NEW AGENTS IN LIPID MANAGEMENT

2022

NEW AGENTS IN LIPID MANAGEMENT

105 years old

101 years old

Overview: maintaining healthy endothelial cells

"Its all atherosclerosis"

Lifestyle

Global risk factor reduction

Weight control

Reducing atherosclerosis risk

Reducing CV events

Wall stress

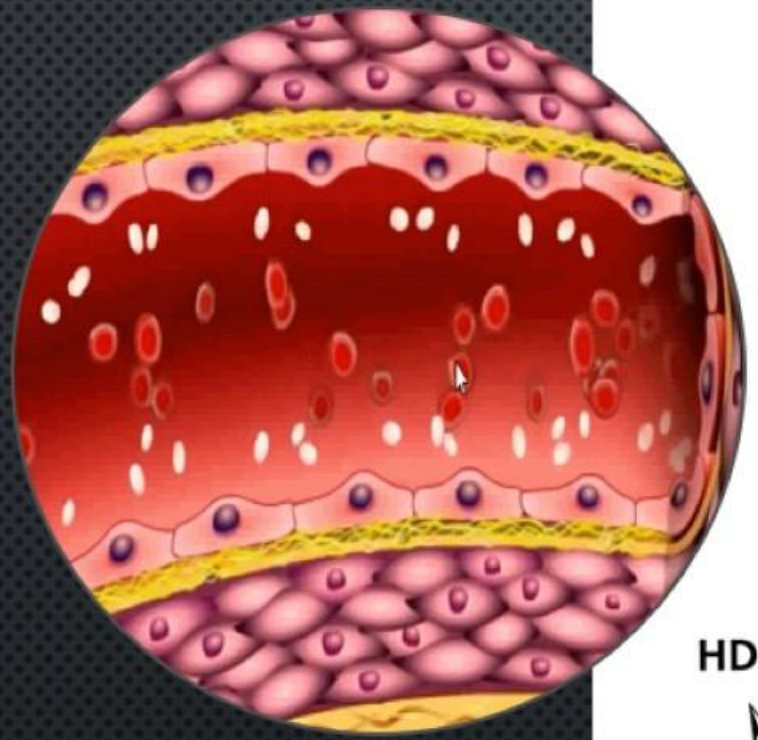
Metabolics

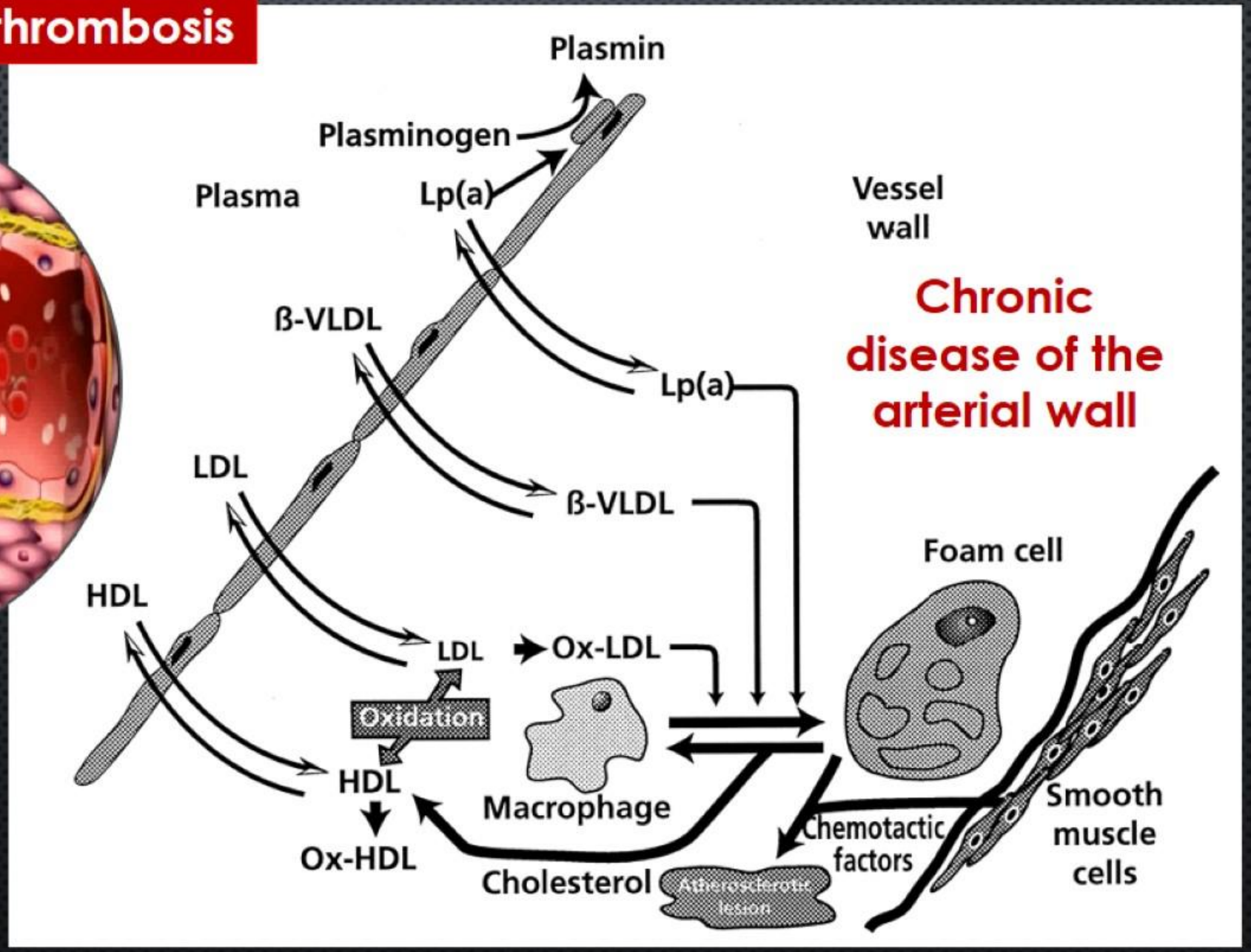
Inflammation

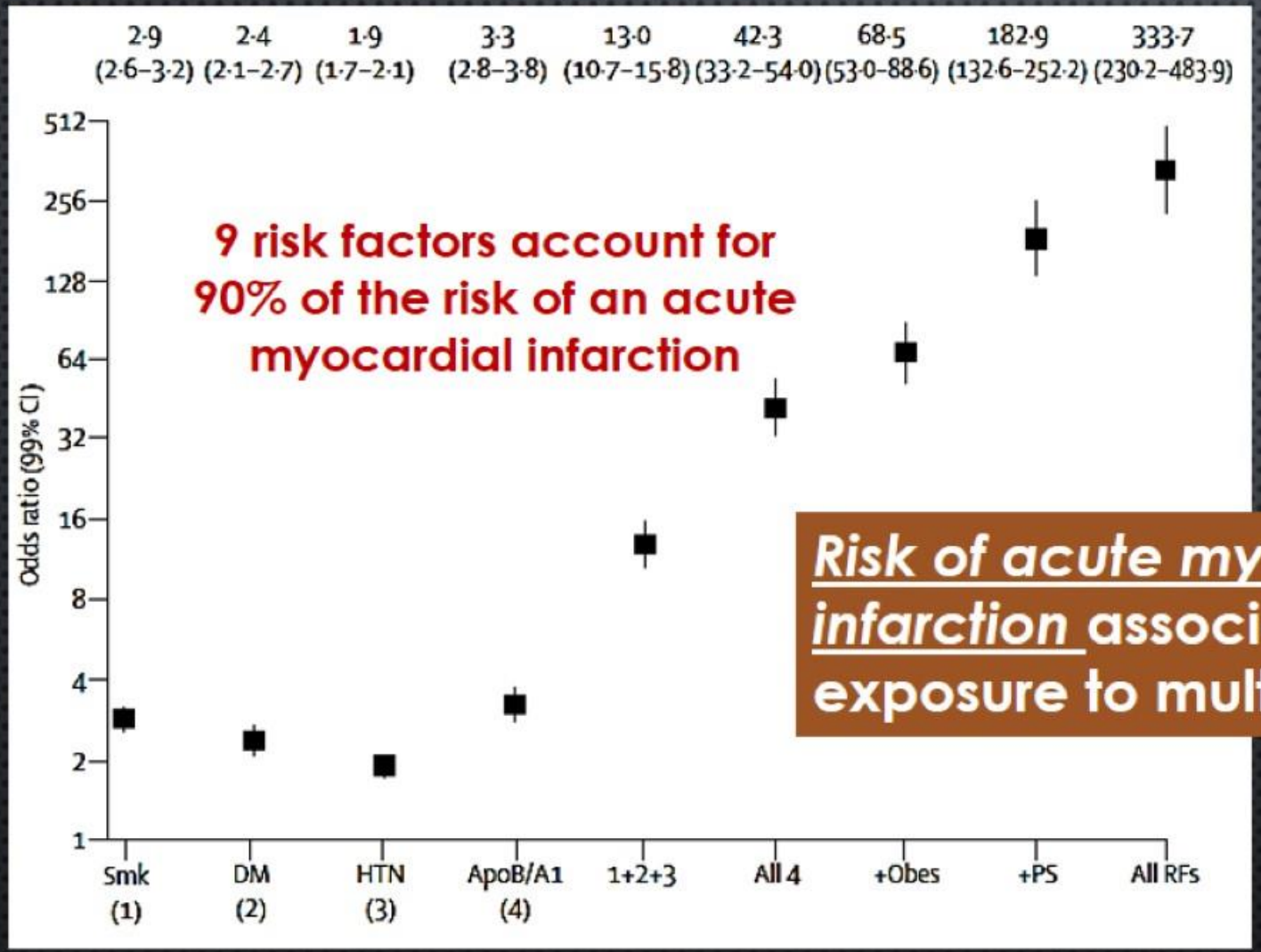
Nine modifiable risk factors predict 90% of first acute MI

Lancet 2004 Sep 11-17;364(9438):937-52
INTERHEART

Lipids and atherothrombosis







Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Tony Dans, Alvaro Avezum, Fernando Lanas, Matthew McQueen, Andrzej Budaj, Prem Pais, John Varigos, Liu Lisheng, on behalf of the INTERHEART Study Investigators*

Summary

Background Although more than 80% of the global burden of cardiovascular disease occurs in low-income and middle-income countries, knowledge of the importance of risk factors is largely derived from developed countries. Therefore, the effect of such factors on risk of coronary heart disease in most regions of the world is unknown.

Methods We established a standardised case-control study of acute myocardial infarction in 52 countries, representing every inhabited continent. 15 152 cases and 14 820 controls were enrolled. The relation of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo), and psychosocial factors to myocardial infarction are reported here. Odds ratios and their 99% CIs for the association of risk factors to myocardial infarction and their population attributable risks (PAR) were calculated.

Risk of acute myocardial infarction **associated with exposure to multiple risk**

Lancet 2004; 364: 937–

CONTROLLING GENETIC BACKGROUND ATHEROTHROMBOSIS RISK OF OBESITY

FinnTwin16 study

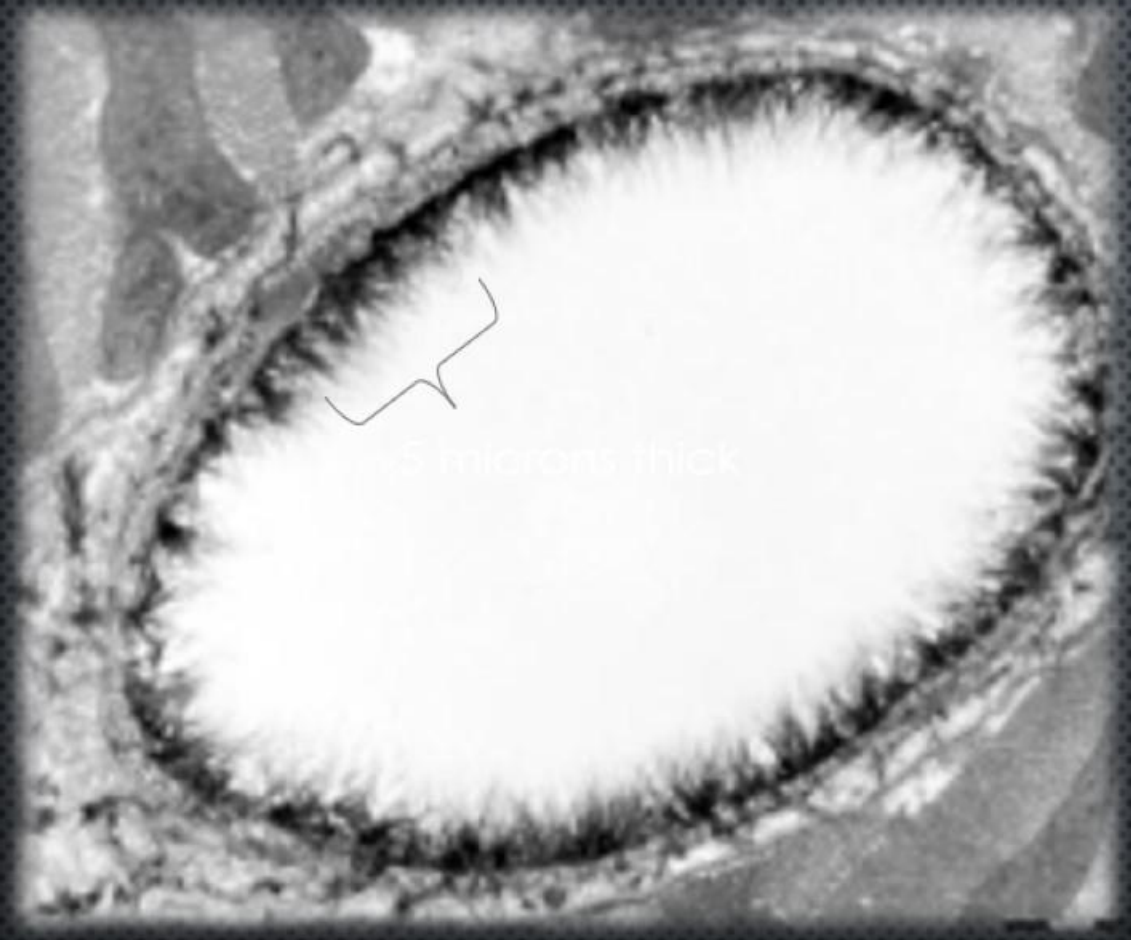
Increased coagulation factors and fibrinolytic activity with increased weight

	Intra-Abd fat dm2	Liver fat	Insulin mU/L	hsCRP mg/L	Fibrinogen g/L	**Liver FAT**	PAI-1	**BMI**
Leaner	0.5	1.25	5	0.9	3.2	**1.25**	4.1	**25.3**
Heavier	1	3.6	9	2	3.4	**3.6**	17.5	**30.5**

Figure 4

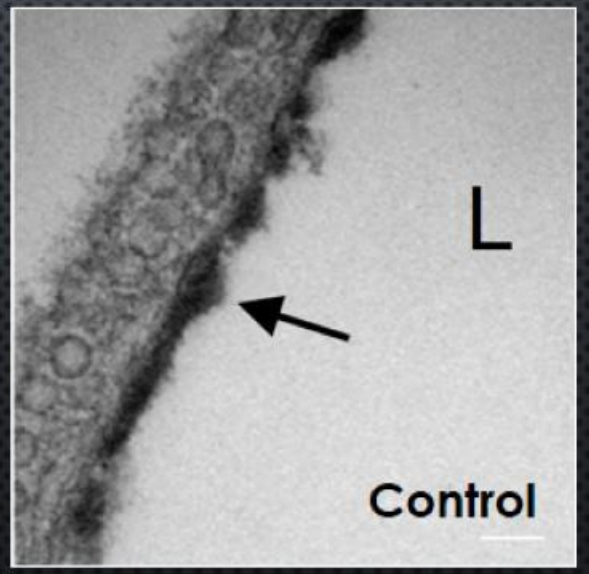
Obesity (2012) 20, 88–94.

