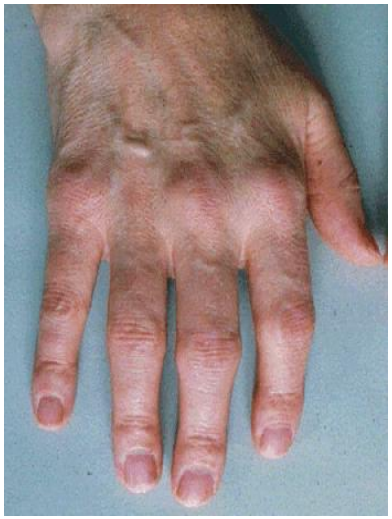
ΠΑΝΕΛΛΗΝΙΟ ΔΙΕΤΑΙΡΙΚΟ ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΠΟΣΙΟ
ΚΑΡΔΙΟΛΟΓΙΑΣ - ΡΕΥΜΑΤΟΛΟΓΙΑΣ
ΚΑΛΑΜΠΑΚΑ, ΟΚΤΩΒΡΙΟΣ 2013

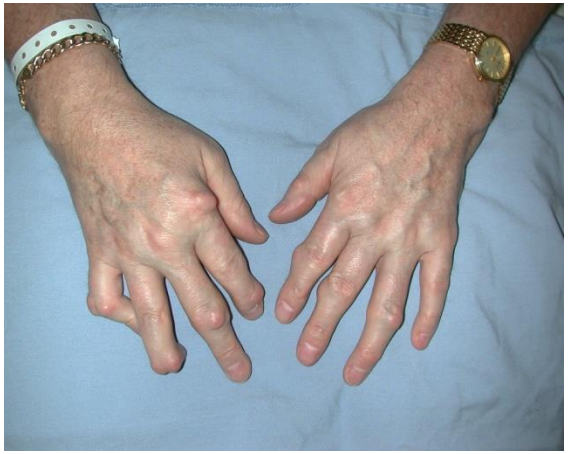
ΦΛΕΓΜΟΝΩΔΗ ΝΟΣΗΜΑΤΑ
ΚΑΙ
ΚΑΡΔΙΑΓΓΕΙΑΚΟΣ ΚΙΝΔΥΝΟΣ
(ΜΟΝΤΕΛΟ = ΡΕΥΜΑΤΟΕΙΔΗΣ ΑΡΘΡΙΤΙΔΑ)

Professor George Kitas, MD, PhD, FRCP
RA Co-morbidity Research Group
Dudley Group NHS Foundation Trust
and
Arthritis Research UK Epidemiology Unit
University of Manchester

RA - symptoms/signs

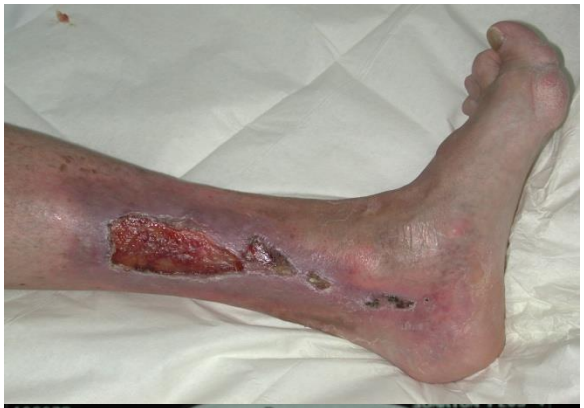
- Joint symptoms
  - Pain
  - Swelling
  - Stiffness

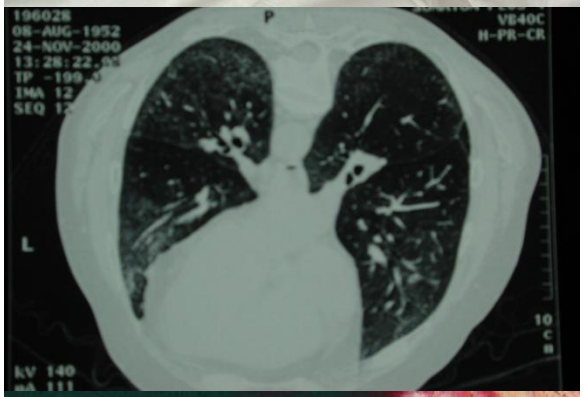


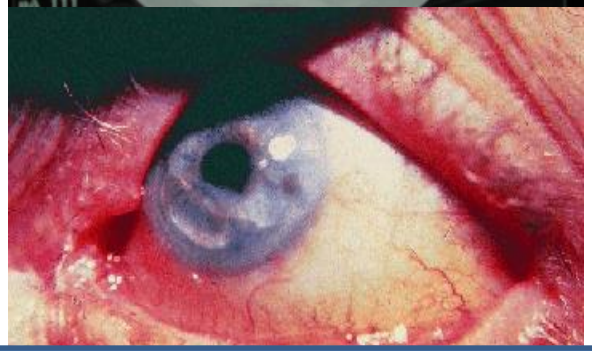


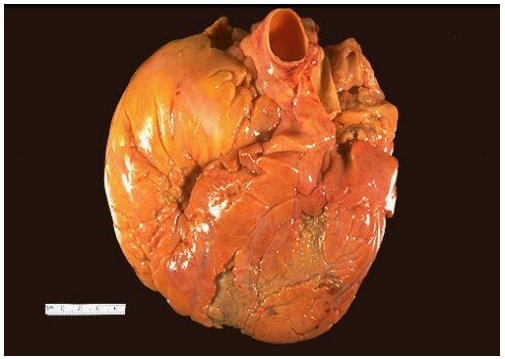
- Constitutional upset
  - Fatigue
  - Weight loss
  - Pyrexia

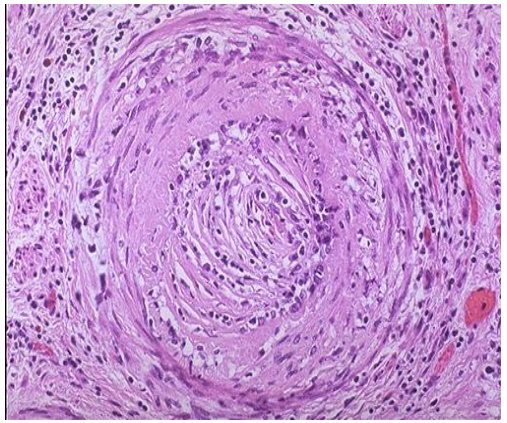
RA - Multi-system involvement



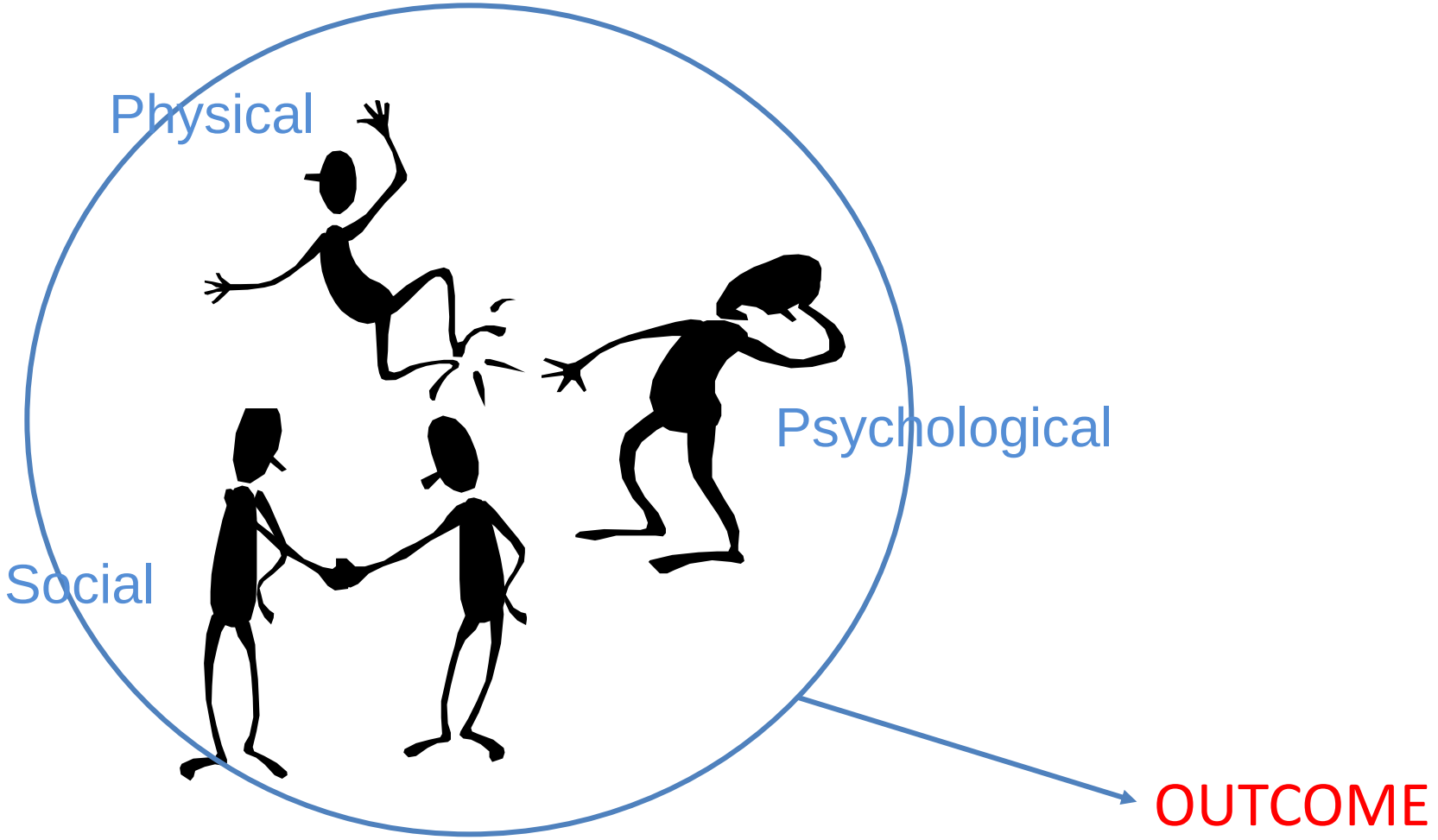








Bio-Psycho-Social impact integration



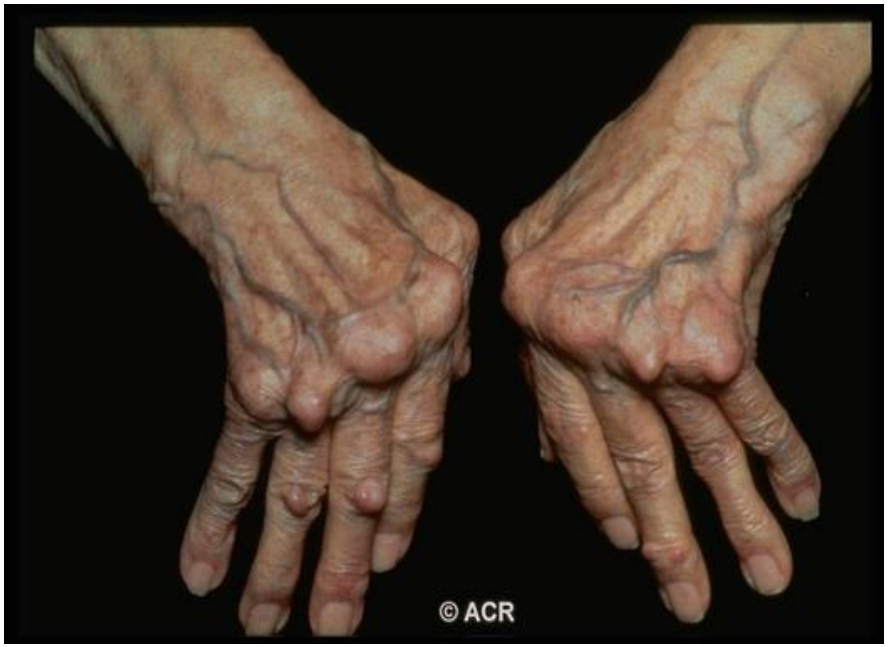
Outline

- What is the problem?
- What is the nature of the problem?
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - Other mechanisms?
- Summary

Outline

- **What is the problem?**
- What is the nature of the problem?
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - Other mechanisms?
- Summary

RA: increased overall mortality

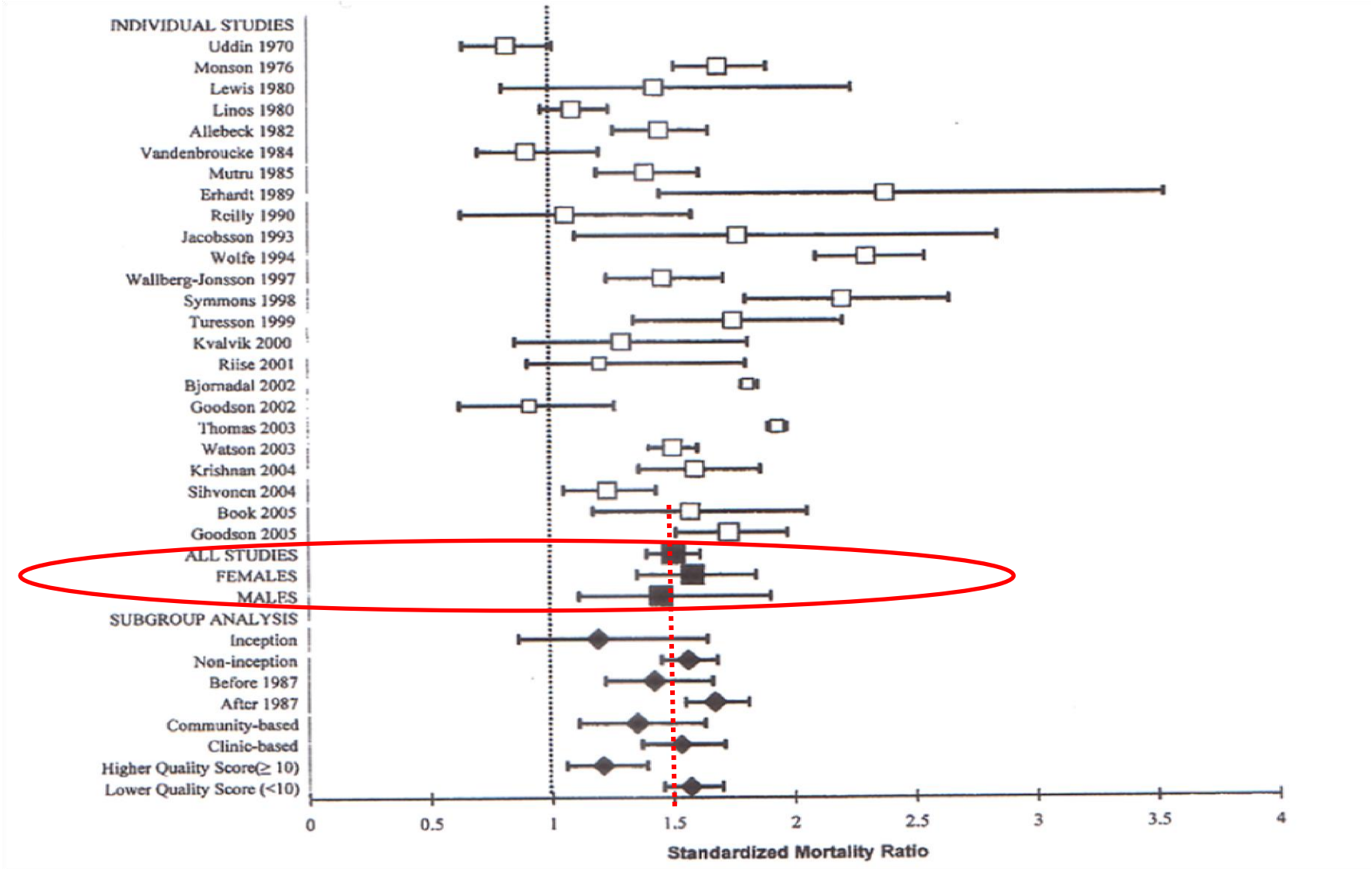


Gloucester : "oh let me kiss these hands"

Lear : "let me wipe them first, they smell of mortality"

King Lear

The problem: CVD mortality in RA



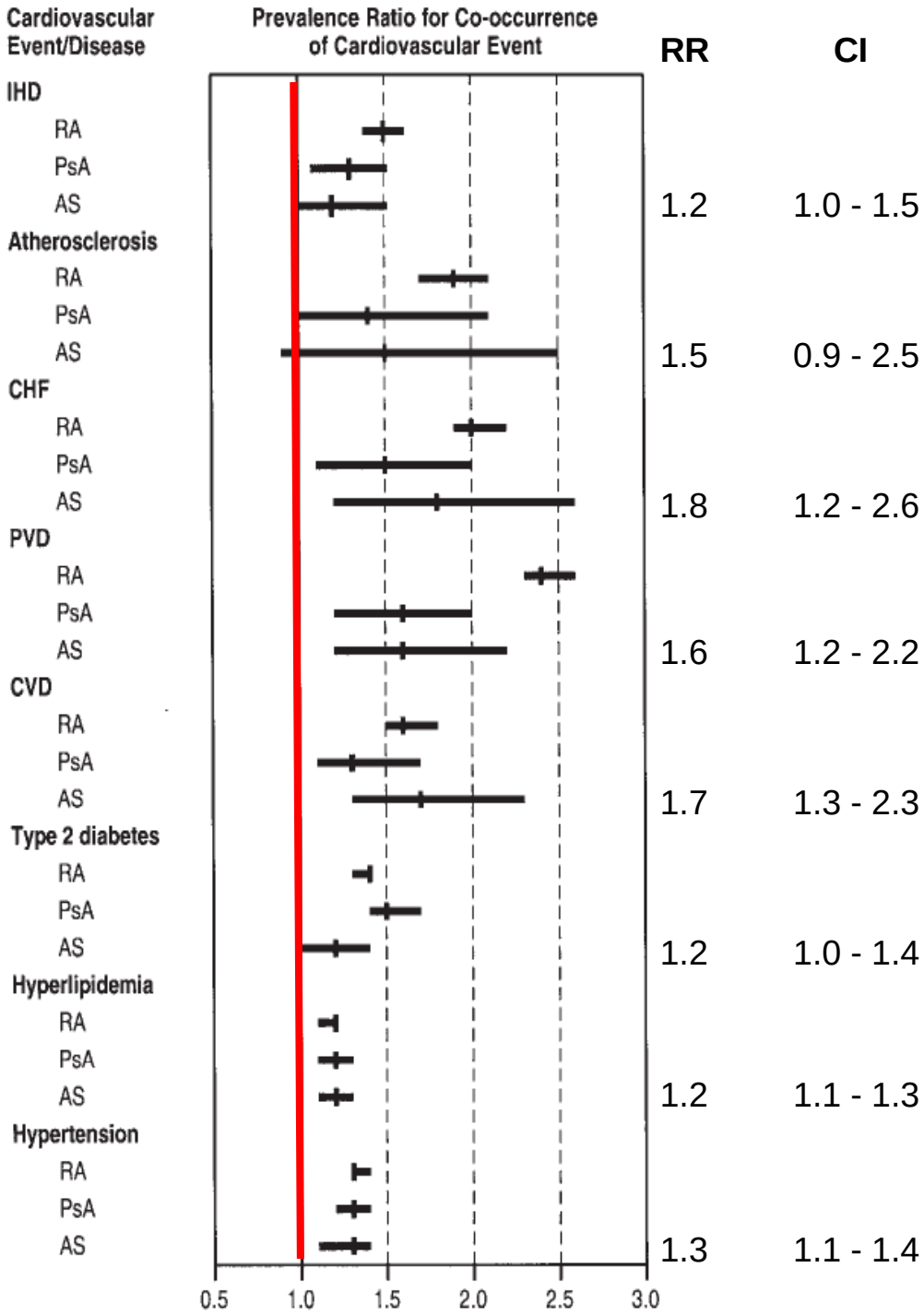
Avina –Zubieta et al, AC&R 2008; 59: 1690

Ischaemic heart disease

Congestive heart failure

Peripheral vascular disease

Cerebrovascular disease



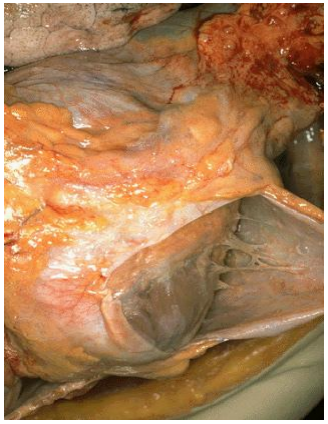
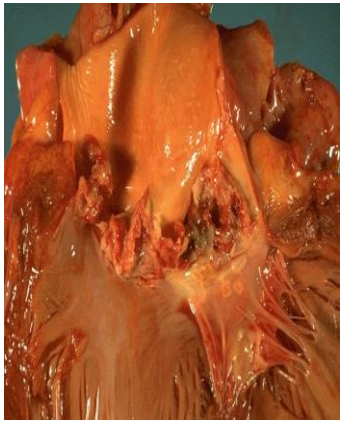
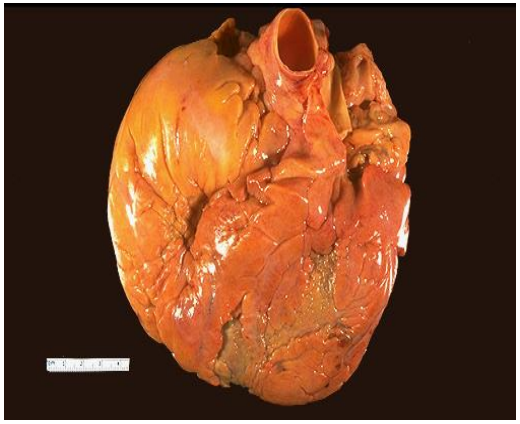
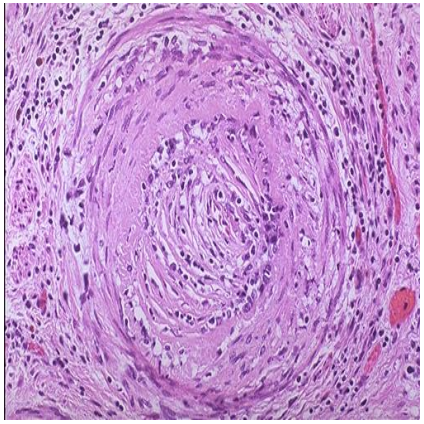
Han et al. J Rheumatol 2006

Outline

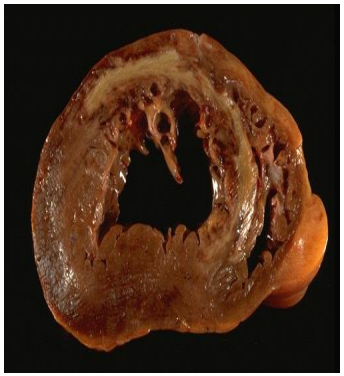
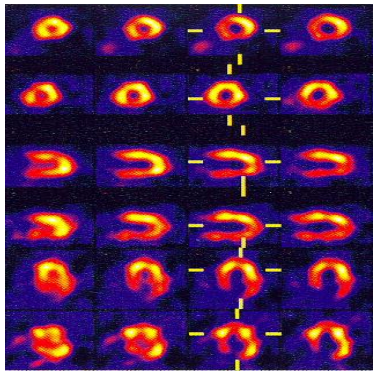
- What is the problem?
- **What is the nature of the problem?**
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - Other mechanisms?
- Summary

Cardiovascular "pathology" in RA

Rheumatoid heart disease (classical inflammation):

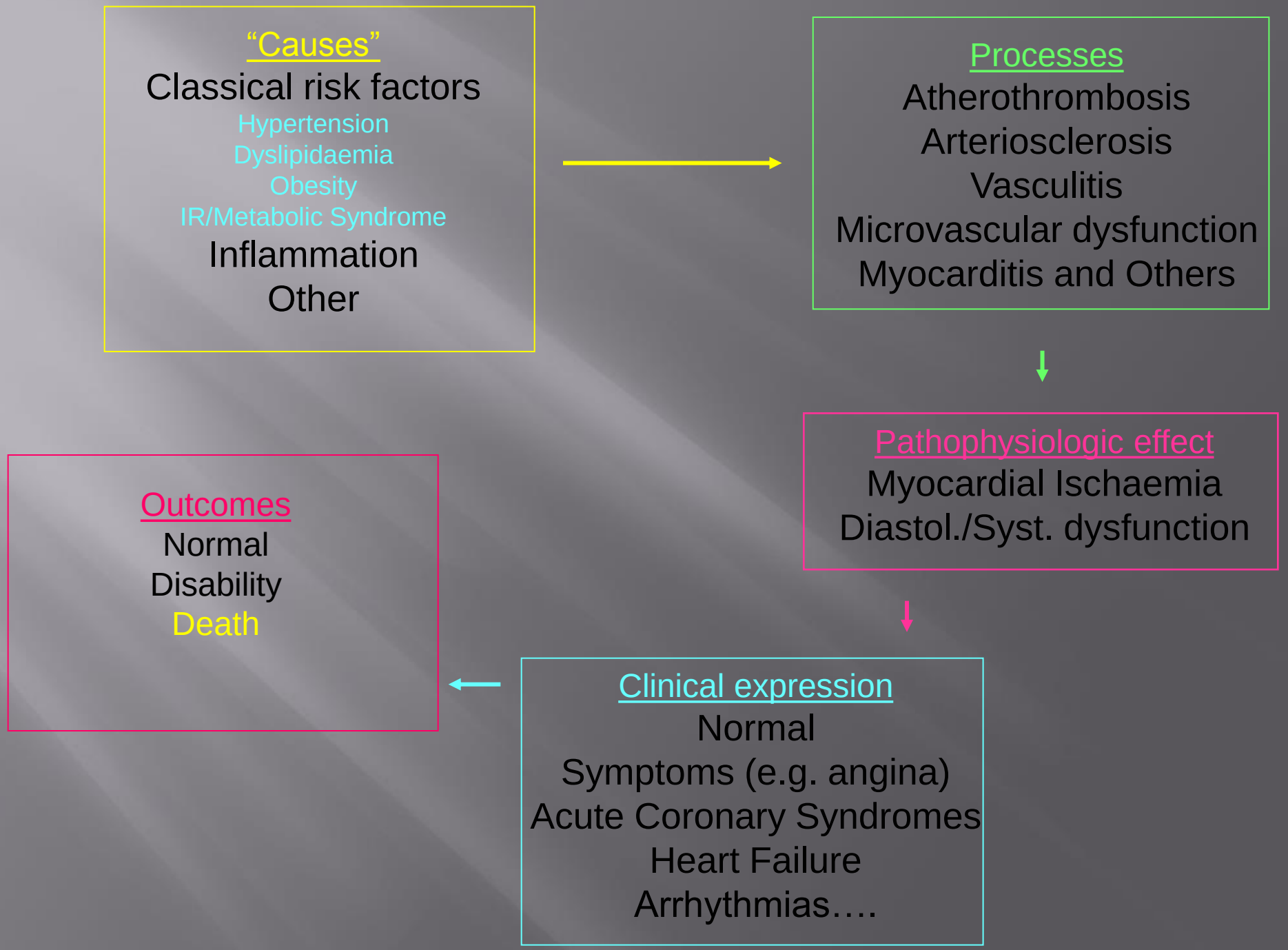
Ischaemic Heart Disease:

Most cardiovascular deaths in RA are due to ischaemic pathologies (i.e. MI, CVA, CHF, sudden death)

Bacon & Kitas, ARD, 1994

Kitas et al: Clin Med 2001


"Causes"
Classical risk factors
Hypertension
Dyslipidaemia
Obesity
IR/Metabolic Syndrome
Inflammation
Other
Processes
Atherothrombosis
Arteriosclerosis
Vasculitis
Microvascular dysfunction
Myocarditis and Others
Pathophysiologic effect
Myocardial Ischaemia
Diastol./Syst. dysfunction
Clinical expression
Normal
Symptoms (e.g. angina)
Acute Coronary Syndromes
Heart Failure
Arrhythmias….
Outcomes
Normal
Disability
Death

Outline

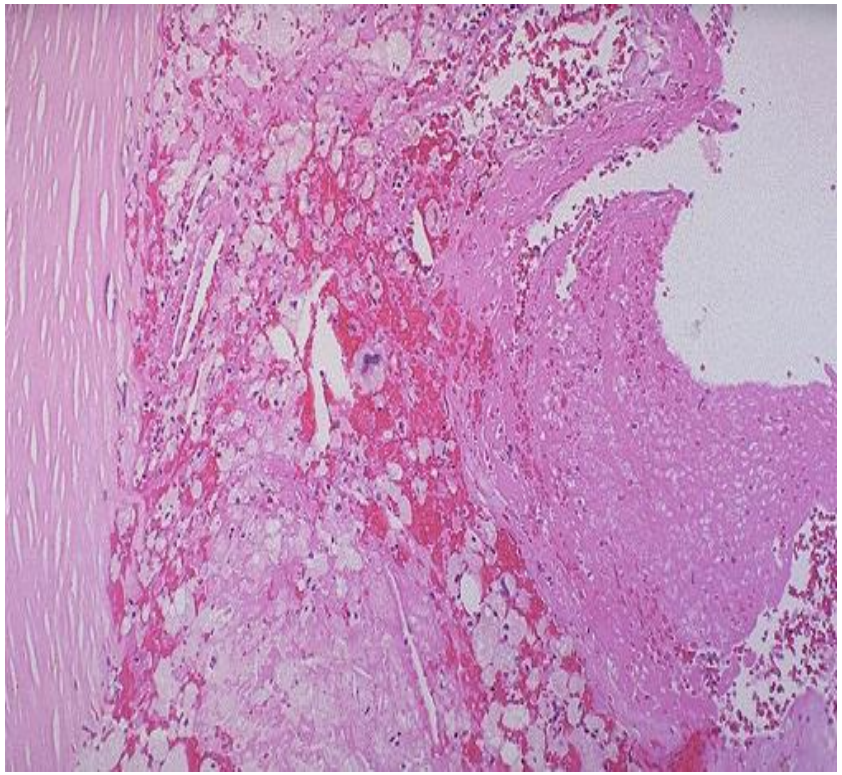
- What is the problem?
- **What is the nature of the problem?**
  - **(Accelerated) Atherosclerosis?**
  - Plaque instability?
  - Other mechanisms?
- Summary

What is the evidence for (accelerated) atherosclerosis in RA?

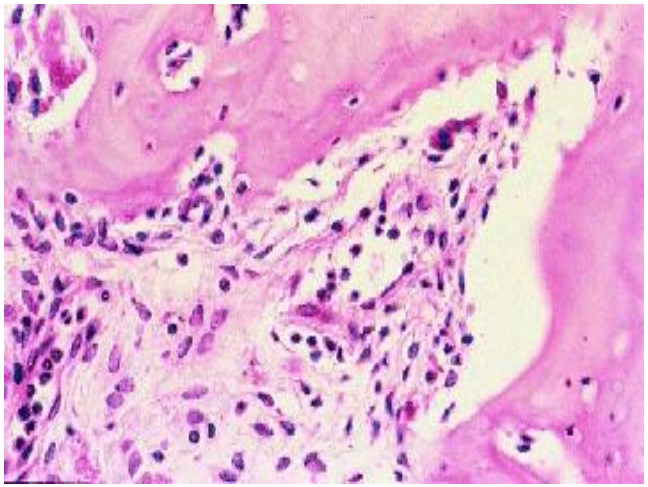
- Theory: the role of inflammation

“INFLAMMATION” et al.

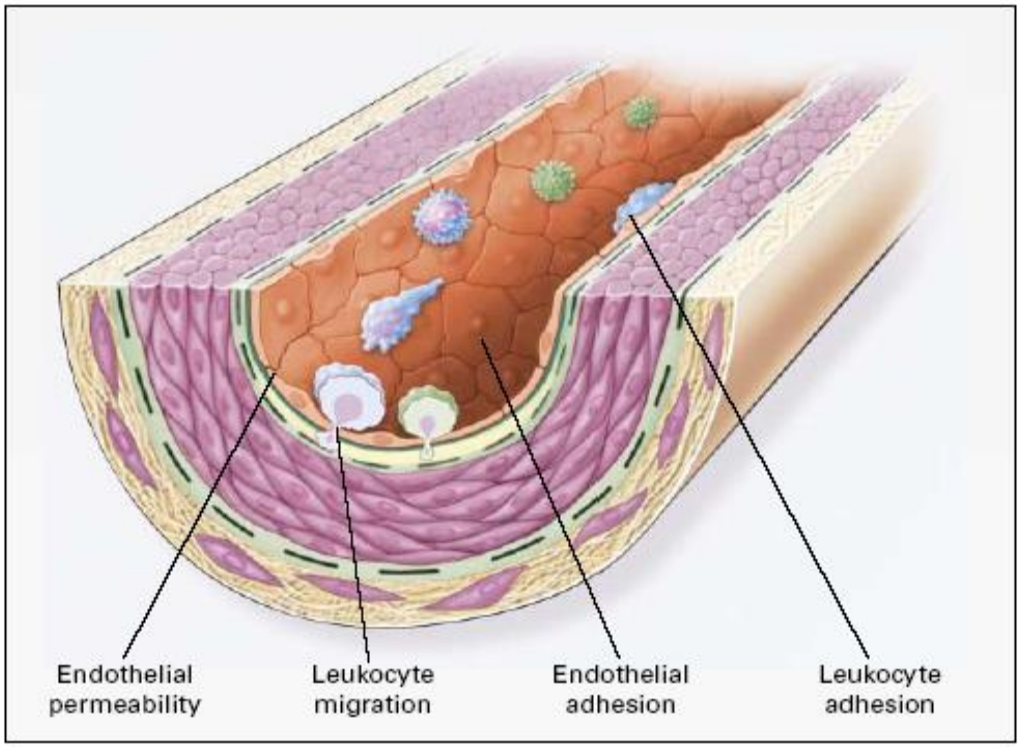
Atherosclerosis is a chronic inflammatory disorder…



…similar to RA…



Stages of atherothrombosis (1):



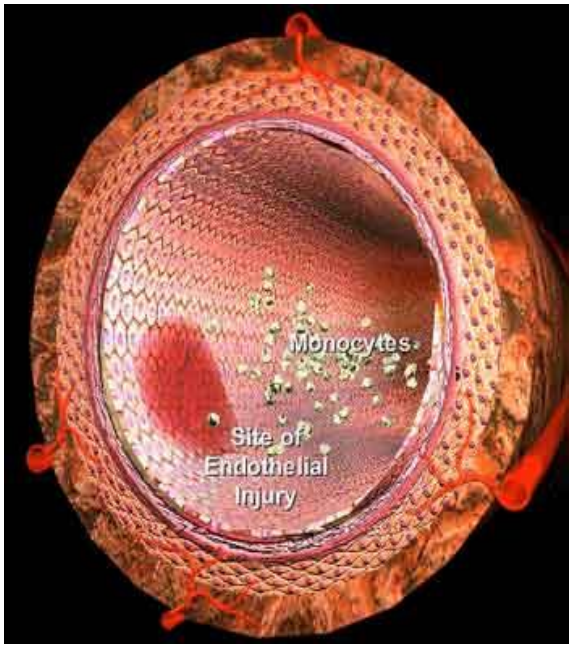
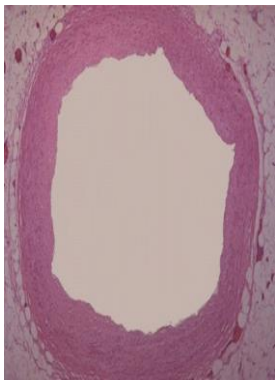
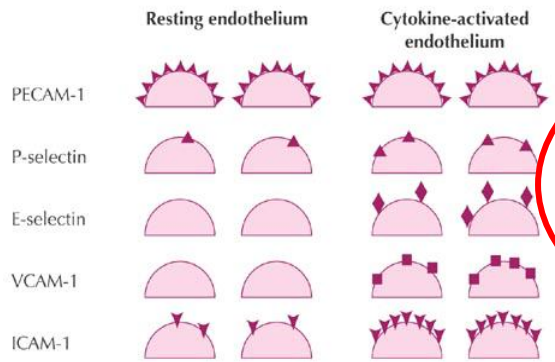
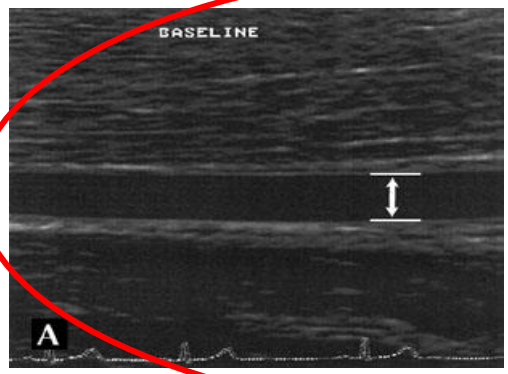
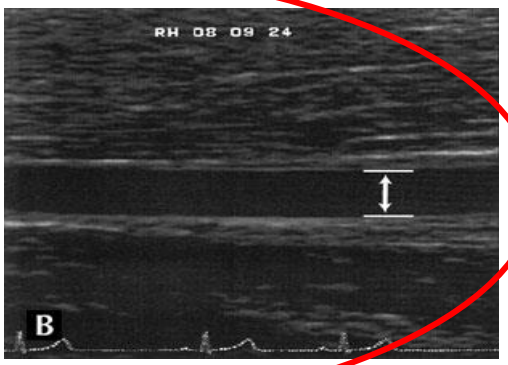


Figure 1. Endothelial Dysfunction in Atherosclerosis.

