Tratamiento de la inflamación y reducción del riesgo cardiovascular

- Inflamación y enfermedad cardiovascular: mecanismos fisiopatológicos.

- Inflamación crónica y riesgo cardiovascular: evidencias clínicas

- Enfermedad cardiovascular en las EIC y su pronóstico.

- Control de la inflamación y reducción del riesgo CV.

- Abordaje de manejo clínico del riesgo cardiovascular en las EIC.

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Papel clave de los Linfocitos y Macrófagos en la producción de citoquinas y el desarrollo de la enfermedad aterosclerótica

The innate immune system in atherosclerosis
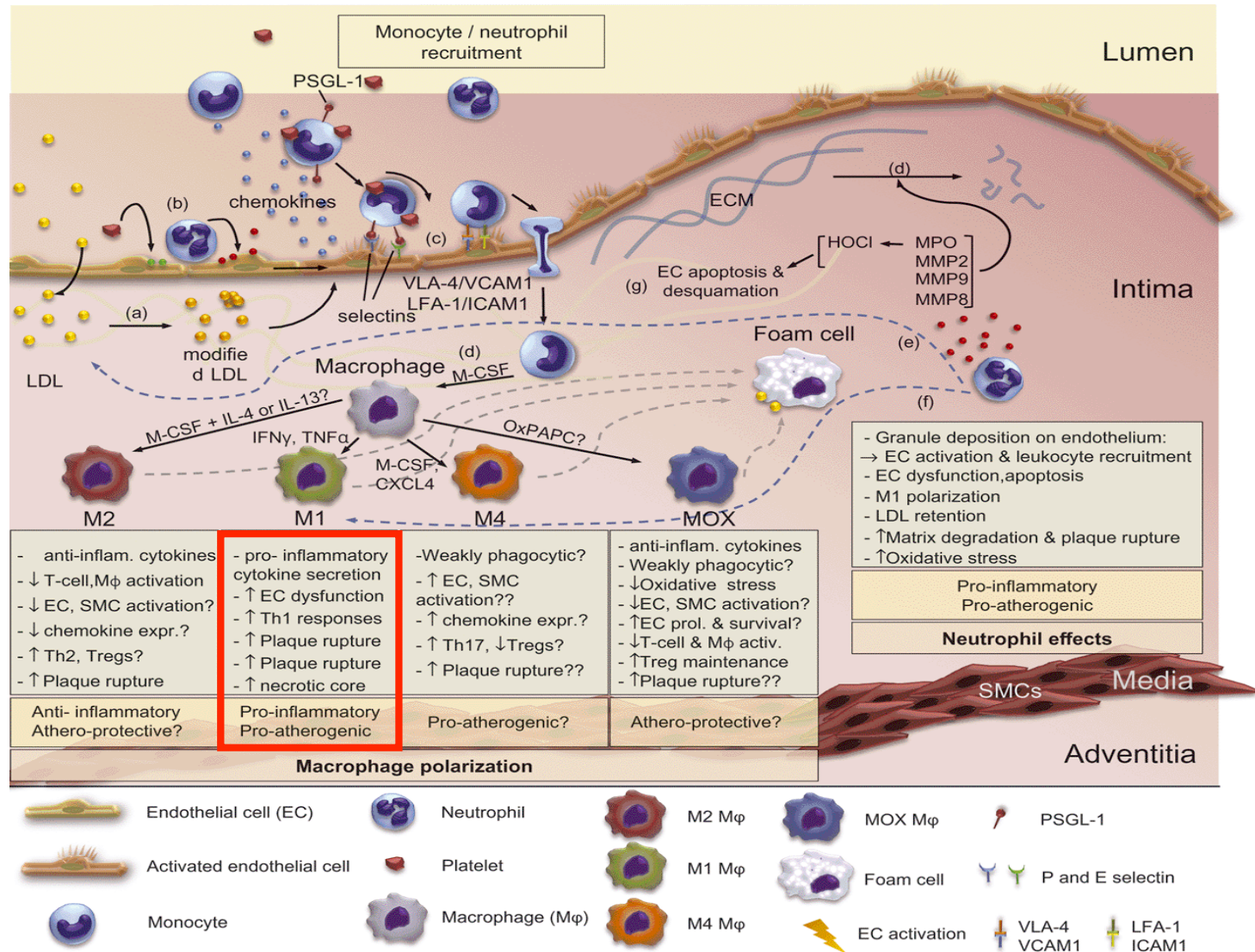
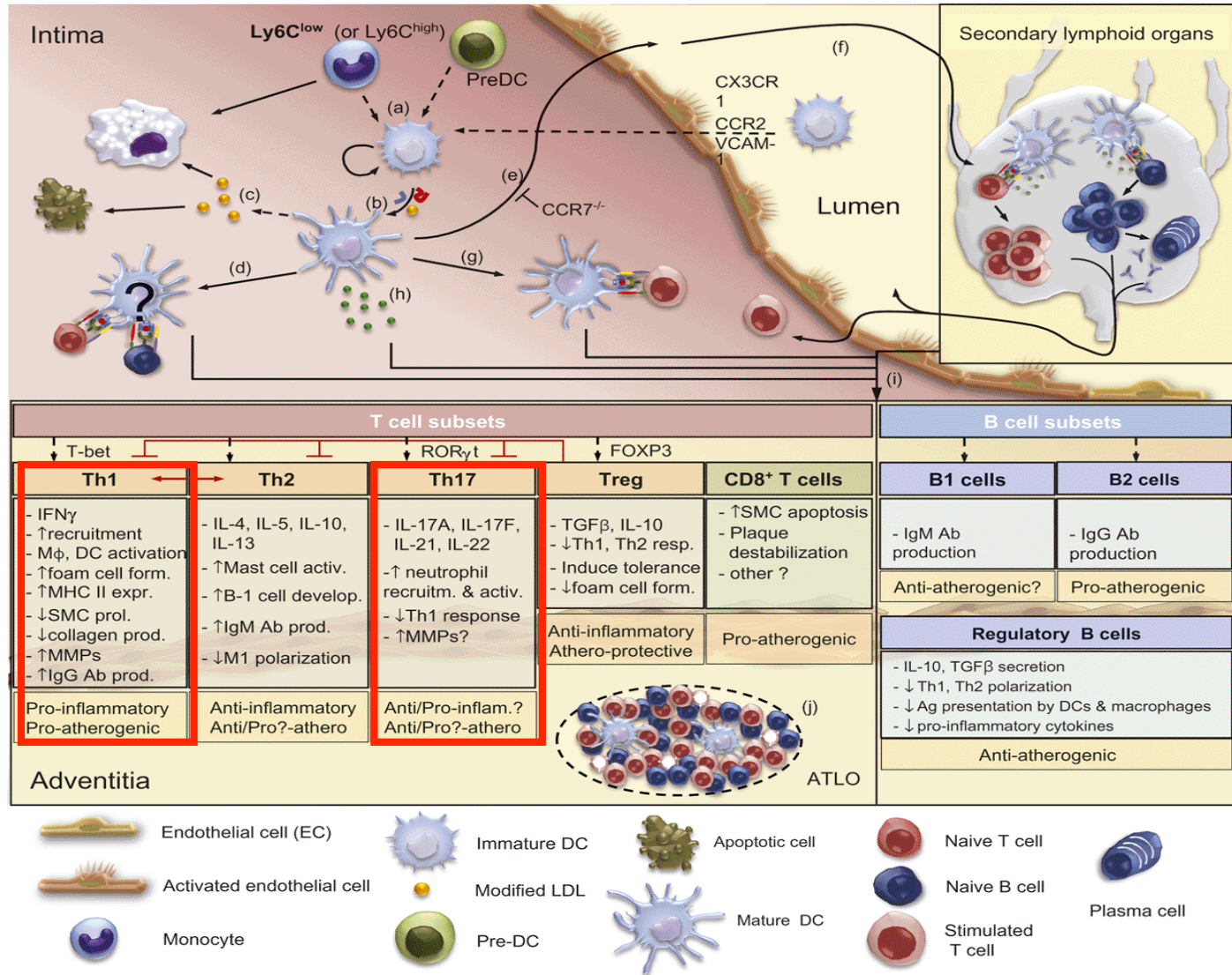Lutgens E. Vascular Biology ESC. 2017

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The adaptive immune system in atherosclerosis

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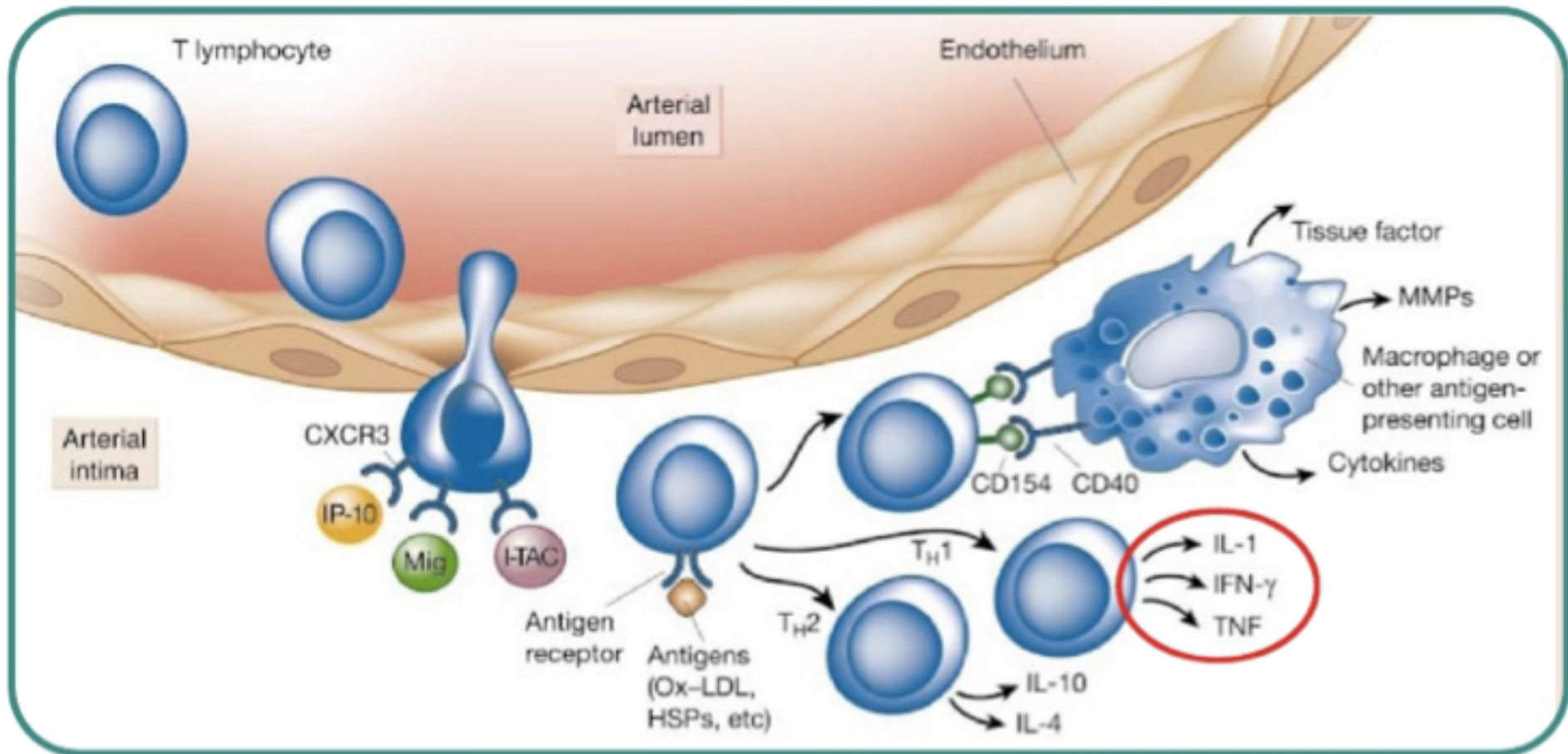
Importancia de la inflamación en el desarrollo de la Enf. Aterosclerótica
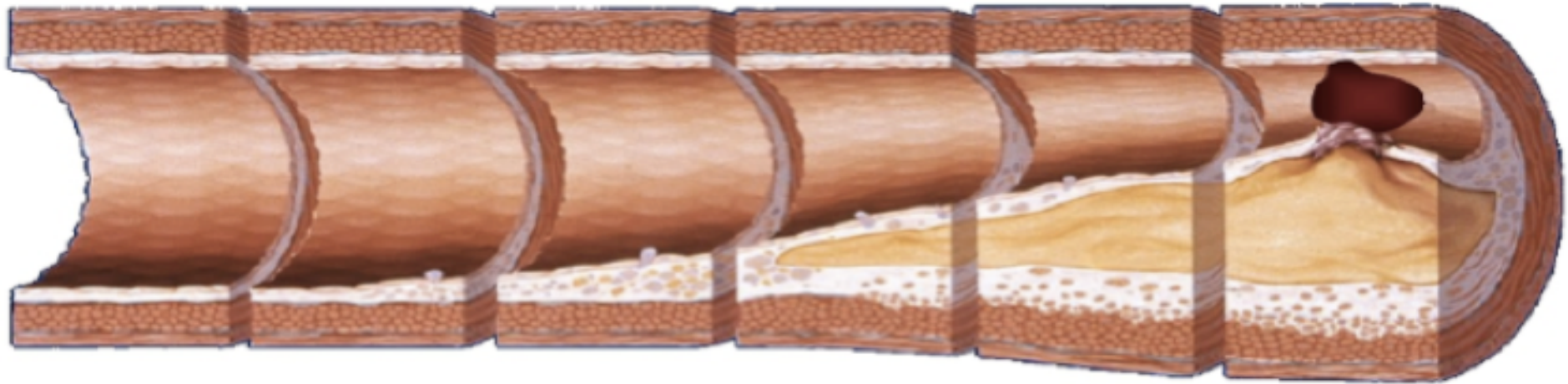
1° & Messenger Inflamm. Chemokines
- IL-1
- TNF-α
- IL-6
- IL-18
- MCP-1

Cellular Adhesion Molecules
- sICAM
- sVCAM
- sSelectins
- sESAM

Acute (& chronic) Phase Reactants
hs-CRP, SAA, Lp-PLA2, WBC

Plaque Destabilization
- MMPs
- IL-18 / IL-17A
- MPO

Plaque Rupture
- CD40L

Endothelial Fxn
- EPCs
- TNF-α

Stary, et al. Circulation.1995;92:1355-1374.

Enfermedades reumáticas inflamatorias crónicas como "*Modelo*"

ARTRITIS REUMATOIDE

Artritis Psoriásica

Espondilitis Anquilosante

Lupus Eritematoso Sistémico

Enfermedad Inflamatoria Intestinal

Psoriasis Cutánea

Esclerosis Sistémica

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INFLAMACIÓN CRÓNICA EN EIC: ATEROSCLEROSIS ACELERADA

Sattar, et al Circulation, 2003;108:2957-2963

Enfermedad Coronaria Microvascular en EIC

Faccine A. EHJ 2016: 37;1799–1806

Enfermedad Cardiovascular en EIC

Riesgo CV en EIC: efecto **ADITIVO**

Dessein, P.H. et al. J Rheumatol 2005; 32, 435-42.

Reducción de la respuesta antiinflamatoria: una nueva aproximación

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Niveles plasmáticos de PCR como predictores de eventos CV en población general

Ischemic heart disease

Copenhagen City Heart Study

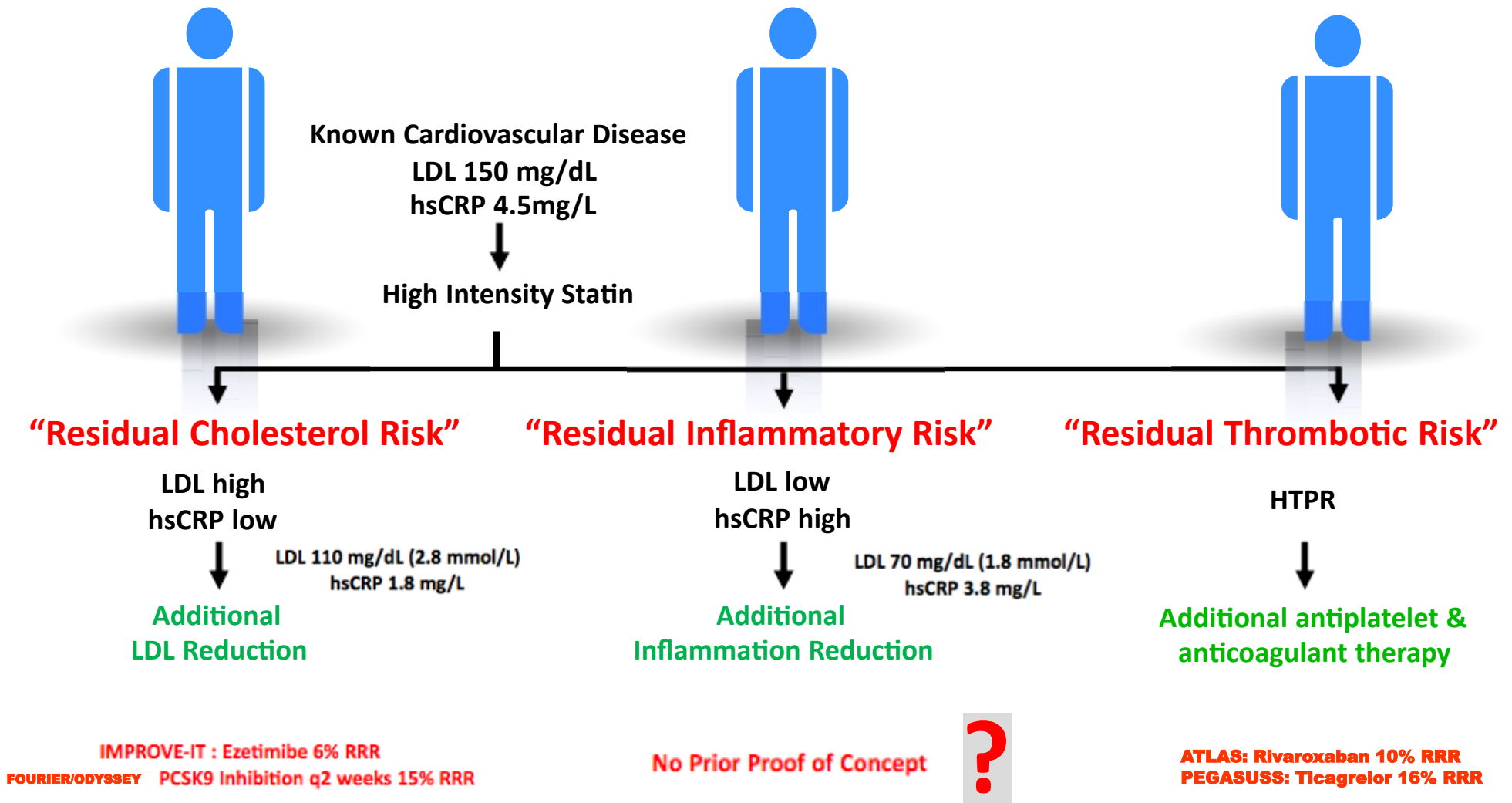| CRP level	No. of participants	No. of events	Hazard ratio (95% CI)	P for trend
Adjusted for age, sex and statin use				<0.001
<1 mg/litre	659	50		
1–3 mg/litre	5370	738		
>3 mg/litre	1905	433		
Adjusted for age, sex, statin use and genotype				<0.001
<1 mg/litre	659	50		
1–3 mg/litre	5370	738		
>3 mg/litre	1905	433		
Multivariable adjusted				<0.001
<1 mg/litre	652	50		
1–3 mg/litre	5294	721		
>3 mg/litre	1842	415		

0.5   1.0   2.0   4.0

CRP levels >3 mg/litre predict ischemic heart disease

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Zacho J et al. N Engl J Med 2008;359:1897–1908

Niveles plasmáticos de PCR como predictores de eventos CV en población general

The Emerging Risk Factors Collaboration*

C-Reactive Protein

C-Index Change (95% CI) vs. Preceding Model

Cardiovascular Disease — 38 studies; 166,596 participants; 13,568 cases

Non–lipid-based model	
Plus total cholesterol	0.0043 (0.0033 to 0.0053)
Plus total and HDL cholesterol	0.0050 (0.0039 to 0.0060)
Plus total and HDL cholesterol and log$_e$ CRP or fibrinogen	0.0039 (0.0028 to 0.0050)

Coronary Heart Disease — 37 studies; 165,586 participants; 8806 cases

Non–lipid-based model	
Plus total cholesterol	0.0114 (0.0093 to 0.0135)
Plus total and HDL cholesterol	0.0104 (0.0084 to 0.0123)
Plus total and HDL cholesterol and log$_e$ CRP or fibrinogen	0.0051 (0.0035 to 0.0066)

Stroke — 33 studies; 153,166 participants; 4732 cases

Non–lipid-based model	
Plus total cholesterol	0.0001 (0.0000 to 0.0002)
Plus total and HDL cholesterol	0.0003 (−0.0001 to 0.0007)
Plus total and HDL cholesterol and log$_e$ CRP or fibrinogen	0.0016 (0.0003 to 0.0030)

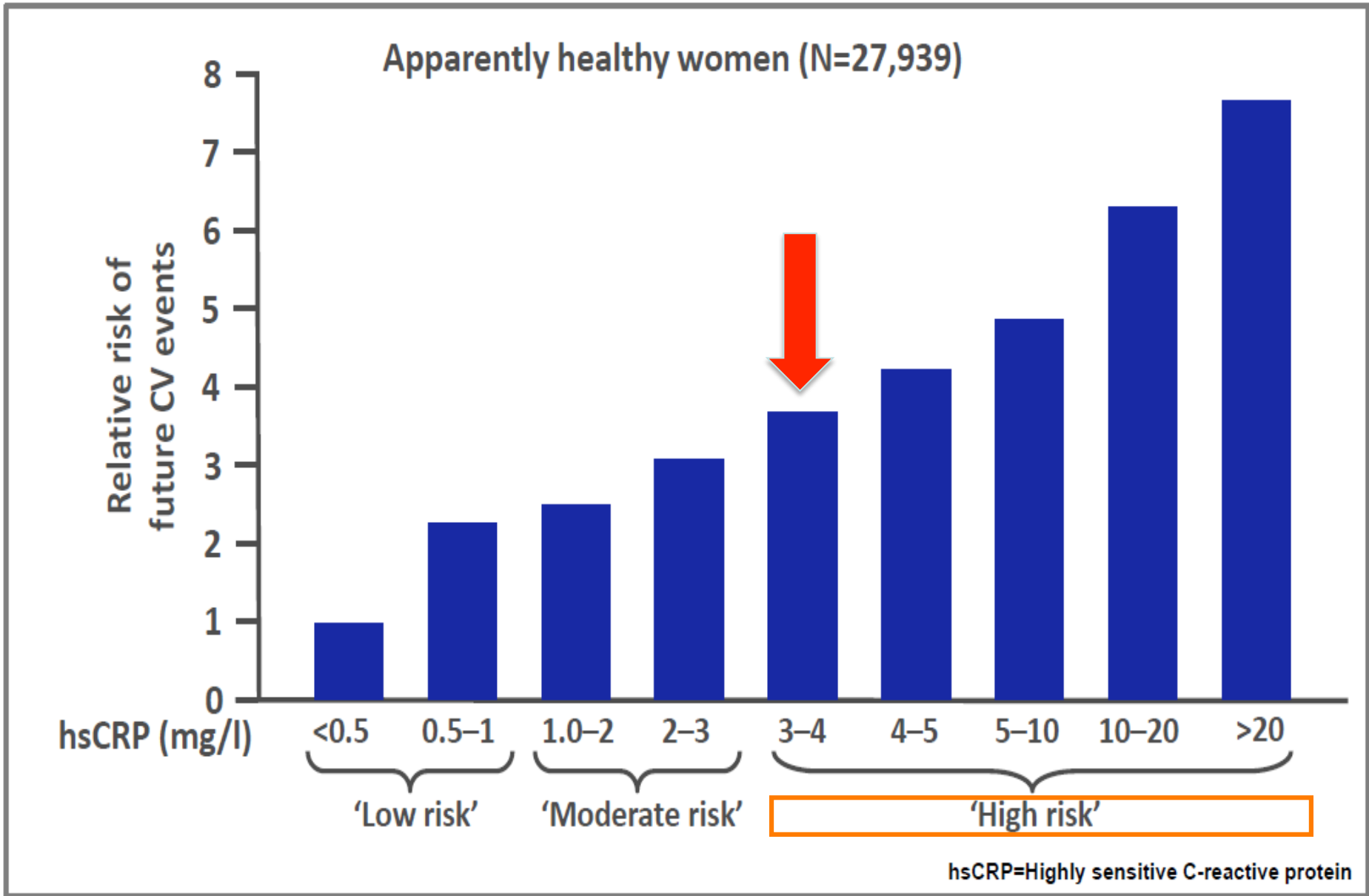Change in C-Index (95% CI), as Compared with Non–Lipid-Based Model

