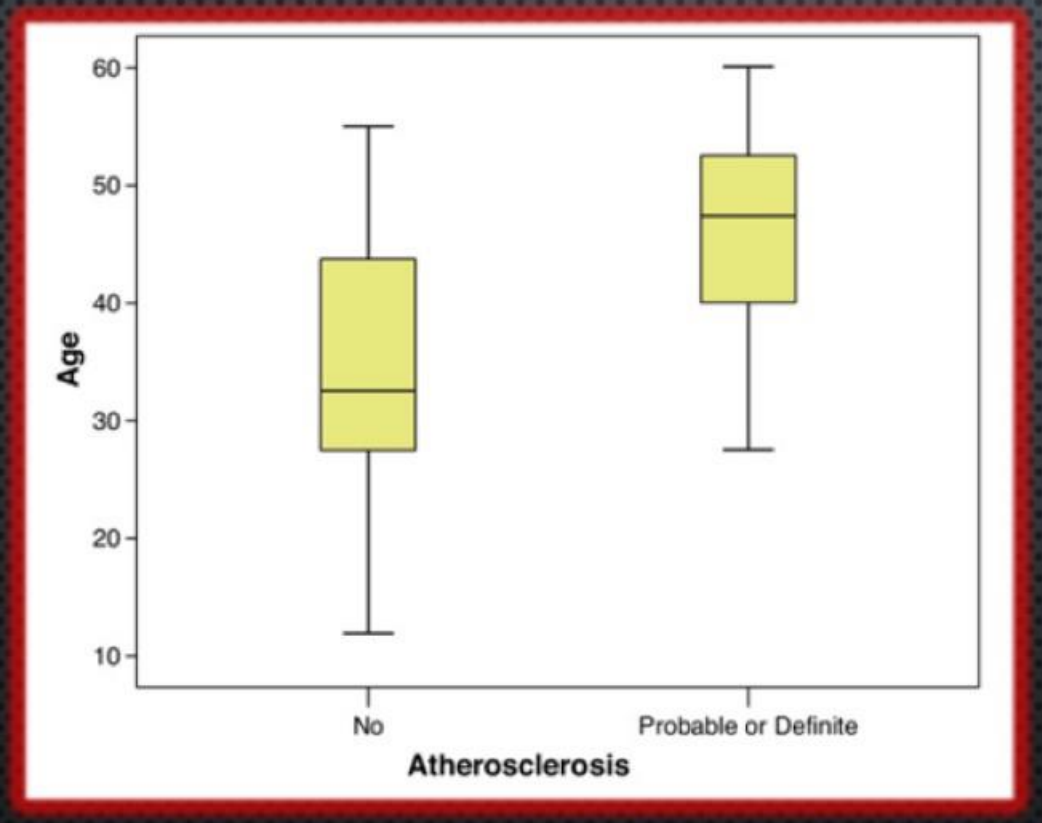
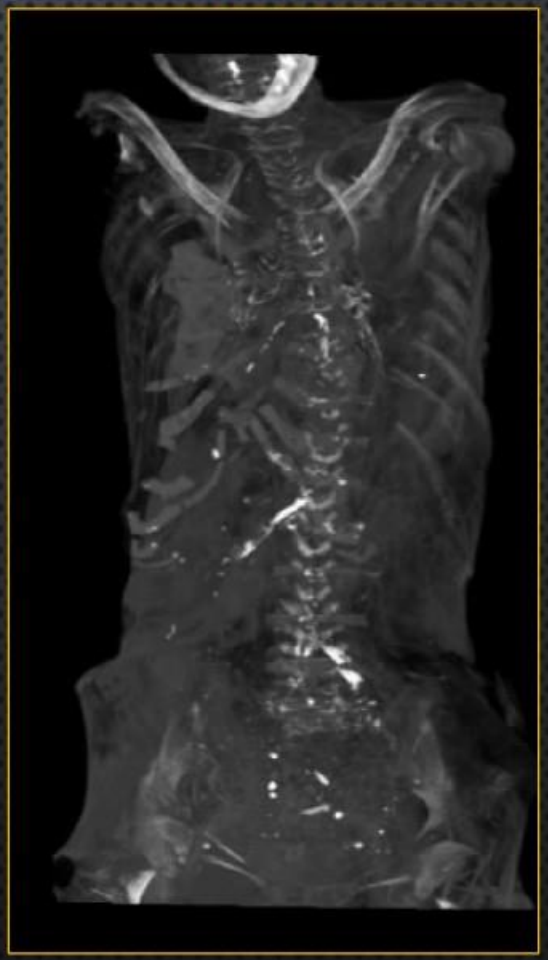
ASCVD RISK REDUCTION THERAPY: BEYOND STATINS



Age at Death of Mummies With and Without Atherosclerosis

Princess



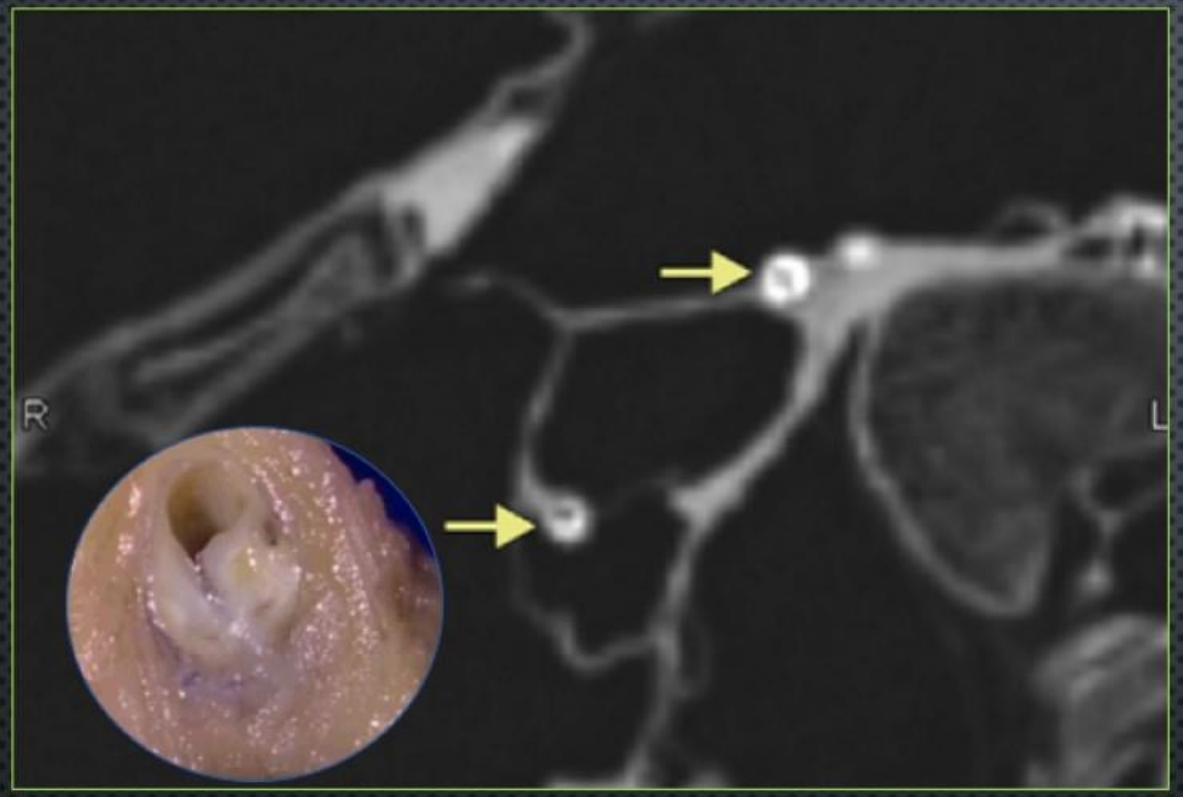
Chilton

OBJECTIVES

1. Recognize the interrelationship of insulin resistance to atherosclerosis
2. Importance of genetic influence on hypertension

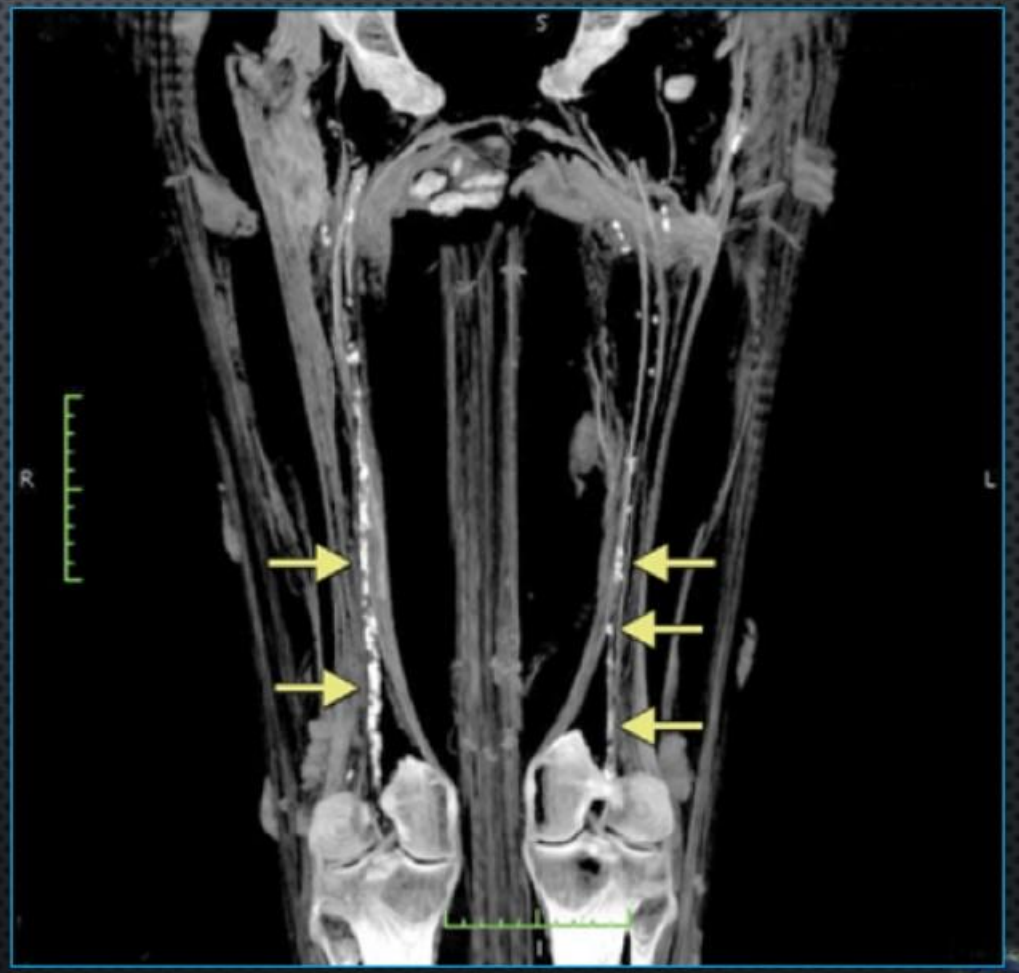
3. Increasing risk of atherosclerosis by duration of high lipids
4. Amplification of CV risk with hypertension and lipids

5. New guidelines
    a. BP
    b. Lipids



Calcifications in the left and right coronary arteries (arrows) in the mummy

Extensive calcifications along the course of the superficial femoral arteries in the mummy of a man who lived during the 18th Dynasty



JACC: CARDIOVASCULAR IMAGING,
VOL. 4, NO. 4, 2011
APRIL 2011:315–27

OVERVIEW: COMPLEXITY OF THE HIGH RISK CARDIO-METABOLIC PATIENT

Environmental epigenetic effects

Birth/mom and dad

Increasing insulin resistance

Cellular dysfunction
Endothelial dysfunction

Common risk factors recognized

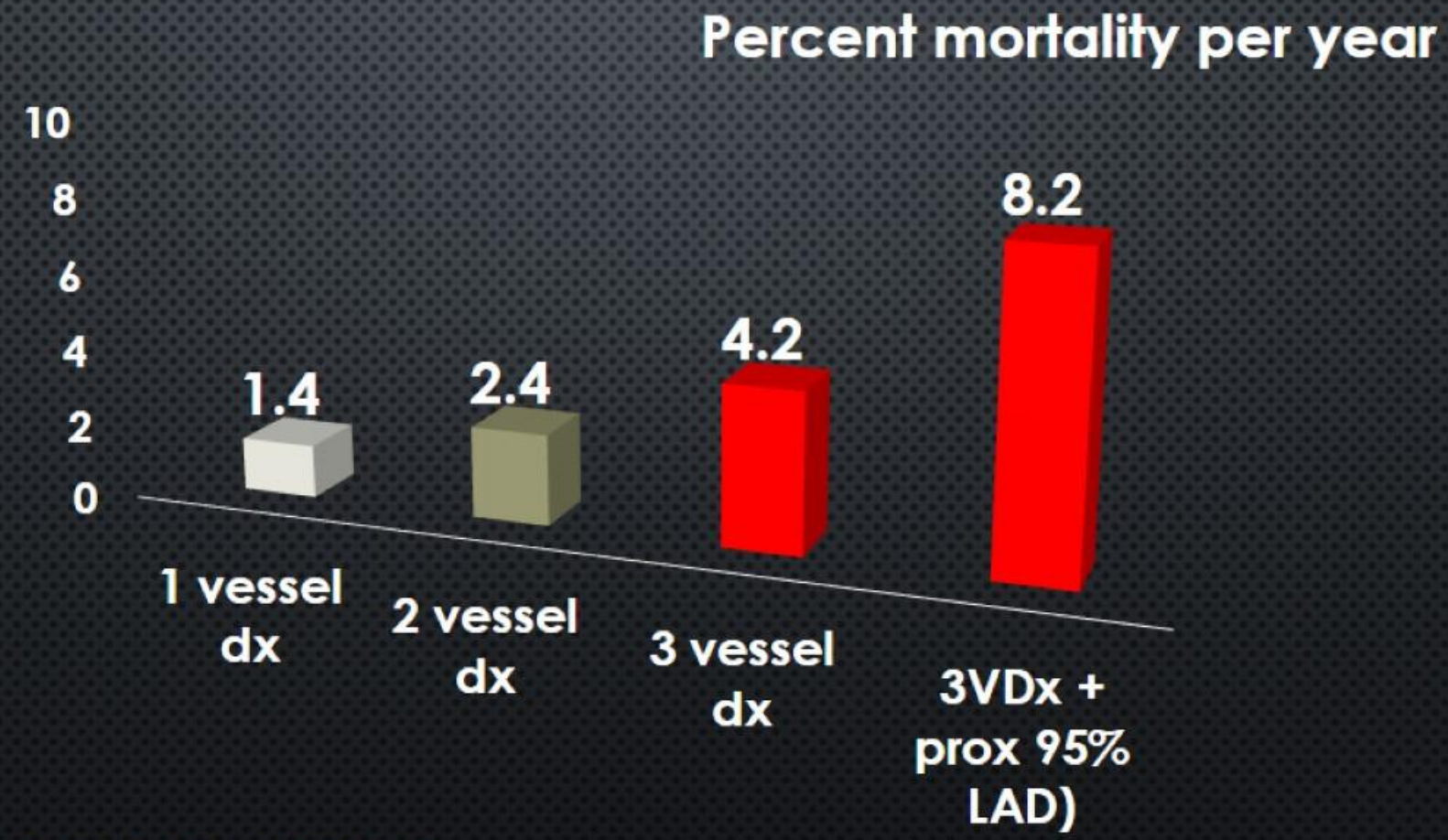
Treatment of numbers ≈ BP <120, LDL <50, hsCRP <0.1 etc

