Cardiology and vascular medicine 2012

Management of vascular inflammation in ACS

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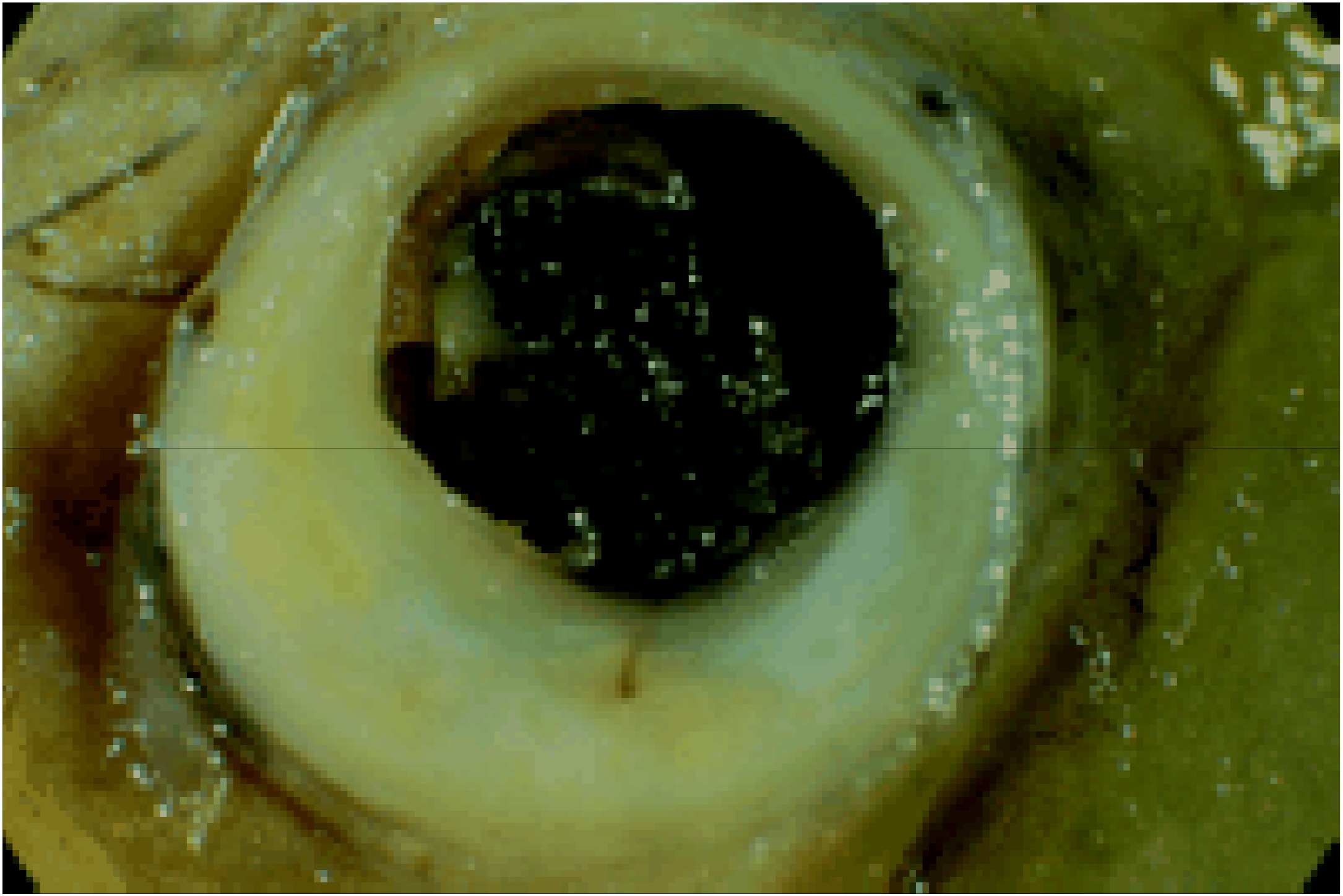
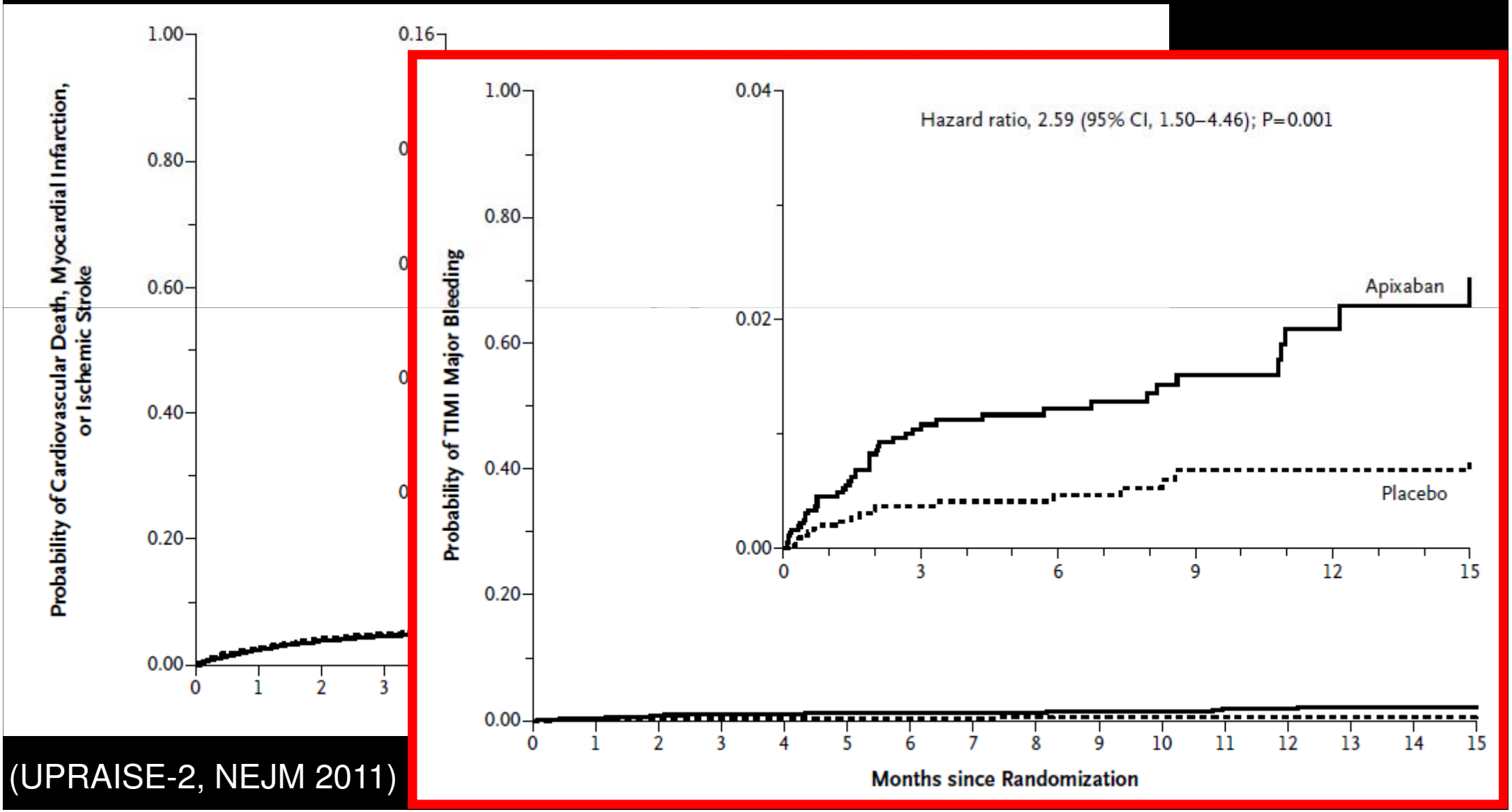


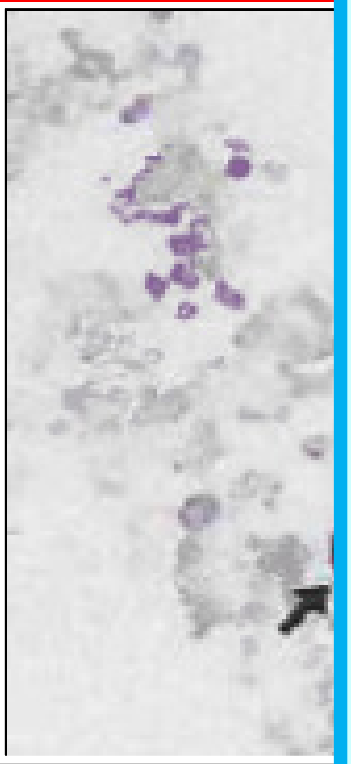
Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (n=7392)



(UPRAISE-2, NEJM 2011)

High Telomerase Activity in Neutrophils from Unstable Coronary Plaques

Immunostai
plaque PM
ant



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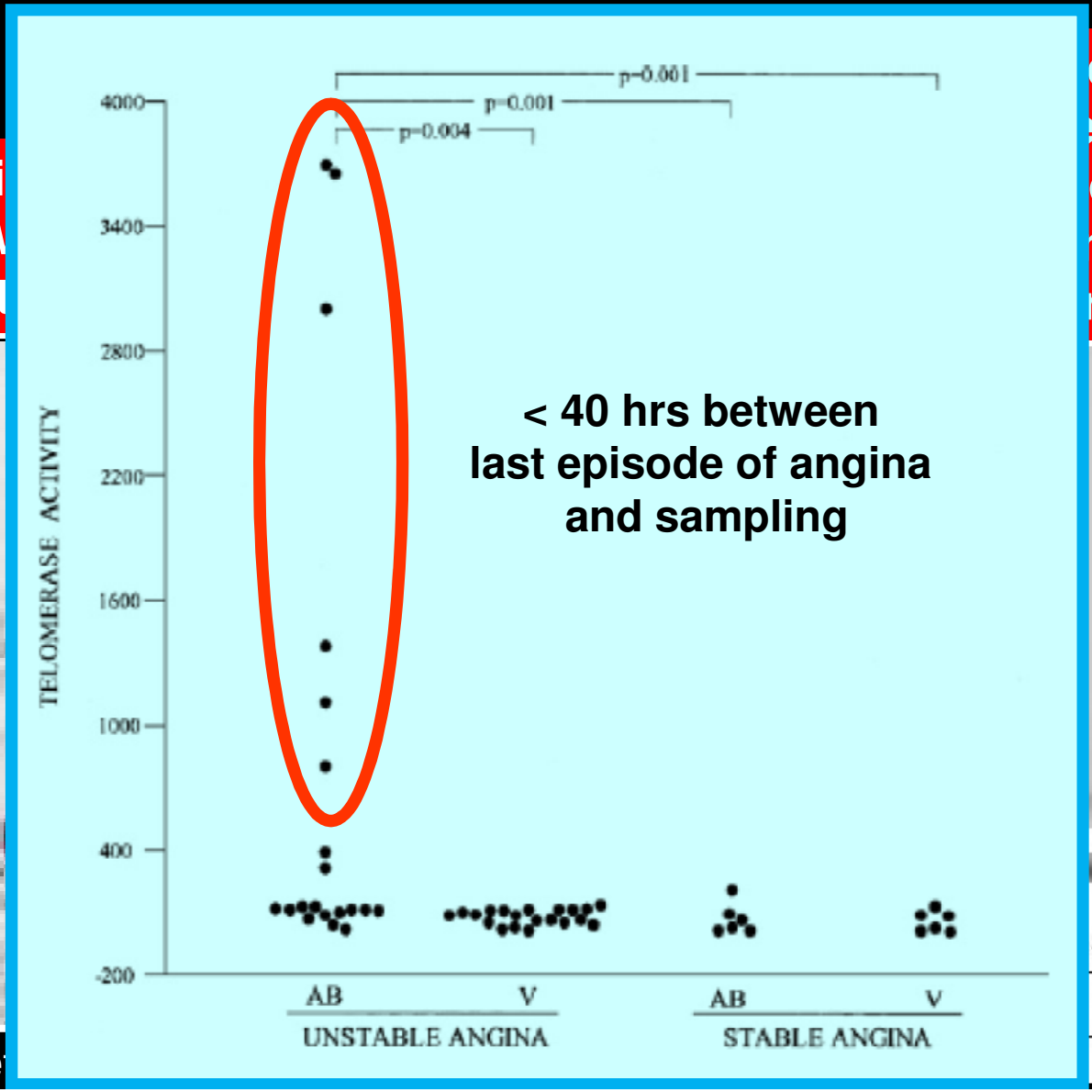

d from PMN
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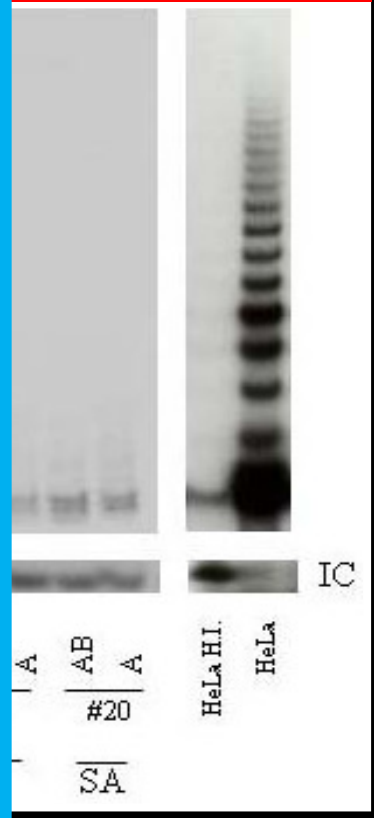
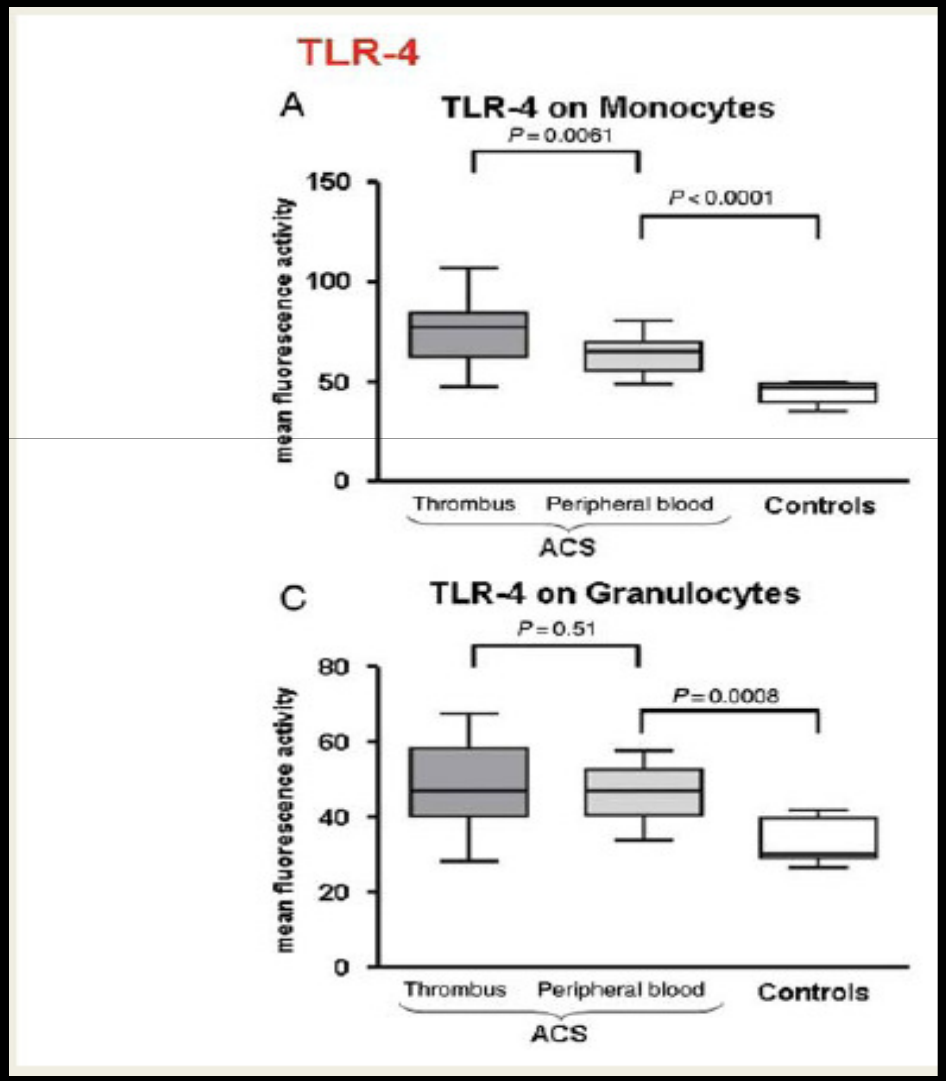
rase activity