High-sensitivity CRP and risk of cardiovascular events: Meta-analisys

Meta-analysis of 54 Prospective Cohort Studies
**hsCRP concentration and risk of cardiovascular events : 2010**

Coronary Heart Disease

All Vascular Deaths

Risk ratio (95% CI)

hsCRP concentration (mg/L)
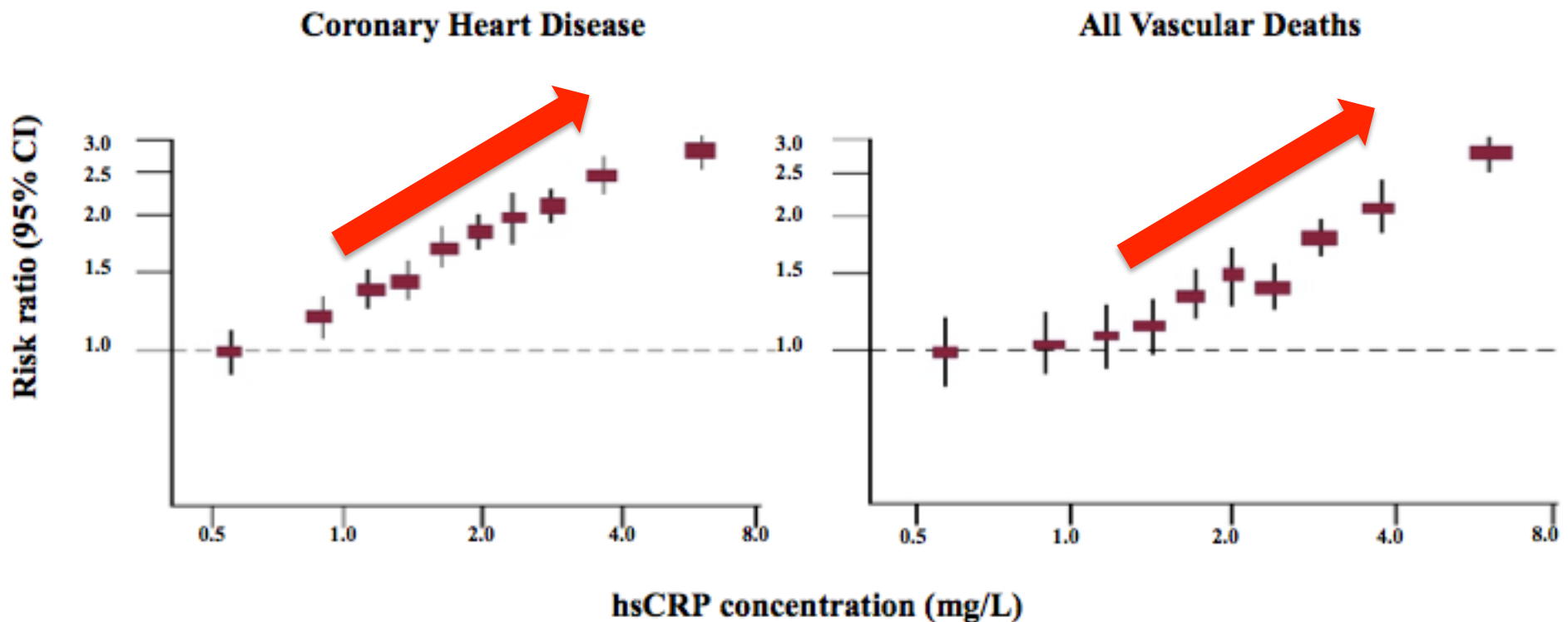
Emerging Risk Factor Collaborators, Lancet January 2010

Apparently healthy women (N=27,939)

Ridker PM et al. Circulation 2004;109:1955-9

Non-rheumatic individuals: interactive effects of CRP and lipid testing as determinants of CV risk

Combined effect of high CRP levels and high Atherogenic Index increases the risk of cardiovascular disease

Atherogenic Index: TC: HDLC
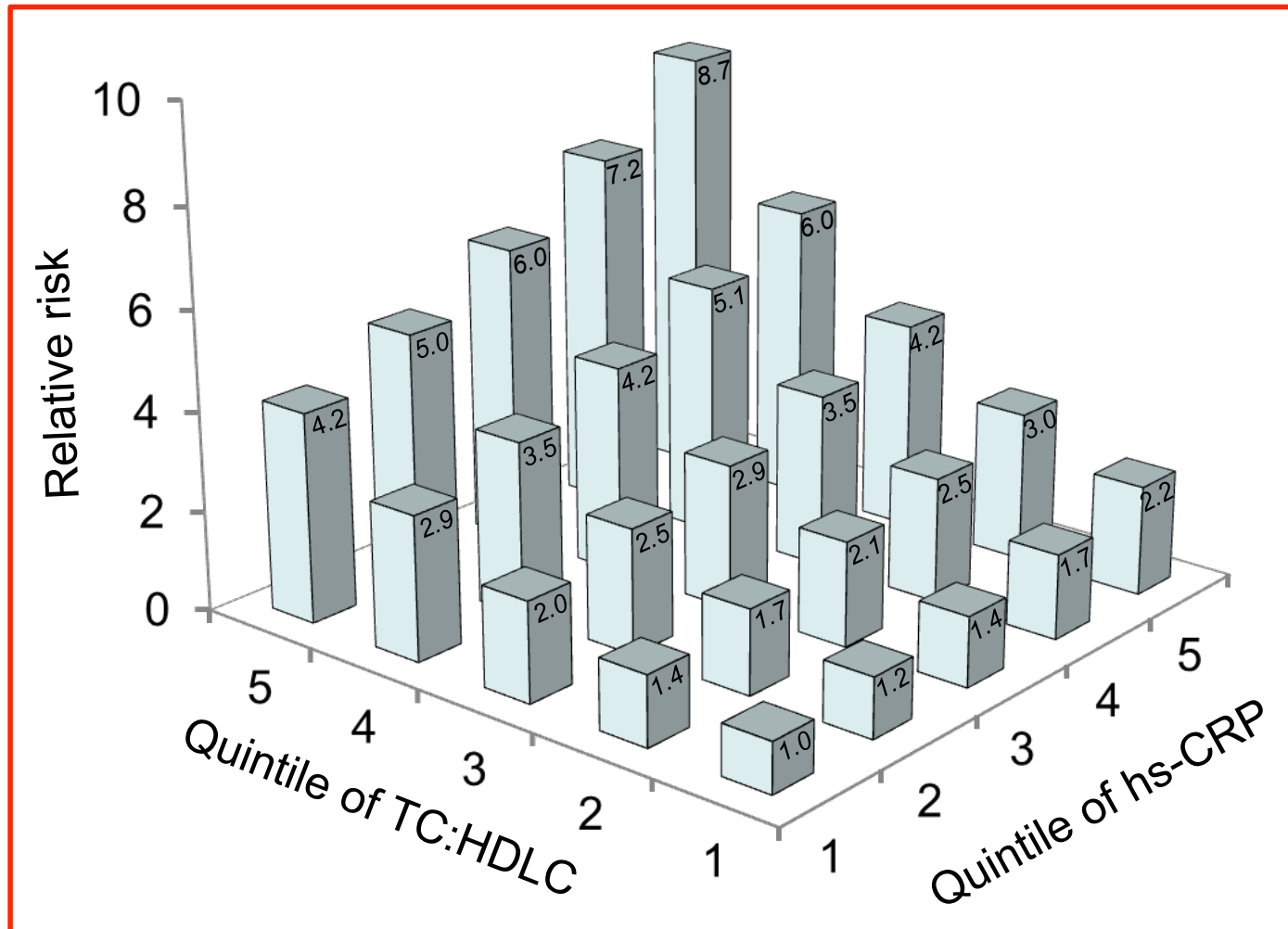
Plasma Concentration of Interleukin-6 and the Risk of Future Myocardial Infarction Among Apparently Healthy Men

404 Apparently healthy men (non-smokers)
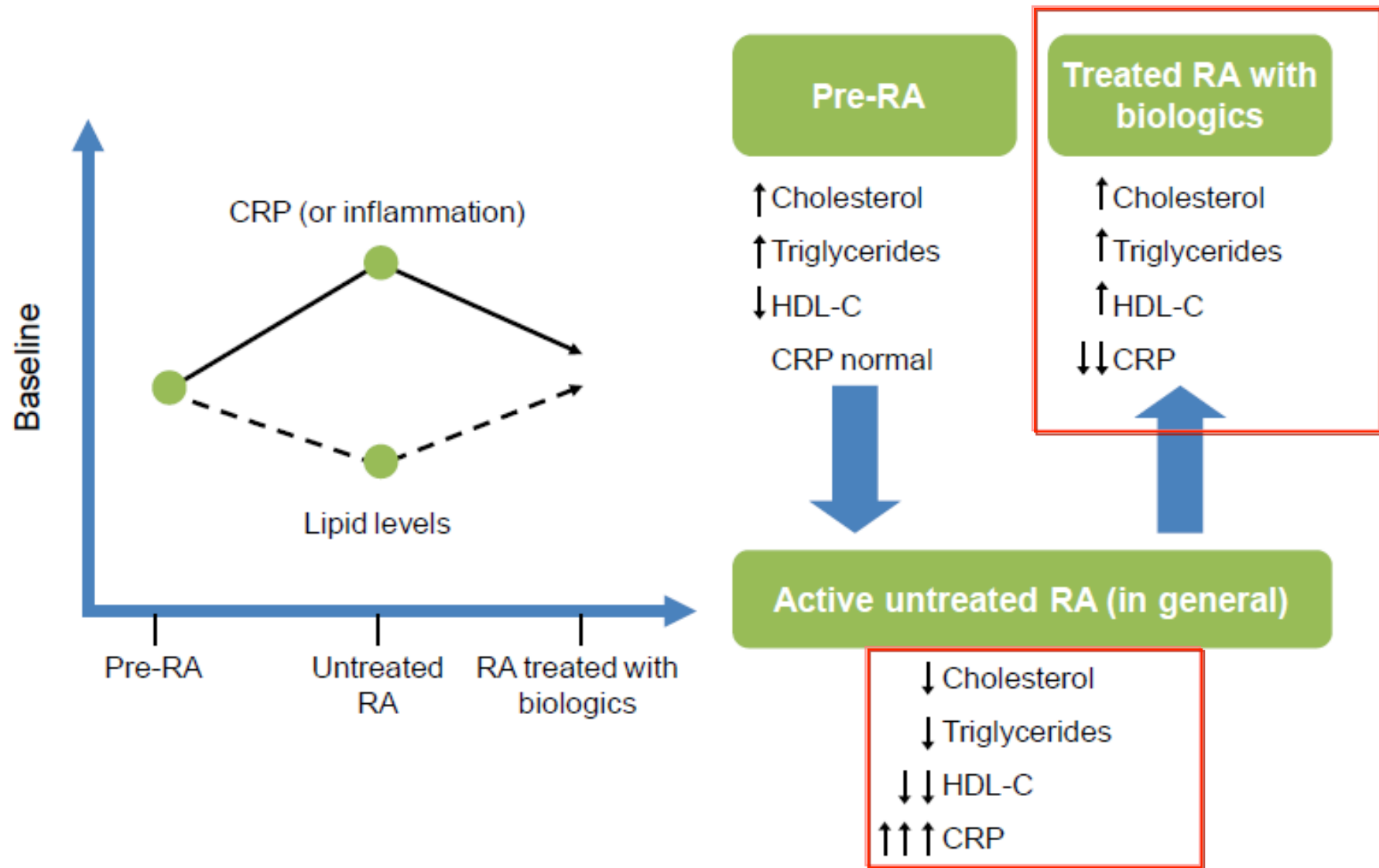
IL-6

Ridker PM et al. Circulation 2000; 101:1767–72.
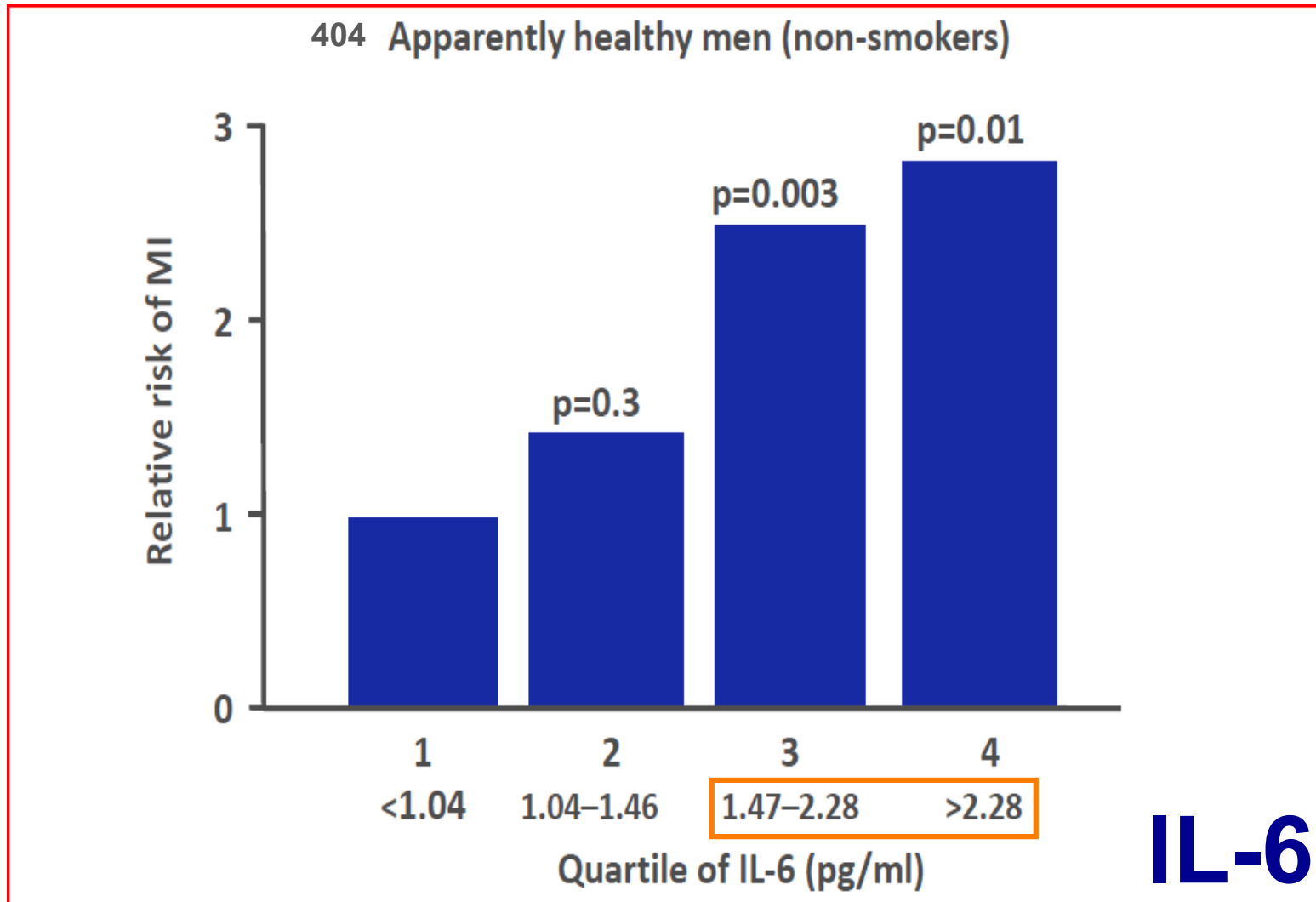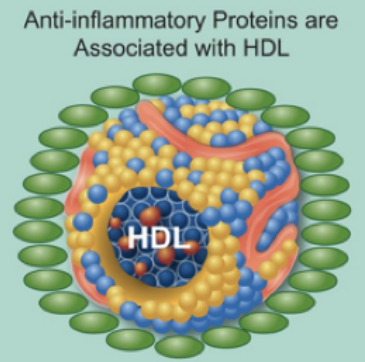
La "Paradoja Lipídica" en AR

Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox

Miguel A González-Gay,[1] Carlos González-Juanatey[2]

Lípidos e Inflamación en AR

1. Choy E and Sattar N. *Ann Rheum Dis* 2009;68:460–469.
2. Genovese MC, et al. *Arthritis Rheum* 2008;58:2968–2980.
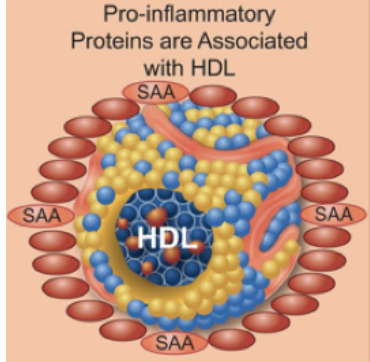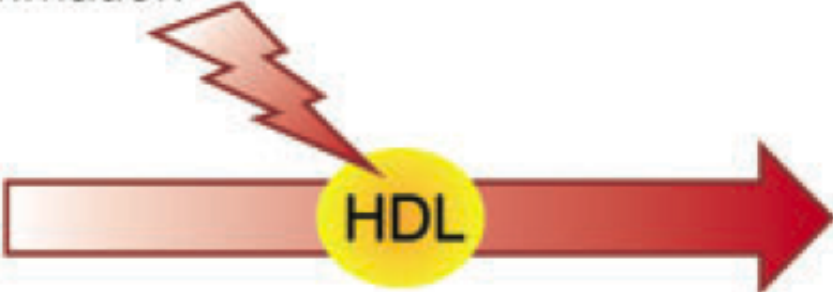3. Gonzalez-Gay and Gonzalez-Juanatey. *Ann Rheum Dis* 2014;73:1281-3.

During an Acute-Phase Reaction, the Composition of HDL Changes Rapidly From Antiatherogenic to Proinflammatory

Efectos de las estatinas relacionados con citoquinas a nivel de la placa aterosclerótica
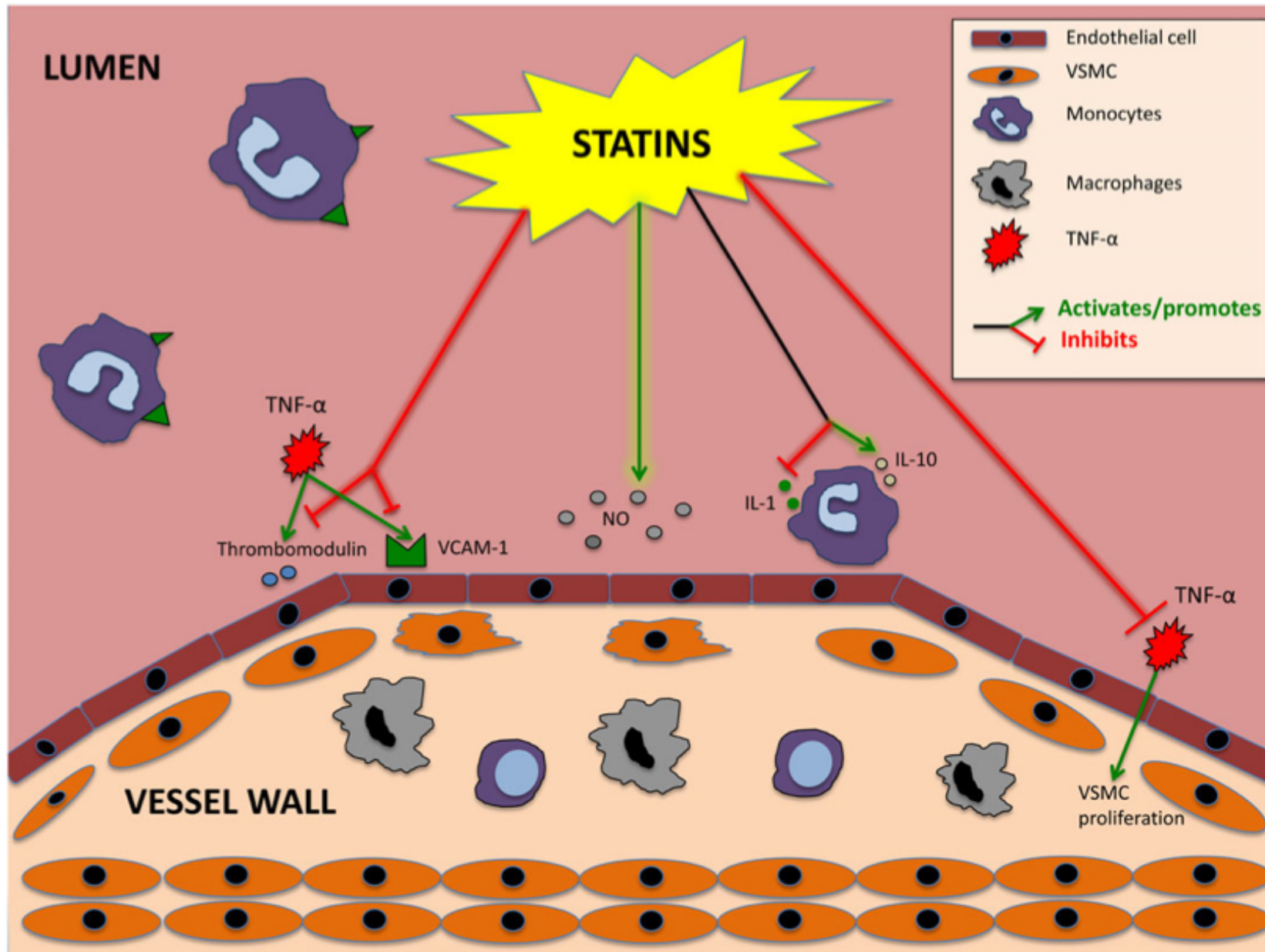
Reducción de la respuesta antiinflamatoria: una nueva aproximación

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Evidencias Clínicas de Enfermedad CV en AR

La **artritis reumatoide (AR)** es una enfermedad inflamatoria sistémica asociada con aumento de la prevalencia de enfermedad cardíaca y alta mortalidad CV.

La **enfermedad CV** es la causa más común de mortalidad prematura en pacientes con AR, con un **riesgo relativo de cerca de 2**, en comparación con controles de la misma edad.

La mortalidad CV en AR es consecuencia de un proceso de **aterosclerosis acelerada**.
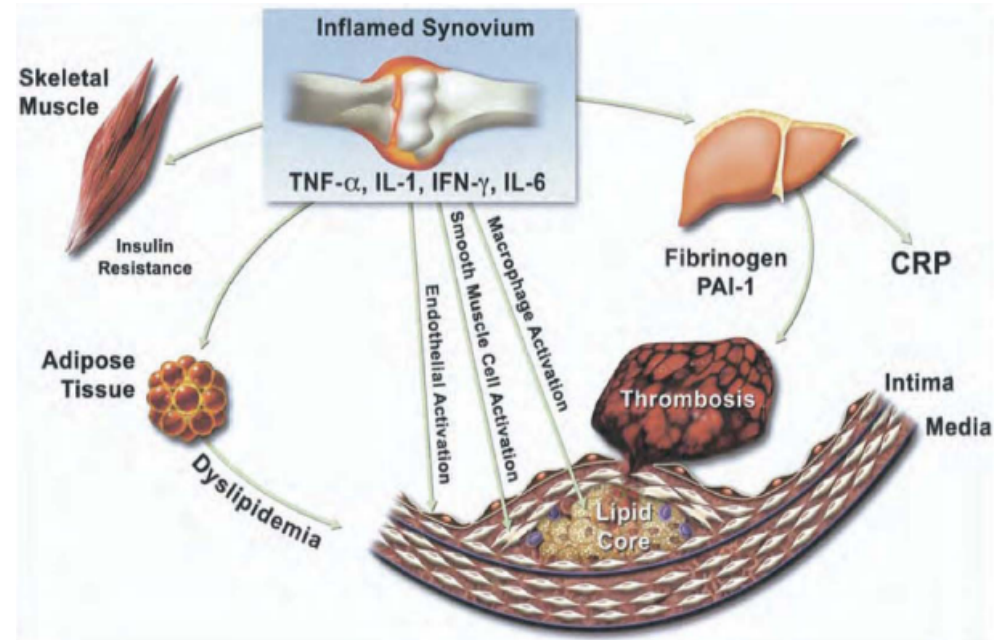
Gonzalez-Gay et al. Semin Arthritis Rheum 2005;35:8-17.