↑ CV risk For > 10yrs

Drugs primary treatment
Rarely lifestyle followed long term

Human awakening as vascular events occur
(Life span shortens 7-13 years)

YEARLY MORTALITY (DEATH) IN MEDICALLY TREATED PATIENTS BY CORONARY ANGIOGRAM

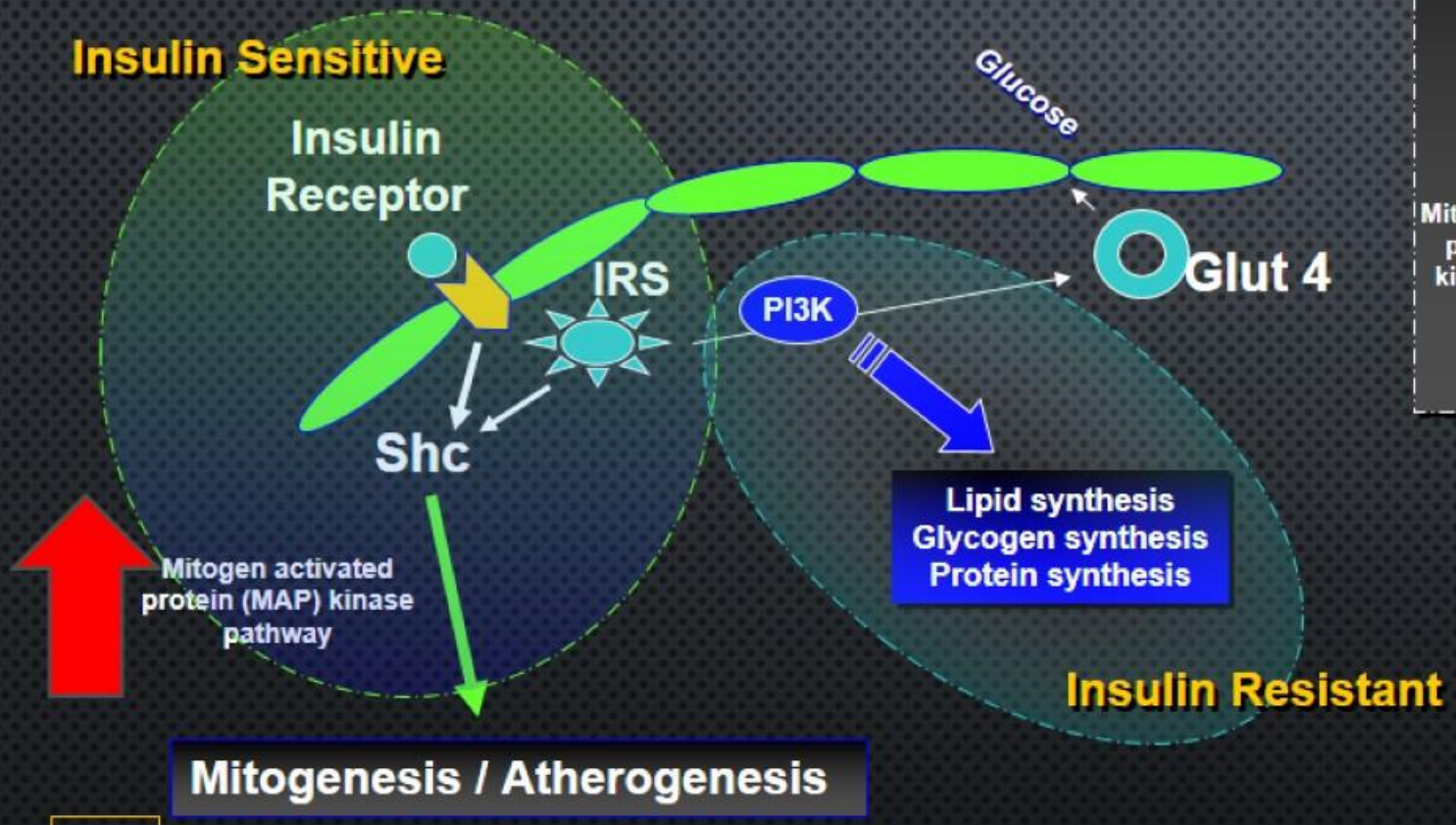


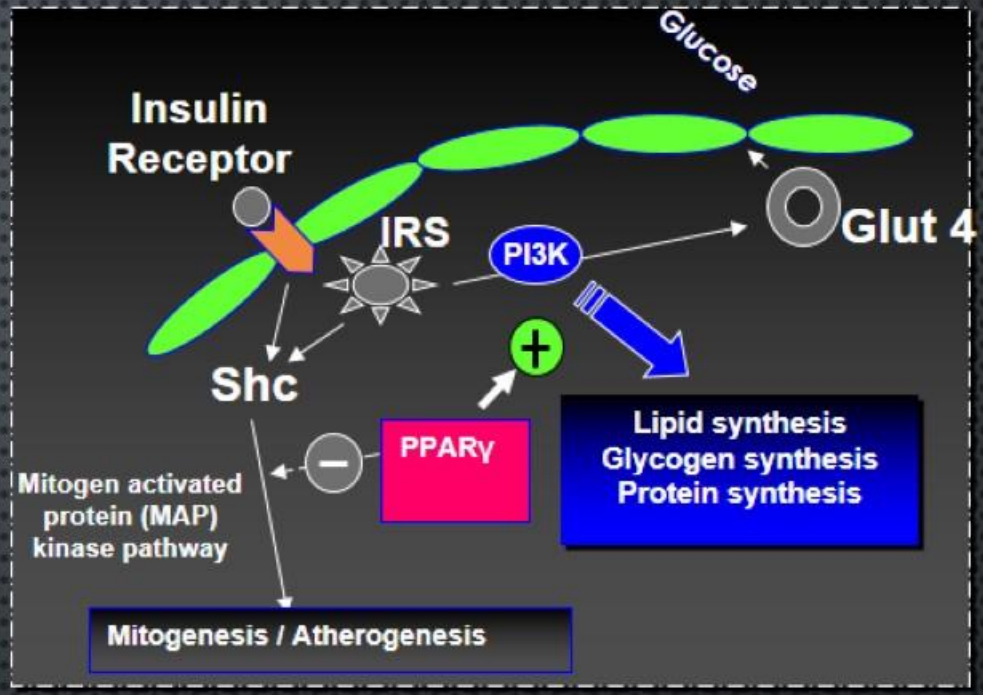
J Am Coll Cardiol. 1996;27:964–1047

Adapted from al Patel et al

BASICS OF INSULIN RESISTANCE

Continued stimulation by insulin





2

Atherosclerosis Supplements 7 (2006) 11–15

WHAT PERCENTAGE YOUNG ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE ATHEROSCLEROSIS?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%

No diabetes

Answer 5 > 70%

Atherosclerosis starts early

High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults

Evidence From Intravascular Ultrasound

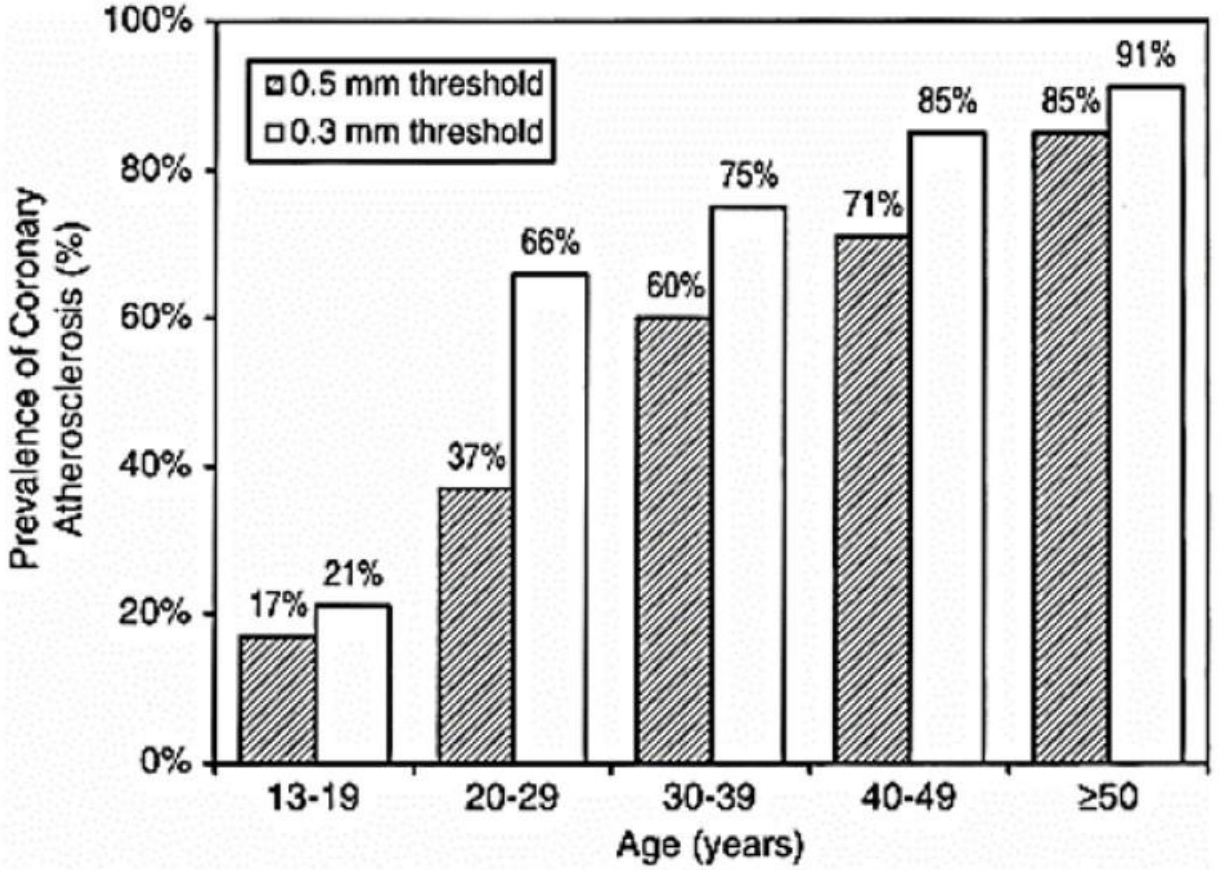
E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

Background—Most of our knowledge about atherosclerosis at young ages is derived from necropsy studies, which have inherent limitations. Detailed, in vivo data on atherosclerosis in young individuals are limited. Intravascular ultrasonography provides a unique opportunity for in vivo characterization of early atherosclerosis in a clinically relevant context.