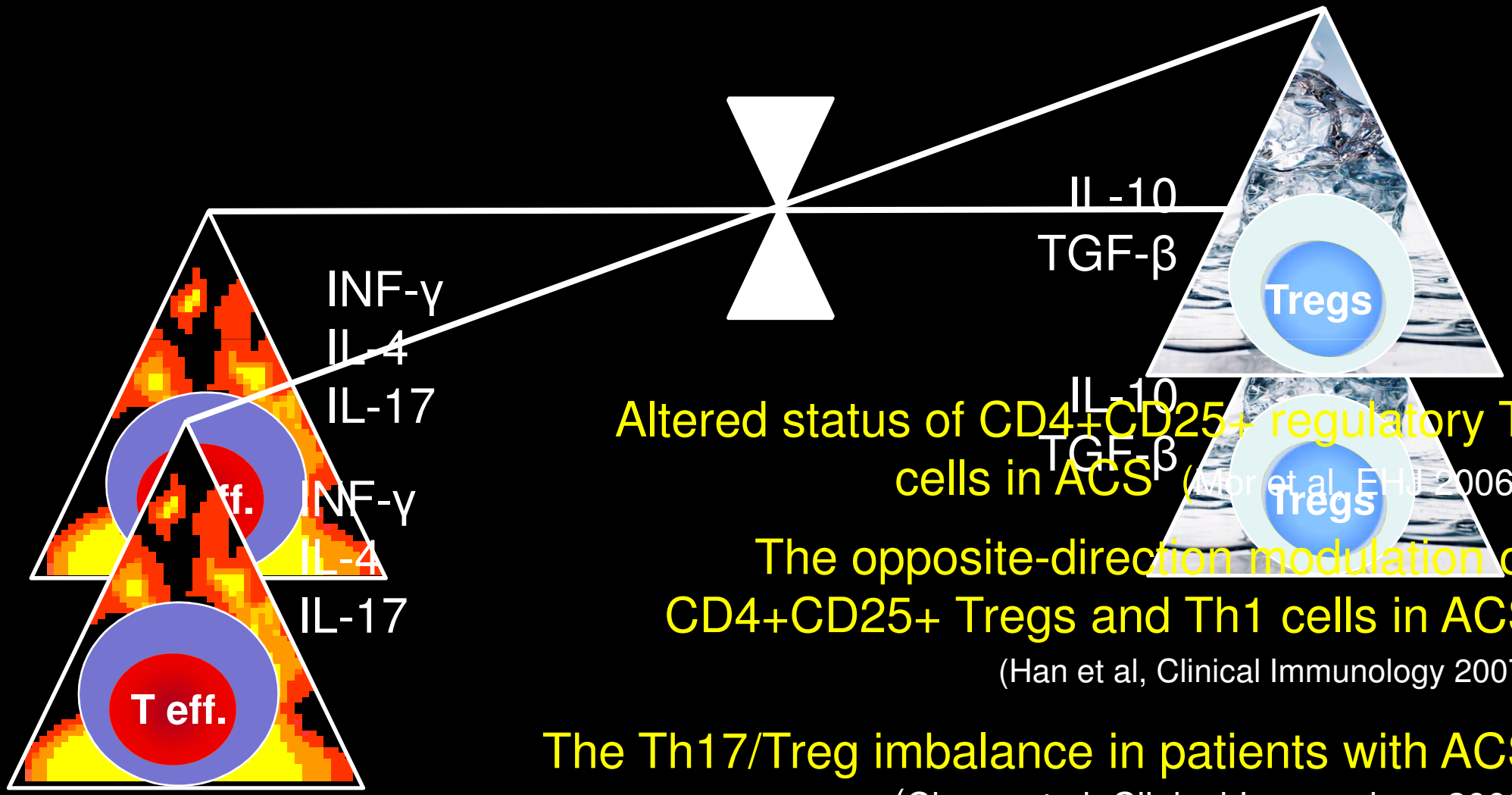


Activation of innate immunity in acute coronary syndromes (n=18)



(Wyss et al, EHJ 2010)

Perturbation of T cell balance in ACS

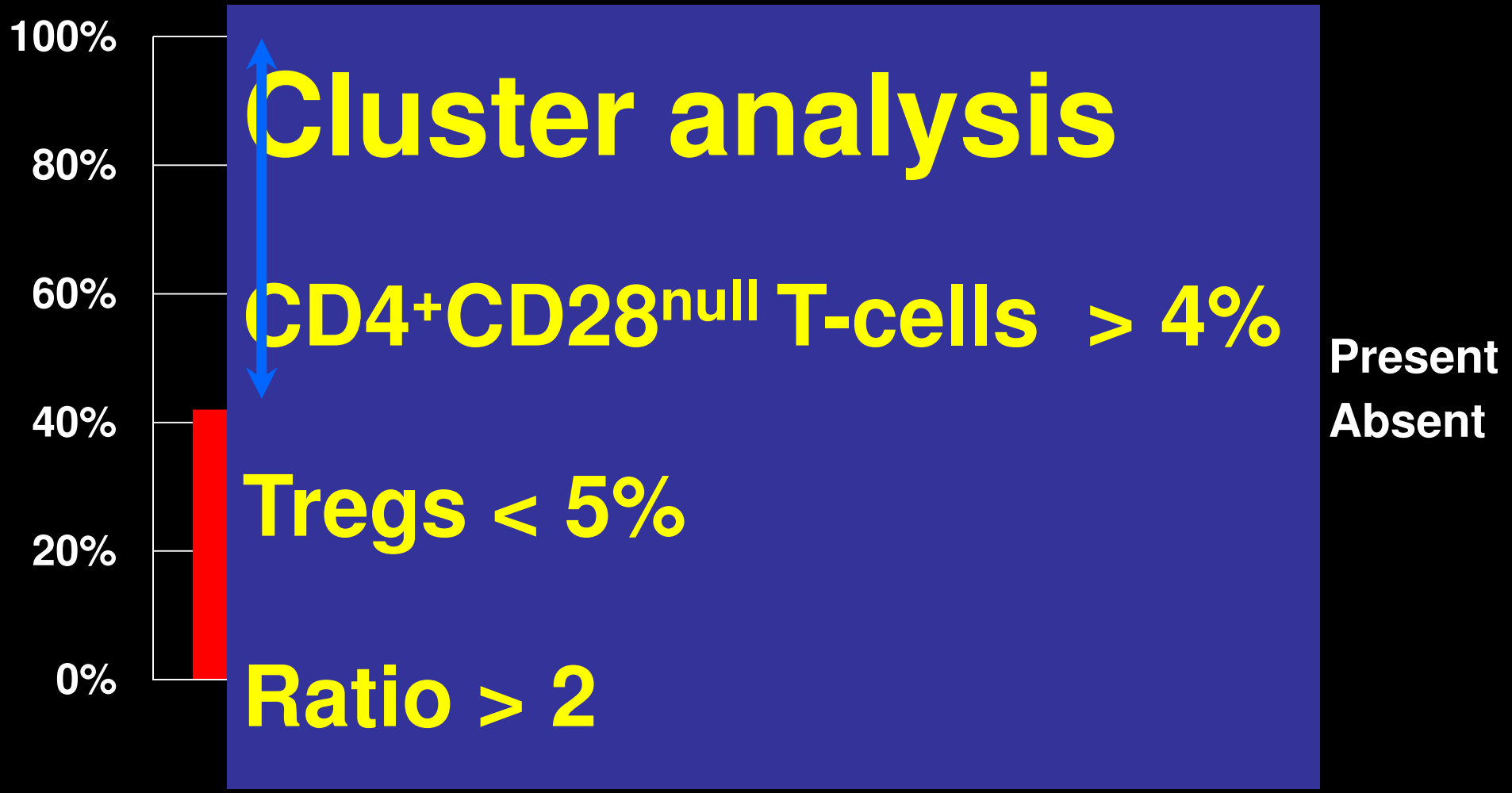


Altered status of CD4+CD25+ regulatory T cells in ACS (Mor et al, EHJ 2006)

The opposite-direction modulation of CD4+CD25+ Tregs and Th1 cells in ACS (Han et al, Clinical Immunology 2007)

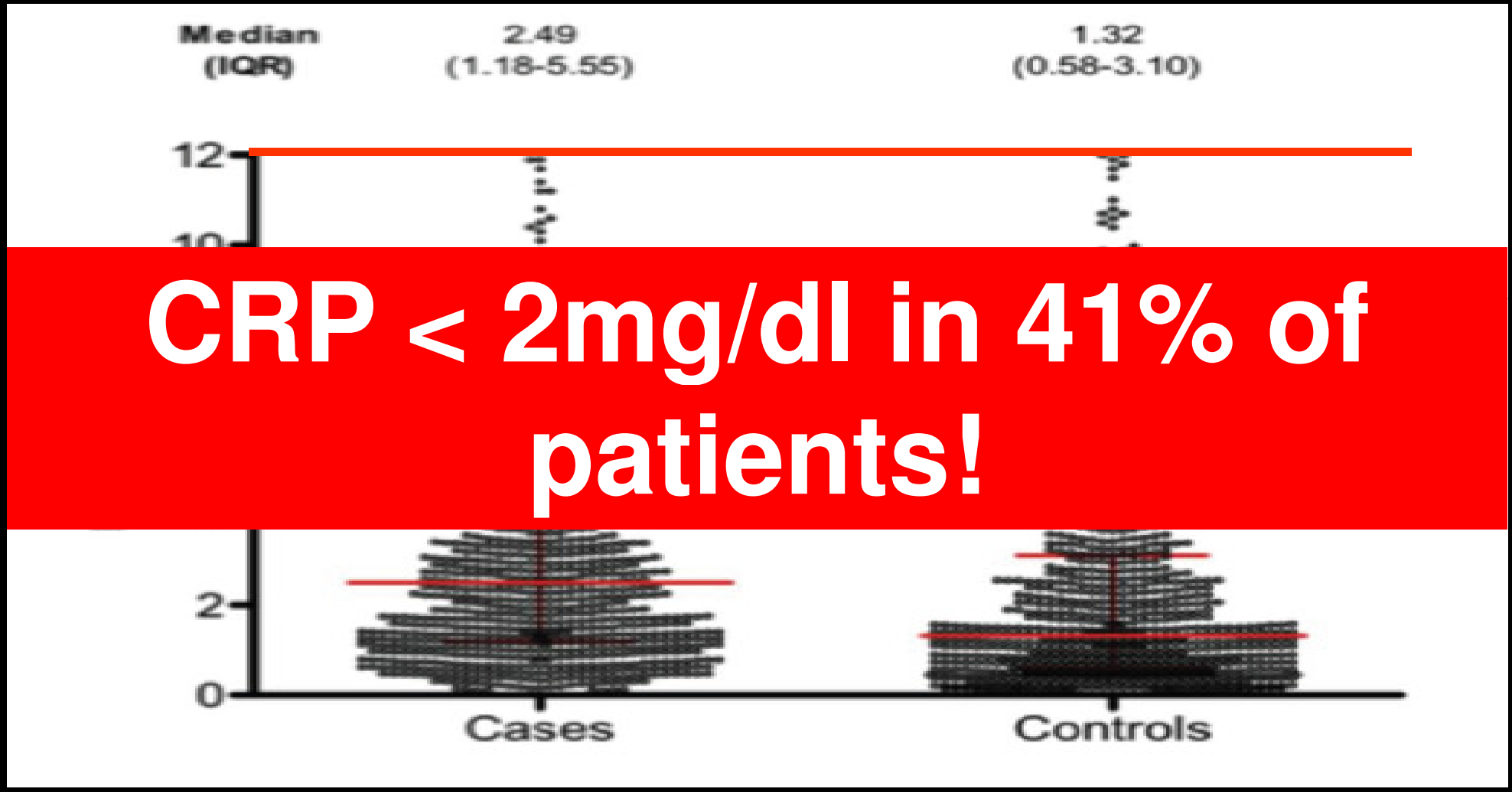
The Th17/Treg imbalance in patients with ACS (Cheng et al, Clinical Immunology 2008)

Cluster analysis according to T cell subsets and their ratio



(Liuzzo et al, submitted)

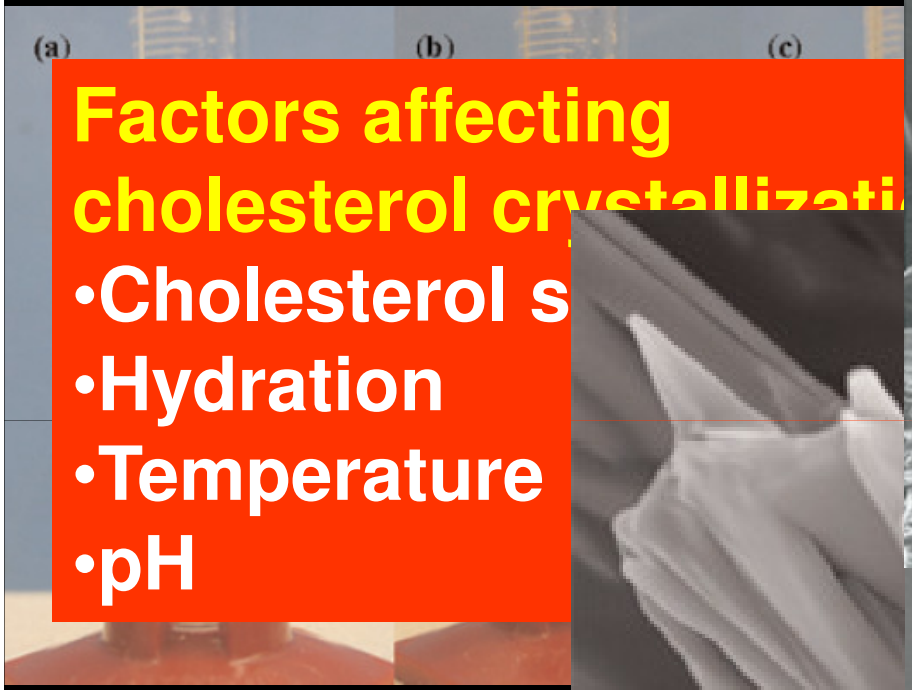
CRP levels at the very onset of first STEMI (n=1099)



CRP < 2mg/dl in 41% of patients!

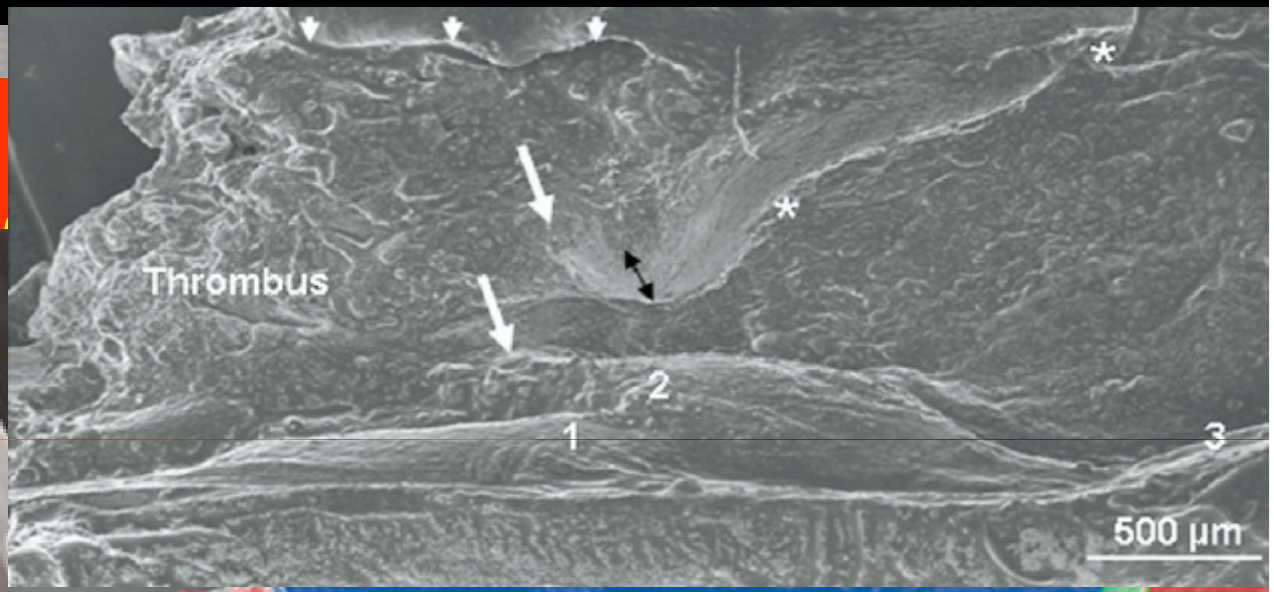
(Cianflone et al, JACC 2011)

