Καρδιακή συν-νοσηρότητα στις χρόνιες φλεγμονώδεις παθήσεις

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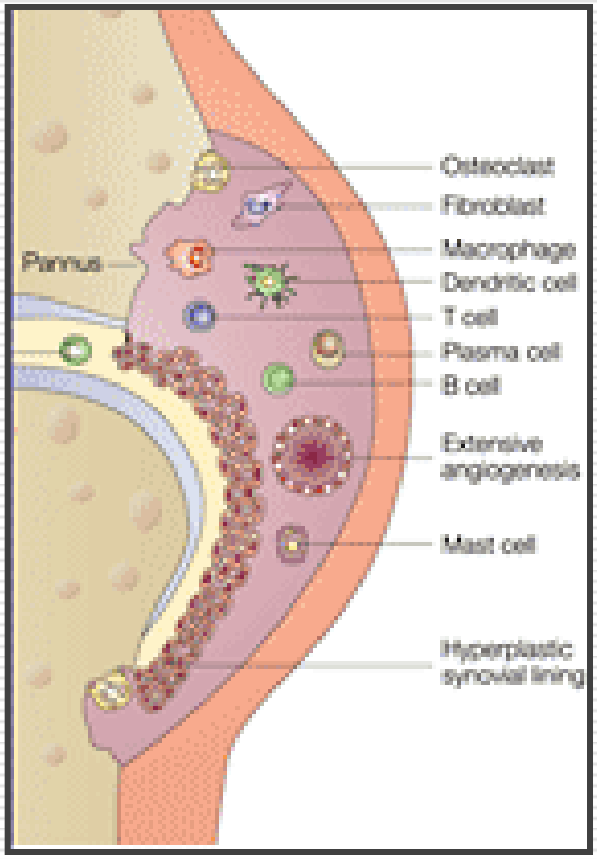
Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων

RA is chronic inflammatory disease with many extraarticular manifestations



- Synovial membrane
  - Synovitis
  - Synovial effusion
- Bone
  - Eroded –RA
  - (Non-eroded – non-RA)
- Cartilage
  - Degradation
  - Destruction

Joint Destruction is the Major Feature of RA

Smolen JS, et al. Nature Rev Drug Disc 2003;2:473-88

Effect of RA on Patients' Quality of Life

- Radiological evidence of joint damage — Within 0–2 years
- 50% become disabled — Within 5 years
- 50%maximal radiological damage is observed — Within 6 years
- 80% become disabled — Within 20 years

(Harris, 1990; Pincus & Callahan, 1986; Scott et al, 1987)

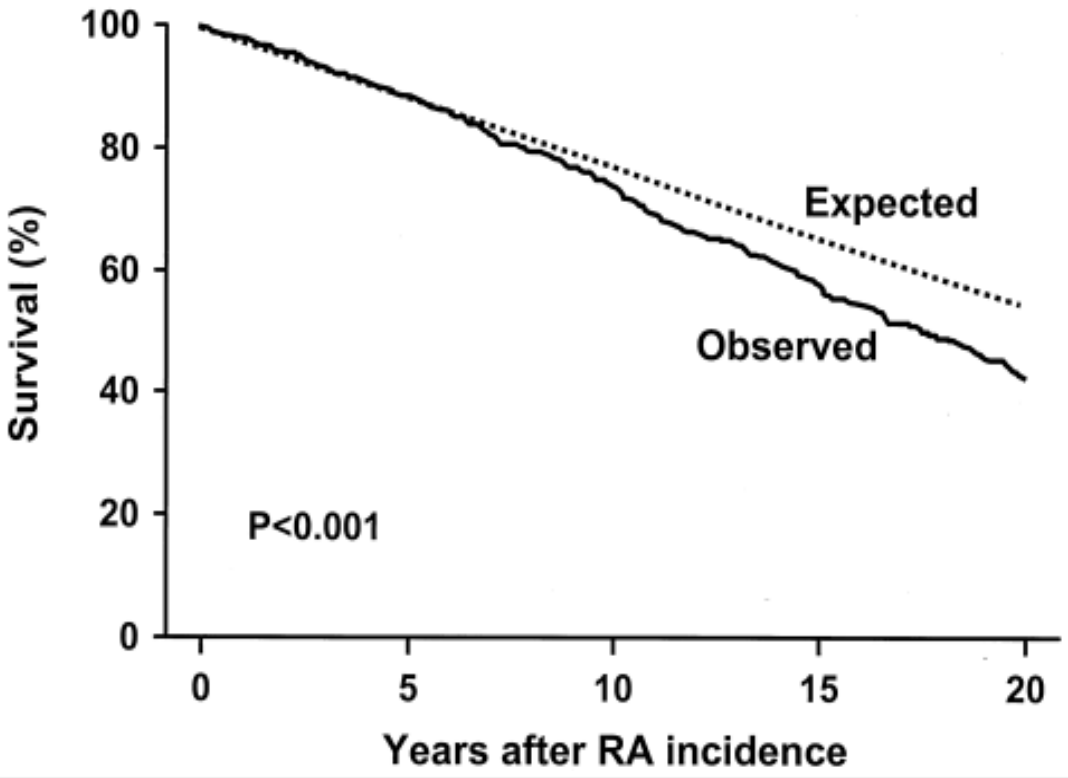
Gabriel SE, Crowson CS, Kremers HM, et al

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

Arthritis Rheum 2003;48:54-8

CONCLUSION

- Survival in RA patients is significantly lower than expected.



