Clinical Review

Management of Cardiovascular Disease Risk in Rheumatoid Arthritis
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ABSTRACT

Objective: To review the management of traditional and nontraditional CVD cardiovascular disease risk factors in rheumatoid arthritis (RA).

Methods: Literature review of the management of CVD risk in RA.

Results: Because of the increased risk of CVD events and CVD mortality among RA patients, aggressive management of CVD risk is essential. Providers should follow national guidelines for the management of traditional CVD risk factors, including dyslipidemia, hypertension, and diabetes mellitus. Similar efforts are needed in counseling on lifestyle modifications, including smoking cessation, regular exercise, and maintaining a healthy body weight. Because higher RA disease activity is also linked with CVD risk, aggressive treatment of RA to a target of low disease activity or remission is critical. Furthermore, the selection of potentially “cardioprotective” agents such as methotrexate and tumor necrosis factor inhibitors, while limiting use of nonsteroidal anti-inflammatory drugs and glucocorticoids, are strategies that could be employed by rheumatologists to help mitigate CVD risk in their patients with RA.

Conclusion: Routine assessment of CVD risk, management of traditional CVD risk factors, counseling on healthy lifestyle habits, and aggressive treatment of RA are essential to minimize CVD risk in this population.

Keywords: rheumatoid arthritis; cardiovascular disease; cardiovascular risk assessment; cardiovascular risk management.

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Rheumatoid arthritis (RA) is a systemic autoimmune condition that contributes to an increased risk for cardiovascular disease (CVD) among affected patients. In persons with RA, the risk of incident CVD and CVD mortality are increased by approximately 50% compared with the general population.1,2 To minimize CVD risk in this population, providers must routinely assess for CVD risk factors3 and aggressively manage both traditional and nontraditional CVD risk factors.

Managing Traditional Risk Factors

As in the general population, identification and management of traditional CVD risk factors are crucial to minimize CVD risk in the RA population. A prospective study of 201 RA patients demonstrated that traditional CVD risk factors were in fact more predictive of endothelial dysfunction and carotid atherosclerosis than were disease-related inflammatory markers in RA.4 Management of traditional risk factors is detailed in the following sections, and recommendations for managing all traditional CVD risk factors are summarized in the Table.

Dyslipidemia

The role of dyslipidemia in atherogenesis is well established, and as a result, lipid levels are nearly universally included in CVD risk stratification tools. However, the interpretation of lipid levels in the context of RA is challenging because of the effects of systemic inflammation on their absolute val-
### Table. Summary of Guidelines for the Management of Traditional Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relevant Guidelines</th>
<th>Screening Method/Frequency</th>
<th>Initiation of Therapy</th>
<th>Recommended Therapies</th>
<th>Treatment Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>ACC/AHA USPSTF109</td>
<td>Lipid panel every 3-5 y in males aged 35 y (25-30 y if high risk) and females aged 45 y (30-35 y if high risk)</td>
<td>Clinical ASCVD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Statins, Ezetimibe, PCSK9 Inhibitors, Bile acid sequestrants, Referral to lipidologist</td>
<td>LDL decrease by 50% if LDL ≥ 190 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL ≥ 190 mg/dL</td>
<td>DM, age 40-75 y 10-y ASCVD risk ≥ 7.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DM, age 40-75 y</td>
<td>BP ≥ 140/90 mm Hg, BP ≥ 130/80 mm Hg&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>ACC/AHA USPSTF53</td>
<td>Yearly blood pressure if normotensive, twice yearly if systolic BP &gt; 120 mm Hg</td>
<td>BP ≥ 140/90 mm Hg, BP ≥ 130/80 mm Hg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ACE inhibitors, ARBs, Thiazide diuretics, CCBs</td>
<td>BP &lt; 130/80 mm Hg</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>ADA USPSTF [<a href="http://care.diabetesjournals.org/content/41/Supplement_1">http://care.diabetesjournals.org/content/41/Supplement_1</a>]</td>
<td>A1c or fasting glucose in patients with HTN, HLP, or BMI ≥ 25 kg/m² (if age 40-70 y) every 3 y</td>
<td>Fasting glucose ≥ 126 mg/dL, OGTT ≥ 200 mg/dL, Random glucose ≥ 200 mg/dL and symptomatic</td>
<td>Metformin, Sulfonylureas, SGLT-2 inhibitors, GLP-1 RA, DPP-4 inhibitors, Thiazolidinediones, Insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A1c ≥ 6.5%</td>
<td>A1c &lt; 7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A1c &lt; 8%&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
<td>US Public Health Service110</td>
<td>Inquire at each office visit</td>
<td>All users who are willing to quit</td>
<td>Nicotine replacement therapy, Bupropion, Varenicline&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Complete cessation</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td>ACC/AHA USPSTF511</td>
<td>Inquiry in adults who are overweight, obese, or have additional CVD risk factors</td>
<td>All patients</td>
<td>2 h 30 min of moderate-intensity exercise weekly (1 hr 15 min if vigorous)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>ACC/AHA TOS Endocrine Society112,113</td>
<td>Measure BMI annually or at each office visit</td>
<td>Overweight (BMI 25.0-29.9) and obese (BMI ≥ 30)</td>
<td>Calorie-restricted diet, Lifestyle programs, Phentermine, Topiramate/phentermine, Lorcaserin, Orlistat, Naltrexone-bupropion, Liraglutide, Bariatric surgery&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Sustained weight loss of at least 3%-5%</td>
</tr>
</tbody>
</table>

