ΕΠΙΣΤΗΜΟΝΙΚΗ ΕΤΑΙΡΕΙΑ ΓΙΑ ΤΗ ΜΥΟΣΚΕΛΕΤΙΚΗ ΥΓΕΙΑ (ΕΠΕΜΥ)
ΡΟΔΟΣ, ΙΟΥΝΙΟΣ 2017

Η ΕΞΕΛΙΞΗ ΤΟΥ ΚΑΡΔΙΑΓΓΕΙΑΚΟΥ ΚΙΝΔΥΝΟΥ ΣΤΑ ΧΡΟΝΙΑ ΦΛΕΓΜΟΝΩΔΗ ΝΟΣΗΜΑΤΑ

(ΚΑΙ ΤΙ ΜΠΟΡΕΙ ΝΑ ΜΑΣ ΠΕΙ ΓΙΑ ΤΗ ΓΗΡΑΝΣΗ)

Professor George Kitas, MD, PhD, FRCP
RA Co-morbidity Research Group
Arthritis Research UK Epidemiology Unit
University of Manchester
College of Life and Environmental Sciences
University of Birmingham
Κεντρο Διερευνησης, Θεραπειας και Αποκαταστασης Ρευματικων Νοσηματων
Νοσοκομειο Υγεια, Αθηνα

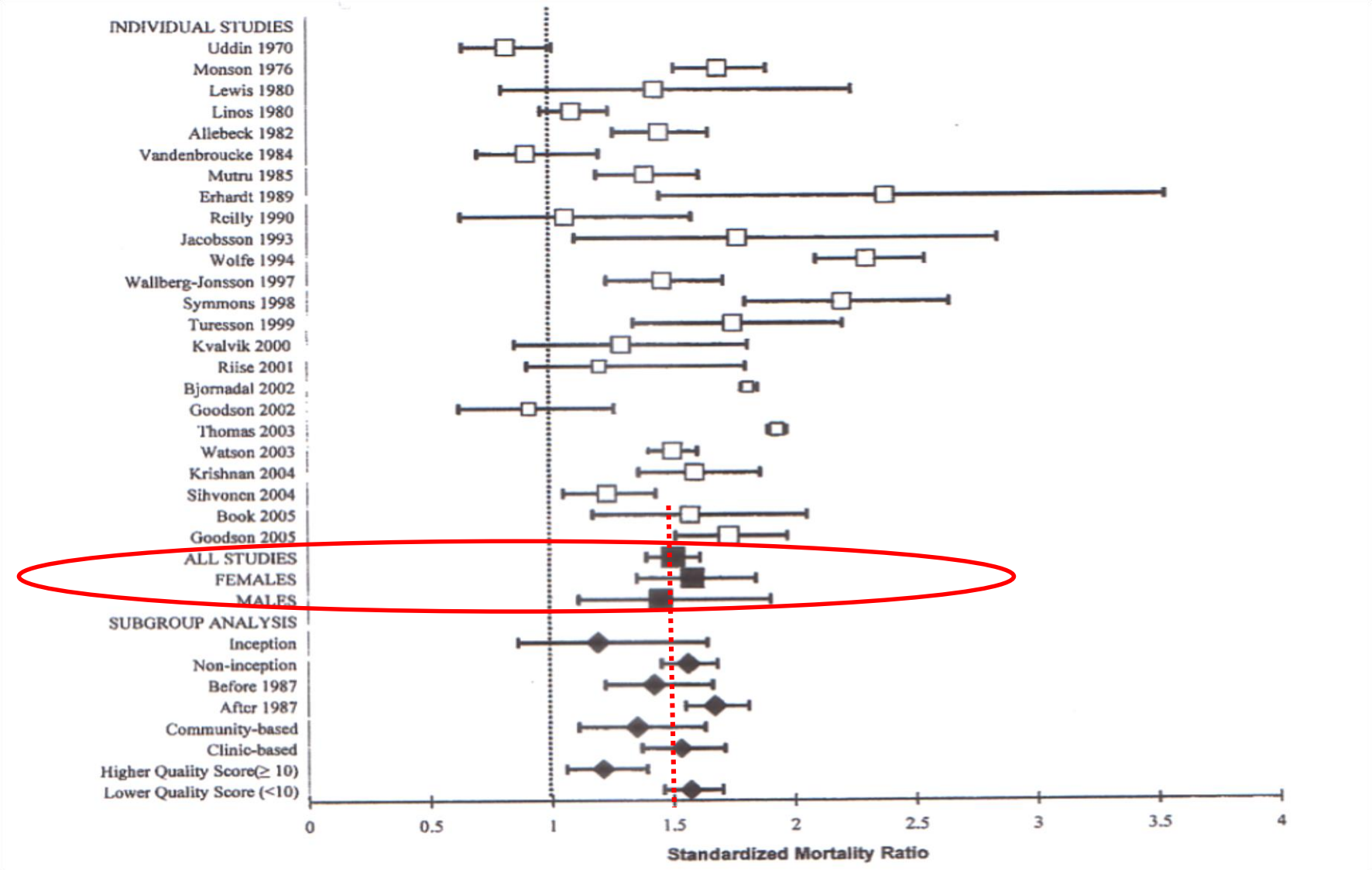
Conflict of interest statement

- **Clinical trials**
  - Global Chief Investigator: Astra-Zeneca
  - Chief Investigator: TRACE RA (partly funded by Pfizer)
  - Principal Investigator: Roche, Pfizer, Abbvie, UCB, BMS, Novartis
- **Unrestricted Grants**
  - Pfizer, (Wyeth), Abbott (Abbvie)
- **Honoraria for lectures / advisory boards**
  - Roche, Abbvie, Pfizer, Novartis, UCB, BMS, Lilly, GSK, MSD, Genesis
- **Congress organisation**
  - Abbvie, BMS, Genesis, MSD, Novartis, Pfizer, Roche, UCB
- **Hospitality**
  - Roche, Abbvie, UCB, Novartis
- **Co-Investigator:** BSRBR (partly funded by the industry)
- **Expert:** NICE (National Institute of Research & Clinical Excellence)

Outline

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

The problem: CVD mortality in RA



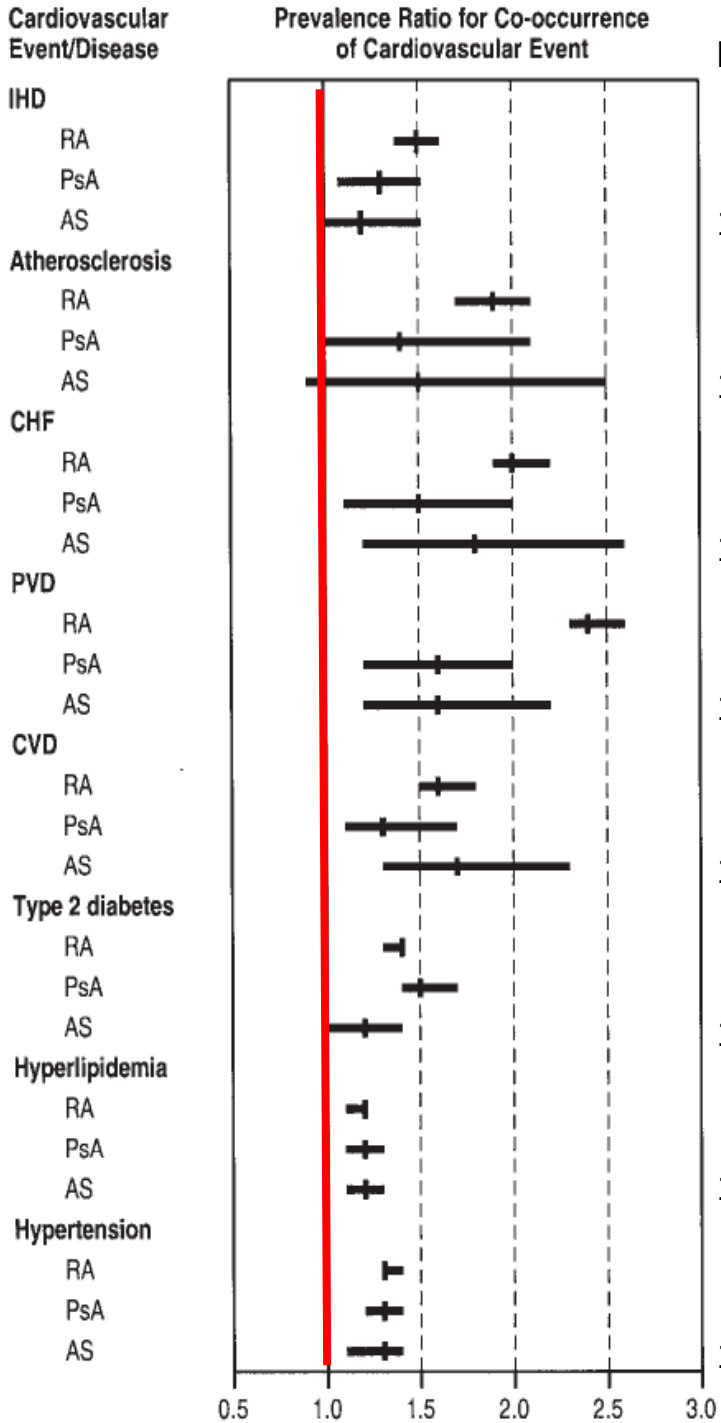
Avina –Zubieta et al, AC&R 2008; 59: 1690

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?