RA and cardiovascular (CV) events

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

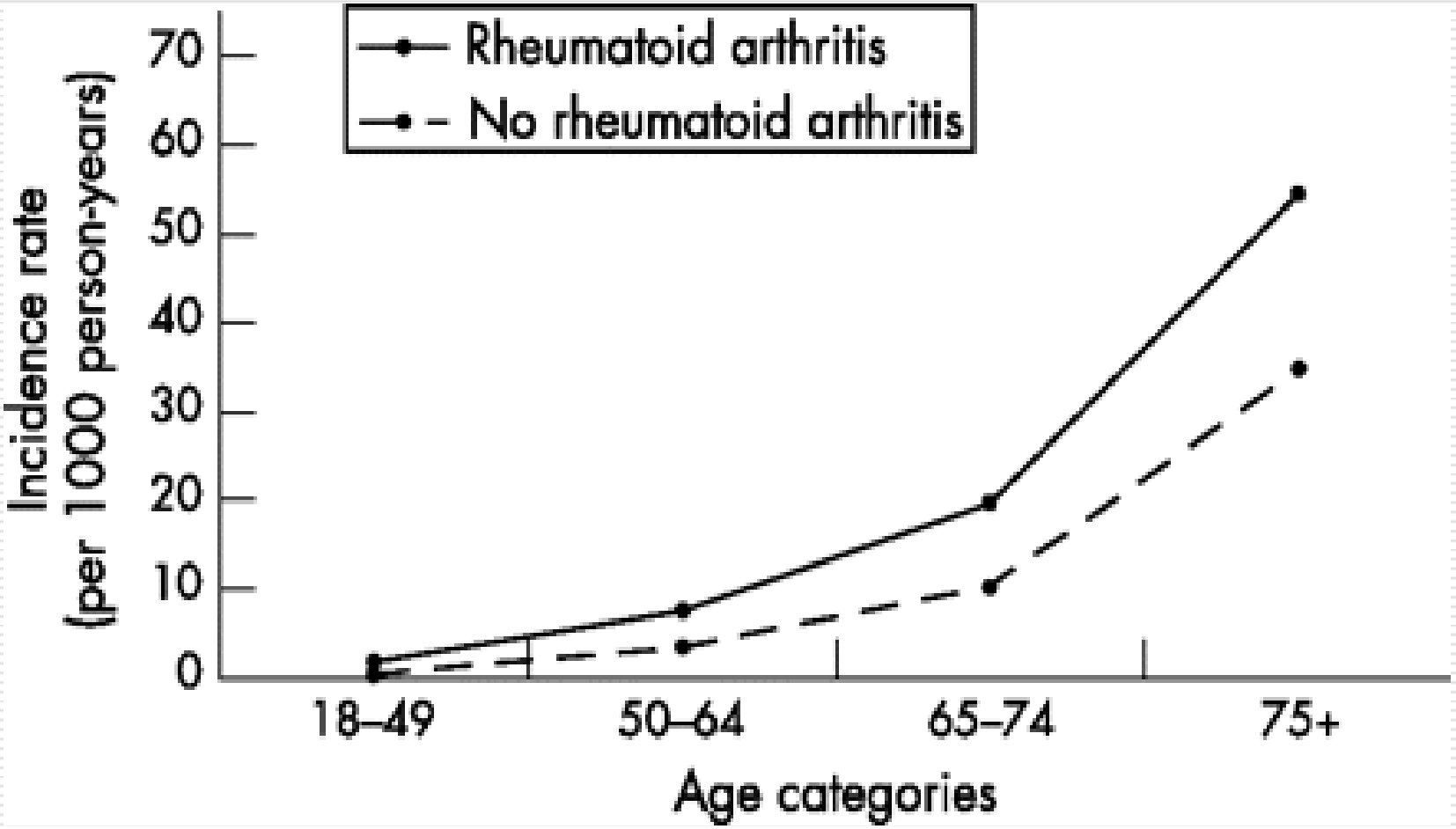
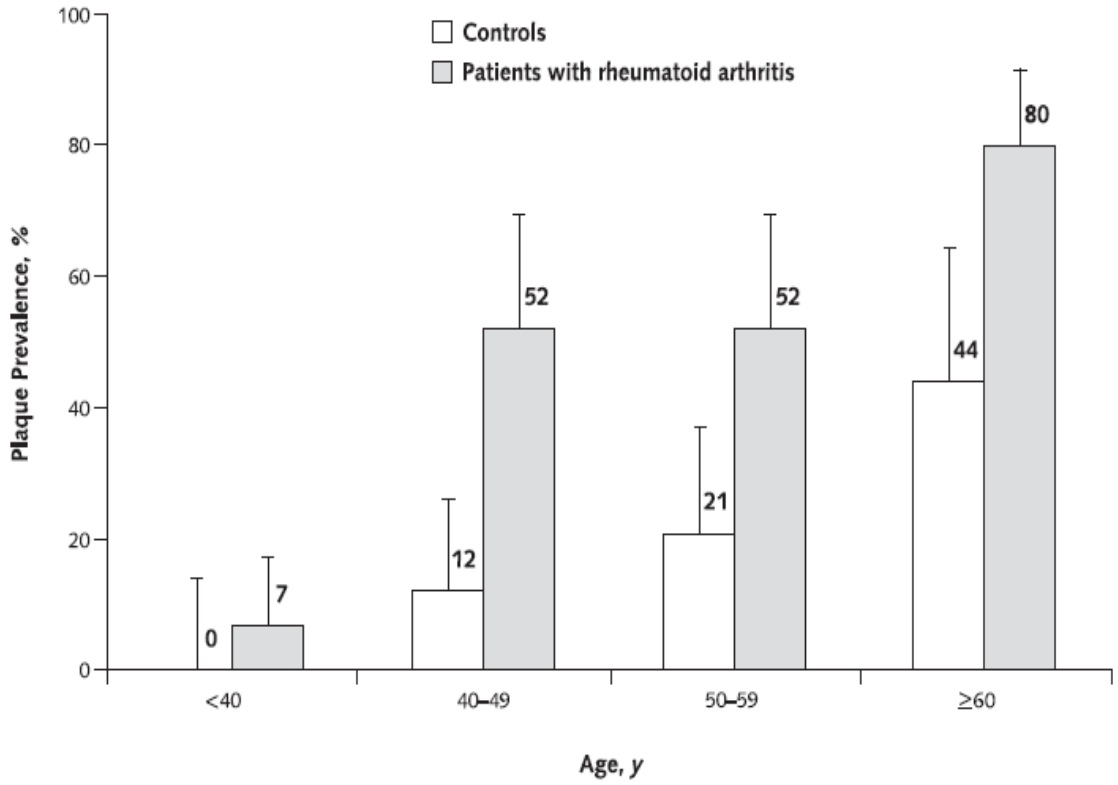


Figure 1 Incidence rates of cardiovascular events among the total study population

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

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



Error bars indicate 95th percentiles.

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

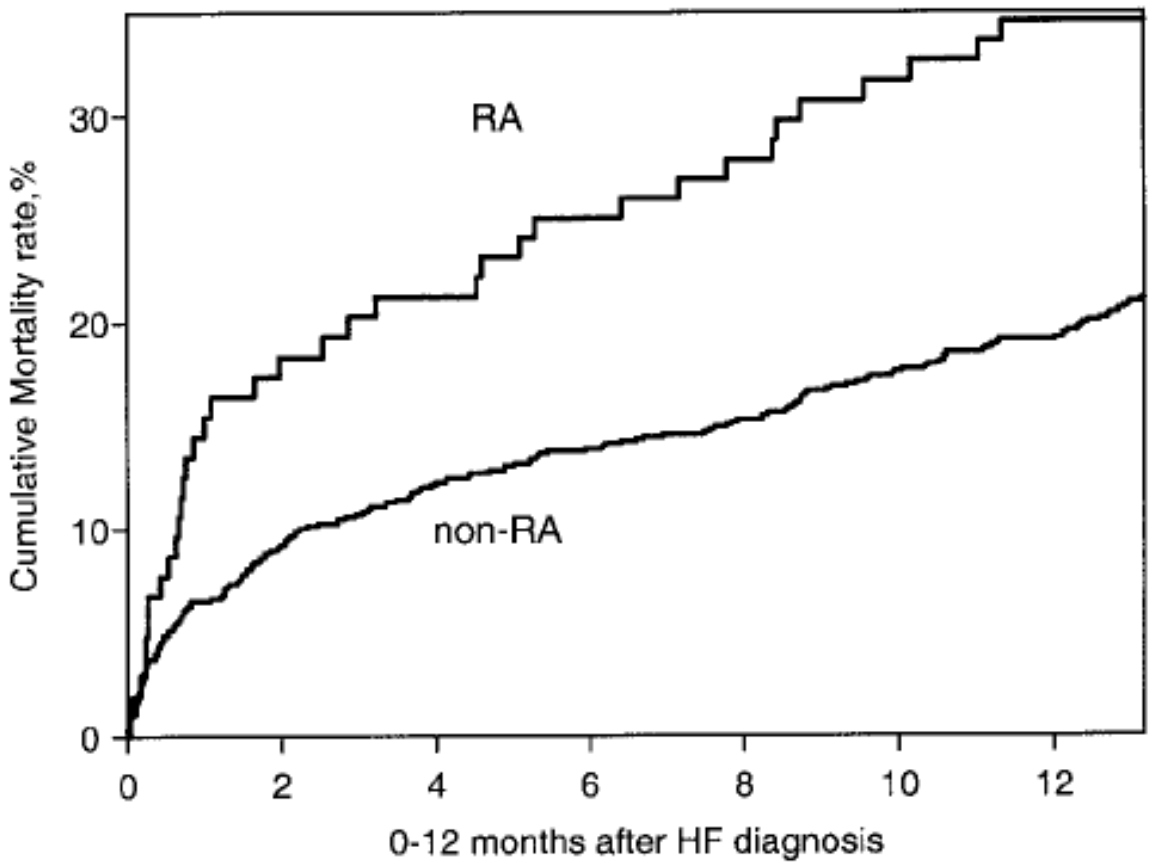


Figure 2. Mortality through 1 year following the onset of heart failure (HF) in the rheumatoid arthritis (RA) and non-RA cohorts.

