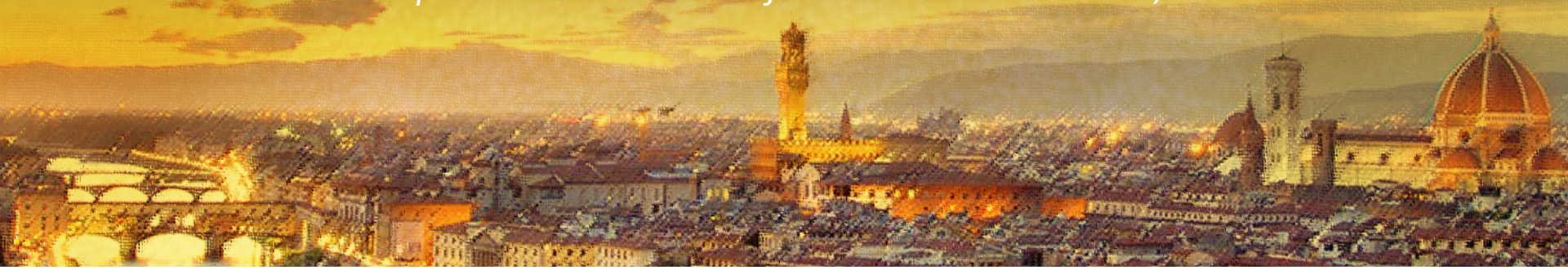
Conoscere e Curare il Cuore 2019

SABATO 2 MARZO

L'INFIAMMAZIONE NELL'ATEROSCLEROSI. PERCHÉ CERCARLA, COME INDIVIDUARLA, IN CHE MODO COMBATTERLA.

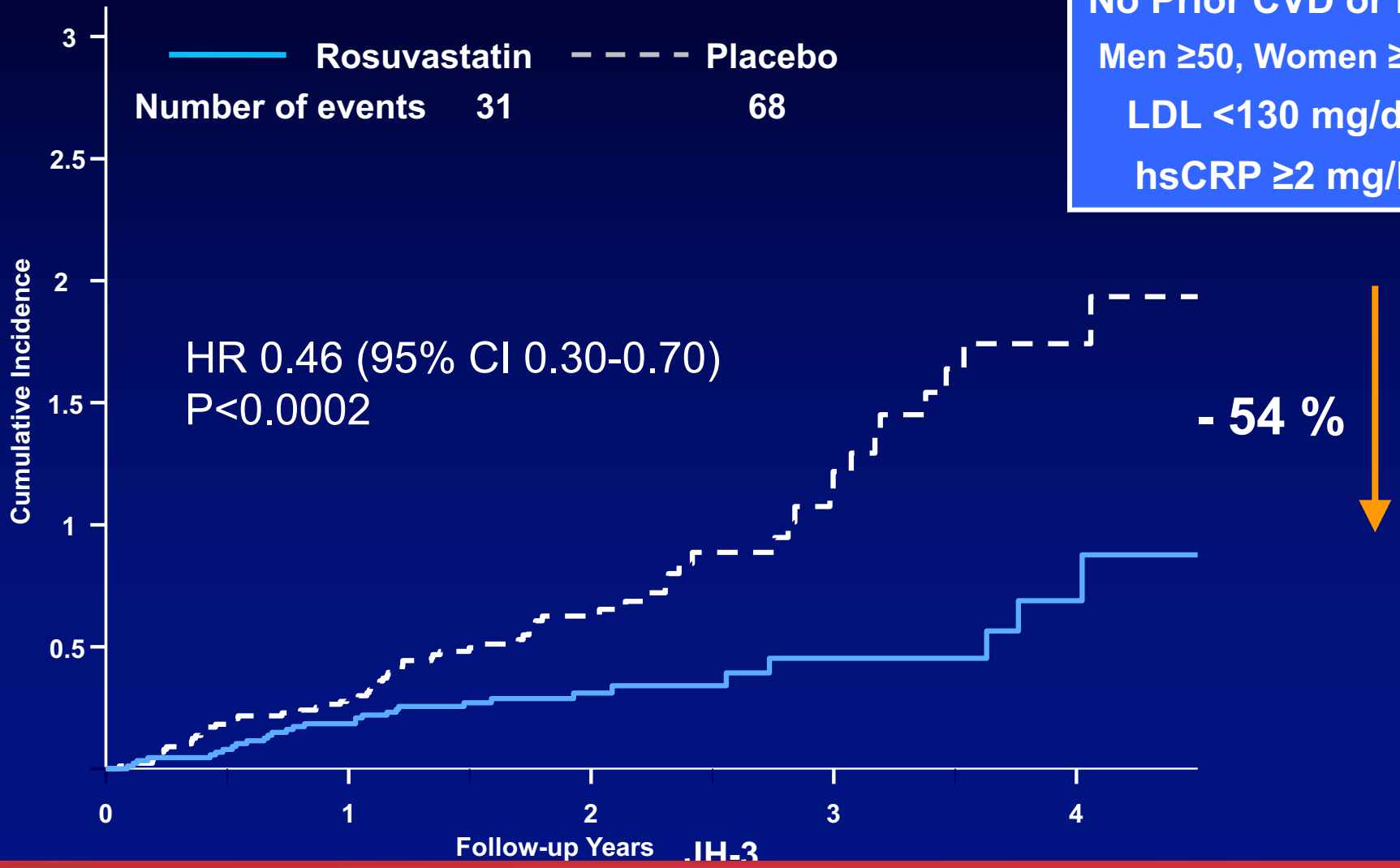
Francesco Prati

U.O.C. Cardiologia d'Urgenza ed Interventistica
A.O. San Giovanni-Addolorata, Roma
Centro per la Lotta contro l'Infarto - Fondazione Onlus, Roma



JUPITER:
Fatal or Nonfatal Myocardial Infarction

No Prior CVD or DM
Men ≥50, Women ≥60
LDL <130 mg/dL
hsCRP ≥2 mg/L



Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
Residual Inflammatory Risk
(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

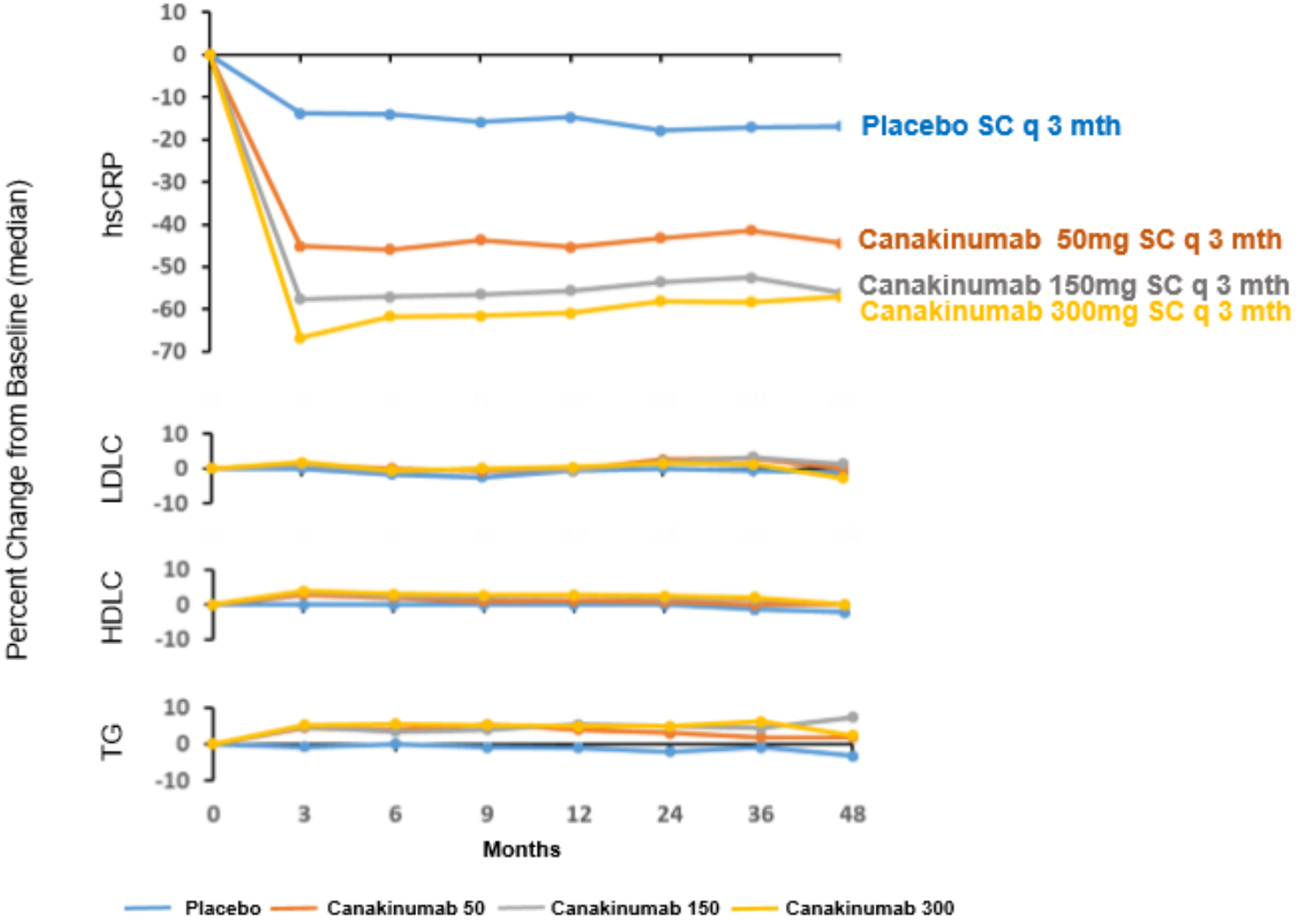
Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Additional Adjudicated Endpoints: Cancer, Infection