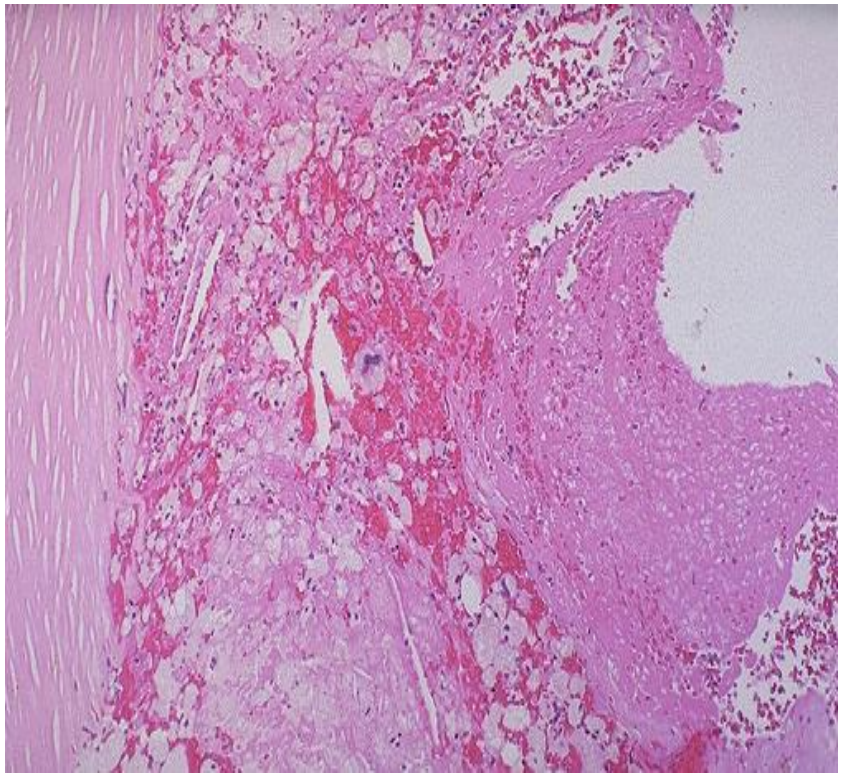
- Summary (back to the future)

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

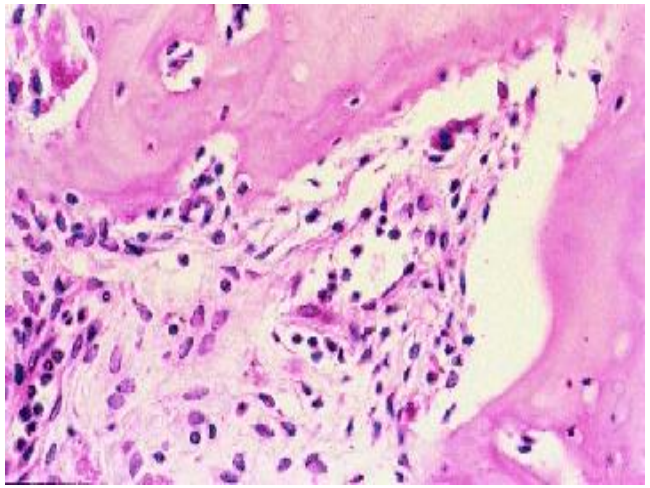
- Theory: the role of inflammation

“INFLAMMATION” et al.

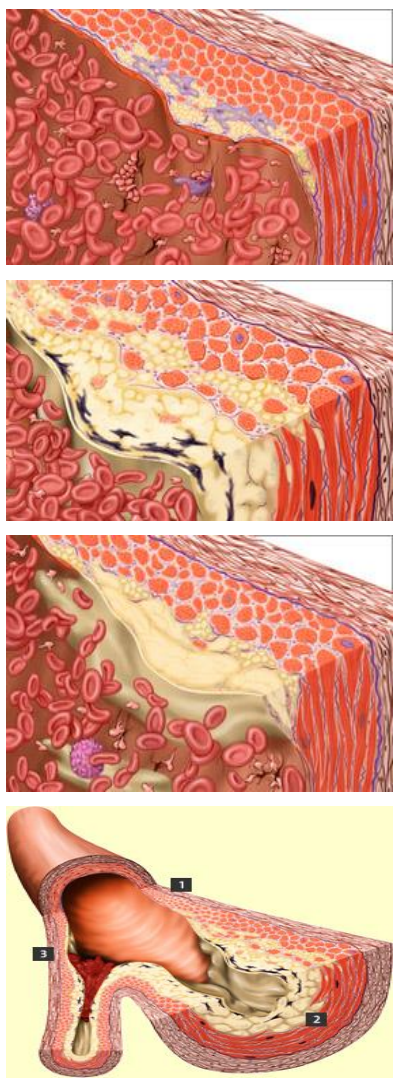
Atherosclerosis is a chronic inflammatory disorder…