A1c, glycated hemoglobin; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; HLP, hyperlipidemia; JNC 8, Eighth Joint National Committee; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT-2, sodium-glucose co-transporter-2; TOS, The Obesity Society; USPSTF, United States Preventive Service Task Force.

<sup>a</sup> Includes patients with history of myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.

<sup>b</sup> If ≥ 65 years old, clinical ASCVD or 10-year ASCVD risk ≥ 10%, or concomitant DM, chronic kidney disease, congestive heart failure, coronary artery disease, cerebrovascular accident, or peripheral arterial disease.

<sup>c</sup> If limited life expectancy, history of severe hypoglycemia, advanced microvascular complications, or significant comorbidity.

<sup>d</sup> Pharmacotherapy should be used in combination with practical in-office counseling and support services (eg, 1-800-QUIT-NOW).

<sup>e</sup> If BMI ≥ 40 or ≥ 35 with obesity-related comorbidities.
ues. Compared to the general population, patients with RA have lower total cholesterol (TC) and low-density lipoprotein (LDL) levels independent of lipid-lowering therapy.\textsuperscript{5,6} Despite this, RA patients are at increased risk for CVD. There is even some evidence to suggest a “lipid paradox” in RA, whereby lower TC (< 4 mmol/L) and LDL levels suggest an increased risk of CVD.\textsuperscript{7,8} In contrast to LDL, higher levels of high-density lipoprotein (HDL) are typically associated with reduced CVD risk, as in the general population.\textsuperscript{8,9} Interestingly, in a cohort of 16,085 RA patients and 48,499 age- and sex-matched controls, there was no significant difference in the relationship between LDL and CVD risk, suggesting that quantitative lipid levels alone may not entirely explain the CVD mortality gap in RA.\textsuperscript{9} As such, there is substantial interest in lipoprotein function within the context of CVD risk in RA. Recent investigations have identified impaired HDL function, with reduced cholesterol efflux capacity and antioxidant properties, as well as increased scavenger receptor expression and foam cell formation, in patients with RA.\textsuperscript{10,11} More research is needed to elucidate how these alterations affect CVD morbidity and mortality and how their measurement could be integrated into improved CVD risk assessment.

Meta-analyses of randomized controlled trials have estimated that lipid-lowering therapy with HMG-CoA reductase inhibitors (statins) reduces the risk of CVD by 25% to 30%; as such, statin therapy has become the standard of care for reduction of CVD risk in the general population.\textsuperscript{12} Benefits for primary prevention of CVD in RA have also been observed; statin therapy was associated with a reduced risk of CVD events (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.20-0.98) and all-cause mortality (HR, 0.43; 95% CI, 0.20-0.92) in a population-based cohort study.\textsuperscript{13} Statins appear to have similar lipid-lowering effects and result in similar CVD risk reduction when used for primary or secondary prevention in RA patients compared to non-RA controls.\textsuperscript{14-16} Additionally, anti-inflammatory properties of statins may act in synergy with disease-modifying antirheumatic drugs (DMARDs) to improve RA disease activity. In a small study of RA patients, statin therapy improved subjective and objective markers of RA disease activity in conjunction with methotrexate.\textsuperscript{17}

