

# Antirheumatic drug therapy and its effects on cardiovascular health

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## Dedication

This project was inspired by and dedicated to Mr. Dick Brunie.

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## Table of Contents

Introduction.....	1
Methotrexate and other DMARDs.....	8
Anti-tumor Necrosis factor alpha drugs.....	11
Glucocorticoids.....	13
HMG-CoA Reductase Inhibitors .....	17
NSAIDs.....	19
Discussion.....	23
Conclusion .....	25
References.....	28
Table 1 .....	41
Abstract.....	42

## Introduction

Rheumatoid arthritis (RA) is a chronic erosive synovitis characterized by autoimmune destruction of synovial joints and inflammation ("Guidelines for the management of rheumatoid arthritis: 2002 Update," 2002; Kirwan, 1995). RA affects 1% of the population and accounts for at least 9 million physician visits yearly ("Guidelines for the management of rheumatoid arthritis: 2002 Update," 2002).

The etiology of RA is not fully understood. In recent years, it has become more widely accepted that the etiology is multifactorial, with several suspected, yet elusive, possible causes. The theories of RA triggers and risk factors include cortisol deficiency, other adrenal hormone deficiencies, infection (Jefferies, 1998), and cigarette smoking (Klareskog et al., 2006). Regardless of the cause, RA is an autoimmune disorder resulting in an immune mediated inflammatory attack on synovial joints. The inflammation associated with the RA disease process results in elevated circulating levels of inflammatory cytokines, including multiple interleukins and tumor necrosis factor-alpha (Barrera et al., 1995).

The chronic, progressive nature of RA leads to physical deformities and significant disability in virtually all patients. The disease inevitably leads to joint destruction (Hickling, Jacoby, & Kirwan, 1998). Recent data show that approximately 35% of RA sufferers in the US claim work disability within ten years of disease onset (Allaire, Wolfe, Niu, & Lavalley, 2008). The use of antirheumatic drug therapy may decrease the inflammatory response and slow progression of joint deformity, but may not completely prevent it (Hickling et al., 1998). As a result, those with RA are often forced to live with the pain and physical limitations this disease causes.

Not only is RA associated with physical morbidity, but it is also associated with decreased life expectancy (Wolfe et al., 1994). An unexpectedly high prevalence of cardiovascular disease (CVD) (del Rincon, Williams, Stern, Freeman, & Escalante, 2001; Fischer, Schlienger, Matter, Jick, & Meier, 2004; Wolfe et al., 1994) may be the cause of the increased mortality. Retrospective data show that those who were later diagnosed with RA were more likely to be hospitalized for a myocardial infarction even before the diagnosis of RA was established (Maradit-Kremers et al., 2005).

¶ There is currently no consensus on why CVD is more prevalent in this population. Researchers have concluded that the increased risk of CVD is independent of traditional risk factors such as male sex, hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and obesity (Crowson et al., 2005; del Rincon et al., 2001). Therefore, evidence points to chronic, systemic inflammation from the RA disease process as a major contributor to the increased prevalence of CVD in this population.

This review discusses the proposed pathogenesis of accelerated CVD in individuals with RA and several drug therapies commonly used to treat RA, including methotrexate, tumor necrosis factor alpha antagonists, glucocorticoids, and non-steroidal anti-inflammatory drugs. The author also addresses the possible role of HMG-CoA reductase inhibitors (statins) for use in those with RA not only to reduce cardiovascular risk, but also as a novel adjunct in the treatment of inflammation. The role of these drugs in promotion or prevention of CVD will be debated, and recommendations will be included for treatment of RA disease activity in conjunction with prevention of CVD.

### *Inflammation and Atherosclerosis*

The exact role that inflammation plays in development of atherosclerosis has been debated for many years. It is now becoming widely accepted that inflammation and immune function play a central role in the progression of atherosclerosis. The first step in atherosclerosis is endothelial cell damage (Stary et al., 1994). Systemic inflammation may accentuate this process, as IFN- $\gamma$  and IL-1 have been shown to damage endothelial cells (Sesin, Yin, Esmon, Buyon, & Clancy, 2005).

Damaged endothelial cells allow the passage of LDLs into the subendothelium (Hahn, Grossman, Chen, & McMahon, 2007; Reiss & Glass, 2006). There, the LDLs become oxidized (Hahn et al., 2007; Stary et al., 1994). Endothelial damage, coupled with the presence of oxidized LDL in the subendothelial layer, induce the expression of endothelial cell surface adhesion molecules (Quinn, Parthasarathy, Fong, & Steinberg, 1987). These surface molecules, including vascular cell adhesion molecule-1 (VCAM-1), recruit monocytes and lymphocytes to the area (Davies et al., 1993). The monocytes then cross into the subendothelium, where they become macrophages and engulf the oxidized LDLs. These lipid-rich macrophages remain as foam cells (Stary et al., 1994).

As these foam cells accumulate, a fatty streak, the next step in the progression of atherosclerosis, is formed in the vessel (Stary et al., 1994). The foam cells further encourage the atherosclerotic process, by releasing inflammatory molecules that increase local inflammation, recruit more monocytes, and induce smooth muscle proliferation (Libby & Ridker, 2004). The inflammatory molecules also recruit B and T lymphocytes, which with direct cell-to-cell contact with macrophages, release metalloproteinases. These metalloproteinases, along with the



cytokine-induced smooth muscle proliferation, alter the matrix of the vessel (Lacraz, Isler, Vey, Welgus, & Dayer, 1994).

