Cardiovascular Effects of Methotrexate in Rheumatoid Arthritis Revisited

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Abstract: Cardiovascular events such as myocardial infarction (MI) and stroke due to enhanced inflammatory atherosclerosis account for increased premature mortality in rheumatoid arthritis (RA). Accumulated evidence suggests that accelerated atherosclerosis and related cardiovascular comorbidities in RA are confounded not only by traditional risk factors (TRF) but also by a number of immune and inflammatory pathways. Since chronic inflammation and autoimmune disorders play a key role in atherosclerosis and related cardiovascular complications in RA, effective suppression of systemic inflammation can be viewed as a strategy for cardiovascular therapy and prevention in this disease. This article overviews some mechanisms of action of methotrexate on TRF, clinical and subclinical manifestations of RA-induced atherosclerosis, and related cardiovascular morbidity and mortality.

Keywords: Atherosclerosis, cardiovascular diseases, inflammation, methotrexate, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which is characterized by enhanced cardiovascular morbidity and mortality [1]. One of the largest meta-analyses of cohort studies with pooled analysis of cardiovascular mortality of 91,916 patients with RA demonstrated a 60% increase in cardiovascular mortality in these patients, who were compared with the general population [2]. Such an increase was largely attributed to the contribution of myocardial infarction (MI) and stroke [3]. Cardiovascular risk in RA is comparable to that in type 2 diabetes [4], viewed by some experts as a justification for cardiovascular prevention, targeting common for RA and diabetes pathways [5].

Accelerated atherosclerosis in RA is driven not only by traditional risk factors (TRF) but also by common for these diseases immune and inflammatory mechanisms [6]. Prior to the onset of RA, TRF are accumulated and trigger systemic rheumatoid inflammation, eventually leading to clinical manifestations of atherosclerosis [7-9]. In fact, risk of unrecognized MI in susceptible individuals prior to the development of RA is 6 times greater than that in non-RA subjects [10]. Cardiovascular events due to rheumatoid inflammation tend to manifest atypically, with symptoms of angina being rarely reported. In patients with established RA, risk of unrecognized MI and sudden death is doubled, compared to non-RA subjects [10]. The rapid increase of vascular events immediately after diagnosing RA suggests that rheumatoid immune disturbances start to play their critical role at that stage [11].

Several lines of evidence suggest that severity of rheumatoid inflammation, characterized by high number of inflamed joints, presence of extraparticular features, intensity of joints functional insufficiency, positivity for Rheumatoid Factor (RF) or Antibodies against Cyclic Citrullinated Proteins (ACCP), and elevated Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and Interleukin-6 (IL-6), confound the development of cardiovascular complications (CVC) in RA [12-14].

Overly expressed proinflammatory cytokines and relatively low levels of antiinflammatory cytokines keep rheumatoid autoimmune pathways persistently activated. Such a disbalance contributes to the endothelial dysfunction, vasoconstriction, lipid peroxidation, hypercoagulation, and atherothrombosis, viewed by most experts as an extraarticular rheumatoid feature [15-18]. Importantly, recent observations revealed that similar cellular infiltrates of monocytes, macrophages, and T-cells in atherosclerotic plaques and inflamed synovial membranes, coupled with the citrullination of fibrinogen and vimentin at both sites, add to the atherosclerotic burden in RA [19].

Apparently, targeting rheumatoid inflammation and autoimmune disorders by effective antiinflammatory agents seems a workable solution to the prevention of cardiovascular events in RA. Dampening rheumatoid inflammation by relatively safe means may reduce cardiovascular risk over a long-term. Cardiovascular effects of the widely-used and relatively safe disease-modifying antirheumatic drug (DMARD) methotrexate (MTX), known as a potent immunosuppressive and antiinflammatory agent, are of particular interest [20,21]. MTX is the first-line DMARD, which is effective for mono- and combined therapy of RA. It is often prescribed at the onset of the rheumatoid joint affection [22].
Early initiation of MTX monotherapy brings about protection for patients with RA, which is comparable to that of biologic agents [23].

The aim of this article is to overview some of the important mechanisms of cardiovascular effects of MTX and related implications for modifying risk factors and reducing cardiovascular and total mortality in RA.