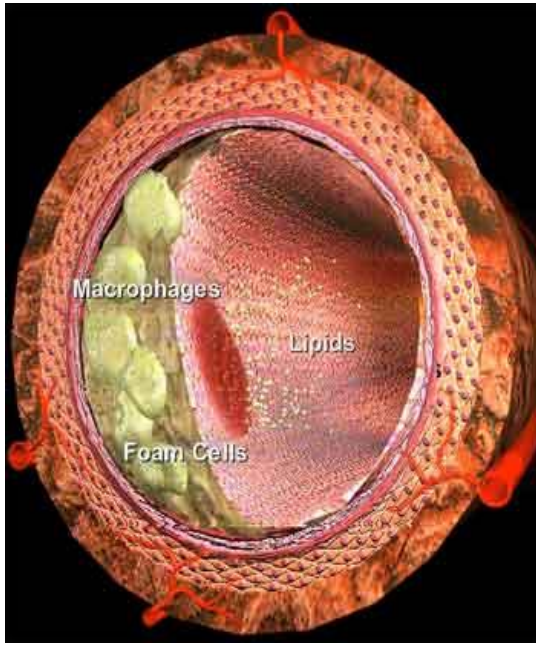


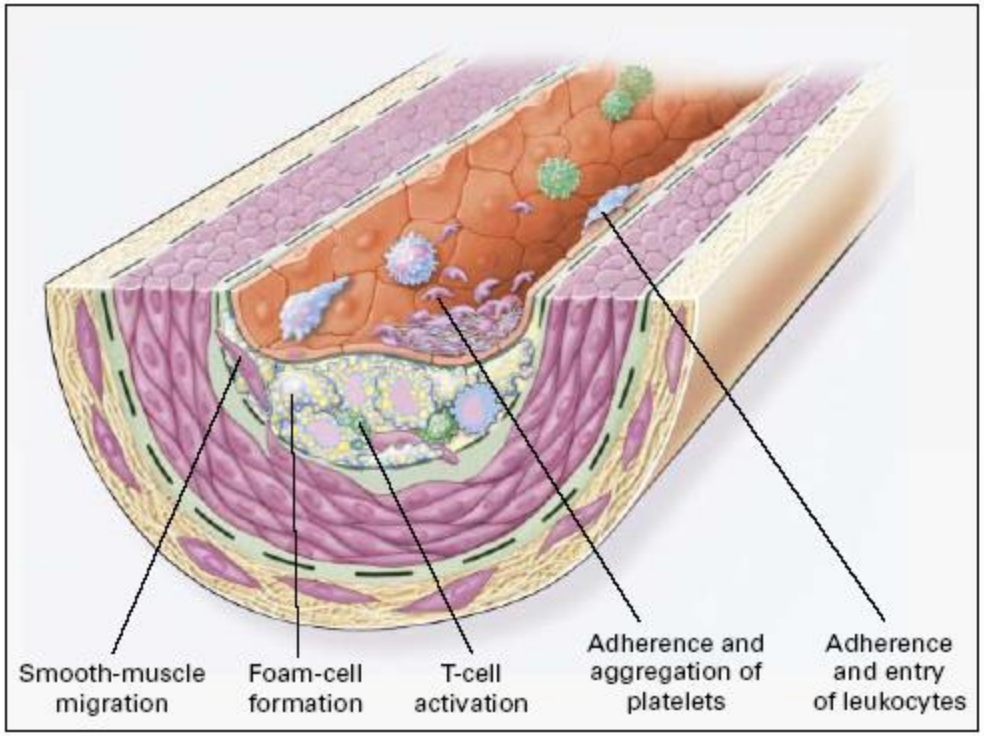






Stages of atherothrombosis (2):





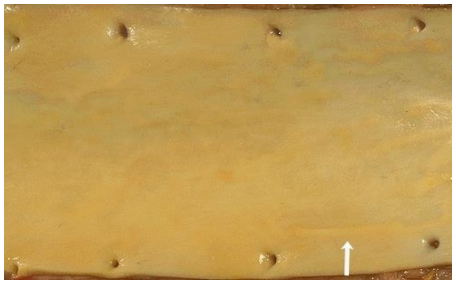
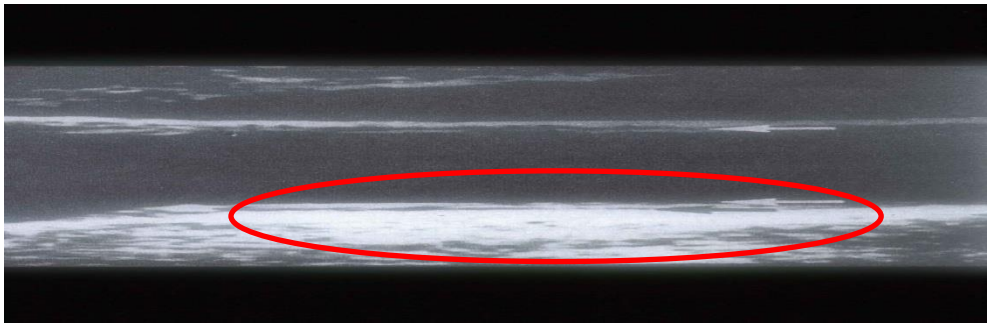
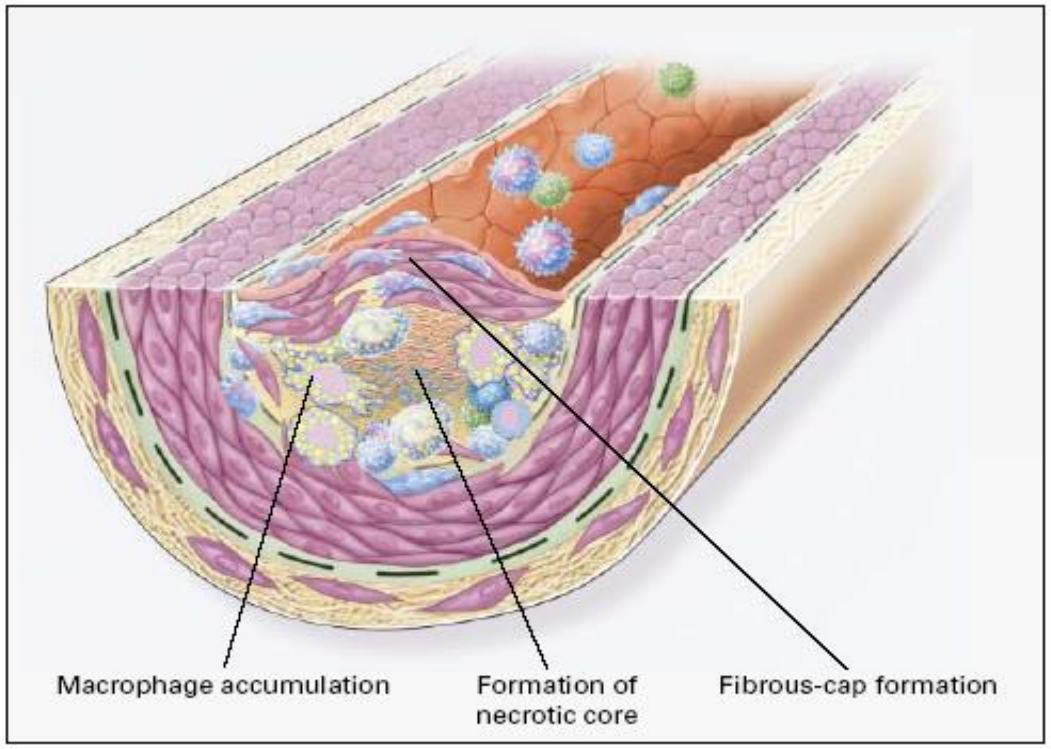


Figure 2. Fatty-Streak Formation in Atherosclerosis.



Stages of atherothrombosis (3):



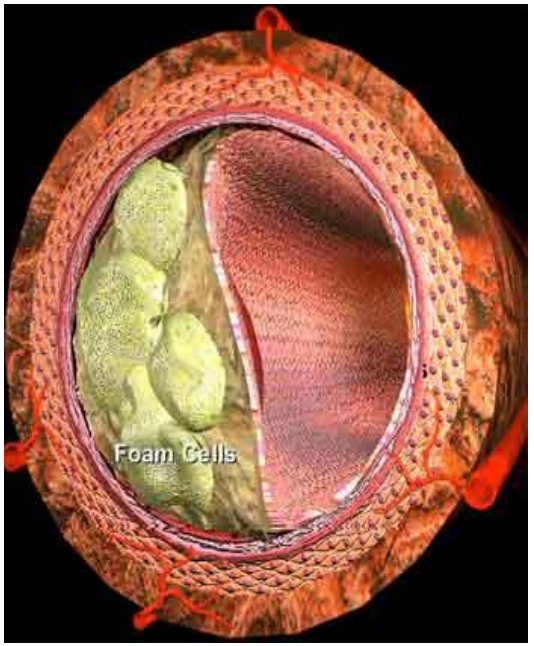
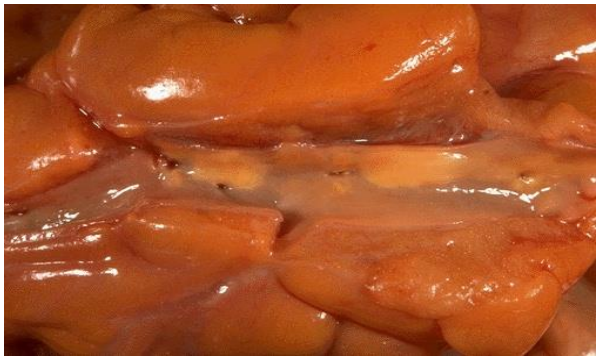
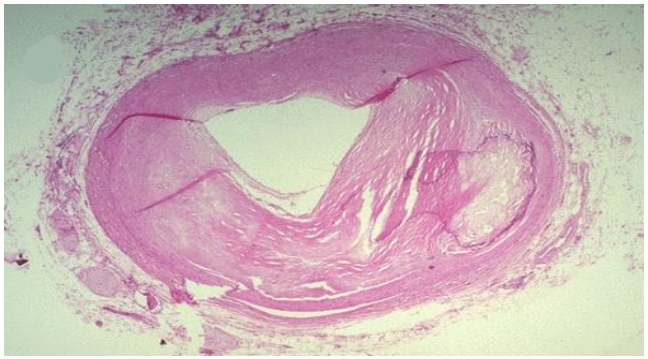


Figure 3. Formation of an Advanced, Complicated Lesion of Atherosclerosis.





Stages of atherothrombosis (4):

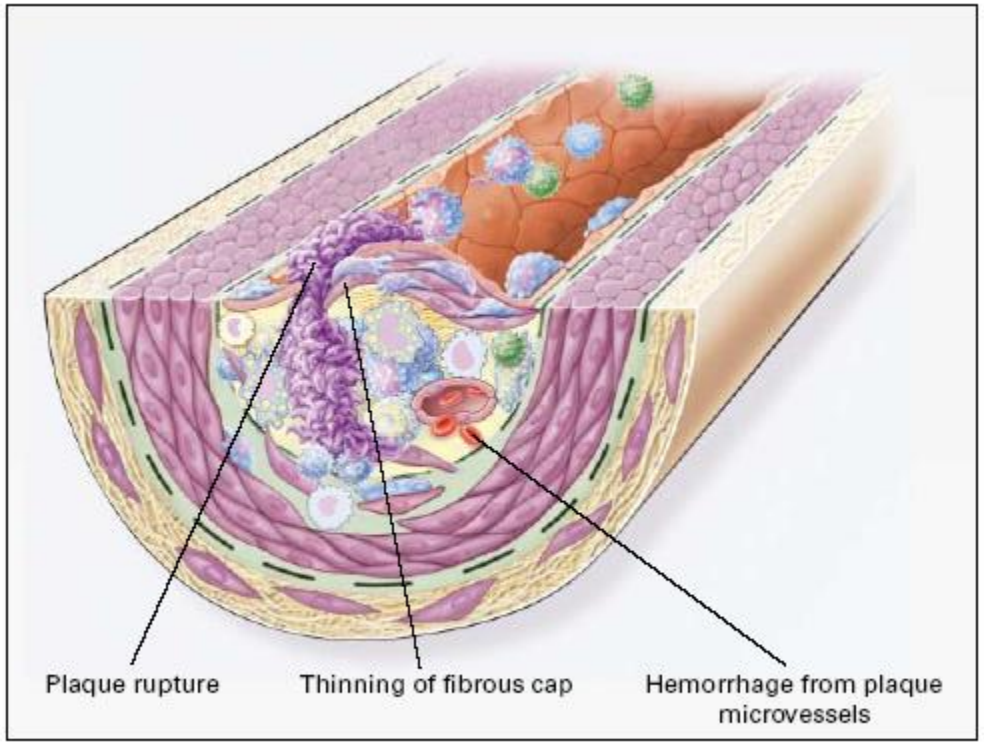
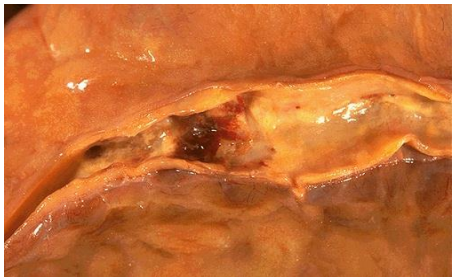
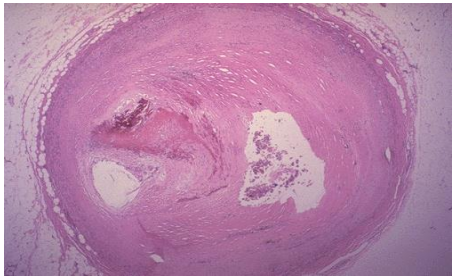
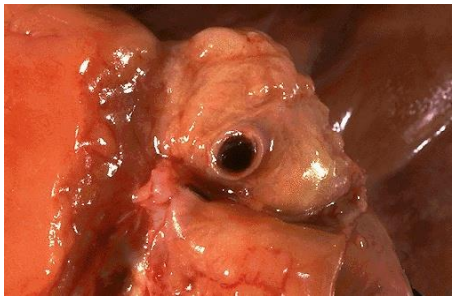
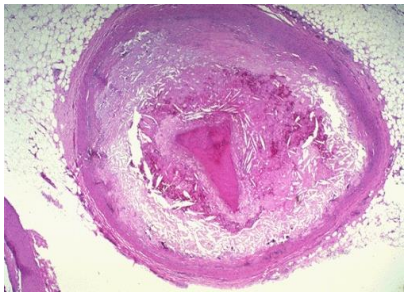


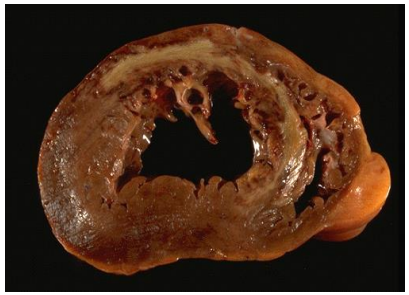
Figure 4. Unstable Fibrous Plaques in Atherosclerosis.











Effect of “inflammation”

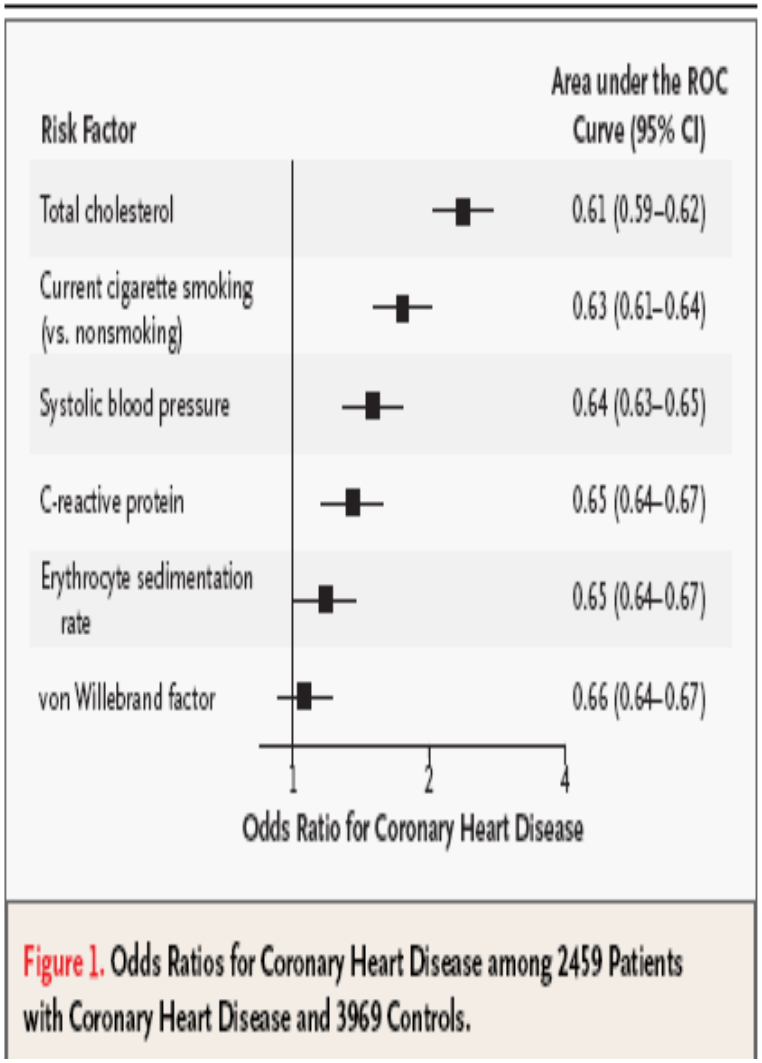
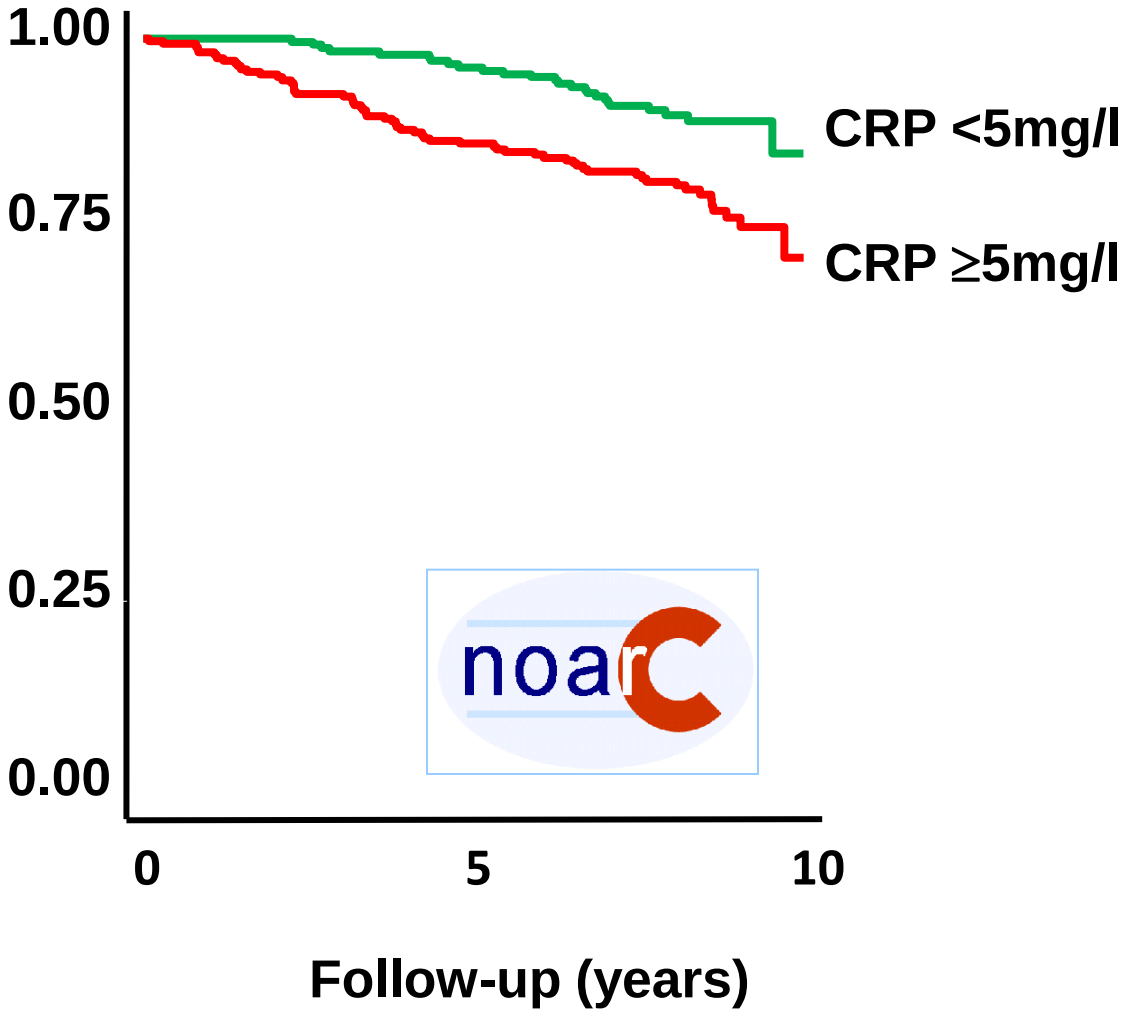


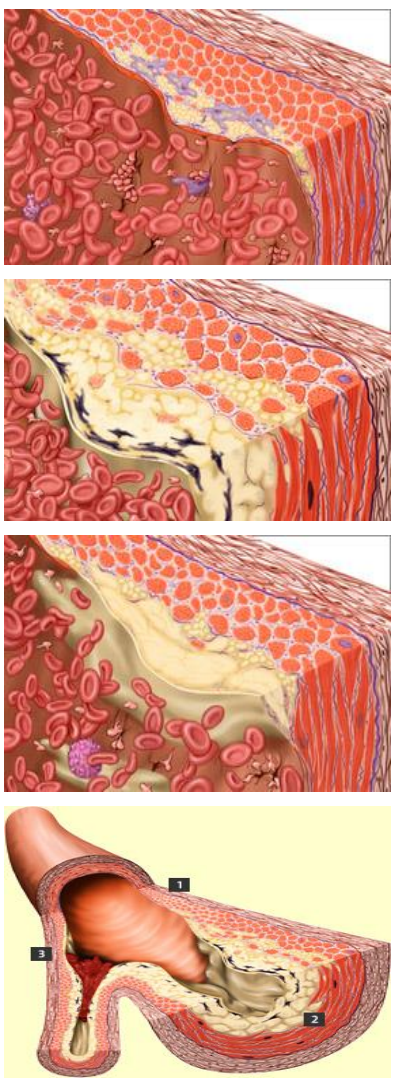
Figure 1. Odds Ratios for Coronary Heart Disease among 2459 Patients with Coronary Heart Disease and 3969 Controls.

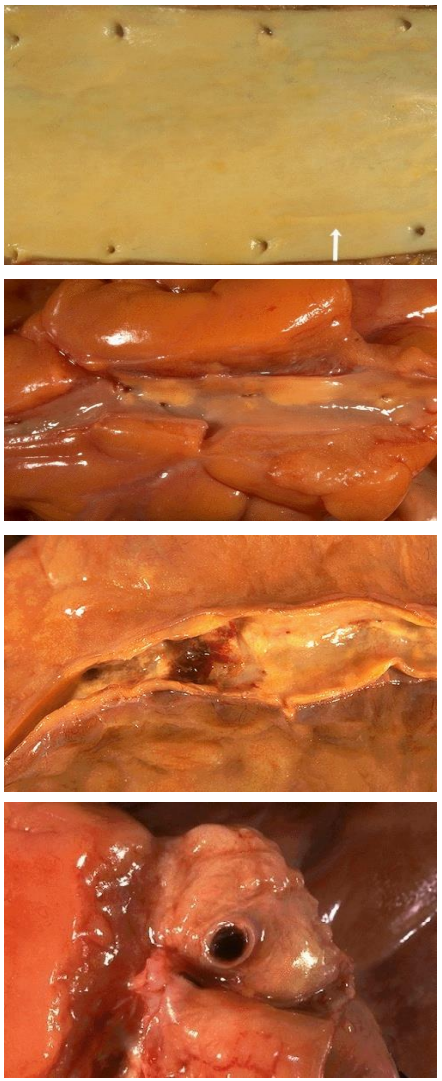


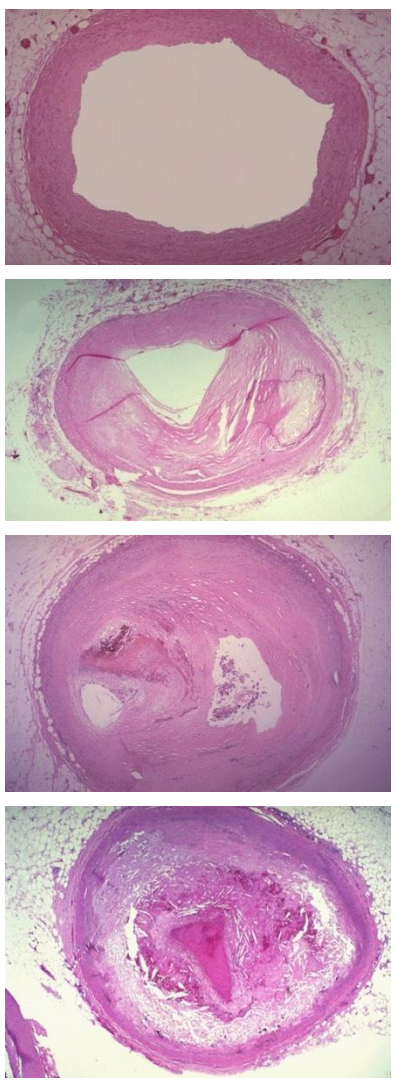
Danesh et al, NEJM, 2004

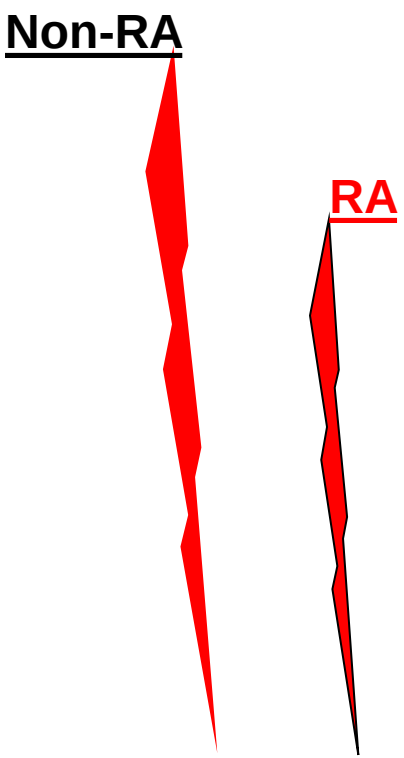
Goodson et al, A&R 2005; 52: 2293

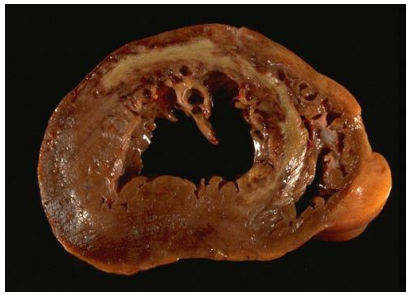
Accelerated atherosclerosis





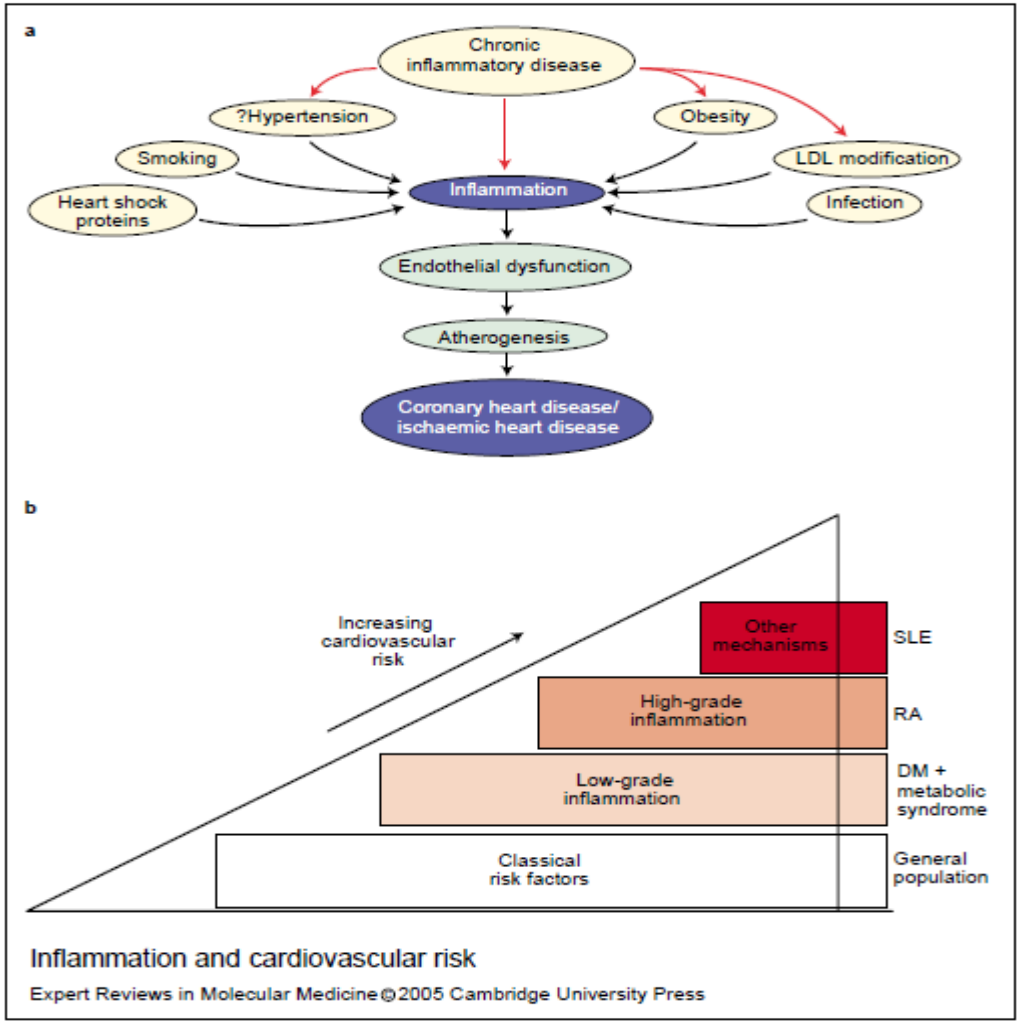






Effect of inflammation

Inflammation → "classical" CVD risk factors → Vasculature
Inflammation → Vasculature



Inflammation and cardiovascular risk

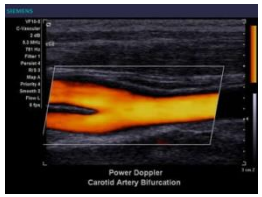
Stevens et al: Exp Rev Mol Med 2005; 7(7): 1-24

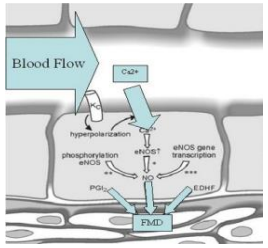
What is the evidence for (accelerated) atherosclerosis in RA?

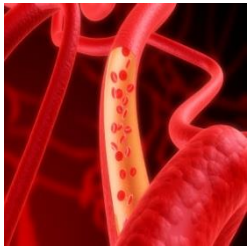
- Theory: the role of inflammation
- Vascular function and morphology studies - biomarkers
  (sub-clinical atherosclerosis)

Vascular Function and Morphology in RA

Aamer Sandoo, BSc, MSc, PhD







•**Sandoo** & Kitas. Current perspectives on the assessment of vascular function and morphology in rheumatoid arthritis. *Int J Clin Rheumatol*. 2013.

•Dimitroulas & **Sandoo** et al. Predictors of asymmetric dimethylarginine levels in patients with rheumatoid arthritis: the role of insulin resistance. *Scand J Rheumatol*. 2013.

•**Sandoo** et al. The role of inflammation, the autonomic nervous system and classical cardiovascular disease risk factors on subendocardial viability ratio in patients with RA: a cross-sectional and longitudinal study. *Arthritis Research and Therapy.* 2012.

•**Sandoo** et al. Anti-TNFalpha therapy transiently improves high density lipoprotein cholesterol levels and microvascular endothelial function in patients with rheumatoid arthritis: a pilot study. *BMC Musculoskeletal Disorders*. 2012.

•**Sandoo** et al. Clinical remission following treatment with tumour necrosis factor-alpha antagonists is not accompanied by changes in asymmetric dimethylarginine in patients with rheumatoid arthritis. *Clinical Biochemistry*. 2012.

•**Sandoo** et al. The role of inflammation and cardiovascular disease risk on microvascular and macrovascular endothelial function in patients with rheumatoid arthritis: a cross-sectional and longitudinal study. *Arthritis Research & Therapy*. 2012.

•**Sandoo** et al. Lack of association between Asymmetric dimethylarginine and *in vivo* Microvascular & Macrovascular Endothelial Function in Patients with Rheumatoid Arthritis. *Clinical Experiments in Rheumatology*. 2012.