Ridker PM et al. N Engl J Med. 2017;377:1119-31

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

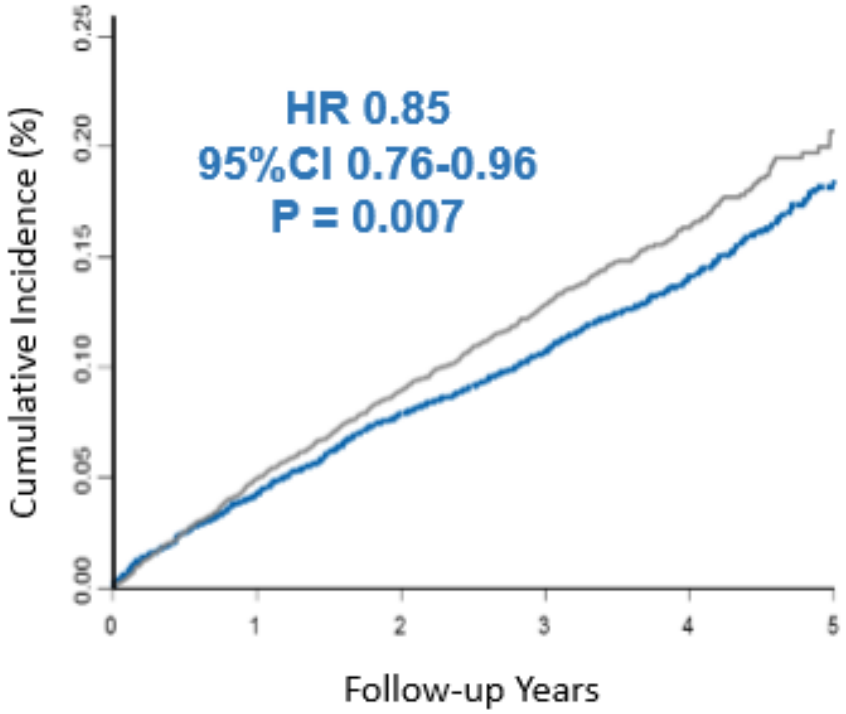


Ridker PM et al. N Engl J Med. 2017;377:1119-31

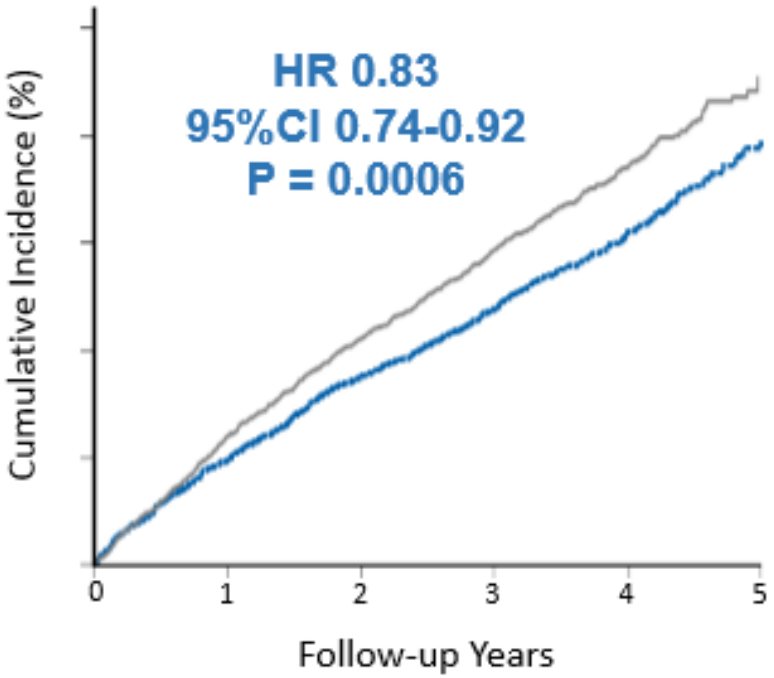
CANTOS: Primary Cardiovascular Endpoints

Placebo SC q 3 months
Canakinumab 150/300 mg SC q 3 months

MACE



MACE - Plus

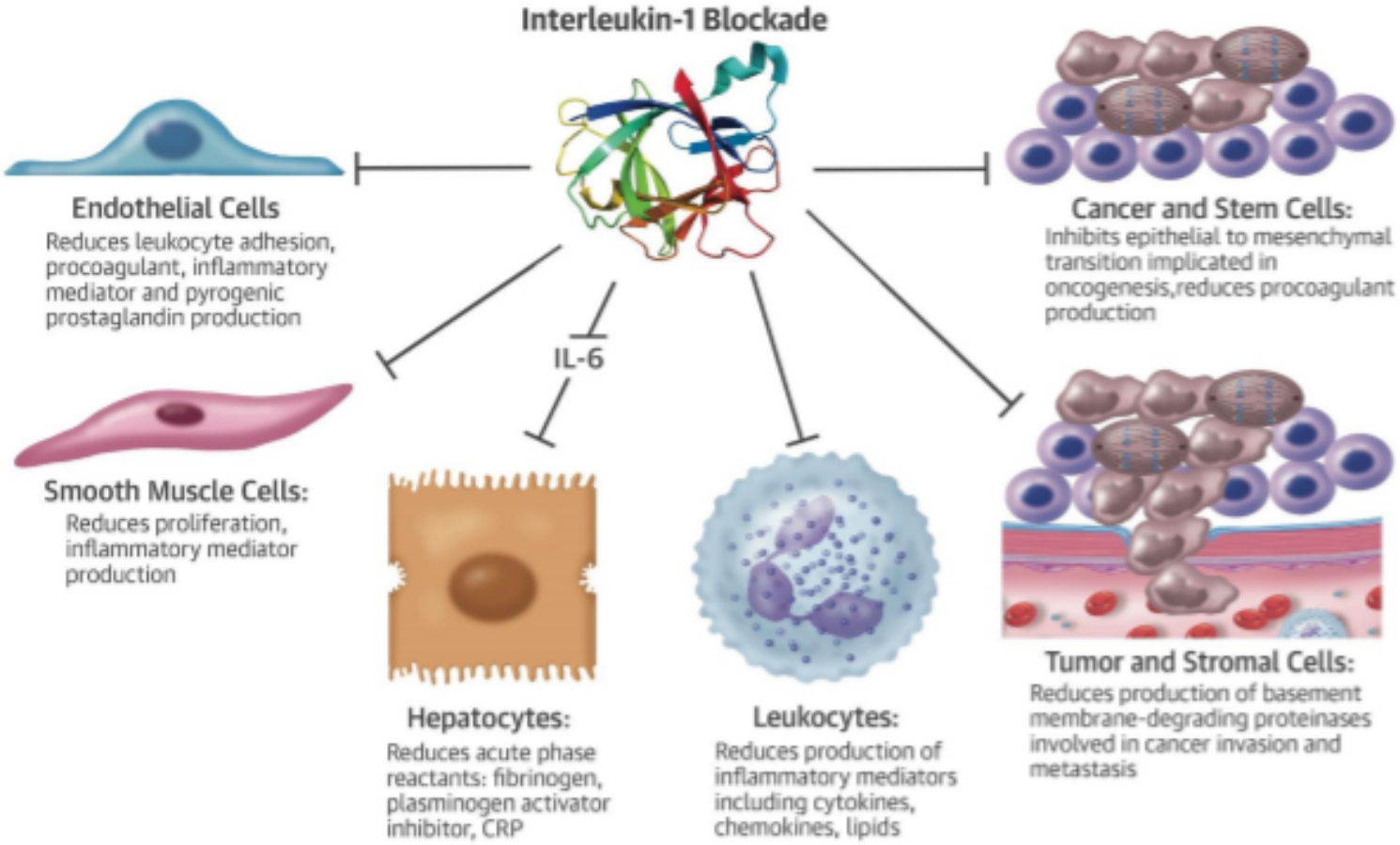


35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM et al. N Engl J Med. 2017;377:1119-31

