Rheumatoid Arthritis and Cardiovascular Disease

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting approximately 1% of the adult general population. Cardiovascular disease is recognized as the leading cause of death in RA patients, accounting for nearly 40% of their mortality. Patients with RA are at a twofold increased risk for myocardial infarction and stroke, with risk increasing to nearly threefold in patients who have had the disease for 10 years or more. Congestive heart failure appears to be a greater contributor to excess mortality than ischemia. This increased cardiovascular disease risk in RA patients seems to be independent of traditional cardiovascular risk factors. Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms such as T-cell activation that subsequently lead to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the congeners of accelerated atherosclerosis observed in RA patients. This paper discusses pathogenic mechanisms, effects of methotrexate, tumor necrosis factor antagonists, steroids, and statins, with a perspective on therapy.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting approximately 1% of the adult general population. It is widely recognized to confer an increased risk of mortality compared with age and sex-matched controls without RA [1]. A pooled analysis of several studies computed a standardized mortality ratio ranging from 0.87 to 3.0 (mean, 1.71) in RA patients and calculated that the lifespan of these patients is shortened by 3 to 18 years [2]. Cardiovascular disease (CVD) is recognized as the leading cause of mortality in RA patients, followed closely by cerebrovascular disease. Together, they account for 35% to 51% of all mortality, with CVD accounting for approximately 40% [3,4].

Cardiovascular Risk in RA Patients

Patients with RA are at a twofold increased risk for myocardial infarction (MI) and stroke, with younger patients at higher risk [5]. The risk increases to nearly threefold in patients who have had the disease for 10 years or more [6]. RA patients are also twice as likely to have an unrecognized MI and sudden cardiac death, and less likely to report symptoms compared with non-RA patients [7]. In RA patients, congestive heart failure appears to be a greater contributor to excess mortality compared with ischemia [8]. Not only do patients with RA have almost twice the risk of developing heart failure, they tend to develop it at an earlier stage of the disease [9]. Even in the absence of clinical heart disease, RA patients exhibit diastolic dysfunction that appears to correlate with the presence of extra-articular manifestations [10,11].

Traditional Cardiovascular Risk Factors

The increased CVD risk in RA patients seems to be independent of traditional cardiovascular risk factors such as age, gender, current smoking status, regular aspirin use, diabetes mellitus, hypercholesterolemia, hypertension, physical activity, family history of early MI, and body mass index [12,13]. Paradoxically, lower body mass index (< 20 kg/m^2) is associated with a higher mortality, probably because those with more severe RA have higher circulating cytokine levels, promoting a catabolic state that lowers weight [14•].

Pathogenesis of CVD in RA

The inability of traditional cardiovascular risk factors to explain the increased CVD mortality in RA patients has prompted exploration of other mechanisms that accelerate atherogenesis in RA, particularly high-grade systemic inflammation. Although, the primary site of inflammation is the synovium, the systemic release of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and

