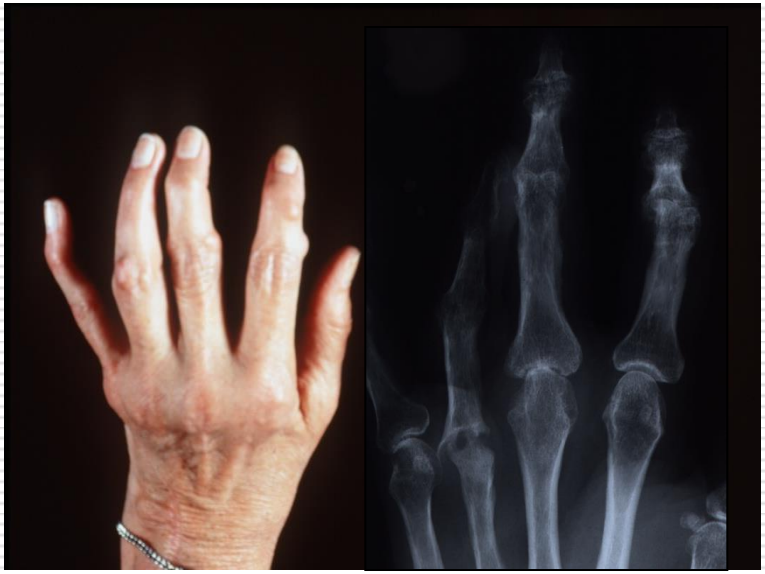
Καρδιαγγειακός κίνδυνος στη ρευματοειδή αρθρίτιδα

Αλέξανδρος Α. Δρόσος

Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων

Rheumatoid Arthritis (RA): A Substantial Burden



- Affects ~0.5%–1% of the European and US population[1-3]
- 3 times more common in women [3]
- Peak age of onset ~60 years[3]

- After 10 years 50% unable to function at work
- After 20 years 90% clinically disabled
- Reduces life expectancy by 3–18 years [4]

[1] Alamanos Y, et al. Semin Arthritis Rheum 2006; 36:182–188; [2] Chen S, et al. *Drug Topics*. 2000;April 3:47-56; [3] Scott DL, et al. *Br J Rheumatol*. 1998;37:546-554; [4] Pincus T, Callahan LF. *J Rheumatol*. 1986;13:841-845.

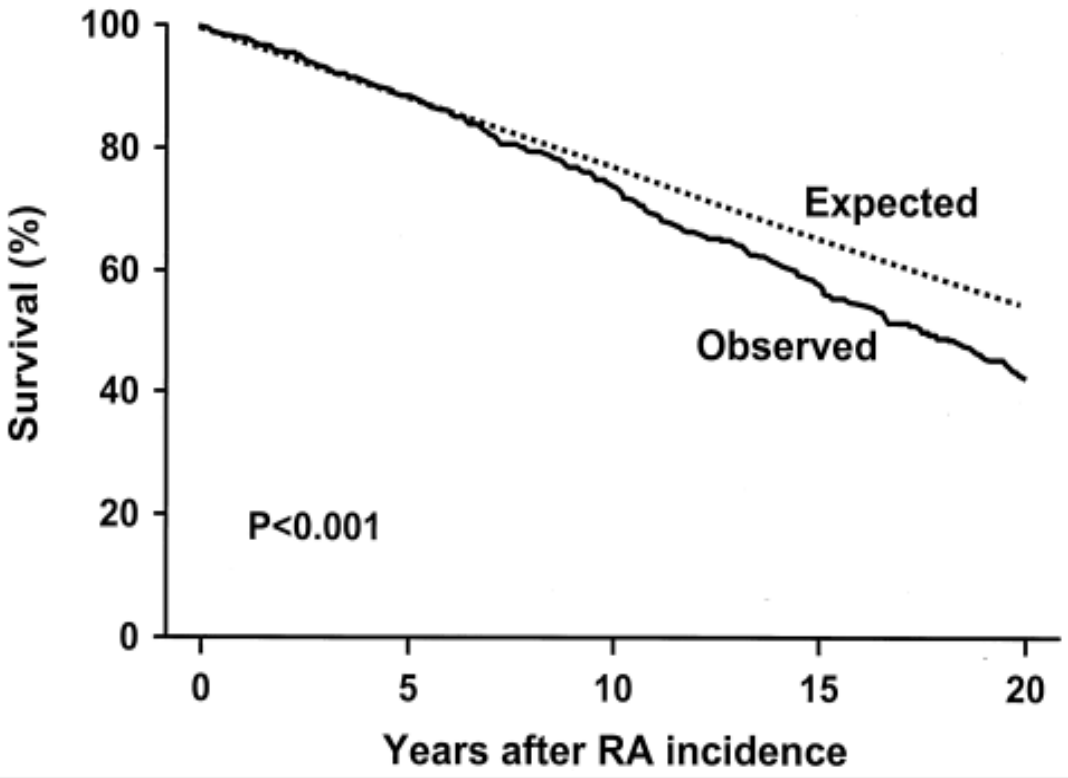
Gabriel SE, Crowson CS, Kremers HM, et al

Survival in Rheumatoid Arthritis A Population-Based Analysis of Trends Over 40 Years

Arthritis Rheum 2003;48:54-8

CONCLUSION

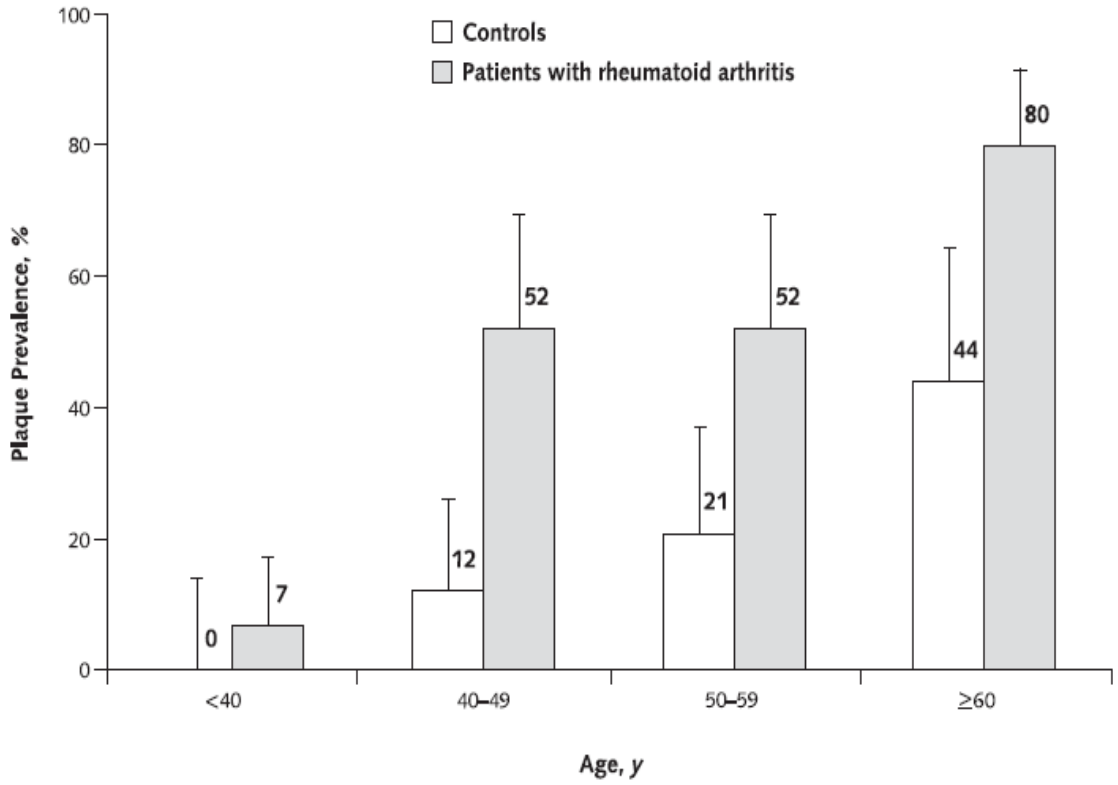
- Survival in RA patients is significantly lower than expected.



RA and cardiovascular (CV) events

- Premature coronary heart disease and cardiovascular disease have been recognized as major determinants of morbidity and mortality in patients with RA
- In active RA, the majority of cardiovascular deaths result from accelerated atherosclerosis

Figure. Prevalence of atherosclerotic plaque in controls and in patients with rheumatoid arthritis, subdivided according to age.



Error bars indicate 95th percentiles.

Roman MJ, et al. Ann Intern Med 2006;144:249-56

Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, et al

Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease

Ann Rheum Dis 2013 (in press)

CONCLUSION

- RA patients without CAD have higher prevalence, extent, and severity of all types of coronary plaque. Residual disease activity associates with presence of higher risk NCP and MP potentially contributing to future adverse cardiac events

Table 1 Baseline demographics and CRF distribution in RA and controls

Variable	RA (150)	Controls (150)	p Value
Age (years)	53±11	53±11	1
Females	131 (87)	131 (87)	1
Diabetes mellitus	26 (17)	26 (17)	1
Hypertension	72 (48)	58 (40)	0.2
Smoking, current	13 (9)	19 (13)	0.3
Family history	6 (4)	90 (60)	<0.0001
Hyperlipidaemia	26 (17)	59 (40)	<0.0001
Body mass index (kg/m^2)	28.9±6.3	30.3±4.6	0.7
RF+	129 (86)	–	–
ACPA+	127 (85)	–	–
Erosions	99 (66)	–	–
RA-duration (years)	11±8	–	–
Tender joint count	1.6±3.4	–	–
Swollen joint count	1.7±2.6	–	–
DAS28-CRP	2.6±1	–	–
DAS28-CRP<3.2	112 (75)	–	–
ESR (mm/h)	27±18	–	–
hsCRP (mg/L)	8.8±13	–	–
IAD	52 (35)	–	–
JRS	15 (10)	–	–
Prednisone	52 (35)	–	–
Prednisone dose (mg)	6.2±4	–	–
DMARDs- concurrent	2±0.8	–	–
MTX	128 (85)	–	–
TNFi-exposed	90 (60)	–	–
TNFi duration (years)	4.2±2.4	–	–

ACPA, anticitrullinated peptide antibodies; CRF, cardiac risk factor; ESR, erythrocyte sedimentation rate; IAD, irreversible articular damage; JRS, joint replacement surgeries; RA, rheumatoid arthritis.

Karpouzas GA, et al. Ann Rheum Dis 2013 (in press)

Table 2 CTA results in RA and controls

Variable	RA (150)	Controls (150)	p Value
Agatston score	84.4±379.30	3.20±11.20	<0.0001
CAC>0	55 (37)	28 (19)	0.005
Agatston score in CAC>0	230.2±602.40	17.7±21.50	0.0002
No coronary plaque	43 (29)	82 (55)	<0.0001
Plaque present			
1-vessel	107 (71)	68 (45)	<0.0001
2-vessel	65 (43)	18 (12)	<0.0001
3-vessel	28 (19)	6 (4)	<0.0001
Segment involvement score (SIS)			
Any plaque	2.02±2.28	0.90±1.25	<0.0001
NCP	1.04±1.19	0.62±0.99	0.0003
MP	0.56±1.20	0.12±0.37	0.0003
CP	0.42±1.03	0.14±0.47	0.009
Segment stenosis score (SSS)			
Any plaque	3.03±4.43	0.98±1.70	<0.0001
NCP	1.45±2.10	0.73±1.30	0.0002
MP	1.03±2.36	0.2±0.68	0.0003
CP	0.55±1.64	0.15±0.54	0.003
Plaque burden score (PBS)			
Any plaque	2.75±3.82	0.98±1.44	<0.0001
NCP	1.22±1.61	0.68±1.10	0.0004
MP	0.91±2.02	0.16±0.51	0.0002
CP	0.62±1.73	0.14±0.47	0.004

CAC, coronary artery calcium; CTA, CT angiography; MP, mixed plaque; NCP, non-calcified plaque; CP, calcified plaque; RA, rheumatoid arthritis.

Karpouzas GA, et al. Ann Rheum Dis 2013 (in press)

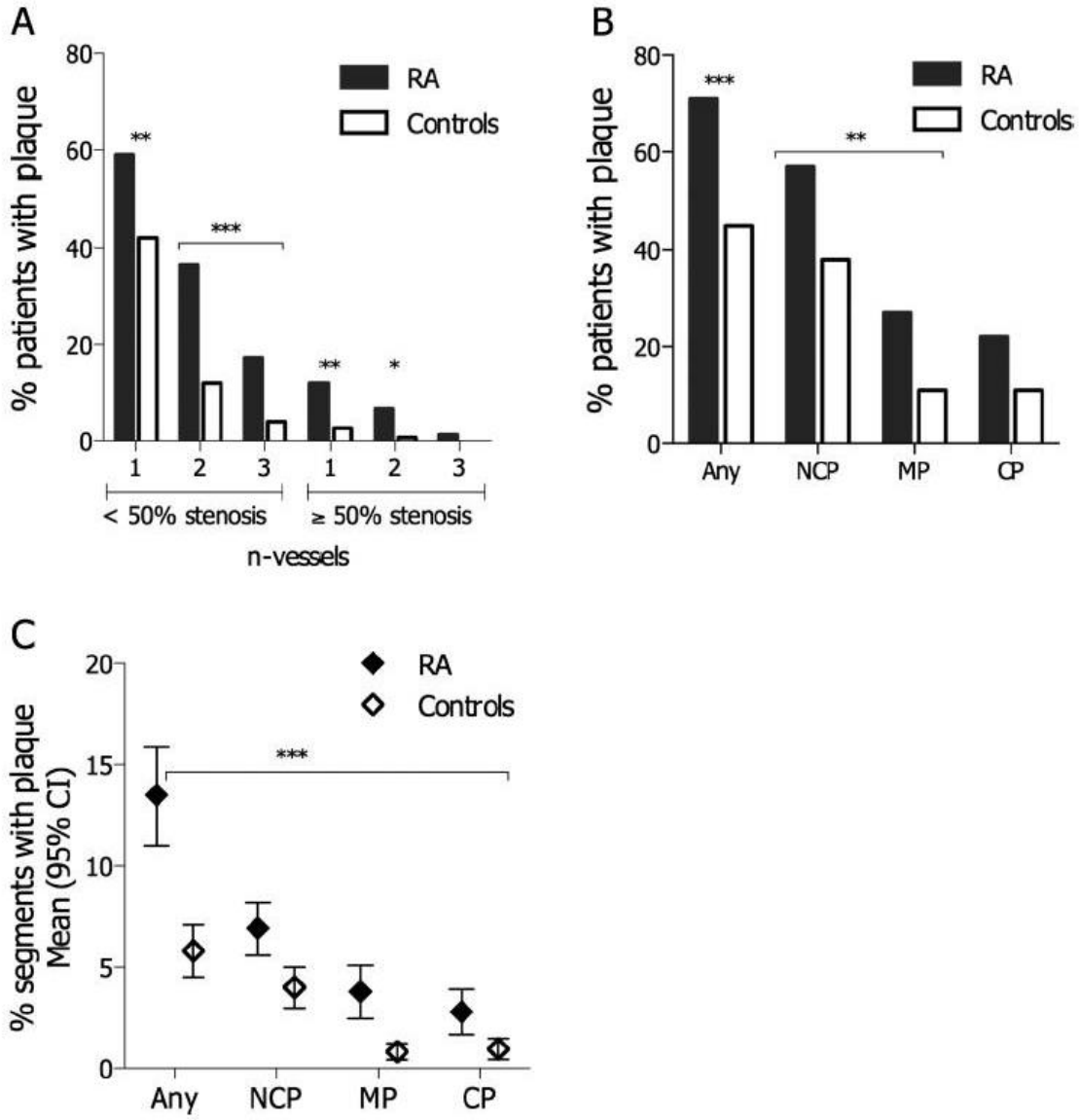


Figure 1 Per patient (panels A and B) and per segment (panel C) analysis of differences in coronary plaque presence and composition in RA and controls. A. Proportions of subjects with one, 2, or ≥3-vessel disease, both non-obstructive (<50%) and obstructive (≥50%); B. Number of patients with any, NCP, MP, or CP in RA and controls. C. Fraction of coronary segments harbouring any plaque, NCP, MP, or CP in RA and controls. Results in mean (95% CI). *p<0.05, **p<0.01, ***p<0.001 for all comparisons between RA and controls. RA, rheumatoid arthritis; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque.