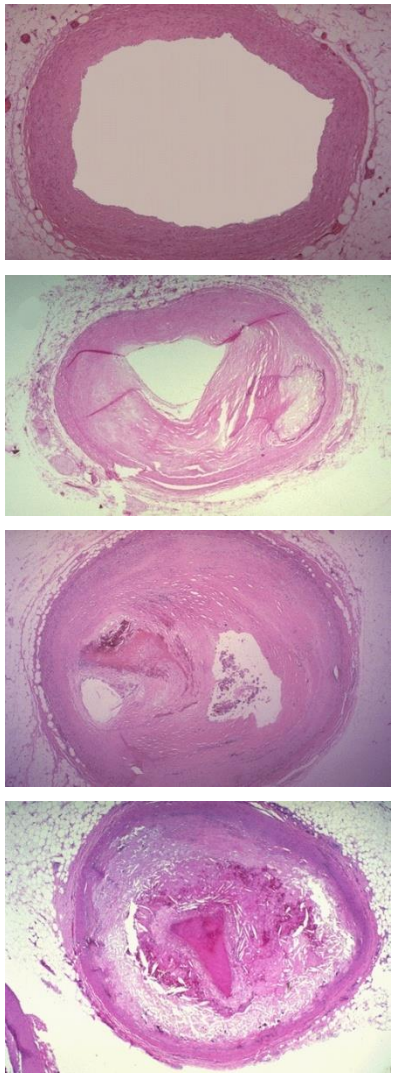


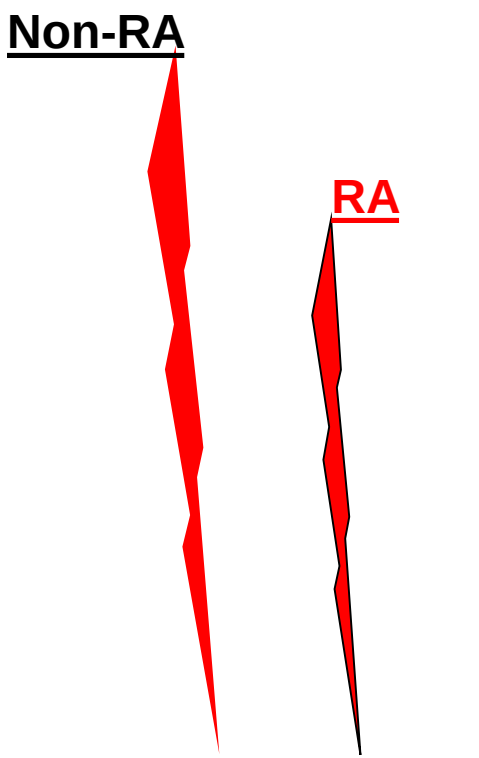
…similar to RA…

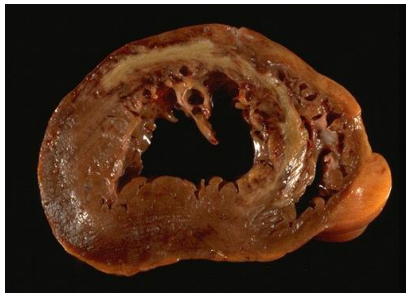


Accelerated atherosclerosis





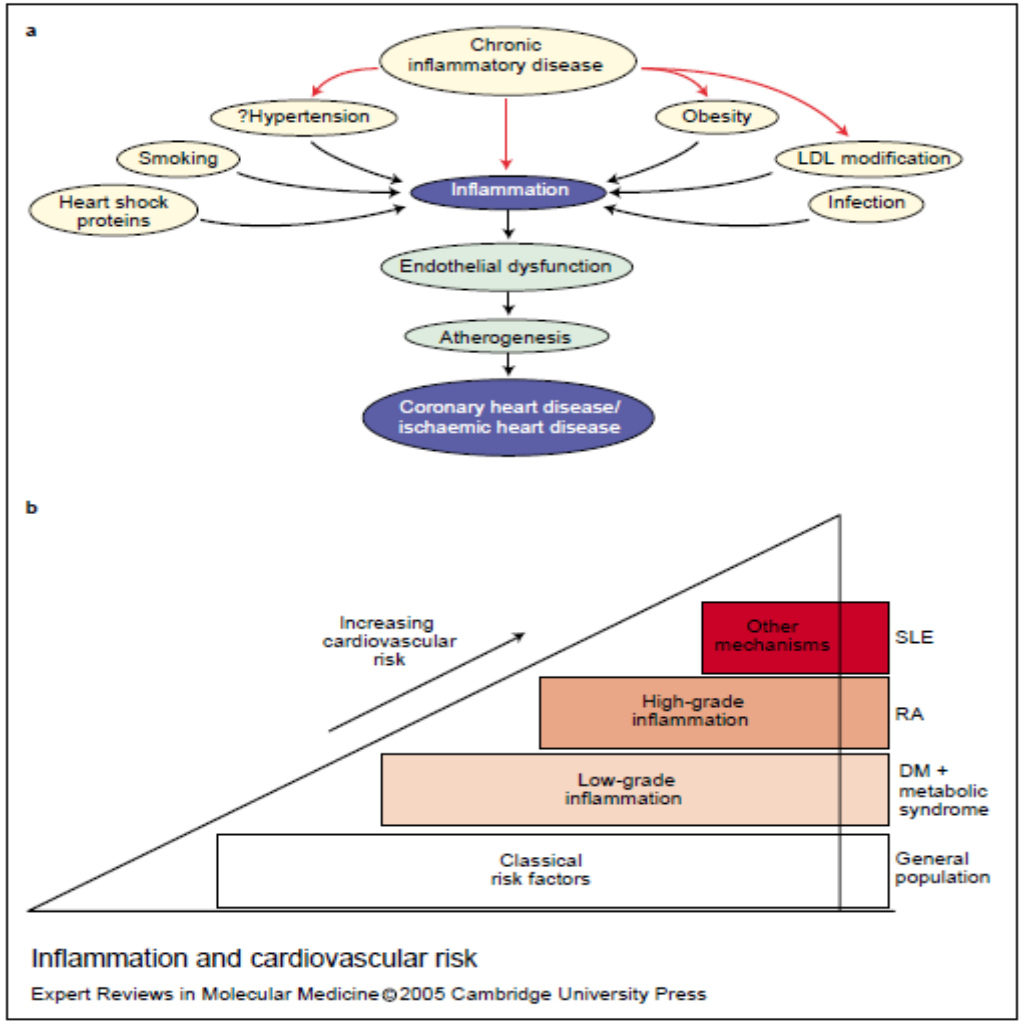




Stevens et al: Exp Rev Mol Med 2005; 7(7): 1-24

Effect of inflammation

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



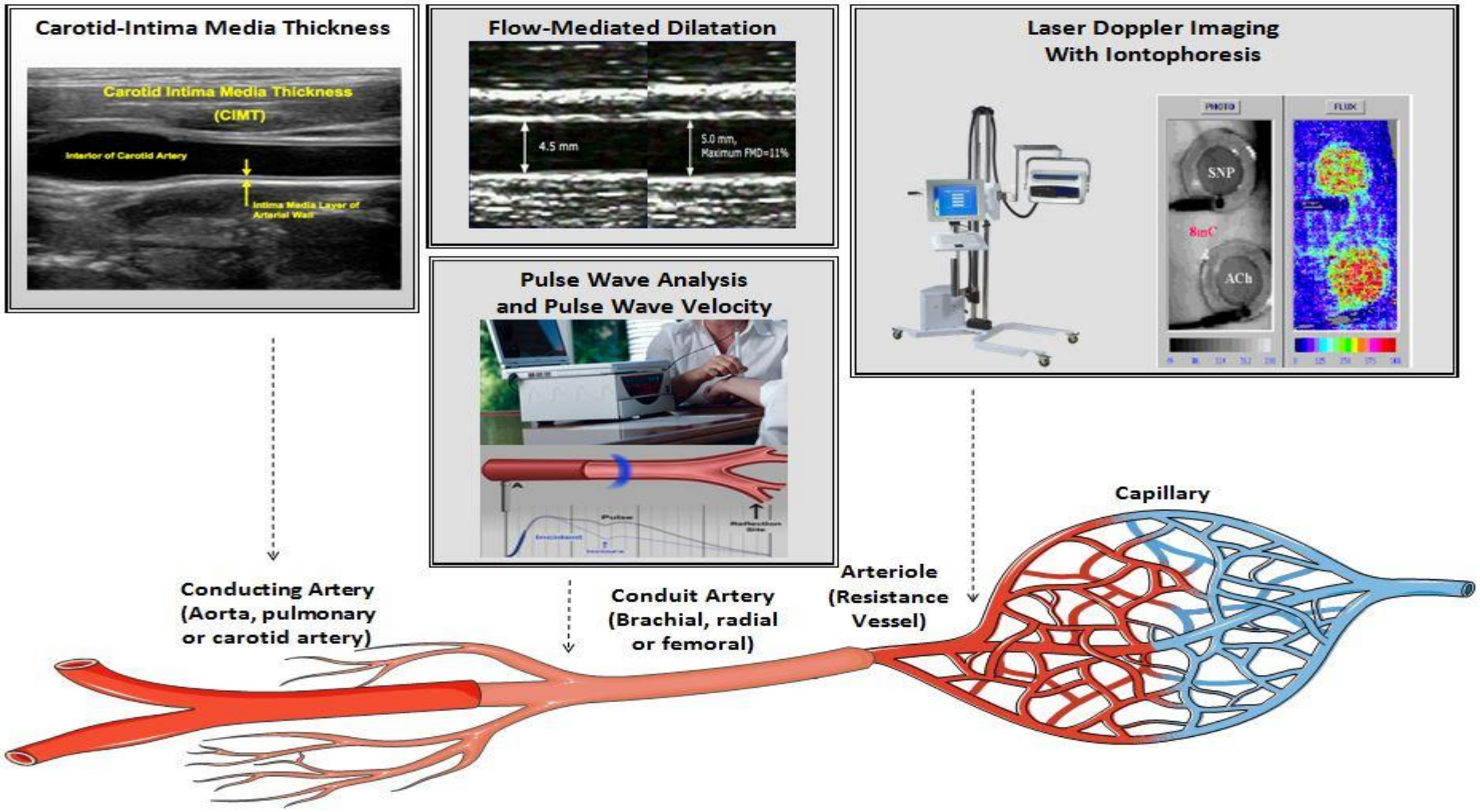
Inflammation and cardiovascular risk

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)

Sub-clinical atherosclerosis: Non-invasive vascular assessments



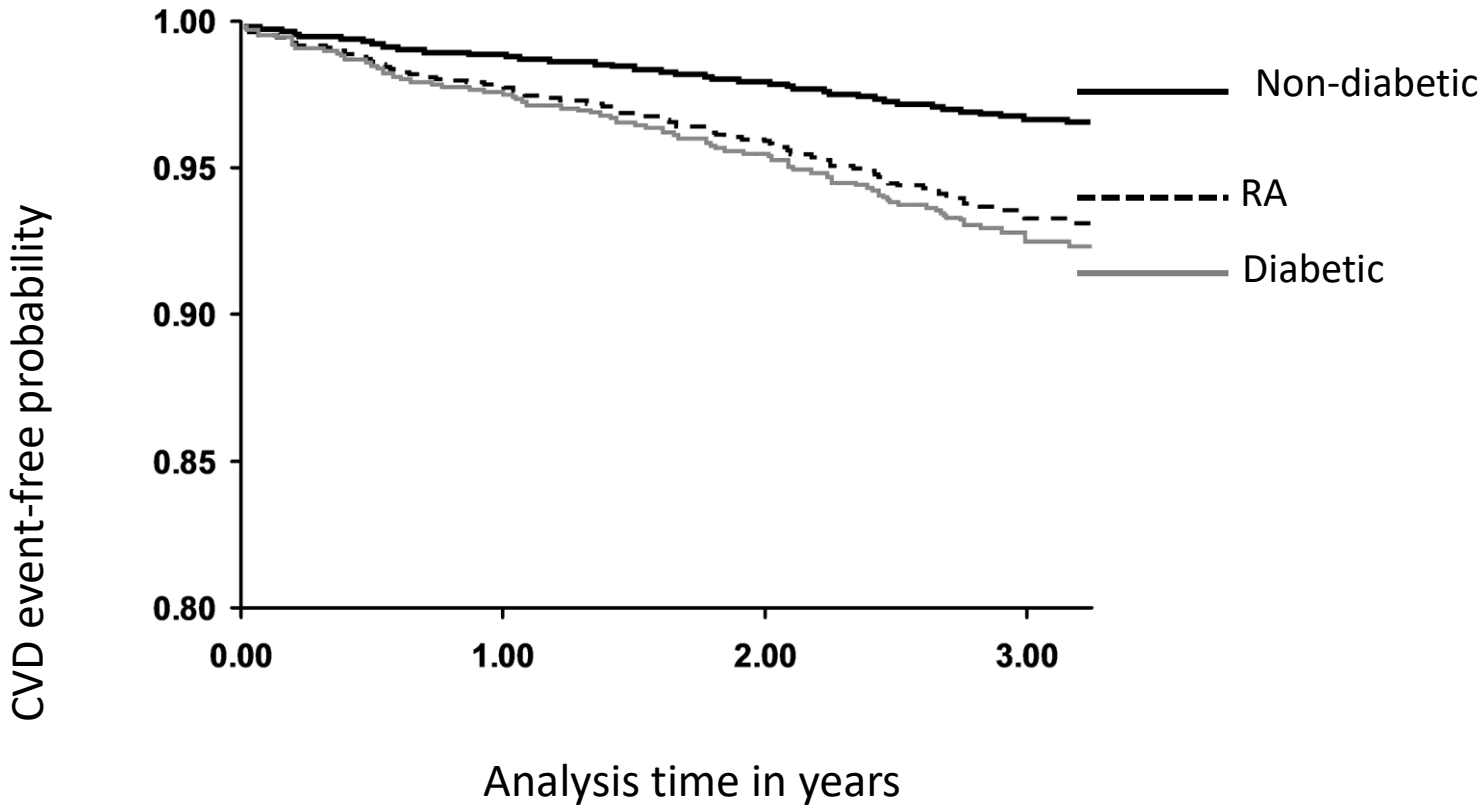
Are they good surrogates of future CVD events in RA?