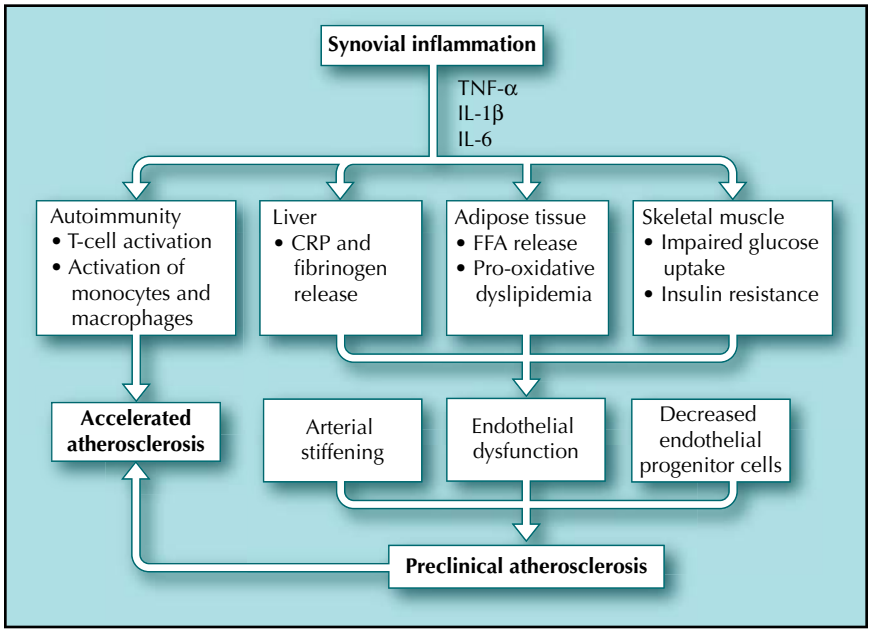

Figure 1. Diagram of the pathophysiology of atherosclerosis in rheumatoid arthritis (RA). RA is associated with the release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, which promote C-reactive protein (CRP) and fibrinogen release from the liver, free fatty acid (FFA) release from the adipose tissue, and impaired uptake of glucose into the skeletal muscle. The resultant pro-oxidative dyslipidemia, insulin resistance, endothelial dysfunction, reduced arterial compliance, and decrease in endothelial progenitor cells promote atherosclerosis. RA patients also have expansion of $CD4^+CD28^{null}$ subtype of T cells, a unique subset of T cells that lack the co-stimulatory CD28 molecule on their surface. These $CD4^+CD28^{null}$ T cells promote activation of T cells, monocytes, and macrophages, which may also be proatherogenic.

IL-6, results in chronically elevated cytokine levels. This alters the function of adipose tissue, skeletal muscle, liver, and vascular endothelium and causes proatherogenic changes that include a distinctive type of dyslipidemia, insulin resistance, prothrombotic effects, oxidative stress, and endothelial dysfunction (Fig. 1) [15].

Pro-oxidative dyslipidemia in RA

TNF-α acts on hepatocytes to induce de novo fatty acid synthesis and on the adipose tissue to stimulate lipolysis. The resulting free fatty acid release along with decreased triglyceride breakdown due to decreased lipoprotein lipase activity leads to hypertriglyceridemia, low total cholesterol levels, low high-density lipoprotein (HDL) levels, and small, dense low-density lipoprotein (LDL) particles, which are easily oxidized and hence proatherogenic [15,16]. Early in the disease course, untreated patients show significant declines in HDL with concomitant elevations in LDL [17]. In addition to lower levels of normal HDL, RA patients seem to have the more proinflammatory HDL, which results in elevated oxidized LDL levels [18]. Oxidized LDL and β2 glycoprotein I interact to form complexes that predispose to atherosclerosis [19]. Elevated lipoprotein(a) levels seen in RA patients might also contribute to atherosclerosis [20,21]. Although TNF-α blockade with infliximab increases total cholesterol and HDL levels, no changes are observed after 2 and 6 weeks of treatment in the total cholesterol to HDL ratio (the atherogenic index) [22]. However, administration of infliximab for 2 years was found to unexpectedly decrease HDL, and a proatherogenic profile developed despite a reduction in systemic inflammation [23].

Insulin resistance in RA

TNF-α inhibits skeletal muscle glucose uptake and stimulates adipose tissue lipolysis, both of which contribute to insulin resistance in RA patients [24–26]. Fatty acids released from adipocytes also elicit a nuclear factor-κB–dependent inflammatory response in macrophages that promotes release of cytokines such as TNF-α and IL-6, perpetuating a vicious cycle [27]. The key role of TNF-α is evident from the observation that TNF antagonists improve insulin sensitivity in RA patients [28].

Prothrombotic state in RA

TNF-α has a procoagulant effect and induces production of procoagulant proteins such as tissue factor from endothelial cells, which can elevate local thrombin concentration and subsequent fibrin deposition [29,30]. TNF-α also induces arterial smooth muscle cells to produce extracellular tissue factor, which ultimately may be responsible for atherosclerotic plaques and tissue factor located in injured arterial walls [31].