Atherosclerotic inflammation

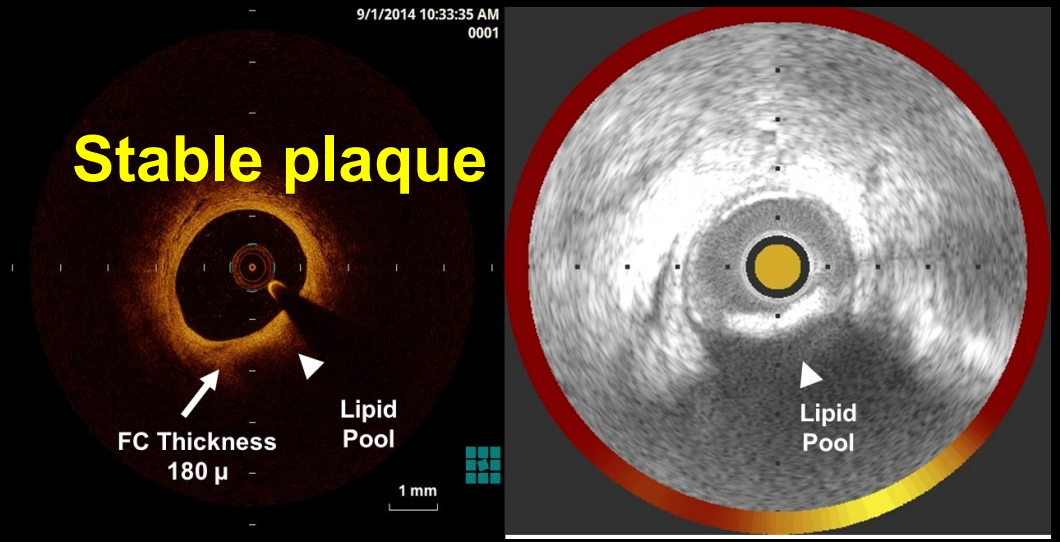
……. sure it counts

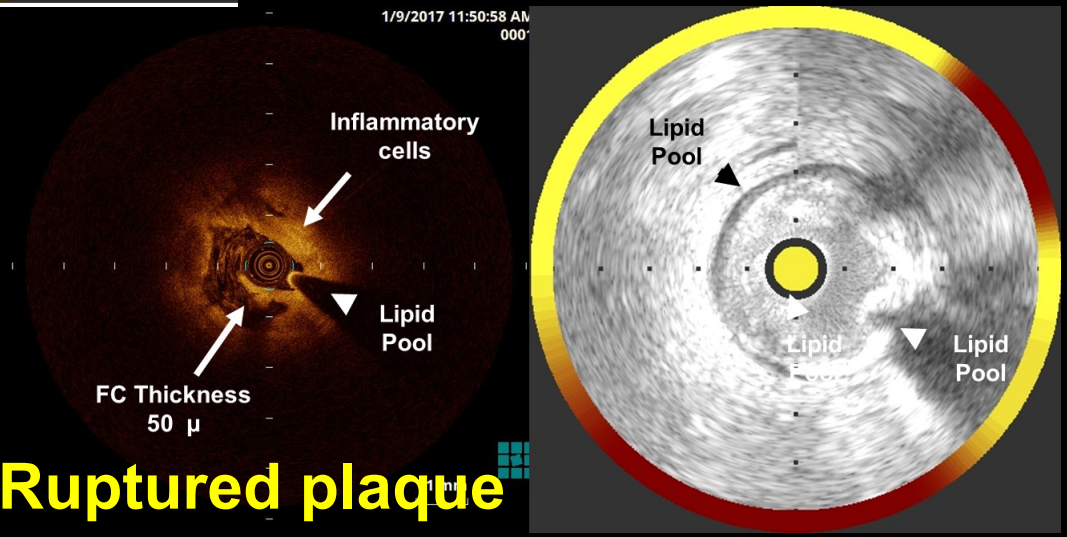


Libby P. Interleukin-1 Beta as a Target for Atherosclerosis: Biologic Basis for CANTOS and Beyond. JACC 2017 (October 31, 2017)

N 99 lesions studied with IVUS-NIRS and OCT

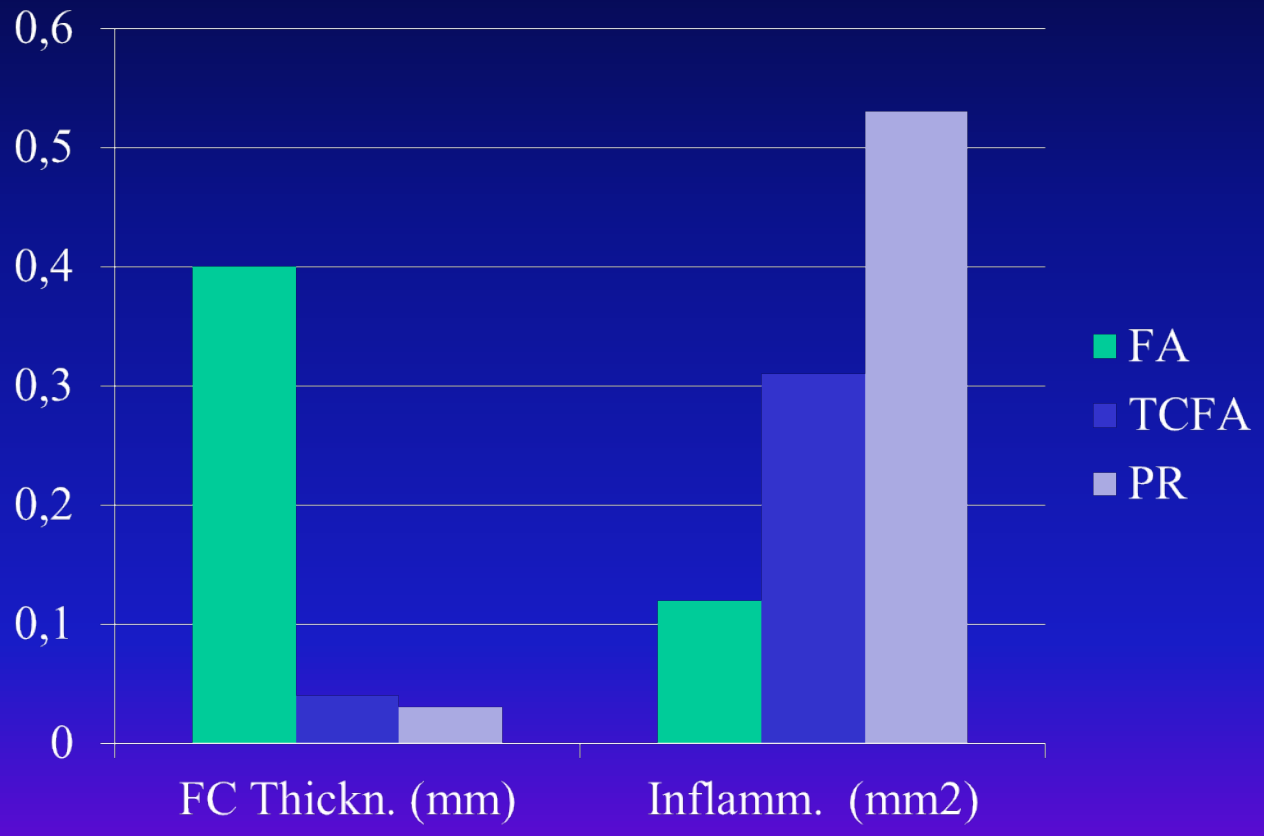
Culprit lesions of ACS pts have small LA (< 4 mm^2, thin FC (< 80 μ) , and superficial inflammation





Prati et al. Int J Cardiol 2018

Culprit plaques have a higher inflammatory content as compared to vulnerable and stable plaques



Narula et al JACC 2013

The New England Journal of Medicine

VOLUME 347 JULY 4, 2002 NUMBER 1

WIDESPREAD CORONARY INFLAMMATION IN UNSTABLE ANGINA

ANTONINO BUFFON, M.D., LUIGI M. BIASUCCI, M.D., GIOVANNA LIUZZO, M.D., GIUSEPPE D'ONOFRIO, M.D., FILIPPO CREA, M.D., AND ATTILIO MASERI, M.D.

ABSTRACT

Background Inflammation within vulnerable coronary plaques may cause unstable angina by promoting rupture and erosion. In unstable angina, activated leukocytes may be found in peripheral and coronary-sinus blood, but it is unclear whether they are selectively activated in the vascular bed of the culprit stenosis.

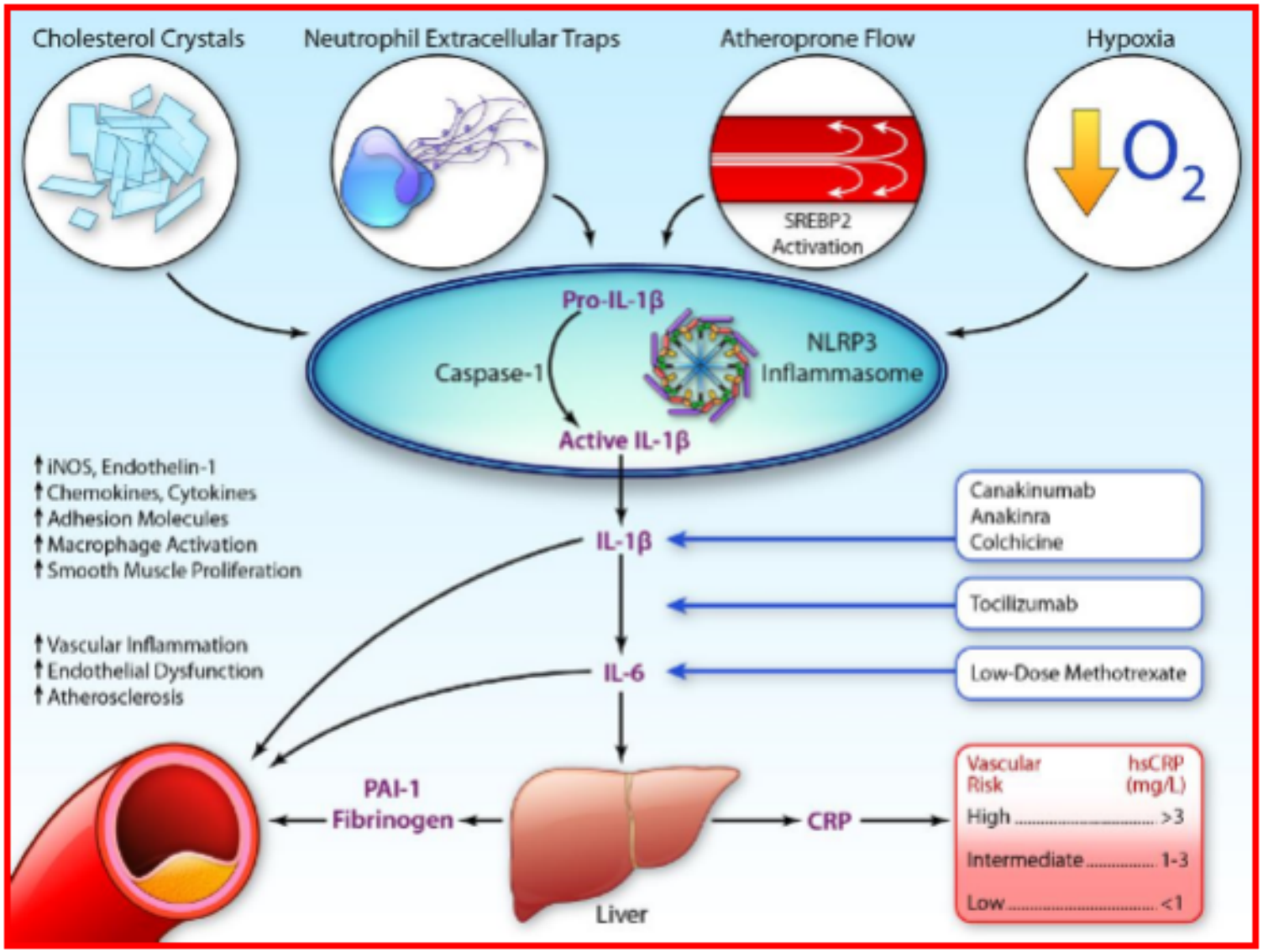
Methods We measured the content neutrophil my-

THE hypothesis that inflammation of a vulnerable plaque is responsible for the development of acute coronary syndromes[1-5] is stimulating a variety of techniques for the detection and stabilization of vulnerable plaques.[6-10] Yet, it is unclear whether the inflammatory process is confined to a single vulnerable plaque or whether it is more widespread in the coronary vasculature.

