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Cardiovascular Disease and Rheumatoid Arthritis: An Update

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Abstract

Patients with rheumatoid arthritis (RA) suffer significantly increased cardiovascular (CV) morbidity and mortality when compared to the general population. Both traditional CV risk factors and high levels of systemic inflammation have been linked to the increased CV risk in RA patients, but significant uncertainty remains regarding the mechanisms through which these factors contribute to CVD. In addition, ongoing questions remain regarding how best to identify RA patients at high risk for CVD, and what primary and secondary prevention strategies are effective at influencing CV outcome. The current review summarizes recent research in this field.

Keywords

Rheumatoid arthritis; Cardiovascular disease; Atherosclerosis; Morbidity; Mortality; Risk factors; Inflammation; Therapy

Introduction

The problem of increased cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is well recognized. Women with RA have a 2-3 fold higher risk of myocardial infarction, even in the absence of traditional coronary risk factors (1-3). While research regarding the increased CV morbidity and mortality in RA patients has burgeoned in recent years, ongoing questions remain regarding 1) the biologic mechanisms contributing to increased CVD in RA, 2) the proper approach to identifying high risk patients, and 3) the effects of both traditional CV prevention strategies as well as RA directed therapies on CV risk in RA.

The below review summarizes work published recently regarding the above topics. Specifically, new literature is reviewed which addresses traditional CV risk factors in RA, including work suggesting a paradoxical association of cholesterol levels with CV outcomes in RA. Mechanistic work linking RA associated inflammation to CV risk is also presented as well as work evaluating potential CV effects of disease modifying therapies.

Traditional CV Risk Factors in RA: What do they tell us?

The prevalence of traditional CV risk factors in RA has been extensively studied (4;5) and their contribution to CV risk in RA is well accepted as evidenced by the recent EULAR CV guidelines (Table 1) (6). New work published by Innala et al. evaluated risk factors for CV

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events in a large Swedish 700 patient early RA cohort of which 442 patients had 5 years of follow-up and 48 patients had new CV events (7). In this work, several traditional CV risk factors including diabetes and treatment for hypertension, in addition to disease activity, were significantly associated with the occurrence of new CV events (7). This confirms previous work by other investigators that both traditional CV risk factors (4;5) as well as systemic inflammation (8) are important in assessing CV risk.

Other recent data in CV outcome studies of RA patients includes work by Van Sijl and colleagues in which renal dysfunction was significantly associated with CV events in a 353 patient cohort followed for 3 years. Although the number of events during the study was relatively low (23), significant associations between both a lower baseline glomerular filtration rate (GFR) as well as a decrease in GFR over the follow-up period with CV events were noted after controlling for other traditional CV risk factors (9). This data is not surprising given the strong association of renal dysfunction with CV risk in the general population, however, further demonstrates the relevance of traditional CV risk factors to the RA population(10). In addition, recent work by Chung et al. has shown that traditional CV risk factors are prevalent in RA, and in particular reported that hypertension may be more common in RA patients compared to control subjects (11).

In contrast to the above work, it is well known from data on body composition that not all traditional CV risk factors behave similarly in patients with RA compared to the general population. A paradoxical effect of body mass index (BMI) on survival in RA patients has been well described in which a low BMI is associated with a threefold increased risk of CV death(12). This is in contrast to the general population in which a lower BMI may be beneficial to cardiovascular risk.

Interestingly, similar paradoxical associations of adverse CV outcome with lower cholesterol levels were recently reported by Myasoedova et al. (13). In work with a population based cohort of 651 patients with RA, patients with lower total cholesterol (TC) and lower low density lipoprotein cholesterol (LDL-C) levels had increased risk of CVD (13). A significant, non-linear association for total cholesterol with risk of CVD was noted showing a 3.3 fold increased risk for TC < 4 mmol/l (95% CI 1.5 to 7.2), and no increased risk for TC > 4mmol/l (p=0.57)(13). Similarly, lower atherogenic ratios, (TC/HDL-C and LDL-C/HDL-C), were associated with increased risk of CVD. As previously reported, systemic inflammation measured by ESR was significantly associated with risk of CVD, but interestingly there were also interactions between LDL-C and ESR for risk of CVD, suggesting that degree of systemic inflammation may affect the associations of cholesterol levels with CVD in RA patients(13).