Hyperhomocysteinemia in RA

Homocysteine is an intermediary amino acid that is produced by removal of a methyl group from methionine, an amino acid regularly consumed in the diet. Hyperhomocysteinemia, considered a potential risk factor for CHD, is seen in RA patients [32,33]. RA patients also have low levels of vitamin B_6 (pyridoxine), which has been correlated with disease activity and severity as well as systemic inflammation, although vitamin B_6 supplementation did not reduce systemic inflammation [34,35]. Pulsed glucocorticoids improve disease activity and decrease homocysteine levels [36]. Although methotrexate decreases disease activity, it reduces plasma and erythrocyte folate levels and, therefore, increases homocysteine levels. This increase can be prevented by supplementation with folic or folinic acid [37].

Immune and autoimmune responses

There is an increasing body of evidence to suggest that atherosclerosis is an inflammatory disorder resulting from interactions between the endothelium, monocytes, and T cells [38]. Many features of immune dysregulation seen in RA patients, such as macrophage, mast cell, and T-cell activation; endothelin production; and neoangiogenesis, are also observed in the pathogenesis of atherosclerosis [39]. Lately, T cells have received special attention in this regard. $CD4^+$ helper T cells are of two subtypes: T-helper 1 (Th1) cells that produce interferon-γ that activates monocytes and macrophages, and Th2 cells that produce cytokines (IL-4, IL-5, and IL-10) that stimulate immunoglobulin production. A unique subset of $CD4^+$ T cells that lack the co-stimulatory CD28 molecule on their surface, called $CD4^+CD28^{null}$ cells, have been implicated in atherosclerotic plaque disruption [40]. RA patients exhibit expansion of the $CD4^+CD28^{null}$ cell population in the peripheral blood, which correlates with higher frequency of extra-articular manifestations, increased carotid artery intima-media thickness (IMT), and decreased flow-mediated vasodilation, lending support to the concept that $CD4^+CD28^{null}$ cells may sustain synovial inflammation and promote atherosclerosis in RA patients [41]. TNF-α downregulates CD28 expression in $CD4^+$ T cells, and TNF antagonists increase its expression [41,42]. A new class of drugs known as co-stimulation blockers (CTLA4Ig), which bind to CD80 and CD86 on antigen-presenting cells (thereby blocking T-cell activation by the CD28 co-stimulatory pathway), appear to hold therapeutic promise [43].

Decreased endothelial progenitor cells

Endothelial progenitor cells (EPCs) are mononuclear cells that are present in bone marrow, peripheral blood, cord blood, and blood vessels. They express specific endothelial markers and have the capacity to facilitate vascular repair at sites of endothelial injury. Low levels of EPCs in the presence of endothelial injury serve as a surrogate marker for progression of CVD [44]. Patients with active RA have low levels of EPCs and elevated plasma levels of asymmetric dimethyl-L-arginine, an endogenous inhibitor of nitric oxide synthesis that may play a role in depressing EPC counts in these patients [45,46]. TNF antagonists improve EPC differentiation and adhesion, and this correlates with clinical improvement [47].

Endothelial dysfunction, inflammation, and arterial stiffness

Several subclinical changes in blood vessels, which often precede development of overt CVD, have been identified. These can be considered surrogate measures of early vascular disease, and the magnitude of their abnormality is usually a predictor of clinical outcome. Among these surrogates are endothelial function, arterial compliance or stiffness, and inflammation. Endothelial cells lining the vascular wall play a pivotal role in both normal and disease states, in large part by releasing a variety of factors, foremost among which is nitric oxide. Absence or reduced activity of nitric oxide not only predisposes the vessel wall to increased vasomotor tone, which could lead to spasm, hypertension, and exacerbation of ischemia, but also predisposes it to increased platelet activation and aggregation, inflammation, and development of atherosclerosis. When it is evident in the human circulation, endothelial dysfunction is a predictor of future development of hypertension, diabetes, progression of atherosclerosis, and adverse cardiovascular events [48–51]. Even in early stages of disease, RA patients with low disease activity and absence of traditional cardiovascular risk factors or overt CVD exhibit decreased flow-mediated vasodilation, a measure of endothelial function [52]. Direct measurements by laser Doppler studies on the hands of RA patients show that they have impaired microvascular reactivity [52]. Treatment with methotrexate, prednisone [53], and TNF antagonists [54] ameliorates endothelial dysfunction. RA patients have systemic inflammatory activation, and the source of this inflammation has long been considered to be from synovial and joint inflammation. Increased levels of soluble adhesion molecules, such as intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, and soluble P-selectin, correlate with markers of CVD activity, such as C-reactive protein [55,56].