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

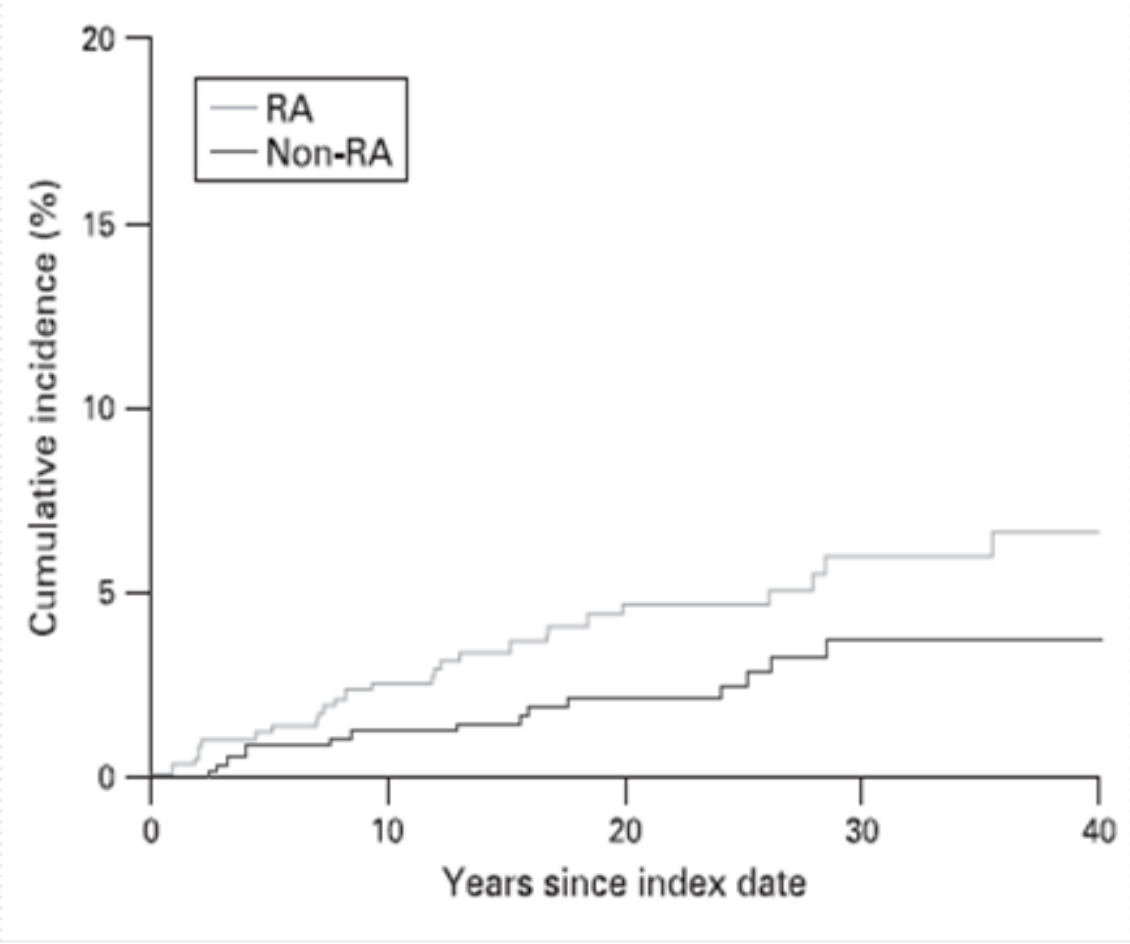


Figure 2 Cumulative incidence of silent myocardial infarction in a population-based incidence cohort of 603 patients with RA and a matched non-RA comparison group of 603 non-RA subjects from the same underlying population. © Increased unrecognized coronary heart disease in rheumatoid arthritis: a population-based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

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

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

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

Arthritis Rheum 2001;44:2737-45

CONCLUSION

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

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

Cardiovascular death in rheumatoid arthritis

Arthritis Rheum 2005;52:722-32

CONCLUSION

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

Turesson C, Jacobsson L, Bergström U

Extra-articular rheumatoid arthritis: prevalence and mortality

Rheumatology (Oxford) 1999;38:668-74

CONCLUSION

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

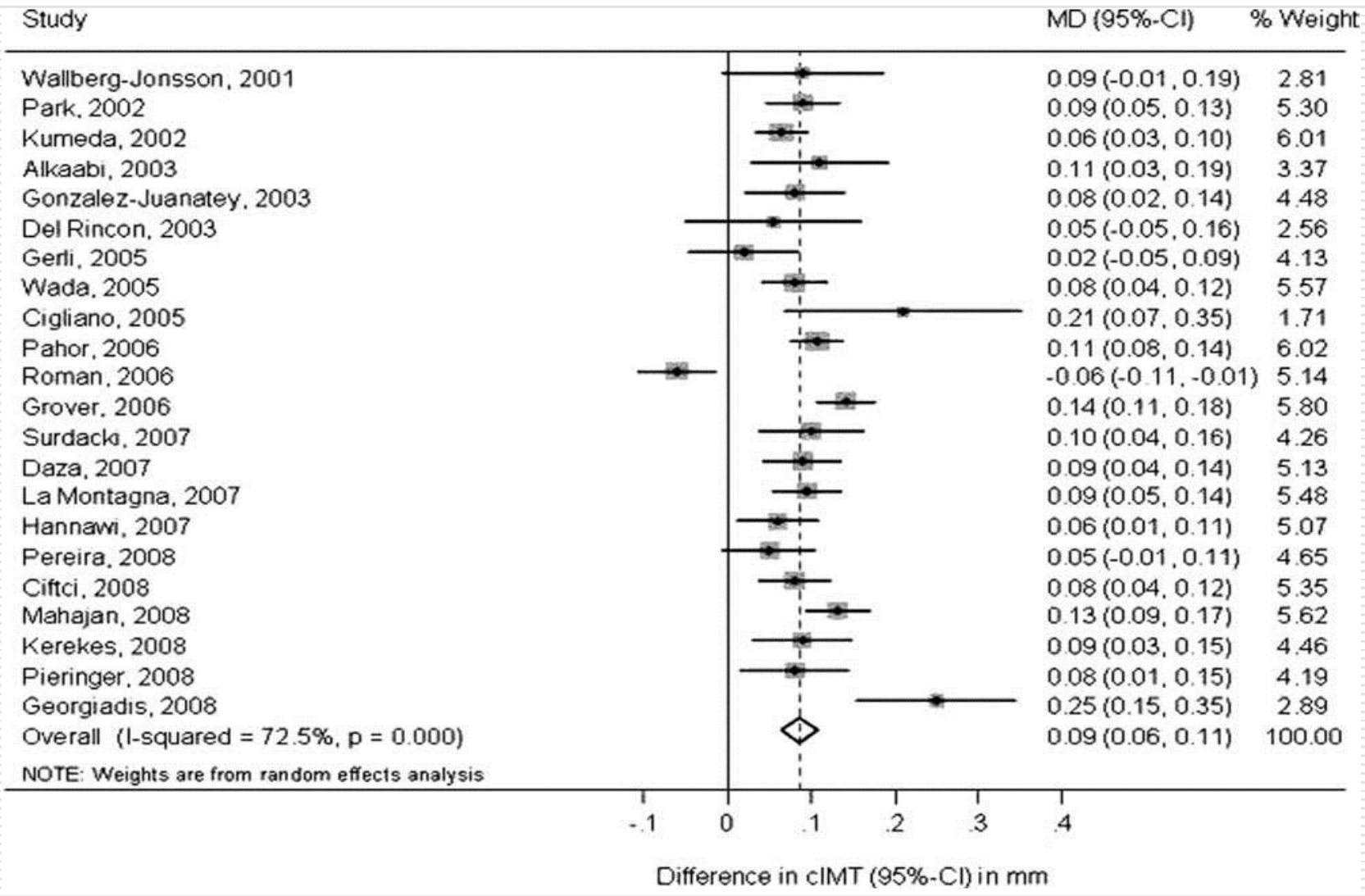
Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP

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

Arthritis Rheum 2002;46:2010-9

CONCLUSION

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



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

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

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

Semin Arthritis Rheum 2011;40:389-97

CONCLUSION

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

Lindhardsen J, Ahlehoff O, Gislason GH, et al

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

Ann Rheum Dis 2011;70:929-34

CONCLUSION

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

Nurmohamed MT, Kitas G

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

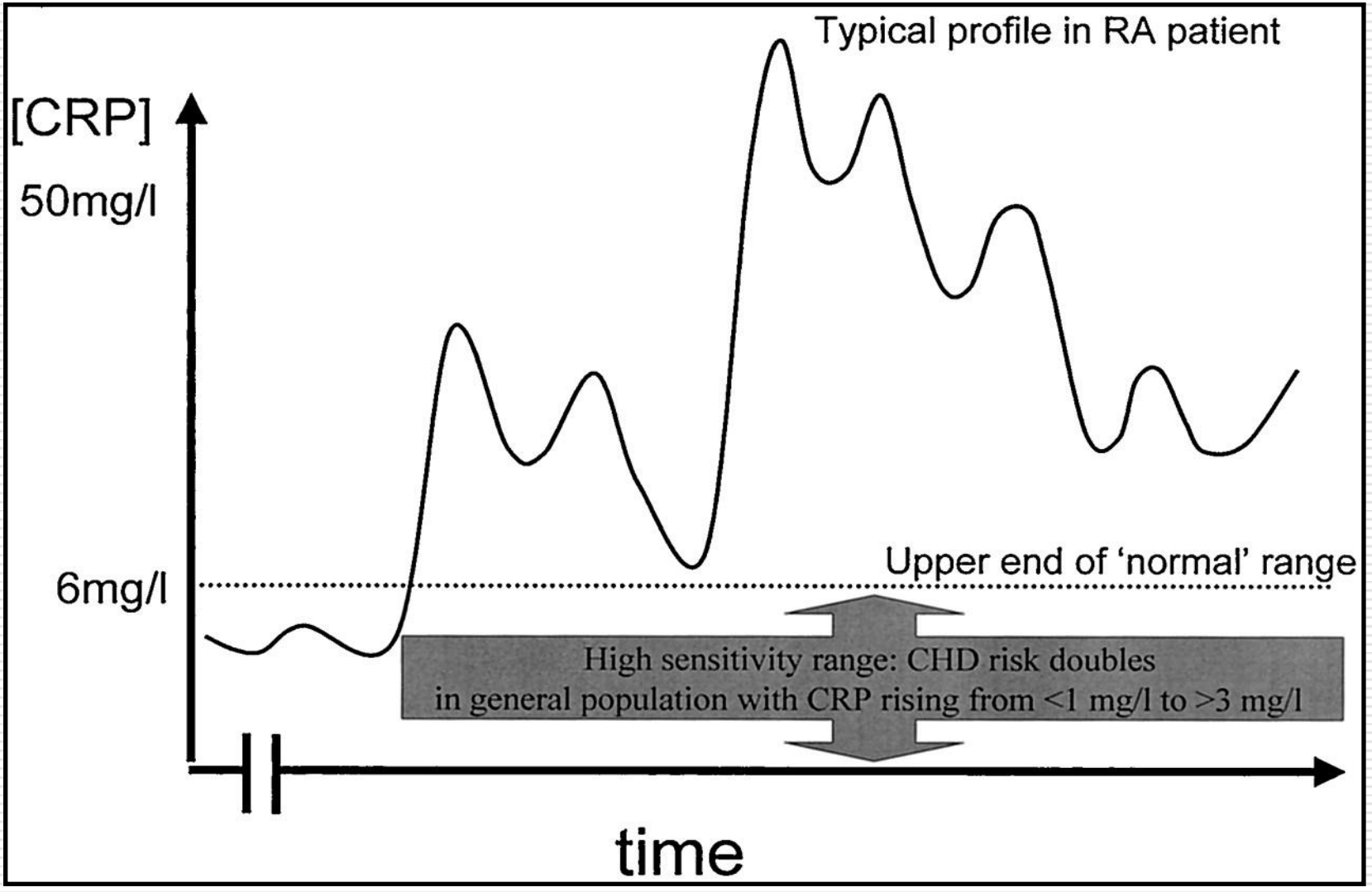
Ann Rheum Dis 2011;70:881-3

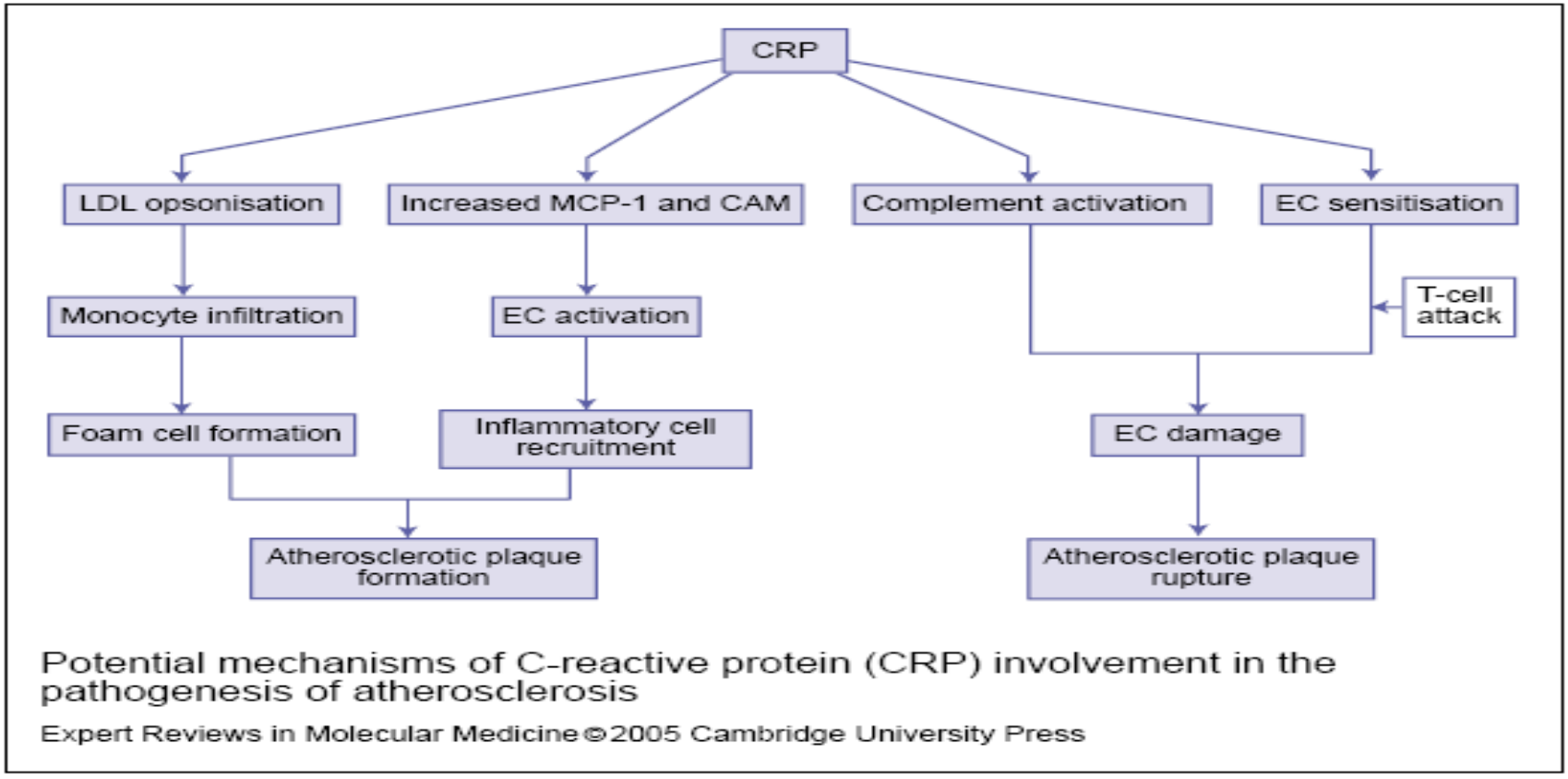
Atherosclerosis in RA

- It is related to classical risk factors