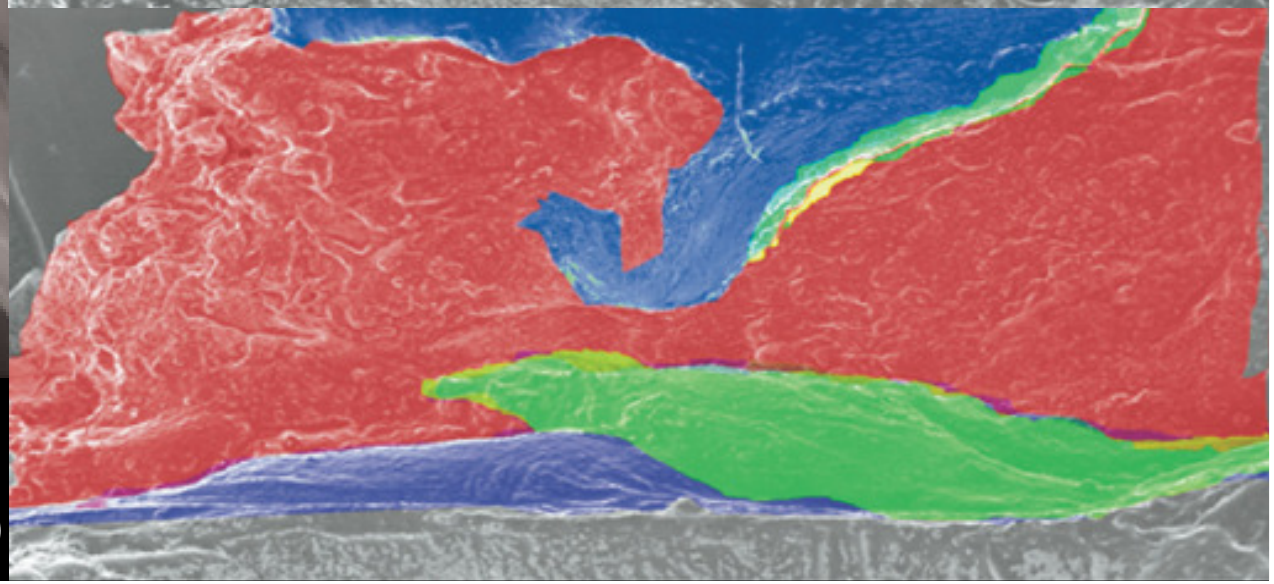
Mechanical triggers of plaque fissure: cholesterol crystals



Factors affecting cholesterol crystallizati

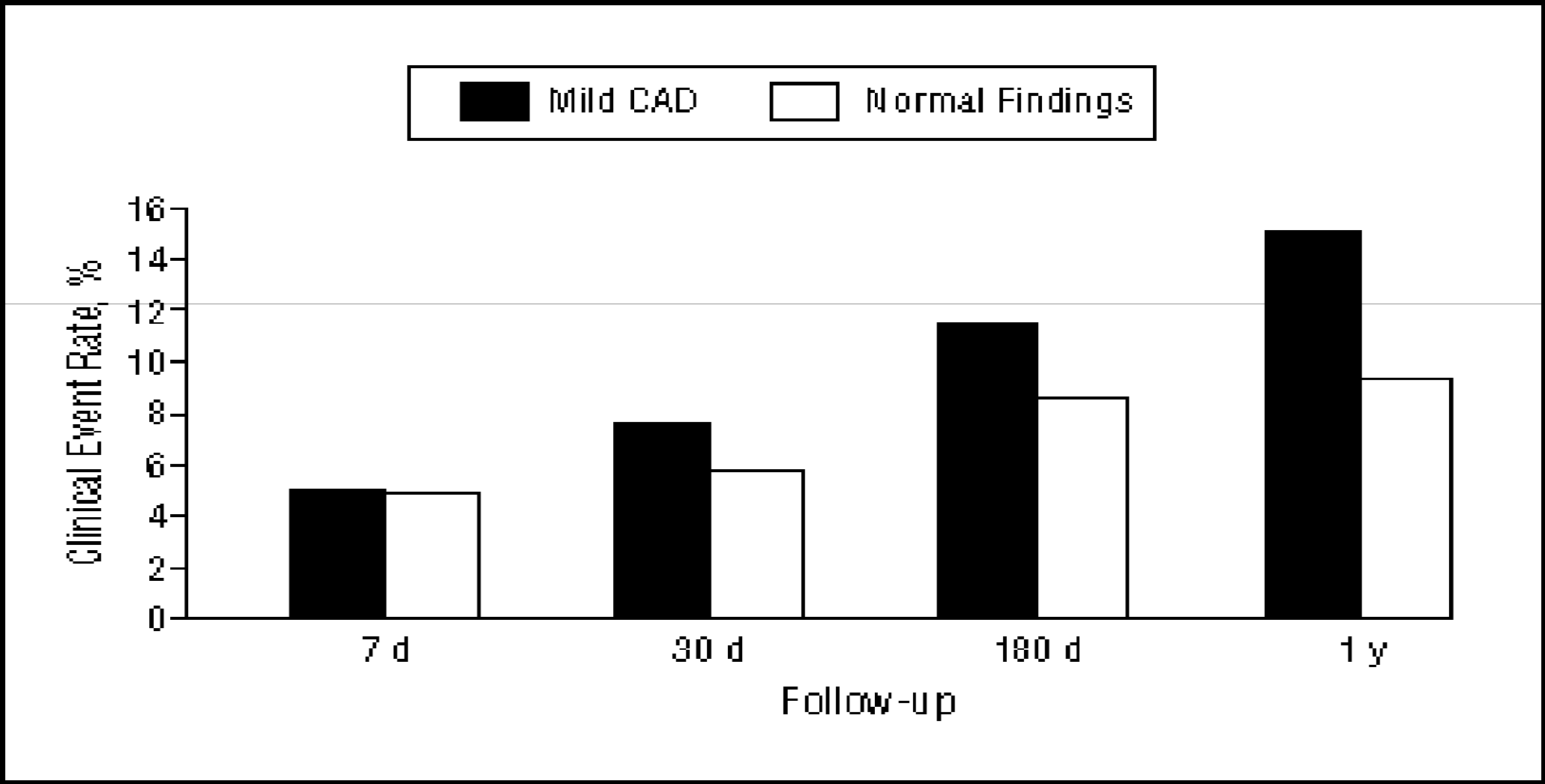
- Cholesterol s
- Hydration
- Temperature
- pH



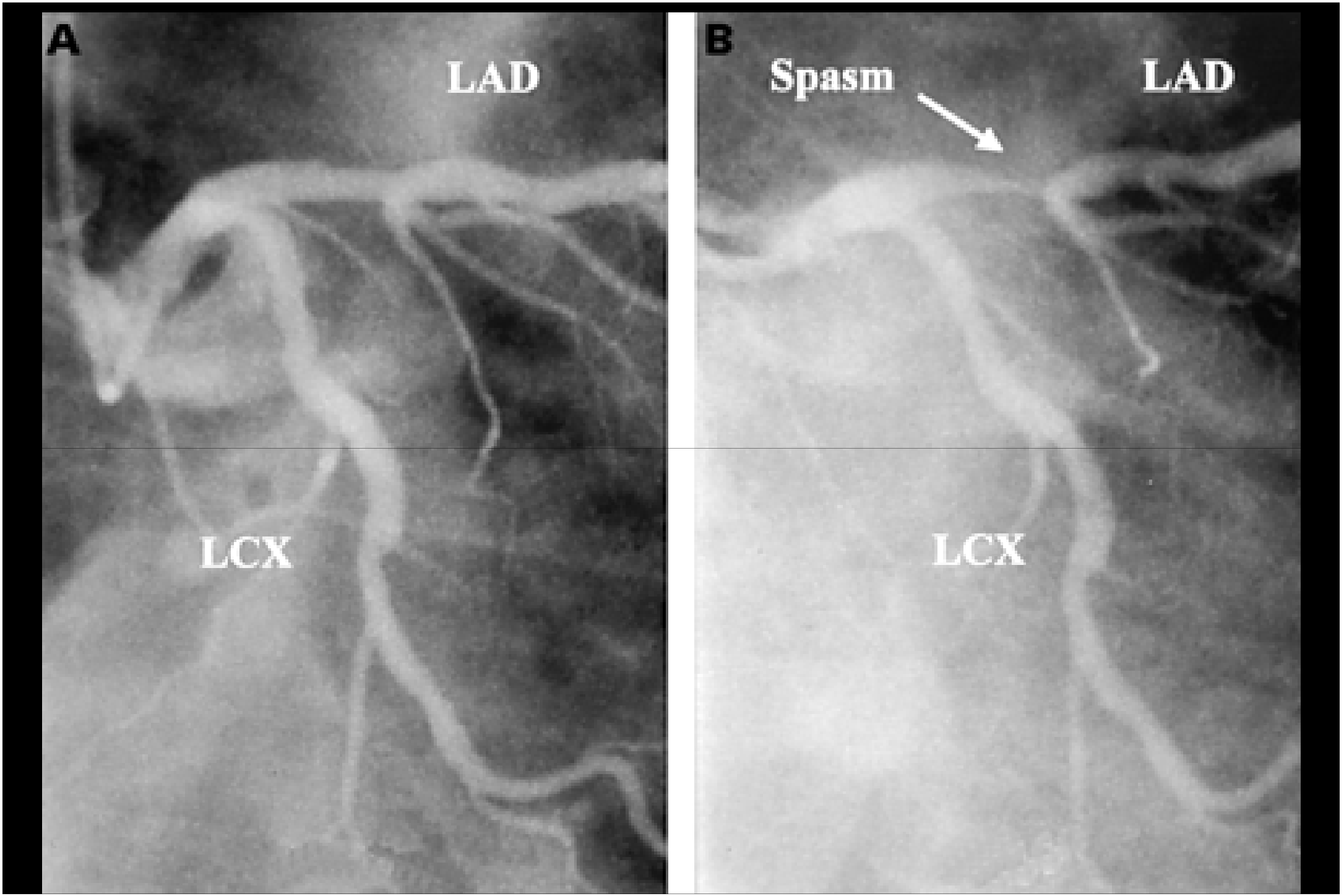


(Abela et al, Clin Cardiol 2005, AJC 2009)

Outcome of patients with NSTE-ACS and normal coronary arteries or mild CAD enrolled in TIMI 11B, TIMI 16 and TIMI 22 (9.1% of 7,656 patients)



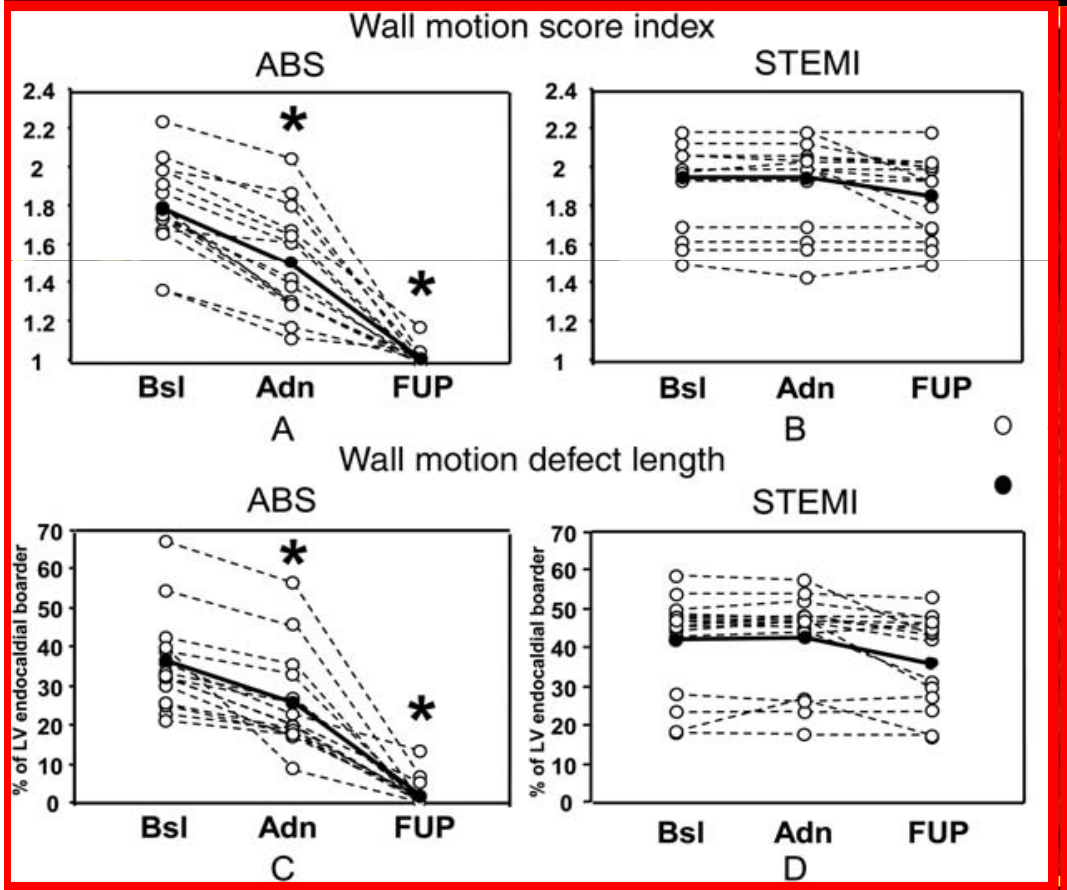
(Bugiardini et al, Arch Intern Med 2006)