Studies have also shown that arterial stiffness, another indicator of subclinical vascular disease that is associated with increased CVD risk, is abnormal in patients with RA [57,58]. Pulse-wave analysis, even in RA patients with normal endothelial dysfunction, was markedly abnormal, indicating reduced arterial compliance [59]. Small and large artery elasticity was found to inversely correlate with markers of inflammation, such as high-sensitivity C-reactive protein, serum amyloid A, and vascular cell adhesion molecule levels [60]. Finally, TNF-antagonist therapy reduces aortic stiffness in RA patients [61••].

Preclinical Atherosclerosis

Preclinical atherosclerosis, often considered a precursor for CVD events, is evident by ultrasound-guided measurement of carotid artery IMT and identification of plaque in the carotid bulb [62,63]. RA patients have a threefold higher incidence of carotid plaque compared with age- and sex-matched controls that is independent of traditional risk factors for CVD [64••].

Newer Therapies

Statins have become the mainstay in management of patients with atherosclerosis. In RA, they not only facilitate clinical improvement as assessed by the disease activity score, but also improve endothelial dysfunction and reduce arterial stiffness [65,66••]. Apart from the

beneficial effects on vascular function of TNF antagonists described earlier in this review, newer therapies for RA have emerged, including the humanized IL-6 antagonist tocilizumab [67].

Conclusions

The concept that RA is a cardiovascular risk factor can be questioned when the confounding direct influence of drugs used to treat RA on CVD risk factors is considered. For example, corticosteroids exacerbate dyslipidemia, increase blood pressure, and adversely affect glucose metabolism, but they also reduce inflammation, making their net effect on vascular risk variable. Similarly, disease-modifying antirheumatic drugs may be protective against CVD risk. Thus, methotrexate abates joint and systemic inflammation and also lowers MI frequency by almost 70% [68]. TNF antagonists improve endothelial dysfunction and arterial stiffness simultaneously, with a reduction in systemic and joint inflammation [54,61••]. However, whether this will translate into true reduction in CVD risk remains unknown. Separating these confounding effects will be crucial in developing a rational recommendation list for managing CVD risk in RA. Although surrogate markers such as endothelial dysfunction, arterial stiffness, and carotid atherosclerosis appear to herald future risk of atherosclerotic disease, it is not certain whether they will also be faithful markers of CVD risk progression when evaluating treatment strategies. Despite these shortcomings, the recently established clinical practice guidelines on CVD risk in RA offer a useful framework [69•]. Cardiologists and rheumatologists need to appreciate that patients with RA, who constitute up to 1% of the population, are at increased CVD risk. Careful monitoring and aggressive treatment of risk factors, similar to what has been proposed for diabetic patients, should be recommended. Patients at increased risk for RA can be monitored by measurement of surrogate or subclinical markers of arterial disease. Glucocorticoids should be used in minimal effective doses, and disease-modifying antirheumatic drug therapy, particularly with methotrexate and TNF antagonists, may improve cardiovascular risk. However, whether early aspirin therapy, aggressive statin use, or angiotensin inhibition are indicated for reduction in cardiovascular risk in patients with RA remains to be investigated.