The above processes encompass a cascade of endothelial damage, plaque formation, and narrowing of the vessel lumen, with circulation of inflammatory cytokines as a possible initiating factor. However, pro-inflammatory molecules may also trigger other dysfunctions in endothelial cells. Exposure to IL-1 and interferon- $\gamma$  may alter endothelial expression of anticoagulation receptors on the endothelial cell surface (Sesin et al., 2005). Additionally, TNF- $\alpha$  blocks the action of nitric oxide synthase, an enzyme responsible for nitric oxide (NO) production in endothelial cells, by degrading mRNA in the enzyme (Yoshizumi, Perrella, Burnett, & Lee, 1993). NO is an important regulator of vasodilation in vessel walls. TNF- $\alpha$  also prevents breakdown of asymmetric dimethylarginine, the enzyme responsible for nitric oxide synthase inhibition (Ito et al., 1999). These actions of TNF- $\alpha$  result in impaired NO bioavailability, which is necessary for proper endothelial function (Yoshizumi et al., 1993).

### *Dyslipidemia*

A characteristic unfavorable lipid pattern is seen in patients with untreated RA (Georgiadis et al., 2006; Park et al., 2002; Park et al., 1999). The primary cause for this poor lipid profile is low concentrations of HDL, which results in an unfavorable ratio of total cholesterol (TC) to HDL. A high TC/HDL ratio is thought to favor atherosclerosis (Lemieux et al., 2001), driven either by high TC or low HDL concentrations. Patients with RA have significantly lower levels of HDL (Georgiadis et al., 2006; Park et al., 2002; Vijayakumar, 2005) and elevated levels of LDL (Georgiadis et al., 2006) when compared to control groups.

HDLs have been described as having a protective effect on cardiovascular health. There is an inverse correlation between RA disease activity and HDL levels (Georgiadis et al., 2006;

Seriolo, Paolino, Sulli, Fasciolo, & Cutolo, 2006). In addition to low HDL levels, RA patients often have dysfunctional pro-inflammatory HDL molecules (McMahon et al., 2006). These pro-inflammatory HDLs are more common in those with systemic inflammation as seen in RA and SLE (McMahon et al., 2006; Navab et al., 2001). In pro-inflammatory HDL, apolipoprotein-A and paroxonase 1 (PON1) are enzymes that do not function correctly on the HDL molecule. Normally functioning apolipoprotein-A is responsible for mobilizing cholesterol from foam cells, and PON1 has a role in protecting LDLs from oxidation (Navab et al., 2001). Therefore, patients with RA have two problems related to their HDL: low levels of HDL (quantitative), and a significant percentage of HDL that do not function effectively (qualitative).

In addition to LDL and HDL abnormalities, elevated triglyceride levels have been demonstrated in patients with RA when compared to controls (Dessein, Joffe, & Singh, 2005; Georgiadis et al., 2006). Circulating inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , promote free fatty acid release and triglyceride synthesis in the liver (Feingold & Grunfeld, 1987; Feingold et al., 1989; Khovidhunkit, Memon, Feingold, & Grunfeld, 2000). These inflammatory cytokines also reduce the actions of lipoprotein lipase in endothelial cells, an enzyme responsible for triglyceride-rich lipid catabolism (Khovidhunkit et al., 2000; Redgrave, Rakic, Mortimer, & Mamo, 1992). Therefore, the high levels of circulating inflammatory molecules may contribute to the pattern of dyslipidemia commonly seen in RA.

### *Hematologic Changes*

Increased levels of several molecules that promote coagulation have been identified in RA subjects including von Willebrand factor, tissue plasminogen activator antigen (McEntegart et al., 2001; McLaren, Alkaabi, Connacher, Belch, & Valenete, 2002), E-selectin, activated factor XII (McLaren et al., 2002), plasma fibrinogen, and fibrin D-dimer (McEntegart et al.,

2001). Elevated levels of these molecules may predispose the individual to thrombosis, especially in the presence of unstable atherosclerotic plaques (discussed earlier). Factor XII may be activated on the surface of endothelial cells and trigger the intrinsic clotting cascade (McLaren et al., 2002). Additionally, circulating cytokines, including IL-1 and interferon- $\gamma$ , induce endothelial cells to change the composition of anticoagulant surface molecules (Sesin et al., 2005).

### *Insulin Resistance*

A significant direct correlation between insulin resistance and severity of inflammatory activity, measured by serum TNF- $\alpha$  and CRP, has been identified (Chung et al., 2008; Hallgren & Berne, 1983). TNF- $\alpha$  has been shown to alter insulin-mediated glucose uptake in skeletal muscle (Hotamisligil et al., 1996). High levels of circulating cytokines, especially TNF- $\alpha$  and IL-6, may act on adipose tissue and the liver to release triglycerides and free fatty acids (described above) (Feingold & Grunfeld, 1987; Feingold et al., 1989; Khovidhunkit et al., 2000), which has been accepted as a part of insulin resistance pathophysiology (Sattar, McCarey, Capell, & McInnes, 2003).

### *Hypertension*

Researchers have noted hypertension in RA patients at greater rates than the general population (del Rincon et al., 2001; Dessein et al., 2005; McEntegart et al., 2001; Panoulas et al., 2007). A recent study found hypertension in over 70% of RA patients (Panoulas et al., 2007). One possible explanation for the increased prevalence of hypertension in RA subjects is the use of non-steroidal anti-inflammatory drugs (NSAIDs), which have been shown to increase mean arterial blood pressure by an average of 3.5 to 5 mm Hg (Chou, 1999). Another possible

explanation is endothelial dysfunction, specifically due to impaired NO reactivity and bioavailability in the presence of active inflammation (Yoshizumi et al., 1993).