The possibility of widespread inflammation of the

Targeting inflammation makes sense

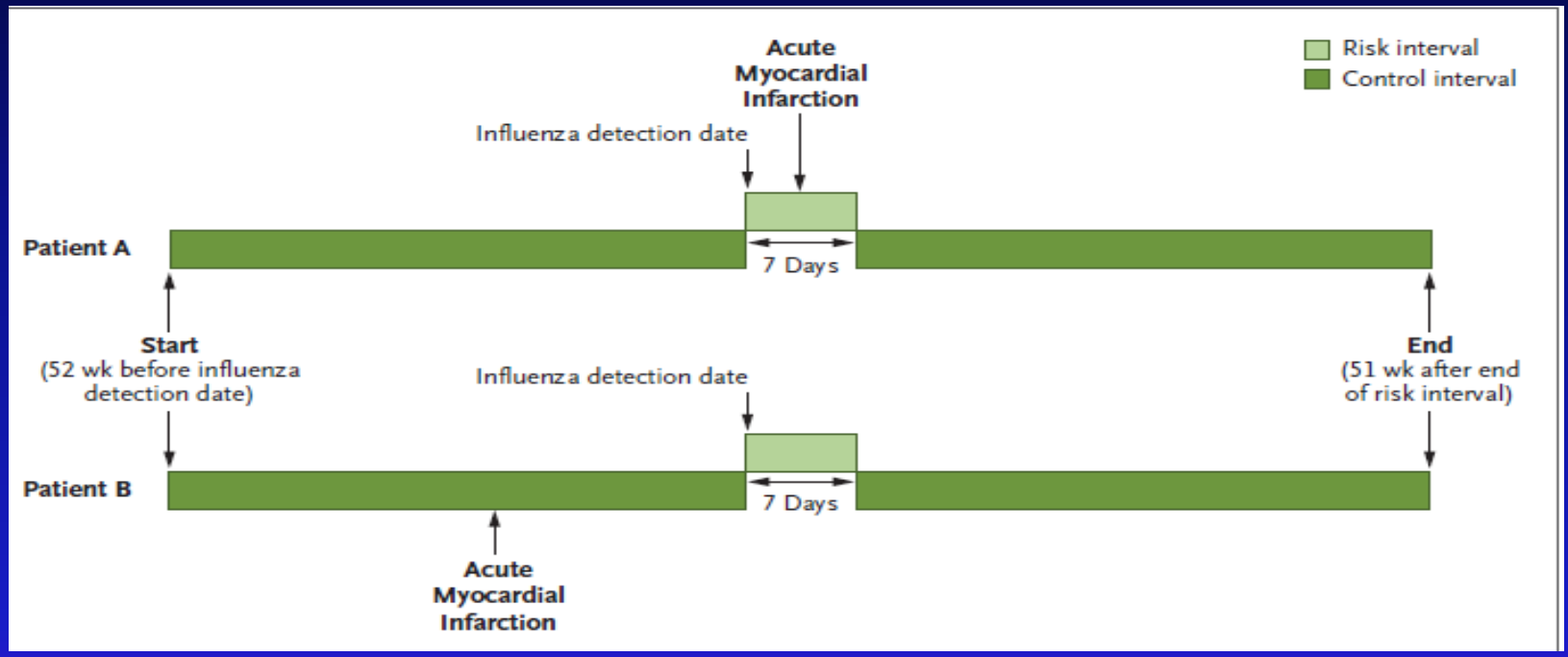
From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotect



Ridker PM. Circ Res 2016;118:145-156.

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.N Engl J Med 2018

Kwong et al.



- 20 admissions for AMI (20.0 admissions per week) during the risk interval
- 344 admissions for AMI (3.3 admissions per week) during the control interval I

Incidence ratio, 6.05

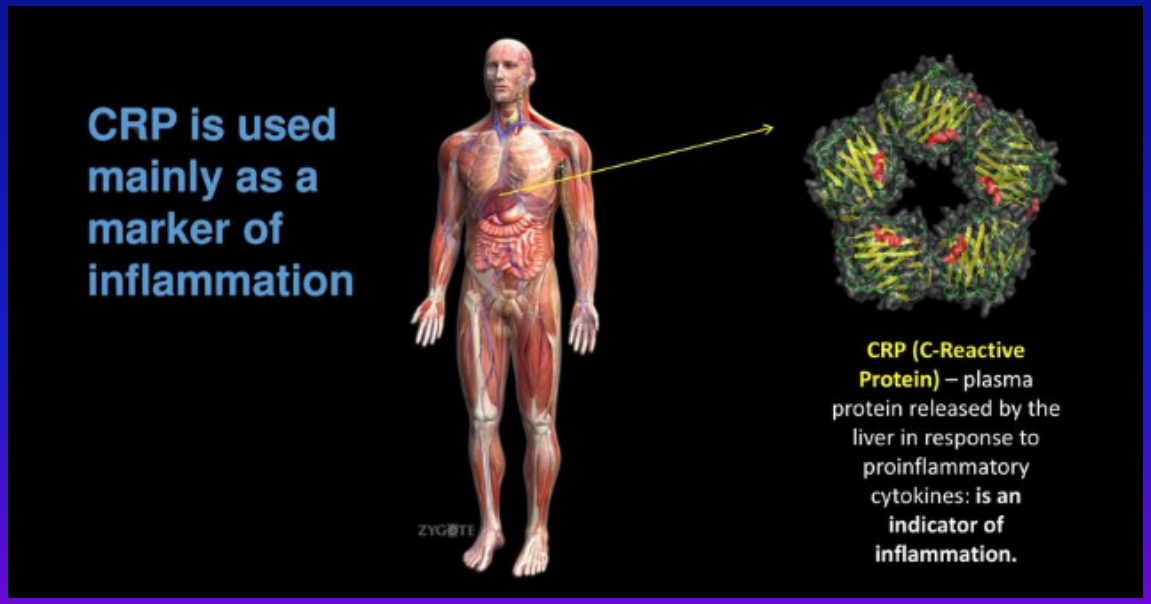
Searching atherosclerotic inflammation

Assessment of inflammtion is currenly based on CRP assessment

What does hsCRP elevation mean?

Limitations of PCR titration

1) low specificity for CAD as many inflammatory diseases can increase CRP values.

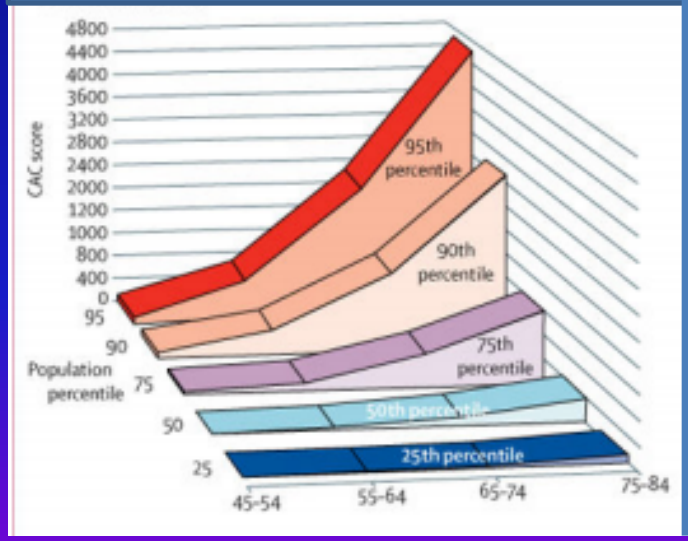


2) CRP surge may not reflect inflamed atherosclerosis

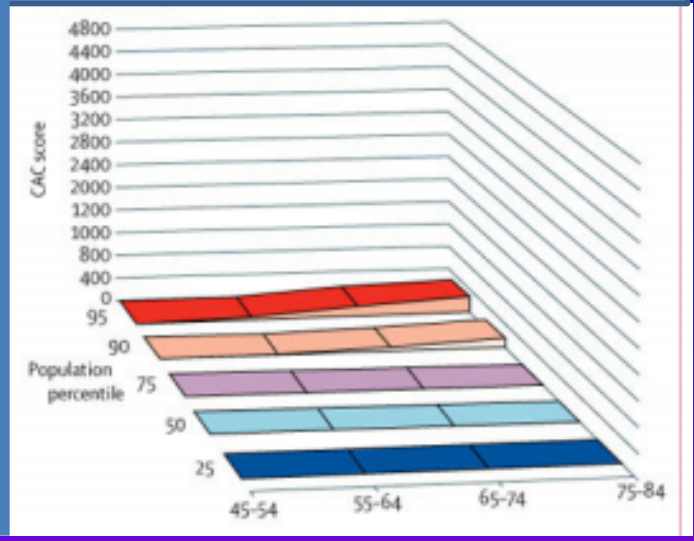
- **The Tsimane aborigines have the lowest reported levels of CAD in the world**

Very LOW Calcium score prevalence

MESA White Men



Tsimane White Men



Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. Lancet 2017;389: 1730–39.

