# Vascular risk management in rheumatoid arthritis patients with/without inflammatory activity

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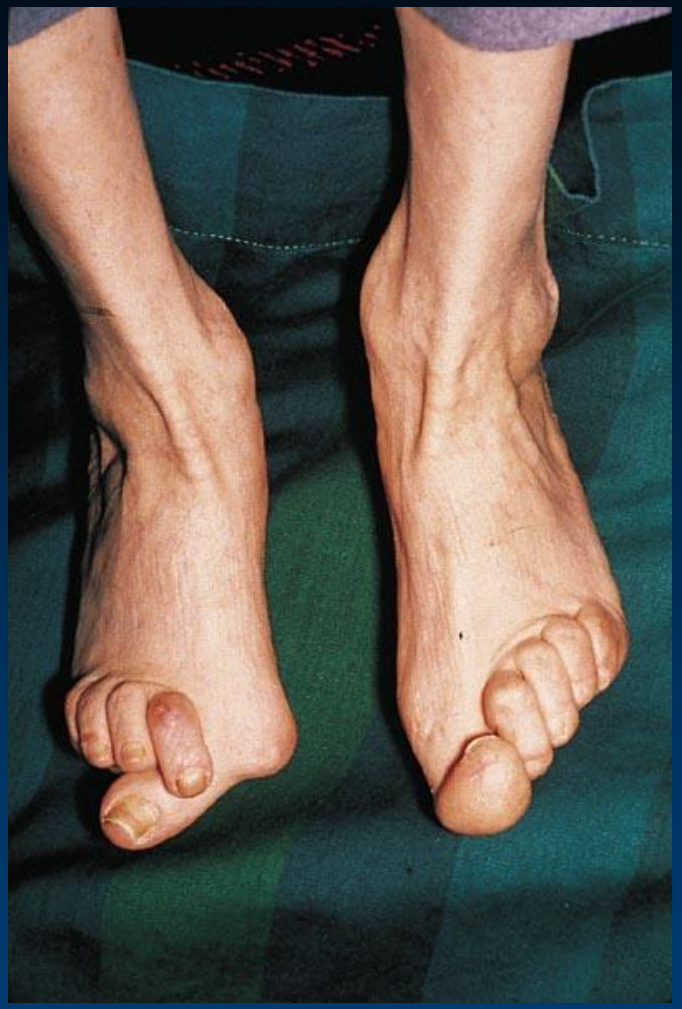
# Cardiovascular risk in rheumatoid arthritis (RA)

- The cardiovascular risk in RA:
  - Increased or not ?
  - Comparison with diabetes?
- Should RA be considered an independent CV-risk factor for which CV-RM is mandatory?
- What is the evidence toward treatment interventions?
  - Antihypertensives & statins
  - Antirheumatic drugs
- CV-RM in the Netherlands
  - Adapted according to disease activity?



# Epidemiology

- RA: most prevalent chronic inflammatory joint disease
  - 1 – 2% Caucasians
- Disease onset
  - 40 - 60 yrs, 3 x more often in women
  - < 16 yrs  Juvenile idiopatic arthritis (JIA)