Sandoo et al: Rheumatology 2011

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

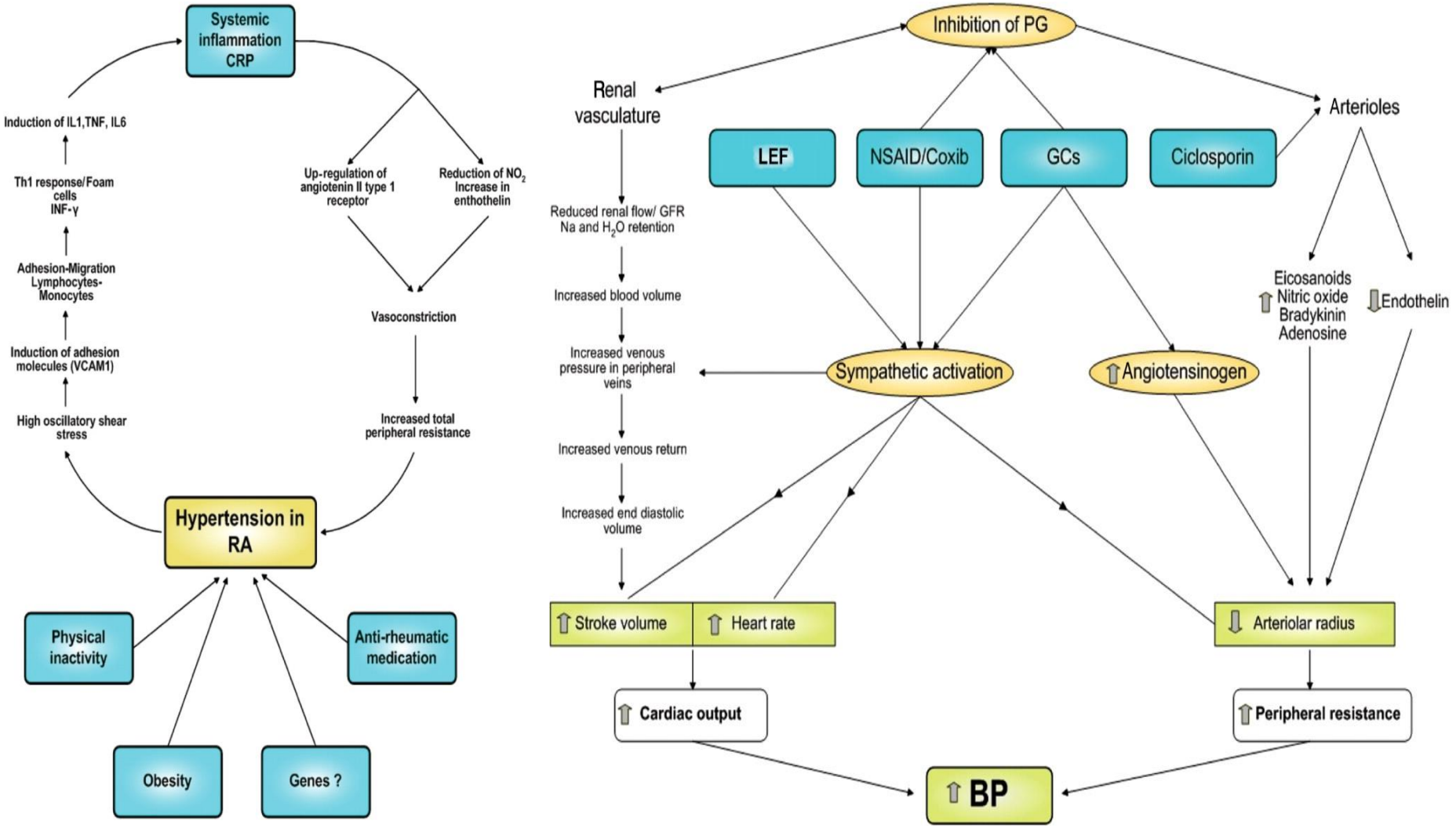
Stamatelopoulos et al, ATVB 2009; 29: 1702

Peters et al, Arthritis Rheum 2009; 61: 1571

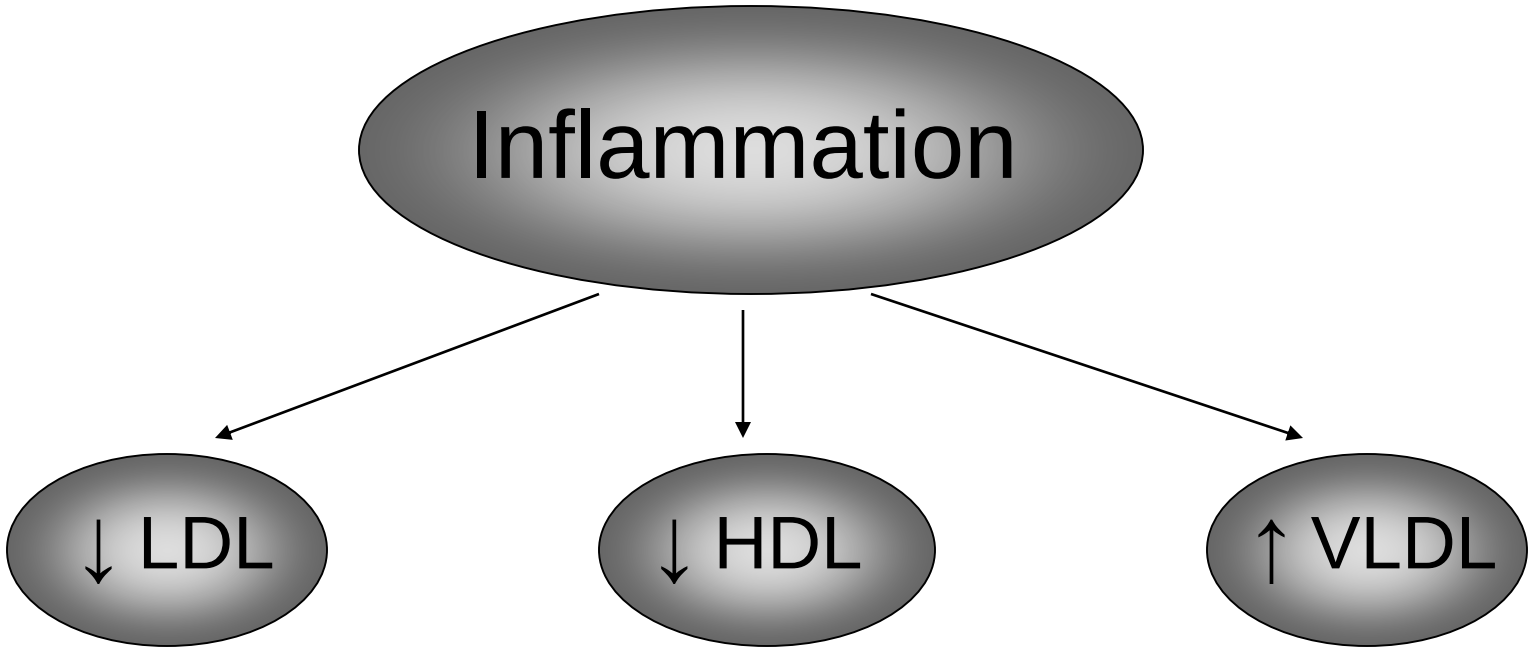
What is the evidence for (accelerated) atherosclerosis in RA?

- 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.)

Mechanisms of hypertension in RA



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



↑ Small dense particles

↑ PAF-AH activity

↑ sPLA2

↑ sphingolipid content

↑ ceruloplasmin & SAA

↑ sPLA2

↑ PAF-AH activity

↓ enzyme activity

(HL,LCAT, PLTP, CETP)

↓ enzyme activity

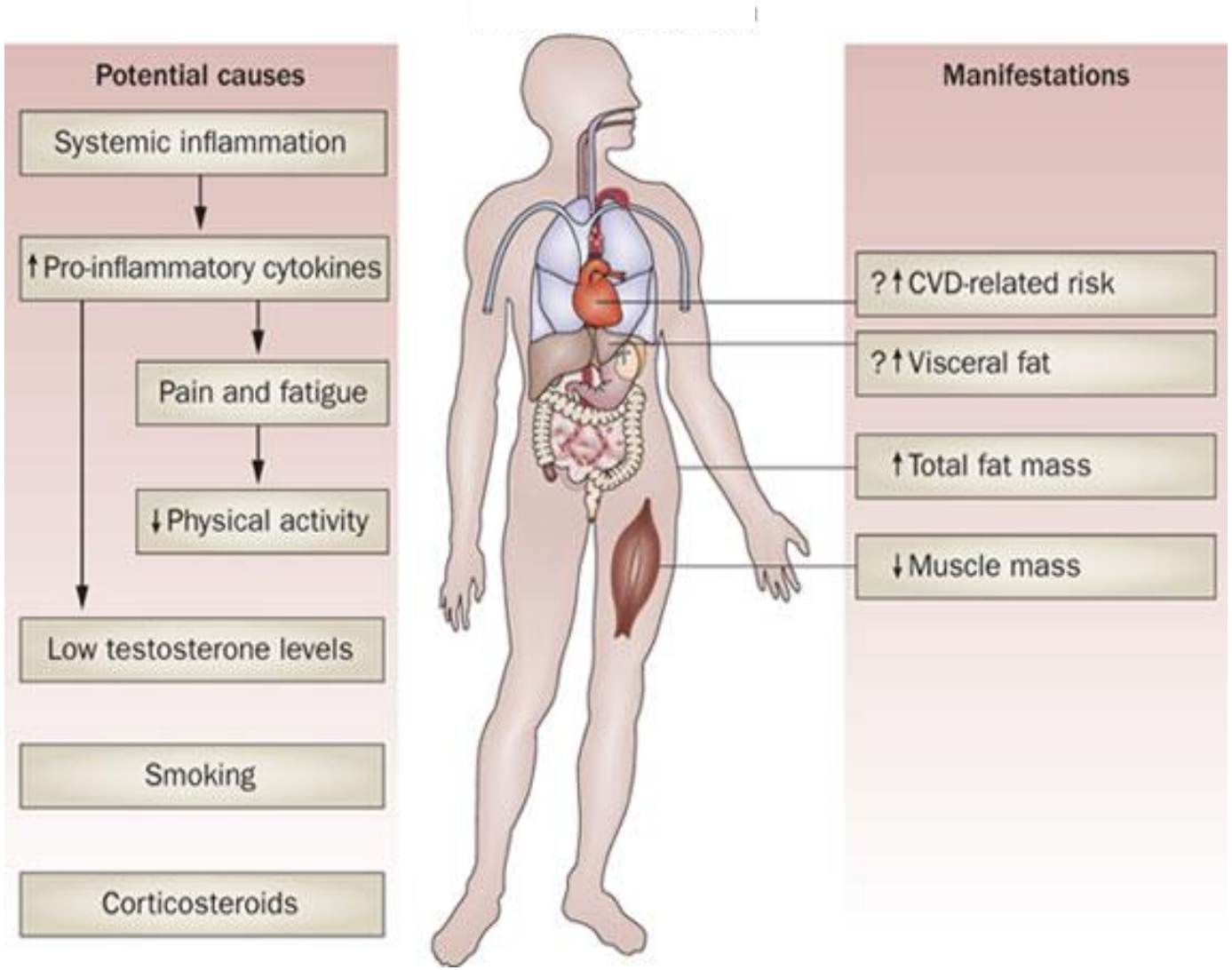
(HL, LPL)