Solomon DH et al. Circulation 2003;107:1303–1307.

Libby P. Am J Med 2008;121:S21–S31.

AR y Eventos Cardiovasculares

529 mujeres con AR
Seguimiento entre 1977- 1996

IAM

Riesgo relativo ajustado para la edad **OR 2,07 (IC 95%: 1,28-3,34)**.
Riesgo relativo ajustado por multivariable **OR 2,00 (IC 95%: 1,23-3,29)**.

Riesgo relativo **AR >10 años** **OR 3,10 (IC 95%: 1,23-3,29)**.

Accidente vascular cerebral

Riesgo relativo ajustado para la edad **OR 1,47 (IC 95%: 0,70-3,08)**.
Riesgo relativo ajustado por multivariable **OR 1,48 (IC 95%: 0,70-3,12)**.

Solomon et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-07.

603 pacientes diagnosticados con AR entre 1955-1995

IAM / Muerte súbita (MS)

Riesgo relativo ajustado por multivariable (IAM) **OR 2,13 (IC 95%: 1,13-4,03)**.
Riesgo relativo ajustado por multivariable (MS) **OR 1,94 (IC 95%: 1,06-3,55)**.

Maradit-Kremers et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402-11.

Factores de riesgo para mortalidad cardiovascular (razones de riesgo-RR-ajustadas por edad en el inicio de la enfermedad y sexo) en 182 pacientes con AR (10 años seguimiento 1996-2005).

Arthritis & Rheumatism

Mortalidad CV (ajustada FRCV) OR 1,79 (95% IC 1,10-3,21)

VARIABLE	RR	(IC 95%)	p
PCR promedio (mg/l)	**1,14**	**1,06-1,23**	**< 0,001**
VSG promedio (mm/1h)	**1,05**	**1,01-1,08**	**0,003**
Terapia con metotrexato	0,86	0,28-2,69	0,800
Factores de riesgo cardiovascular			
En 1996	1,78	0,64-4,90	0,266
Durante el seguimiento	1,46	0,52-4,09	0,475
Epitopo compartido HLA-DRB1*04	**4,15**	**1,15-15,0**	**0,030**
HLA-DRB1*0401	1,63	0,54-4,91	0,385
HLA-DRB1*0404	**6,65**	**1,98-22.33**	**0,002**

Gonzalez-Gay MA, Gonzalez-Juanatey C et al. Arthritis Rheum 2007;57:125-32

RA and MACE

Risk of Cardiovascular Mortality in Patients With Rheumatoid Arthritis: A Meta-Analysis of Observational Studies

Arthritis & Rheumatism — AMERICAN COLLEGE OF RHEUMATOLOGY

J. ANTONIO AVIÑA-ZUBIETA,[1] HYON K. CHOI,[1] MOHSEN SADATSAFAVI,[2] MAHYAR ETMINAN,[2] JOHN M. ESDAILE,[1] AND DIANE LACAILLE[1]   Arthritis Rheum. 2008;59(12):1690-7.

24 studies

111,758 patients with RA
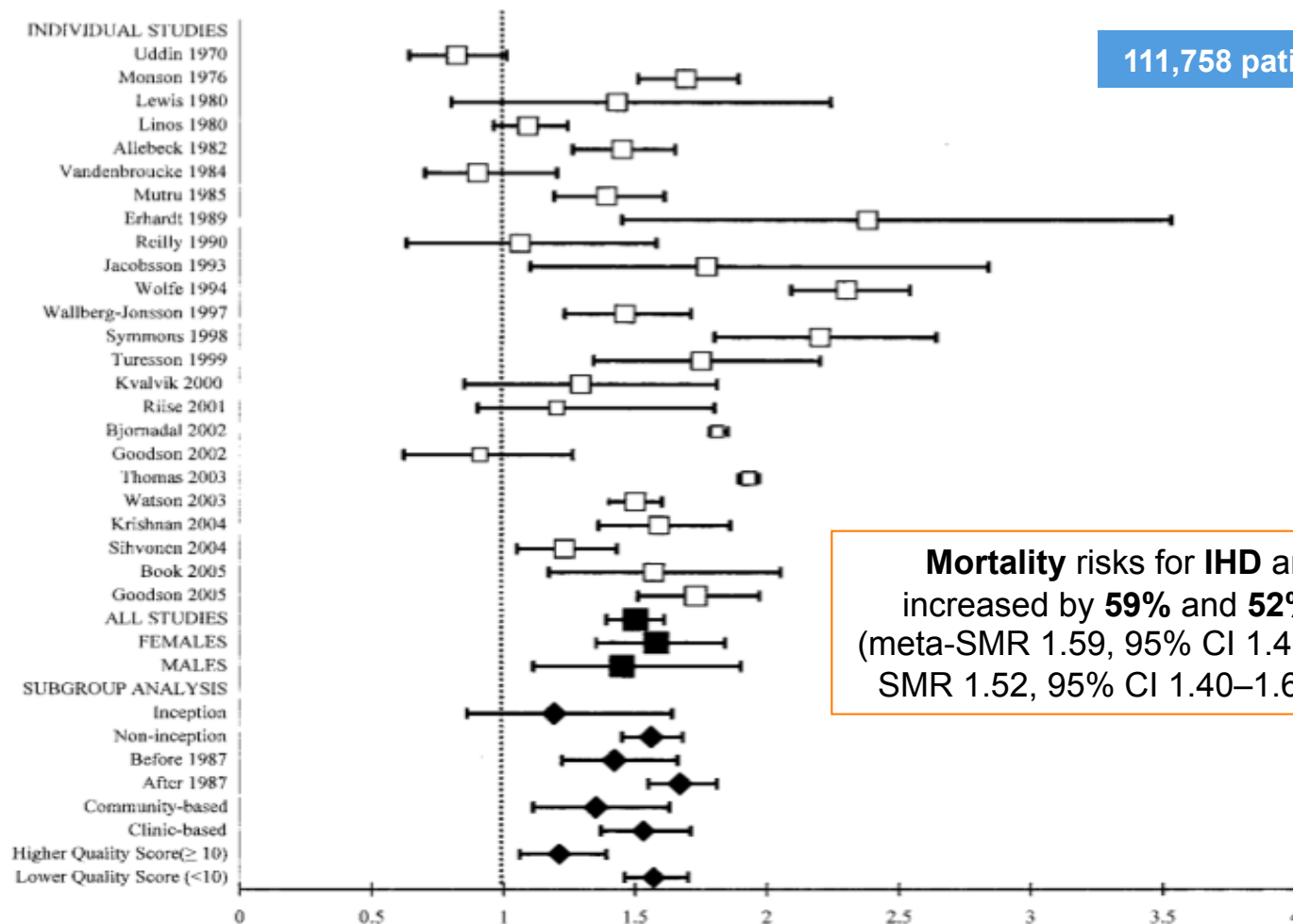
Mortality risks for **IHD** and **CVA** were increased by **59%** and **52%**, respectively (meta-SMR 1.59, 95% CI 1.46–1.73 and meta-SMR 1.52, 95% CI 1.40–1.67, respectively).

Aterosclerosis Carotídea Subclínica en AR

	AR	Controles	
CIMT	0,779 ± 0,164	0,699 ± 0,129 mm	p = 0,01

47 pacientes AR larga evolución sin FRCV ni ECV previa
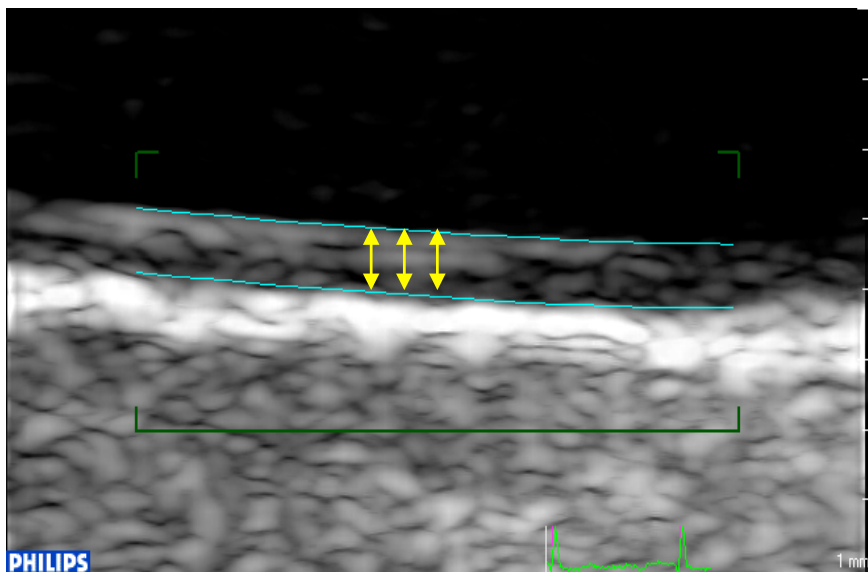
p = 0,03

	AR	Controles
Placas carotídeas	34%	15%

Gonzalez-Juanatey C et al. Medicine (Baltimore) 2003; 82:407-13.

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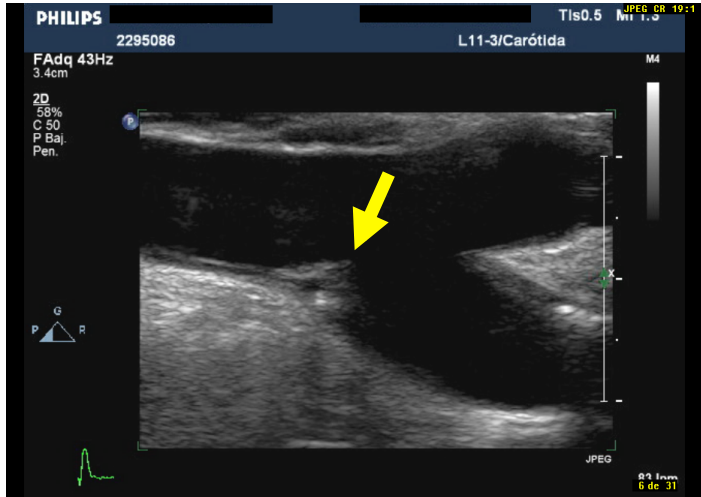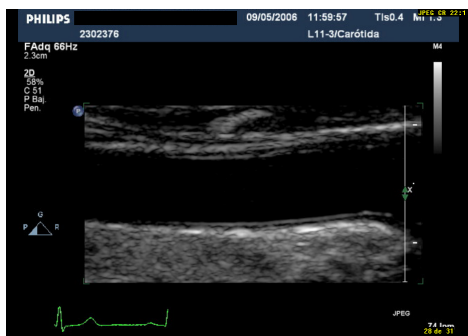
Predictores independientes de aterosclerosis subclínica en pacientes con AR

CIMT	OR (95% CI)	P
Edad >60 años al estudio	6,80 (1,77 to 26,11)	0,005

Placas (+)	OR (95% CI)	P
Duración enf.	1,13 (1,02 to 1,27)	0,024
Edad al estudio	1,40 (1,94 to 2,07)	0,097

Correlación entre los Valores Promedio de PCR y el IMT de la Carótida en 47 Pacientes con AR sin Enfermedad CV Clínicamente Evidente

C = Cuartil

Gonzalez-Gay MA et al. J Rheumatol 2005; 32:1219-23
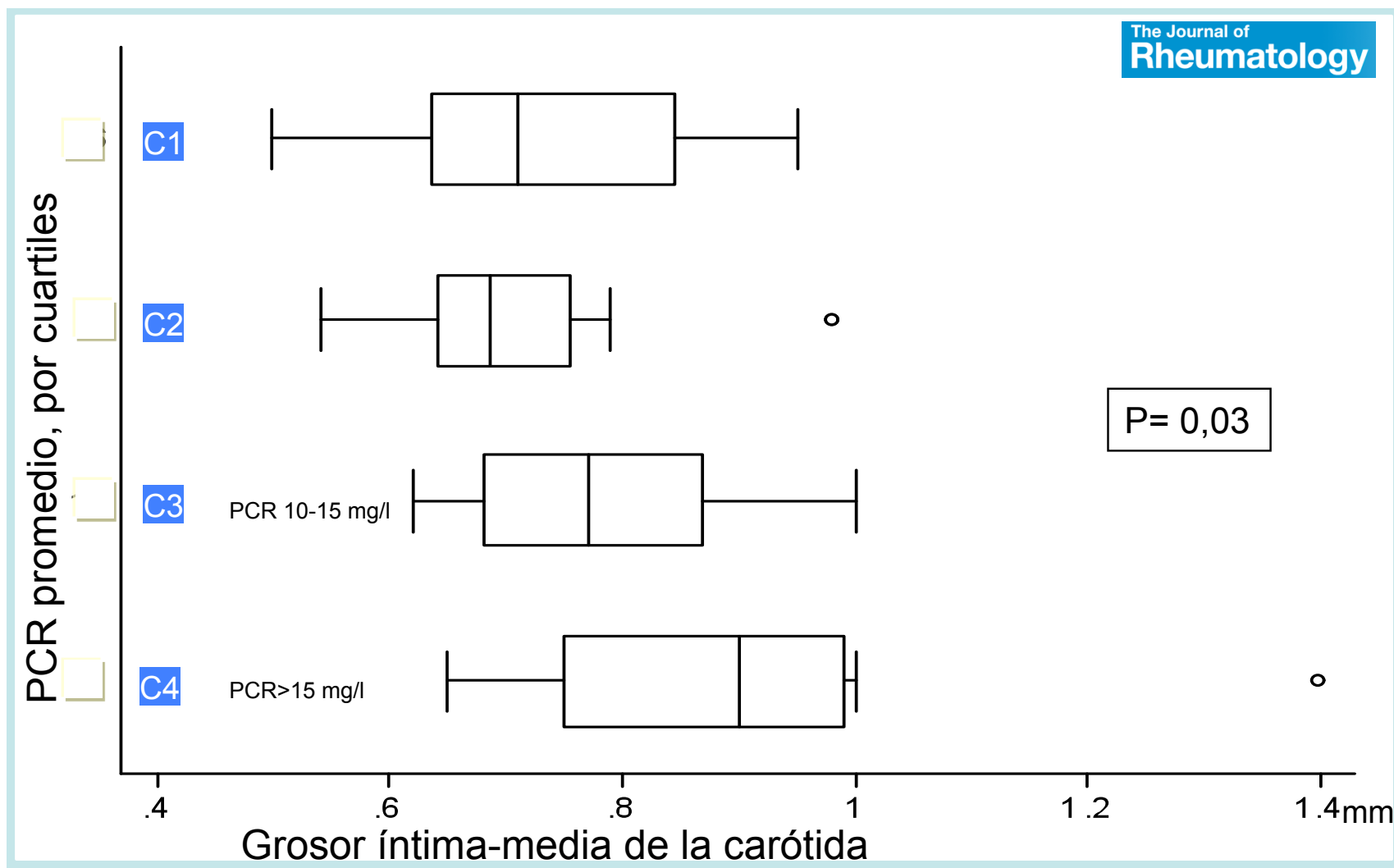
RA and CV disease

Coronary Atherosclerosis

CT-scan: Coronary Artery Calcium (CAC) Score
Early RA (n=70); Established RA (n=71); Controls (n=86)

Disease duration

Chung C et al. Arthritis Rheum 2005 52; 3045-56
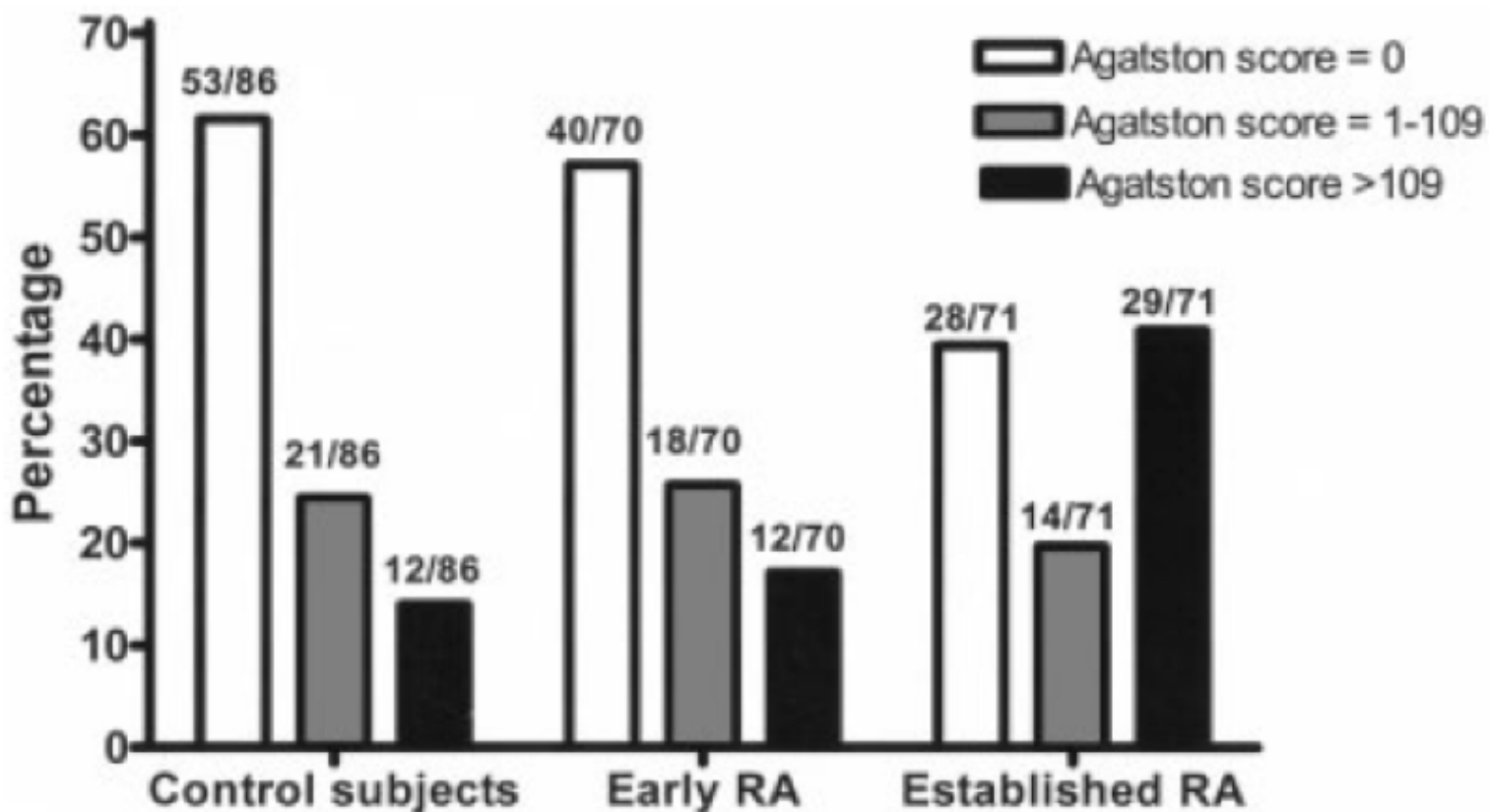
RA and CV disease

Aortic Inflammation

F-FDG-PET/CT-scan. **Ascending Aortic Inflammation in RA patients** without clinical CVD (n=91)
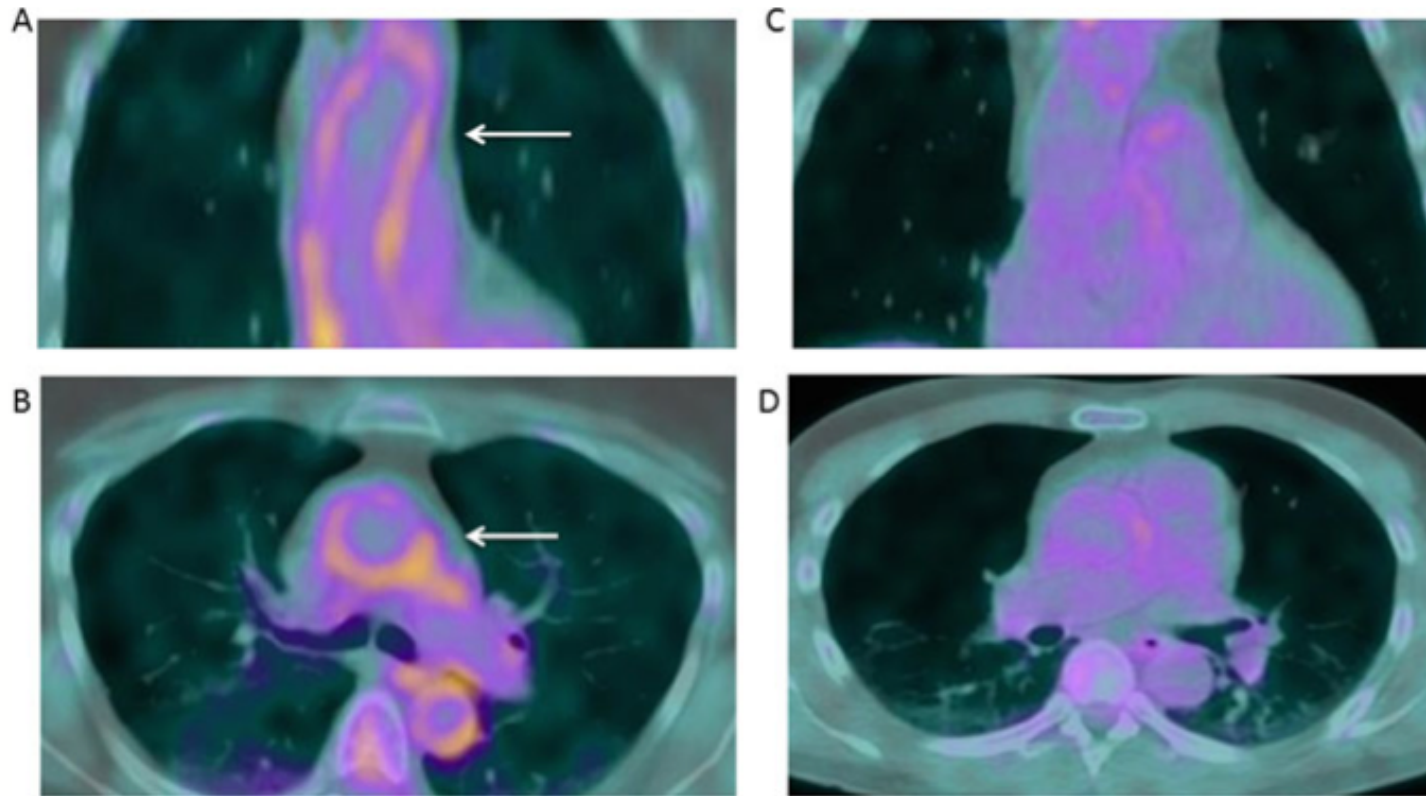
Traditional **CV risk factors** (HTA/BMI) and **RA disease characteristics** (rheumatoid nodules and the DAS28 using the C-reactive protein level in anti-CCP antibody–positive individuals) were independently associated with ascending aortic FDG uptake in RA patients without clinical CVD.