Disclosures

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Gabriel SE: **The epidemiology of rheumatoid arthritis.** *Rheum Dis Clin North Am* 2001, **27:**269–281.
2. Van Doornum S, McColl G, Wicks IP: **Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis?** *Arthritis Rheum* 2002, **46:**862–873.
3. Reilly PA, Cosh JA, Maddison PJ, et al.: **Mortality and survival in rheumatoid arthritis: a 25 year prospective study of 100 patients.** *Ann Rheum Dis* 1990, **49:**363–369.
4. Wolfe F, Mitchell DM, Sibley JT, et al.: **The mortality of rheumatoid arthritis.** *Arthritis Rheum* 1994, **37:**481–494.
5. Solomon DH, Goodson NJ, Katz JN, et al.: **Patterns of cardiovascular risk in rheumatoid arthritis.** *Ann Rheum Dis* 2006, **65:**1608–1612.
6. Solomon DH, Karlson EW, Rimm EB, et al.: **Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis.** *Circulation* 2003, **107:**1303–1307.
7. Maradit-Kremers H, Crowson CS, Nicola PJ, et al.: **Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study.** *Arthritis Rheum* 2005, **52:**402–411.
8. Nicola PJ, Crowson CS, Maradit-Kremers H, et al.: **Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis.** *Arthritis Rheum* 2006, **54:**60–67.
9. Nicola PJ, Maradit-Kremers H, Roger VL, et al.: **The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years.** *Arthritis Rheum* 2005, **52:**412–420.
10. Di Franco M, Paradiso M, Mammarella A, et al.: **Diastolic function abnormalities in rheumatoid arthritis. Evaluation by echo Doppler transmitral flow and pulmonary venous flow: relation with duration of disease.** *Ann Rheum Dis* 2000, **59:**227–229.
11. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J: **The increased risk of ventricular diastolic dysfunction and congestive heart failure in patients with rheumatoid arthritis is independent of the duration of the disease.** *Sem Arthritis Rheum* 2005, **35:**132–133.
12. del Rincon ID, Williams K, Stern MP, et al.: **High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors.** *Arthritis Rheum* 2001, **44:**2737–2745.
13. Solomon DH, Curhan GC, Rimm EB, et al.: **Cardiovascular risk factors in women with and without rheumatoid arthritis.** *Arthritis Rheum* 2004, **50:**3444–3449.
14.• Escalante A, Haas RW, del Rincon I: **Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation.** *Arch Intern Med* 2005, **165:**1624–1629.

This is an interesting study describing body mass index as a function of systemic inflammation. It also states that decreased body mass index was paradoxically associated with increased mortality in RA patients.

15. Sattar N, McCarey DW, Capell H, McInnes IB: **Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis.** *Circulation* 2003, **108:**2957–2963.
16. Hurt-Camejo E, Paredes S, Masana L, et al.: **Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile [see comment].** *Arthritis Rheum* 2001, **44:**2761–2767.