Karpouzas GA, et al. Ann Rheum Dis 2013 (in press)

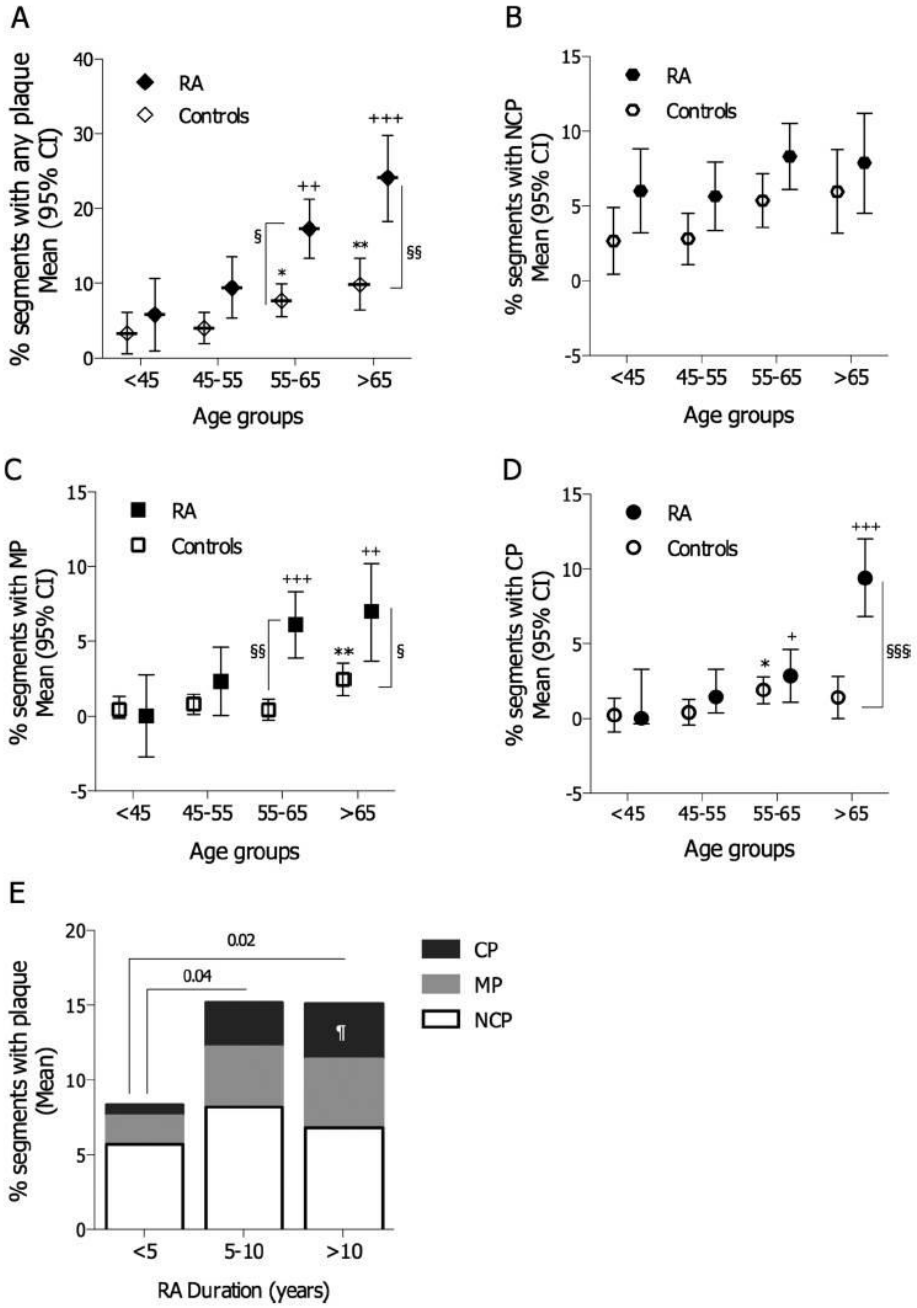


Figure 2 Coronary segment involvement with various plaque types by age group (A–D) and disease duration (E). RA, rheumatoid arthritis; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque; *p<0.05, **p<0.01 vs controls <45 years; +p<0.05, ++p<0.01, +++p<0.001 vs RA patients <45 years; §p<0.05, §§p<0.01, §§§p<0.001 compared to the difference between RA and controls <45 years; ¶p<0.05 vs disease duration <5 years.

Karpouzas GA, et al. Ann Rheum Dis 2013 (in press)

Semb AG, Rollefstad S, Provan SA, Kvien TK, et al

Carotid Plaque Characteristics and Disease Activity in Rheumatoid Arthritis

J Rheumatol 2013;40:359–68

CONCLUSION

- Patients with RA had more CP compared with controls and patients in CDAI remission, and controls had more stable CP than patients with active disease; these findings point to the importance of achieving remission in RA

Van Halm VP

Patients with rheumatoid arthritis have more vulnerable arterial plaques, but lowering disease activity may stabilize this threat

J Rheumatol 2013;40:348-9

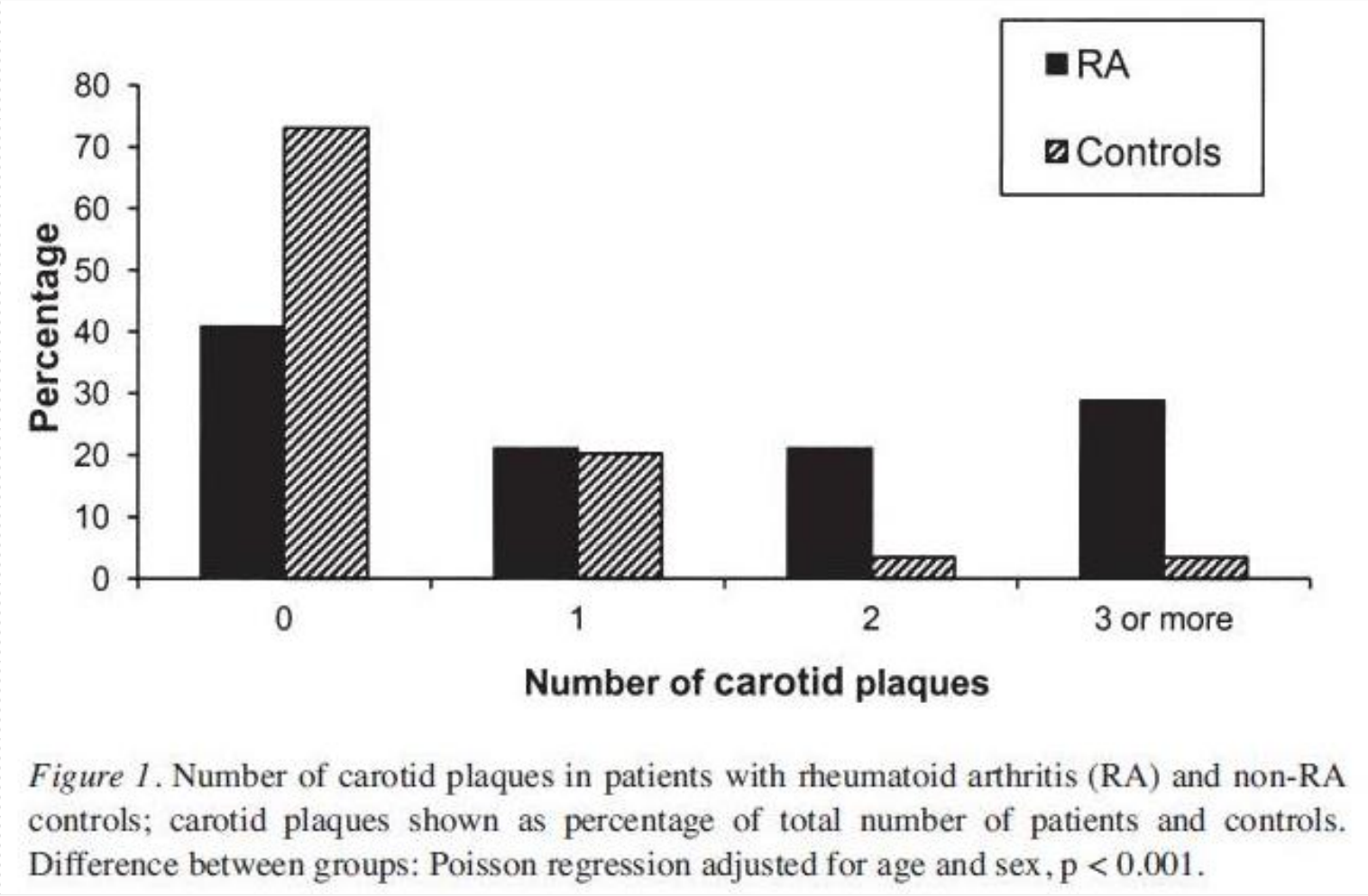


Figure 1. Number of carotid plaques in patients with rheumatoid arthritis (RA) and non-RA controls; carotid plaques shown as percentage of total number of patients and controls. Difference between groups: Poisson regression adjusted for age and sex, $p < 0.001$.

Semb AG, et al. J Rheumatol 2013;40:359–68

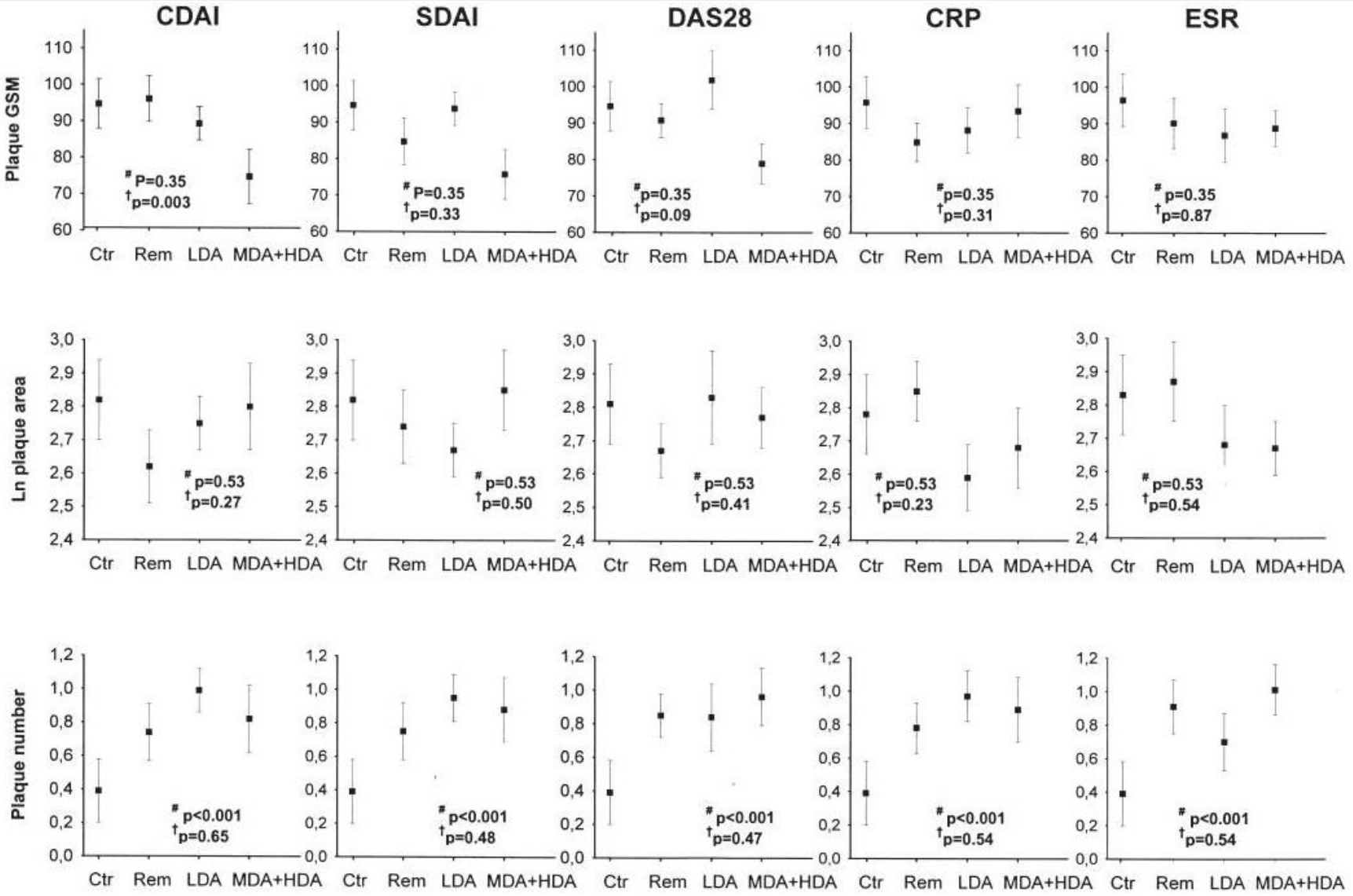


Figure 2. Characteristics of carotid artery plaque according to disease activity in patients with rheumatoid arthritis (RA) and controls. Different methods were used to compare patients and controls and trend within RA disease activity: mixed models with random intercepts were used to analyze plaque area and GSM; Poisson regression analysis was used to compare number of plaques between patients and controls. All data were adjusted for age, sex, smoking, and systolic blood pressure and are presented as least-square means with standard error. Trend analyses were performed by linear contrasts within each model. #RA vs controls; †trend in RA disease activity. CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; DAS28: Disease Activity Score based on 28-joint counts; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Ctr: controls; Rem: remission; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; GSM: Gray-Scale Median. **Semb AG, et al. J Rheumatol 2013;40:359–68**