Aterosclerosis Carotídea y Predicción de Síndrome Coronario Agudo en AR

599 pacientes AR y sin SCA previo Seguimiento 3 años
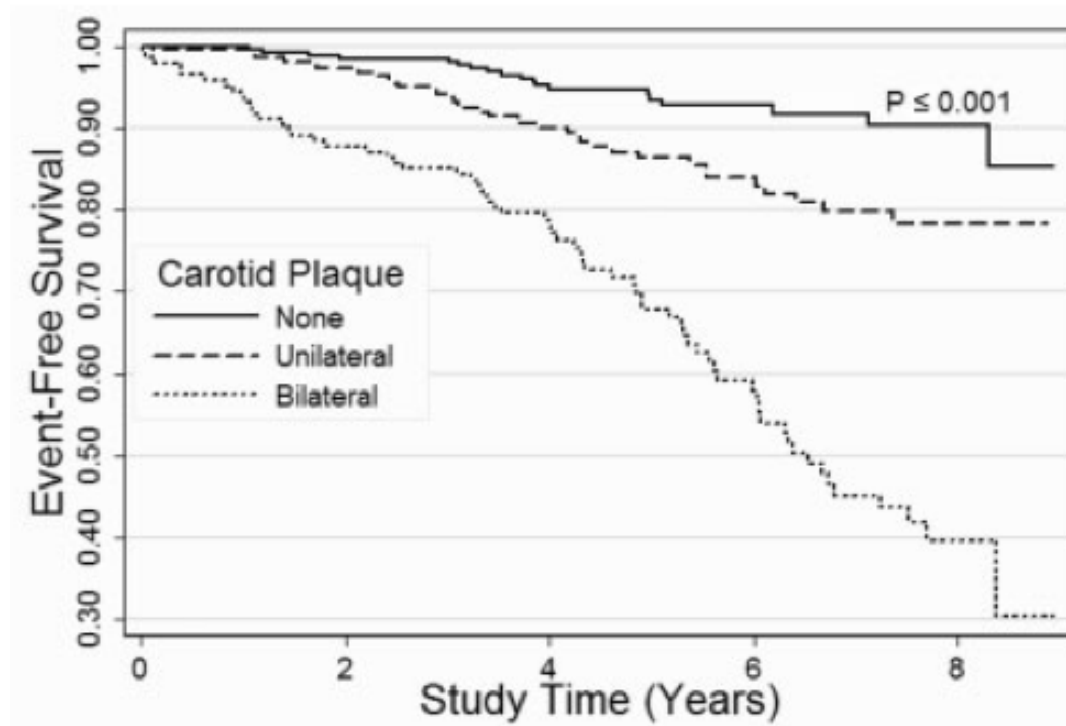
Incident acute coronary syndromes (n = 599)

	Events	Person-years	Rate (95% CI)*
Plaque			
None	17	1,581	1.1 (0.6–1.7)
Unilateral	22	877	2.5 (1.7–3.8)
Bilateral	27	628	4.3 (2.9–6.3)

* Per 100 person-years. 95% CI = 95% confidence interval.

Evans MR et al. Arthritis Rheum 2011; 63:1211-20

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JUPITER

Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death
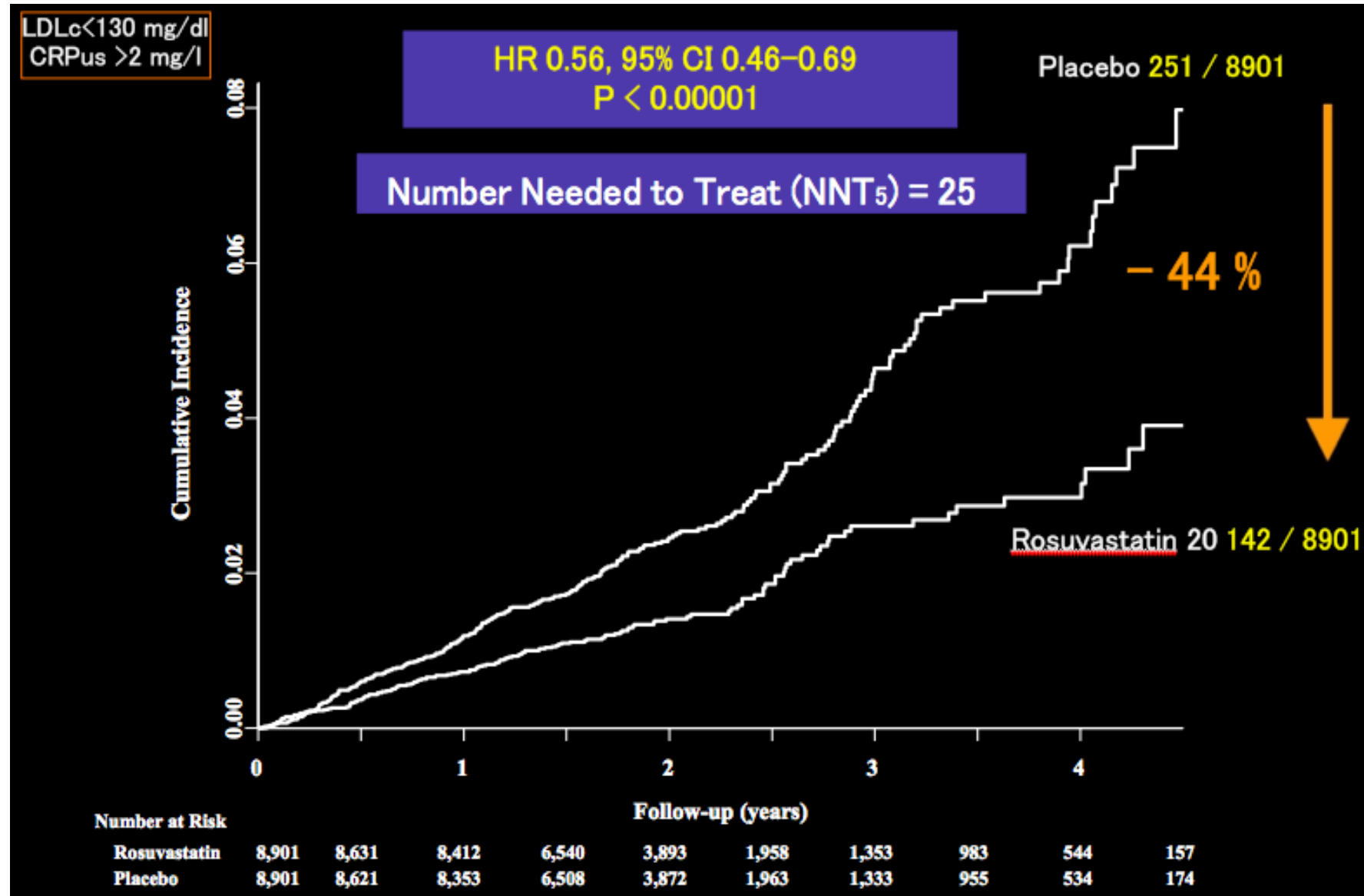
JUPITER
LDL reduction, hsCRP reduction or both?

Ridker et al NEJM 2008;359:2195-2207
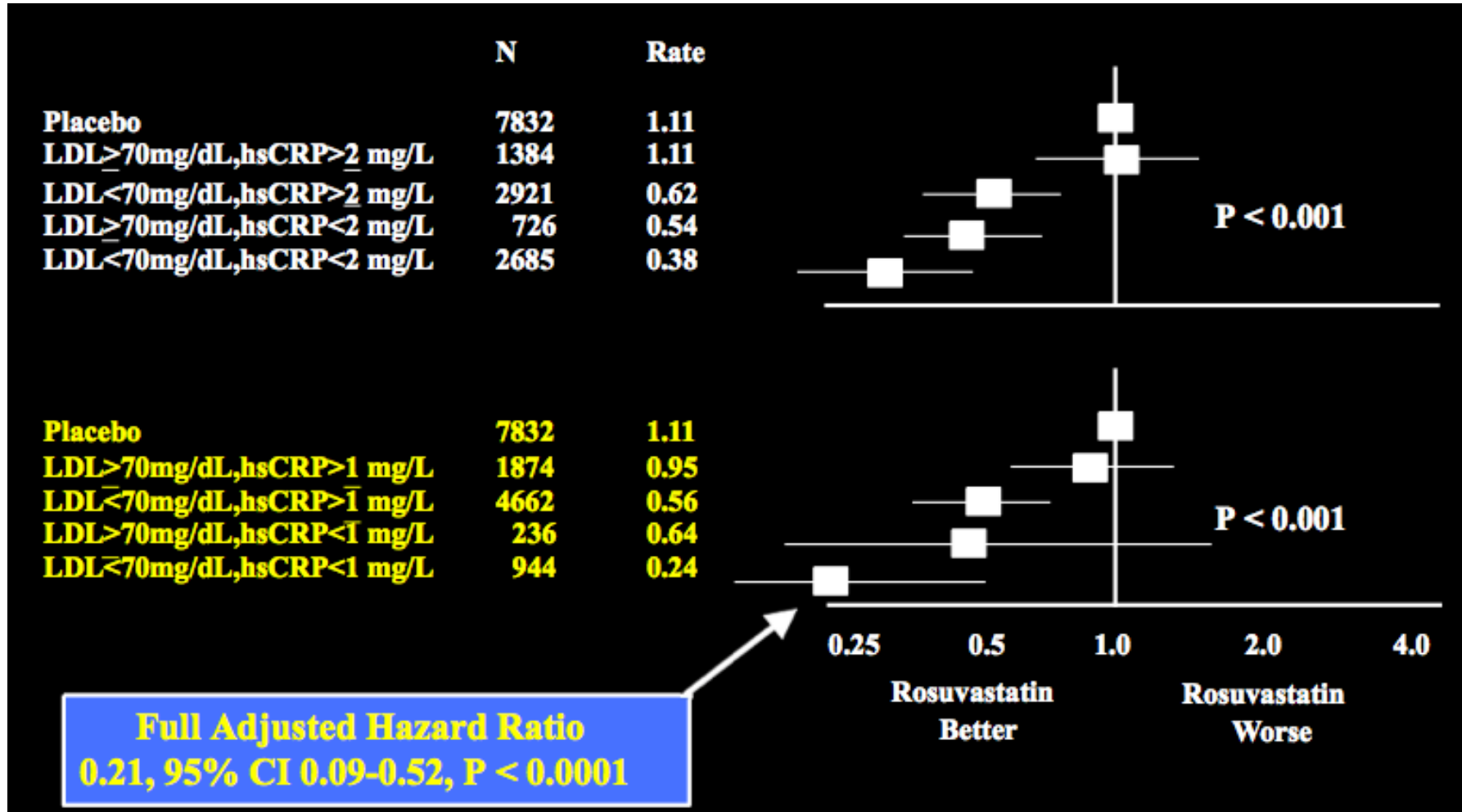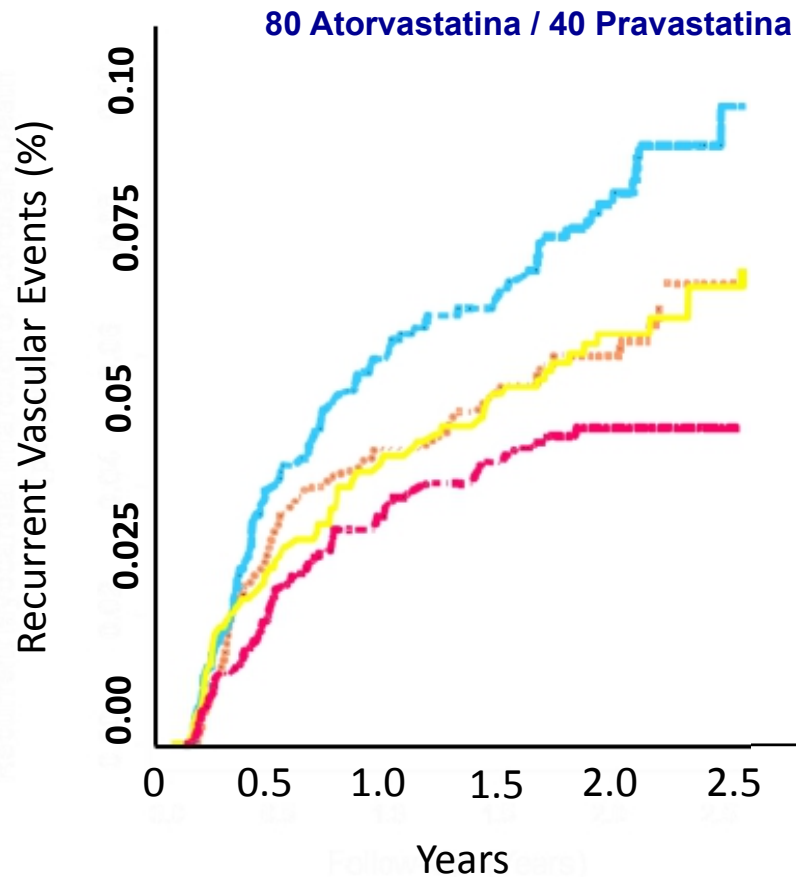
PROVE-IT

Ridker et al, NEJM 2005;352:20-8

IMPROVE-IT

Bohula et al, Circulation 2015;132:1224-33

■ LDL >70 mg/dL hsCRP > 2mg/L	■ LDL <70 mg/dL hsCRP > 2mg/L	■ LDL > 70 mg/dL hsCRP < 2mg/L	■ LDL <70 mg/dL hsCRP < 2mg/L
Neither Goal Achieved	LDL Goal Achieved	hsCRP Goal Achieved	Dual Goals Achieved

Eur Heart J 2016;37:1729-22

Riesgo Inflamatorio Residual

PROVE-IT
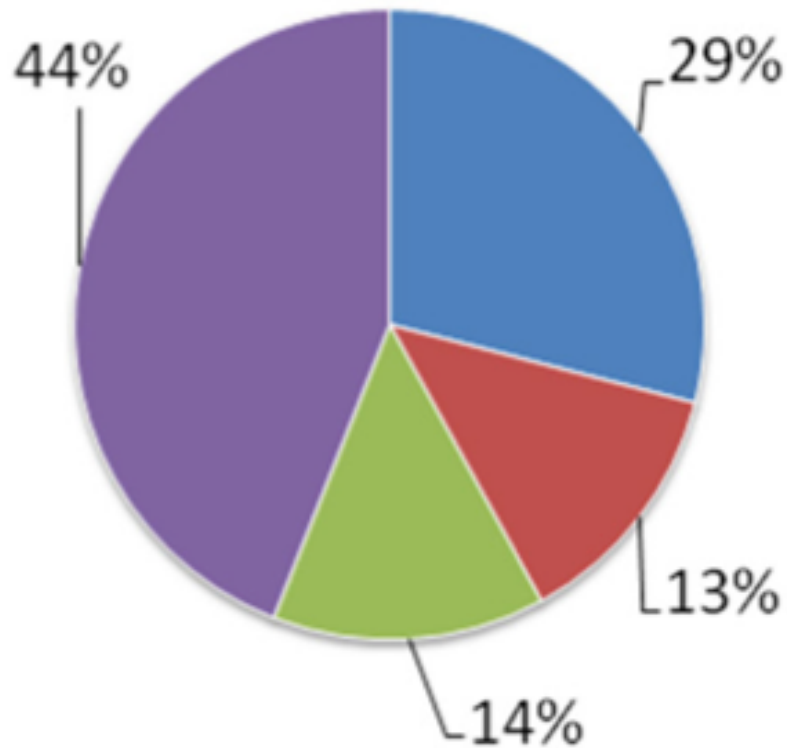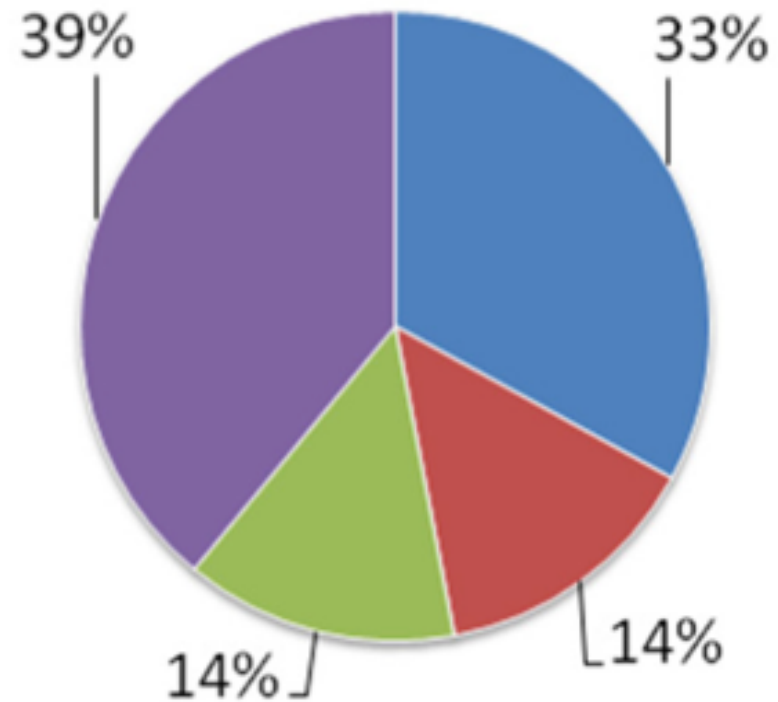
44%   29%

13%

14%

IMPROVE-IT

39%   33%

14%

14%

Residual Inflammatory Risk	Residual Cholesterol Risk	Both	Neither
hsCRP ≥ 2 mg/L LDLC < 70 mg/dL	hsCRP < 2 mg/L LDLC ≥ 70 mg/dL	hsCRP ≥ 2 mg/L LDLC ≥ 70 mg/dL	hsCRP < 2 mg/L LDLC < 70 mg/dL

Circulation Res 2017;120:617-19

Riesgo Inflamatorio Residual

Registro VIRGO
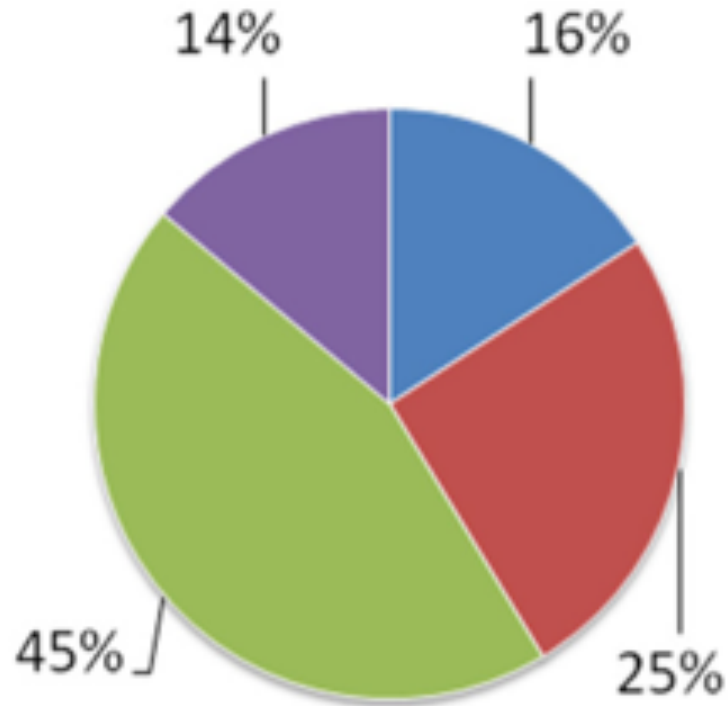
14% 16%

45% 25%

■ Residual Inflammatory Risk	■ Residual Cholesterol Risk	■ Both	■ Neither
hsCRP ≥ 2 mg/L LDLC < 70 mg/dL	hsCRP < 2 mg/L LDLC ≥ 70 mg/dL	hsCRP ≥ 2 mg/L LDLC ≥ 70 mg/dL	hsCRP < 2 mg/L LDLC < 70 mg/dL

Estatinas/AR: Actividad Inflamatoria

116 pacientes ATORVASTATINA 40mg	Estudio TARA (Atorvastatina en AR)		
6 meses	**Atorvastatina** (n=58)	**Placebo** (n=58)	p
DAS28	-0,52 (-0,75/-0,25)	0,03 (-0,23/0,28)	0,004
PCR (mg/l)	-0,46 (-0,64/-0,28)	0,12 (-0,09/-0,34)	<0,0001
VSG (mm/h)	-5,03 (-8,4/-1,67)	1,91 (-1,61/5,54)	0,005
LDLc (mmol/l)	-1,40 (-1,63/-1,17)	-0,07 (-0,23/0,10)	<0,0001

	Methotrexate status at baseline				Difference	p
	Not taking (n=29)	p	Taking (n=29)	p		
DAS28	−0·40 (−0·74 to −0·06)	0·02	−0·59 (−0·97 to −0·21)	0·004	0·19 (−0·31 to 0·69)	0·46
Erythrocyte sedimentation rate (mm/h)	−4·17 (−6·88 to −1·47)	0·004	−5·90 (−12·28 to 0·49)	0·069	1·72 (−5·06 to 8·51)	0·61
C-reactive protein (log mg/L)	−0·40 (−0·67 to −0·13)	0·006	−0·52 (−0·77 to −0·27)	0·0002	0·12 (−0·24 to 0·49)	0·51

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McCarey et al. Lancet 2004; 363:2015-21

¿Puede el control de la inflamación, en ausencia de una reducción lipídica, disminuir los eventos CVs?

Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease

Vessel Wall   Macrophage/Monocyte   Adipose Tissue   NLRP3 Inflammasome

Upstream Targets and Biomarkers

5-LO Inhibitors
FLAP Inhibitors

Adalimumab
Infliximab → TNF-α

IL-1β
IL-18

Canakinumab
Anakinra
Colchicine

Anti-CAMs
SIRT activators

Leukotriene Function

Tocilizumab → IL-6

CCR2 CCR5 Antagonists

MMP-9

Low Dose Methotrexate

Darapladib
Varespladib

ICAM-1
VCAM
P-selectin
E-selectin

Monocyte Recruitment

Liver

Lp-PLA2
sPLA2

PAI-1

Downstream Targets and Biomarkers

Vascular risk hsCRP (mg/L)	
High	> 3 mg/L
Intermediate	1-3 mg/L
Low	< 1 mg/L

3.0
2.0
1.0

CRP

CRP RNA - Antisense Anti-CRPs

Fibrinogen

SAA

Terapia Convencional en AR: Metotrexato

1.240 pacientes con **AR** (sgto 18 años): Metotrexato proporcionó una reducción de la mortalidad global 60%, por reducción mortalidad CV 60%.

Choi et al. Lancet. 2002; 359:1173-7.

Nelson-Aalen cumulative hazard estimates

Calendar year of onset
- Earlier than 1970
- 1970-1980
- After 1990

Follow up in years

logrank p= 0.001
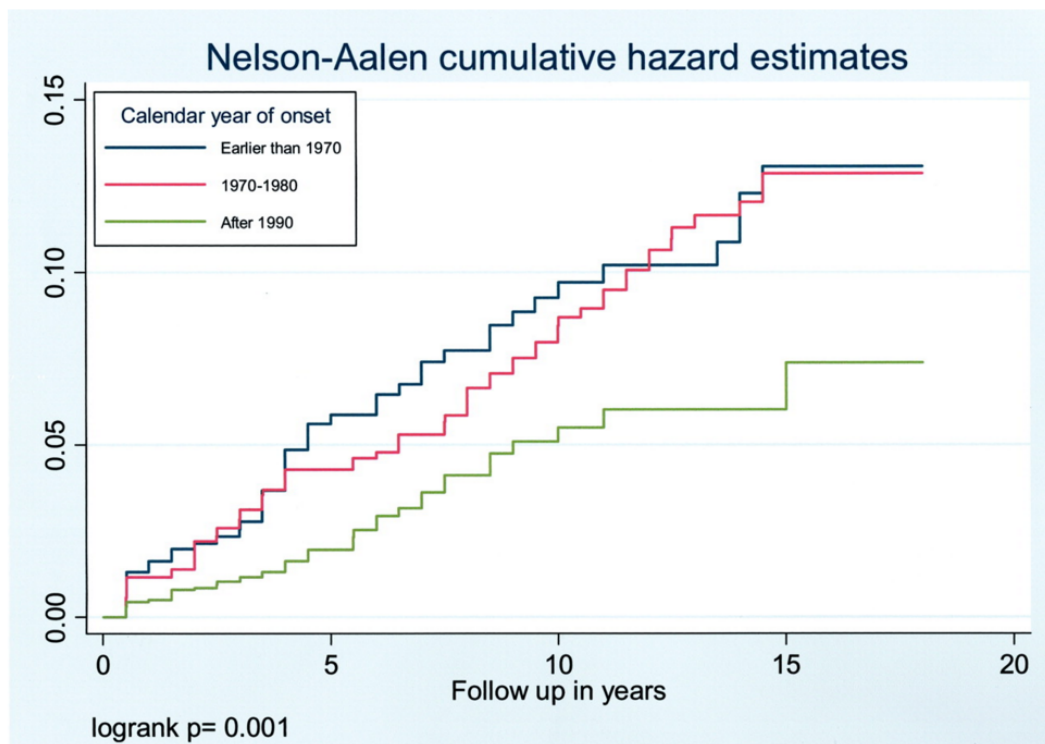
3.862 pacientes con AR seguidos de 1980 a 1997
Disminución significativa de infarto agudo del miocardio con Metotrexato

Krishnan et al. Circulation 2004; 110:1774-9.