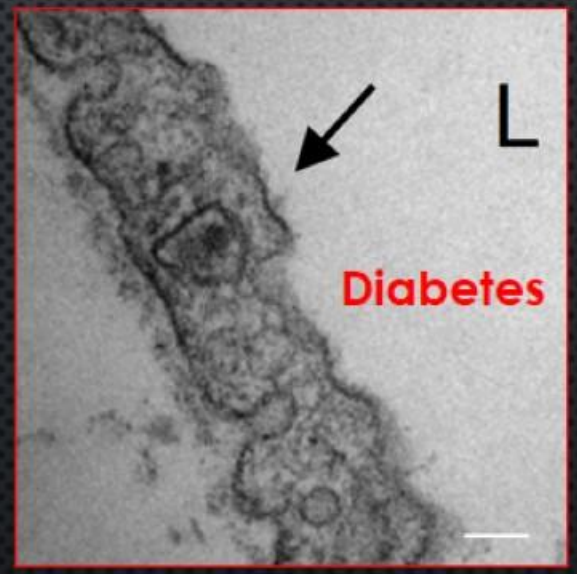
Translational science of atherosclerosis



Endothelial cells are shielded from direct exposure to flowing blood by a **highly hydrated mesh-glycocalyx**

Protein concentration gradients across this layer are essential for **control of transvascular fluid** exchange





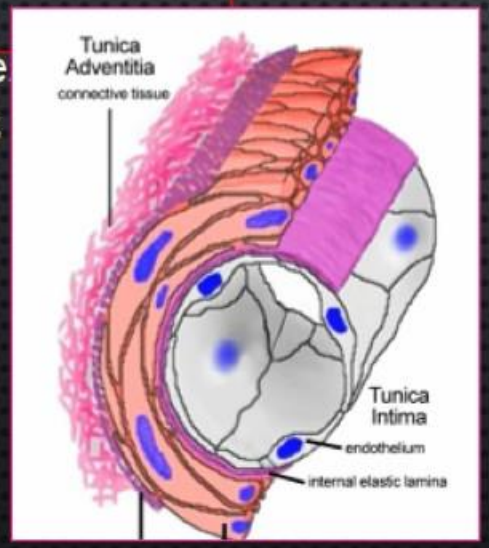
Loss of glycocalyx with diabetes

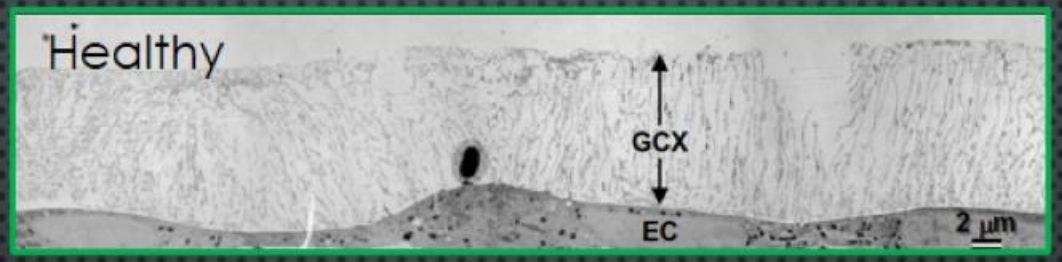
Diabetologia (2022) 65:879–894

Importance of the endothelium/glycocalyx

Damage to glycocalyx

-High glucose concentrations
-Reactive oxygen species
-Inflammatory mediators
-increased permeability
-LDL
-Wall stre
-others





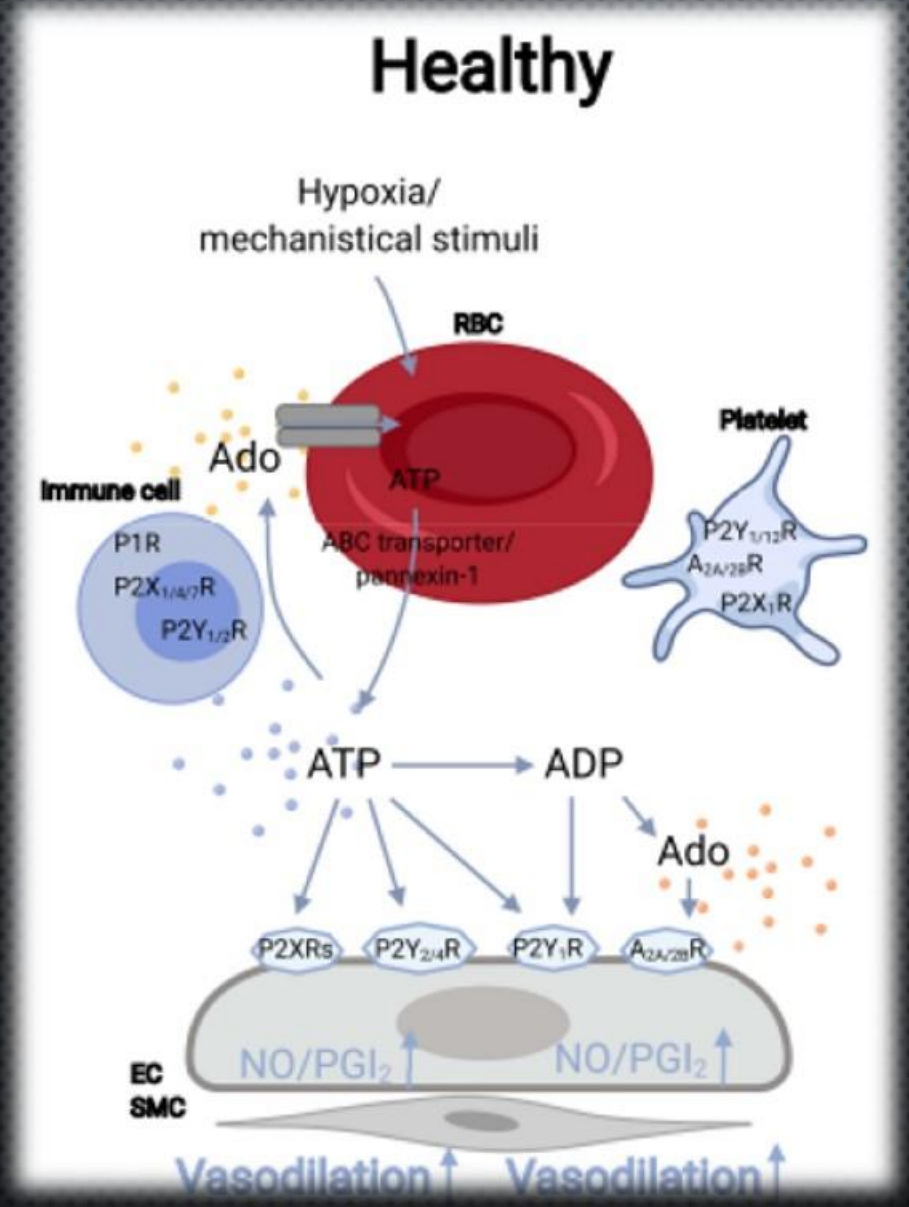
eGlx is lost from the vascular wall including glomerular circulation

Important functions of endothelial cell

- Actively signal WBC during **inflammation**
- Blood clotting
- Blood pressure control
- Angiogenesis / fluids
- Release NO
- Glucose
- **Barrier to lipids**

PLoS One 8(2):e55852
Am J Physiol Renal Physiol

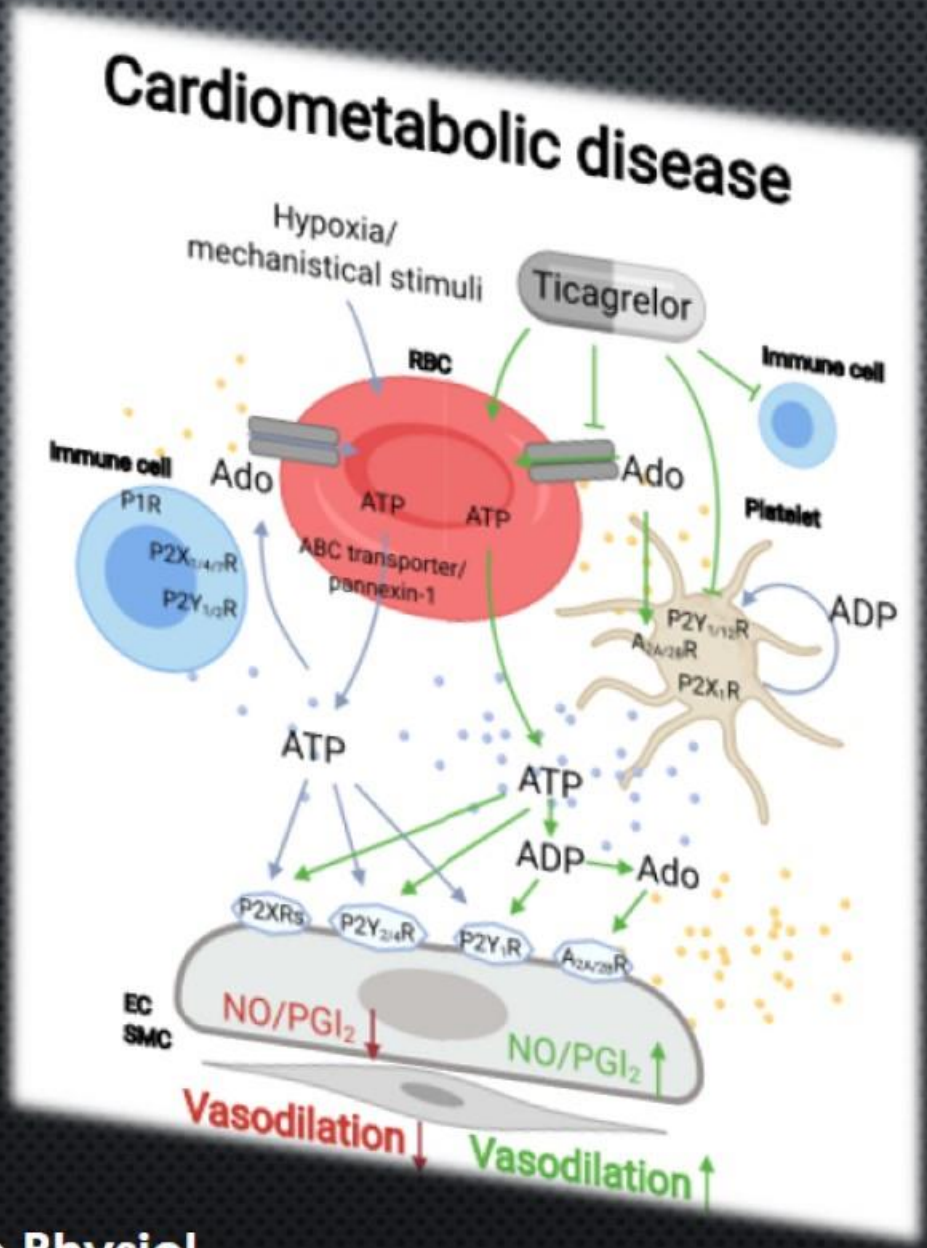
Endothelial cells orchestrates vascular changes



Ticagrelor inhibits adenosine uptake in red blood cells & ↑ ATP

ATP (↓ DM) can activate P2Y R on the endothelium, ↑nitric oxide (NO) and prostacycline

Diabetes
ADP-mediated P2Y 12 R activation

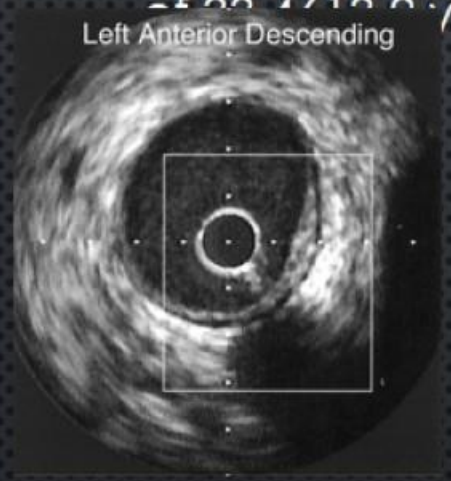


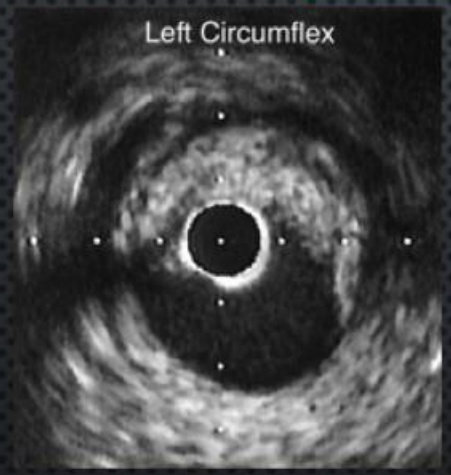
AJP-Heart Circ Physiol
doi:10.1152/ajpheart.00570.2020

Epidemiology

High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults

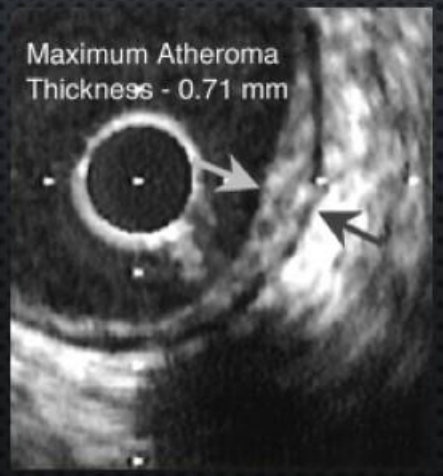
Donor population consisted of
146
men and 116 women (mean age
ears)





Characteristics of Donor Population

Characteristic	
Age, y	33.4±13.2
Male sex, n (%)	146 (56)
Hypertension, n (%)	39/260 (15)
Smoking, n (%)	126/164 (77)
White race, n (%)	227 (86.6)
Body mass index, kg/m^2	25.2±5.9