- RA disease process

Other risk factor of atherosclerosis in RA patients

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


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



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

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

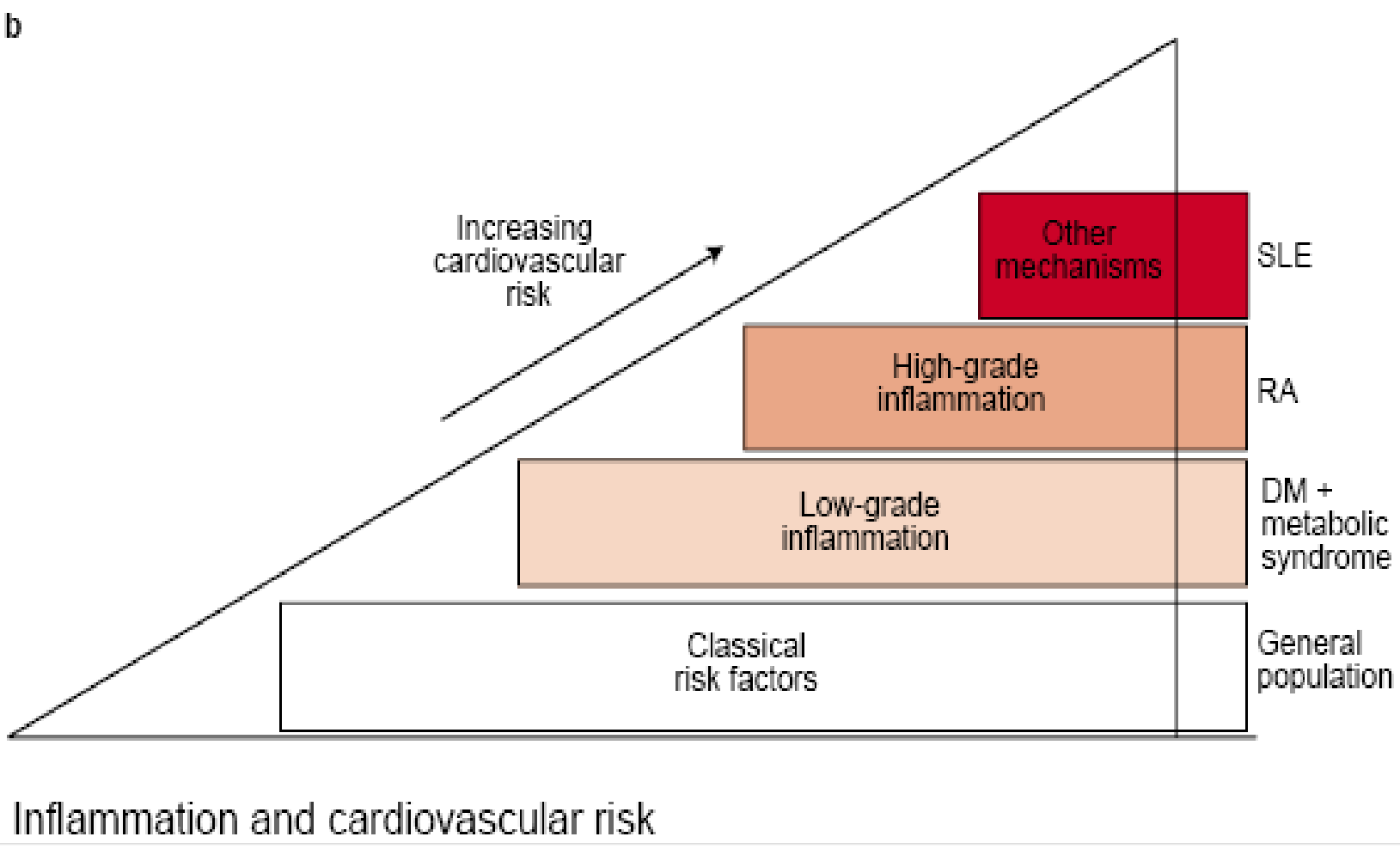
Galarraga B, Khan F, Kumar P, Pullar T, Belch JJ

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

Rheumatology (Oxford) 2008;47:1780-4

CONCLUSION

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



Inflammation and cardiovascular risk

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

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

Arthritis Rheum 2008;58:2723-34

CONCLUSION

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

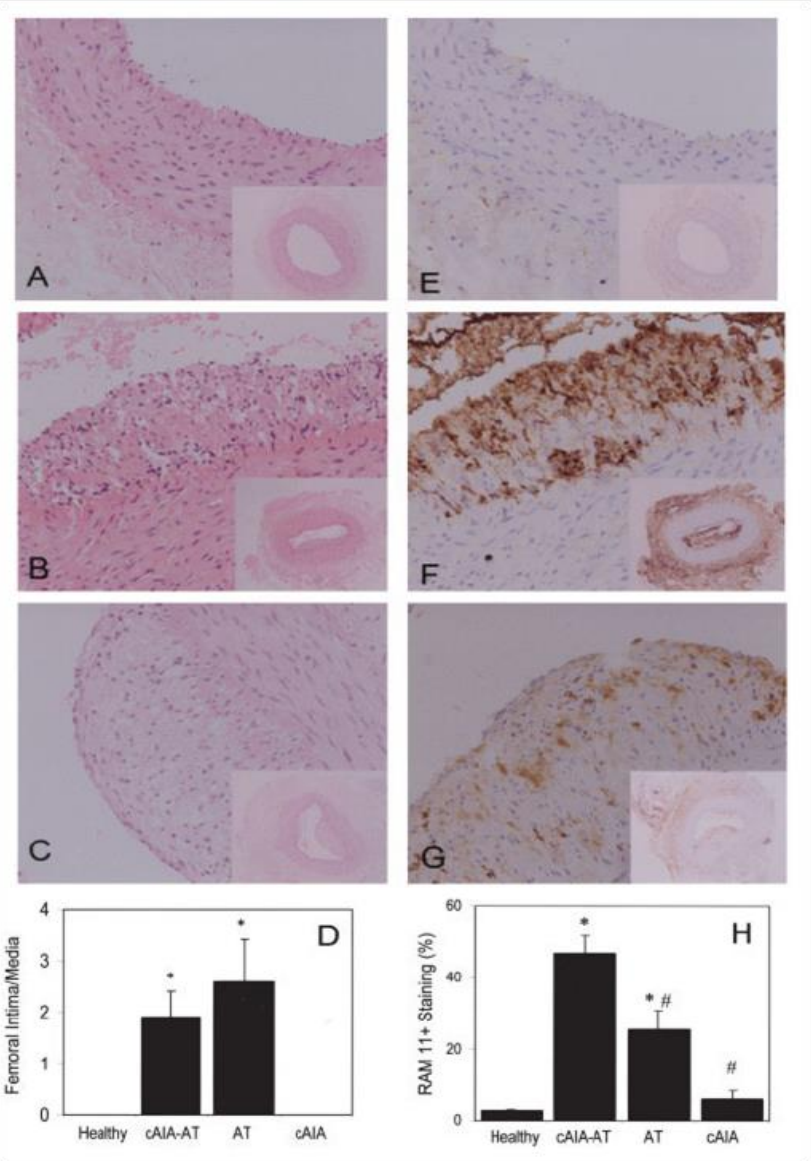
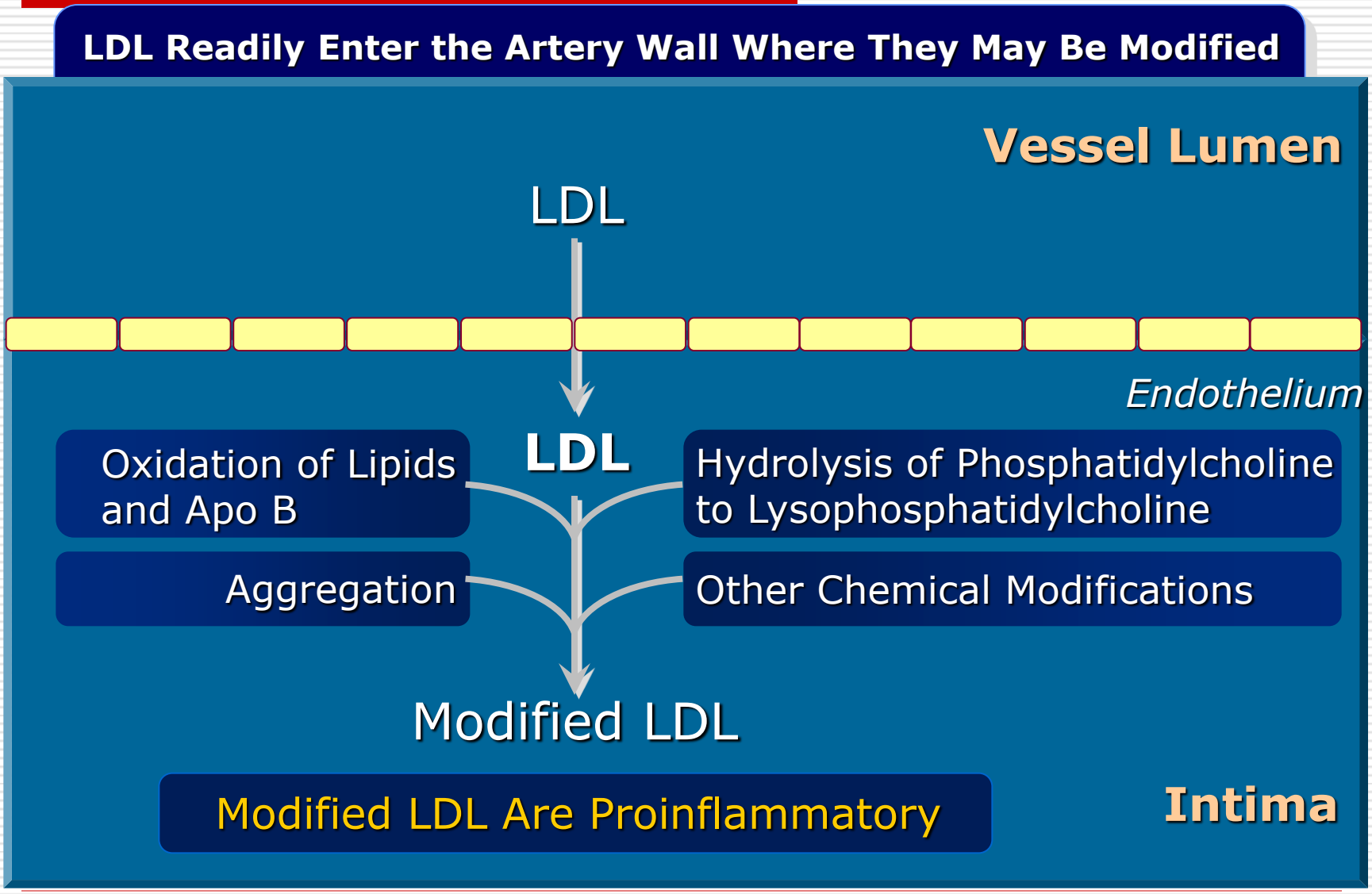