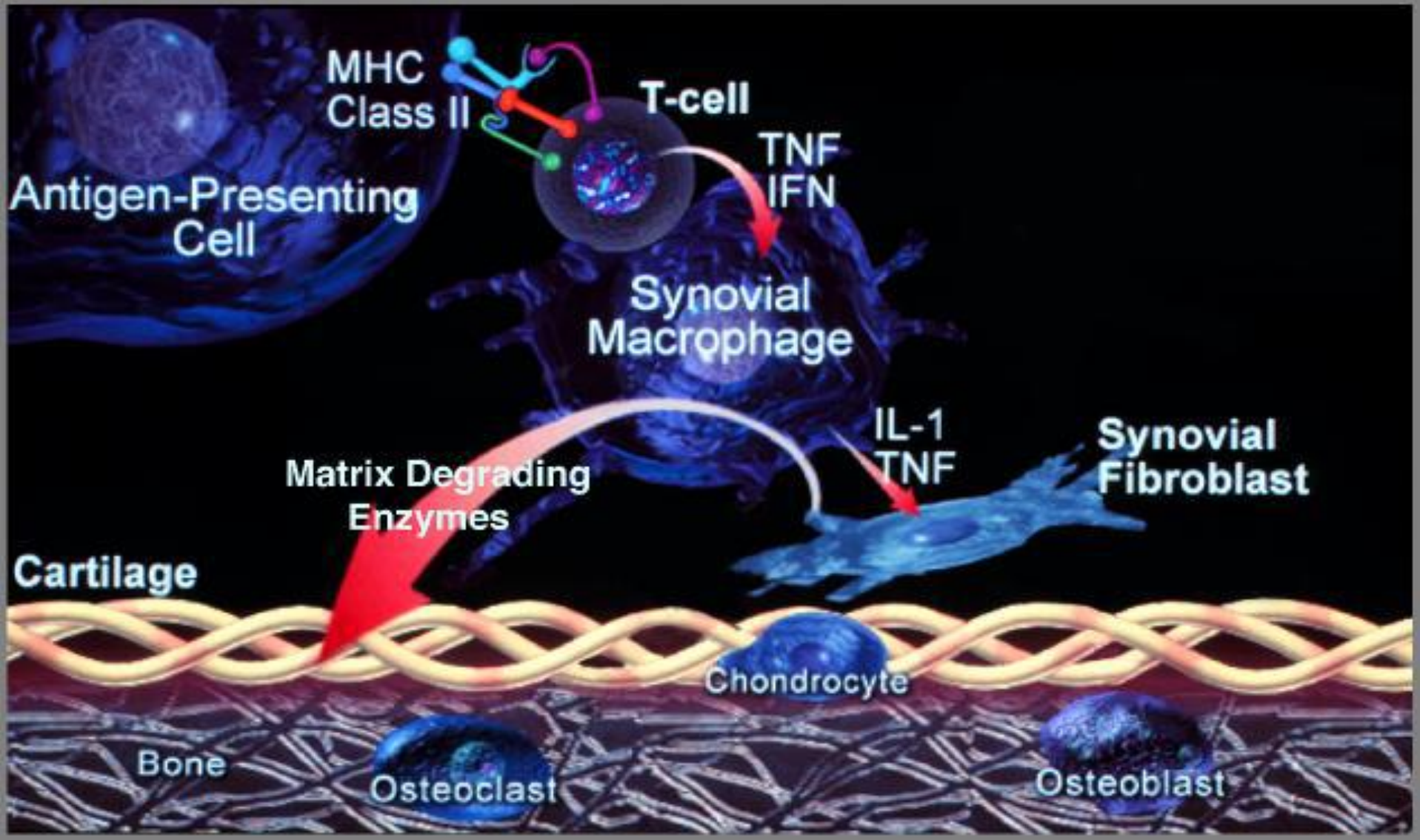
# Pathogenesis I

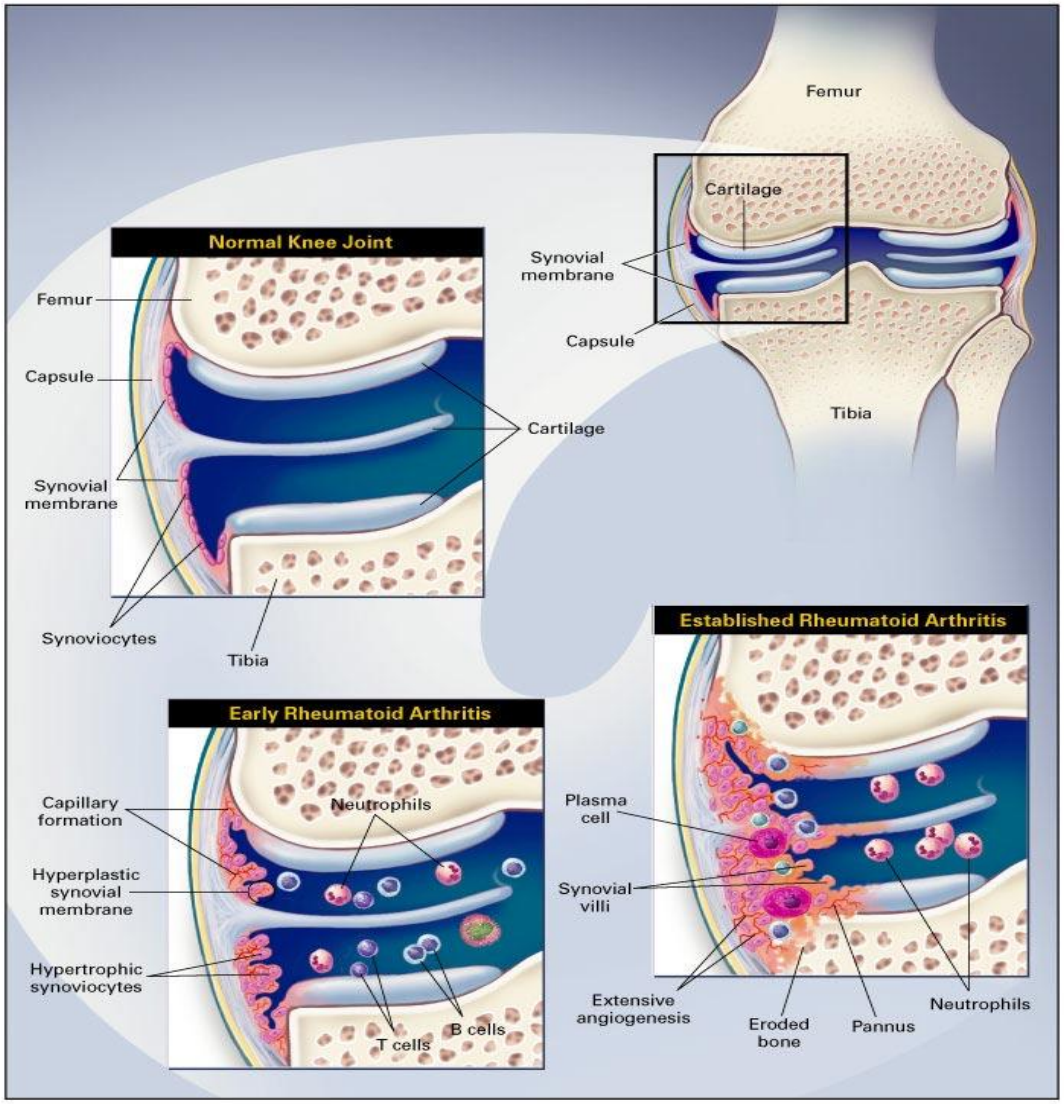
- Genetic factors
  - HLA-class II antigens (HLA-DR4 and -DR1)
  - Hereditary (susceptibility) component
- Hormonal factors
  - Higher risk in fertile women
  - Lower disease activity during pregnancy
- Initial infectious component?

# Pathogenesis II

- T-cell mediated inflammation:
  - Arthritogenic peptides bind to antigen-presenting cell (APC, macrophage)
  - APC binds T-cell
  - T-cell activation ==> cytokine production ==> inflammatory reaction against auto-antigens of the synovium of the joint

# Cells and Cytokines in the Arthritic Joint




Femur
Cartilage
Synovial membrane
Capsule
Tibia
Normal Knee Joint
Femur
Capsule
Synovial membrane
Synoviocytes
Tibia
Cartilage
Early Rheumatoid Arthritis
Capillary formation
Hyperplastic synovial membrane
Hypertrophic synoviocytes
Neutrophils
T cells
B cells
Established Rheumatoid Arthritis
Plasma cell
Synovial villi
Extensive angiogenesis
Eroded bone
Pannus
Neutrophils

# Extra-articular manifestations

- Fatigue, loss of weight, fever, anemia
- Pulmonary: pleuritis, noduli, fibrosis