Evans MR, Escalante A, Battafarano DF, et al

Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis

Arthritis Rheum 2011;63:1211-20

CONCLUSION

- Atherosclerosis is strongly associated with ACS in RA. RA patients with carotid plaque, multiple CV risk factors (particularly diabetes mellitus or hypertension), many swollen joints, and a high cumulative dose of glucocorticoids, as well as RA patients who are men, are at high risk of ACS

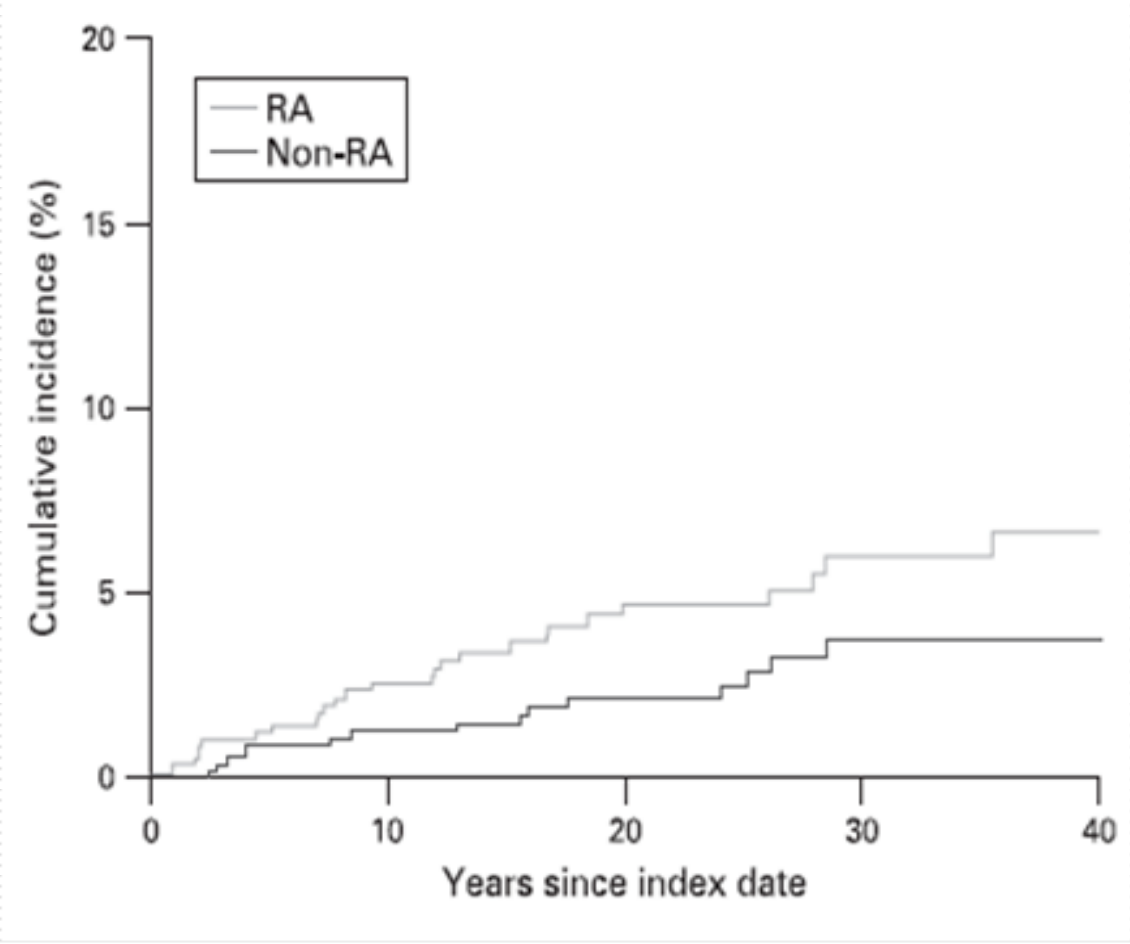


Figure 2 Cumulative incidence of silent myocardial infarction in a population-based incidence cohort of 603 patients with RA and a matched non-RA comparison group of 603 non-RA subjects from the same underlying population. © Increased unrecognized coronary heart disease in rheumatoid arthritis: a population-based study. **Arthritis Rheum 2005;52:402–11. Reprinted with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.**

Gabriel SE. Ann Rheum Dis 2008;67 Suppl 3:iii30-4

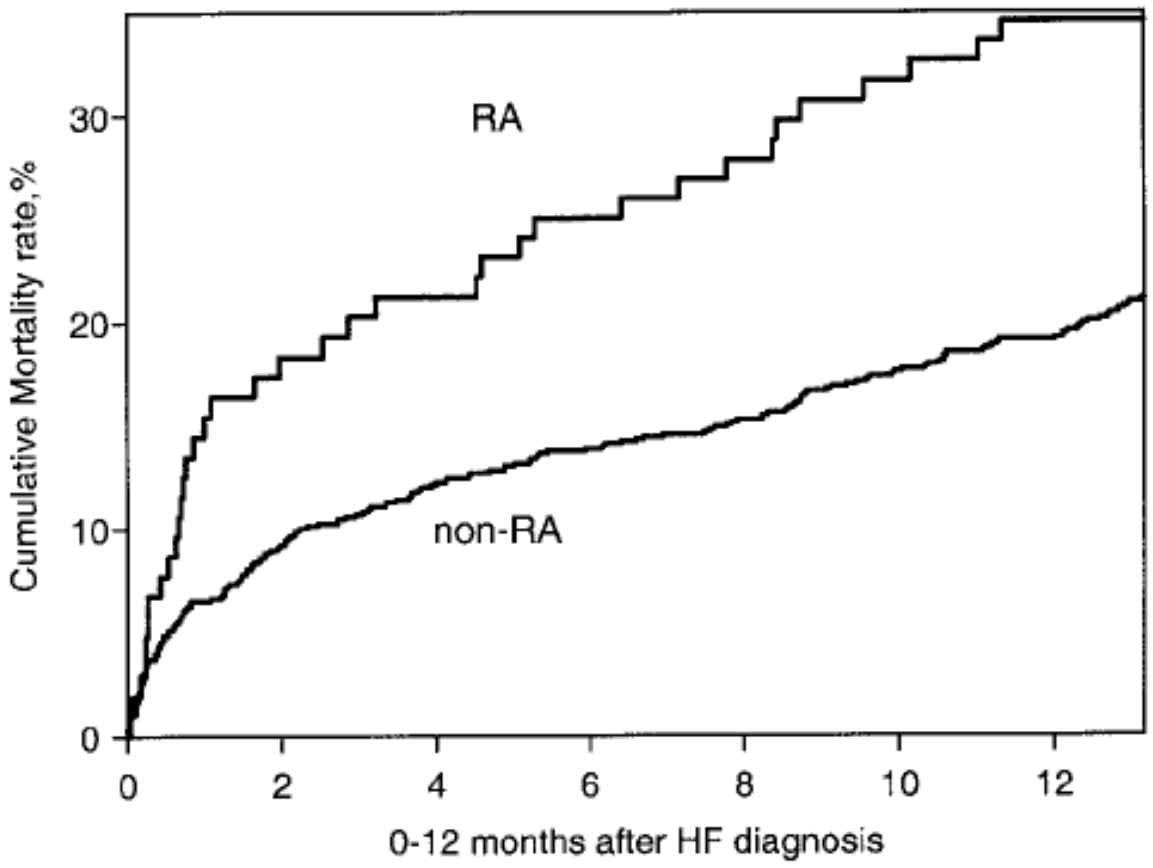


Figure 2. Mortality through 1 year following the onset of heart failure (HF) in the rheumatoid arthritis (RA) and non-RA cohorts.

Davis JM 3rd, et al. Arthritis Rheum 2008;58:2603-11

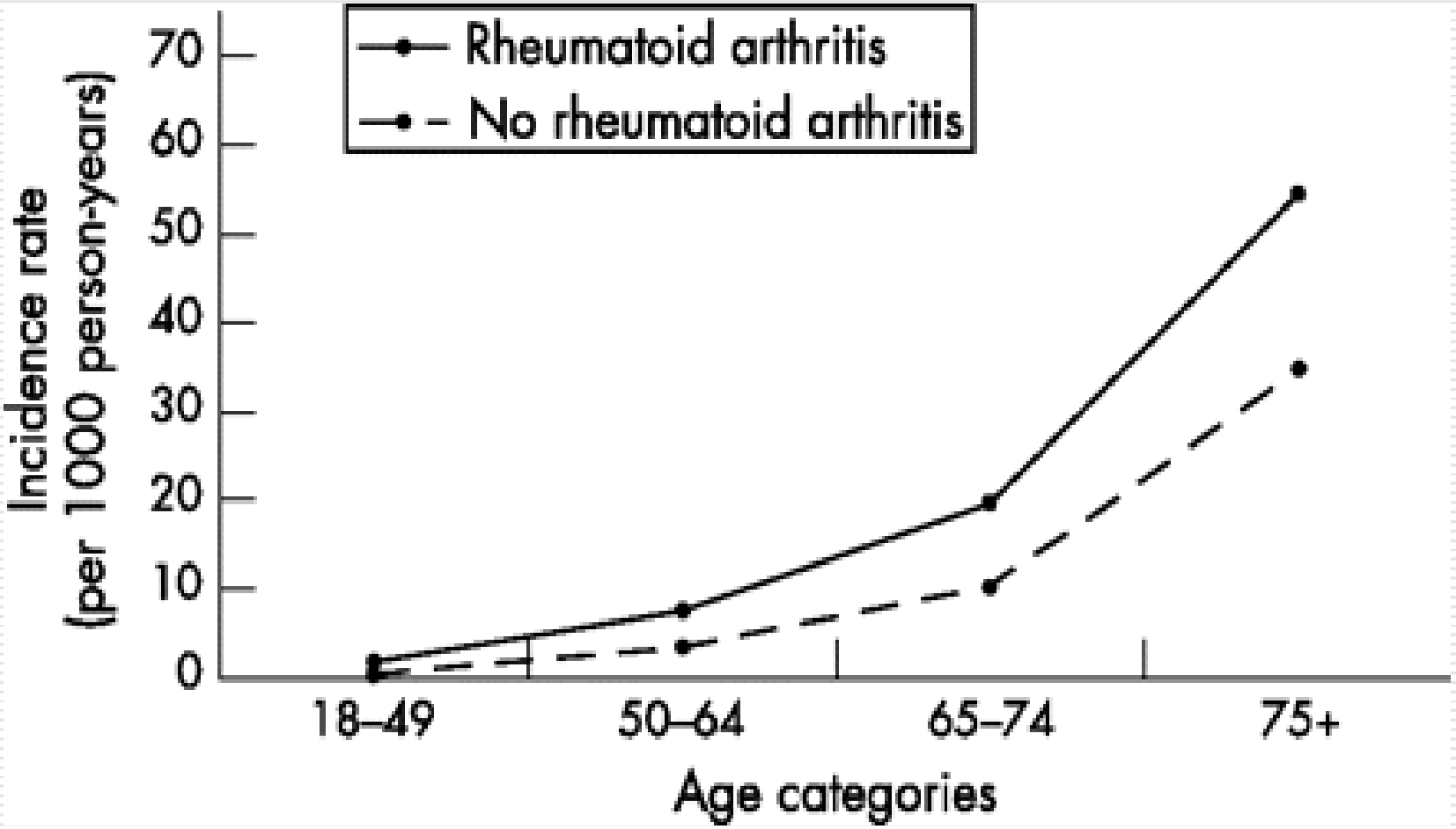


Figure 1 Incidence rates of cardiovascular events among the total study population

Solomon DH, et al. Ann Rheum Dis 2006;65:1608-12

Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al

Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies

Ann Rheum Dis 2012;71:1524-9

CONCLUSION

- Published data indicate that the risk of incident CVD is increased by 48% in patients with RA compared to the general population

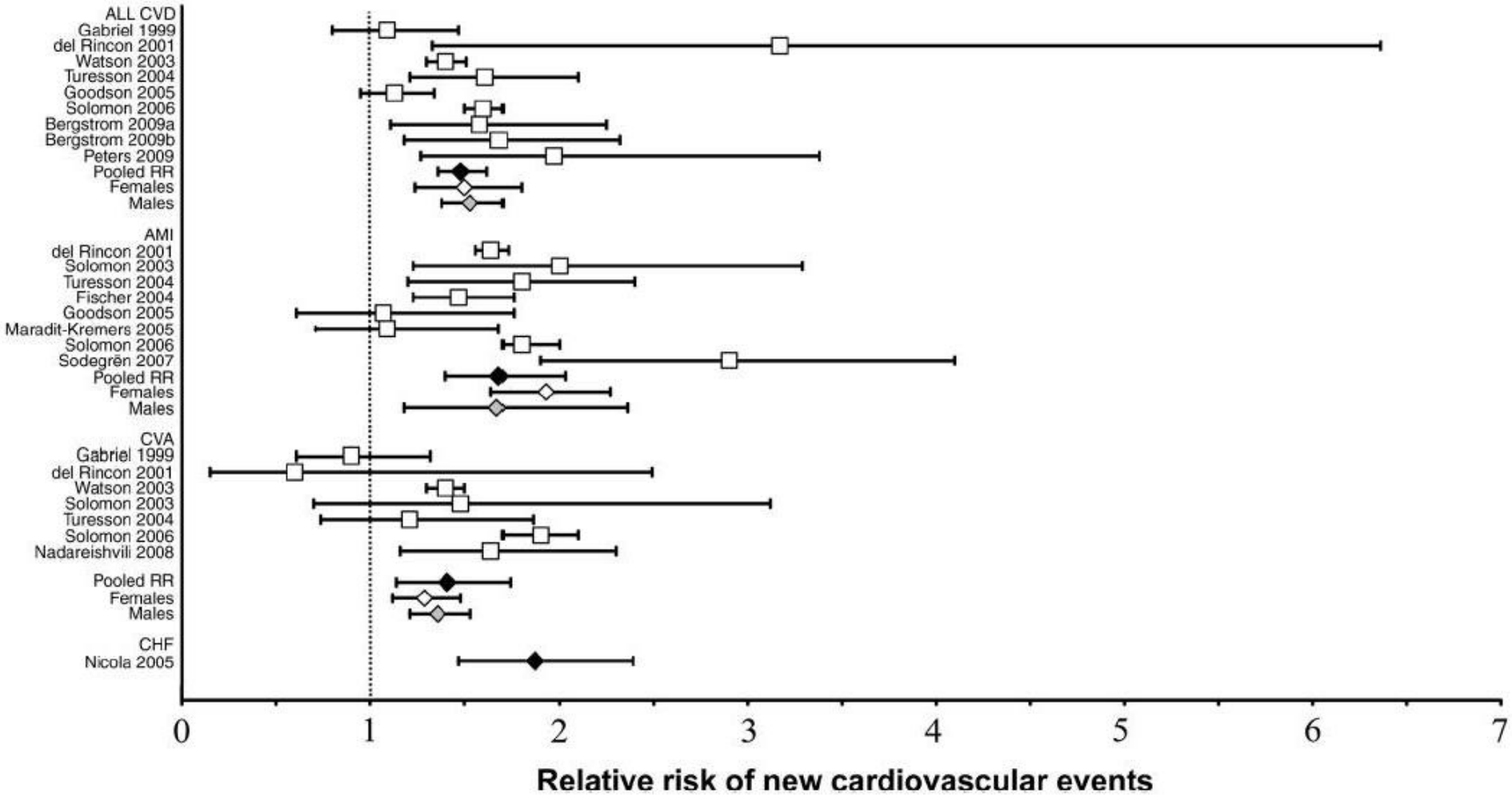


Figure 2 Meta-analysis of studies on overall and cause-specific cardiovascular diseases in patients with rheumatoid arthritis.