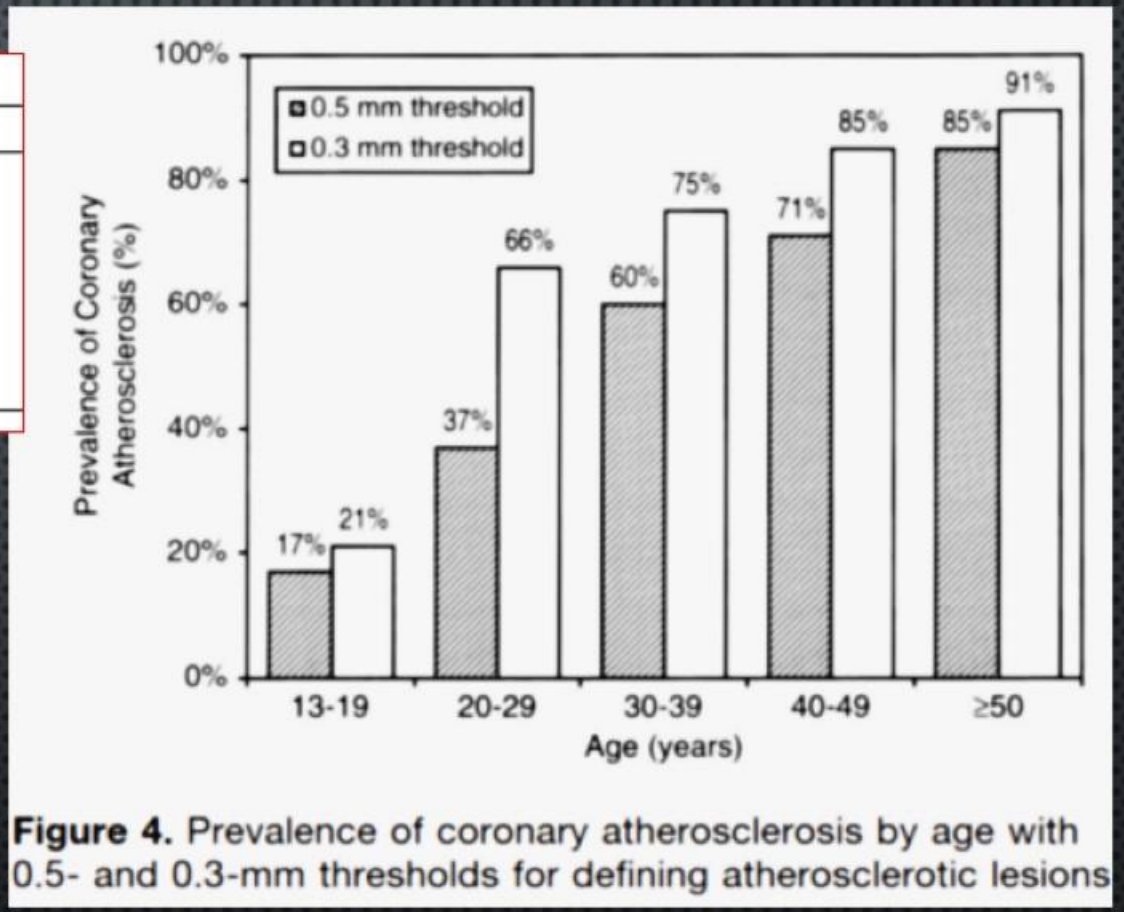
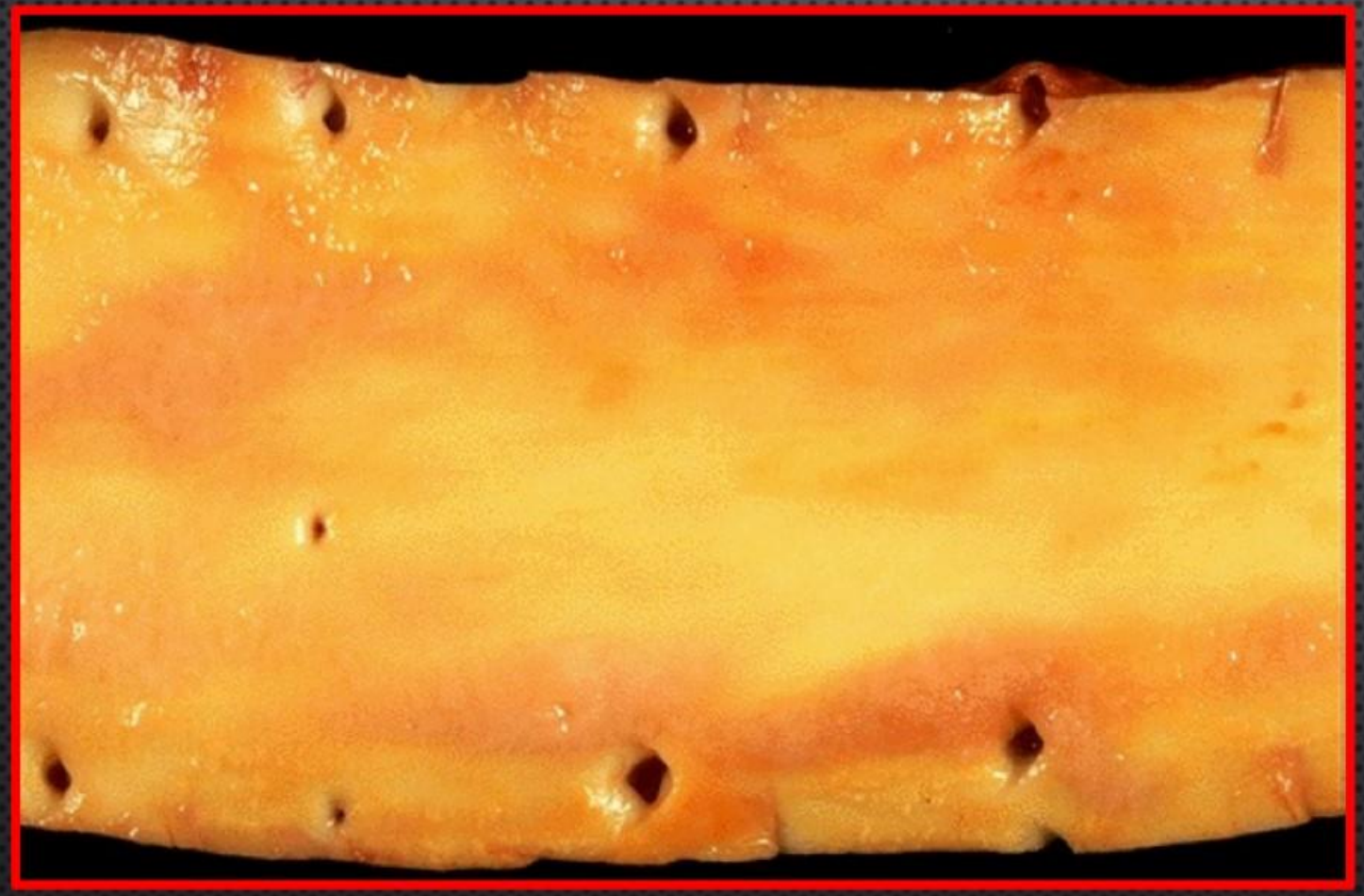
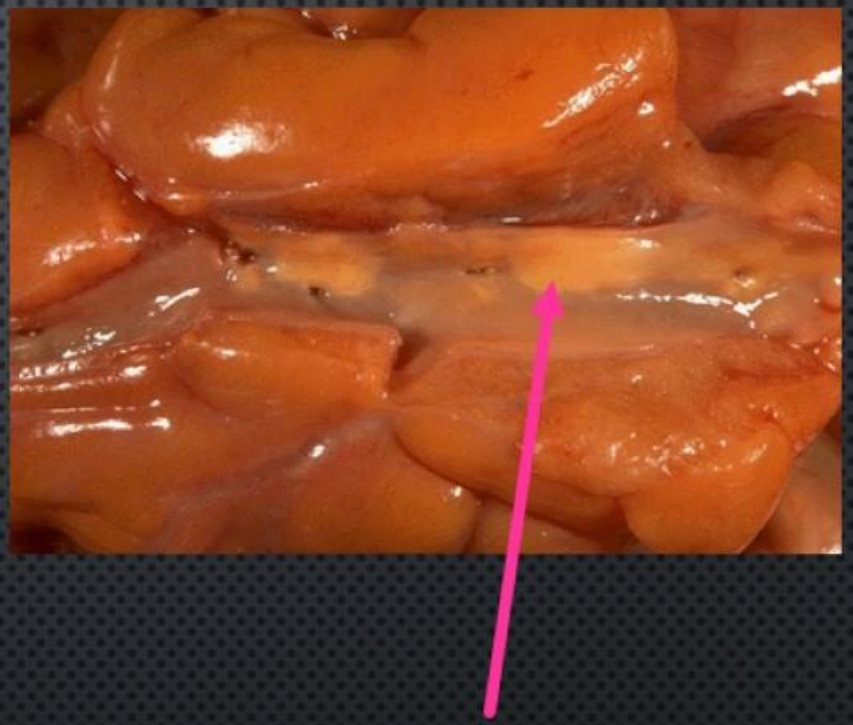


Figure 4. Prevalence of coronary atherosclerosis by age with 0.5- and 0.3-mm thresholds for defining atherosclerotic lesions

Circulation Volume 103, Issue 22, 5 June 2001, Pages 2705-2710

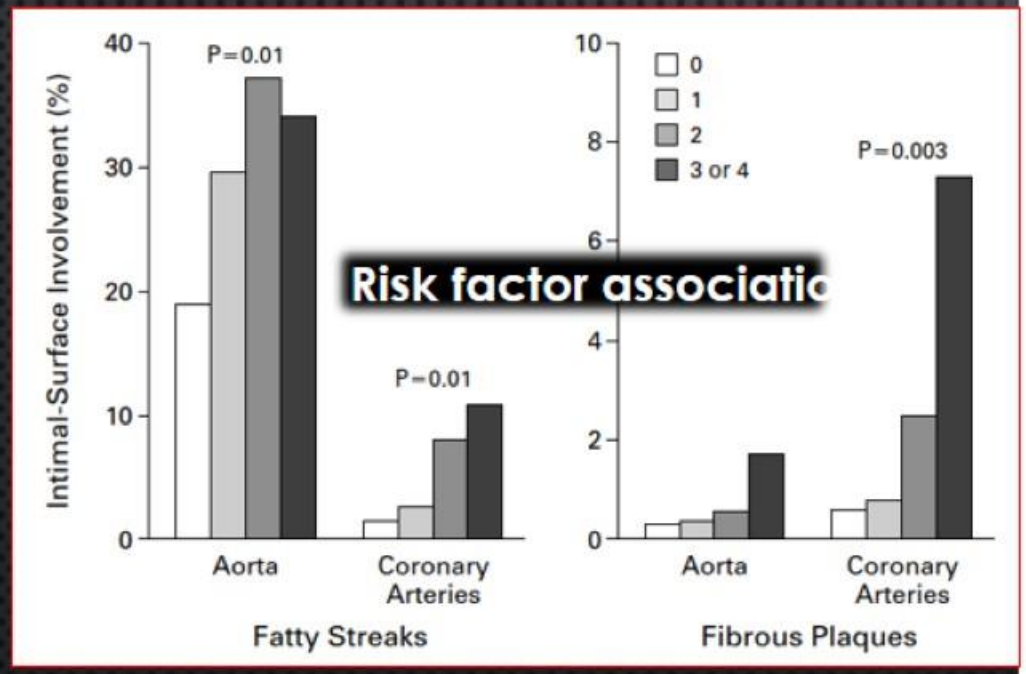




This is about as normal as an adult aorta in America gets. **The faint reddish staining is from hemoglobin that leaked from RBC's following death. The surface is quite smooth, with only occasional faint small yellow lipid streaks visible**

Atherosclerosis starts early in life

Autopsies on 204 young persons 2 to 39 years of age



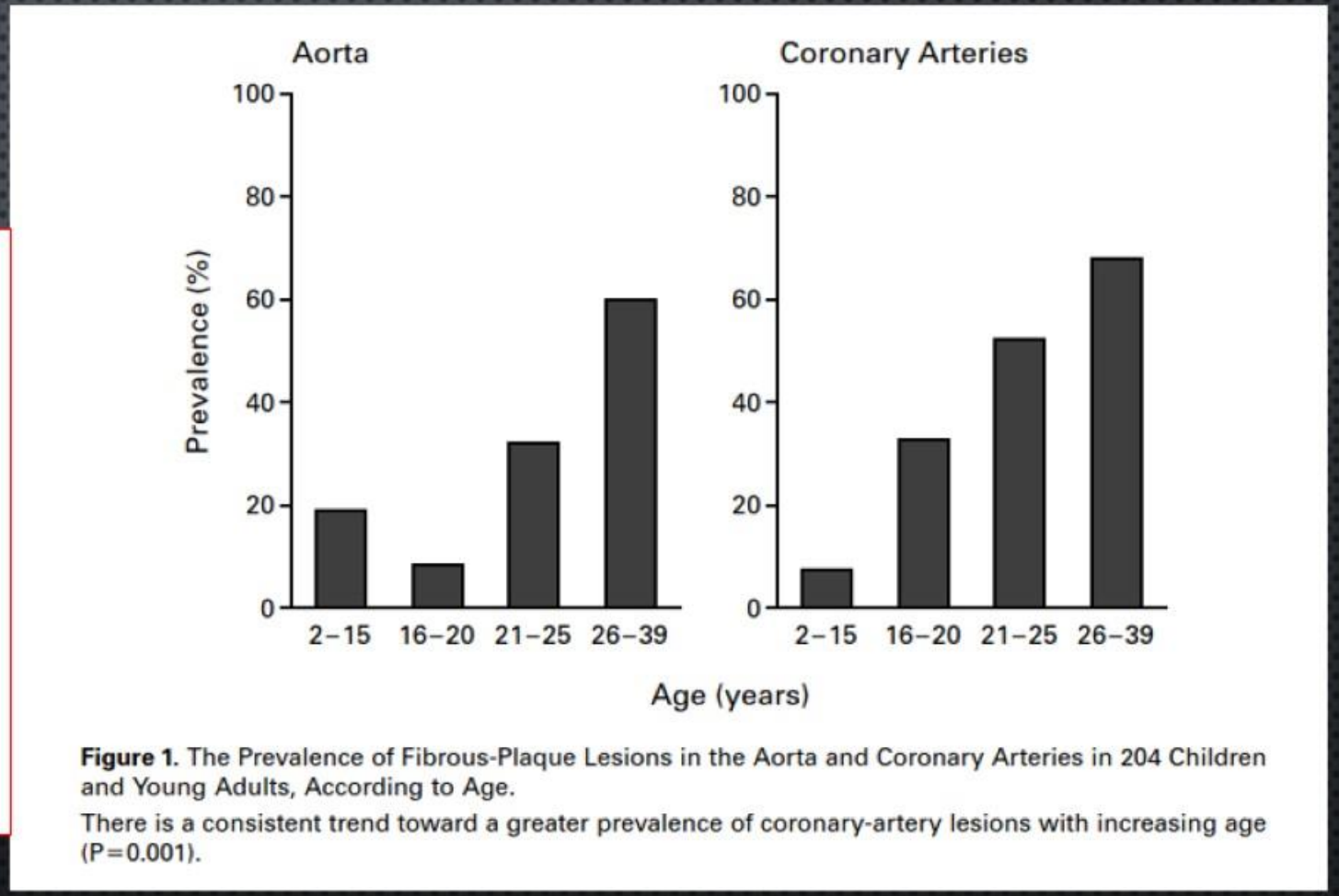


Figure 1. The Prevalence of Fibrous-Plaque Lesions in the Aorta and Coronary Arteries in 204 Children and Young Adults, According to Age.

There is a consistent trend toward a greater prevalence of coronary-artery lesions with increasing age (P=0.001).

N Engl J Med 1778;338:1650-6

Am J Cardiol 2002;90(suppl):3L–7L

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

Production of a proatherosclerotic metabolite, trimethylamine-N-oxide (TMAO) (microbial metabolism)

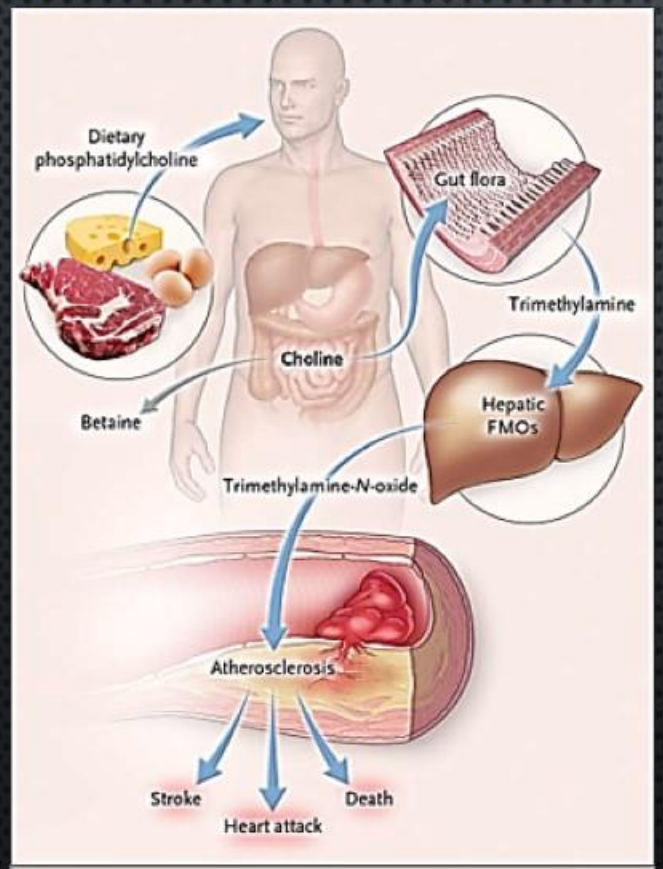
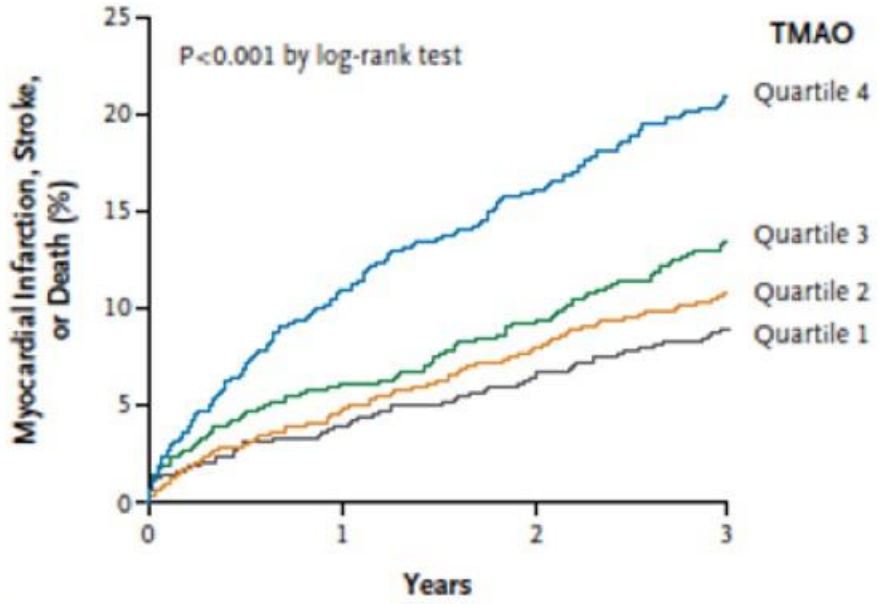


Figure 3. Pathways Linking Dietary Phosphatidylcholine, Intestinal Microbiota, and Incident Adverse Cardiovascular Events.