The Apolipoprotein-related Mortality Risk (AMORIS) study also evaluated the predictive values of TC and triglycerides (TG) for CV events in patients with and without RA (14). While both TC and TG were significant predictors of acute MI and stroke in patients without RA, the predictive values in RA patients were not consistent (14). Additional studies are needed to confirm and better understand the implications of these findings, however, the two studies described above raise interesting questions regarding the impact/significance of increases in cholesterol levels associated with RA therapies.

Traditional CV Risk Factors in RA: How should/do we manage them?

The EULAR guidelines for cardiovascular risk management in patients with RA incorporate several standard traditional CV risk factors/guidelines with a suggestion to adjust CVD risk scores by a factor of 1.5 dependent on presence of RA duration >10 years, RF/CCP positivity, and extra-articular manifestations(6) (Table1). The 2011 American Heart Association's Guidelines for Prevention of CVD in Women incorporate RA as a major risk

factor for CVD in women, indicating regular traditional CV risk factor screening. These guidelines also suggest that women with prior CVD events should be screened for autoimmune conditions including RA (15).

Despite this increased awareness of CV risk in RA, recent data suggests that adherence to both primary and secondary prevention strategies is low in the RA population. Toms et al. studied a cohort of RA patients without established CVD or diabetes and found that in the high risk group, 2-26% (depending on risk stratification group), had sufficiently high risk to require statin therapy, although the majority of them (58-95%) were not treated (16). Bartels and colleagues studied RA patients enrolled in Medicare who were older than age 65 and had both RA and concomitant CVD (90%), diabetes (46%), or hyperlipidemia (64%) (17). In this high risk cohort with CVD, 30% of the RA patients studied saw a PCP less than once per year and 1 in 3 lacked annual cholesterol screening (17). Finally, Lindhardsen et al. reported a marked discrepancy in secondary prevention in RA patients discharged from the hospital after suffering a first myocardial infarction (MI). In this Danish registry containing 877 RA patients, (out of 66,107 total registry patients), RA was associated with a significantly lower initiation of aspirin, beta blockers, and statins thirty days after discharge, although no difference in use of renin angiotensin system blockers or clopidogrel was noted (18). These differences in initiation of aspirin, beta blockers, and statins were maintained at day 180 (18). In addition, adherence to statins was lower in RA patients relative to non-RA patients, while no significant differences were found in adherence to other drugs (18).

The above studies raise several questions regarding CV prevention strategies in RA patients, including whether undertreatment may contribute to the increased CV burden in RA. However, it is not known whether the use of therapies such as statins in primary and secondary prevention strategies will have similar beneficial effects in RA patients as seen in the general population. A large, randomized placebo controlled study of atorvastatin in 4,000 RA patients (TRACE RA; <http://www.dgoh.nhs.uk/tracera/>) is in progress to examine this question.

In the interim, several studies have used available data to evaluate the potential beneficial effects of statins in RA patients. Sheng et al. evaluated a population based cohort of OA and RA patients in Scotland who were categorized into statin exposed or statin-unexposed groups according to statin use during follow up (19). In primary prevention analysis of RA patients (n=430), statins were associated with reduced CV events and all cause mortality (adjusted HR 0.45 (95% CI 0.20-0.98) and 0.43 (95% CI 0.25-0.72) respectively(19). However, no reduction of CV events or mortality was seen in secondary prevention both in RA (n= 78) and the OA population (n=247) studied(19). Certainly, the interpretation of this study is somewhat limited by the retrospective nature of the study and the relatively small sample size.

Semb et al. also examined secondary prevention lipid lowering therapy outcomes in 87 RA patients who participated in the IDEAL study (total n=8888) in which patients were randomized to either atorvastatin or simvastatin therapy and followed for CV event. In this work, patients with RA and previous MI had similar rates of CV events on lipid lowering therapy as those without RA (20). Interestingly, baseline cholesterol levels (both TC and LDL-C) were significantly lower in the RA group than in patients without RA although they experienced comparable lipid-lowering effects with treatment (20). Finally, De Vera et al. studied the effects of statin discontinuation on risk of acute MI in RA patients(21). During 15,669 person-years of follow-up 264 acute MIs occurred and statin discontinuation was associated with a 67% increased risk of MI in adjusted analysis (21). Taken together, this data suggests potential benefits of statin use in RA patients and continued adherence to modified CV guidelines until conclusive data from studies such as TRACE are available.

RA Associated Inflammation: A known link to CV risk in RA, but how?