Avina-Zubieta JA, et al. Ann Rheum Dis 2012;71:1524-9

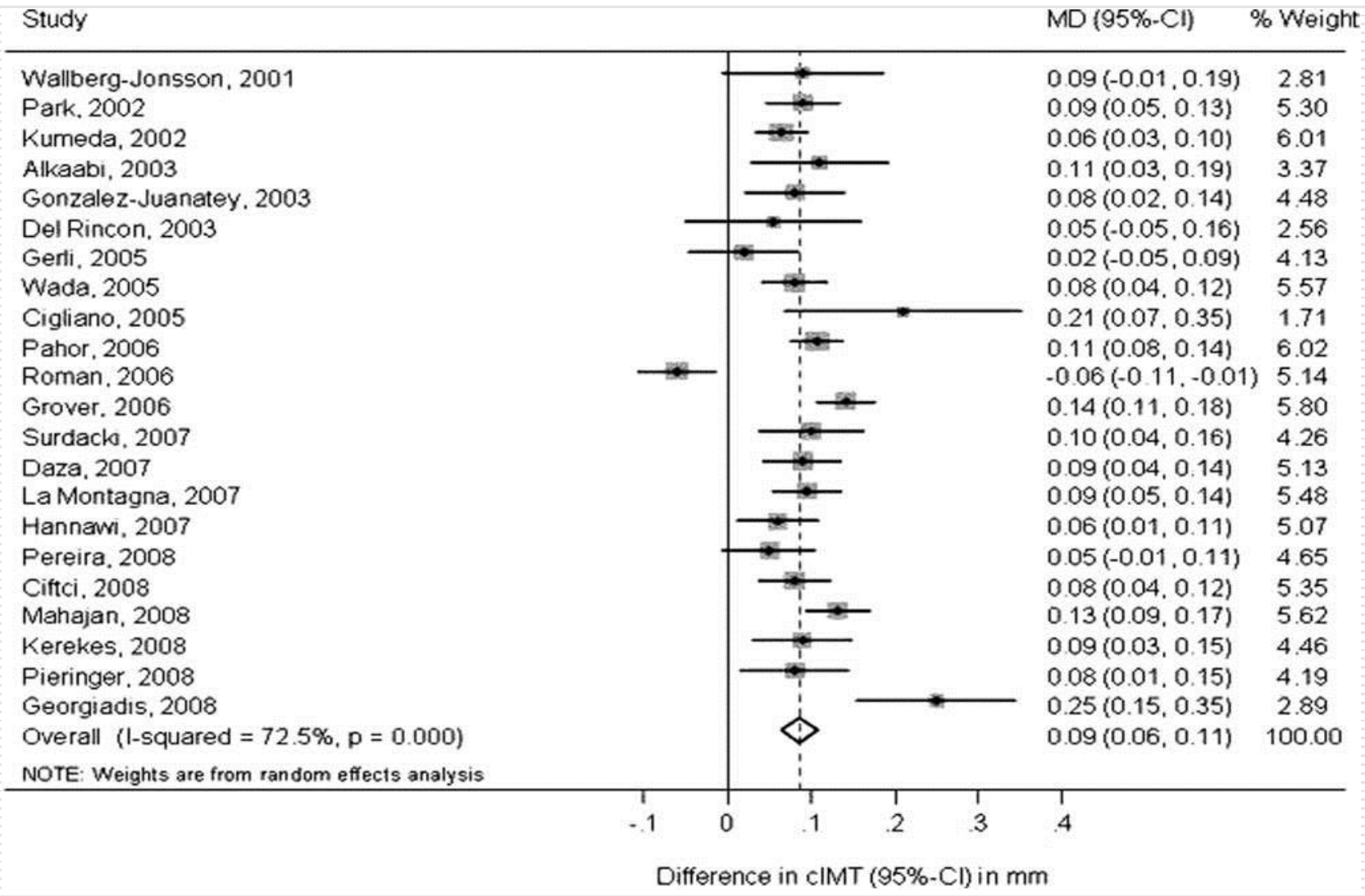
van Sijl AM, Peters MJ, Knol DK, et al

Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis

Semin Arthritis Rheum 2011;40:389-97

CONCLUSION

- Our observations support the current evidence base for an increased cardiovascular burden in RA and support the use of cIMT in observational studies in RA patients



van Sijl AM et al. Semin Arthritis Rheum. 2011;40:389-97

Corrales A, Parra JA, González-Juanatey C, et al

Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis

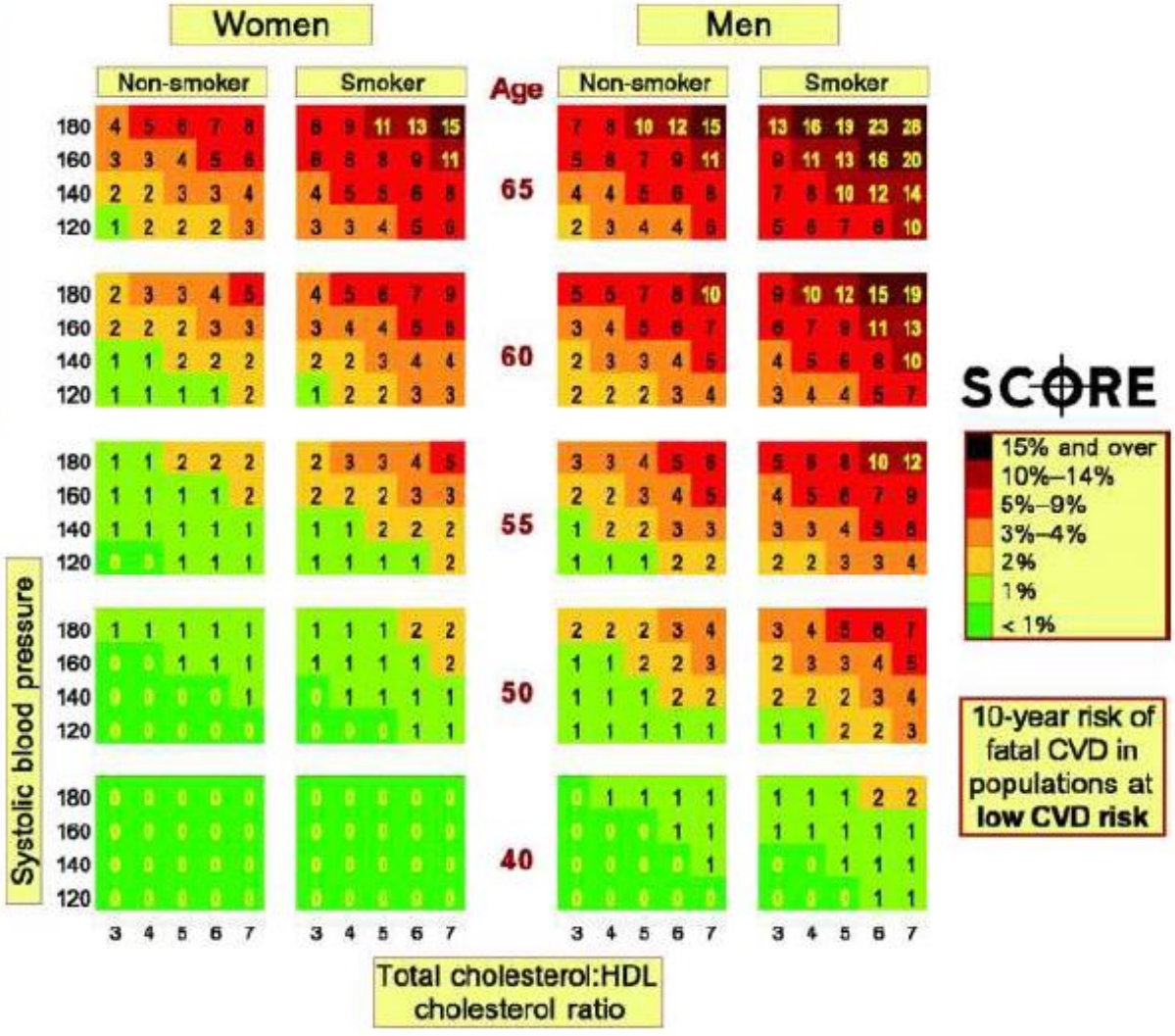
Ann Rheum Dis 2013 (in press)

CONCLUSION

- Carotid ultrasonography is more sensitive than CACS for the detection of subclinical atherosclerosis in RA

PA - εκτίμηση καρδιαγγειακού κινδύνου

- ♂
- 60 χρ.
- Κάπνισμα: (+)
- ΣΑΠ = 150 mm Hg
- Χοληστερόλη: 285 mg/dl
- HDL: 45 mg/dl
- PA x 15 χρ.
- RF/anti-CCP: (+)



Conroy R et al. Eur Heart J 2003;24:987-1003

González-Gay MA, González-Juanatey C, Llorca J

Carotid ultrasound in the cardiovascular risk stratification of patients with rheumatoid arthritis: when and for whom?

Ann Rheum Dis 2012;71:796-8

CONCLUSION

- The presence of abnormal carotid IMT (>0.90 mm) or carotid plaques would lead to these patients being considered as having high CV risk regardless of the results derived from the modified SCORE

Mavrogeni S, Dimitroulas T, Sfikakis PP, Kitas GD

Heart involvement in rheumatoid arthritis: Multimodality imaging and the emerging role of cardiac magnetic resonance

Semin Arthritis Rheum 2013. [Epub ahead of print]

Cardiovascular risk factors in RA

- Traditional risk factor for CVA
- Inflammation of disease process
- Treatment of RA

Traditional risk factors for CVA are more frequent found in RA than in control patients

- Obesity
- Smoking
- Hypertension
- Physical inactivity
- Dyslipidemia
- Insulin resistance

Han C, et al. J Rheumatol 2006;33:2167-72; Solomon DH, et al. Ann Rheum Dis 2010;69:2114-7; Gonzalez A, et al. Ann Rheum Dis 2008;67:64-9

- Traditional CV risk factors appear to differ significantly between RA cases and controls include:

Insulin resistance	Dyslipidemia
Abnormal fat distribution	Hypertention
Cigarette smoking	Diabetes mellitus
Lack of physical activity	

- All the above are elevated in RA compared to controls

Liao KP, Solomon DH. Rheumatology (Oxford) 2013;52:45-52

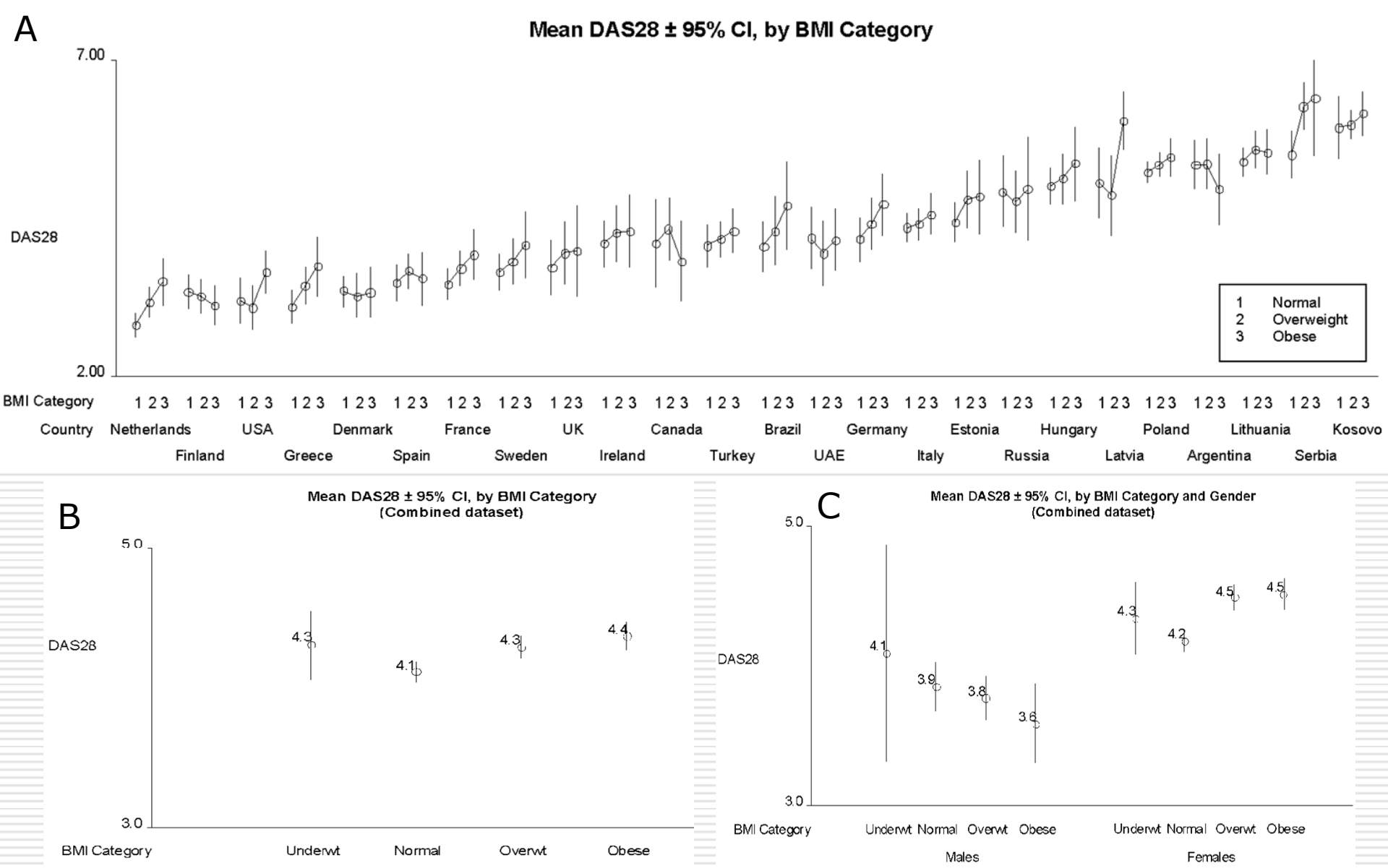
Παχυσαρκία και ΡΑ

Η παχυσαρκία στη ΡΑ σχετίζεται με:

