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Rheumatoid Arthritis and Cardiovascular Disease: Update on Treatment Issues

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Abstract

Purpose of review—This review examines thresholds for treatment of traditional cardiovascular disease (CVD) risk factors among RA patients and whether RA-specific treatment modulates cardiovascular risk.

Recent findings—There are substantial data demonstrating an increased CVD risk among patients with RA. Both traditional CVD risk factors and inflammation contribute to this risk. Recent epidemiologic studies strengthen the case that aggressive immunosuppression with biologic DMARDs, such as TNF antagonists, is associated with a reduced risk of CVD events. However, to data, there are no randomized controlled trials published regarding the management of CVD in RA.

Summary—Epidemiologic evidence continues to accumulate regarding the relationship between the effects of traditional CVD risk factors and RA-specific treatments on CV outcomes in RA. The field needs randomized controlled trials to better guide management.

Keywords

rheumatoid arthritis; cardiovascular disease; risk stratification; coronary; treatment

Introduction

The risk of cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA)[1–5], but no disease-specific treatment strategies have been agreed on. RA increases CVD morbidity by 1.5 - 2-fold compared to the general population[4,6*], with recent evidence supporting the notion that the mortality gap between patients with RA and those in the general population has widened[7]. Many factors contribute to the elevated CVD risk in RA, but it cannot be explained by traditional cardiovascular risk factors alone [8–11]. RA-specific factors –immune dysregulation, systemic inflammation, plaque instability, impaired coronary reserve, elevated thrombotic markers, or specific treatments (i.e. oral glucocorticoids or nonsteroidal anti-inflammatory drugs)–likely also contribute to the increased CVD risk. Thus, traditional CVD risk factors and RA specific risk factors must be addressed to improve CV outcomes.

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In this review, we examine: 1) whether thresholds for prevention and treatment of traditional cardiovascular risk factors should be altered in RA patients and 2) how RA-specific treatment modulates CVD risk.

Should Thresholds for Treatment of Traditional CVD Risk Factors be Altered in RA Patients?

Prior studies show that the prevalence of traditional cardiovascular risk factors is increased in RA patients. Several traditional risk factors, such as dyslipidemia, type 2 diabetes mellitus (DM), hypertension (HTN), physical inactivity, advanced age, male gender, family history of CVD, cigarette smoking, and altered BMI predict CVD in RA patients[12,13]. As well, HTN, elevated LDL, and DM often go untreated or undertreated in this population [14**, 15*,16]. Whereas obesity is widely appreciated as a CVD risk factor in the general population and RA, rheumatoid cachexia may also confer an elevated CVD risk in RA patients [17]. Recent cardiology and rheumatology management guidelines acknowledge the higher risk of CVD in RA patients[18,19], but what remains unclear is whether treatment thresholds in RA patients should be altered to account for these CVD risk factors. In this section, we examine the elevated risk conferred by various traditional CVD risk factors and provide recommendations regarding management.

Dyslipidemia

Despite the increased risk of CVD in RA patients, the prevalence of dyslipidemia does not appear to differ significantly between RA patients and the general population[10]. Lipid levels may be altered by RA disease activity although the data is conflicting. In early RA, some studies demonstrate decreased levels of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels [20,21], whereas others demonstrate increased levels of TC, LDL, and high density lipoprotein (HDL) levels[22,23]. Although reports of lipid profiles in patients with established RA vary, growing evidence suggests that lower TC and LDL levels result in paradoxically elevated CVD risk in RA patients[24,25*]. The majority of recent studies of lipid profiles in RA patients show that tumor necrosis factor (TNF) inhibitors and tocilizumab worsen lipid levels[26–29*]. As well, a recent study found that hydroxychloroquine may improve the atherogenic profile[30*].