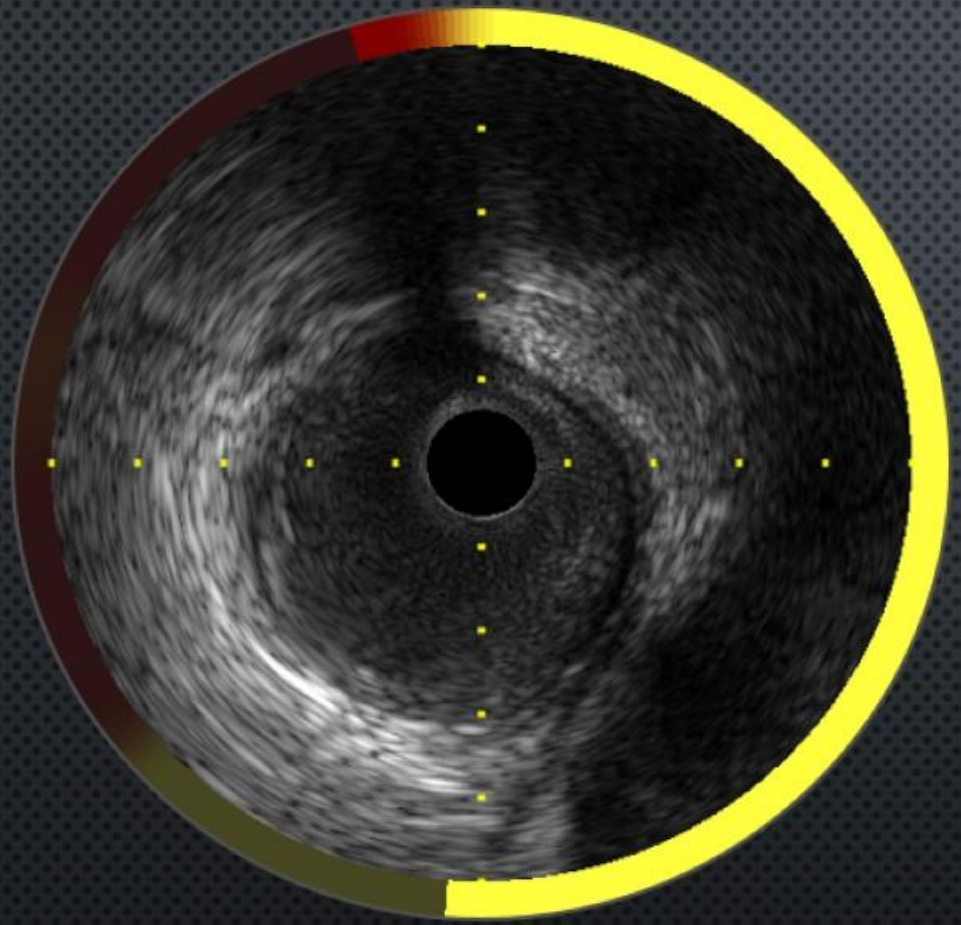
Methods and Results—Intravascular ultrasound was performed in 262 heart transplant recipients 30.9±13.2 days after transplantation to investigate coronary arteries in young asymptomatic subjects. The donor population consisted of 146 men and 116 women (mean age of 33.4±13.2 years). Extensive imaging of all possible (including distal) coronary segments was performed. Sites with the greatest and least intimal thickness in each CASS segment were measured in multiple coronary arteries. Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic. A total of 2014 sites within 1477 segments in 574 coronary arteries (2.2 arteries per person) were analyzed. An atherosclerotic lesion was present in 136 patients, or 51.9%. The prevalence of atherosclerosis varied from 17% in individuals <20 years old to 85% in subjects ≥50 years old. In subjects with atherosclerosis, intimal thickness and area stenosis averaged 1.08±0.48 mm and 32.7±15.9%, respectively. For all age groups, the average intimal thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in men and 51.7% in women).

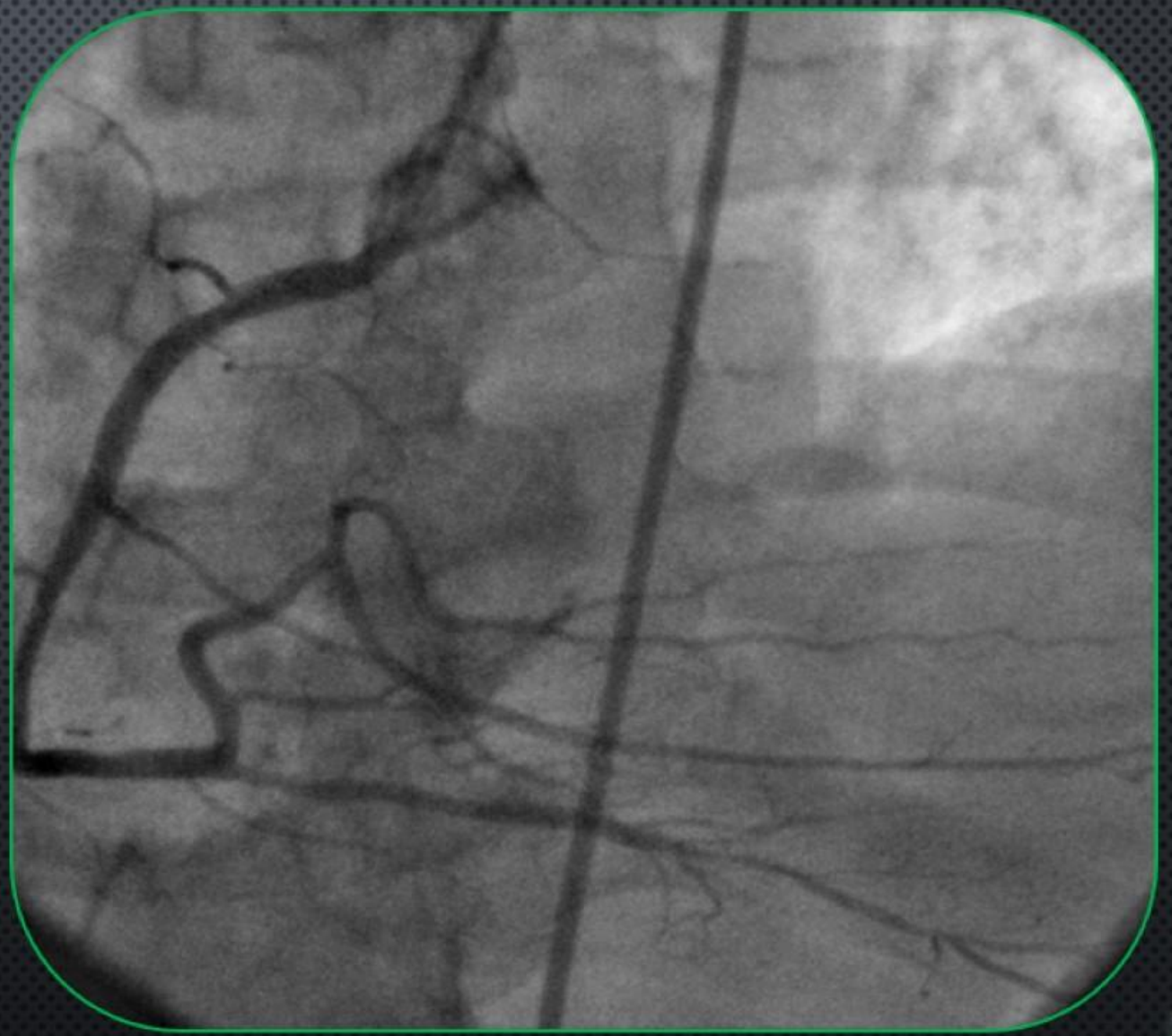
Conclusions—This study demonstrates that coronary atherosclerosis begins at a young age and that lesions are present in 1 of 6 teenagers. These findings suggest the need for intensive efforts at coronary disease prevention in young adults.

(*Circulation*. 2001;103:2705-2710.)

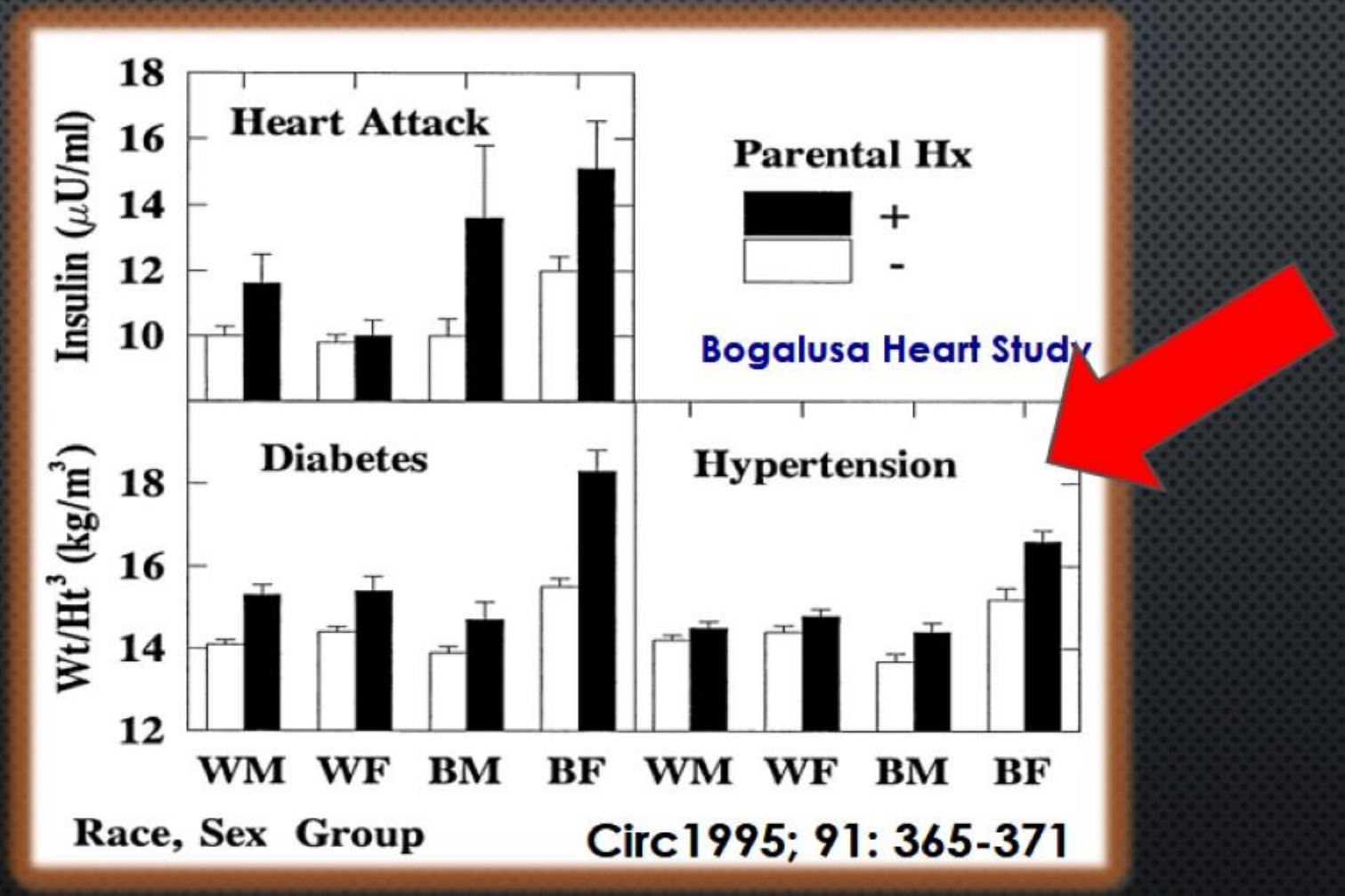


Circulation. 2001;103:2705-2710





IMPORTANCE OF GENETIC FACTORS WHEN PICKING YOUR PARENTS

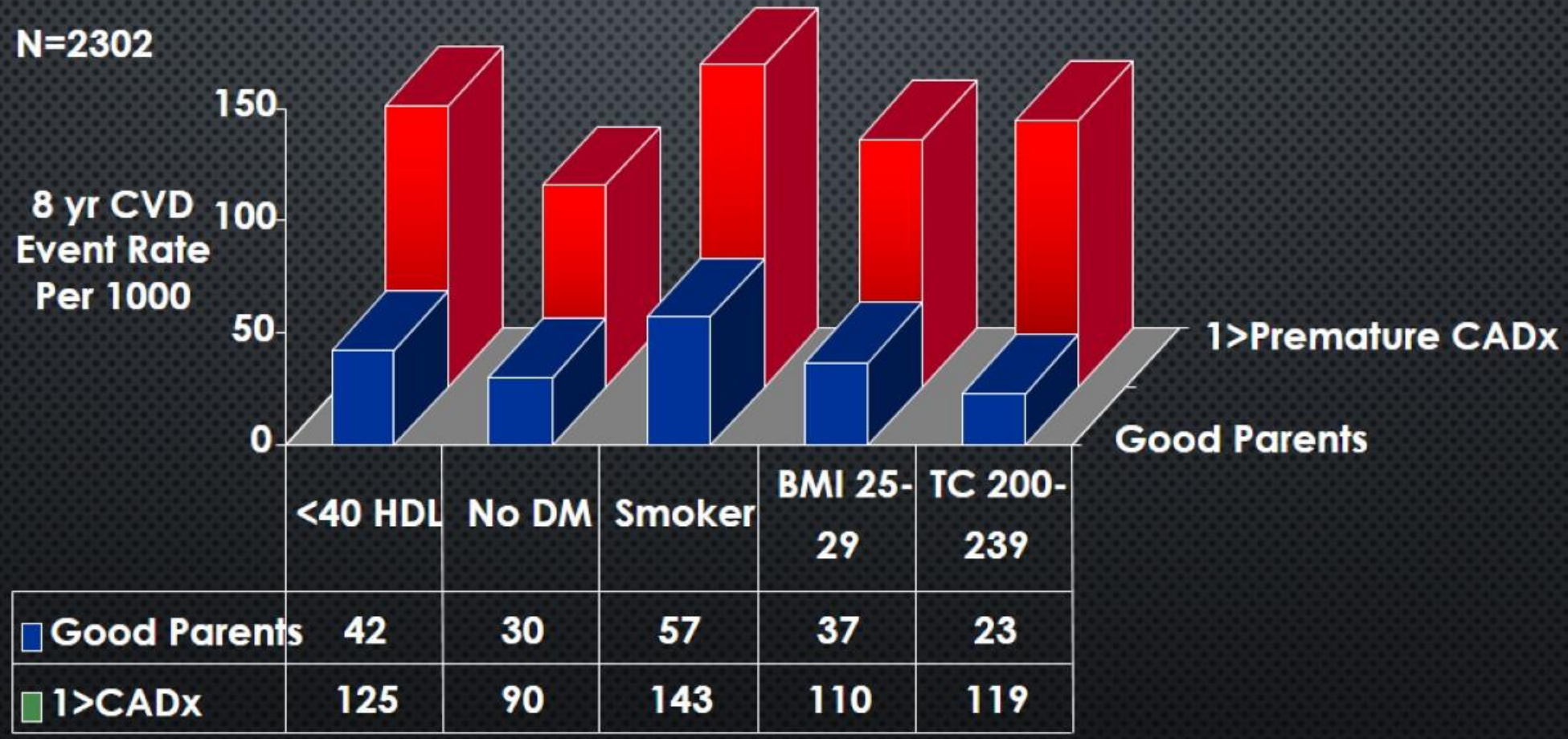


Selected risk factor variables in offspring ages 18 to 31 years by parental history of disease, race, and sex