While statins provide robust reduction in CVD risk, some individuals cannot tolerate statin therapy or do not achieve goal LDL levels with statin therapy. Select non-statin LDL-cholesterol-lowering agents have shown promise for reducing CVD events in the general population.\textsuperscript{18} Ezetimibe, which inhibits cholesterol absorption in the small intestine, very modestly reduced CVD events when added to atorvastatin (relative risk [RR], 0.94; 95% CI, 0.89-0.99) in a double-blind randomized controlled trial.\textsuperscript{19} Novel monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibit the internalization of surface LDL receptors, promoting LDL clearance. Two PCSK-9 inhibitors, alirocumab and evolocumab, were approved by the US Food and Drug Administration (FDA) after randomized controlled trials demonstrated their efficacy in lowering LDL by approximately 60% and reducing CVD events by approximately 15% in patients on maximum-tolerated statin therapy.\textsuperscript{20-22} To date, non-statin LDL-cholesterol-lowering agents have been subject to limited study in RA.\textsuperscript{23}

Identification and management of dyslipidemia offers an opportunity for substantial CVD risk reduction at the RA population level. Unfortunately, current rates of lipid screening are inadequate in this high-risk group. In a study of 3298 Medicare patients with RA, less than half of RA patients with an indication underwent appropriate lipid screening.\textsuperscript{24} Additionally, statins are often underutilized for both primary and secondary prevention in RA patients. Only 27% of RA patients meeting National Cholesterol Education Program Adult Treatment Panel III criteria were initiated on statin therapy in a population-based cohort study.\textsuperscript{25} Among patients discharged after a first myocardial infarction (MI), the odds of receiving lipid-lowering therapy were 31% lower for RA patients (odds ratio [OR], 0.69; 95% CI, 0.58-0.82).\textsuperscript{26} Similar to the general population, adherence to statins in RA patients appears to be poor.\textsuperscript{27-30} This raises particular concern considering that a population-based cohort study of RA patients demonstrated a 67% increased risk of MI associated with statin discontinuation, regardless of prior MI status.\textsuperscript{27} Providers—rheumatologists, primary care providers, and cardiologists alike—need to remain vigilant in efforts to assess CVD risk to identify patients who will benefit from lipid-lowering therapy and to emphasize the importance to patients of statin adherence. Novel models of health-care delivery, health technologies, and patient
engagement in care may prove useful for improving lipid screening and management in RA.

**Tobacco Use**

Cigarette smoking is a shared risk factor for both CVD and RA. Large cohort studies have identified a dose-dependent increased risk of incident RA, particularly seropositive RA, among smokers.\textsuperscript{31-34} Tobacco smoking has also been associated with increased levels of inflammation and RA disease activity.\textsuperscript{35} The consequences of tobacco use in the general population are staggering. Among individuals over the age of 30 years, tobacco use is responsible for 12% of all deaths and 10% of all CVD deaths.\textsuperscript{36} Similar findings are observed in RA; a recent meta-analysis estimated there is a 50% increased risk of CVD events in RA related to smoking tobacco.\textsuperscript{37} In the general population, smoking cessation markedly lowers CVD risk, and over time CVD risk may approach that of nonsmokers.\textsuperscript{38,39} Thus, regular counseling and interventions to facilitate smoking cessation are critical to reducing CVD risk in RA patients. RA-specific smoking cessation programs have been proposed, but have yet to outperform standard smoking cessation programs.\textsuperscript{40}

**Diabetes Mellitus**

It is estimated that almost 10% of the US population has diabetes mellitus (DM), which in isolation portends substantial CVD risk.\textsuperscript{41} There is an increased prevalence of DM in RA, perhaps owing to factors such as physical inactivity and chronic glucocorticoid use, though a higher level of RA disease activity itself has been associated with increased insulin resistance.\textsuperscript{42-45} In a cohort of 100 RA patients who were neither obese nor diabetic, RA patients had significantly higher fasting blood glucose and insulin levels than age- and sex-matched controls. These findings were even more pronounced in RA patients with higher levels of disease activity.\textsuperscript{44} Similar to the general population, DM is associated with poor CVD outcomes in RA.\textsuperscript{37} Therefore, both appropriate management of diabetes and control of RA disease activity are vitally important to minimize CVD risk related to DM.