### *C-Reactive Protein (CRP)*

Inflammation causes an elevation in serum CRP levels, and patients with RA have been found to have higher levels of CRP compared to the general population (Dessein et al., 2005). CRP is an acute-phase inflammatory marker that may predict coronary events (Danesh et al., 2004). An elevated level of serum CRP is also linked to vascular damage and is a reliable predictor of cardiovascular morbidity (Libby & Ridker, 2004). Additionally, increased serum CRP levels from systemic inflammation are associated with impaired endothelial reactivity (Fichtlscherer et al., 2000) and inhibition of NO bioavailability (Venugopal, Devaraj, Yuhanna, Shaul, & Jialal, 2002).

### *Homocysteine*

Homocysteine plays a role in the development of atherosclerosis (Harpel, Chang, & Borth, 1992) and promotes prothrombotic activity (Harpel et al., 1992). Elevation of serum homocysteine is an independent risk factor for CVD (Eikelboom, Lonn, Genest, Hankey, & Yusuf, 1999) and is common in patients with RA (Hernanz, Plaza, Martin-Mola, & De Miguel, 1999).

### *Antirheumatic Drug Therapy and CVD*

A clear association has been described between systemic inflammation and the progression of atherosclerosis, dyslipidemia, hypercoagulability, insulin resistance, and hypertension. Drug therapies used to treat the RA disease process aim to decrease systemic inflammation by reducing levels of circulating inflammatory markers, and consequently should delay the onset or slow advancement of CVD in this population.

## Methotrexate and Other DMARDs

Methotrexate (MTX), a disease-modifying antirheumatic drug (DMARD), is the gold standard drug choice for treatment of RA (Nurmohamed, van Halm, & Dijkmans, 2002). MTX inhibits dihydrofolate reductase, an enzyme involved in production of RNA and DNA precursors for lymphocyte proliferation. Without proper levels of nucleic acid products necessary for lymphocyte development, fewer lymphocytes are free to circulate and contribute to joint inflammation in the patient with RA (Cronstein, 1997). MTX is the drug of choice for treatment of RA because it exhibits better long-term reduction in symptoms when compared to other DMARDs, such as sulfasalazine, gold salts, antimalarial drugs, cyclosporine, and azathioprine (Nurmohamed et al., 2002).

MTX use leads to elevations in plasma homocysteine levels. This increase in serum homocysteine levels further increases with MTX and sulfasalazine (SSZ) combination therapy, but not with use of SSZ alone (Haagsma et al., 1999). As previously mentioned, hyperhomocysteinemia promotes clotting (Harpel et al., 1992) and is an independent risk factor for CVD (Eikelboom et al., 1999). However, folic acid supplementation during MTX therapy decreases homocysteine levels (Slot, 2001) and reduces incidence of MTX toxicity without affecting its therapeutic efficacy (Cronstein, 1997).

Several studies have suggested the benefits of MTX may extend beyond symptomatic relief from RA disease activity. In a study involving over 1,200 participants, Choi and colleagues (2002) demonstrated that MTX reduces the risk of death due to CVD by 70% in patients being treated for RA. This statistically significant effect was not dose-dependent, and a similar reduction in mortality was not seen with other DMARDs (Choi, Hernan, Seeger, Robins, & Wolfe, 2002). Additionally, subjects with severe RA who did not show response to MTX,

measured by degree of inflammatory activity, had a four-fold increase in mortality when compared with the general population. Those who did respond clinically to MTX therapy showed only a slight increase in mortality compared to the general population (Krause, Schleusser, Herborn, & Rau, 2000).

Other studies have evaluated the effects of MTX on CVD-related morbidity. Suissa and colleagues found that the use of any DMARD, including the traditional drugs other than MTX, lowers the risk of acute MI (Suissa, Bernatsky, & Hudson, 2006). A retrospective cohort study involving over 7,000 patients with RA revealed a significant decrease in the incidence of vascular disease in patients treated with MTX versus those who did not receive MTX. This effect was most evident in low cumulative doses of MTX, especially when paired with folic acid supplementation (Prodanovich et al., 2005). Furthermore, MTX and other DMARD use was associated with decreased risk of hypertension, diabetes, and dyslipidemia (van Halm, Nurmohamed, Twisk, Dijkmans, & Voskuyl, 2006).

A logical mechanism for the reduction of morbidity and mortality associated with CVD in patients with RA is by reducing the circulating levels of inflammatory markers. In support of this argument, MTX has been shown to significantly reduce levels of CRP, a predictor of coronary events (Dessein, Joffe, & Stanwix, 2002). Therefore, use of MTX therapy in patients with RA may show promise to reduce the incidence of CVD in this population.

Leflunomide is a DMARD that inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH). DHODH is an enzyme responsible for pyrimidine ribonucleotide uridine monophosphate (rUMP) synthesis. Inhibition of DHODH by leflunomide results in inadequate production of rUMP, a product which is necessary for proper lymphocyte development (Fox et al., 1999). When compared to placebo, MTX, or sulfasalazine, leflunomide

therapy has been found to be associated with increased incidence of hypertension. Furthermore, drug-induced hypertension has been documented in up to 2% of those receiving Leflunomide (Smolen & Emery, 2000).