•**Sandoo** et al. Vascular function and morphology in rheumatoid arthritis: a systematic review. *Rheumatology* (Oxford). 2011.

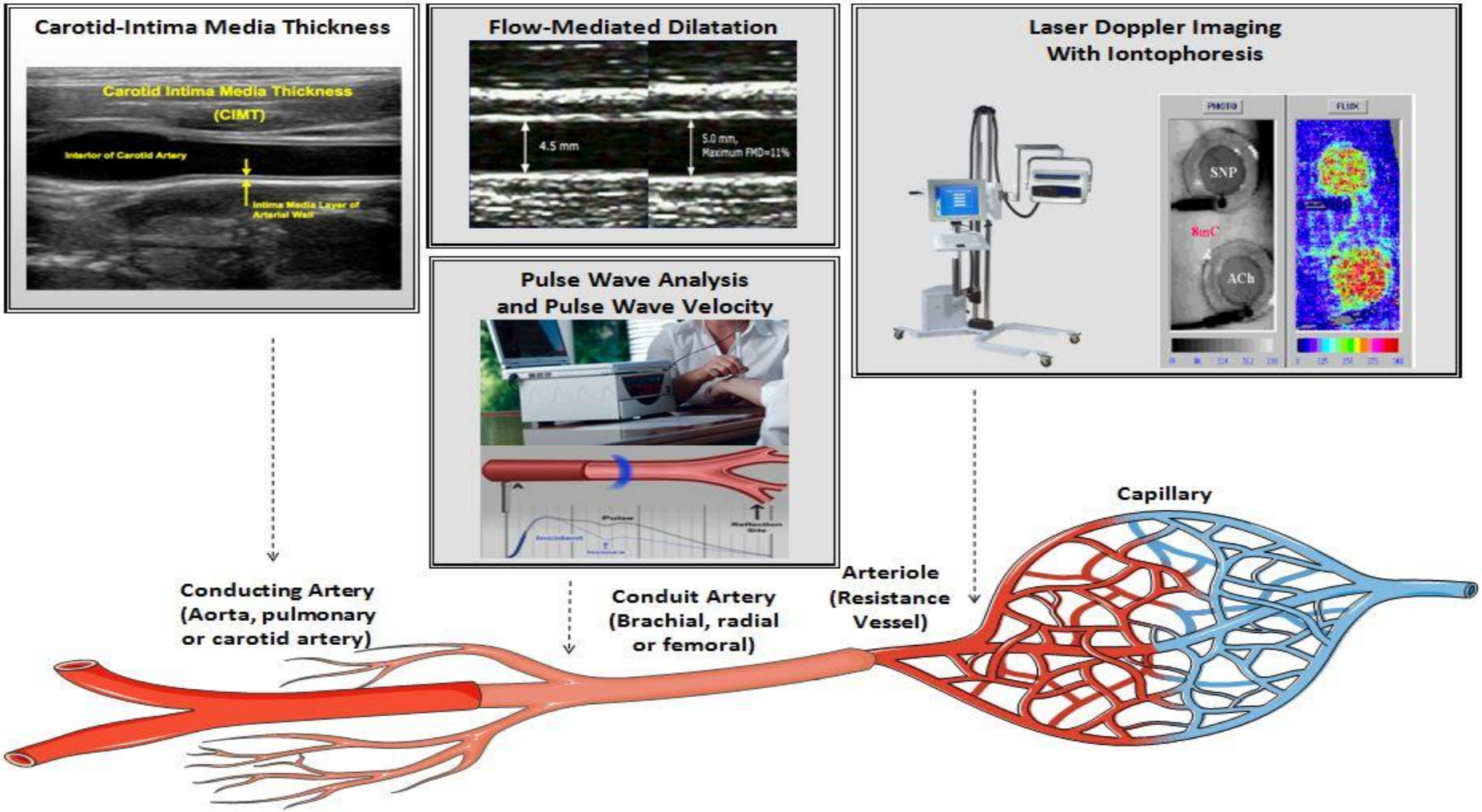
•**Sandoo** et al. The association between microvascular and macrovascular endothelial function in patients with rheumatoid arthritis: a cross-sectional study. *Arthritis Research & Therapy.* 2011.

•**Sandoo** et al. Anti-TNFα therapy may lead to blood pressure reductions through improved endothelium-dependent microvascular function in patients with rheumatoid arthritis. *Journal of Human Hypertension.* 2011.

•**Sandoo** et al. The endothelium and its role in regulating vascular tone. *The Open Cardiovascular Medicine Journal*. 2010.

•**Sandoo** et al. Short-term effects of rituximab on flow-mediated dilatation may be mediated by intravenous glucocorticoids . *Arthritis and Rheumatism*. 2009.

Sub-clinical atherosclerosis: Non-invasive vascular assessments



Are they good surrogates of future CVD events in RA?

Sandoo et al: Rheumatology 2011

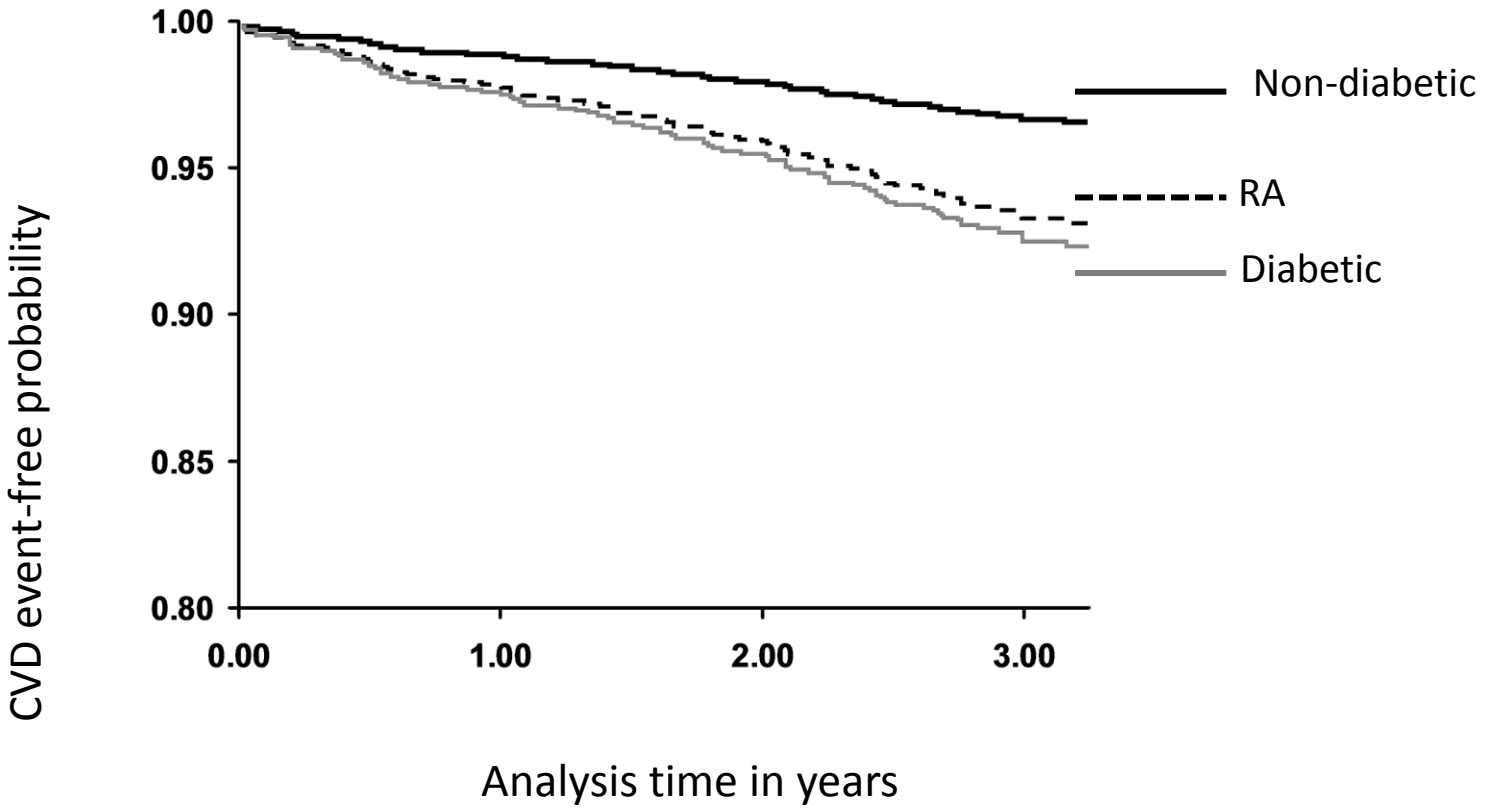
Summary – Vascular function and morphology in RA:

- Sub-clinical atherosclerosis appears to be more pronounced in RA compared to controls – equal to Type 2 DM
- Classical CVD risk factors appear to have a greater impact than systemic inflammation on most vascular parameters
- Changes in microvascular and macrovascular endothelial function are independent of each other
- Classical CVD risk factors and inflammation have different effects on vascular smooth muscle cells and endothelial cells

What is the evidence for (accelerated) atherosclerosis in RA?

- Theory: the role of inflammation
- Vascular function and morphology studies - biomarkers
  (sub-clinical atherosclerosis)
- Epidemiology: **RA = DM type 2**
  (DM type 2 = CHD equivalent)

CVD morbidity in RA = DM



Nurmohamed & Kitas: ARD 2011; 70: 881

John et al: Curr Opin Cardiology 2011: 26:327–333

Linhardsen et al, ARD 2011; 70: 929

Stamatelopoulos et al, ATVB 2009; 29: 1702

Peters et al, Arthritis Rheum 2009; 61: 1571

What is the evidence for (accelerated) atherosclerosis in RA?

- Theory: the role of inflammation
- Vascular function and morphology studies - biomarkers
  (sub-clinical atherosclerosis)
- Epidemiology: RA = DM type 2
  (DM type 2 = CHD equivalent)
- Abundance of classical and novel risk factors
  - Hypertension
  - Dyslipidaemia
  - Obesity – Cachexia – Insulin resistance
  - Physical Inactivity
  - Multiple other factors (e.g. drugs, smoking, RhF etc.)

Hypertension in RA

Vasileios Panoulas MD, PhD, MRCP

Senior Lecturer in Cardiology, Imperial College London

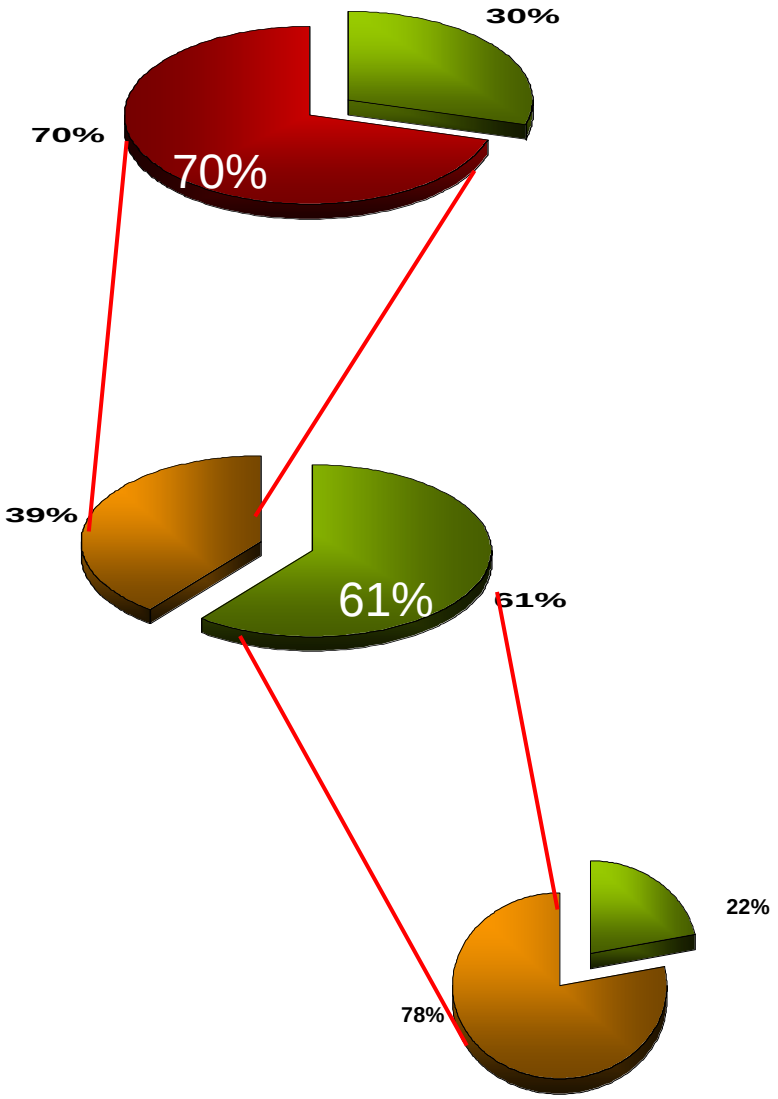
- **Panoulas VF**, et al. Target organ damage in patients with rheumatoid arthritis: the role of blood pressure and heart rate. *Atherosclerosis* 2010 Mar;209(1):255-60.
- **Panoulas VF**, et al. Lack of an association of GNB3 C825T polymorphism and blood pressure in patients with rheumatoid arthritis. *Clin Exp Hypertens*. 2009 Aug;31 (5):428-439
- **Panoulas VF** et al. Association of interleukin-6 (IL-6)-174G/C gene polymorphism with cardiovascular disease in patients with rheumatoid arthritis: The role of obesity and smoking. *Atherosclerosis*. 2009 May;204(1):178-83.
- **Panoulas VF**, et al. Galectin -2 *(LGALS2)* 3279C/T polymorphism may be independently associated with diastolic blood pressure in patients with rheumatoid arthritis. *Clin Exp Hypertens*. 2009 Apr;31(2):93-104
- **Panoulas VF**, et al. Transforming growth factor beta 1 *869 T/C*, but not interleukin-6 *-174G/C* polymorphism, associates with hypertension in rheumatoid arthritis. *Rheumatology (Oxford)*. 2009 Feb;48(2):113-8.
- **Panoulas VF**, et al. Polymorphisms of the endothelin-1 gene associate with hypertension in patients with rheumatoid arthritis. *Endothelium.* 2008 Jul-Aug;15(4):203-12.
- **Panoulas VF**, et al. Hypertension in rheumatoid arthritis. *Rheumatology (Oxford)*. 2008 Sep;47(9):1286-98. Epub 2008 May 8. Review.
- **Panoulas VF**, et al. Serum uric acid is independently associated with hypertension in patients with rheumatoid arthritis. *J Hum Hypertens*. 2008 Mar;22(3):177-82. Epub 2007 Oct 25.
- Toms TE*, **Panoulas VF***, et al. "Cardiovascular" drugs in Rheumatoid Arthritis: Killing two birds with one stone? *Immun., Endoc. & Metab. Agents in Med. Chem*. 2008 ;8:259-274
- **Panoulas VF** et al.. Six step management of hypertension in patients with rheumatoid arhtirits. *Future Rheumatology*, 2008 Feb;3(1):21-35
- **Panoulas VF**, et al. Long-term exposure to medium-dose corticosteroid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2008 Jan;47(1):72-5.
- **Panoulas VF**, et al. Association of serum uric acid with cardiovascular disease in rheumatoid arthritis. *Rheumatology (Oxford)* 2007; 46(9):1466-1470.
- **Panoulas VF**, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2007; 46(9):1477-1482.

Hypertension in RA

- Of the total RA population in 2^0 care, 70% are hypertensive…

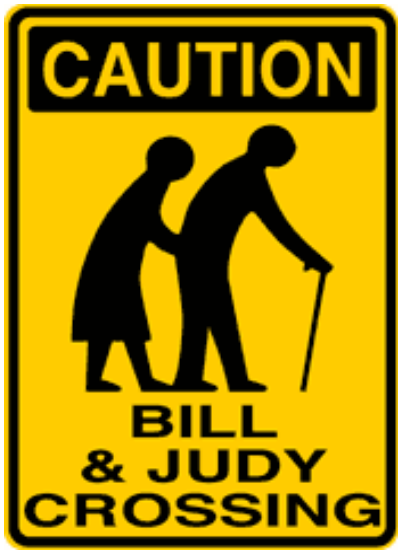
- Of those with hypertension, 40% remain undiagnosed...

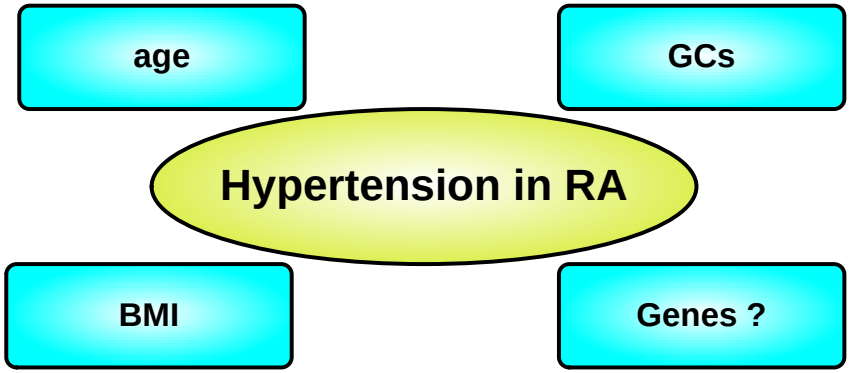
- Of those diagnosed, ~80% are sub-optimally controlled….

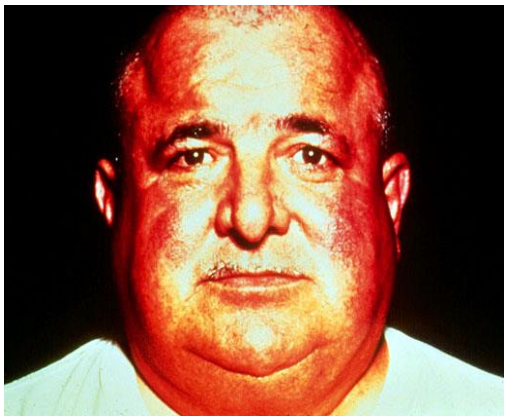


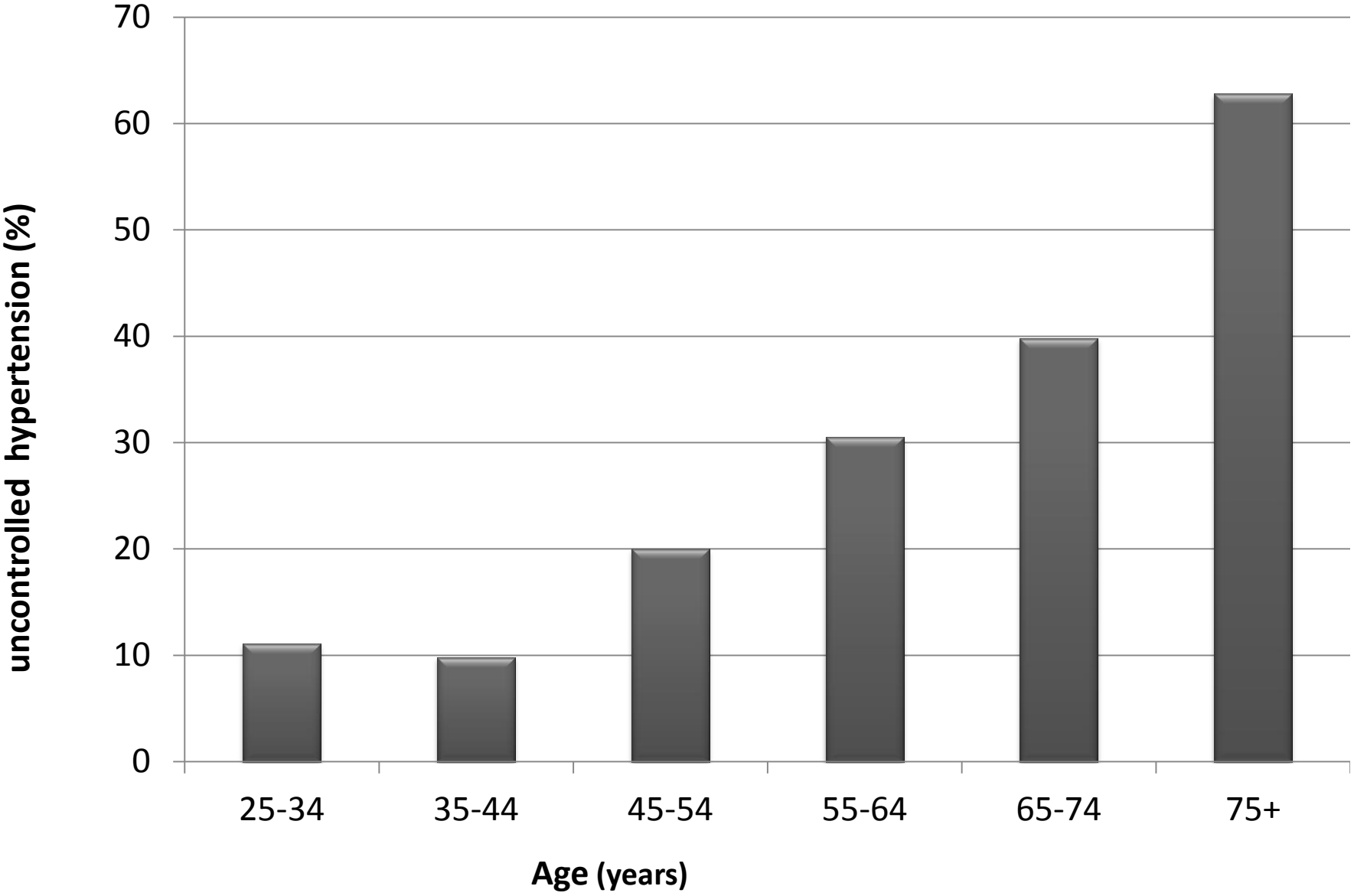
Panoulas et al: Rheumatology 2007; 46: 1477

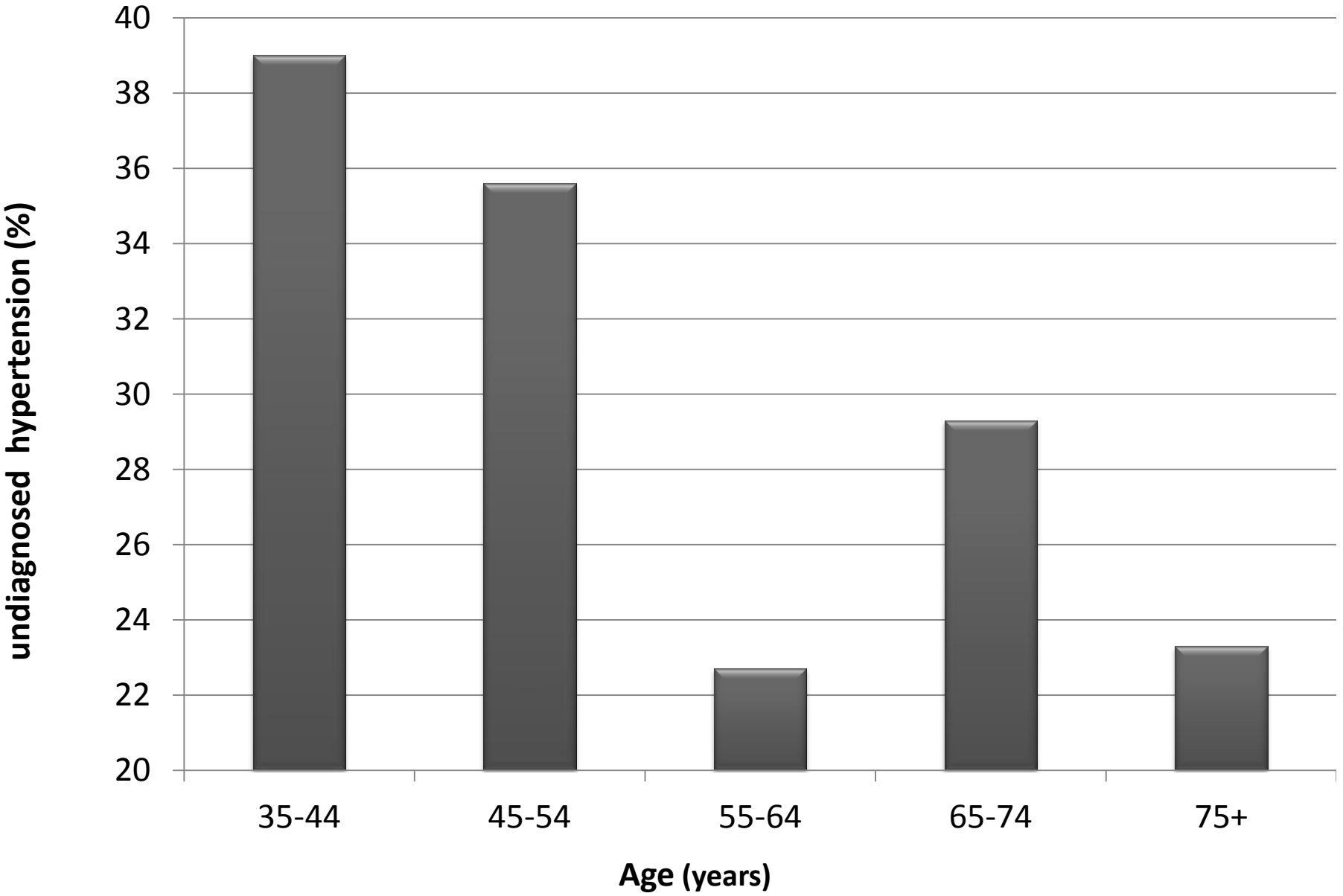
In RA patients hypertension associates with:





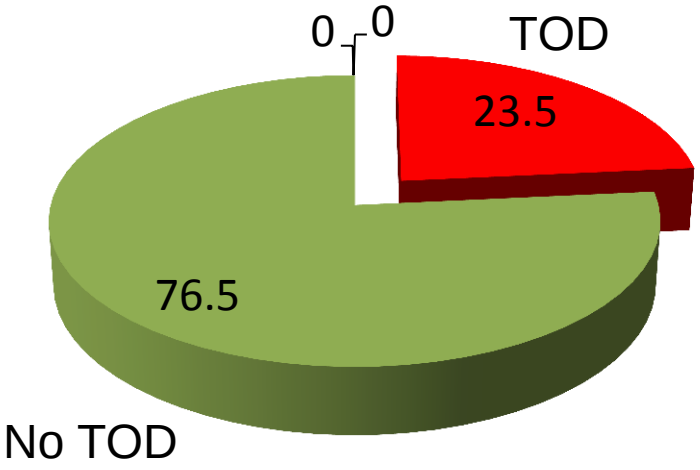



70
60
50
40
30
20
10
0
uncontrolled hypertension (%)
25-34
35-44
45-54
55-64
65-74
75+
Age (years)

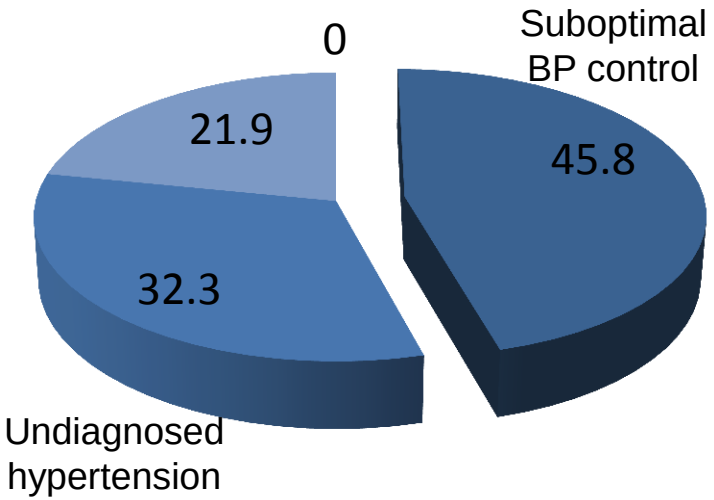

40
38
36
34
32
30
28
26
24
22
20
undiagnosed hypertension (%)
35-44
45-54
55-64
65-74
75+
Age (years)

Target organ damage in RA

Of the total RA population

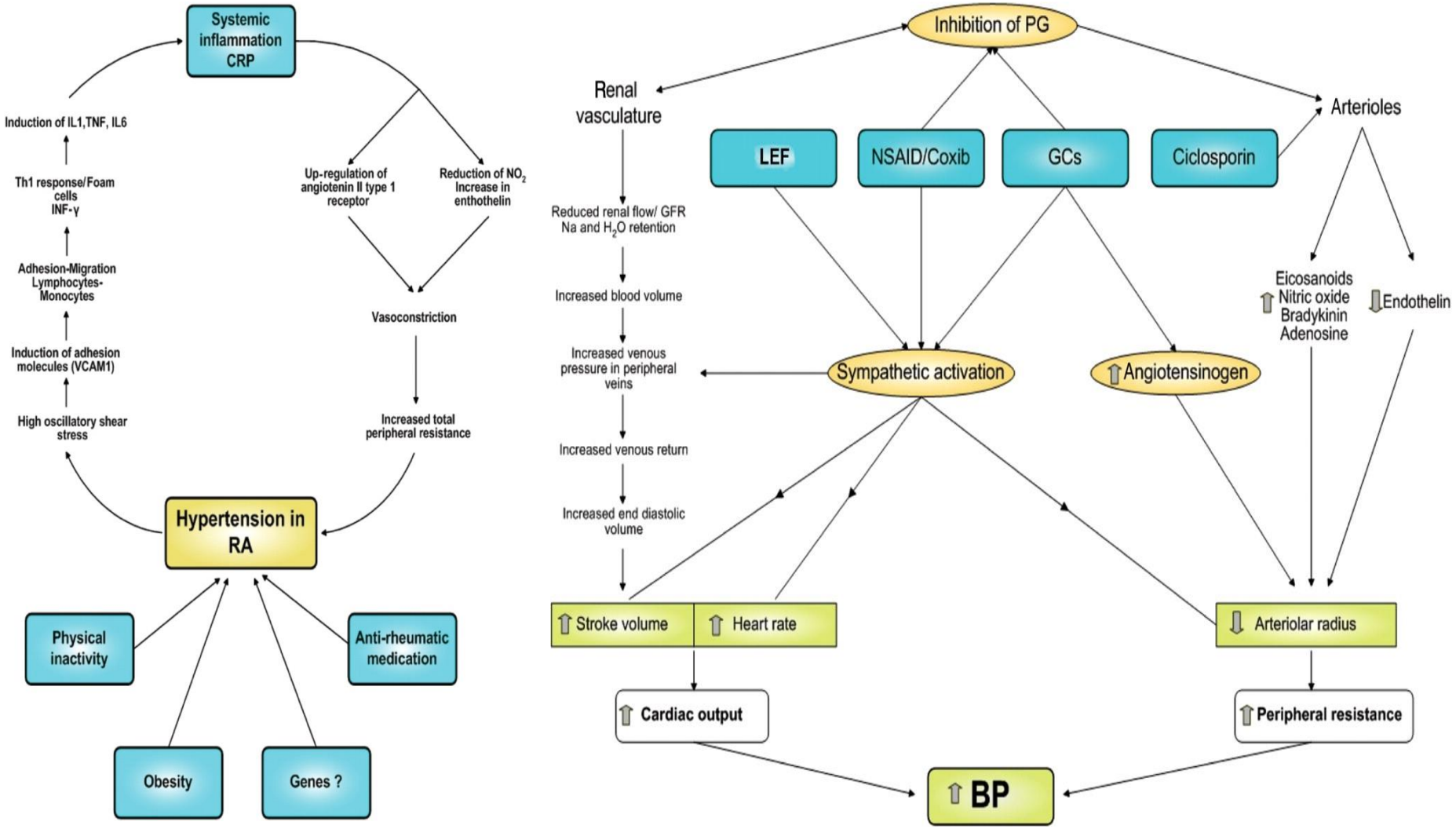


Of those with TOD



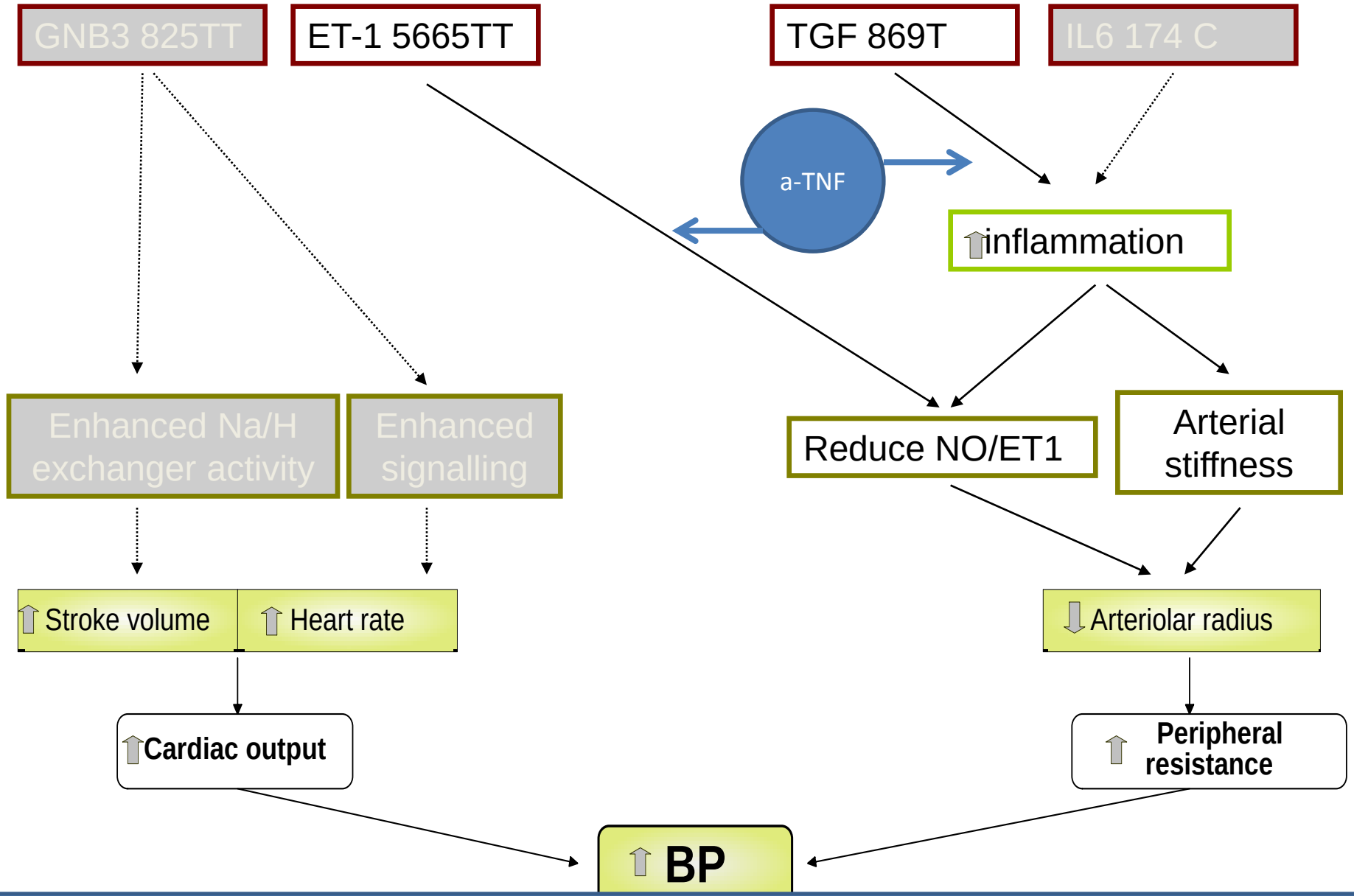
Panoulas VF et al. Target organ damage in patients with rheumatoid arthritis: the role of blood pressure and heart rate. *Atherosclerosis* 2010 Mar;209(1):255-60.