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Anti-TNF-α y Resistencia a la Insulina
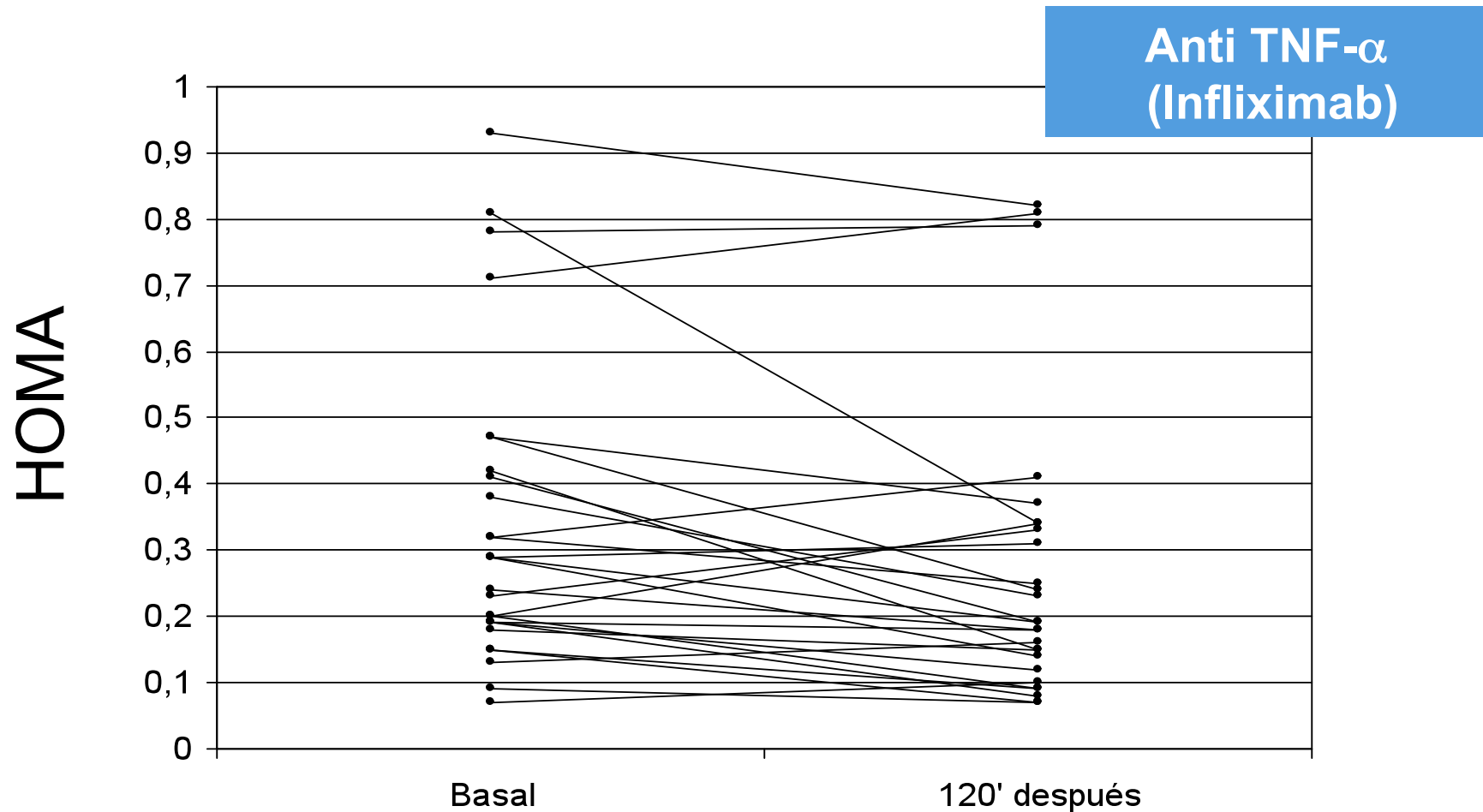
Mejora rápida de la resistencia a la insulina después de administración de Infliximab
27 pacientes con AR de larga evolución y en tratamiento crónico
durante 1 año con anti-TNF-α (**INFLIXIMAB**).

Terapia a largo plazo con Adalimumab mejora la Función Endotelial en pacientes con AR refractaria a Metotrexato

Anti TNF-α (Adalimumab)

7.4±2.8%

4.5±4.0%

p< 0.001
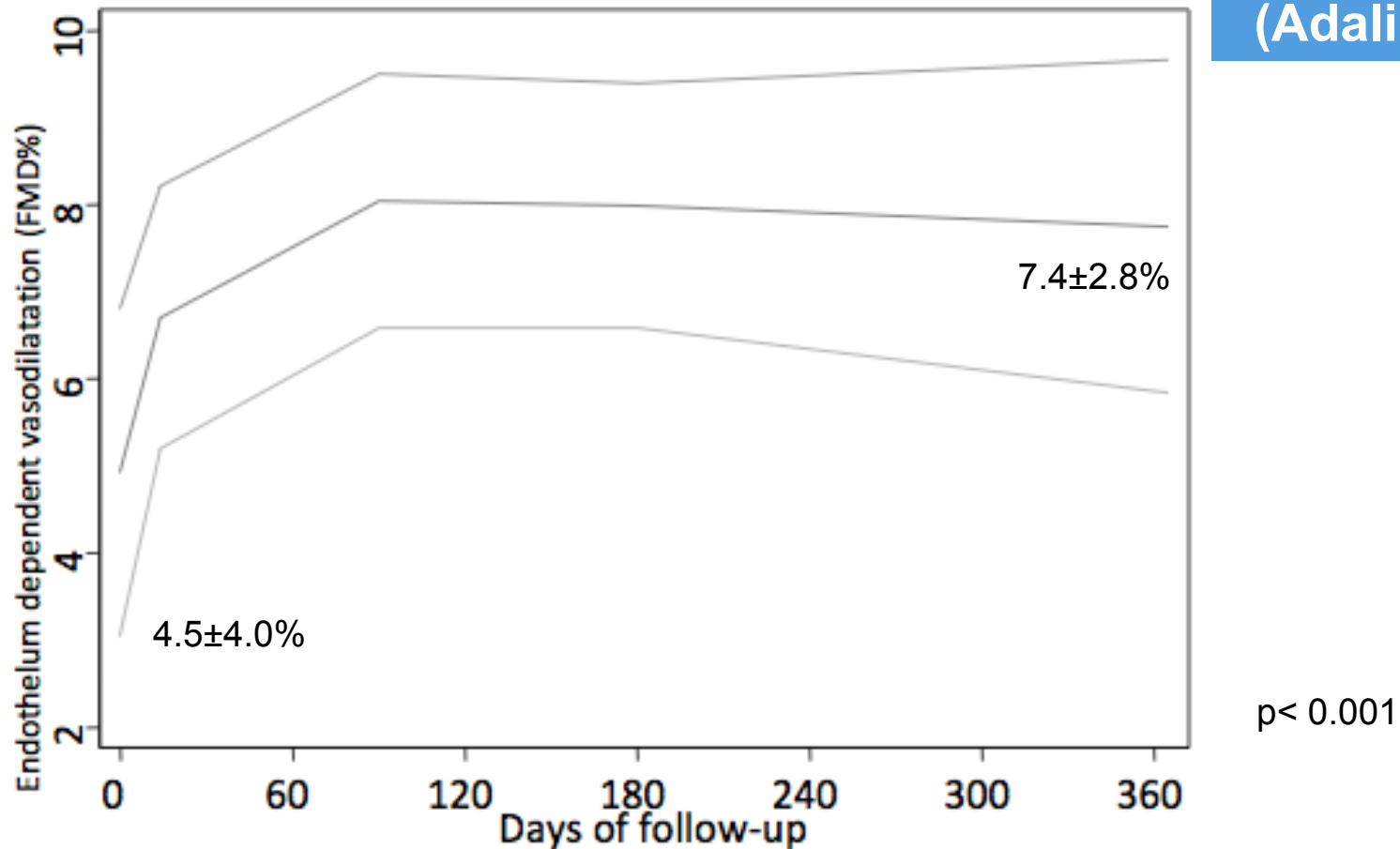
34 pacientes con AR refractarios al tto. con Metotrexato que inician tto. con Adalimumab:
Efecto activo de adalimumab sobre la función endotelial desde el inicio del tto.

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Anti-TNF-α and vascular inflammation in RA

Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation and Stiffness in Patients With Rheumatoid Arthritis

Kaisa M. Mäki-Petäjä, PhD; Maysoon Elkhawad, MRCS; Joseph Cheriyan, FRCP;
Francis R. Joshi, MRCP; Andrew J.K. Östör, MBBS, FRACP; Frances C. Hall, FRCP, DPhil;
James H.F. Rudd, PhD, MRCP; Ian B. Wilkinson, FRCP, DM

Background—Rheumatoid arthritis (RA) is a systemic inflammatory condition associated with increased cardiovascular risk. This is not fully explained by traditional risk factors, but direct vascular inflammation and aortic stiffening may play a role. We hypothesized that patients with RA exhibit aortic inflammation, which can be reversed with anti-tumor necrosis factor-α therapy and correlates with aortic stiffness reduction.

Methods and Results—Aortic inflammation was quantified in 17 patients with RA, before and after 8 weeks of anti-tumor necrosis factor-α therapy by using ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography coregistration. Concomitantly, 34 patients with stable cardiovascular disease were imaged as positive controls at baseline. Aortic fluorodeoxyglucose target-to-background ratios (TBRs) and aortic pulse wave velocity were assessed. RA patients had higher baseline aortic TBRs in comparison with patients who have cardiovascular disease (2.02 ± 0.22 versus 1.74 ± 0.22, $P=0.0001$). Following therapy, aortic TBR fell to 1.90 ± 0.29, $P=0.03$, and the proportion of inflamed aortic slices (defined as TBR >2.0) decreased from $50 \pm 33\%$ to $33 \pm 27\%$, $P=0.03$. Also, TBR in the most diseased segment of the aorta fell from 2.51 ± 0.33 to 2.05 ± 0.29, $P<0.0001$. Treatment also reduced aortic pulse wave velocity significantly (from 9.09 ± 1.77 to 8.63 ± 1.42 m/s, $P=0.04$), which correlated with the reduction of aortic TBR ($R=0.60$, $P=0.01$).

Conclusions—This study demonstrates that RA patients have increased aortic ^{18}F-fluorodeoxyglucose uptake in comparison with patients who have stable cardiovascular disease. Anti-tumor necrosis factor-α therapy reduces aortic inflammation in patients with RA, and this effect correlates with the decrease in aortic stiffness. These results suggest that RA patients exhibit a subclinical vasculitis, which provides a mechanism for the increased cardiovascular disease risk seen in RA. (*Circulation*. 2012;126:2473-2480.)

Circulation
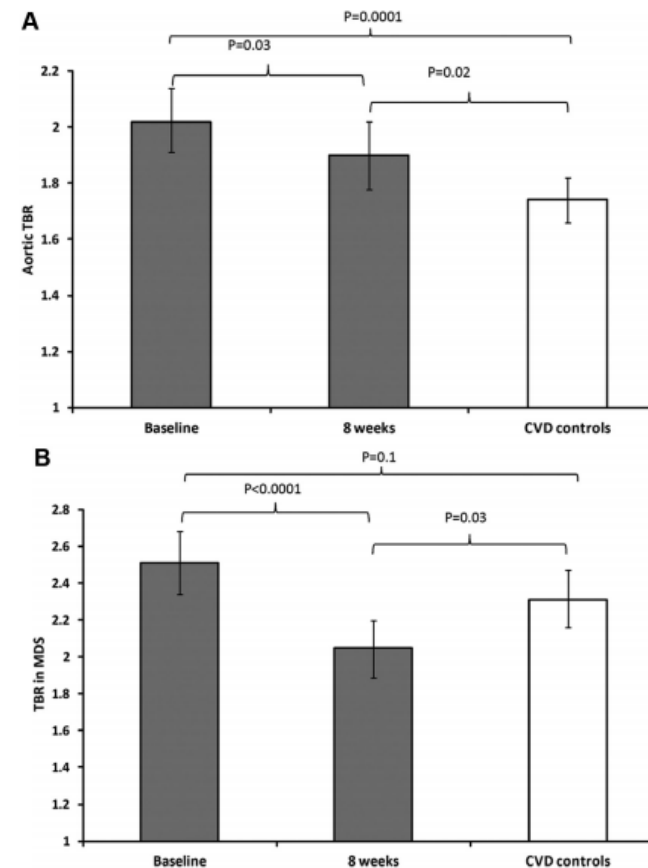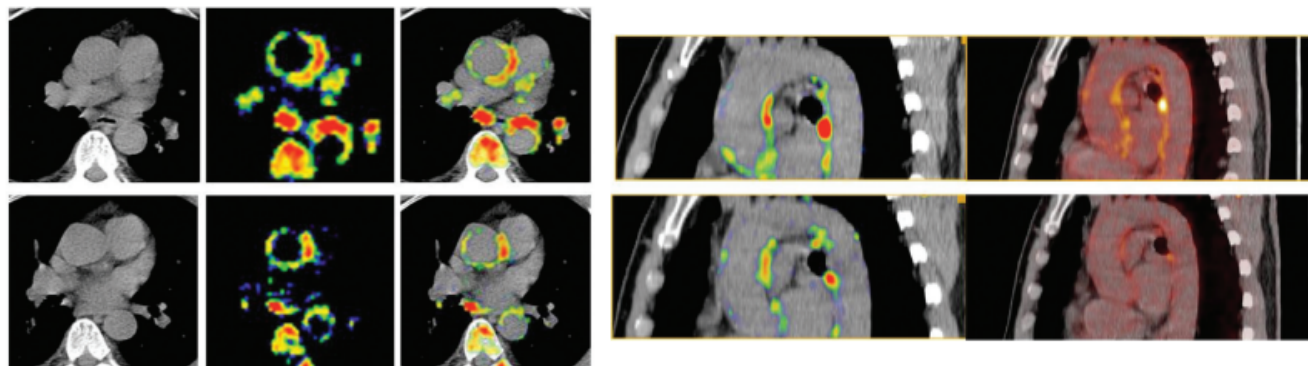
Table 3. The Effect of Anti-TNF-α Therapy on Disease Activity, Inflammatory Markers, and Hemodynamics

	Baseline	8 wk	P
DAS28 score	6.52 ± 0.78	4.38 ± 1.61	<0.0001
CRP, mg/L*	11.0 (4.0–29.0)	3.0 (2.0–10.0)	0.007
ESR, mm/h*	22 (8.5–41.0)	13.0 (7.0–17.0)	0.04
MAP, mm Hg	104 ± 11	104 ± 12	0.9
Augmentation index, %	31 ± 11	33 ± 11	0.4
Brachial PWV, m/s	9.00 ± 1.23	8.56 ± 1.11	0.06
Aortic PWV, m/s	9.09 ± 1.77	8.63 ± 1.42	0.04
Baseline diameter, mm	3.94 ± 0.59	3.91 ± 0.68	0.8
FMD, %	3.54 ± 2.34	6.66 ± 3.17	0.003
GTN response, %	9.53 ± 4.26	8.29 ± 5.63	0.9

British Society of Rheumatology Biologics Register

Reducción de la incidencia de IAM en pacientes con AR respondedores al tratamiento con bloqueadores del TNF-α.

Table 3. Incidence rates of verified first MI in nonresponders and responders to anti-TNFα treatment*

	Nonresponders (n = 1,638)	Responders (n = 5,877)
Person-years	1,815	9,886
No. of reported MIs	17	35
Rate of MIs per 1,000 person-years (95% CI)	9.4 (5.5–15.0)	3.5 (2.5–4.9)
Incidence rate ratio	Referent	0.38 (0.21–0.67)
Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22–0.68)
Incidence rate ratio, multivariate analysis†	Referent	0.36 (0.19–0.69)
Incidence rate ratio by sex, multivariate analysis†		
Male patients	Referent	0.31 (0.12–0.81)
Female patients	Referent	0.46 (0.20–1.06)

* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Adjusted for age, sex, disease severity, body mass index, social deprivation, smoking history, comorbidity, and baseline drug use.

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Dixon et al. Arthritis Rheum 2007; 56:2905-2912.

Review-meta-analysis: anti-TNF-α and CV events in RA

Table 1. Characteristics of studies included in the systematic review*

Author, year (ref.)	Source	Therapy comparison	Outcome	N	Disease duration, years	Followup time
St.Clair et al, 2004 (32)	Multinational study	INF vs. MTX	MI	1,040	0.8	54 weeks
Van de Putte et al, 2004 (33)	Multinational study	ADA vs. placebo (previous DMARD)	MI	544	11	26 weeks
Emery et al, 2008 (34)	Multinational study	ETN vs. MTX	Cardiovascular event	542	0.8	52 weeks
Geborek et al, 2002 (12)	Swedish registry	INF, ETN vs. leflunomide	MI	369	14	NR
Wolfe and Michaud, 2004 (15)	American registry	INF, ETN vs. DMARD†	CHF	13,171	15	NR
Jacobsson et al, 2005 (24)	Swedish registry, administrative data	INF, ETN vs. DMARD	Cardiovascular event, MI, CHF, CVA	983	11	4 years
Carmona et al, 2007 (16)	Spanish registry	Anti-TNFα vs. MTX	Cardiovascular event, CHF, CVA, mortality	1,578	NR	5 years
Curtis et al, 2007 (18)	American insurance claims	INF, ETN vs. MTX	CHF	2,121	NR	21 months
Cole et al, 2007 (17)	American veterans	INF, ETN, ADA vs. RA control group	CHF, mortality	203	NR	NR
Dixon et al, 2007 (14)	British registry	INF, ETN, ADA vs. DMARD	MI	10,755	12	1.7 years
Wolfe and Michaud, 2007 (35)	American registry	INF, ETN, ADA vs. RA control group‡	MI	25,343	NR	NR
Jacobsson et al, 2008 (36)	Swedish registry	TNF vs. DMARD	Cardiovascular event, MI, CVA	26,383	NR	NR
Listing et al, 2008 (13)	German registry	INF, ETN, ADA vs. DMARD	CHF	4,248	9	NR
Naranjo et al, 2008 (37)	Multinational study	TNF vs. DMARD	Cardiovascular event, MI, CVA	4,363	11	NR
Setoguchi et al, 2008 (19)	American insurance claims	INF, ETN vs. MTX	CHF	5,593	NR	2.5 years
Solomon et al, 2008 (38)	American registry	TNF vs. DMARD	Cardiovascular event	10,870	7	2 years

Anti-TNF-α therapy was associated with a reduced risk for all **CV events** (RR 0.46), **MI** (RR 0.81), and **CVA** (RR 0.69).

IL-6 Tocilizumab improves the proatherothrombotic profile of rheumatoid arthritis patients modulating endothelial dysfunction, NETosis, and inflammation
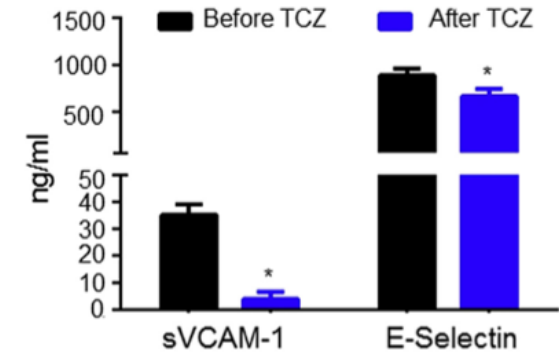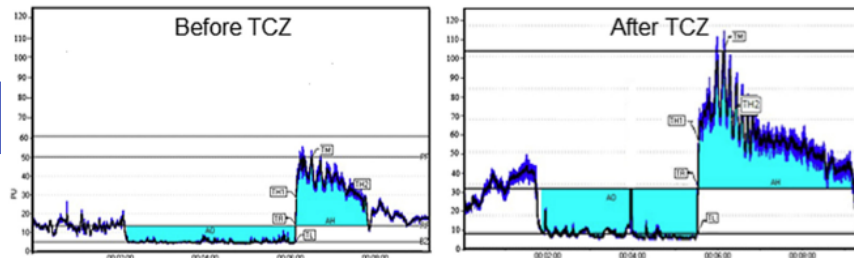
TRANSLATIONAL RESEARCH
The Journal of Laboratory and Clinical Medicine

20 pacientes con AR. Tocilizumab 162mg/semana. Sgto 6 meses

Función endotelial

	Before TCZ	After TCZ	p value
PF	71.23 ± 6.06	87.17 ± 10.10*	0.010
AH	2314.03 ± 300.73	3846.54 ± 575.64*	0.041
BZ-PF	1098.23 ± 109.65	1324.37 ± 167.19	0.360
TH1	2.39 ± 0.85	1.48 ± 0.37	0.390
TH2	48.44 ± 9.80	42.11 ± 3.80	0.430

Estrés oxidativo
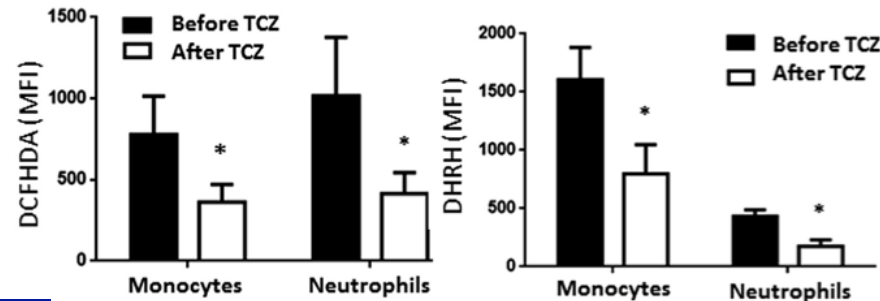
Producción de Peróxidos y peroxinitritos en monocitos y neutrófilos de pacientes con AR antes y después del tto. con TCZ

Estado Protrombótico

Mejora del estado protrombótico de pacientes con AR tras tto. con TCZ
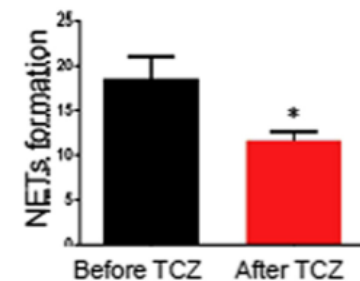
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