↑ sphingolipid content

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

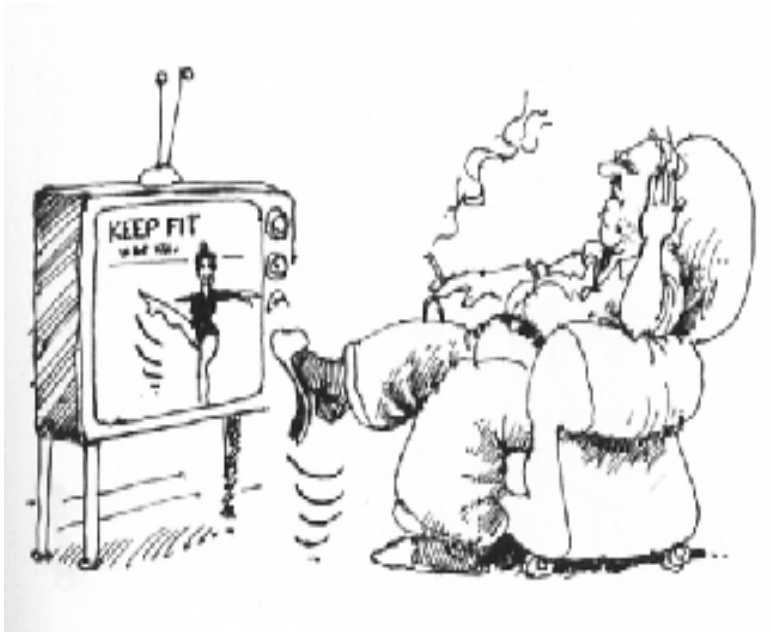
Toms T et al: RA susceptibility genes associate with dyslipidaemia in RA. ARD 2011

Body composition - Rheumatoid cachexia



Summers et al: Nature Rev. Rheumatol. 2010

Physical inactivity in RA



- Highly prevalent
- Very low levels of activity
- Various reasons
- Associates with:
  - vascular dysfunction
  - multiple CVD risk factors
  - basal metabolic rate
  - abnormal CV response to stress

Metsios et al. Open Cardiovasc Med J. 2010 Feb 23;4:89-96
Metsois et al. Eur J Cardiovasc Prev Rehabil. 2009 Apr;16(2):188-94
Sandoo et al. Arthritis Res Ther. 2012 Nov 28;14(6):R258
Van Zanten et al. Biol Psychol. 2008 Jan;77(1):106-10

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

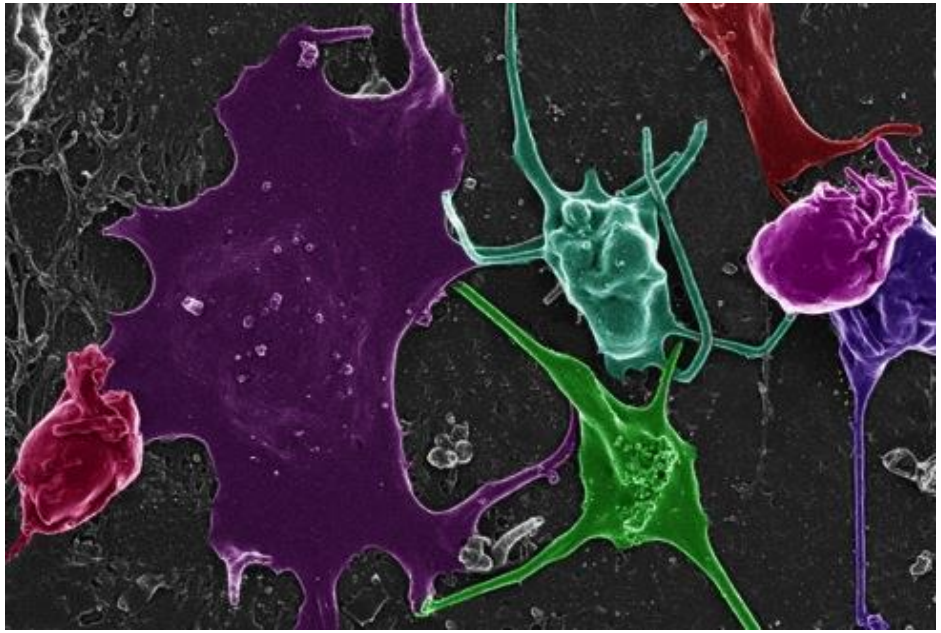
Outline

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

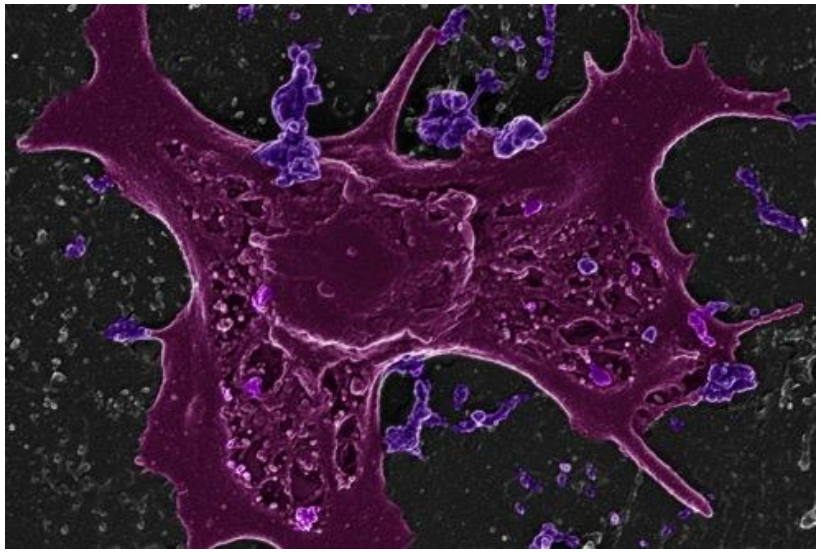
What is the evidence for plaque instability and pro-thrombotic phenomena?

- 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

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?

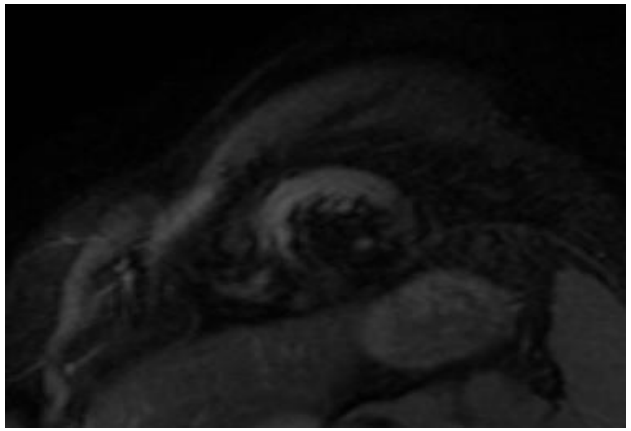
- **What is the nature of the problem?**
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - **Other mechanisms?**

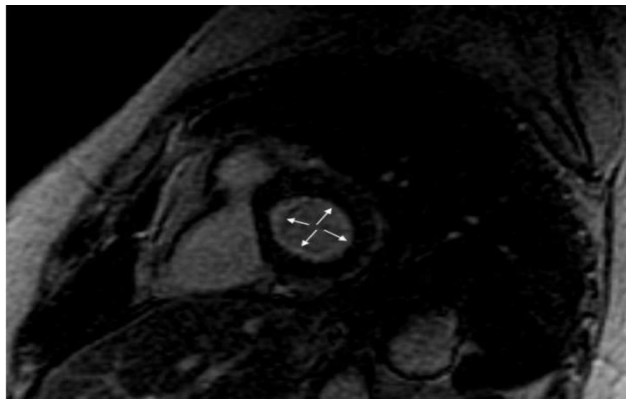
- Summary (back to the future)

Microvascular disease / dysfunction

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

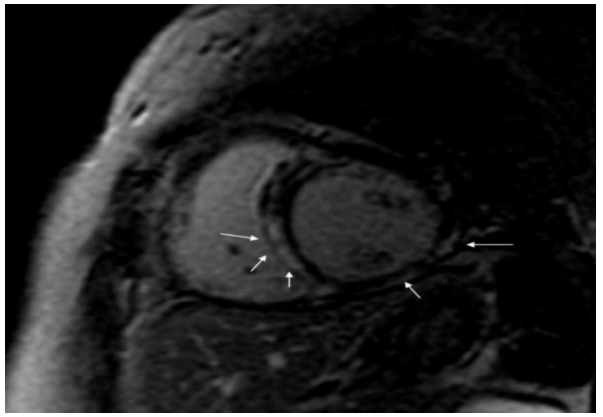
Myocarditis
STIR T2 (Oedema Imaging)