A study investigating 107,908 patients receiving DMARD therapy, including MTX, leflunomide, anti-malarials, gold salts, cyclosporine, or azathioprine, showed that use of any DMARD resulted in a 20% decreased risk for acute MI (Suissa et al., 2006). Alternatively, a study investigating 3,501 RA patients compared various antirheumatic therapies and the incidence of MI or stroke. The DMARDs included in the study were MTX, leflunomide, azathioprine, and cyclosporine. The results indicate that when compared to MTX monotherapy, the patients receiving the other cytotoxic DMARDs had an 80% increased risk for suffering a cardiovascular event (Solomon et al., 2006). Since MTX may be cardioprotective, these results do not necessarily indicate the other DMARDs directly cause MI or stroke, however it does support the argument that MTX is a superior choice for antirheumatic therapy.

### Anti-Tumor Necrosis Factor Alpha Drugs

Another class of antirheumatic drugs, the biologics, modify RA disease progression by disabling specific cytokines in the body. Infliximab, a commonly prescribed drug for treatment of moderate to severe RA, is a chimeric IgG monoclonal antibody that targets TNF- $\alpha$  and neutralizes its activity (*PDR*, 2007). It is commonly combined with MTX to treat the symptoms of RA and prevent progression of the disease. Other anti-TNF- $\alpha$  drugs include etanercept and adalimumab. With anti-TNF- $\alpha$  therapy the adverse effects of TNF- $\alpha$  are less evident. These effects include release of additional pro-inflammatory molecules such as interleukins, amplification of leukocyte migration and activation, release of acute phase reactants, and destruction of tissue (*PDR*, 2007). Based on the known actions of TNF- $\alpha$ , anti-TNF- $\alpha$  therapy should decrease disease activity, reduce levels of pro-inflammatory cytokines, improve endothelial function, decrease progression of atherosclerosis, improve lipid profiles, and decrease insulin resistance. Therefore, anti-TNF- $\alpha$  therapy should improve cardiovascular health of individuals with significant RA disease activity.

In a study by Hurlimann and associates (2002), flow-mediated vasodilation improved after 12 weeks of infliximab therapy. This evidence suggests that the endothelial damaging effects of TNF- $\alpha$  may be significantly reduced with infliximab. Similar results were seen in another study, but the improvement in endothelial function was transient, disappearing four weeks after the infusion (Gonzalez-Juanatey et al., 2004). However, since infliximab is often administered by IV infusion every eight weeks, the cumulative effects of a temporary increase in endothelial function may vastly improve cardiovascular health for these patients receiving the drug for an extended period of time.



Investigation into the effects of infliximab on cardiovascular events is also promising. RA patients receiving anti-TNF- $\alpha$  therapy with either infliximab or etanercept have been found to have a lower risk of suffering a first cardiovascular event than those who do not receive these drugs (Jacobsson et al., 2005). When compared to MTX, infliximab shows no deleterious or protective effect on the incidence of cardiovascular events (Solomon et al., 2006). However, these results indicate that if MTX is accepted as being cardioprotective, infliximab similarly improves cardiovascular health.

Limited evidence also supports that infliximab improves the dyslipidemic pattern commonly seen in RA patients. In a small study by Seriola et al. with infliximab therapy, HDL levels were found to increase significantly (Seriolo et al., 2006). Higher levels of HDL have a protective effect on cardiovascular health, and although total cholesterol may increase with use of infliximab, the increase in HDL is still proposed to be beneficial.

## Glucocorticoids

Glucocorticoids (GCs) are excellent anti-inflammatory medications. They inhibit several components of the inflammatory process including cytokines, inflammatory enzymes, adhesion molecules, and permeability factors (Bijlsma, Boers, Saag, & Furst, 2003). GCs are widely used to suppress inflammation in a variety of acute disease processes, including RA disease flares. GCs have been found to provide rapid and dramatic improvement in functioning and reduce joint damage in patients with RA ("Guidelines for the management of rheumatoid arthritis: 2002 Update," 2002; Hickling et al., 1998; Kirwan, 1995). Unfortunately, the symptoms and joint damage resume with GC discontinuation, regardless of concomitant DMARD use (Hickling et al., 1998). This results in a large percentage of RA patients developing functional dependence on GC for long-term disease suppression ("Guidelines for the management of rheumatoid arthritis: 2002 Update," 2002).

Long-term GC therapy in chronic inflammatory disease remains controversial due to the widely accepted list of adverse effects associated with GC use. The proposed adverse effects of GC therapy on cardiovascular functioning include hypertension (Whitworth, 1987), elevation of blood glucose (Delaunay et al., 1997), accelerated atherosclerosis (Da Silva et al., 2006; "Guidelines for the management of rheumatoid arthritis: 2002 Update," 2002; Kalbak, 1972), and lipid disturbances (Bijlsma et al., 2003).

However, in a “chicken or the egg” style argument, these unfavorable cardiovascular changes may progress as a direct result of systemic inflammation, as formerly described. Therefore, these adverse cardiovascular effects may actually be due to the underlying systemic inflammation for which the GC is prescribed. Consequently, the anti-inflammatory activity of GCs may in fact reduce cardiovascular risk by decreasing systemic inflammation (Bijlsma et al.,

2003; Pham et al., 2006). This suggestion remains a topic of debate and requires further investigation. Nevertheless, the data from studies assessing CVD in patients receiving GC therapy may be difficult to interpret since those who require GCs arguably have more inflammatory disease activity than those who do not require GC therapy.