Statin use in RA patients has been demonstrated to decrease TC and LDL levels in a randomized placebo-controlled trial [31]. A population-based retrospective study using a cohort from Scotland demonstrated that statin therapy was associated with reduced CV events and all-cause mortality in primary prevention [32*]. Lipid-lowering effects with statin treatment were similar in RA and non-RA control groups in patients randomized to atorvastatin or simvastatin therapy over a five-year period [33*]. A recent study noted that RA patients discontinuing statin therapy experienced an increased risk of myocardial infarction, although the results of observational “stopping trials” are difficult to interpret [34*]. Observational studies are unlikely to provide all of the answers. To this end, a randomized placebo-controlled study of atorvastatin in approximately 3,000 RA patients is in progress (TRACE-RA; http://www.dgoh.nhs.uk/tracera/http://www.dgoh.nhs.uk/tracera/). This study randomized patients with slight elevation in LDL (100–130 mg/dL) to test

whether a more aggressive lipid treatment strategy than what is recommended in the general population is warranted [35].

Until results from this study are available, we recommend annual lipid profile screening and adherence to the current general population guidelines.

Diabetes

While DM is a clear risk factor for CVD in the general population, its influence on future CVD risk in RA patients is less clear. Although there are strong epidemiological data supporting an association between RA and insulin resistance[36], studies including diabetes as a covariate did not find a statistically significant relationship with CVD, although several were underpowered[1, 8, 10, 37]. In the QUEST-RA study, diabetes emerged as an independent risk factor in multivariate analyses but only for stroke[38]. A recent prospective study reported that diabetes mellitus was significantly predictive of a new CV event in patients with early RA[39*].

Given these conflicting data, at least annual screening of hemoglobin A1c in patients with active disease, chronic corticosteroid use, or those at high risk for CVD seems warranted. Treatment targets for DM should adhere to general population standards.

Hypertension

Studies assessing the prevalence of HTN in RA do not suggest an increase in risk compared to the general population[40*]. After disease onset, hypertension appears to be more common among patients with RA compared to those without [41]. A population-based cohort study evaluating patients with newly diagnosed RA showed that the 10-year absolute risk of a CVD event rose significantly if hypertension was present[12]. A recent multi-ethnic study of atherosclerosis demonstrated that rates of undiagnosed hypertension are higher in RA patients compared to a non-RA cohort[14**]. Hypertension can be particularly difficult to control in RA patients using treatment with NSAIDs, chronic corticosteroids, or DMARDs associated with increased blood pressure (i.e. leflunomide and cyclosporine)[42, 43, 44].

Given these findings, it is important to regularly monitor blood pressure levels and treat based on general population guidelines for hypertension.

Cigarette smoking

Cigarette smoking is considered one of the strongest environmental risk factors for RA incidence and progression, particularly in genetically predisposed individuals[45]. In RA patients, cigarette smoking is associated with anti-citrullinated peptide antibody production and increases the risk of joint erosions and extra-articular manifestations[46]. In seropositive RA males, cigarette smoking is associated with increased disease severity [47]. However in a population-based incidence cohort of subjects with RA, cigarette smoking imparted less risk for the development of CVD in RA patients compared to the non-RA group[10].

Smoking cessation should be emphasized in RA patients, particularly to improve disease activity but also given the probable CVD benefit.

Body Mass Index (BMI)

While obesity is a well-documented traditional CVD risk factor in the population, low BMI is also shown to be associated with increased risk of death due to CVD in RA patients[48, 17]. Although it remains unclear whether individuals with RA have an elevated BMI compared to the general population[49], obese patients with RA tend to have worse disease activity and a significantly elevated CVD risk[50,51]. Rheumatoid cachexia may be equally important [52], although a recent small observational prospective study did not demonstrate low BMI to be a significant predictor of new CV events [39*].

Given the elevated CVD risk, regular monitoring of BMI and encouragement of healthy diet and regular exercise for RA patients is likely to be of significant CVD benefit.

Does Treatment of RA Modulate Cardiovascular Risk?