Mechanisms of hypertension in RA



Panoulas VF, et al. Hypertension in rheumatoid arthritis. *Rheumatology* 2008;47(9):1286-98.

Genes, Inflammation and Hypertension in RA



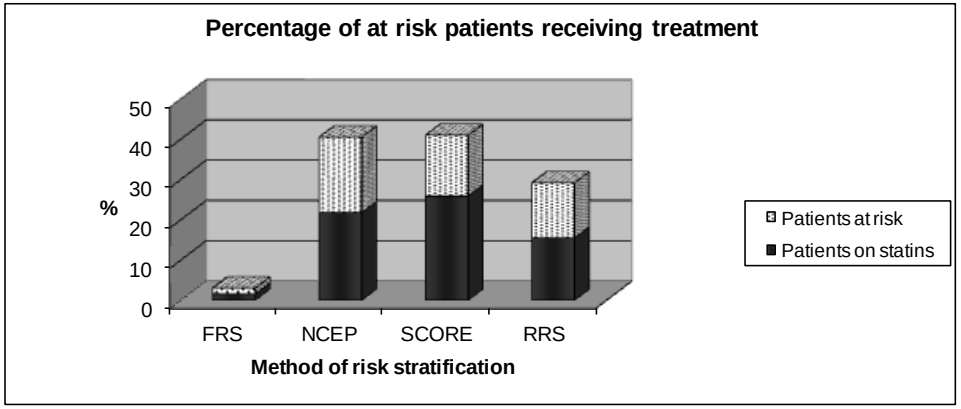
Dyslipidaemia in RA

Tracey Toms, MBBS, PhD, MRCP

- Toms et al. Apolipoprotein E gene polymorphisms are strong predictors of inflammation and dyslipidaemia in RA. J Rheum. 2012
- Toms et al. Dyslipidaemia in rheumatological autoimmune disease. Open Cardiovasc Med. 2011
- Toms et al. Rheumatoid arthritis susceptibility genes associate with lipid levels in patients with rheumatoid arthritis. Ann Rheum Dis. 2011
- Toms et al. Are lipid ratios less susceptible to change with systemic inflammation than individual lipid components in patients with rheumatoid arthritis? Angiology. 2011
- Toms et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: Evidence for substantial under treatment of lipid associated cardiovascular risk. Ann Rheum Dis. 2010
- Toms et al. Dyslipidaemia in rheumatoid arthritis: The role of inflammation, drugs, lifestyle and genetic factors. Curr Vasc Pharmacol. 2010
- Toms et al. Prevalence of risk factors for statin induced myopathy in rheumatoid arthritis patients. Musculosketelal Care. 2010
- Toms et al. Methotrexate therapy associates with a reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60 – more than just an anti-inflammatory effects? A cross sectional study. Arthritis Res Ther. 2009
- Toms et al. Lack of association between glucocorticoid use and the presence of the metabolic syndrome in patients with rheumatoid arthritis: A cross sectional study. Arthritis Res Ther. 2008

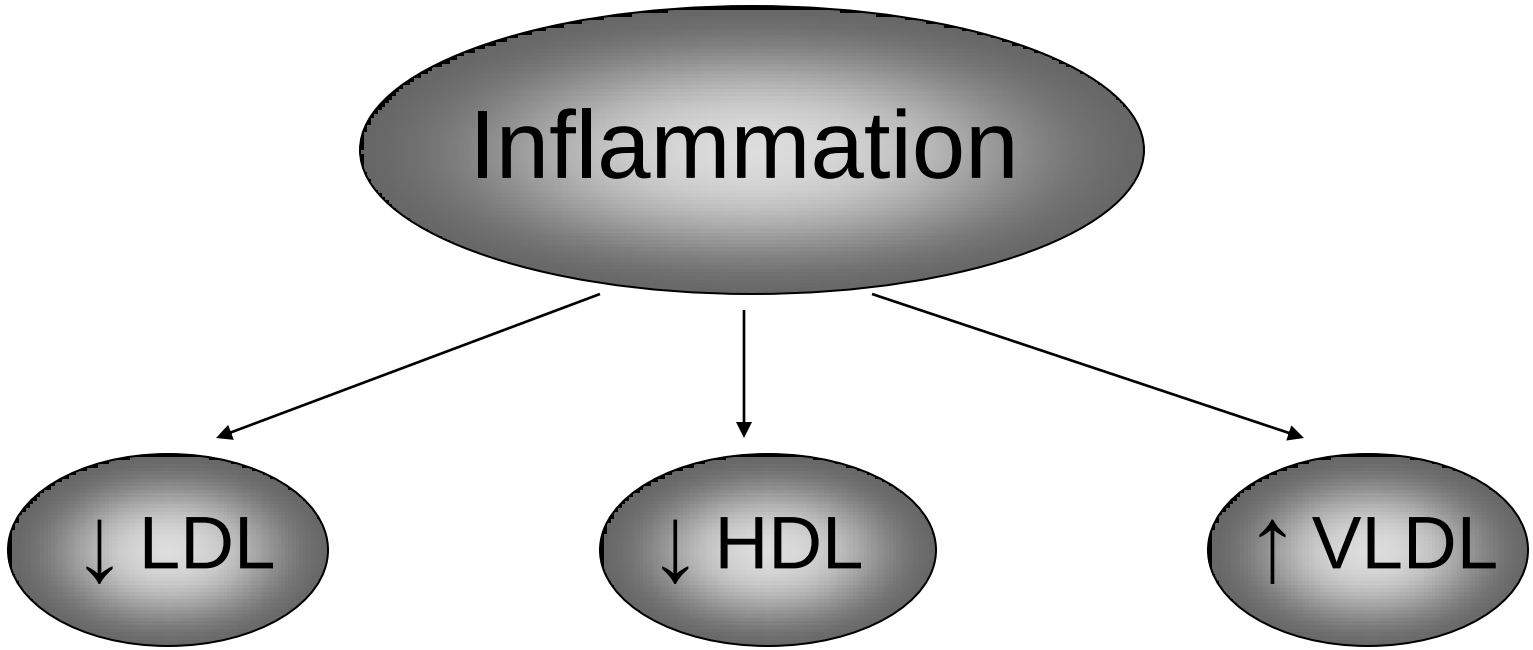
Prevalence of NCEP defined dyslipidaemia and the CVD risk this confers:

Prevalence = 56.8%



Independent predictors of NCEP defined dyslipidaemia:

↑ Likelihood	DYSLIPIDAEMIA	↓ Likelihood
Female		HCQ
Prednisolone		CRP
Older age		



↑ Small dense particles

↑ PAF-AH activity

↑ sPLA2

↑ sphingolipid content

↑ ceruloplasmin & SAA

↑ sPLA2

↑ PAF-AH activity

↓ enzyme activity

(HL,LCAT, PLTP, CETP)

↓ enzyme activity

(HL, LPL)

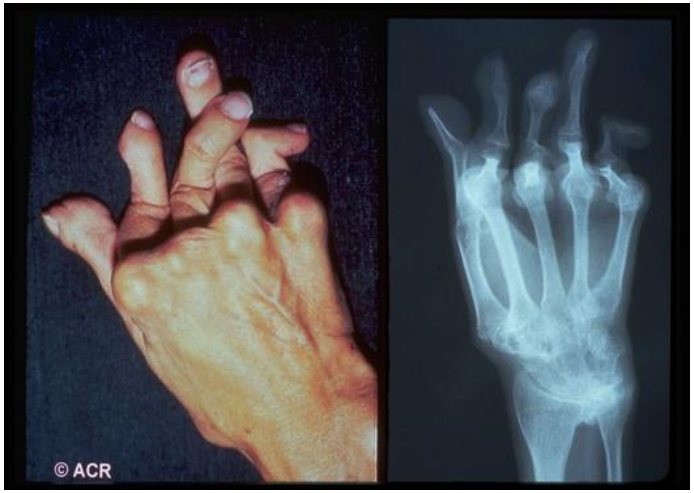
↑ sphingolipid content

Toms T et al: Curr Vasc Pharmacol 2010; 8: 301

Toms T et al: RA susceptibility genes associate with dyslipidaemia in RA. ARD 2011

RA susceptibility/severity genes

?



Lipid metabolism genes

Toms T et al: RA susceptibility genes associate with dyslipidaemia in RA. ARD 2011

ARTHRITIS & RHEUMATISM
Vol. 65, No. 8, August 2013, pp 2015–2023
DOI 10.1002/art.38021

The Impact of Inflammation on Metabolomic Profiles in Patients With Arthritis

Stephen P. Young,[1] Sabrina R. Kapoor,[2] Mark R. Viant,[1] Jonathan J. Byrne,[1] Andrew Filer,[3] Christopher D. Buckley,[2] George D. Kitas,[4] and Karim Raza[2]

Objective. **Inflammatory arthritis is associated with systemic manifestations including alterations in metabolism. We used nuclear magnetic resonance (NMR) spectroscopy–based metabolomics to assess metabolic fingerprints in serum from patients with established rheumatoid arthritis (RA) and those with early arthritis.**

Methods. **Serum samples were collected from newly presenting patients with established RA who were naive for disease-modifying antirheumatic drugs, matched healthy controls, and 2 groups of patients with synovitis of ≤3 months' duration whose outcomes were determined at clinical followup. Serum metabolomic profiles were assessed using 1-dimensional ^{1}H-NMR spectroscopy. Discriminating metabolites were identified, and the relationships between metabolomic profiles and clinical variables including outcomes were examined.**

Results. **The serum metabolic fingerprint in established RA was clearly distinct from that of healthy controls. In early arthritis, we were able to stratify the patients according to the level of current inflammation, with C-reactive protein correlating with metabolic differences in 2 separate groups ($P < 0.001$). Lactate and lipids were important discriminators of inflammatory burden in both early arthritis patient groups. The sensitivities and specificities of models to predict the development of either RA or persistent arthritis in patients with early arthritis were low.**

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. The identification of metabolic alterations may provide insights into disease mechanisms operating in patients with inflammatory arthritis.**

The etiology of rheumatoid arthritis (RA) is not fully understood but involves both genetic and environmental factors. In addition to synovitis, there are widespread systemic effects mediated by proinflammatory cytokines that impact on metabolism. Tumor necrosis factor α, interleukin-1 (IL-1), and IL-6 all promote

Dr. Kapoor's work was supported by an Arthritis Research UK Clinical PhD Studentship (grant 18552). The nuclear magnetic resonance data were acquired at the Henry Wellcome Building for Biomolecular Nuclear Magnetic Resonance Spectroscopy at the University of Birmingham; the facility is funded by the Wellcome Trust (grant 066490/Z/01/A).

[1]Stephen P. Young, PhD, Mark R. Viant, PhD, Jonathan J. Byrne, PhD: University of Birmingham, Birmingham, UK; [2]Sabrina R. Kapoor, MBChB, MSc, MRCP, Christopher D. Buckley, MBBS, FRCP, DPhil, Karim Raza, BMBCh, FRCP, PhD: University of Birmingham and the Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK; [3]Andrew Filer, MD, MRCP, PhD: University of Birmingham and the University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [4]George D. Kitas, MD, FRCP, PhD: University of Birmingham and the Dudley Group of Hospitals NHS Foundation Trust, Birmingham, UK.

Drs. Young and Kapoor contributed equally to this work.

Dr. Kitas has received consulting fees from AstraZeneca (less than $10,000) and speaking fees and/or honoraria for Advisory Board service from Roche, Abbott, Pfizer, Novartis, UCB, and Bristol-Myers Squibb (less than $10,000 each) and has received unrestricted grants from Pfizer.

Lipid metabolites “low” in very early, active or persistent inflammatory arthritis…

Table 2. Metabolites contributing to the differentiation between groups, determined by analysis of PLS-DA weightings*

Metabolite, ppm	RA patients versus controls	Patients with early arthritis before versus after resolution of inflammation	Patients with persistent arthritis versus patients with resolving arthritis (group 1)	Patients with persistent arthritis versus patients with resolving arthritis (group 2)	Patients with persistent RA versus patients with resolving arthritis (group 1)	Patients with persistent RA versus patients with resolving arthritis (group 2)
LDL-CH3, 0.80	Low (6.30)	Low (3.03)	Low (6.81)	Low (2.87)	–	–
LDL-CH2, 1.21	Low (7.06)	Low (31.81)	Low (7.40)	Low (6.89)	–	Low (1.58)
3-hydroxybutyrate, 1.18, 1.19	High (4.21)	High (7.90)	–	High (6.87)	–	–
Lactate, 1.31, 4.11	High (54.51)	–	Low (12.85)	High (27.90)	Low (12.74)	High (16.98)
Alanine, 1.46, 1.48	Low (20.00)	Low (2.15)	–	–	–	Low (3.84)
Acetylglycine, 2.03	High (48.67)	High (17.41)	High (6.55)	High (6.80)	High (4.57)	Low (1.94)
Methylguanidine, 2.81	Low (10.17)	–	High (92.72)	Low (38.15)	High (34.76)	Low (6.51)
Taurine, 3.26	High (8.12)	High (9.11)	–	High (15.73)	–	High (8.66)
Glucose, 3.25, 3.88	High (16.8)	High (12.72)	–	High (11.55)	–	High (7.49)
Lipid, 5.32	Low (2.36)	Low (2.53)	–	–	–	–
Urea, 5.79	–	High (1.32)	High (3.90)	–	High (1.25)	–

*“High” indicates that the metabolite was at a higher concentration in the rheumatoid arthritis (RA; column 2), early arthritis before resolution (column 3), persistent arthritis (columns 4 and 5), or persistent RA (columns 6 and 7) phenotypes. Nuclear magnetic resonance chemical shifts (in parts per million), which identify the location of the major peaks in the spectra, are shown for each metabolite. Values in parentheses are the variable importance of the projection for each metabolite. PLS-DA = partial least-squares discriminant analysis; LDL-CH3 = low-density lipoprotein CH3.

…and correlate with CRP…

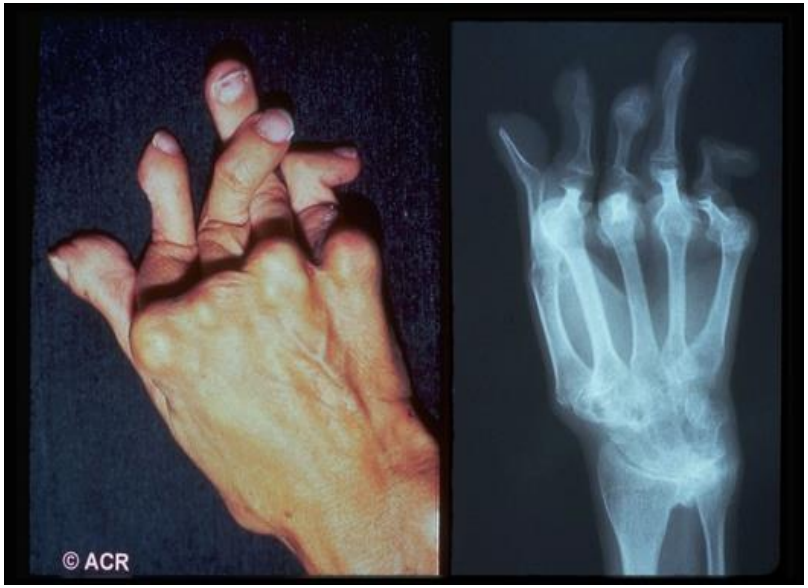
Table 3. Metabolites most strongly correlated with CRP level in patients with early arthritis in groups 1 and 2*

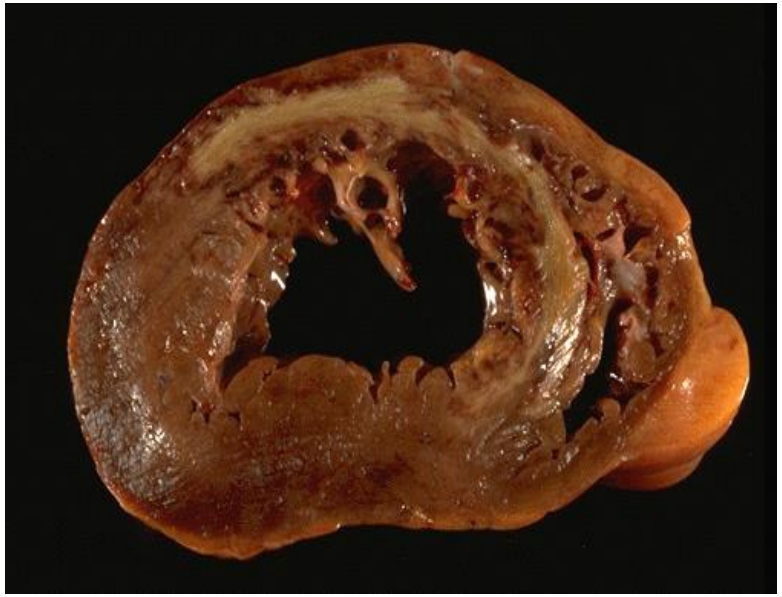
Ranked importance	Metabolites identified in patient group 1 (ppm)	Metabolites identified in patient group 2 (ppm)
1	Choline (3.20, 3.22, 3.23)	LDL lipids (1.24–1.27)
2	LDL lipids (1.24–1.27)	Acetylglycine (2.03, 3.71, 3.76)
3	Lactate (1.31, 1.33, 4.11)	Glucose (3.24–3.26, 3.41, 3.48, 3.68–3.69, 3.88)
4	Acetylglycine (2.03, 3.71, 3.76)	Fatty acids (0.8–0.84, 2.22–2.24)
5	Urea (5.77, 5.78, 5.79, 5.80, 5.81, 5.82)	Methylguanidine (2.81)
6	Glucose (3.24–3.26, 3.41, 3.48, 3.68–3.69, 3.88)	Lactate (1.31, 1.33)
7	Methylguanidine (2.81)	Threonine (3.58)
8	Methylhistidine (3.70)	Homocysteine (3.86)
9	Cholesterol (0.91)	Glycine (3.55)
10	Taurine (3.42)	Taurine (3.42)
11	Threonine (3.58)	Methylxanthine (3.49)
12	Fatty acids (0.8–0.84, 2.22–2.24)	Choline (3.20, 3.22, 3.23)
13	Methylxanthine (3.49)	Methylhistidine (3.70)
14	Homocysteine (3.86)	Cholesterol (0.91)

* Metabolites were identified using the partial least-squares regression analysis model and represent the regions of the spectra which had the greatest influence on the correlation with C-reactive protein (CRP) level. Values in parentheses are the nuclear magnetic resonance chemical shifts (in parts per million), which identify the location of the major peaks in the spectra. LDL = low-density lipoprotein.

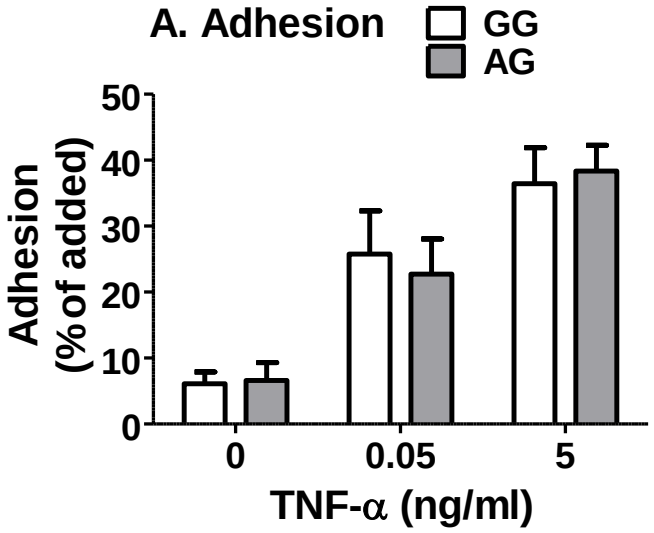
Young et al, A&R 2013

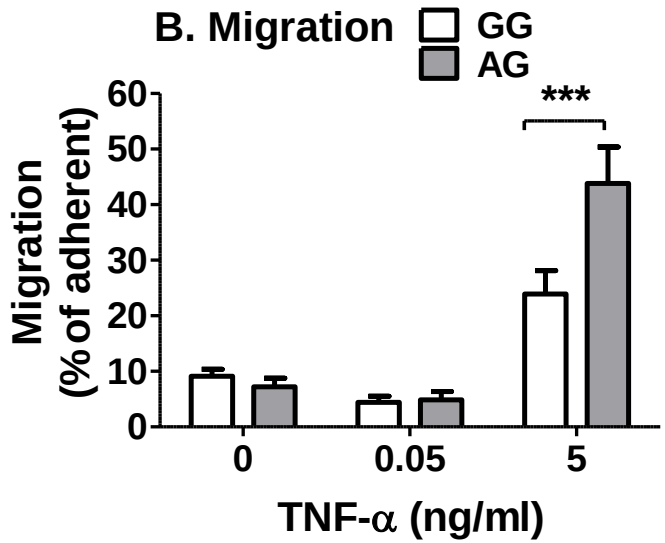
…which correlates with damage / adverse outcome



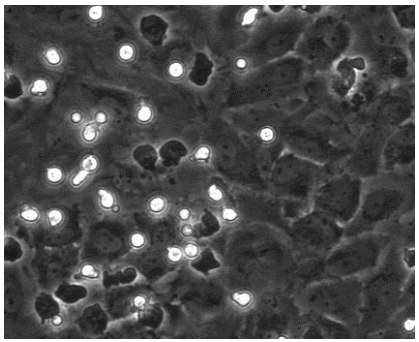


PTPN22 R620W enhances neutrophil activation and function in RA and controls

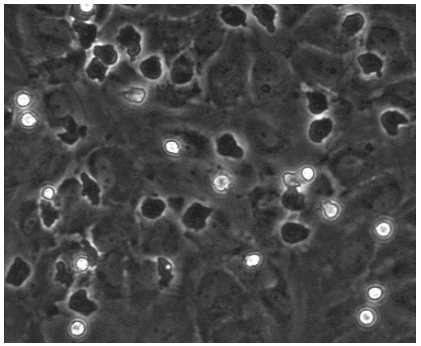


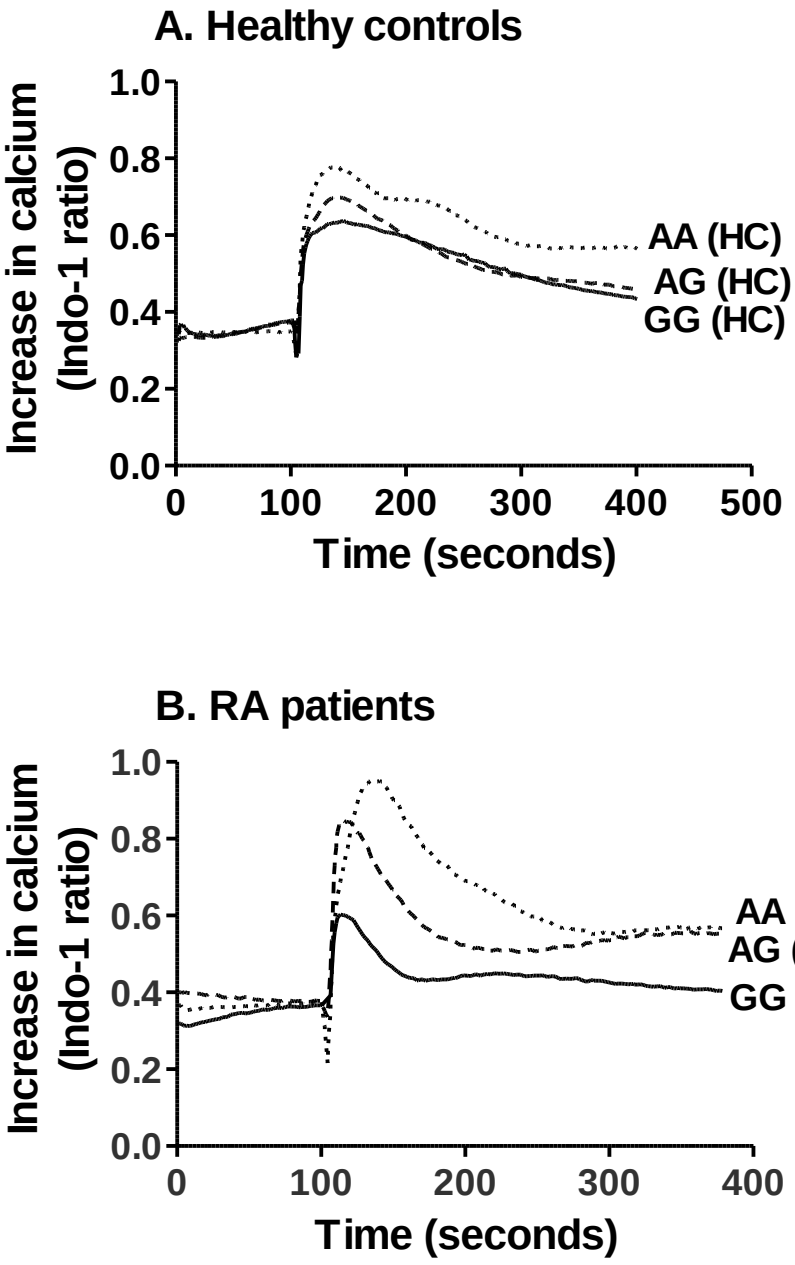


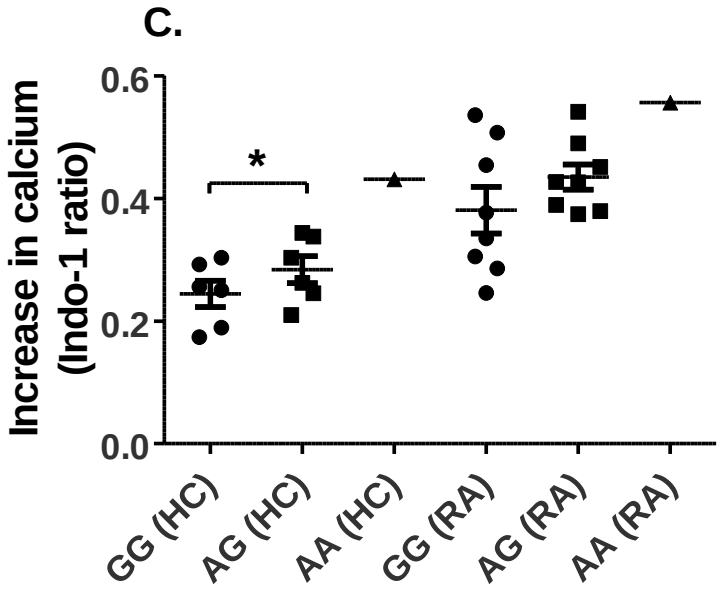
C. GG neutrophils



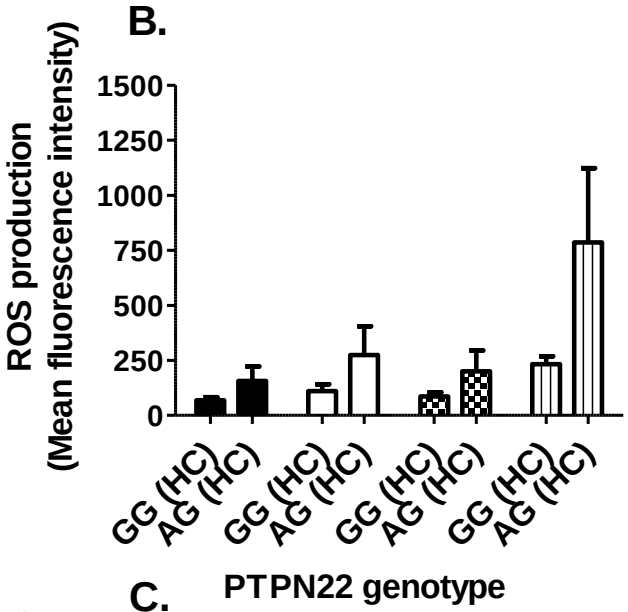
D. AG neutrophils

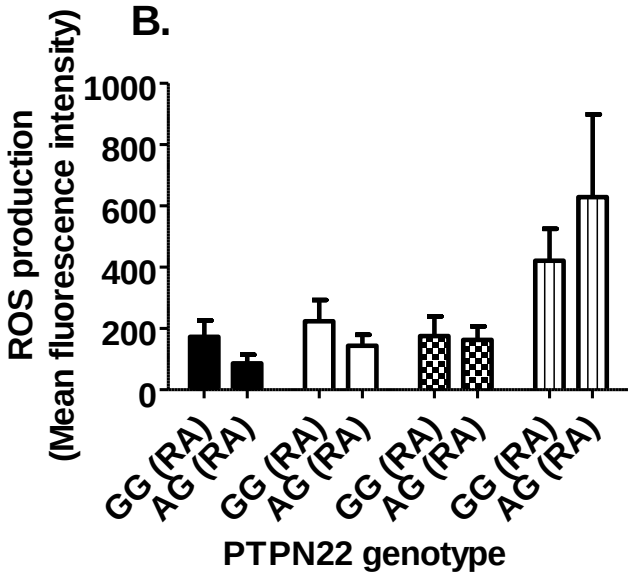


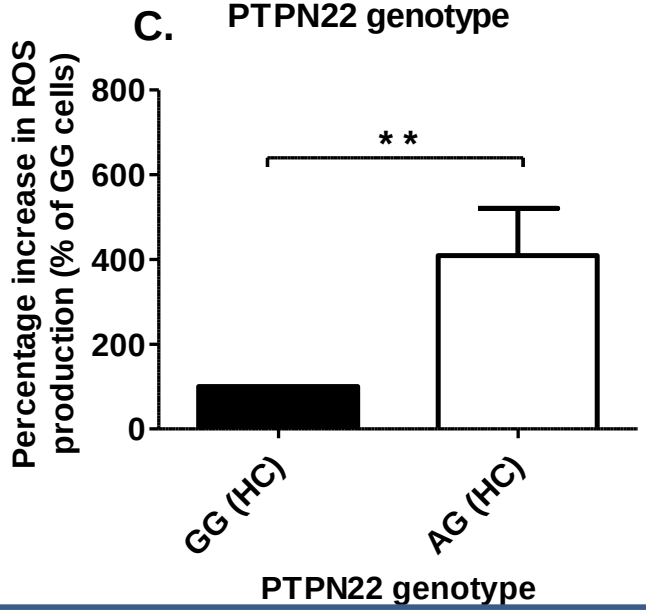

A. Healthy controls
Increase in calcium (Indo-1 ratio)
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
Time (seconds)
AA (HC)
AG (HC)
GG (HC)
B. RA patients
Increase in calcium (Indo-1 ratio)
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time (seconds)
AA (RA)
AG (RA)
GG (RA)

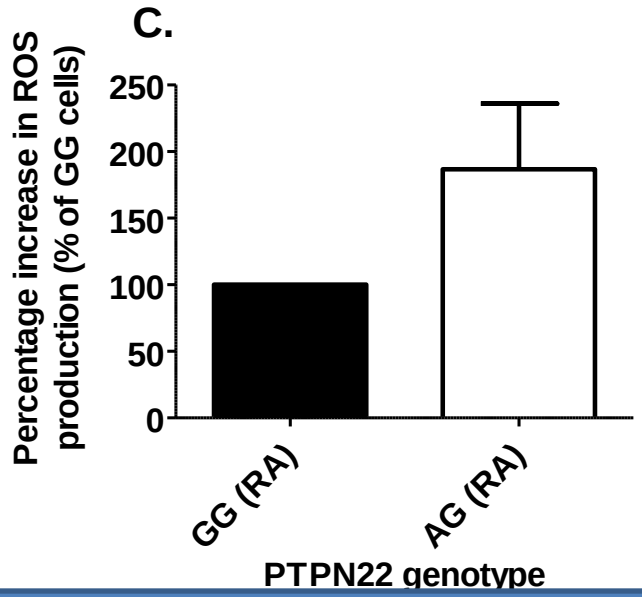

C.
Increase in calcium (Indo-1 ratio)
0.6
0.4
0.2
0.0
*
GG (HC)
AG (HC)
AA (HC)
GG (RA)
AG (RA)
AA (RA)

Heterozygosity for PTPN22 R620W enhances neutrophil ROS production from HC and RA patients after TNF-α priming.