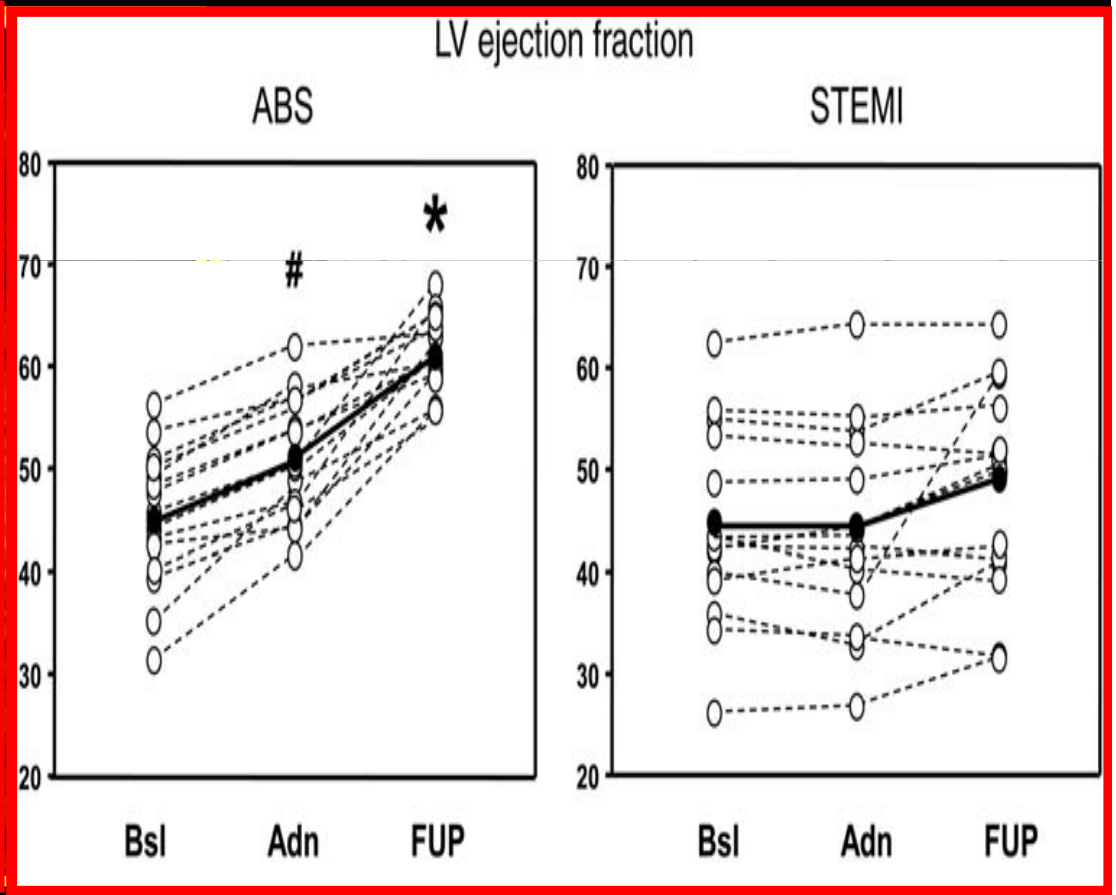

A
LAD
LCX
B
Spasm
LAD
LCX

Tako-Tsubo: role of coronary microvascular dysfunction

Perfusion defect at baseline

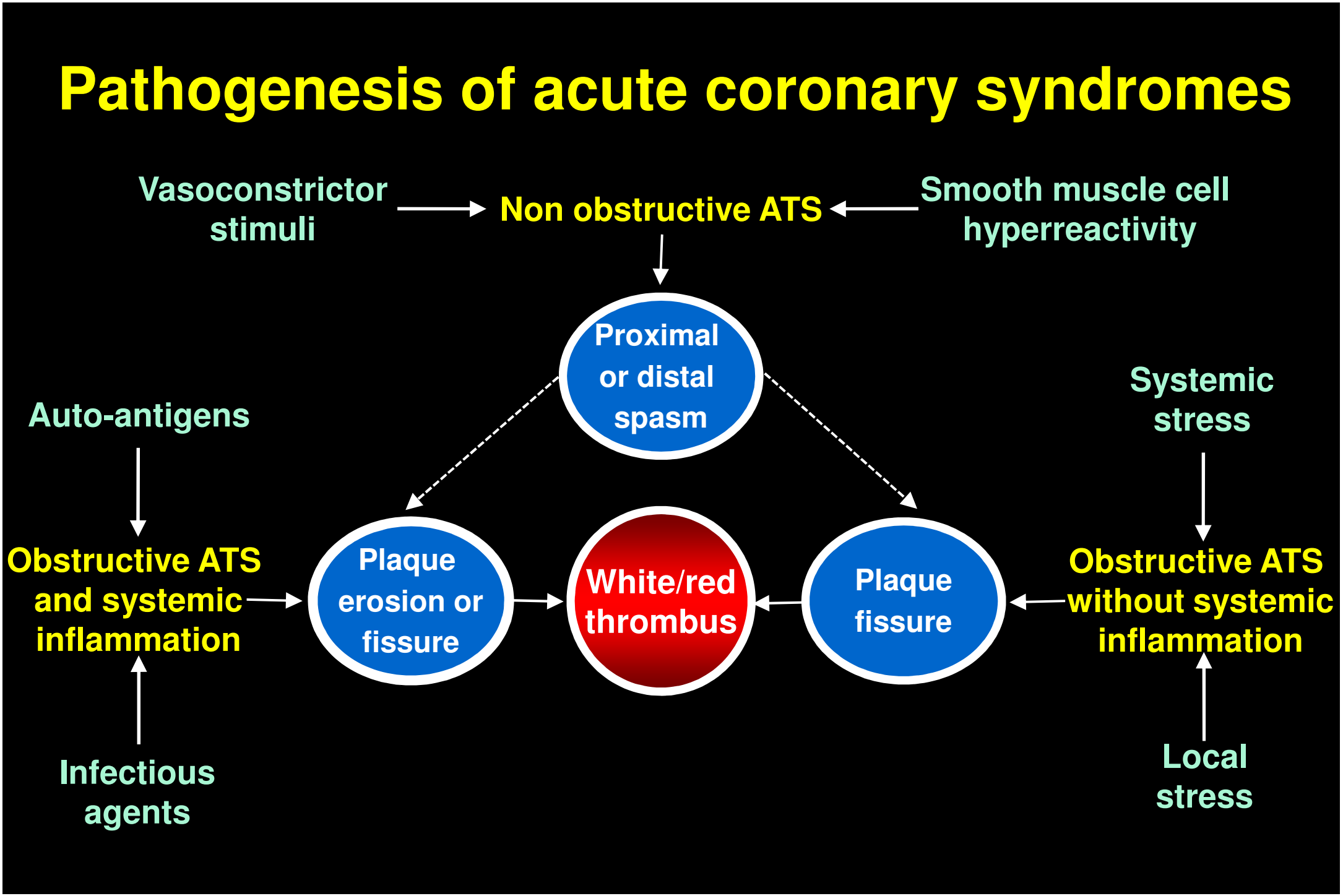
Transient improvement during ADN

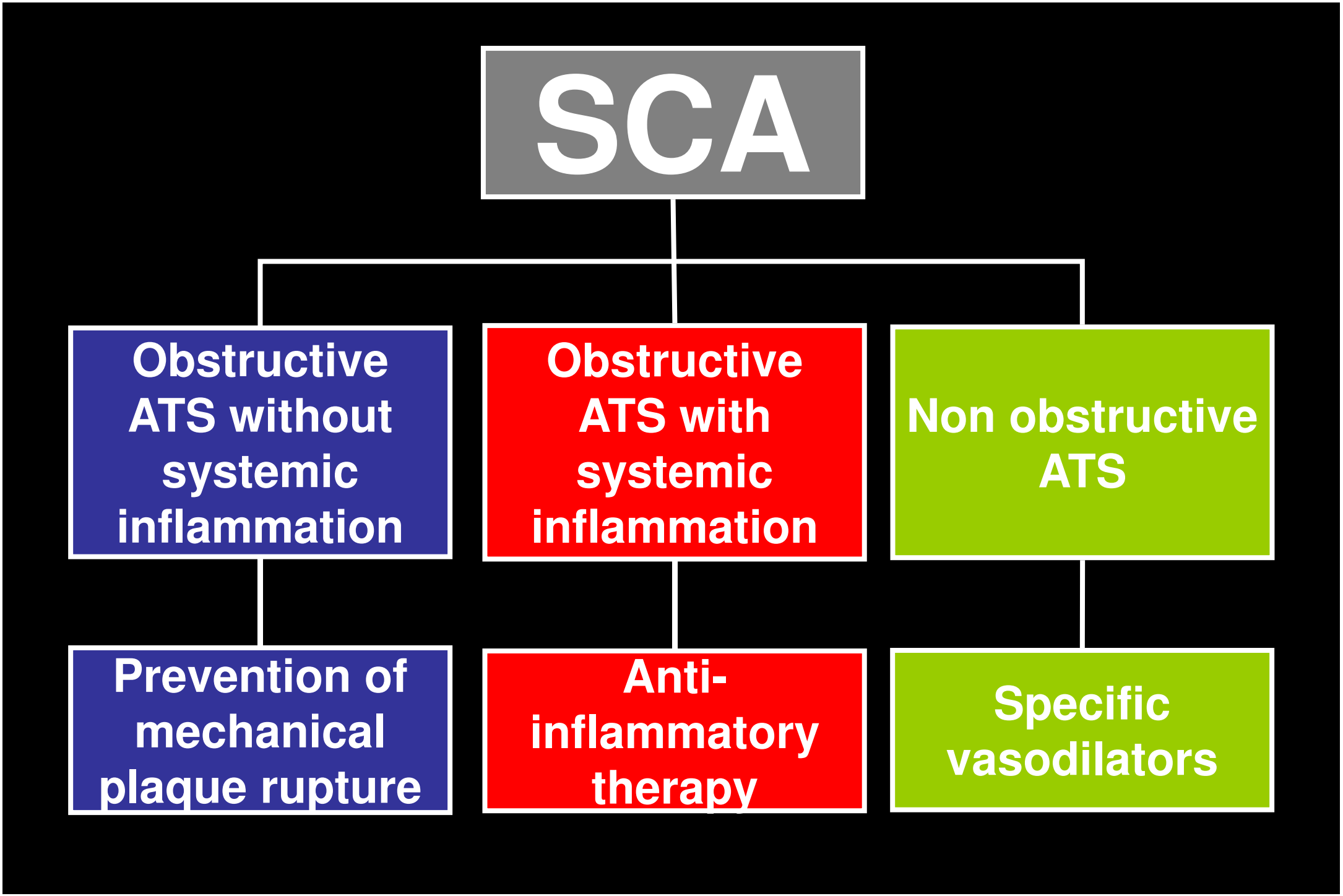




(Galiuto et al, EHJ 2010)

Pathogenesis of acute coronary syndromes




SCA
Obstructive ATS without systemic inflammation
Obstructive ATS with systemic inflammation
Non obstructive ATS
Prevention of mechanical plaque rupture
Anti-inflammatory therapy
Specific vasodilators

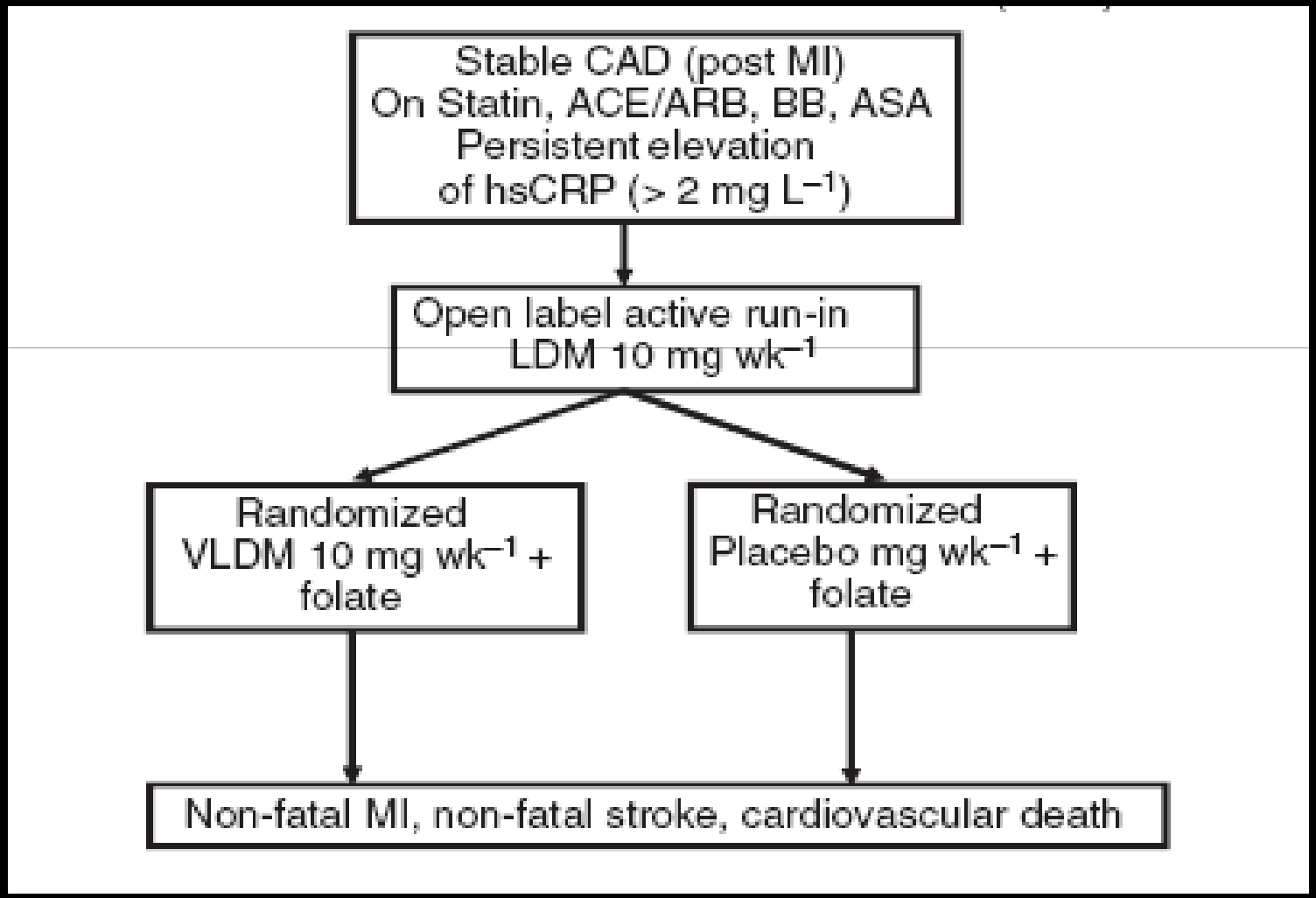
How to target inflammation in ACS?

DMARDs	• Methotrexate
Key cytokine blockers	• IL-1β blockers
T cell modulators	• Statins
Antibiotics Vaccines	• Influenza vaccination

Low dose methotrexate and CVD: observational evidence

Cohort	Group	HR* (95% CI)	Endpoint	Exposure
Wichita Choi 2002	RA	0.4 (0.2–0.8) 0.3 (0.2–0.7) 0.4 (0.3–0.8)	Total mortality CV mortality CV mortality	LDM LDM LDM < 15 mg wk^{-1}
Netherlands van Helm 2006	RA	0.3 (0.1–0.7) 0.2 (0.1–0.5) 0.2 (0.1–1.2) 0.2 (0.1–0.5)	CVD CVD CVD CVD	LDM only LDM + SSZ LDM + HCQ LDM + SSZ + HCQ
Miami VA Pradanovich 2005	Psoriasis RA 	0.7 (0.6–0.9) 0.5 (0.3–0.8) 0.8 (0.7–1.0) 0.6 (0.5–0.8)	CVD CVD CVD CVD	LDM LDM < 15 mg wk^{-1} LDM LDM < 15 mg wk^{-1}
CORRONA Solomon 2006	RA	0.6 (0.3–1.2) 0.4 (0.2–0.8)	CVD CVD	LDM TNF-inhibitor
QUEST-RA Narango 2008	RA	0.85 (0.8–0.9) 0.82 (0.7–0.9) 0.89 (0.8–1.0)	CVD MI Stroke	LDM LDM LDM
UK Norfolk 2008	RA, PSA	0.6 (0.4–1.0) 0.5 (0.3–1.1)	Total mortality CV mortality	LDM LDM

Cardiovascular inflammation reduction trial (CIRT)

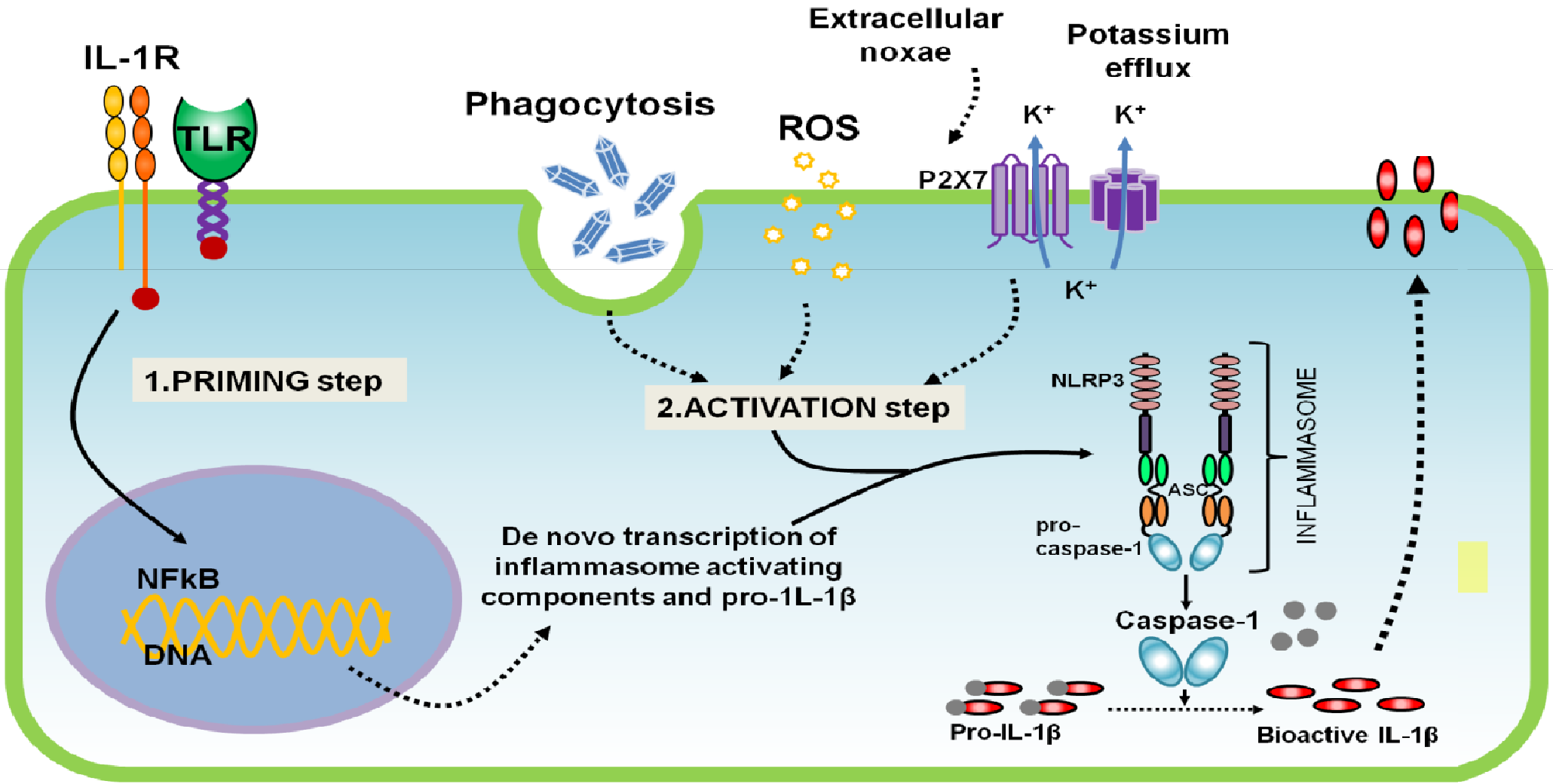


(Ridker et al , J Throm Haemost 2009)

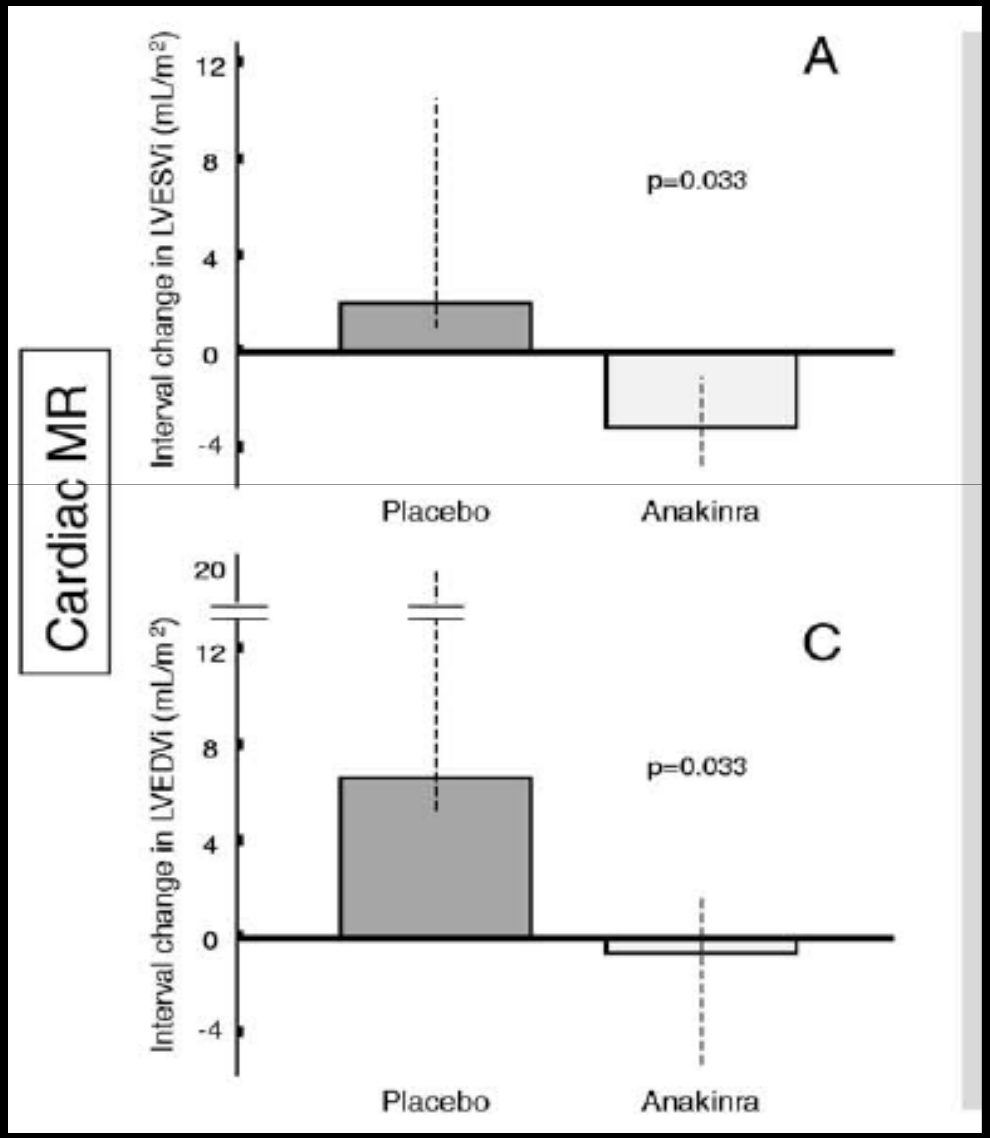
How to target inflammation in ACS?