- Cardiac: peri/myocarditis, valve disorders
- Eyes: (epi)scleritis
- Vasculitis: ulcers, renal disorders, ischemic intestinal diseases, neuropathy
- Sicca-syndrome (Sjögren)
- Noduli
- Felty-syndrome: splenomegaly and leucopenia
- Amyloidosis

# Mortality in RA

- Increased total mortality
  - > 10 years disease
- Decreased life expectancy 4 – 18 years
- Men and women

# Causes of death

- Infections
- Lymphoproliferative disorders
- Gastrointestinal illnesses
- **Cardiovascular disease**
  - Most important cause of death
  - RA patient: up to 2.2 fold increased risk for cardiovascular death

# Determinants of mortality

- Decreased functional capacity
- Higher “joint-count”/ disease activity”/ ESR
- Corticosteroids
- Rheumatoid nodules
- Other extra-articular manifestations
- Presence of rheumatoid factor/aCCP

# Carré-investigation*

- Ongoing, prospective study
- Prevalent & incident CVD, underlying risk factors
- Rheumatoid arthritis (RA) patients
  - 1987 ACR criteria
- Aged between 50 – 75 yrs
- Disease duration up to 12 years
- N = 353
- Started in 2001
- Follow-up: at least 15 years
- Comparison group: participants of the Hoorn study**

