APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

2' edizione

MANIFESTAZIONI CARDIOVASCOLARI
E METABOLICHE IN REUMATOLOGIA

4 - 5 aprile 2014

Gestione del paziente reumatologico relativamente al rischio cardiovascolare

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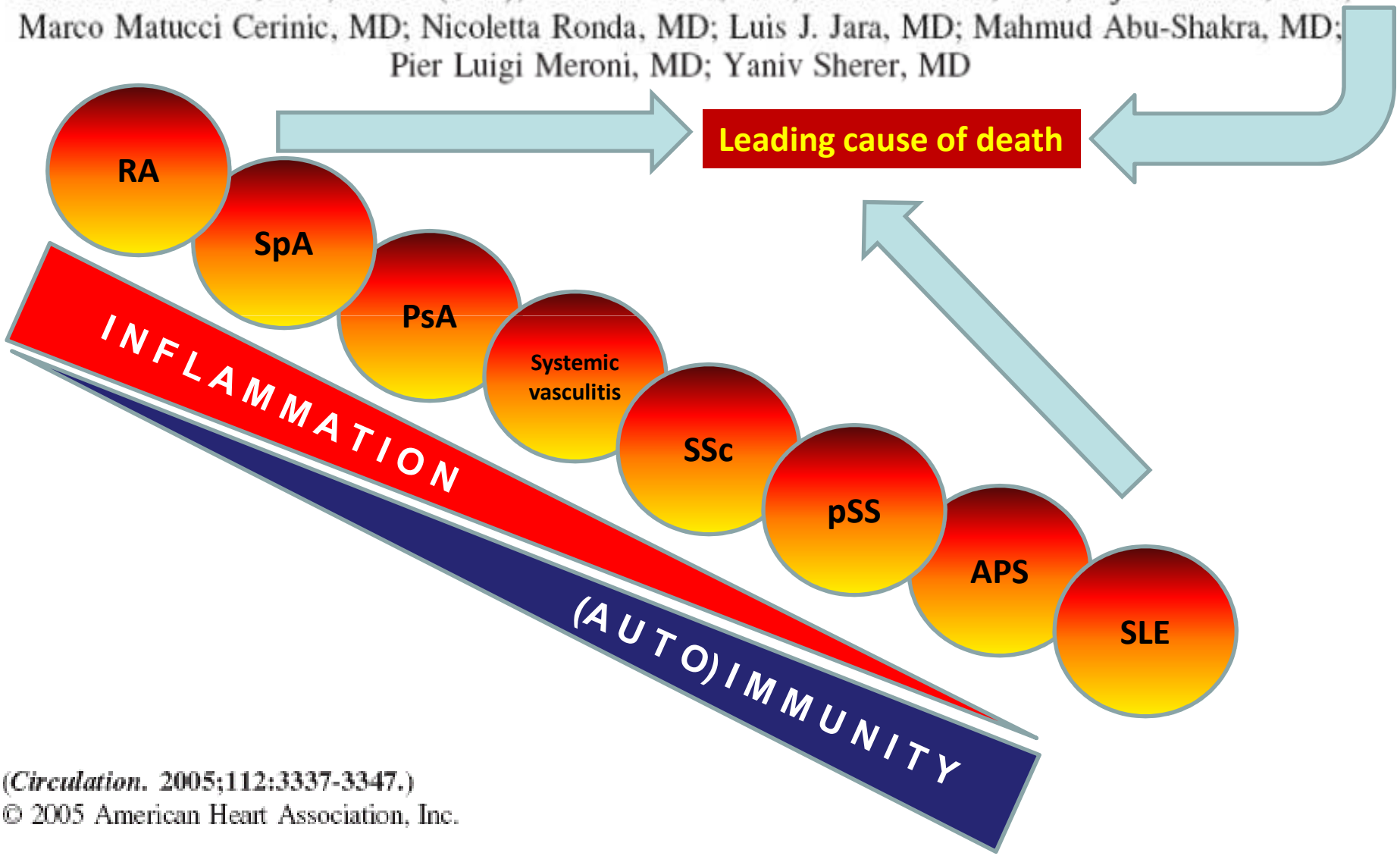
Università di Perugia

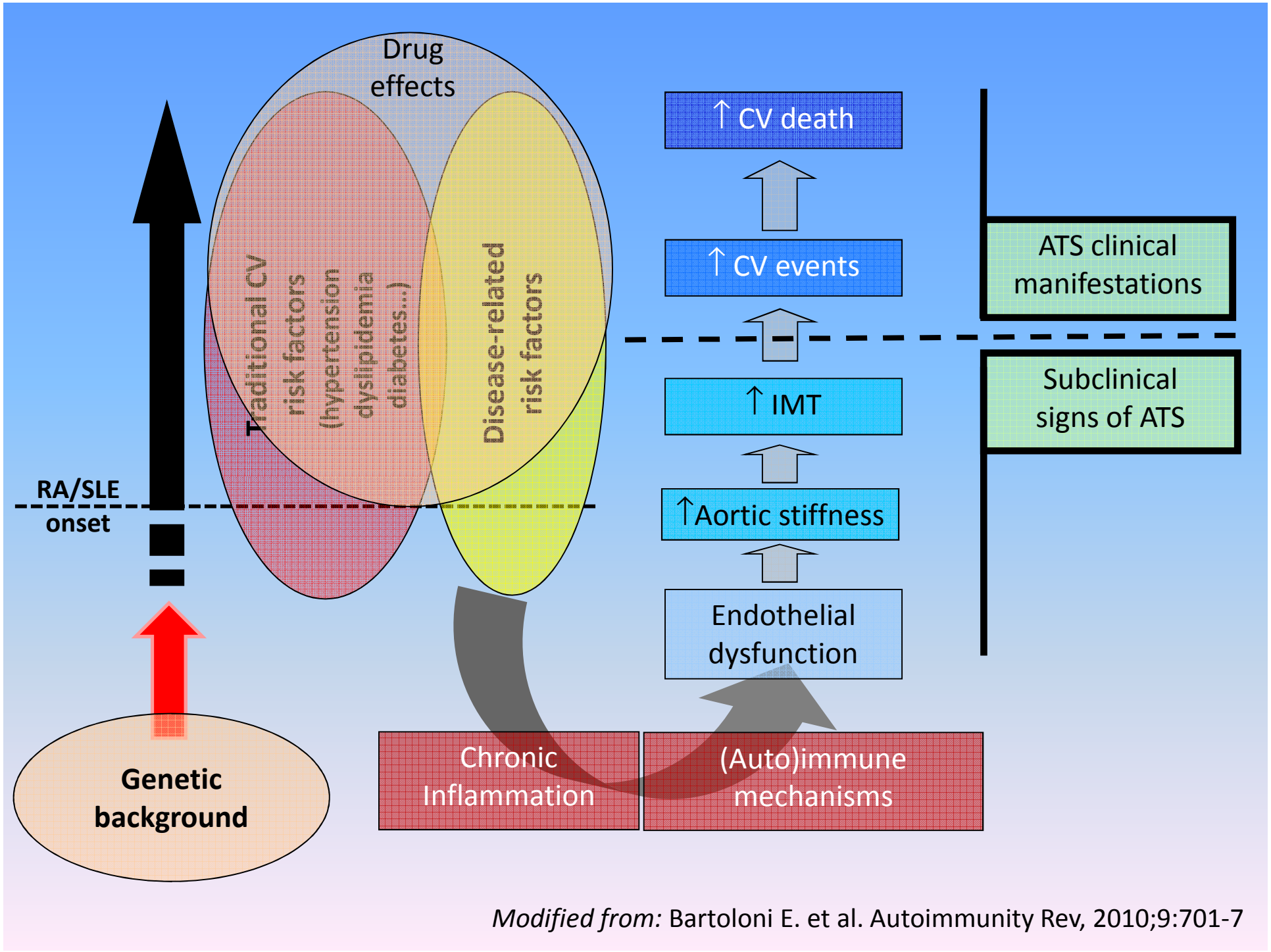
Contemporary Reviews in Cardiovascular Medicine

Accelerated Atherosclerosis in Autoimmune Rheumatic Diseases

Yehuda Shoenfeld, MD, FRCP (Hon); Roberto Gerli, MD; Andrea Doria, MD; Eiji Matsuura, PhD; Marco Matucci Cerinic, MD; Nicoletta Ronda, MD; Luis J. Jara, MD; Mahmud Abu-Shakra, MD; Pier Luigi Meroni, MD; Yaniv Sherer, MD



(*Circulation.* 2005;112:3337-3347.)



Modified from: Bartoloni E. et al. Autoimmunity Rev, 2010;9:701-7

Continuum of RA/SLE-specific and traditional risk factors for CVD

RA/SLE-specific CV risk factor		Traditional CV risk factor
Disease duration	↓ HDL/ ↑ pro-inflamm.HDL	Old age
Disease activity	Cytokine dysregulation	Hypertension
Autoantibodies	C-reactive protein	Lipid dysregulation
- anti-ApoA-I	Oxidative stress	Smoking
- anti-HDL	Homocysteine	Male gender
- anti-LPL	Insuline-resistance	Diabetes mellitus
- anti-oxLDL		Menopause
- aPL		High BMI
- Rheumatoid factor		
- anti-CCP		
- T-cell dysfunction		

Modified from: Skaggs BJ et al. Nat Rev Rheumatol 2012;8:214-223

Traditional cardiovascular risk factors in rheumatoid arthritis: A meta-analysis

Source	Participants (*n*) RA/CTRL	Age (mean) RA/CTRL	Women (%) RA/CTRL	SMK	HTN	DM	DL
Popa et al. (2007) [17]	56/56	55/55	71/71	NC	NC	NC	C
Roman et al. (2006) [3]	98/98	47/48	94/94	NC	C	C	NC
Pedersen et al. (2006) [18]	515/769	49/48	71/62	C	NC	NC	NC
Pamuk et al. (2006) [19]	63/34	51/53	89/88	NC	C	NC	NC
Maradit-Kremers et al. (2005) [13]	603/603	58/58	73/73	C	C	C	C
Gerli et al. (2005) [20]	101/75	63/61	73/71	NC	C	C	C
del Rincon et al. (2005) [15]	234/102	59/59	90/88	NC	NC	C	C
Chung et al. (2005) [22]	70/86	51/52	61/65	NC	C	NC	NC
Stolt et al. (2003) [23]	679/847	NC/NC	72/71	C	NC	NC	NC
Dessein et al. (2002) [9]	79/39	52/56	84/85	NC	C	C	NC
McEntegart et al (2001) [6]	76/641	57/NC	83/NC	NC	NC	C	NC
Jonsson et al. (2001) [24]	39/39	52/52	77/77	NC	C	C	NC
Hutchinson et al. (2001) [25]	239/239	60/60	67/67	C	NC	NC	NC
Lazarevic et al. (1992) [26]	69/65	49/45	86/75	NC	NC	NC	C
Magaro et al. (1991) [27]	35/20	NC/NC	NC/NC	NC	NC	NC	C

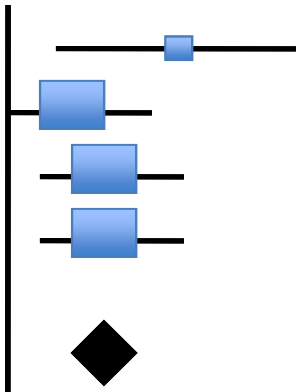
RA: rheumatoid arthritis patients; **CTRL:** controlli; **SMK:** smoking; **HTN:** hypertension; **DM:** diabetes mellitus; **DL:** dyslipidaemia; **NC:** not characterized; **C:** characterized

Boyer JF et al. Joint Bone Spine 2011;78:179-83

Traditional cardiovascular risk factors in rheumatoid arthritis: A meta-analysis

Study or sub-category	RA n/N	Controls n/N	Odds Ratio 95% CI	Weight %	Odds Ratio 95% CI
Hutchinson	100/184	52/167		8.40	2.61 [1.70,4.08]
Stoll	192/399	204/495		31.87	1.32 [1.01,1.73]
Maradit-Kremers	170/425	144/473		27.59	1.52 [1.16,2.01]
Pedersen	253/407	316/614		32.15	1.55 [1.20,2.00]
Total (95% CI)	1415	1749		100	1.56 [1.35,1.80]

Total events: 715 (RA), 716 (Controls)
Test for heterogeneity: Chi^2 =7, df=3 (P=o.o7). I^2=57.2%
Test for overall effect: Z=6.06 (P<0.00001)



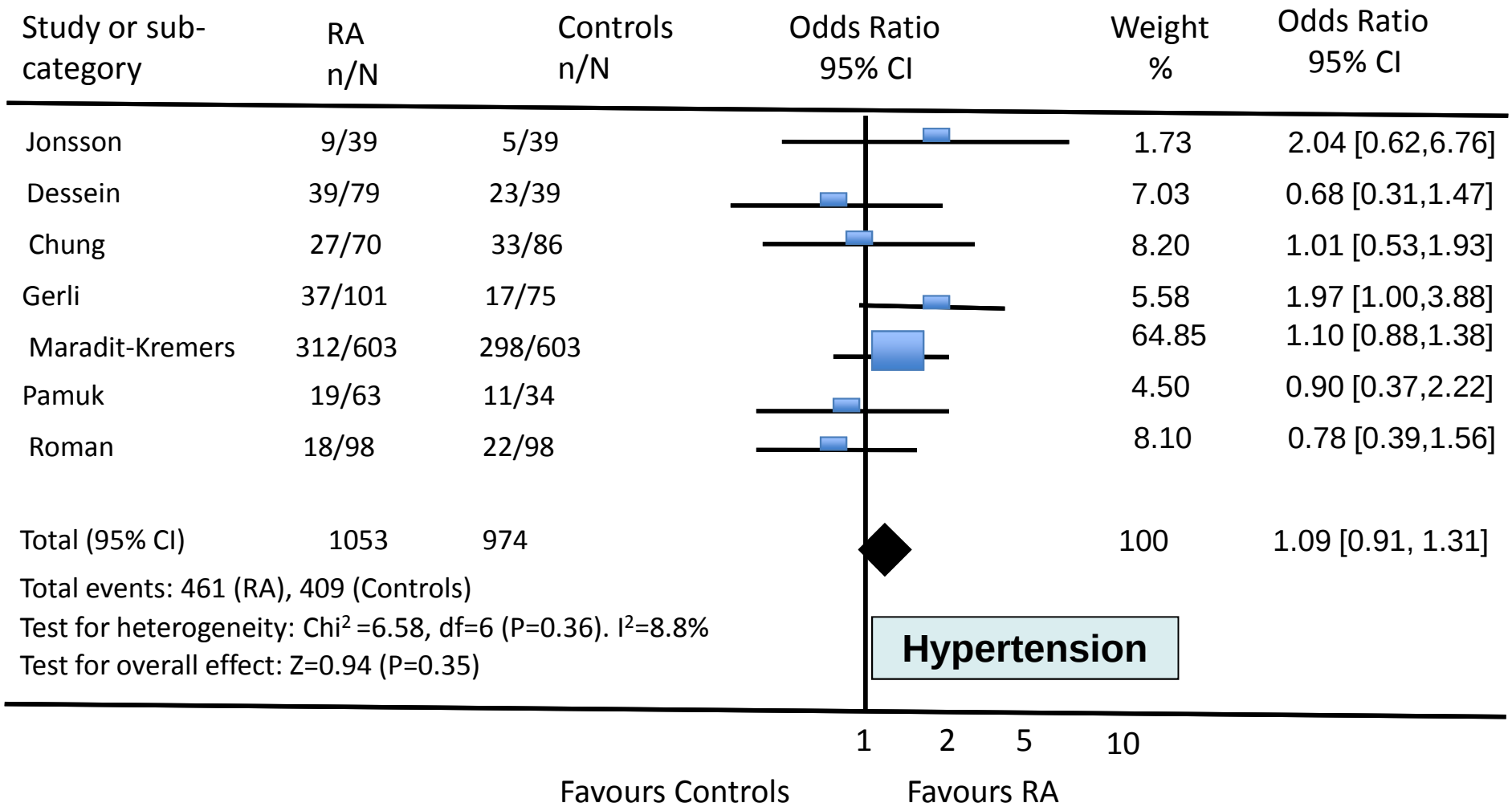
Smoking

1 2 5

Favours Controls Favours RA

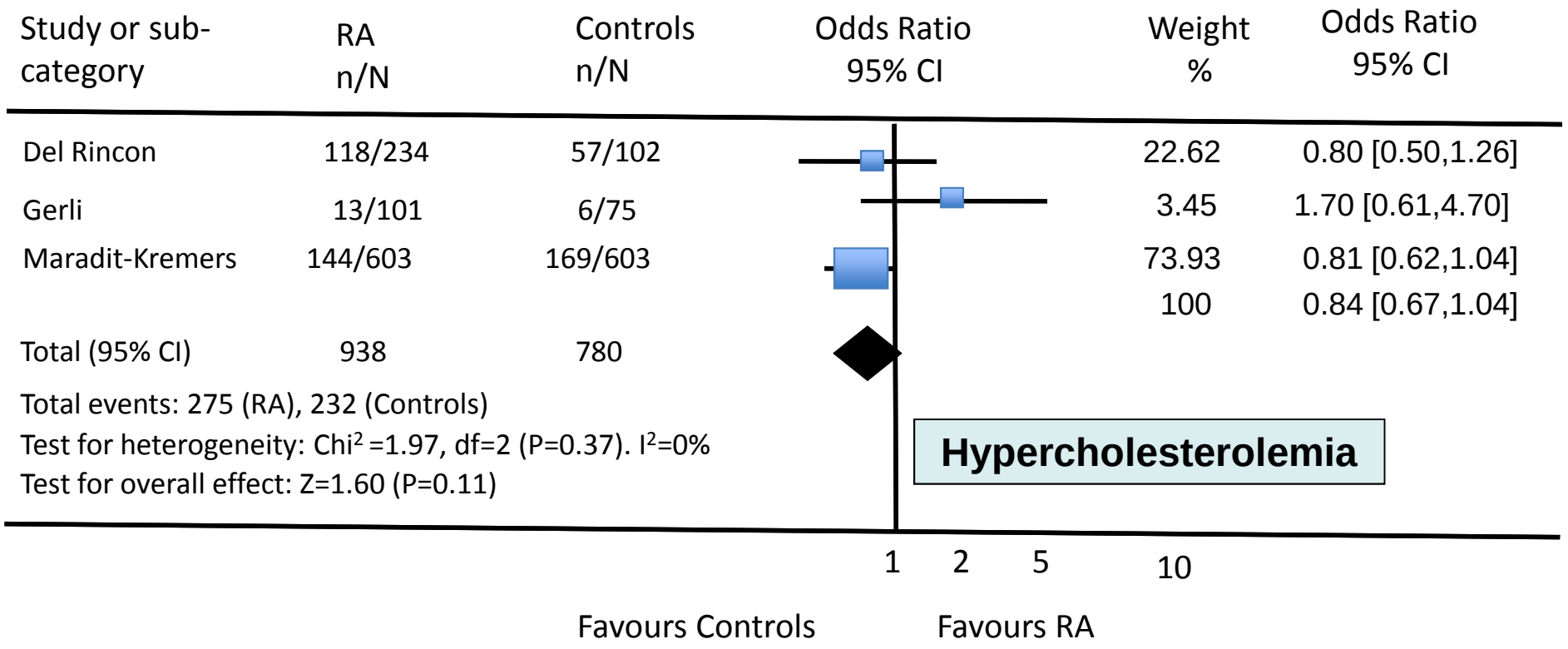
Boyer JF et al. Joint Bone Spine 2011;78:179-83

Traditional cardiovascular risk factors in rheumatoid arthritis: A meta-analysis



Boyer JF et al. Joint Bone Spine 2011;78:179-83

Traditional cardiovascular risk factors in rheumatoid arthritis: A meta-analysis



Boyer JF et al. Joint Bone Spine 2011;78:179-83

Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients?