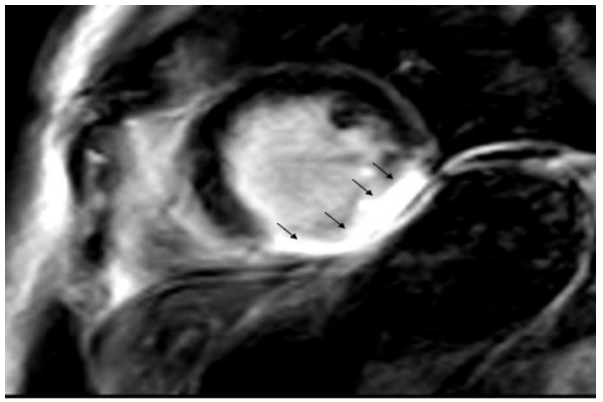




Diffuse subendocardial fibrosis
due to vasculitis

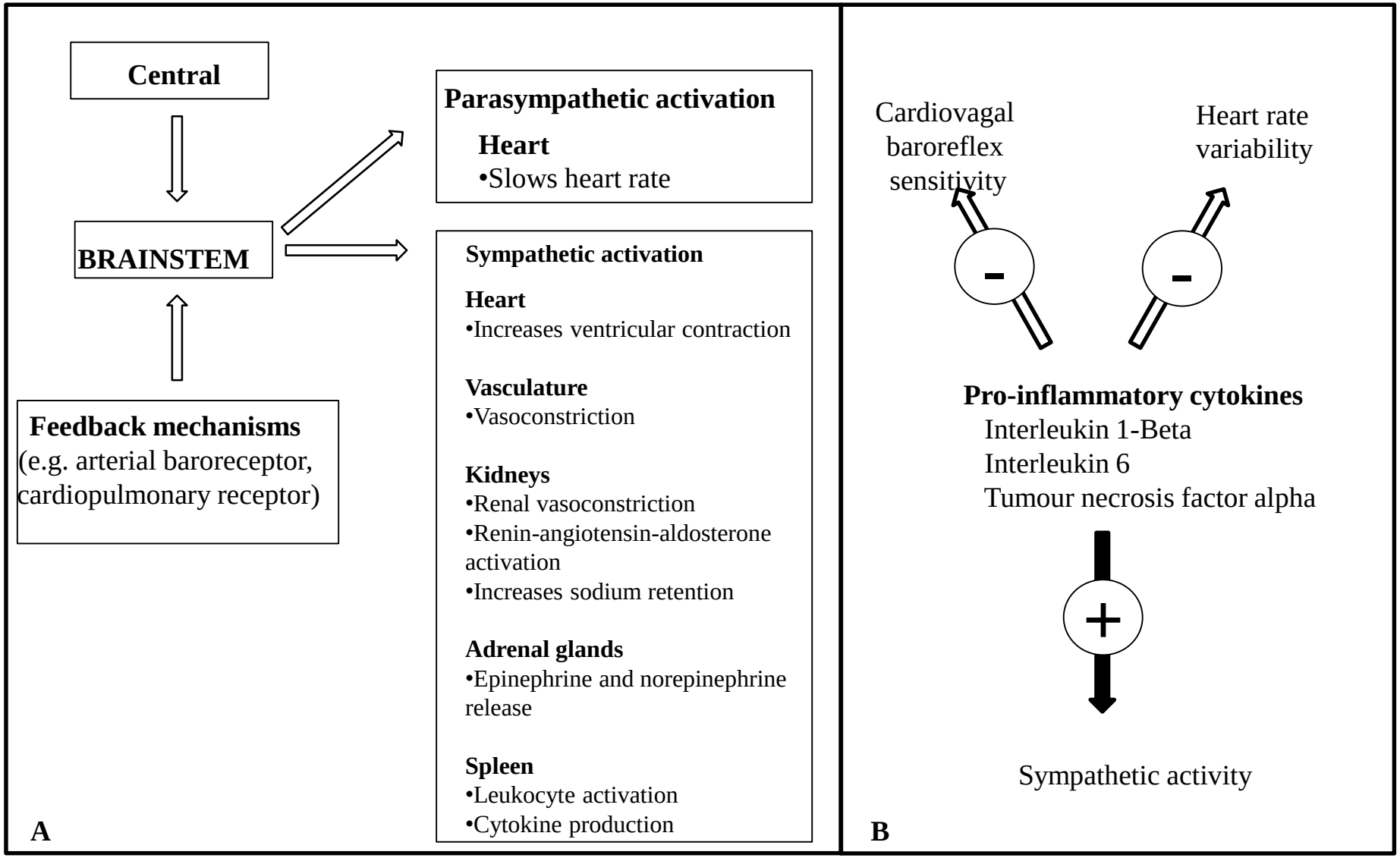
Myocarditis.
Late gadolinium enhancement (LGE) in
IVS, inferior and lateral wall of LV





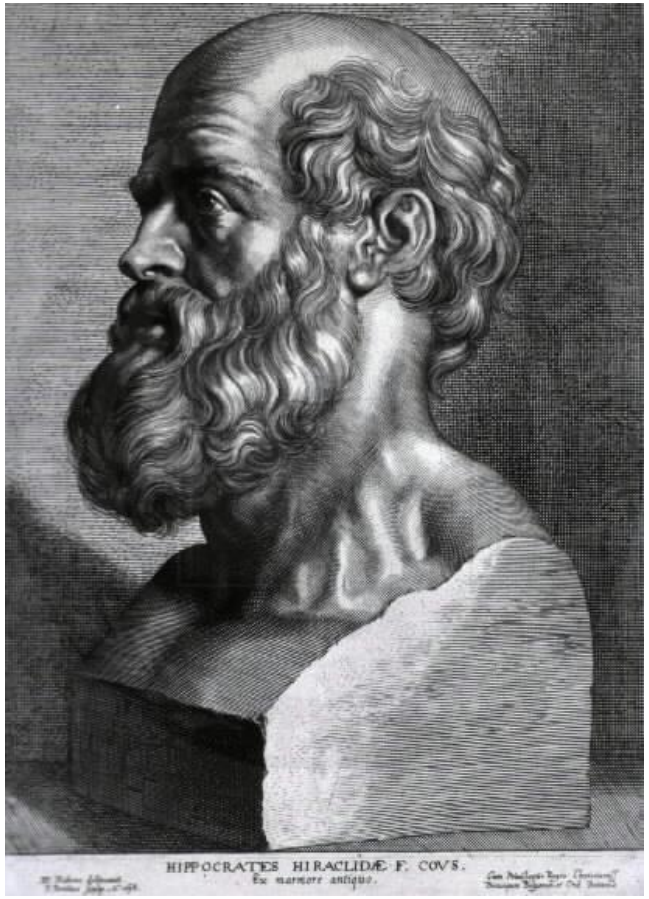
Myocardial infarction

Autonomic dysfunction



Ahmed Adlan et al (several)

(SOME) INTERVENTIONS

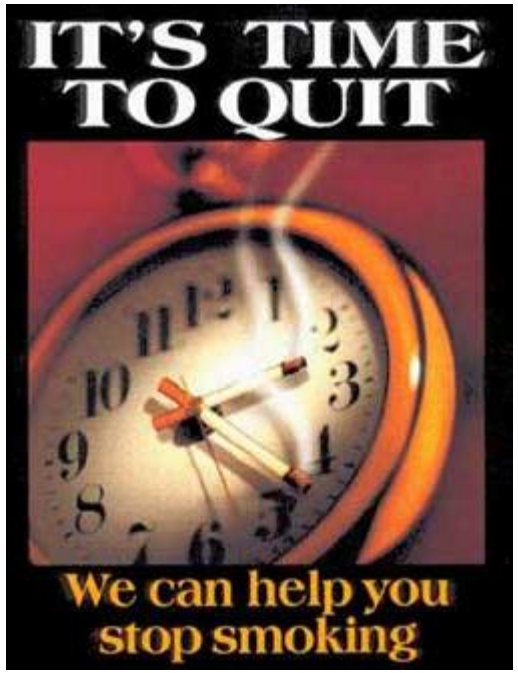


If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.

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.

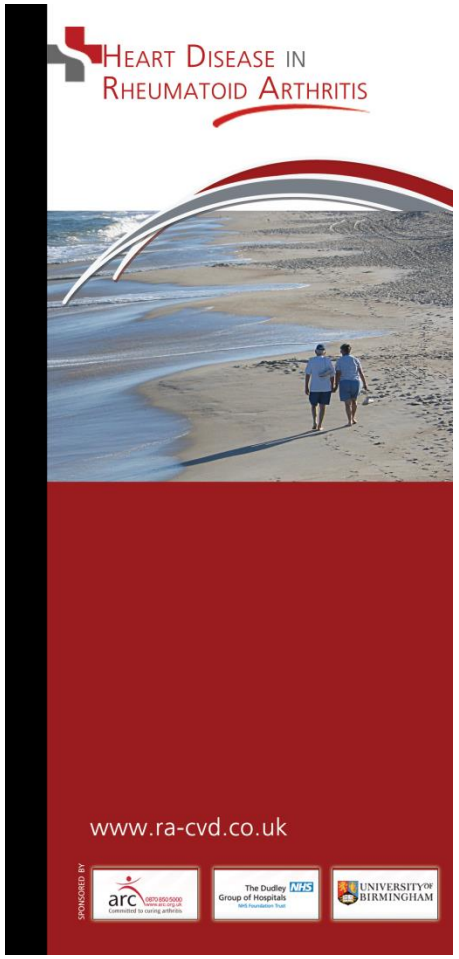
Regimen, in *Hippocrates*, trans. W. H. S. Jones (1931), Vol. 4, 229

Smoking cessation programmes

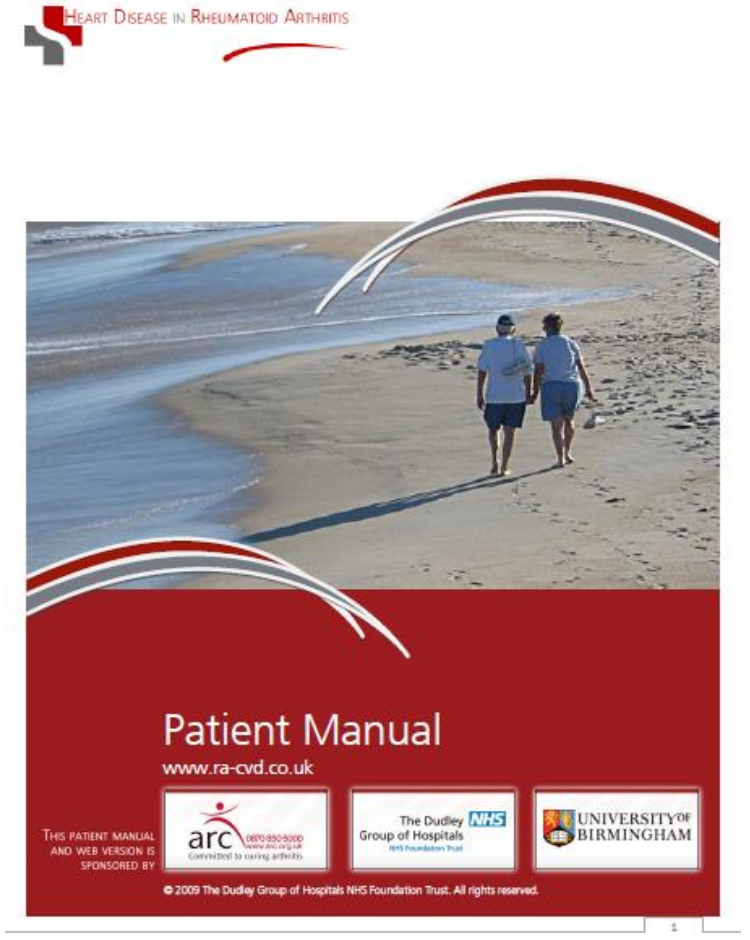


Educational material produced

Standard leaflet



Patient manual to accompany a detailed <u>cognitive behavioural</u> small group patient education course