*van Halm et al. Ann Rheum Dis 2009; **Hoogeveen et al. ATVB 1998

# Cardiovascular disease & RA

- Increased cardiovascular risk in RA!
  - Carré-investigation
    - Doubled prevalence of CVD*
    - Doubled incidence of CVD**
    - Comparable to type 2 diabetes
    - Only partially explained by CV-risk factors

* van Halm et al. Ann Rheum Dis 2009, **Peters et al. Arthritis Care Res 2009

# RA and DM in Denmark*

- National databases
  - Hospital admissions
  - Outpatients clinic visits
  - Medication registries
- Nationwide population registry
  - n = 4.311.022 ( > 16 yrs)
  - 1 Jan 1997 – 31 Dec 2006
- New diagnoses
  - 10.447 RA & 130.215 DM
- New myocardial infarctions
  - RA IRR: 1.7 (95% C.I.: 1.5 – 1.9)
  - DM IRR: 1.7 (95% C.I.: 1.6 – 1.8)

* Lindhardsen et al. Ann Rheum Dis 2011

# CV-risk in RA

## CV-risk factors vs disease severity markers*

- CORRONA-study
  - 17,000 RA patients
  - Both traditional CV-risk factors + RA severity markers contribute towards the CV-risk

- Targeting CV-risk aimed at
  - Traditional CV-risk factors
  - RA-disease activity

*Solomon et al Ann Rheum Dis 2010

# Cardiovascular endpoint trials in RA

- Antihypertensive agents
  - No clinical trials (ClinicalTrials.gov)
  - ACE inhibitors & angiotensin receptor(AT1)-inhibitors*
- Statins
  - Anti-inflammatory properties**
  - Secondary prevention trials (TNT/IDEAL)***
    - Statins in patients with previous MI
    - RA patients vs non RA-patients
      - similar
  - Large primary prevention trial
    - TRACE-RA
      - RCT in 4000 RA patients
        - » Atorvastatin for 5 – 6 yrs
        - » Stopped in 2012, too low rate of CV-events

*Dahlbeth Rheumatol 2005, Price EWWR 2005; **McCarey Lancet 2004
***Semb A&R 2012

# DMARDs and Cardiovascular risk

- Case-control study*
  - 613 RA patients
    - 72 with confirmed incident cardiovascular disease
    - 541 controls
  - Reference treatment: Never MTX/SSZ/HCQ use
  - Index treatment ever DMARD use
- Model corrected for age, gender, smoking & disease duration*
  - Methotrexate use OR 0.2
  - SSZ
- Systematic review**
  - Risk reduction by MTX: 20 – 30%

*van Halm et al. Arthritis Res Ther 2006, **Westlake et al Rheumatology 2010

# TNF-blockers I*

- CORRONA database*
  - Prospective cohort
  - 103 out-patient clinics in North America
    - 10,156 patients with RA
    - 1-10-2001 – 31-12-2006
    - Follow-up: 23 months
  - TNF-blockers vs MTX vs non MTX-DMARDs
    - End-points
      - Fatal and non-fatal MI, stroke/TIA

*Greenberg et al Ann Rheum Dis 2010

# Results

- 88 events

**Table 3** Adjusted risk of composite* cardiovascular events by DMARD and steroid exposure

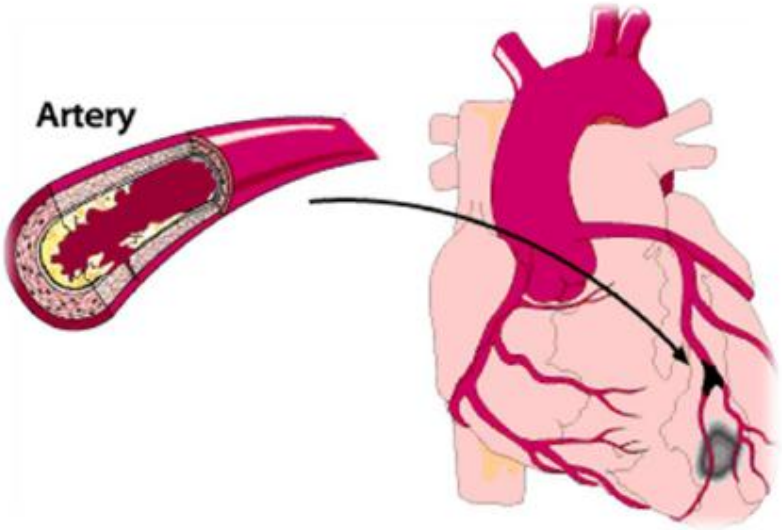
| | Exposure periods (N) | HR | 95% CI |
|---|---|---|---|
| TNF antagonists | 4585 | 0.39 | 0.19 to 0.82 |
| Methotrexate | 4791 | 0.94 | 0.49 to 1.80 |
| Other non-biological DMARDs | 1724 | Referent | – |
| Prednisone | | | |
| None | 6689 | Referent | – |
| <7.5 mg daily | 3141 | 1.78 | 1.06 to 2.96 |
| ≥7.5 mg daily | 1090 | 2.62 | 1.29 to 5.31 |