While considerable evidence suggests that the extent of systemic inflammation predicts poor cardiovascular outcome in patients with RA (4;8;22-24), ongoing questions remain regarding the mechanisms which link systemic inflammation to increased cardiovascular risk. Recent work by Giles et al. reported that both higher swollen joint counts and higher average C-reactive protein levels were associated with incident as well as progressive carotid plaque in a 158 patient RA cohort followed over 3 years (25). Additional research in the last year has further evaluated potential mechanistic links between this RA-associated inflammation and CV risk.

The function and structure of HDL has previously been shown to be altered in the setting of systemic inflammation in animal models of inflammation (26-29), in patients with acute inflammatory responses after surgery or during infection (26;29), and in patients with rheumatic disease including active RA (30;31). The anti-atherogenic function of HDL occurs through its ability to promote cholesterol efflux from artery wall cells (32), and protect LDL against oxidation (33-37). The former function of cholesterol efflux had not previously been evaluated in patients with RA but was recently shown to be a strong inverse predictor of both coronary artery disease and carotid intima media thickness (IMT) in non-RA patients (38). In recently published work, the cholesterol efflux capacity of HDL was also evaluated in patients with RA (39). In this work, HDL from RA patients with high disease activity measured by a disease activity score using 28 joint count (DAS28) > 5.1, had significantly decreased ability to promote cholesterol efflux compared to HDL from patients with low disease activity/clinical remission (DAS28 < 2.6) (39). In addition, a significant correlation was noted between cholesterol efflux and disease activity measured by the DAS28 in all RA patients ($r = -0.39$, $p = 0.01$); higher RA disease activity was associated with decreased efflux by HDL (39). A similar significant correlation was observed with ESR and this association remained in limited multivariate analysis controlling for smoking, diabetes, and prednisone use (39).

Additional work has attempted to understand the changes in HDL's protein structure which occur in the setting of systemic inflammation from active RA and which may account for impairment in its anti-atherogenic functions. Watanabe et al. examined HDL from RA patients using proteomic analysis and identified 78 different proteins in the HDL complexes (40). Twelve of these proteins including several acute phase proteins and complement factors were significantly increased in RA patients with non-protective, pro-inflammatory HDL compared to RA patients with normal anti-oxidant HDL (40). This data suggests a potential mechanism by which systemic inflammation alters HDL's protein cargo with subsequent effects on its protective capacity.

Endothelial dysfunction has also been linked to systemic inflammation and the development of early atherosclerosis (41;42). New work by Sidibe et al. recently demonstrated that VE-cadherin, an endothelium-specific adhesion molecule of importance for endothelium integrity, is lysed by stimulation of endothelial cells with tumor necrosis factor α (TNF α) (43). In addition, in a cohort of 63 patients with early RA, circulating levels of the extracellular domain of VE-cadherin (VE-90) were positively correlated with RA disease activity at baseline and one year follow-up, suggesting a potential mechanism through which active RA may induce endothelial damage and predispose to atherosclerosis (43).

Lastly, interesting work published by Giles et al. recently described increased citrullination in the myocardium of patients with RA compared to the myocardium of controls including patients with scleroderma and fatal myocarditis (44). Average anti-citrulline staining was 59% higher for the RA group compared to combined non-RA group. While further study is

necessary, this data may suggest another mechanism through which RA directly predisposes patients to increased cardiovascular disease (44).

Measures of Subclinical Atherosclerosis: Do they help us?

Due to the difficulty of obtaining long term data on CV events in large numbers of RA patients, work continues to evaluate measures of subclinical atherosclerosis in RA as potential measures of CV risk. Until recently, only one study had shown a direct link between a measure of subclinical atherosclerosis and adverse CV outcome (45). However, Evans et al. recently described a 636 patient RA cohort in which 66 incident acute coronary events occurred in 3,403 person years of follow up (46). In this cohort, the presence of unilateral carotid plaque at baseline was associated with a two and a half fold increased risk of acute coronary syndrome (ACS) (46). The presence of plaque in both internal carotid arteries nearly quadrupled the ACS incidence compared to patients without carotid plaque (46). This work validates the idea that atherosclerosis contributes significantly to ACS in RA patients, and also provides data that suggest carotid ultrasound may be useful for assessing CV risk in RA (46).