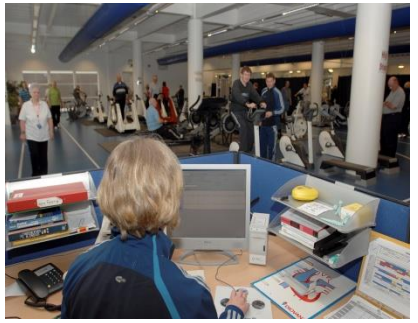


Individualised exercise interventions **Action Heart Dudley**

- **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**








Promoting **Autonomous Physical Activity** and Well-being in Rheumatoid Arthritis Patients

Dr Peter C. Rouse

J.L . Duda, J.J.C.S. Veldhuijzen van Zanten, G. Metsios, N. Ntoumanis, C., Yu, & G. D., Kitas

Rouse et al., In the beginning: Role of autonomy support on the motivation, mental health and intentions of participants entering an exercise referral scheme. *Psychology and Health, (2011).*

Yu et al., Motivation-related predictors of physical activity engagement and subjective vitality in rheumatoid arthritis patients: A test of basic needs theory. *British Journal of Health Psychology, (Submitted)*

TRIAL OF ATORVASTATIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS (TRACE RA) (ISRCTN: 41829447)

G. D. Kitas, P. Nightingale, J. Armitage, N. Sattar,
TRACE RA Consortium, J.J. Belch, D.P. Symmons

Outline

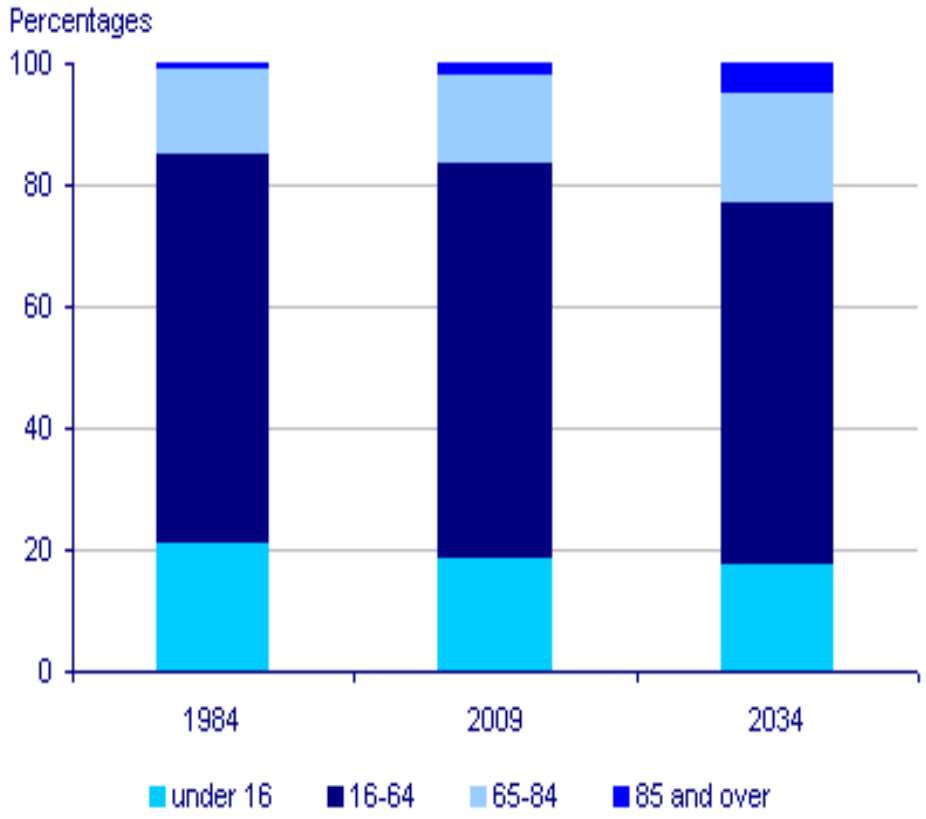
- What is the problem?
- What is the nature of the problem?
  - (Accelerated) Atherosclerosis?
  - Plaque instability?
  - Other mechanisms?
- **Summary (back to the future)**

Looking to the future

MUSCULOSKELETAL AGEING

MRC – Arthritis Research UK Centre for Musculoskeletal Ageing Research

Strategic Need:
We are an Ageing Population



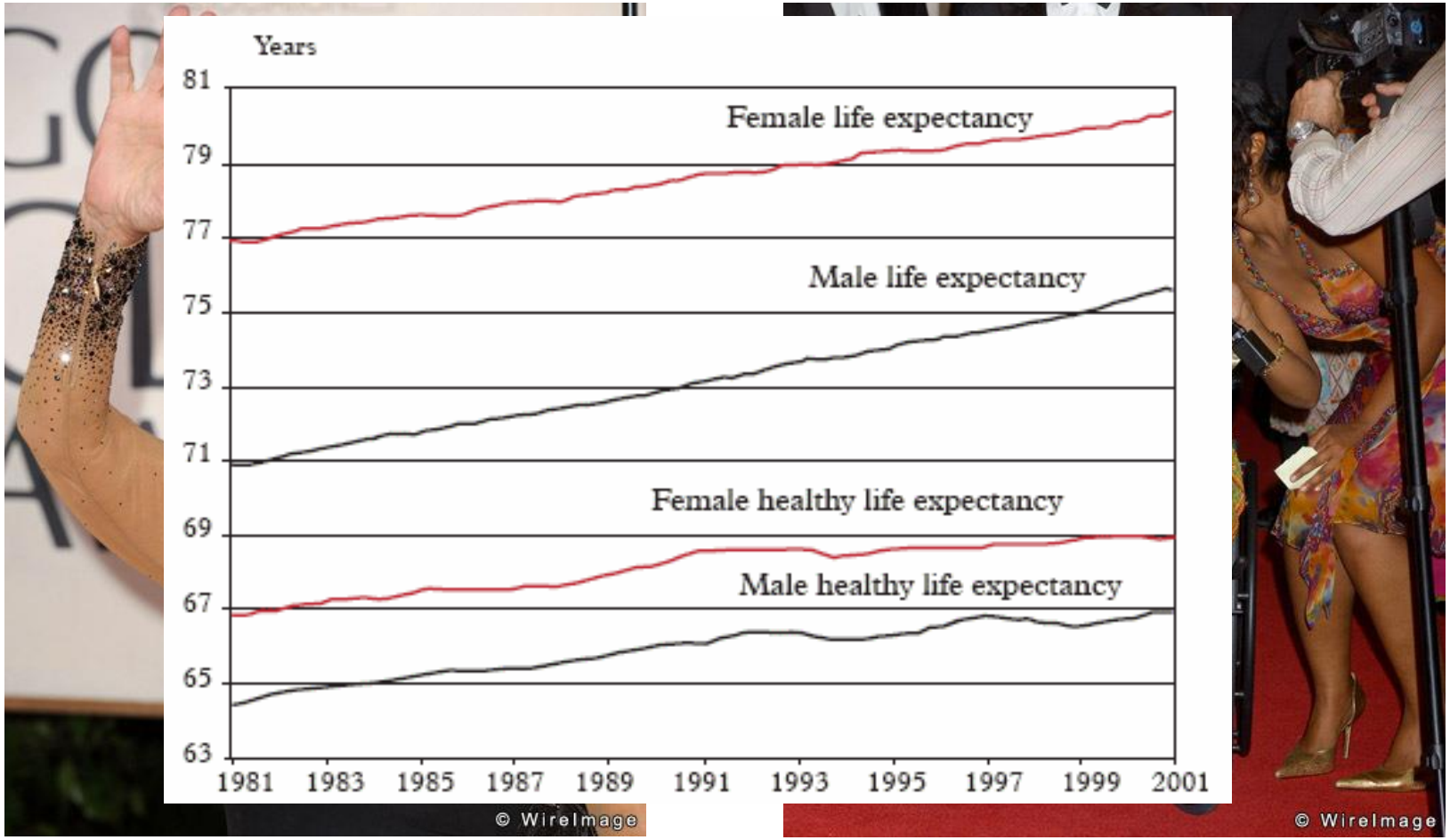
Between 1984-2009:

- **Number of individuals in UK aged ≥65 years increased by 1.7 million**
- **Number of individuals aged ≥85 years more than doubled to 1.4 million**

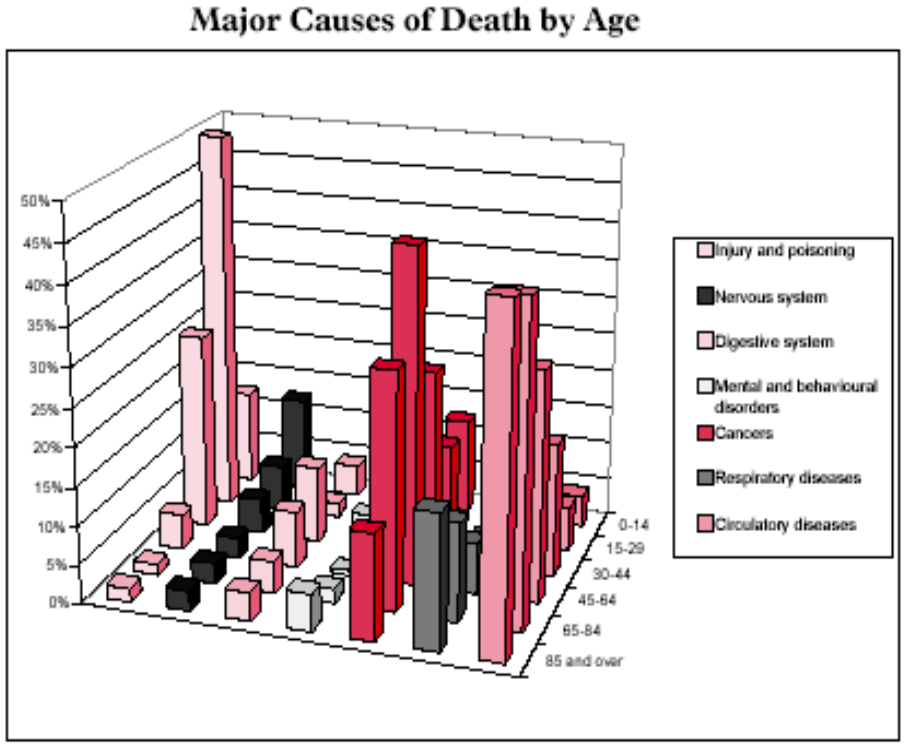
By 2034:

