Clustering of cardiovascular risk factors in rheumatoid arthritis: the rationale for using statins

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ABSTRACT

Atherosclerosis may be more prevalent and more extensive in individuals with rheumatoid arthritis (RA) compared with the general population. Despite the fact that traditional and novel cardiovascular disease (CVD) risk factors are clinically important in these patients, it seems that inflammation - a key feature of RA - plays a crucial role in atherogenesis.

Reducing the CVD burden in patients with RA is a more complex process than in the general population, mostly due to inadequate inflammation suppression as well as multiple concomitant drug therapy. Furthermore, there is no current consensus on whether RA patients should be treated as individuals at high-risk for vascular events. Statins have proved their efficacy in reducing CVD events in the general population. Despite the fact that they are not specifically indicated in RA, there is evidence supporting a beneficial effect on CVD risk factors as well as disease activity and progression.

The present review considers the traditional and novel as well as the RA-specific CVD risk factors. The current evidence supporting the use of statins in this patient population is also discussed.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects about 1% of the population and is characterised by chronic and erosive synovitis of the peripheral joints (1-4). RA patients have reduced life expectancy (by 3-18 years) compared with the general population (5-9), although this finding is not supported by all studies (10, 11). This discrepancy may be attributed to the changing natural history of RA leading to decreased mortality (5), different RA definition and disease duration (8), as well as to the fact that the more recent studies included patients with milder disease (12). A review that analysed 21 observational studies concluded that RA patients have an increased risk of death; most of these studies evaluated RA patients with a disease duration of 10 years or longer (8).

Epidemiology of cardiovascular disease (CVD) in RA

The excess vascular disease burden in RA has been known for many years (5, 13-16). Approximately 40%-50% of the mortality in RA is attributed to CVD; this is similar to what is observed in the general population (5, 7). However, CVD in RA patients presents about a decade earlier than in the general population, suggesting that RA is an independent risk factor for premature atherosclerosis (3, 17).

Cardiovascular morbidity and mortality

The heart can be affected in RA, mostly in the form of structural lesions such as pericarditis, valve abnormalities and endocardial rheumatoid nodules (7, 16, 18). However, the cardiac manifestations of RA usually remain clinically silent and do not appear to account for the increased CVD mortality (7, 16, 18). This finding suggests that atherosclerosis contributes to the causes of death in RA patients (18).

The majority of studies showed that RA is associated with increased CVD mortality (5, 6, 19-28), while others failed to detect such an association (29, 30). Standard CVD mortality ratios in RA patients range between 1.13 and 5.25, though this includes seropositive patients and patients with inflammatory polyarthritis, even without an established diagnosis of RA (3, 31). A study published in 1995 that evaluated approximately 1200 deaths in RA women in Finland showed that there was a 34% excess of deaths from CVD (19). A Swedish study reported a standardised
mortality ratio (SMR) of 1.46 for CVD and 1.54 for ischaemic heart disease (IHD) for patients with RA (23). Data from approximately 114,000 women participating in the Nurses’ Health Study showed that RA was associated with a relative risk (RR) of 2.0 (adjusted for cardiovascular risk factors) for myocardial infarction (MI) compared with women without RA (26). Another study showed a similar increase in male and female RA patients compared with the general population (32). RA patients have an increased 30-day mortality rate after the first CVD event compared with the general population (33). Recurrent cardiac CVD events after acute coronary syndromes (ACS) also occur more frequently in these patients compared with non-RA individuals (57.5% vs 30%, p = 0.013) (34).

Measures of disease activity, such as C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), may independently predict mortality in patients with RA or inflammatory polyarthritis (35, 36). Moreover, CVD events in RA patients are frequently silent and therefore unrecognised before a fatal event (3). It was reported that the SMR for CVD was 1.93 in RA patients with disease onset in the 1990s; however, hospital admissions for CVD were not increased suggesting that events may go unrecognised (21). Additionally, RA patients less frequently report symptoms of angina and more frequently experience sudden deaths compared with the general population (37). Finally, an ACS presents with chest pain only in 4/5 RA patients (34).