FRAMINGHAM OFFSPRING STUDY

"PICKING YOUR PARENTS"

Both parents w/o CVD <55 man (<65 women)(Good)



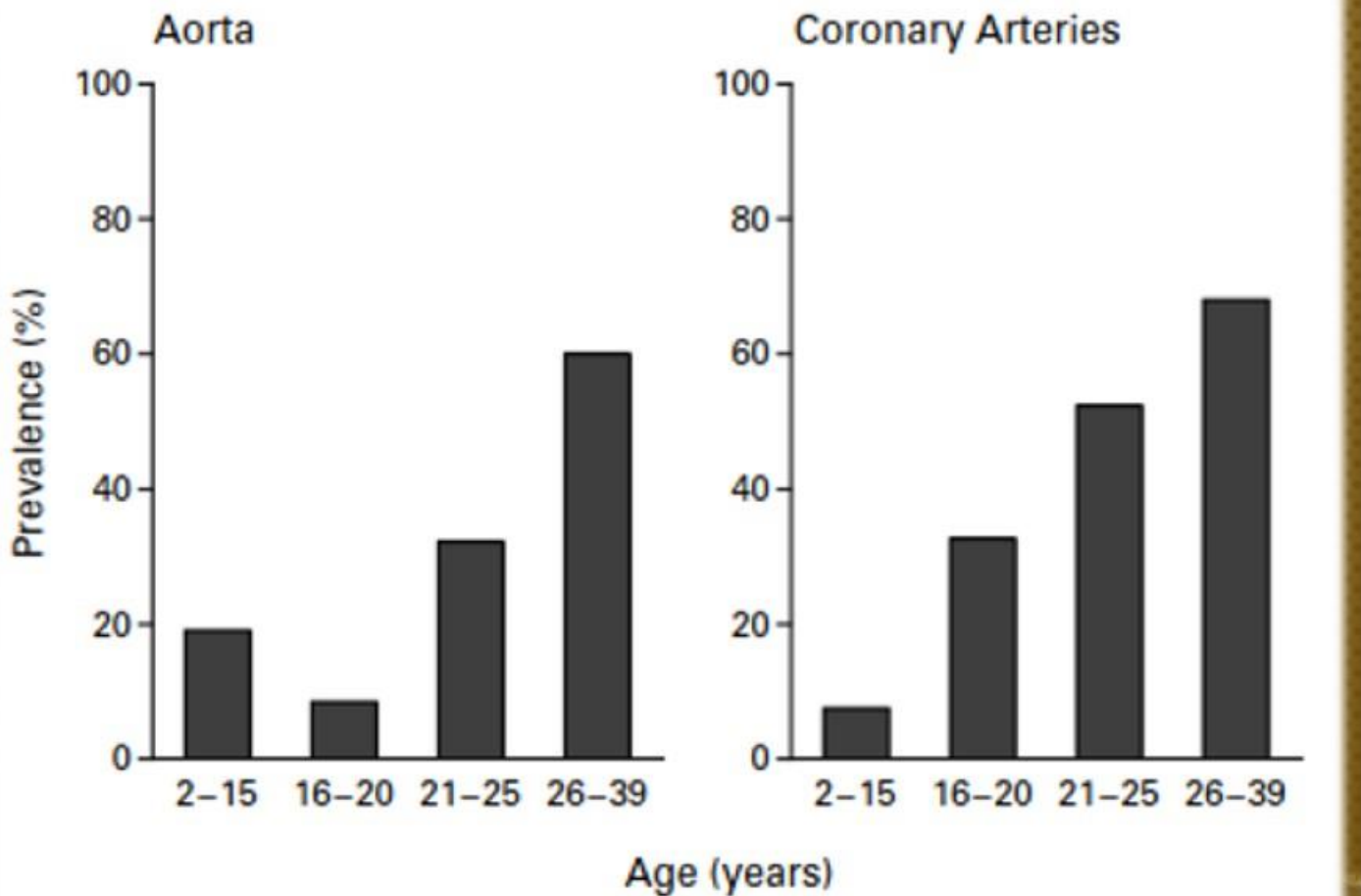
	<40 HDL	No DM	Smoker	BMI 25-29	TC 200-239
Good Parents	42	30	57	37	23
1>CADx	125	90	143	110	119

p=all significant

JAMA May 12, 2004;291:2204-2211

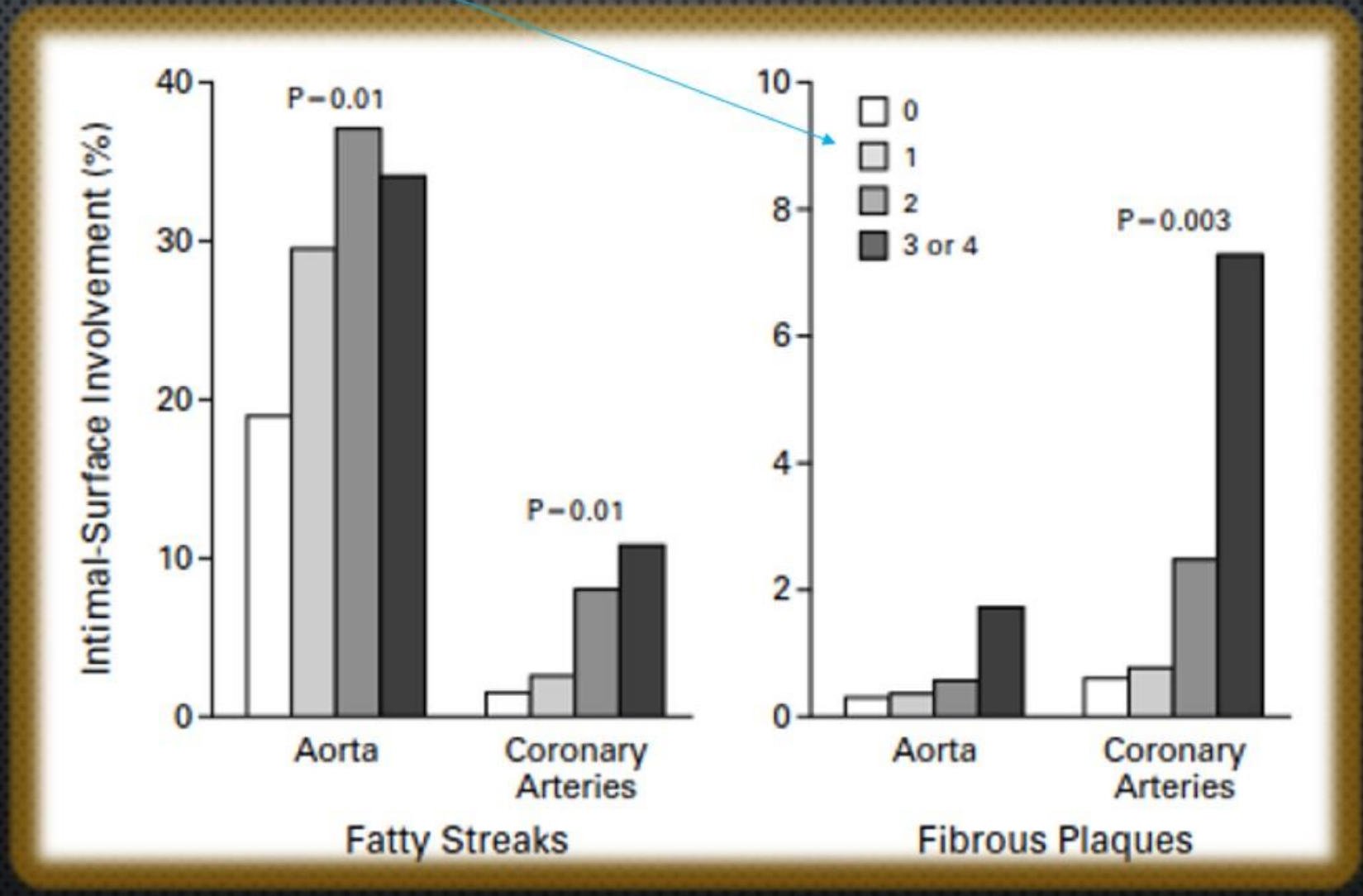
LANDMARK PAPER: BOGALUSA HEART STUDY

- AUTOPSIES ON 204 YOUNG PERSONS 2 TO 39 YEARS…TRAUMA



N Engl J Med 1998;338:1650-6

Cardiovascular risk factors increase the amount of disease



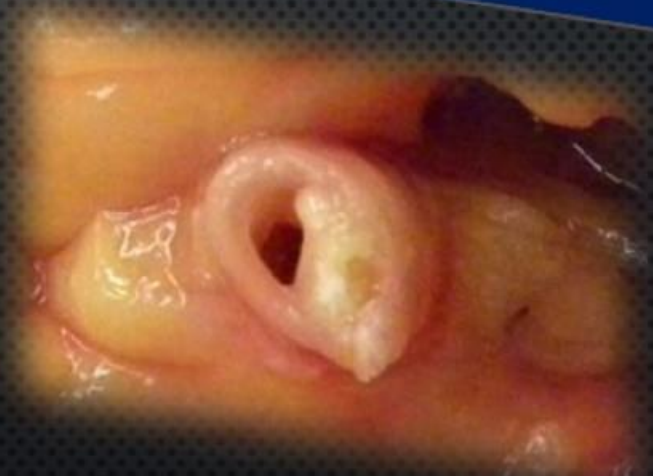
N Engl J Med 1998;338:1650-6

AUTOPSY RESULTS BY AGE 21-29

85% coronary arteries have fatty streaks

Time
Genetics
Metabolism
Inflammation

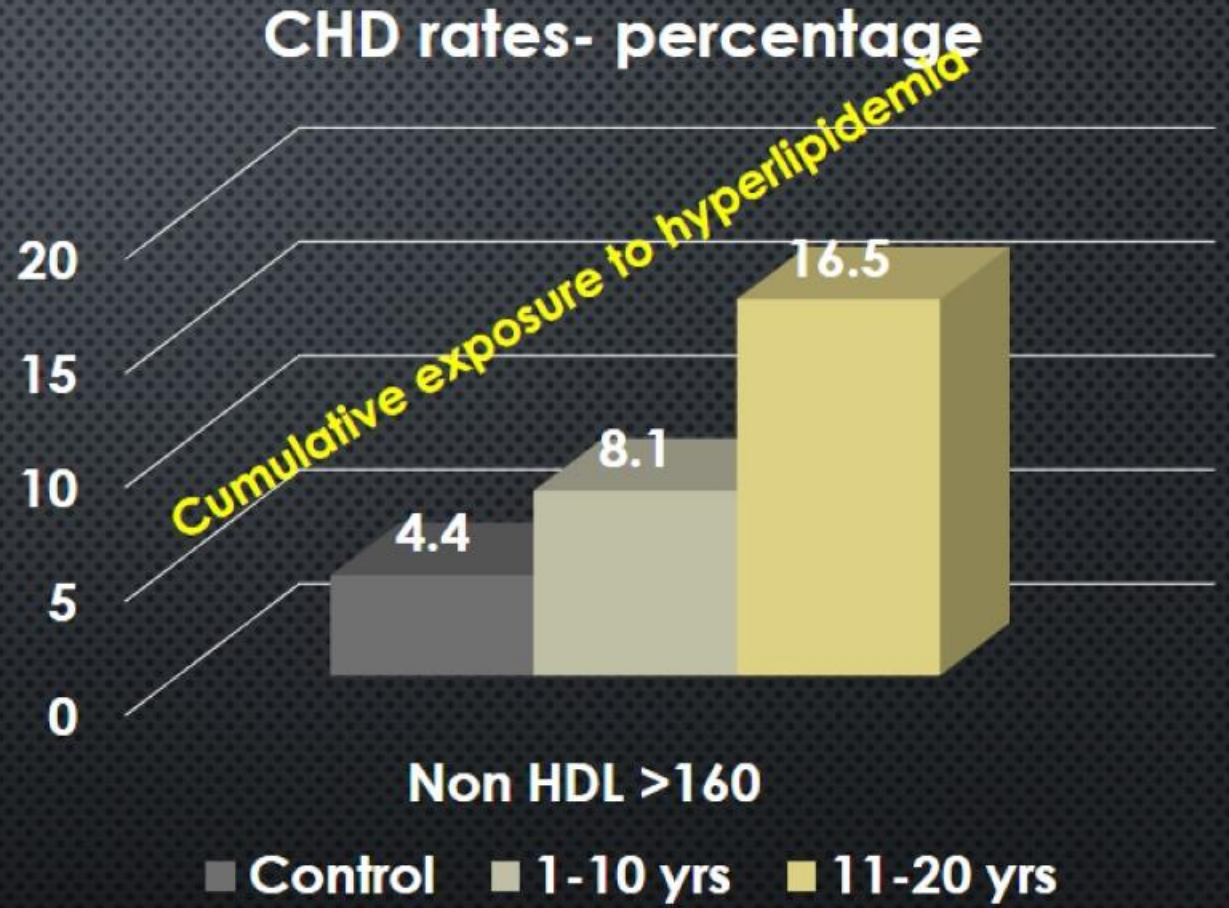
50-69% have coronary atheroma



N Engl J Med 1998;338:1650-6

YEARS OF HIGH LIPID INCREASED CV EVENTS

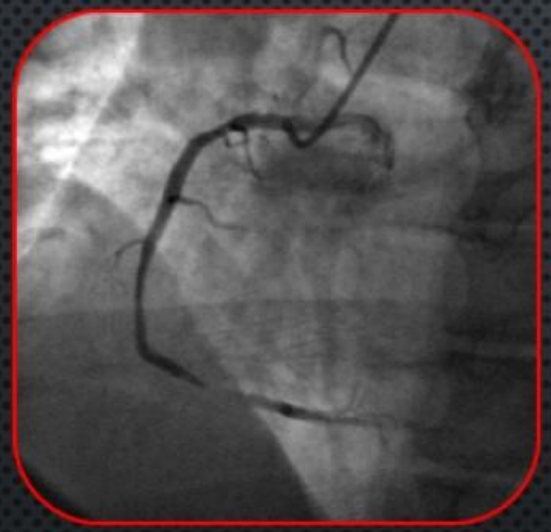
- Framingham Offspring Cohort data- identify adults without incident cardiovascular disease to 55 years of age (n=1478)
- Moderate hyperlipidemia (non–high-density lipoprotein cholesterol≥160 mg/dL (35-50 y/o)
- Median 15-year follow-up
- CHD rates were significantly elevated among adults with prolonged hyperlipidemia exposure by 55 years of age