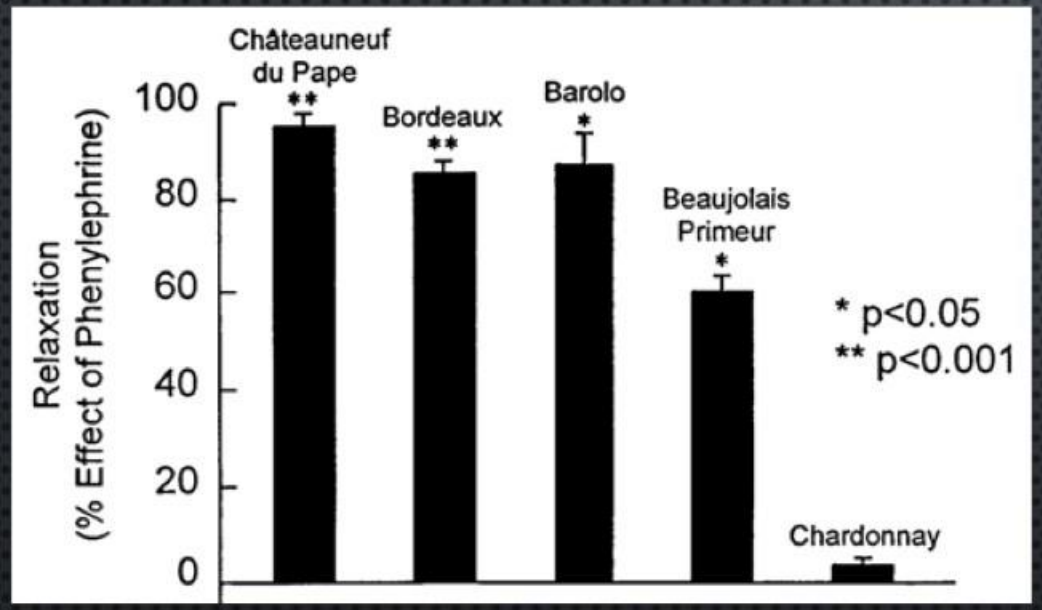
No. at Risk				
Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Figure 2. Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level.

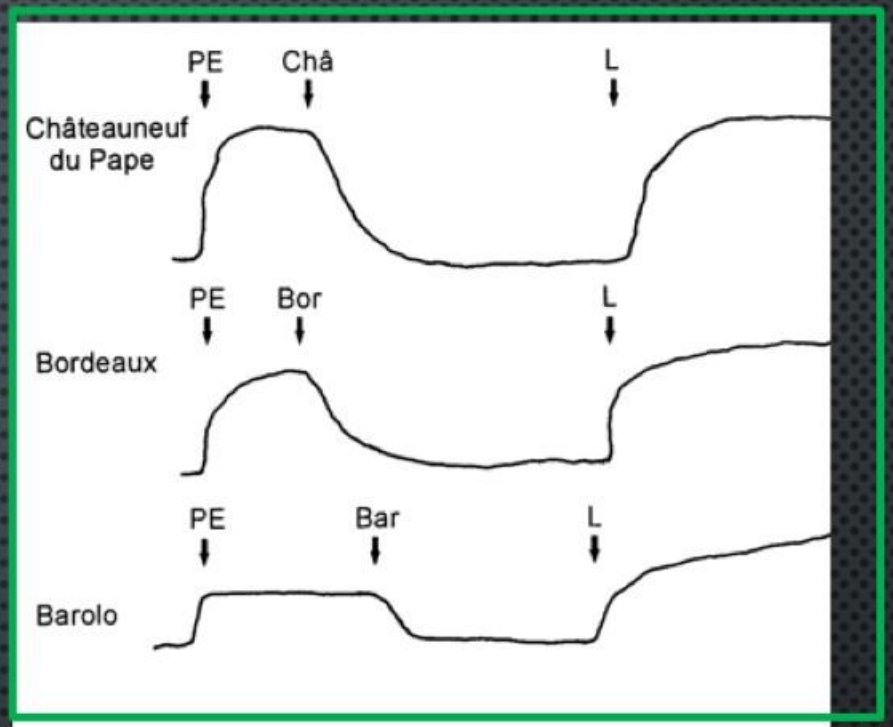
Data are shown for 4007 participants in the clinical-outcomes study. The P value is for all comparisons.

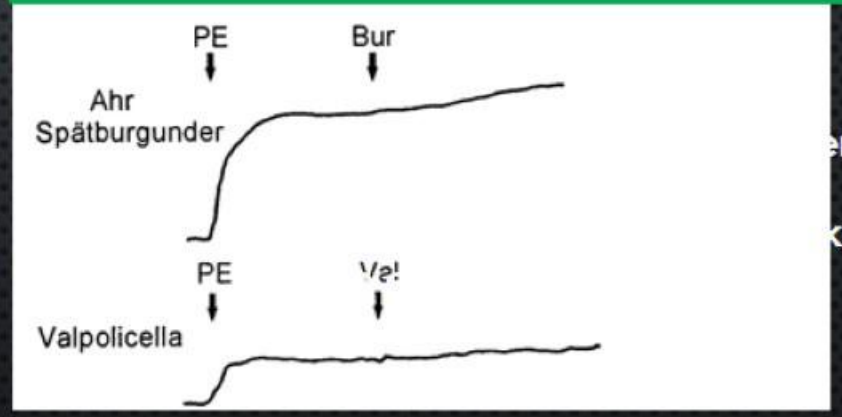
N Engl J Med 2013;368:1575-84

Effects of red and white wine on endothelium-dependent vasorelaxation -human coronary arteries



Strong NO vasorelaxation-blocked by l-nmma





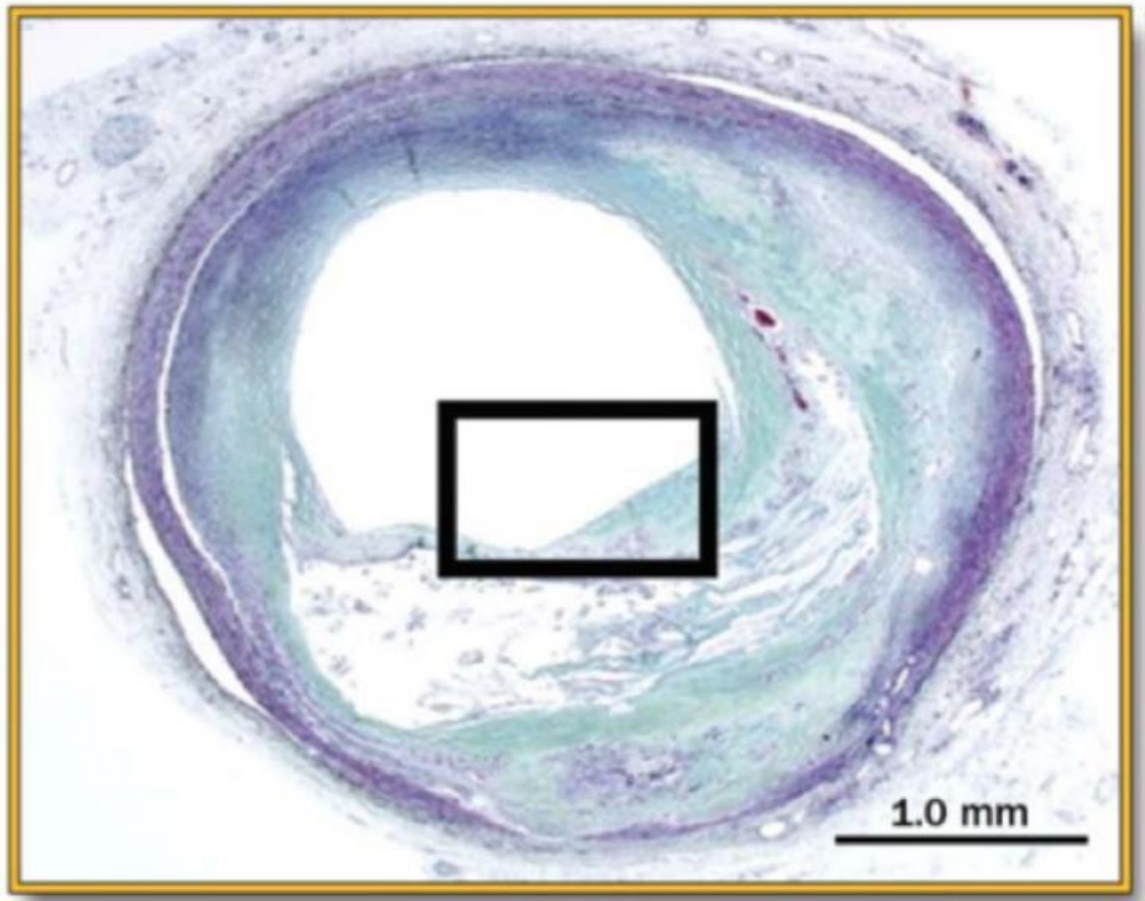
Notice: *ethanol* itself had no effect on vascular tone

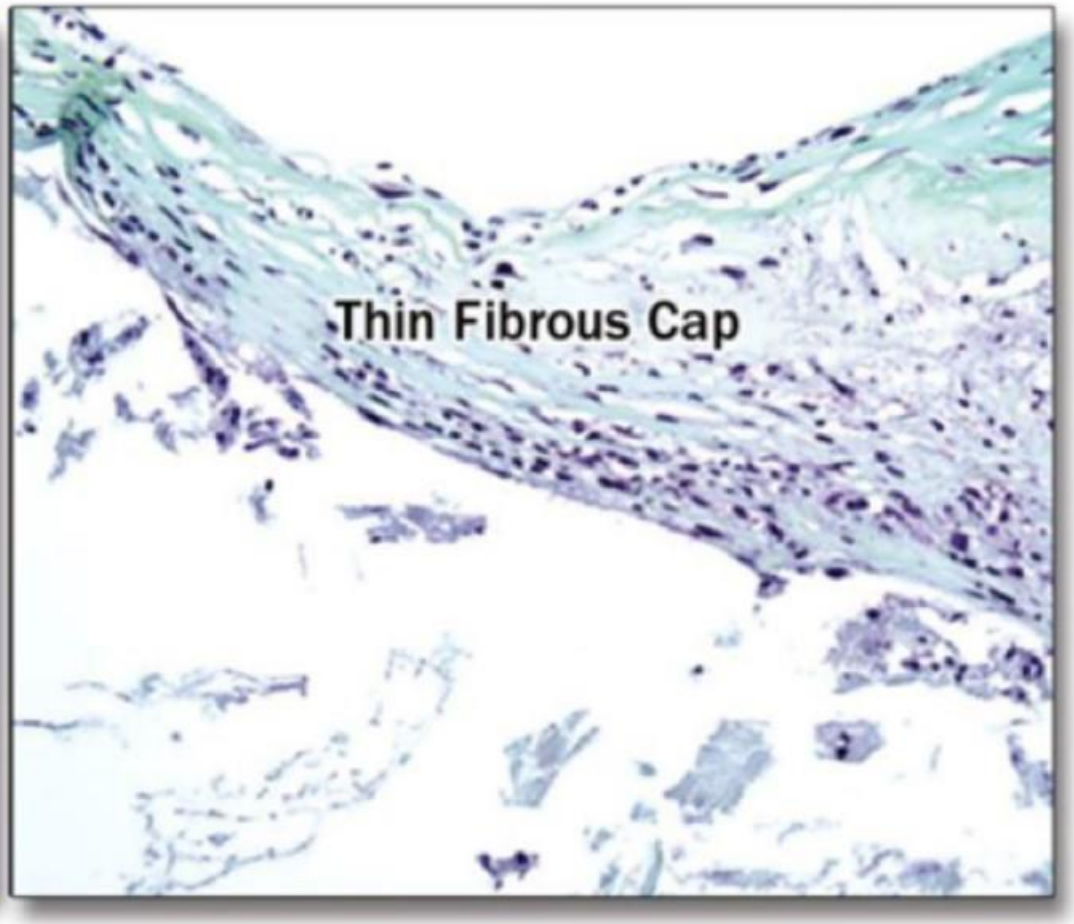
Food for thought

journals.physiology.org/journal/ajphea
t 1998;h1183

Prevention is the best

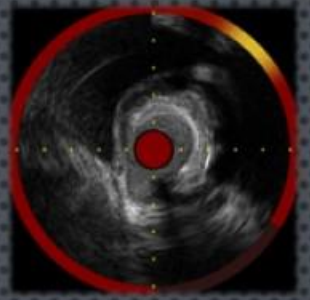
Human Coronary Thin-Cap Fibroatheroma



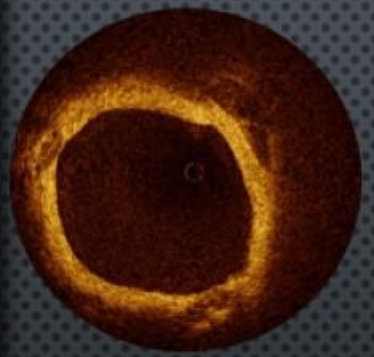


consist of
thinner fibrous caps and more lipid-

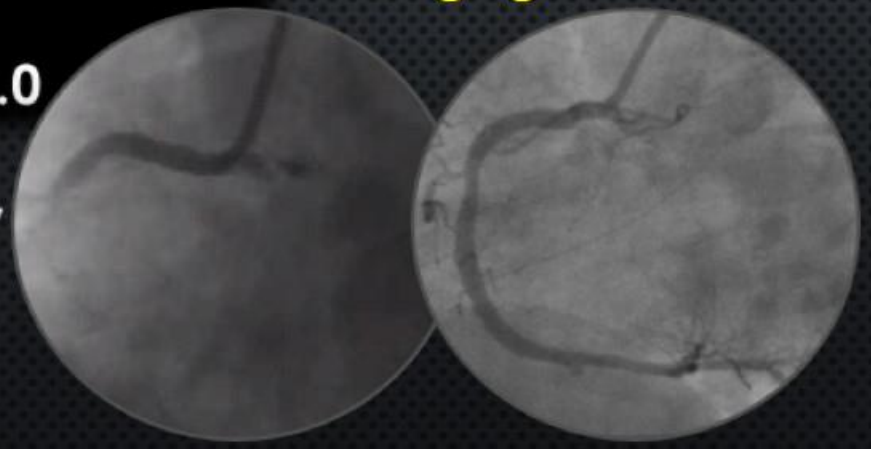
RISK FACTORS OF ACUTE CORONARY SYNDROME



- INDEPENDENT RISK FOR CV EVENTS-CLINICAL
  - DIABETES-INSULIN P<0.005
  - PRIOR CABG P<0.02
- IVUS LESIONS (P<0.001)
  - PLAQUE BURDEN >70%
  - THIN CAP
  - MIN LUMEN AREA <4.0