The excess CVD morbidity and mortality in RA can also be attributed to the fact that these patients have more severe IHD at the time of diagnosis (16). It was recently shown that RA patients are more likely to have multiple-vessel coronary artery disease (CAD) (as assessed by angiography) compared with non-RA individuals (38). Moreover, the odds ratio (OR) for severe coronary calcification in patients with RA duration greater than 10 years was 3.4, after adjustment for age, sex and CVD risk factors, compared with controls (39).

Cardiovascular comorbidity

If the findings of the majority of the studies are right and RA is indeed associated with increased CVD mortality, RA patients would be expected to have raised CVD comorbidity (5). This issue has been investigated in several studies (40-46). Hypertension, angina pectoris and chest pain were more prevalent in RA patients compared with non-RA individuals (40, 41, 43). Moreover, RA patients without known CVD have an increased prevalence of silent myocardial ischaemia (as assessed by non-invasive electrocardiographic monitoring and/or myocardial perfusion scanning) (5, 47). RA patients also have increased common carotid intima-media wall thickness (IMT), an accepted marker of subclinical atherosclerosis (48-53).

Interestingly, a recent study retrospectively evaluated the incidence of non-cardiac vascular disease in a cohort of 609 RA patients (54). The 30-year cumulative incidence rate of cerebrovascular and peripheral arterial events was estimated to be 32.2% (54). Specifically, the prevalence of cerebrovascular events was 21.6%, higher than the reported incidence rate of 12.6%-19.5% expected in non-RA individuals (54). Moreover, the incidence of peripheral arterial disease (PAD) was 19.6%, higher than the reported 14.9% rate in high-risk individuals (elderly, diabetic or smokers) (54).

Pathophysiology of CVD in RA

The pathogenesis of CVD is complex. Briefly, the arteries are exposed to risk factors leading to endothelial dysfunction and atherosclerosis (55). The precise mechanism of atherosclerosis in RA remains unclear; most likely multiple proatherogenic abnormalities interact and result in the increased prevalence of atherosclerosis (56). In this context, we will consider the traditional, novel and disease-specific CVD risk factors in RA.

Traditional and novel CVD risk factors

1. Lipid profile

Several studies assessed lipid and lipoprotein levels in RA patients (57-64). Most studies showed that untreated RA is accompanied by decreased total cholesterol (TC) and high density lipopro-
CVD in RA are conflicting. One study found that smoking increases CVD risk before the onset of seropositive inflammatory polyarthritis (84), while another failed to identify it as a predictor of CVD in RA patients (85). Current cigarette use is associated with the presence of carotid atherosclerotic plaques (50, 86) and with more severe coronary artery calcification in RA patients (39).

4. Glucose metabolism
Impaired glucose tolerance has been reported in RA patients and is associated with inflammatory activity as estimated by acute phase reactant levels (4, 87). More than 70% of RA patients demonstrate insulin resistance (55); however, one study failed to detect an increased prevalence of diabetes in RA patients compared with the general population (88). Insulin resistance often occurs as a feature of the metabolic syndrome (MetSyn) along with lipid abnormalities (89, 90). A recent study reported that patients with RA and MetSyn are at increased risk of having moderate to high disease activity score (DAS28), a validated score, which comprises of ESR, patient-assessed global score, visual analogue pain score and swollen and tender joint counts (both 0-28) (91). The presence of MetSyn, even without overt diabetes, is associated with increased prevalence of vascular disease (92).

Treatment with disease-modifying anti-rheumatic agents (DMARDs), anti-TNF agents or corticosteroids reverses the impaired glucose handling in RA patients (69, 93-95). This situation may be analogous to the impaired lipid profile in RA patients treated with corticosteroids (see section 1, above).

5. Body mass index (BMI)
Obesity is a risk factor for CVD (4). RA patients, however, may present with decreased BMI (rheumatoid cachexia) (96). A recent retrospective study showed that in RA patients, a low BMI (< 20 kg/m²) was a predictor of increased CVD mortality, after adjustment for other risk factors and malignancies (97).

RA is often associated with inactivity, but regular physical activity is an important strategy to prevent CVD (98).