**MECHANISMS OF ACTION OF METHOTREXATE**

MTX is an antimetabolite, or a substance chemically similar to its natural metabolite with which the drug competes in the process of DNA synthesis and cell reparation. The principal mechanism of action of MTX lies with its antifolate activity [24]. The drug exerts a cytotoxic effect due to the inhibition of dihydrofolatereductase (DHFR) and related decrease of intracellular levels of tetrahydrofolate, a carbon carrier in the DNA synthesis. The inhibition of DHFR disrupts DNA synthesis, which underlies antiproliferative pathways in a range of clinical conditions, including MTX overdose [25, 26].

Several mechanisms of low-dose MTX therapy have been explored, with the formation of an endogenous antiinflammatory mediator adenosine being considered the main driver of the efficiency in inflammatory disorders [27]. Adenosine-dependent actions of MTX inhibit the proliferation of endothelial cells and synovial fibroblasts, adhesion of white blood cells to the endothelium, and their migration to the inflamed tissues through capillaries and venules.

MTX dampens systemic inflammation in RA by modulating synthesis of proinflammatory and immunoregulatory cytokines that may decrease the risk of atherothrombotic events [28]. On one hand, MTX suppresses the synthesis of interleukin (IL)-1, IL-6, IL-8, leukotrienes, and tumor necrosis factor (TNF)-α [29-31], on the other, it increases production of antiinflammatory cytokines, such as IL-4 and IL-10 [32, 33]. Th2-related cytokines IL-4 and IL-10, which are produced in response to MTX, inhibit the expression of Th1-related cytokines IL-2 and interferon (INF)-γ, bringing about an immunomodulatory effect.

MTX-induced immunomodulatory effect translates into vascular effects, retarding the course of atherothrombosis. The beneficial effects of MTX on the vessel wall in RA were reported not only due to the long-term therapy, but also in response to a single dose of MTX, which dropped levels of acute-phase proteins, inhibited neutrophils’ chemotaxis, reduced reactive oxygen radicals, and lowered adhesion of leukocytes to the endothelium [34].

A bulk of evidence also suggests that there may be several indirect effects of MTX therapy on the course of atherogenesis and its complications in RA. In fact, it is hypothesized that the enhanced production of adenosine, induced by G-proteins and adenyylate cyclase, and T-cell activation drive most vascular effects of MTX [35, 36]. Large amounts of adenyylate cyclase are found in basal ganglia, vessel wall, and platelets. A2A and A1 receptors of endogenous adenosine play an important role in the regulation of coronary blood flow, oxygen consumption by the myocardium, and metabolism of brain cells [37, 38]. The activation of A2A and A1 receptors, triggered by MTX, may dilate coronary vessels and enhance blood flow in the myocardium.

It is now well known that MTX improves (reverses) cholesterol (C) transport in patients with RA. Such an effect is mediated by adenosine, interacting with its receptors on macrophages and thereby activating enzymes, which are engaged in the metabolism and reverse transport of C from the vessel wall to the liver [39]. The increased expression of the 27-hydrolase gene leads to the transformation of C to more soluble 27-OH-cholesterol, whereas the increased expression of ATP-binding cassette transporter - A1 (ABCA1) contributes to C transport from endothelial cells to HDL particles [40]. In fact, ABCA1 and 27-hydroxylase, antiatherogenic proteins, stimulate the efflux of C. The inhibition of ABCA1 disrupts C and phospholipids elimination from cells, thus leading to the formation of their complexes with apoA1, which, in turn, reduces the formation of HDL particles.

Adenosine reduces the number of foam cells in the vessel wall in *in-vitro* conditions. Using a cell culture (human THP-1 monocytes/macrophages), it was shown that the activation of adenosine receptor A2A by MTX reverses transport of C and reduces formation of foam cells [35], suggesting that the antiatherogenic effect of MTX is not limited to its direct antiinflammatory action.

Notably, there is evidence that MTX promotes the interaction of insulin with its receptor, enhancing glucose influx into the cells [41], which may have implications for overcoming insulin resistance in RA. Plausible mechanisms of the improved glucose metabolism may also include direct stimulatory effect of adenosine on the glucose influx [42].