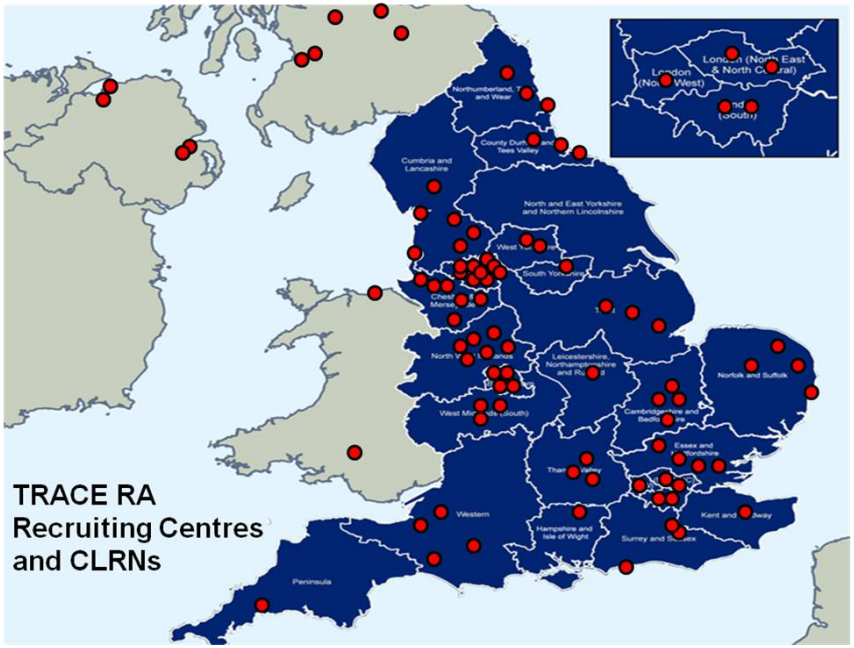








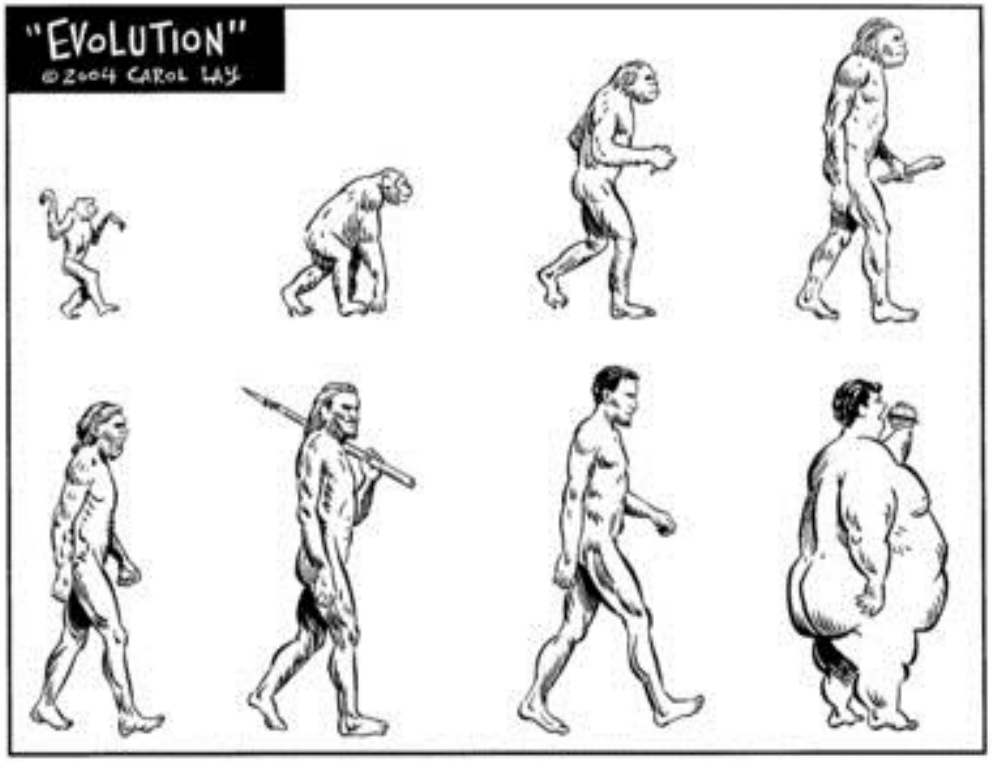
Bayley R et al; (submitted)



TRACE RA

TRial of **A**torvastatin for the primary prevention of **C**ardiovascular **E**vents in patients with **R**heumatoid **A**rthritis

Obesity in RA

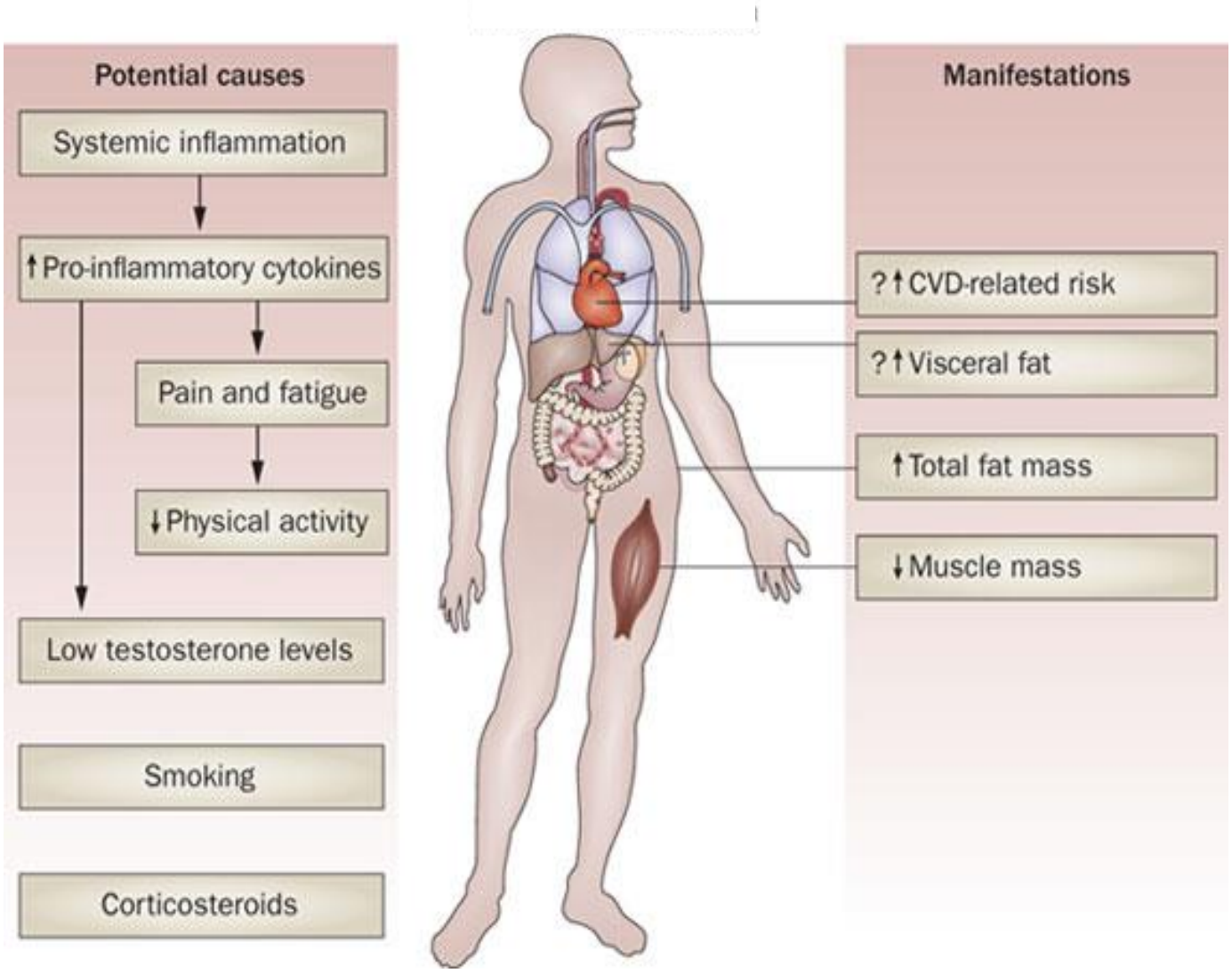


Reprinted from The Funny Times / PO Box 18530 / Cleveland Heights, OH 44118
phone: (216) 371-8600 / e-mail: ft@funnytimes.com

Stavropoulos-Kalinoglou et al

Metsios et al

Body composition - Rheumatoid cachexia



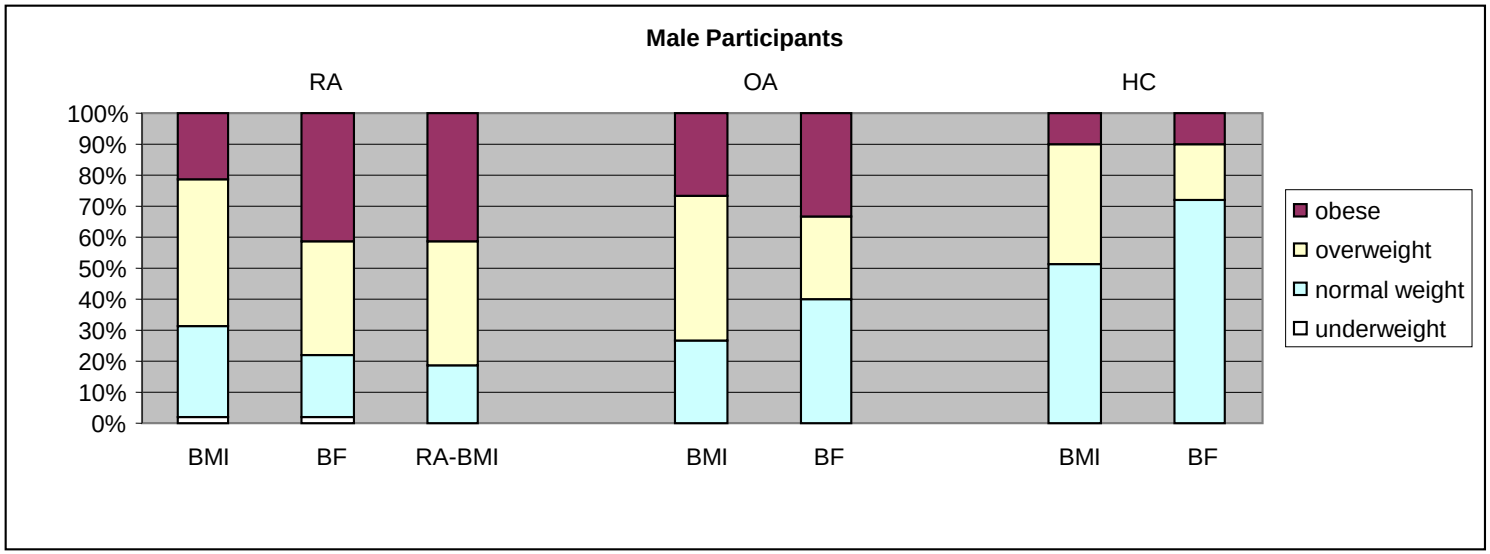
Summers et al: Nature Rev. Rheumatol. 2010

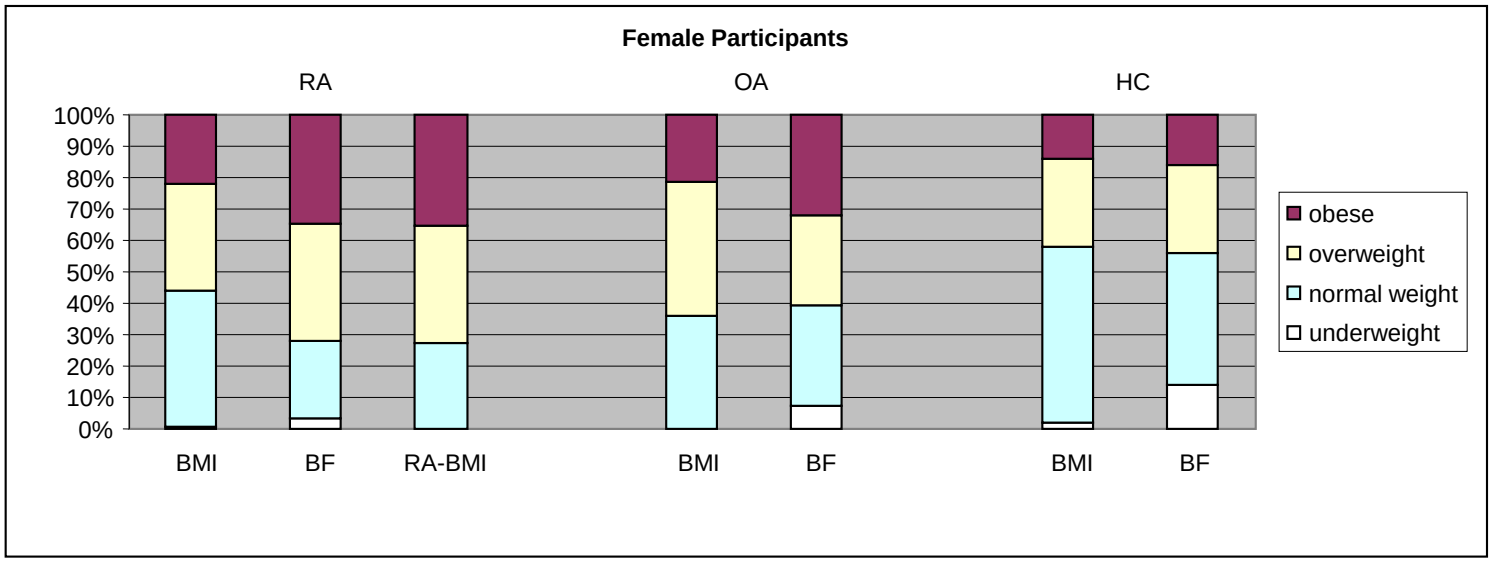
Cachexia and Obesity in RA: two sides of the same coin?

Antonios Stavropoulos-Kalinoglou, BSc, MSc, PhD

- Stavropoulos-Kalinoglou A, et al. *Anti-tumour necrosis factor alpha therapy improves insulin sensitivity in normal-weight but not in obese patients with rheumatoid arthritis.* Arthritis Res Ther. 2012
- Nevill AM, et al. *Inverted BMI rather than BMI is a better proxy for percentage of body fat.* Ann Hum Biol. 2011
- Stavropoulos-Kalinoglou A, et al. *Obesity in rheumatoid arthritis*. Rheumatology (Oxford). 2011
- Summers GD, et al. *Rheumatoid cachexia and cardiovascular disease*. Nat Rev Rheumatol. 2010
- Metsios GS, et al. *Rheumatoid cachexia and cardiovascular disease.* Clin Exp Rheumatol. 2009
- Stavropoulos-Kalinoglou A, et al. *What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation.* Int J Obes (Lond). 2010
- Stavropoulos-Kalinoglou A, et al. *Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis.* Clin Rheumatol. 2009
- Stavropoulos-Kalinoglou A, et al. *Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis.* Ann Rheum Dis. 2009
- Stavropoulos-Kalinoglou A, et al. *Cigarette smoking associates with body weight and muscle mass of patients with rheumatoid arthritis: a cross-sectional, observational study.* Arthritis Res Ther. 2008
- Metsios GS, et al. *New resting energy expenditure prediction equations for patients with rheumatoid arthritis.* Rheumatology (Oxford). 2008
- Metsios GS, et al. *Blockade of tumour necrosis factor-alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia.* Rheumatology (Oxford). 2007
- Metsios GS, et al. *Cigarette smoking significantly increases basal metabolic rate in patients with rheumatoid arthritis.* Ann Rheum Dis. 2008
- Stavropoulos-Kalinoglou A, et al. *Redefining overweight and obesity in rheumatoid arthritis patients.* Ann Rheum Dis. 2007

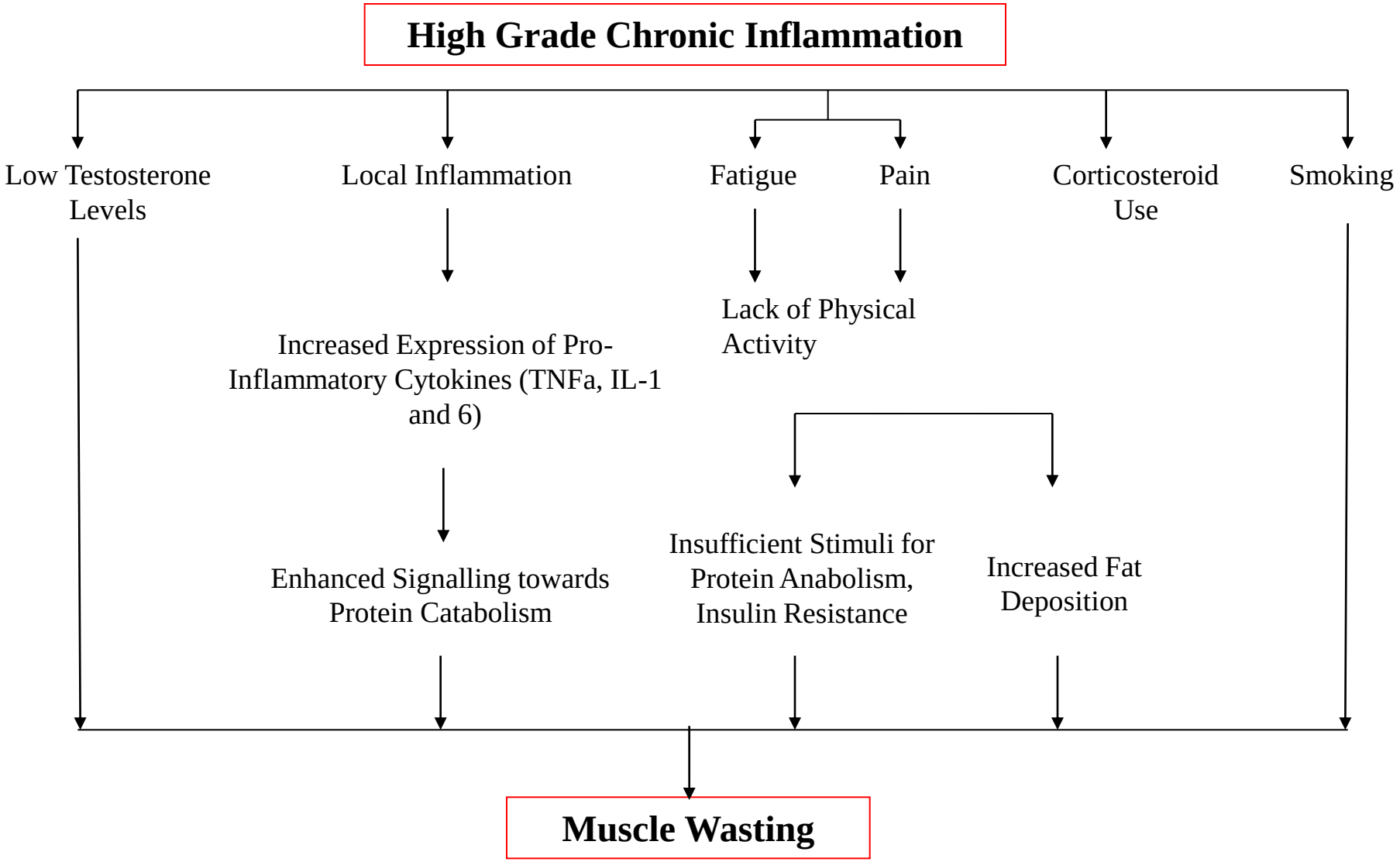
Standard BMI thresholds misclassify “fatness” in RA patients





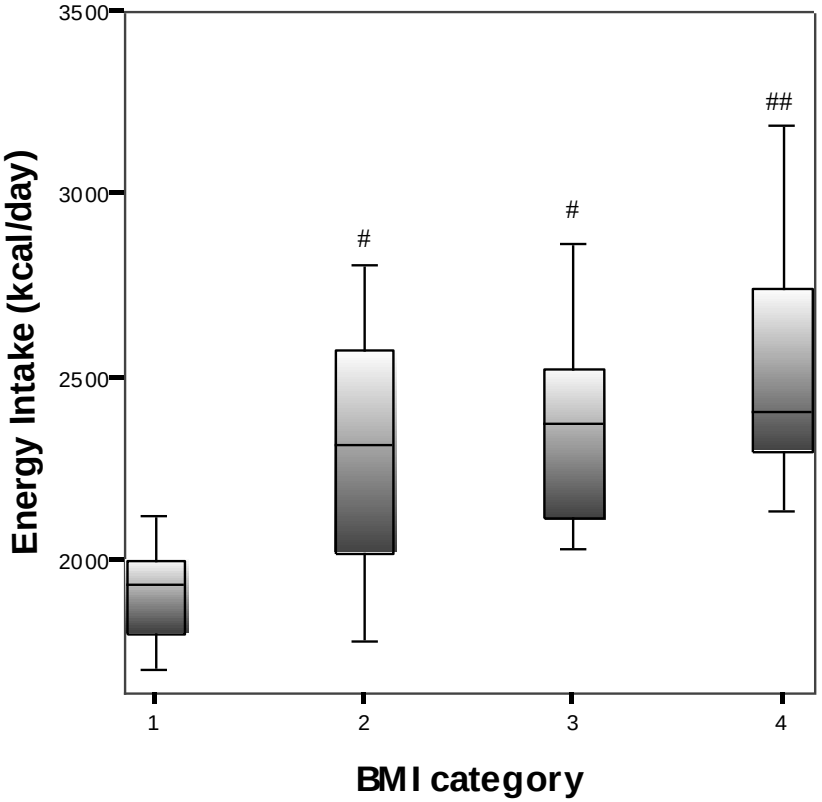
Stavropoulos-Kalinoglou et al: ARD 2007; 66: 1316

Possible mechanisms of muscle wasting in RA

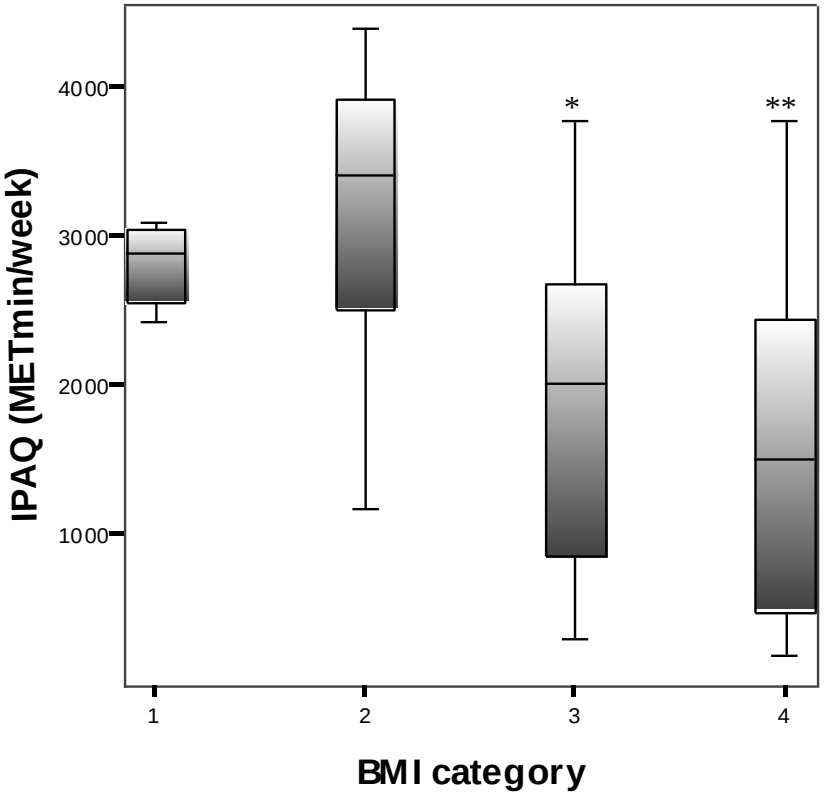


Conventional factors affecting BC in RA

Poor nutrition may drive underweight/ muscle wasting



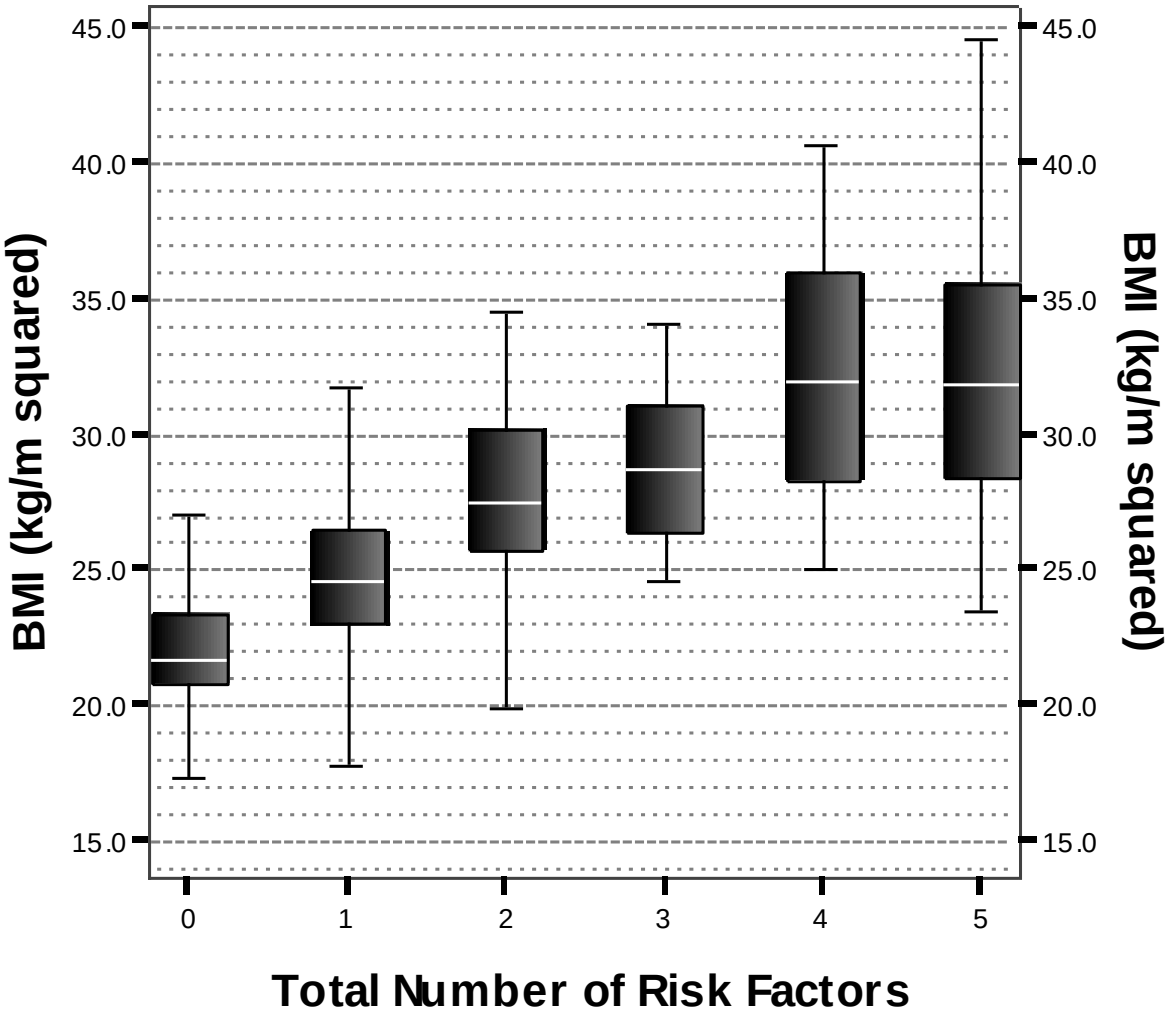
Low levels of physical activity may drive obesity



Scope for Nutritional Planning?

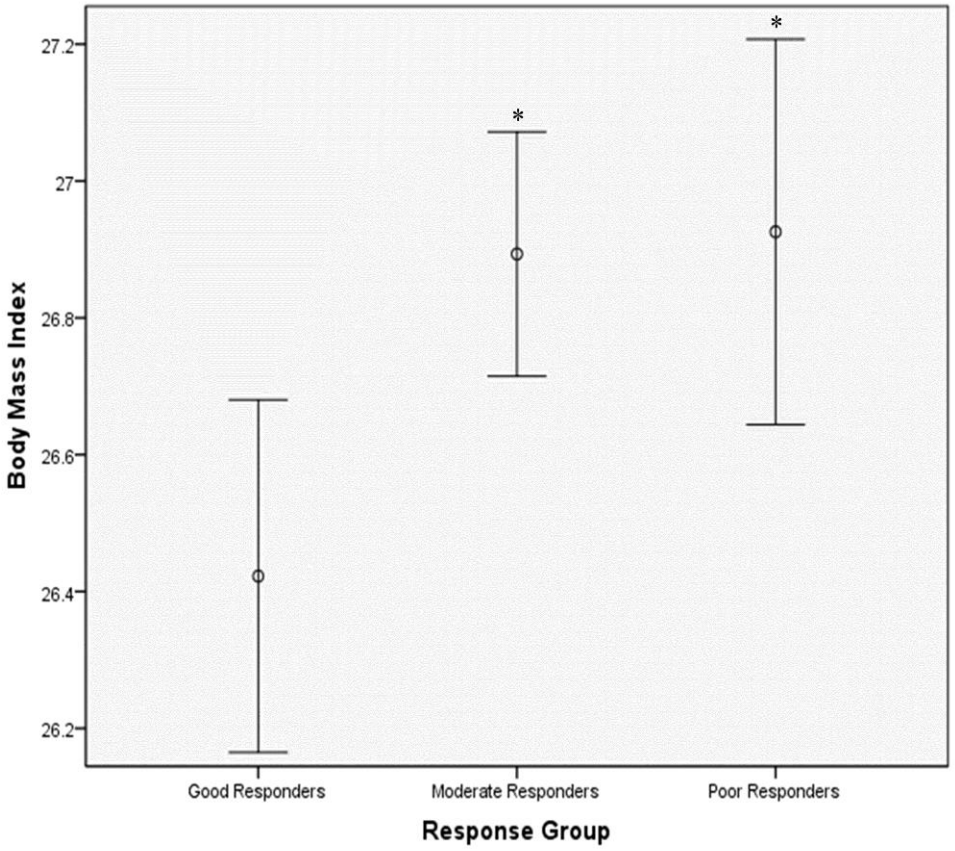
BMR calculation re-adjustment!

Impact of obesity on CVD risk



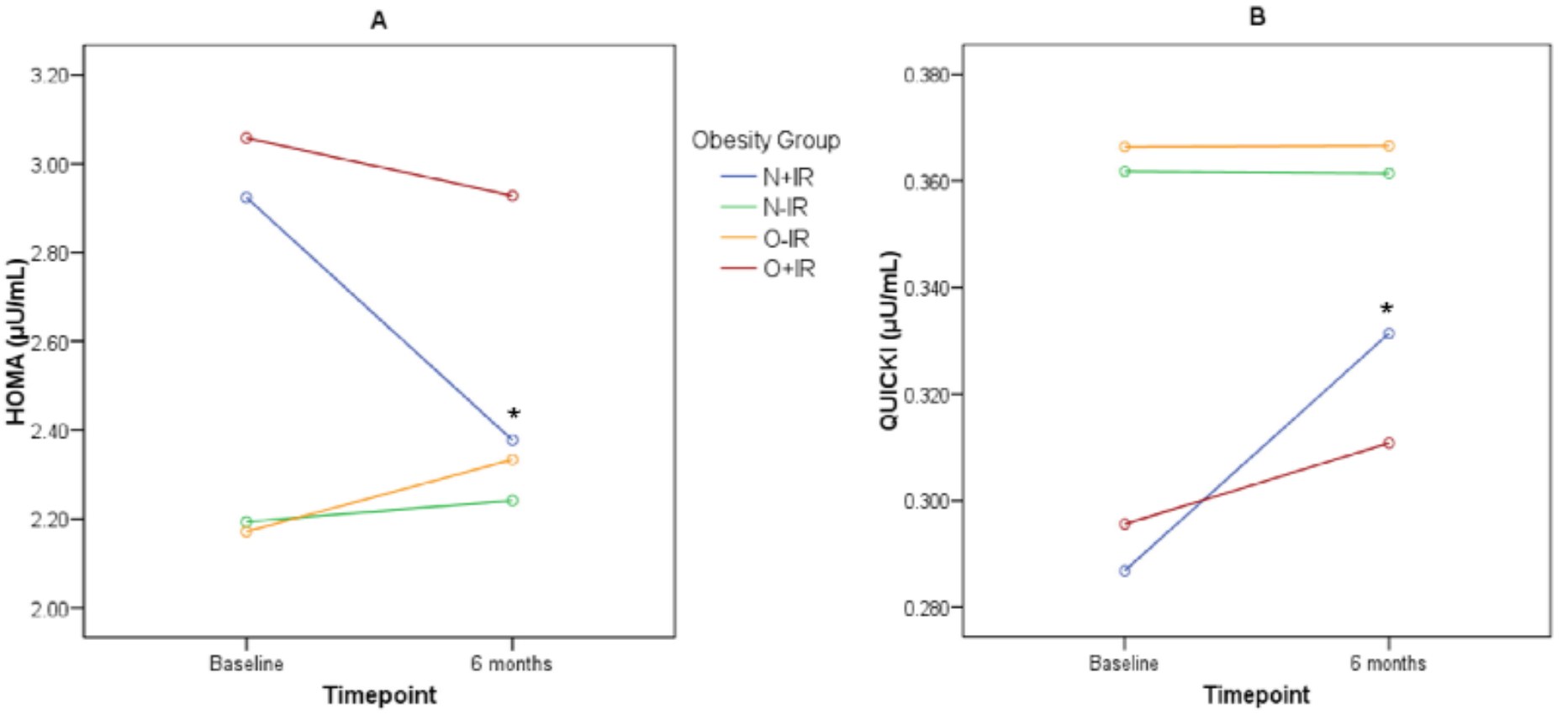
Obesity affects treatment response…

Patients with lower BMI respond better to anti-TNFα treatment than patients with higher BMI



…and reduces additional benefits of treatment

Insulin sensitivity increases in normal-weight but not in obese RA patients treated with anti-TNFα for 6-months



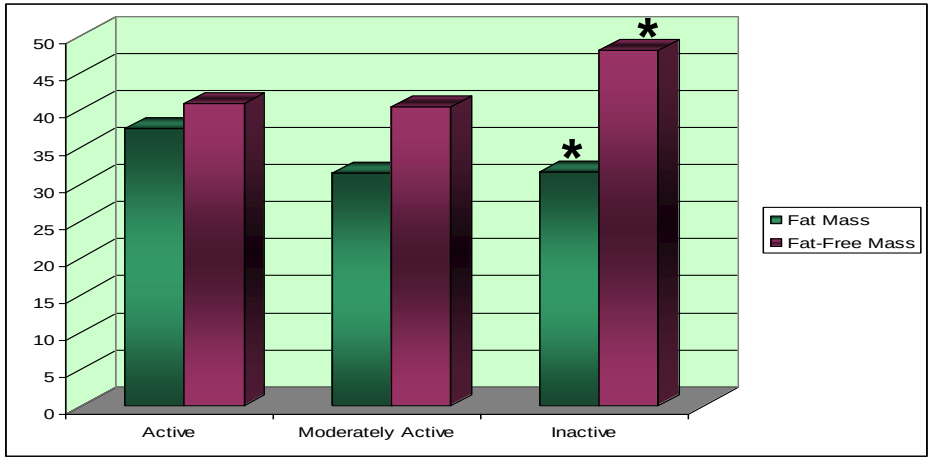
Physical Activity and RA

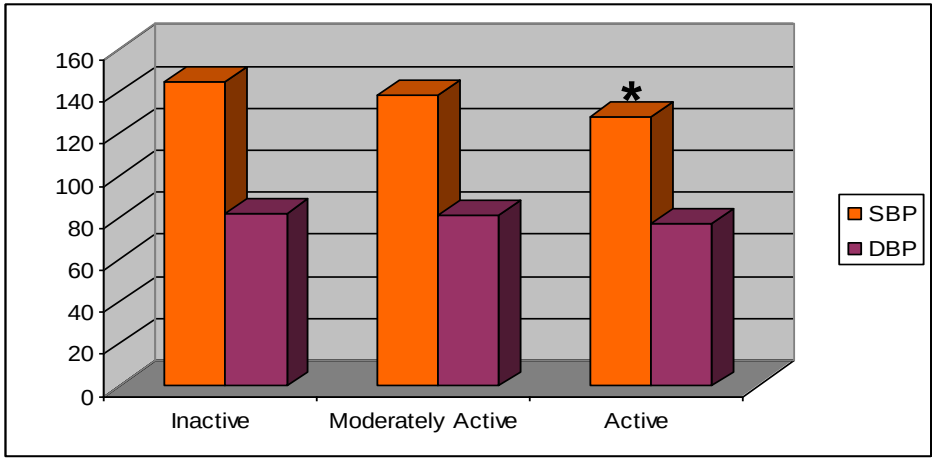
George Metsios, MSc, PhD
Reader in Clinical Exercise Physiology

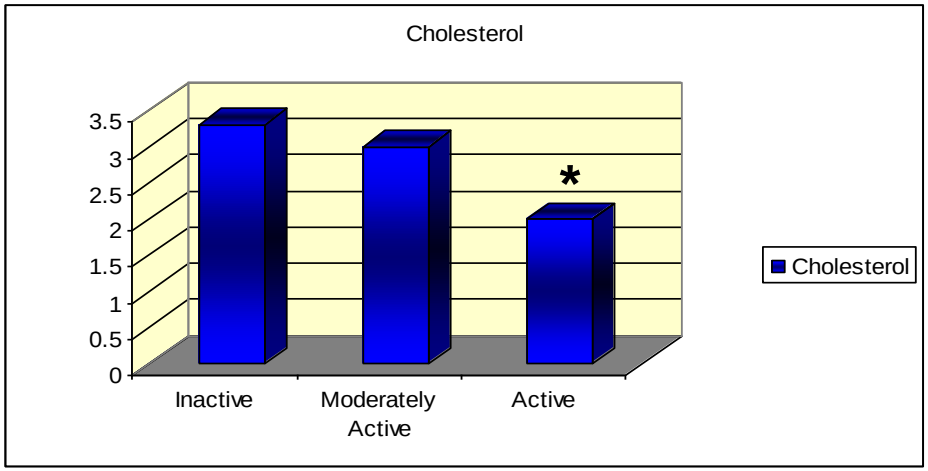
1. Metsios et al. (2008). Rheumatoid Arthritis, Cardiovascular Disease and Physical Exercise: A Systematic Review. Rheumatology, 47(3):239-48
2. Metsios et al. (2009). Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. European Journal of Cardiovascular Prevention and Rehabilitation, 16(2):188-94
3. Stavropoulos-Kalinoglou et al. (2010). What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. International Journal of Obesity, 34(2):295-301
4. Metsios et al. (2010). Vascular Function and Inflammation in Rheumatoid Arthritis: The Role of Physical Activity. Invited Review. The Open Cardiovascular Medicine Journal, 23;4:89-96.
5. Metsios GS, et al. (2011). Disease activity and low physical activity associate with number of hospital admissions and length of hospitalisation in patients with rheumatoid arthritis. Arthritis Res Ther. 2011 Jun 29;13(3):R108.
6. Stavropoulos-Kalinoglou et al. (2012) Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis. doi:10.1136/annrheumdis-2012-202075
7. Metsios et al. (2013). Indvidualised exercise improves endothelial function in patients with rheumatoid arthritis. Ann Rheum Dis. 2013 Jul 31. doi: 10.1136/annrheumdis-2013-203291 (in press)

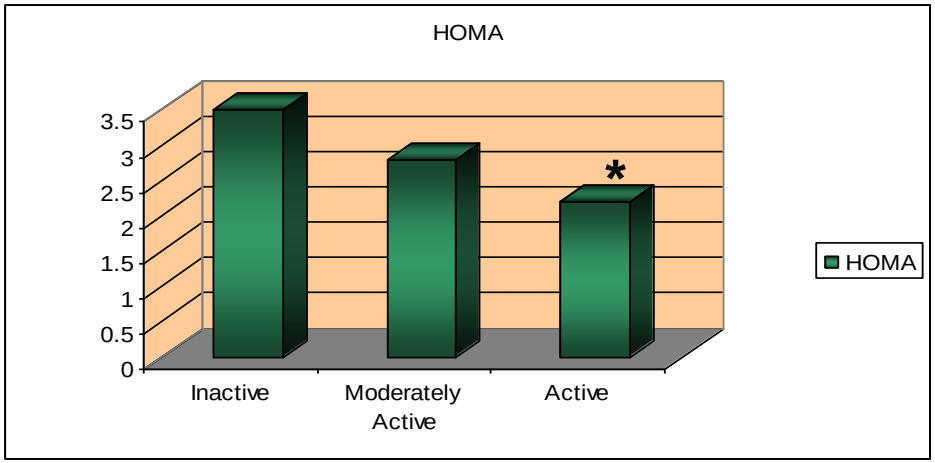
Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis.