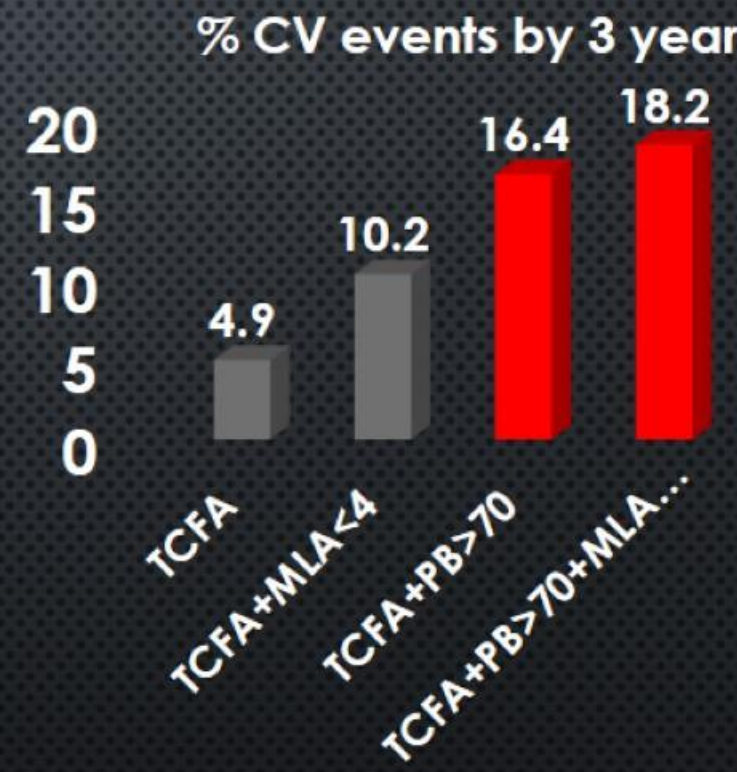


Life changing moment



A Prospective Natural-History Study of Coronary Atherosclerosis

Mild disease at baseline by IVUS but represents major CV risk by 3 years

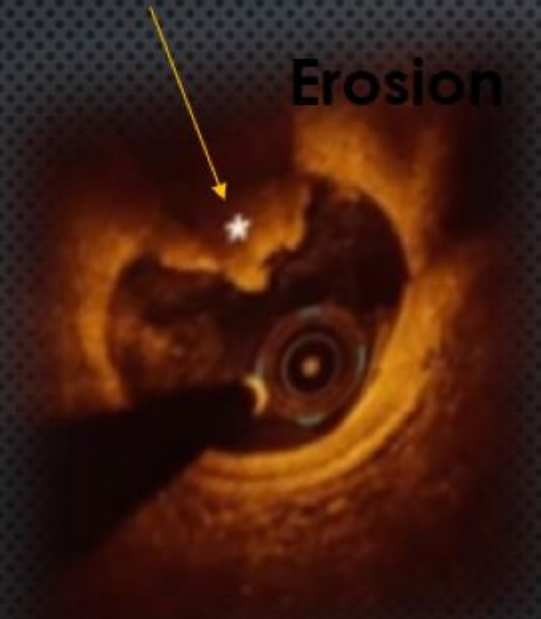


Stone et al N Engl J Med 2011;364:226-35

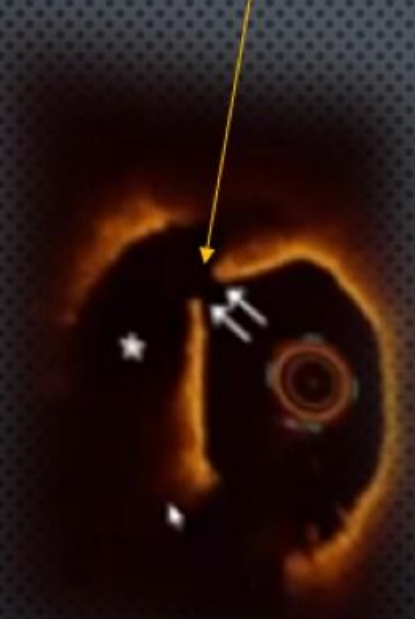
Increased atheroprothrombotic state in diabetes

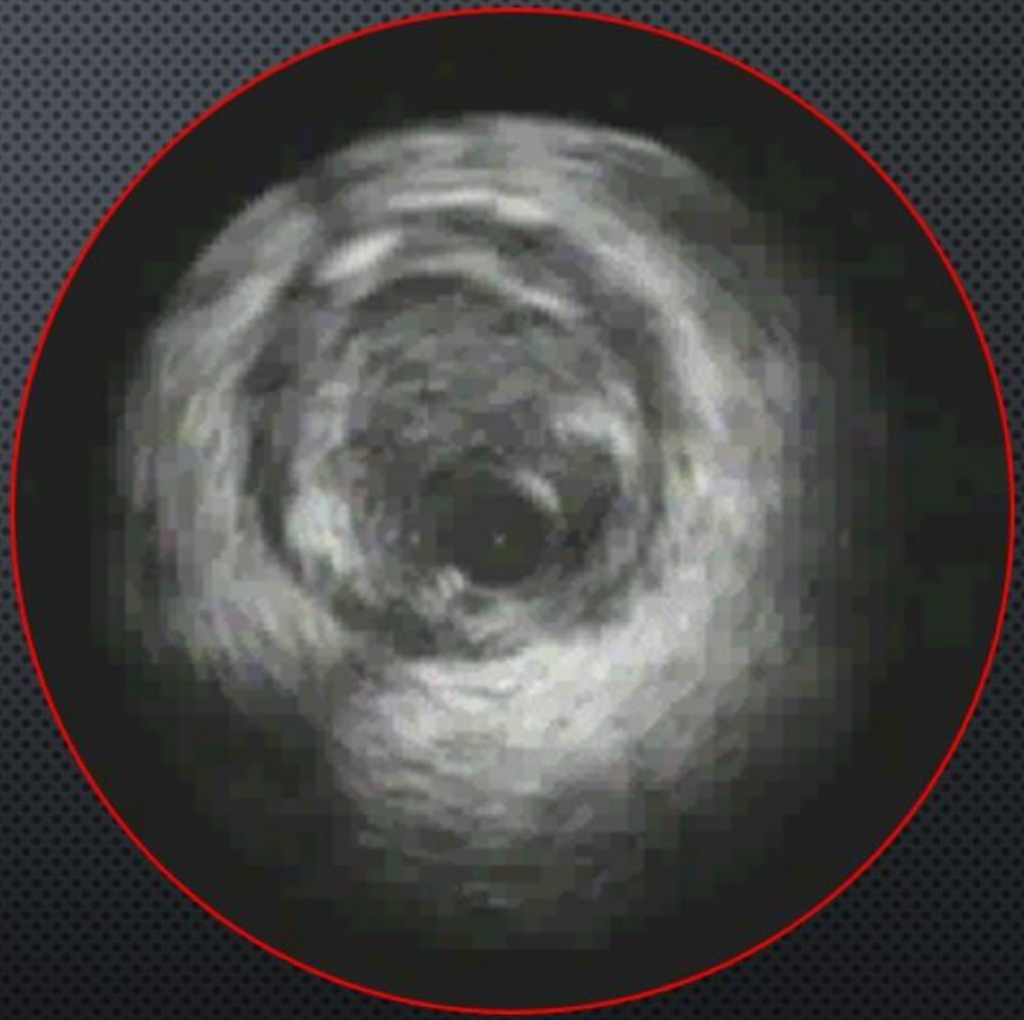
Platelet rich thrombus

Erosion

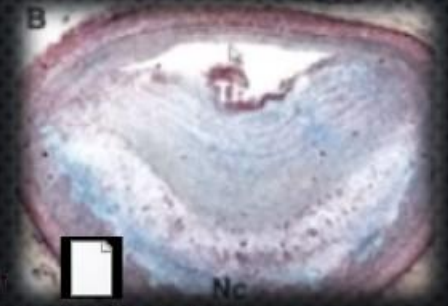


Thin fibrous cap <65u





No endothelial cells



Fibrous cap rupture

Thromb Haemost 1999; 82 (Suppl.): 1–3

Humans (carotid tissue) and statins

Atherosclerotic plaques were surgically removed from both treated and untreated (control) patient groups for histological analysis (N-24)(3 months statins vs control)

Statin treated patients: plaques had significantly less lipid content and less inflammatory cell infiltration

Statin treated: reduction in matrix degradation enzymes

Higher collagen content in statin-treated plaques

Translational

Pravastatin Treatment Increases Collagen Content and Decreases Lipid Content, Inflammation, Metalloproteinases, and Cell Death in Human Carotid Plaques

Implications for Plaque Stabilization

Milita Crisby, MD; Gunilla Nordin-Fredriksson, MD; Prediman K. Shah, MD; Juliana Yano, BS; Jenny Zhu, BS; Jan Nilsson, MD, PhD

Background—The clinical benefits of lipid lowering with statins are attributed to changes in plaque composition leading to lesion stability, but supporting clinical data from human studies are lacking. Therefore, we investigated the effect of 3 months of pravastatin treatment on composition of human carotid plaques removed during carotid endarterectomy.

Methods and Results—Consecutive patients with symptomatic carotid artery stenosis received 40 mg d pravastatin (n=11) or no lipid-lowering therapy (n=13; control subjects) for 3 months before scheduled carotid endarterectomy. Carotid plaque composition was assessed with special stains and immunocytochemistry with quantitative image analysis. Plaques from the pravastatin group had less lipid by oil red O staining (8.2±8.4% versus 23.9±21.1% of the plaque area, $P<0.05$), less oxidized LDL immunoreactivity (13.3±3.6% versus 22.0±6.5%, $P<0.001$), fewer macrophages (15.0±10.2% versus 25.3±12.5%, $P<0.05$), fewer T cells (11.2±9.3% versus 24.3±13.4%, $P<0.05$), less matrix metalloproteinase 2 (MMP-2) immunoreactivity (3.6±3.9% versus 8.4±5.3%, $P<0.05$), greater tissue inhibitor of metalloproteinase 1 (TIMP-1) immunoreactivity (9.0±6.2% versus 3.1±3.9%, $P<0.05$), and a higher collagen content by Sirius red staining (12.4±3.1% versus 7.5±3.5%, $P<0.005$). Cell death by TUNEL staining was reduced in the pravastatin group (17.7±7.8% versus 32.0±12.6%, $P<0.05$).

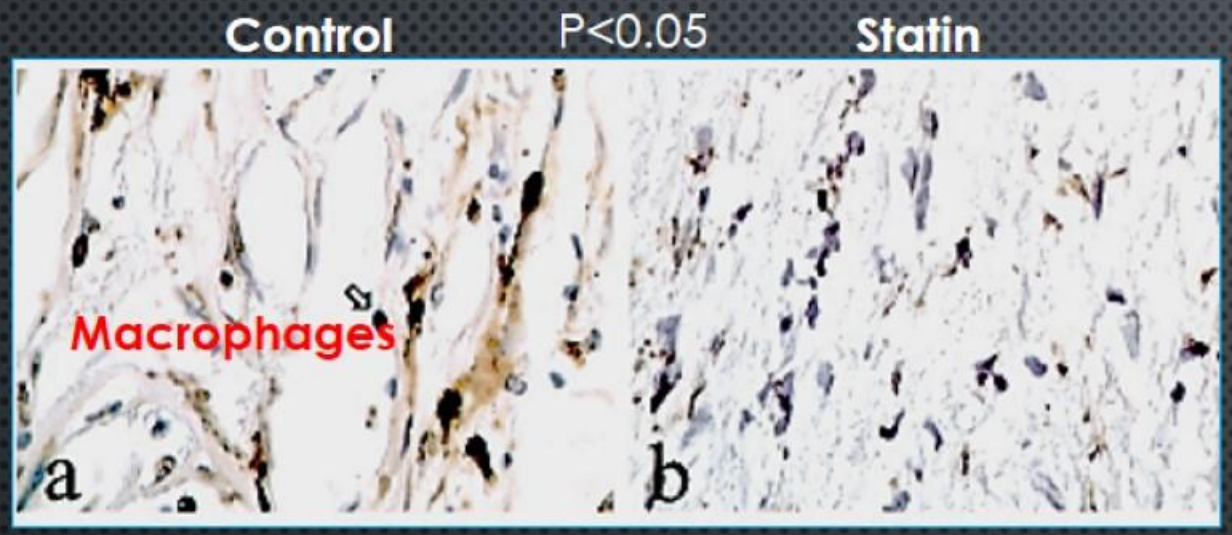
Conclusions—Pravastatin decreased lipids, lipid oxidation, inflammation, MMP-2, and cell death and increased TIMP-1 and collagen content in human carotid plaques, confirming its plaque-stabilizing effect in humans. (*Circulation.* **2001; 103:926-933.**)

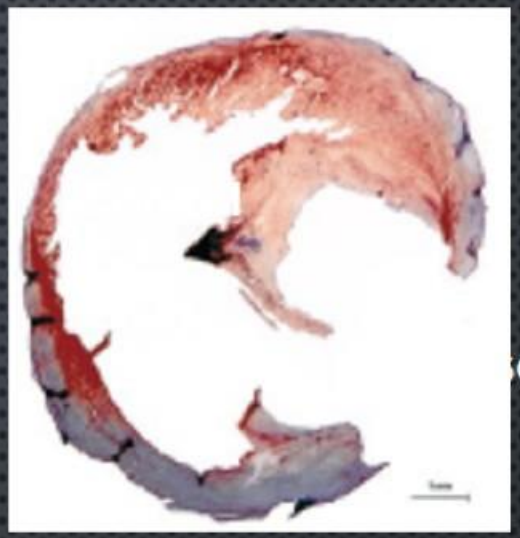
Oil red O stain for lipid

Immunoreactivity for oxidized LDL

Circulation. 2001;103:926-933

Humans (carotid tissue) and statins



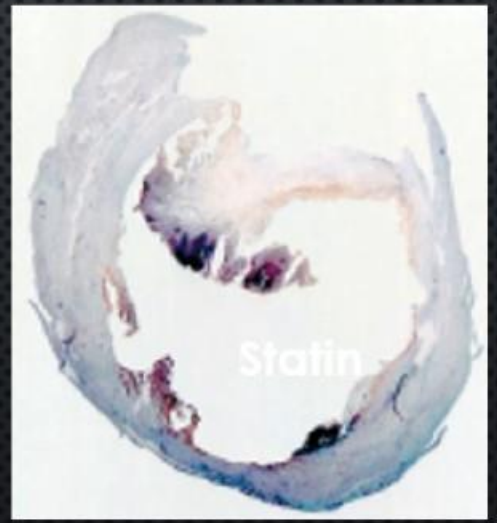


ed MMP2

TABLE 6. MMP, TIMP, and Collagen Content

Subjects	Collagen	*P*	MMP-1	*P*	MMP-2	*P*
Control (n=13)	7.5±3.5		10.4±4.7		8.4±5.3	
Pravastatin (n=11)	12.4±3.1	0.003	8.2±5	NS	3.6±3.9	0.03

Data are presented as percentage of plaque area, mean±SD.



Circulation. 2001;103:926-933

New clinical trials & guidelines

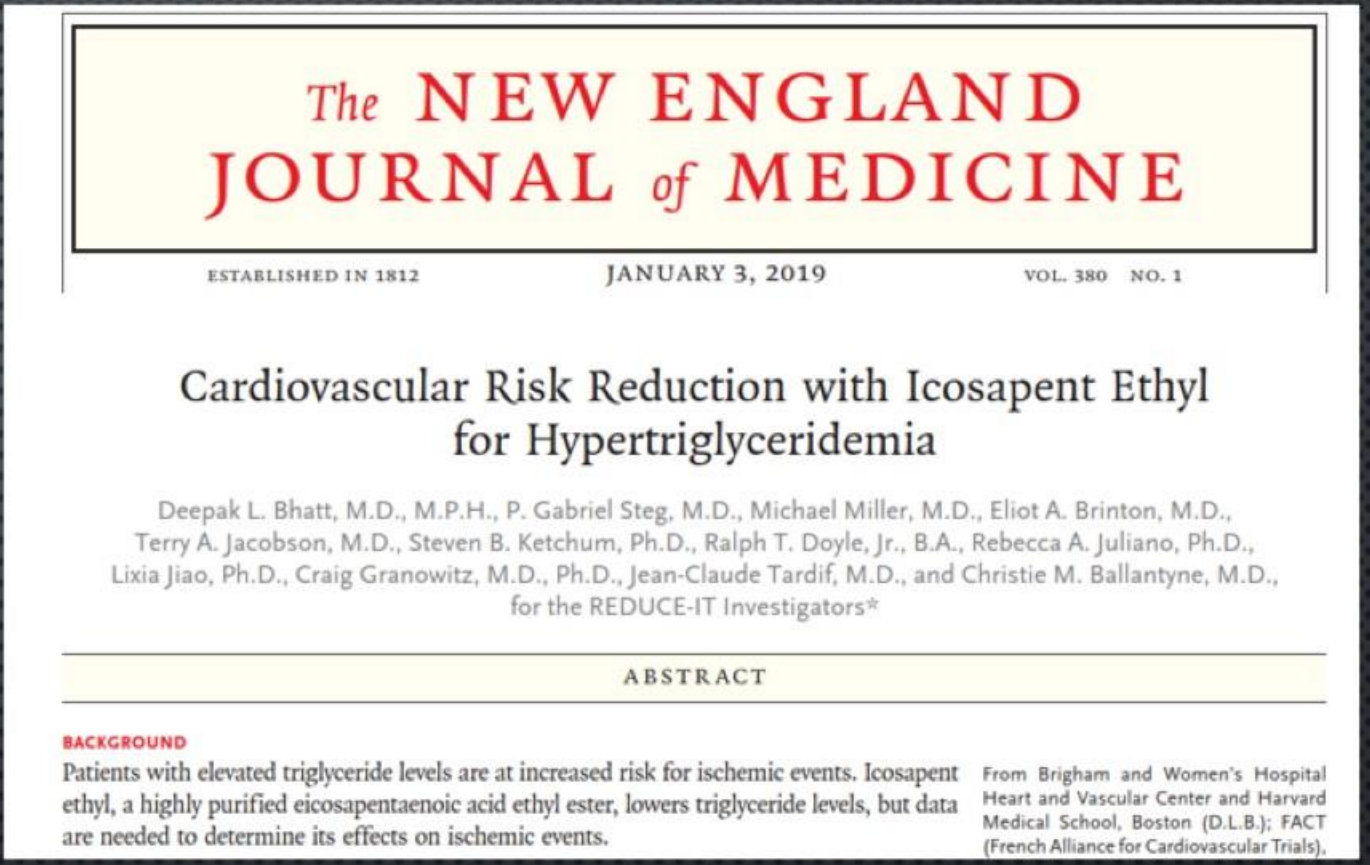
EPA/PCSK9/ Bempedoic acid /IL 1b

REDUCE IT

Multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other

Fasting triglyceride level of 135 to 499 mg per deciliter and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter

2 g of icosapent ethyl twice daily vs control



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ABSTRACT

BACKGROUND

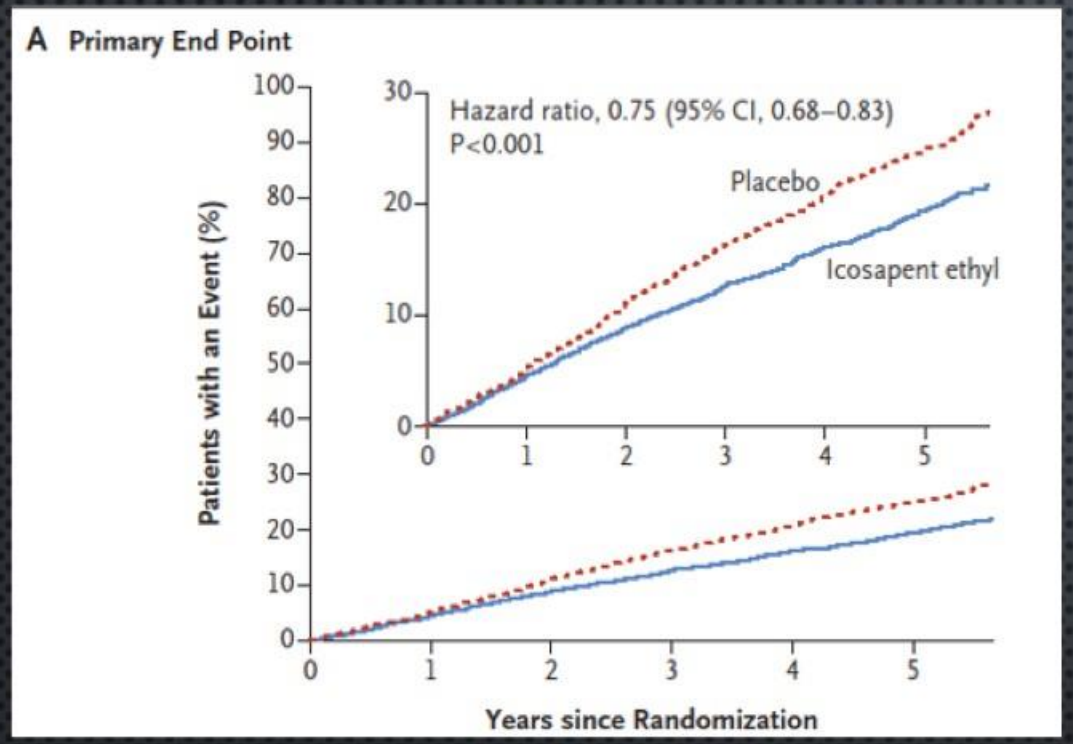
Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials),

Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years.

N Engl J Med 2019;380:11-22



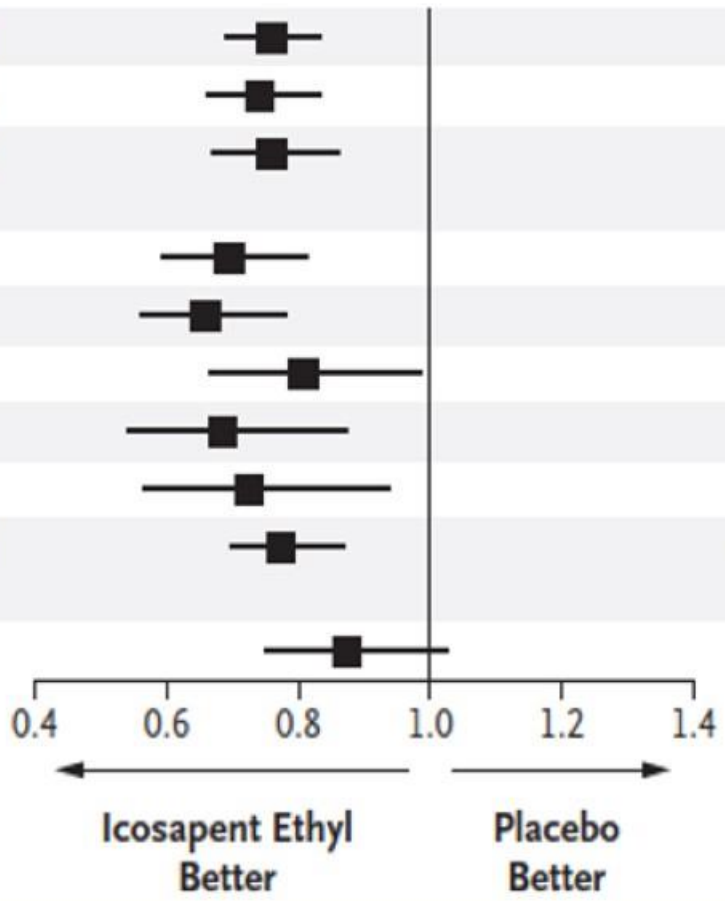
Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Risk stratum				0.14
Secondary-prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65–0.81)	
Primary-prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70–1.10)	
Region				0.30
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	551/2906 (19.0)	713/2905 (24.5)	0.74 (0.66–0.83)	
Eastern Europe	143/1053 (13.6)	167/1053 (15.9)	0.84 (0.67–1.05)	
Asia–Pacific	11/130 (8.5)	21/132 (15.9)	0.49 (0.24–1.02)	
Ezetimibe use				0.64
No	649/3827 (17.0)	834/3828 (21.8)	0.75 (0.67–0.83)	
Yes	56/262 (21.4)	67/262 (25.6)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8)	715/2895 (24.7)	0.73 (0.65–0.82)	
Female	154/1162 (13.3)	186/1195 (15.6)	0.82 (0.66–1.01)	
Race				0.18
White	646/3691 (17.5)	812/3688 (22.0)	0.77 (0.69–0.85)	
Other	59/398 (14.8)	89/401 (22.2)	0.60 (0.43–0.83)	
Age				0.004
<65 yr	322/2232 (14.4)	460/2184 (21.1)	0.65 (0.56–0.75)	
≥65 yr	383/1857 (20.6)	441/1906 (23.1)	0.87 (0.76–1.00)	

Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina

REDUCE IT

N Engl J Med 2019;380:11-22

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



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N Engl J Med 2019;380:11-22

Recommendations for Hypertriglyceridemia

Referenced studies that support recommendations are summarized in Online Data Supplements 31 and 32.

COR	LOE	Recommendations
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [2.0 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.[S4.5.2-1]

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

IMPORTANCE Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

OBJECTIVE To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

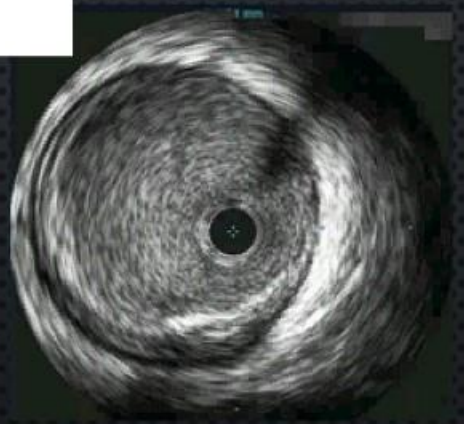
Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions page 2426

GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial

N= Monthly **evolocumab**(420mg)(n = 484)orplacebo(n = 484)

Evolocumab (420 mg) or placebo administered monthly via subcutaneous injection for 76 weeks



Primary endpoint: change in **Percent atheroma volume**(PAV)from baseline to week 78 measure by intravascular ultrasound (IVUS)

JAMA.2016;316(22):2373-2384.doi:10.1001/jama.2016.16951

Table 1. Baseline Characteristics of Patients in the Randomized Population Who Received Study Drug (N = 968)[a]

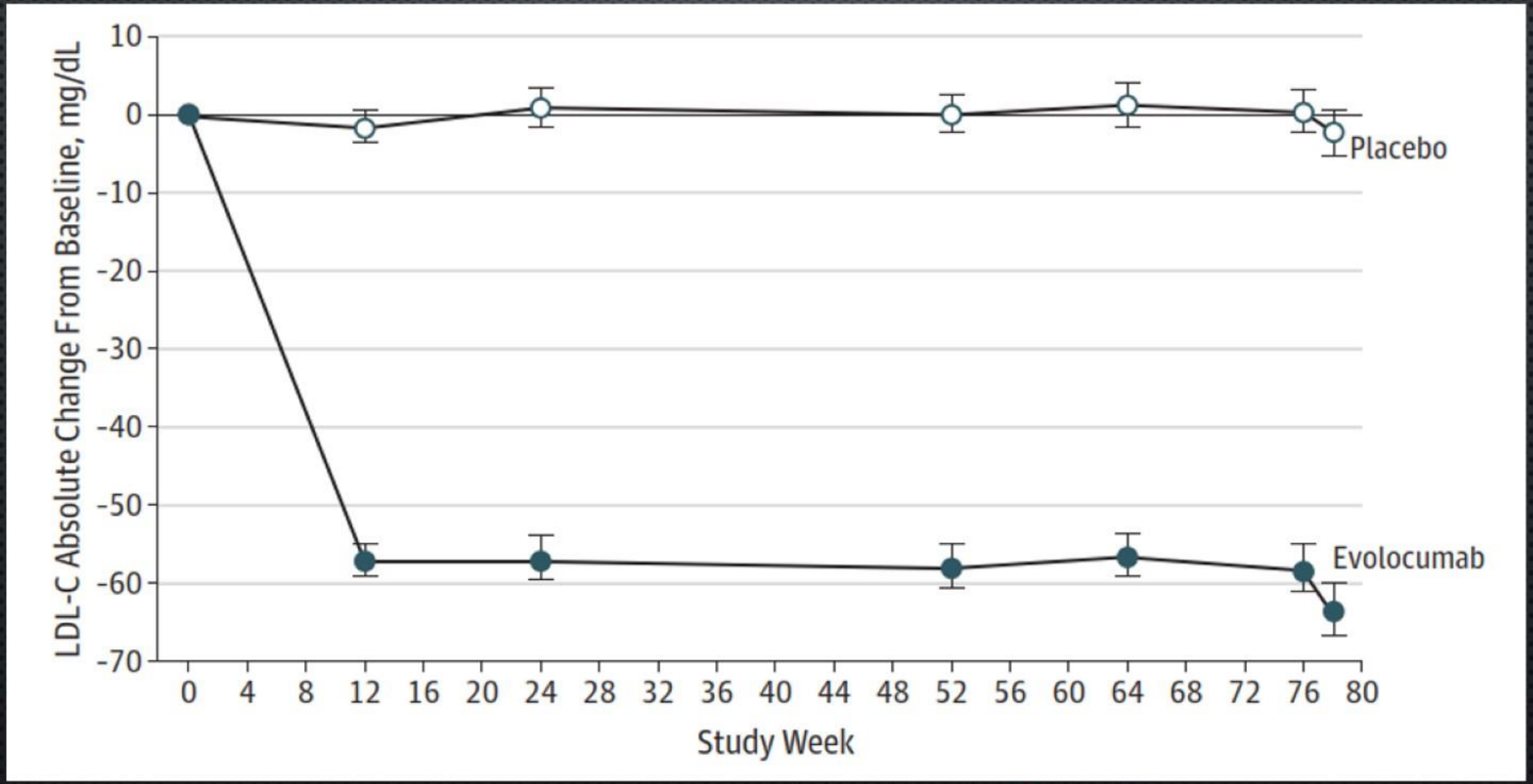
Parameter	No. (%)	
	Placebo (n = 484)	Evolocumab (n = 484)
Age, mean (SD), y	59.8 (8.8)	59.8 (9.6)
Men	350 (72.3)	349 (72.1)
Race/ethnicity		
White	452 (93.4)	456 (94.2)
Black or African American	5 (1.0)	4 (0.8)
Asian	16 (3.3)	14 (2.9)
Native Hawaiian or other Pacific islander	0	1 (0.2)
American Indian or Alaska native	2 (0.4)	0
Multiple	6 (1.2)	7 (1.4)
Other	3 (0.6)	2 (0.4)

JAMA.2016;316(22):2373-2384.doi:10.1001/jama.2016.16951

GLAGOV

Table 2. Baseline and On-Treatment Biochemical Measures and Blood Pressure in the Randomized Population Who Received Study Drug[a]

Parameter	Baseline		On-Treatment		*P* Value[b]
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	
Cholesterol, mean (95% CI), mg/dL					
TC	166.2 (163.1 to 169.2)	166.1 (163.0 to 169.2)	169.1 (166.3 to 172.0)	108.6 (106.0 to 111.3)	<.001
LDL-C[c]	92.4 (90.0 to 94.8)	92.6 (90.1 to 95.0)	93.0 (90.5 to 95.4)	36.6 (34.5 to 38.8)	<.001
HDL-C	45.4 (44.2 to 46.5)	46.7 (45.5 to 47.8)	47.1 (46.0 to 48.2)	51.0 (49.8 to 52.1)	<.001
Triglycerides, median (IQR), mg/dL[d]	124.5 (90.0 to 173.0)	117.0 (88.0 to 155.0)	130.5 (100.3 to 177.2)	105.1 (82.5 to 141.6)	<.001
non-HDL-C, mean (95% CI), mg/dL	120.8 (117.9 to 123.7)	119.4 (116.5 to 122.3)	122.0 (119.3 to 124.7)	57.7 (55.2 to 60.2)	<.001
TC:HDL-C, mean (95% CI)	3.9 (3.8 to 4.0)	3.7 (3.6 to 3.9)	3.8 (3.7 to 3.9)	2.3 (2.2 to 2.3)	<.001
Apolipoprotein, mean (95% CI), mg/dL					
B	81.9 (80.1 to 83.6)	81.1 (79.3 to 82.9)	83.5 (81.8 to 85.2)	42.4 (40.8 to 44.0)	<.001
A-I	139.5 (137.2 to 141.9)	140.5 (138.3 to 142.8)	145.4 (143.4 to 147.4)	151.6 (149.5 to 153.7)	<.001
B:A-I	0.60 (0.59 to 0.62)	0.59 (0.58 to 0.61)	0.59 (0.57 to 0.60)	0.29 (0.28 to 0.30)	<.001
hsCRP, median (IQR), mg/L[d,e]	1.6 (0.8 to 3.4)	1.6 (0.8 to 3.4)	1.4 (0.7 to 3.0)	1.4 (0.7 to 3.0)	.47
Lp(a), median (IQR), mg/dL	10.9 (3.9 to 50.7)	12.1 (4.6 to 57.1)	8.9 (3.9 to 48.1)	7.1 (2.5 to 46.7)	.07