Based on the accumulating evidence of an increased association of systemic inflammation with increased CVD risk [39*, 53–55, 56*, 57, 58*, 59], the implication is that better control of disease activity in RA patients will result in improved CVD outcomes. However, it is not currently known whether the relationship between systemic inflammation and CVD risk is causal or simply an association. To date, no randomized controlled trial has directly evaluated whether anti-inflammatory agents reduce CVD event rates, in either RA or the general population. While a number of studies have evaluated the effects of whether effective treatment of RA improves cardiovascular outcome, these studies are conflicted and are unfortunately limited by study design and a low number of events. In this section, we attempt to highlight the most recent literature focusing on how individual treatment options may specifically modulate active inflammation and CVD risk factors in RA patients.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The relationship of NSAIDs to cardiovascular morbidity and mortality in RA patients remains controversial. Several earlier clinical trials demonstrated a higher risk of adverse CVD outcomes for patients treated with selective COX2 inhibitors compared to placebo[60–63]. Epidemiological studies of CVD outcomes in large population-based groups have also suggested increased toxicity of non-selective NSAIDs[64–66]. Subgroup analyses demonstrated that factors such as age>80 years, hypertension, prior CV events, presence of RA or COPD may identify patients at high risk[67]. However, little data exists regarding the CVD safety of NSAID use in cohorts of patients with chronic inflammatory disease. A previous meta-analysis of nine randomized controlled trials in patients with osteoarthritis and RA found that use of non-selective NSAIDs, compared to placebo, had no significant effect on CVD events in these patients [68]. Similar results from a primary care-based inception cohort of patients with inflammatory polyarthritis showed that NSAID use does not appear to be associated with increased cardiovascular disease or all-cause mortality[69]. While there are conflicting data regarding these agents' safety in RA, one should employ similar caution regarding use of NSAIDs in RA patients as with the general population.

Corticosteroids

Corticosteroid studies demonstrate contradictory results regarding their impact on CVD risk. Previous studies demonstrate considerable detrimental effects of corticosteroids on blood pressure, insulin resistance, hypertension, body weight and fat distribution[70–72]. This risk appears dose-dependent, given that the use of corticosteroids in high cumulative doses has been associated with increased CVD mortality, MI, and heart failure[73]. While previous studies suggest an adverse impact on lipid profiles, corticosteroids may also have cardioprotective effects mediated by their anti-inflammatory effects. Corticosteroids may actually improve the lipid profile by increasing HDL levels and lowering the TC to HDL ratio [74–76]. Furthermore, a recent systematic literature review assessing the CVD risk in RA patients using low dose corticosteroids (defined as <10mg/day of prednisone) demonstrated weak association with CVD risk. However, a trend of increasing major CV events was identified[77].

Given the concerns raised, we suggest that corticosteroid dosing be limited to the shortest duration possible.

Methotrexate (MTX)

MTX has been associated with reductions in CVD [78], ranging from 15% to 85%[37, 79, 80]. However, in studies including TNF inhibitors, reductions in MTX-associated CVD have not been observed [81*,82]. Recent systematic reviews also demonstrate overall cardiovascular benefits with MTX in RA, although the results have been heterogenous[83**, 84]. A recent meta-analysis demonstrated that MTX use among patients with systemic inflammation primarily due to RA was associated with a 21% lower CVD risk, with little evidence of between-study heterogeneity [83**] (Figure 1). The evidence for benefit is strongest for a reduction in the overall CVD morbidity and mortality and weakest for stroke outcomes. A large randomized, double-blind, placebo-controlled trial known as CIRT (Cardiovascular Inflammation Reduction Trial) is currently funded by the NIH to assess the effect of MTX (15–20 mg weekly) in the secondary prevention of myocardial infarction, stroke, and cardiovascular death among patients with known prior cardiovascular disease who have DM or metabolic syndrome[85]. The potential impact of CIRT is significant in that if MTX is shown to improve CVD outcomes, this would not only lend support to the hypothesis of the significant role of inflammation in the development of CVD, but would also provide a novel treatment for patients with chronic cardiovascular disease.

Until results from the CIRT are known, we recommend continuing MTX as a DMARD in RA patients, but cannot definitively comment on its CVD benefits.