European Journal of Cardiovascular Prevention and Rehabilitation, 16(2):188-94







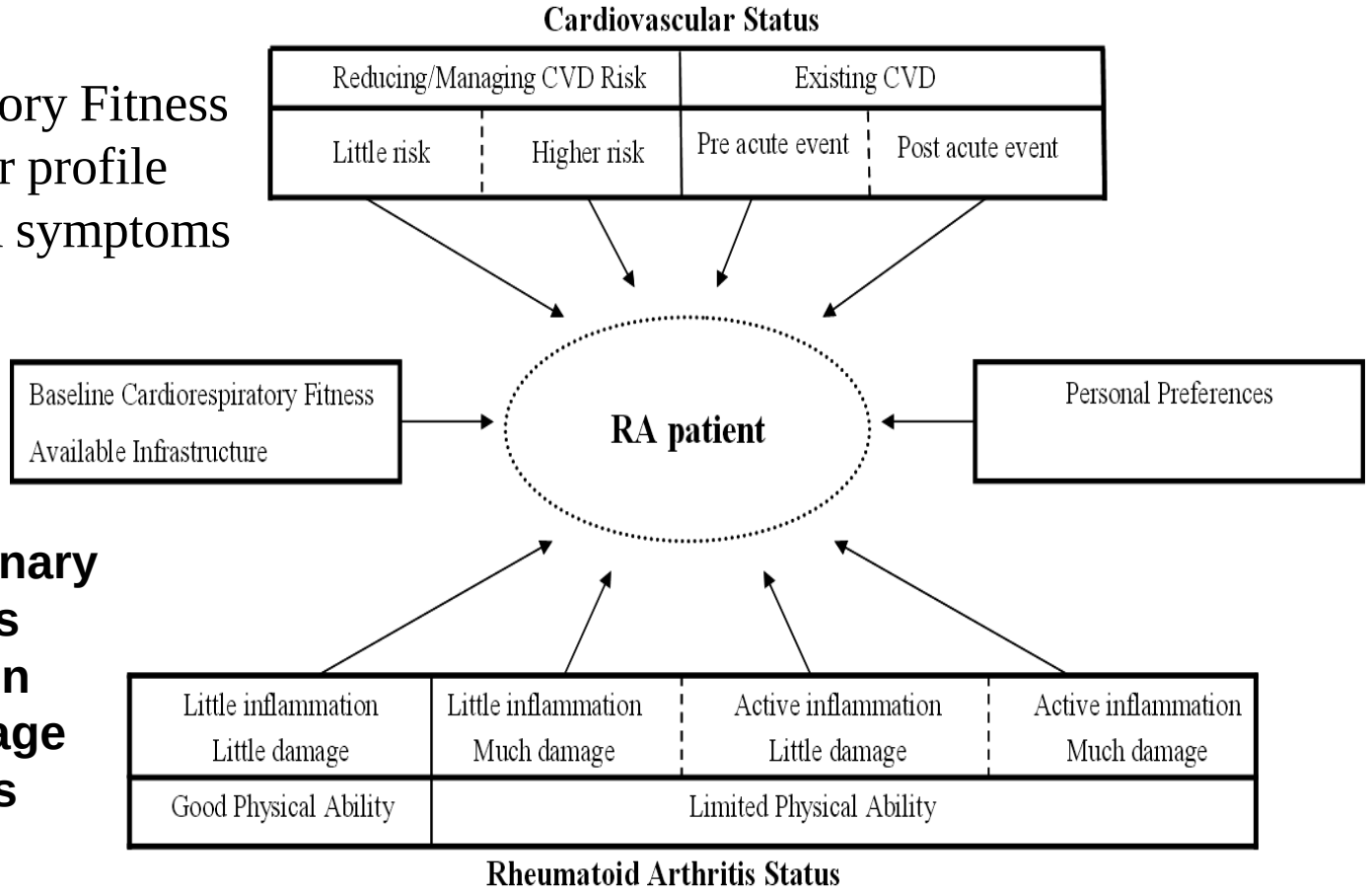


CRP significantly higher in physically inactive patients

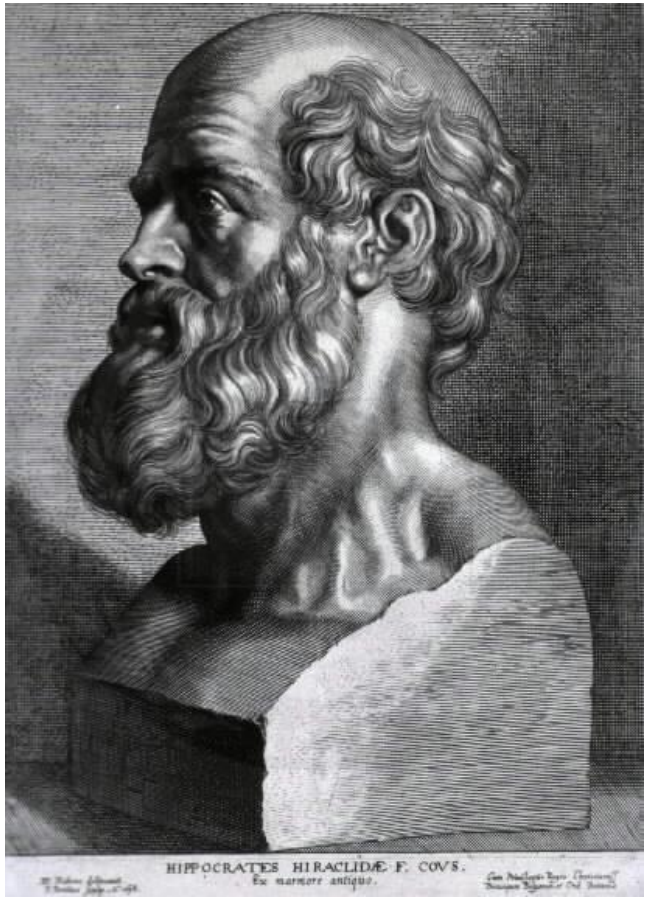
Summary – Physical Inactivity in RA

- RA patients have much lower than the recommended levels of physical activity
- However, they CAN and SHOULD exercise with the following benefits:

↑ Cardio-respiratory Fitness
↑ Cardio-vascular profile
↓ Disease-related symptoms



A multidisciplinary approach is necessary in order to engage RA patients



If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.

Eating alone will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health.

Regimen, in *Hippocrates*, trans. W. H. S. Jones (1931), Vol. 4, 229

Dr Holly John, MB, PhD, FRCP

Patient Education on Cardiovascular Disease in Rheumatoid Arthritis

1. John H, Hale ED, Treharne GJ, Kitas GD. Patient education on cardiovascular aspects of rheumatoid disease: An unmet need. Rheumatology 2007; 46: 1513-1516.

2. John H, Kitas G, Toms T, Goodson N. Cardiovascular Co-morbidity in Early Rheumatoid Arthritis. Best Pract Res Clin Rheumatol 2009; 23: 71-82.

3. John H, Hale ED, Treharne GJ, Carroll D, Kitas GD. "All singing from the same hymn sheet": Health professionals' perceptions of developing patient education material about the cardiovascular aspects of rheumatoid arthritis. Musculoskeletal Care 2009; 7: 258-71.

4. John H, Hale ED, Treharne GJ, Carroll D, Kitas GD. "Extra information a bit further down the line": Rheumatoid arthritis patients' perceptions of developing educational material about the cardiovascular disease risk. Musculoskeletal Care 2009;7:272-87.

5. John H, Treharne GJ, Hale ED, Panoulas V, Carroll D, Kitas GD. Development and initial validation of a heart disease knowledge questionnaire for people with rheumatoid arthritis. Pt Educ Couns 2009; 77: 136-43.

6. John H, Hale ED, Bennett P, Treharne GJ, Carroll D, Kitas GD. Translating patient education theory into practice: developing material to address the cardiovascular education needs of people with rheumatoid arthritis. Pt Educ Couns 2011; 84: 123-7.

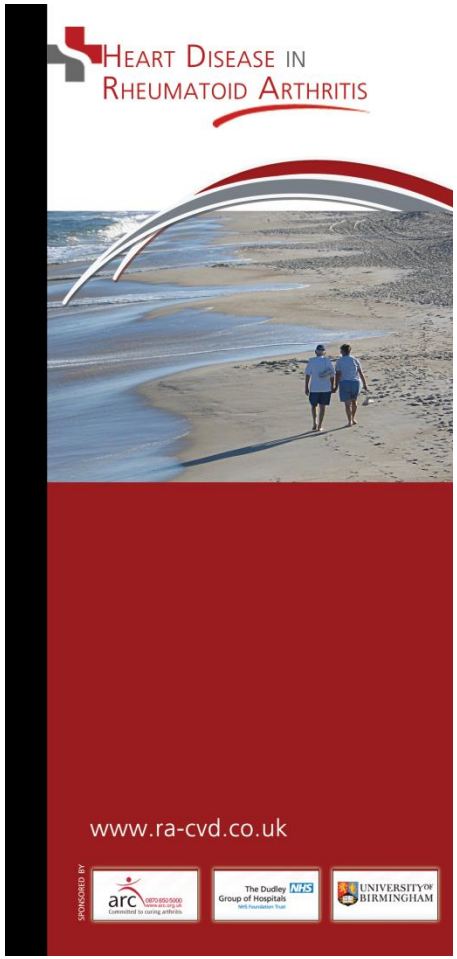
7. John H, Carroll D, Kitas GD. Cardiovascular education for people with rheumatoid arthritis; what can existing patient education programmes teach us? Rheum 2011; 50: 1751-9.

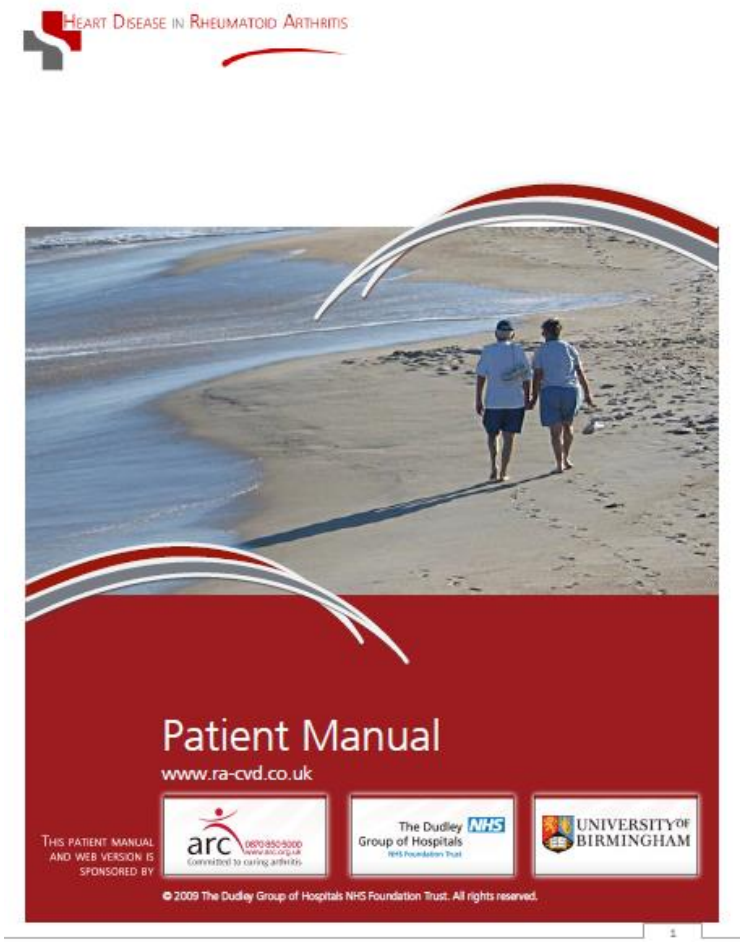
8. John H, Toms TE, Kitas GD. Rheumatoid arthritis: is it a coronary heart disease equivalent? Curr Opin Card 2011; 26: 327-33.

9. John H, Hale ED, Treharne GJ, Korontzis K, Obrenovic K, Carroll D, et al. Patient evaluation of a novel patient education leaflet about heart disease risk among people with rheumatoid arthritis. Musculoskeletal Care 2011; 9: 194-9.

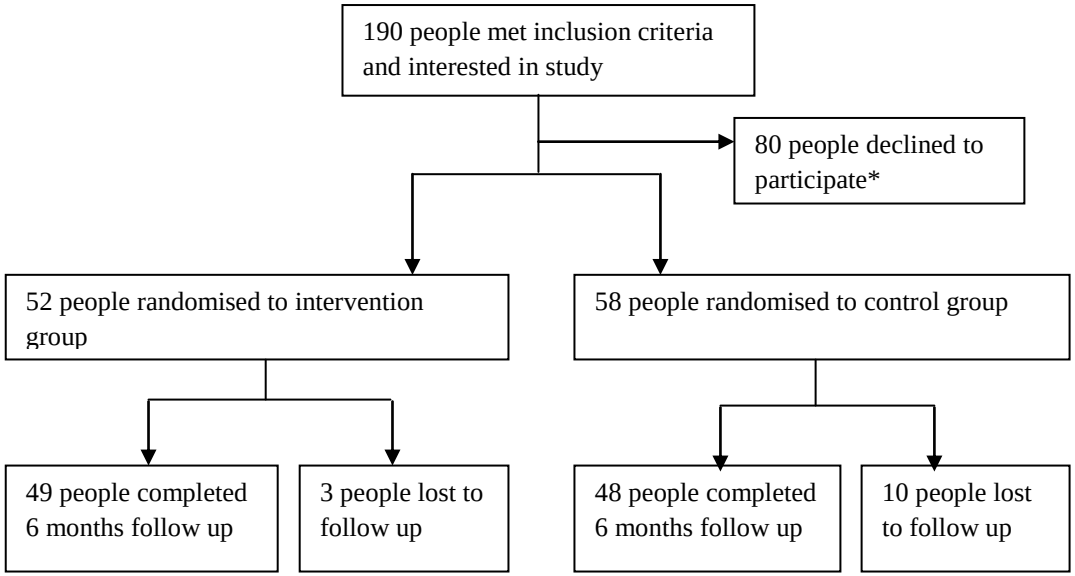
10. John H, Hale ED, Treharne GJ, Carroll D, Kitas GD. A randomised controlled trial of a cognitive behavioural patient education intervention versus a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease. Rheum 2013; 52: 81-90.

Educational material produced
a)standard leaflet
b) patient manual to accompany a detailed cognitive behavioural small group patient education course





A randomised controlled trial of a cognitive behavioural patient education intervention versus a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease.

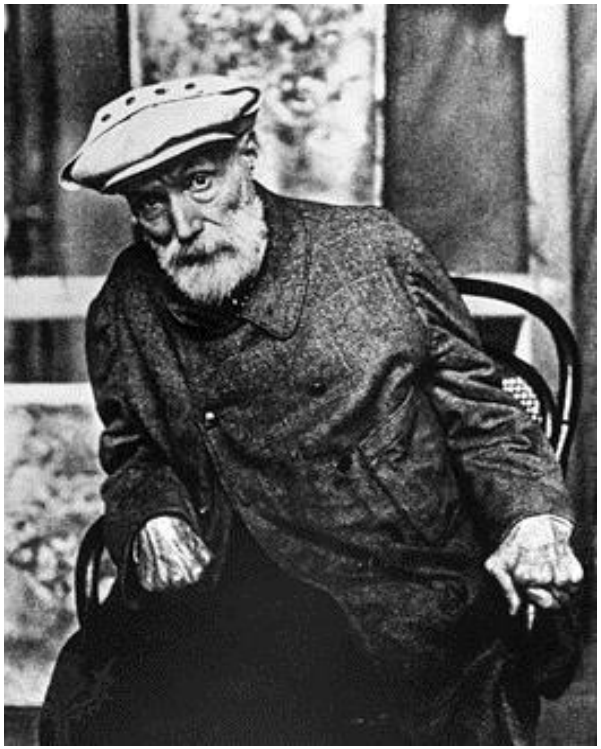


*Reasons included did not have the time, could not fit it in, other commitments, could not get time off work, do not want to make any more visits to hospital and not interested.

Results

- At 6 months the intervention group had:
  - Significantly improved knowledge scores
  - Significantly improved behavioural intentions to
    - Increase exercise
    - Eat a low fat diet
    - Lose weight
  - **Significantly lower diastolic blood pressure**

Development and evaluation of **individualised** exercise interventions to improve cardiorespiratory health in patients with RA



"One must from time to time attempt things that are beyond one's capacity."

Pierre-Auguste Renoir

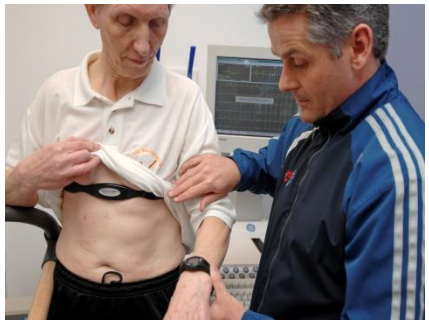
Action Heart - Dudley

- Largest cardiac rehab centre in the country
- Independent charity – *Beacon Status*
- Open to general public (+/- GP referral)
- Research active

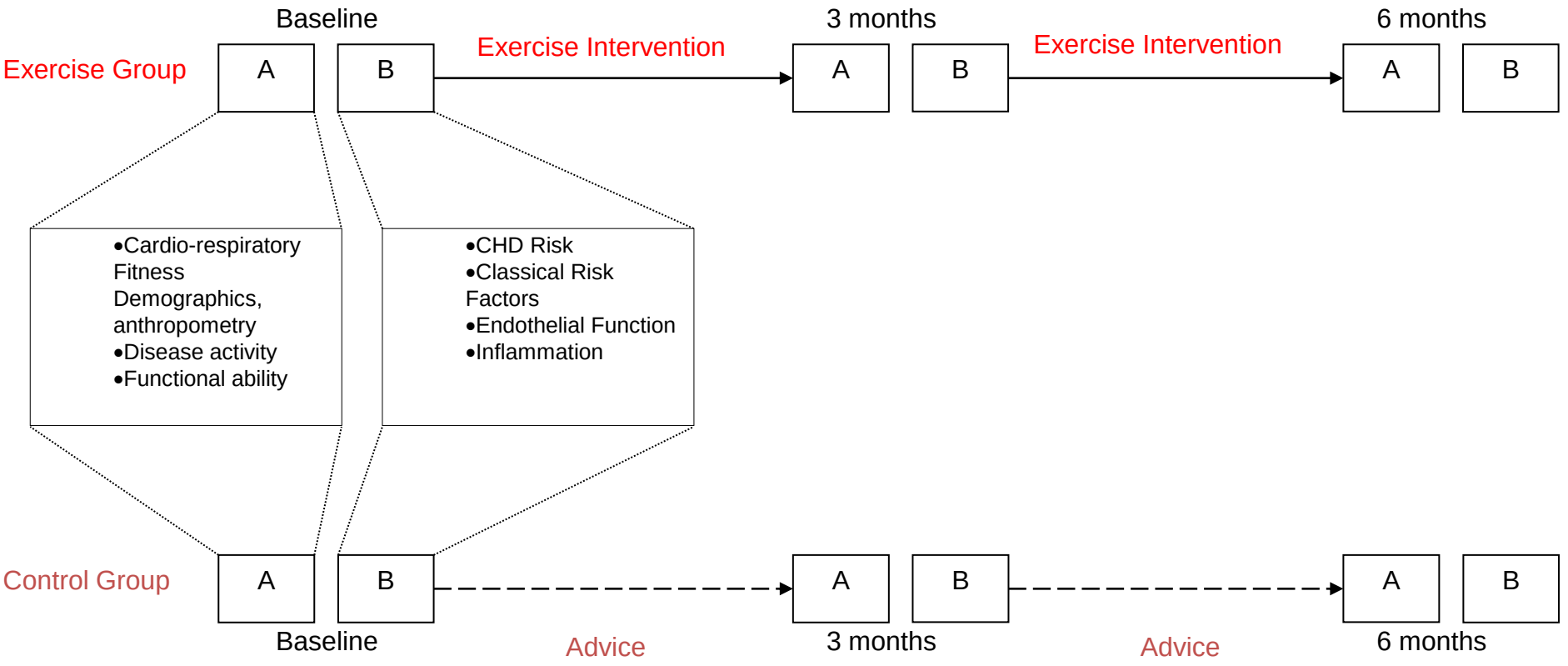
- **Specialised in:**
  - Primary and Secondary CVD Prevention
  - People with musculoskeletal disability
  - Morbidly obese





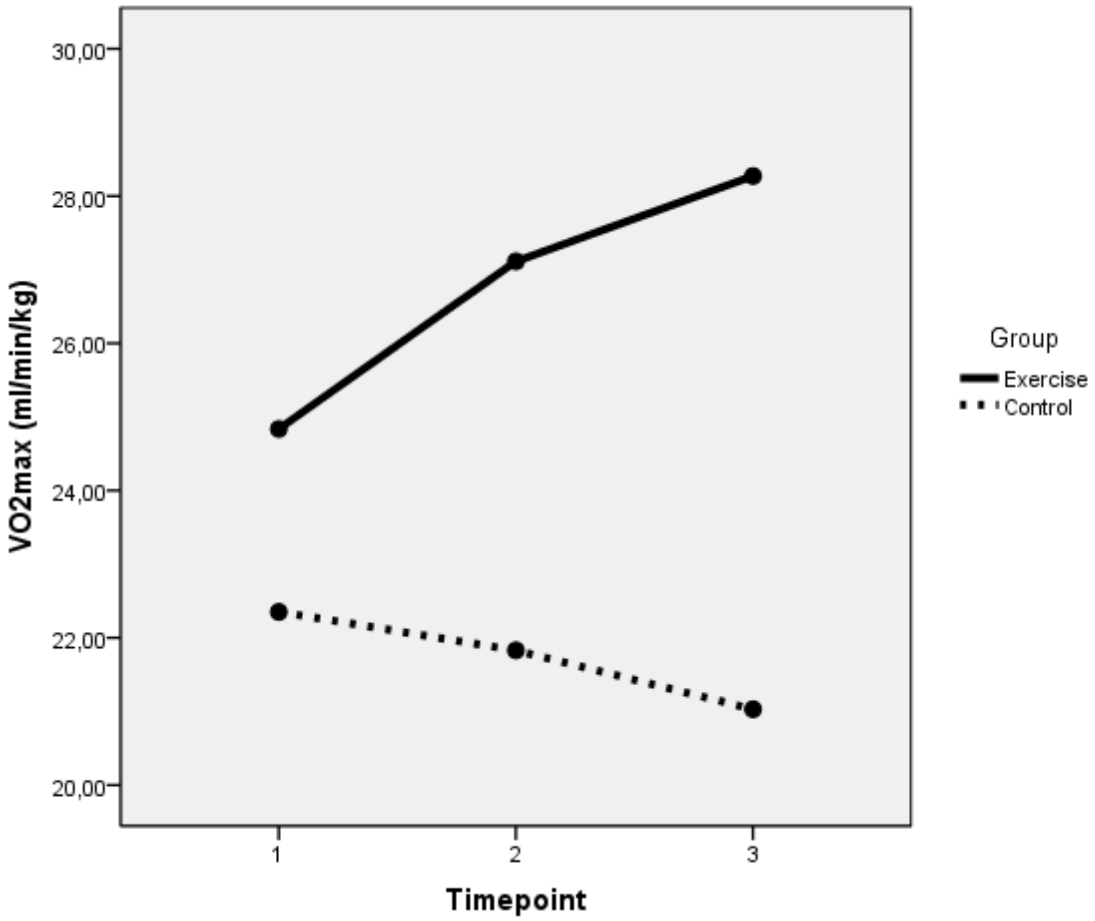
Study Design



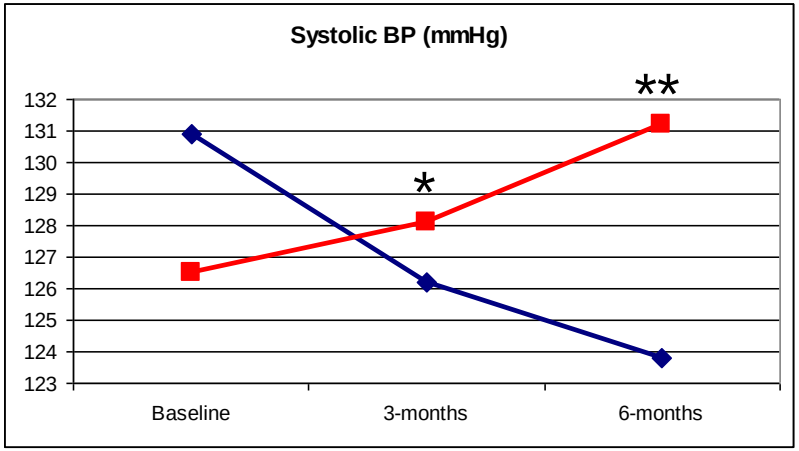
Stavropoulos-Kalinoglou et al. Ann Rheum Dis. 2013

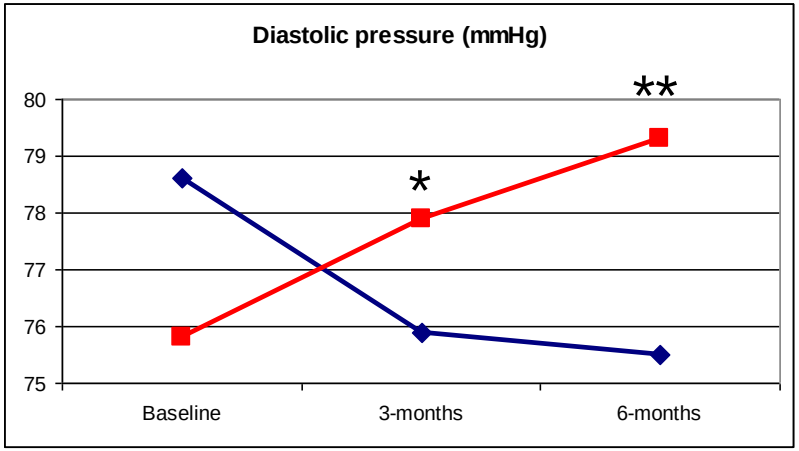
Improvement in Fitness

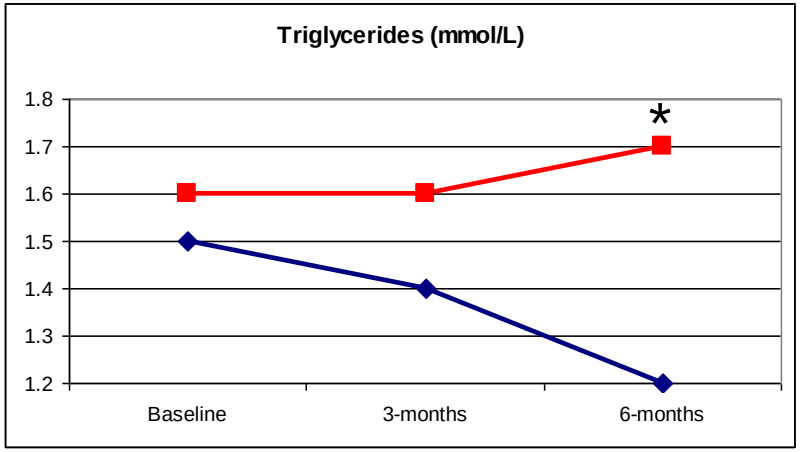
- Attendance: 88% (patients coming to the gym)
- Adherence: 76% (patients reaching their targets for each exercise)