A Gonzalez,[1] H Maradit Kremers,[1] C S Crowson,[2] K V Ballman,[2] V L Roger,[3] S J Jacobsen,[4] W M O'Fallon,[2] S E Gabriel[5]

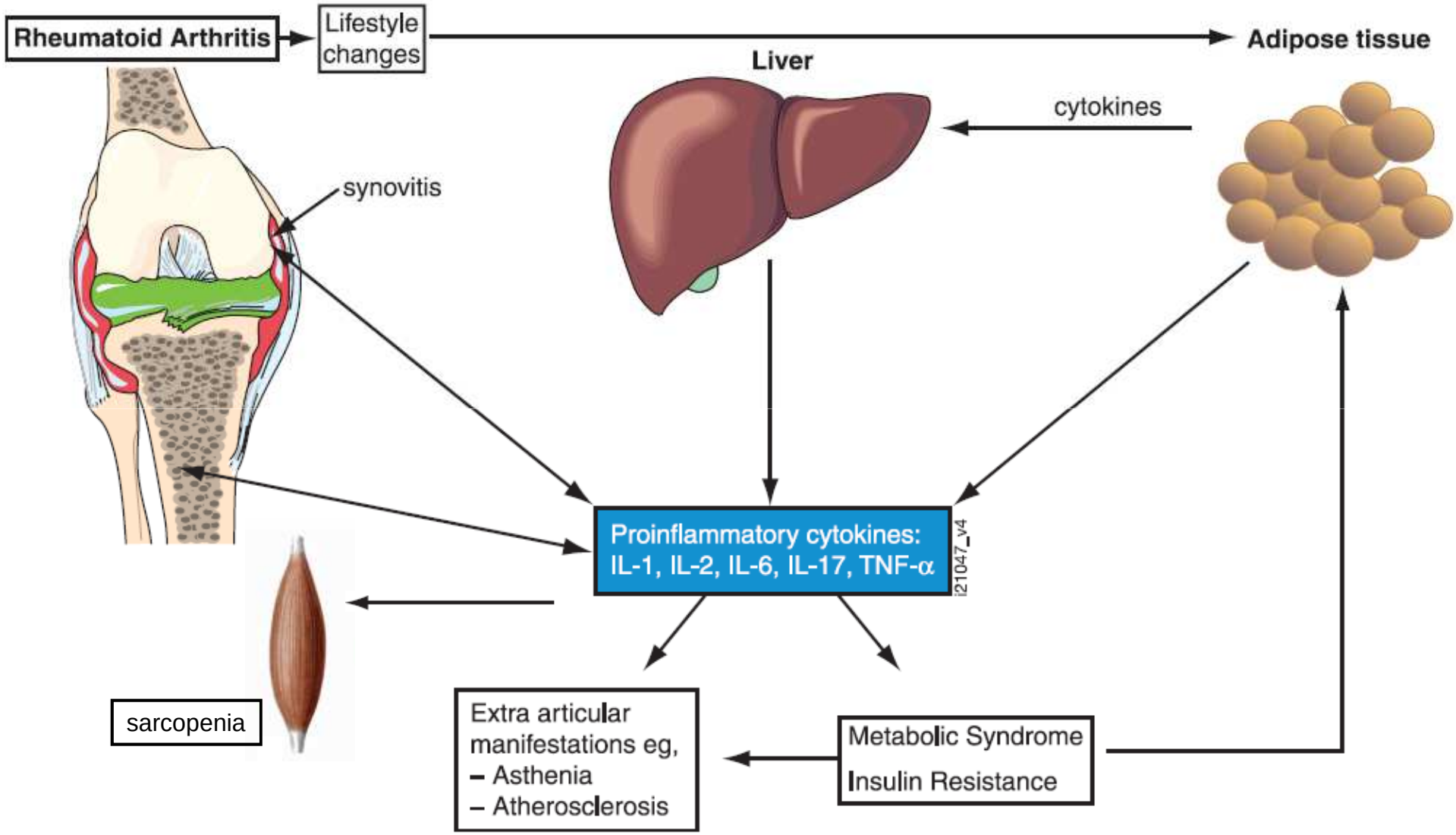
*Ann Rheum Dis 2008;**67**:64-9*

Table 2 Incidence rates (events/100 person-years), rate ratios (rheumatoid arthritis (RA)/non-RA), and 95% confidence intervals of the cardiovascular (CV) risk factors that developed during follow-up in RA and non-RA subjects*

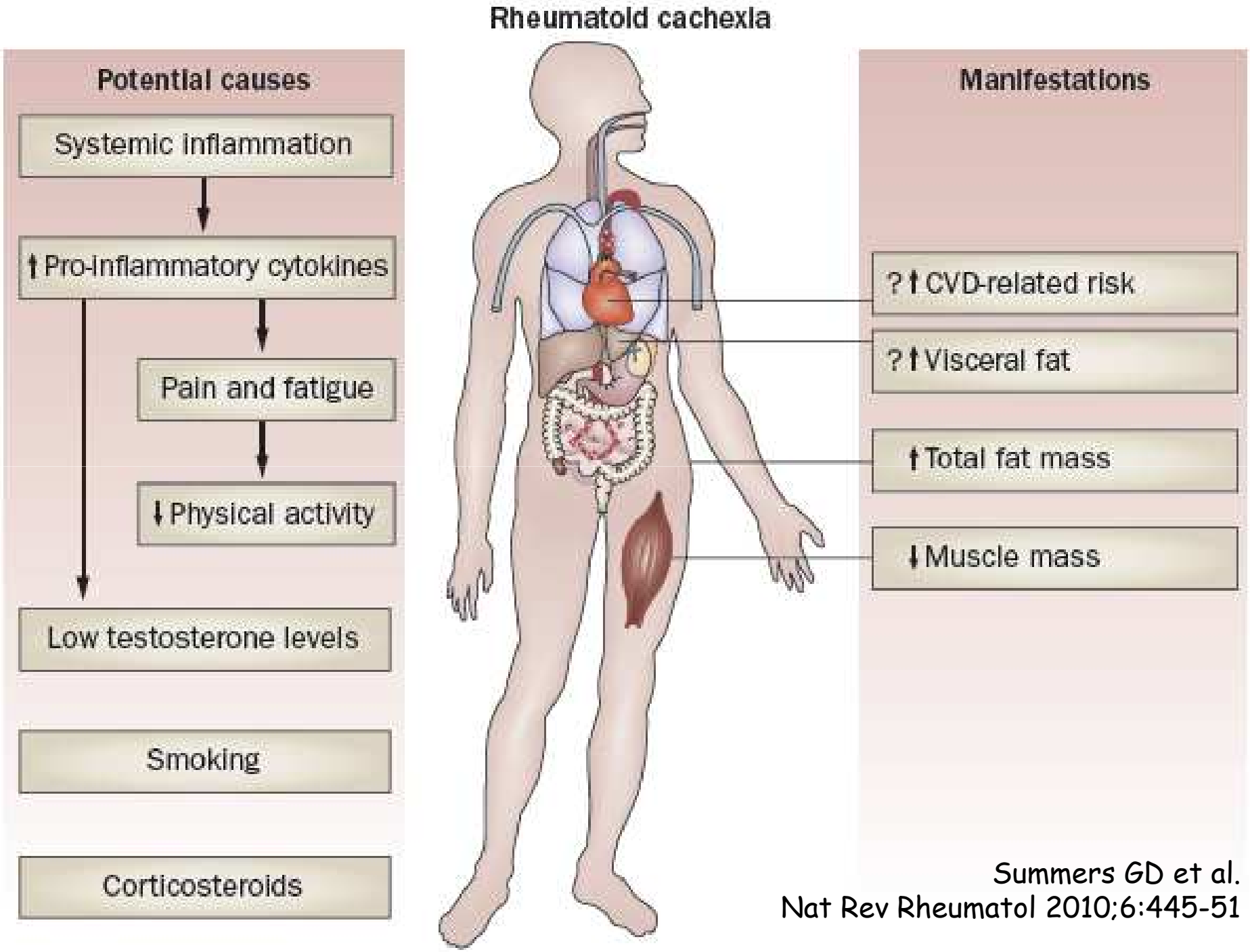
	Rate per 100 person-years (no. of cases)		
Cardiovascular risk factors	**RA**	**Non-RA**	**Rate ratio (95% CI)**
Hypertension	3.67 (179)	3.59 (215)	1.02 (0.84–1.25)
Dyslipidaemia	2.71 (158)	3.64 (228)	0.75 (0.61–0.91)†
High BMI (≥30 kg/m^2)	0.47 (35)	0.63 (54)	0.75 (0.48–1.13)
Low BMI (<20 kg/m^2)	1.17 (83)	0.65 (53)	1.79 (1.28–2.54)†
Diabetes mellitus	0.79 (66)	1.02 (98)	0.78 (0.57–1.06)

*Subjects with the risk factor at baseline were removed from the analysis of that specific risk factor.
† Significant ($p<0.05$) values.
BMI, body mass index.

Rheumatoid synovitis effects on adipose tissue and muscle mass



Wasko MC et al. Arthritis Care Res 2011;4:512-21



Summers GD et al.
Nat Rev Rheumatol 2010;6:445-51

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Atherosclerosis 220 (2012) 11–21

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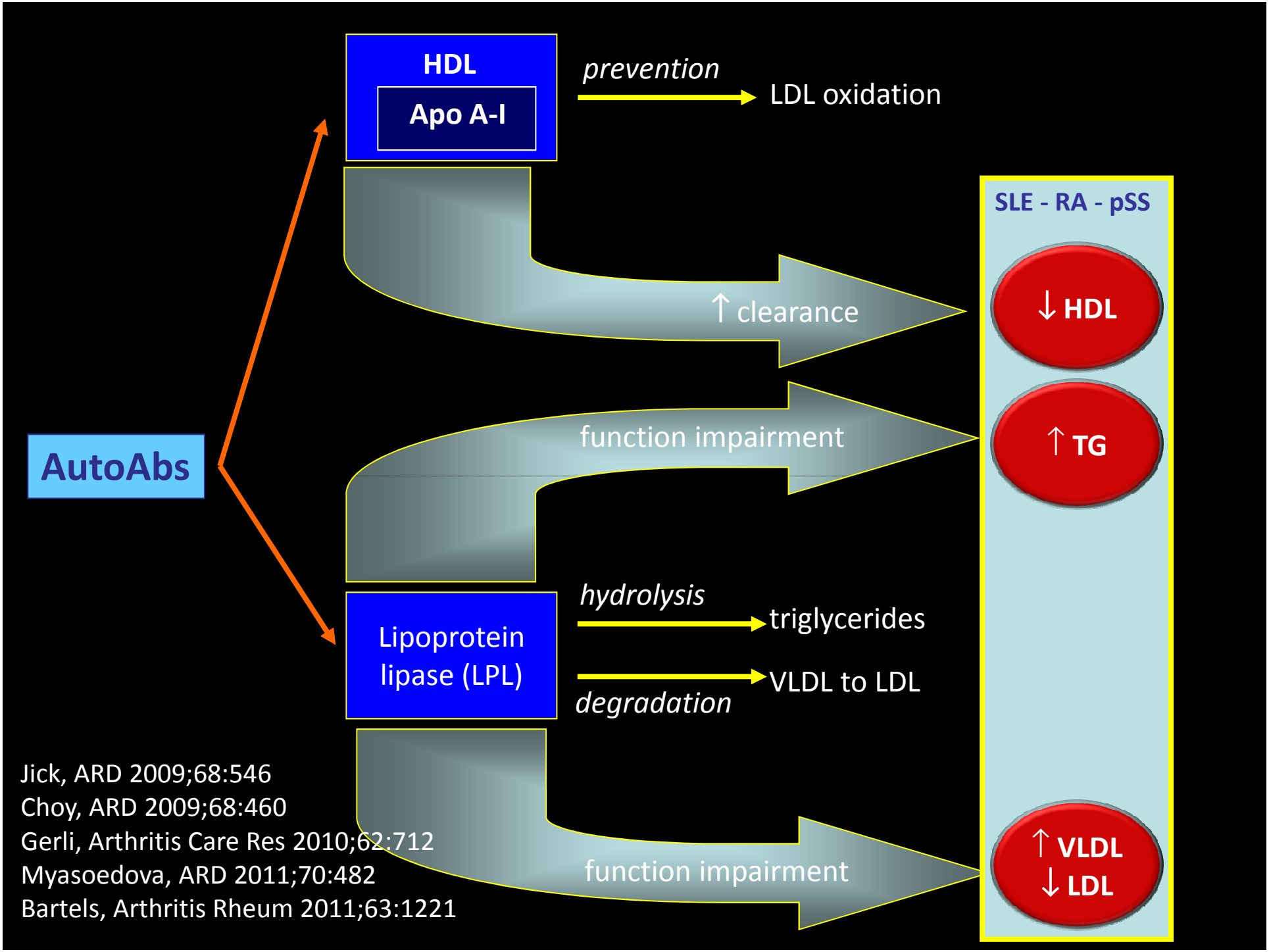
journal homepage: www.elsevier.com/locate/atherosclerosis

Emerging role of high density lipoproteins as a player in the immune system

Giuseppe Danilo Norata[a,b,*], Angela Pirillo[b,f], Enrico Ammirati[c,d,e], Alberico Luigi Catapano[a,f,**]

Table 2:
HDL and immune-mediated disorders.

Disease	*HDL plasma levels*	*1st Author*	*(Year)*
Systemic lupus erythematosus	↓	Borba EF	(2006)
Rheumatoid arthritis	↓	Myasoedova E	(2010)
Sjögren's sindrome	↓	Gerli R	(2006)
Ankylosing spondilitis	↓	Mathieu S	(2010)
Psoriatic arthritis	↓	Juarez-Rojas J	(2008)
Crohn's disease	↓	van Leuven SI	(2007)
Ulcerative colitis	↓	Biyyani RS	(2010)
Multiple sclerosis	↑	Salemi G	(2010)

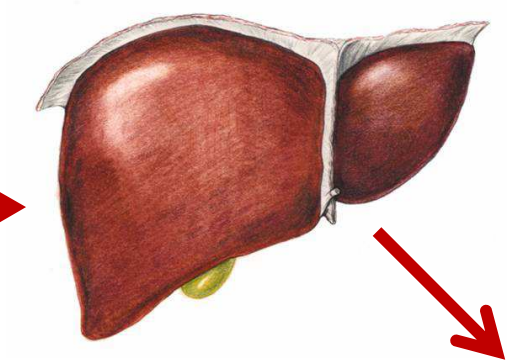


Jick, ARD 2009;68:546
Choy, ARD 2009;68:460
Gerli, Arthritis Care Res 2010;62:712
Myasoedova, ARD 2011;70:482
Bartels, Arthritis Rheum 2011;63:1221