- Ενεργότητα της νόσου
- Δομικές βλάβες
- Λειτουργική ικανότητα – ποιότητα ζωής
- Επιβίωση

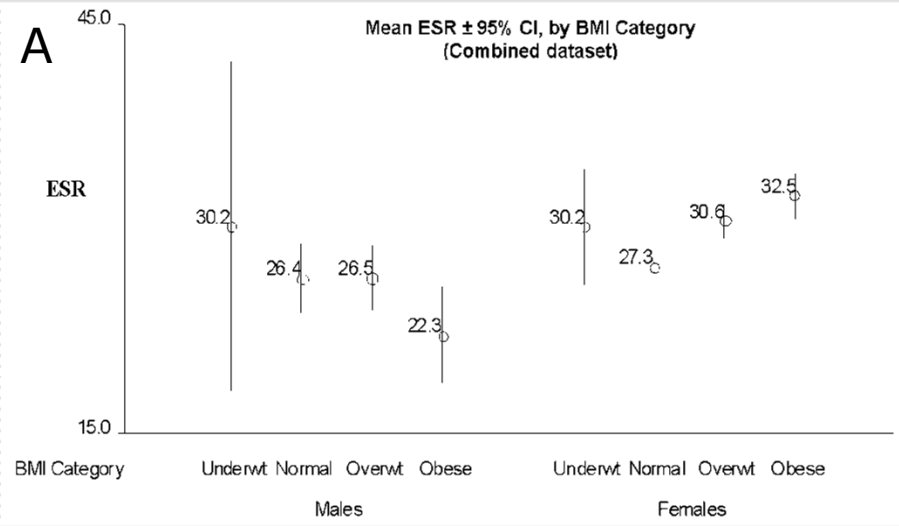
Van den Berg MH. J Clin Rheumatol 2007;13:181-6
Metsios GS. Eur J Cardiovasc Prev Rehabil 2009;16:188-94

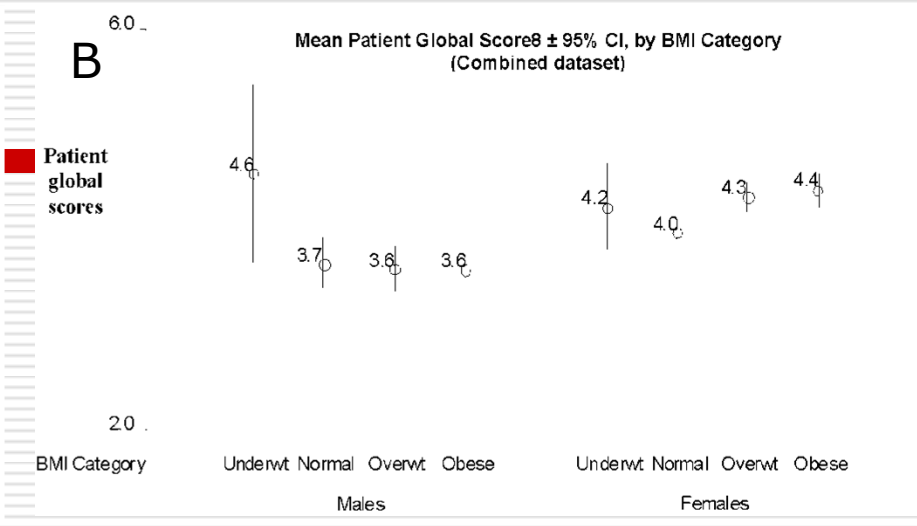
QUEST-RA From January 2005 to April 2008: 6004 patients from 70 clinics in 25 countries

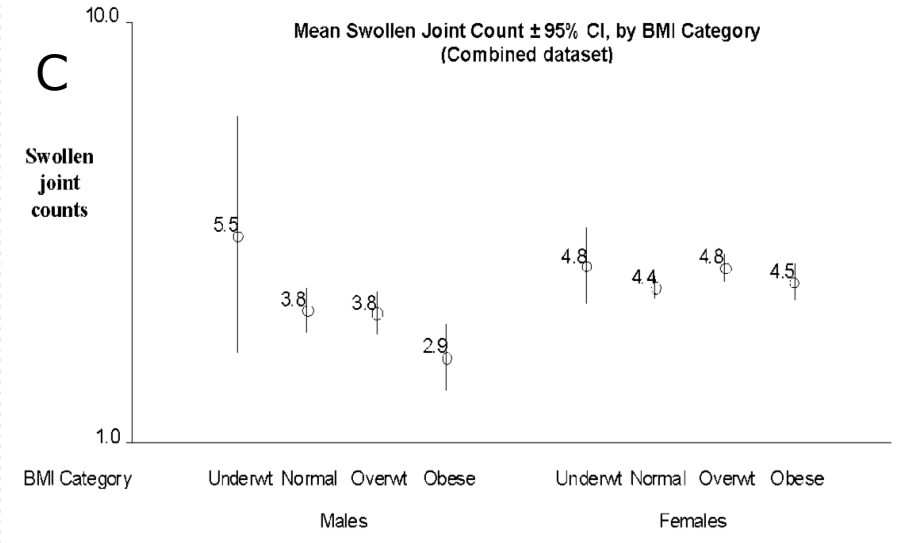


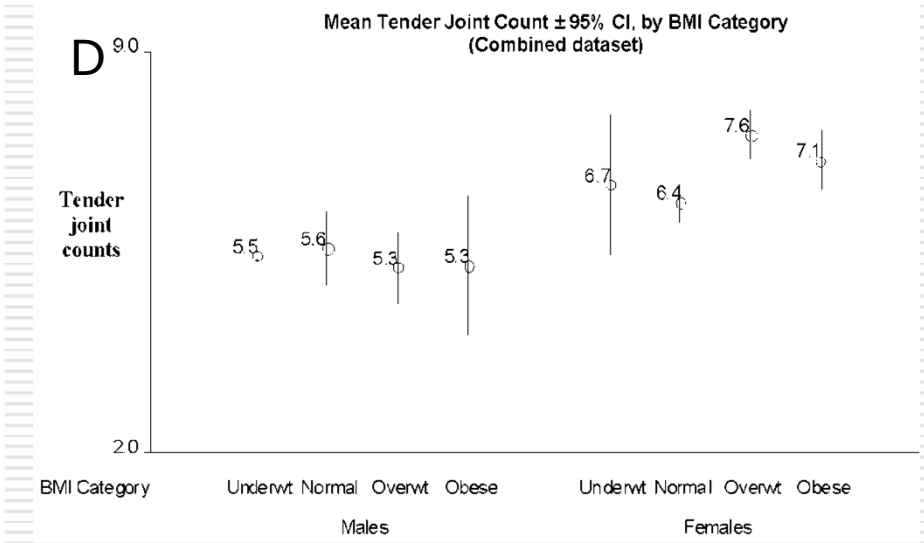
Plots showing the mean DAS28 scores and the 95% confidence intervals (y-axis) by BMI category (x-axis), i.e. normal, overweight and obese, (a) for each country participating in the QUEST-RA study, (b) for the combined dataset and (c) for female and male patients separately

Jawaheer D, et al; Quest RA Study. Clin Exp Rheumatol 2010;28:454-61









Plots showing the mean (a) ESR, (b) Patient Global Scores, (c) Swollen Joint Counts, and (d) Tender Joint Counts, with 95% confidence intervals (y-axis) by BMI category (x-axis) in the combined dataset, for female and male patients separately.

Jawaheer D, et al; Quest RA Study. Clin Exp Rheumatol 2010;28:454-61

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 1, January 15, 2008, pp 42–50
DOI 10.1002/art.23255

ORIGINAL ARTICLE

Physical Inactivity in Patients With Rheumatoid Arthritis: Data From Twenty-One Countries in a Cross-Sectional, International Study

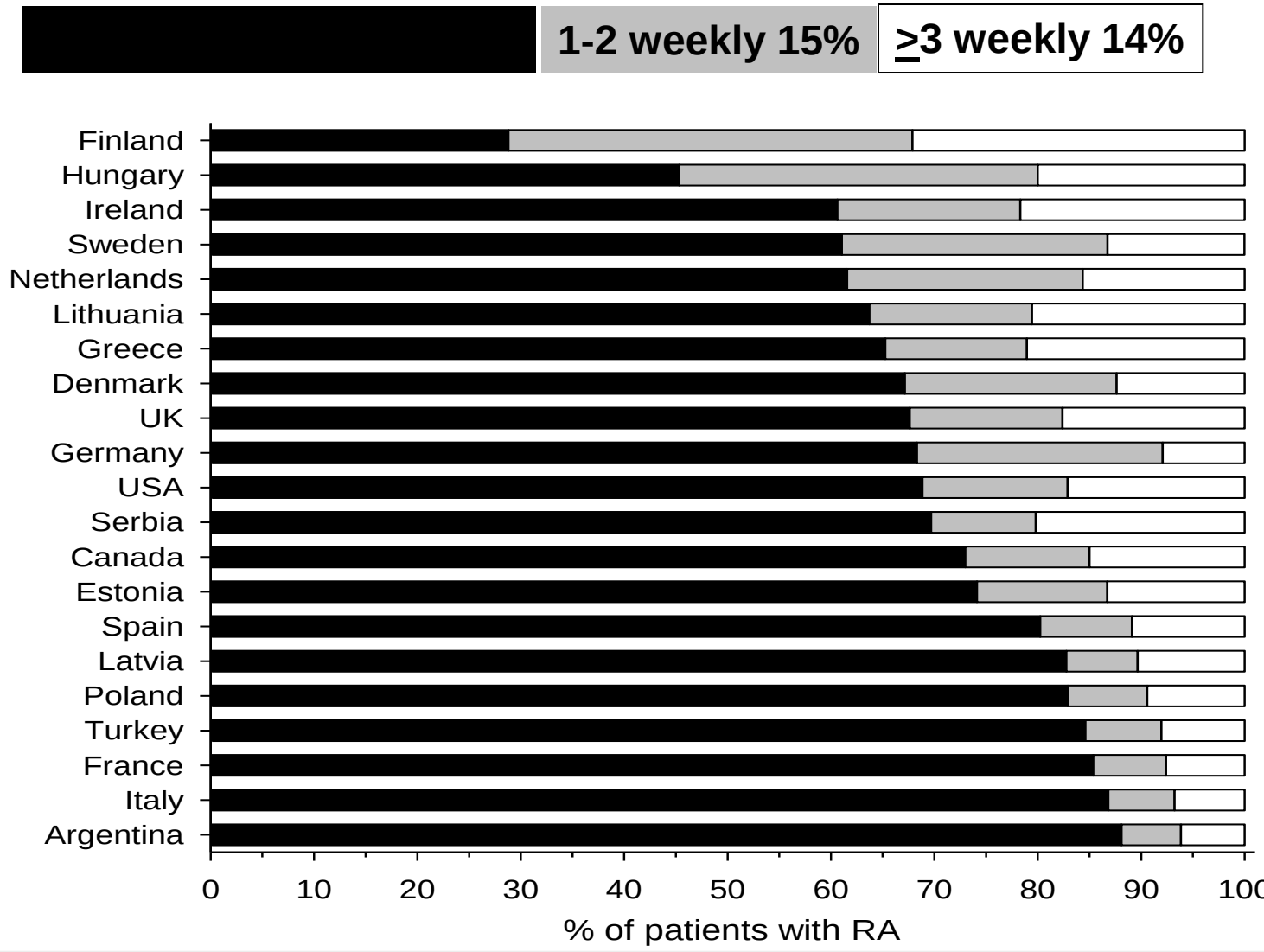
TUULIKKI SOKKA,[1] ARJA HÄKKINEN,[2] HANNU KAUTIAINEN,[3] JEAN FRANCIS MAILLEFERT,[4] SERGIO TOLOZA,[5] TROELS MØRK HANSEN,[6] JAIME CALVO-ALEN,[7] ROLF ODING,[8] MARGARETH LIVEBORN,[8] MARGRIET HUISMAN,[9] RIEKE ALTEN,[10] CHRISTOF POHL,[10] MAURIZIO CUTOLO,[11] KAI IMMONEN,[12] ANTHONY WOOLF,[13] EITHNE MURPHY,[14] CLAIRE SHEEHY,[14] EDEL QUIRKE,[14] SELDA CELIK,[15] YUSUF YAZICI,[16] WITOLD TLUSTOCHOWICZ,[17] DANUTA KAPOLKA,[18] VLADO SKAKIC,[19] BERNADETTE ROJKOVICH,[20] RAILI MÜLLER,[21] SIGITA STROPUVIENE,[22] DAINA ANDERSONE,[23] ALEXANDROS A. DROSOS,[24] JURIS LAZOVSKIS,[25] AND THEODORE PINCUS,[16] ON BEHALF OF THE QUEST-RA GROUP

QUEST-RA:

How often do you exercise aerobically (sweating, increased heart rate, shortness of breath) for at least one-half hour (30 minutes)? Please check only one.