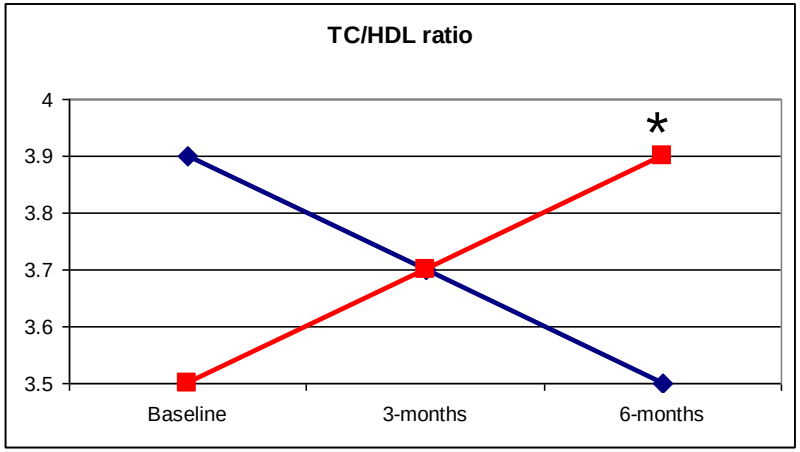


CVD risk factors





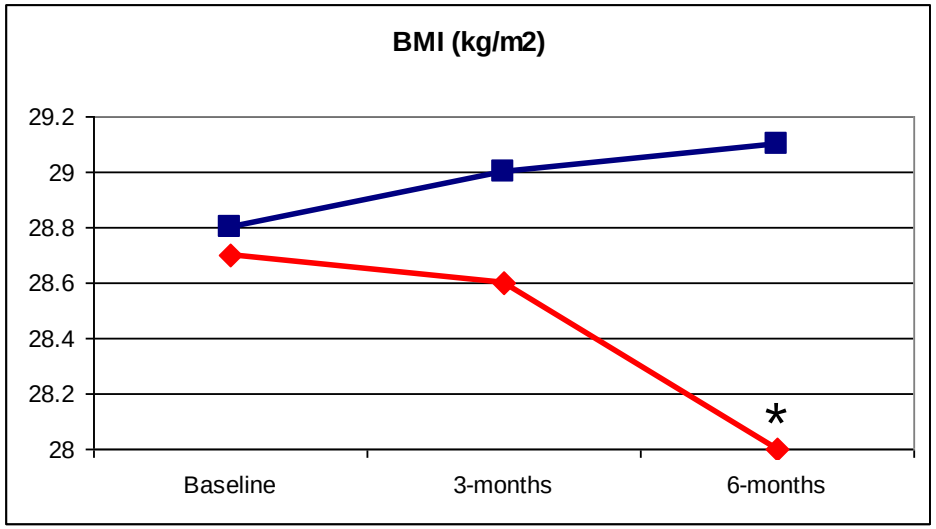


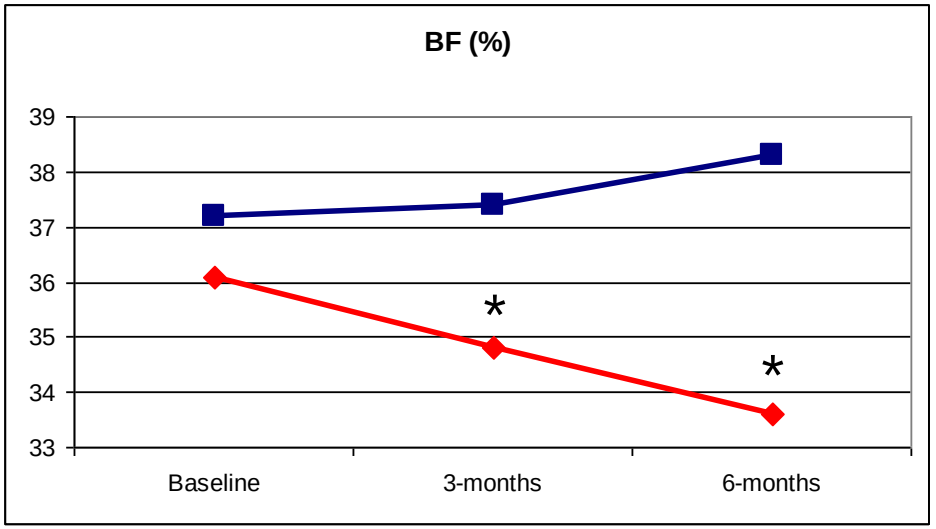


Exercise Group

Control Group

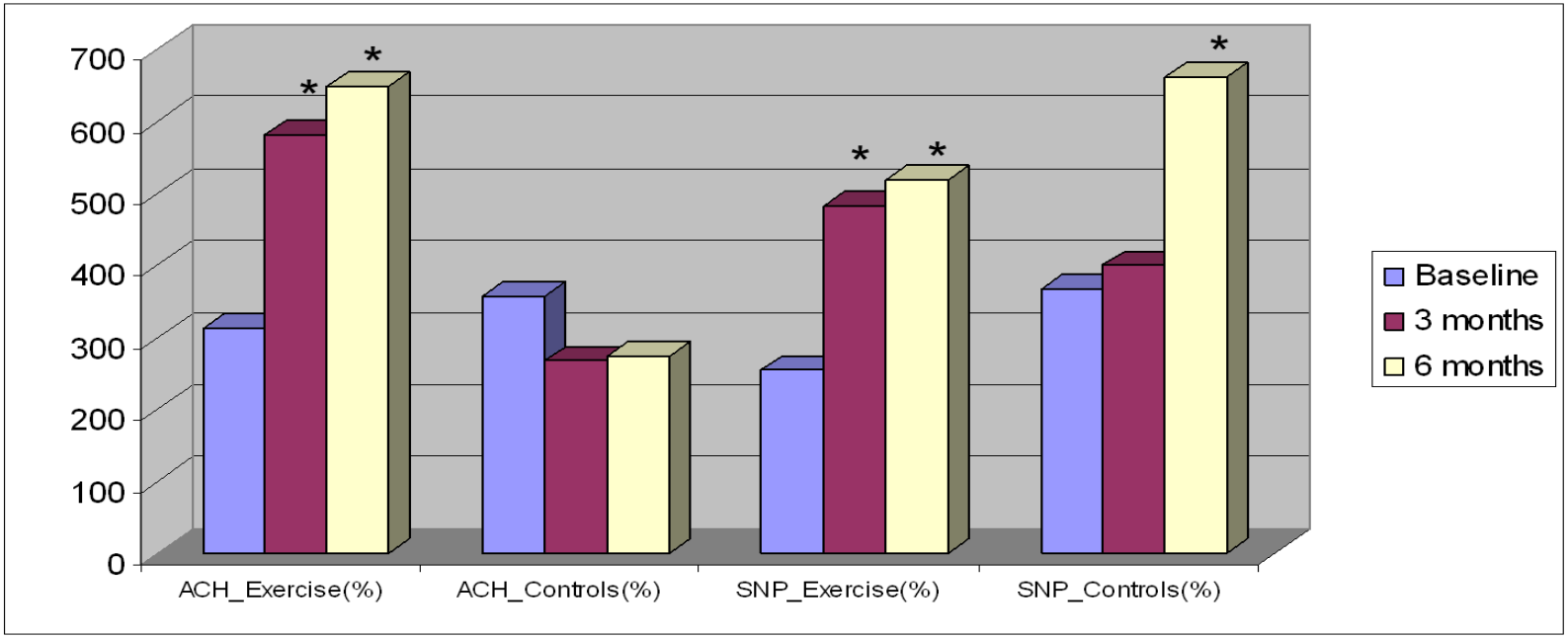
Body composition



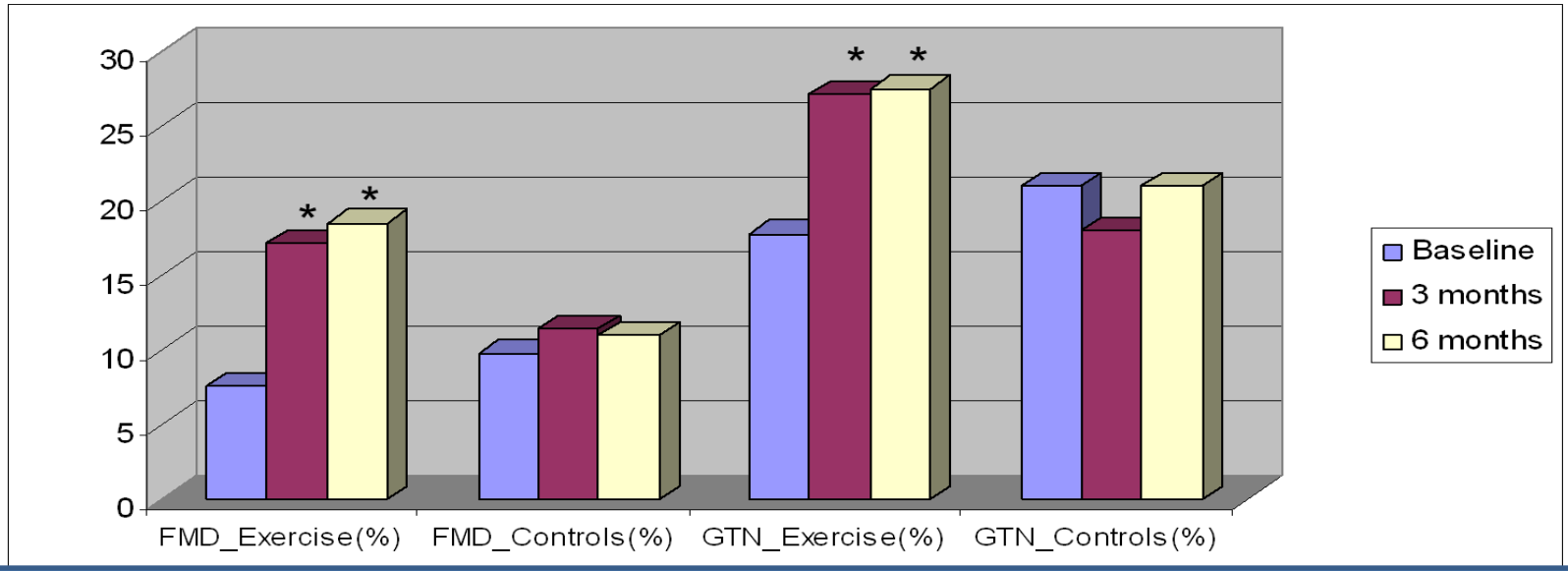


Endothelial function

Exercise and MICRO-vascular Function



Exercise and MACRO-vascular Function



Metsios et al., Ann Rheum Dis. 2013 Jul 31.

What is the evidence for (accelerated) atherosclerosis in RA?

- Theory: the role of inflammation
- Vascular function and morphology studies - biomarkers
  (sub-clinical atherosclerosis)
- Vascular work + Epidemiology: **RA = DM type 2**
  (DM type 2 = CHD equivalent)
- Abundance of classical and novel risk factors
  - Hypertension
  - Dyslipidaemia
  - Obesity – Cachexia – Insulin resistance
  - Physical Inactivity
  - Multiple other factors (e.g. drugs, smoking, RhF etc.)

RA treatment effects on CVD risk factors

• NSAIDs / Coxibs	Hypertension
• Hydroxychloroquine	↓ Lipids, DM
• Methotrexate	↓ Met. Syndrome ↑ Homocysteine
• Steroids	Hypertension Dyslipidaemia Insulin resistance
• Biologics	Lipids, BP Body composition

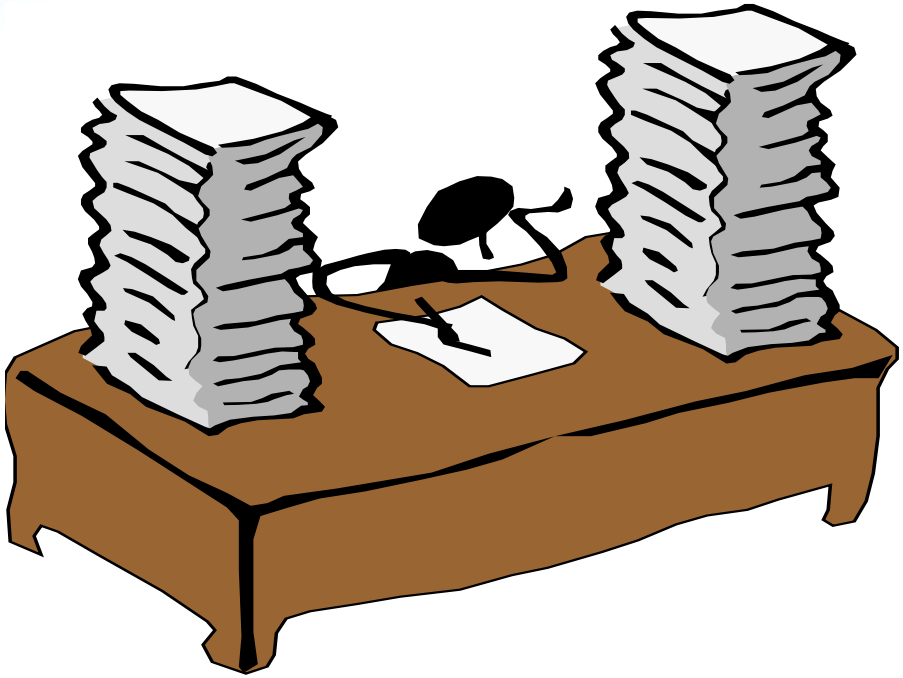
Gasparyan et al: Curr Vasc Pharmacol 2011 Toms et al: Curr Vasc Pharmacology 2010

Multiple interactions between “classical” and “novel” risk factors

- Rheumatoid Factor
- ACPA
- Rheumatoid Nodules
- Disability
- Less antiTNF response
- ↑basal metabolic rate – rheumatoid cachexia

John et al: Best Practice & Research Clinical Rheumatology 23 (2009) 71–82

Assessing attribution is difficult



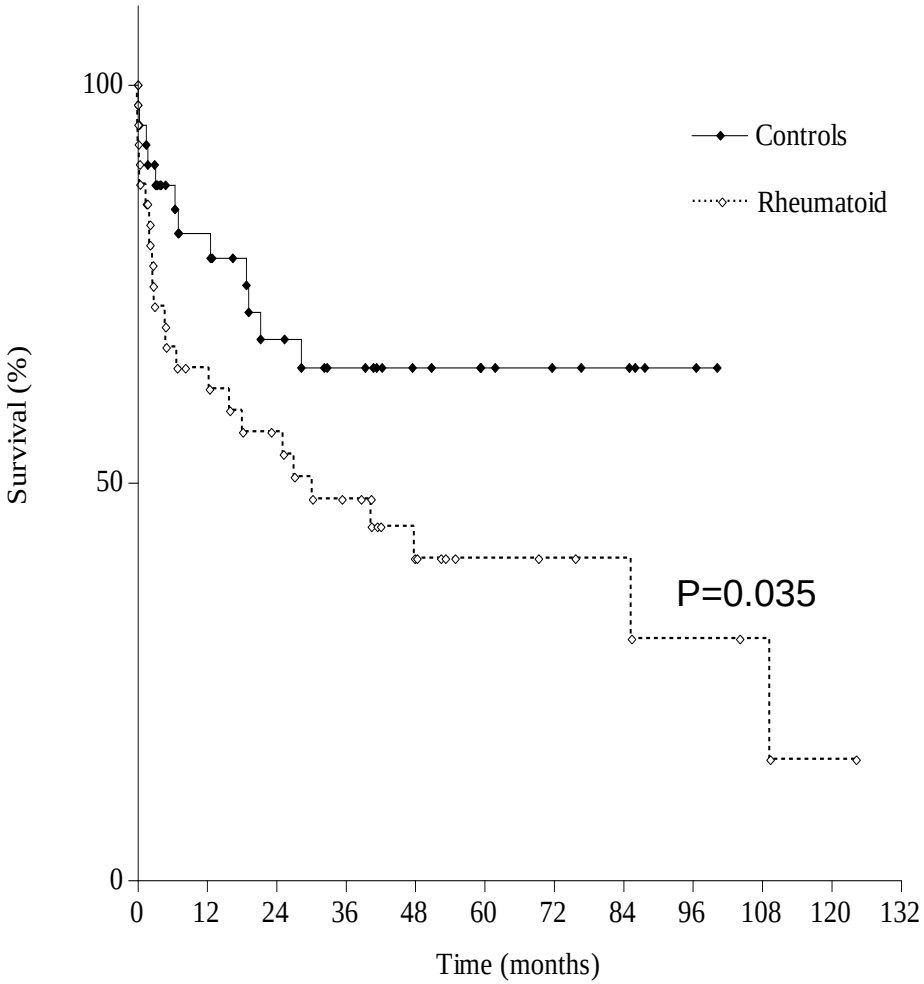
Outline

- What is the problem?
- **What is the nature of the problem?**
  - (Accelerated) Atherosclerosis?
  - **Plaque instability?**
  - Other mechanisms?
- Summary

What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate

Increased case fatality / re-infarction in RA



RA: N=40
Case-matched controls for
Age, sex, risk factors, ACS

RA:
20% no chest pain (***)
Delayed thrombolysis
Less cardiac Ix
Less cardiac rehabilitation

Douglas et al, ARD 2006 // Rantapaa-Dahlqvist et al, ARD 2007 // Gabriel SE et al, Am J Med 2008 // …

What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate
- Unstable (coronary) plaque phenotype (by 64 slice CT angiography)

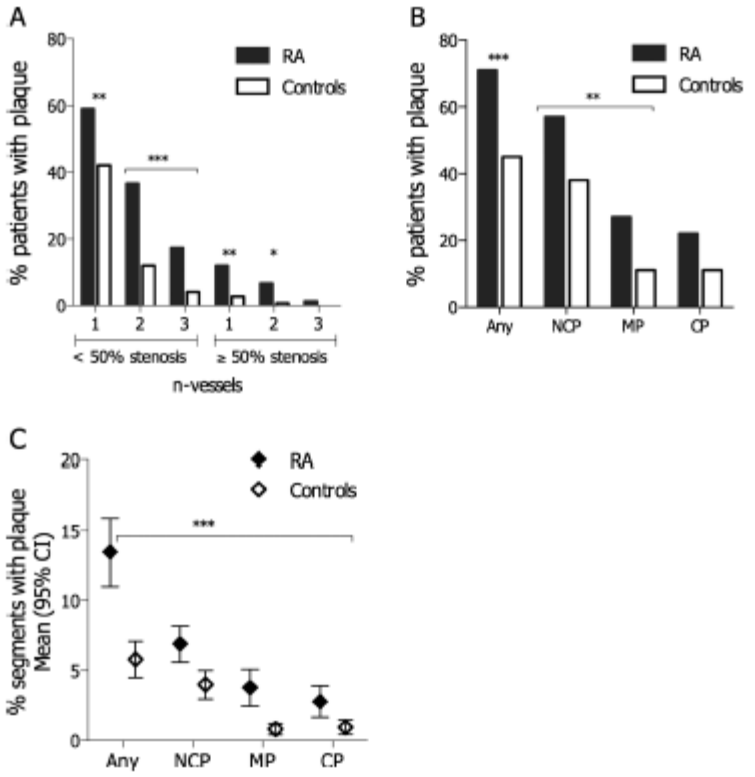


Figure 1 Per patient (panels A and B) and per segment (panel C) analysis of differences in coronary plaque presence and composition in RA and controls. A. Proportions of subjects with one, 2, or ≥3-vessel disease, both non-obstructive (<50%) and obstructive (≥50%); B. Number of patients with any, NCP, 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 et al, ARD 2013

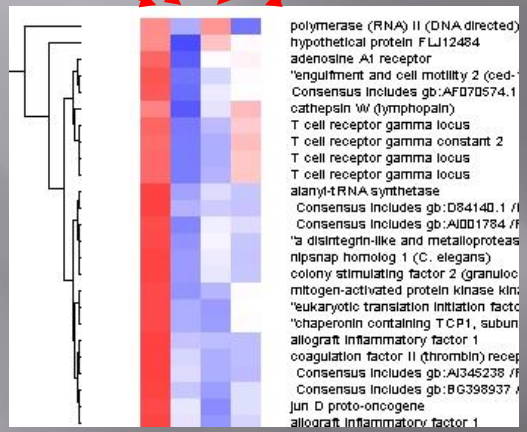
What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate
- Unstable (coronary) plaque phenotype (by 64 slice CT angiography)
- Unstable (carotid) plaque phenotype (using gene microarrays)

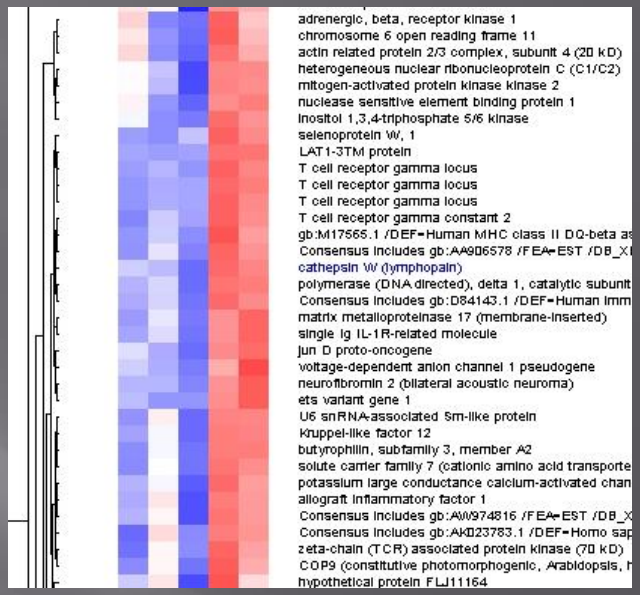
Expression Data Analysis

Hierarchial Clustering of Expression Data using Li&Wong dChip method

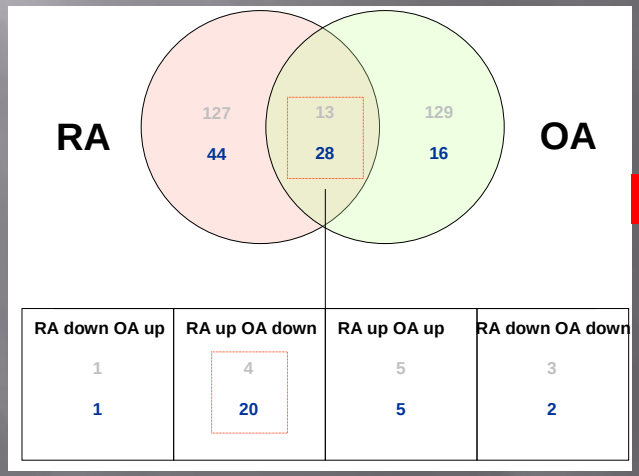
RA+IHD RA-IHD OA+IHD OA-IHD



RA-IHD RA+IHD



SAM Statistical Analysis of Microarray Data
By Bootstrapping to account for Multiplicity



Gene List

Genes up-regulated 2 Fold or Greater only in RA+ID vs RA-IHD

T cell receptor gamma locus

Granzyme 2

Cathepsin W (lymphopain)

Jagged 1 (Alagille syndrome)

mitogen-activated protein kinase kinase 2

natural killer cell group 7 sequence

p53 regulated PA26 nuclear protein

Halligan E et al, Rheumatology 2004

What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate
- Unstable (coronary) plaque phenotype (by 64 slice CT angio)
- Unstable (carotid) plaque phenotype (using gene microarrays)
- Autopsy studies

Autopsy study: Aubry MC et al, J. Rheumatol. 2007; 34(5):937

- *…there was less histologic evidence of atherosclerosis but greater evidence of inflammation and instability in RA patients (n=41) compared to controls (n=82, matched for age, sex, CVD history and autopsy date)…*

- *"…these differences suggest that the mechanisms responsible for CVD morbidity and mortality may be different in patients with RA"*

What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate
- Unstable (coronary) plaque phenotype (by 64 slice CT angio)
- Unstable (carotid) plaque phenotype (using gene microarrays)
- Autopsy studies
- Augmented response to stress in RA

Physiological Responses to Mental Stress in Rheumatoid Arthritis

Jet Veldhuijzen van Zanten, MSc, PhD

Paine NJ, Bosch JA & Veldhuijzen van Zanten JJCS (2012). Inflammation and the vascular responses to acute mental stress: implications for the triggering of myocardial infarction. *Current Pharmaceutical Design, 18: 1494-501*

Veldhuijzen van Zanten JJCS, Carroll D, Ring C & Kitas GD (2005). Increased C reactive protein in response to acute stress in patients with rheumatoid arthritis. *Annals of Rheumatic Diseases. 64, 1299-1304*

Veldhuijzen van Zanten JJCS, Kitas GD, Carroll D & Ring C (2008). Increase in systemic vascular resistance during acute mental stress in patients with rheumatoid arthritis with high inflammation. *Biological Psychology, 77,* 106-10

Summary: stress-induced responses in RA

Increased risk for acute cardiovascular events in rheumatoid arthritis patients

$\rightarrow$

… could be mediated by stress-induced inflammatory and vascular response specific to those RA patients with high disease activity combined with increases in haemodynamic, rheological, and coagulation factors, over and above the high baseline levels

What is the evidence for plaque instability and pro-thrombotic phenomena?

- Higher re-infarction rate
- Unstable (coronary) plaque phenotype (by 64 slice CT angio)
- Unstable (carotid) plaque phenotype (using gene microarrays)
- Autopsy studies
- Augmented response to stress in RA
- Derangement of haemostasis

Thrombotic factors and CVD in RA

Dr Karen MJ Douglas

BSc, MBChB, FRCP, MD

• K Douglas, AV Pace et al. Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome, *Heart*, 2006

• T Dimitroulas, K Douglas, et al. Derangement of hemostasis in rheumatoid arthritis: association with demographic, inflammatory and metabolic factors, *Clinical Rheumatology*, 2013

• T Dimitroulas, K Douglas et al. Lack of association between polymorphisms of thrombogenic genes and disease susceptibility in rheumatoid arthritis. *Rheumatology International,* 2013

Derangement of hemostasis in rheumatoid arthritis: association with demographic, inflammatory and metabolic factors

Results

- RA patients had higher levels of coagulation factors than controls.
- After correction for age and sex, having RA predicted increased:
  - tPA (β=0.32, $p<0.001$),
  - PAI-1 (β=0.33, $P<0.001$)
  - Fibrinogen (β=0.38, $P<0.001$)
  - PF1+2 (β=0.33, $P<0.001$),
  - TM (β=0.19, $P=0.03$) levels
- CRP correlated positively with
  - tPA ($P<0.05$)
  - fibrinogen ($P<0.001$)
  - TM ($P<0.05$),
  - PF1+2 ($P<0.001$)
  - vWF ($P<0.001$)

In RA:

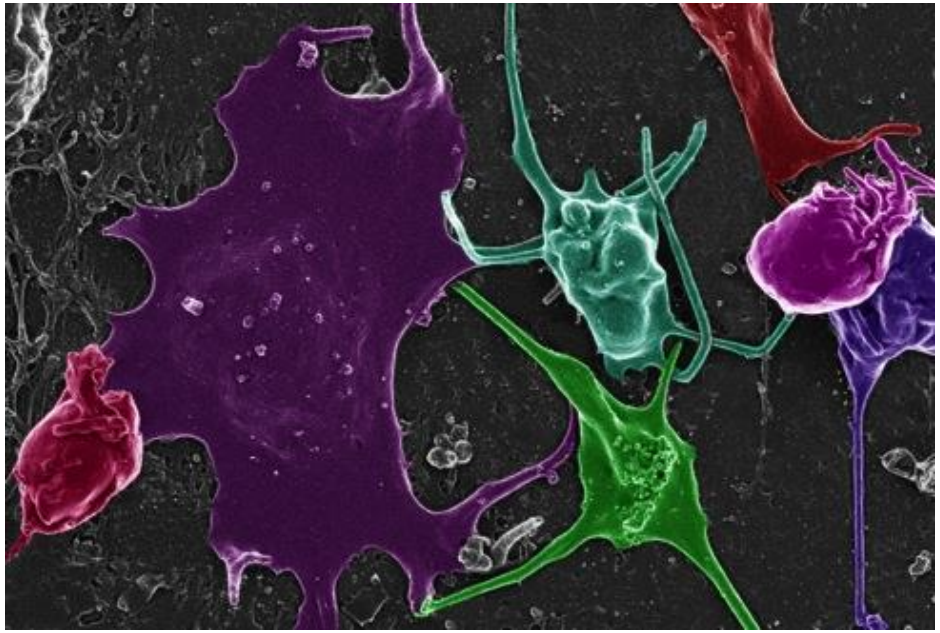
- Age influenced:
  - tPA ($P<0.001$)
  - fibrinogen ($P<0.01$)
  - TM ($P<0.05$)
  - PF1+2 ($P<0.001$)
  - vWF ($P<0.01$).
- Metabolic factors & coag
  - hypertriglyceridaemia (tPA, $P<0.05$; PAI-1, $P<0.05$; Protein C, $P<0.05$)
  - insulin resistance (tPA, $P<0.01$; PAI-1, $P<0.01$; vWF, $P<0.05$).

Platelets in RA

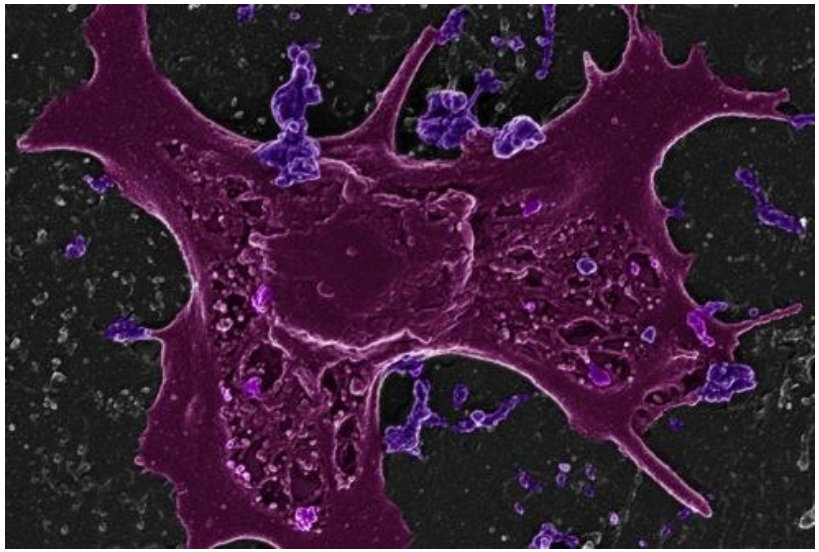
Dr. Armen Gasparyan, MD, PhD, FESC
Assoc. Professor of Medicine

•**Gasparyan AY**, Ayvazyan L, Pretorius E, Kitas GD: Platelets in Rheumatic Diseases: Friend or Foe? Curr Pharm Des. 2013 Apr 2.
•**Gasparyan AY**, Ayvazyan L, Cocco G, Kitas GD.
•Adverse cardiovascular effects of antirheumatic drugs: implications for clinical practice and research.Curr Pharm Des. 2012;18(11):1543-55
•Shanker J, **Gasparyan AY**, Kitas GD, Kakkar VV.
•Platelet function and antiplatelet therapy in cardiovascular disease: implications of genetic polymorphisms.Curr Vasc Pharmacol. 2011 Jul 1;9(4):479-89.
•**Gasparyan AY**, Ayvazyan L, Mikhailidis DP, Kitas GD.Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17(1):47-58
•**Gasparyan AY**, Stavropoulos-Kalinoglou A, Mikhailidis DP, Douglas KM, Kitas GD.Platelet function in rheumatoid arthritis: arthritic and cardiovascular implications.Rheumatol Int. 2011 Feb;31(2):153-64
•**Gasparyan AY**, Sandoo A, Stavropoulos-Kalinoglou A, Kitas GD.Mean platelet volume in patients with rheumatoid arthritis: the effect of anti-TNF-α therapy.Rheumatol Int. 2010 Jun;30(8):1125-9
•**Gasparyan AY**, Stavropoulos-Kalinoglou A, Toms TE, Douglas KM, Kitas GD.Association of mean platelet volume with hypertension in rheumatoid arthritis. Inflamm Allergy Drug Targets. 2010 Mar;9(1):45-50
•**Gasparyan AY**, Stavropoulos-Kalinoglou A, Mikhailidis DP, Toms TE, Douglas KM, Kitas GD. The rationale for comparative studies of accelerated atherosclerosis in rheumatic diseases. Curr Vasc Pharmacol. 2010 Jul;8(4):437-49.

RA and platelets



Activated Platelet and shedding of microparticles in RA



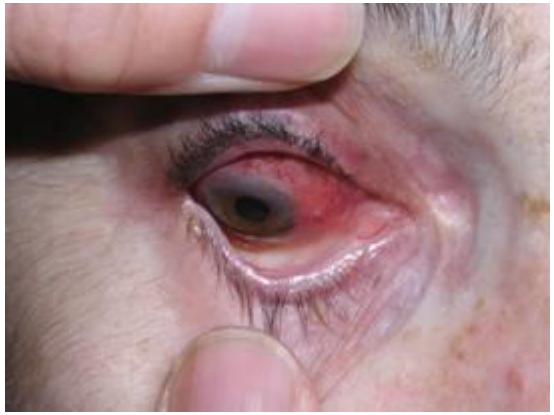
Membrane damage and shedding of microparticles in RA and diabetes

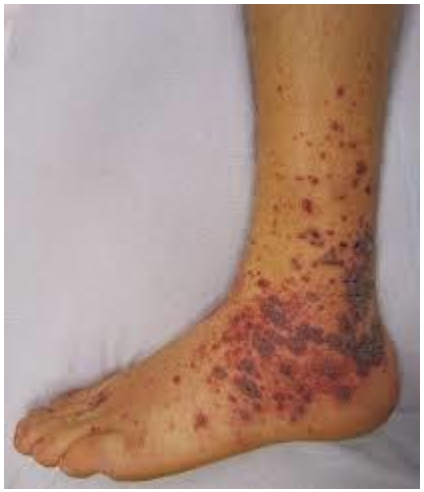
Outline

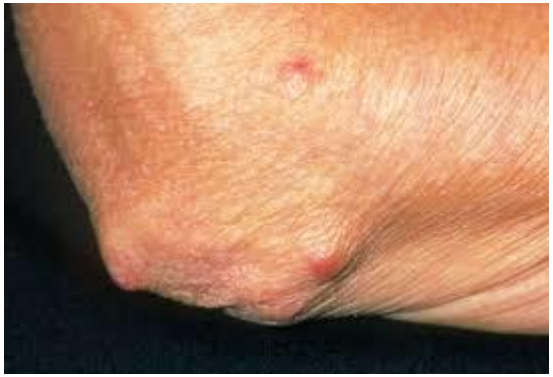
- What is the problem?
- **What is the nature of the problem?**
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - **Other mechanisms?**
- Summary (back to the future)

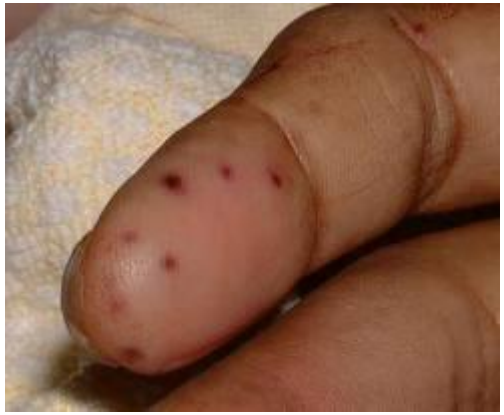
What is the evidence for **microvascular** disease / dysfunction in RA?

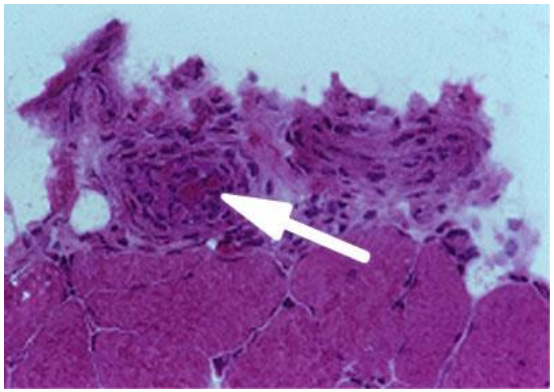
- **Disease phenotype: rheumatoid vasculitis**

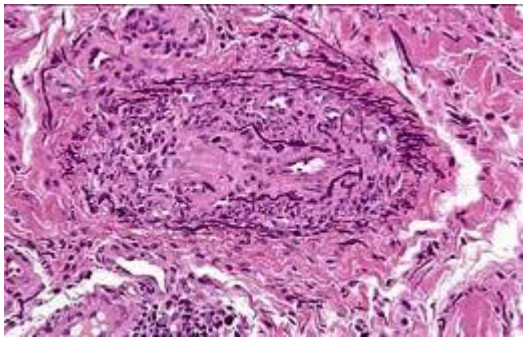








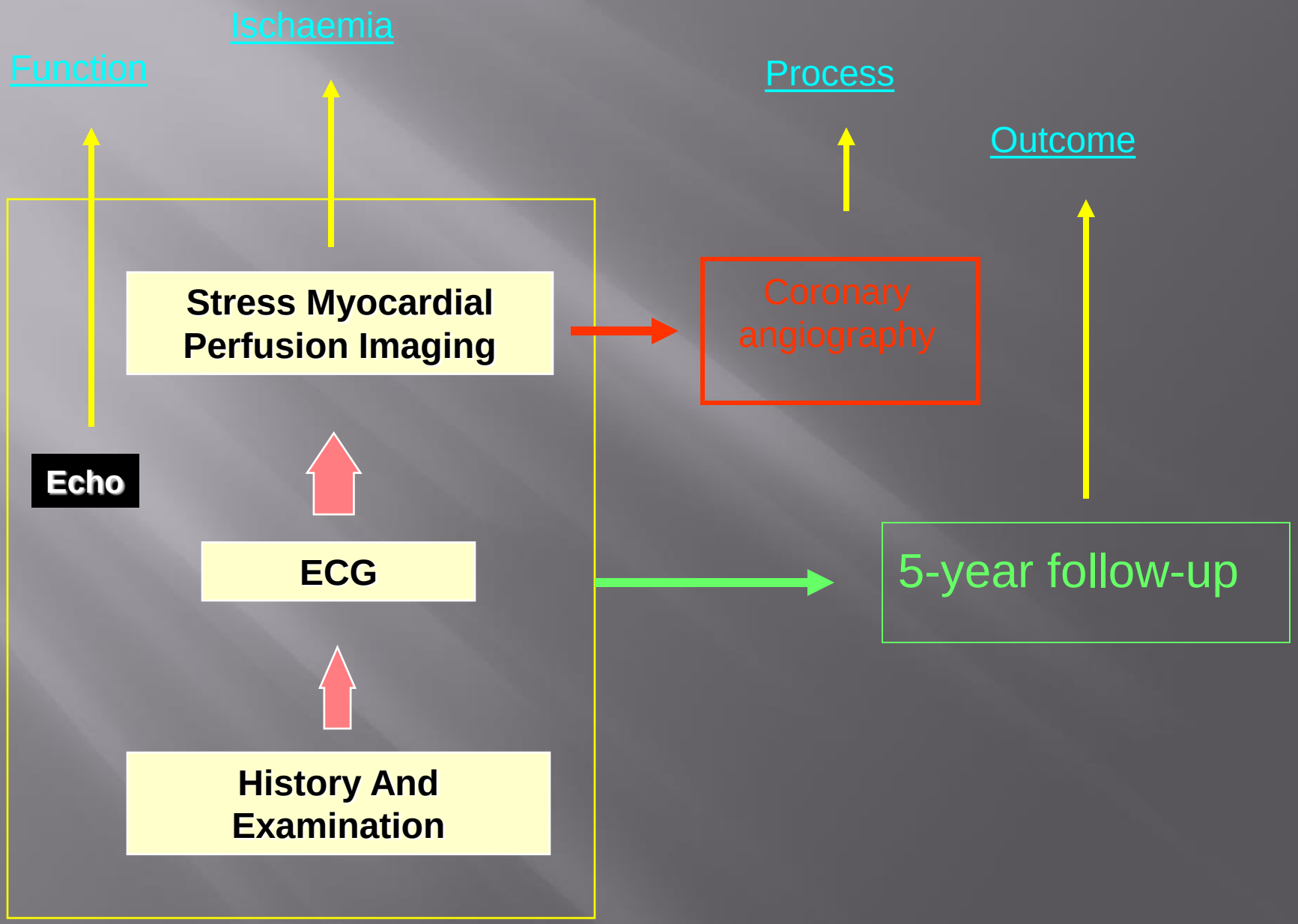




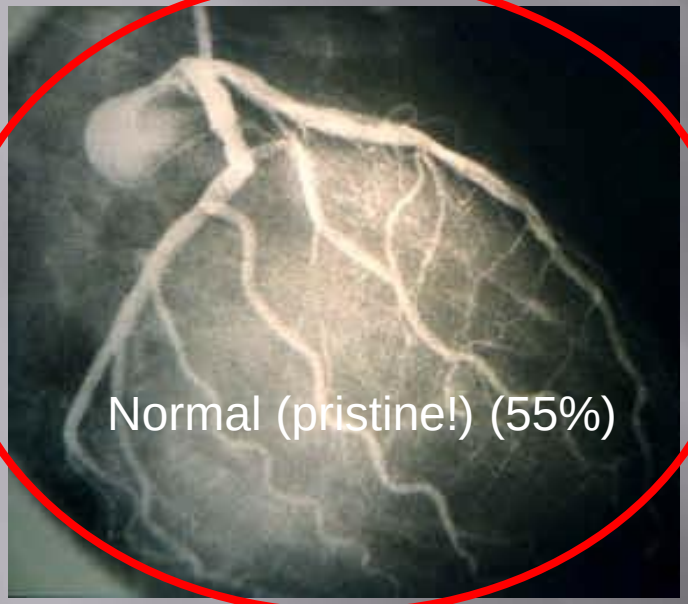
What is the evidence for **microvascular** disease / dysfunction in RA?

