Cardiovascular Disease in Rheumatoid Arthritis

Release Date: 08/24/2011

Expiration Date: 08/24/2014

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FACULTY AND ACCREDITOR DISCLOSURE STATEMENTS:

Katrin Holt *has no actual or potential conflict of interest in relation to this program.*

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Program Overview:

To provide nurse and pharmacists with an understanding cardiovascular disease and effects on rheumatoid arthritis.

OBJECTIVES:

After completing this program, participants will be able to:

- Understand and describe the pathophysiology of cardiovascular disease in rheumatoid arthritis.
- List traditional and novel risk factors predisposing RA patients to an elevated cardiovascular risk.
- Describe European League Against Rheumatism **(**EULAR) recommended guidelines for identifying CVD in RA patients, and understand the importance of multiplication factors for national risk assessment models.
- Understand the controversial role of NSAIDs and glucocorticoids in RA treatment, and describe preferred treatment options and durations of therapy.
- Describe EULAR preferred treatment guidelines for CVD in RA.

Cardiovascular Disease in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by synovial joint inflammation and destruction. Significant attention is placed on early, aggressive intervention to reduce severity of disease with induction of remission as the primary goal. However, cardiovascular disease (CVD) is the main cause of mortality in rheumatoid arthritis patients, accounting for as much as 50% of all reported deaths. [1-4] The risk for cardiovascular disease in RA is significantly increased versus the general population and often undertreated, leading to a decrease in life expectancy.[4-7] In RA, traditional and novel risk factors along with certain prescribed and over-the-counter medications play a role in the development and exacerbation of CVD.[1-3,6-8] The following article will focus on the pathophysiology of CVD in RA, guidelines for identifying CVD risk in RA patients, and the current treatment options available.

The Pathophysiology of Cardiovascular Disease in Rheumatoid Arthritis

Cardiovascular disease is an inflammatory disorder causing endothelial injury and dysfunction. Smoking, hypertension, and diabetes along with increased levels of modified low-density lipoprotein (LDL) have been implicated as factors that cause endothelial dysfunction.[9] Endothelial injury caused by traditional risk factors leads to an increase in adhesion molecules (vascular cell adhesion molecule 1, intercellular adhesion molecule 1), allowing for the passage of monocytes into the artery wall. [9, 10] Macrophages are produced in response to monocytes uptake of oxidized LDL trapped inside the artery wall. Furthermore, macrophages transform into foam cells after scavenging LDL. Modified LDL in the arterial wall continues to attract macrophages and T cells, causing an increase in cytokines, chemokines and growth factors to perpetuate the inflammatory cycle, leading to plaque development and future cardiovascular events.[9-12]

In RA, active disease and extraarticular manifestations like rheumatoid nodules, vasculitis, and RA related lung disease are associated with increased cardiovascular risk, morbidity and mortality, enhancing atherosclerosis.[1] Reportedly, the risk for experiencing a first cardiovascular event is increased by as much as 60% in RA patients, especially for myocardial

infarction (MI), reducing the average lifespan by as much as 18 years.[1, 13] An increased risk of cardiovascular events may begin prior to the diagnosis of RA and that risk continues to elevate in patients with prolonged disease duration.[1, 4,14] The inflammatory components in RA are very similar to the ones seen in CVD, leading theorists to believe that RA patients may experience CVD at an accelerated rate due to novel and traditional risk factors (**Table 1**).[11] Atherosclerotic plaque contains several inflammatory elements common in RA, including macrophages, cytokines (TNF-α, IL-1), T lymphocytes (CD4, CD28), and C-reactive protein (CRP). Theorists believe that elevated systemic levels of TNF-α play a dual role in RA, promoting synovial joint destruction along with accelerating atherosclerosis. In RA, tumor necrosis factor alpha (TNF-α) works in the synovial joint to initiate the release of other inflammatory cytokines, matrix metalloproteinases and osteoclasts that are responsible for bone erosions and joint damage.[4, 9, 15] In CVD, TNF-α impairs glucose uptake into skeletal muscle, creating a prothrombotic environment along with augmenting LDL adhesion to vascular endothelium to promote the development and rupture of plaque.[1, 11, 12, 16] Another known predictor of future cardiovascular events is the hepatic production of CRP which is also thought to be influenced by TNF-α. CRP has been shown to induce adhesion molecules (ICAM-1, VCAM-1), promoting the progression of plaque formation and rupture. Reportedly, RA patients have also been shown to display elevated levels of fibrinogen, von Willibrand factor and tissue plasminogen activator (tPA), increasing the likelihood of thrombosis.[11, 12]