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

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Paul M Ridker MD MPH
Eugene Braunwald Professor of Medicine
Harvard Medical School
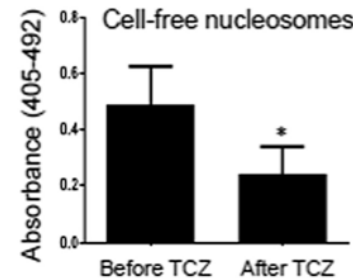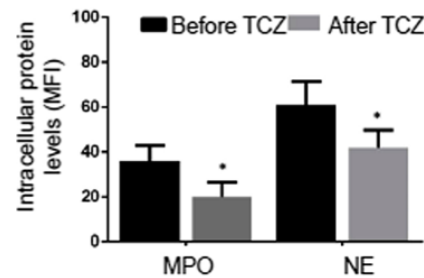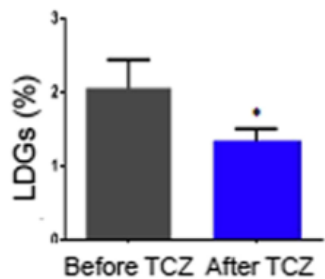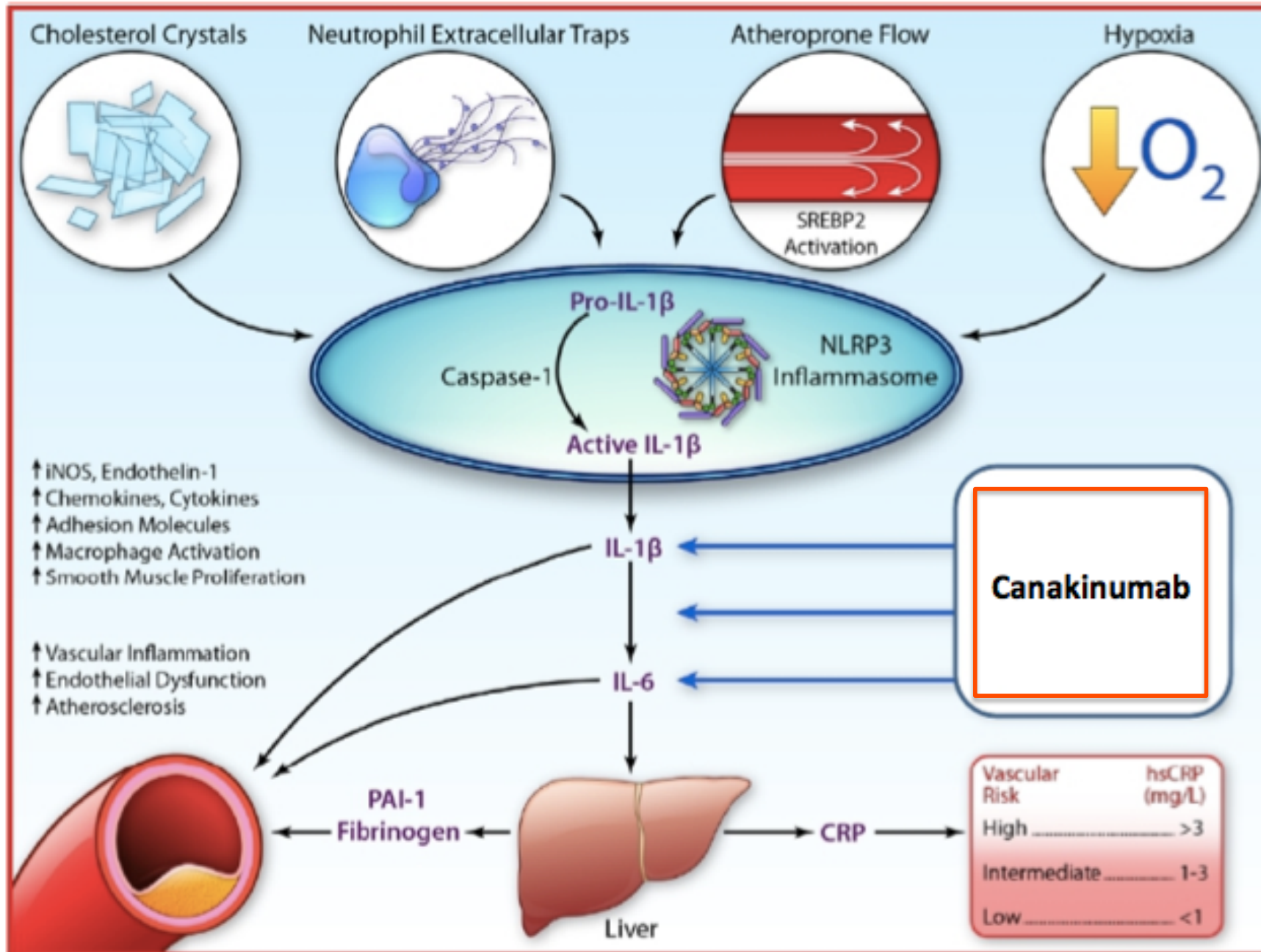Director, Center for
Cardiovascular Disease Prevention
Brigham and Women's Hospital
Boston, MA USA
pridker@partners.org

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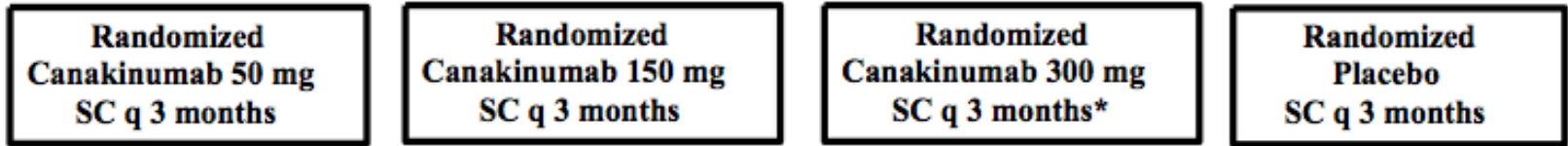
Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)

Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality

Ridker PM. N Engl J Med 2017; 377:1119-1131

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

39 countries
> 1000 investigators

17482 Screened

7377 Excluded Prior to Entering Randomization Process
- 146 refused consent
- 71 child-bearing potential
- 44 age out of range
- 251 no documented MI
- 3390 hsCRP < 2 mg/L
- 728 exclusionary concomitant disease
- 1873 tuberculosis risk factors
- 104 infectious disease
- 76 immunocompromised state
- 27 life threatening condition
- 574 withdrew consent
- 137 site closure
- 81 physician decision
- 49 unable to contact
- 7 adverse event
- 11 died
- 139 other reasons

10105 Entered Into Randomization Process

44 Failed Randomization Process
- 41 Invalid randomization
- 3 major GCP violations

10061 Successfully Randomized

3344 placebo
18.1% discontinued study drug
3335 known final vital status
9 unknown final vital status

2170 canakinumab 50mg
16.7% discontinued study drug
2161 known final vital status
9 unknown final vital status

2284 canakinumab 150mg
19.2% discontinued study drug
2279 known final vital status
5 unknown final vital status

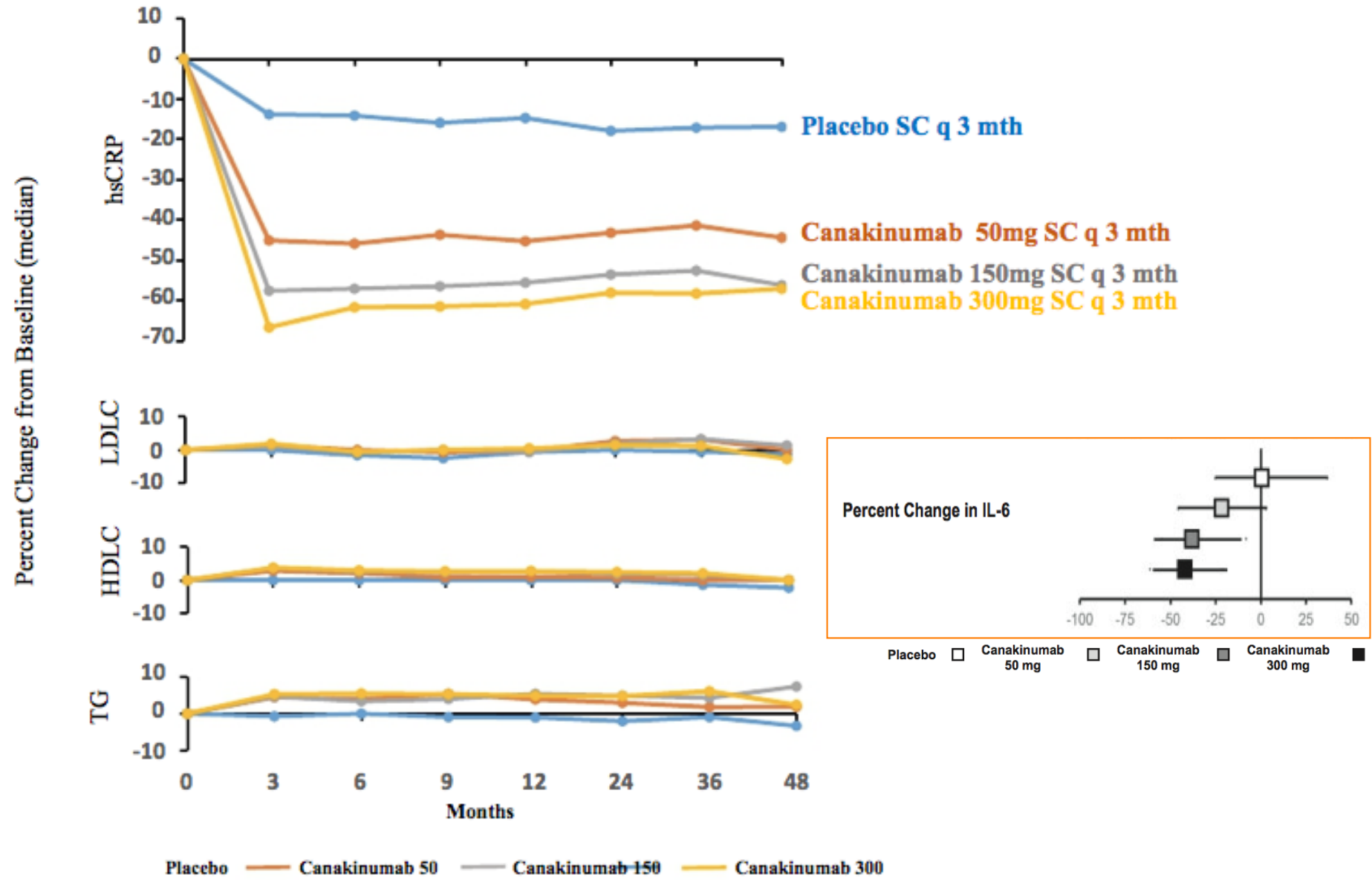**2263 canakinumab 300mg**
20.1% discontinued study drug
2259 known final vital status
4 unknown final vital status

Ridker PM. N Engl J Med 2017; 377:1119-1131

CANTOS - Baseline Clinical Characteristics

		Canakinumab SC q 3 months		
Characteristic	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Female (%)	25.9	24.9	25.2	26.8
Current smoker (%)	22.9	24.5	23.4	23.7
Diabetes (%)	39.9	39.4	41.8	39.2
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Prior Revascularization (%)	79.6	80.9	82.2	80.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0
Triglycerides (mg/dL)	139	139	139	138
hsCRP (mg/L)	4.1	4.1	4.2	4.1

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

Placebo SC q 3 mth

Canakinumab 50mg SC q 3 mth

Canakinumab 150mg SC q 3 mth
Canakinumab 300mg SC q 3 mth

Percent Change in IL-6

Placebo □   Canakinumab 50 mg ▨   Canakinumab 150 mg ▨   Canakinumab 300 mg ■

Placebo —— Canakinumab 50 —— Canakinumab 150 —— Canakinumab 300

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CANTOS: Primary Cardiovascular Endpoint (MACE)

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

—— Placebo SC q 3 months

----- Canakinumab 150/300 SC q 3 months

HR 0.85
95%CI 0.76-0.96
P = 0.007

35% reduction in IL6

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE

Cumulative Incidence (%)

Follow-up Years

Ridker PM. N Engl J Med 2017; 377:1119-1131

CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

Ridker PM. N Engl J Med 2017; 377:1119-1131
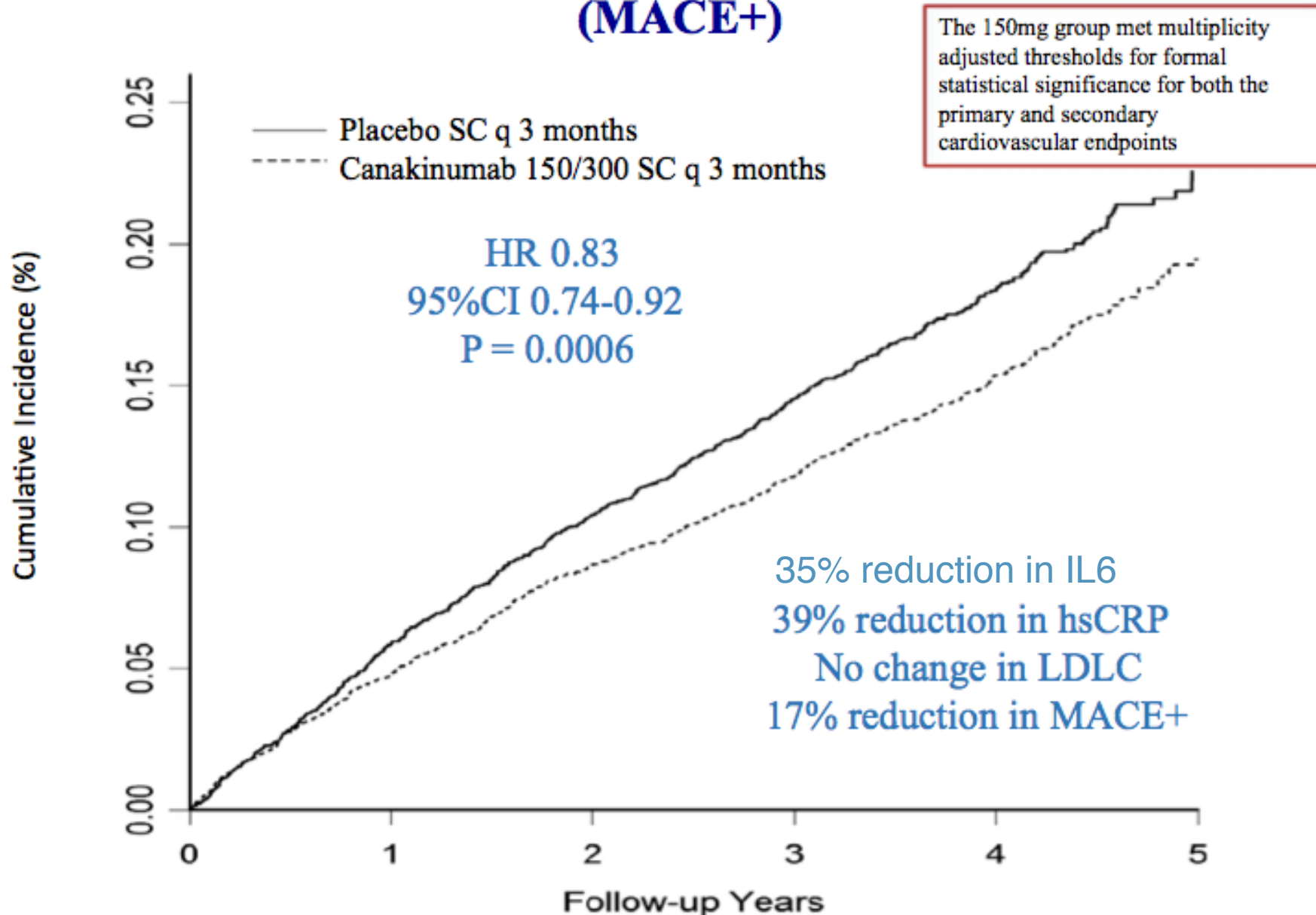
CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

Endpoint	Placebo (N=3347)	Canakinumab SC q 3 months			P-trend
		50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	
Primary	1.00	0.93	0.85	0.86	0.020
Secondary	1.00	0.90	0.83	0.83	0.002
Myocardial Infarction	1.00	0.94	0.76	0.84	0.028
Urgent Revascularization	1.00	0.70	0.64	0.58	0.005
Any Coronary Revascularization	1.00	0.72	0.68	0.70	<0.001
Stroke	1.00	1.01	0.98	0.80	0.17
Cardiac Arrest	1.00	0.72	0.63	0.46	0.035
CV Death	1.00	0.89	0.90	0.94	0.62
All Cause Mortality	1.00	0.94	0.92	0.94	0.39

Ridker PM. N Engl J Med 2017; 377:1119-1131

CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)

Placebo
Canakinumab (on treatment hsCRP ≥ 2mg/L
Canakinumab (on treatment hsCRP < 2 mg/L

HR	(95%CI)	P
1.0	(referent)	(referent)
0.91	(0.81-1.03)	0.14
0.74	(0.65-0.83)	0.0001

HR 0.74
95%CI 0.65-0.83
P=0.0001
for those with on-treatment hsCRP < 2 mg/L

Cumulative Incidence (%)

Follow-up Years

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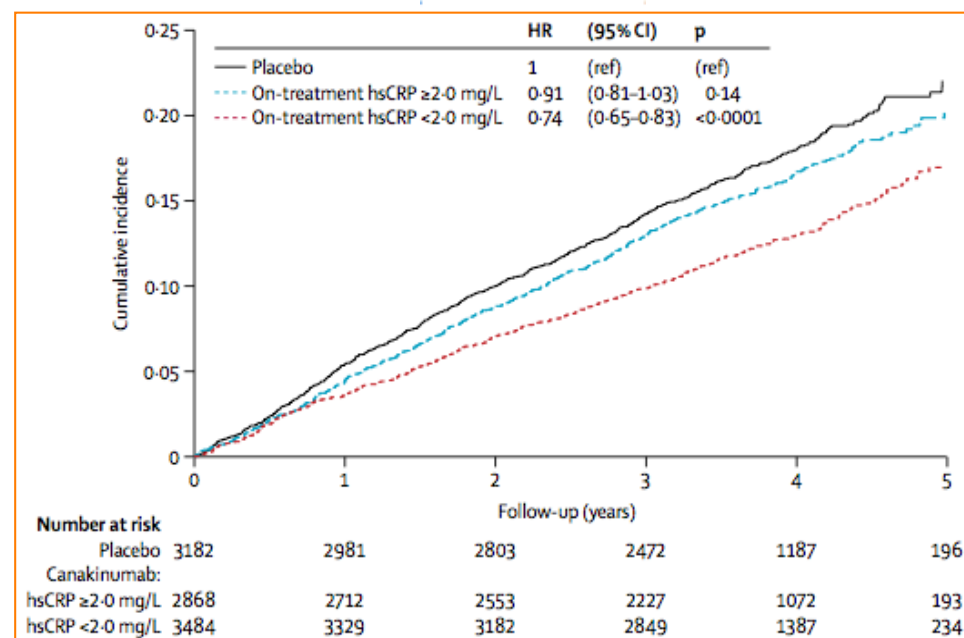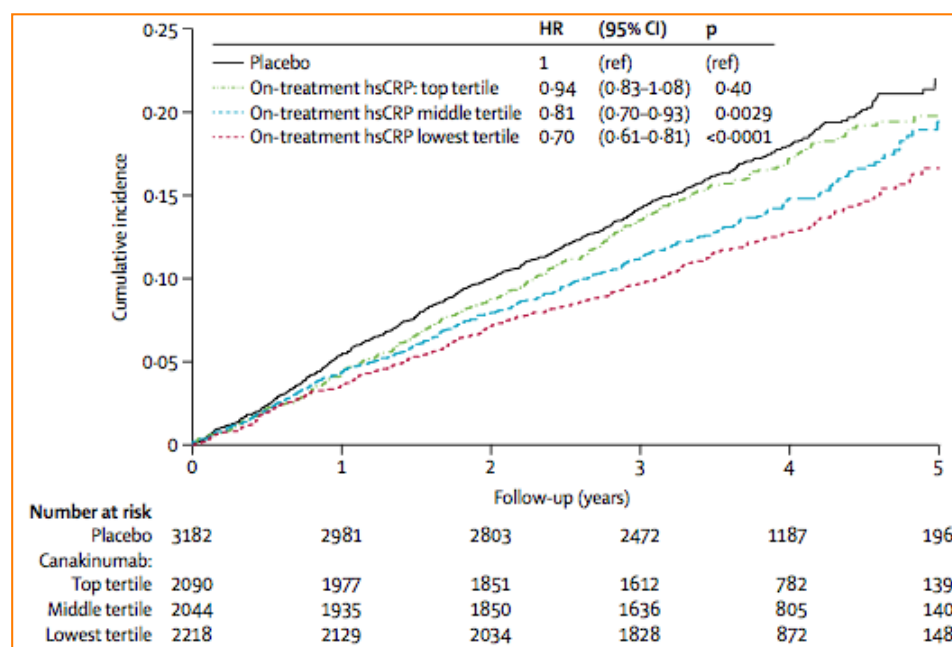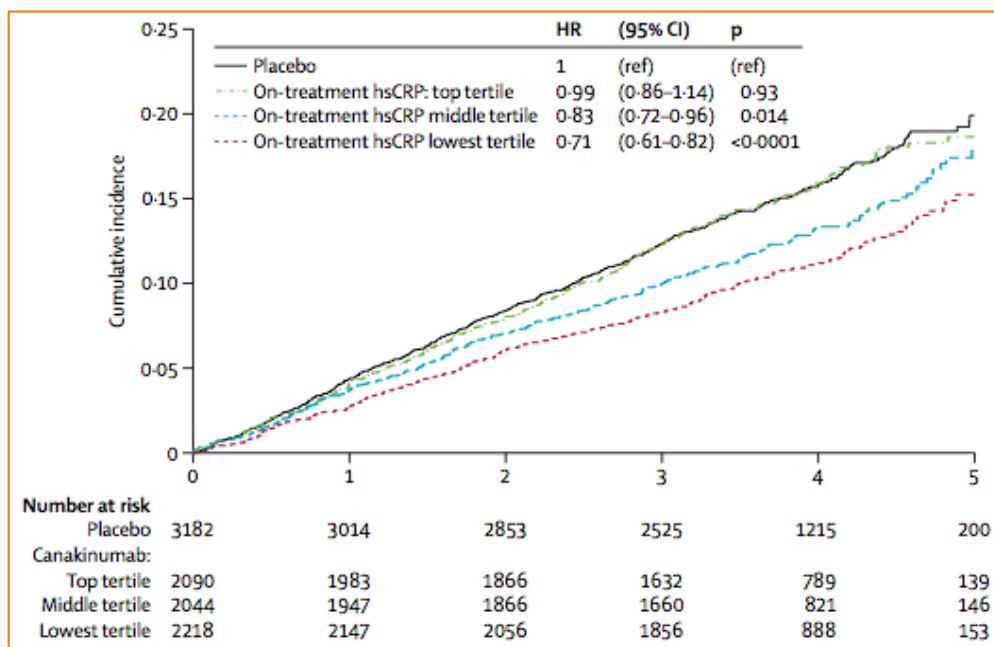Ridker PM. N Engl J Med 2017; 377:1119-1131

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

THE LANCET

MACE

	HR	(95% CI)	p
Placebo	1	(ref)	(ref)
On-treatment hsCRP ≥2·0 mg/L	0·95	(0·84–1·09)	0·48
On-treatment hsCRP <2·0 mg/L	0·75	(0·66–0·85)	<0·0001

MACE+

	HR	(95% CI)	p
Placebo	1	(ref)	(ref)
On-treatment hsCRP ≥2·0 mg/L	0·91	(0·81–1·03)	0·14
On-treatment hsCRP <2·0 mg/L	0·74	(0·65–0·83)	<0·0001

MACE — Number at risk

	0	1	2	3	4	5
Placebo	3182	3014	2853	2525	1215	200
Canakinumab: hsCRP ≥2·0 mg/L	2868	2724	2574	2258	1087	195
hsCRP <2·0 mg/L	3484	3353	3214	2890	1411	243

MACE+ — Number at risk

	0	1	2	3	4	5
Placebo	3182	2981	2803	2472	1187	196
Canakinumab: hsCRP ≥2·0 mg/L	2868	2712	2553	2227	1072	193
hsCRP <2·0 mg/L	3484	3329	3182	2849	1387	234

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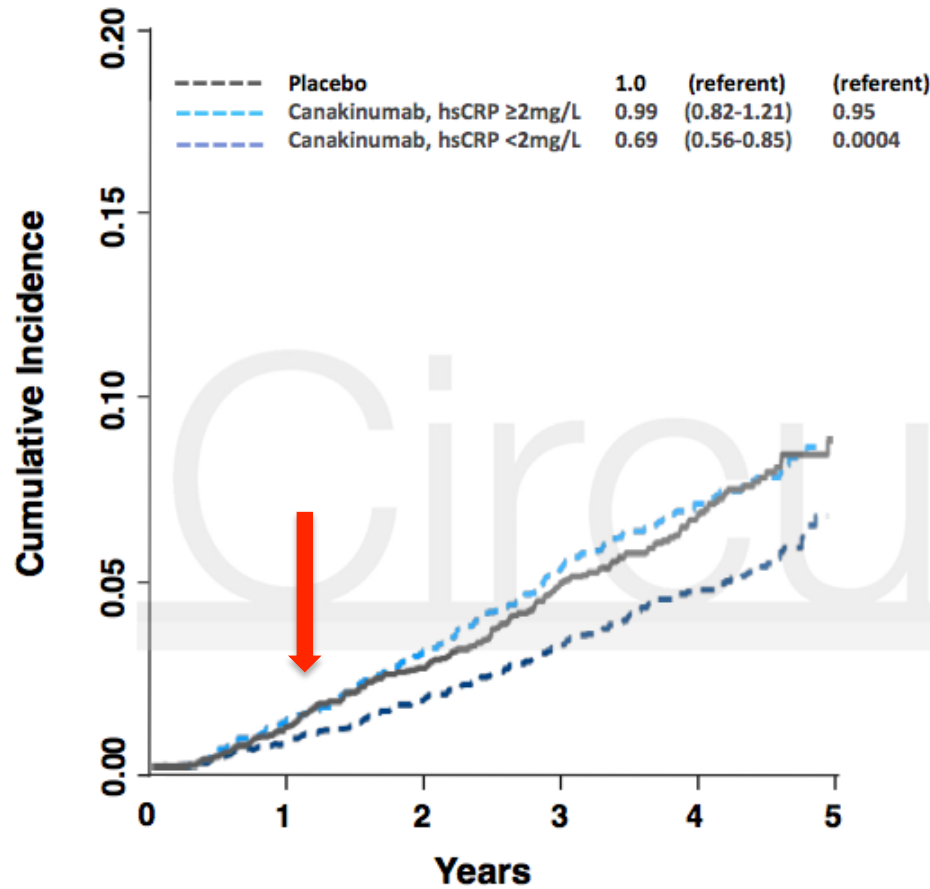
THE LANCET