DMARDs	• Methotrexate
Key cytokine blockers	• IL-1β blockers
T cell modulators	• Statins
Antibiotics Vaccines	• Influenza vaccination

IL-1β activation

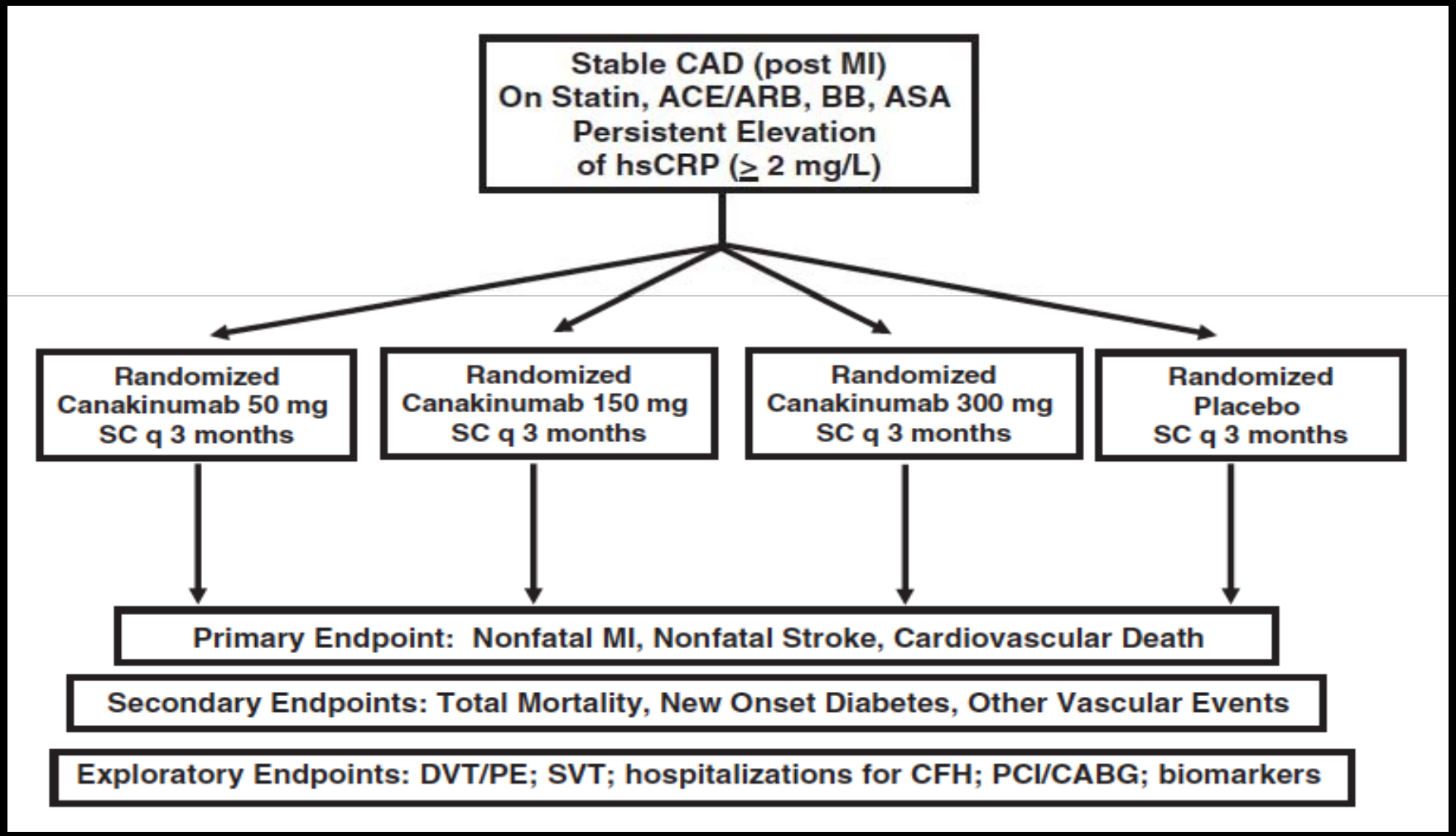


IL-1R blockade with anakinra prevents adverse cardiac remodeling after STEMI (n=10)



(Abbate et al, AJC 2010)

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

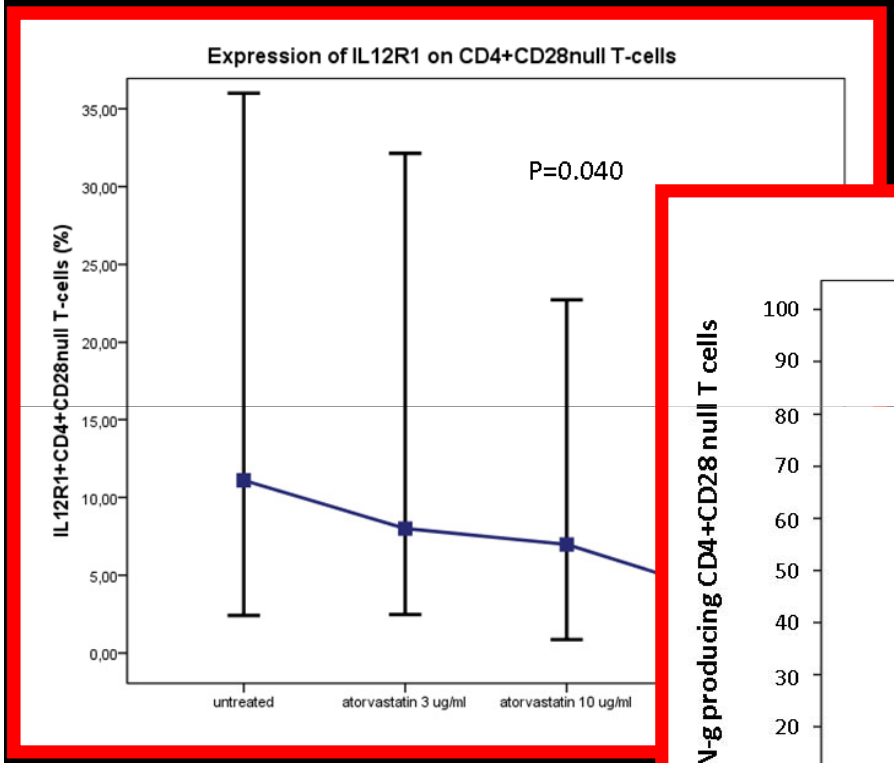


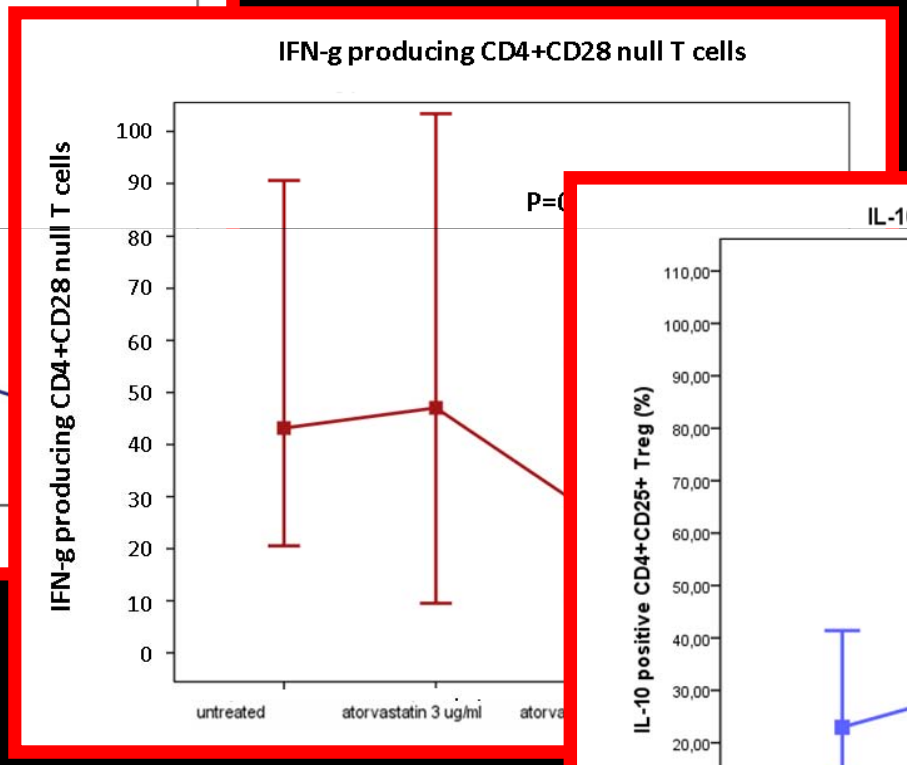
(Ridker et al , Am Heart J 2011)

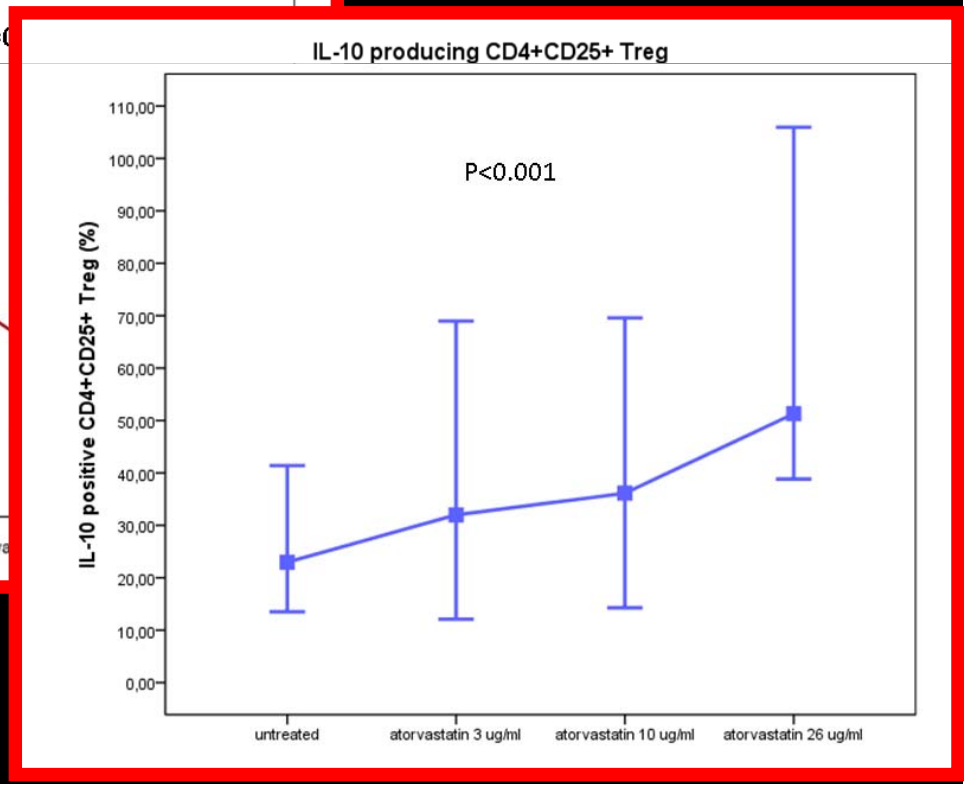
How to target inflammation in ACS?

DMARDs	• Methotrexate
Key cytokine blockers	• TNFα or IL-1β blockers
T cell modulators	• Statins
Antibiotics Vaccines	• Influenza vaccination

In vitro effects of atorvastatin on CD4+CD28null and on CD25+ T cells





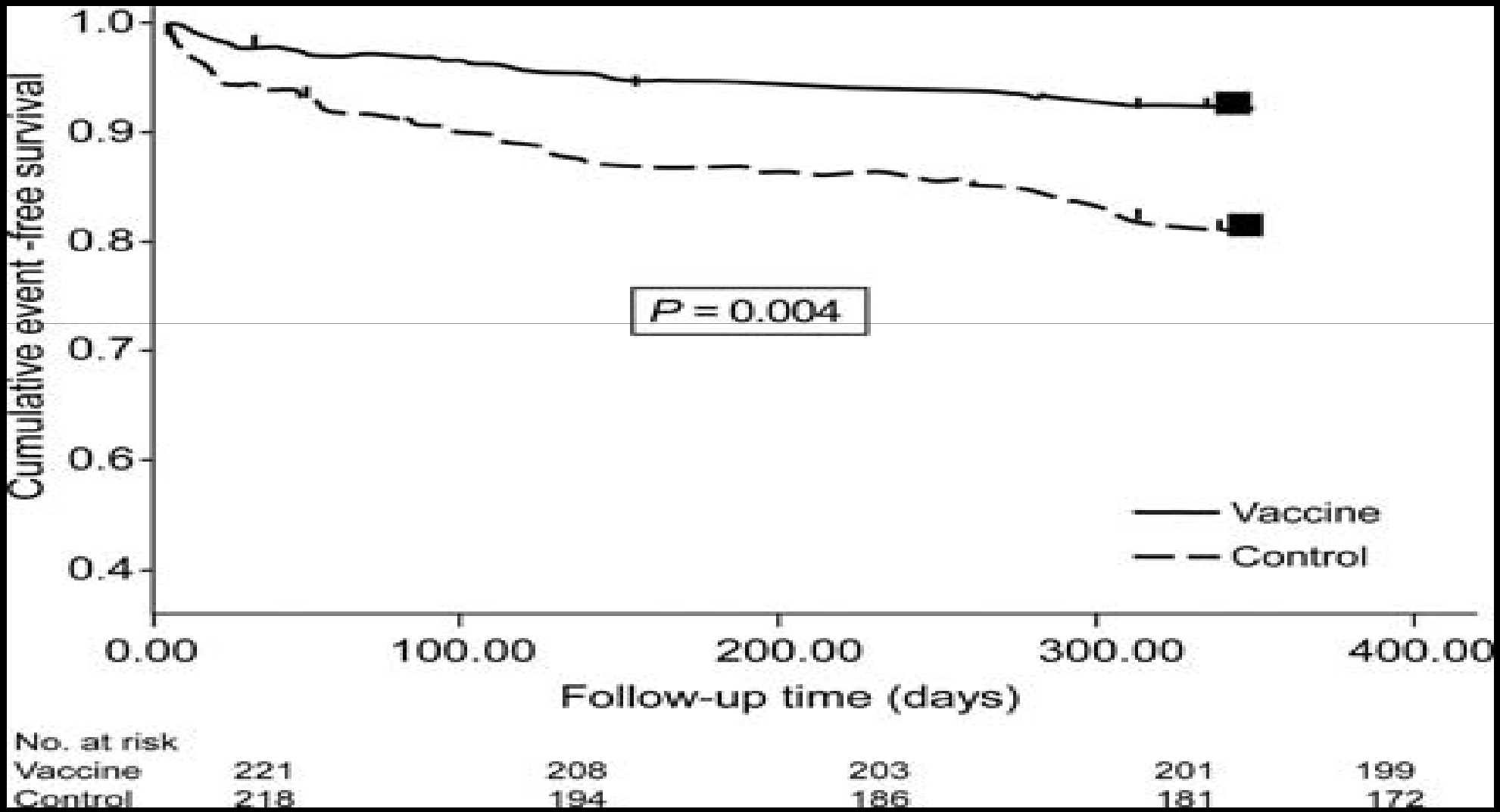


(Campioni et al, submitted)

How to target inflammation in ACS?