Adjusted for age, gender, smoking status, diabetes, hypertension, dyslipidemia, previous myocardial infarction (MI) or stroke and modified health assessment questionnaire score, aspirin use, naproxen use, non-selective non-steroidal anti-inflammatory drug use and cyclooxygenase-2 inhibitor use.
*Composite includes MI, transient ischaemic attack/stroke and cardiovascular-related deaths.
DMARDs, disease-modifying antirheumatic drugs; TNF, tumour necrosis factor.

Greenberg et al Ann Reum Dis 2010

# Plaque instability and RA*

## Superior Protection Against Vulnerable Coronary Plaque in CAD-naive TNFi vs. DMARD- Responders with Rheumatoid Arthritis (RA)




George A Karpouzas, Naser Ahmadi, Tae-Young Choi, Fereshteh Hajsadeghi, Silvia Munoz, Matthew J Budoff

*Harbor-UCLA Medical Center, Torrance CA*

Karpouzas et al. Ann Rheum Dis 2013

# Plaque composition in RA vs non RA

- 150 RA patients vs 150 matched controls
- 64 slice CT-angiography
  - Plaques
    - Standardized AHA 15 segment model
    - Non-calcified (NCP), mixed (MP), calcified (CP)

**Table 2** CTA results in RA and controls

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

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

# Plaque-investigation

- Within RA patients
  - Low disease activity
    - TNF-blockers/DMARDs vs DMARDs only
      - 65% less vulnerable plaques
- Therapeutic advantages?
  - Earlier/more often/preferential TNF-blockers??
- Prospective investigations necessary

Karpouzas et al  Ann Rheum Dis 2013

# Excess cardiovascular risk in RA

- Explained by
  - Cardiovascular risk factors
  - The chronic inflammatory process
- Atherosclerosis = Inflammatory disease
- RA = Inflammatory disease
- Inflammation in RA => facilitates atherosclerosis development
- RA is new, independent, cardiovascular risk factor

➔ Cardiovascular risk management

# Cardiovascular risk management

- Cardiovascular profile assessment
  - Blood pressure, lipid profile, etc
- Assessment of 10-years cardiovascular disease (CVD) risk
  - Framingham and SCORE risk calculators
  - Netherlands: specific table

# Cardiovascular risk management
## - “general population” -

- Life style recommendations for all persons
- Treatment with antihypertensives/statins
  - 10-years CVD-risk (SCORE) above certain value (The Netherlands: 20% (non)fatal CVD)

# “EULAR task force: EULAR recommendations for cardiovascular risk management in patients with RA and other inflammatory arthritis”*

*Peters et al. Arthritis Rheum 2010

# Recommendations I

- RA, like diabetes, is a high risk condition for CVD
  - Recommendation: B
- Adequate control of disease activity
  - Recommendation: B
- Cardiovascular risk assessment for all patients with RA
  - Risk profile
    - National guidelines
    - Annually
  - Risk assessment should be repeated when anti-rheumatic treatment is changed
    - Recommendation: C

# Recommendations II

- Risk score models should be adapted for RA patients by a 1.5 multiply factor when:
  - Disease duration of more than 10 years;
  - Presence of RF or anti-CCP positivity;
  - Presence of extra-articular manifestations;
    - Recommendation: C
- Total cholesterol/HDL-cholesterol ratio should be used with SCORE
  - Recommendation: C
- Treatment thresholds & goals should be according to national guidelines
  - Recommendation: C