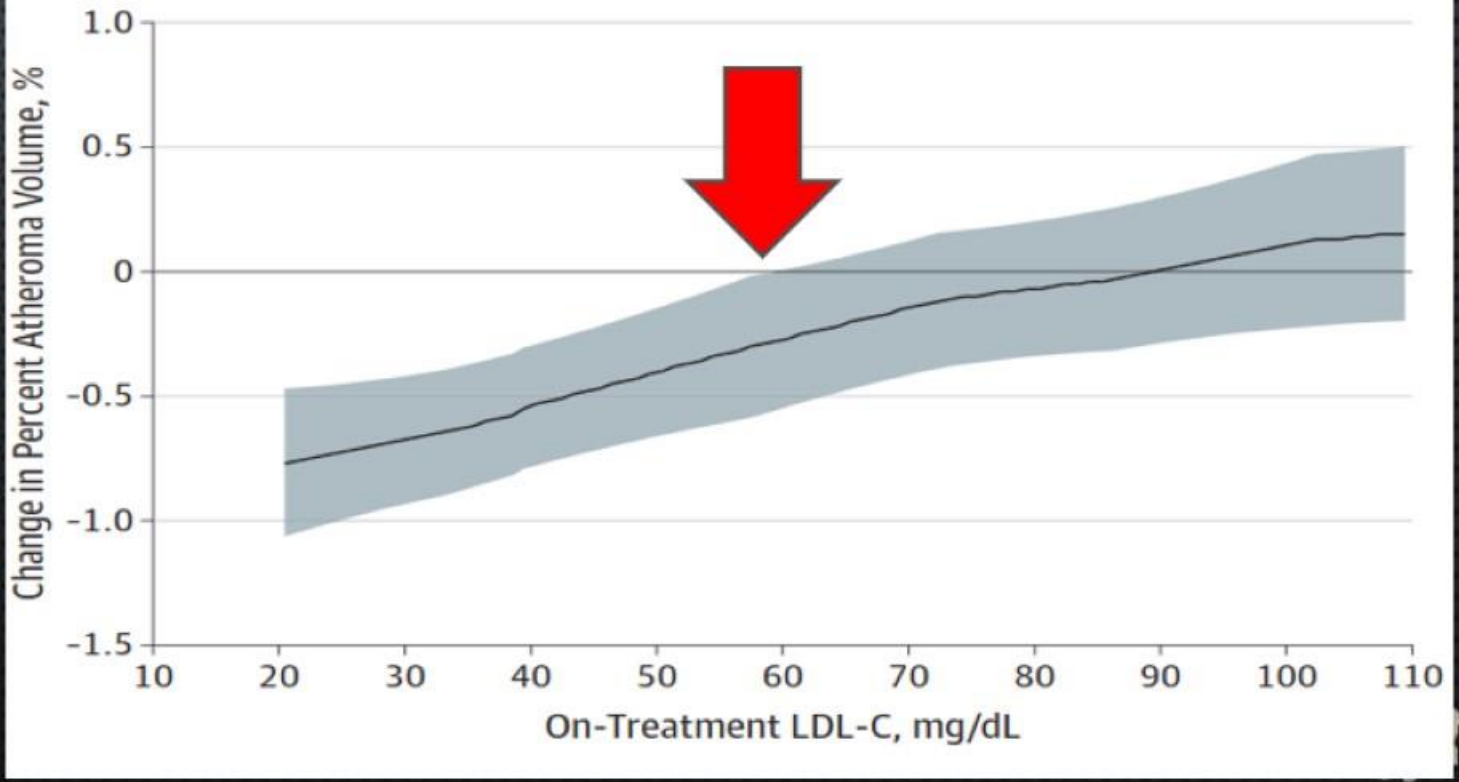
JAMA.2016;316(22):2373-2384.doi:10.1001/jama.2016.16951

Table 3. Primary and Secondary Study End Points as Evaluated on Intravascular Ultrasonography

Parameter	Placebo (n = 423)	Evolocumab (n = 423)	Between Group Differences, Least Squares Means (95% CI)	*P* Value
Follow-up at 78 wk				
Percent atheroma volume				
Mean (95% CI)	37.3 (36.5 to 38.1)	35.6 (34.8 to 36.4)	−1.7 (−2.8 to −0.6)	.002
Median (95% CI)	36.8 (35.7 to 37.8)	35.7 (34.8 to 36.5)		

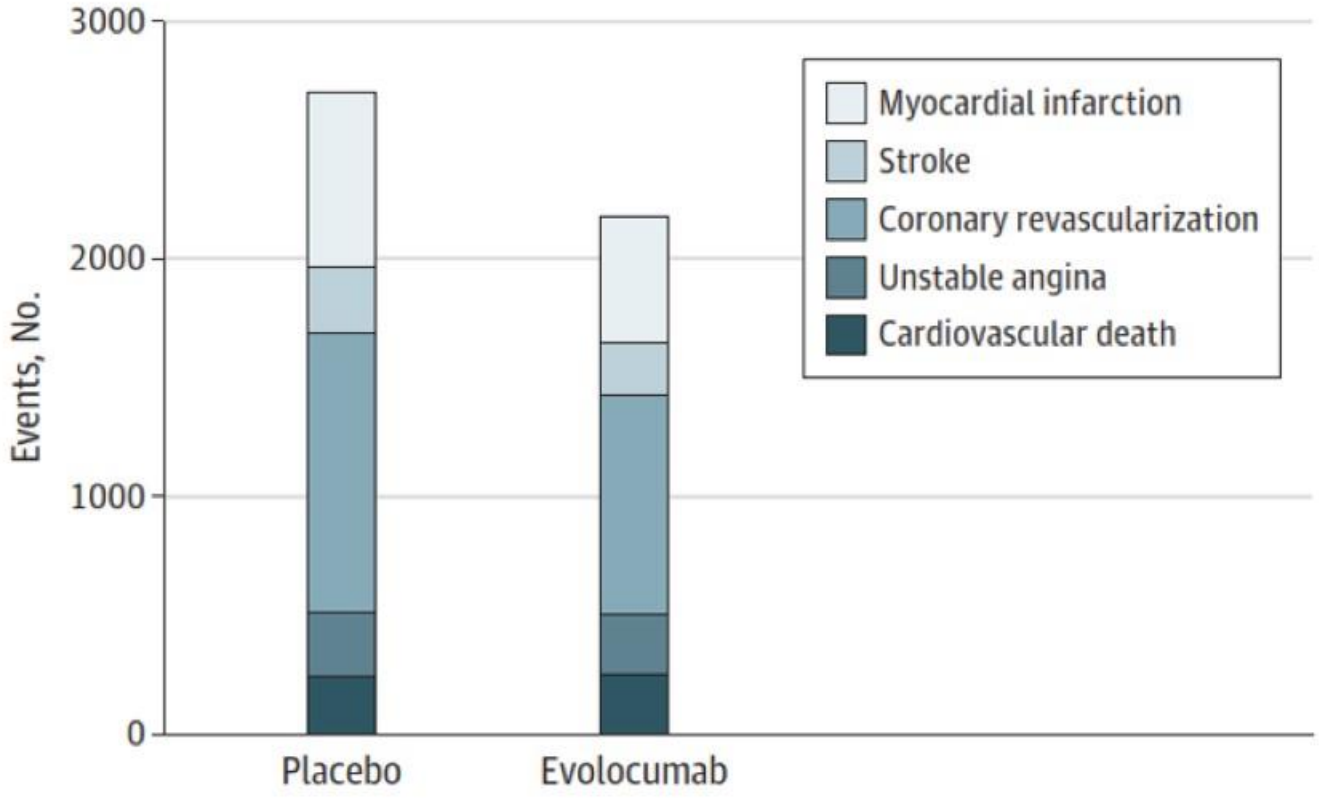
Primary endpoint: change in **Percent atheroma volume** (PAV) from baseline to week 78 measure by intravascular ultrasound (IVUS)

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume

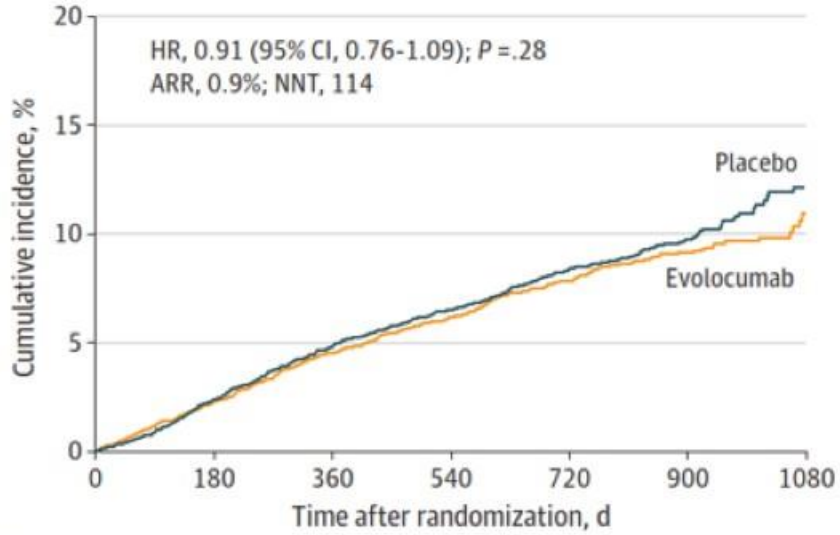


JAMA.2016;316(22):2373-2384.doi:10.1001/jama.2016.16951

Figure 3. Total Events During Follow-up by Randomization Group for Components of the Primary End Point



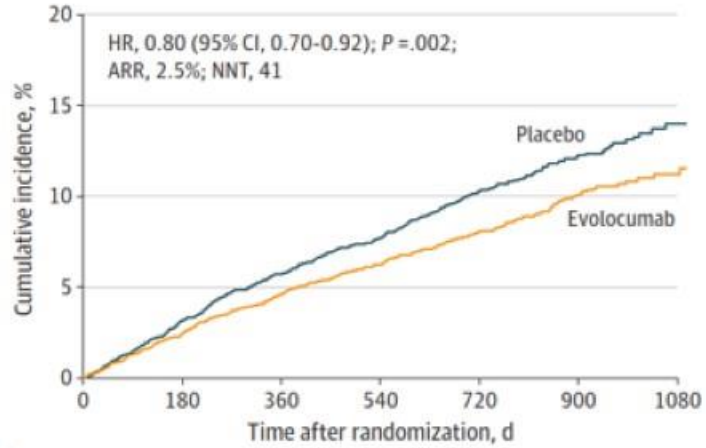
D No diabetes and no metabolic syndrome



No. at risk

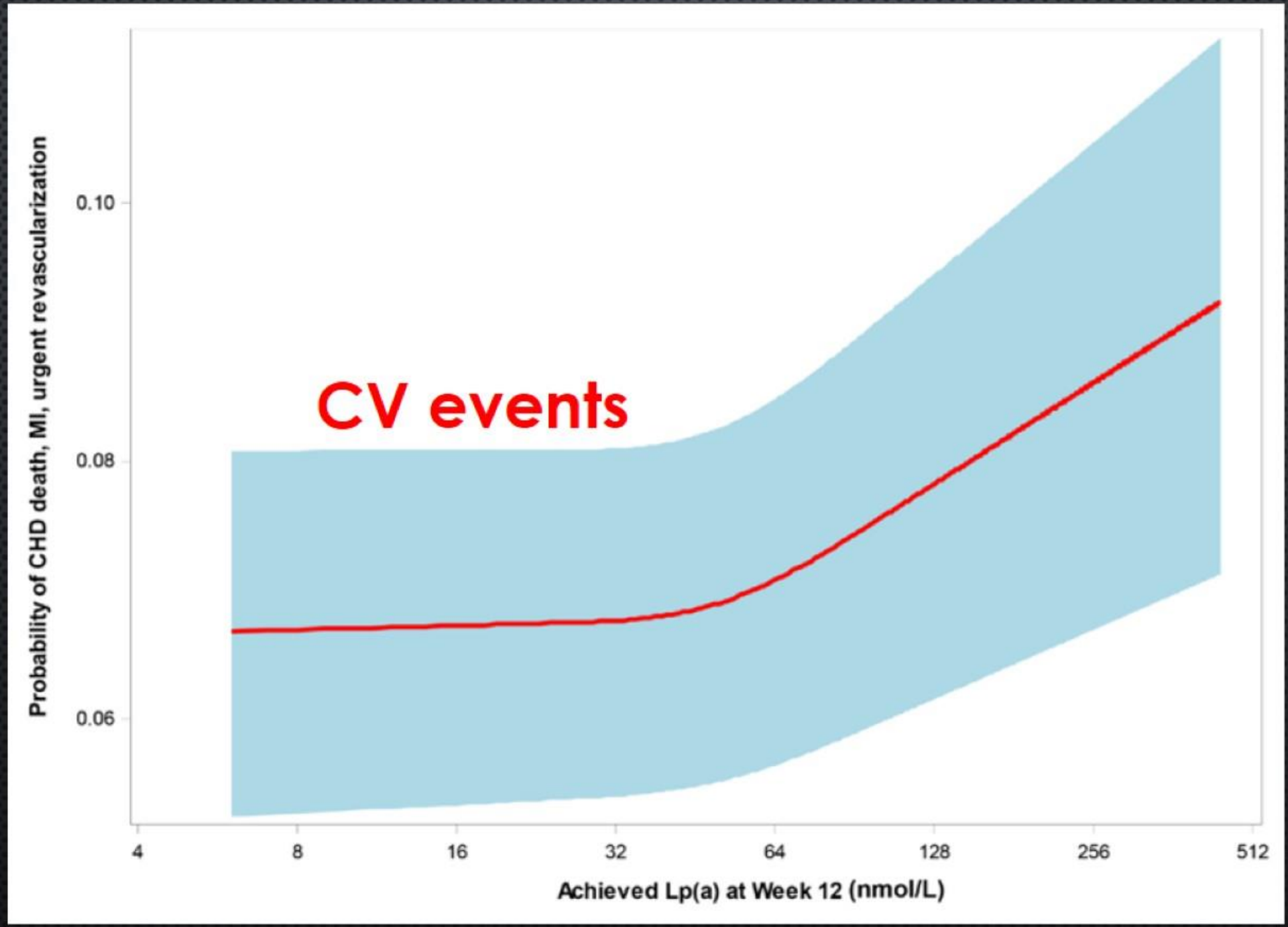
Placebo	4402	4268	4145	3878	2537	1294	299
Evolocumab	4359	4246	4129	3878	2586	1294	273

C Metabolic syndrome and no diabetes



No. at risk

Placebo	3799	3668	3558	3385	2243	1086	252
Evolocumab	3833	3729	3632	3464	2335	1154	267


Probability of CHD death, MI, urgent revascularization
0.10
0.08
0.06
CV events
4
8
16
32
64
128
256
512
Achieved Lp(a) at Week 12 (nmol/L)

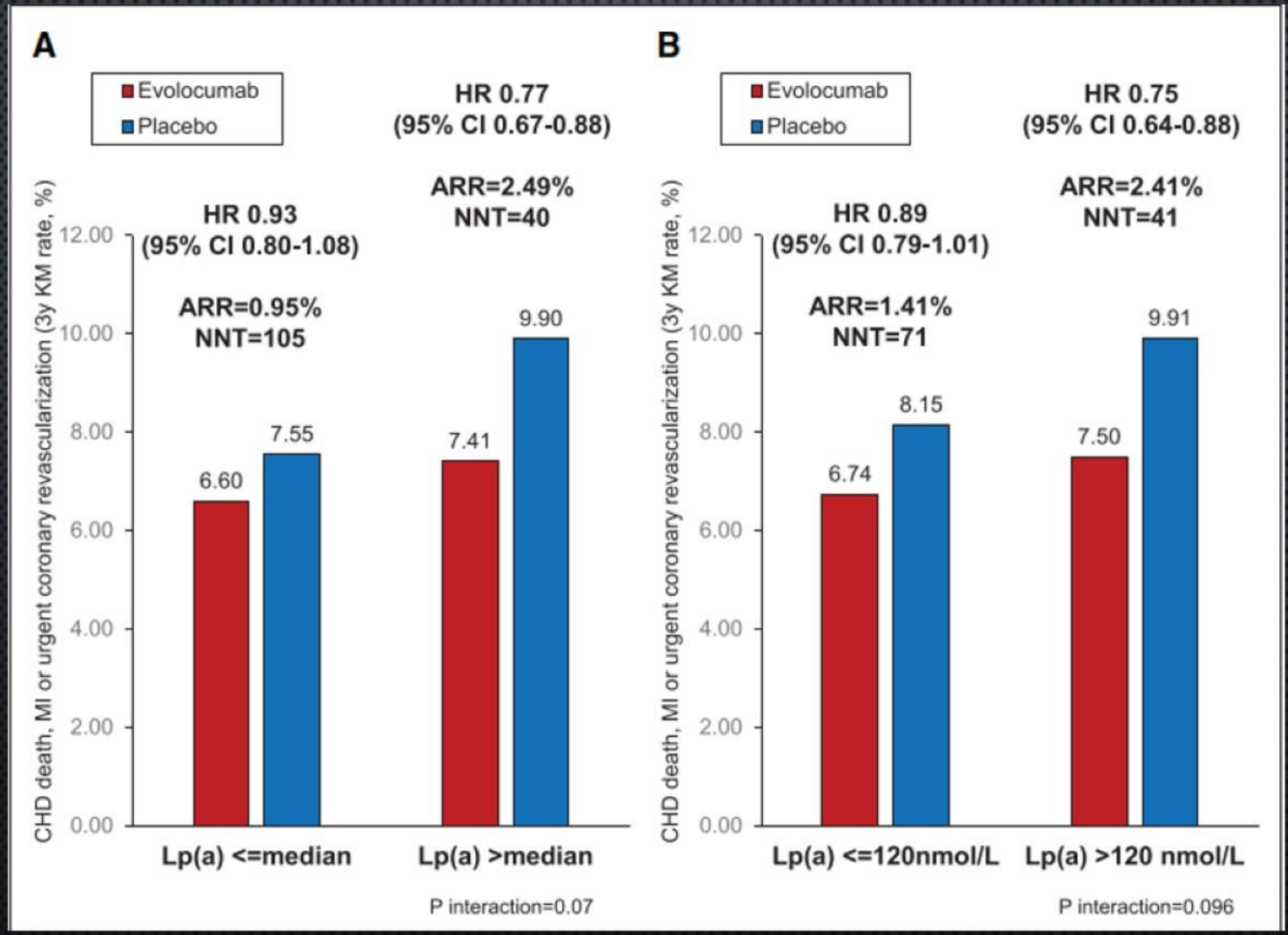

A
Evolocumab
Placebo
HR 0.77
(95% CI 0.67-0.88)
ARR=2.49%
NNT=40
HR 0.93
(95% CI 0.80-1.08)
ARR=0.95%
NNT=105
CHD death, MI or urgent coronary revascularization (3y KM rate, %)
12.00
10.00
8.00
6.00
4.00
2.00
0.00
6.60
7.55
7.41
9.90
Lp(a) <=median
Lp(a) >median
P interaction=0.07
B
Evolocumab
Placebo
HR 0.75
(95% CI 0.64-0.88)
ARR=2.41%
NNT=41
HR 0.89
(95% CI 0.79-1.01)
ARR=1.41%
NNT=71
CHD death, MI or urgent coronary revascularization (3y KM rate, %)
12.00
10.00
8.00
6.00
4.00
2.00
0.00
6.74
8.15
7.50
9.91
Lp(a) <=120nmol/L
Lp(a) >120 nmol/L
P interaction=0.096

Table 1Comparison of Safety of PCSK9 Inhibitors

	Inclisiran (ORION Meta-Analysis) (4)	Alirocumab (ODYSSEY Outcomes) (2)	Evolocumab (FOURIER) (3)
New-onset diabetes	11.6% (inclisiran) vs. 11.4% (placebo); RR: 1.02 (95% CI: 0.9–1.2)	9.6% (alirocumab) vs. 10.1% (placebo)	8.1% (evolocumab) vs. 7.7% (placebo); HR: 1.05 (95% CI: 0.94–1.17)
LPa	**Unclear**	Reduced	Reduced

Table 1
Trial comparison: FOURIER versus ODYSSEY OUTCOMES.