DYSLIPIDAEMIA INDUCED BY INFLAMMATION

IL-6
TNF-α

LIVER

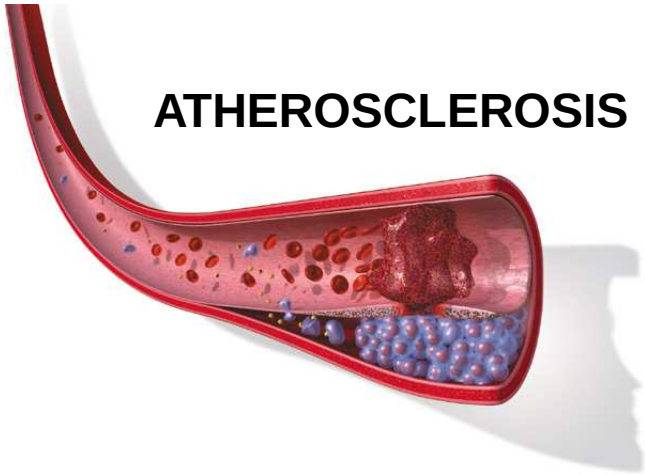


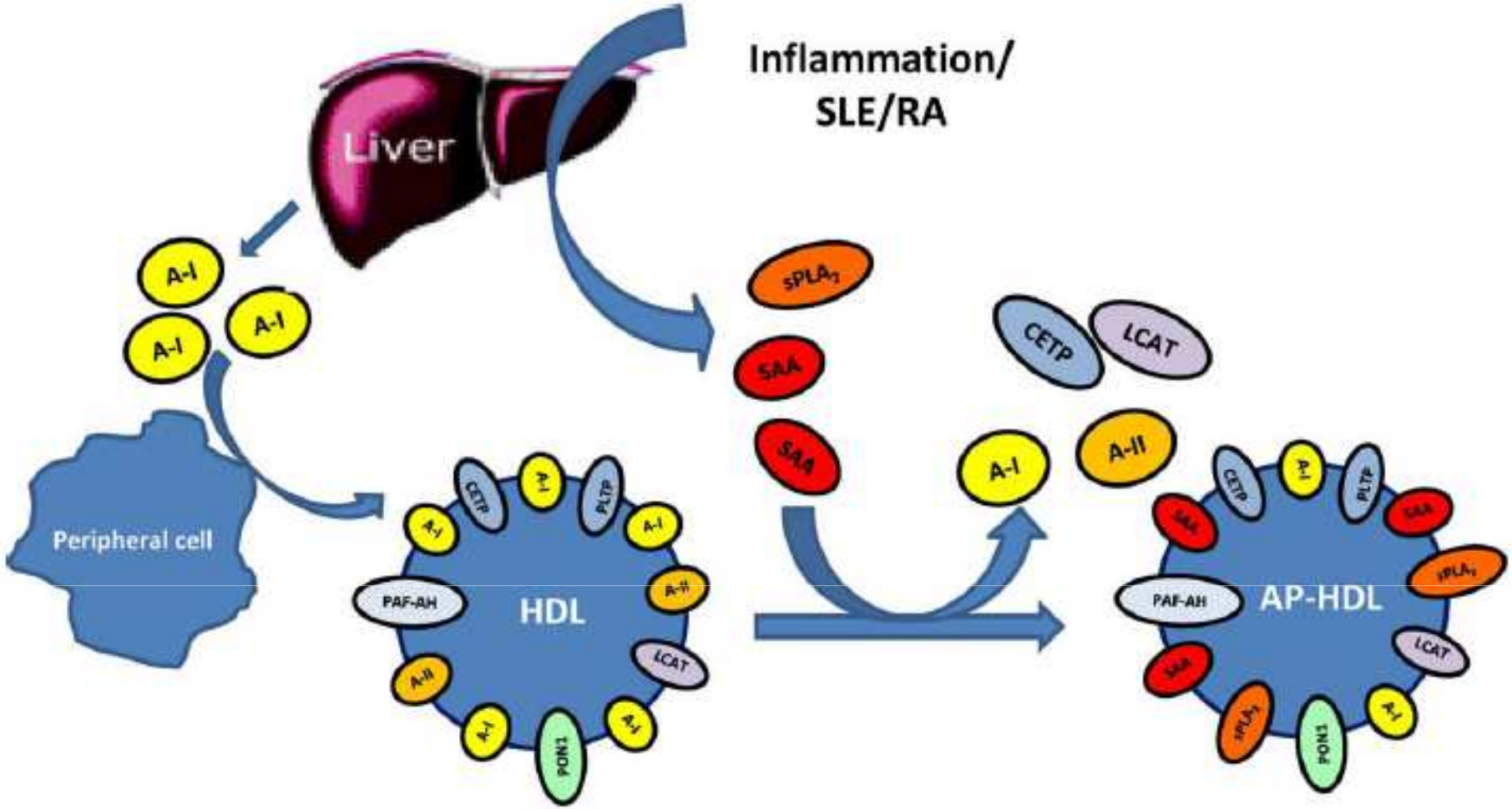
CRP

↓ **Total cholesterol**
HDL

↑ **Triglycerides**
Small dense LDL
ApoB/ApoAI

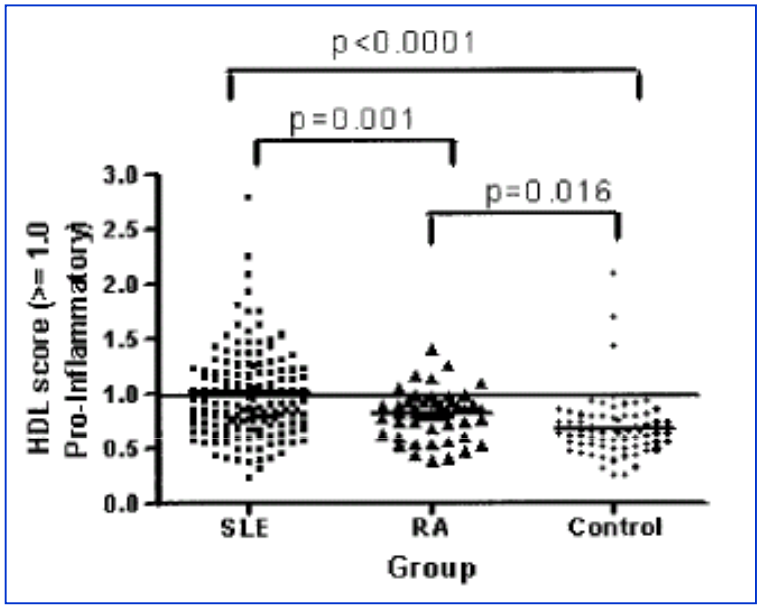
ATHEROSCLEROSIS

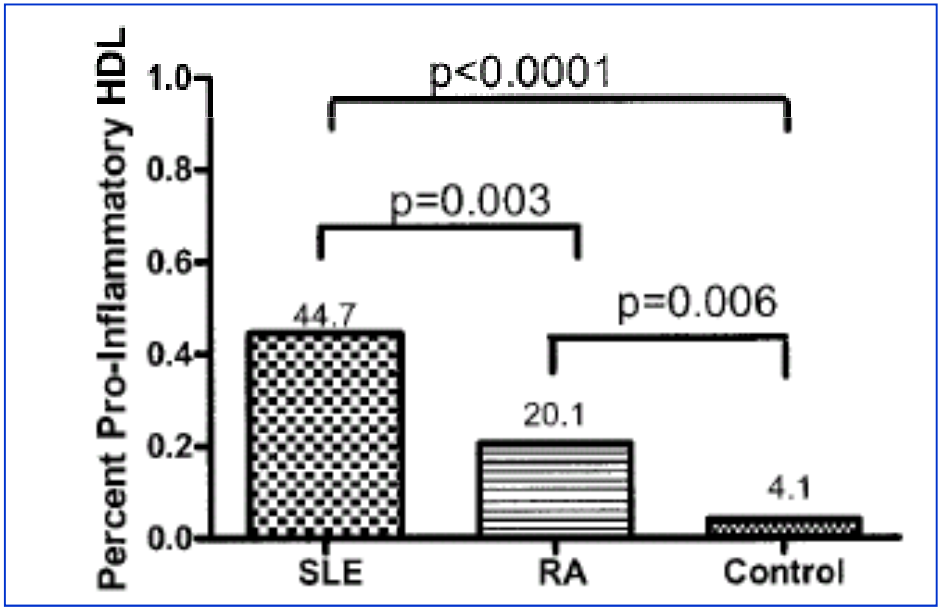




A-I, AII: Apo-AI, Apo-AII
PAF-AH: platelet-activating factor acetylhydrolase
LCAT: cholesterol acyltransferase
PON1: serum paraoxonase
SAA: serum amyloid A
sPLA: serum phospholipase A2

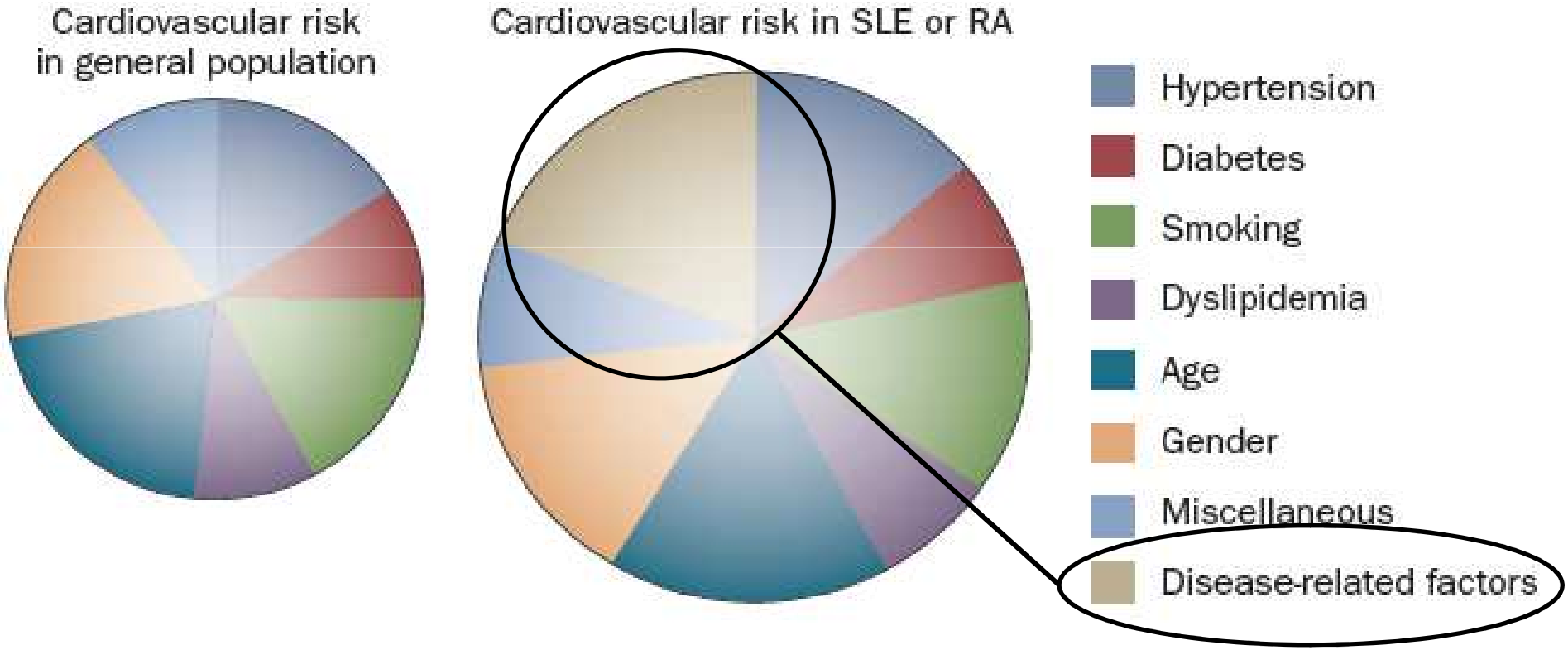
Proinflammatory HDL as a biomarker for atherosclerosis in patients with SLE and RA





McMahon M et al. Arthritis Rheum 2006;54:2541-9

Hypothetical distribution of cardiovascular risk factors in patients SLE or RA in comparison with the general population



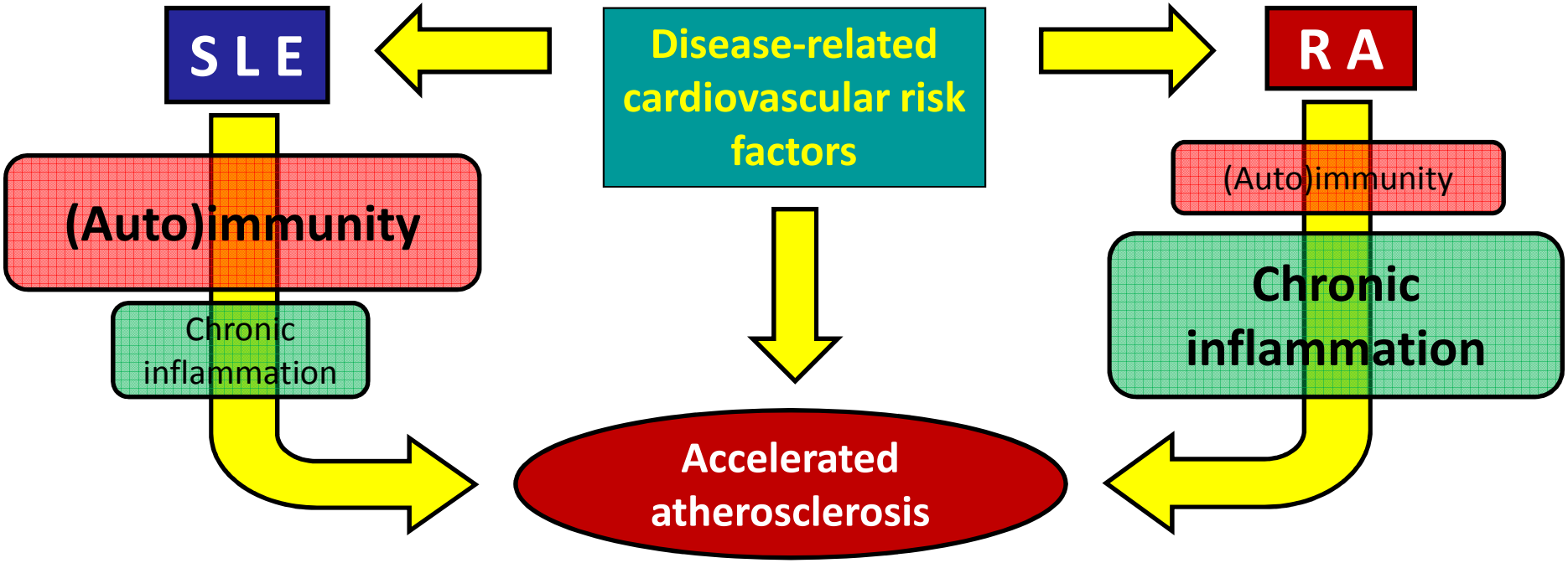
Symmons DPM & Gabriel S. Nat Rev Rheumatol 2011;7:399-408

Arthritis Care & Research
Vol. 63, No. 2, February 2011, pp 178–183
DOI 10.1002/acr.20322

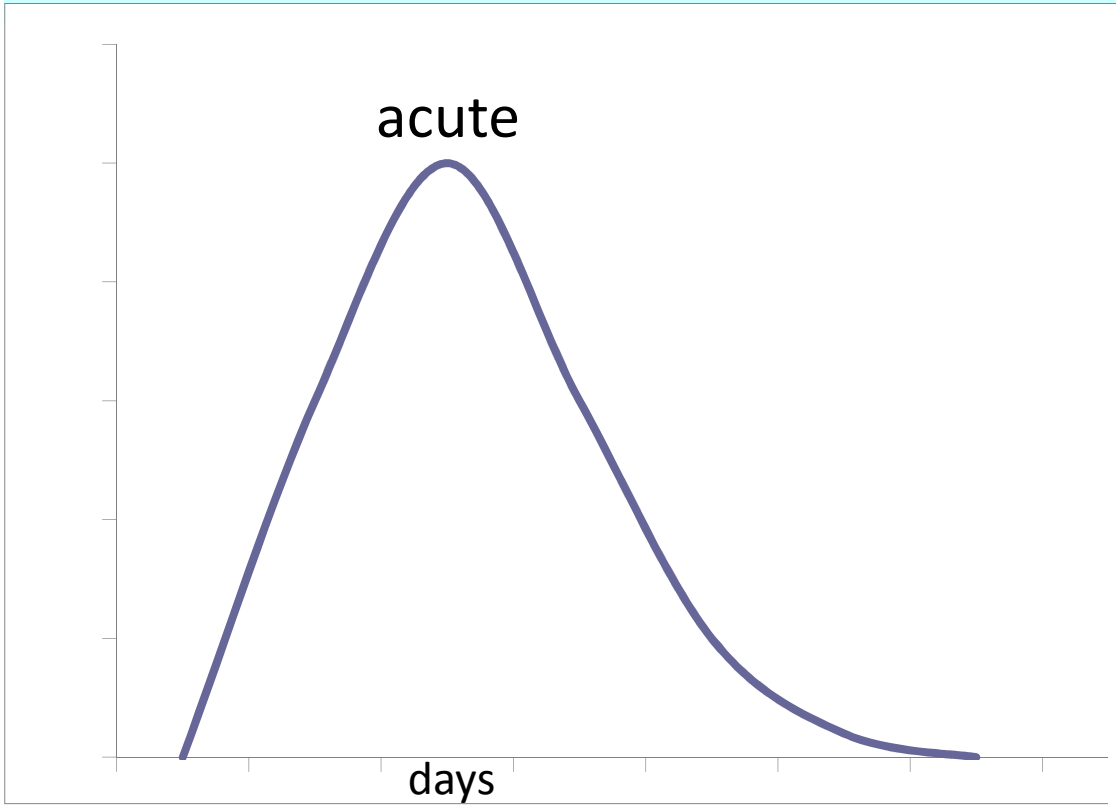
REVIEW ARTICLE

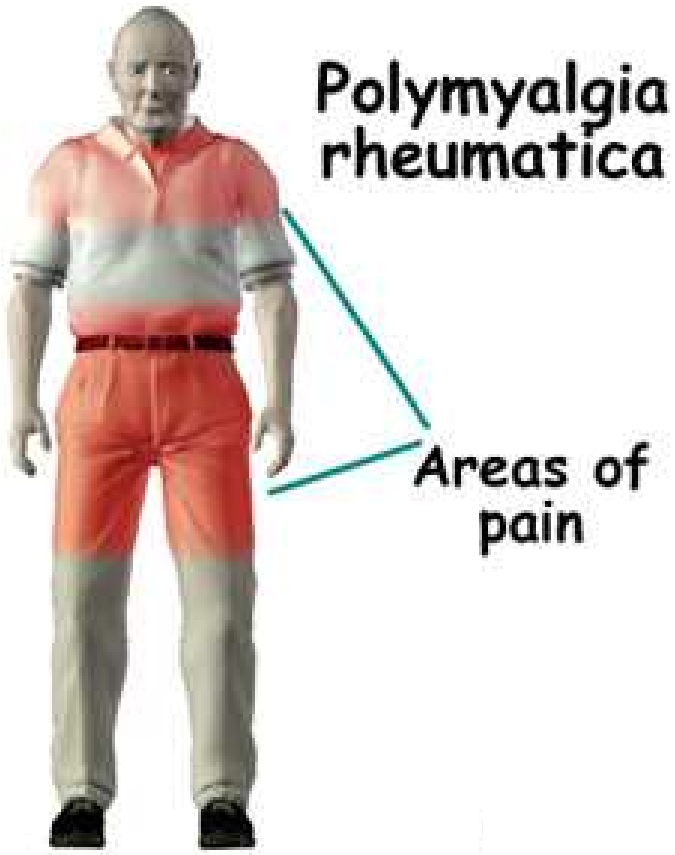
Inflammatory and Autoimmune Mechanisms in the Induction of Atherosclerotic Damage in Systemic Rheumatic Diseases: Two Faces of the Same Coin

ELENA BARTOLONI,[1] YEHUDA SHOENFELD,[2] AND ROBERTO GERLI[1]



Acute vs Chronic Inflammation

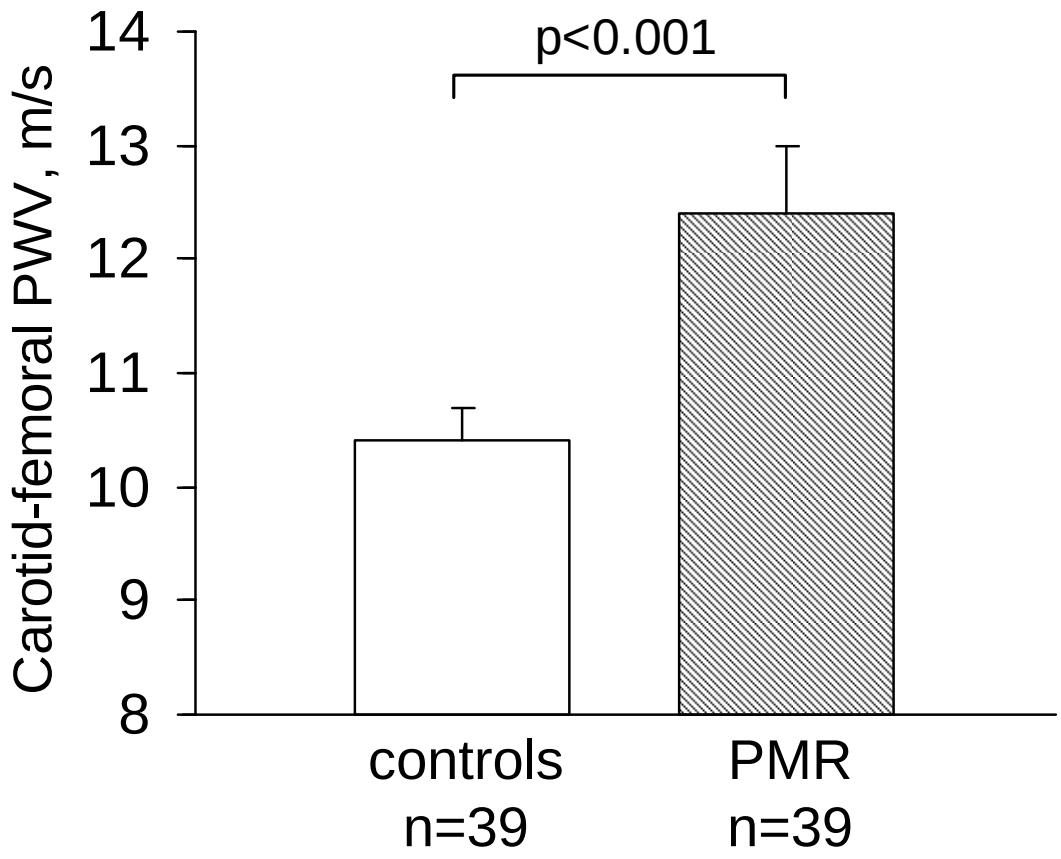




Inflammation → Repair

Aortic stiffness is increased in polymyalgia rheumatica

	controls	pts	p
Number	42	38	
age, ys	70 (6)	71 (8)	n.s.
men, %	45	45	n.s.
SBP, mmHg	134(12)	134(14)	n.s.
DBP, mmHg	77(7)	75(9)	n.s.



Schillaci G, Bartoloni E, Pucci G, *et al*. *Ann Rheum Dis* (2012).