TNF inhibitors

TNF-α is an inflammatory cytokine known to contribute to the pathogenesis of RA and has an atherogenic effect on the endothelial cells lining arterial walls [86]; it may contribute to vascular instability and atherosclerosis progression[87]. As a result, TNF inhibitor therapy has been postulated to have a potential cardioprotective effect. In patients with RA, recent epidemiological studies have shown conflicting results. Data from a large registry study shows significant reductions in fatal and nonfatal CVD outcomes associated with TNF

inhibitors[81*]. In contrast, another study from the U.S. Veterans Administration database did not demonstrate a reduction in the rate of composite CVD endpoints, but did appear to reduce stroke risk [88*]. Similarly, a study from the Swedish Rheumatology Registry found no decrease in the risk of acute coronary syndrome with TNF-inhibitor therapy, including in a subgroup of patients with a good or moderate EULAR response [89*]. Given the known atherogenic effects of TNF-α, there has been significant literature surrounding the effect of TNF inhbitors on the lipid profile[75, 90, 91*, 92, 93*], with recent literature suggesting that these agents are associated with significant increases of TC, HDL, and TG levels, although LDL levels and the atherogenic index again remained unaffected[94*]. Therefore, the presumed cardioprotective effects of TNF inhibitors in RA patients do not seem to be explained by changes in the lipid profile, given that long-term treatment appears to have no effect on the atherogenic index or LDL levels. While increased HDL levels may offer benefit towards improved CVD outcomes, this has yet to be confirmed by prospective studies with long-term follow-up.

Among patients with RA, we recommend continuing use of TNF-inhibitors as DMARD therapy, with annual lipid screening and management based on current general population guidelines.

Non-TNF Biologic DMARDs

Newer agents in RA treatment demonstrate conflicting results regarding CVD risk. Long-term safety analysis of rituximab, a human-murine chimeric monoclonal antibody against CD20 approved for the treatment of refractory RA demonstrated no notable differences in serious CVD events during placebo-controlled periods[95,96]. Recent studies evaluating the effect of rituximab on the lipid profile and endothelial dysfunction have shown conflicting results. [97,98]. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, has been associated with CRP reductions within two weeks of initiation of treatment[99]. However, studies on tocilizumab demonstrate an adverse impact on lipid profiles[100,101*], with a recent meta-analysis demonstrating persistent elevations of TC, LDL, and HDL for years after initiating treatment[102]. Thus far, increased CVD events have not been demonstrated in patients treated with tocilizumab. Similarly, tofacitinib, a new oral Janus Kinase inhibitor, recently approved by the FDA for use in patients with RA, is also associated with significantly increased mean LDL levels as compared with placebo [103**]. Larger studies, with long-term follow-up are needed to determine the relationship between these newer agents and the risk of CVD. It is possible that they will have beneficial effects on CVD risk, but more data need to be collected to understand the CVD risk-benefit profile of these agents.

Conclusion

We have focused on treatment effects on CVD in patients with RA. However, targeting preventive treatments requires accurate estimation of CVD risk. Multiple studies demonstrate the limitations of general population CVD risk stratification methods among patients with RA [104**, 105, 106*], and this remains an active area of investigation. Future

research is needed to develop and validate RA-specific CVD risk algorithms to provide effective primary and secondary prevention in RA patients.

We suggest clinicians maintain a high level of suspicion for CVD and its risk factors in RA. Until treatment trials have been completed, regular screening for traditional CVD risk factors, education of patients and primary care providers, and aggressive management of each risk factor is prudent. Treating to target with an aggressive DMARD strategy may also lead to reduced CVD risk. However, this is still an unproven hypothesis.

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Key Points

- Substantial data demonstrates increased CVD risk among RA patients.
- This review examines whether thresholds for treatment of traditional CVD risk factors should be altered among RA patients and whether RA-specific treatment modulates CVD risk.
- While well-designed, randomized controlled trials are necessary, accumulating epidemiological data supports careful risk factor management and the possibility that disease suppression may reduce CVD risk in RA.