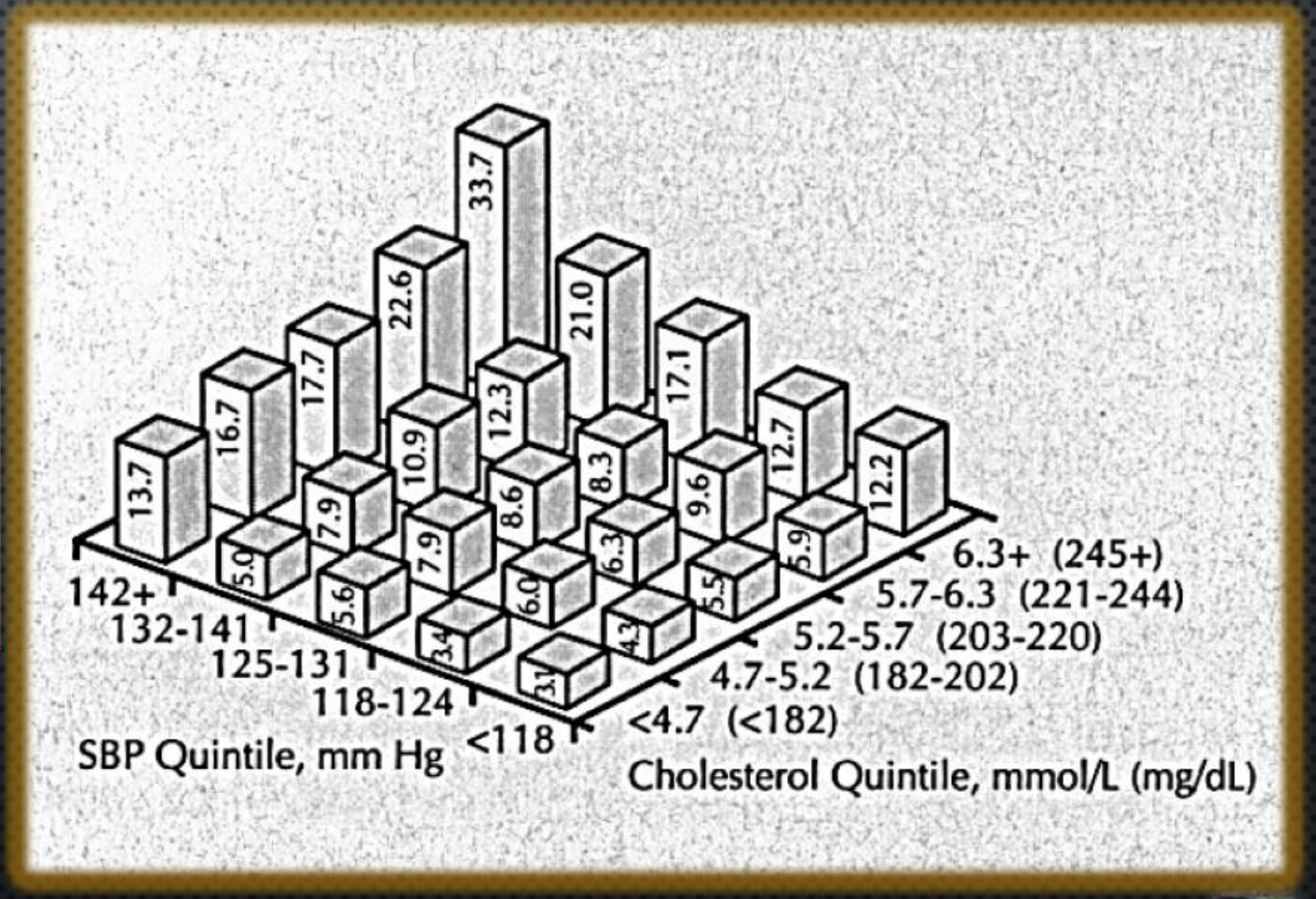
Circulation 2015;131:451-458

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

N=316 099

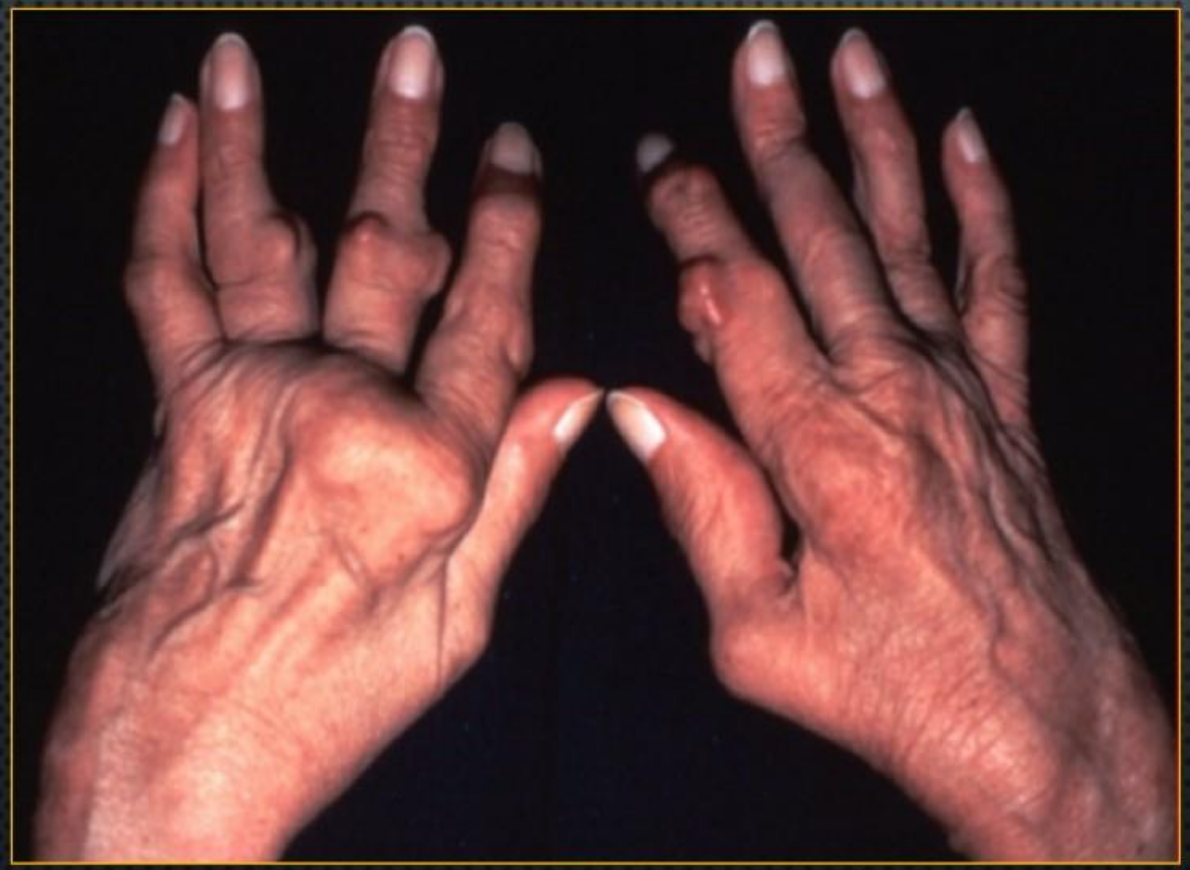


Time
Genetics
Metabolism
Inflammation



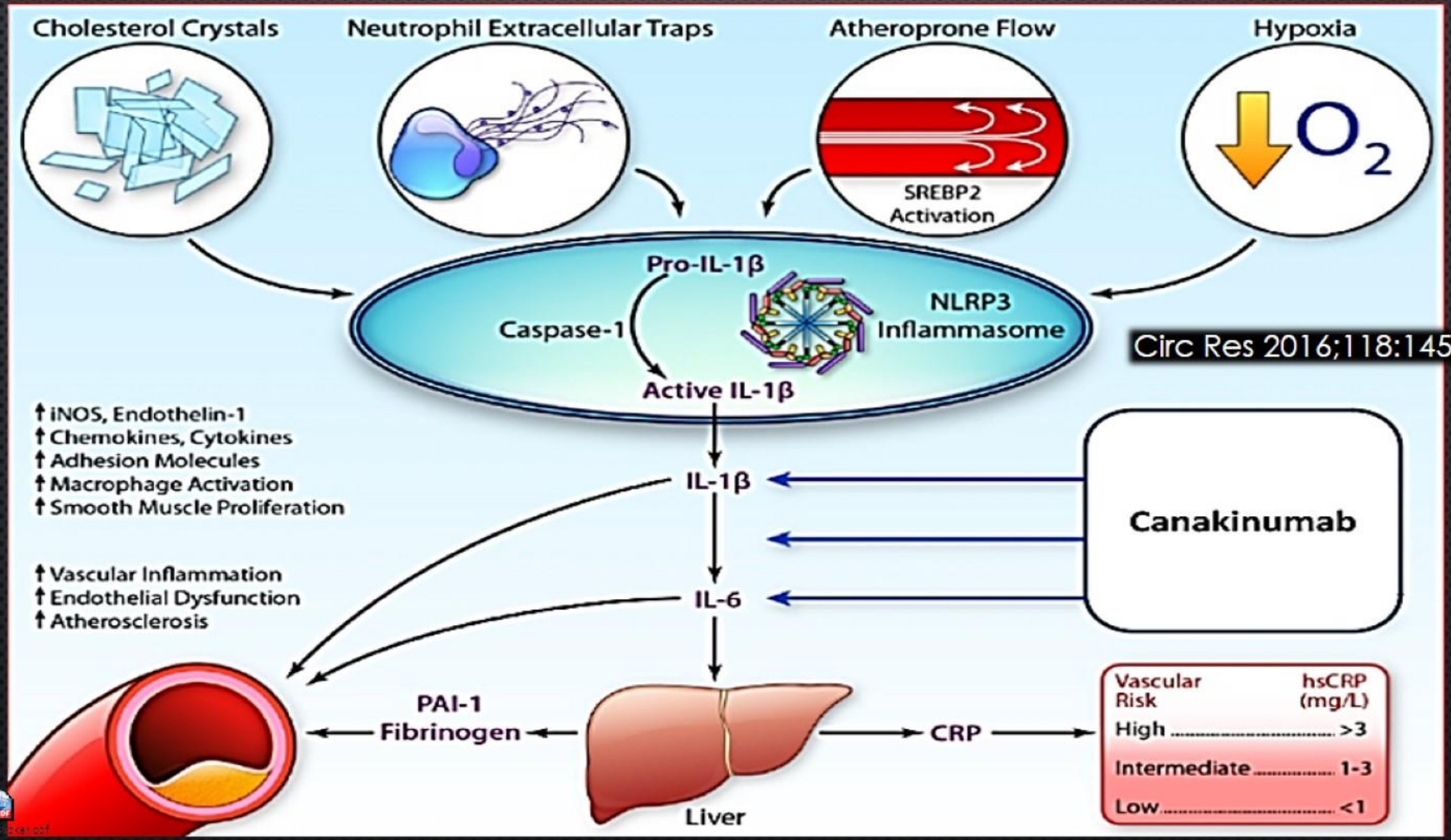
Arch Intern Med. 1992;152:56-64

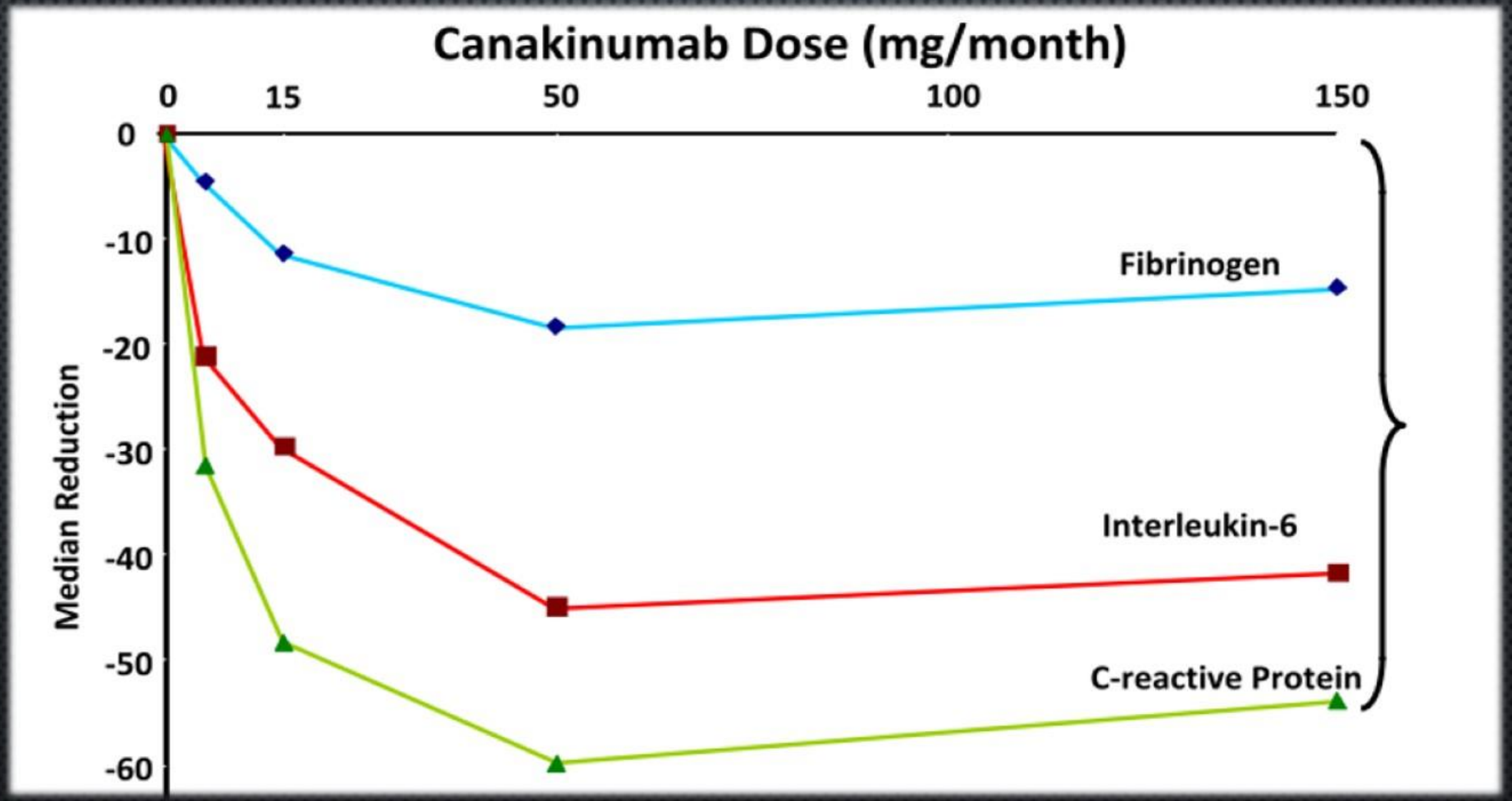
TARGETING INFLAMMATION



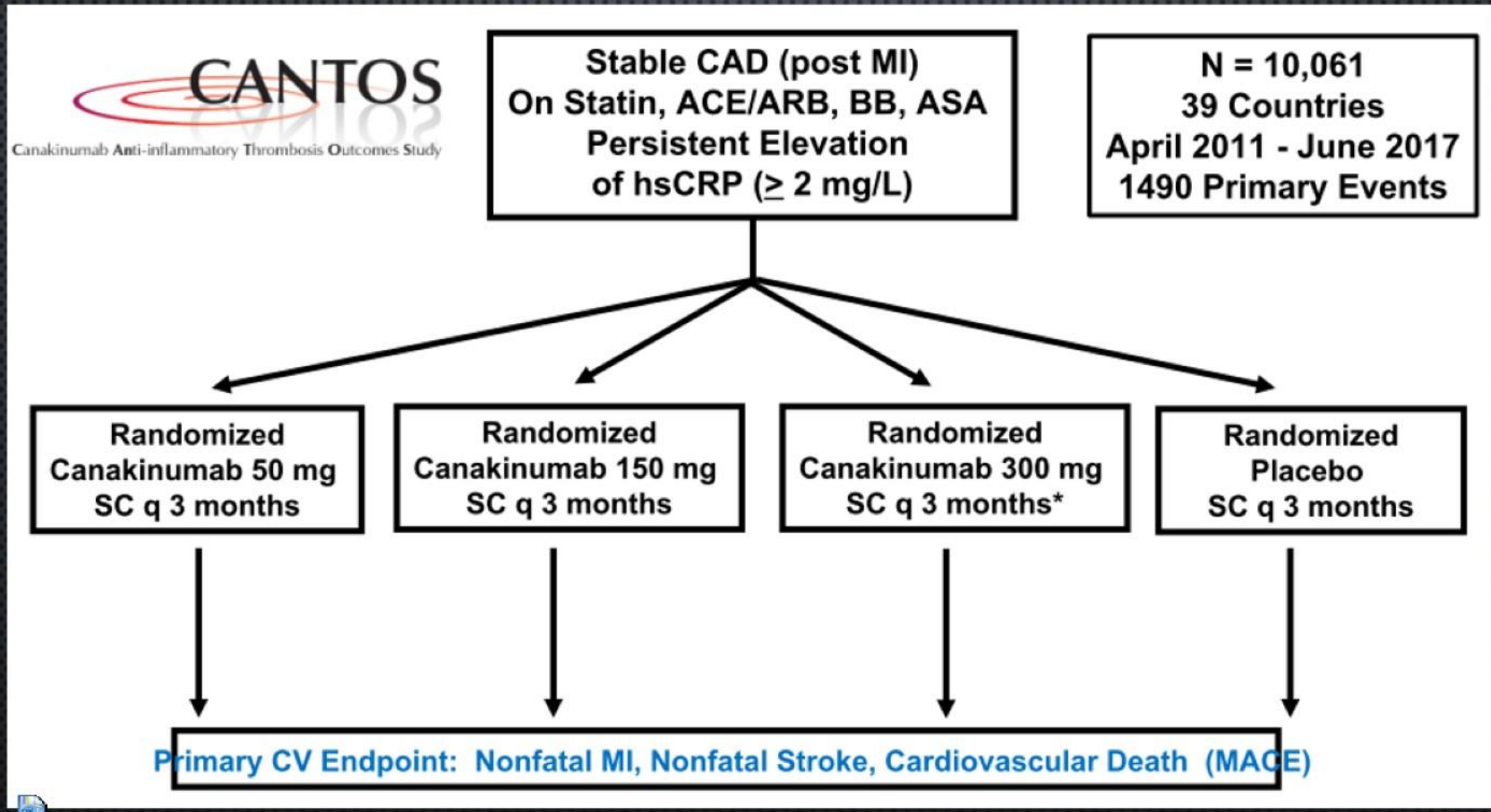
High inflammatory state

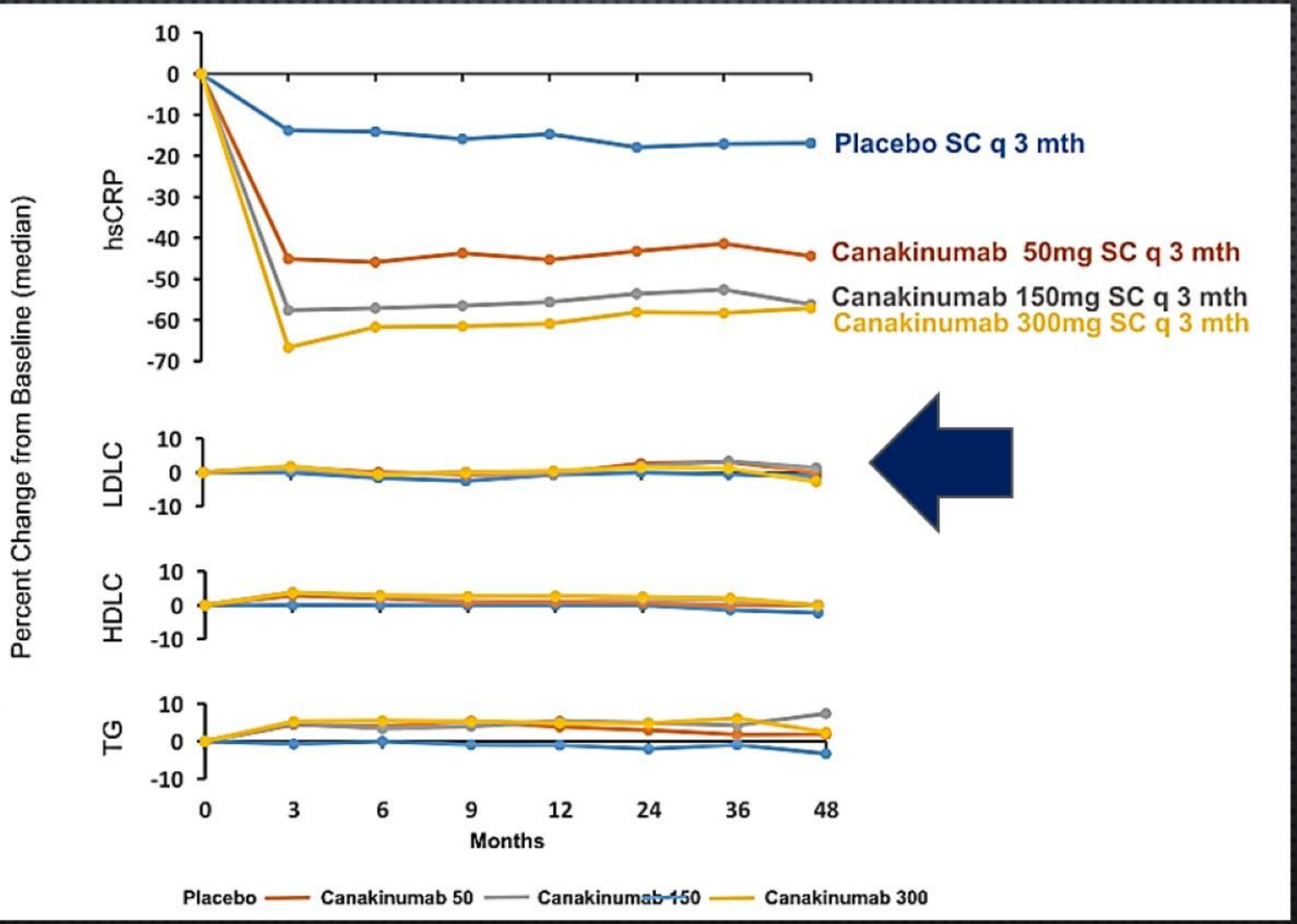
Significant increase in CV events


Cholesterol Crystals
Neutrophil Extracellular Traps
Atheroprone Flow
Hypoxia
SREBP2 Activation
O_2
Pro-IL-1β
Caspase-1
NLRP3 Inflammasome
Active IL-1β
Circ Res 2016;118:145-156
↑ iNOS, Endothelin-1
↑ Chemokines, Cytokines
↑ Adhesion Molecules