Toll-like receptors (TLRs), known to detect microbes and tissue damage along with inducing proinflammatory genes, have recently been implicated in the pathophysiology of both RA and CVD. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) induce an immune response through activation of TLRs, leading to the production of proinflammatory substances. Injured tissue releases substances classified as DAMPs. In the absence of infection, DAMPs have been implicated in activating the immune response seen in both RA and CVD. Rheumatoid arthritis patients exhibit an increased level of TLR-2 and TLR-4 in the synovial joint. More studies are required to determine the exact pathogenesis of TLRs in both RA and CVD along with the possible therapeutic benefits and detriments of TLR inhibition.[14]

During periods of active inflammatory disease, patients display a tendency toward decreased total cholesterol (TC) and significantly depressed HDL levels. Even with a decrease in TC, the risk for cardiovascular events is increased. Reportedly, an inverse relationship exists between inflammation and cholesterol. Furthermore, physical inactivity associated with pain from joint erosion and destruction compounds dyslipidemias experienced in RA. Tumor necrosis factor, responsible for driving inflammation in RA, depresses TC levels (especially HDL); thereby, creating an unfavorable ratio between TC and HDL. However, HDL levels typically improve with control of the disease, reducing the cardiovascular risk.[1, 10, 11]

Cachexia is a phenomenon related to dyslipidemia in RA. Patients with cachexia display low body weight and subsequently low body mass index (BMI). The BMI is a measure of weight and height, giving an approximate measure of total body fat. The high inflammatory state in RA is thought to cause cytokine mediated loss of lean muscle mass.[1, 17] Patients with rheumatoid related cachexia generally have higher fat content as lean body mass is substituted by fat, yielding a state similar to obesity. High fat content seen in obese patients is known to cause hypertension, insulin resistance and dyslipidemias, leading to an increased chance of experiencing a cardiovascular event.[17] In a trial completed by Kremers et al, RA patients experiencing low BMI at the initiation of the study displayed a four-fold increase in cardiovascular death versus non-RA participants. Furthermore, RA patients developing a low BMI during the study were reportedly three times as likely to die from a cardiovascular event.[17]

Diabetes and insulin resistance (IR) have long been known as independent risk factors for CVD. While only a modest increase in diabetes has been reported in RA patients, insulin resistance (IR) has been well documented.[18, 19] Disease activity may be correlated with IR, occurring more often in patients with higher levels of inflammation and/or glucocorticoid use. Scientific studies comparing the risk to induce CVD have lead to mounting evidence suggesting the equivalence of RA versus diabetes in the ability to increase risk.[1, 7, 20] One study by Peters et al showed that RA patients experienced a cardiovascular related event twice as often as the general population. Likewise, the elevated risk was roughly equivalent at 2.14 and 2.04 between RA and type 2 diabetic patients respectively. The odds ratio was reportedly 3.1 in the studied RA patients versus 2.3 in the diabetic patients.[1, 7] Of note, the study reported that the

Framingham risk score for CVD may underestimate the true risk in RA patients.[7] The increased incidence of CVD in RA similar to that seen in diabetic patients has lead to European League Against Rheumatism (EULAR) guidelines recommending RA be considered a condition that predisposes the patient to a higher CVD risk.[6] Furthermore, the French Agency for Healthcare Product Safety (AFSSAPS) has published clinical practice guidelines for CVD in RA, stating RA should be considered an independent risk factor for CVD based on clinical trial evidence and expert opinion.[21]