Aortic stiffness is increased in polymyalgia rheumatica and improves after steroid treatment

	controls	pts	p
Number	42	38	
age, ys	70 (6)	71 (8)	n.s.
men, %	45	45	n.s.
SBP, mmHg	134(12)	134(14)	n.s.
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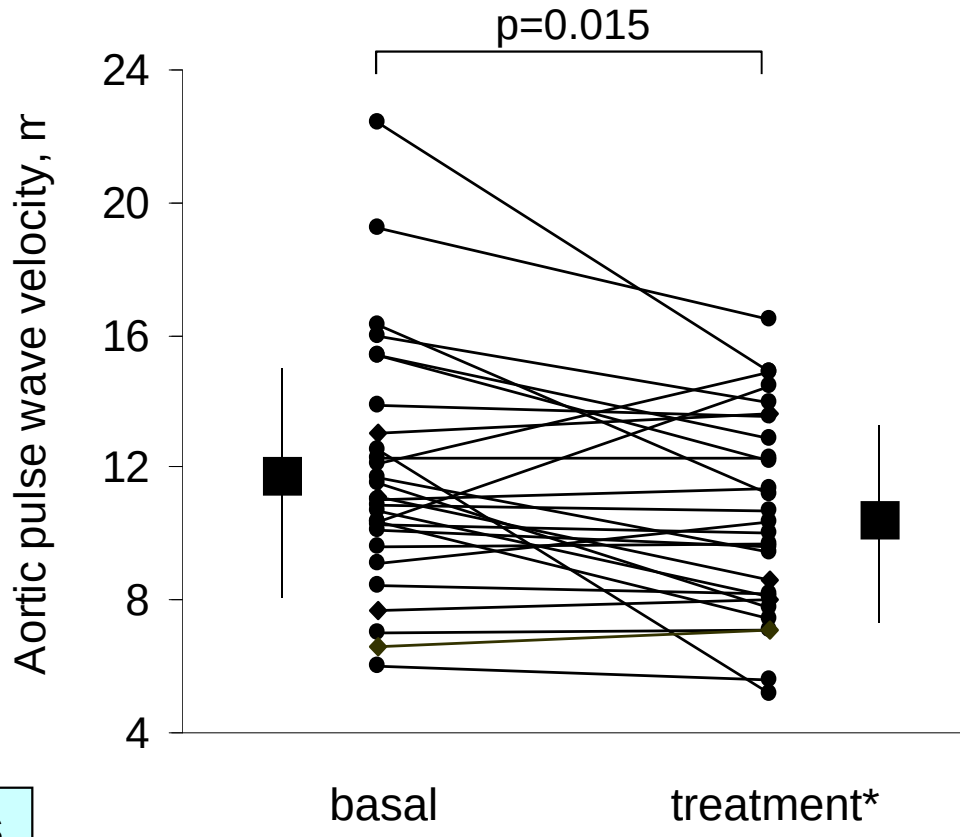

* Prednisone: 15 mg/day for 30 days

Schillaci G, Bartoloni E, Pucci G, *et al. Ann Rheum Dis* (2012).

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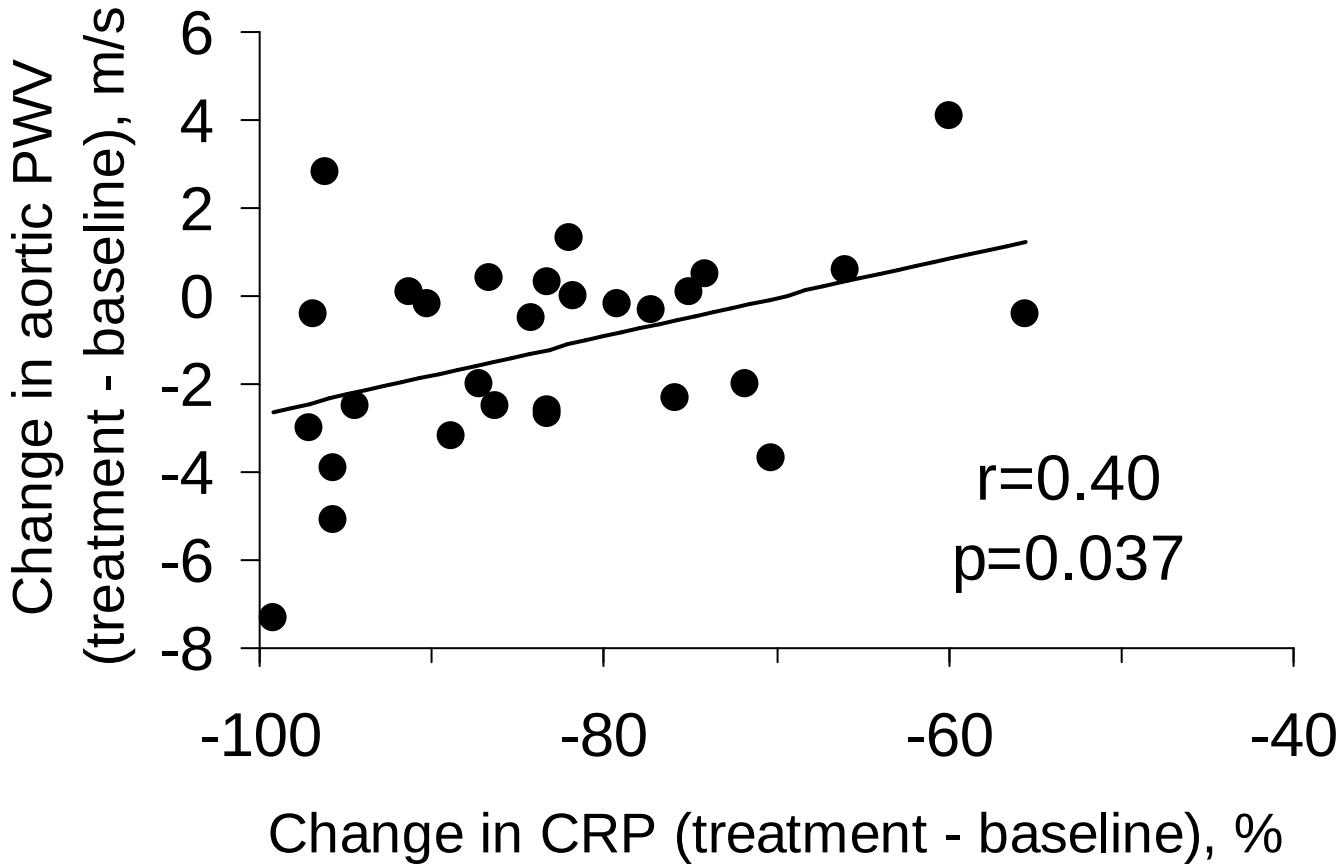
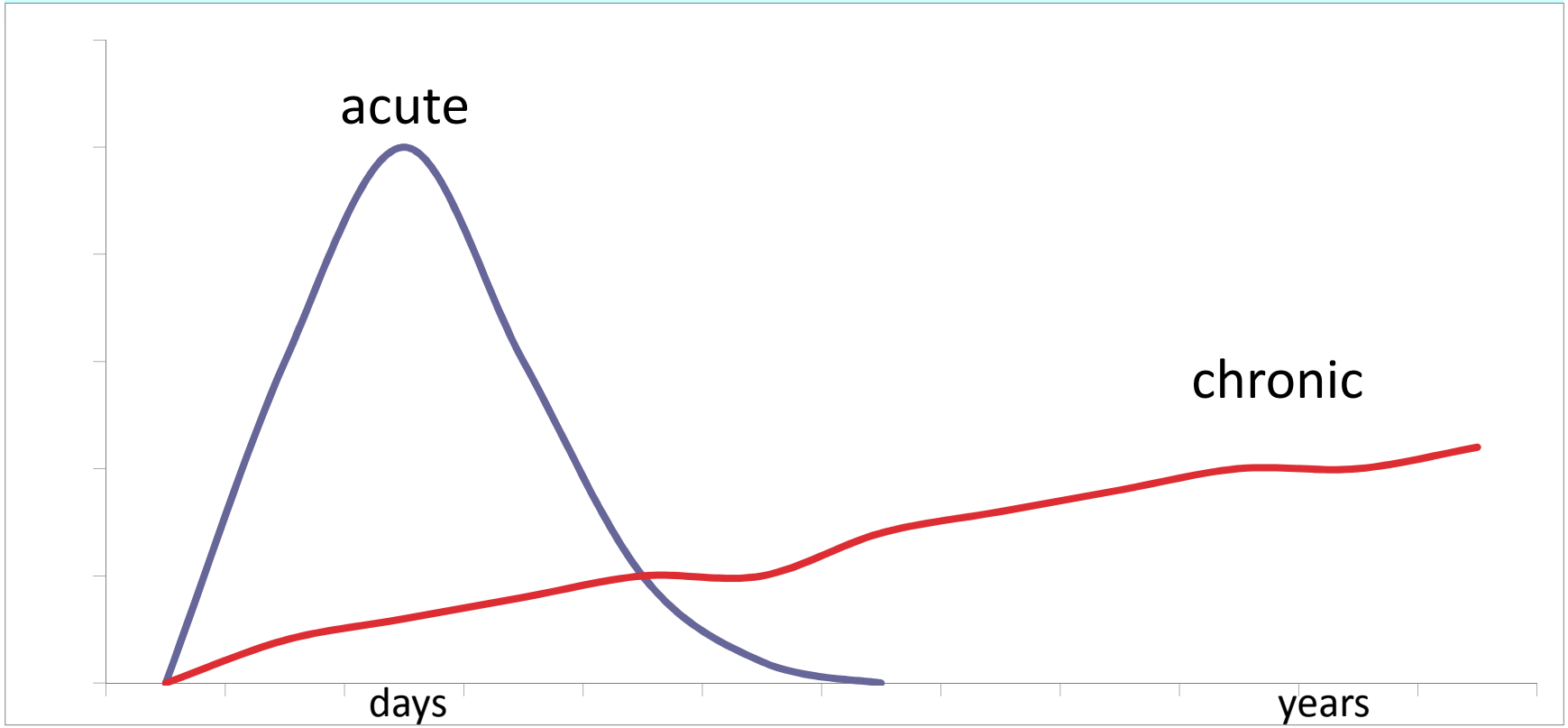


Schillaci G, Bartoloni E, Pucci G, *et al*. *Ann Rheum Dis* (2012).

Acute vs Chronic Inflammation



Inflammation → Repair

Inflammation → Disease Damage

EXTENDED REPORT

Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity

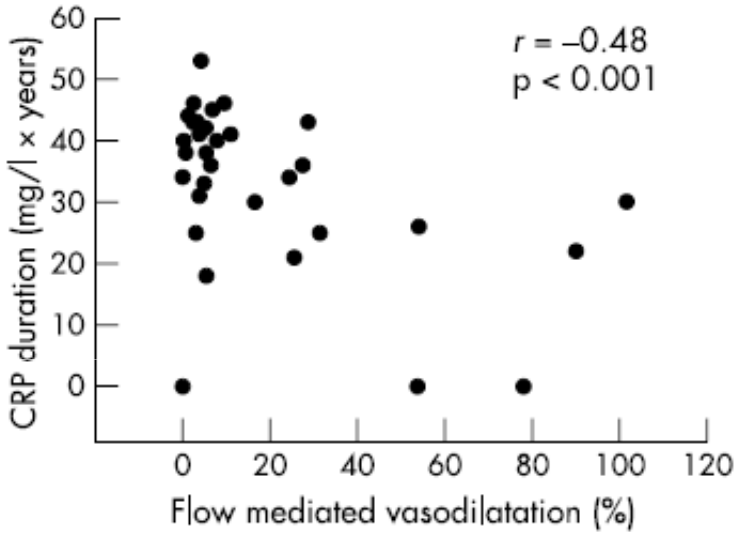


Table 3 Univariate correlations of flow mediated vasodilatation with selected variables in patients with RA

	R	p
Age	0.22	NS
LDL cholesterol	−0.45	<0.001
HDL cholesterol	−0.11	NS
Triglycerides	0.09	NS
Homocysteine	0.22	NS
Erythrocyte sedimentation rate	0.01	NS
Actual CRP	−0.44	<0.001
Average CRP	−0.47	<0.001
CRP duration	−0.48	<0.001
Systolic blood pressure	0.21	NS
Diastolic blood pressure	0.12	NS
Disease activity score	0.24	NS
Disease duration	−0.29	NS

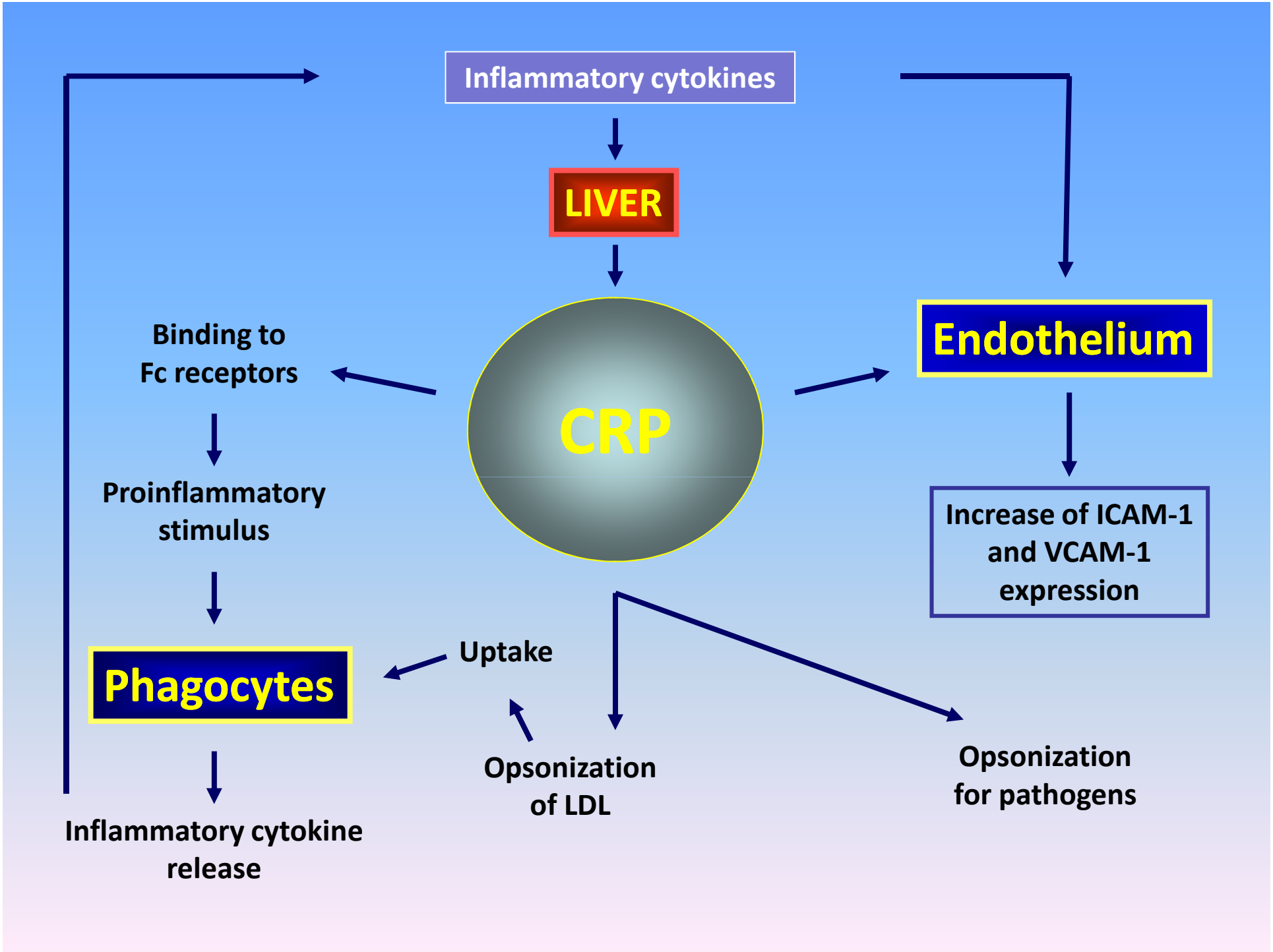
CRP, C reactive protein; DAS, Disease Activity Score; actual CRP, CRP at the moment of ultrasound examination; average CRP, the average of CRP levels evaluated at different times during the disease (at least four determinations/year); CRP duration, average CRP multiplied by the disease duration in years.

Table 4 Independent predictors of brachial artery flow mediated vasodilatation in patients with RA

Predictor	β	R^2	p
Brachial artery diameter	−0.28	0.22	<0.01
CRP duration	−0.44	0.37	<0.01
LDL cholesterol	−0.40	0.50	<0.01

CRP duration, average CRP multiplied by the disease duration in years.

Vaudo G *et al.* Ann Rheum Dis 2004;63:31-5


Inflammatory cytokines
LIVER
CRP
Binding to
Fc receptors
Proinflammatory
stimulus
Phagocytes
Inflammatory cytokine
release
Endothelium
Increase of ICAM-1
and VCAM-1
expression
Uptake
Opsonization
of LDL
Opsonization
for pathogens

Inflammatory cytokines involved in atherosclerosis and autoimmunity

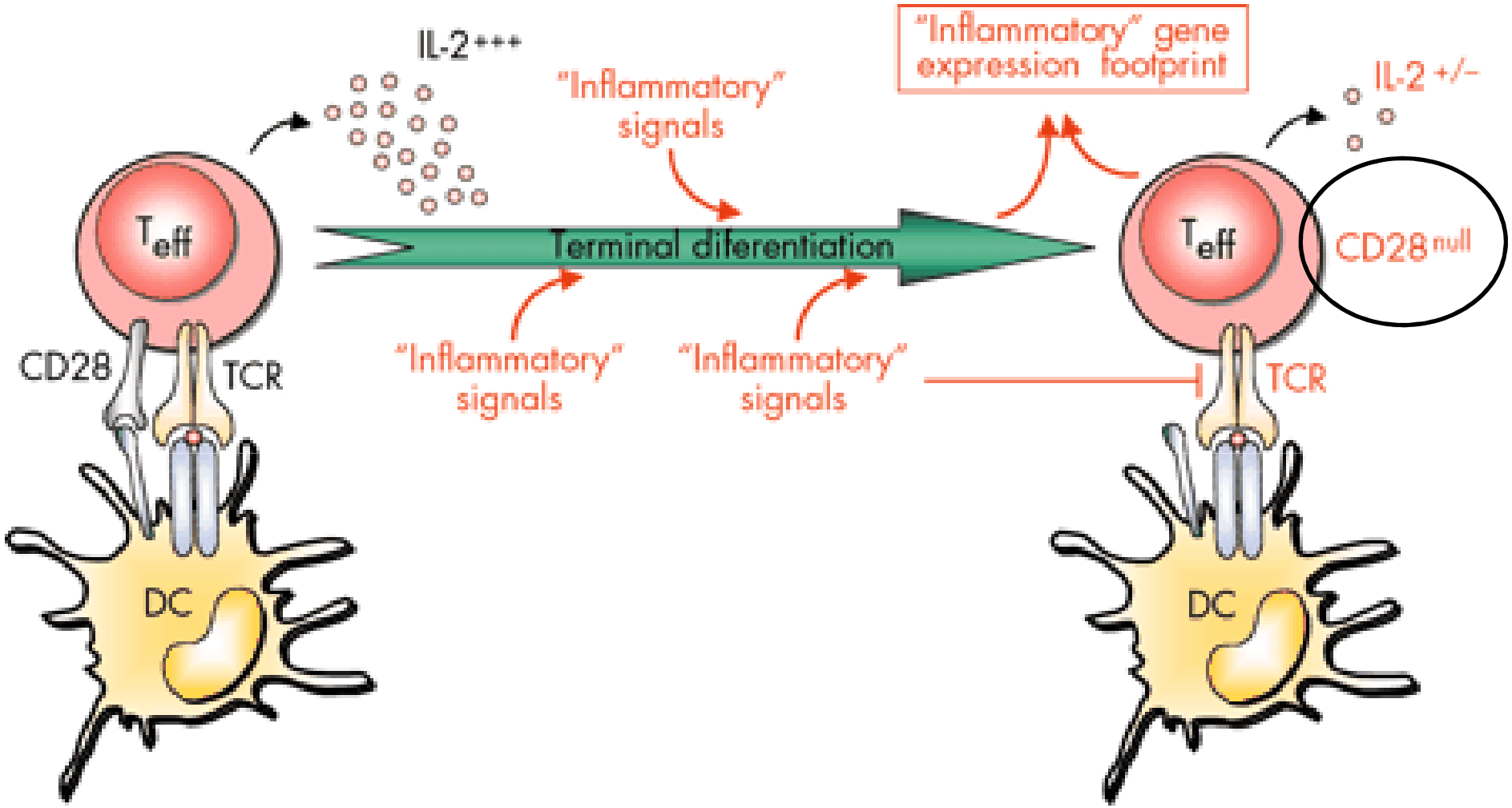
Cytokine	Atherosclerosis	Rheumatoid arthritis	Systemic lupus erythematosus
TNF-α	Increases adhesion molecules on endothelial surface Recruits inflammatory cells to vascular wall Promotes foam cell formation Promotes insulin resistance	Involved in pathogenesis of arthritis Inhibition likely protective for CVD development	May be elevated, potential role in lupus nephritis; correlates with CVD
IL-17	Absence of IL-17 signaling is protective for atherosclerosis development in mice	Involved in pathogenesis of arthritis Predicts microvascular endothelial function and macrovascular compliance May have prothrombotic effects	Elevated in SLE but link with CVD unknown
IL-6	Increased in atherosclerotic plaques Accelerates atherosclerosis in mice Inhibition of signaling can reverse plaque Its blockade may have deleterious effects on lipids	Involved in pathogenesis of arthritis Correlates with coronary calcium scores Likely contributes to abnormal lipid profiles	Link to CVD unknown
Type I interferons	Increased in atherosclerotic plaques Enhances inflammatory cell activation and plaque destabilization	Some patients may have elevated levels but role in RA-associated CVD is undefined	Plays a major role in SLE pathogenesis Contributes to endothelial dysfunction, poor vascular repair, platelet activation, foam cell formation and increased CV risk in SLE