A well-known article by Whitworth (1987) states that exogenous GC use may result in iatrogenic hypertension in up to 20% of patients. However, this statistic was in reference to patients with iatrogenic Cushing's syndrome, which implies use of a much higher GC dose than necessary for symptomatic relief in most patients with RA. Furthermore, 80% of those with naturally occurring Cushing's syndrome in this study were found to have hypertension (Whitworth, 1987). Perhaps this is evidence that synthetic GCs have less mineralocorticoid effect, and therefore less salt-retaining action, than their endogenous equivalent. Low-dose GC therapy, defined as less than 20 mg/day of prednisone, which is appropriate for use in RA symptom reduction, has shown no correlation with blood pressure elevation (Jackson, Beevers, & Myers, 1981).

Glucocorticoid therapy is associated with dose-dependent hyperglycemia (Gurwitz et al., 1994) via increased hepatic glucose production (Delaunay et al., 1997), decreased insulin production, and increased insulin resistance (Bijlsma et al., 2003; Delaunay et al., 1997). When GCs are discontinued, these effects are usually rapidly reversed (Da Silva et al., 2006) and few go on to develop persistent diabetes mellitus (Bijlsma et al., 2003; Hricik, Bartucci, Moir, Mayes, & Schulak, 1991). On the other hand, GC use has also been attributed with improved peripheral insulin sensitivity (Hallgren & Berne, 1983). This paradoxical phenomenon is consistent with the idea that widespread inflammation contributes to progression of insulin resistance.

Treatment of RA disease activity, including the use of GCs, improves lipid profiles. A small study comparing lipid profiles of 58 patients before receiving RA drug therapy and after 12 months of MTX and low-dose prednisone use showed an improvement in disease activity, a reduction in inflammatory markers, and favorable changes in lipid levels. The alteration in lipids included an increase in HDLs without altering LDLs. Consequently, TC was increased, but TC/HDL and LDL/HDL ratios improved (Georgiadis et al., 2006). A similar study with 42 RA patients described a 21% increase in HDL levels after MTX and prednisolone therapy, which is more than can be expected with statin use (Park et al., 2002).

Studies investigating the incidence of cardiovascular events such as stroke or MI in RA patients receiving GC therapy do not reflect these beneficial results. When compared to patients receiving MTX monotherapy, those receiving oral GC monotherapy for treatment of RA had a 50% increase in cardiovascular events (Solomon et al., 2006). In a similar study, GCs were found to increase the risk of acute MI in patients with RA (Suissa et al., 2006). However, since MTX is cardioprotective and reduces the incidence of cardiovascular events, it may be unjust to compare it with GCs. A better analysis may be to compare patients taking GCs with those who have not received DMARD therapy.

A study by Davis and colleagues (2007) compared the effects of GCs on the incidence of cardiovascular events in rheumatoid factor (RF) positive and RF-negative patients. The results indicate a significantly increased risk of cardiovascular events in RF-positive patients receiving GCs, but no increased risk for RF-negative patients receiving GCs. Perhaps these results suggest yet another inflammatory process involving RF that contributes to the complex progression of CVD in patients with RA.

The conflicting data on the effects of GCs in RA reflect the controversy surrounding their use for long-term therapy. GCs remain one of the most powerful and cost effective drug therapies for symptomatic relief of RA, yet traditional theory, largely based on older studies, sparks a fear of increased cardiovascular side effects. However, many of these studies were based on doses that are much higher than commonly used to treat RA (Da Silva et al., 2006; Whitworth, 1987), and may be consequently irrelevant in this discussion. Future investigations of long-term, low-dose GC use in subjects with RA, who are not compared to the general population for rates of CVD, will be the most influential studies in determining the cardiovascular safety of GC use in the treatment of RA.

## HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, or statins, are effective cholesterol lowering drugs. Statins inhibit the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A into mevalonate, a precursor to cholesterol synthesis. The result is a decrease in circulating levels of total cholesterol, LDLs, and triglycerides, while increasing HDL levels (*PDR*, 2007).

The decrease in cardiovascular mortality demonstrated in patients taking statins cannot fully be explained by the cholesterol-lowering effects alone (Costenbader & Coblyn, 2005). In fact, in the ASCOT-LLA trial, which involved over 10,000 subjects without dyslipidemia, atorvastatin was found to significantly reduce cardiovascular events (Sever et al., 2003). In a process unrelated to the HMG-CoA reductase inhibition, statins have been shown to rapidly improve endothelial function (Fabian et al., 2004). Improved endothelial function was also seen using fluvastatin in as little as 15 minutes after administration (Tiefenbacher et al., 2004). This illustrates a potential cardioprotective effect beyond the cholesterol modifying function of statins.

Support of the possibility that a mild anti-inflammatory effect of statins may provide cardiovascular benefit is growing (Abud-Mendoza et al., 2003; Costenbader & Coblyn, 2005; Palinski & Napoli, 2002). In a small study by Abud-Mendoza and colleagues (2003), statins reduced erythrocyte sedimentation rate (ESR) and CRP levels in RA patients who did not respond to traditional DMARDs. When statins were added to DMARD therapy in a different study, CRP decreased by 50%, and ESR decreased by 28% (McCarey et al., 2004). Clinically, RA patients receiving statin therapy reflect this effect with symptomatic improvement measured by swollen joint count (McCarey et al., 2004) and subjective scores on American College of Rheumatology disease activity scales (Abud-Mendoza et al., 2003).

Histologic studies offer promising results as well. In mice treated with simvastatin, researchers observed a significant decrease in both synovial hyperplasia and in cartilage and bone erosion (Leung et al., 2003). Similar effects were seen with human cells in vitro as simvastatin reduced synovial cell proliferation (Leung et al., 2003). These results suggest that statins may prevent RA disease progression and articular damage.