17. Park YB, Lee SK, Lee WK, et al.: **Lipid profiles in untreated patients with rheumatoid arthritis.** *J Rheumatol* 1999, **26:**1701–1704.
18. McMahon M, Grossman J, FitzGerald J, et al.: **Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis.** *Arthritis Rheum* 2006, **54:**2541–2549.
19. Tabuchi M, Inoue K, Usui-Kataoka H, et al.: **The association of C-reactive protein with an oxidative metabolite of LDL and its implication in atherosclerosis.** *J Lipid Res* 2007, **48:**768–781.
20. Dursunolu D, Evrengul H, Polat B, et al.: **Lp(a) lipoprotein and lipids in patients with rheumatoid arthritis: serum levels and relationship to inflammation.** *Rheumatol Int* 2005, **25:**241–245.
21. Asanuma Y, Kawai S, Aoshima H, et al.: **Serum lipoprotein(a) and apolipoprotein(a) phenotypes in patients with rheumatoid arthritis [see comment].** *Arthritis Rheum* 1999, **42:**443–447.
22. Vis M, Nurmohamed MT, Wolbink G, et al.: **Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis.** *J Rheumatol* 2005, **32:**252–255.
23. Dahlqvist SR, Engstrand S, Berglin E, Johnson O: **Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy.** *Scand J Rheumatol* 2006, **35:**107–111.
24. Paolisso G, Valentini G, Giugliano D, et al.: **Evidence for peripheral impaired glucose handling in patients with connective tissue diseases.** *Metab Clin Exp* 1991, **40:**902–907.
25. Dessein PH, Stanwix AE, Joffe BI: **Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis.** *Arthritis Res* 2002, **4:**R5.
26. Hotamisligil GS, Arner P, Caro JF, et al.: **Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance.** *J Clin Invest* 1995, **95:**2409–2415.
27. Liang CP, Han S, Senokuchi T, Tall AR: **The macrophage at the crossroads of insulin resistance and atherosclerosis.** *Circ Res* 2007, **100:**1546–1555.
28. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, et al.: **Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis.** *Clin Exp Rheumatol* 2006, **24:**83–86.
29. Bauer KA, ten Cate H, Barzegar S, et al.: **Tumor necrosis factor infusions have a procoagulant effect on the hemostatic mechanism of humans.** *Blood* 1989, **74:**165–172.
30. Kirchhofer D, Tschopp TB, Hadvary P, Baumgartner HR: **Endothelial cells stimulated with tumor necrosis factor-alpha express varying amounts of tissue factor resulting in inhomogenous fibrin deposition in a native blood flow system. Effects of thrombin inhibitors.** *J Clin Invest* 1994, **93:**2073–2083.
31. Schecter AD, Spirn B, Rossikhina M, et al.: **Release of active tissue factor by human arterial smooth muscle cells [see comment].** *Circ Res* 2000, **87:**126–132.
32. Clarke R, Daly L, Robinson K, et al.: **Hyperhomocysteinemia: an independent risk factor for vascular disease [see comment].** *N Engl J Medicine* 1991, **324:**1149–1155.
33. Roubenoff R, Dellaripa P, Nadeau MR, et al.: **Abnormal homocysteine metabolism in rheumatoid arthritis.** *Arthritis Rheum* 1997, **40:**718–722.
34. Chiang E-PI, Bagley PJ, Selhub J, et al.: **Abnormal vitamin B(6) status is associated with severity of symptoms in patients with rheumatoid arthritis.** *Am J Med* 2003, **114:**283–287.
35. Chiang E-PI, Selhub J, Bagley PJ, et al.: **Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis.** *Arthritis Res Ther* 2005, **7:**R1404–R1411.
36. Lazzerini PE, Capecchi PL, Bisogno S, et al.: **Reduction in plasma homocysteine level in patients with rheumatoid arthritis given pulsed glucocorticoid treatment.** *Ann Rheum Dis* 2003, **62:**694–695.
37. van Ede AE, Laan RF, Blom HJ, et al.: **Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis.** *Rheumatology* 2002, **41:**658–665.
38. Ross R: **Atherosclerosis—an inflammatory disease.** *N Engl J Med* 1999, **340:**115–126.
39. Pasceri V, Yeh ET: **A tale of two diseases: atherosclerosis and rheumatoid arthritis.** *Circulation* 1999, **100:**2124–2126.
40. Liuzzo G, Goronzy JJ, Yang H, et al.: **Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes.** *Circulation* 2000, **101:**2883–2888.
41. Gerli R, Schillaci G, Giordano A, et al.: **CD4+CD28- T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients.** *Circulation* 2004, **109:**2744–2748.
42. Bryl E, Vallejo AN, Matteson EL, et al.: **Modulation of CD28 expression with anti-tumor necrosis factor alpha therapy in rheumatoid arthritis [see comment].** *Arthritis Rheum* 2005, **52:**2996–3003.
43. Kremer JM, Westhovens R, Leon M, et al.: **Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig.** *N Engl J Med* 2003, **349:**1907–1915.
44. Hill JM, Zalos G, Halcox JPJ, et al.: **Circulating endothelial progenitor cells, vascular function, and cardiovascular risk.** *N Engl J Med* 2003, **348:**593–600.
45. Grisar J, Aletaha D, Steiner CW, et al.: **Depletion of endothelial progenitor cells in the peripheral blood of patients with rheumatoid arthritis.** *Circulation* 2005, **111:**204–211.
46. Surdacki A, Martens-Lobenhoffer J, Wloch A, et al.: **Elevated plasma asymmetric dimethyl-L-arginine levels are linked to endothelial progenitor cell depletion and carotid atherosclerosis in rheumatoid arthritis.** *Arthritis Rheum* 2007, **56:**809–819.
47. Ablin JN, Boguslavski V, Aloush V, et al.: **Effect of anti-TNFalpha treatment on circulating endothelial progenitor cells (EPCs) in rheumatoid arthritis.** *Life Sci* 2006, **79:**2364–2369.
48. Halcox JP, Schenke WH, Zalos G, et al.: **Prognostic value of coronary vascular endothelial dysfunction [see comment].** *Circulation* 2002, **106:**653–658.
49. Schachinger V, Britten MB, Zeiher AM: **Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease.** *Circulation* 2000, **101:**1899–1906.
50. Perticone F, Ceravolo R, Pujia A, et al.: **Prognostic significance of endothelial dysfunction in hypertensive patients.** *Circulation* 2001, **104:**191–196.
51. Vita JA, Keaney JF Jr: **Endothelial function: a barometer for cardiovascular risk? [comment].** *Circulation* 2002, **106:**640–642.
52. Arosio E, De Marchi S, Rigoni A, et al.: **Forearm haemodynamics, arterial stiffness and microcirculatory reactivity in rheumatoid arthritis [see comment].** *J Hypertens* 2007, **25:**1273–1278.
53. Bergholm R, Leirisalo-Repo M, Vehkavaara S, et al.: **Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis.** *Arterioscler Thromb Vasc Biol* 2002, **22:**1637–1641.
54. Hurlimann D, Forster A, Noll G, et al.: **Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis.** *Circulation* 2002, **106:**2184–2187.
55. Littler AJ, Buckley CD, Wordsworth P, et al.: **A distinct profile of six soluble adhesion molecules (ICAM-1, ICAM-3, VCAM-1, E-selectin, L-selectin and P-selectin) in rheumatoid arthritis.** *Br J Rheumatol* 1997, **36:**164–169.