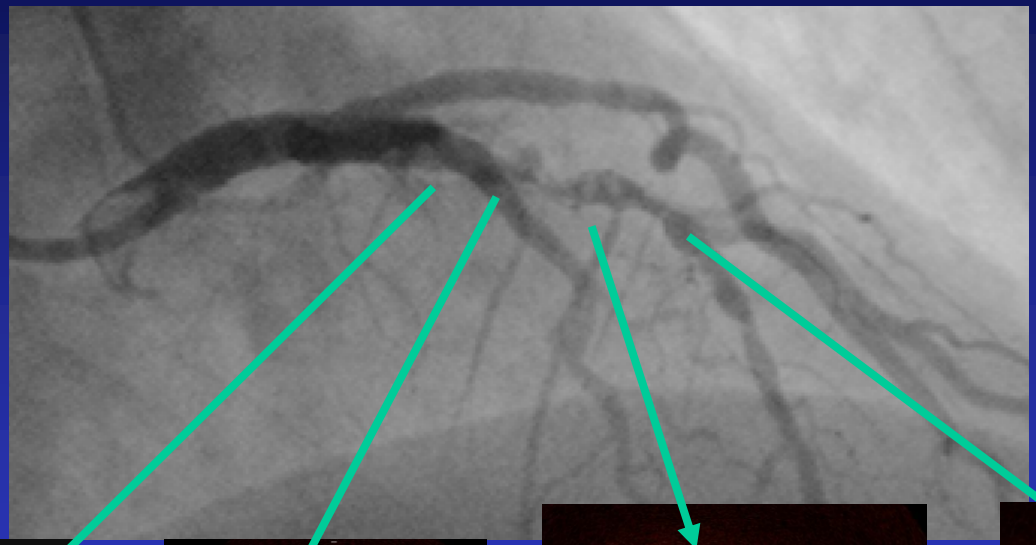
- **High levels of CRP, related environmental exposure to infections.**

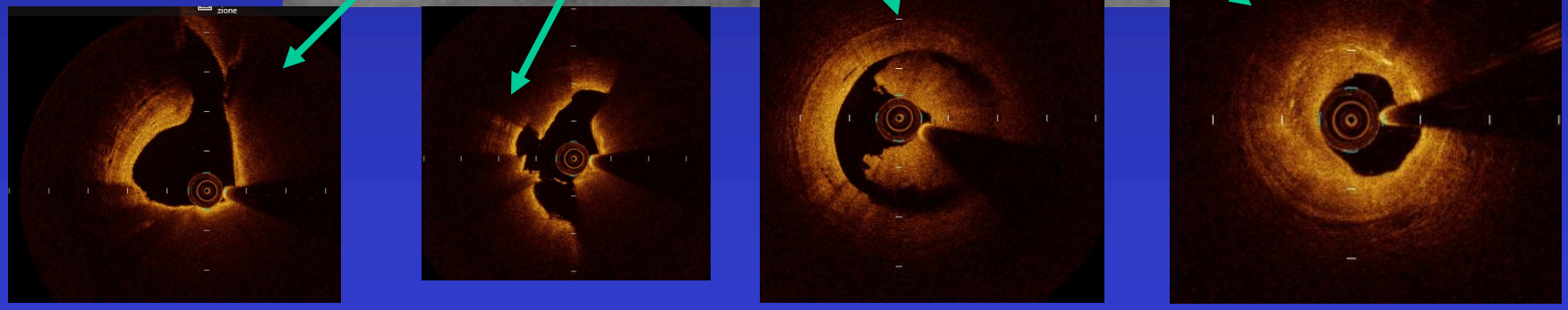
- **Hs-CRP concentrations higher than 3.0 mg/L reported in 51% of Tsimane**
- **Mean CRP : 3.7 mg/**

Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. Lancet 2017;389: 1730–39.

3) A single ACS culprit coronary plaque cannot be responsible for hsCRP surge

FR. Male 55 Y





Inflammatory Markers and Onset of Cardiovascular Events

Results From the Health ABC Study

Cesari et al. Circulation 20013

TABLE 2. Inflammatory Markers Levels (Median, Interquartile Range) According to Incident CHD, Stroke, and CHF Events

	No Events (n=1950)	CHD Events (n=188)	P*	Stroke Events (n=60)	P*	CHF Events (n=92)	P*
IL-6, pg/mL	1.68 (1.16–2.54)	2.11 (1.40–3.13)	<0.001	2.41 (1.78–3.17)	<0.001	2.62 (1.62–4.35)	<0.001
CRP, mg/L	1.61 (0.98–3.01)	1.74 (1.04–3.10)	0.193	1.99 (1.04–3.60)	0.102	2.70 (1.47–4.41)	<0.001
TNF-α, pg/mL	3.02 (2.35–3.86)	3.50 (2.67–4.66)	<0.001	3.20 (2.38–4.42)	0.212	3.40 (2.67–5.33)	<0.001

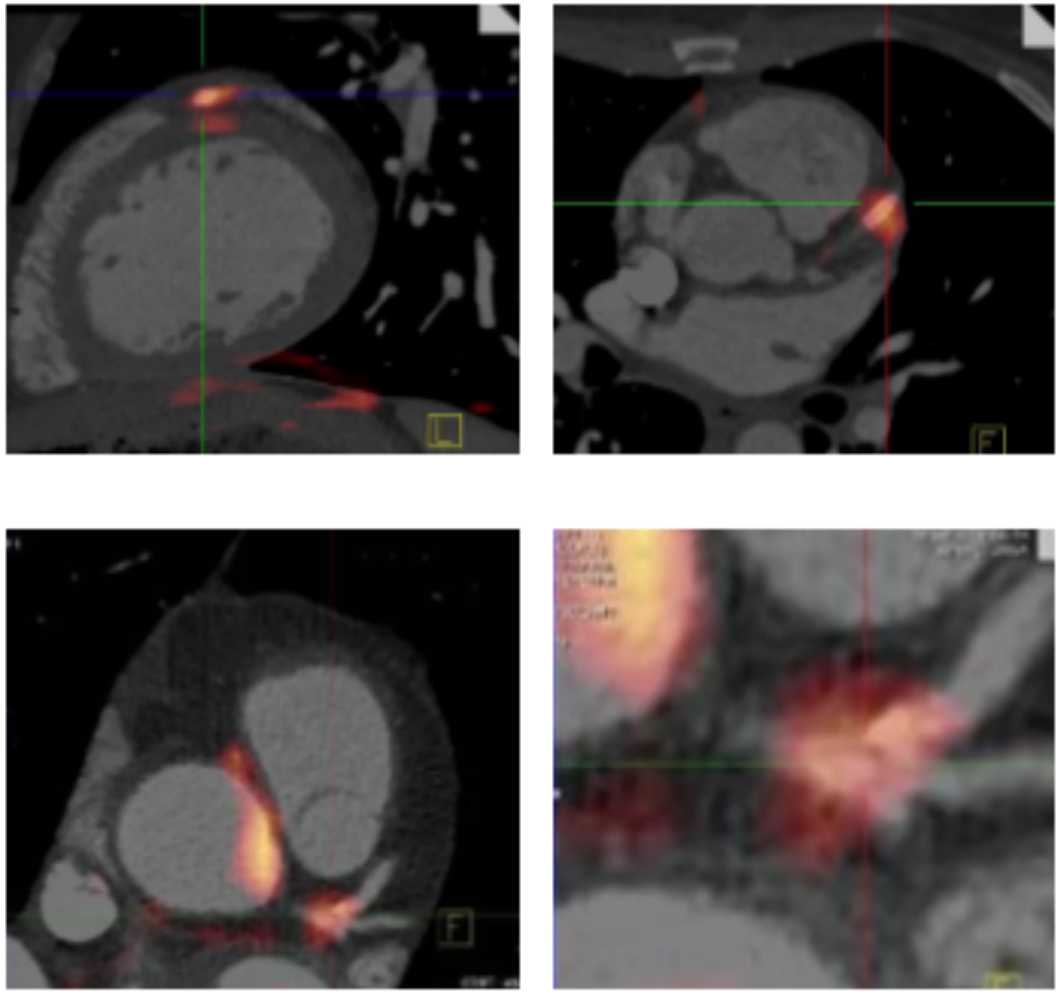
*P values vs No Events are based on Mann-Whitney *U* statistics.

- There is need for adequate, precise standardized assay
- Current assays of inflammatory are limited to CRP assessment

Can we image inflammatory cells in atherosclerotic lesions?