Serologic studies of inflammatory markers also support the anti-inflammatory and immunomodulatory effects of statins. Statin use has been associated with a decrease in expression of major histocompatibility complex class II (MHC-II), a molecule involved in the activation and maturation of T-lymphocytes (Kwak, Mulhaupt, Myit, & Mach, 2000). Statins may also suppress T-cell-macrophage communication (Leung et al., 2003), which induces cytokine release in the complex cascade of the inflammatory process (Lacraz et al., 1994). As T-lymphocyte function is reduced with statin use, fewer pro-inflammatory cytokines will be released. This has manifested as decreased levels of interferon- $\gamma$ , TNF- $\alpha$ , interleukin-2, interleukin-6, interleukin-8 (Leung et al., 2003).

## NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common choice for pain relief in patients with RA. NSAIDs produce analgesia and reduce inflammation by inhibition of cyclooxygenase (COX) enzymes, which are involved in prostaglandin synthesis (Kurth, Hennekens, Buring, & Gaziano, 2004; *PDR*, 2007). The functions of prostaglandins in the human body are vast. These functions primarily include propagation of pain and inflammation, and stimulation of mucosal protective functions in the GI tract (Bombardier et al., 2000; *PDR*, 2007).

The COX-1 isoenzyme is found constitutively in the gastrointestinal mucosa, where it produces prostaglandins necessary for proper mucosal function (Bombardier et al., 2000; Meade, Smith, & DeWitt, 1993). The COX-1 enzyme is also found on the platelet surface and is integral in production of thromboxane A<sub>2</sub>, a strong platelet aggregator and vasoconstrictor (Antman et al., 2007; Kurth et al., 2004; *PDR*, 2007).

¶ Alternatively, the COX-2 isoenzyme generates prostaglandins that induce inflammation and pain (Bombardier et al., 2000; Meade et al., 1993). The COX-2 isoenzyme, which is also found on the endothelial cell surface, is expressed during periods of shear stress (Antman et al., 2007; Topper, Cai, Falb, & Gimbrone, 1996) and produces prostacyclin, an antithrombotic and vasodilator (Antman et al., 2007; Kurth et al., 2004). A sensitive balance exists between COX-1 and COX-2 actions regarding the tendency to form blood clots (Antman et al., 2007).

Traditional NSAIDs are non-selective and block both the COX-1 and COX-2 enzyme simultaneously. At low doses, aspirin irreversibly inhibits the COX-1 enzyme with no effect on COX-2 (*PDR*, 2007). In large doses, however, aspirin non-selectively and irreversibly blocks both the COX-1 and COX-2 enzymes in peripheral tissues, which may result in gastric irritation



and GI bleeding (*PDR*, 2007). The newer, COX-2 specific inhibitors, are selective for the COX-2 enzyme, which should provide more effective analgesia, since COX-2 is the isoenzyme primarily involved in inflammation and pain (*PDR*, 2007). These drugs provide the anti-inflammatory and analgesic effects of traditional NSAIDs and aspirin, without the frequency of adverse GI side effects (Bombardier et al., 2000; Silverstein et al., 2000).

Since aspirin irreversibly inhibits COX-1 on platelets, it reduces production of thromboxane A<sub>2</sub>, therefore acting as an antithrombotic medication (Kurth et al., 2004). For that reason, in addition to its classic use as an analgesic, aspirin is widely used in low doses in prevention of cardiovascular events. Although patients with RA face an increased risk of CVD, the diagnosis of RA alone has not been enough to recommend prophylactic aspirin therapy (Pham et al., 2006) as the risk of side effects may outweigh the possible benefits for this population.

Non-selective NSAIDs reversibly inhibit both COX-1 and COX-2 and exhibit a milder anti-platelet activity versus aspirin, and for only a portion of the dosing interval (Kurth et al., 2004; Schafer, 1995). Naproxen may have the best anti-platelet activity of non-selective NSAIDs as it has a prolonged duration of action and has been shown to reduce rates of acute MI (Kurth et al., 2004; Solomon, Glynn, Levin, & Avorn, 2002).

When aspirin is used in combination with nonselective NSAIDs, such as ibuprofen or naproxen, the anti-platelet effect of aspirin is decreased (Catella-Lawson et al., 2001; Pham et al., 2006). A possible explanation for this phenomenon is that non-selective NSAIDs compete for the binding site of the COX-1 isoenzyme on platelets. As these non-selective COX inhibitors are eliminated from the bloodstream, the COX-1 enzyme is no longer inhibited from producing its prothrombotic products. Alternatively, aspirin covalently binds COX-1 for the life

of the platelet, which results in more anti-platelet activity over time (Kurth et al., 2004; Schafer, 1995).

Safety of COX-2 specific inhibitors has been a subject of controversy in recent years due to the possible increased CVD risk associated with their use. They work by selectively blocking the action of the COX-2 isoenzyme (*PDR*, 2007) with the goal of reducing inflammation and providing analgesia, without the bleeding risk or GI irritation of traditional NSAIDs and aspirin. Theoretically, inhibition of the COX-2 enzyme without simultaneous inhibition of the COX-1 enzyme should cause elevated levels of thromboxane A<sub>2</sub> and decreased levels of prostacyclin. Since prostacyclin is a natural anti-platelet and thromboxane is prothrombotic, the patient receiving COX-2 inhibitor therapy would then be at elevated risk for thrombosis and cardiovascular events (Kurth et al., 2004).