DMARDs	• Methotrexate
Key cytokine blockers	• IL-1β blockers
T cell modulators	• Statins
Antibiotics Vaccines	• Influenza vaccination

Influenza vaccination reduces cardiovascular events in patients with ACS (n=439)

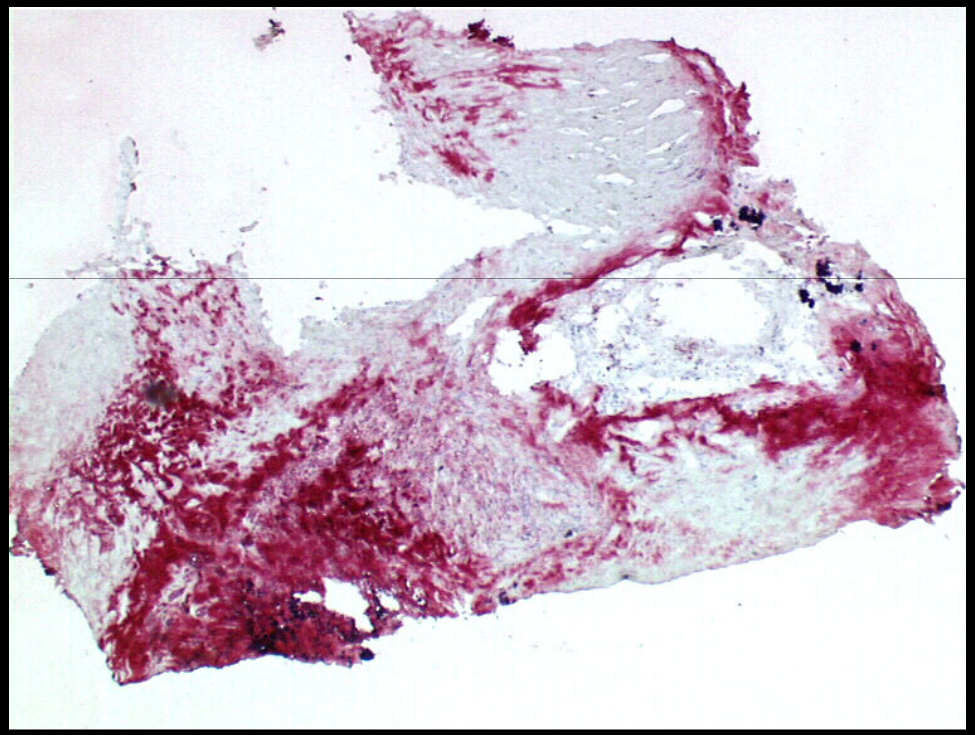


(Phrommintikul et al, EHJ 2011)

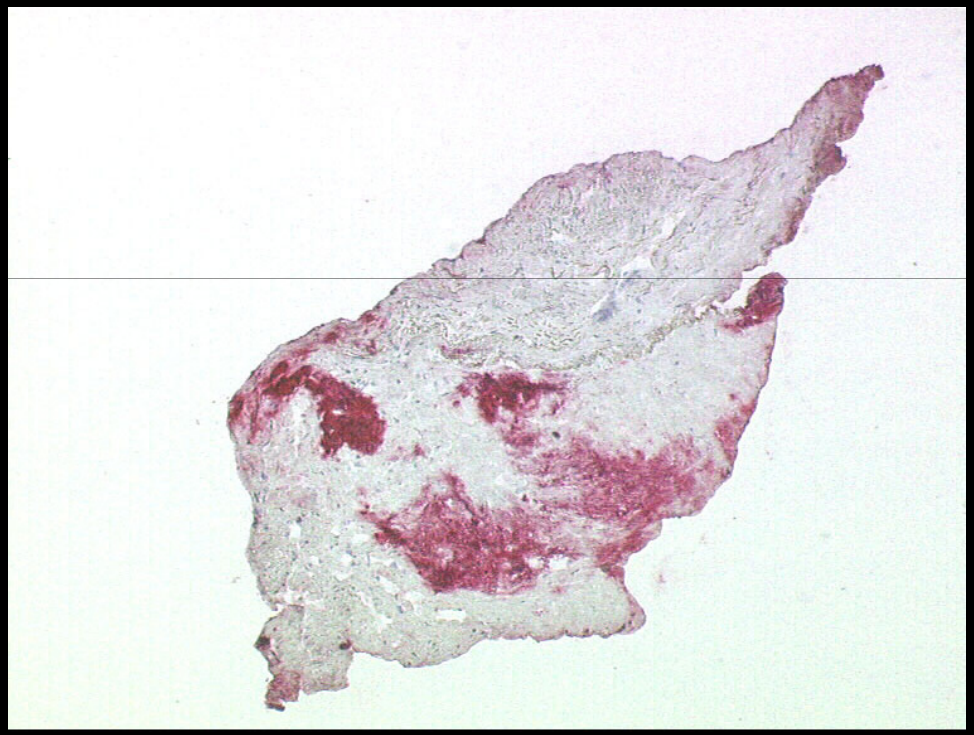
Anti-inflammatory treatment of ACS

- Innate immunity: ongoing CRT of methotrexate and of IL-1 blockers in ACS are testing this therapeutic target
- Adaptive immunity: T cell repertoire perturbation is a potential new target which needs to be tested in CRT
- Triggers: the promising results with influenza vaccination suggests that reduction of infectious burden is another potential new target

Ox-LDL in atherectomy specimens from stable and unstable plaques



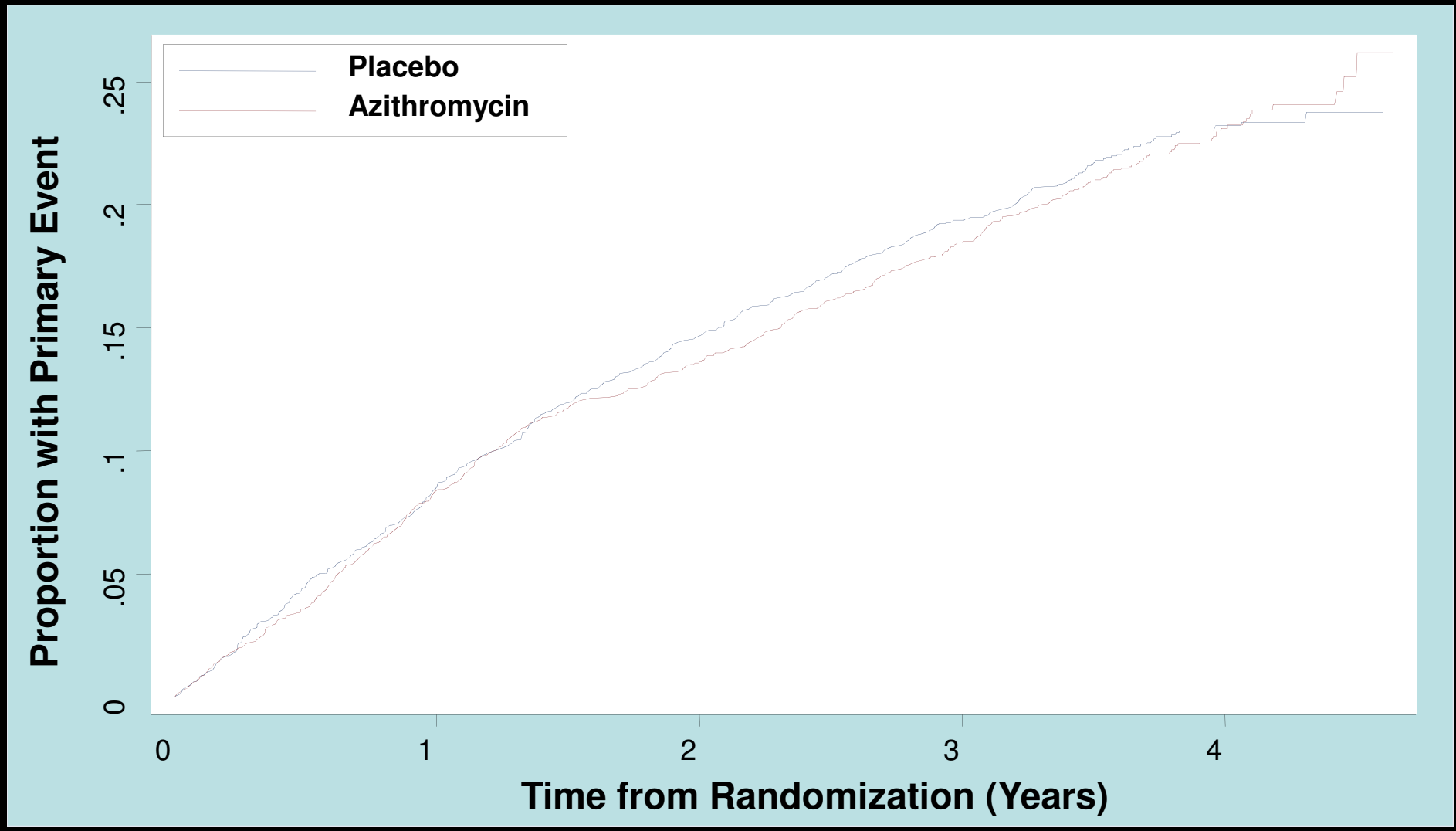
Stable Angina



Unstable angina

(Niccoli et al, J Cardiovasc Med 2007)

ACES: Primary Endpoint Rate



(Grayston et al, NRJM 2005)

Current Pharmaceutical Design, 2011, *17*, 000-000

Anti-inflammatory Treatment of Acute Coronary Syndromes

R. Della Bona, G. Liuzzo, D. Pedicino, and F. Crea*

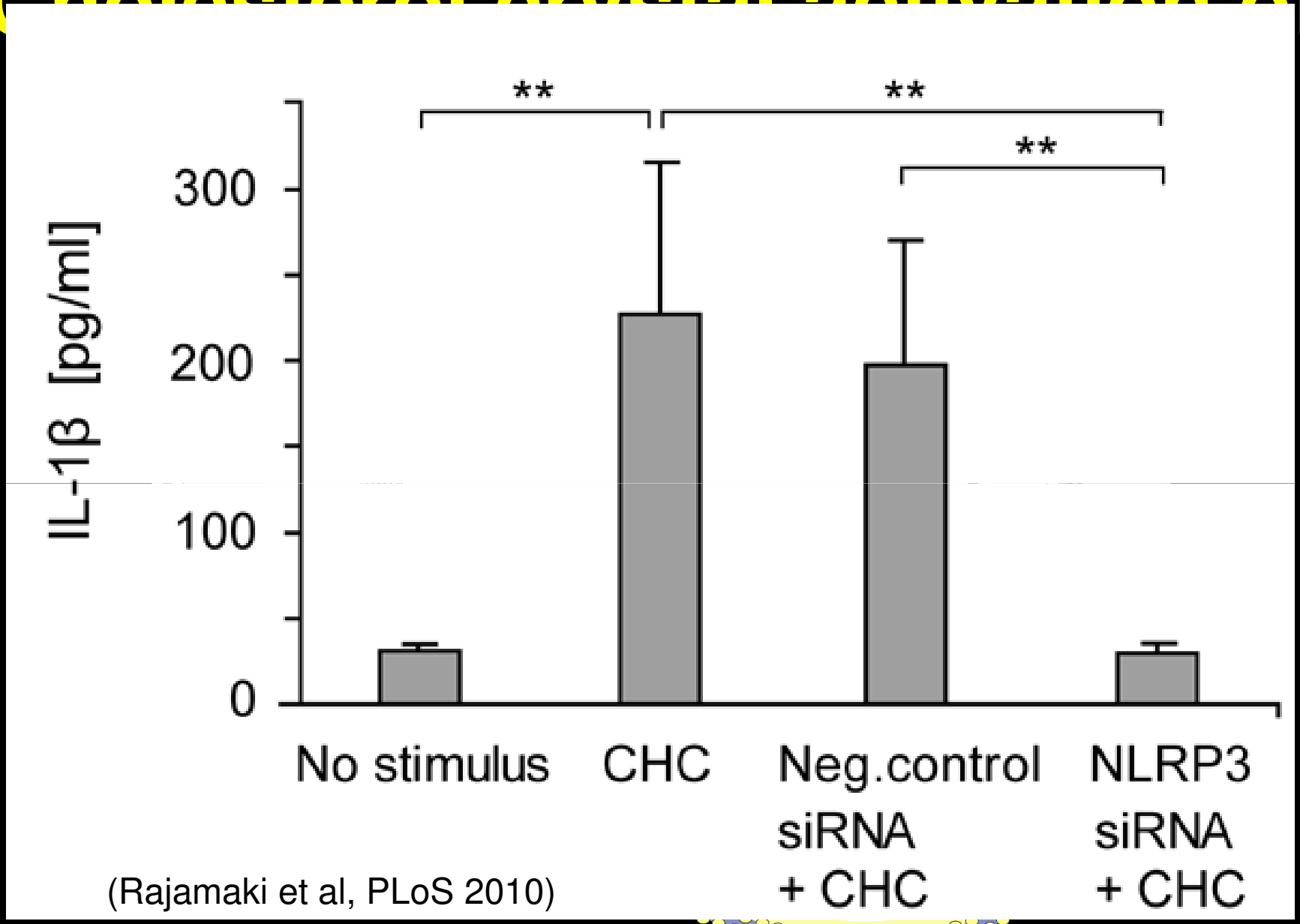
Institute of Cardiology, Catholic University, Rome, Italy

Abstract: The past decade has seen a steady growth in the treatment options available for Acute Coronary Syndromes (ACS), as a consequence of our better understanding of ACS pathophysiology. Administration of fibrinolytics in ST-elevation myocardial infarction, and of potent antiplatelet and anticoagulant drugs in all ACS, has allowed us to considerably improve their outcome. Yet, the rate of adverse cardiac events at early follow-up ranges from 15% to 20%. Thus, to further improve the outcome of ACS or to prevent their occurrence, it is important to identify new therapeutic target.

A number of experimental and clinical studies have highlighted the key role of inflammation in all phases of atherosclerosis, from fatty streaks to disrupted plaques and raised levels of inflammatory markers have been associated to a poor outcome despite optimal treatment, including myocardial revascularization. In this review, we will focus on inflammation as a possible new therapeutic target of ACS, discussing the anti-inflammatory treatments in four sections: 1) non specific anti-inflammatory drugs; 2) specific antagonists of key cytokines; 3) T-cell modulation; 4) immunization as promising therapeutic modality against atherosclerosis.

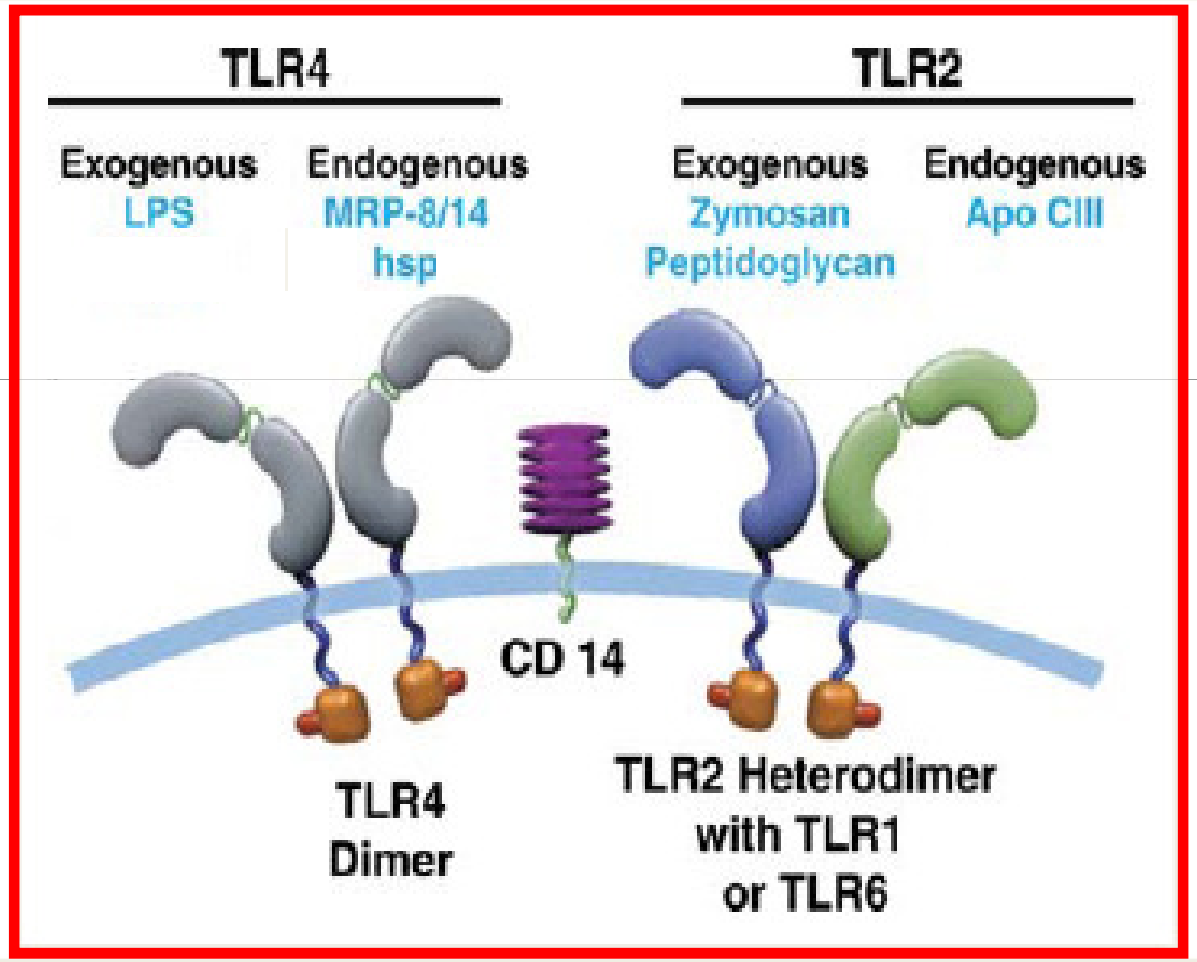
Keywords: Acute Coronary Syndrome, Inflammation, Methotrexate, Glucocorticoids, Statins, NSAIDs, COX, Key cytokines antagonists, TNF, IL-1, T-cells.