Identifying Cardiovascular Disease Risk in Rheumatoid Arthritis

Recent EULAR guidelines recommend using either a Framingham score or the model most often used in Europe called the Systemic Coronary Risk Evaluation (SCORE) for assessing cardiovascular risk in all RA patients.[6] Used in the U.S., Framingham's was designed for the general population to predict a person's 10 year risk for experiencing a cardiovascular event and to determine the need for medical intervention. Patient risk is divided into three categories of low (‹10%), intermediate (10% - 20%) and high risk (›20%), taking into consideration age, cholesterol and blood pressure levels, gender and smoking status. Both models consider classic risk factors for CVD in hopes of targeting patients at the highest risk for experiencing a cardiovascular related event.[22] Because RA is considered to significantly increase the risk for CVD, EULAR recommendations state that all patients with rheumatoid arthritis should undergo yearly cardiovascular risk assessments, using either Framingham's or SCORE. However, emerging evidence suggests that a factor of 1.5 to 1.6 should be multiplied to either risk evaluation model to more accurately determine an RA patient's CVD risk. Studies have reported that the risk evaluation models may underestimate CVD risk in women and in inflammatory diseases like RA, implicating exclusion of non-traditional risk factors in both models as the primary reason for the variance.[1, 7, 22] Since RA patients display both classic and non-traditional risk factors, EULAR guidelines recommend multiplying risk evaluation scores by a factor of 1.5 in patients displaying two out of the three criteria: patients with disease duration ›10 years, RF (rheumatoid factor) or anti-CCP (anti-cyclic citrullinated peptide) positive, and/or extra-articular manifestations.[6] Assessment of CVD in patients displaying low disease activity or remission may be reevaluated every 2 to 3 years, increasing assessments to every year if disease activity

levels rise in patients with existing high cardiovascular risk per EULAR recommendations. Furthermore, patients in remission or displaying low disease activity may be assessed every 2 to 3 years, increasing assessments to every year if disease activity levels rise in patients with existing high cardiovascular risk. Incorporating blood pressure assessments and laboratory monitoring of cholesterol (non-fasting) during regular rheumatologic visits is also encouraged. Lastly, patients who switch or change treatment should be reassessed.[6]

The Controversial Role of NSAIDs and Glucocorticoids in RA

Hypertension, insulin resistance, and lipid abnormalities promote the progression of atherosclerosis and cardiovascular events. RA patients are more likely to require antihypertensive medications, statins and aspirin.[7] Systemic inflammation inherent in RA leads many patients to adopt a sedentary lifestyle, requiring a multitude of prescribed and over-the-counter medications and promoting lipid abnormalities, insulin resistance and hypertension.[1, 3, 7, 8, 19]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed medications known to reduce inflammation and pain associated with RA related joint destruction. Nonselective NSAIDs like ibuprofen and naproxen display anti-inflammatory properties through the inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes responsible for converting arachidonic acid into prostaglandins. Selective NSAIDs such as celecoxib were designed to inhibit primarily COX-2 in the hopes of reducing gastrointestinal complications.[23-25] However, COX-2 enzymes also play an important role in CVD with detrimental and protective effects. COX-2 enzymes have been identified in fatty streaks, enhancing monocyte adhesion to endothelial cells and the development of atherosclerosis.[24] Plaque stability and rupture are both associated with COX-2 dependent prostaglandins.[26] Besides playing a role in plaque stabilization, another beneficial effect occurs during myocardial infarction as COX-2 levels are increased, limiting infarct size and decreasing chances for myocardial rupture.[27] While NSAID associated COX inhibition decreases inflammation and pain, cardiovascular risk becomes elevated for myocardial infarction and other events. Beginning in 2001, increased reports of cardiovascular events were noted with the use of

selective COX-2 inhibitors. Although selective COX-2 inhibitors reportedly elevate CV risk more than nonselective NSAIDs, the Advisory Committee for the US Food and Drug Administration required revision of all NSAID labels to reflect the possibility for the increased risk of myocardial infarction and stroke in February of 2005. [23-25, 28]