**Hypertension**

Though not a universal finding, there may be an increased prevalence of hypertension in RA patients.\textsuperscript{31,46} Nonsteroidal anti-inflammatory drug (NSAID) and glucocorticoid use may play a role in the development of hypertension, while DMARDs appear to exert a less substantial effect on blood pressure.\textsuperscript{47,48} At least one study found that DMARD initiation (particularly for methotrexate and hydroxychloroquine) was associated with significant, albeit small, declines in both systolic and diastolic blood pressure over the first 6 months of treatment.\textsuperscript{49}

Despite its potentially higher prevalence in this population, hypertension is both underdiagnosed and undertreated in RA patients.\textsuperscript{24,50-52} This is an important deficiency to target because, as in the general population, hypertension is associated with an increased risk of MI (RR, 1.84; 95% CI, 1.38-2.46) and composite CVD outcomes (RR, 2.24; 95% CI, 1.42-3.06) in RA.\textsuperscript{37} Thresholds for initiation and escalation of antihypertensive therapy are not specific to the RA population; thus, diagnosis and management of hypertension should be informed by the American College of Cardiology/American Heart Association guidelines, treating those with in-office blood pressures exceeding 140/90 mm Hg (> 130/80 mm Hg if aged > 65 years or with concomitant CVD, DM, chronic kidney disease, or 10-year atherosclerotic cardiovascular disease risk > 10%), typically with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, or thiazide diuretics as comorbidities may dictate or allow.\textsuperscript{53} Also, the use of NSAIDs and glucocorticoids should be minimized, particularly in those with concomitant hypertension.

**Physical Activity**

Likely due to factors such as articular pain and stiffness, as well as physical limitations, RA patients are more sedentary than the general population.\textsuperscript{54,55} In a study of objectively assessed sedentary behavior in RA patients, greater average sedentary time per day and greater number of sedentary bouts (> 20 min) were associated with increased 10-year risk of CVD as assessed by the QRISK2.\textsuperscript{56} Conversely, the beneficial effects of exercise are well documented. Light to moderate physical activity has been associated with improved cardiovascular outcomes, greater physical function, higher levels of HDL, as well as reduced systemic inflammation and disease activity, and improved endothelial function in RA patients.\textsuperscript{57-61} While there has been concern that physical activity may
result in accelerated joint damage, even high-intensity exercise was shown to be safe without causing significant progression of joint damage.\textsuperscript{58}

**Obesity, Weight Loss, and Diet**

While obesity is clearly associated with CVD risk in the general population, this relationship is much more complex in RA, as underweight RA patients are also at higher risk for CVD and CVD-related mortality.\textsuperscript{62-64} One potential explanation for this finding is that pathological weight loss resulting in an underweight body mass index (BMI) is an independent predictor of CVD. In a study of US Veterans with RA, higher rates of weight loss (> 3 kg/m\textsuperscript{2} /year) were associated with increased CVD mortality (HR, 2.27; 95% CI, 1.61-3.19) independent of BMI.\textsuperscript{65} Systemic inflammation in RA can lead to “rheumatoid cachexia,” characterized by decreased muscle mass, increased adiposity, and increased CVD risk despite a normal or potentially decreased BMI.\textsuperscript{66} Practitioners should be mindful of not only current body weight, but also patients’ weight trajectories when counseling on lifestyle practices such as healthy diet and regular exercise in RA patients. For obese individuals with RA, healthy weight loss should be encouraged. Interestingly, bariatric surgery in RA patients may improve RA disease activity in addition to its known effects on body weight and DM.\textsuperscript{67}

Counseling on healthy diet with a focus on limiting foods high in saturated- and trans-fatty acids and high glycemic index foods, and increasing consumption of fruits, vegetables, and mono-unsaturated fatty acids is a well-accepted and common practice to help minimize CVD risk in the general population.\textsuperscript{68} No studies to date have investigated the effect of specific diets on CVD risk in RA patients, and thus we recommend adherence to general population recommendations.

