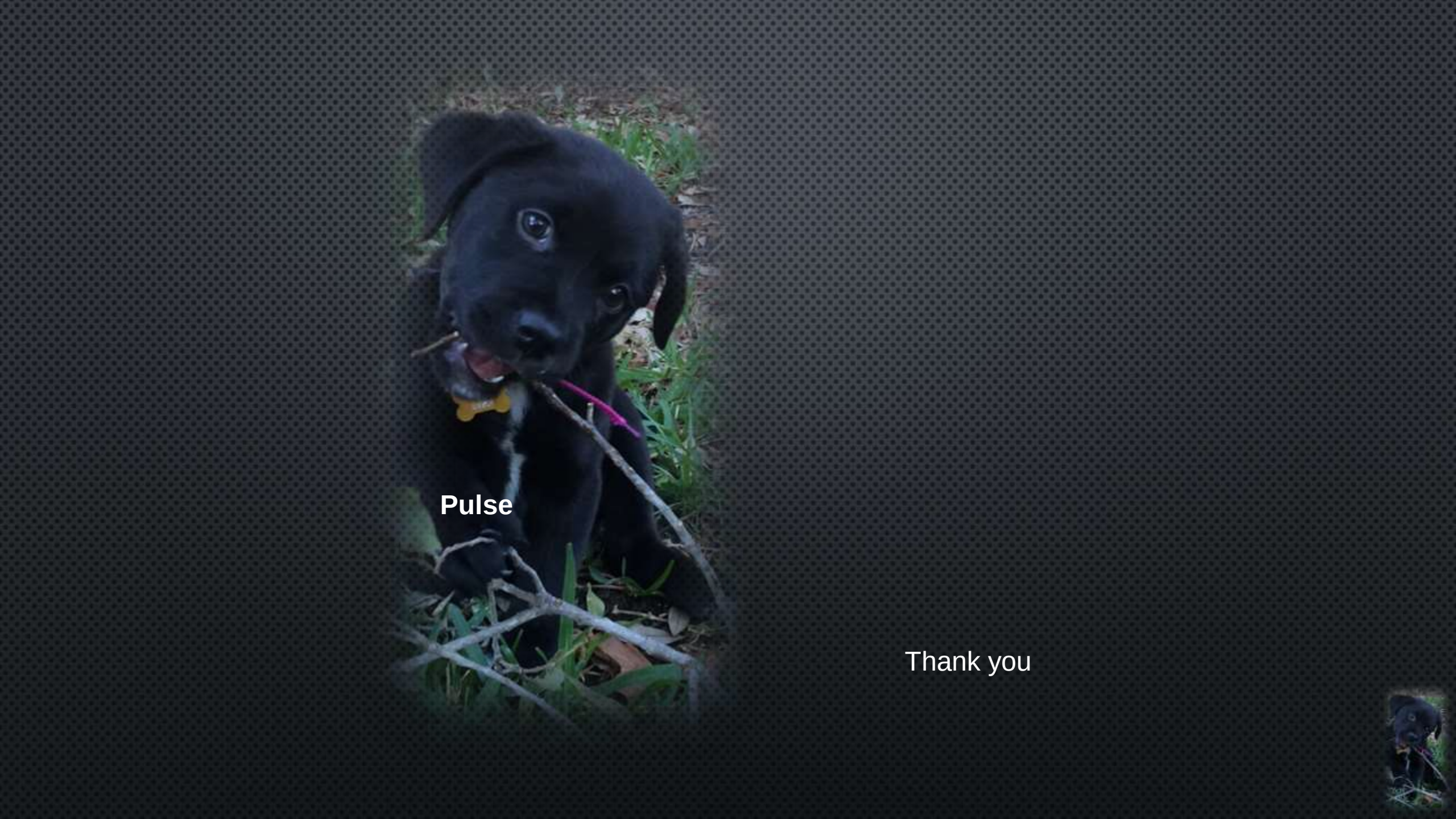


N Engl J Med 2013;368:1575-84

TAKE HOME MESSAGE

- CV EVENT REDUCTION
  - STATINS WORK!
  - PCSK9 STILL IN INVESTIGATION
  - BET INHIBITORS NOT READY
  - LIPIDS ARE ONLY A SMALL PIECE OF THE PIE
- TRANSLATIONAL MEDICINE REQUIRES MORE THAN A REDUCED "NUMBER"
- WEIGHT LOSS IS STILL THE MOST POWERFUL LIFE SAVING TREATMENT…BUT HARDEST

Answers to long life are in here



Thank you