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

THE LANCET

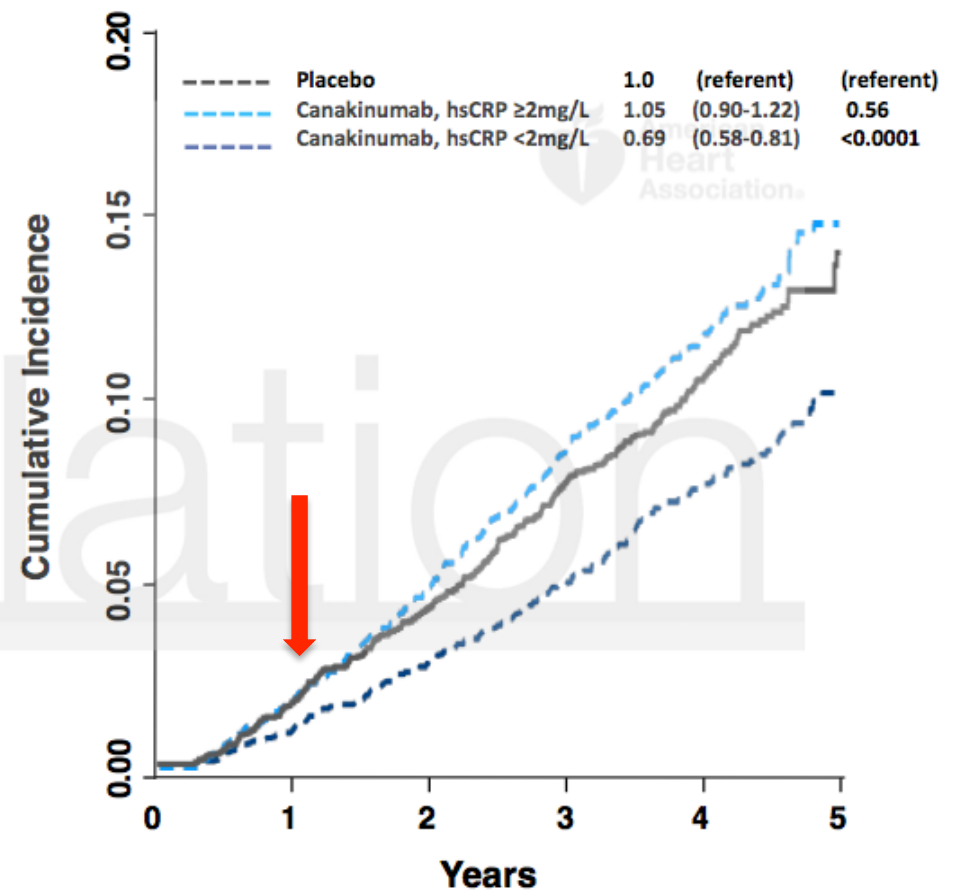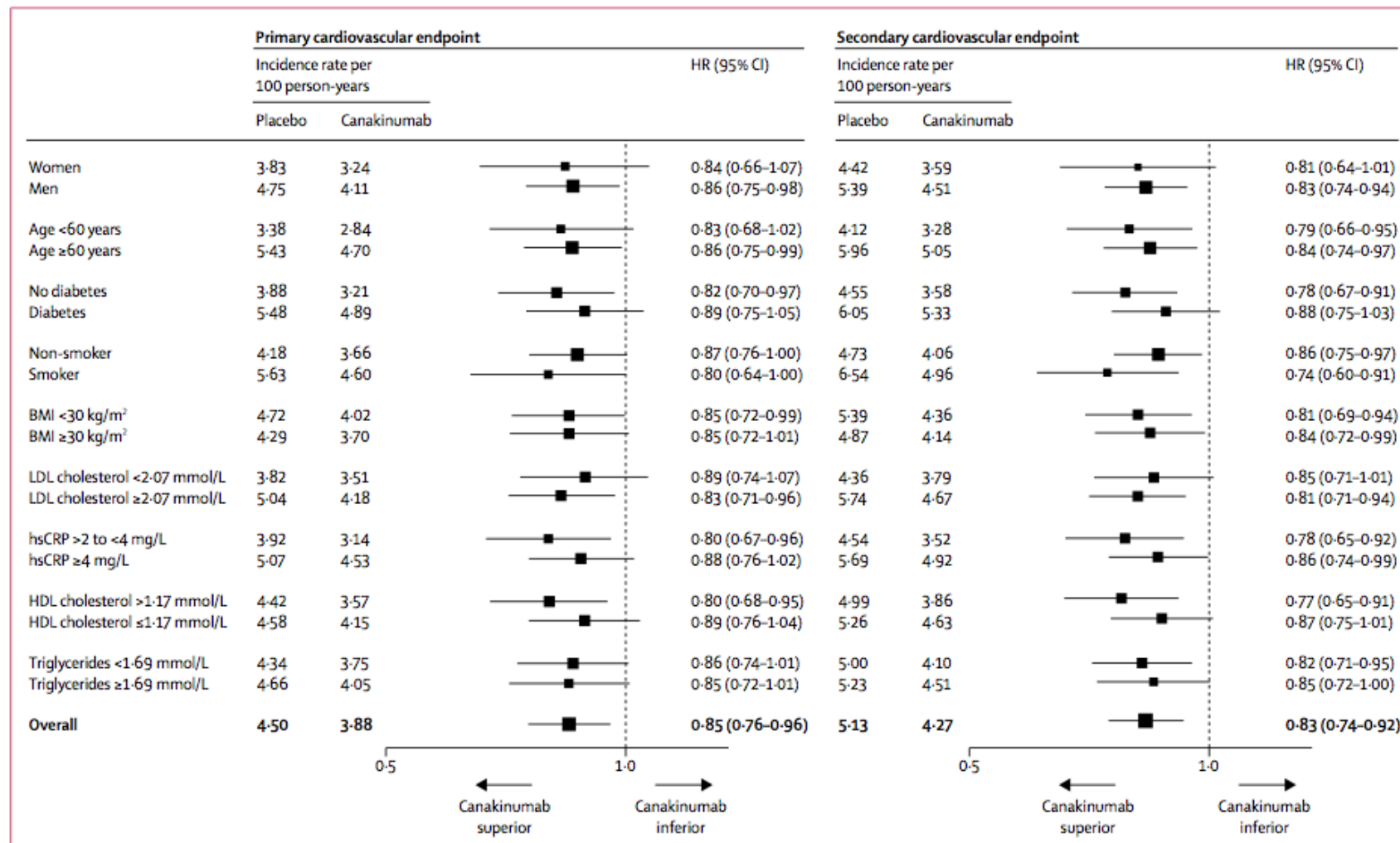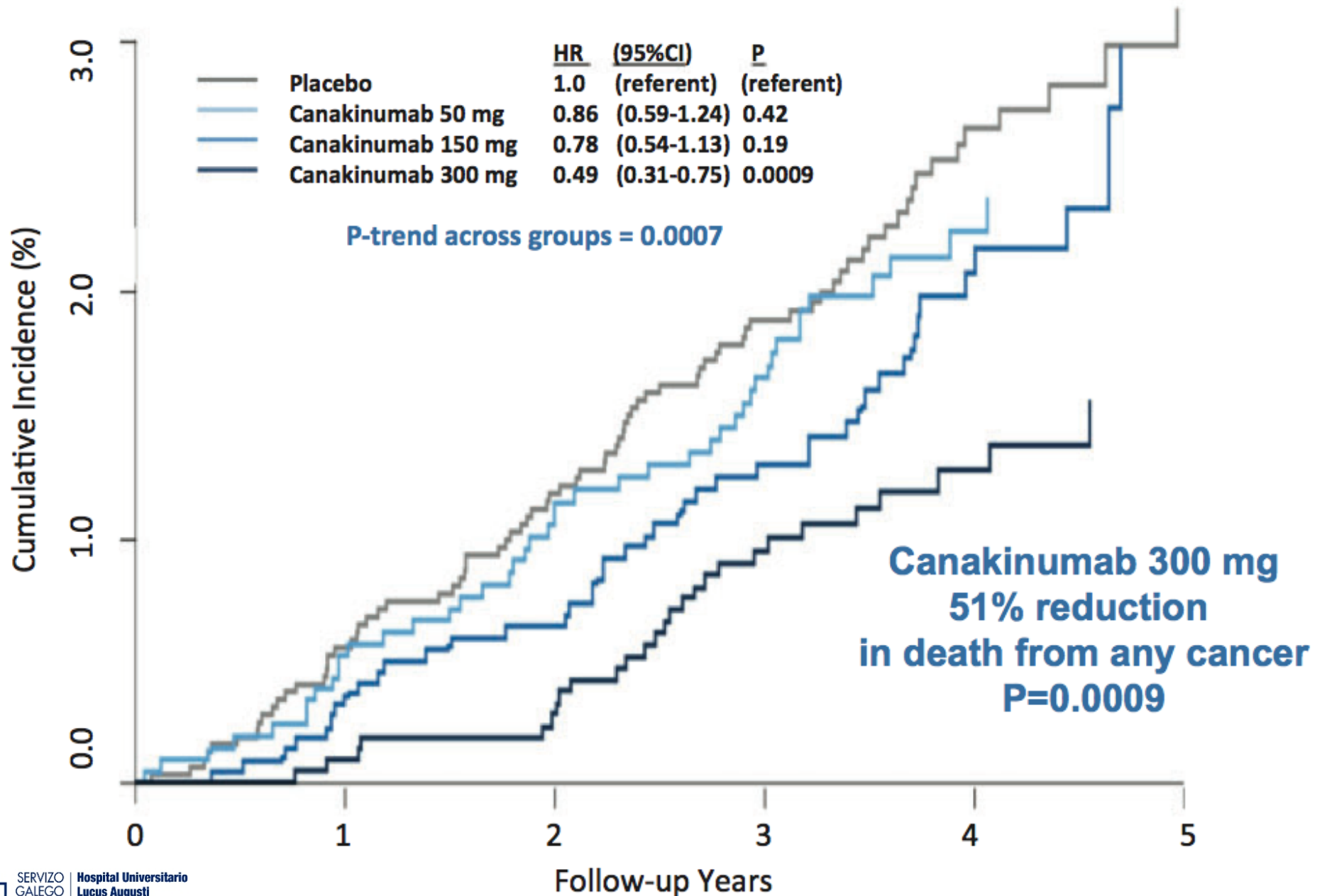|	Placebo (n=3182)	Canakinumab, hsCRP ≥2 mg/L at 3 months (n=2868)	Canakinumab, hsCRP <2 mg/L at 3 months (n=3484)	p_trend across categories
Myocardial infarction, stroke, or death from any cause				
Incidence rate (n)	5·39 (614)	5·38 (553)	3·96 (508)	..
HR[adj] (95% CI)	1 (ref)	0·93 (0·83–1·05)	0·73 (0·65–0·82)	..
p value	Ref	0·25	<0·0001	<0·0001
Cardiovascular death				
Incidence rate (n)	1·74 (211)	1·83 (198)	1·22 (164)	..
HR[adj] (95% CI)	1 (ref)	0·99 (0·82–1·21)	0·69 (0·56–0·85)	..
p value	Ref	0·95	0·0004	0·0004
All-cause mortality				
Incidence rate (n)	2·79 (338)	3·14 (339)	1·96 (264)	..
HR[adj] (95% CI)	1 (ref)	1·05 (0·90–1·22)	0·69 (0·58–0·81)	..
p value	Ref	0·56	<0·0001	<0·0001

Incidence rates are calculated per 100 person-years of exposure. Covariates included in the adjusted multivariable model include age, sex, smoking status, hypertension, diabetes, body-mass index, baseline concentration of hsCRP, and baseline concentration of LDL cholesterol. HR[adj]=adjusted hazard ratio. hsCRP=high-sensitivity C-reactive protein.

Table 3: Incidence rates and adjusted hazard ratios for additional prespecified cardiovascular endpoints in CANTOS, according to on-treatment hsCRP concentrations at 3 months, <2 mg/L or ≥2 mg/L

Circulation

CANTOS - Cardiovascular Mortality

Placebo	1.0	(referent)	(referent)
Canakinumab, hsCRP ≥2mg/L	0.99	(0.82-1.21)	0.95
Canakinumab, hsCRP <2mg/L	0.69	(0.56-0.85)	0.0004

CANTOS - All Cause Mortality

Placebo	1.0	(referent)	(referent)
Canakinumab, hsCRP ≥2mg/L	1.05	(0.90-1.22)	0.56
Canakinumab, hsCRP <2mg/L	0.69	(0.58-0.81)	<0.0001

Ridker PM. Circulation published online December 22, 2017

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

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	Primary cardiovascular endpoint				Secondary cardiovascular endpoint			
	Incidence rate per 100 person-years			HR (95% CI)	Incidence rate per 100 person-years			HR (95% CI)
	Placebo	Canakinumab			Placebo	Canakinumab		
Women	3·83	3·24		0·84 (0·66–1·07)	4·42	3·59		0·81 (0·64–1·01)
Men	4·75	4·11		0·86 (0·75–0·98)	5·39	4·51		0·83 (0·74–0·94)
Age <60 years	3·38	2·84		0·83 (0·68–1·02)	4·12	3·28		0·79 (0·66–0·95)
Age ≥60 years	5·43	4·70		0·86 (0·75–0·99)	5·96	5·05		0·84 (0·74–0·97)
No diabetes	3·88	3·21		0·82 (0·70–0·97)	4·55	3·58		0·78 (0·67–0·91)
Diabetes	5·48	4·89		0·89 (0·75–1·05)	6·05	5·33		0·88 (0·75–1·03)
Non-smoker	4·18	3·66		0·87 (0·76–1·00)	4·73	4·06		0·86 (0·75–0·97)
Smoker	5·63	4·60		0·80 (0·64–1·00)	6·54	4·96		0·74 (0·60–0·91)
BMI <30 kg/m²	4·72	4·02		0·85 (0·72–0·99)	5·39	4·36		0·81 (0·69–0·94)
BMI ≥30 kg/m²	4·29	3·70		0·85 (0·72–1·01)	4·87	4·14		0·84 (0·72–0·99)
LDL cholesterol <2·07 mmol/L	3·82	3·51		0·89 (0·74–1·07)	4·36	3·79		0·85 (0·71–1·01)
LDL cholesterol ≥2·07 mmol/L	5·04	4·18		0·83 (0·71–0·96)	5·74	4·67		0·81 (0·71–0·94)
hsCRP >2 to <4 mg/L	3·92	3·14		0·80 (0·67–0·96)	4·54	3·52		0·78 (0·65–0·92)
hsCRP ≥4 mg/L	5·07	4·53		0·88 (0·76–1·02)	5·69	4·92		0·86 (0·74–0·99)
HDL cholesterol >1·17 mmol/L	4·42	3·57		0·80 (0·68–0·95)	4·99	3·86		0·77 (0·65–0·91)
HDL cholesterol ≤1·17 mmol/L	4·58	4·15		0·89 (0·76–1·04)	5·26	4·63		0·87 (0·75–1·01)
Triglycerides <1·69 mmol/L	4·34	3·75		0·86 (0·74–1·01)	5·00	4·10		0·82 (0·71–0·95)
Triglycerides ≥1·69 mmol/L	4·66	4·05		0·85 (0·72–1·01)	5·23	4·51		0·85 (0·72–1·00)
Overall	4·50	3·88		0·85 (0·76–0·96)	5·13	4·27		0·83 (0·74–0·92)

0·5   1·0

Canakinumab superior ← → Canakinumab inferior

CANTOS: Additional Outcomes (per 100 person years of exposure)

Adverse Event	Placebo (N=3347)	Canakinumab SC q 3 months			P-trend
		50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	
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

* P-value for combined canakinumab doses vs placebo

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Ridker PM. N Engl J Med 2017; 377:1119-1131

CANTOS: Dose-dependent Benefits on All-Cause Cancer Mortality

CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer

	HR	(95%CI)	P
Placebo	1.0	(referent)	(referent)
Canakinumab 50 mg	0.77	(0.49-1.20)	0.25
Canakinumab 150 mg	0.61	(0.39-0.97)	0.034
Canakinumab 300 mg	0.33	(0.18-0.59)	0.00008

P-trend across groups = 0.0003

Canakinumab 300 mg
67% reduction
in incident lung cancer
P =0.00008

Cumulative Incidence (%)

Follow-up Years

Ridker PM. N Engl J Med 2017; 377:1119-1131
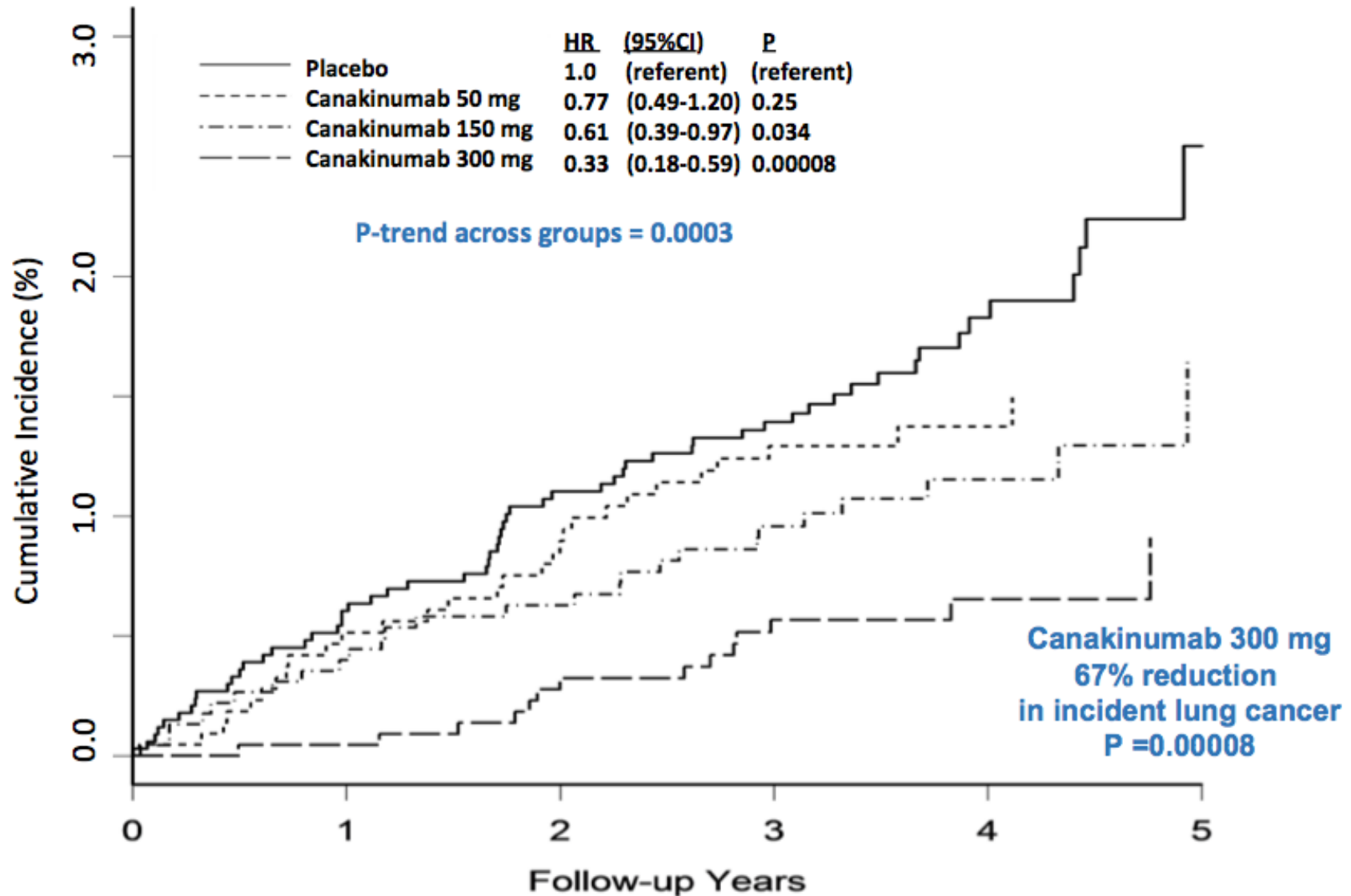
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Fatal Lung Cancer

	HR	(95%CI)	P
Placebo	1.0	(referent)	(referent)
Canakinumab 50 mg	0.71	(0.40-1.26)	0.24
Canakinumab 150 mg	0.64	(0.36-1.14)	0.13
Canakinumab 300 mg	0.23	(0.10-0.54)	0.0002

P-trend across groups = 0.0002

Canakinumab 300 mg
77% reduction
in fatal lung cancer
P =0.0002

Cumulative Incidence (%)

Follow-up Years
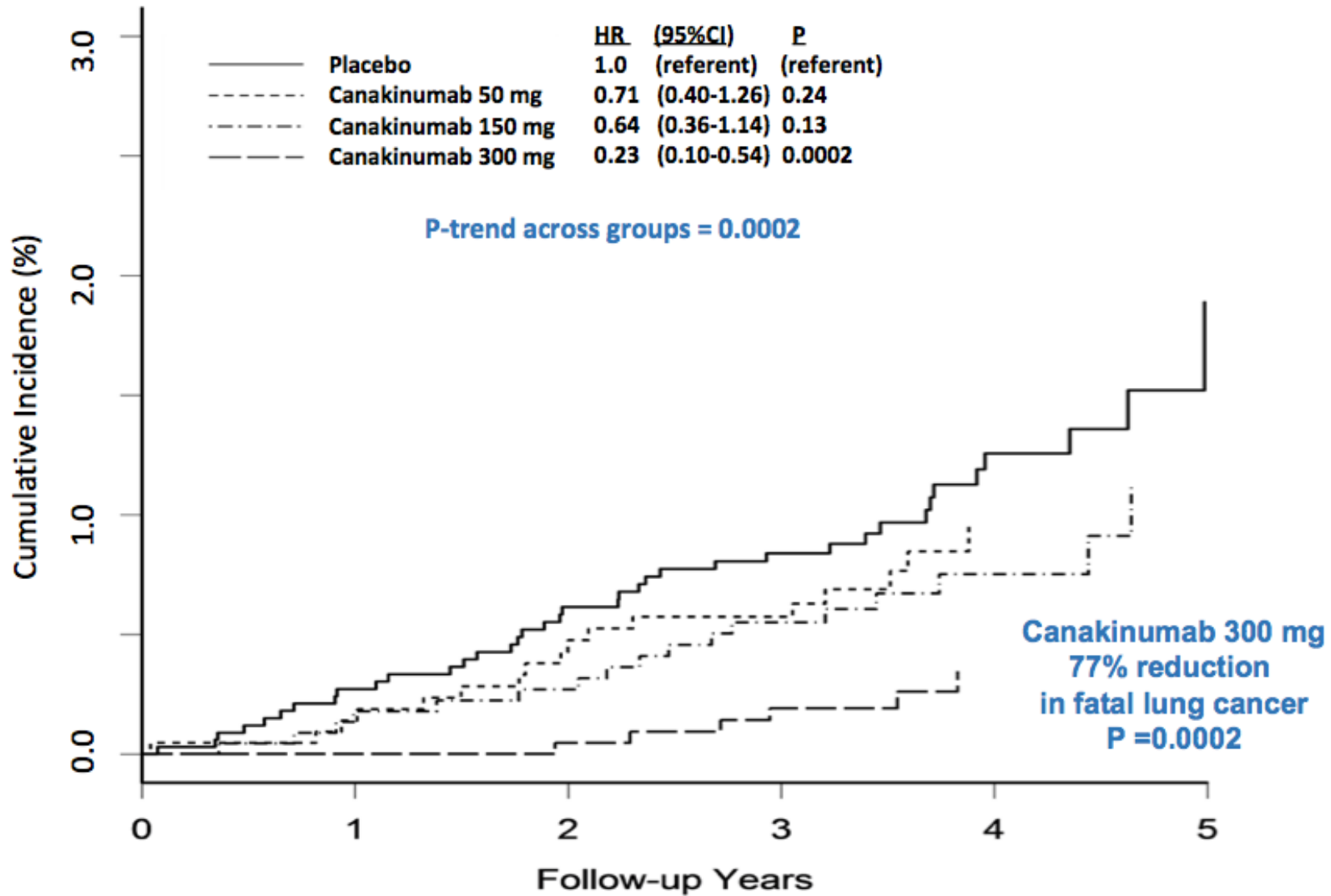
Riesgo Inflamatorio Residual:
Terapia personalizada en C. Isquémica

Teoría inflamatoria en C. Isquémica

Known Cardiovascular Disease
LDL 150 mg/dL
hsCRP 4.5mg/L

↓

High Intensity Statin

"Residual Cholesterol Risk"

LDL high
hsCRP low

↓ LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/ODYSSEY   PCSK9 Inhibition q2 weeks 15% RRR

"Residual Inflammatory Risk"

LDL low
hsCRP high

↓ LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

No Prior Proof of Concept
Canakinumab 150mg sc q3 months 15%RRR

"Residual Thrombotic Risk"

HTPR

↓

Additional antiplatelet &
anticoagulant therapy

ATLAS: Rivaroxaban 10% RRR
PEGASUSS: Ticagrelor 16% RRR

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Ongoing trials of inflammation in CAD

Methotrexate

Cardiovascular inflammation reduction trial (CIRT)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent elevation
of hsCRP (> 2 mg L^{-1})

↓

Open label active run-in
LDM 10 mg wk^{-1}

Randomized
VLDM 10 mg wk^{-1} +
folate

Randomized
Placebo mg wk^{-1} +
folate

Non-fatal MI, non-fatal stroke, cardiovascular death

Colchicine

Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)

Post MI within the last 30 days
On statin, ACE/ARB, BB, ASA
Completed any planned percutaneous
revascularization procedures

Randomized
Colchicine 0.5mg
once at day

Randomized
Placebo 0.5mg
once at day

Non-fatal MI, non-fatal stroke, CV death,
resuscitated CV arrest, hospitalization for
angina requiring coronary revascularization

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Reducción de la respuesta antiinflamatoria: una nueva aproximación

- Inflamación y enfermedad cardiovascular: mecanismos fisiopatológicos.