- 3 or more times per week
- 1 – 2 times per week
- 1 – 2 times per month
- I do not exercise regularly

QUEST-RA: Self-reported level of physical exercise



Sokka et al. Arthritis Rheum 2008;59:42-50

Σωματική δραστηριότητα και ΡΑ

Οι ασθενείς με ΡΑ:

- Λιγότερο δραστήριοι σε σχέση με το γενικό πληθυσμό
- Παρουσιάζουν χειρότερο λιπιδαιμικό προφίλ
- Υψηλή ΑΠ
- Παχυσαρκία

Van den Berg MH. J Clin Rheumatol 2007;13:181-6
Metsios GS. Eur J Cardiovasc Prev Rehabil 2009;16:188-94

Manavathongchai S, Bian A, Rho YH, Oeser A, et al

Inflammation and Hypertension in Rheumatoid Arthritis

J Rheumatol 2013 Sep 1. [Epub ahead of print]

CONCLUSION

- HTN in patients with RA is not associated with generalized systemic inflammation or insulin resistance, but is associated with increasing concentrations of homocysteine and leptin

Serelis J, Papagiotakos DB, Mavrommati M, Skopouli FN

Cardiovascular Disease Is Related to Hypertension in Patients with Rheumatoid Arthritis: A Greek Cohort Study

J Rheumatol 2011;38:236-41

CONCLUSION

- Hypertension was an important risk factor for CVD development in patients with RA
- Late RA onset and inadequate early control of disease activity (as attested by CRP) remain additional risk factors. Leflunomide treatment may have a contributing effect. Early and effective treatment of RA and strict control of hypertension may modify the burden of CVD in RA patients

Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD, Drosos AA

Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment--a prospective, controlled study

Arthritis Res Ther 2006;8:R82

Table 1

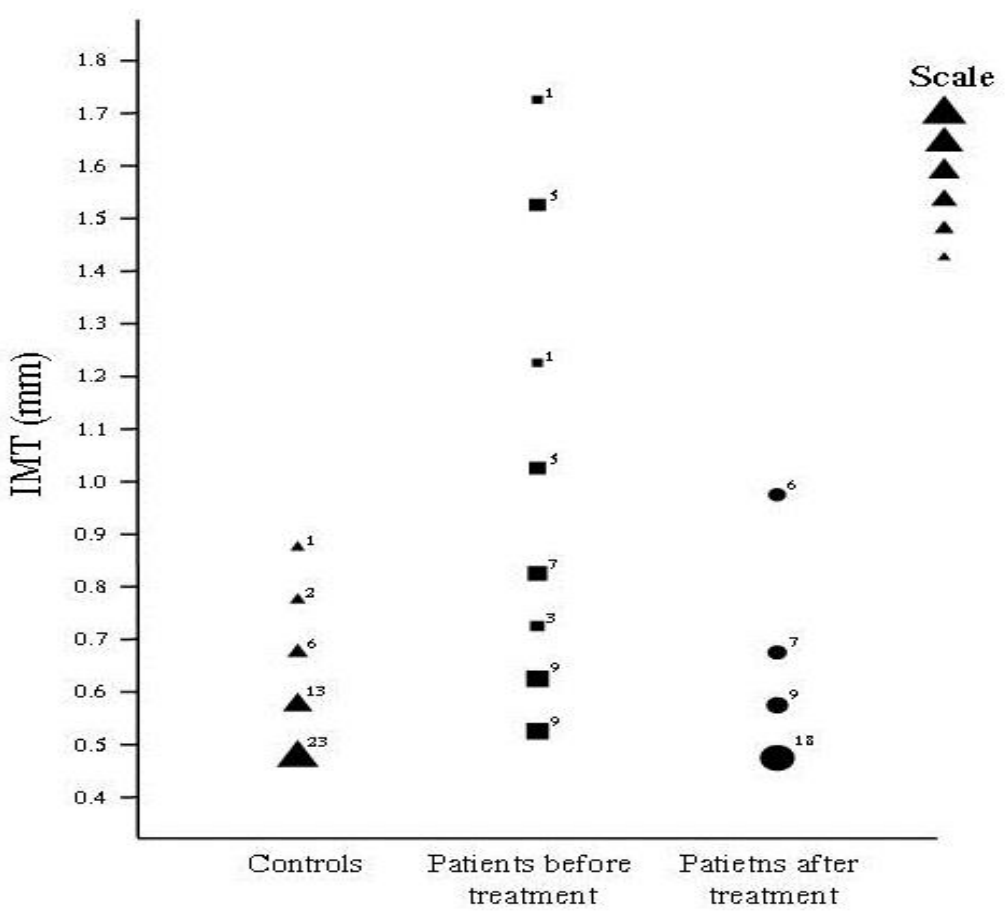
Clinical characteristics and lipid profile of patients with early rheumatoid arthritis and controls

	Controls ($N = 63$)	Patients	
		Baseline ($N = 58$)	Post treatment ($N = 56$)
Sex (male/female)	20/43	14/44	13/43
Age (years)	58.4 ± 17.7	53.6 ± 15.3	54.7 ± 14.8
Body mass index (kg/m^2)	25.8 ± 17.7	25.5 ± 3.3	25.8 ± 3.1
IgM rheumatoid factor (+/-)	0/0	45/13	44/13
C-reactive protein (mg/dl)	2.1 ± 1.3	28.15 ± 20.75	4.60 ± 4.20[a]
ESR (mm/h)	5.2 ± 3.1	48.0 ± 19.7	14.6 ± 8.7[a]
DAS-28	-	5.8 ± 0.9	2.7 ± 1.0[a]
TC (mg/dl)	190.4 ± 33.9	216.5 ± 50.3[b]	228.1 ± 42.1[c]
LDL-C (mg/dl)	126.5 ± 31.3	141.6 ± 42.3[b]	140.4 ± 32.4
HDL-C (mg/dl)	51.1 ± 7.4	47.5 ± 11.8[2]	60.7 ± 13.4[a]
NonHDL-C (mg/dl)	139.3 ± 30.2	172.0 ± 46.3[b]	167.4 ± 37.4
Triglycerides (mg/dl)	97.1 ± 28.3	133.0 ± 58.2[b]	131.5 ± 56.1
TC/HDL-C	3.7 ± 0.9	4.9 ± 1.3[b]	3.8 ± 0.8[a]
LDL-C/HDL-C	2.5 ± 0.8	3.0 ± 1.0[b]	2.4 ± 0.6[a]
Apolipoprotein B (mg/dl)	93 ± 19	103 ± 28[b]	105 ± 30
Apolipoprotein A-I (mg/dl)	144 ± 23	127 ± 27[d]	152 ± 22[a]

Values represent the mean ± standard deviation. [a]$p < 0.001$ and [c]$p < 0.05$ compared to the baseline values; [b]$p < 0.001$ and [d]$p < 0.01$ compared to the control group. DAS-28, disease activity for 28 joint indices score; ESR, erythrocyte sedimentation rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Georgiadis AN, et al. Arthritis Res Ther 2006;8:R82

IMTs measurements before and after treatment



- Common carotid artery IMTs were higher in RA patients compared to controls (0,82±0,29 vs 0,57 ±0,11, p<0,05).
- After 1 year therapy a decrease of the IMTs was noted (0,63±0,196 vs 0,57±0,11, p<0,001).
- Three patients (1 man, 2 women) and 2 controls (1 man and 1 woman) had focal plaques.

Georgiadis AN, et al. Semin Arthritis Rheum 2008;38:13-9

del Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A

High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors

Arthritis Rheum 2001;44:2737-45

CONCLUSION

- The increased incidence of CV events in RA patients is independent of traditional CV risk factors. This suggests that additional mechanisms are responsible for CV disease in RA

Maradit-Kremers H, Nicola PJ, Crowson CS, Vallman KV, Gabriel SE

Cardiovascular death in rheumatoid arthritis

Arthritis Rheum 2005;52:722-32

CONCLUSION

- These results indicate that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with RA

Turesson C, Jacobsson L, Bergström U

Extra-articular rheumatoid arthritis: prevalence and mortality

Rheumatology (Oxford) 1999;38:668-74

CONCLUSION

- In this series, serositis and cutaneous vasculitis were predominant extra-articular manifestations of RA

Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP

Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients

Arthritis Rheum 2002;46:2010-9

CONCLUSION

- Excess mortality in the early years of IP is confined to patients who are seropositive for RF

Hjeltnes G, Hollan I, Førre Ø, Wiik A, et al

Anti-CCP and RF IgM: predictors of impaired endothelial function in rheumatoid arthritis patients

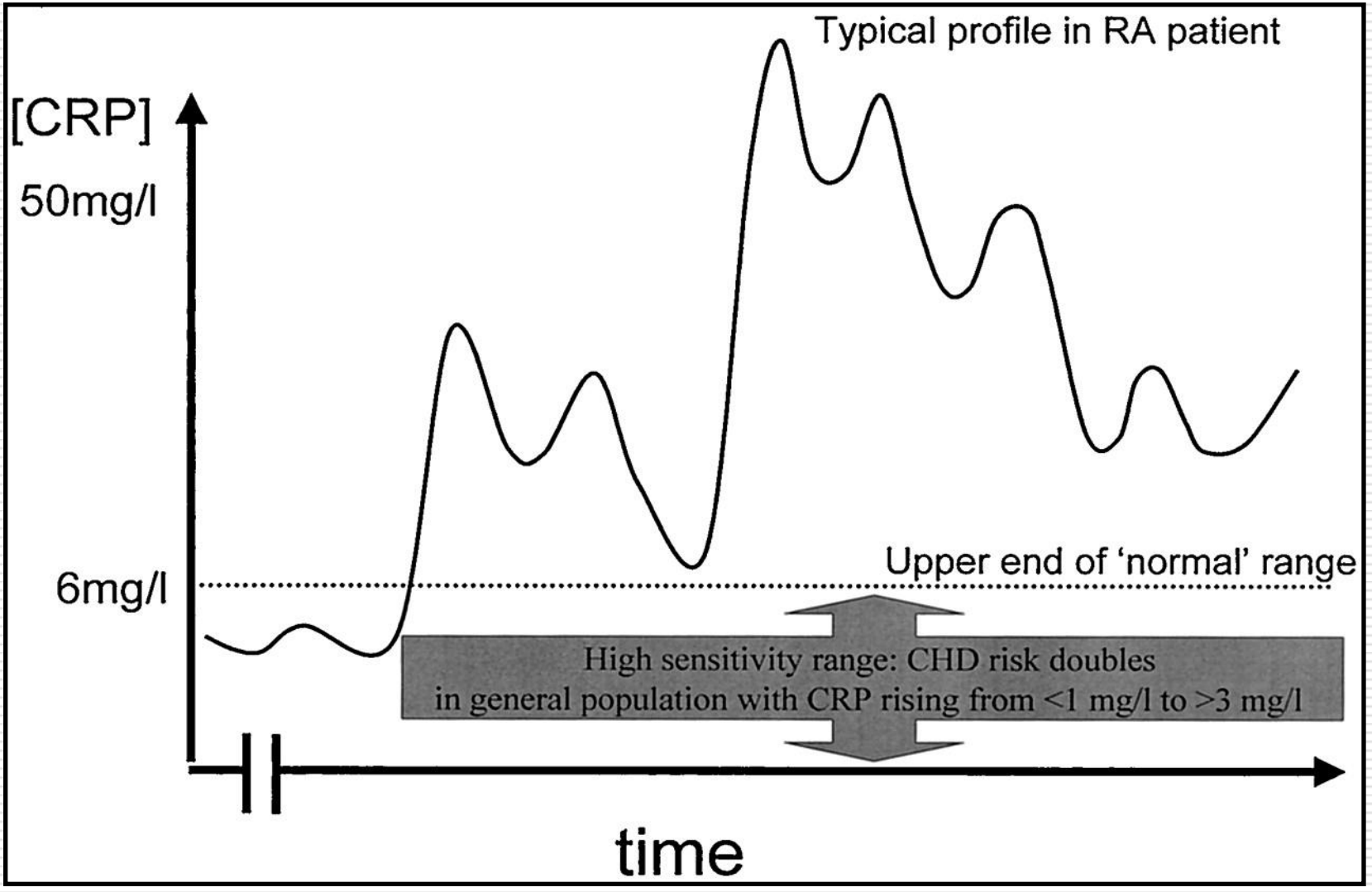
Scand J Rheumatol 2011;40:422-7

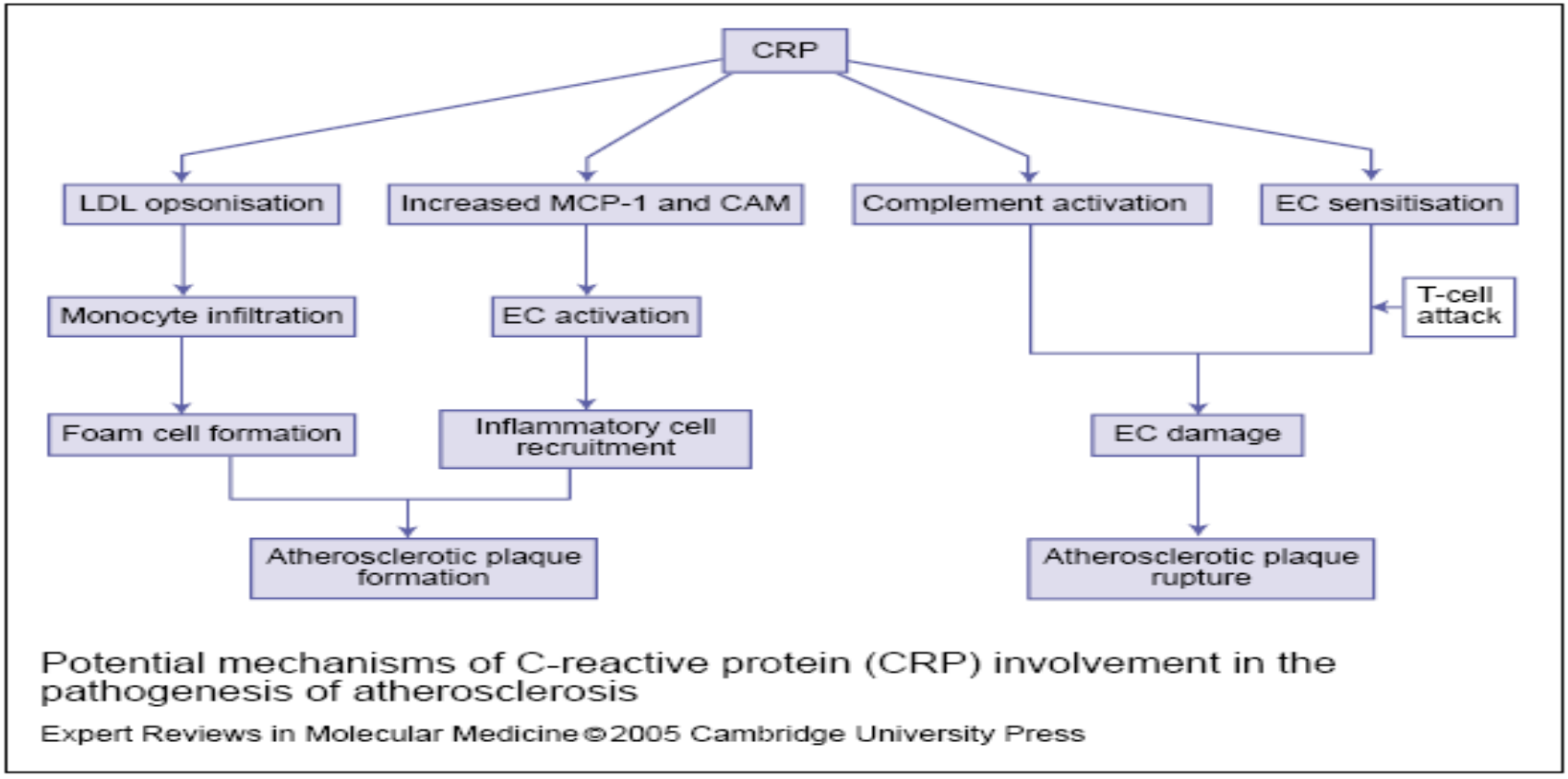
CONCLUSION

- The presence of anti-CCP antibodies and RF IgM was related to impaired endothelial function independent of other cardiovascular risk factors in RA patients

Other risk factor of atherosclerosis in RA patients

- Systemic inflammation (↑ CRP)
- High disease activity (DAS-28 >4.2)
- Extra-articular manifestations (nodules, plurisy)
- Long-standing disease
- Disability (HAQ >1.5)
- Presence of autoantibodies (RF, CCP)


Typical profile in RA patient
[CRP]
50mg/l
6mg/l
Upper end of 'normal' range
High sensitivity range: CHD risk doubles
in general population with CRP rising from <1 mg/l to >3 mg/l
time



Potential mechanisms of C-reactive protein (CRP) involvement in the pathogenesis of atherosclerosis

Figure 2. Potential mechanisms of C-reactive protein (CRP) involvement in the pathogenesis of atherosclerosis. Currently it remains uncertain whether CRP is pathogenically involved in atherosclerosis or just an epiphenomenon, reflecting other processes. Evidence is emerging that CRP is localised within atherosclerotic lesions and might be produced locally by vascular smooth muscle cells (VSMCs) or macrophages. It might be involved in foam-cell formation [by increased uptake of CRP-opsonised low-density lipoprotein (LDL) by macrophages], endothelial cell (EC) activation [resulting in enhanced expression of cellular adhesion molecules (CAMs) and induction of monocyte chemotactic protein (MCP-1)], complement activation, and sensitisation of ECs to damage by cytotoxic T cells.