Results of studies evaluating this possibility are mixed and seem to vary with the type of COX-2 specific inhibitor (Antman et al., 2007). In 2004, Merck voluntarily removed rofecoxib from the market due to evidence that its use increased risk for cardiovascular events (Antman et al., 2007; Bombardier et al., 2000). The Vioxx Gastrointestinal Outcomes Research Study (VIGOR trial) showed an increased risk of MI with rofecoxib versus naproxen (Bombardier et al., 2000). If naproxen provides CV benefit as proposed above, it is uncertain if these results are due to the protective effect of naproxen or the adverse effects of rofecoxib (Kurth et al., 2004). Regardless, this evidence led to a withdrawal of rofecoxib and a “black box warning” for celecoxib, the only COX-2 inhibitor that is currently available, stating that there may be an increase in cardiovascular risk (Antman et al., 2007).

Studies investigating CV risk with celecoxib have not shown the same results as those evaluating rofecoxib and expert opinion is split on whether all COX-2 specific inhibitors should

be discontinued. One major study, the Celecoxib Long-Term Arthritis Safety Study (CLASS trial) investigated over 8,000 participants and showed no significant difference in CV risk for celecoxib versus ibuprofen or diclofenac (Silverstein et al., 2000). Another study evaluating over 107,000 subjects found no increase in acute MI with COX-2 specific inhibitor use (Suissa et al., 2006). Nevertheless, it is recommended that COX-2 inhibitors only be prescribed to patients receiving no relief from traditional NSAIDs or those who are at high risk for GI bleeding, with careful cardiovascular risk evaluation. Furthermore, the use of COX-2 inhibitors should be limited to the lowest possible dose for the shortest possible duration in the attempt to minimize any possible deleterious effects on the CV system (Antman et al., 2007).

The use of NSAIDs for pain control may play a role in elevation of blood pressure and hypertension in patients with RA. The means for this possible blood pressure elevation is unclear and debatable. The VIGOR trial evaluating the effects of the COX-2 specific inhibitor rofecoxib showed a mean elevation of systolic blood pressure of 4.6mm Hg in rofecoxib patients versus a 1.0 mm Hg systolic BP increase in those taking naproxen (Bombardier et al., 2000; Nurmohamed et al., 2002). This supports the decisions made by Merck and the FDA to discontinue use of rofecoxib and establish CV precautionary measures for COX-2 specific inhibitor use. Conversely, the CLASS trial showed 1.7% of those taking celecoxib had hypertension versus 2.3% of those taking traditional NSAIDs (Nurmohamed et al., 2002; Silverstein et al., 2000), strengthening the argument that celecoxib does not impose the same CV risks as rofecoxib.

## Discussion

Patients with RA face a higher risk of cardiovascular morbidity and mortality (McEntegart et al., 2001; Park et al., 1999; Wolfe et al., 1994). Inflammation and the molecular products of the inflammatory cascade play a central role in the advancement of CVD in this population, as outlined in table 1. As the complex interaction between inflammation and CVD becomes clearer, compelling reasons for controlling inflammation in patients with RA extending beyond symptomatic relief have begun to emerge. Reduction of inflammation by common RA drug therapies improves the cardiovascular profile of RA patients. MTX reduces mortality, including death due to CV causes (Choi et al., 2002; Krause et al., 2000), and lowers the risk of acute MI (Suissa et al., 2006). Anti-TNF- $\alpha$  therapy with infliximab improves lipid profiles (Seriolo et al., 2006) and lowers risk of suffering a first CV event (Jacobsson et al., 2005).

GCs have historically held the reputation of causing adverse CV consequences, but recent information suggests that low-dose therapy, commonly used to treat RA, may not have the same harmful effects as high-dose therapy (Bijlsma et al., 2003; Da Silva et al., 2006; Jackson et al., 1981; Whitworth, 1987). In fact, GCs may actually improve CV health by effectively reducing inflammation throughout the body, thereby slowing progression of CV disease (Bijlsma et al., 2003; Pham et al., 2006).

NSAIDs and aspirin are great options for pain control because they reduce inflammation and provide analgesia, though they do not alter progression of RA. They have also been used for years as anti-platelet medications for those with high CV risk. However, a common side effect is gastric ulceration and gastrointestinal bleeding. COX-2 specific inhibitors produce less GI disturbance, but have been linked with CV events.

Statins have not traditionally been used to treat RA, yet recent research suggests that they may help to prevent CVD in this population. Statins have been found to not only help correct the lipid disturbances commonly seen in RA patients (McCarey et al., 2004), but they also moderately reduce inflammation (Abud-Mendoza et al., 2003; Costenbader & Coblyn, 2005; Kwak et al., 2000; Leung et al., 2003; McCarey et al., 2004) and improve disease activity (Abud-Mendoza et al., 2003; Leung et al., 2003; McCarey et al., 2004).

## Conclusion

In conclusion, special care must be taken for RA patients and those with other chronic inflammatory diseases, such as SLE, psoriasis, psoriatic arthritis, or crohn's disease, with regular monitoring and screening of cardiovascular health. No guidelines exist to start screenings earlier in such patients, however the possible propagation of CVD with inflammatory disease warrants diligent treatment. Symptoms that may be disregarded as new or worsening musculoskeletal pain of the upper body should warrant suspicion for cardiac ischemia in this population.

Traditional drug therapies used to treat RA, including MTX and TNF- $\alpha$  antagonists, provide cardiovascular benefit. All patients with RA, especially those with cardiovascular risk factors, should be on MTX. Not only is it a superior choice for RA disease modification, but it also clearly reduces the risk for CVD related morbidity and mortality. If the patient does not tolerate MTX, other DMARDs are acceptable choices for controlling the RA disease process, but these patients may require more aggressive CVD prevention and blood pressure monitoring.