56. Klimiuk PA, Sierakowski S, Latosiewicz R, et al.: **Soluble adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and vascular endothelial growth factor (VEGF) in patients with distinct variants of rheumatoid synovitis.** *Ann Rheum Dis* 2002, **61:**804–809.
57. Blacher J, Asmar R, Djane S, et al.: **Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients.** *Hypertension* 1999, **33:**1111–1117.
58. Boutouyrie P, Tropeano AI, Asmar R, et al.: **Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study.** *Hypertension* 2002, **39:**10–15.
59. Van Doornum S, McColl G, Jenkins A, et al.: **Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function [see comment].** *Arthritis Rheum* 2003, **48:**72–80.
60. Wong M, Toh L, Wilson A, et al.: **Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation.** *Arthritis Rheum* 2003, **48:**81–89.
61.•• Maki-Petaja KM, Hall FC, Booth AD, et al.: **Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy [see comment].** *Circulation* 2006, **114:**1185–1192.
This study describes the beneficial effects of TNF-α antagonists on arterial stiffness.
62. Ebrahim S, Papacosta O, Whincup P, et al.: **Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study.** *Stroke* 1999, **30:**841–850.
63. Del Rincon I, Williams K, Stern MP, et al.: **Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects.** *Arthritis Rheum* 2003, **48:**1833–1840.
64.•• Roman MJ, Moeller E, Davis A, et al.: **Preclinical carotid atherosclerosis in patients with rheumatoid arthritis.** *Ann Inter Med* 2006, **144:**249–256.
This cross-sectional study illustrates the high prevalence of carotid plaque, and thus preclinical atherosclerosis, in RA patients.
65. McCarey DW, McInnes IB, Madhok R, et al.: **Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial.** *Lancet* 2004, **363:**2015–2021.
66.•• Maki-Petaja KM, Booth AD, Hall FC, et al.: **Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis.** *J Am Coll Cardiol* 2007, **50:**852–858.
This study outlines the beneficial effects of statins on three things: inflammation, endothelial dysfunction, and arterial stiffness.
67. Nishimoto N, Kishimoto T: **Interleukin 6: from bench to bedside.** *Nat Clin Pract Rheumatol* 2006, **2:**619–626.
68. Choi HK, Hernan MA, Seeger JD, et al.: **Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study.** *Lancet* 2002, **359:**1173–1177.
69.• Giles JT, Post W, Blumenthal RS, Bathon JM: **Therapy insight: managing cardiovascular risk in patients with rheumatoid arthritis.** *Nat Clin Pract Rheumatol* 2006, **2:**320–329.
This is a good consensus paper.