Kahlenberg JM et al. Annu Rev Med. 2013;64:249–63

Impact of type I interferons on the vasculature and atherosclerotic lesions

Endothelial cells (ECs)
Increased EC apoptosis
Decreased levels and function of reparative EC progenitors
Inhibition of proangiogenic pathways, including VEGF and IL-1β
Upregulation of IL-18 which interferes with normal EC progenitor differentiation
Macrophages
Increased macrophage recruitment into atherosclerotic lesions
Upregulation of TLR4, with increased TNF-α, IL-12, and MMP-9 production
Upregulation of scavenger receptor A, thereby priming for foam cell formation
T cells
Increased T cell recruitment into atherosclerotic lesions
Promotion of T cell-mediated smooth muscle cell death and plaque instability

Knight JS & Kaplan MJ. Curr Opin Rheumatol 2013;25:597-605



switch regulation by TNFα

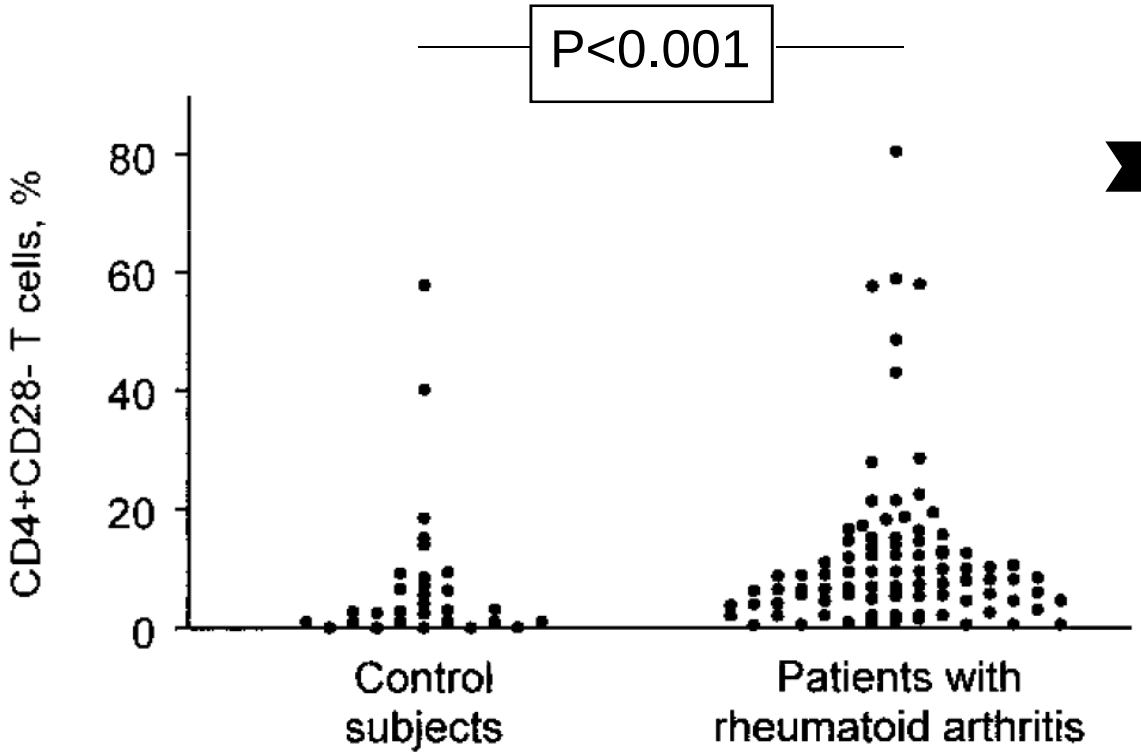
"Antigen mode" → **"Inflammation mode"**

Modified from: Clark J et al. Ann Rheum Dis 2011;64:70-6

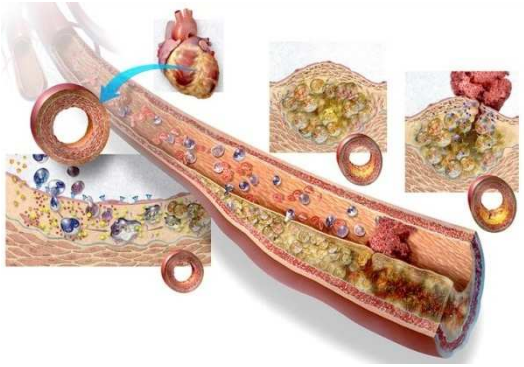
CD4+CD28− T Lymphocytes Contribute to Early Atherosclerotic Damage in Rheumatoid Arthritis Patients

Roberto Gerli, MD; Giuseppe Schillaci, MD; Andrea Giordano, MD; Elena Bartoloni Bocci, MD; Onelia Bistoni, BiolSc; Gaetano Vaudo, MD; Simona Marchesi, MD; Matteo Pirro, MD; Federica Ragni, MD; Yehuda Shoenfeld, MD, FRCP; Elmo Mannarino, MD

(*Circulation. 2004;109:2744-2748.*)

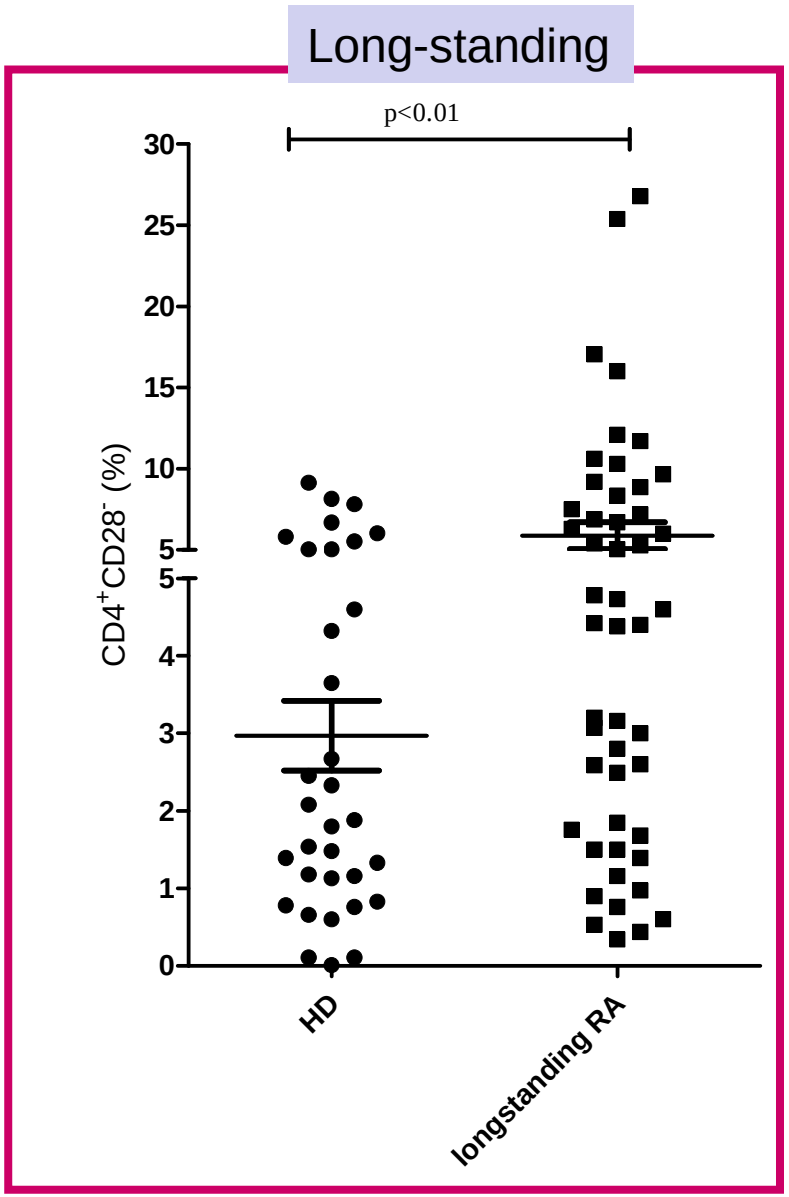


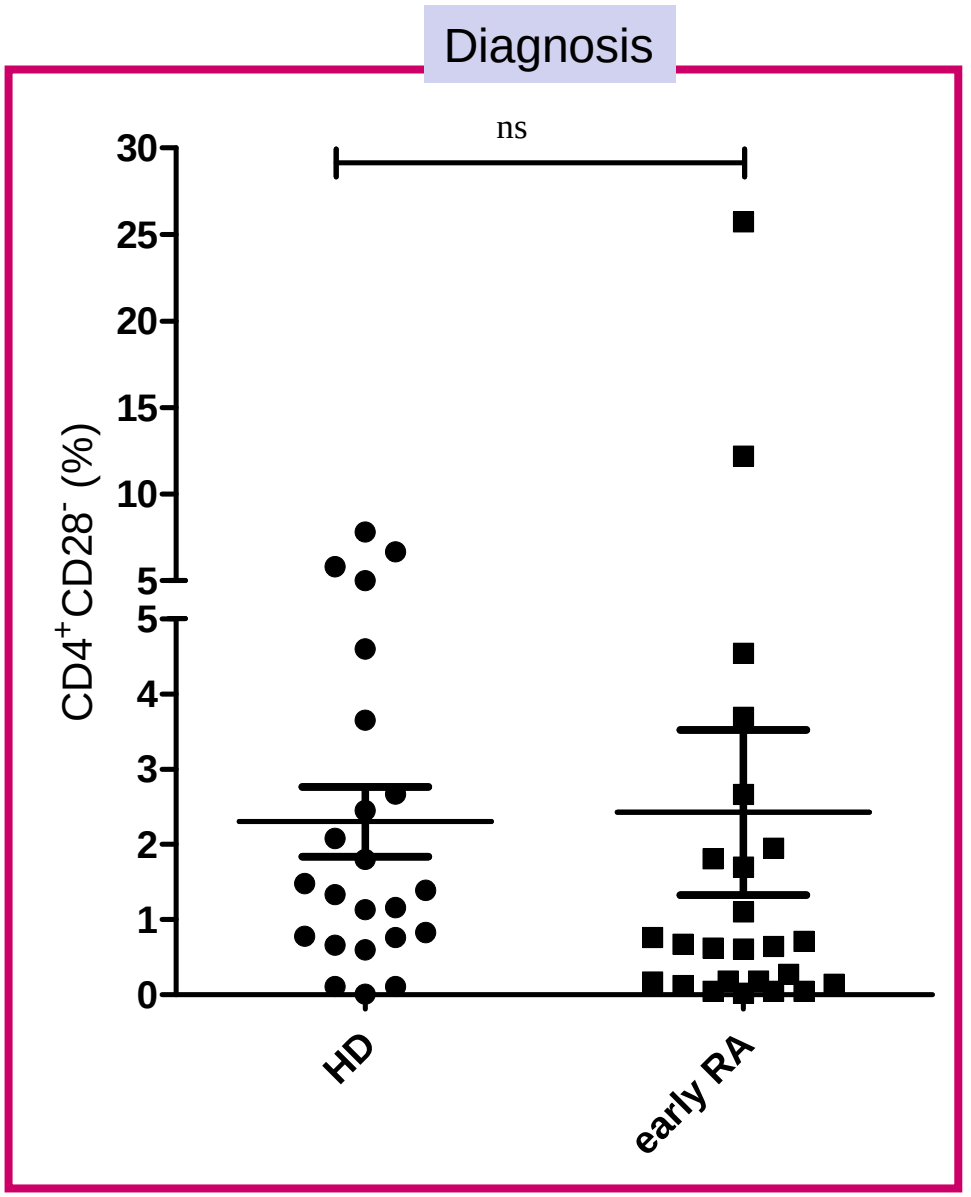
Arterial wall damage



Increased frequency of CD4+CD28- T cells in RA peripheral blood

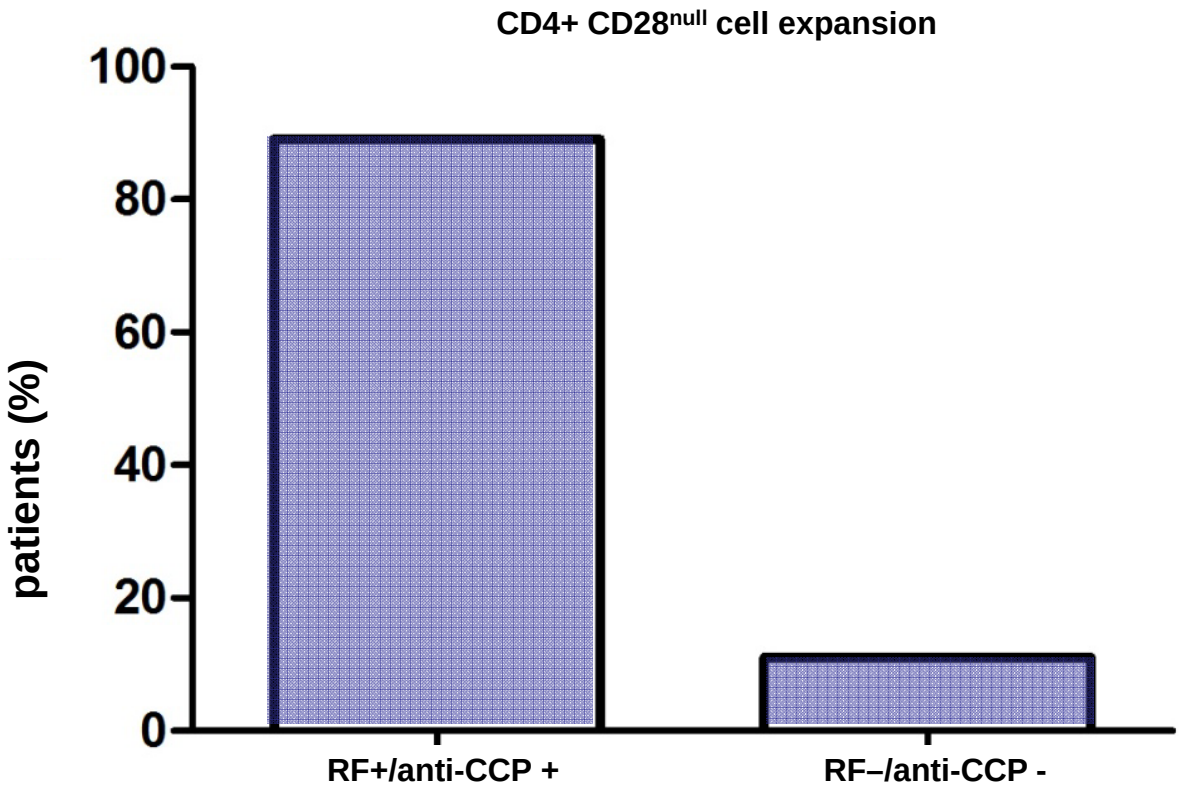
Percentage of circulating $CD4^+CD28^-$ lymphocytes in patients with rheumatoid arthritis at onset and with long-standing disease





Mirabelli G, Bartoloni E et al. Manuscript in preparation

CD4+ CD28^{null} expansion/non expansion in seropositive and seronegative RA patients



Bartoloni E et al. Manuscript in preparation

Different roles for anti–CCP and $CD4^{+}CD28^{null}$ cells in the acceleration of ATS in RA

Table 1. IMT thickness values at different carotid artery districts in rheumatoid arthritis patients according to the presence or absence of circulating anti-CCP antibodies and peripheral blood expansion of $CD4+CD28^{null}$ cells*

	Anti-CCP+	Anti-CCP−
With $CD4+CD28^{null}$ expansion		
No. of patients	7	9
IMT, mean ± SD mm		
Carotid artery*	1.00 ± 0.15†	0.99 ± 0.17‡
Common carotid	0.99 ± 0.15†	0.95 ± 0.14‡
Internal carotid	0.89 ± 0.17†	0.85 ± 0.23‡
Without $CD4+CD28^{null}$ expansion		
No. of patients	35	19
IMT, mean ± SD mm		
Carotid artery*	0.87 ± 0.17	0.82 ± 0.14
Common carotid	0.82 ± 0.13	0.78 ± 0.14
Internal carotid	0.80 ± 0.22§	0.71 ± 0.13

Gerli R. et al. Arthritis Rheum 2009;60:631

Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis

Table 1 Intima-media thickness values at different carotid artery districts (mm; mean (SD)) in patients with RA subdivided according to the presence of absence of serum anti-CCP antibodies

	Normal controls n = 75	Total patients with RA n = 81	Patients with RA anti-CCP– n = 29	Patients with RA anti-CCP+ n = 52	Anti-CCP– versus anti-CCP+P
Age (mean (SD))	61 (13)	63 (10)	62 (10)	63 (11)	0.54
Sex (males %)	29.3	28.4	13.7	36.5	0.02 (ξ^2)
Disease duration (years)	–	11 (9)	10 (7)	13 (10)	0.41
Common carotid	0.81 (0.24)	0.84 (0.22)†	0.82 (0.18)	0.85 (0.24)	0.44
Carotid bifurcation	0.89 (0.24)	1.02 (0.25)†	1.05 (0.26)	1.01 (0.24)	0.52
Internal carotid	0.74 (0.23)	0.76 (0.21)†	0.70 (0.16)	0.80 (0.23)	0.03
Carotid artery*	0.86 (0.25)	0.87 (0.19)†	0.85 (0.16)	0.89 (0.20)	0.47

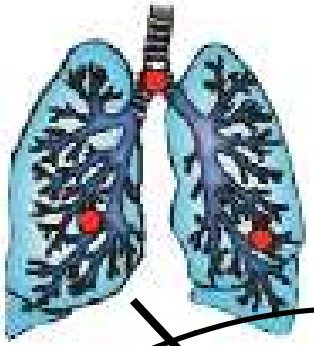
*Values of carotid artery are the average of common carotid, carotid bifurcation and internal carotid intima-media thickness values.
†$p<0.05$ versus normal controls.
RA, rheumatoid arthritis; anti-CCP, anti-cyclic citrullinated peptides.