Opposing theories exist for NSAID associated cardiovascular risk. One theory suggests the increase in cardiovascular risk may be related to an imbalance in COX-2 dependent prostacyclin (PGI2) and thromboxane A-2 (TXA2).[11, 24, 29] COX-2 inhibition by NSAIDs leaves TXA2 relatively unopposed, causing increased platelet aggregation, predisposing patients to an increased cardiovascular risk.[11, 27, 30] However, a second theory suggests that the balance between COX-1 and COX-2 or prostacyclin and thromboxane only display a small percentage of the problem. The theory proposes that all NSAIDs produce dose-dependent changes in prostaglandins throughout the body, especially with high doses of selective or nonselective NSAIDs in susceptible patients.[25] According to a very recent trial conducted by Sven et al, ibuprofen, celecoxib, rofecoxib and lumiracoxib were all associated with an increased risk for myocardial infarction versus placebo. The incidence of stroke was increased in all NSAIDs studied, including naproxen, ibuprofen, diclofenac and subsequent selective COX-2 inhibitors. Furthermore, overall incidence for cardiovascular death exceeded 30% for all NSAIDs studied, excluding naproxen.[28] Because naproxen has been deemed the safest of all NSAIDs, many clinical trials are comparing all other NSAIDs against naproxen to evaluate CV risk.[24, 27] One such study found that patients taking diclofenac displayed a 52% greater risk of having serious CVD or death versus naproxen with rofecoxib and celecoxib being the worst offenders. Moreover, patients taking ibuprofen were reported to have a 25% increased risk versus naproxen.[24] However, another trial studying cardiovascular events in patients taking NSAIDs showed a significant recurrence rate in patients with a previous history of acute myocardial infarction (AMI). Nabumetone reportedly had the highest recurrence rates followed by naproxen, celecoxib, ibuprofen and etodolac.[31] Clinically based evidence suggests cardiovascular risk is highest among patients with existing cardiovascular disease, long duration of use and high dosage levels with all types of NSAIDs.[23, 29] Regardless of the actual cause for CVD, the risk for myocardial events remains elevated for several weeks after discontinuation of use, especially in patients with an inflammatory disease. The continued risk is thought to be

caused by a rebound effect on the vasculature, reactivating platelets and destabilizing arterial plaques.[32] Since 2005, more attention has been focused on the ability of all types of NSAIDs to increase blood pressure, decrease the effectiveness of antihypertensive medications, aggravate congestive heart failure (CHF) and increase the incidence of myocardial infarction.[23-25, 28]

Already prevalent in RA, hypertension occurs in up to 73% of patients.[1] According to the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), for every 20/10 mmHg above 115/75 mmHg, the cardiovascular risk doubles.[33] Elevation in blood pressure is another NSAID related side effect. Minimal increases in blood pressure ranging from 3 to 5 mmHg have been documented since the 1980s. The resulting blood pressure increases may antagonize antihypertensive medications while necessitating prescriptive medications in some prehypertensive patients.[25, 27, 29] The degree of elevation is dose dependent and varies between NSAIDs with naproxen raising blood pressure minimally and diclofenac reportedly having the worst effect. [25, 29]

New onset heart failure associated with NSAID use has also been reported in patients with a history of heart disease. Approximately 20% of CHF exacerbations leading to hospitalization are linked to NSAID use. Patients with existing heart failure may experience exacerbations as a result of NSAID-induced increases in vascular resistance. Additionally, a higher risk for CHF exacerbations occurs in elderly patients concomitantly taking NSAIDs and diuretics. Elderly patients are more prone to renal effects resulting from NSAID drug interactions with the renin-angiotensin-aldosterone system, and prostaglandins. Furthermore, diuretics and angiotensin-converting enzyme inhibitors (ACEI) taken by heart failure patients may interact with NSAIDs, increasing the risk for CHF exacerbations.[24, 26]