Efficacy	FOURIER	ODYSSEY OUTCOMES
Patient population	Stable ASCVD	ACS
Baseline LDL-C (mg/dL)	92	92
High intensity statin use (%)	69	89
Ezetimibe use (%)	5	3
Target LDL-C (mg/dL)	No	Yes (25–50)
Follow up duration (years)	2.2	2.8
Absolute change in LDL-C (mg/dL)	−56	−48
% change in LDL-C (on-treatment arm)	−59%	−55%
% change in Lp(a)	−27%	−24%
% change in Triglyceride	−16%	−10%
Primary endpoint relative reduction	15%	15%
All-cause mortality relative reduction	+4%	−15%*

* Nominally significant due to hierarchical statistical testing.

Recommendations for Patients With Diabetes Mellitus

Referenced studies that support recommendations are summarized in Online Data Supplements 11 and 12.

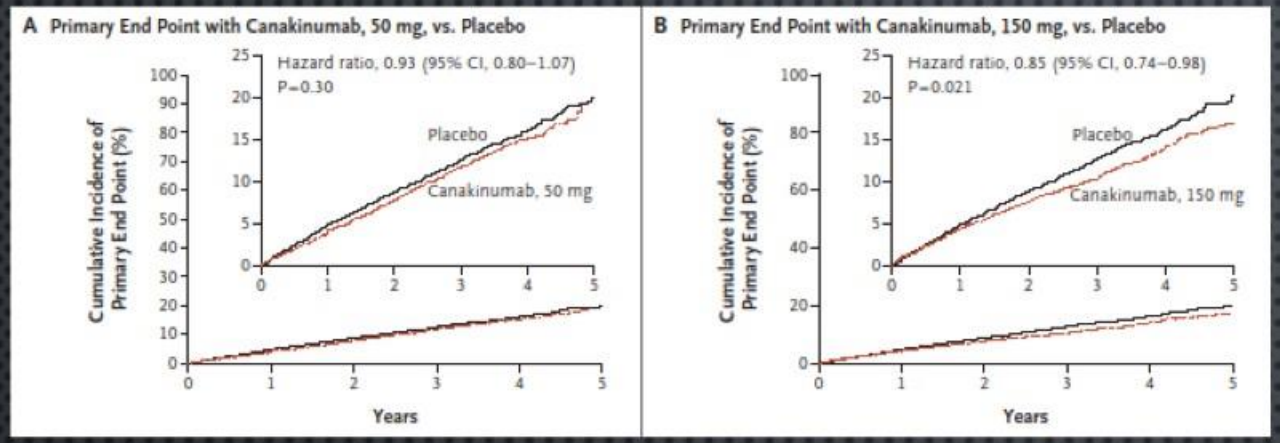
COR	LOE	Recommendations
I	A	1. In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.[S4.3-1–S4.3-9]

Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
Long duration (≥10 years for type 2 diabetes mellitus[S4.3-20] or ≥20 years for type 1 diabetes mellitus[S4.3-6]
Albuminuria ≥30 mcg of albumin/mg creatinine[S4.3-25]
eGFR <60 mL/min/1.73 m^2[S4.3-25]
Retinopathy[S4.3-19]
Neuropathy[S4.3-16]
ABI <0.9[S4.3-22,S4.3-24]

Circulation. 2019;139:e1082–e1143

Reduce hsCRP (inflammation) but not LDL: CV events were reduced



Dose ranging study is important

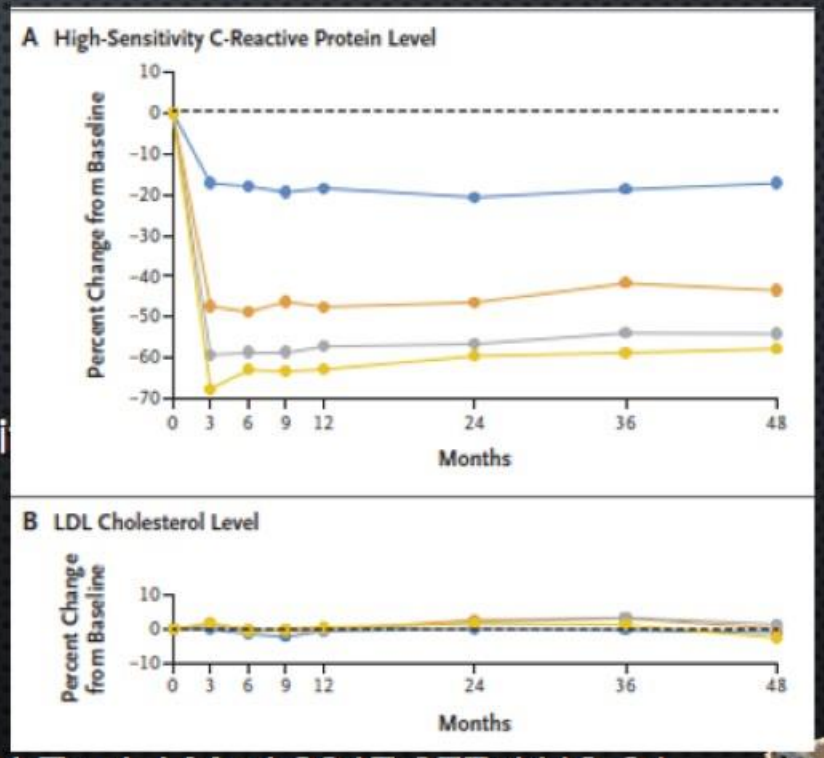

The NEW ENGLAND JOURNAL of MEDICINE

SEPTEMBER 21, 2017

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

ABSTRACT

Randomized, double-blind trial of canakinumab, a therapeutic monoclonal
antibody targeting interleukin-1β, involving 10,061 patients with **previous myocardial infarction** and a **hsCRP >2** mg or more per li



Primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

N Engl J Med 2017;377:1119-31

Canakinumab was associated with a higher incidence of fatal infection than

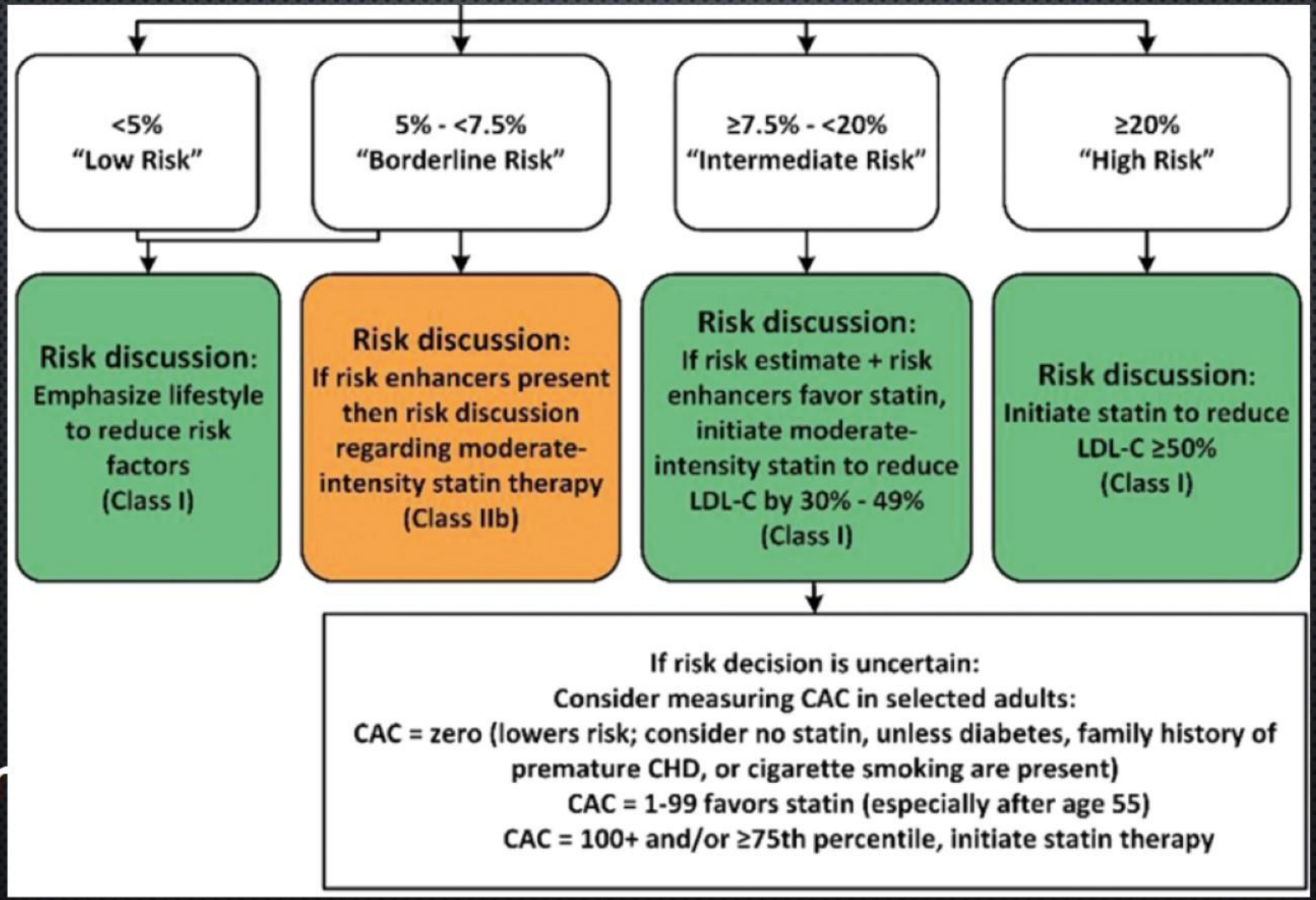
Table 2. Incidence Rates and Hazard Ratios for Major Clinical Outcomes and All-Cause Mortality.*

Clinical Outcome	Placebo Group (N=3344)	Canakinumab				P Value for Trend across Doses vs. Placebo
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)	
Primary end point†						
Incidence rate per 100 person-yr (no. of patients)	4.50 (535)	4.11 (313)	3.86 (320)	3.90 (322)	3.95 (955)	0.02
Hazard ratio (95% CI)	1.00	0.93 (0.80–1.07)	0.85 (0.74–0.98)	0.86 (0.75–0.99)	0.88 (0.79–0.97)	
P value	—	0.30‡	0.021§	0.031‡	0.02	
Any coronary revascularization						
Incidence rate per 100 person-yr (no. of patients)	3.61 (421)	2.53 (191)	2.49 (205)	2.56 (209)	2.53 (605)	<0.001
Hazard ratio (95% CI)	1.00	0.72 (0.60–0.86)	0.68 (0.58–0.81)	0.70 (0.59–0.83)	0.70 (0.62–0.79)	
P value	—	<0.001	<0.001	<0.001	<0.001	
Any stroke						
Incidence rate per 100 person-yr (no. of patients)	0.74 (92)	0.73 (58)	0.74 (63)	0.60 (51)	0.69 (172)	0.17
Hazard ratio (95% CI)	1.00	1.01 (0.72–1.41)	0.98 (0.71–1.35)	0.80 (0.57–1.13)	0.93 (0.72–1.20)	
P value	—	0.95	0.91	0.20	0.58	
Myocardial infarction						
Incidence rate per 100 person-yr (no. of patients)	2.43 (292)	2.20 (169)	1.90 (159)	2.09 (174)	2.06 (502)	0.03
Hazard ratio (95% CI)	1.00	0.94 (0.78–1.15)	0.76 (0.62–0.92)	0.84 (0.70–1.02)	0.84 (0.73–0.97)	
P value	—	0.56	0.005	0.07	0.02	

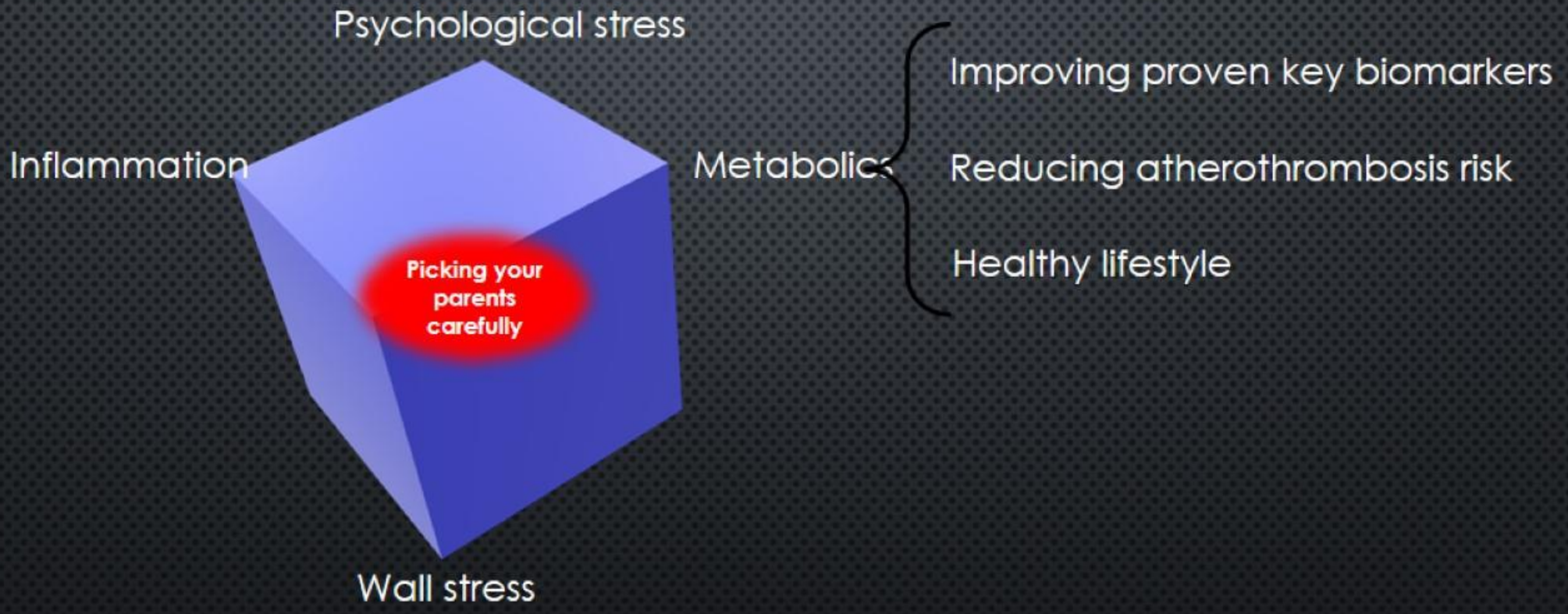
Primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death

N Engl J Med 2017;377:1119-31

Sur


<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

CLOSING SUMMARY



Precision medicine vs/& organizational guidelines