Figure 3. Neointimal hyperplasia and macrophage staining in injured femoral arteries. A–C, Hematoxylin and eosin–stained sections of femoral arteries from a healthy rabbit (A), a rabbit with both chronic AIA and atherosclerosis (B), and a rabbit with atherosclerosis alone (C), harvested 4 weeks after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

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

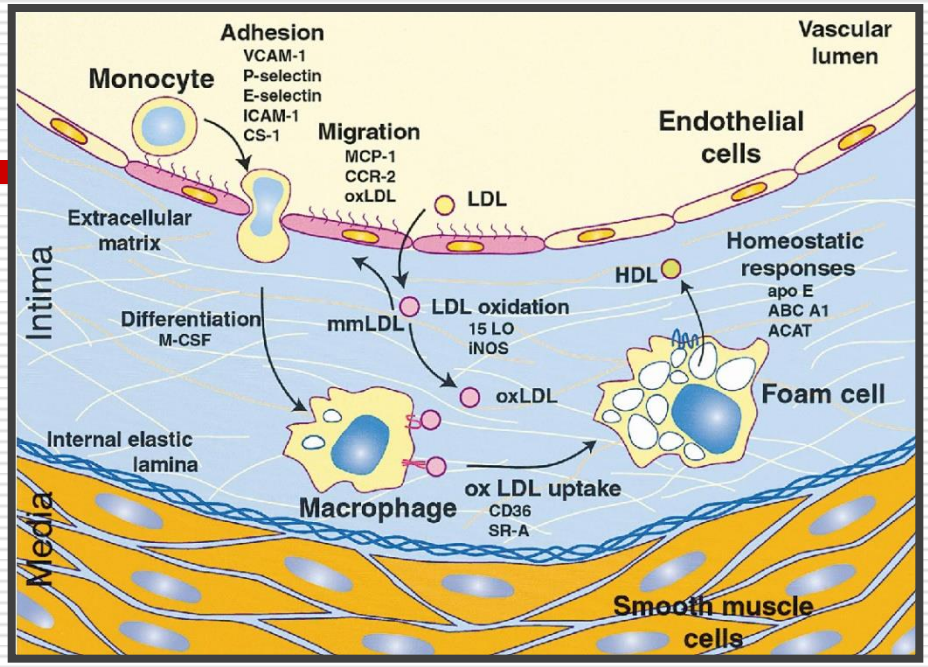
Role of LDL in Inflammation

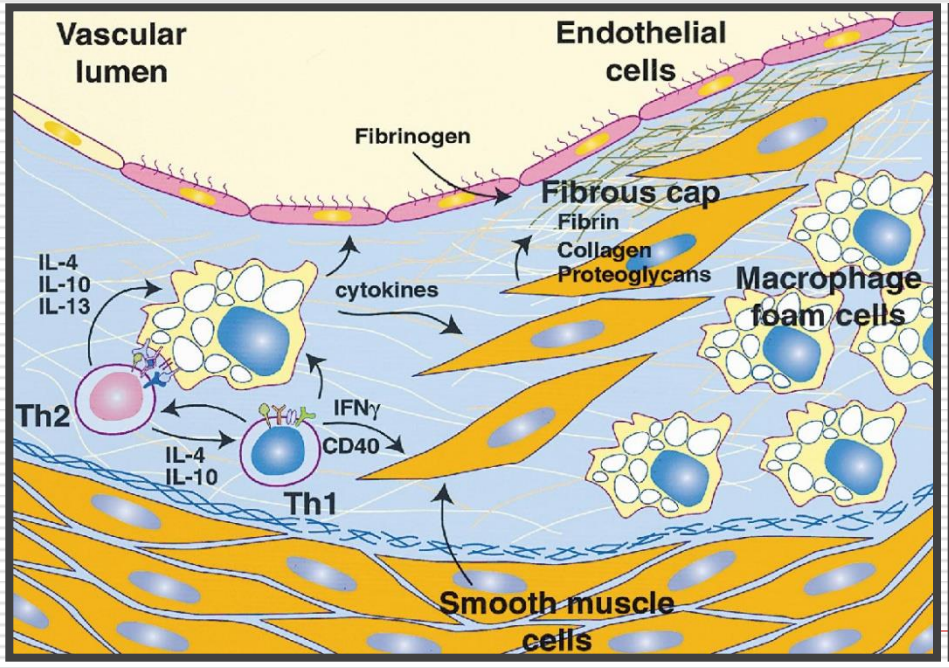


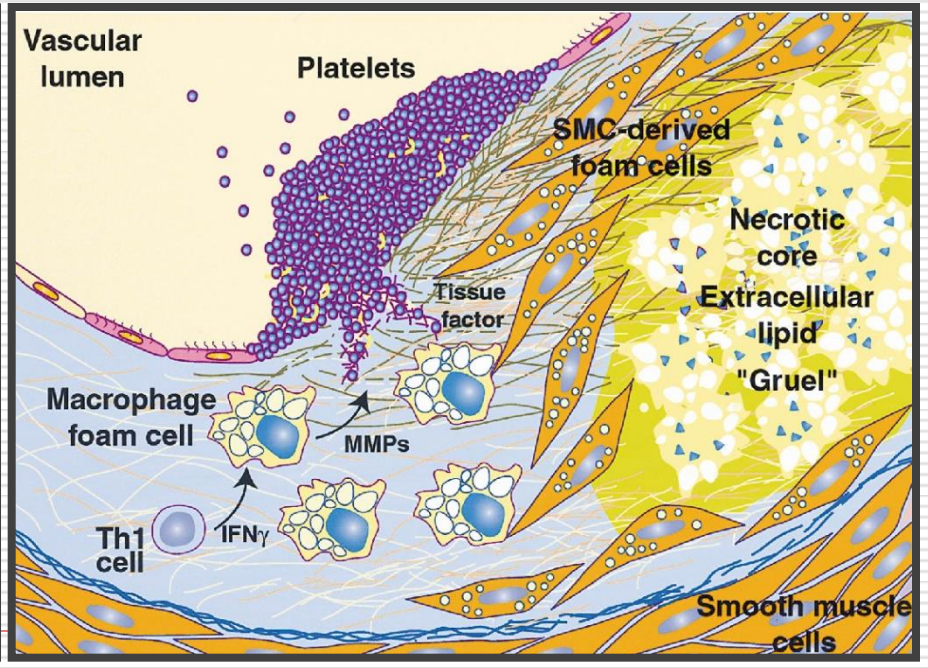
Steinberg D, et al. N Engl J Med. 1989;320:915-924.