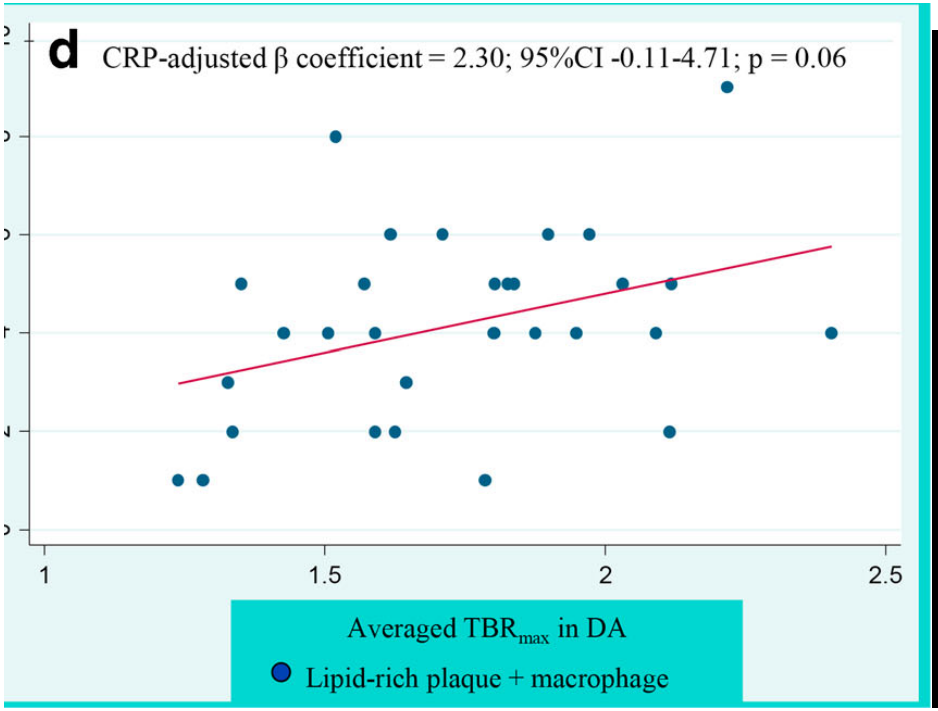
- Pheripheral arteries?
- Coronary district?

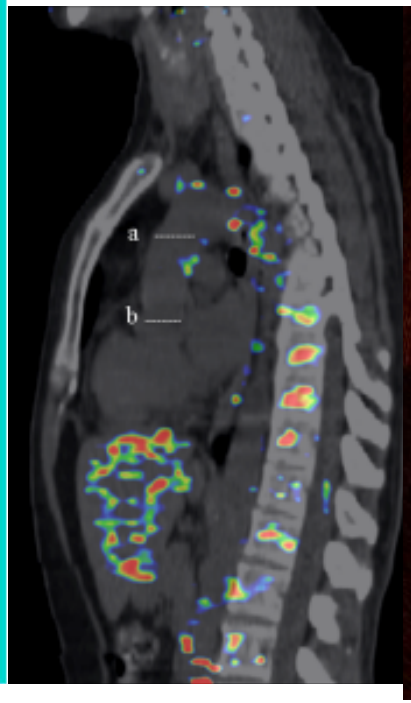
Coronary FDG-PET/CT Imaging

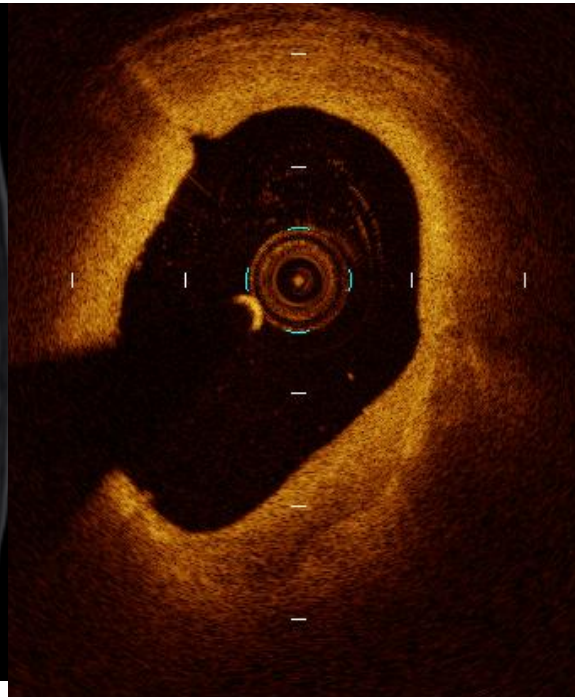


PET have a high sensitivity, but limited spatial resolution

Relation between thoracic aortic inflammation and features of plaque vulnerability in the coronary tree in patients with ACS
An FDG-positron emission tomography and OCT study
Nevio Taglieri et al Eur J Nucl Med Mol Imaging 2018



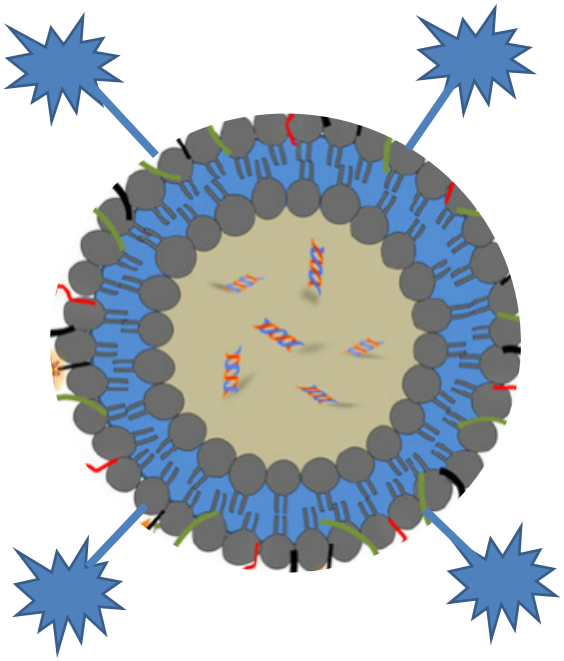




Significant association between averaged FDG uptake (TBR_{max}) in descending aorta and the number of lipid-rich plaques with macrophages even after adjustment for CRP values

Probes

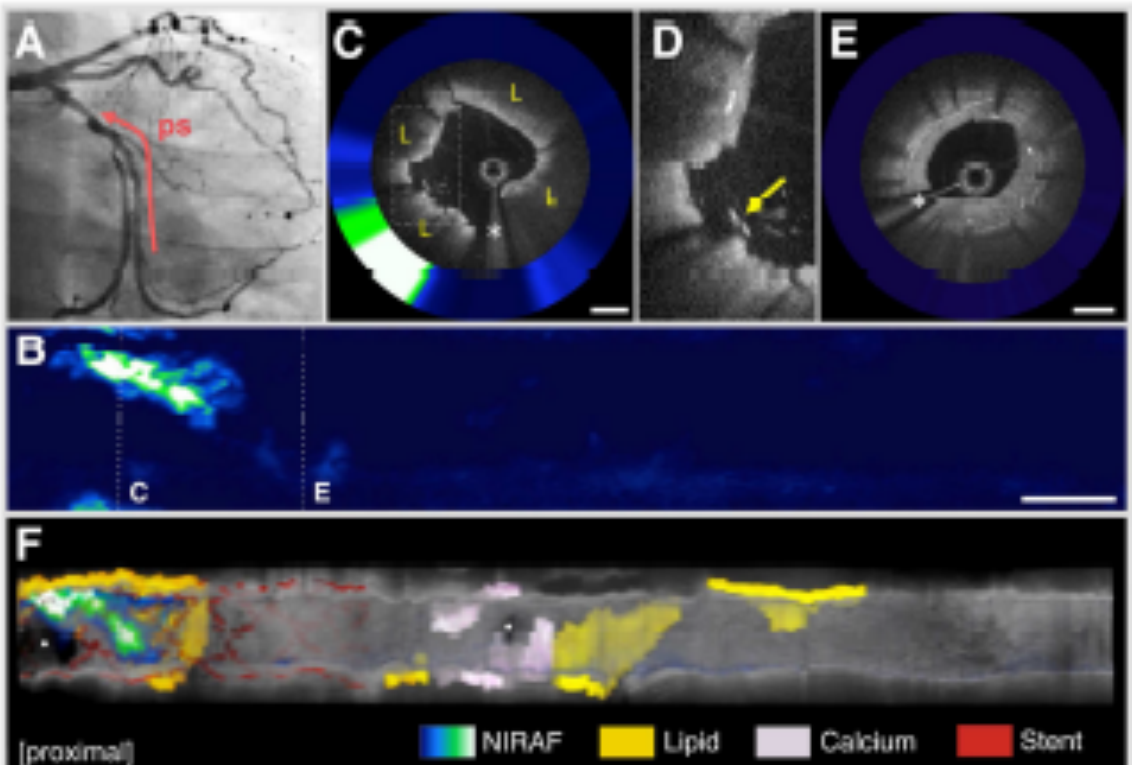
- Moiety: antibody or specific ligand with high affinity for the desired target molecule.
- Modified to facilitate uptake by specific cells.