Cholesterol crystal activation of



(Rajamaki et al, PLoS 2010)

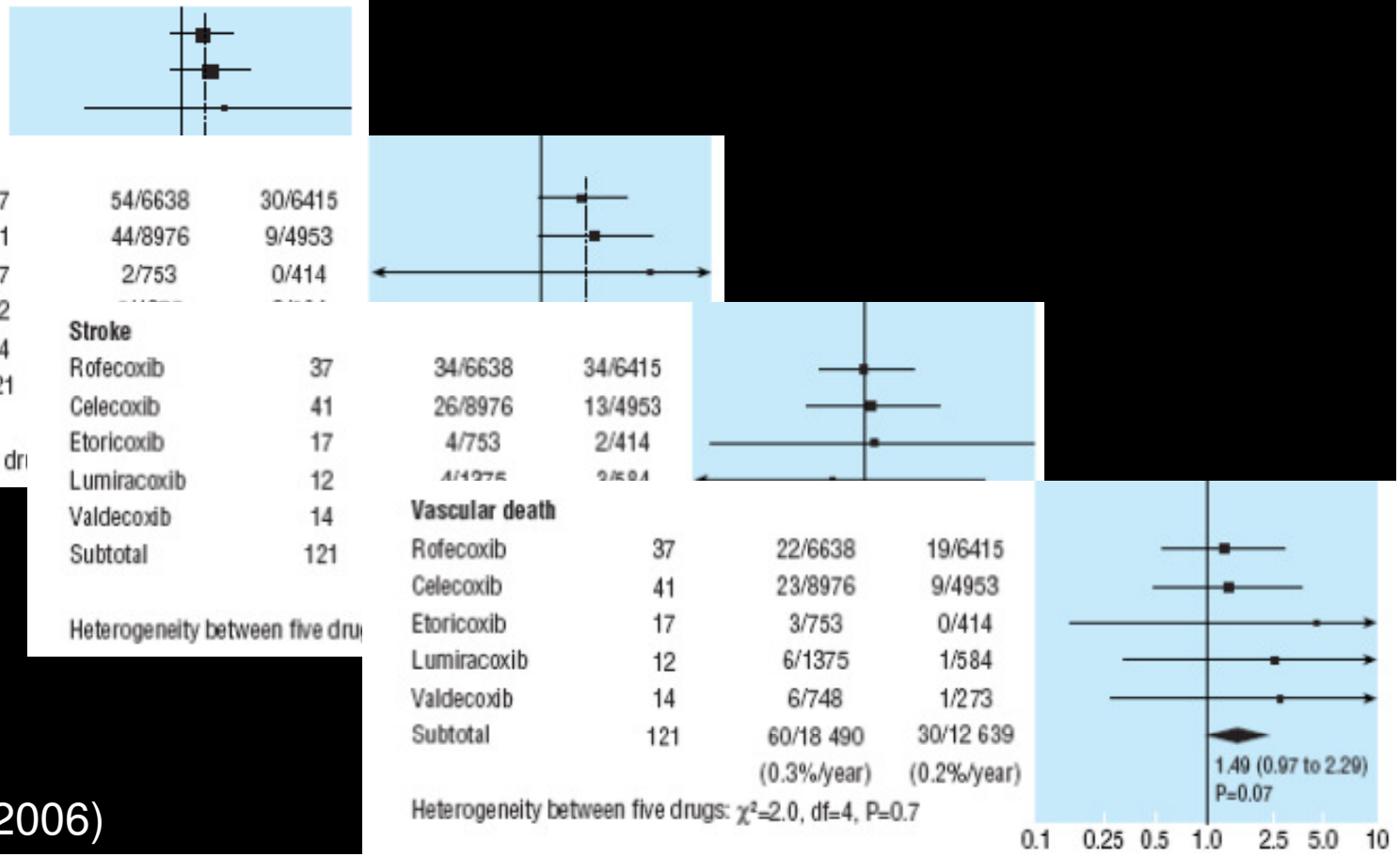
Activation of innate immunity



(Wyss et al, EHJ 2010)

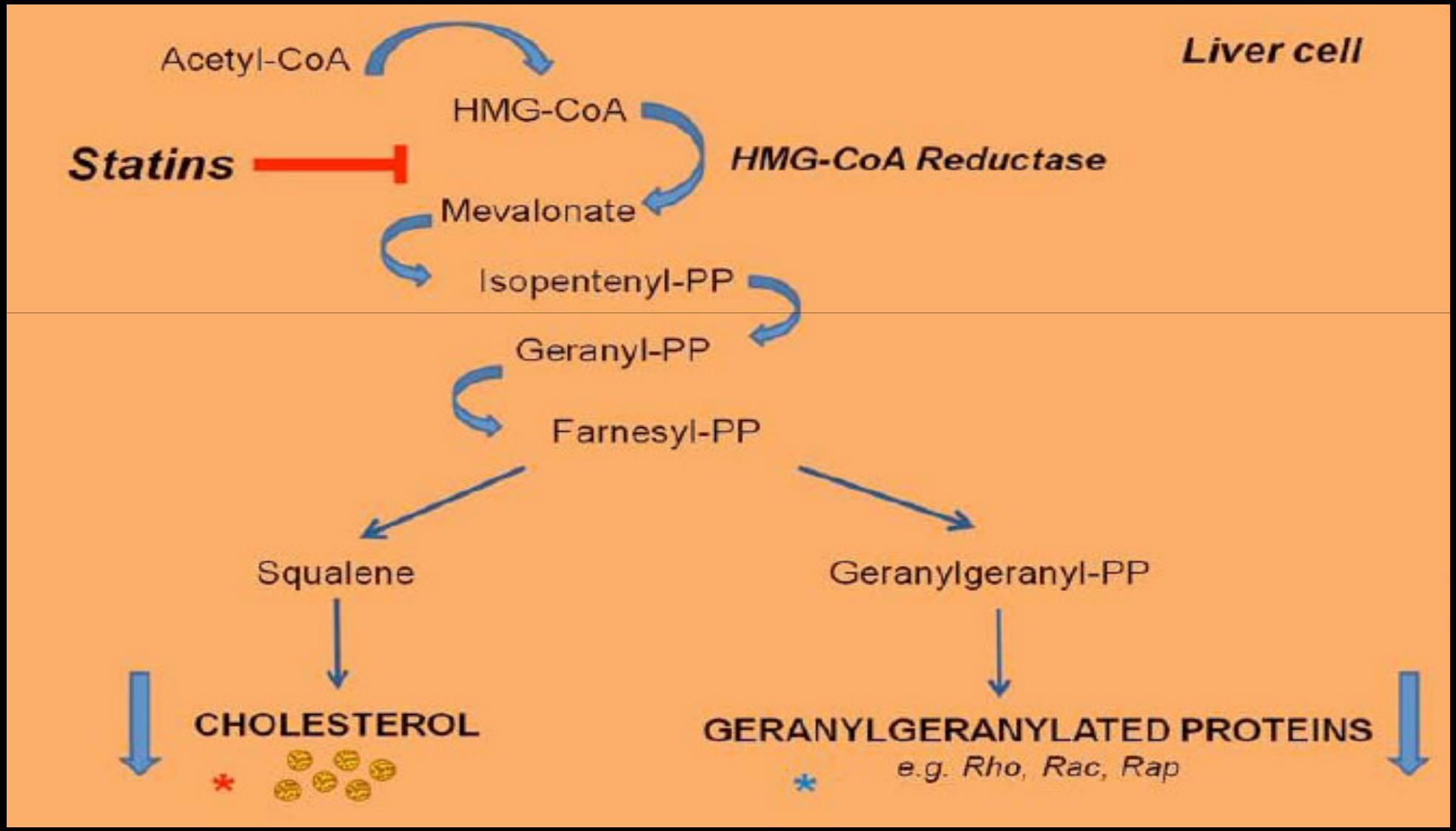
COX-2 inhibition and risk of CV events: meta-analysis of randomised trials

COX 2 inhibitor	No of trials	Events/person years: Allocated COX 2 inhibitor	Events/person years: Allocated placebo
Vascular events			
Rofecoxib	37	98/6638	72/6415
Celecoxib	41	84/8976	29/4953
Etoricoxib	17	7/753	2/414
Lumiracoxib	12		
Valdecoxib	14		
Subtotal	121		
Heterogeneity between five drugs:			
Myocardial infarction			
Rofecoxib	37	54/6638	30/6415
Celecoxib	41	44/8976	9/4953
Etoricoxib	17	2/753	0/414
Lumiracoxib	12		
Valdecoxib	14		
Subtotal	121		
Heterogeneity between five dr			
Stroke			
Rofecoxib	37	34/6638	34/6415
Celecoxib	41	26/8976	13/4953
Etoricoxib	17	4/753	2/414
Lumiracoxib	12		
Valdecoxib	14		
Subtotal	121		
Heterogeneity between five dru			
Vascular death			
Rofecoxib	37	22/6638	19/6415
Celecoxib	41	23/8976	9/4953
Etoricoxib	17	3/753	0/414
Lumiracoxib	12	6/1375	1/584
Valdecoxib	14	6/748	1/273
Subtotal	121	60/18 490 (0.3%/year)	30/12 639 (0.2%/year)
Heterogeneity between five drugs: χ^2=2.0, df=4, P=0.7			

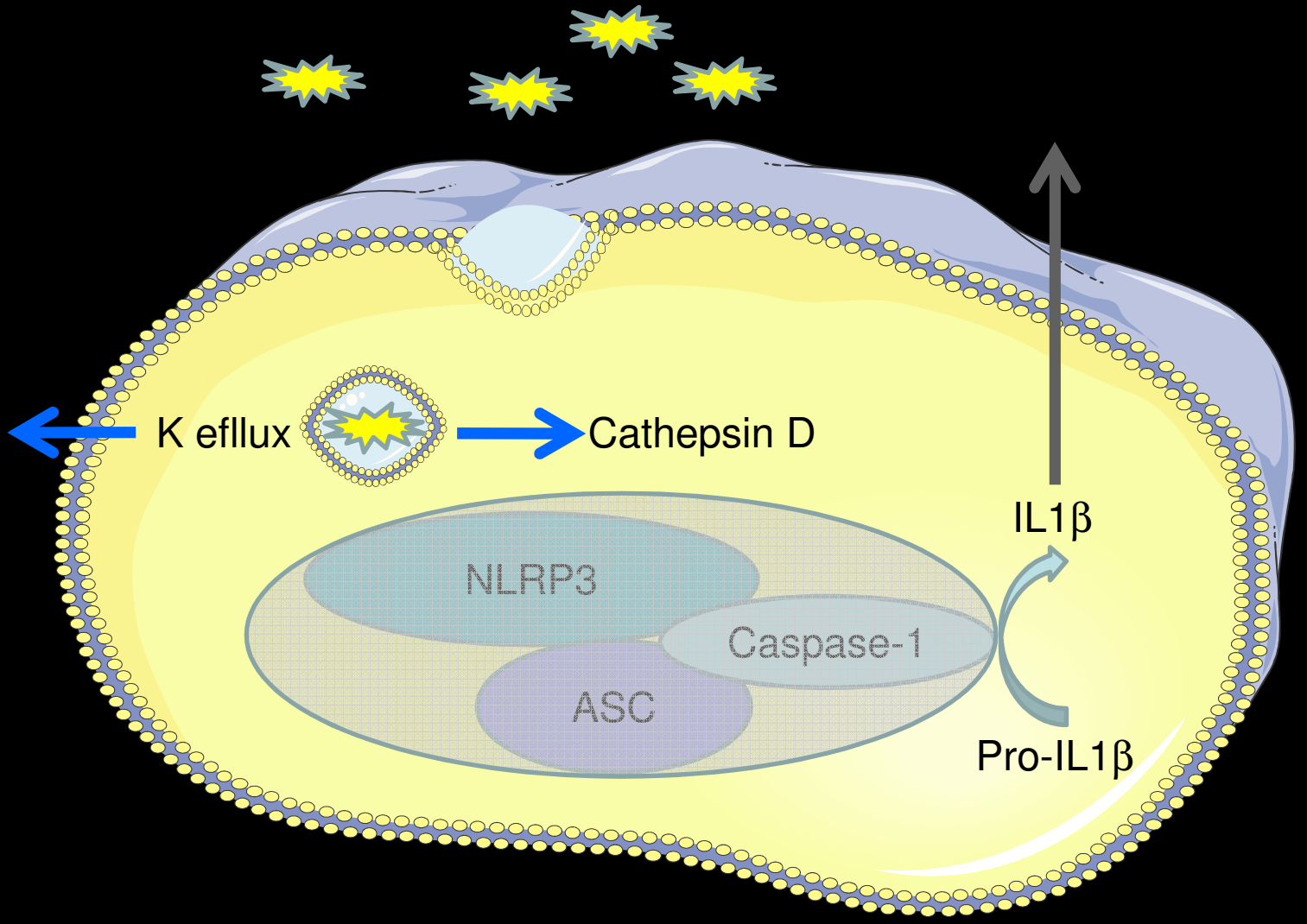


(Kearney et al, BMJ 2006)

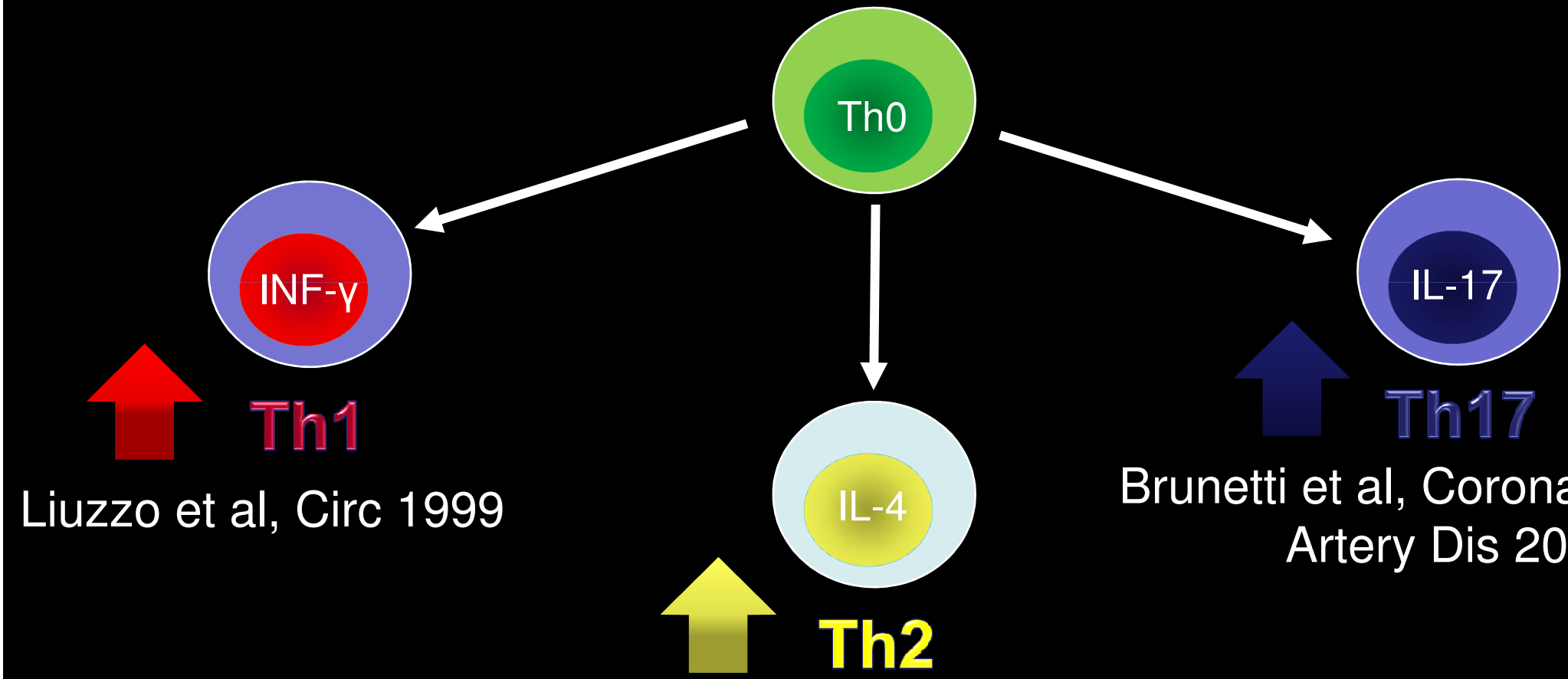
Mechanisms of anti-inflammatory action of statins