To sum up, mechanisms of MTX action in RA are complex. The main antiinflammatory effects and related cardiovascular protection in the course of MTX therapy may be associated with the activation of adenosine receptors, modulation of pro- and antiinflammatory cytokines, and regulation of lipids and glucose metabolism.

**METHOTREXATE THERAPY REDUCES CARDIOVASCULAR MORBIDITY AND MORTALITY**

The reduced mortality rates in patients with chronic inflammatory arthritis, who are treated with MTX, are largely attributable to the antiinflammatory effects [43, 44]. In a landmark US-based cohort study of 5,626 patients with RA, followed up for 25 years, MTX therapy was associated with a 70% decline in total mortality (adjusted Hazard Ratio [HR] 0.3, 95% Confidence Interval [CI] 0.09-0.53) [43]. In another US-based study of 1,015 male patients with RA estimated mortality rates were twice as high as those in the general population and were independently associated with higher ESR and RF concentrations, increased DAS28, and prednisone use, among other covariates [44]. MTX therapy in that study was associated with a 37% decline in total mortality (HR 0.63, 95% CI 0.42-0.96) [44].

Several studies have specifically analyzed the effects of MTX therapy on cardiovascular risk, comorbidities, and mortality in RA. Some of these studies are presented in Table 1. These are mostly US-based retrospective analyses of large cohorts. Not all of these studies prove comprehensive cardiovascular protection on MTX therapy.
Table 1. Studies of cardiovascular implications of methotrexate therapy in patients with RA

<table>
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<tr>
<th>References</th>
<th>Study Design</th>
<th>Patient and Therapy Characteristics</th>
<th>Outcome Measures</th>
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<tr>
<td>Choi HK, et al. [45]</td>
<td>Prospective cohort study, 6-year follow-up</td>
<td>588 patients with RA on MTX, mean age 57 years, mean MTX dose 13 mg/week, maximum dose 25 mg/week</td>
<td>All-cause and cardiovascular mortality</td>
<td>Cardiovascular mortality HR for MTX use compared to no MTX use 0.3, 95% CI 0.2-0.7</td>
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<td>van Halm VP, et al. [46]</td>
<td>Case-control study</td>
<td>613 patients, of whom 72 (mean age 67 years) with CVD. Mono- or combined therapy with SSZ, HCQ, or MTX. Drug-naive patients served as controls</td>
<td>Incidents of CVD (coronary, cerebral, or peripheral arterial disease)</td>
<td>Corrected ORs of CVD risk for 'only MTX ever' group 0.16, 95% CI 0.04-0.66, 'MTX and SSZ ever' 0.20, 0.08-0.51, 'MTX, SSZ and HCQ ever' 0.2 (0.08-0.54)</td>
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<tr>
<td>Hochberg MC, et al. [47]</td>
<td>Prospective cohort study, 3.9-year follow-up</td>
<td>16752 patients with newly-diagnosed RA (mean age 60 years), of whom 27% developed cardiovascular manifestations, 22.7% were on MTX for at least 1 year prior to cardiovascular manifestations</td>
<td>Cardiovascular manifestations (pericarditis, vasculitis, CAD, CHF, stroke)</td>
<td>HR of cardiovascular manifestations for prior MTX use 0.65, 95% CI 0.59-0.72</td>
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<tr>
<td>Naranjo et al. [48]</td>
<td>Retrospective multicenter cohort study (QUEST-RA)</td>
<td>4363 patients from 15 countries (mean age 57 years, disease duration 11 years)</td>
<td>Incidence of angina, MI, coronary disease, coronary bypass surgery, and stroke</td>
<td>Adjusted HR of vascular events for those exposed to MTX 0.85, 95% CI 0.81-0.89, adjusted HR of MI 0.82, 0.74-0.91</td>
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<td>Prodanovich S, et al. [49]</td>
<td>Retrospective cohort study</td>
<td>6707 patients, mean age of those with CVD - 69.4 years. Patients were stratified to those on MTX therapy &lt;7.5 mg/week and &gt;30 mg/week</td>
<td>Incidence of vascular disease (CAD, stroke, peripheral arterial disease)</td>
<td>RR of vascular disease on MTX, compared to no MTX, was reduced to 0.83, 95% CI 0.71-0.9. Low cumulative dose of MTX was associated with further risk reduction to 0.65, 0.52-0.8</td>
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<td>Greenberg JD, et al. [50]</td>
<td>Cohort study to compare cardiovascular risk on TNF antagonists and nonbiologic therapies (CORRONA registry)</td>
<td>10156 patients were followed for a median of 23 months. 4969 patients were exposed to MTX therapy (mean age 59 years, median disease duration 6 years).</td>
<td>Incidence of non-fatal MI, non-fatal stroke or transient ischemic attack, and cardiovascular-related death</td>
<td>TNF antagonists reduced adjusted risk of composite cardiovascular events (HR 0.39, 95% CI 0.19 to 0.82), whereas MTX did not (HR 0.94, 0.49-1.8)</td>
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<td>Suissa S, et al. [51]</td>
<td>Nested case-control study to compare risk of MI on biologics and nonbiologics</td>
<td>107905 patients (average age 54 years), 558 with MI at follow-up</td>
<td>Incidence of MI</td>
<td>MI risk reduced due to DMARD therapy (adjusted Rate Ratio 0.80, 95% CI 0.65-0.98) but not biologic therapy (1.3, 0.92-1.83). MTX effect was borderline (0.81, 0.60-1.08)</td>
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<td>Bernatsky S, et al. [52]</td>
<td>Case-control study</td>
<td>41885 patients (average age 51 years). During followup, 520 hospitalizations for CHF occurred.</td>
<td>Incidence of hospitalizations for CHF</td>
<td>Adjusted RR of CHF for current use of any DMARD, compared to no current use, was 0.7, 95% CI 0.6-0.9; for MTX 0.8, 0.6-1.0; for refeocortisol 1.3, 1.0-3.1</td>
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<tr>
<td>Myasoedova E, et al. [53]</td>
<td>Incidence cohort study</td>
<td>795 patients (mean age 55 years), of whom 92 developed CHF during followup (mean 9.7 years)</td>
<td>Incidence of CHF</td>
<td>HR for CHF development on MTX, compared to nonusers of MTX, 0.5, 95% CI 0.3-0.9</td>
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</table>