Aspirin (ASA) was first introduced in tablet form in 1899. Low dose ASA has long been used for the ability to irreversibly inhibit COX-1 and thromboxane A_2 platelet thrombotic effects; thereby, reducing the risk for stroke, myocardial infarction and cardiovascular related deaths.[26] However, several trials have reportedly demonstrated that concomitant NSAID use may negate the cardioprotective effects of ASA. During the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARA), patients at the highest risk for experiencing a

cardiovascular event were reportedly taking ibuprofen and ASA.[26] Research suggests that nonselective NSAIDS pose the greatest threat, increasing the risk for myocardial infarction two-fold.[24] Arachidonic acid is irreversibly acetylated by ASA in close proximity to its catalytic site. However, ibuprofen taken two hours prior to ASA reversibly binds to the catalytic site, making it unavailable for ASA inhibition. Selective COX-2 inhibitors do not appear to have the same effect.[24, 27]

The American Heart Association issued treatment considerations for patients with inflammatory conditions in regards to NSAID use. Nonpharmacological treatment is recommended initially using physical therapy and heat/cold therapy followed by the lowest risk medication if pain is still uncontrolled. The lowest effective doses of acetaminophen (APAP), aspirin (ASA) and even narcotic medications are preferred for short term use. Patients requiring long term treatment with uncontrolled pain relief on APAP, ASA or narcotics may consider NSAID treatment, realizing cardiovascular and cerebrovascular risks are elevated with NSAID use. Nonselective NSAIDs like naproxen are preferred. Patients not controlled on naproxen may try more COX-2 selective medications.[27] EULAR recommends caution in prescribing COX-2 selective and nonselective NSAIDs. Extreme caution is recommended in patients with existing CVD or CV risk factors. However, EULAR states elevation in CV risk due to selective and nonselective NSAIDs is not well established; therefore, further trials are warranted.[6]

Glucocorticoids are widely used in RA for their immunosuppressant and antiinflammatory abilities to slow the progression of joint destruction and decrease pain.[34] Like NSAIDs, glucocorticoids increase blood pressure. However, glucocorticoids are also known to cause lipid abnormalities and insulin resistance, increasing cardiovascular risk.[1, 8, 13, 35] Clinical trials evaluating cardiovascular risk associated with glucocorticoid use has reported conflicting results. A study by Wei et al evaluated prednisolone equivalents in the ability to increase the risk for CVD. Patients continually using corticosteroids had a higher risk for CVD with the most risk occurring in patients taking daily doses ≥7.5 mg. A dose-dependent increase in the incidence of heart failure was also noted. Low–dose corticosteroids demonstrated similar results to non-users, except for the incidence of heart failure. Consequently, the cumulative systemic exposure to glucocorticoids may be as important as the dose.[34] A case-control analysis by Wolfe and

Michaud studied myocardial infarction and its risk factors in RA. Prednisone was associated with an increased risk of myocardial infarction along with the future development of diabetes and hypertension. Risk for myocardial infarction increased as the dose increased.[36] However, severe RA is associated with increased incidences of myocardial infarction. Subsequently, the increased risk for CVD in RA may be partly associated with disease severity as well as corticosteroid use.[11, 36] On the other hand, corticosteroids may also have a protective effect against CVD. Patients with early disease taking prednisone have shown increases in HDL and decreases in C-reactive protein (CRP) levels.[1, 35] Additionally, use of corticosteroids in patients with a recent history of CVD have reported decreased incidences of cardiovascular events.[37] A trial by Boers et al studied lipid response to combination therapy, including glucocorticoid treatment. Patients with early, active RA disease generally present with low HDL and high total cholesterol levels, increasing CV risk. Patients taking combination therapy with glucocorticoids demonstrated significant increases in HDL and TC levels. However, the HDL:TC ratio decreased, reducing CV risk.[38] Mounting data suggest that the anti-inflammatory properties of glucocorticoids control the development of atherosclerosis in certain patient populations.[1, 10, 11, 35] Because of the conflicting data suggesting corticosteroids negatively impact lipid levels, glucose levels, and blood pressure as well as positively impacting inflammation, EULAR guidelines recommend using the lowest effective doses of corticosteroids for the shortest period of time.[6]