Cholesterol crystal activation of inflammasome



Activation of adaptive immunity

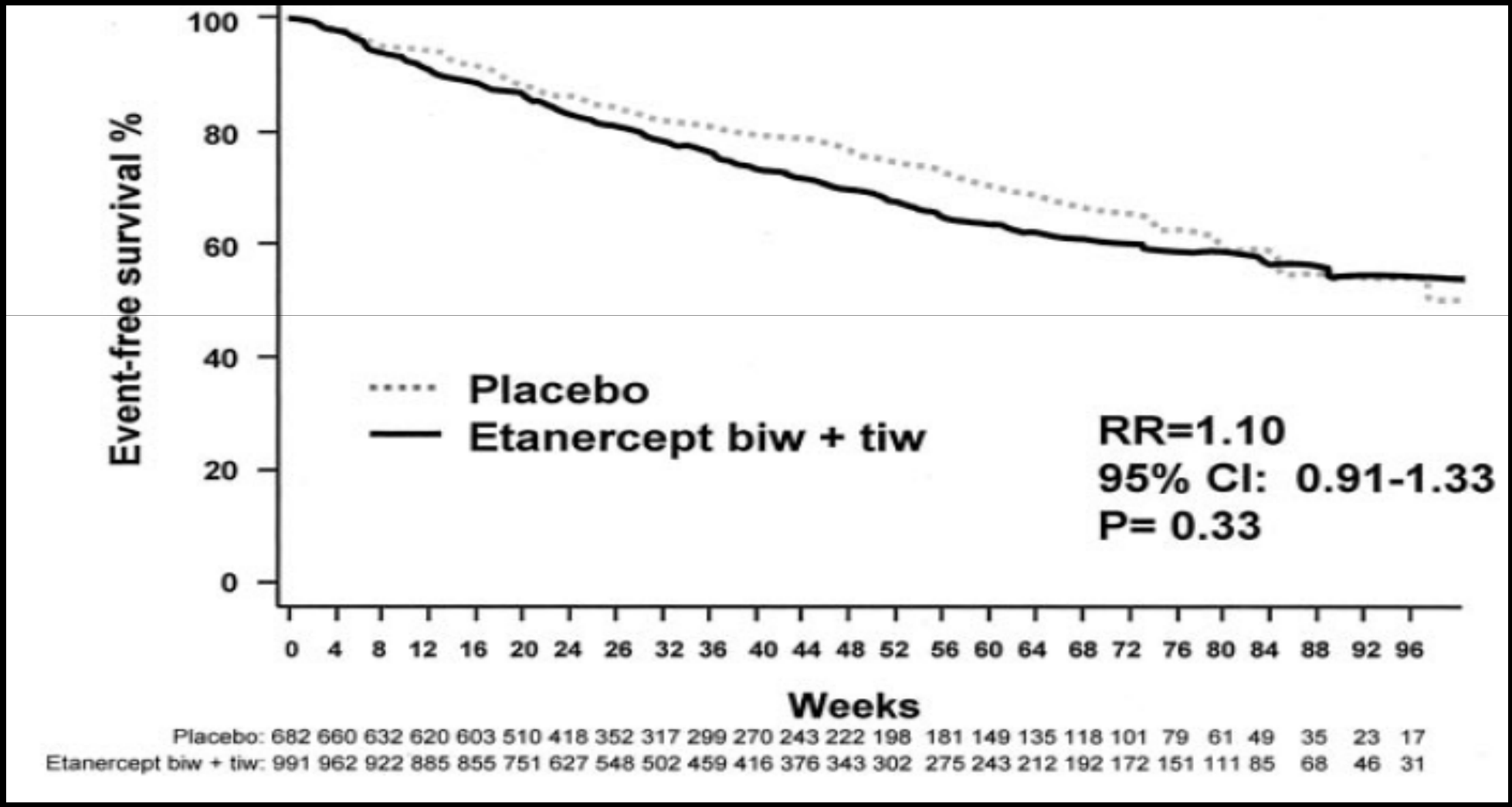


Liuzzo et al, Circ 1999

Brunetti et al, Coronary Artery Dis 2008

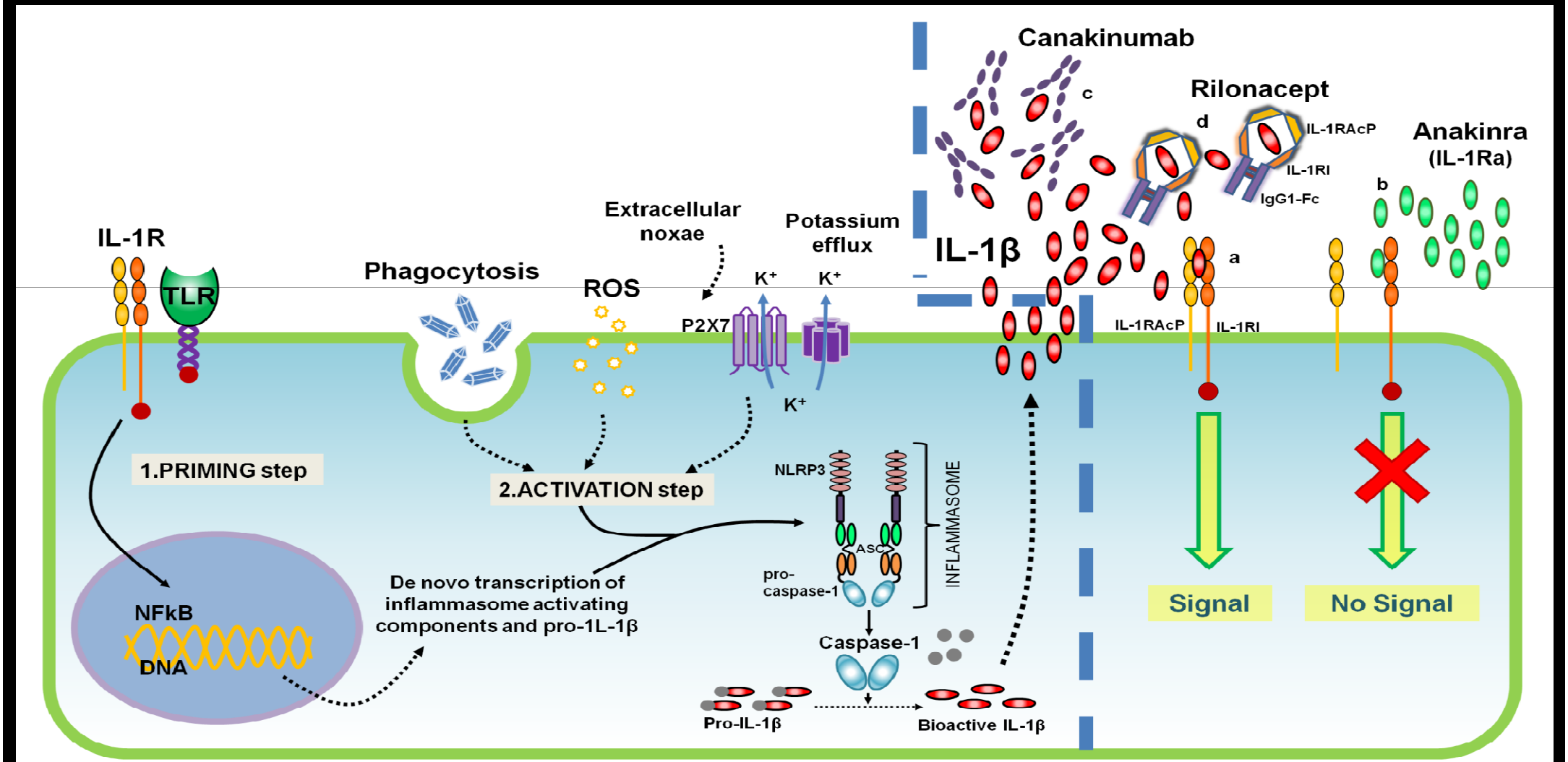
Eid et al, Circulation 2009

Targeted Anticytokine Therapy in Patients With Chronic Heart Failure (n=1675)

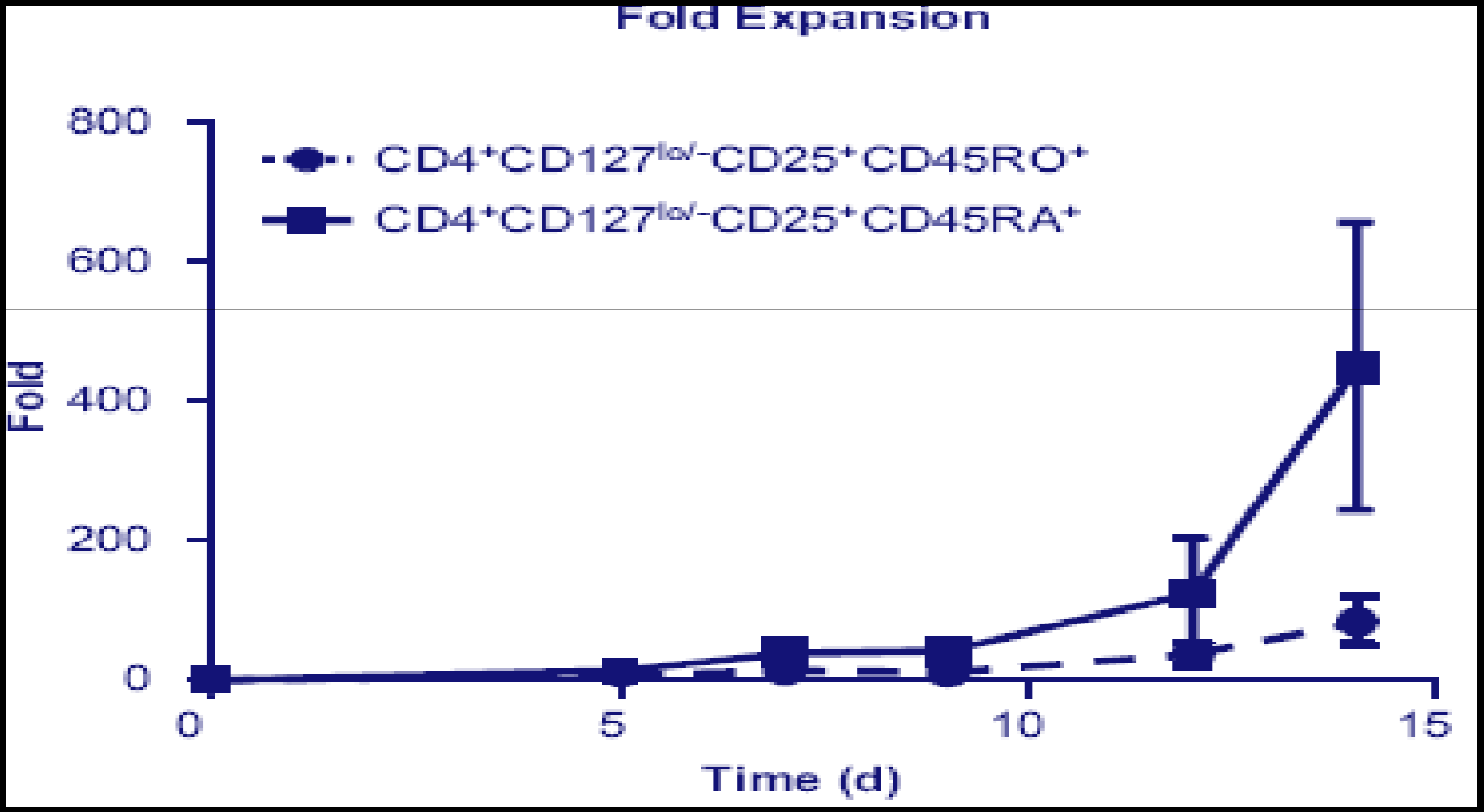


(Mann et al, Circulation 2004)

IL-1β activation and blockers



Expansion of Human T reg From Patients With T1DM



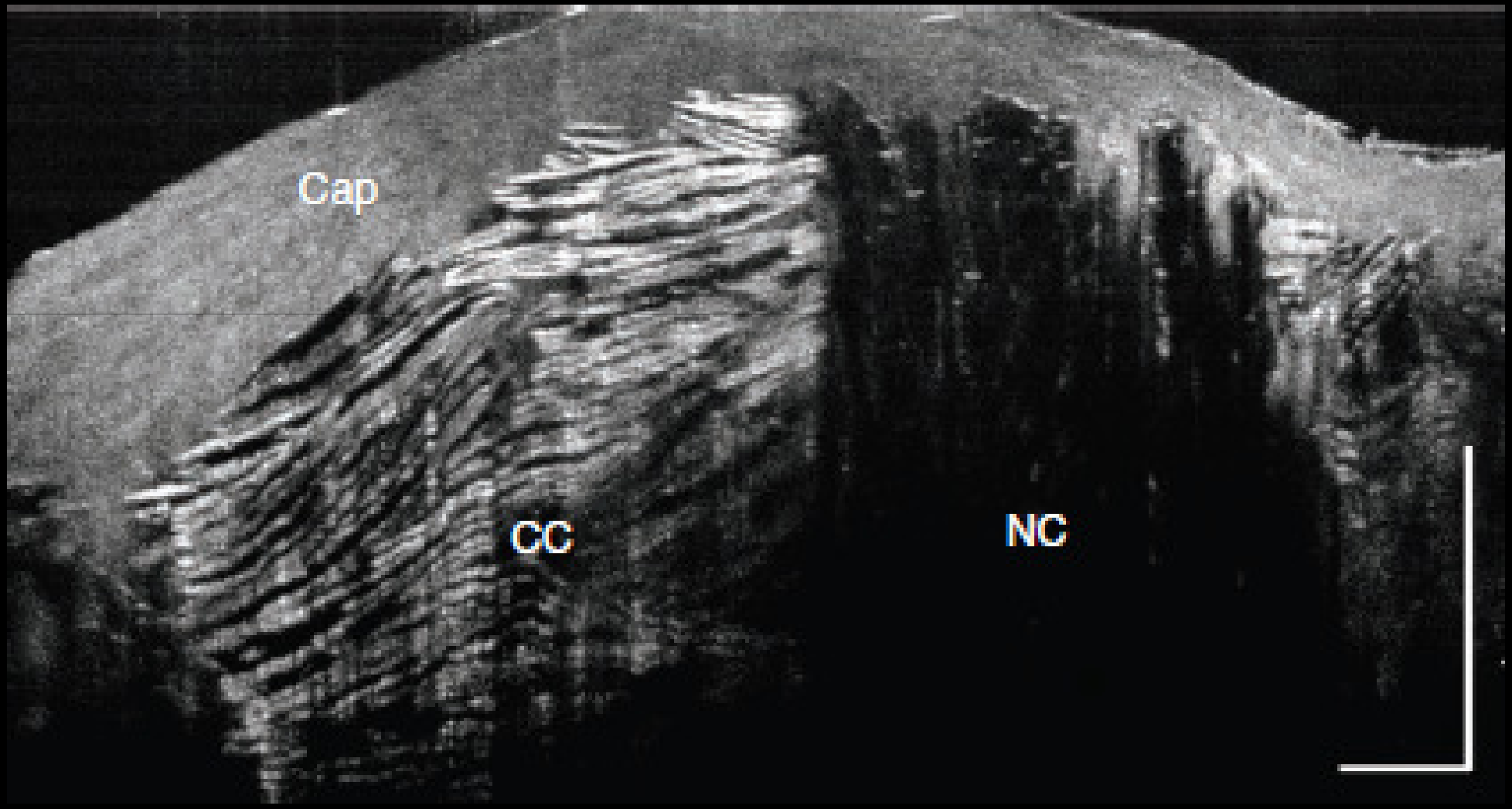
(Putnam et al, Diabetes 2009)

In RA utilization of DMARDs is associated to a lower CV risk (n=4363)

	CV all types	Myocardial infarction	Stroke
Methotrexate	0.85 (0.81–0.89)[d]	0.82 (0.74–0.91)[d]	0.89 (0.82–0.98)[e]
Glucocorticoids	0.95 (0.92–0.98)[d]	0.96 (0.91–1.00)	0.98 (0.93–1.03)
Antimalarials	0.98 (0.94–1.02)	0.94 (0.85–1.03)	0.87 (0.76–1.01)
Sulfasalazine	0.92 (0.87–0.98)[f]	0.82 (0.69–0.98)[e]	0.90 (0.79–1.03)
Gold	0.99 (0.95–1.03)	1.04 (0.98–1.10)	0.98 (0.89–1.07)
Leflunomide	0.59 (0.43–0.79)[f]	0.52 (0.26–1.06)	0.91 (0.65–1.28)

(Naranjo et al, Arthritis Research & Therapy 2008)

Cholesterol crystal by micro-OCT



(Liu et al, Nature Med 2011)