# Recommendations III

- Statins and/or ACE-inhibitors are preferred treatment options
  - Recommendation: C
- The role of COXIBs and most NSAIDs regarding CVD risk is not well established
  - Follow-up of blood pressure
    - Recommendation: C
- Corticosteroids: lowest dose possible
  - Recommendation: C
- Smoking cessation
  - Recommendation: C

# Other guidelines

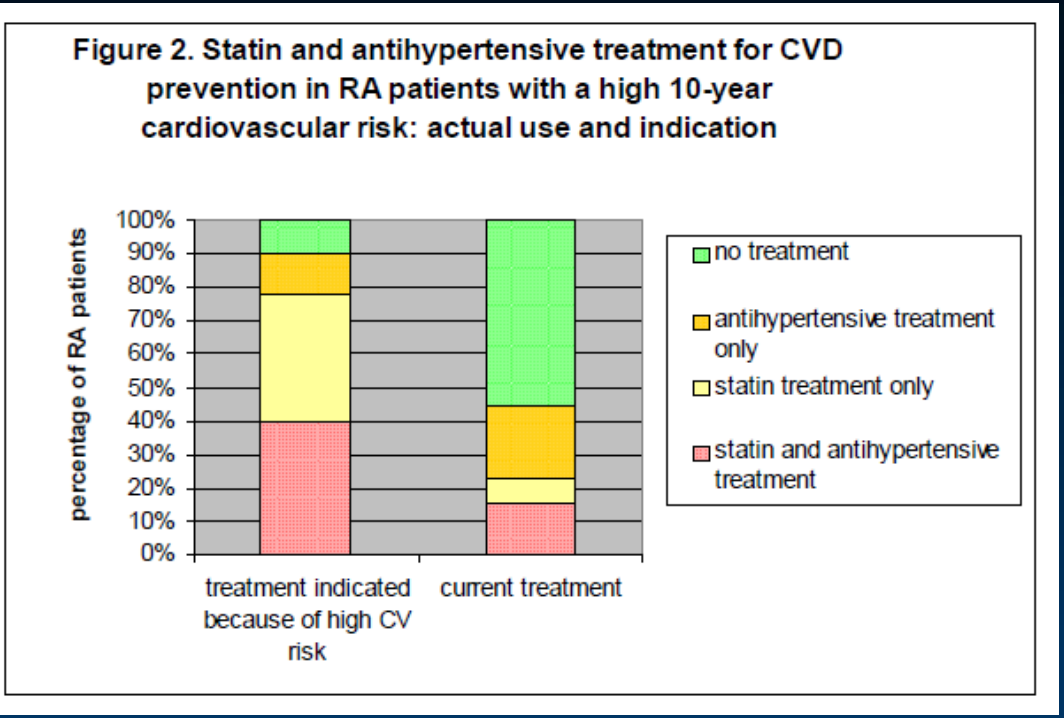
- Dutch Multidisciplinary CV-RM Guideline (2011)
  - Add 15 years to the actual age
    - No differentiation according to disease activity
- UK guideline (2014)
  - RA included as category which increases CV risk (HR: 1.4)
- Several other adaptations of risk models suggested
- Unmet need for RA specific risk model(s)

# CV-RM implementation program - Preliminary results I - *

- 2012
  - CV-RM implementation in RA
  - 2 centers (Reade, Amsterdam and St Antonius Hospital, Sneek)
- At baseline (n = 390)
  - Mean age 58 yrs
  - Females 71%
  - 10 yrs (adapted) CV risk
    - < 10% 16%
    - 10 – 20% 15%
    - > 20% 69%

*I. van den Oever et al , submitted

# Results II




- One year follow-up
  - Antihypertensives were used in all indicated cases
  - Statins in 70% of indicated cases

# Conclusions & Take home messages I

- Increased CV risk in RA
  - Comparable to diabetes
  - Explained by
    - Traditional cardiovascular risk factors
    - Chronic underling inflammatory process
- CV-RM
  - Existing recommendations differ
    - RA specific CV-risk prediction models lacking
    - Poor implementation of CV-RM in clinical practice

# Conclusions & Take home messages II

- **Future research agenda**
  - CV-endpoint trials
    - Statins and antihypertensives
    - Biologicals
- **But do not wait with CV-RM!**
  - Screening and treatment of CV-risk factors (by whom?)
  - No evidence to adapt CV-RM according to disease activity
    - Increased CV-risk already before clinical onset of RA
  - Effective suppression of the inflammatory process

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