Treating Cardiovascular Disease in Rheumatoid Arthritis

The treatment of CVD in RA should be determined by national guidelines, using Framingham's and SCORE in the US and Europe respectively.[6] However, EULAR guidelines recommend statins, ACEI, and angiotensin II blockers for their additive benefit as an anti-inflammatory.[6] Additionally, antirheumatic medications display their own unique properties in reducing cardiovascular risk.[1, 8, 13, 35, 37, 39]

Statins are traditionally used for primary and secondary prevention of CVD, decreasing LDL up to 55%, triglycerides up to 30% with modest increases of HDL between 5 to 15%.[40] In addition to the lipid effects, statins have demonstrated the ability to reduce inflammation by decreasing CRP levels between 15 to 25%, inhibiting the expression of adhesion molecules,

MHC II, cytokine release, and modifying smooth muscle and endothelial cell apoptosis.[8, 10, 13, 41, 42] According to a study by Okamoto et al, RA patients taking atorvastatin reported significant improvements in pain control, number of swollen and tender joints in addition to improved lipid profiles. Another trial by McCarey et al compared atorvastatin in RA patients versus placebo, reporting a 50% reduction in CRP, 28% reduction in erythrocyte sedimentation rate, significant improvements in the 28-joint Disease Activity Score (DAS28), and number of swollen joints.[42] However, another trial studied the regulatory T cell response in RA patients taking atorvastatin. Regulatory T cells (Treg) play an important part in the prevention of autoimmune diseases, controlling CD4 and CD25 expression. While the exact etiology of RA is unknown, Treg reduction is speculated to be involved. Patients who received atorvastatin demonstrated enhanced Treg functions and upregulation, improving disease activity.[43] The ability to produce favorable lipid effects in addition to the anti-inflammatory properties determined the reasons for EULAR to choose statins as a preferred treatment option.[6]

ACE inhibitors and ARBs are used in many cardiovascular disease states for their beneficial effects on the renin-angiotensin-aldosterone system.[33] Angiotensin I is converted to angiotensin II through angiotensin-converting enzyme cleavage. Functions of angiotensin II include regulating blood pressure and fluid status along with enhancing inflammatory processes.[44] ACE inhibitors and angiotensin receptor blockers (ARBs) have pleiotropic effects on the immune system, kidney, arterial wall, cardiomyocyte functions, and adipose tissue.[45] The progression of atherosclerosis is inhibited by ACEI through a reduction in NADPH activity and activation of signaling pathways, reducing endothelial dysfunction. Reportedly, RA patients have increased levels of ACE and renin in synovial fluids.[44] However, ACEI and ARBs are thought to possess anti-inflammatory properties resulting from the down regulation of angiotensin II induction of TNF-α and IL-6. Animal studies have reported beneficial effects of quinapril and candasarten on collagen induced arthritis, reducing TNF-α concentrations in the affected joint.[44] According to Flammer et al, RA patients taking high-dose ramipril reportedly demonstrate improved endothelial function, reducing cardiovascular events. Similarly, quinapril has been shown to reduce articular production of TNF-α.[46] Contrastingly, Tikiz et al reported no significant improvement in endothelial function using quinapril 10mg in RA patients.[47] However, Flammer et al refute the reported results stating the quinapril dose was to low for

proper ACE inhibition.[46] Because of the potential benefits achieved through improved endothelial function and reduction in inflammatory markers, EULAR recommends ACEI and ARBs as preferred options for treatment in RA patients.[6]