**Managing RA-related CVD Risk Factors**

**Disease Activity**

In addition to traditional risk factors, several studies have identified associations between the level of RA disease activity and risk of CVD. In a cohort of US Veterans with RA, CVD-related mortality increased in a dose-dependent manner with higher disease activity categories. In stark contrast, the CVD mortality rates of those in remission paralleled the rates from the general population (standardized mortality ratio [SMR], 0.68; 95% CI, 0.37-1.27).\textsuperscript{69} In a separate cohort of 1157 RA patients without prior CVD, achieving low disease activity was associated with a lower risk of incident CVD events (HR, 0.65; 95% CI, 0.43-0.99).\textsuperscript{70} Additionally, high disease activity has been associated with surrogate markers of CVD and other CVD risk factors including NT-proBNP and systolic blood pressure.\textsuperscript{71,72} While no randomized controlled trial data is available to inform this recommendation, observational data suggest RA should be aggressively treated (ideally to achieve and maintain remission or low disease activity) to minimize CVD risk. While keeping this treatment goal in mind, the differential effects of specific RA therapies on CVD must also be considered.

**Glucocorticoids and NSAIDs**

With the expanding repertoire of DMARDs available and more aggressive treatment approaches, the role of glucocorticoids and NSAIDs in RA treatment is decreasing over time. While their efficacy for improving pain and stiffness is well established, concern regarding their contribution to CVD risk in RA patients is warranted.

Glucocorticoids are known to have detrimental effects on traditional CVD risk factors such as hypertension, insulin resistance, and dyslipidemia in the general population, as well as in RA patients.\textsuperscript{73,74} In a meta-analysis of predominantly observational studies of RA patients, glucocorticoid use was associated with an increased risk of CVD events (RR, 1.47; 95% CI, 1.34-1.60), including MI, congestive heart failure (CHF), and cerebrovascular accident (CVA).\textsuperscript{75} Evidence is conflicting in regards to a clear dose threshold that leads to increased CVD risk with glucocorticoids, though higher doses are associated
As RA patients requiring glucocorticoids typically have higher disease activity, confounding by indication remains a complicating factor in assessing the relative contributions of glucocorticoid use and RA disease activity to elevated CVD risk in many analyses. The increased CVD risk with NSAID use is not specific to RA and has been well established in the general population. In the previously mentioned meta-analysis, an increased overall risk of CVD events was observed with NSAID use in RA (RR, 1.18; 95% CI, 1.01-1.38). It should be noted that cyclo-oxygenase 2 (COX-2) inhibitors, in particular rofecoxib (now removed from the market), appeared to drive the majority of this risk (RR, 1.36; 95% CI, 1.10-1.67 in COX-2 inhibitors and RR 1.08, 95% CI, 0.94-1.24 in nonselective NSAIDs), suggesting a potential differential risk among NSAIDs. While naproxen has been thought to carry the lowest risk of CVD based on initial studies, this has not been universally observed, including in a recent randomized controlled trial of more than 24,000 RA and osteoarthritis patients.

Providers should use the lowest possible dose and duration of glucocorticoids and NSAIDs to achieve symptom relief, with continual efforts to taper or discontinue. Candidates for glucocorticoid and NSAID therapy should be selected carefully, and use of these therapies should be avoided in those with prior CVD or at high risk for CVD based on traditional CVD risk factors. Most importantly, providers should focus on utilizing DMARDs for the management of RA, which more effectively treat RA as well as reduce CVD risk.

**Methotrexate**

Methotrexate (MTX), a mainstay in the treatment of RA, is a conventional DMARD observed to improve overall survival and mitigate CVD risk in multiple RA cohorts. In a recent meta-analysis comprised of 236,525 RA patients and 5410 CVD events, MTX use was associated with a 28% reduction in overall CVD events across 8 studies (RR, 0.72; 95% CI, 0.57-0.91), substantiating similar findings in a prior meta-analysis. MTX use was specifically associated with a decreased risk of MI (RR, 0.81; 95% CI, 0.68-0.96). Case-control and cohort studies have cited a 20% to 50% reduced risk of CHF with MTX use. The potential cardioprotective effect of MTX appears to be both multifactorial and complex, likely mediated through both direct and indirect mechanisms. MTX directly promotes anti-atherogenic lipoprotein function, improves endothelial function, and scavenges free radicals. Indirectly, MTX likely reduces CVD risk by effectively reducing RA disease activity. Based on these and other data, MTX remains the cornerstone of DMARD therapy in RA patients when targeting CVD risk reduction.