↑ Macrophage Activation
↑ Smooth Muscle Proliferation
IL-1β
IL-6
Canakinumab
↑ Vascular Inflammation
↑ Endothelial Dysfunction
↑ Atherosclerosis
PAI-1
Fibrinogen
CRP
Liver
Vascular Risk
hsCRP (mg/L)
High >3
Intermediate 1-3
Low <1



Ridker PM, et al; Circulation 2012; 126:2739-2748

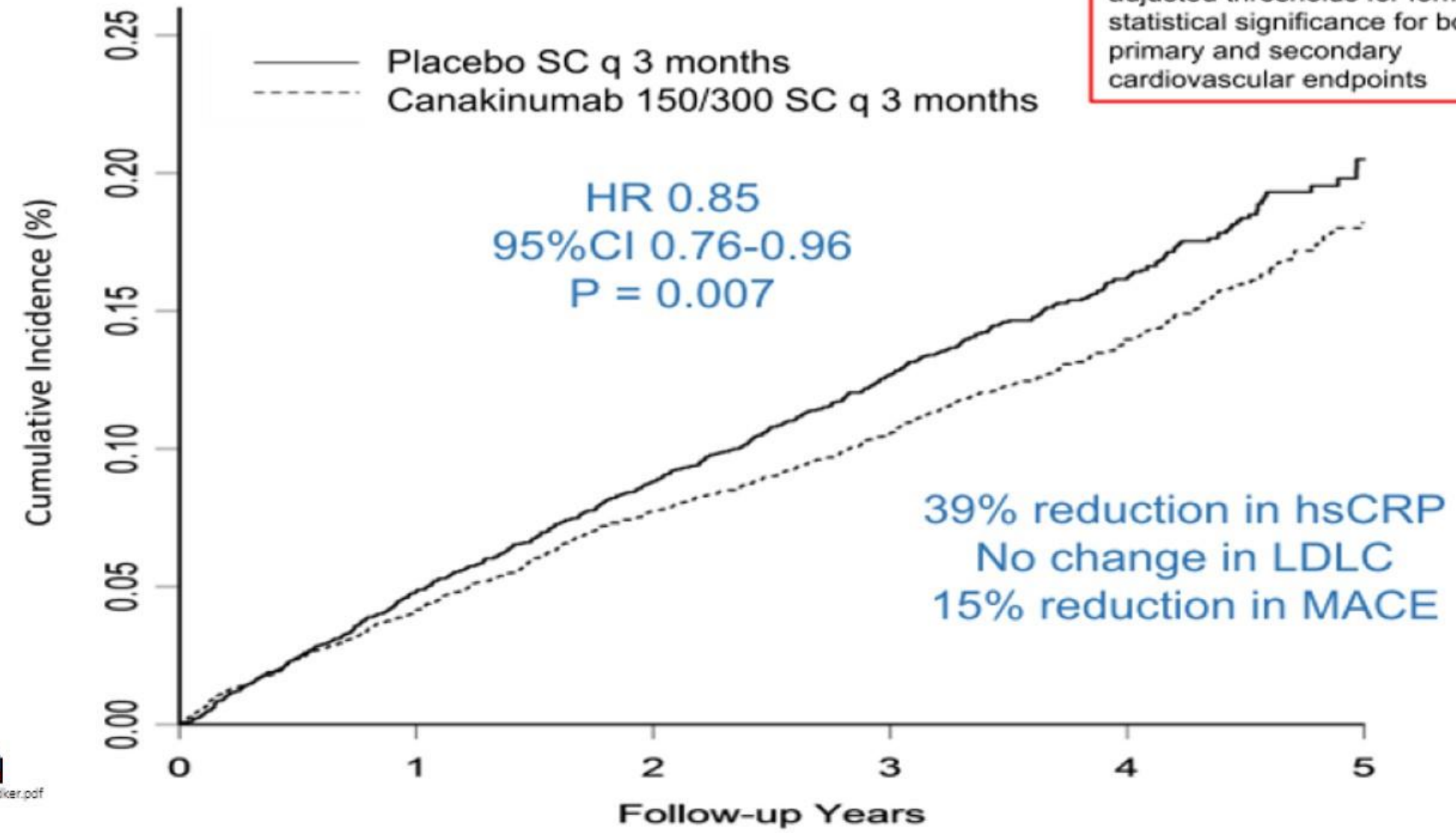

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study
Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥ 2 mg/L)
N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events
Randomized
Canakinumab 50 mg
SC q 3 months
Randomized
Canakinumab 150 mg
SC q 3 months
Randomized
Canakinumab 300 mg
SC q 3 months*
Randomized
Placebo
SC q 3 months
Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)