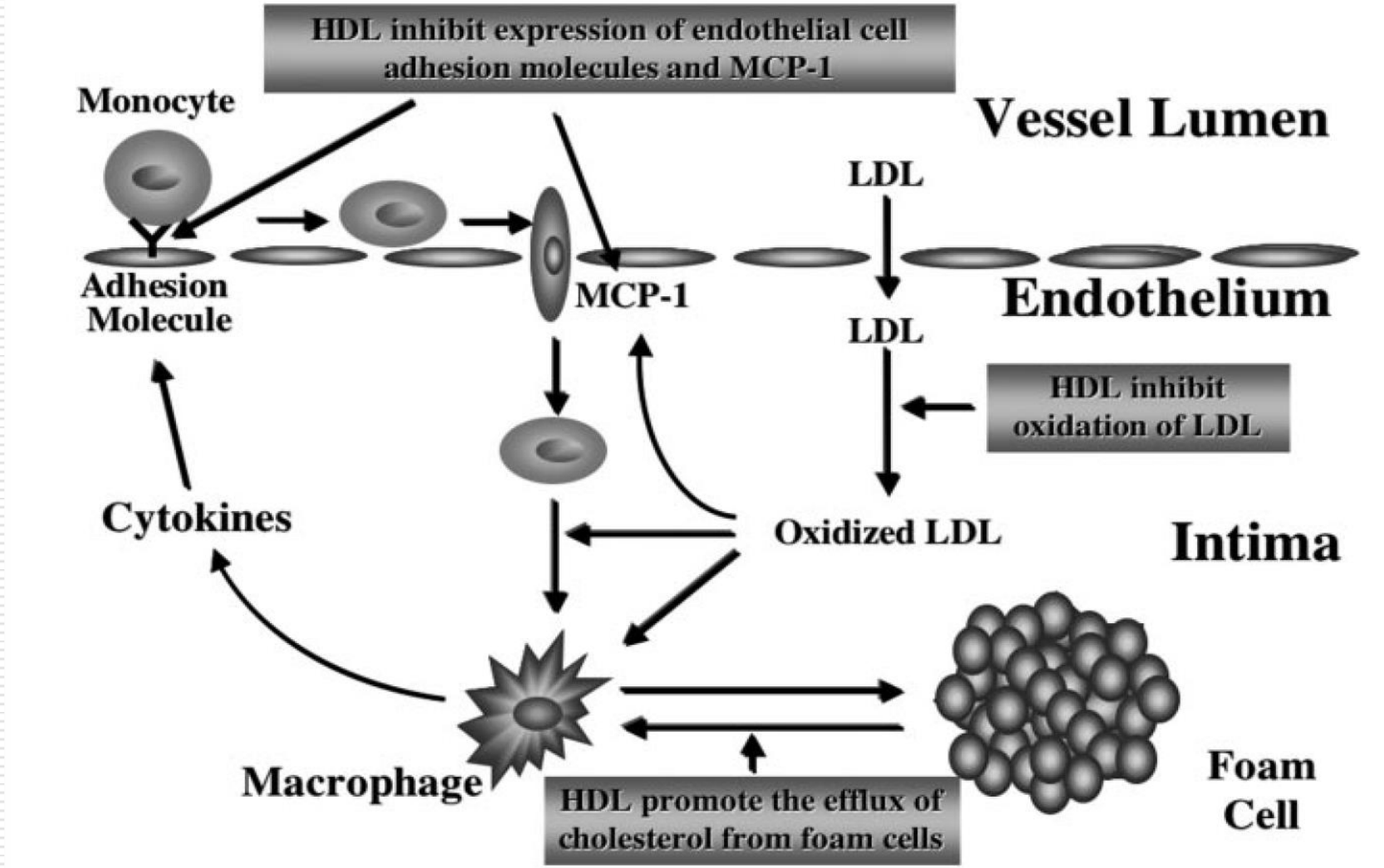
Pathophysiology of atherosclerosis

Glass CK, et al. Cell. 2001; 104:503-516





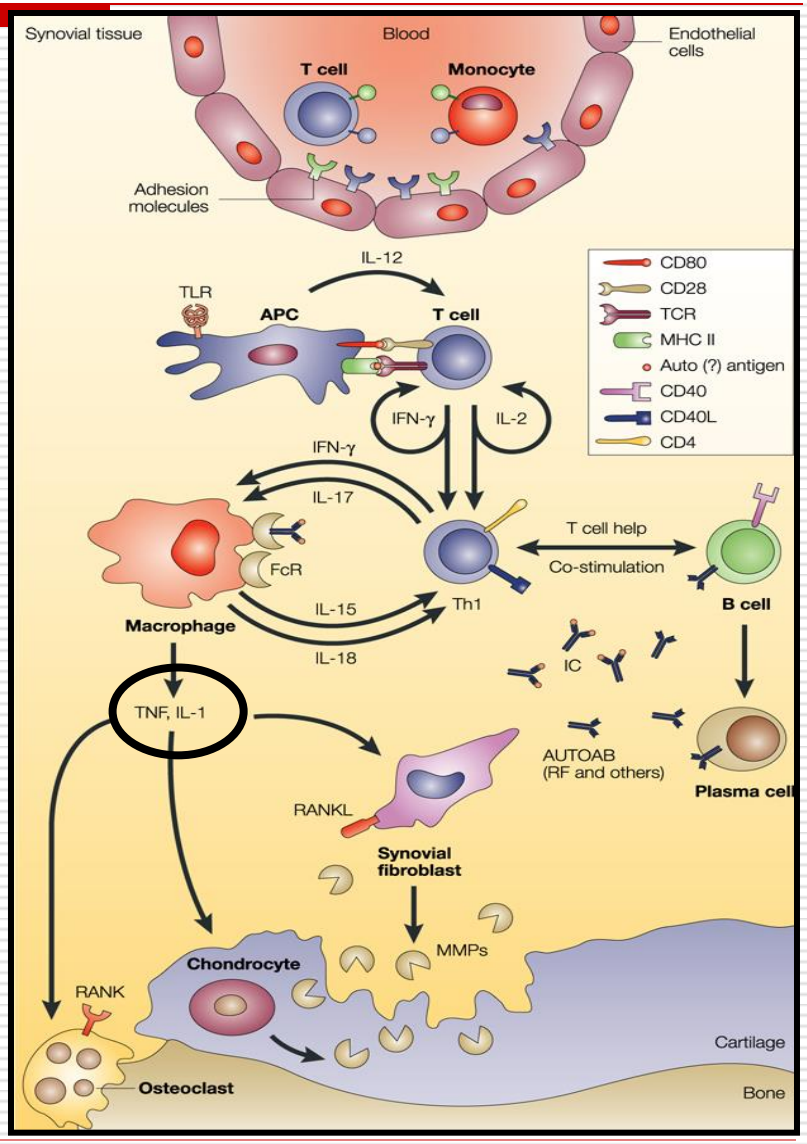




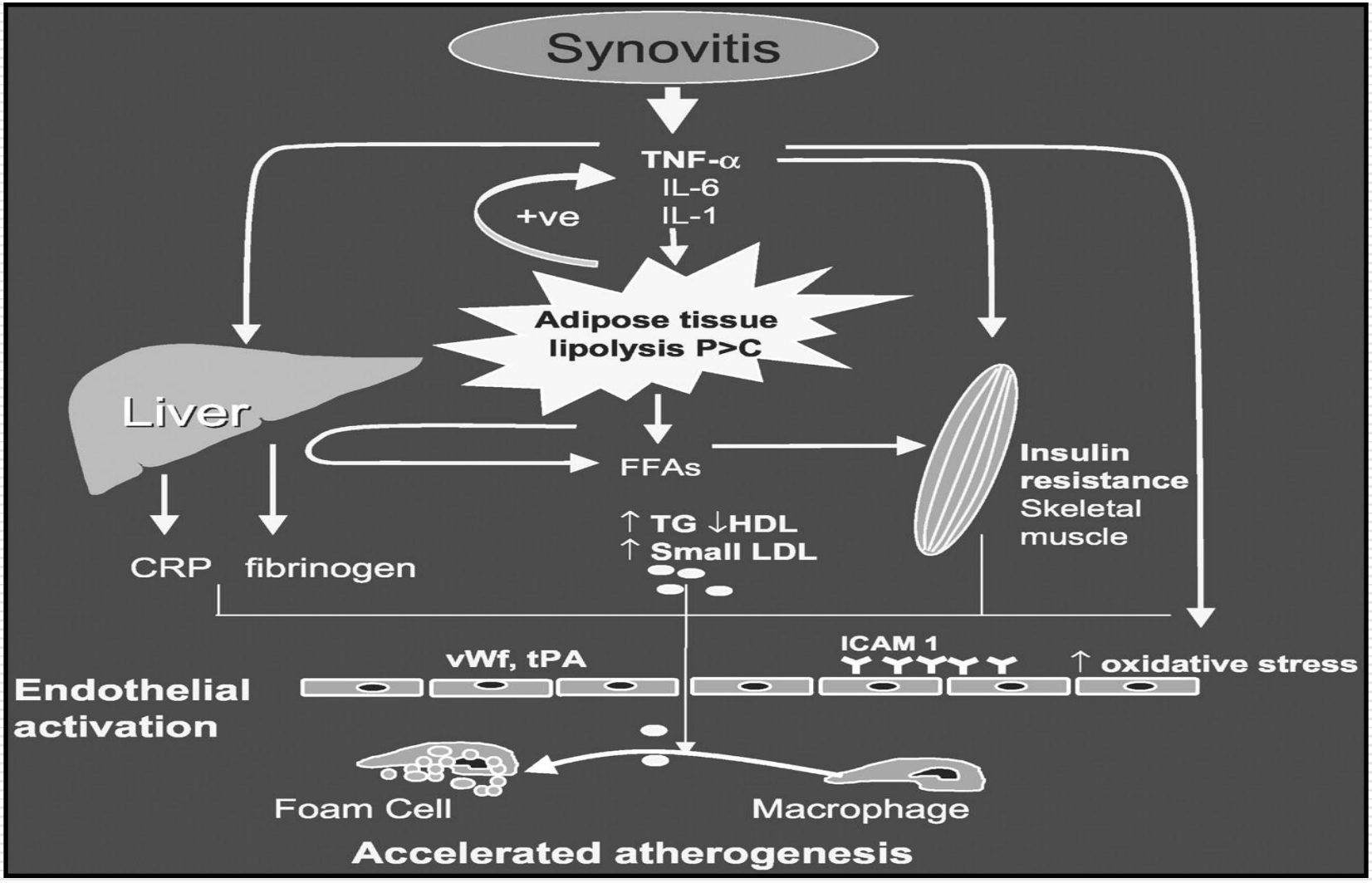
Barter PJ, et al. Circ Res 2004;95:764-72