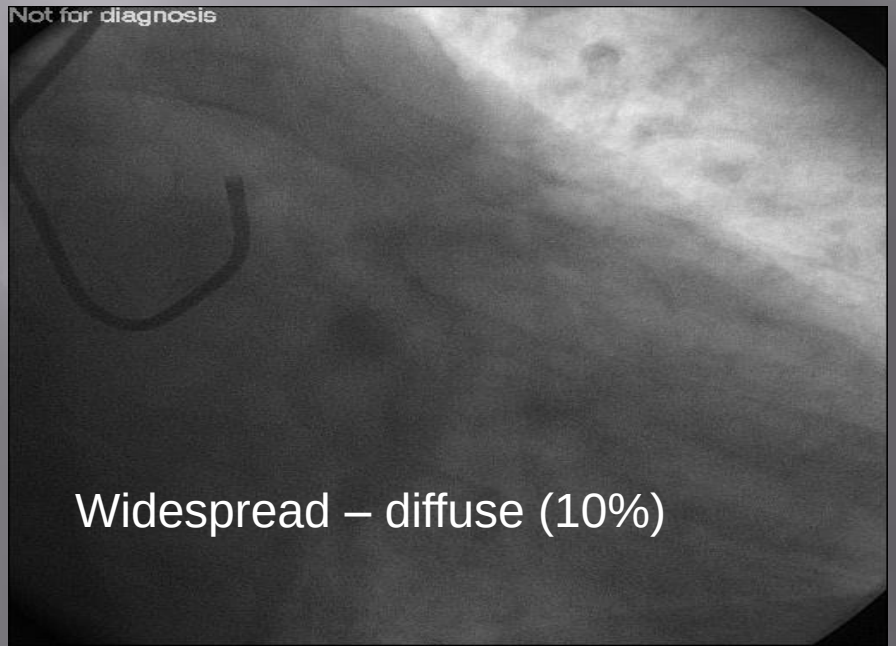
- Disease phenotype: rheumatoid vasculitis
- **Thallium scans**

RA (N=80) vs. OA (N=40)

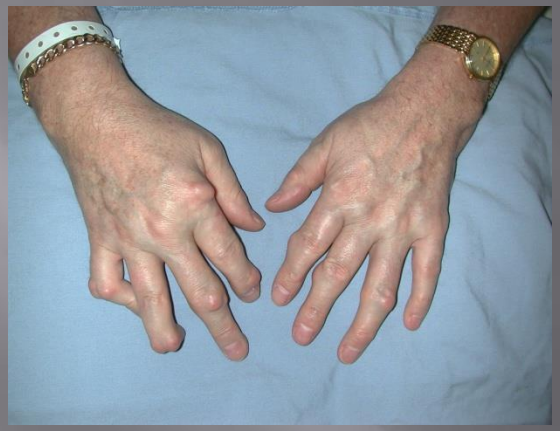


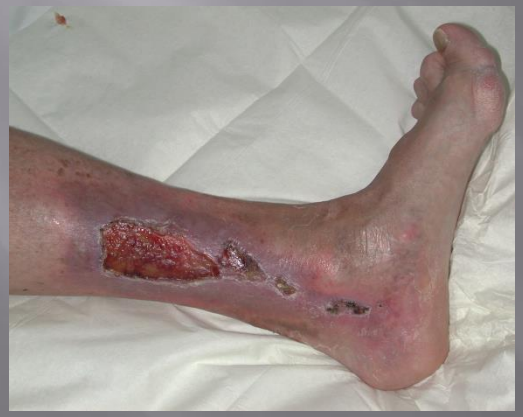
Patterns of Coronary artery involvement in RA patients with high risk MPI

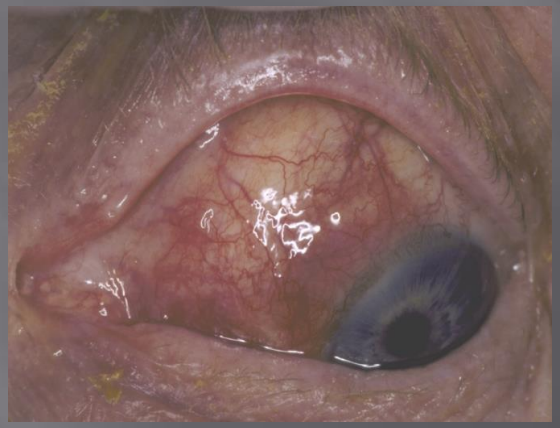




Is microvascular disease reversible?



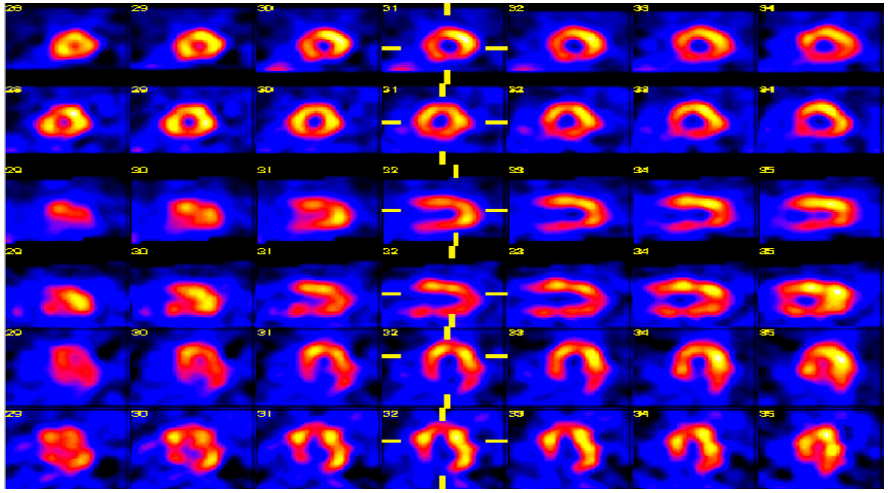


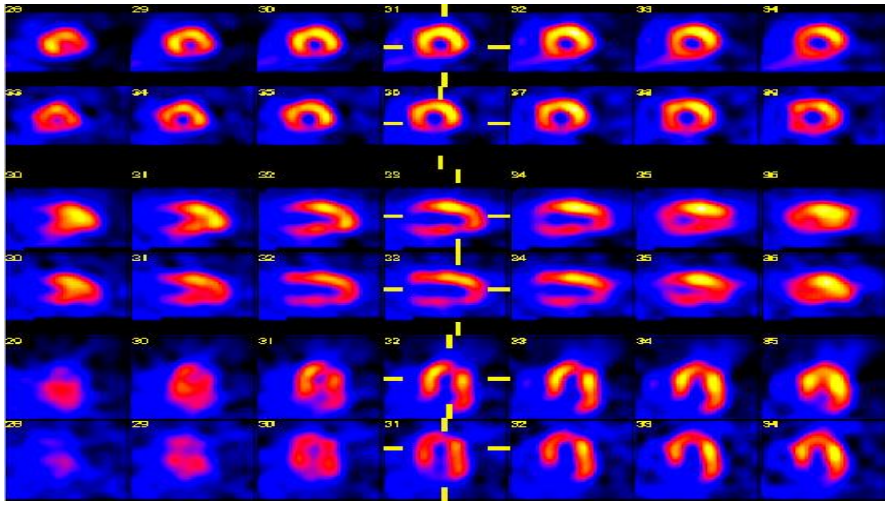


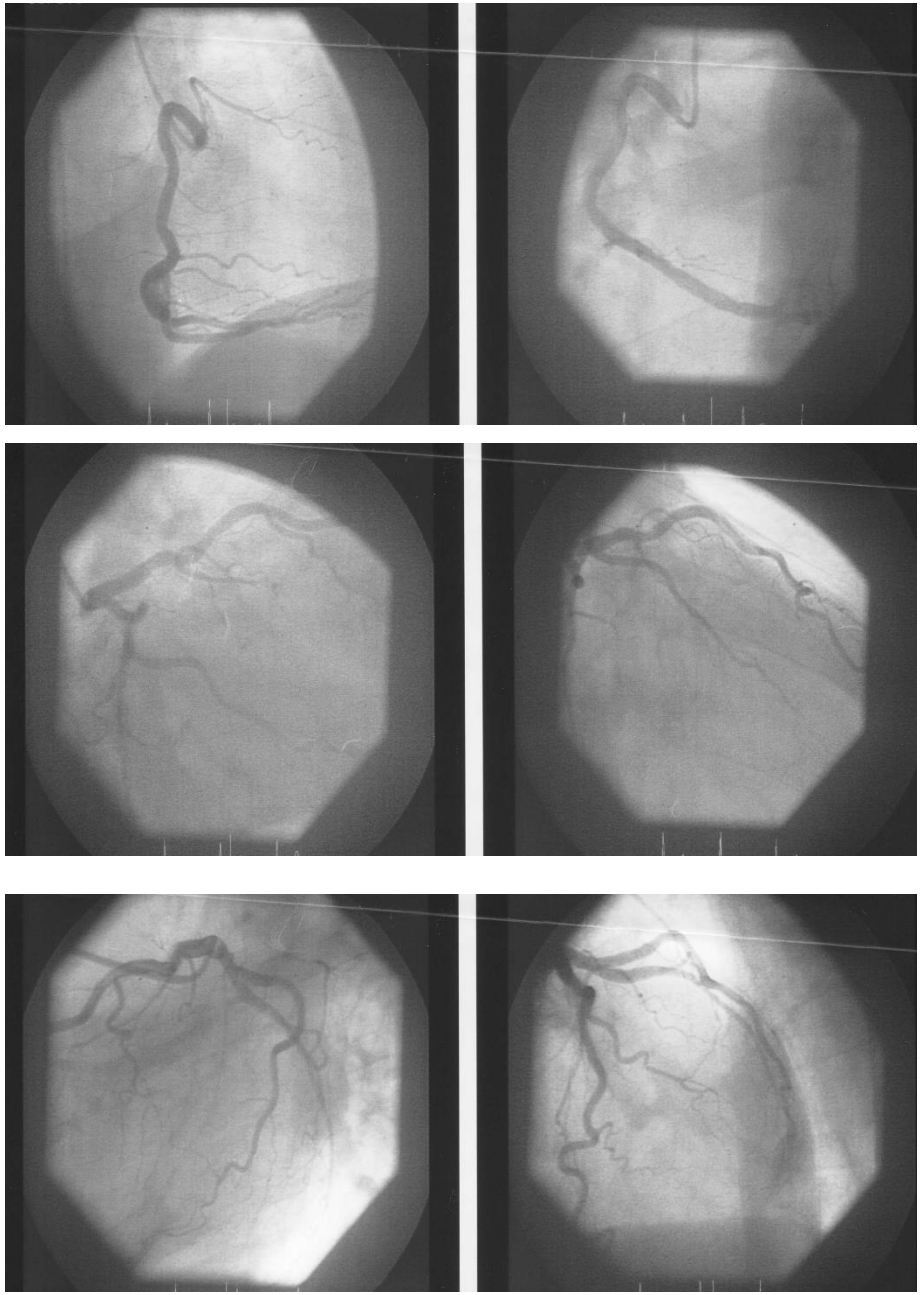
49 years
Non-smoker
Not hypertensive
High cholesterol
Manual labourer
No FH of CAD

RA x 26 years

Non-atherosclerotic processes:
Microvascular dysfunction?
Myocarditis?







Banks et al, A&R 1999

Raza, Banks & Kitas: J Rheumatol 2006

What is the evidence for **microvascular** disease / dysfunction in RA?

- Disease phenotype: rheumatoid vasculitis
- Thallium scans
- **Stress contrast echo – coronary angiography**

Rheumatology (Oxford). 2013 Jan;52(1):76-80. doi: 10.1093/rheumatology/kes349. Epub 2012 Nov 26.

Myocardial ischaemia without obstructive coronary artery disease in rheumatoid arthritis: hypothesis-generating insights from a cross-sectional study.

Toutouzas K, Sfikakis PP, Karanasos A, Aggeli C, Felekos I, Kitas G, Zampeli E, Protogerou A, Stefanadis C.

Source

1st Department of Cardiology, Hippokration Hospital, Athens Medical School, Athens, Greece. ktoutouz@gmail.com

Abstract

OBJECTIVE:

RA is associated with increased cardiovascular events, reportedly to equal diabetes mellitus (DM). The presence of myocardial ischaemia was assessed in asymptomatic high-risk RA patients and compared with patients with DM and a healthy control group.

METHODS:

Eighteen consecutive non-diabetic RA patients without known cardiovascular disease who developed a new carotid atheromatic plaque during the last 3 years were matched 1:1 for traditional cardiovascular risk factors with asymptomatic type 2 DM patients and 1:2 with asymptomatic non-RA, non-DM control subjects. After dobutamine stress contrast echocardiography with wall-motion and perfusion evaluation, coronary angiography was performed in those with positive stress tests.

RESULTS:

Ischaemia by echocardiography was found in 67% of RA patients; this was significantly higher than controls (31%, P = 0.019) but comparable to those with DM (78%, P = 0.71). Angiography performed in eight consenting RA patients was normal in four, revealed non-flow-limiting coronary atheromatic lesions in two and significant lesions in two patients. RA patients with ischaemia had CRP serum levels significantly higher by six-fold compared with those with normal stress echocardiography.

CONCLUSION:

Asymptomatic RA patients may display myocardial ischaemia at similar levels to DM patients but with low prevalence of obstructive coronary artery disease. Microvascular abnormalities associated with increased inflammatory response may account for these findings. Their exact nature and significance require further evaluation.

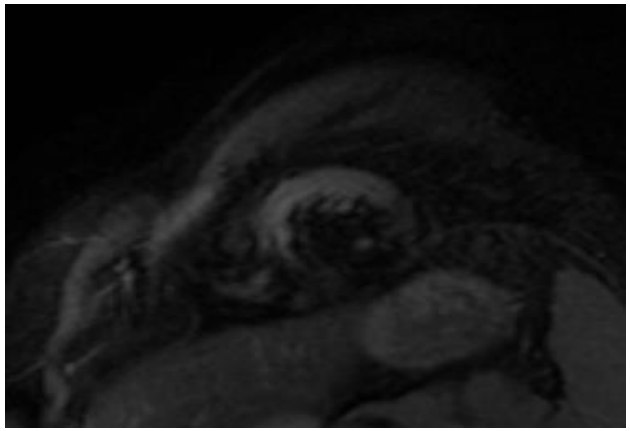
What is the evidence for **microvascular** disease / dysfunction in RA?

- Disease phenotype: rheumatoid vasculitis
- Thallium scans
- Stress contrast echo – coronary angiography
- CMR

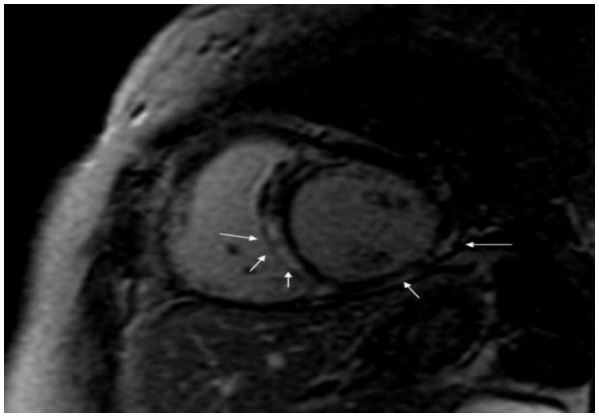
Dr. Sophie Mavrogeni, MD
Onasseion Hospital, Athens

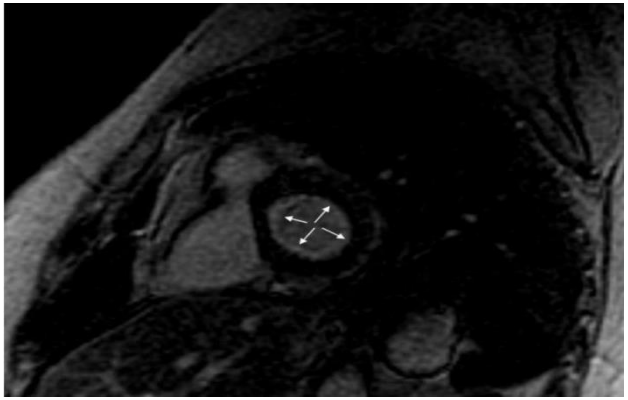
- Mavrogeni S, Dimitroulas T, Sfikakis PP, Kitas GD. Heart involvement in rheumatoid arthritis: Multimodality imaging and the emerging role of cardiac magnetic resonance. Semin Arthritis Rheum. 2013 Jun 17.
- Mavrogeni S, Sfikakis PP, Gialafos E, Karabela G, Stavropoulos E, Sfendouraki E, Panopoulos S, Kolovou G, Kitas GD. Diffuse, subendocardial vasculitis. A new entity identified by cardiovascular magnetic resonance and its clinical implications. Int J Cardiol. 2013 May 3.
- Mavrogeni S, Dimitroulas T, Chatziioannou SN, Kitas G. The role of multimodality imaging in the evaluation of Takayasu arteritis. Semin Arthritis Rheum. 2013 Feb;42(4):401-12.
- Mavrogeni S, Dimitroulas T, Kitas GD. Multimodality imaging and the emerging role of cardiac magnetic resonance in autoimmune myocarditis. Autoimmun Rev. 2012 Dec;12(2):305-12.
- Dimitroulas T, Mavrogeni S, Kitas GD. Imaging modalities for the diagnosis of pulmonary hypertension in systemic sclerosis. Nat Rev Rheumatol. 2012 Feb 7;8(4):203-13.
- **Mavrogeni S**, Sfikakis PP, Gialafos E, Bratis K, Karabela G, Stavropoulos E, Spiliotis G, Sfendouraki E, Panopoulos S, Bournia V, Kolovou G, Kitas GD. Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases. Arthritis Care Res (Hoboken). 2013 Sep 19. doi: 10.1002
- **Mavrogeni S**, Karabela G, Stavropoulos E, Gialafos E, Sfendouraki E, Kyrou L, Kolovou Imaging patterns of heart failure in rheumatoid arthritis evaluated by cardiovascular magnetic resonance. Int J Cardiol. 2013 May 30

Myocarditis
STIR T2 (Oedema Imaging)

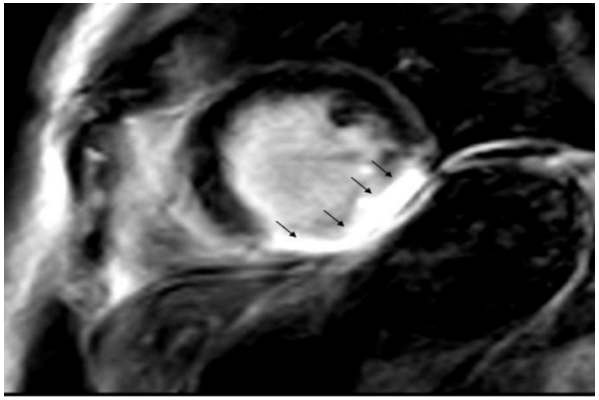


Myocarditis.
Late gadolinium enhancement (LGE) in IVS, inferior and lateral wall of LV





Diffuse subendocardial fibrosis due to vasculitis



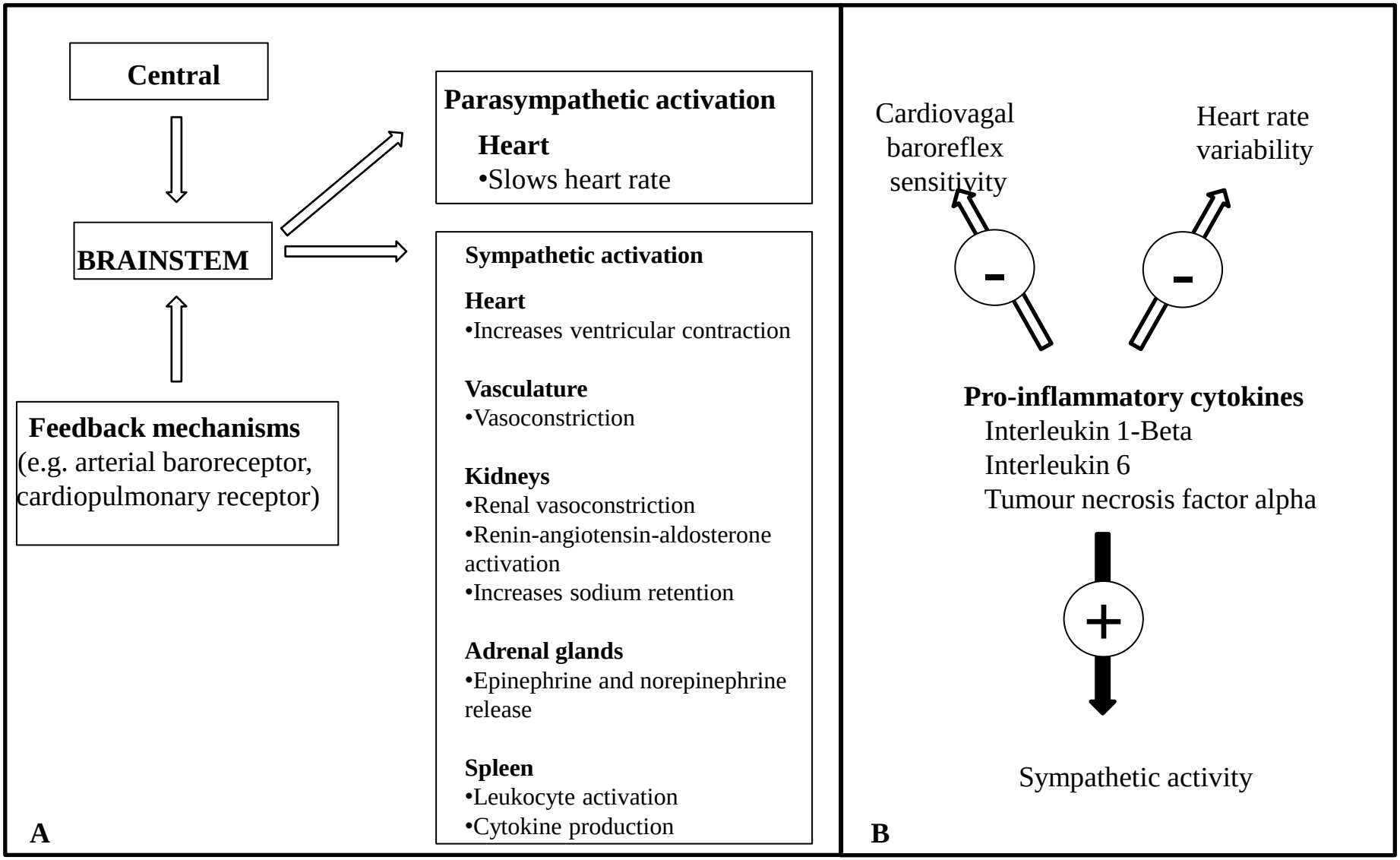
Myocardial infarction

What is the evidence for **microvascular** disease / dysfunction in RA?

- Disease phenotype: rheumatoid vasculitis
- Thallium scans
- Stress contrast echo – coronary angiography
- CMR

Evidence for any other mechanisms?

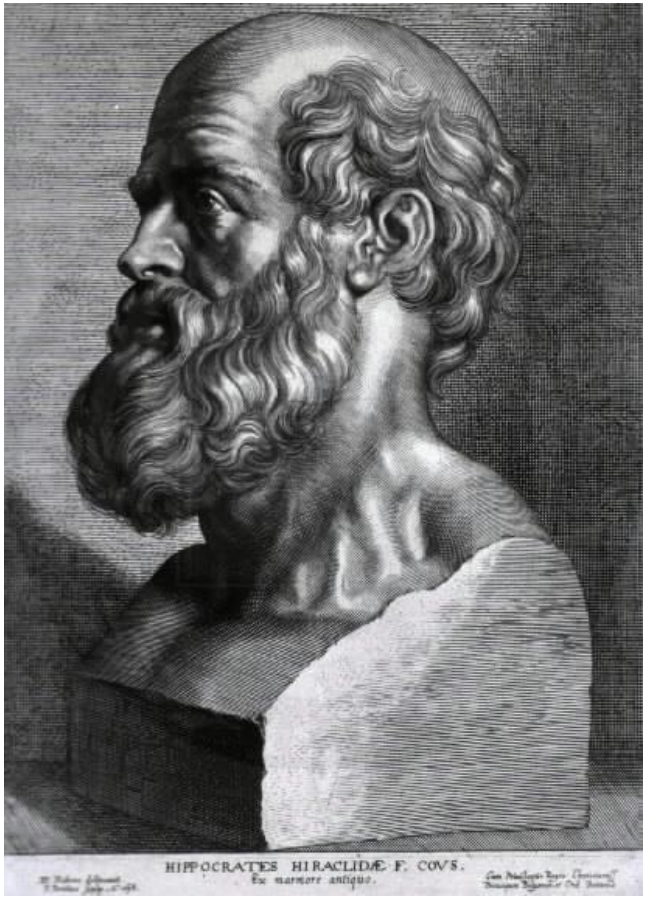
- Autonomic dysfunction



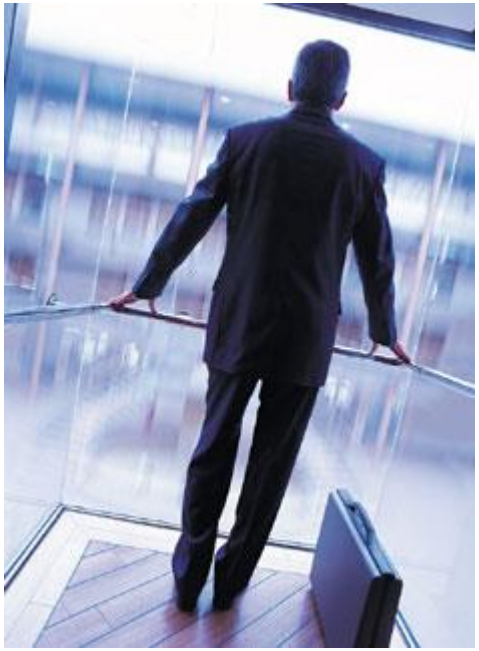
Ahmed et al (submitted)

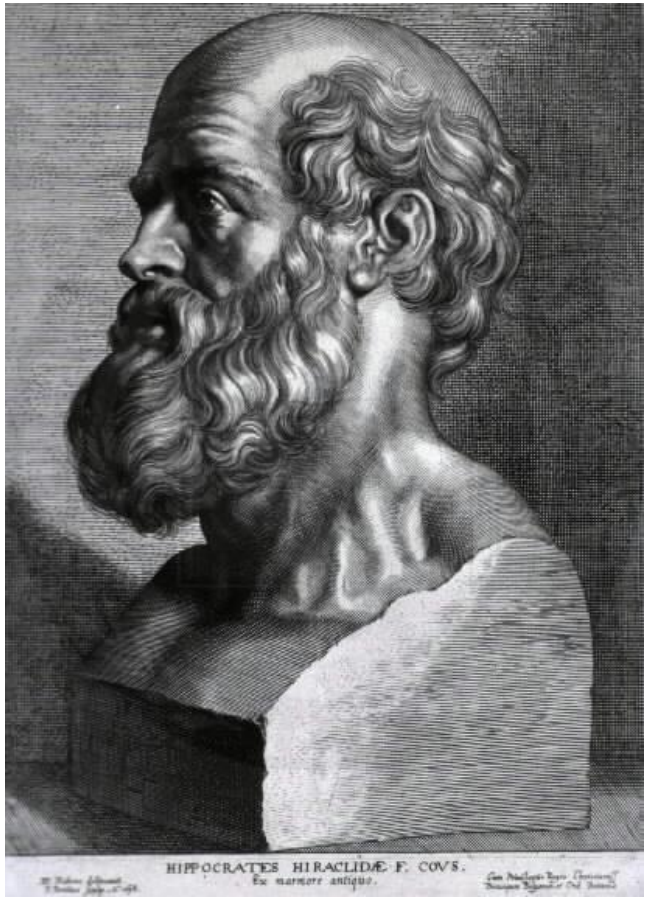
Outline

- What is the problem?
- What is the nature of the problem?
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - Other mechanisms?
- **Summary**



"the <u>patient</u> should be the focus of care"





There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance.

— Hippocrates

Law sect. 4, in *Hippocrates*, trans. W. H. S. Jones (1923), Vol. 2, 265.

Summary

- CVD is remains an important co-morbidity in RA – but is it as important for mortality as in the past?
- There is some evidence for accelerated atherosclerosis
  - Driven mostly by classical risk factors
  - Aggressive identification is required
  - Optimal management for RA still unknown
- There is good evidence for plaque instability
  - Driven mostly by inflammatory mechanisms
  - Aggressive suppression of inflammation may be helping here
- The importance of processes other than atherosclerosis, particularly microvascular disease, is re-emerging and needs a lot of investigation in terms of pathogenesis, clinical importance and relevance to outcome.
- Specifically designed clinical trials are needed but are very challenging and may require international collaborations

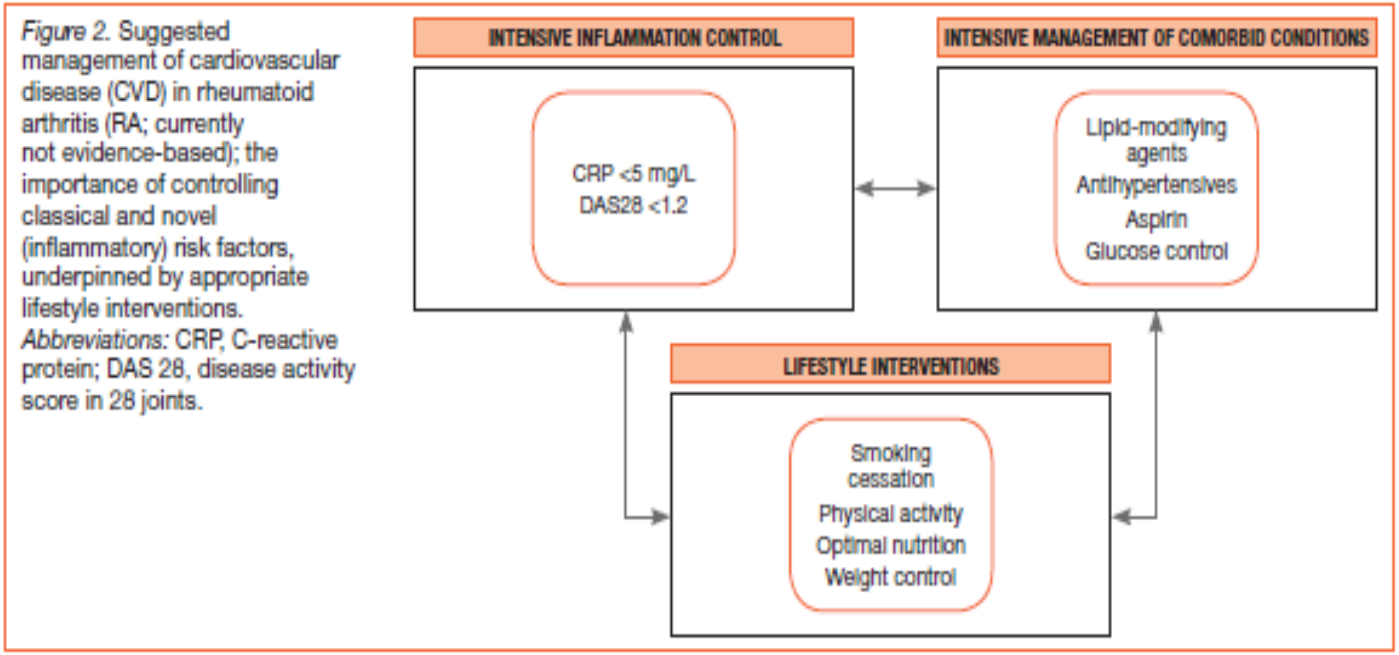


Figure 2. Suggested management of cardiovascular disease (CVD) in rheumatoid arthritis (RA; currently not evidence-based); the importance of controlling classical and novel (inflammatory) risk factors, underpinned by appropriate lifestyle interventions. *Abbreviations:* CRP, C-reactive protein; DAS 28, disease activity score in 28 joints.

Hot Topics Rheumatol Volume 1 • Issue 1 • Year 2013
ISSN 2282-5096

John & Kitas, 2013 *Toms et al: Immun., Endoc. & Metab. Agents in Med. Chem., 2008, 8, 259-274*

A practical approach

- Address system failures
- Address the INDIVIDUAL patient
- Use knowledge from other disease entities
- Facilitate the generation of RA-specific evidence through research

- **Use common sense**

Thanks to:

Research Fellows

- Giorgos Metsios
- Antonis Stavropoulos-Kalinoglou
- Vasilis Panoulas
- Dimitris Daousis
- Theodoros Dimitroulas
- Kostas Korontzis
- Tracey Toms
- Holly John
- Aamer Sandoo
- Armen Gasparyan
- Matt Banks
- Karen Douglas
- Jackie Smith
- Rebecca Storey
- Jet v van Zanten
- Gareth Treharne
- Liz Hale

Collaborators

- Yiannis Koutedakis (Birmingham + Greece)
- Doug Caroll (Birmingham)
- Joan Duda (Birmingham)
- Anton Wagenmakers (Birmingham)
- Deborah Symmons (Manchester)
- Jill Belch (Dundee)
- Jane Armitage (Oxford)
- Piet van Riel (Nijmegen)
- Anne Grete Semb (Oslo)
- Tore Kvien (Oslo)
- Petros Sfikakis (Athens)
- Sophie Mavrogeni (Athens)
- Janet Lord (Birmingham)
- George Karpouzas (LA)

Thanks to:

Funding bodies

- Arthritis Research UK
- British Heart Foundation
- Medical Research Council
- Welcome Trust
- Nuffield Foundation
- Lupus UK
- Sjogren's Syndrome Association
- BBSRC
- NIHR
- Dudley R&D
- UK CRN

The TRACE RA consortium