- **Designed to be detected by various modalities**
  - Ultrasound (microbubbles)
  - SPECT and PET (radioactive isotopes)
  - MRI (paramagnetic compounds)
  - CT (iodinated compounds)
  - Optical imaging (fluorochromes)

First-In-Human Dual-Modality OCT and Near-Infrared Autofluorescence Imaging of Coronary Artery Disease

Giovanni J. Ughi, JACC imaging 2018

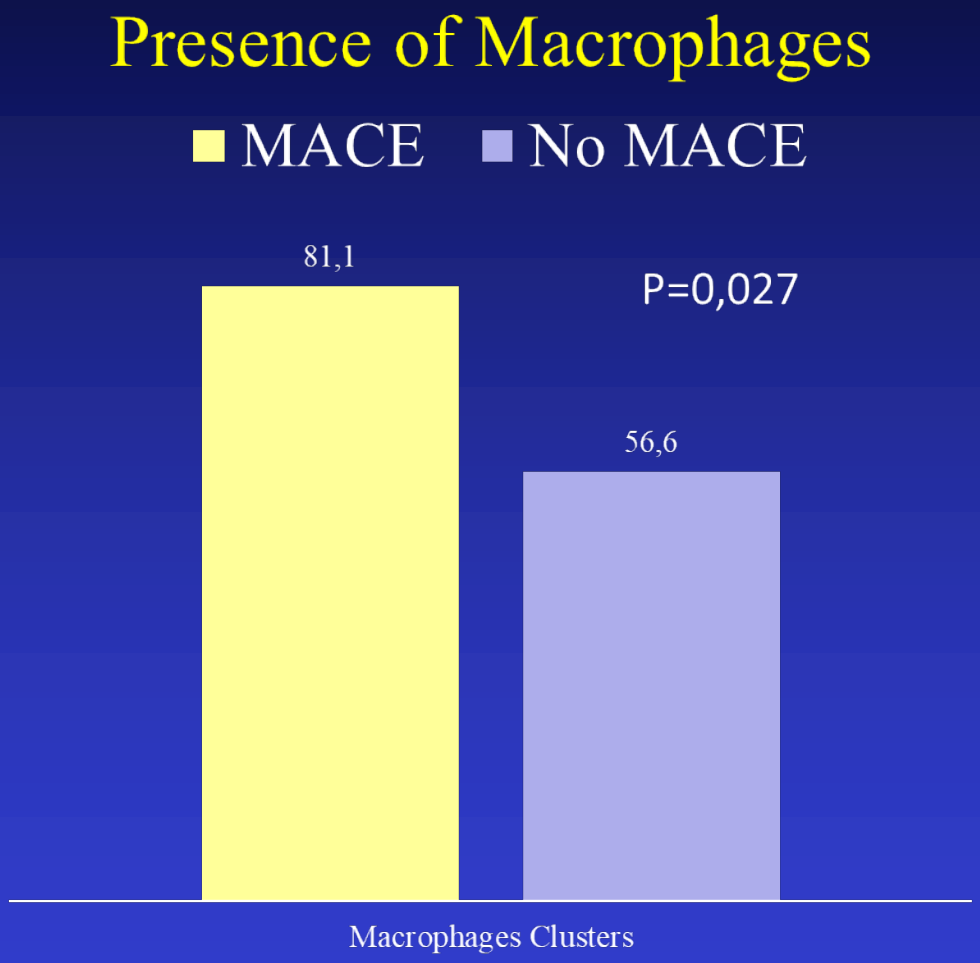


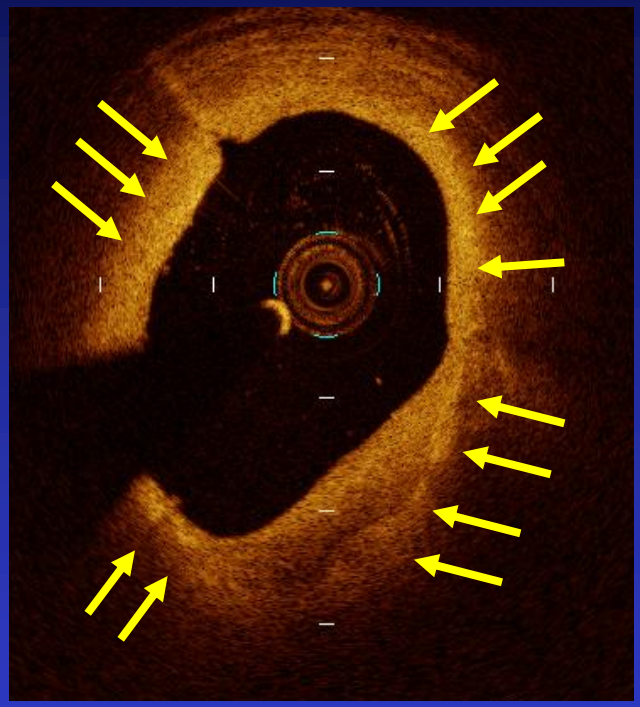
- **Excellent sensitivity and temporal resolution**
- **Invasive technique**

CLIMA Study.