Hydroxychloroquine, methotrexate and other disease-modifying antirheumatic drugs (DMARDs) are commonly used in RA to slow down disease progression, improve pain, and induce remission. However, certain prescribed RA medications come with additional cardiovascular benefits. Hydroxychloroquine (HCQ), classified as an antimalarial medication, has been used in the treatment of systemic lupus erythematosus (SLE) and RA since 1955.[39] Relatively safe, hypoglycemia is a unique and rare side effect associated with HCQ. As previously stated, impaired fasting glucose levels are implicated in the development of CVD, especially in RA patients. Reportedly, RA patients taking HCQ for over a four-year time frame reduce the likelihood of developing diabetes by over 75%. A trial by Penn et al studied the effects of HCQ on glucose levels in RA and SLE patients, reporting lower fasting glucose levels in both disease states. Furthermore, postmenopausal patients had more significant reductions in fasting glucose levels. Interestingly, the data associated patients taking prednisone with lower fasting glucose levels while improved β cell function requiring lower insulin levels were most prominent in non-prednisone users.[39] Additional cardiovascular benefits resulting from HCQ administration include increased HDL levels and decreased LDL levels along with possible antithrombotic properties.[10, 11, 39] Methotrexate (MTX), used extensively in RA, is associated with an overall reduction in cardiovascular risk of 35%. Incidentally, myocardial infarction has been reportedly reduced up to 18% after one year of use.[11, 37] Lastly, patients taking TNF-α inhibitors have demonstrated a reduced overall mortality rate and risk for first time CVD events.[8, 12, 13, 37] The inhibitory effects studied in trials has shown increased HDL levels, improved insulin sensitivity, and improved endothelial function.[12, 19, 48] According to Gonzalez-Gay et al, insulin resistance improved immediately upon administration of a TNF inhibitor with the most significant effects seen in patients with the highest amount of resistance.[19] Another trial found a reduction in prothrombotic markers after both short and long-term treatment with TNF inhibitors, reducing proinflammatory cytokines in long-term users.[48] Contrastingly, patients with a history of congestive heart failure taking TNF inhibitors were found to be at an increased mortality rate.[37]

National and EULAR Guidelines Help Improve Cardiovascular Health in RA

Cardiovascular disease leads to significant morbidity and mortality in RA patients. EULAR guidelines have updated recommendations, alerting healthcare professionals to the increased risks in order to obtain cardiovascular health and adequate control of disease activity. National guidelines such as Framingham's and SCORE should be used to determine cardiovascular risk. A multiplication factor of 1.5 to the risk score model has been suggested in certain RA patients to obtain true cardiovascular risk. Treatment of CVD in RA patients should follow national guidelines with statins, ACEI and ARBs preferred for their possible anti-inflammatory properties. Special attention is warranted with NSAID and glucocorticoid use as cardiovascular effects have been reported. Additionally, smoking cessation is always strongly recommended in all patients. Patient and healthcare professional education in cardiovascular risk management is strongly encouraged to improve the excessive morbidity and mortality rates seen in RA.

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Table 1. Nontraditional CV Risk Factors in RA	
RA activity	Radiographic joint erosions
Degree of Inflammation	Small and Large joint swelling
Hypothyroidism	Insulin resistance
Longer disease duration[a]	Increased clotting potential
Vasculitis	Low BMI
Corticosteroid use[b]	RF positive[c]

Source: References 1-4, 10-12

[a] ≥ 8 years duration

[b] Doses ≥ 7.5mg daily

[c] RF= Rheumatoid Factor

Table 2. EULAR Recommended Medications in RA

Statins	↑HDL, ↓LDL, ↓TG, ↓CRP, ↓ESR reduced swollen & tender joints improved pain control
ACEI/ARBs	↓NADPH, ↓TNF-α, ↓Il-6 improved endothelial function
Hydroxychloroquine	↑HDL, ↓LDL, ↓fasting glucose levels improvedβfunction antithrombotic properties
TNF-αInhibitors	**↑HDL, ↑insulin sensitivity** **improved endothelial function**

Source: References 1,6,8,13,35,37,39