Karpouzas and colleagues recently studied the characteristics of coronary plaque in RA patients using cardiac computed tomography angiography (CTA) (47). Initial work in 74 RA patients and 74 matched controls revealed that asymptomatic RA pts have a higher prevalence, extent, and severity of “vulnerable” non-calcified coronary plaque compared to controls (47). Specifically, non-calcified plaque was present in 54% of diseased arterial segments in RA pts vs. 21% in controls ($p = 0.0001$) (47). Additional follow-up work in 150 RA patients suggested an association of systemic inflammation (high CRP) with the presence of vulnerable coronary plaque on CTA (48). Interestingly, this data in part echoes work from a previous autopsy study by Aubry and colleagues in which RA patients had significantly more “vulnerable” plaques compared to autopsy controls. In the latter work, a vulnerable plaque was defined by the number of inflammatory cells (>25) per high power field and a thin fibrous cap (<65 μ m thick) (49).

Other recent studies of subclinical atherosclerosis in RA patients include measurements of flow mediated dilatation and small artery elasticity which continue to suggest evidence of premature atherosclerosis in patients with both early and longstanding RA (50;51).

CV Effects of RA Therapies

Due to the strong association of systemic inflammation with increased CV risk in epidemiologic studies of RA patients (8), better control of RA disease activity with new disease modifying therapies has been hoped to improve CV outcomes. Unfortunately, studies in this regard are plagued with the challenge of assessing an outcome which requires many years of follow up, (CV events), in an overall heterogeneous population with a relatively rare disease, (RA), for this type of study. Despite these caveats, recent research has progressed in the area, albeit sometimes with conflicting results. In the last section of this review, new data is discussed related to the effects of RA disease modifying therapies on both CV risk factors and CV morbidity and mortality.

Effects of RA Therapies on Traditional CV Risk Factors

High levels of systemic inflammation in patients with RA have previously been associated with suppression of total, LDL, and HDL cholesterol levels (52). Not surprisingly, effective treatment of RA has been associated with increases in cholesterol levels, particularly total and HDL cholesterol levels, albeit in most but not all studies (53). Past work by Boers et al. identified a significant inverse correlation of HDL and total cholesterol levels with disease

activity in patients treated with non biologic DMARDs (sulfasalazine and/or methotrexate + prednisone). Improvement in disease activity measured by the DAS28 was linearly associated with the total cholesterol/HDL ratio, the so-called “atherogenic index,” due primarily to increases in HDL-C levels (54).

More recent work has evaluated the effects of biologic therapies on lipid profiles in RA patients. Analysis from the etanercept in rheumatoid arthritis (ETRA) study showed significant increases in TC, TG, LDL-C and apoA-1 levels after 4 months of etanercept therapy (55). Interestingly, when stratified for EULAR response, significant changes in lipid profiles were noted only in the EULAR responders. These patients had increases in TC and apoA-1 at 4 months as well as one year after therapy initiation (55). Recent work by Curtis and colleagues with a retrospective database study also reported increases in cholesterol levels including TC, HDL-C, and LDL-C in RA patients not on lipid-lowering therapies who were treated with TNF- inhibitors (56).

Tocilizumab, a monoclonal antibody against the IL-6 receptor, markedly decreases C reactive protein levels and has been associated with increases in total, HDL, and LDL cholesterol levels(57;58). A recent meta-analysis of six Japanese initial trials and five long-term extension studies with tocilizumab showed that TC, HDL-C, and LDL-C levels all increased during the first year of tocilizumab treatment, but did not continue to increase during the extension studies with the atherogenic index remaining stable throughout 5 years (59).

Further research may seek to better understand to what extent the increases in cholesterol levels with newer RA therapies are mediated by drug specific mechanisms, versus non specific mechanisms related to the body’s physiologic response to decreases in disease activity and systemic inflammation. Both the TNF-inhibitors and tocilizumab have also been associated with potential CV protective effects including improvement in peripheral insulin sensitivity (60;61) and decreases in arterial stiffness (62). Recent data also suggests an improvement in blood pressure with use of the TNF inhibitors (63;64), and tocilizumab was recently reported to improve hemoglobin A1C levels in a small study of diabetic patients with RA (65). Finally, the recently noted paradoxical associations of lower cholesterol levels with worse CV outcomes in RA patients (13) may suggest that the CV consequences of increases in cholesterol with effective therapy are not entirely straightforward.