RA = Rheumatoid Arthritis; HR = Hazard Ratio; OR = Odds Ratio; RR = Relative Risk; MTX = Methotrexate; SSZ = Sulfasalazine; HCQ = Hydroxychloroquine; DMARD = Disease-modifying Antirheumatic Drug; TNF = Tumor Necrosis Factor; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease; CHF = Chronic Heart Failure; MI = Myocardial Infarction; QUEST-RA = QUESTionnaires in SToandard Monitoring of Patients with Rheumatoid Arthritis Program; CORRONA = Consortium of Rheumatology Researchers of North America RA registry.
A landmark study of 1,240 patients with RA, followed up for 6 years at the Wichita Arthritis Center (US), demonstrated a 70% decrease in the risk of cardiovascular mortality due to the exposure to various doses of MTX (HR 0.3, 95%CI 0.2-0.7, P<0.001) [45]. In the same study, MTX did not have a significant effect on noncardiovascular mortality (HR 0.6, 95%CI 0.2-1.2). Also, in a case-control study of 613 patients with RA, MTX alone or in combination with other DMARDs (sulfasalazine and/or hydroxychloroquine) demonstrated a significant reduction of the risk of atherosclerotic vascular morbidity [46], though the number of cardiovascular events in that study was relatively low (72). In a much larger cohort of 16,752 patients, who were followed up for 4 years, the exposure to MTX decreased the risk of both atherosclerotic and nonatherosclerotic vascular manifestations (HR 0.65, 95% CI 0.59-0.72) [47].

The notorious multicenter QUEST-RA study (Questionnaires in STandard Monitoring of Patients with Rheumatoid Arthritis Program) proved that prolonged MTX therapy was associated with a 15% decrease in the risk of all cardiovascular disorders and an 18% decrease in the risk of MI, irrespective of the prevalence of cardiovascular risk factors, RA activity, and patients’ functional status [48]. Similar trends in the risk reduction were apparent for leflunomide, sulfasalazine, glucocorticoids, and biologic agents. Cases of fatal atrial fibrillation were particularly related to lipid-regulating but not to antihypertensive effects of MTX.