Percent Change from Baseline (median)
hsCRP
LDLC
HDLC
TG
10
0
-10
-20
-30
-40
-50
-60
-70
Placebo SC q 3 mth
Canakinumab 50mg SC q 3 mth
Canakinumab 150mg SC q 3 mth
Canakinumab 300mg SC q 3 mth
0
3
6
9
12
24
36
48
Months
Placebo
Canakinumab 50
Canakinumab 150
Canakinumab 300

		Canakinumab SC q 3 months			
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Primary Endpoint					
IR (per 100 person years)	4.5	4.1	3.9	3.9	0.020
HR	1.0	0.93	0.85	0.86	
95%CI	(referent)	0.80-1.07	0.74-0.98	0.75-0.99	
P	(referent)	0.30	0.021*	0.031	
Secondary Endpoint					
IR (per 100 person years)	5.1	4.6	4.3	4.3	0.003
HR	1.00	0.90	0.83	0.83	
95%CI	(referent)	0.78-1.03	0.73-0.95	0.72-0.94	
P	(referent)	0.11	0.005*	0.004	

CANTOS: Primary Cardiovascular Endpoint (MACE)

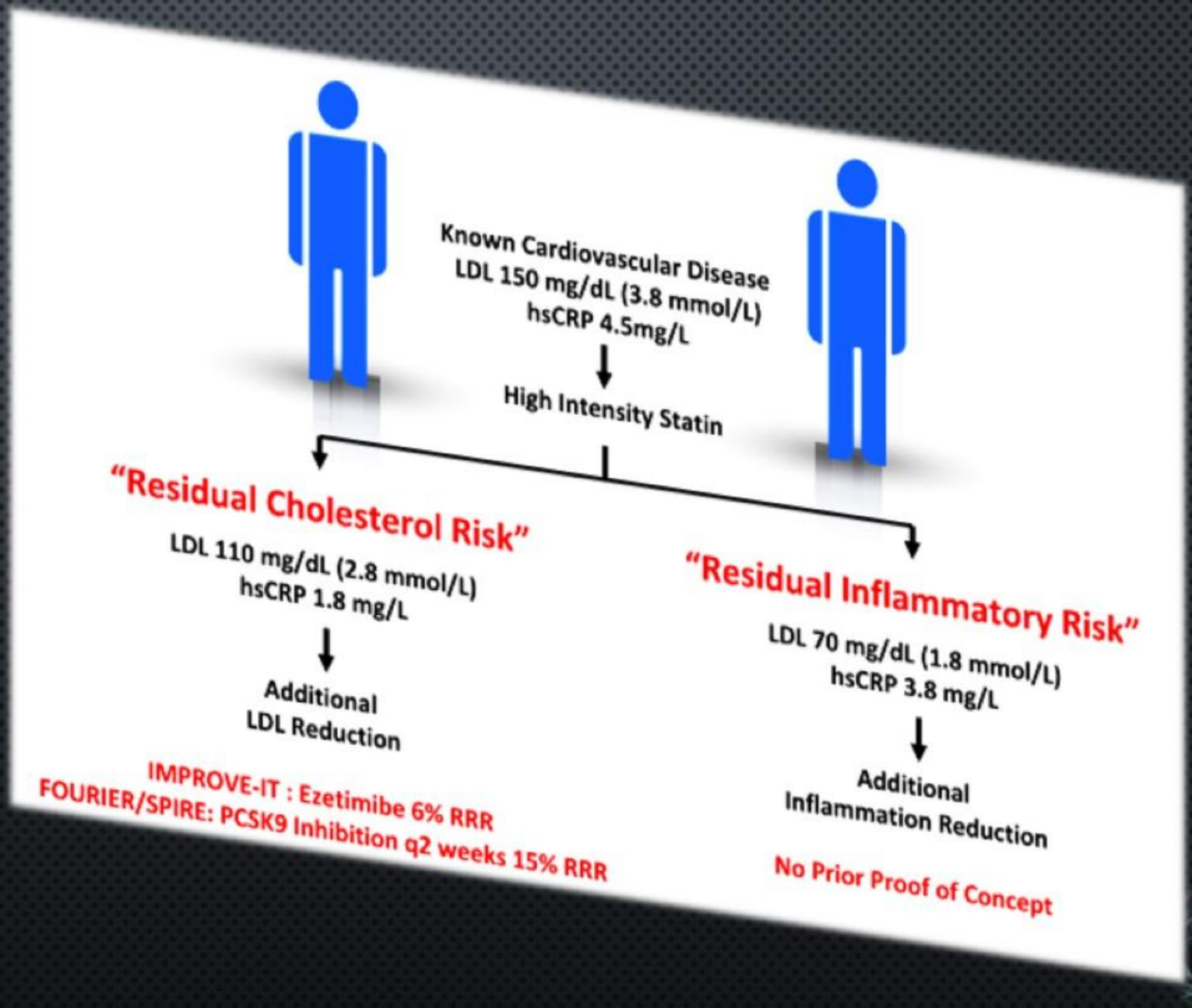
The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



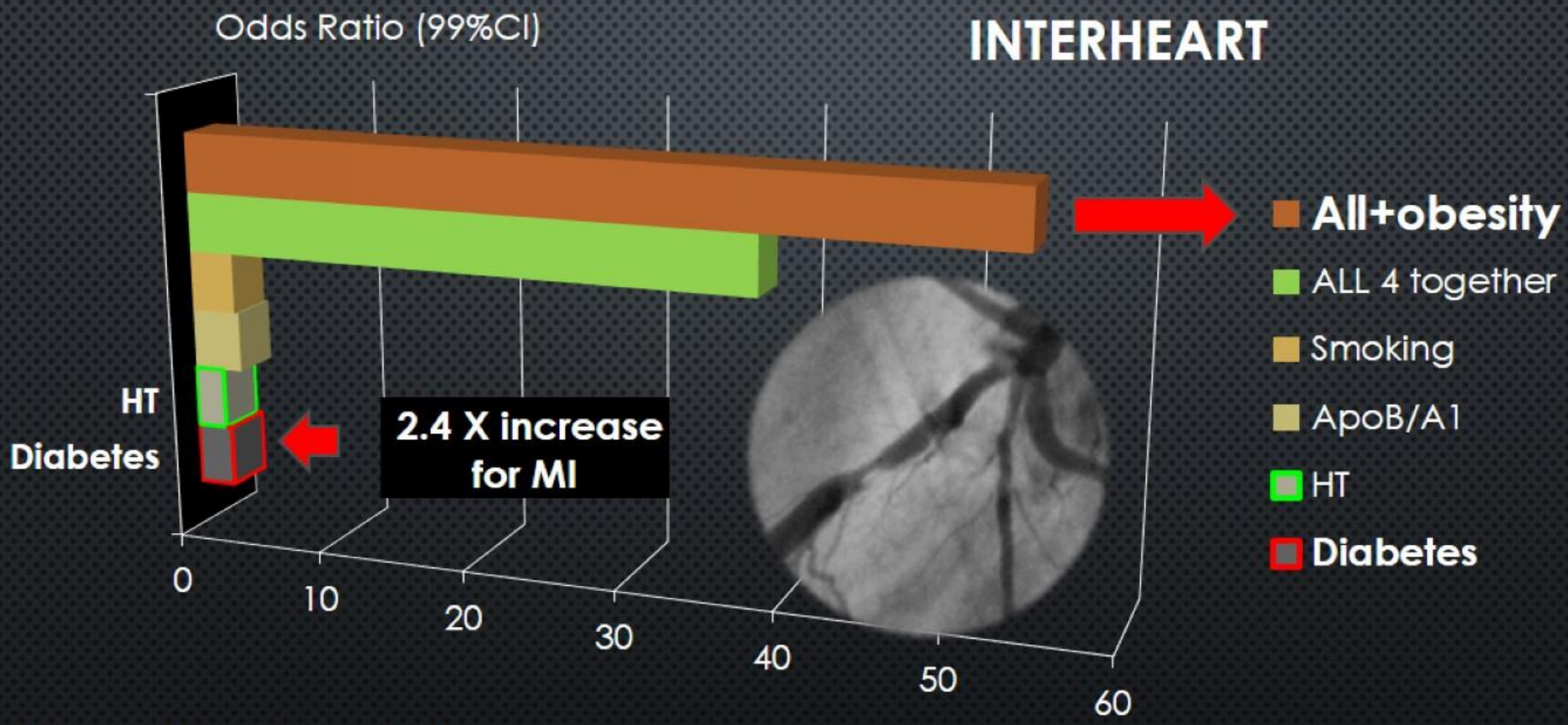
_Ridker.pdf

		Canakinumab SC q 3 months			
Adverse Event	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

Translational biology



RISK OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH SELECTED CV RISK FACTORS-80% FROM 4 MAJOR FACTORS

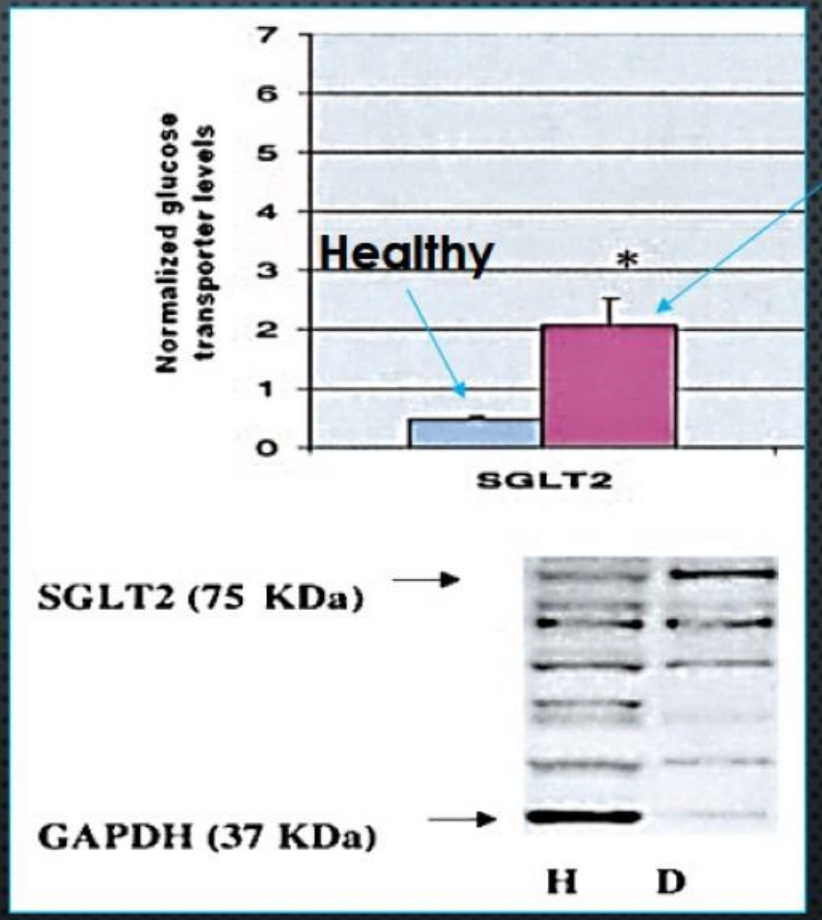


Adapted from Yusuf et al

Lancet 2004; 364: 937–52

INCREASED PROTEIN EXPRESSION OF SGLT2 IN TYPE 2 DM

- INSULIN RESISTANCE / T2DM
- HYPERGLYCEMIA INCREASES THE FILTERED LOAD OF GLUCOSE AT THE GLOMERULUS, AND GLOMERULAR HYPERFILTRATION ITSELF IS ALSO ASSOCIATED WITH DIABETES
- GLUCOSE TRANSPORTERS IN HUMAN RENAL PROXIMAL TUBULAR CELLS IN T2DM