Predictors at multivariate analysis: **age**
smoking
anti-CCP antibodies

Gerli R. et al. Ann Rheum Dis 2008;67:724

Hypothetical model for molecular pathogenesis of ACPA-positive rheumatoid arthritis

Environmental factors (smoke, others…) on genetic backgroung



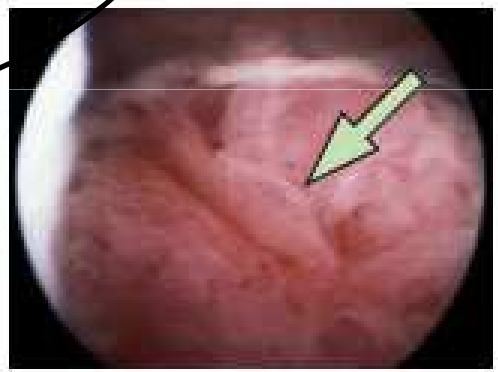
ACPA

Humoral immunity

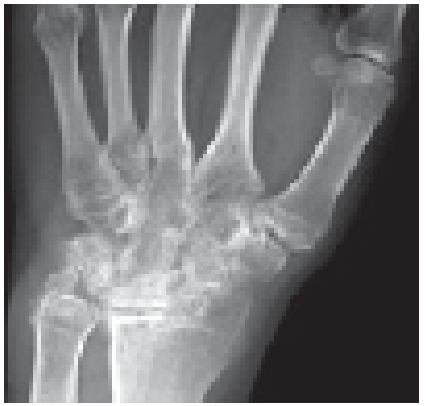
RF

Immune response

Inflammatory response

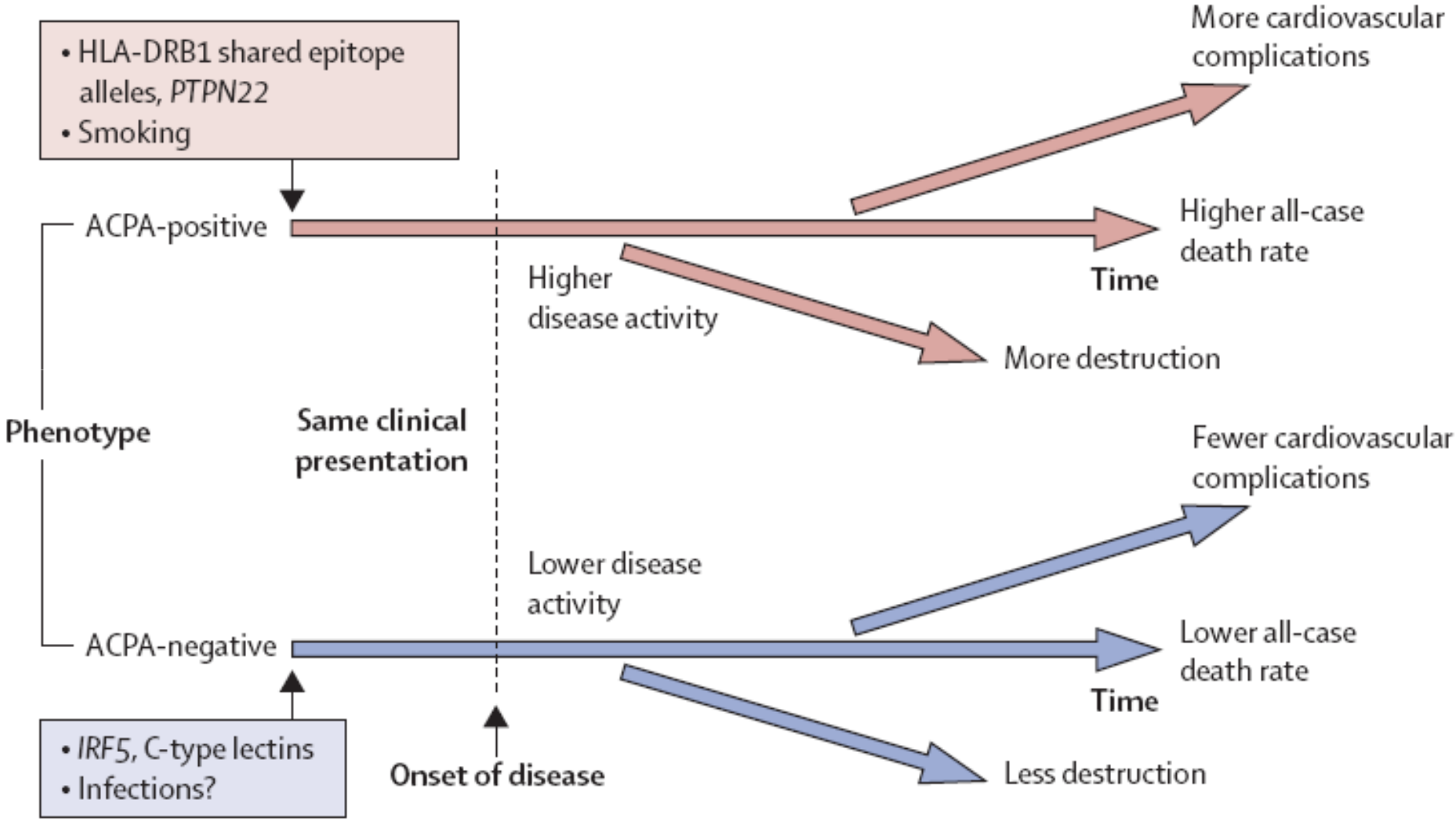


Synovial inflammation



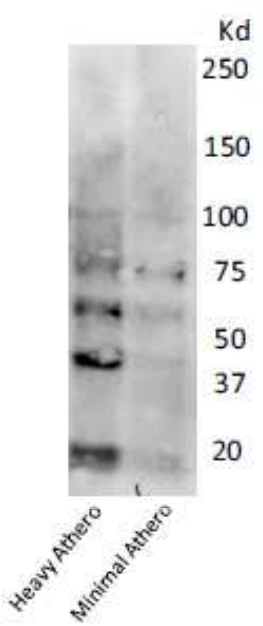
Joint destruction

Different risk factors, immune events and disease course between 2 major RA subsets

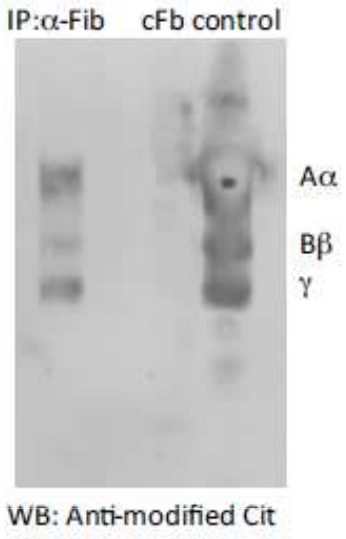


Klareskog L et al. Lancet 2009;373:659-72

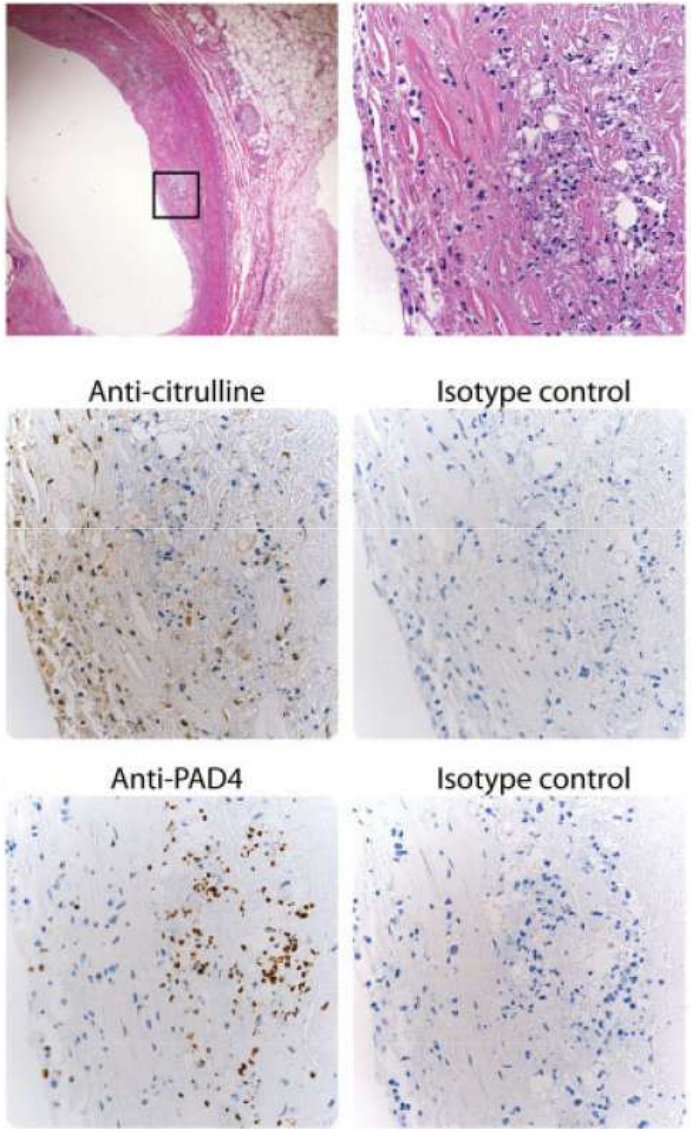
Presence of citrullinated proteins in atherosclerotic plaque

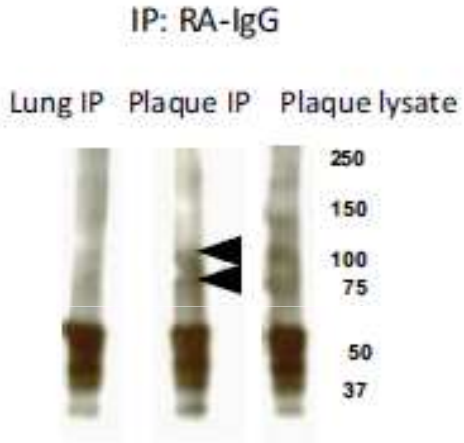


Multiple citrullinated proteins



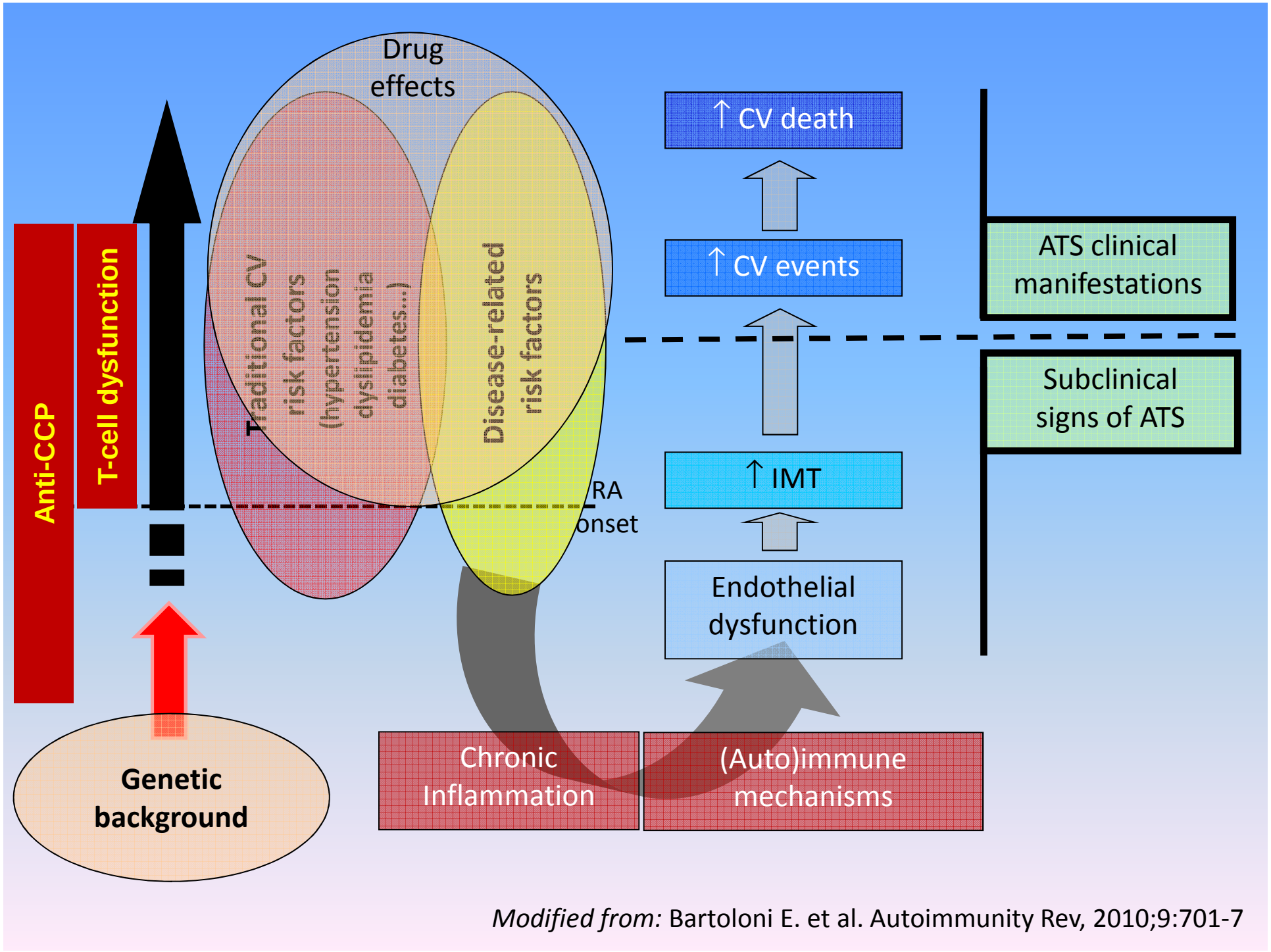
Citrullinated fibrinogen





Reactivity of ACPA+ RA IgG against citrullinated proteins

Sokolove J et al. Arthritis Rheum 2013;65:1719-24



Modified from: Bartoloni E. et al. Autoimmunity Rev, 2010;9:701-7

Cardiovascular disease assessment in rheumatoid arthritis: a guide to translating knowledge of cardiovascular risk into clinical practice

Anne Grete Semb,[1] Silvia Rollefstad,[1] Piet van Riel,[2] George D Kitas,[3,4] Eric L Matteson,[5] Sherine E Gabriel[5]

ARD Online First, published on March 7, 2014

We recommend starting with these simple procedures:

1. CVD risk factor recording and evaluation using risk calculators available for the general population

2. Referral of patients with high CVD risk to a primary care physician or a cardiologist skilled in this subject for follow-up

3. Providing information about excess CVD risk and how to modify it to the patients as major stakeholders

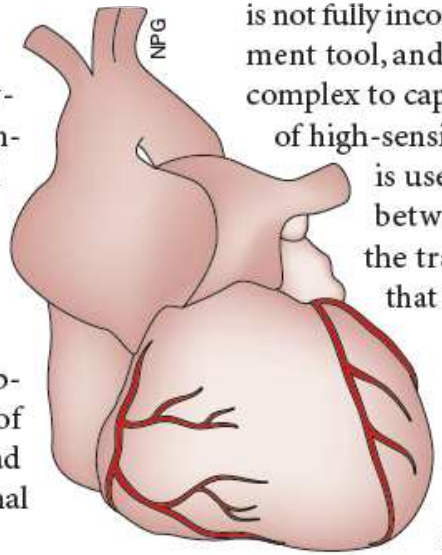
Treating cardiovascular risk in RA requires multidisciplinary care

Rekha Mankad and Sherine E. Gabriel

Rheumatoid arthritis is associated with an excess risk of cardiovascular disease, but current cardiovascular risk models might not be adequate to fully predict individual risk in a patient with this disease. Does the solution lie in closer collaboration between rheumatologists and cardiologists?

Mankad, R. & Gabriel, S. E. *Nat. Rev. Rheumatol.* advance online publication 18 March 2014;

coronary risk evaluation (SCORE) underestimate cardiovascular risk in patients with RA, especially in those with low-to-intermediate risk levels; conversely, the QRisk II model was found to overestimate risk in the patient with RA. Thus, presently, our ability to assess cardiovascular risk in the patient with RA is suboptimal. Under-recognition of an individual's risk could lead to undertreatment of traditional risk factors.



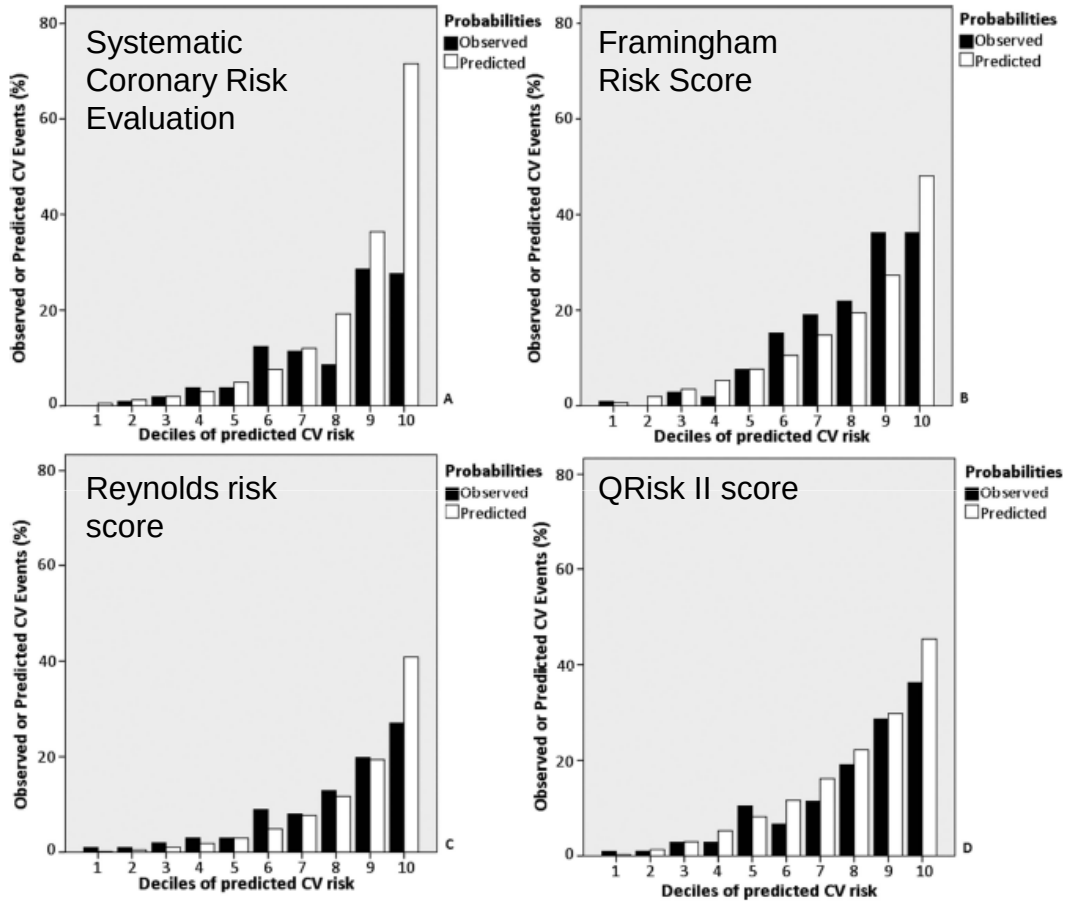
the increased cardiovascular risk in RA,[5] yet is not fully incorporated into any risk assessment tool, and this role is likely to be too complex to capture by mere measurement of high-sensitivity C-reactive protein, as is used in the RRS. An interplay between the inflammation and the traditional risk factors exists that is not fully understood.[5]

Inflammation and immune mechanisms are known to underlie the atherosclerotic process.[6] Thus, in RA, the control of inflammation could reduce the

> "...presently, our ability to assess cardiovascular risk in the patient with RA is suboptimal"

A consensus statement with recommendations for management of patients with RA and CVD was published in 2010.[10] These expert-panel-derived guidelines outline recommendations for screening for cardiovascular risk, treating cardiovascular risk factors and appropriate use of rheumatic disease therapies, including methotrexate and low-dose corticosteroids. However, many questions remain unanswered. Continued collaboration between rheumatologists and cardiologists will enhance our understanding of

Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis



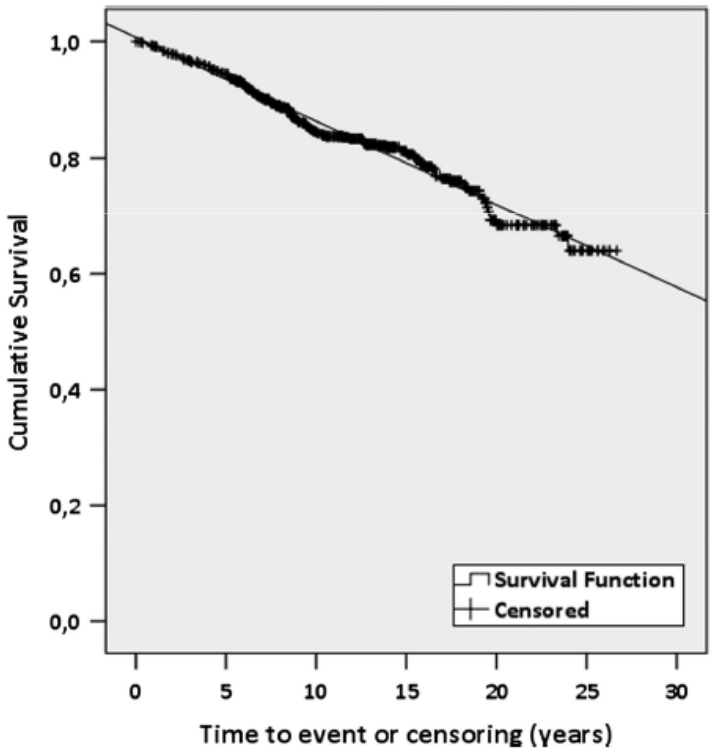
Commonly used CV risk models for 10-year risk of CVD tend to either underestimate or overestimate CV risk in a large portion of RA patients

$\rightarrow$ less accurate predictions of CV risk in RA compared to the general population

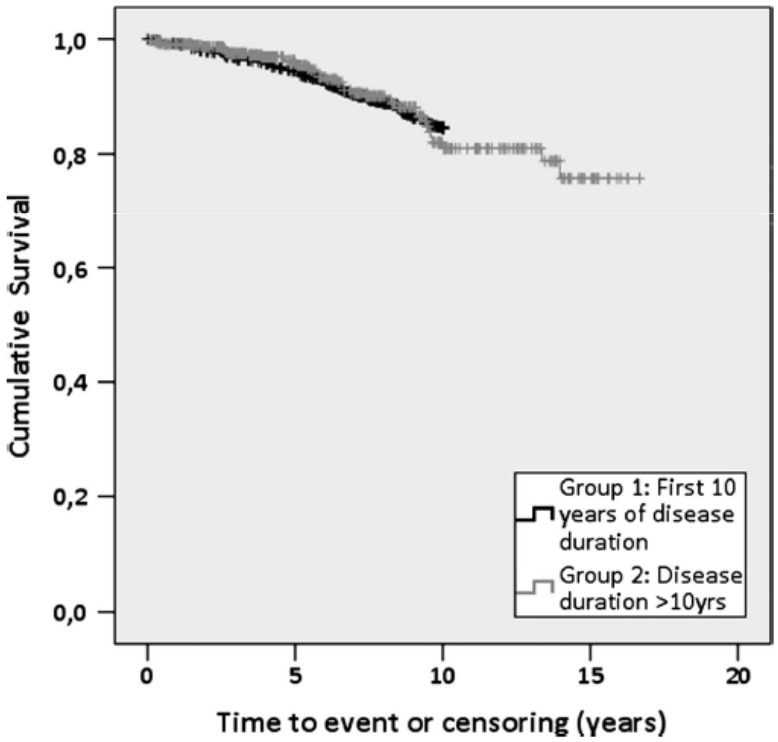
Arts EEA et al Ann Rheum Dis 2014

The effect of disease duration on the risk of cardiovascular disease in rheumatoid arthritis patients

Disease duration until CV event or censoring in RA

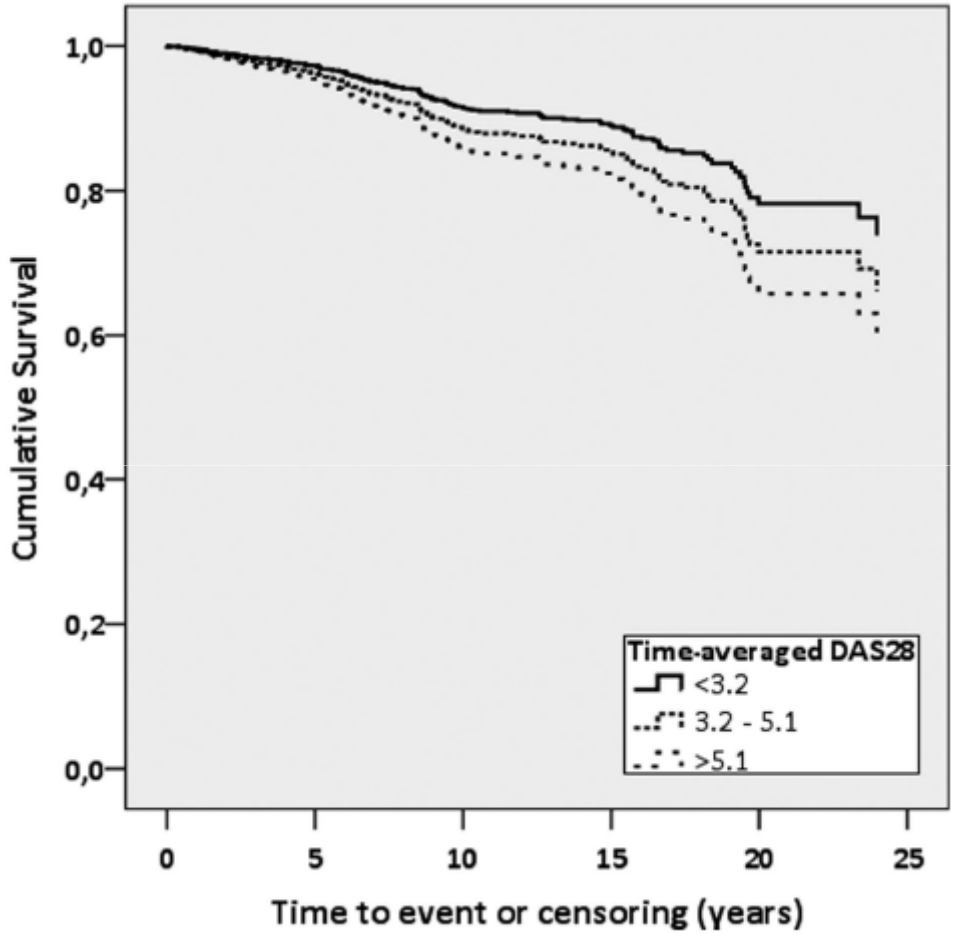


Survival distribution for patients at risk for CVD before or after 10 ys of disease duration



Arts EEA et al Ann Rheum Dis 2014

The effect of disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients

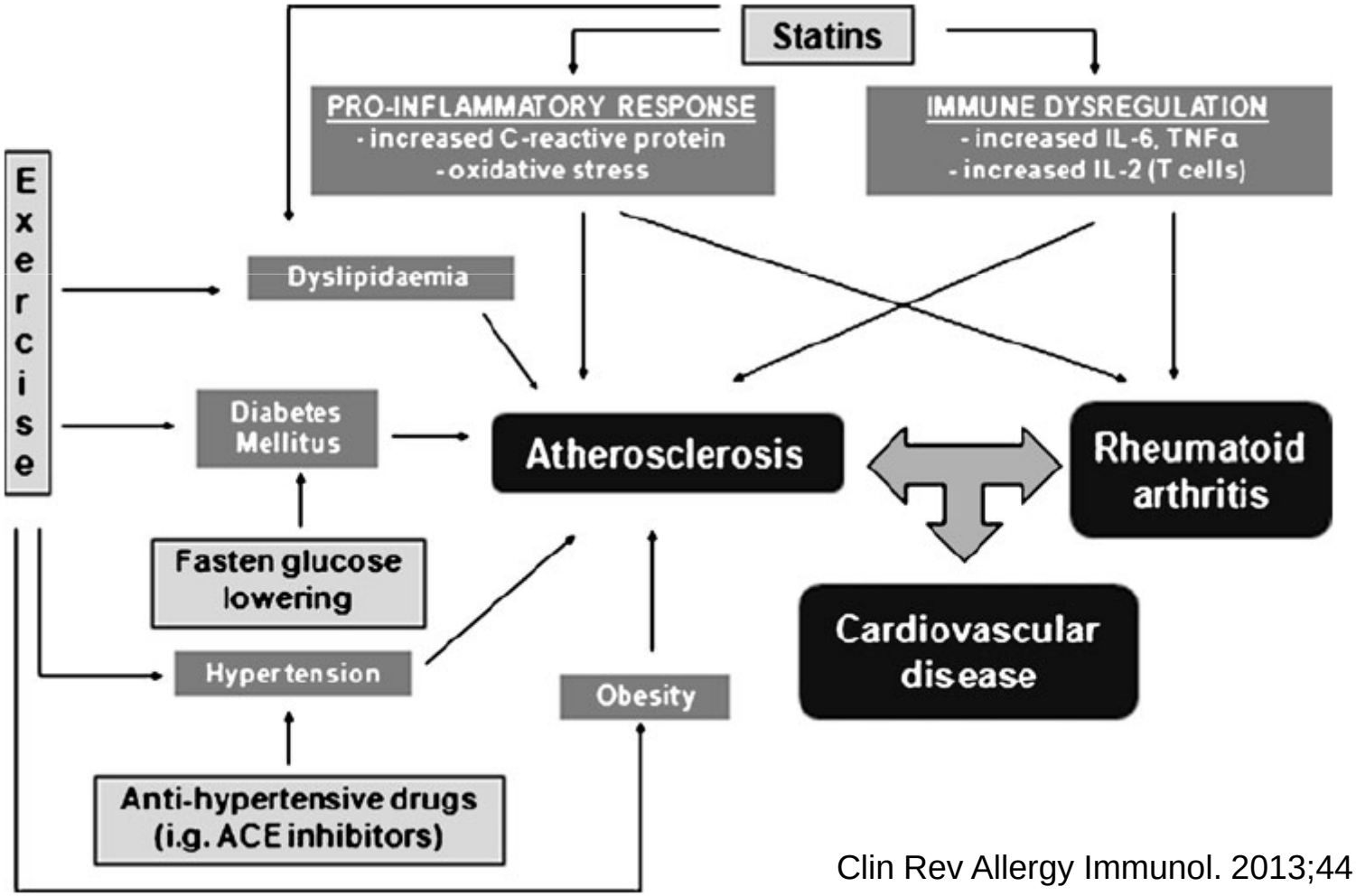


Survival distributions for RA patients divided into 3 groups based on the time-averaged 28 joint disease activity score (<3.2, 3.2–5.1, >5.1).

Arts EEA et al Ann Rheum Dis 2014

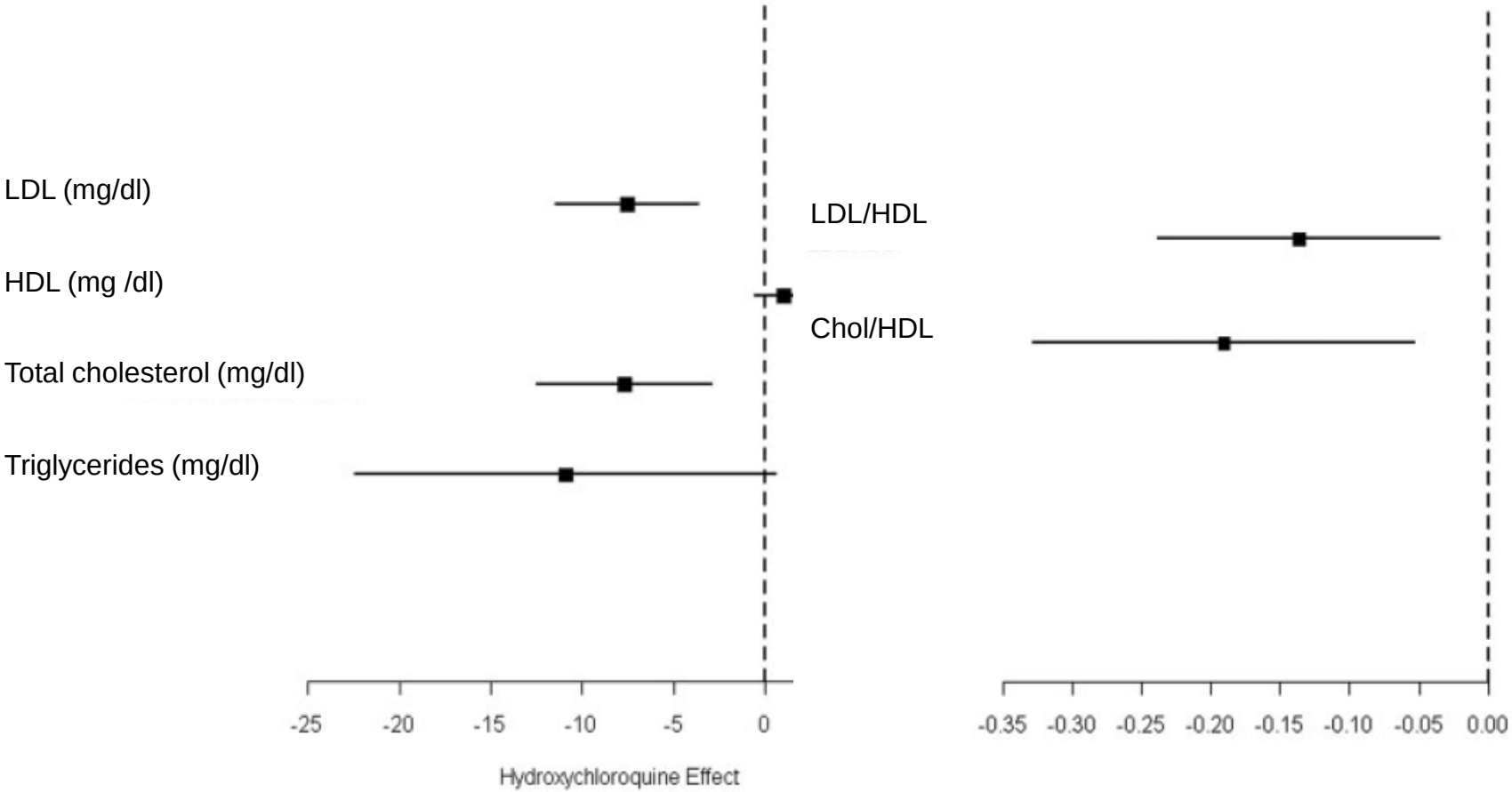
Cardiovascular Risk in Rheumatoid Arthritis and Systemic Autoimmune Rheumatic Disorders: a Suggested Model of Preventive Strategy

Elena Bartoloni • Alessia Alunno • Onelia Bistoni • Roberto Gerli



Clin Rev Allergy Immunol. 2013;44:14-22

Hydroxychloroquine Use Associated With Improvement in Lipid Profiles in Rheumatoid Arthritis Patients

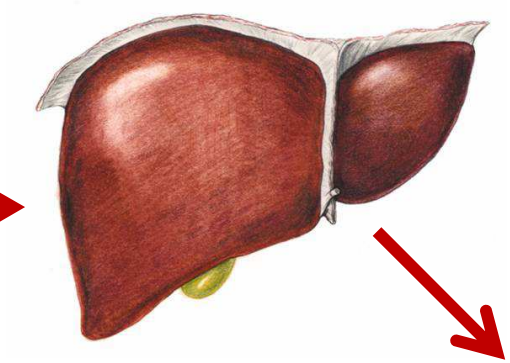


Morris S et al. Arthritis Care Res 2011;4:530-4

DYSLIPIDAEMIA INDUCED BY INFLAMMATION

IL-6
TNF-α

LIVER

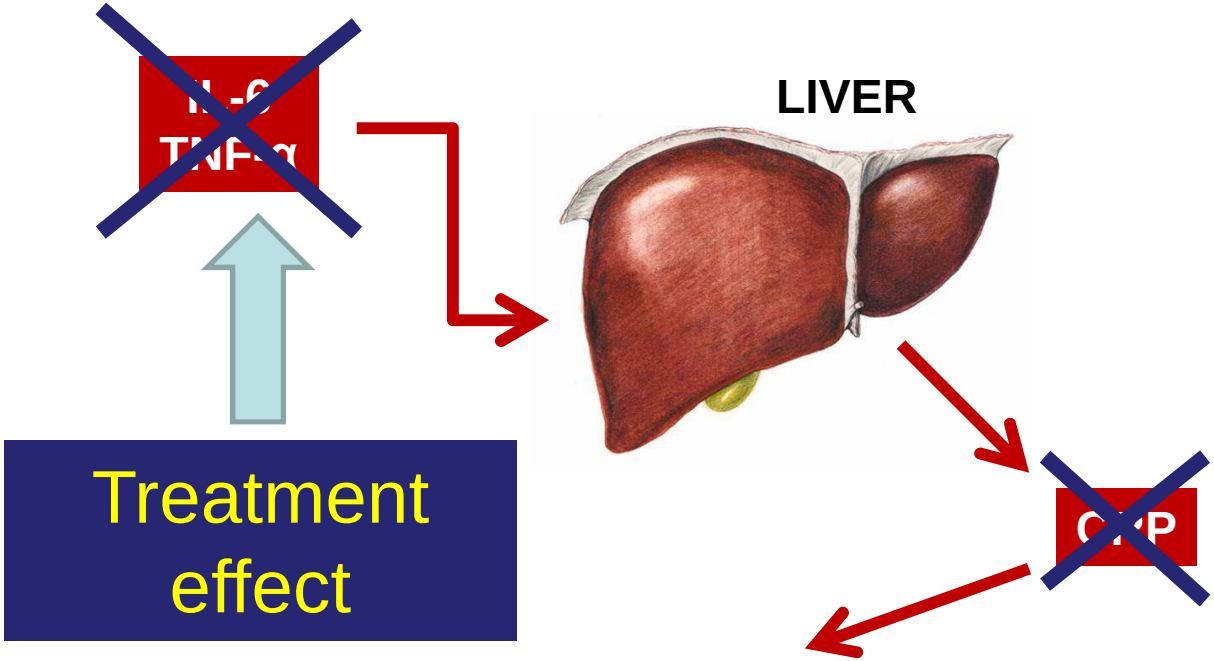


CRP

↓ **Total cholesterol**
HDL

↑ **Triglycerides**
Small dense LDL
ApoB/ApoAI

DYSLIPIDAEMIA INDUCED BY INFLAMMATION



- Total cholesterol
- HDL
- **Triglycerides**
- Small dense LDL
- ApoB/ApoAI

Effects of the anti-IL-6 receptor antibody, tocilizumab, on serum lipid levels in patients with RA