Effects of RA Therapies on CV Morbidity and Mortality

Work by several groups has recently studied the effects of disease modifying therapies on CV morbidity and mortality in patients with RA. Greenberg et al. examined the association of CV events with TNF inhibitor use compared with non-biological DMARDs use in the Consortium of Rheumatology Researchers of North America (CORRONA) registry of 10,156 RA patients. In this work a total of 88 CV events occurred, including 26 MIs, 45 transient ischemic attacks (TIA)/strokes and 17 CV-related deaths. Patients using a TNF inhibitor experienced a reduced risk of CV endpoint compared with users of non-biological DMARDs although interestingly methotrexate was not associated with a reduced CV risk (HR 0.94, 95% CI 0.49 to 1.80)(66). In contrast, Lunt et al. reported findings from the British Society for Rheumatology Biologics Register (BSRBR) cohort study in which 322 CV deaths occurred and no protective CV benefits were noted in anti-TNF-treated patients compared to patients treated with non biologic DMARDs (67). Similar results were noted in a large study from the US Veterans Administration database (20,811 RA patients) in which TNF inhibitors did not reduce the rate of composite CVD end-point, although appeared to reduce stroke risk in subsequent analysis(68). Finally, work from the Swedish Rheumatology Register examined a cohort of early RA patients and found no decrease in risk of acute coronary syndrome with anti-TNF therapy, including no decreased risk in a

subgroup of patients meeting EULAR response criteria with TNF-I use(69). The latter finding was in contrast to an earlier BSRBR study which found a reduced risk of MI among responders to TNF-I therapy, albeit in patients with established RA, not early RA(70).

Taken together, the above studies clearly demonstrate the range of results from various cohort studies, with inconsistencies likely stemming in part from the heterogeneity of the cohorts as well as other factors including variable numbers of CV events in each study. Two large systemic reviews have recently been published addressing the question of TNF-I and risk of CV events in RA patients. Westlake et al. included a total of 20 articles and concluded that TNF-antagonists appeared to overall reduce the likelihood of CVD in RA patients, although the reduction was not as consistent as studies with methotrexate (71). In a meta-analysis by Barnabe et al., anti-TNF therapies were also associated with a reduced risk of CV events, and randomized controlled trials demonstrated a trend toward decreased CV risk although underpowered in this regard (72). A randomized clinical trial of tocilizumab and etanercept powered to detect differences in rates of hard CV outcomes is currently in progress. (US National Library of Medicine. *ClinicalTrials.gov* [online], <http://clinicaltrials.gov/ct2/show/NCT01331837> (2011).)

Conclusions

In conclusion, while many questions remain regarding the increased CV risk associated with RA, recent research continues to show progress in our understanding of risk factors and mechanisms related to CVD in RA, as well as the status of care and need for further work. Recent data support the importance of traditional CV risk factors, while also challenge the idea that all traditional CV risk factors behave similarly in patients with RA as in patients without RA (13). New mechanistic studies suggest that RA-associated inflammation may directly affect lipoproteins such as HDL, altering its protein structure and anti-atherogenic function(39;40), as well as directly compromise endothelial integrity through cytokines like TNF α (43). Additional work is needed to better define mechanisms which predispose RA patients to increased CV risk, so that preventive strategies and targeted therapeutics may be developed. Targeted CV therapeutics may be particularly important to those RA patients who continue to have active disease, despite currently available disease modifying therapies. Finally, while large outcome studies of CV events remain the gold standard in assessing the effects of RA therapies on CV risk, difficulties in obtaining this data as seen by discrepancies in recent data sets, reinforce the need for continued research in other measures of subclinical atherosclerosis and vascular function.

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Table 1

The 10 EULAR evidence-based recommendations for cardiovascular (CV) risk management in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

Recommendations	Level of evidence	Strength of recommendation
1 RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden	2b–3	B
1 Adequate control of disease activity is necessary to lower the CV risk	2b–3	B
1 CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed	3–4	C
1 Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria:	3–4	C
1. <ul style="list-style-type: none"> • Disease duration of more than 10 years 		
1. <ul style="list-style-type: none"> • RF or anti-CCP positivity 		
1. <ul style="list-style-type: none"> • Presence of certain extra-articular manifestations 		
1 TC/HDL cholesterol ratio should be used when the SCORE model is used	3	C
1 Intervention should be carried out according to national guidelines	3	C
1 Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options	2a–3	C-D
1 The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors	2a–3	C
1 Corticosteroids: use the lowest dose possible	3	C
1 Recommend smoking cessation	3	C

ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2 inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

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