6. Hyperhomocysteinaemia
Hyperhomocysteinaemia has been proposed as a risk factor for vascular disease (99). Homocysteine levels are elevated in RA patients (100) and are further increased in RA patients with comorbid CVD (5). This increase may partially be due to concomitant methotrexate (MTX) therapy (101). Folic acid supplementation in RA patients on MTX is crucial for the maintenance of normal plasma homocysteine levels (102, 103).

7. Prothrombotic markers
The concentrations of several prothrombotic markers, such as fibrinogen, tissue plasminogen activator (tPA), D-dimers and von Willebrand factor (vWF) are increased in RA (43). Moreover, PAI-1 and vWF concentrations were associated with an increased rate of CVD events in seropositive RA patients (104). Activated platelets play a role in the pathogenesis of vascular disease (105-107). Platelet characteristics, such as platelet-derived microparticles and platelet count, are often elevated in RA individuals (108, 109).

8. Impaired renal function
Renal involvement in RA is a common finding with clinical significance, since it worsens the course and the mortality associated with the disease (110). Chronic kidney disease prevalence has been reported to exceed 20% in RA (55). Moreover, renal dysfunction is often associated with an increased risk of vascular events (111). Renal dysfunction in RA originates either from the disease itself (rheumatoid nephropathy), secondary to renal amyloidosis, but may also be due to the nephrotoxic effects of anti-rheumatic agents (110). The rise in serum creatinine levels and the persistent proteinuria in this population are mostly due to the effects of drugs, while haematuria is mostly disease-related (112).

9. Oxidative stress
Oxidised LDL (oxLDL) is considered an important feature of atherosclerotic plaque formation (4). Lipid peroxidation and oxidative activity are increased in RA patients and they are directly correlated with acute phase reactants (113). However, a recent study showed that the concentration of malondialdehyde (MDA), an index of lipid peroxidation, was increased in RA patients compared with controls (p< 0.03), while total oxidative status levels were decreased in patients compared with controls (p< 0.008) (114).

RA-specific CVD risk factors
The increased prevalence of CVD mortality and morbidity in RA cannot be fully explained by the presence of traditional risk factors (4, 45). Therefore, other factors may be responsible for any accelerated atherosclerosis seen in RA patients.

The conditions described below are not only attributed to RA patients, but most are also implicated in the pathogenesis of CVD in the general population. However, these conditions are predominately present in RA.

1. Inflammation
Atherosclerosis is associated with low-grade inflammation, sharing similar pathogenetic mechanisms with RA (18, 115-118). Atherosclerosis seems to be a chronic inflammatory process resulting from interactions between plasma lipoproteins, cellular components (such as monocytes, T-cells, endothelial and smooth muscle cells) and extracellular components of the arterial wall (117). High-grade systemic inflammation is the hallmark of RA (119). Overlapping pathogenic features between the two diseases include the presence of pro-inflammatory cytokines (TNF-α, IL-6), elevated levels of acute phase reactants [CRP, fibrinogen, serum amyloid A (SAA), neo-angiogenesis, T-cell activation, and the local expression of leukocyte adhesion molecules] (120).

The links between high-grade inflammation and CVD in RA are complex (119, 121). For example, it has been shown that carotid IMT is elevated in RA patients and is independently associated with inflammation markers, such as CRP (122, 123). Moreover, cytokines released from the inflamed
synovial tissue, have a proatherogenic role, possibly through their adverse long-term effects in lipid profile and peripheral insulin sensitivity, as well as their prothrombotic and pro-oxidative effects (15, 119). This is further supported by the finding that the inhibition of TNF-α reduces atherosclerosis (124).

There is evidence of an inverse relationship between CRP and HDL-C levels in RA (58, 60, 62). Moreover, elevated ESR in RA patients has been associated with CVD events (85). TNF-α and IL-1 are implicated in cholesterol metabolism (125). Specifically, they both influence lipoprotein lipase activity, while IL-1 additionally induces the production of SAA (125). SAA acts either by displacing apolipoproteins A-I and A-II, enhancing the catabolism of HDL (126), or by inhibiting lecithin-cholesterol acyltransferase activity, resulting in changes in the distribution of HDL subclasses (127).