N 1003 pts with OCT assessment of proximal LAD artery

MACE: Cardiac death and or MI at one year

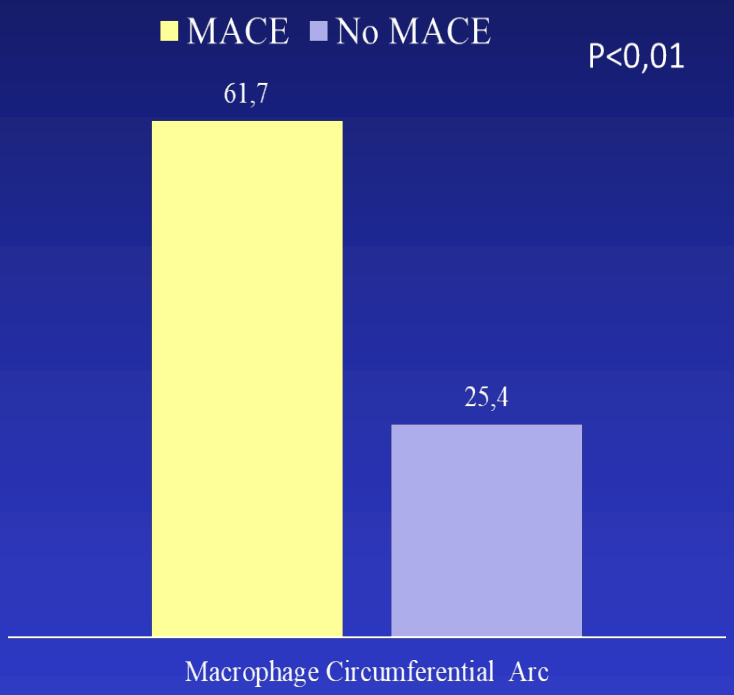


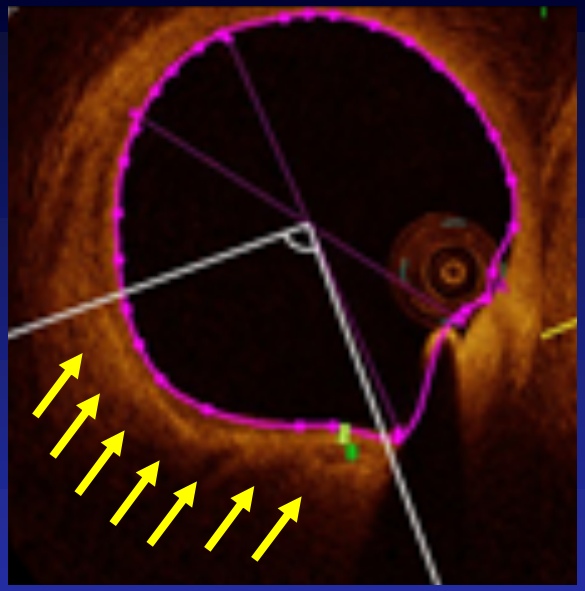


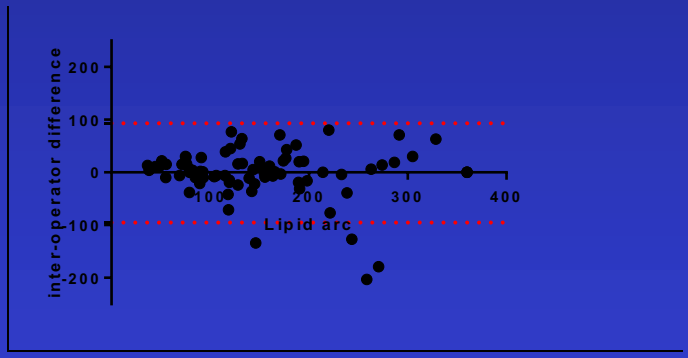
European Heart Journal submitted

CLIMA Study

Circumferential Arc of Macrophages > 70 Grades





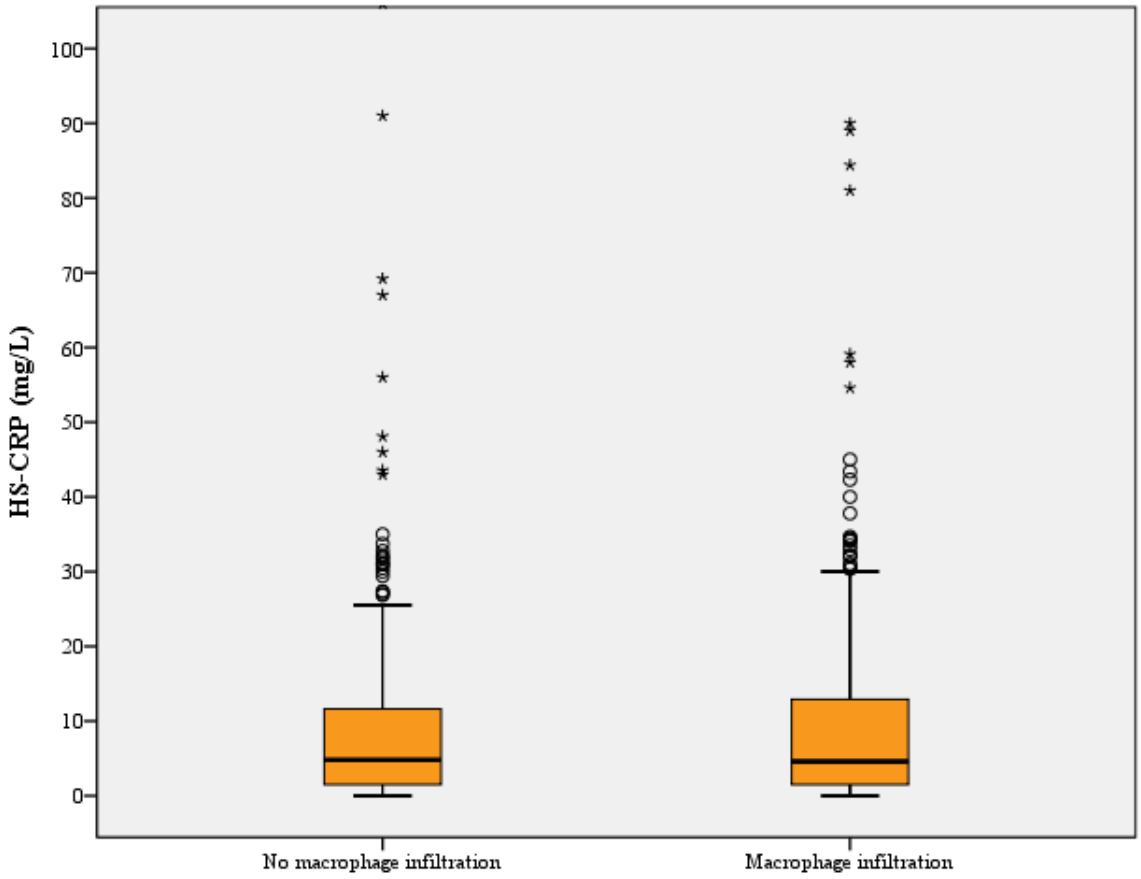


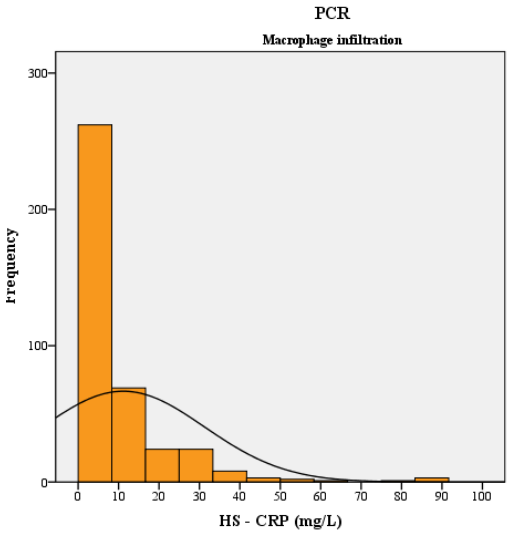
Good correlation for Interobsever measurements

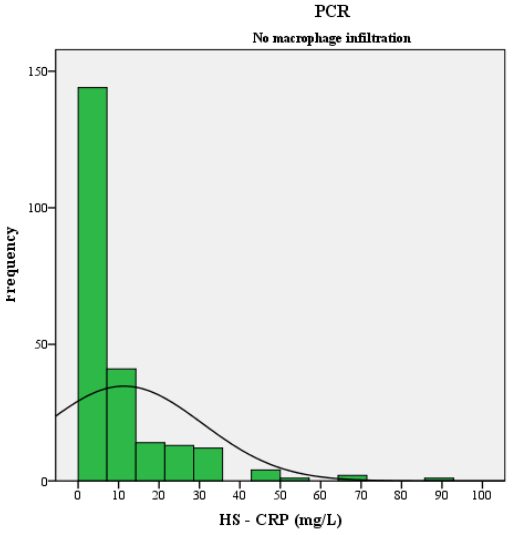
Unpublished data

CLIMA data

PCR (mg/L) distribution according to presence of macrophage infiltration





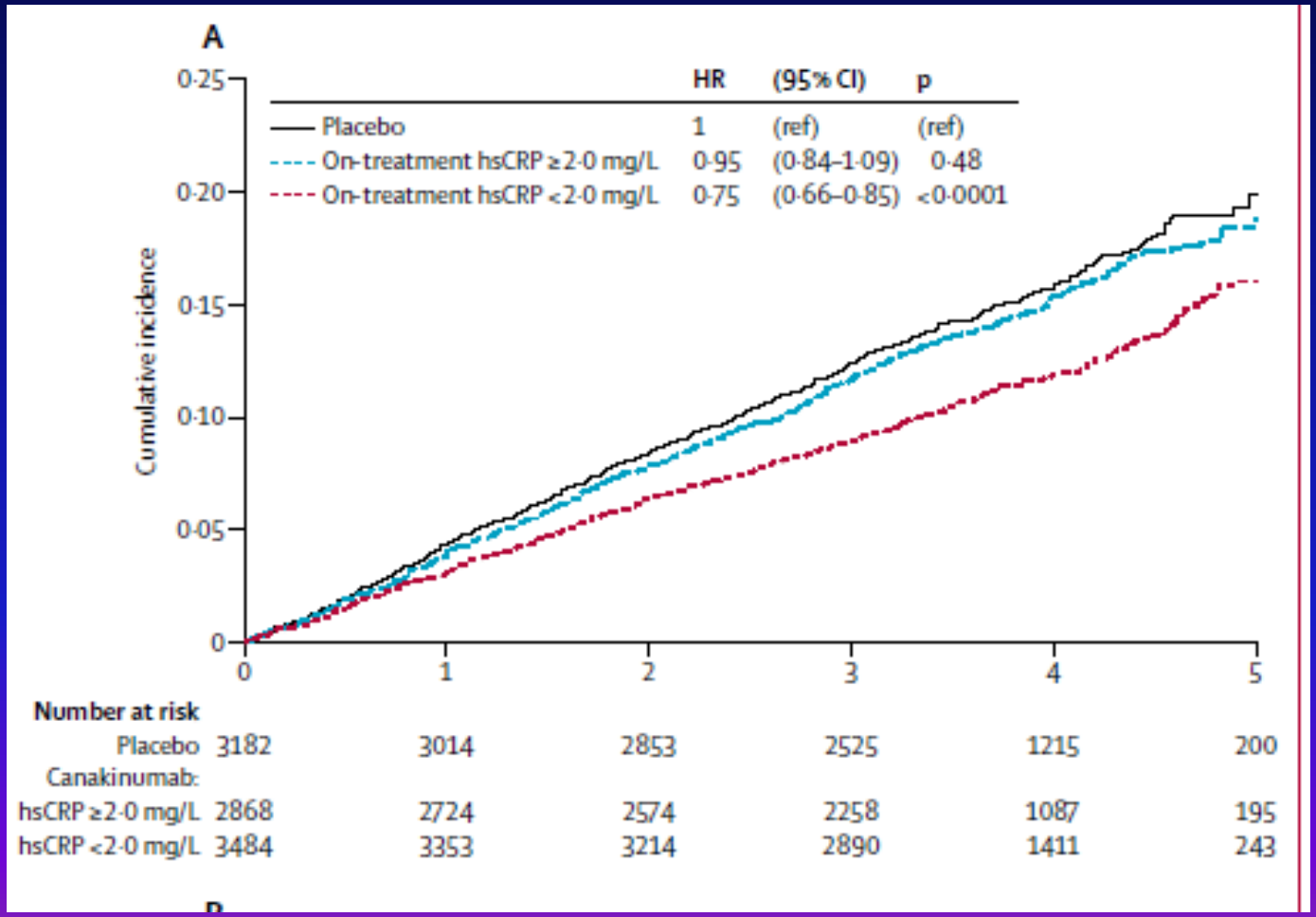


Statistics

Macrophage infiltration	**Median**	**4.60 (IQ 1.5-13.0)**	
No Macrophage infiltration	**Median**	**4.80 (IQ 1.5-11.8)**	**p=0.989**

Ready to adopt anti inflammatory drug strategies?

Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018



Benefit–Risk Balance of Canakinumab (CANTOS)

1000 Patients Treated with Canagliflozin for 3.7 years

Canakinumab 150 mg

Benefit

- 6 MACE events prevented
  - 5 MIs prevented
- 11 fewer coronary PCI/CABG
  - 2 fewer hosp. UA → UR
- 1 fewer fatal cancer
- 11 fewer arthritis
  - 4 fewer gouty arthritis

Risk

- 1 excess fatal infection
- 1 excess leukopenia
- 1 excess thrombocytopenia
- No excess liver toxicity
- No excess injection site reactions
- No excess hemorrhage

No effect on stroke, CV death or all-cause mortality

Inflammatory Hypothesis for Atherothrombosis
Totality of Evidence

Pro

- CANTOS
  (Canakinumab: anti-IL1β)
- ? LoDoCo
  (Colchicine)

Con

- Lp-PLA2 inhibition
  (Darapladib; 2 negative trials: STABILITY, SOLID-TIMI 52)
- Steroids ↑ atherogenesis
- NSAIDs ↑ CVD risk
- Anti-TNF-α agents ↑ mortality

Validation of the inflammatory hypothesis implies that targeting of molecules involved in inflammation reduces CV risk

CVOTs Addressing the Inflammatory Hypothesis of Atherothrombosis

Trial	Type	Blind	Power (1-β)	MDD (δ)	Cohort	Time period
CIRT (N=7,000) Methotrexate vs Placebo	Superiority	DB	90%-95% (514 events)	HR 0.75	Post-MI + T2DM or metabolic syndrome	2013-2019
LoDoCo2 (N=4,230) Colchicine vs Placebo	Superiority	DB	90% (331 events)	HR 0.70	Stable CAD	2014-2019
COLCOT (N=4,500) Colchicine vs Placebo	Superiority	DB	90% (301 events)	NR	Post-MI <30d	2015-2019

These trials are likely have a greater impact on the inflammatory hypothesis given the safety, tolerability, & affordability of methotrexate and colchicine

Conclusions

Treatment of coronary inflammation is a

- An interesting concept of personalized medicine
- Further studies are needed to prove the safety/efficacy profile of Canakinumab and address cost-effectiveness
- Further studies are needed to prove the safety/efficacy profile of other anti-inflammatory drugs (Colchicine, Methotrexate)
- In the next future there is need to explore other solutions

  (Imaging may help) to address inflammation
- We have to retain the concept that high PCR in the unstable clinical setting means higher risk and assessment of PCR (with its limitations) is worth doing