Galarraga B, Khan F, Kumar P, Pullar T, Belch JJ

C-reactive protein: the underlying cause of microvascular dysfunction in rheumatoid arthritis

Rheumatology (Oxford) 2008;47:1780-4

CONCLUSION

- Systemic inflammation (CRP) is independently associated with microvascular dysfunction in patients with RA
- This strong correlation is independent of other conventional vascular risk factors

Largo R, Sánchez-Pernaute O, Marcos ME, et al

Chronic arthritis aggravates vascular lesions in rabbits with atherosclerosis: A novel model of atherosclerosis associated with chronic inflammation

Arthritis Rheum 2008;58:2723-34

CONCLUSION

- The onset of chronic AIA in animals with atherosclerosis resulted in the local and systemic up-regulation of mediators of tissue inflammation and plaque instability associated with a higher incidence of aortic lesions

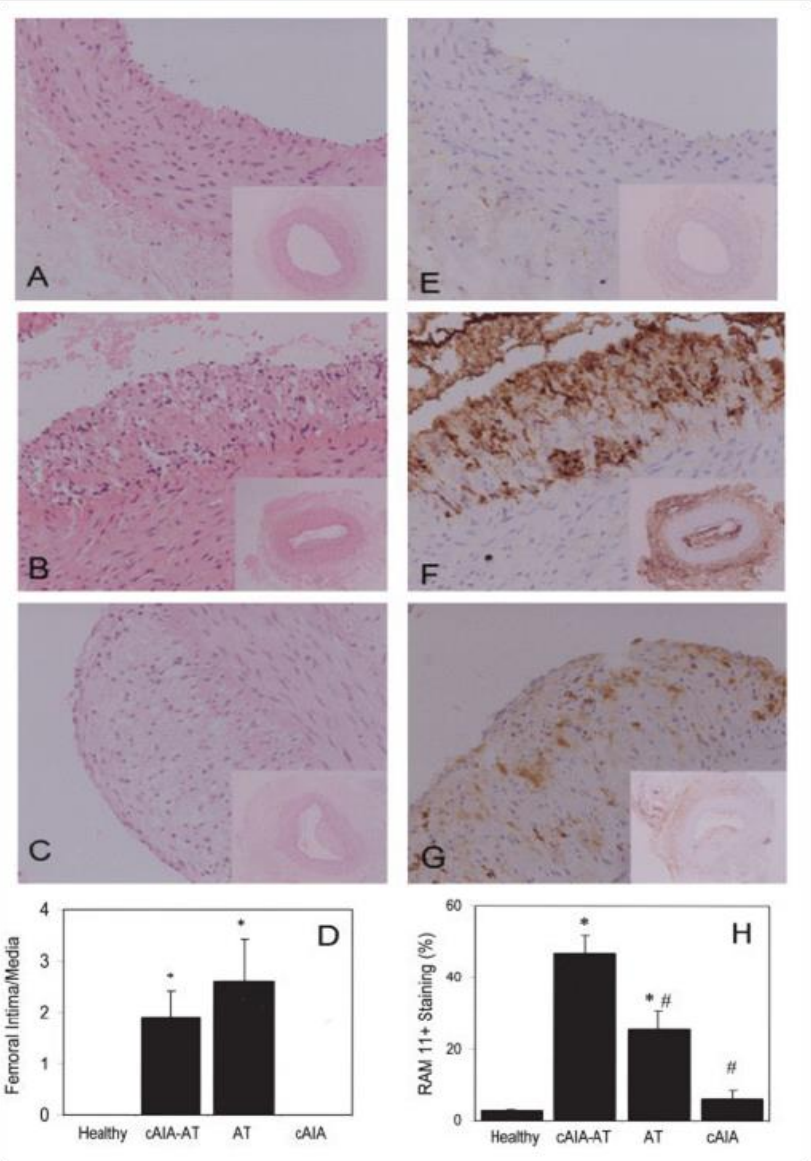


Figure 3. Neointimal hyperplasia and macrophage staining in injured femoral arteries. A–C, Hematoxylin and eosin–stained sections of femoral arteries from a healthy rabbit (A), a rabbit with both chronic AIA and atherosclerosis (B), and a rabbit with atherosclerosis alone (C), harvested 4 weeks after vascular injury. A complete section of each vessel is shown in each inset. D, Intima-media thickness ratio in the femoral arteries of each group of animals. E–G, RAM11-stained sections of femoral arteries from a healthy rabbit (E), a rabbit with both chronic AIA and atherosclerosis (F), and a rabbit with atherosclerosis alone (G). A complete section of each vessel is shown in each inset. H, Proportion of RAM11 staining in the femoral arteries of each group of animals. Bars in D and H show the mean and SEM (n 10–15 rabbits per group). P 0.05 versus healthy controls; # P 0.05 versus rabbits with both chronic AIA and atherosclerosis. No femoral lesions were seen in rabbits with chronic AIA alone.
Original magnification 200; 40 in insets.)

Largo R, et al. Arthritis Rheum 2008;58:2723-34

Giles JT, Post WS, Blumenthal RS, Polak J, Petri M, Gelber AC, Szklo M, Bathon JM.

Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis.

Arthritis Rheum 2011;63:3216-25

Objectives

- To explore predictors of change in measures of carotid atherosclerosis among RA patients without CV at baseline

Methods

- 158 RA patients were investigated
- RA patients underwent carotid ultrasonography at 2 time points separated by a mean ± SD of 3.2 ± 0.3 years.
- The average yearly change in the mean maximal intima-media thickness (IMT) of the common carotid artery (CCA) and the internal carotid artery (ICAs) and with incident or progressive plaque in the ICA/carotid bulb, were explored.

Giles JT, et al. Arthritis Rheum 2011;63:3216-25

Results

- The maximal CCA-IMT increased in 82% and the maximal ICA-IMT increased in 70%. Incident plaque was observed in 14% of those without plaque at baseline. Plaque progression was observed in 5% of those with plaque at baseline
- Among RA predictors, the adjusted average yearly change in the maximal CCA-IMT was significantly greater in patients with earlier RA than in those with established disease
- Higher swollen joint counts and higher CRP levels were both associated with incident or progressive plaque

Giles JT, et al. Arthritis Rheum 2011;63:3216-25

Innala L, Möller B, Ljung L, Magnusson S, et al

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

Arthritis Res Ther 2011;13:R131

CONCLUSION

- The occurrence of new CV events in very early RA was explained by traditional CV risk factors and was potentiated by high disease activity. Treatment with DMARDs decreased the risk. The results may have implications for cardio-protective strategies in RA

Table 1 Demographic and clinical data in early RA at baseline (T0) and after five years (T5)

Variables	T0 (*n* = 700)	T5 (*n* = 442)
Sex, f/m	481/219	301/141
Age at onset of symptoms (years)	55.2 (14.3)	55.1 (14.2)
Duration of symptoms at inclusion (mo)	6.6 (3.3)	6.7 (3.2)
RF, n (%)	489 (76.4)	na
ANA, n (%)	130 (25.0)	na
Anti-CCP, n (%)	373 (67.8)	na
SE, n (%)	330 (56.9)	na
PTPN22 Tvariant, n (%)	167 (34.0)	na
ESR (mm)	31.5 (23.7)	20.0 (19.9)***
CRP (mg/l)	22.0 (24.6)	11.1 (14.3)***
DAS28[1]	4.8 (1.4)	3.2 (1.3)***
HAQ[1]	0.9 (0.6)	0.6 (0.52)***
Tender joints[1]	6.7 (5.8)	2.6 (3.7)***
Swollen joints[1]	7.4 (5.2)	3.2 (4.1)***
VAS pain (mm)[1]	44.5 (25.2)	28.7 (20.7)***
VAS global (mm) [1]	45.3 (24.9)	29.8 (20.6)***
AUC DAS28 (6 mo)[1,2]	-	25.8 (7.1)
AUC DAS28 (12 mo)[1,2]	-	47.2 (13.5)
AUC DAS28 (24 mo)[1,2]	-	87.5 (26.0)
Extra-articular disease, n (%)[3]	-	21 (3.0)
Presence of nodules, n (%)	-	78 (20.7)

Mean (S.D.) or n (%).

*** $P < 0.001$, ** $P < 0.01$, paired t-test, for all patients who had reached the five-year follow-up, that is, who had data at both baseline (T0) and at follow-up (T5). NA, not analysed

[1] Regularly collected data from the RA-registry for 314 patients.

[2] AUC for DAS28 6, 12 and 24 months after inclusion.

[3] Criteria used for severe extra-articular manifestations: pericarditis, pleuritis, interstitial lung disease, Felty's syndrome, neuropathy, scleritis/episcleritis, glomerulonephritis, major cutaneous vasculitis and vasculitis involving other organs [26]. RA, rheumatoid arthritis; RF, rheumatoid factor; ANA, anti-nuclear antibodies; Anti-CCP, anti-cyclic citrullinated peptide/protein; SE, shared epitope; PTPN22, protein tyrosine phosphatise nonreceptor type 22; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score; HAQ, Health Assessment Questionnaire; VAS, visual analogous scale; AUC, area under the curve.

Innala L, et al. Arthritis Res Ther 2011;13:R131

Table 2 Cardiovascular risk factors and treatment in early RA at baseline (T0) and after five years (T5)

Variables	T0 (*n* = 700)	T5 (*n* = 442)
Hypertension, n (%)	170 (24.5)	164 (37.4)***
BP systolic, mmHg	144.1 (22.6)	141.2 (21.8)**
BP diastolic, mmHg	82.7 (10.3)	81.0 (9.6)**
Diabetes mellitus, n (%)	48 (7.1)	41 (9.5)**
BMI	26.3 (4.5)	25.8 (4.3)*
Smoking, present, n (%)	196 (29.8)	92 (22.4)***
Smoking, ever, n (%)	451 (69.5)	-
Previous CVE, n (%)	72 (10.4)	-
s-Cholesterol, mmol/L	5.6 (1.1)[1]	na
s-HDL, mmol/L	1.5 (0.5)[1]	na
s-Triglycerides, mmol/L	1.5 (0.7)[1]	na
Statin treatment, n (%)	54 (8.1)	71 (16.4)***
NSAIDs, n (%)	386 (58.5)	357 (82.4)***
COX-2 inhibitors, n (%)	82 (12.3)	112 (25.7)***
Corticosteroids, ever, n (%)	197 (29.1)	367 (72.7)***
Corticosteroids, months (T0 to T5)	-	22.3 (24.0)
DMARDs ≤3 months after inclusion, n (%)	-	393 (88.9)
DMARDs, ever, n (%)	-	429 (96.8)
DMARDs months (T0 to T5)	-	51 (16.4)
Methotrexate ever, n (%)	-	361 (81.5)
Biologicals, ever, n (%)	-	62 (14.2)

Mean (SD) or n (%).

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, paired t-test, for all patients who had reached the five-year follow-up, that is, who had data at both baseline (T0) and at follow-up (T5). na, not analysed

[1]analysed at baseline or as soon as possible during follow-up

BMI, Body mass index; BP, blood pressure; COX-2, cyclo-oxygenase-2; CVE, cardiovascular event; DMARDs, disease-modifying anti-rheumatic drugs; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis

Innala L, et al. Arthritis Res Ther 2011;13:R131

Table 4 Importance of potential risk factors for a new CVE in early- RA followed for five years.

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

Innala L, et al. Arthritis Res Ther 2011;13:R131

Lindhardsen J, Ahlehoff O, Gislason GH, et al

The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study

Ann Rheum Dis 2011;70:929-34

CONCLUSION

- RA is associated with the same risk of MI as DM, and the risk of MI in RA patients generally corresponded to the risk in non-RA subjects 10 years older

Nurmohamed MT, Kitas G

Cardiovascular risk in rheumatoid arthritis and diabetes: how does it compare and when does it start?

Ann Rheum Dis 2011;70:881-3

Protogerou A, Zampeli E, Tentolouris N, et al

Subclinical femoral atheromatosis in rheumatoid arthritis: comparable prevalence to diabetes mellitus in a case-control study

Ann Rheum Dis 2012;71:1534-6

CONCLUSION

- Subclinical femoral atheromatosis in RA is analogous to DM, further confirming the territorial unrestricted acceleration of the atheromatic process in these patients. Cardiovascular risk stratification based on both carotid and femoral plaque detection in RA should be addressed prospectively

van Halm VP, Peters MJL, Voskuyl AE, Boers M, et al

Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE´ Investigation

Arthritis Rheum 2013;65:1675-83

CONCLUSION

- The prevalence of CVD in RA is increased to an extent that is at least comparable to that of DM2. This should have implications for primary cardiovascular prevention strategies in RA