- Inflamación crónica y riesgo cardiovascular: evidencias clínicas

- Enfermedad cardiovascular en las EIC y su pronóstico.

- Control de la inflamación y reducción del riesgo CV.

- **Abordaje de manejo clínico del riesgo cardiovascular en las EIC.**

Manejo RCV en EIC

CÁLCULO DEL RIESGO CARDIOVASCULAR

Control INFLAMACIÓN

Control FRCV clásicos

EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update

R Agca,[1] S C Heslinga,[1] S Rollefstad,[2] M Heslinga,[1] I B McInnes,[3] M J L Peters,[4] T K Kvien,[5] M Dougados,[6] H Radner,[7] F Atzeni,[8] J Primdahl,[9,10,11] A Södergren,[12] S Wallberg Jonsson,[12] J van Rompay,[13] C Zabalan,[14] T R Pedersen,[15] L Jacobsson,[16,17] K de Vlam,[18] M A Gonzalez-Gay,[19] A G Semb,[20] G D Kitas,[21] Y M Smulders,[4] Z Szekanecz,[22] N Sattar,[23] D P M Symmons,[24] M T Nurmohamed[25]

El decálogo de Recomendaciones para el Manejo de RCV en AR y otras Poliartritis Inflamatorias

Table 1 Overarching principles and recommendations

	Level of evidence	Strength of recommendation	Level of agreement (SD)
Overarching principles			
A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA.			
B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD.			
C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS			
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)

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Agca R, et al. Ann Rheum Dis. 2016;0:1-12

El decálogo de Recomendaciones para el Manejo de RCV en AR y otras Poliartritis Inflamatorias

Table 1 Overarching principles and recommendations

	Level of evidence	Strength of recommendation	Level of agreement (SD)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)
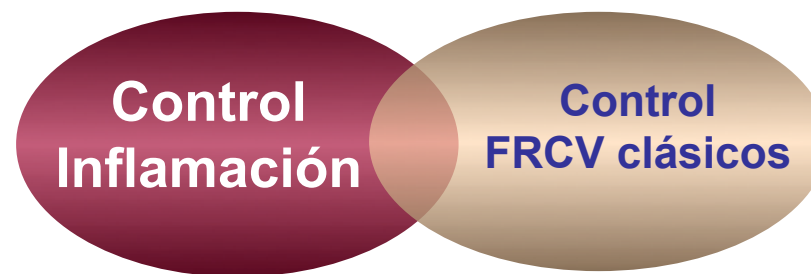
Control Inflamación — Control FRCV clásicos

Agca R, et al. Ann Rheum Dis. 2016;0:1-12

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2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Recommendations for autoimmune disease

Recommendations	Class[a]	Level[b]	Ref[c]
The use of a 1.5 factor risk multiplier for CV risk in rheumatoid arthritis should be considered, particularly if disease activity is high.	IIa	B	177
The use of a 1.5 risk multiplier for CV risk in immune inflammatory diseases other than rheumatoid arthritis may be considered on a patient-by-patient basis, depending on disease activity/severity.	IIb	C	177

CV risk assessment in the general population

Cardiovascular risk evaluation

Reynolds Risk Score
Calculating Heart and Stroke Risk for Women and Men

Gender	○ Male ○ Female
Age	[____] Years (Maximum age must be 80)
ⓘ Do you currently smoke?	○ Yes ○ No
ⓘ Systolic Blood Pressure (SBP)	[____] mm/Hg
ⓘ Total Cholesterol	[____] mg/DL (or) [____] mmol/L
ⓘ HDL or "Good" Cholesterol	[____] mg/DL (or) [____] mmol/L
ⓘ High Sensitivity C-Reactive Protein (hsCRP)	[____] mg/L
ⓘ Did your Mother or Father have a heart attack before age 60 ?	○ Yes ○ No
	Calculate 10 year risk

Reynolds Risk Score is designed to predict your risk of having a future heart attack, stroke, or other major heart disease in the next 10 years.

Cardiovascular risk evaluation

FRAMINGHAM RISK SCORE to predict 10 year ABSOLUTE RISK of CHD EVENT
ST ALBANS & HEMEL HEMPSTEAD NHS TRUST : CARDIOLOGY DEPARTMENT

This risk assessment only applies to assessment for **PRIMARY PREVENTION** of CHD, in people who do not have evidence of established vascular disease.
Patients who *already* have evidence of vascular disease usually have a >20% risk of further events of over 10 years, and require vigorous **SECONDARY PREVENTION**.
People with a Family History of premature vascular disease are at higher risk than predicted; Southern Europeans and some Asians may have a lower risk in relation to standard risk factors.

STEP 1: Add scores by sex for Age, Total Cholesterol, HDL-Cholesterol, BP, Diabetes and Smoking. (If HDL unknown, assume 1.1 in Males, 1.4 in Females)

Age	M	F
30-34	-1	-9
35-39	0	-4
40-44	1	0
45-49	2	3
50-54	3	6
55-59	4	7
60-64	5	8
65-69	6	8
70-74	7	8

Total Cholesterol	M	F
< 4.1	-3	-2
4.1 – 5.1	0	0
5.2 – 6.2	1	1
6.3 – 7.1	2	1
7.2	3	3

HDL Cholesterol	M	F
< 0.9	2	5
0.9 - 1.16	1	2
1.17 - 1.29	0	1
1.30 - 1.55	0	0
≥1.56	-2	-3

Systolic BP		Diastolic BP				
Male	<80	80-84	85-89	90-99	≥100
<120	0	0	1	2	3
120-129	0	0	1	2	3
130-139	1	1	1	2	3
140-159	2	2	2	2	3
≥160	3	3	3	3	3
Female	<80	80-84	85-89	90-99	≥100
<120	-3	0	0	2	3
120-129	0	0	0	2	3
130-139	0	0	0	2	3
140-159	2	2	2	2	3
≥160	3	3	3	3	3

If Systolic and Diastolic BP fall into different categories, use score from higher category

Diabetes	M	F
No	0	0
Yes	2	4

Smoking	M	F
No	0	0
Yes	2	2

Categorisation of 10 year Risk of CHD Event

Very Low risk	< 10%
Low risk	< 15%
Moderate risk	15-20%
High risk	> 20%

STEP 2: Use total score to determine Predicted 10 year Absolute Risk of CHD Event (Coronary Death, Myocardial Infarction, Angina) by sex

Total Score	≤-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	3	14	15	16	≥17
10 year Risk: Male		<2%	3%	3%	4%	5%	7%	8%	10%	13%	16%	20%	25%	31%	37%	45%	53%	53%	53%	53%
10 year Risk: Female	<1%	2%	2%	2%	3%	3%	4%	4%	5%	6%	7%	8%	10%	11%	13%	15%	18%	20%	24%	27%

STEP 3: Compare Predicted 10 year Absolute Risk with "Average" and "Ideal" 10 year Risks, to give Relative Risks

| Age	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74
"Average" Male	3%	5%	7%	11%	14%	16%	21%	25%	30%
"Ideal" Male	2%	3%	4%	4%	6%	7%	9%	11%	14%
"Average" Female	<1%	<1%	2%	5%	8%	12%	12%	13%	14%
"Ideal" Female	<1%	1%	2%	3%	5%	7%	8%	8%	8%

"Ideal" risk represents
Total Cholesterol = 4.1 - 5.1
HDL = 1.2 (Male), 1.4 (Female)
BP < 120/80
No Diabetes, Non Smoker

People with an absolute risk of ≥20% should be considered for treatment: with a Statin to achieve a Total Cholesterol <5 and/or LDL cholesterol <3.2 with anti-hypertensives to achieve a BP ≤160/90 (ideally ≤140/80)

from Wilson PWF, et al   Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47   Dr John Bayliss
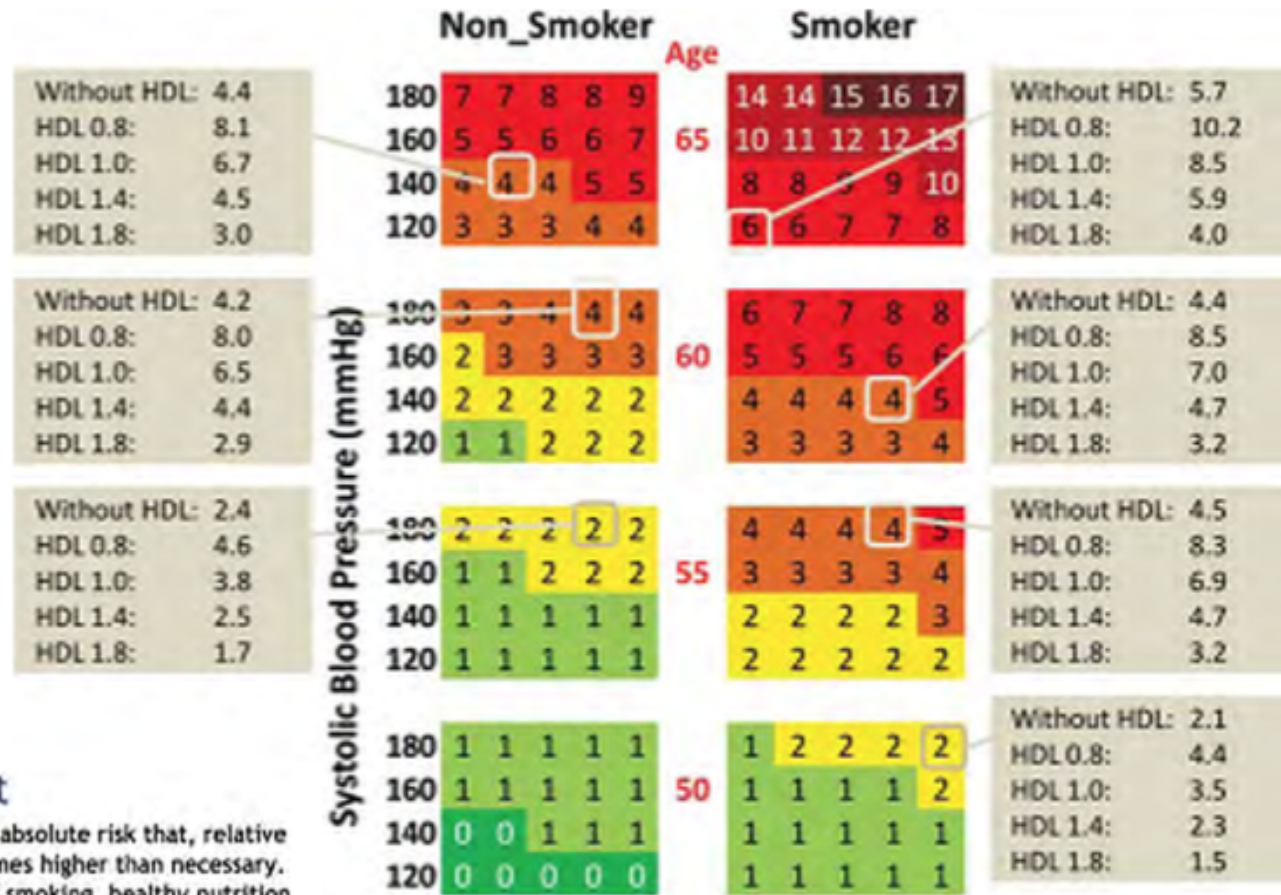
The Framingham risk score includes: age, sex, total and HDL cholesterol, blood pressure, diabetes, and smoking to derive an estimated risk of developing CHD within 10 years.

Wilson PW et al. Circulation 1998;97:1837–1847.

Cardiovascular risk evaluation
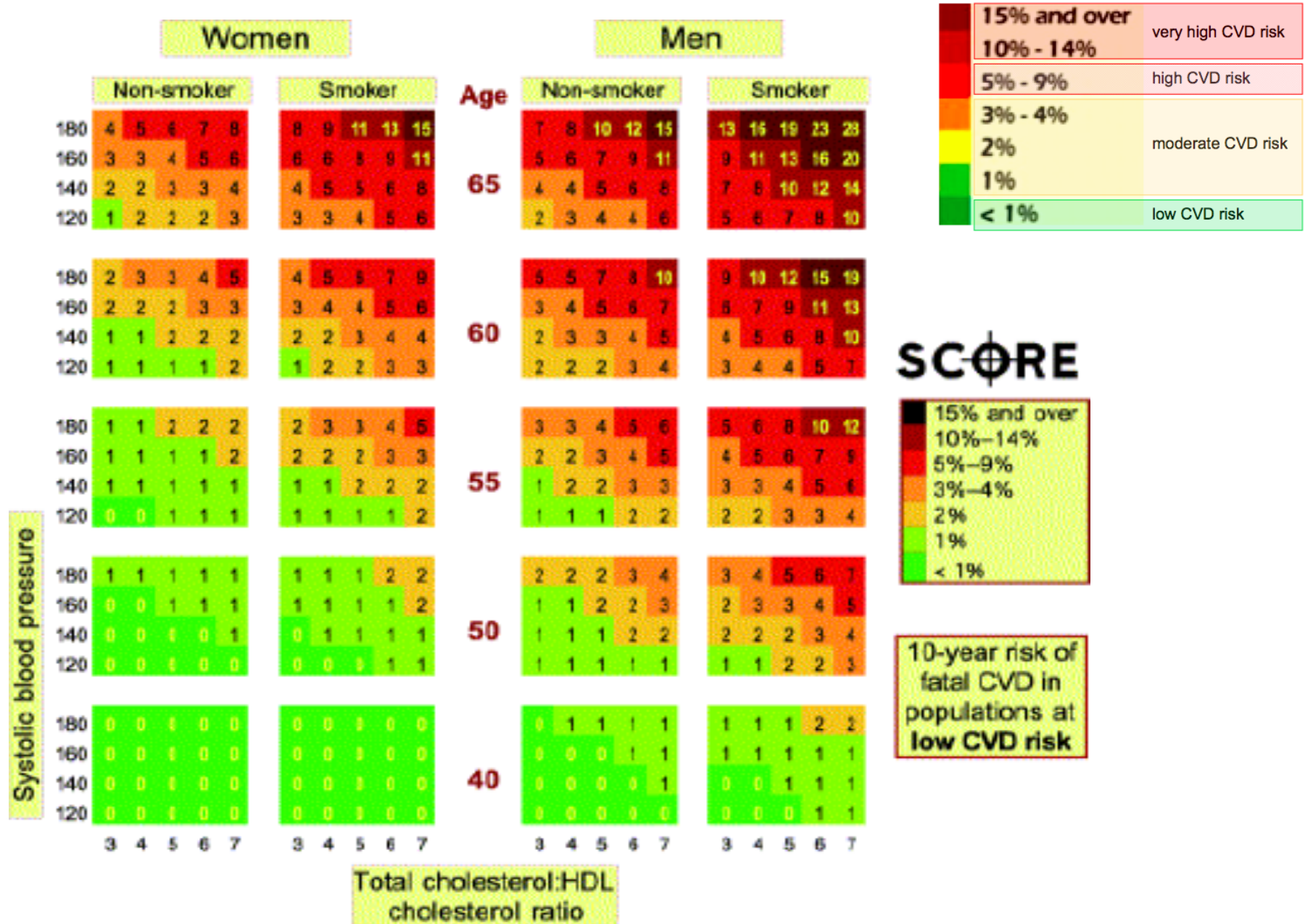
SCORE: Low CV Risk Chart

Total Cholesterol / HDL-Colesterol

Relative CV risk in young patients

Relative Risk Chart

This chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary. This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication
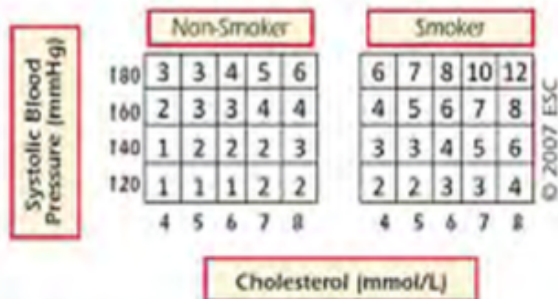
Please note that this chart shows RELATIVE not absolute risk. The risks are RELATIVE to 1 in the bottom left. Thus a person in the top right hand box has a risk that is 12 times higher than a person in the bottom left

ESTRATIFICACIÓN DEL RIESGO CV

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Piepoli MF et al. Eur Heart J. 2016. Aug 27.

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.
Moderate risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

Objetivo de control de Colest-LDL en función del Riesgo CV

| Recomendaciones	Clase[a]	Nivel[b]
En personas de MUY ALTO RIESGO cardiovascular (enfermedad cardiovascular establecida, diabetes tipo 2 ó 1 con FRCV ó LOD, ERC severa, SCORE ≥ 10%), el objetivo es c-LDL < 70 mg/dL y/o una reducción de c-LDL > 50% si el objetivo no puede alcanzarse.	I	A
En pacientes de RIESGO ALTO (FRCV muy elevado ó SCORE ≥ 5% a < 10%, Diabetes tipo 1 ó 2 sin FRCV ni LOD, ERC moderada, se debe considerar como objetivo un c-LDL < 100 mg/dL.	I	A
En pacientes de RIESGO MODERADO (SCORE > 1% a ≤ 5%) se debe considerar como objetivo un c-LDL < 115 mg/dL.	I	A

[a]Clase de recomendación.[b]Nivel de evidencia. ERC: Enfermedad Renal Crónica. LOD: Lesión Órgano Diana. FRCV: Factor de Riesgo Cardiovascular. c-LDL: Colesterol unido a lipoproteínas de baja densidad.

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"Cuanto más bajo mejor" parece ser cierto tanto para cLDL como para PCRus tanto en prevención primaria como secundaria
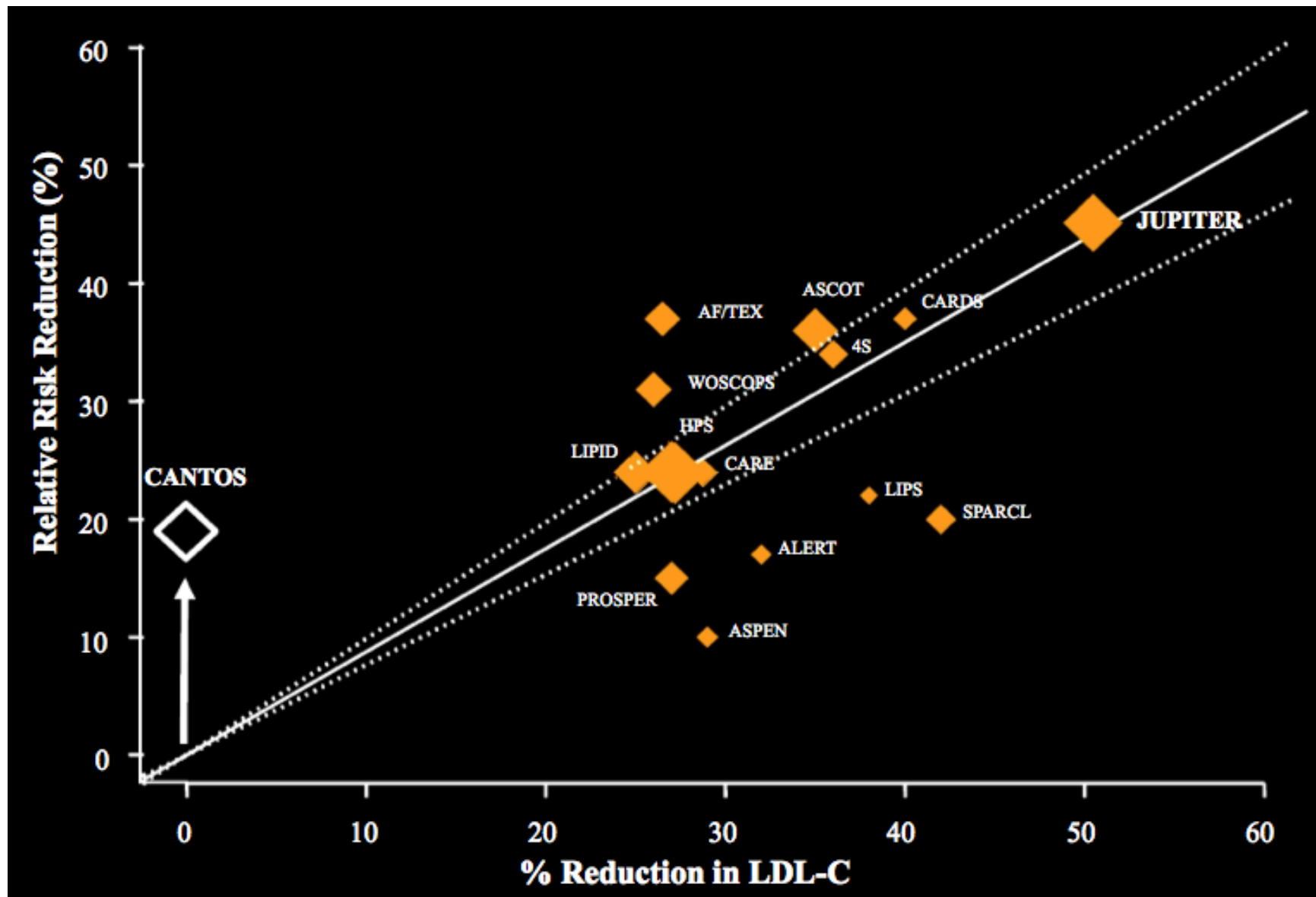
Conclusiones

- La inflamación sistémica y local a nivel de la placa de ateroma juega un papel clave en el desarrollo de la enfermedad aterosclerótica.

- La inflamación sistémica crónica se ha relacionado con el aumento del riesgo cardiovascular en población general y en los pacientes con EIC.

- La teoría del "riesgo inflamatorio" CV se demuestra en prevención secundaria (C. Isquémica Crónica). CANTOS

- Es necesario un abordaje global del riesgo CV centrado en el control de los FRCV y la inflamación, sobre todo en pacientes con EIC.

MUCHAS GRACIAS

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