TNF and Joint Damage

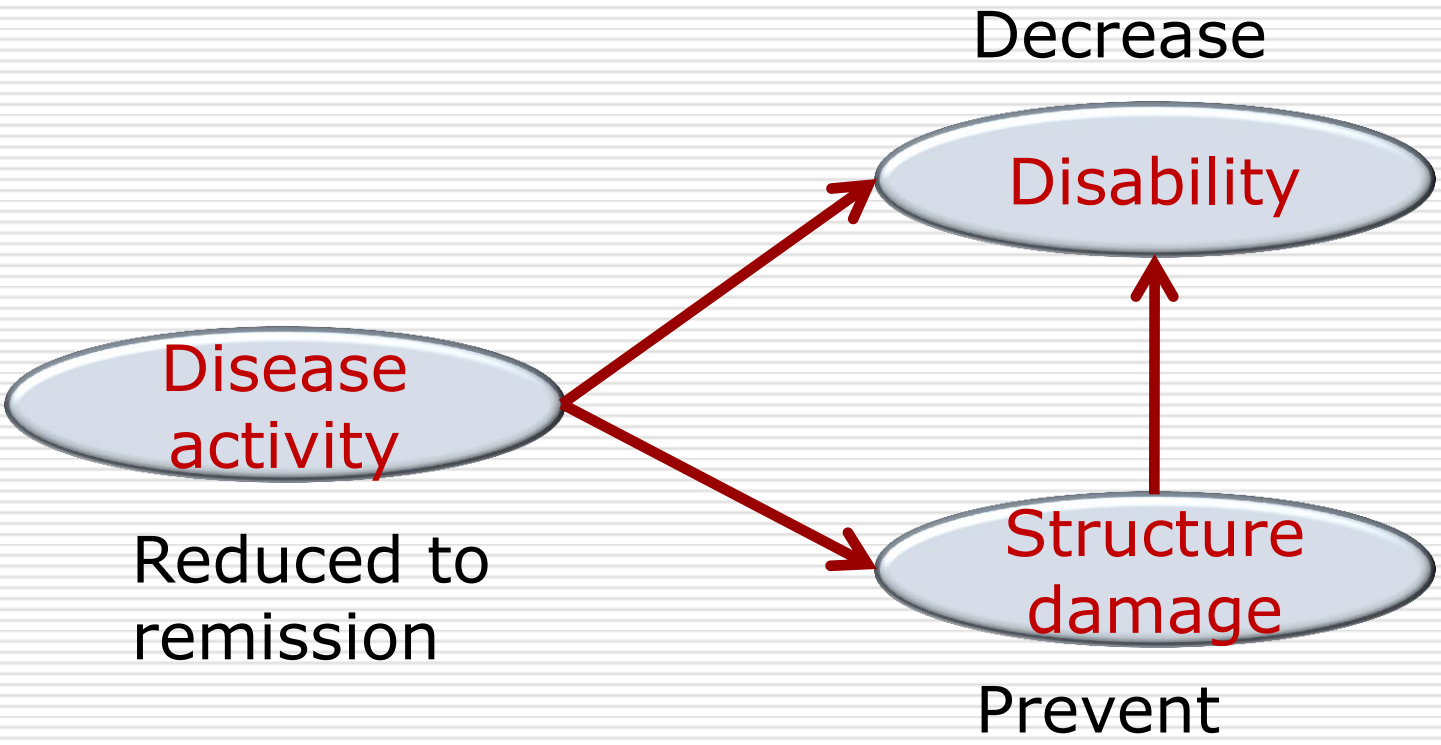
- Recruitment of white blood cells in inflamed synovium
- Induction of inflammatory cytokine production (eg, IL-1, IL-6)
- Increased metalloproteinase synthesis; cartilage degradation
- Increased RANKL expression; bone resorption
- Stimulation of fibroblast proliferation



Smolen JS and Steiner G. Nat Rev Drug Discov 2003;2:473-88


Synovitis
TNF-α
IL-6
IL-1
+ve
Adipose tissue
lipolysis P>C
Liver
FFAs
Insulin
resistance
Skeletal
muscle
↑ TG ↓HDL
↑ Small LDL
CRP
fibrinogen
vWf, tPA
ICAM 1
↑ oxidative stress
Endothelial
activation
Foam Cell
Macrophage
Accelerated atherogenesis

Objective of RA treatment



Targets of therapy in RA

Clinical remission
DAS-28 <2,6

↓

Maintenance of quality of live

↓

Inhibition of structural damage

Provan SA, Semb AG, Hisdal J et al

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

Ann Rheum Dis 2011;70:812-7

CONCLUSION

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

Westlake SL, Colebatch AN, Baird J, et al

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

Rheumatology (Oxford) 2010;49:295-307

CONCLUSION

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

Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA

Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis

Ann Rheum Dis 2005;64:765-6

CONCLUSION

- The results suggest that infliximab treatment may have beneficial effects on insulin sensitivity in the most insulin resistant patients with RA and AS

Wasko MC, Kay J, Hsia EC, Rahman MU

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

Arthritis Care Res 2011;63:512-21

CONCLUSION

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

Greenberg JD, Kremer JM, Curtis JR et al

Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis

Ann Rheum Dis 2011;70:576-82

CONCLUSION

- TNF antagonist use was associated with a reduced risk of cardiovascular events in patients with RA

Askling J, Dixon W

Influence of biological agents on cardiovascular disease in rheumatoid arthritis (Editorial)

Ann Rheum Dis 2011;70:561-2

Barnabe C, Martin BJ, Ghali WA

Systematic review and meta-analysis: Anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis

Arthritis Care Res 2011;63:522-9

CONCLUSION

- Anti-TNFα therapy is associated with a reduced risk of all cardiovascular events, MI, and CVA in observational cohorts.

Morris SJ, Wasko MC, Antohe JL, et al

Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients

Arthritis Care Res 2011;63:530-4

CONCLUSION

- Use of HCQ in this RA cohort was independently associated with a significant decrease in LDL, total cholesterol, LDL/HDL, and total cholesterol/HDL. Considering these results, its safety profile, and low cost, HCQ remains a valuable initial or adjunct therapy in this patient population at high risk for CVD

Conclusions

- Cardiovascular disease and premature atherosclerosis are frequently observed in RA patients
- High disease activity and systemic inflammation are responsible for premature atherosclerosis
- Early intervention with DMARDs especially MTX, and/or anti-TNF therapy reduces the risk of cardiovascular disease in these patients

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Aviña-Zubieta JA, Abrahamowicz M, Choi HK, et al

Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study

Ann Rheum Dis 2011;70:990-5

CONCLUSION

- This large population-based study indicates that GC use is not associated with an increased risk of CVA in cases with RA

van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE

Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study

Arthritis Res Ther 2006;8:R151

CONCLUSION

- We hypothesize that DMARD use, in particular MTX use, results in powerful suppression of inflammation, thereby reducing the development of atherosclerosis and subsequently clinically overt CVD

Evans MR, Escalante A, Battafarano DF, et al

Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis

Arthritis Rheum 2011;63:1211-20

CONCLUSION

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