2. Endothelial dysfunction
An early step in the atherosclerotic process is endothelial cell injury (18, 128). Endothelial dysfunction (ED), expressed as reduced vasodilator ability, derives from the effects of classic risk factors (such as hypercholesterolaemia and hypertension) as well as other stimuli (such as inflammatory cytokines) (129, 130). There is considerable – although indirect – evidence of systemic endothelial activation in RA, as expressed by elevated levels of ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (119,131). However, a recent study showed that the levels of ED markers (ICAM-1, VCAM-1) were similar in RA and non-RA individuals, after controlling for traditional and non-traditional CVD risk factors (131). Microalbuminuria, a marker of endothelial injury, is common in RA and is associated with increased serum CRP levels (132). Studies that “directly” assessed endothelial function showed that there is indeed ED in RA patients and this is associated with inflammatory markers (133-136). Vasculitis, a feature of RA, although rarely affecting the coronary arteries, may cause ED distant from the primary inflammatory location (18, 137). This might be a triggering factor for atherosclerosis (18). Chronic ED might lead to enhanced susceptibility of the arteries to both traditional and RA-specific risk factors (18). Finally, many of the traditional and novel CVD risk factors (such as insulin resistance, oxidised LDL, dyslipidaemia) can promote ED (119).

3. Immunopathogenesis
T-cells in atherosclerotic plaques modulate lesion progression, determine the grade of inflammation and therefore plaque stability (138). An atypical CD4+CD28 subpopulation of T-cells is present in the peripheral blood of RA patients (139). These cells induce endothelial damage (3). It was recently shown that RA patients with persistent circulating CD4+CD28 T-cells had greater ED and carotid atherosclerosis compared with patients without these cells (140).

4. Drug-related CVD risk factors
Corticosteroids usually exert adverse effects on the lipid profile (74); however, corticosteroids at low doses reverse the atherogenic lipid profile in RA (75, 141). Corticosteroids also promote insulin resistance and the occurrence of diabetes (142, 143). Most studies suggest that they do not increase CVD risk in RA (3, 76, 85). However, a recent study showed that corticoid exposure resulted in higher incidence of carotid plaque in RA patients, independent of CVD risk factors (144). Therefore, it seems that the relationship between corticosteroid use and CVD in RA is complex.

NSAIDs are commonly used in RA. The administration of both selective (cyclo-oxygenase-2 inhibitors, COX-2 inhibitors) and non-selective NSAIDs has been associated with an increased risk of CVD and cerebrovascular events (145-147). A recent meta-analysis of randomised clinical trials showed that the allocation to a COX-2 inhibitor resulted in a 42% relative increase in the incidence of serious vascular events compared with placebo (rate ratio 1.42, 95% CI 1.13 to 1.78, p = 0.003), and this was mostly attributed to an increased risk of MI (148). Another important finding of this meta-analysis was the fact that it seems that not all non-selective NSAIDs are the same in terms of vascular risk. Specifically, high dose regimens of some traditional NSAIDs, such as diclofenac (risk ratio 1.63, 95% CI 1.12 to 2.37) and ibuprofen (risk ratio 1.51, 95% CI 0.96 to 2.37) but not naproxen (risk ratio 0.92, 95% CI 0.67 to 1.26), are associated with an excess vascular event rate, compared with placebo (148). Furthermore, NSAID administration was associated with an increased rate of first-time MI several weeks after the cessation of therapy and this risk was enhanced in RA (149). NSAIDs can also increase blood pressure and induce renal dysfunction in the general population (120).

MTX therapy has been associated with decreased CVD morbidity and mortality in RA (3, 150, 151); however, one study showed that MTX may promote atherosclerosis in RA patients who already had signs of atherosclerotic disease (152). MTX may induce renal dysfunction (153), but this was not confirmed in another study (154). Additionally, MTX increases plasma homocysteine levels (101). Finally, the effects of anti-TNF-α agents are complex; anti-TNF-α agents have been shown to decrease plaque formation (155) and to reduce the incidence of first-time CVD event [relative risk (RR) 0.46 vs not treated with anti-TNF-α agents] (156). However, a recent study showed that progression of subclinical atherosclerosis (assessed by IMT) occurs in chronically treated RA patients with the anti-TNF-α blocker infliximab (157). This observation suggests that the beneficial effect of anti-TNF-α therapy is mediated by an effect on the process leading to unstable plaques rather than with a decrease in the progression of carotid IMT. On the other hand, these agents may promote heart failure (155, 158).