Diabetes 2005;54:3427–3434

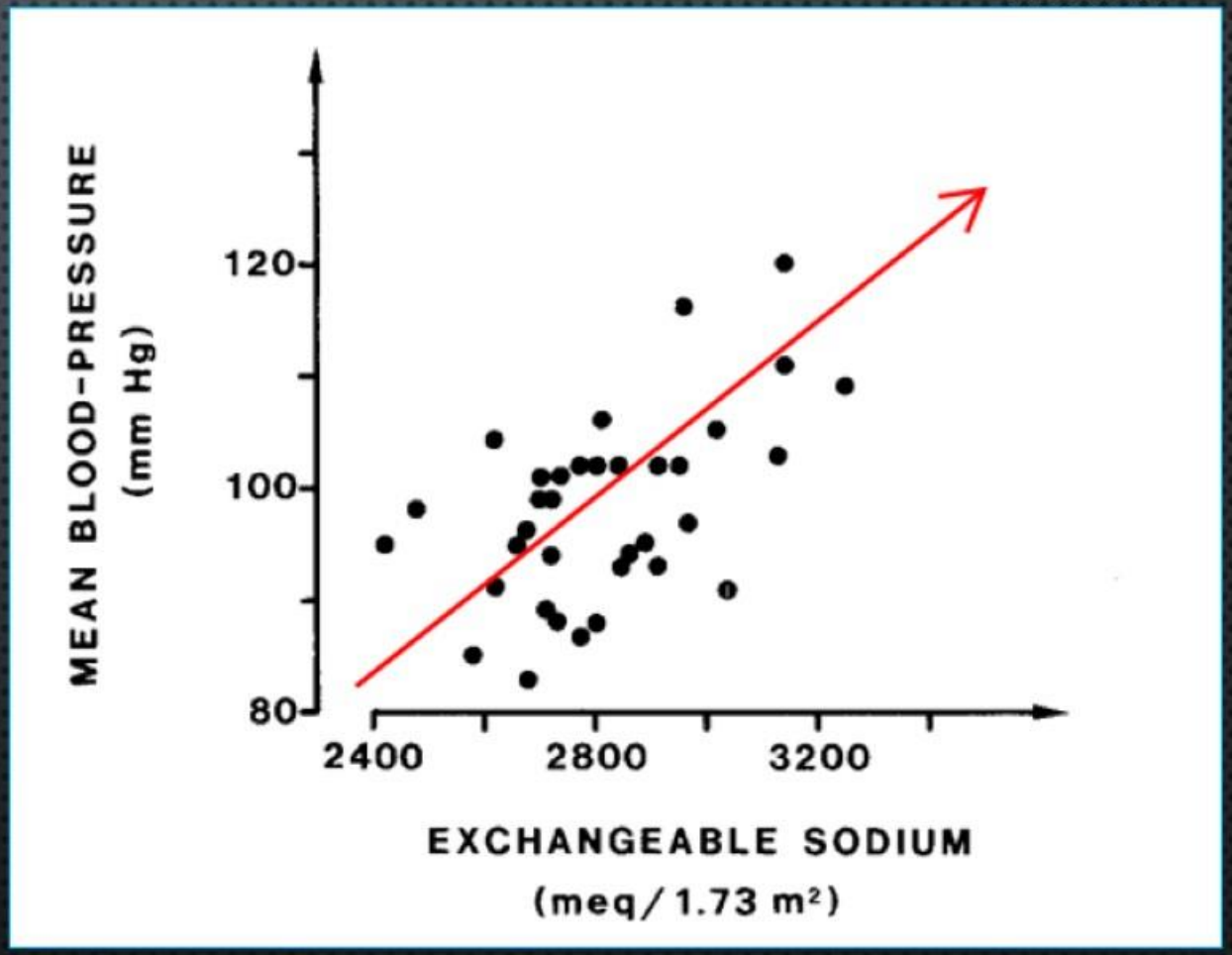
High volume of sodium in diabetes patients leads to increased blood pressure

10% higher volume of exchangeable sodium than in non-diabetes patients without significant differences in volume of circulating plasma

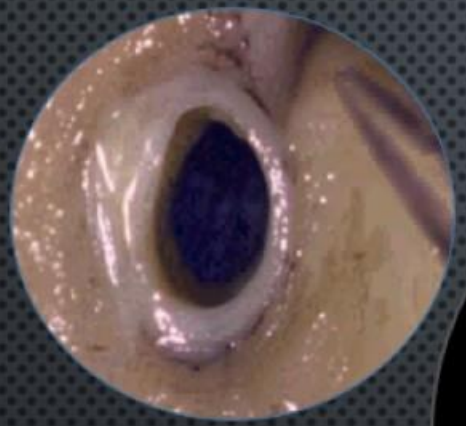
SGLT2 inhibition improved insulin resistance-animal study

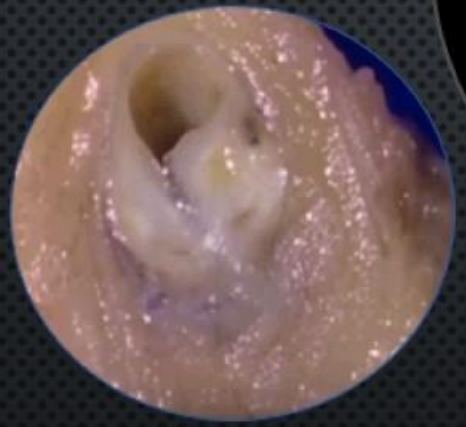
SGLT2 expression increased in diabetes animals

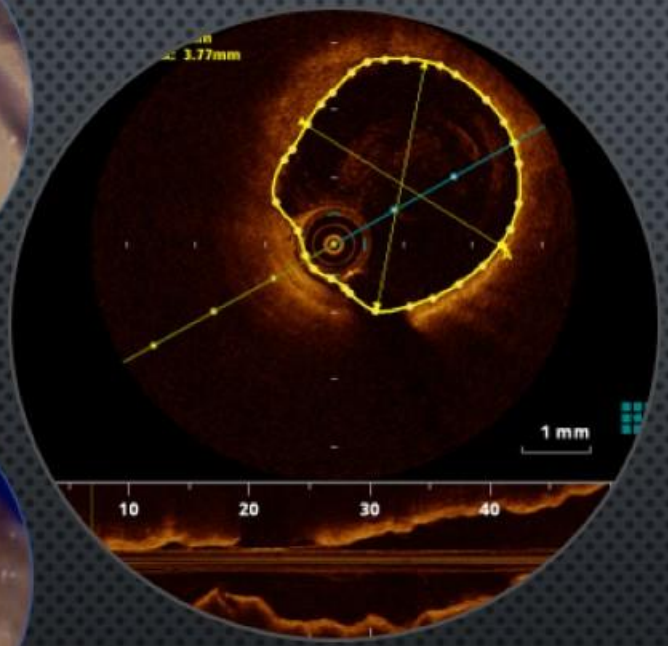
Human

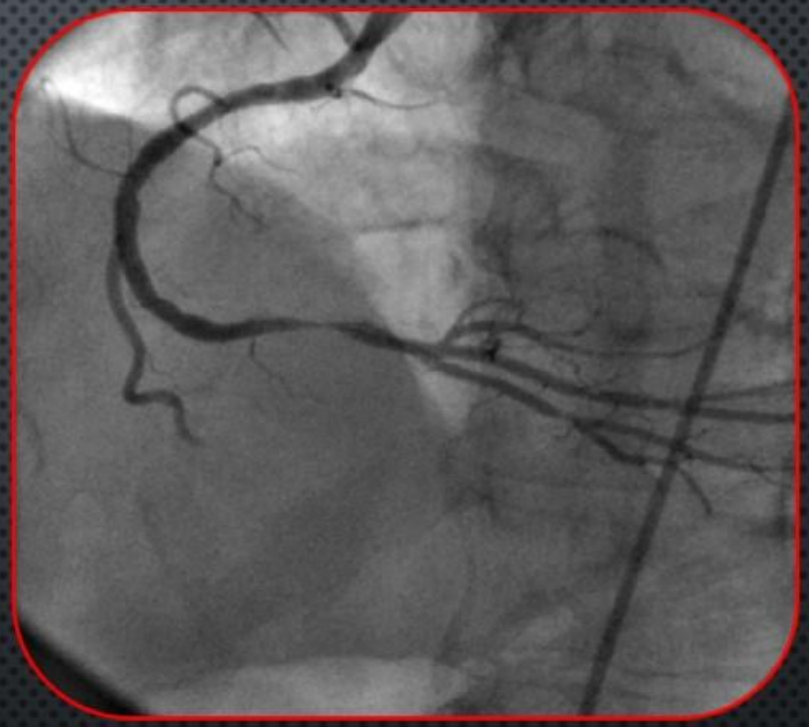


Endocrinology, March 2016, 157(3):1029–1042
Diabetalogia (1987) 30:610-617






3.77mm
1 mm
10
20
30
40



Closing highlights

2017 UPDATE

Higher-risk patients with clinical ASCVD: age >65 years, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic PAD with prior MI or stroke, history of non-MI related coronary revascularization, residual coronary artery disease with >40% stenosis in >2 large vessels, HDL-C <40 mg/dL for men and <50 mg/dL for women, hs-CRP >2 mg/L, or metabolic syndrome

JACC 2017;70:1785 guidelines

GUIDELINES-2017 (NON STATIN OR ADDITIONAL LOWERING)

IMPROVE-IT (EZETIMIDE)

Patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m2, and smoking.

PCSK-9 inhibitor

Clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. The clinician–patient discussion should consider the extent of available scientific evidence for net ASCVD risk- reduction benefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements **(refrigeration).**

JACC 2017;70:1785 guidelines

CV events per year

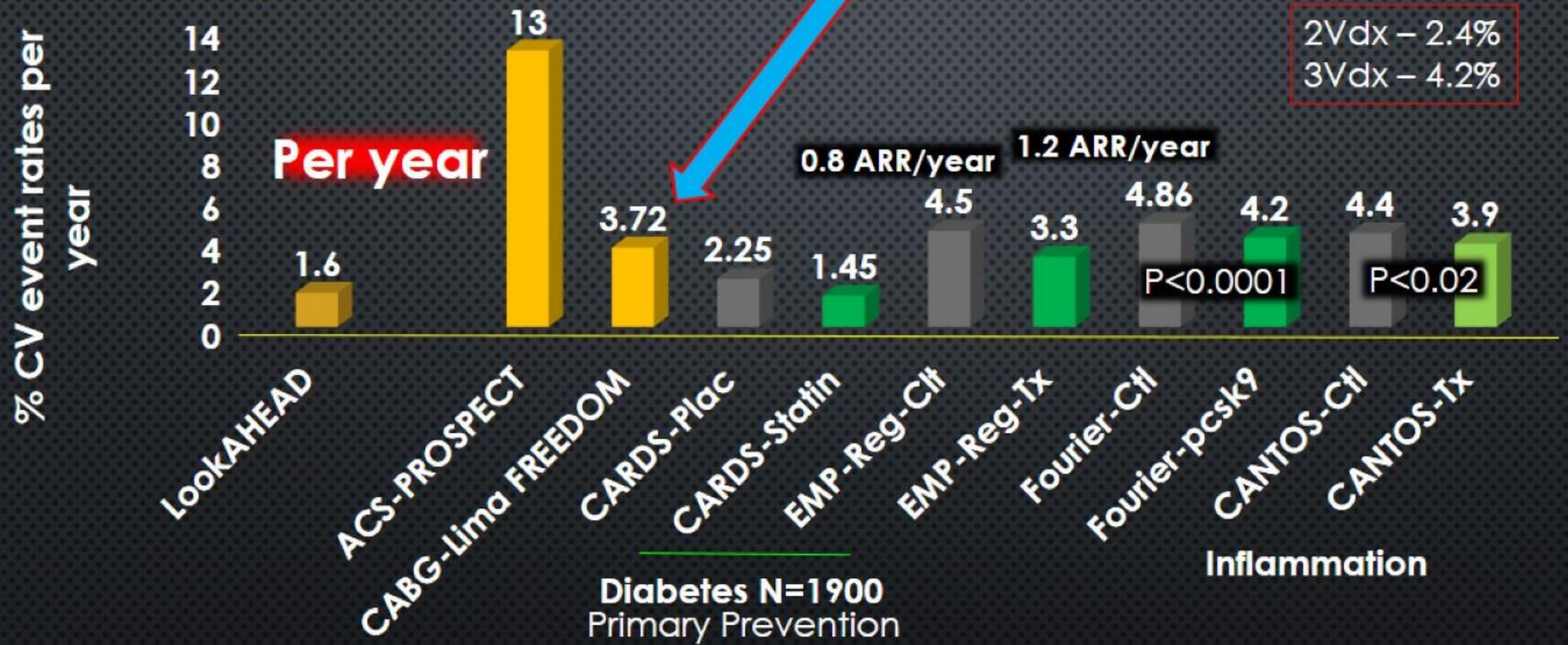
We need better treatments

ACS-N=697

PCI

Our "life saving surgery?" not good enough

2Vdx – 2.4%
3Vdx – 4.2%



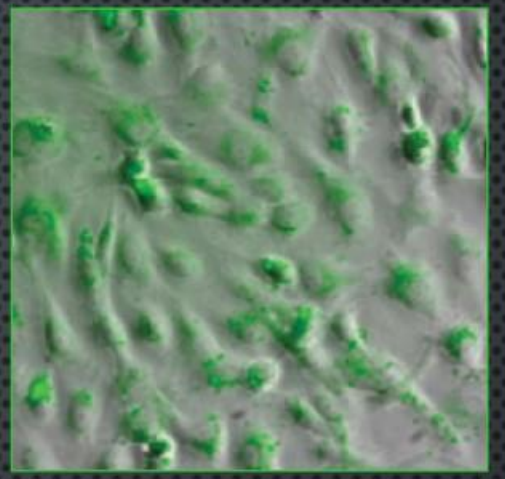
<6% @ 10 yrs best

N Engl J Med 2012;367:2375-84
Lancet. 2004 Aug 21-27;364(9435):685-96
DOI: 10.1056/NEJMoa1707914 CANTOS

Thank you

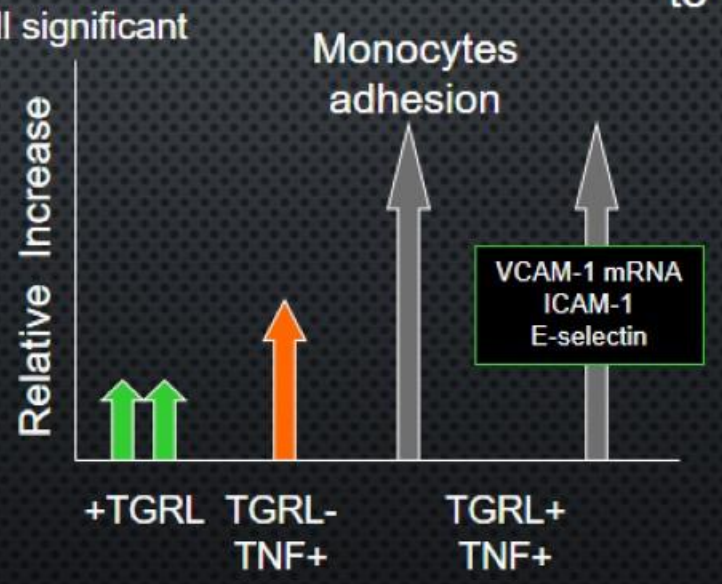
Lifestyle wins

PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE



TGRL electron transfer-based fluorescence bound to HAECs treated for 2hrs

- TGRL ALONE NO INFLAMMATION IN HAEC
- TGRL ENHANCED INFLAMMATORY RESPONSE 10X TO CYTOKINE STIMULATION



HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al Circ Res Feb 2007;100:000