A dose-dependent effect of MTX on CVD was analyzed in a cohort of 6,707 patients with RA (90% males) by Prod'homme S, et al [49]. Overall, a 17% decrease in the risk of cardiovascular disorders was noted due to MTX therapy (Relative Risk [RR] 0.83). Low-dose MTX therapy (<7.5 mg/week) was associated with decreased risk of all cardiovascular diseases (RR=0.65, 95%CI 0.52-0.8) while high-dose therapy (>30 mg/week) did not have such effect (RR=1.0; 95%CI 0.83-1.22). The absence of the effect might be due to the high intensity of rheumatoid inflammation, requiring high doses of MTX.

An analysis of the CORRONA (Consortium of Rheumatology Researchers Of North America RA) registry also did not demonstrate any effect of MTX on a composite cardiovascular risk reduction (HR 0.94, 95% CI 0.49-1.8) [50]. Therapy with TNF antagonists in the CORRONA study proved to significantly reduce the composite cardiovascular risk (HR 0.39, 95% CI 0.19 to 0.82), though there were limitations owing to the small number of cardiovascular events (88 for a cohort of 10,156 subjects) over a relatively short followup (23 months). A much larger North American cohort study (107,908 patients) did not find any cardiovascular benefit of biologic therapy and simply a borderline effect of MTX on reduction of MI risk (Rate Ratio 0.81, 95%CI 0.60-1.08) [51]. Likewise, MTX was found to have a borderline effect on the reduction of the risk of hospitalizations due to heart failure (0.8, 95%CI 0.6-1.0) [52]. Finally, a study of 795 patients, of whom 92 developed heart failure during the followup, reported a 50% heart failure risk reduction for those on MTX, compared to nonusers of MTX (0.5, 95%CI 0.3-0.9) [53].

To sum up, MTX therapy brings about cardiovascular protection in RA by controlling systemic inflammation and reducing related risk of atherosclerotic vascular events [54, 55]. Notably, a pooled analysis of 8 prospective and 2 retrospective cohort studies on MTX with a total of 66,334 subjects with inflammatory arthritis, who developed 6,235 cardiovascular events, demonstrated a 21% cardiovascular disease and an 18% MI risk reduction [55]. Such a significant cardiovascular risk reduction persisted after adjustment for underlying disease severity and concomitant use of other drugs.

**METHODS: THERAPY AND CARDIOVASCULAR RISK FACTORS IN RA**

Several cross-sectional and longitudinal studies have evaluated the influence of MTX on separate cardiovascular risk factors and markers, which may confound the drug's effects on cardiovascular morbidity and mortality (Table 2) [56-60]. Limitations of these studies are related to small number of patients, short followup periods, and absence of proper controls for concomitant use of multiple antiinflammatory drugs, and primarily glucocorticoids.

MTX therapy dampens systemic inflammation and reduces levels of inflammatory markers, which may alter lipid profiles. A pilot 3-month study of MTX therapy and reduced saturated fatty acids diet in RA demonstrated a significant decrease of CRP without meaningful alterations of lipids [56]. A one-year study of 39 patients with RA on MTX therapy revealed improvements in the course of arthritis in 27 patients with a significant elevation of HDL-C (P<0.001) and nonsignificant decrease of the atherogenic index (LDL-C/HDL-C ratio) [57]. In another cohort of 58 patients with early RA one-year stable MTX therapy at 15.5 mg/week along with low-dose prednisone significantly decreased atherogenic index that correlated with decreased ESR and CRP [58].

Decreased triglyceride and increased HDL-C were also noted in the UK-based Dudley cohort of 387 patients, which was due to the regular long-term MTX therapy [59]. Logistic regression analysis proved that MTX use is associated with low risk of the metabolic syndrome in RA in the same cohort (adjusted Odds Ratio 0.517, 95%CI 0.33-0.81, P=0.004) [59] that may be due to lipid-regulating but not to antihypertensive effects of MTX therapy [60].

Altogether, preliminary longitudinal and retrospective cohort studies suggest that MTX suppresses systemic inflammation and regulates cholesterol transport, thereby decreasing atherogenic index. Specifically designed and properly controlled long-term prospective studies are warranted to confirm these results.