5. Genetic factors
There are functional polymorphisms related with major histocompatibility complex (MHC) expression that are
associated with increased susceptibility to RA, MI and multiple sclerosis (159). This finding provides a potential explanation for the susceptibility to these diseases (3). In this regard, an association between HLA-DRB1*04 shared epitope alleles and endothelial dysfunction has been reported (136).

6. Abnormal angiogenesis
Endothelial progenitor cells (EPC) are important for the normal revascularisation after endothelial damage and their plasma levels are elevated after vascular damage (3). There is evidence that the plasma EPC count is decreased in patients with RA (160). This finding may partially explain the high incidence of atherosclerosis in RA (3).

7. Disease severity and duration
RA patients with disease duration greater than 6 years and the presence of ≥ 5 tender joints have an abnormal common carotid IMT (51). This is in agreement with an older study in RA patients that showed that there was an increase of 1.33 in mortality rate for every additional swollen joint (161). Additionally, in a series of 47 long-term actively treated RA patients without traditional CVD risk factors or clinically evident CVD, patients with extraarticular disease had a greater carotid IMT compared with patients without extraarticular manifestations (53). In this study, disease duration was the best predictor of the presence of carotid plaques. Moreover, patients with rheumatoid factor (RF)-positive arthritis have a RR of 1.61 for total mortality (9).

Effects of statins on CVD risk factors and clinical events
The evidence discussed above suggests that the increased CVD prevalence in RA is not adequately explained by traditional risk factors, and that it probably originates from the high-grade systemic inflammation occurring in these patients. Since complete suppression of inflammation is rarely achieved in RA, even with the new DMARDs, vascular disease incidence will continue to be high (15). This has led to the consideration of alternative agents in this population. An appealing option is statins.

To our knowledge, no studies evaluated the effect of statins on CVD mortality in RA patients. However, there are numerous studies evaluating the use of statins in the general population, in primary and in secondary prevention, that provide convincing evidence of a decrease by about 25-50% in cardiovascular mortality and morbidity (162-165).

The “pleiotropic effects” of statins may contribute to the benefit observed, since this cannot be readily explained by their lipid-lowering effects alone (166). It is beyond the scope of the present review to address all the pleiotropic effects of statins; however, we will consider their effects on parameters that: a) are known CVD risk factors, and, b) are commonly present in RA patients. Since the lipid profile in RA patients depends on disease activity and on the treatment used, it is not evident how RA patients may benefit from statin administration. If RA patients are indeed at a high risk for CVD, LDL-C treatment targets may need to be < 100 mg/dL (2.6 mmol/l) as outlined in several guidelines (167).

Statins may decrease blood pressure (168). Their effect on glucose metabolism is controversial; statin administration has been associated with decreased, unchanged or even increased onset of diabetes in the general population (169). Statins have a neutral effect on homocysteine levels in hypercholesterolaemic patients (170); a finding that may be important in dyslipidaemic RA patients on MTX therapy. Moreover, RA patients with or without impaired renal function might benefit from the use of statins; there is evidence that the administration of statins has a beneficial effect on serum creatinine and uric acid levels as well as on creatinine clearance in patients with dyslipidaemia, IHD or PAD (171-176).

CRP levels and ESR are associated with atherosclerosis in RA patients (35, 36, 177). Several studies have shown that statin administration in RA patients results in significant declines in these two parameters (178-182). Moreover, other inflammatory markers, such as IL-1, IL-6, IL-8 and TNF-α, have been shown to decline in both experimental (183-185) and clinical studies (178) after statin administration. Furthermore, fluvastatin can prevent complement-mediated inflammation in animal models (186). Statins also selectively inhibit leukocyte function antigen-1 (LFA-1)-mediated adhesion and costimulation of lymphocytes, resulting in a suppression of the inflammatory response (187).

Statins have favourable effects on endothelial function in RA patients (188) and in the general population (189, 190). For example, simvastatin (40 mg/day) improved endothelial function, as measured by flow-mediated dilation of the brachial artery, compared with placebo; this improvement was more evident in those with higher baseline CRP levels (188). Atorvastatin administration was associated with a significant reduction in arterial stiffness in 29 RA patients, and this improvement was more evident in patients with more active disease (191).