While GCs are excellent in reducing inflammation and RA symptoms, they may increase blood pressure and be deleterious to the cardiovascular system. Nonetheless, healthcare providers may not need to fear low-dose GC use in RA patients because GCs are extremely effective and beneficial for many RA patients, and they do not exert the same adverse effects as large doses. If a patient does require long-term GC use to control the RA disease process, make sure to closely monitor BP since GCs have been correlated with hypertension.

Although it is not indicated to start patients with RA on statins unless they have documented dyslipidemia, it is beneficial to use statins a bit more liberally to correct dyslipidemia in patients with RA as it may also reduce joint pain and destruction. In the RA patient, statin use will lead to decreased pain and disability, slowed disease progression, and

prevention of CVD by both modifying cholesterol and reducing inflammation. Furthermore, it may be reasonable to consider RA as an additional CVD risk factor equivalent when determining lipid goals and treating dyslipidemia aggressively.

Celecoxib, the only COX-2 specific inhibitor currently available, is a good choice for RA patients who are prone to GI disturbance with traditional NSAID use. Unfortunately, COX-2 selective inhibitors have recently been correlated with increased CV risk due to the unfavorable side effects of rofecoxib, although it does not appear that celecoxib causes the same undesirable effects on the cardiovascular system. Nonetheless, COX-2 inhibitors should be used with utmost caution. It is important to be aware of the possibility that the drugs in this class could lead to CV events; however, this is mostly based on theory and evidence from rofecoxib trials.

Obviously, a patient should always be placed on a medication regimen cautiously due to the risk of adverse reactions, which can occur even in the most benign drugs. However, a reasonable suggestion for RA drug therapy is to first achieve pain relief and modify disease progression, and thereafter adjust medications and dosages to keep ESR and CRP low. These lab values are a measurable reflection of inflammatory activity. If ESR and CRP are kept within normal limits, one can presume other circulating inflammatory markers are also at a minimum, perhaps sparing the cardiovascular system from their damaging effects.

Future studies investigating cardiovascular health in systemic inflammatory diseases, such as RA, will be extremely beneficial. Since RA patients have a lower life expectancy than the general population with a high rate of deaths attributable to CVD (Wolfe et al., 1994), knowledge in this area can only help our chances of improving life expectancy in this group. Additionally, the drugs used to combat inflammation may be used as prototypes for cardiovascular drugs for the general population. If inflammation causes CVD, RA patients can

be used as models for developing effective new treatments to prevent progression of CVD in those with less severe inflammatory activity in the general population.

Clinicians need to work with patients to individualize therapy to maximize control of symptoms. Closely monitoring degree of inflammatory activity is a good indicator of RA disease control. If symptoms are not well controlled, or if serum CRP or ESR levels are elevated, critical damage to the cardiovascular system could be taking place. Tight control of the RA disease process may add years to the RA patient's life.



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Table 1

*Cardiovascular actions of inflammatory molecules*

Cytokine	Action	Proposed result	Source
TNF-alpha	Blocks action of endothelial nitrous oxide synthase (ENOS)	Decreased NO bioavailability	(Yoshizumi et al., 1993)
	Prevents breakdown of asymmetric dimethylarginine (which inhibits ENOS)	Decreased NO bioavailability	(Ito et al., 1999)
	Promotes hepatic free fatty acid release	Dyslipidemia	(Feingold & Grunfeld, 1987)
	Promotes hepatic triglyceride synthesis	Dyslipidemia	(Khovidhunkit et al., 2000)
	Blocks action of lipoprotein lipase	Decreased triglyceride catabolism	(Khovidhunkit et al., 2000; Redgrave et al., 1992)
	Alters insulin mediated glucose uptake in skeletal muscle	Insulin resistance	(Hotamisligil et al., 1996)
IL-1	Decreased expression of anticoagulation receptors on endothelial cell surface	Promotes coagulation	(Sesin et al., 2005)
	Damages endothelial cells	Promotes atherosclerosis	(Sesin et al., 2005)
IL-6	Promotes hepatic free fatty acid release	Dyslipidemia	(Khovidhunkit et al., 2000)
Interferon- $\gamma$	Damages endothelial cells	Promotes atherosclerosis	(Sesin et al., 2005)
	Decreases expression of anticoagulation receptors on endothelial cell surface	Promotes coagulation	(Sesin et al., 2005)
CRP	Decreases NO bioavailability	Vascular dysfunction	(Venugopal et al., 2002)
	Impaired endothelial function/reactivity to NO	Vascular dysfunction	(Fichtlscherer et al., 2000)

## Abstract

**Objective:** Rheumatoid arthritis (RA) is a disabling disorder associated with an increased incidence of cardiovascular disease (CVD) and a decreased life expectancy. This review investigates why CVD is more abundant in this population and how antirheumatic drug therapy affects cardiovascular (CV) health.

**Method:** This review was conducted using the MEDLINE database.

**Results:** Evidence supports inflammation playing a major role in progression of CVD.

Traditional antirheumatic drug therapy combats these effects on the CV system, as methotrexate and anti-TNF $\alpha$  drugs improve CV risk. Glucocorticoids remain controversial as they have a poor side effect profile, but some propose the anti-inflammatory effects are cardioprotective. Some COX-2 selective inhibitors have been associated with increased risk of CV events. HMG-CoA reductase inhibitors may be a future option for treating RA since they correct dyslipidemia and exhibit anti-inflammatory effects.

**Conclusion:** Treatment plans for individuals with RA must be tailored to reduce RA progression and prevent CVD.