**Hydroxychloroquine**

Emerging evidence suggests that hydroxychloroquine (HCQ), an antimalarial most often utilized in combination with alternative DMARDs in RA, prevents DM and has beneficial effects on lipid profiles. A recent meta-analysis compiled 3 homogenous observational studies that investigated the effect of HCQ on incident DM. RA patients ever exposed to HCQ had a 40% lower incidence of DM (HR, 0.59; 95% CI, 0.49-0.70). Increased duration of HCQ use was shown to further reduce risk of incident DM. The aforementioned meta-analysis also pooled 5 studies investigating the effect of HCQ on lipid profiles, with favorable mean differences in TC (–9.82 mg/dL), LDL (–10.61 mg/dL), HDL (4.13 mg/dL), and triglycerides (–19.15 mg/dL) in HCQ users compared to non-users. Given these favorable changes to traditional CVD risk factors, it is not surprising that in a retrospective study of 1266 RA patients without prior CVD, HCQ was associated with significantly lower risk of incident CVD. While external validation of these findings is needed, HCQ is an attractive conventional DMARD to be used in RA for CVD risk reduction. Moreover, its combination with MTX and sulfasalazine also shows promise for CVD risk reduction.

**TNF Inhibitors**

Tumor necrosis factor (TNF) inhibitors are often the initial biologic DMARD therapy used in RA patients not responding to conventional DMARDs. In the previously described meta-analysis, TNF inhibitors were associated with similar reductions in CVD events as MTX (RR, 0.70; 95% CI, 0.54-0.90). Of note, there was a trend toward reduced risk of CHF (RR, 0.75; 95% CI, 0.49-1.15) in this same meta-analysis, an area of concern with TNF inhibitor use due to a prior randomized controlled trial demonstrating worsening clinical status in patients with
existing moderate-to-severe CHF treated with high-dose infliximab. Current RA treatment guidelines recommend avoiding TNF inhibitor use in individuals with CHF.

Aside from the risk of CHF exacerbation, TNF inhibitors appear to be cardioprotective. Similar to MTX, the mechanism by which TNF inhibition reduces cardiovascular risk is complex and likely due to both direct and indirect mechanisms. Substantial research has been conducted on the effect of TNF inhibition on lipids, with a recent meta-analysis demonstrating increases in HDL and TC, with stable LDL and atherogenic index over treatment follow-up. A subsequent meta-analysis not limited to RA patients yielded similar results. In addition to quantitative lipid changes, alteration of lipoprotein function, improvement in myocardial function, reduced aortic stiffness, improved blood pressure, and reduced RA disease activity may also be responsible for cardioprotective benefits of these agents.

Non-TNF Biologic and Traditional Synthetic DMARDs

Tocilizumab, an IL-6 inhibitor, can potently increase LDL levels, but it does not appear to increase the risk of CVD events and may actually promote more favorable anti-atherogenic lipoprotein function. Although these quantitative lipid changes received significant attention in the wake of early reports detailing this effect, similar lipid changes appear to accompany other DMARDs including TNF inhibitors and tofacitinib. There have been few studies evaluating the risk of CVD with other non-TNF inhibitor biologic DMARDs and traditional synthetic DMARDs, warranting future study.

Conclusion

To mitigate the increased risk of CVD in RA, primary care and subspecialty providers alike must be aware of this heightened risk in RA, perform frequent assessments of CVD risk, and aggressively manage both traditional and nontraditional CVD risk factors. The differential roles in this effort may not be clear; thus, we have proposed a co-management strategy detailed in the Figure. Clear communication between providers is of the utmost importance to ensure effective management of CVD risk.

Given limited evidence for RA-specific CVD risk assessments and traditional risk factor treatment targets, management should follow pertinent national guidelines.
The importance of lifestyle counseling should not be overlooked, with a focus on smoking cessation, healthy diet and body weight, and regular aerobic exercise. Finally, rheumatologists should aggressively manage RA using a treat-to-target approach, minimize the use of glucocorticoids and NSAIDs, and preferentially select DMARDs that have been associated with lower CVD risk. Through this comprehensive approach, recent trends of improved CVD outcomes in RA will hopefully become more widespread.

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References