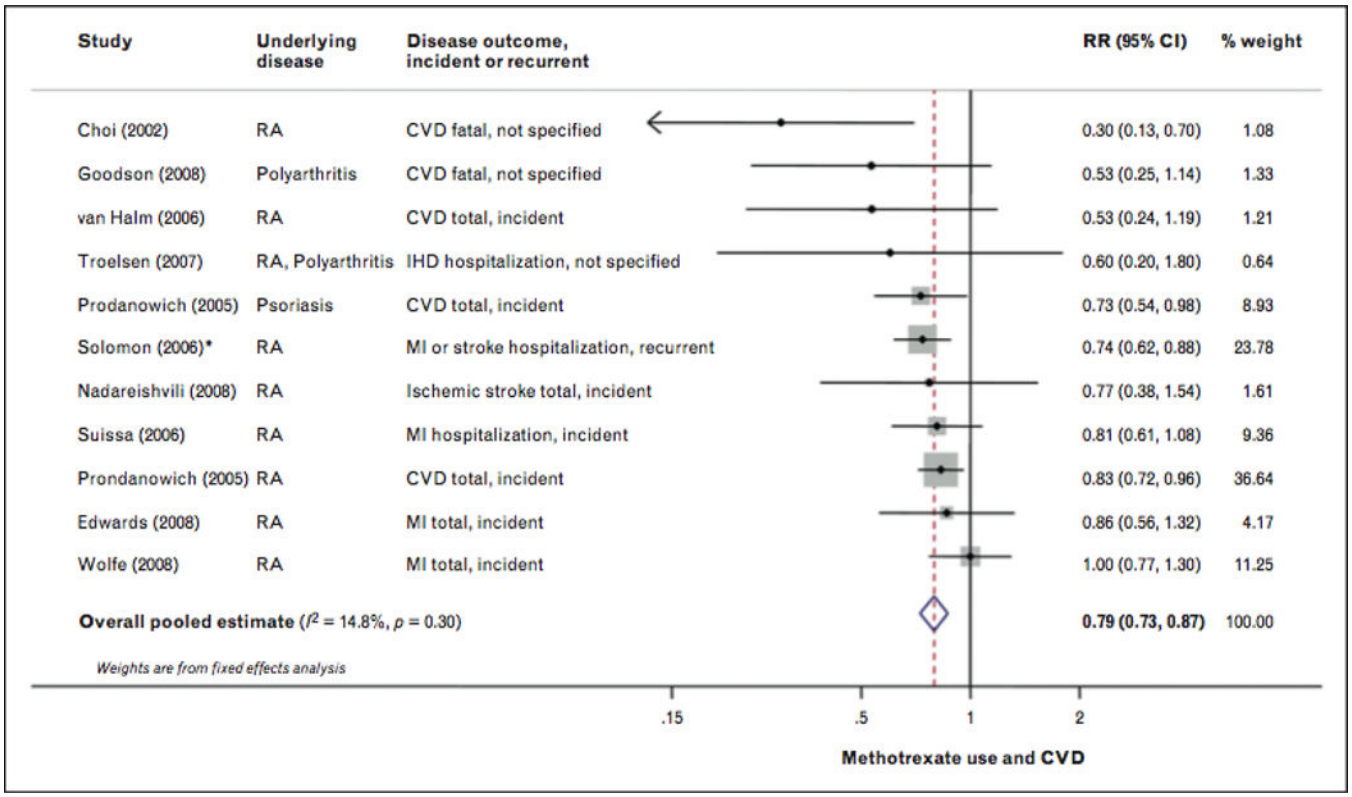

FIGURE 1.

Risk for cardiovascular disease associated with methotrexate use, including eight prospective and two retrospective cohort studies, 66334 participants and 6235 events. Random-effects meta-analysis was used to calculate the overall pooled RR, in the presence of statistical between-study heterogeneity (*P*>0.10]. Solid diamonds and lines are study-specific RRs ond 95% Cls, respectively; the size of each box is weighted by the inverse variance of each study. Dashed line and open diamond are pooled RR and 95% CI, respectively, combining each study-specific RR. *Assessed other RA medication compared with methotrexate as the reference group. The RR of methotrexate versus other RA medications wos calculated by pooling the inverse RRs of all other RA medications, using fixed-effects meta-analysis. CI, confidence interval; IHD, ischaemic heart disease; RA, rheumatoid arthritis. Adapted from [85■■].