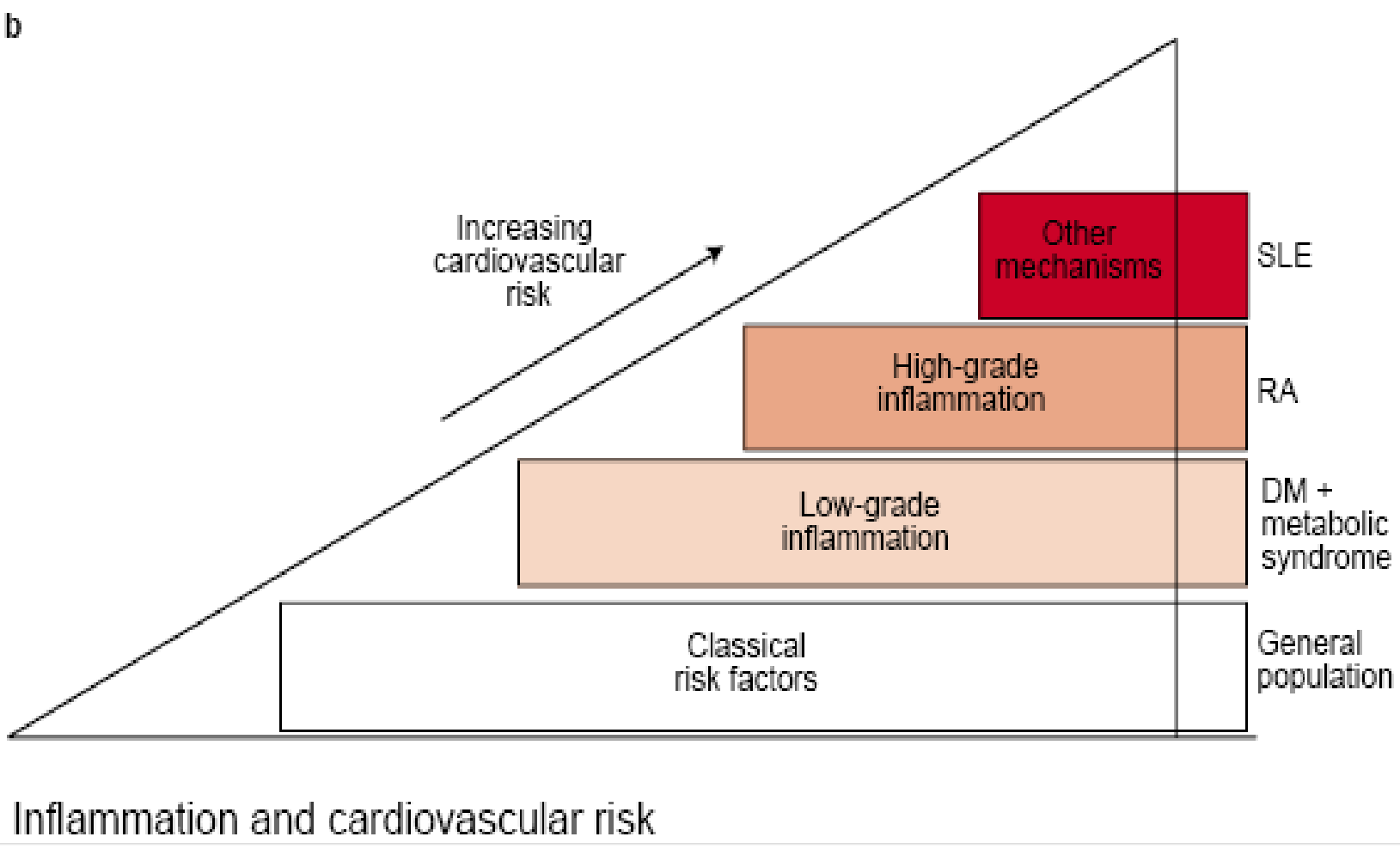
Young SP, Kapoor SR, Viant MR, Byrne JJ, Filer A, et al

The impact of inflammation on metabolomic profiles in patients with arthritis

Arthritis Rheum 2013;65:2015-23

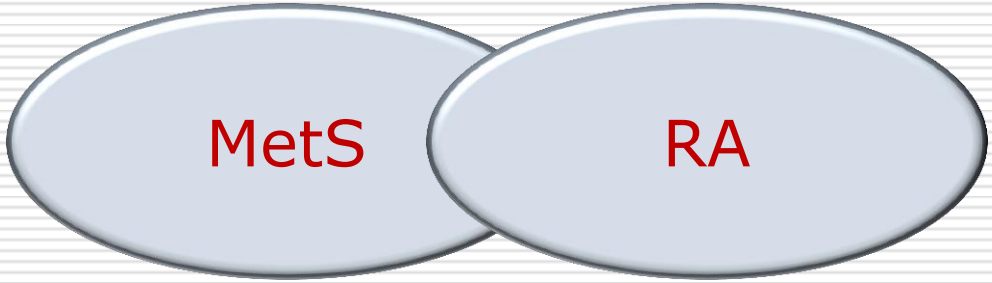
CONCLUSION

- The metabolic fingerprint reflects inflammatory disease activity in patients with synovitis, demonstrating that underlying inflammatory processes drive significant changes in metabolism that can be measured in the peripheral blood



Inflammation and cardiovascular risk

Key soluble biomarkers that are associated with different stages of the atherosclerosis pathway in the metabolic syndrome and RA



↑ TNF, ↑ IL-6, ↑ CRP,
↑ leptin, ↑ resistin, ↑/↓ adiponectin,
↑ insulin, ↑ glucose

↑ TNF, ↑ IL-1, ↑ IL-6, ↑ CRP, ↑ SAA,
↑ leptin, ↑ adiponectin, ↑ visfatin,
↑ insulin, ↑ glucose

↓

Endothelial dysfunction: ↑ MCP-1, ↑ sICAM-1, ↑ sVCAM-1,
↑ sE-selectin, ↓ sL-selectin, ↑ VWF, ↑ tPA, ↑ PAI-1

↓

Plaque instability: ↑ MMP9, ↑ myeloperoxidase, ↑ sCD40L

↓

Cardiac overload/Ventricular dysfunction: ↑ NT-proBNP

SSA: serum amyloid
PAI-1: plasminogen activator inhibitor-1

Kozera L, et al. Rheumatology (Oxford) 2011;50:1944-54

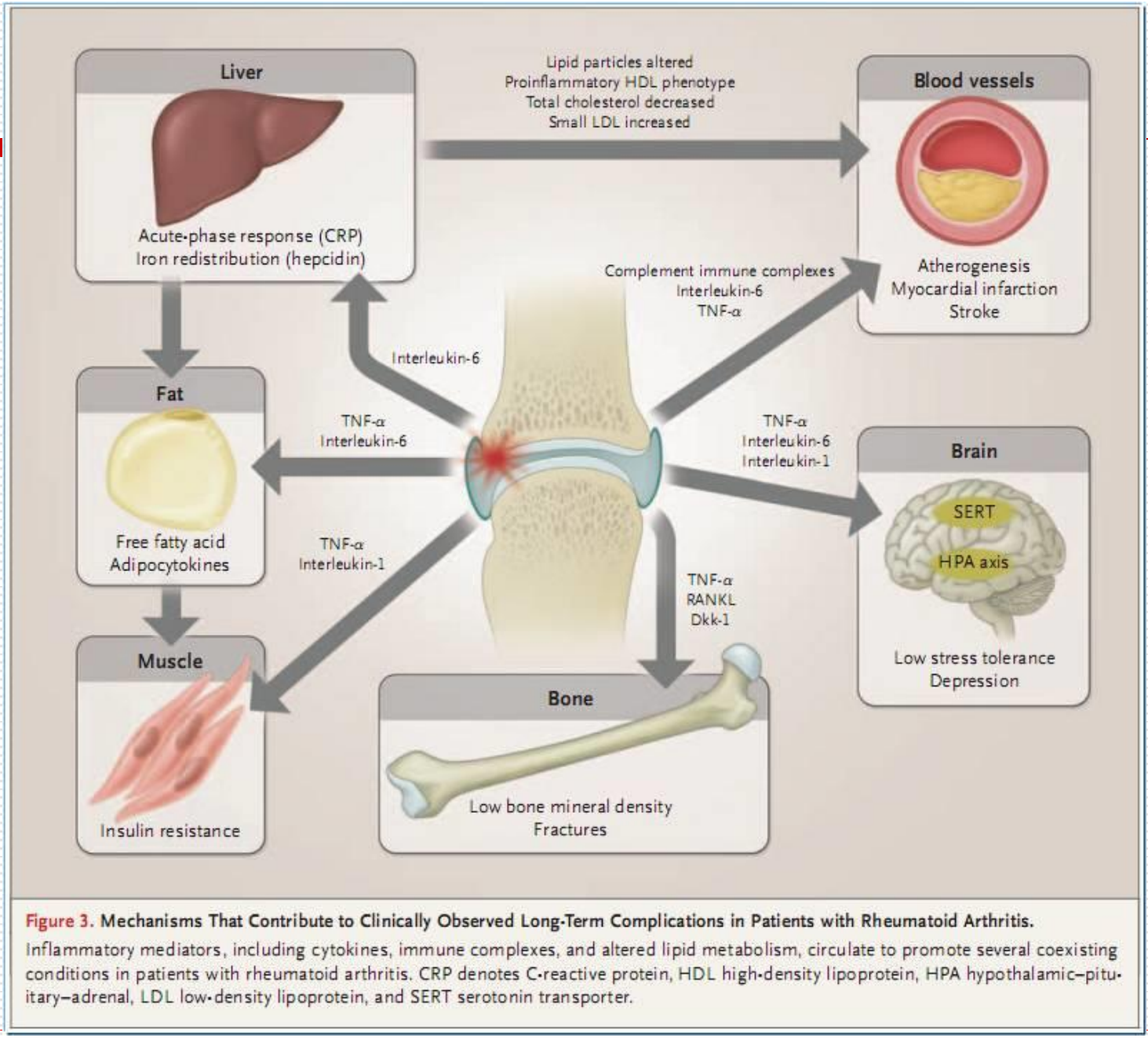


Figure 3. Mechanisms That Contribute to Clinically Observed Long-Term Complications in Patients with Rheumatoid Arthritis.

Inflammatory mediators, including cytokines, immune complexes, and altered lipid metabolism, circulate to promote several coexisting conditions in patients with rheumatoid arthritis. CRP denotes C-reactive protein, HDL high-density lipoprotein, HPA hypothalamic–pituitary–adrenal, LDL low-density lipoprotein, and SERT serotonin transporter.

McInnes I, Schett G. NEJM 2011;365:2205-19

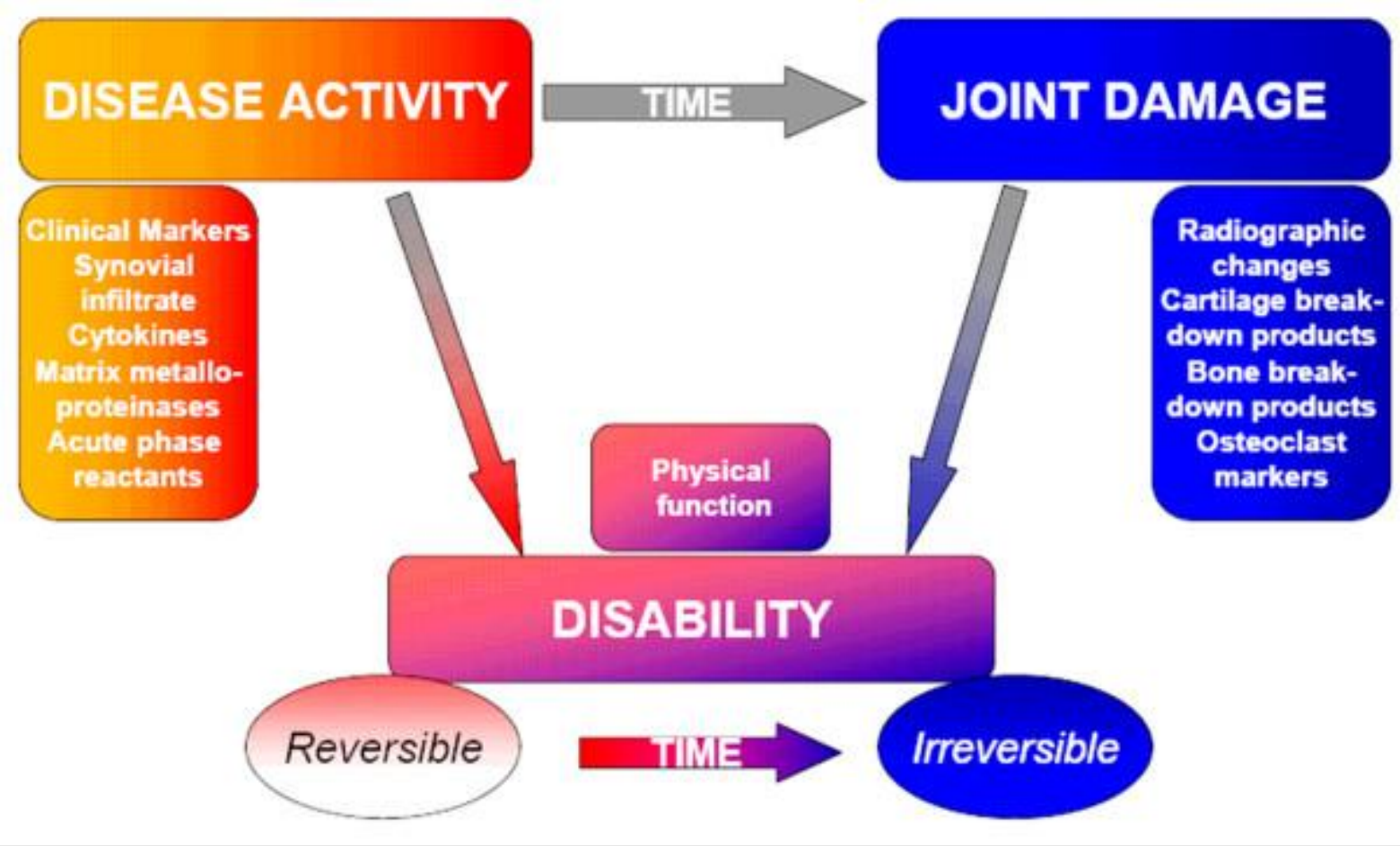
Cardiovascular risk factors in RA

Treatment of RA

- Coxibs and NSAIDs
- Steroids

The first extent prothrombolic effects while steroids have deleterious effects on lipids, obesity, blood pressure and insulin resistance

Bolten WW. Ann Rheum Dis 2006;65:7-13
Da Silva JA, et al. Ann Rheum Dis 2006;65:285-93



Smolen JS et al. Arthritis Res Ther 2008;10:208.

Targets of therapy in RA

Clinical remission
DAS-28 <2,6

↓

Maintenance of quality of live

↓

Inhibition of structural damage

Provan SA, Semb AG, Hisdal J et al

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

Ann Rheum Dis 2011;70:812-7

CONCLUSION

- Patients with active RA, but not those in remission, had significantly increased levels of CVD risk markers

Wasko MC, Kay J, Hsia EC, Rahman MU

Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: Risk reduction in a chronic inflammatory disease

Arthritis Care Res 2011;63:512-21

CONCLUSION

- Controlling inflammation may improve insulin sensitivity and subsequently reduce the risk of developing type 2 DM in RA patients. This may also reduce the risk of CVD in this high-risk group

Solomon DH, Peters MJL, Nurmohamed MT, Dixon W

Motion for Debate: the Data Support Evidence-Based Management Recommendations for Cardiovascular Disease in Rheumatoid arthritis

Arthritis Rheum 2013;65:1675-83

Kozera L, Andrews J, Morgan AW

Cardiovascular risk and rheumatoid arthritis--the next step: differentiating true soluble biomarkers of cardiovascular risk from surrogate measures of inflammation

Rheumatology (Oxford) 2011;50:1944-54

CONCLUSION

- RA is a risk factor for CVD
- Traditional risk factors and inflammation predict CVD in RA and should be aggressively managed
- Long-term CV outcomes should be prospectively examined in future studies

Conclusions

- Cardiovascular disease and premature atherosclerosis are frequently observed in RA patients
- Classical factors and systemic inflammation are responsible for premature atherosclerosis
- Early intervention with DMARDs especially MTX, and/or anti-TNF therapy reduces structural damage development
- This early intervention may have a beneficial effect on the cardiovascular risk in these patients

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