- **23% of population ≥65 years**
- **5% of population ≥85 years**

Strategic Need:
We are not all Ageing Well

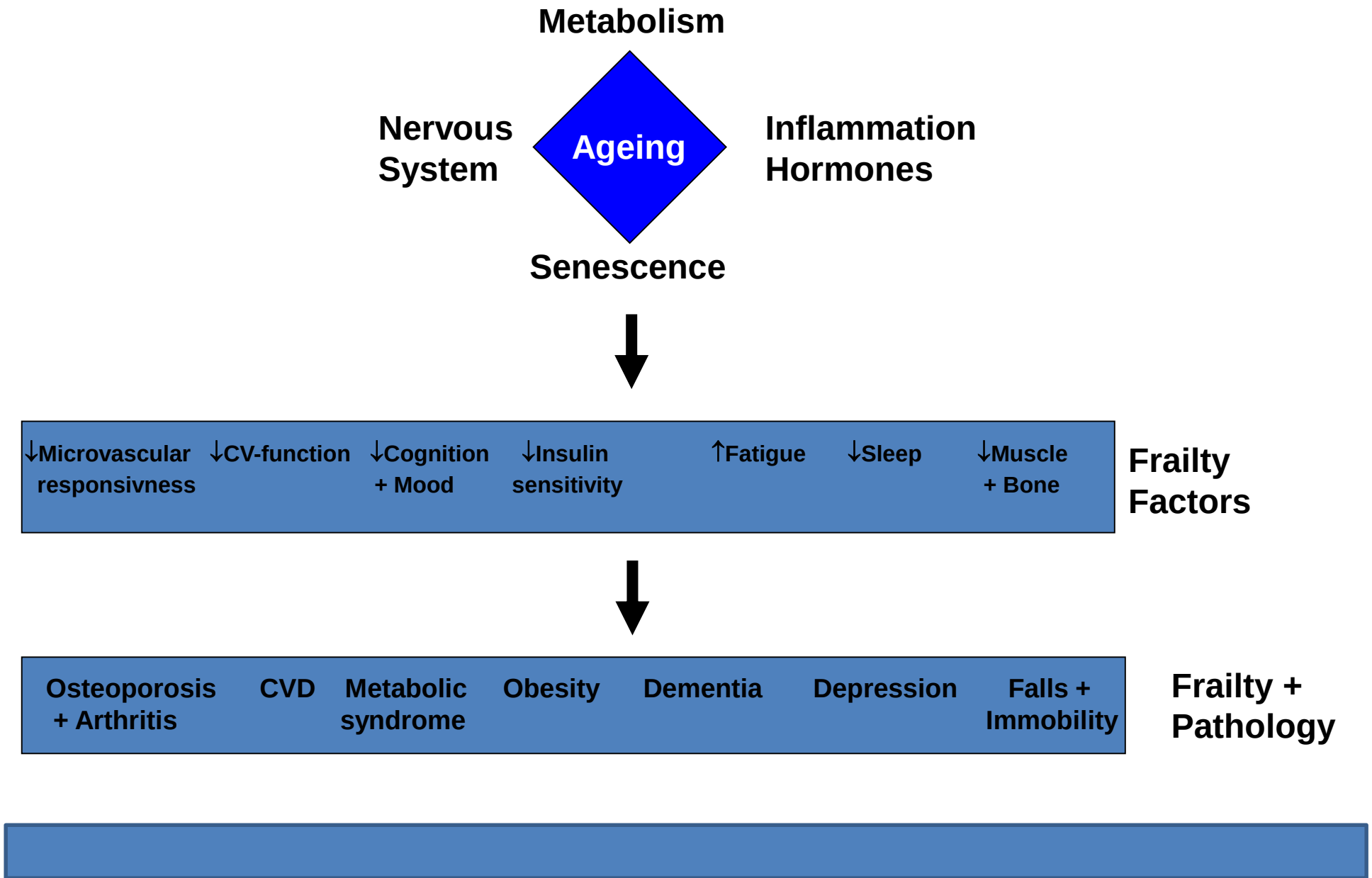


Strategic Need:
Death is cheap, Unsuccessful Ageing is expensive

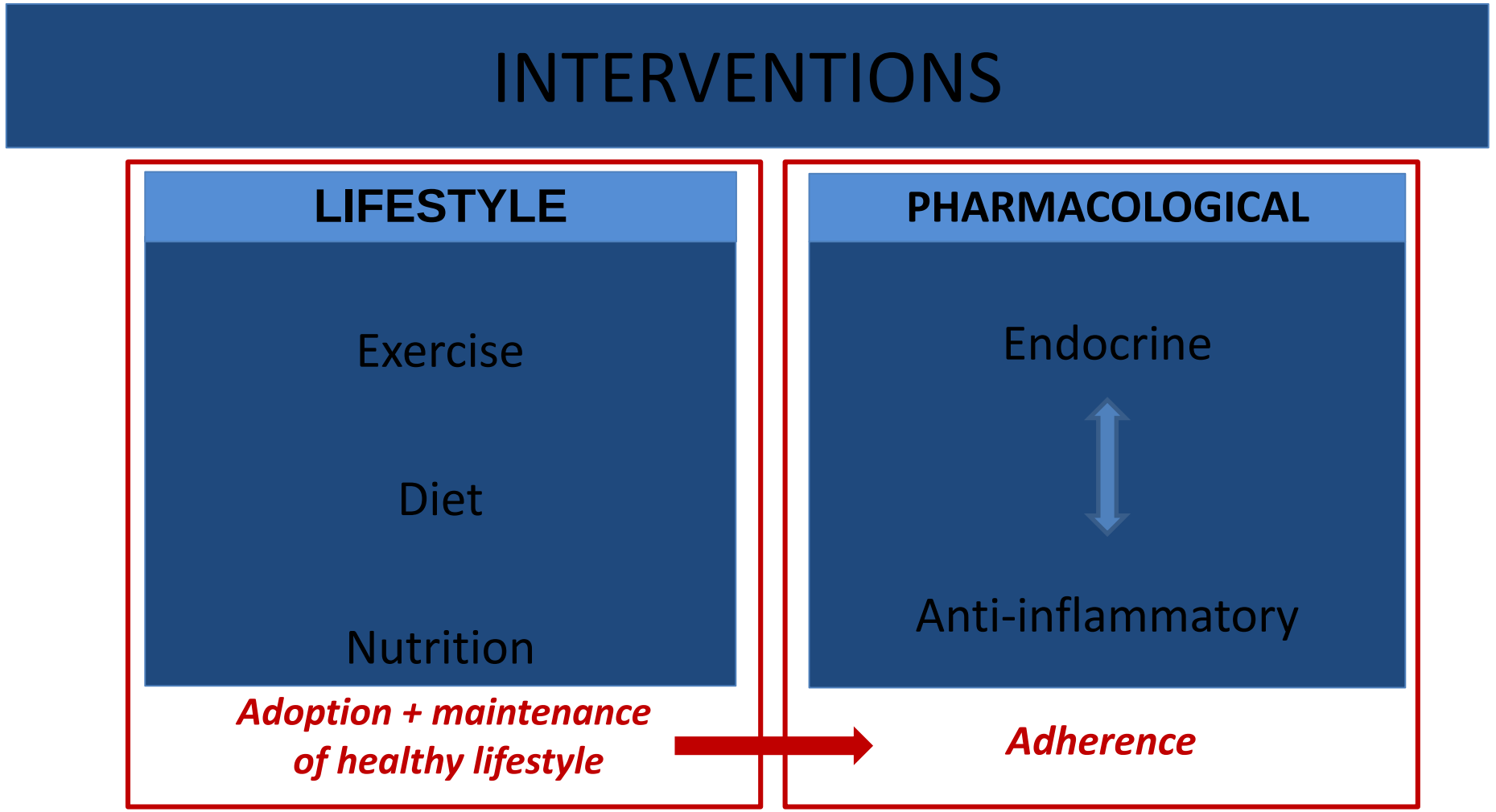


- Falls: 1 in 3 adults >65 fall each year
- Physical frailty and inactivity: 17% of men and 13% of women aged 65-74 are physically inactive. Cost £8.2bn (excludes £2.5bn for obesity);
- Osteoporosis: 3m affected in UK, results in 300,000 fractures, cost £1.7 billion;
- Arthritis: >6m patients, 1% of gross national product;
- Incontinence: 1 in 4 older adults affected ; 2% of NHS budget, £1.4 bn
- …….

Vision: To understand Human Ageing in order to prevent Musculoskeletal Frailty


Metabolism
Nervous System
Ageing
Inflammation Hormones
Senescence
↓Microvascular responsivness
↓CV-function
↓Cognition + Mood
↓Insulin sensitivity
↑Fatigue
↓Sleep
↓Muscle + Bone
Frailty Factors
Osteoporosis + Arthritis
CVD
Metabolic syndrome
Obesity
Dementia
Depression
Falls + Immobility
Frailty + Pathology

Lifestyle and Pharmacological Interventions in Healthy Ageing



Lifestyle and Pharmacological Interventions in Healthy Ageing

Pharmacological

Endocrine ⟷ **Anti-inflammatory**

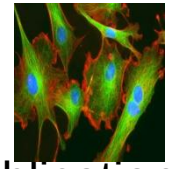
- 11beta-HSD1 inhibition
- Anti-cytokine therapy
  - Anti-TNFalpha
  - Anti-IL6R
  - IL-1RA

ARUK-MRC Centre for Musculoskeletal Ageing Research

What will significant Impact look like?

£££££

Increased funding,
Improved leverage



Publications in basic and applied ageing research

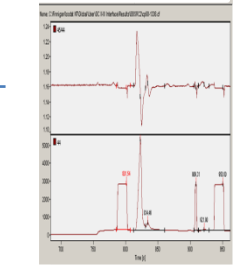
Validating Interventions in different settings

Arthritis Research UK

MRC Medical Research Council

ageUK

Influencing health + research policy



Evidence base for interventions

Consolidated industry links

Increased research capacity and collaborations

Public engagement at national level

UNIVERSITY OF BIRMINGHAM

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)
- Steve Young (Birmingham)
- Helen Griffiths (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