Statins also exert immunomodulatory effects (192-194). They inhibit the expression of MHC class II antigens, and therefore inhibit MHC-II-mediated T-cell activation (195). In an experimental model of RA, simvastatin inhibited not only the development but also clinically evident collagen-induced arthritis at doses that would not alter cholesterol levels in vivo (185). This study indicates that statins may have a role in the treatment of Th-1 driven autoimmune diseases, such as RA (185).

The effect of different statins on thrombosis, fibrinolysis and angiogenesis is conflicting (196-199). However, such effects may be relevant because there is a prothrombotic diathesis in RA (see section Traditional and novel CVD risk factors, part 7 above).

Statins also have antioxidant properties (189,190). In RA patients, simvastatin 40 mg/day significantly decreased both oxLDL levels and oxLDL/LDL ratio (p< 0.001 and p = 0.03, respectively) (188).

In January of 2006 the initiation of a large clinical trial (involving more than 3,500 patients with RA) was announced (200). This trial will evaluate the ability of statins to reduce the incidence of heart attacks and strokes in
RA patients with a calculated risk for a CVD-related event of less than 20% over ten years.

**Effects of statins on RA activity and progression**

There are limited clinical data on the effect of statins on RA activity and progression. The first open-label study, only included 8 patients and showed that simvastatin (10 mg/day) reduced the number of tender joints (p = 0.02) and patient self-assessment of disease activity (p = 0.03) after 12 weeks (179). However, the number of swollen joints, patient self-assessment of pain and physician global assessment of disease activity did not change significantly (179).

Another open-label study evaluated the effect of atorvastatin (20 mg/day) in 5 patients with refractory RA (182). All of the RA patients experienced an improvement of over 20% as defined by the American College of Rheumatology response criteria (ACR20) (182). The same investigators thereafter conducted an 8-week study in 15 RA patients, who received simvastatin (40 mg/day) and hydroxychloroquine (182). Nine of the ten simvastatin patients, compared with none of the hydroxychloroquine patients, achieved an ACR50 response (182).

In the only randomised, placebo-controlled double blind study (178), 116 RA patients were randomised to atorvastatin (40 mg/day) or placebo, as an adjunct to current DMARD therapy. The primary outcome was change in DAS28 (178). The two groups were comparable at baseline, except for MTX treatment rate (29 patients in the atorvastatin group vs 15 patients in the placebo group, p = 0.007). After 6 months, DAS28 in the atorvastatin group was significantly reduced [-0.50 (95% CI –0.75 to –0.25)] compared with the placebo group [0.03 (95% CI –0.23 to 0.28)] (p = 0.004) (178). This difference between the two groups persisted after adjustment for MTX therapy. The European League Against Rheumatism (EULAR) criteria for a good or moderate response were met in 31% of the atorvastatin patients and in 10% of the placebo patients (p = 0.006). CRP levels and ESR decreased by 50% and 28%, respectively, in the atorvastatin group relative to placebo. Moreover, several individual disease activity variables improved in patients allocated to atorvastatin (178). The investigators recommend statin therapy in dyslipidaemic RA patients. A novel potential role for statins in RA was recently reported (199). Fluvastatin (a lipophilic statin) but not pravastatin (a hydrophilic statin) induces apoptosis of RA synoviocytes in vitro suggesting a potential therapeutic role in the pathogenesis of synovial cell proliferation (199).

These findings provide indirect evidence of the usefulness of statins in RA patients. However, caution is required in this population in regard of concomitant drug therapy. For example, co-administration of a statin with MTX may increase the risk of hepatotoxicity (197).

**Conclusions**

RA is likely to be associated with increased CVD morbidity and mortality. These patients have a clustering of traditional, novel and disease-specific risk factors that may rank them as high risk individuals for the development of CVD. Statins do not have specific indications in RA. However, some evidence exists supporting a favourable effect on CVD risk factors as well as disease activity and progression. Further research is required to determine whether RA should be added to the list of vascular risk factors as well as to define the long-term effect of statins on CVD morbidity and mortality in RA.

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