An important issue arises as to whether MTX therapy influences atherosclerotic risk markers in RA. A few preliminary studies examining intimal-medial thickness and atherosclerotic plaques of the common carotid and femoral arteries in small cohorts, revealed no changes between those treated and nontreated with MTX over 3-24 months [61-63]. Biologists seem to exert a more pronounced effect on the arterial intima [63], though large prospective studies are still pending to evaluate vascular benefits of MTX and its comparators.

Finally, there are concerns that cardioprotective benefits of MTX therapy may be diminished by the inhibition of homocysteine-methionine pathway and the resultant hyper-
mocysteinemia, a modifiable cardiovascular risk factor [64-66]. Indeed, hyperhomocysteinemia is often reported in patients with RA on low-dose MTX therapy (5-25 mg/week) [67], and particularly in male patients, subjects with advanced radiological damage [68], and those exposed to combined MTX and sulfasalazine therapy [69]. A recent US-based cohort study distinguished hyperhomocysteinemia as a factor independently tripling the risk of hypertension in RA [70]. Elevated homocysteine can damage endothelial cells, trigger LDL oxidation, contribute to the production of proinflammatory HDL and asymmetric dimethylarginine, and thereby enhance atherothrombosis [71-73].

Currently available evidence, derived from small prospective cohort studies, suggests that continuous folic acid supplementation overcomes MTX-induced hyperhomocysteinemia that may contribute to the overall cardiovascular protection in RA [74-76]. And a recent Cochrane systematic review of 6 trials with 624 patients supported a protective effect of supplementation with low-dose of folic acid (below 7 mg/week), which allows to reduce the incidence of MTX-induced gastrointestinal adverse effects and hepatic dysfunction [77]. That systematic review also proved the crucial role of folic acid supplementation in avoiding MTX discontinuation for any reason, though no data were presented on cardiovascular risk. Further large prospective studies on the effect of folic acid supplementation on cardiovascular morbidity and mortality in RA are still pending.

**CONCLUSION**

RA is a chronic progressive inflammatory disorder with enhanced cardiovascular risk. Numerous (auto)immune and inflammatory pathways leading to atherothrombosis in RA have been explored. Proinflammatory cytokines, which are produced by macrophages/monocytes, neutrophils, platelets, and other immune cells, induce rheumatoid inflammation in the joints’ synovium and vascular wall, subsequently damaging the endothelium, altering cholesterol transport, and enhancing thrombogenicity [78-80]. Continuous suppression of the production of proinflammatory cytokines is therefore a strategy to tackle with the highly prevalent cardiovascular risk factors and comorbidities in RA.
MTX is the first-line DMARD, which is widely used for mono- and combined therapy of RA. With earlier and uninterrupted use of MTX, it is possible to effectively control the immune inflammation in the joints and vascular walls, thereby improving cardiovascular and total mortality in RA. Several systematic reviews and meta-analyses of observational cohorts prove that despite the availability of numerous synthetic DMARDs, potently suppressing inflammatory pathways in RA, MTX with its moderate antiinflammatory properties retains its position as a relatively safe drug with beneficial thrombogenic and atherogenic profiles [54, 55, 81, 82]. It is plausible that MTX therapy may have better outcomes with folic acid supplementation. Large prospective studies are warranted to comparatively assess cardiovascular implications of MTX, biologics, and other antiinflammatory agents. One such prospective, one-year cardiovascular imaging study, which is called Coronary Artery Disease Evaluation in Rheumatoid Arthritis (CADERA), is now underway to examine 120 patients with early, treatment naïve RA, randomized to MTX and combinations of MTX with synthetic DMARDs [83].

In the meanwhile, low-dose MTX is actively promoted as a safe and potentially effective means for secondary prevention of cardiovascular events in high-risk non-RA cohorts [84]. The success of the recently launched Cardiovascular Inflammation Reduction Trial (CIRT), comparing cardiovascular implications of MTX at a target dose of 20 mg/week versus placebo in post-MI non-RA population, may provide further evidence in support of the inflammatory hypothesis of atherogenesis and justify the use of antiinflammatory agents for cardiovascular prevention in the general population [21].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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REFERENCES


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- Cuones, E.; Chan, E.S.; Reiss AB. Methotrexate in atherogenesis and cholesterol metabolism. *Cholesterol*, 2011, 503028.