Characteristics	TCZ group ($n = 9$)		
	Baseline	After 3 months	*P*
Total cholesterol (mg/dl)[a]	190.6 ± 40.6	227.0 ± 40.9	0.011
HDL-cholesterol (mg/dl)[a]	54.5 ± 10.6	68.1 ± 7.80	0.015
LDL-cholesterol (mg/dl)[a]	119.7 ± 28.0	146.4 ± 32.5	0.011
Triglyceride (mg/dl)[a]	106.2 ± 52.8	122.3 ± 90.4	NS
Apo A-1 (mg/dl)[a]	120.1 ± 22.3	144.7 ± 12.7	0.017
Apo A-2 (mg/dl)[a]	22.5 ± 5.40	29.8 ± 3.82	0.011
Apo B (mg/dl)[a]	92.1 ± 19.3	102.3 ± 19.3	0.093
Apo B/Apo A-1	0.77 ± 0.10	0.70 ± 0.13	NS
Atherogenic index[a]	3.50 ± 0.31	3.35 ± 0.58	NS
CRP (mg/dl)[a]	3.39 ± 1.69	0.26 ± 0.59	0.011
SAA (μg/dl)[a]	191.4 ± 195.6	13.6 ± 25.8	0.011
IL-6 (pg/dl[a])	23.4 ± 23.0	48.2 ± 54.5	NS
DAS28-ESR	6.95 ± 0.38	3.31 ± 1.31	0.011

Differences from baseline were analyzed using nonparametric paired Wilcoxon test

[a] M ± SD

Kawashiri S et al. Rheumatol Int 2011;31:451–6

Beneficial Cardiovascular Effects of Low-dose Glucocorticoid Therapy in Inflammatory Rheumatic Diseases

Glucocorticoid therapy and incidence of subclinical atherosclerosis

Study	Type	No. Patients	No. Controls	Daily Dose	Cumulative Dose	GC Duration, yrs	Subclinical Atherosclerosis	Results	Comments
Gonzalez-Juanatey 2003[3]	Case-control	RA 47	47		15.9 g mean	≥ 5	cIMT plaque	No correlation cumulative PDN-plaque	
Gonzalez-Juanatey 2003[4]	Case-control	RA 55	31	Mean 10 mg/day		≥ 5	FMD	No correlation cumulative PDN-FMD	
Gonzalez-Juanatey 2004[5]	Case-control	RA 47	47	Mean 10 mg/day			LVDD	No correlation cumulative PDN-LVDD	
del Rincon 2004[6]	Prosp	RA 427	220	Mean 6.4 mg	Low 5–6.0 mg, medium 6–16 mg, high 16–122 mg	Mean 7.5	cIMT, plaque, ABI	Increased plaque/ ABI in higher dose	cIMT/plaque/ABI with duration of exposure
Hafström 2007[7]	Prosp	Early RA 34	31	DMARD + PDN 7.5 mg/day vs DMARD		2 ± 2	cIMT plaque, FMD	No difference	Higher total cholesterol in PDN
Vettori 2010[8]	Case-control	50 SSc	41	Low-medium (5–15 mg/day) in 62%	30% no PDN, 28% < 5 g, 16% 5–10 g, 26% > 10 g		IMT > 0.9 mm plaque	OR 1.15 in higher cumulative dose	
Giles 2011[9]	Prosp	158 RA	No		Median 3.1 g (0–9.1)		cIMT/plaque progression at mean 3.2 yrs	Association cumulative PDN-cIMT progression	Lower cIMT progression in PDN users on statin therapy

cIMT: carotid intima-media thickness; ABI: ankle-brachial index; FMD: flow-mediated vasodilation; LVDD: left ventricular diastolic dysfunction; GC: glucocorticoid; PDN: prednisone; Prosp: prospective; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug.

Bartoloni E et al. J Rheumatol. 2012;39:1758-62

Beneficial Cardiovascular Effects of Low-dose Glucocorticoid Therapy in Inflammatory Rheumatic Diseases

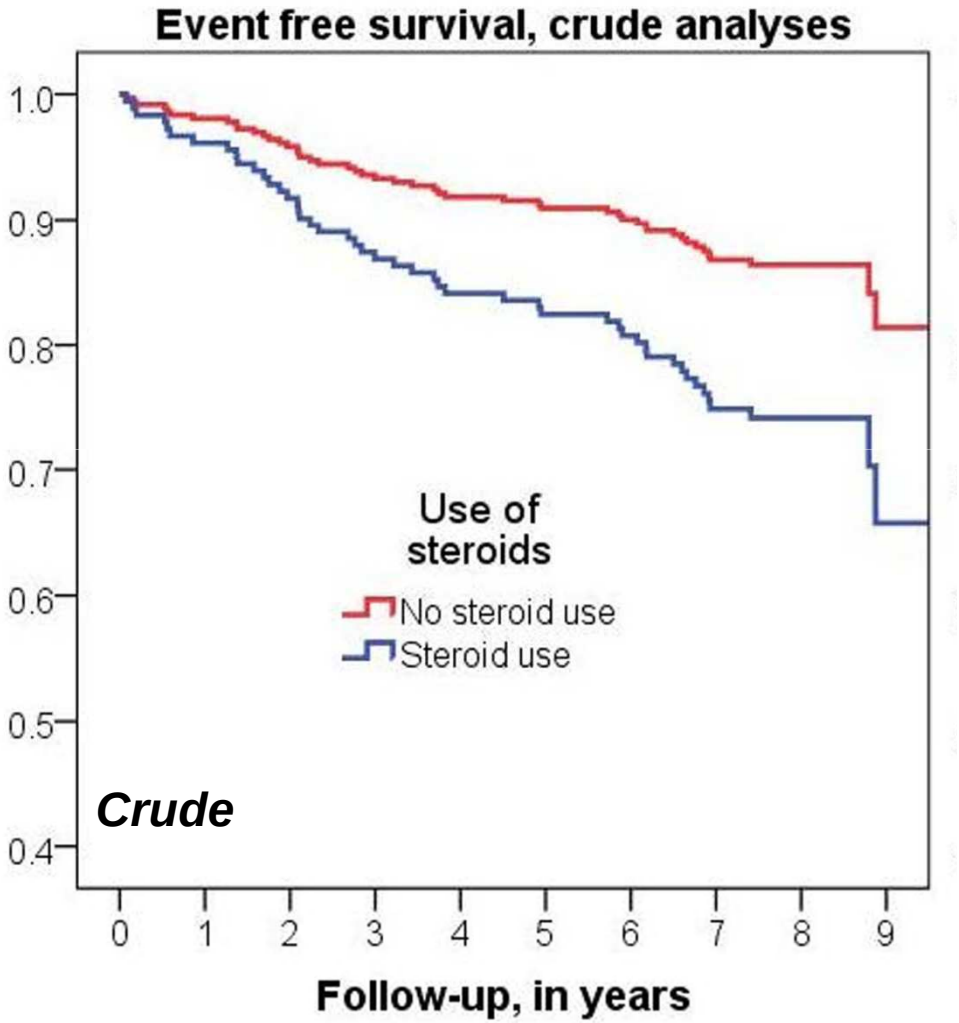
Glucocorticoid therapy and risk of cardiovascular events

Study	Type	No. Patients	No. Controls	Average Daily Dose	Duration of GC	CV Outcome	Results	Comments
Wei 2004[13]	Cohort 5 yrs	COPD, IBD, arthritis 68.781	82.202	Low (topic), medium < 7.5 mg/day, high ≥ 7.5 mg/day		MI, HF, ictus	RR 2.56 ≥ 7.5 mg/day	Increased risk in continuous vs intermittent use
Souverein 2004[14]	Case-control 10 yrs	RA, COPD 50.656	50.656	Low < 7.5, medium 7.5–20, high ≥ 20 mg/day		MI, ictus, TIA, HF	OR 1.25 in ever-use	OR 2.6 HF current user
Huiart 2006[15]	Case-control 7 yrs	COPD 371	1.864	Mean 3.7 mg/day		Fatal/nonfatal MI	RR 2.01 in current exposure	RR 3.22 current exposure ≥ 25 mg/day
Huiart 2005[16]	Case-control 7 yrs	COPD 371	1.864	Inhaled low < 50, medium 50–200, high > 200 μg/day		Fatal/nonfatal MI	RR 0.68 (0.47-0.99) in medium dose	No association with duration inhaled GC use
Varas-Lorenzo 2007[17]	Case-control 3 yrs	4.795 RA; COPD, asthma, CTD	20.000	Low-medium ≤ 10, high > 10 mg/day		Fatal/nonfatal MI	OR 1.42 in current use, OR 2.15 current high dose	
Solomon 2006[18]	Case-control 6 yrs	RA 3.501	RA 9.460	Low < 10, medium 10–20, high > 20 mg/day		MI, stroke	OR 1.5	No dose effect
Davis 2007[19]	Retro 13 yrs	RA 603	No	7.7 mg/day	Median 2.1 yrs	MI, stroke, CV death	HR 2.11 in highest dose (> 7 mg/day)	In RF+, inc. risk with higher cumulative exposure/average daily dose, recent exposure
Naranjo 2008[20]	Cohort 22 mo	RA 4.363	No			MI, angina, stroke	HR 0.95 (0.92–0.98)	
Kremers 2007[21]	Retro	PMR 364	Yes	3.5 mg/day	Median 1.7 yrs	MI, HF, ictus, PAD	HR 0.61 (0.37–1.01)	No association with cumulative dose decrease 50% past exposed (> 1 yr)
Mazzantini 2012[1]	Retro 60 mo	PMR 222	No	4.4 ± 2.6 g cumulative	Mean 46 ± 22 mo	MI, PAD	GC duration - MI at univariate	No association cumulative/ duration at multivariate

COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease; CTD: connective tissue disease; HF: heart failure; PAD: peripheral artery disease; MI: myocardial infarction; RA: rheumatoid arthritis; RF: rheumatoid factor; Retro: retrospective; RR: risk ratio; TIA: transient ischemic attack; HR: hazard ratio; PMR: polymyalgia rheumatica.

Bartoloni E et al. J Rheumatol. 2012;39:1758-62

Kaplan-Meier survival curve of RA patients who were using or not steroids at baseline



Van Sijl AM et al. PlosOne 2014;9:e87965

Glucocorticoid dose thresholds associated with CV mortality in RA

Glucocorticoid exposure	CV mortality			
	No. of deaths	No. of person-years	HR (95% CI), adjusted for glucocorticoid propensity	
			Unadjusted	Adjusted
Daily dose				
None	48	3,646	1.0 (referent)	1.0 (referent)
<5 mg	16	585	2.07 (1.17–3.65)†	1.82 (1.03–3.22)
5–7 mg	28	1,647	1.28 (0.80–2.05)	1.07 (0.67–1.72)
8–15 mg	24	575	3.17 (1.94–5.17)	2.27 (1.36–3.79)
≥15 mg	4	72	4.08 (1.47–11.32)	3.21 (1.14–8.97)
Cumulative dose				
None	31	2,372	1.0 (referent)	1.0 (referent)
<9 gm	14	1,430	0.95 (0.47–1.95)	0.70 (0.37–1.31)
9–39.9 gm	23	1,323	0.93 (0.45–1.87)	1.08 (0.63–1.88)
≥40 gm	52	1,398	2.32 (1.36–3.96)	2.05 (1.29–3.27)
Dose/time				
N				t)
<				16)
1.9				81)
≥				75)

With 5 mg/day, it would take 21.9 years to reach 40-gm cumulative dose threeshold

Del Rincon I et al. Arhtritis Rheumatol. 2014;66:264-72

arthritis research&therapy

RESEARCH ARTICLE Open Access

Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study

Co-variates	HR	CI 95%	*P*-value
ESR, baseline	1.018/+	1.005, 1,030	<0.01
Triglycerides	1.853/mmolL^{-1}	1.376, 2.496	<0.001
Hypertension	2.809/+	1.575, 5.008	<0.001
Female sex	0.449	0.249, 0.808	<0.01
DMARDs[1]	0.887/mo	0.856, 0.918	<0.001

Extended Cox multiple regression model, with fixed and time-dependent covariates.

[1]Time-dependent co-variate

Global Chi square (LR) = 131.45 on 5df ($P < 0.001$)

CI, confidence interval; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; HR, hazard ratio; RA, rheumatoid arthritis

RHEUMATOLOGY

Original article

The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review

Sarah L. Westlake[1], Alexandra N. Colebatch[2], Janis Baird[3], Patrick Kiely[4], Mark Quinn[5], Ernest Choy[6], Andrew J. K. Ostor[7] and Christopher J. Edwards[2]

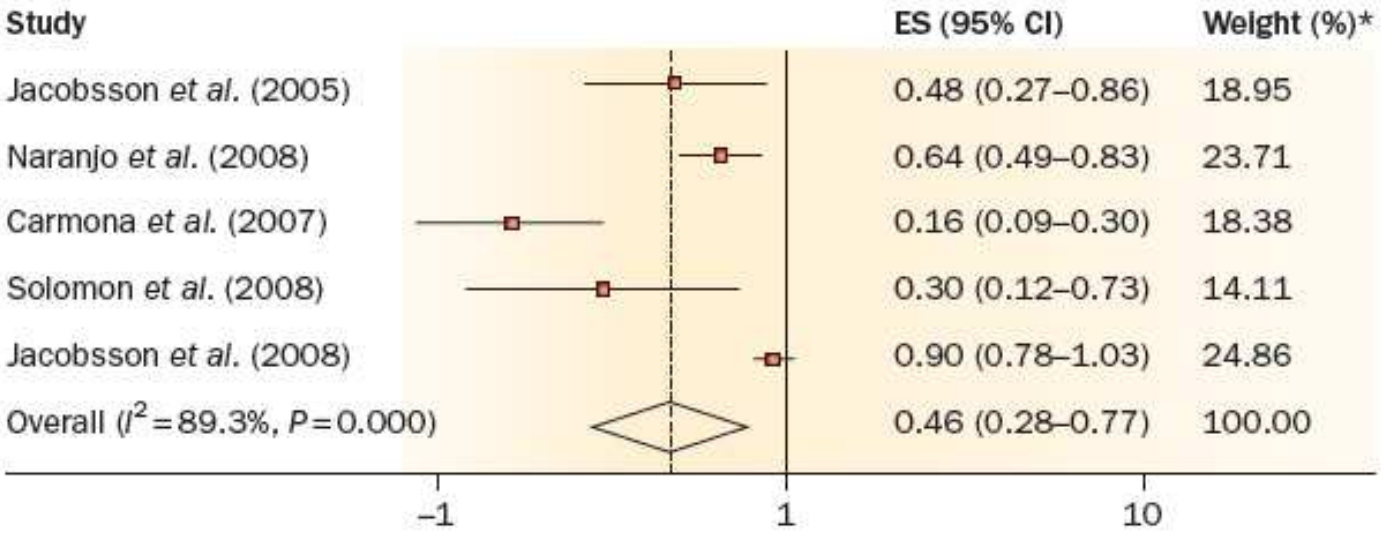
Conclusion. The current evidence suggests that MTX use is associated with a reduced risk of CVD events in patients with RA. This suggests that reducing the inflammation in RA using MTX not only improves disease-specific outcomes but may also reduce collateral damage such as atherosclerosis.

Rheumatology 2010;49:295-307

Cardiovascular risks of TNF antagonists versus nonbiologic DMARDs

Endpoint	Number of events	Hazard ratio	95% CI
Composite endpoint (including cardiovascular deaths)	82‡	0.39	0.19–0.82
Composite endpoint (excluding cardiovascular deaths)	66	0.35	0.16–0.74
Nonfatal myocardial infarction	25	0.24	0.06–0.95
Nonfatal TIA or stroke	41	0.44	0.18–1.09

*Data from a multi-centered US observational RA registry of 10,156 patients comparing the rates of cardiovascular events among patients with RA prescribed anti-TNF agents versus nonbiologic DMARDs excluding methotrexate.[63] ‡The incidence rate was 7.51 per 1,000 patient-years (95% CI 3.95–11.07) for the reference group of nonbiologic DMARD users and 2.93 (95% CI 1.74–4.13) for anti-TNF therapy users. Abbreviation: TIA, transient ischemic attack. Adapted with permission from Greenberg, J. D. *et al. Ann. Rheum. Dis.* **70**, 576–582 (2011).[63]



Greenberg, J. D. *et al. Nat. Rev. Rheumatol. 2011;15:13-21*

Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti–tumor necrosis factor therapy

Table 2. Incidence rates of verified first MI in DMARD-treated and anti-TNFα–treated patients*

	All patients		Male patients		Female patients	
	DMARD (n = 2,170)	Anti-TNFα (n = 8,659)	DMARD (n = 615)	Anti-TNFα (n = 2,072)	DMARD (n = 1,555)	Anti-TNFα (n = 6,587)
Person-years	2,893	13,233	831	3,199	2,062	10,034
No. of reported MIs	17	63	10	27	7	36
Rate of MIs per 1,000 person-years (95% CI)	5.9 (3.4–9.4)	4.8 (3.7–6.1)	12.0 (5.8–22.1)	8.4 (5.5–12.2)	3.4 (1.4–7.0)	3.6 (2.5–5.0)
Incidence rate ratio	Referent	0.81 (0.47–1.38)	Referent	0.70 (0.34–1.45)	Referent	1.06 (0.47–2.37)
Incidence rate ratio, adjusted for age and sex	Referent	1.13 (0.65–1.96)	Referent	0.92 (0.43–0.98)	Referent	1.39 (0.62–3.14)
Incidence rate ratio, multivariate analysis†	Referent	1.44 (0.56–3.67)	Referent	0.96 (0.26–3.55)	Referent	2.07 (0.62–6.88)

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)

Dixon WG et al. Arthritis Rheum 2007;56:2905-12

Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study

Sella A Provan, Anne Grete Semb, Jonny Hisdal, et al.

Ann Rheum Dis 2011;**70**:812-817

Table 2 Cardiovascular risk markers compared across groups

Variable	Active RA (n=82)	RA in remission (n=31)	Population controls (n=86)	p Value (active vs remission)	p Value (active vs control)	p Value (remission vs control)
Soluble biomarkers						
CRP (mg/l)	8.65 (1.49)	5.35 (2.30)	3.13 (1.39)	0.001	<0.000	0.09
Total cholesterol (mmol/l)	5.22 (0.13)	5.77 (.20)	5.84 (0.12)	0.02	<0.000	0.77
HDL cholesterol (mmol/l)	1.60 (0.06)	1.61 (0.09)	1.72 (0.06)	0.90	0.14	0.33
Atherogenic index	3.58 (0.13)	3.81 (0.20)	3.67 (0.12)	0.23	0.17	0.24
lnNT-proBNP (pmol/l)	2.09 (0.11)	1.99 (0.17)	2.09 (0.11)	0.04	0.04	0.61
Peripheral biomarkers						
RHI	2.02 (0.07)	2.60 (0.11)	2.13 (0.07)	<0.000	0.29	<0.000
Brachial systolic pressure (mm Hg)	134.47 (2.01)	126.47 (3.07)	127.34 (1.85)	0.03	0.01	0.81
Central biomarkers						
PWV (m/s)	8.09 (0.16)	7.31 (0.23)	7.84 (0.14)	0.003	0.21	0.05
AIx	22.57 (1.05)	18.35 (1.53)	18.20 (0.95)	0.02	0.002	0.93
Central systolic pressure (mm Hg)	124.64 (1.94)	116.20 (2.85)	117.33 (1.77)	0.01	0.005	0.74
IMT (mm)	0.76 (0.02)	0.73 (0.03)	0.74 (0.02)	0.38	0.45	0.75
Composite risk score						
Framingham	10.93 (0.64)	10.11 (0.90)	10.15 (0.53)	0.44	0.34	0.97
SCORE	3.38 (0.27)	2.46 (0.38)	2.88 (0.23)	0.04	0.15	0.34

Estimated marginal mean (SE) presented with adjustments for age and sex.
AIx, augmentation index; BMI, body mass index; CRP, high sensitivity C reactive protein; Framingham, Framingham risk score; HDL cholesterol, high density lipoprotein; IMT, intima-median thickness; lnNT-proBNP, natural logarithm of N-terminal pro-brain natriuretic peptide; PWV, pulse wave velocity; RHI, reactive hyperaemia index; SCORE, European Society of Cardiology SCORE risk calculator.

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